

IMAGES IN GASTROENTROLOGY AND HEPATOLOGY

Part II

**J. C. Walsh
A. B. R. Thomson**

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CANMED OBJECTIVES

Medical Expert

The discussion of complex cases provides the participants with an opportunity to comment on additional focused history and physical examination. They would provide a complete and organized assessment. Participants are encouraged to identify key features, and they develop an approach to problem-solving.

The case discussions, as well as the discussion of cases around a diagnostic imaging, pathological or endoscopic base provides the means for the candidate to establish an appropriate management plan based on the best available evidence to clinical practice. Throughout, an attempt is made to develop strategies for diagnosis and development of clinical reasoning skills.

Communicator

The participants demonstrate their ability to communicate their knowledge, clinical findings, and management plan in a respectful, concise and interactive manner. When the participants play the role of examiners, they demonstrate their ability to listen actively and effectively, to ask questions in an open-ended manner, and to provide constructive, helpful feedback in a professional and non-intimidating manner.

Collaborator

The participants use the “you have a green consult card” technique of answering questions as fast as they are able, and then to interact with another health professional participant to move forward the discussion and problem solving. This helps the participants to build upon what they have already learned about the importance of collegial interaction.

Manager

The participants are provided with assignments in advance of the three day GI Practice Review. There is much work for them to complete before as well as afterwards, so they learn to manage their time effectively, and to complete the assigned tasks proficiently and on time. They learn to work in teams to achieve answers from small group participation, and then to share this with other small group participants through effective delegation of work. Some of the material they must access demands that they use information technology effectively to access information that will help to facilitate the delineation of adequately broad differential diagnoses, as well as rational and cost-effective management plans.

Health Advocate

In the answering of the questions and case discussions, the participants are required to consider the risks, benefits, and costs and impacts of investigations and therapeutic alliances upon the patient and their loved ones.

Scholar

By committing to the pre- and post-study requirements, plus the intense three day active learning Practice Review with colleagues is a demonstration of commitment to personal education. Through the interactive nature of the discussions and the use of the “green consult card”, they reinforce their previous learning of the importance of collaborating and helping one another to learn.



Professional

The participants are coached how to interact verbally in a professional setting, being straightforward, clear and helpful. They learn to be honest when they cannot answer questions, make a diagnosis, or advance a management plan. They learn how to deal with aggressive or demotivated colleagues, how to deal with knowledge deficits, how to speculate on a missing knowledge byte by using first principles and deductive reasoning. In a safe and supportive setting they learn to seek and accept advice, to acknowledge awareness of personal limitations, and to give and take 360° feedback.

Knowledge

The basic science aspects of gastroenterology are considered in adequate detail to understand the mechanisms of disease, and the basis of investigations and treatment. In this way, the participants respect the importance of an adequate foundation in basic sciences, the designing of clinical research studies to provide an evidence-based approach, the relevance of their management plans being patient-focused, and the need to add “compassionate” to the Three C’s of Medical Practice: competent, caring and compassionate.

“They may forget what you said, but they will never forget how you made them feel.”

Carl W. Buechner, on teaching.

“With competence, care for the patient. With compassion, care about the person.”

Alan B. R. Thomson, on being a physician.



PROLOGUE

Like any good story, there is no real beginning or ending, just an in-between glimpse of the passing of time, a peek into a reality of people's minds, thoughts, feelings, and beliefs. The truth, as I know, has a personal perspective which drifts into the soul of creation. When does life begin, when does an idea become conceived, when do we see love or touch reality? A caring, supportive, safe, and stimulating environment creates the holding blanket, waiting for the energy and passion of those who dream, invent, create – disrupt the accepted, challenge the conventional, ask questions with forbidden answers. Be a child of the 60s. Just as each of us is a speck of dust in the greater humanity, the metamorphosis of the idea is but a single sparkle in the limitlessness of the Divine Intelligence. We are the ideas, and they are us. No one of us is truly the only parent of the idea, for in each of us is bestowed the intertwined circle of the external beginning and the end.....during a visit to the Division of Gastroenterology at the University of Ottawa several years ago, the trainees remarked how useful it would be to have more than two hours of learning exchange, a highly interactive tutorial with concepts, problem solving, collegial discussion, the fun and joys of discovery and successes. Ms. Jane Upshall of BYK Canada (Atlanta, Nycomed), who had sponsored two of these visiting Professorships, encouraged the possibility of the development of a longer program. Her successor, Lynne Jamme, supported the initial three-day educational event for the trainees enrolled in the GI training program at the University of Ottawa. With her entrepreneurial foresight, wisdom, and enthusiasm, the idea began. Lynne's commitment to an event which benefited many of the future clinicians, who will care for ourselves and our loved ones, took hold. Then, thanks to the GI program directors in Ottawa and the University of Western Ontario, Nav **Saloojee** and Jamie Gregor, more trainees were exposed, future GI fellows talked with other trainees, and a grass roots initiative began. Had it not been for Nav and Jamie's willingness to take a risk on something new, had they not believed in me, then there would have been no further outreach. Thank you, Lynne, Nav, and Jamie. You were there at the beginning. I needed you.

By 2008, all but one GI program in the country gave their trainees time off work to participate in the three-day event, GI Practice Review (GI-PR). The course is 90% unsponsored, and is gratis to the participants, (except for the cost of their enthusiastic participation!) I am happy to give back to the subspecialty that gave me so much for 33 years. I hope GI-PR is helpful to all trainees. I know that from these future leaders there will arise those who will continue to dedicate and donate their time, energy, and ability to the betterment of those who contribute to the continued improvement of our medical profession. The clinicians, the teachers, the researchers.

In a short span of eight years, more than 300 fellows, coming from all the 14 training programs in Canada, have participated in the small group sessions in the GI practice review. I thank the training program directors who have supported GI-PR. Special appreciation as well to their many staff physicians who worked without their trainees for the three days of each program.

The idea for the electronic and hard copy summary of the "list of facts" came from the trainees who wished for an aide memoir. But the GI-PR is about more than lists and facts - it is about problem formulation, case discussions, review of endoscopy, histopathology, motility, diagnostic imaging. It is about having fun working together to learn. The subterfuge to gain interest in the basic sciences is the use of clinical scenarios to show the way to the importance of first principles. While the lists are here, the experience is in the performance.



The child will grow, the images will expand, the learning of all aspects of our craft will develop and flourish amongst persons of good will. Examinations will become second nature, as each clinical encounter, each person, each patient, becomes our test, the determination of clinical competence, of caring, of compassion. May these three Cs become part of each of our life's narrative. And from this start comes Capstone Academic Publishing, an innovation for the highest quality and value in educational material, made available at cost, speaking in tongues, in the languages of many cultures, with the dialect of the true North strong and free, so that knowledge will be free at last. Outstanding medical practice and true dedication to those from whom we receive both a privilege and pleasure of care, comes from much more than the GI-PR can give you, much more than Q & As, descriptions of diagnostic imaging or endoscopy stills or videos, histopathology or motility. True, we need all of these to jump over a very high bar. But to be a truly outstanding physician, you need to care for and care about people, and you must respect the dignity and rights of all others. You must strike a balance between love and justice, and you place your family and friends at the top of your wish-list of lifetime achievements.

For the skeptics who ask "What do you want from me?" I simply say "You are the future; I trust that in time you too will help young people to be the best they can be."

May good luck, good health, modesty, peace, and understanding be with you always. Through medicine, all persons of the world may come to share caring, respect, dignity, and justice.

Sincerely,
Alan Thomson

Emeritus Distinguished University Professor, U of A
Adjunct Professor, Western University, London, Canada



ACKNOWLEDGEMENTS

Patience and patients go hand in hand. So also does the interlocking of young and old, love and justice, equality and fairness. No author can have thoughts transformed into words, no teacher can make ideas become behavior and wisdom and art, without those special people who turn our minds to the practical - of getting the job done!

Thank you, Naiyana, for translating those scribbles (called my handwriting), into the still magical legibility of the electronic age. Sarah, thank you for your hard work and creativity.

My most sincere and heartfelt thanks go to the excellent persons at JP Consulting, and CapStone Academic Publishers. Jessica, you are brilliant, efficient, dedicated, and caring. Thank you most sincerely.

When Rebecca, Maxwell, Megan, Henry, Felix, Toby, Grady and Jasper, ask about their Grandad, I will depend on James and Anne, Matthew and Allison, Jessica and Matt, and Benjamin to be understanding, generous, kind and forgiving. For what I was trying to say and to do was to make my professional life focused on the four Cs and an “H”; competence, caring, compassion, and composure, as well as humor - and to make my very private personal life dedicated to family – to you all.



DEDICATIONS

For Jeremy, who makes me believe that I can accomplish anything,
For my little loves Michael, Dennis & Julia, who fill my life with joy,
and
For all the Canadian women physicians who support and raise each other higher.

Joanna Walsh

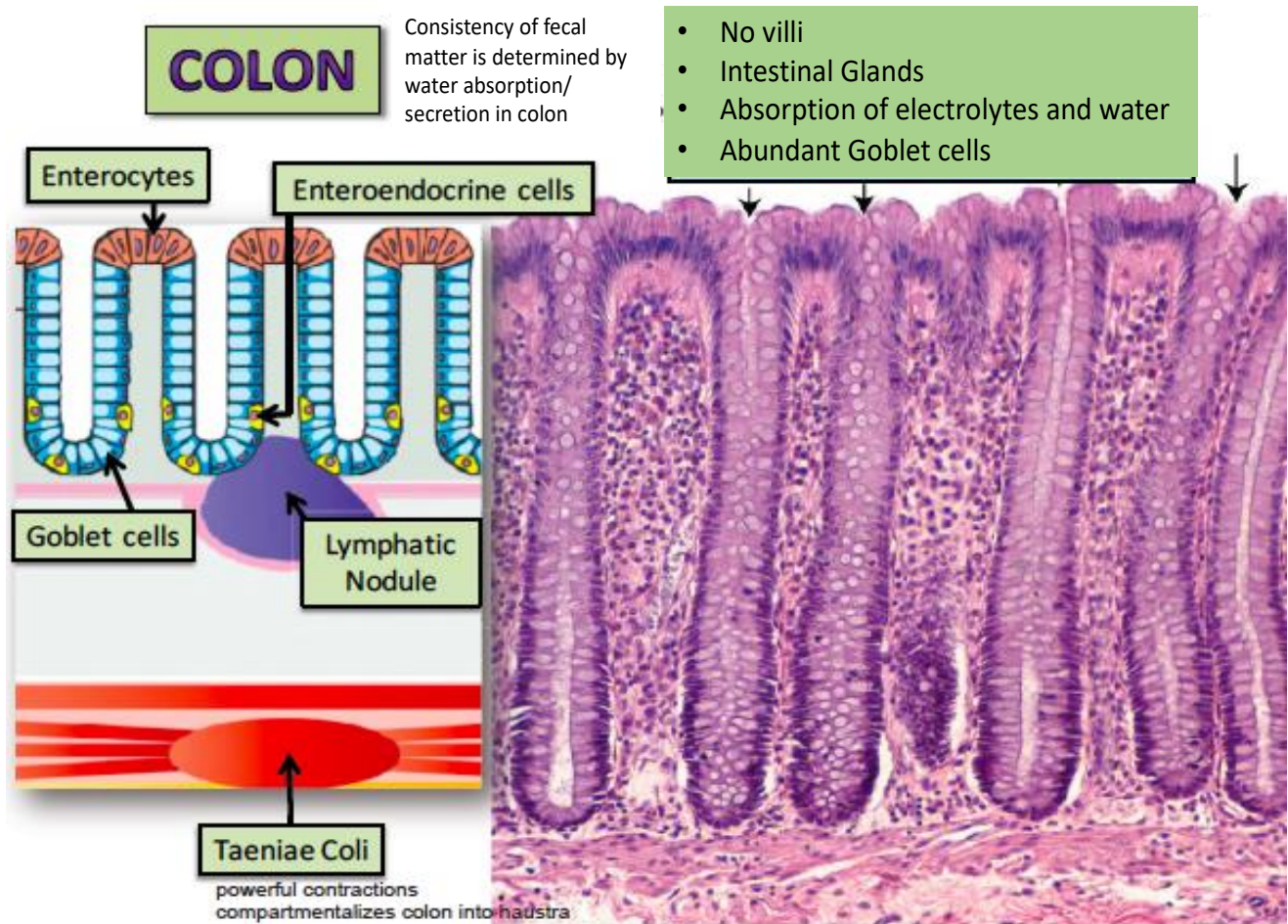
This book is dedicated to Jeannette for her strength, courage and commitment to survive
the year of 2020.

Alan Thomson





NORMAL HISTOLOGY

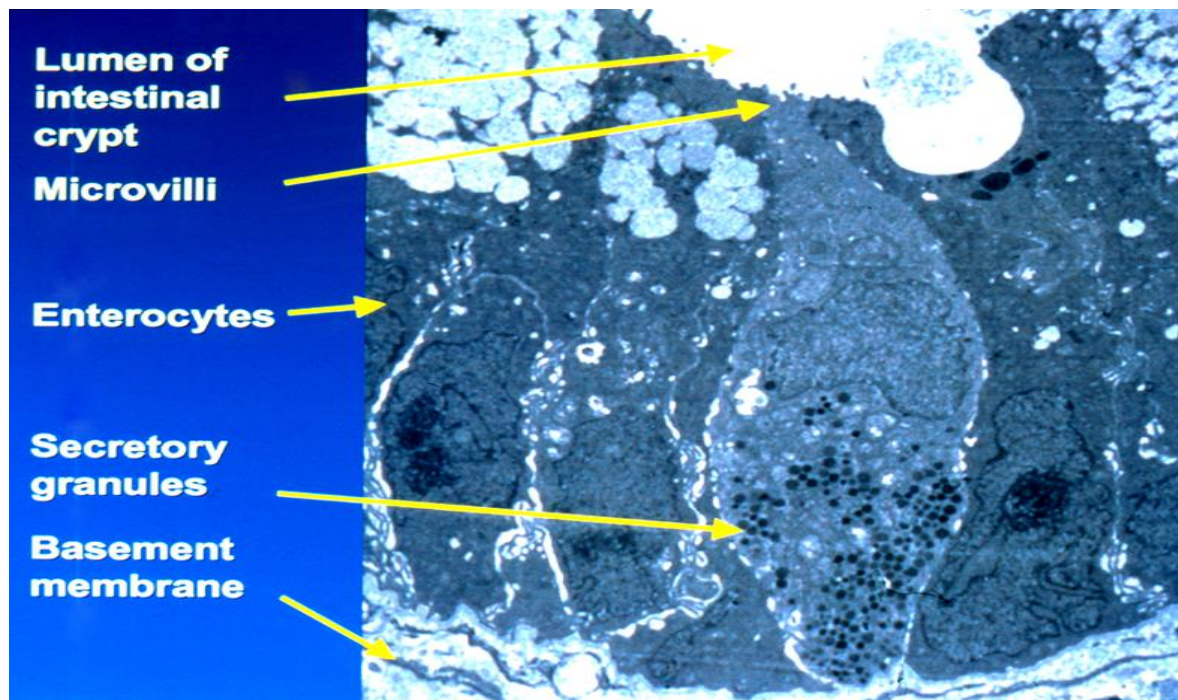


- The wall of the colon is comprised of an inner circular and an outer longitudinal muscle layer, the “muscularis propria”.
- The longitudinal muscle layer is discontinuous, running in three 6-to-10 mm wide bands (teniae coli) from the cecum to the rectum.
- There is no muscle between the teniae coli, leading to three bulges in the wall of the colon, called the “haustra”.
- The haustra are between the teniae coli
- Because these muscles are tonically contracted and then suddenly relax, their size changes with contraction and relaxation of the muscle bands.
- When the muscle coats contract, the flat mucosal surface of the colon appears as folds, known as the semilunar folds or the plicae semilunaris.
- The cecum, ascending and descending colon are less mobile than the transverse colon and sigmoid colon, each of which has a mesentery.
- The right column contains Paneth cells.



- The ileocecal valve (ICV) appears as two transverse folds.
- The ICV is anatomically not a sphincter, but has a resting tone of 20 mm Hg and so is capable of functioning in this manner.
- When the terminal ileum is distended, the ICV pressure falls so that small intestinal contents pass into the cecum.
- The (vermiform) appendix is attached to the medial wall of the cecum of adults. Its function in humans is unknown.
- The S-shaped sigmoid colon is angulated, particularly at the rectosigmoid junction, where the colon begins to have a peritoneal surface.
- The colonic mucosa becomes smoother in the rectum, which passes between the sacrum and the uterus in females, or between the sacrum and the bladder in males.
- The inner circular muscle of the colon becomes thicker and ends as the internal anal sphincter (IAS).
- A layer of elastic fibers and the outer longitudinal layer of the rectum separate the IAS from the outer external anal sphincter (EAS).
- The EAS is skeletal muscle, and is under voluntary control.

Enterochromaffin Cell

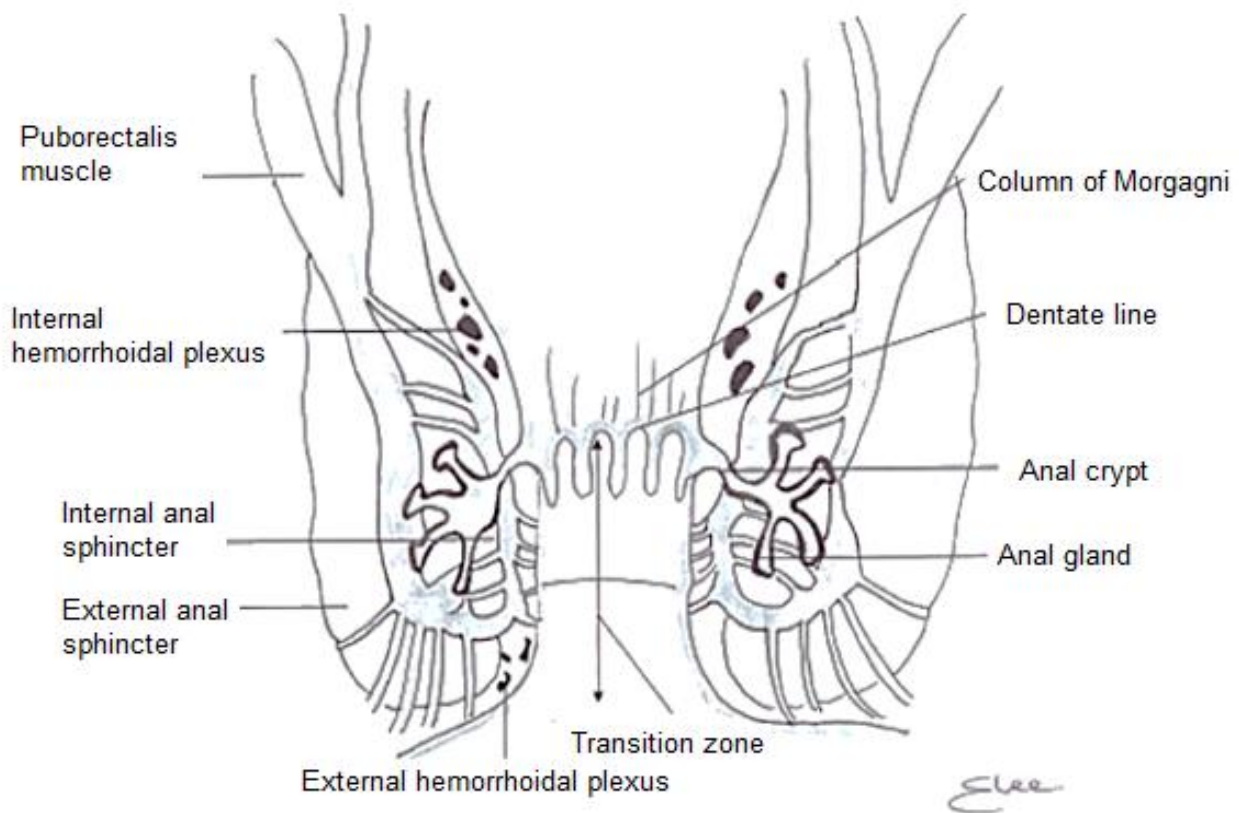


Courtesy of Dr. Spiller RC.



ANORECTAL AND PERIANAL DISEASE

➤ The Anatomy of the Anal Region



Adapted from: Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 8th Edition. Saunders / Elsevier, Philadelphia, 2006, Figure 122-1, page 2834.

Rectal Prolapse (aka Rectal Procidentia)

➤ Definition

- Intussusception of the rectum, internally on itself, through the anus
 - Partial
 - protrusion of the mucosa
 - Complete
 - protrusion of all layers

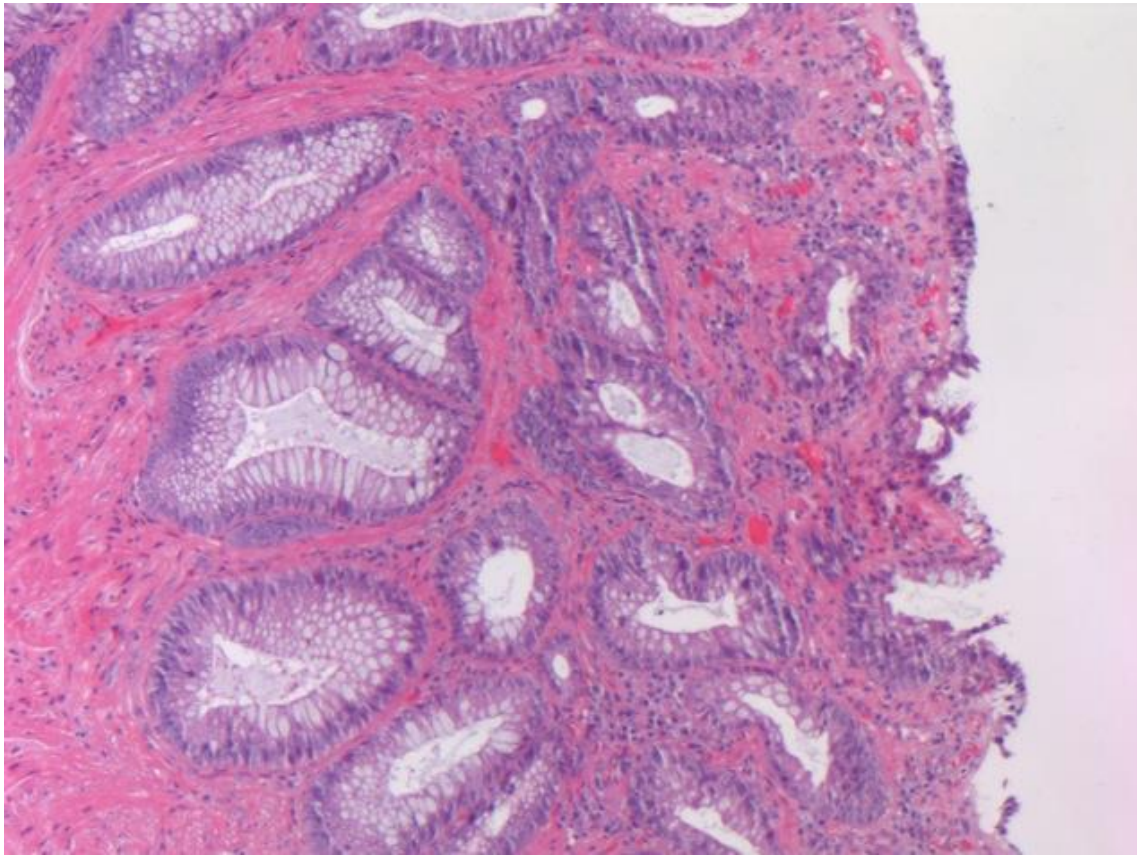
➤ Demography

- 15% to 30% of women with rectal prolapse have pelvic floor dysfunction or anatomic defects, e.g., rectocele, cystocele, enterocele



➤ Histopathology

Mucosal Prolapse



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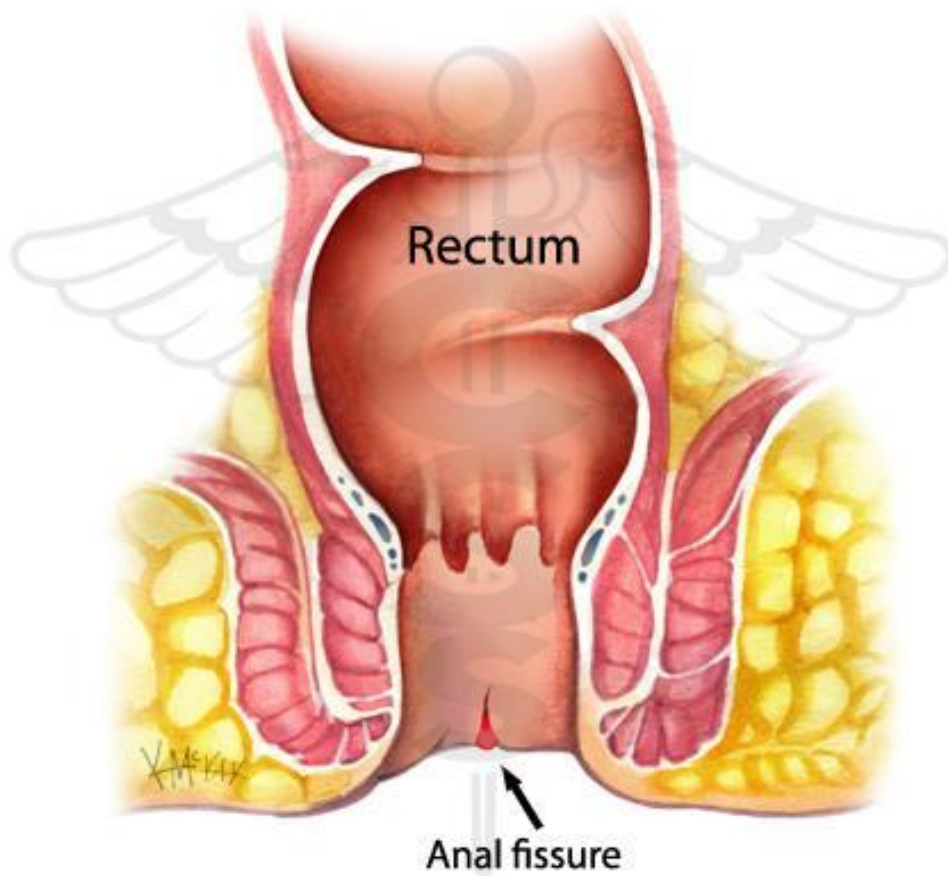
- Mucosal prolapse may be given different names by the pathologist but common features are serrated changes in the epithelium with smooth muscle splaying upwards between the crypts.
 - Mucosal prolapse type polyp / features consistent with mucosal prolapse – may be used when only the features described above are present
 - Inflammatory cloacogenic polyp – may be used when anal squamous mucosa is present in the sample
 - Solitary rectal ulcer (syndrome) – may be used when there is a clinical description of rectal ulceration and a biopsy shows erosion / ulcer



Anal Fissure

➤ Definition

- A longitudinal cut in the anoderm
- Position
 - Mid posterior, 90%
 - Anterior, 10%
- Constipation → stretch strains spasm – fissure?
- Anal area “Animus”
- Sharp pain in anus



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Perianal Fistulas in Crohn Disease (CD)

- Demography
 - 20-30 % of patients with CD have fistulas
 - 50% of patients with Crohn colitis and perianal fistulas end with ileostomy
- Pathology
 - Often multiple, also located laterally or centrally
 - Often wide with undermined edges
 - Limited pain, lack of reactive sphincter spasm
 - Covered with indurated firm cap-like skin fold
 - Reddish violet edematous perianal skin with radial pronounced furrows
 - Limited tendency to healing

Perianal Fistulas



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Perianal Fistulas



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- Histopathology
 - Fistulization
 - Peri-enteric / perianal abscess formation

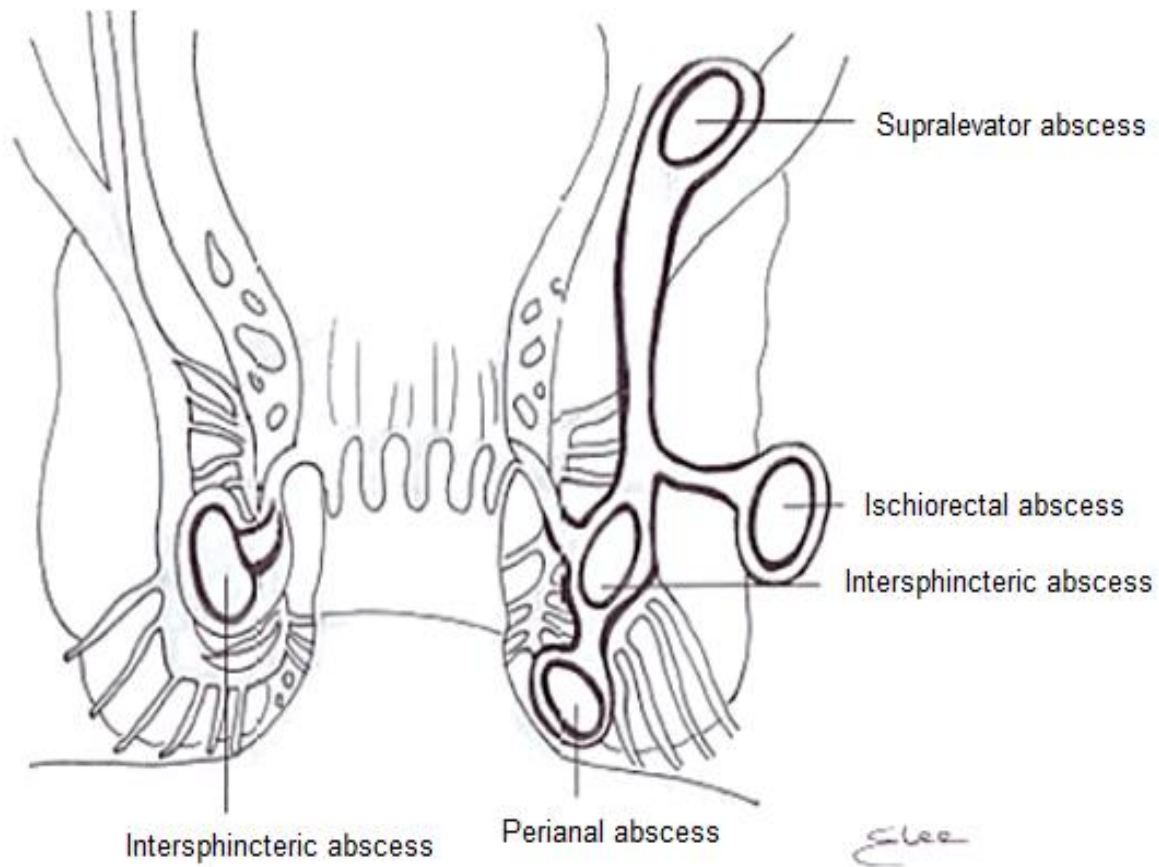


Fistula-in-ano

➤ Definition

- A tunnel that connects an internal opening, usually at an anal crypt at the base of the columns of Morgagni, with an external opening, usually on the anal skin" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 2267).

➤ Classification of Abscesses of Anal Region Based of their Location



Adapted from: Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 8th Edition. Saunders / Elsevier, Philadelphia, 2006, Figure 122-3, page 2843.



Hemorrhoids

- Definition
 - Dilated vascular channels
- Position
 - 3, 7, 11 o'clock positions
- Surface
 - Internal
 - Above dentate line
 - Covered by columnar or transitional mucosa
 - External
 - Below dentate line
 - Covered by squamous mucosa
- Endoscopy

Hemorrhoids, retroflexed view



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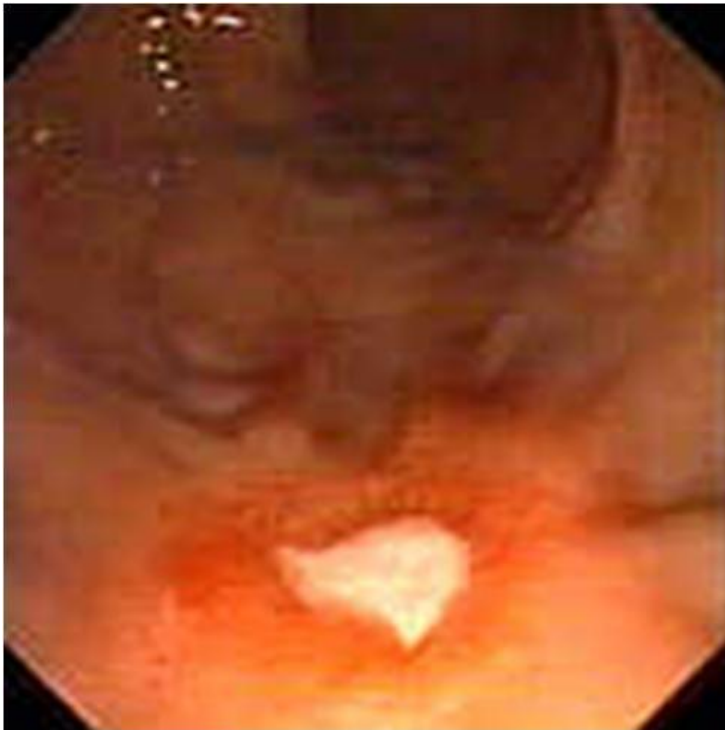
Solitary Rectal Ulcer Syndrome (SRUS)

➤ Definition

- Single or multiple ulcers, polypoid lesion
- Typical pathology
 - Lamina propria replaced by fibromuscular tissue
 - Muscularis mucosae hypertrophied and splayed (“prolapse type features”), with muscle fibres extending between crypts, towards the lumen
- Pathogenesis: “occult or overt rectal prolapse with paradoxical contraction of the pelvic floor during defecation....” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 2080).
- Usual site of prolapse of rectal mucosa is anterior wall of the rectum, 7 cm to 10 cm above the verge of the anus.

➤ Endoscopy

Solitary Rectal Ulcer Syndrome

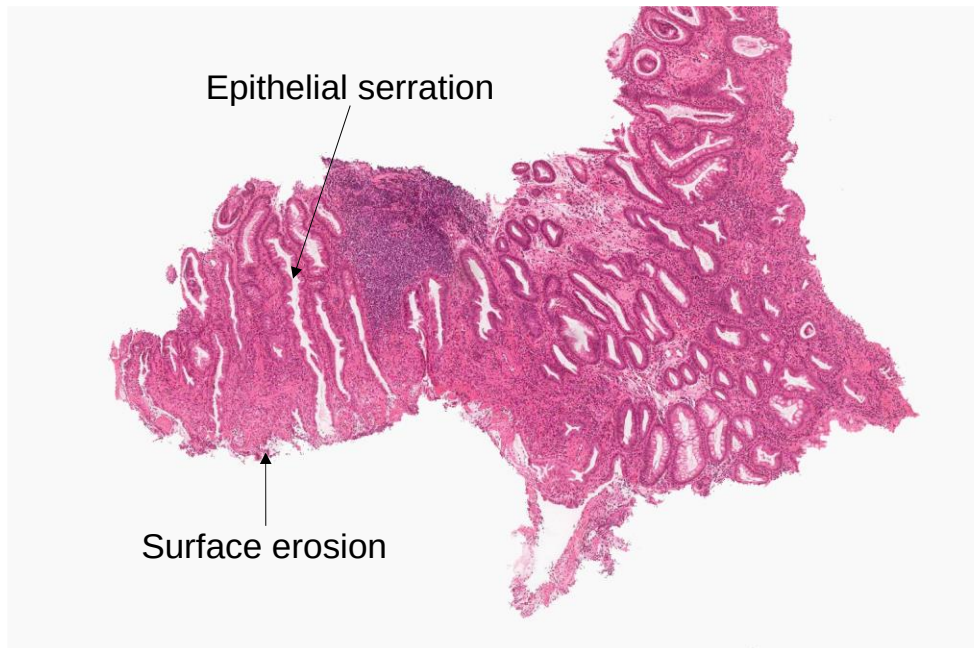


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➤ Histopathology

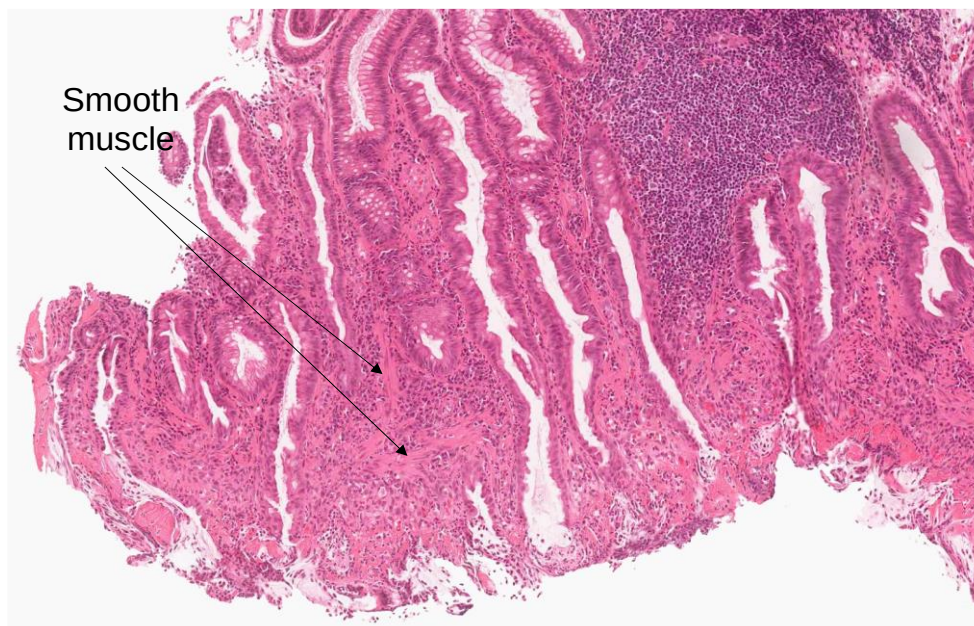
Solitary rectal ulcer syndrome (H&E, 40X)



SRUS / mucosal prolapse showing serrated crypts and surface erosion

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Solitary rectal ulcer syndrome (H&E, 100X)



SRUS / mucosal prolapse showing smooth muscle strands within the lamina propria

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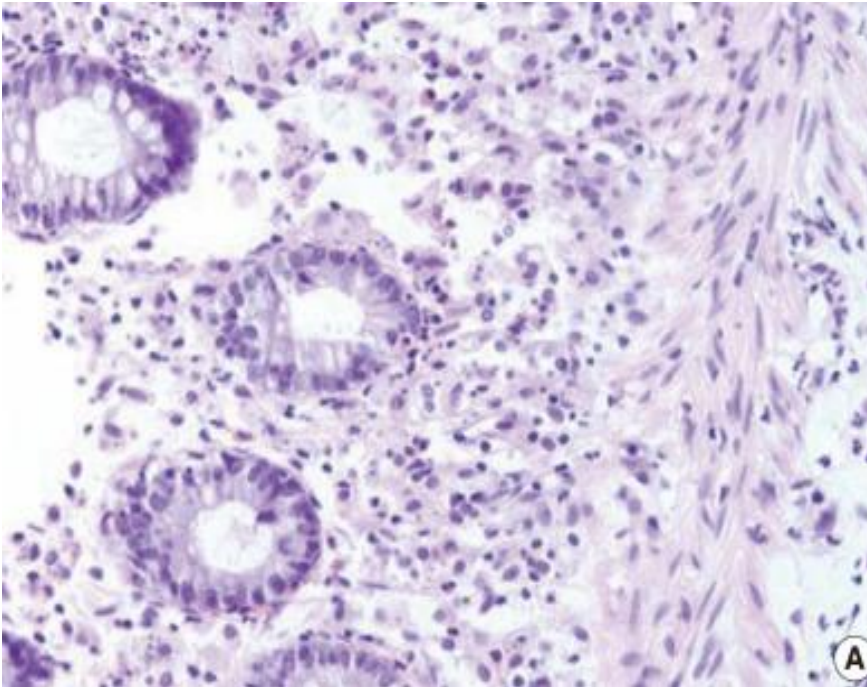


Malakoplakia of Colon

- Definition
 - A rare granulomatous disease of infectious etiology
- Demography
 - More common in persons exposed to chemotherapy, immunosuppression for organ transplantation, or with AIDs.
- Pathology
 - Malakoplakia may be suspected on colonoscopy by the presence of yellowish, friable mucosal lesions.
 - The pigment is lipofuscin within macrophages.
 - The focal form (as compared to the diffuse or isolated [to the rectosigmoid area] form) may be associated with adenomatous polyps or CRC.
- Histopathology
- Give histological features associated with colonic **malakoplakia**, and indicate (*) which feature is considered to be diagnostic.
 - Macrophages
 - Sheets of large, pale macrophages
 - Cytoplasm may contain coliform bacteria
 - Inclusion bodies*
 - In cytoplasm
 - Laminated
- In the context of malakoplakia, give the meaning of von Hanseman cells, and Michaelis-Gutmann bodies.
 - Von Hanseman cells
 - Coliform bacteria in the cytoplasm of macrophages in the colonic mucosal biopsies
 - Michaelis-Gutmann bodies
 - Laminated intracytoplasmic inclusion bodies



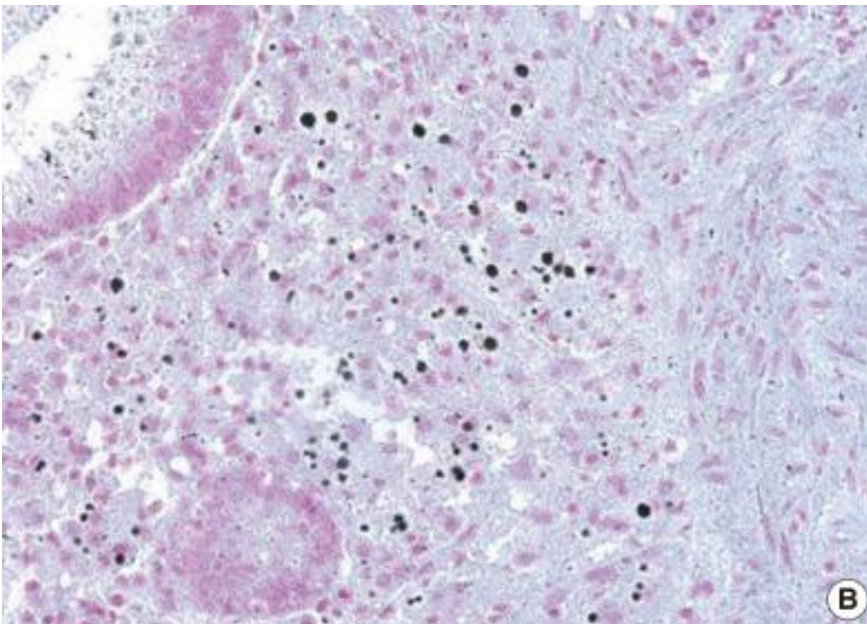
Malakoplakia of Colon



Michaelis-Gutmann bodies are positively stained on von Kossa stain.

(A) Hematoxylin and eosin stain.

(B) von Kossa stain



Printed with permission: Bae GE, et al. Korean Journal of Pathology 2013; 47(2): 163-166.



DEFECATION

Constipation

➤ Definition

- IBS, constipation
 - Unlike irritable bowel syndrome, constipation (IBS-C) predominant chronic idiopathic constipation (CIC) does not have pain component
- Slow proximal colonic transit but normal distal transit suggests slow transit constipation. Normal proximal colonic transit but slow distal transit suggests pelvic dyssynergy or anorectal dysfunction
- Only slow transit constipation will respond to subtotal colectomy with ileorectal anastomosis
- With dilation of both the colon and rectum, as well as normal anal sphincter function, proctocolectomy and an ileoanal anastomosis may be suitable; if anal sphincter function is abnormal, an ileostomy needs to be performed

Please see: Chaun H. Chapter 56. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 3: Constipation, page 741-745.

➤ Diagnostic imaging

Rectal filling defect: FOB positive in 55 year old woman on NSAIDs for osteoarthritis

Colonic Filling Defect: Air contrast barium enema



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➤ Endoscopy

Melanosis Coli



- Chronic laxative abuse

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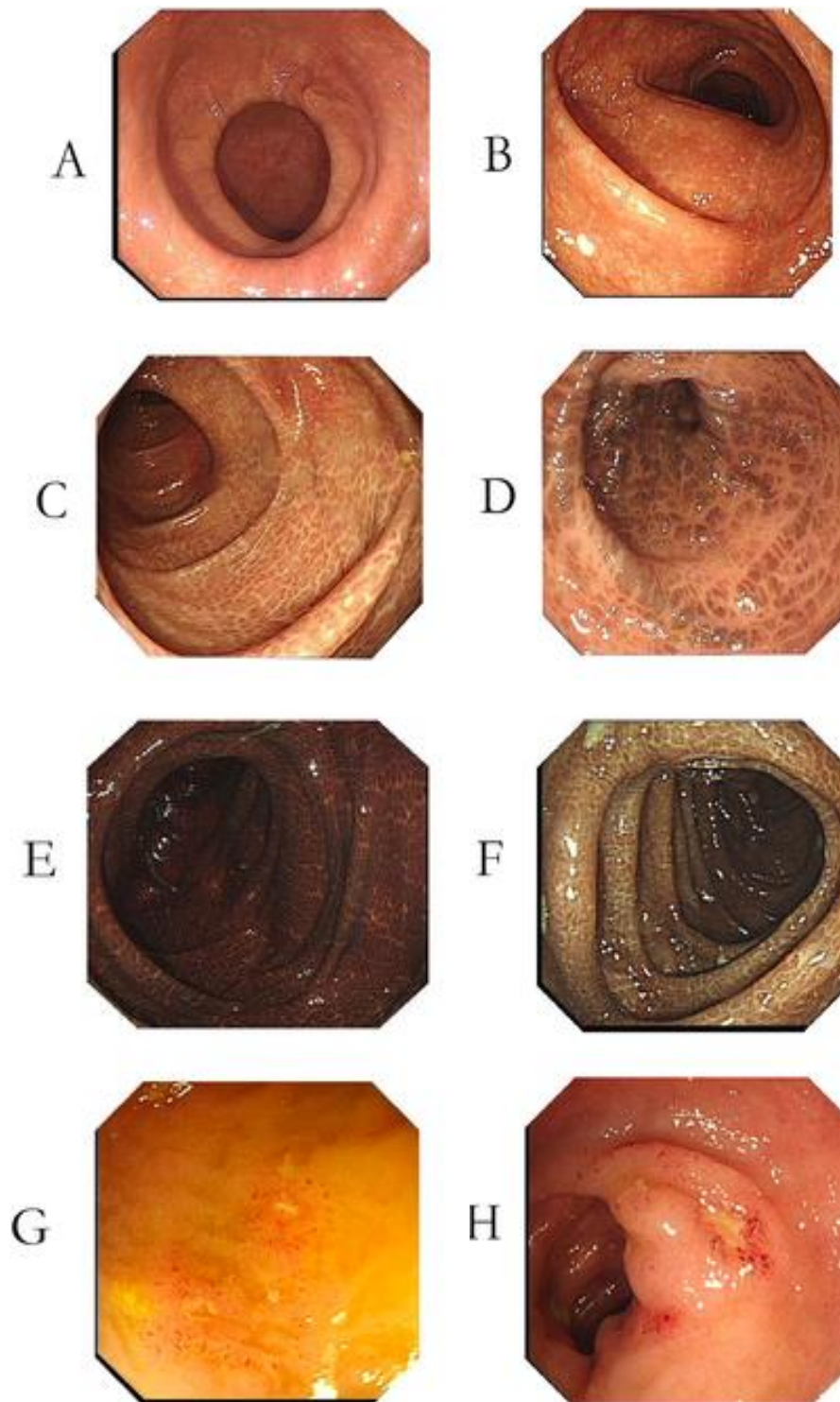
Melanosis Coli



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Melanosis Coli

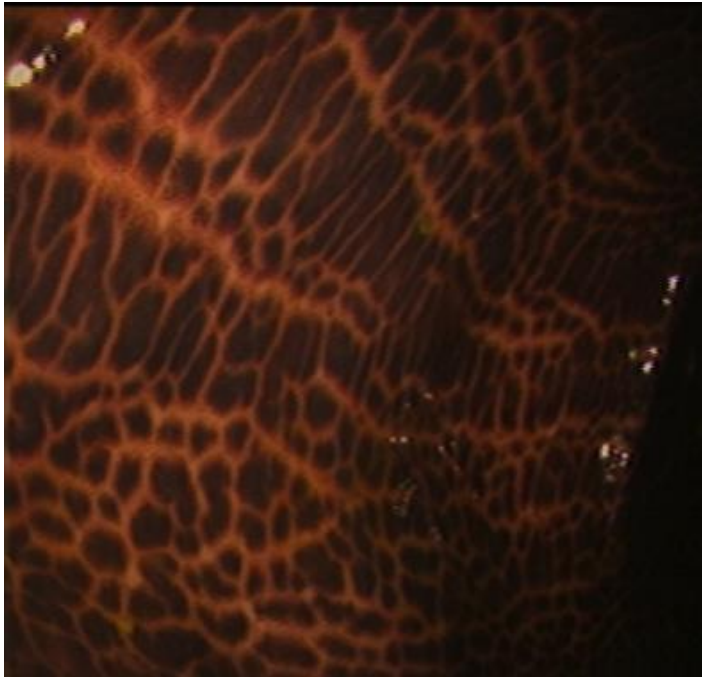


- Melanosis coli of different grades and distal ileum ulcer.
 - (A), (B): Melanosis coli Grade I, macroscopically appearing as light brown colonic mucosa, without clear boundary with normal mucosa
 - (C), (D): Melanosis coli Grade II, macroscopically appearing as brown colonic mucosa, with clear linear or non-continuous boundary with normal mucosa.
 - (E), (F): Melanosis coli Grade III, macroscopically appearing as dark black colonic mucosa with linear or spotted boundary with normal mucosa
 - (G), (H): Distal ileum ulcers endoscopically discovered at six patients suffering from melanosis coli.
- The ulcers were multiple, small, and superficial, and mucosa around the ulcers seems normal. Pathology of the ulcers was all nonspecific inflammation.

Printed with permission: Liu ZH, et al. PLOS ONE 2017;12(10): e0186668.



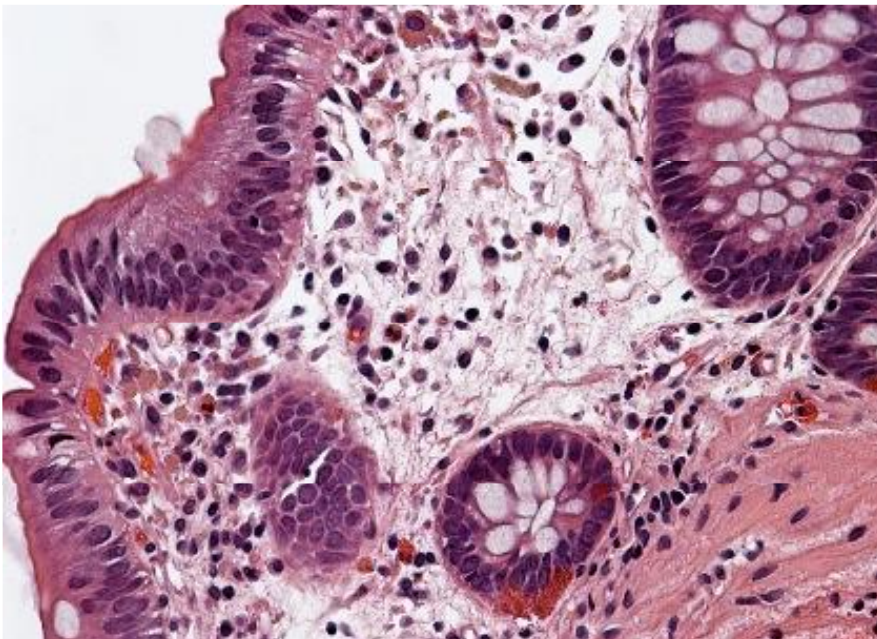
Melanosis Coli



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➤ Histopathology

Melanosis Coli



Courtesy of Dr. Aducio Thiesen, University of Alberta, Edmonton



Cathartic Colon

➤ Diagnostic imaging

Cathartic Colon



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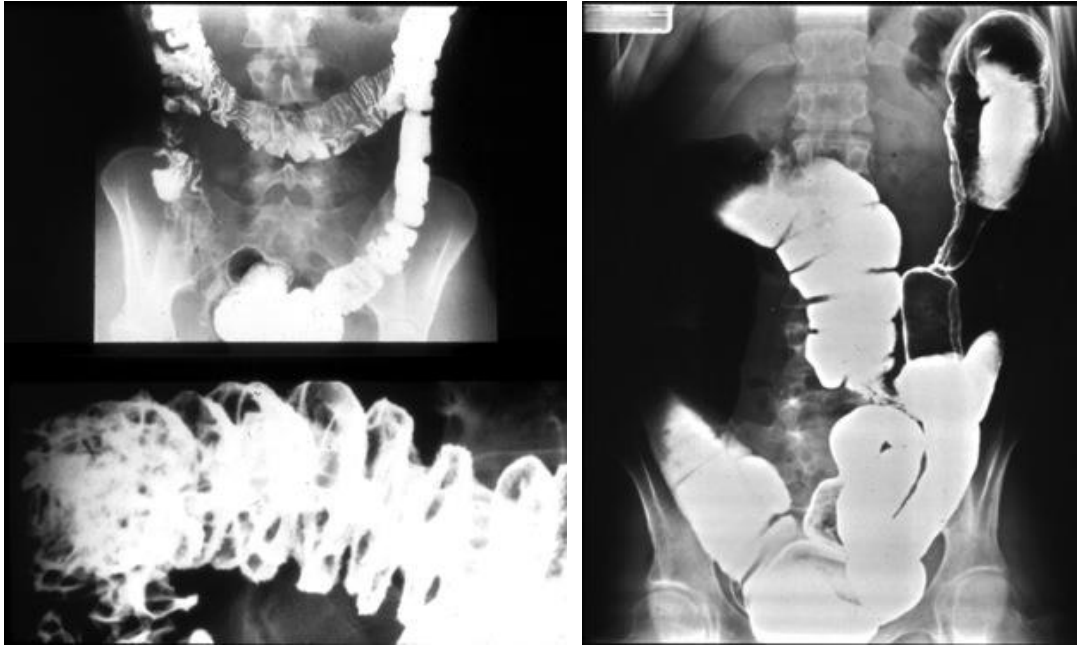
Cathartic Colon



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Cathartic Colon



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Cathartic Colon



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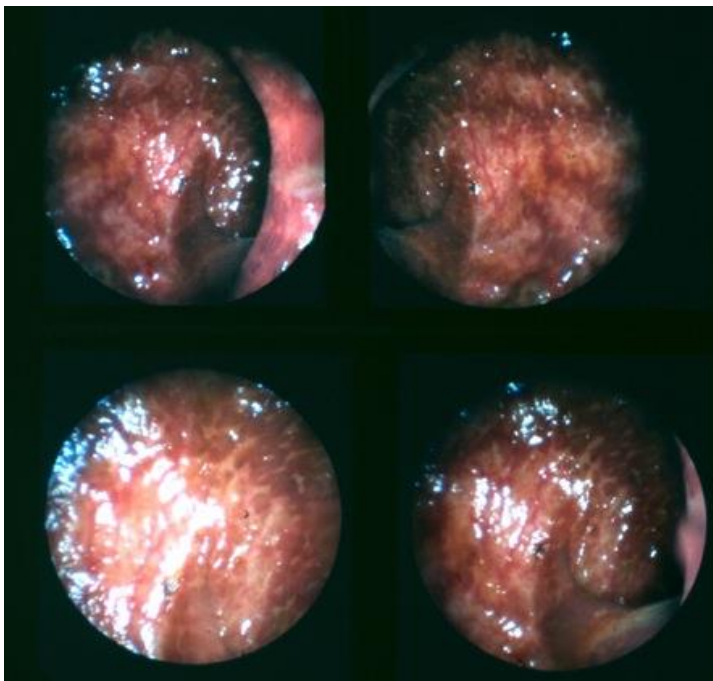
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➤ Endoscopy

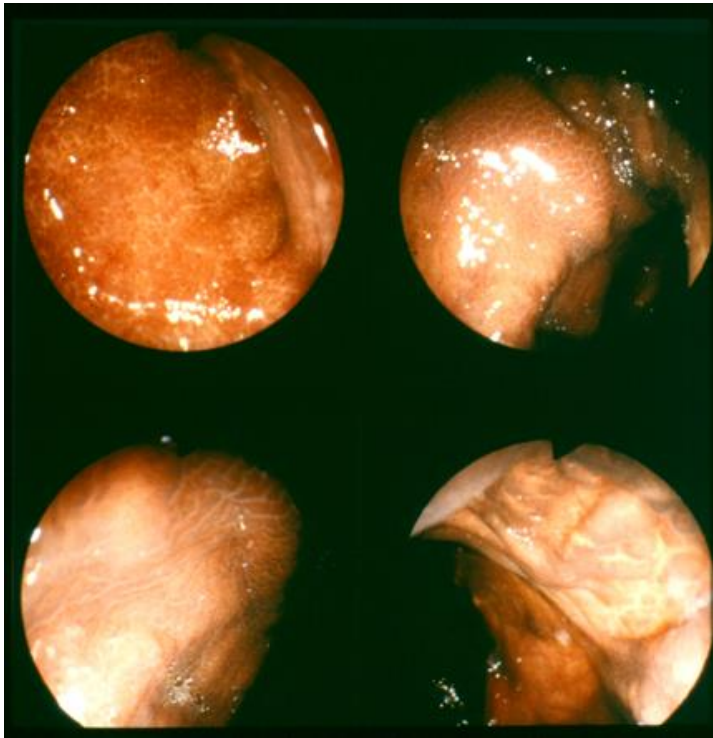
Cathartic Colon



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Cathartic Colon



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➤ Histopathology

Melanosis (High power)



- Mild mucosal infiltration with inflammatory cells
- Hypertrophy of muscularis mucosae
- Atrophy of outer muscle layer
- Proximal colon worse than distal colon

Courtesy of Professor Guito Tytgat, Netherlands



Melanosis coli (Low power)



Lipofuscin pigment within histocytes in the lamina propria

Courtesy of Professor Guito Tytgat, Netherlands

Megacolon

➤ Definition

- Colon persistently increased in diameter associated with longstanding constipation.
- Differentiate between colon inertia and outlet obstruction

➤ Diagnostic imaging

Megacolon on Abdominal Film



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ULCERATIVE COLITIS (UC)

➤ Demography

- Incidence $8/10^5$ person-years
- Prevalence $150/10^5$

Approximate figures, USA, Canada and Europe

➤ Diagnostic imaging

- Radiography
 - Wall thickening
 - Pericolonic fat stranding
 - “Backwash” ileitis (acute inflammation)
 - Hyperenhancement of colonic wall
 - Enlargement of vasa recti
- Fat attenuation in thickened bowel wall

❖ Air contrast barium enema

- Normal pattern
- Loss of haustration – spasm and irritability
- Contraction and decreased distensibility (widening of retrorectal space)
- Abundant secretions of blood, mucus and pus
 - flocculent barium
- Minute ulcerations or spicules
- Large ulcers (collar-button)
- Hazy / fuzzy or grossly ragged contour
- Pseudopolyps
- Backwash ileitis

“You have to put the puck in the net”

PW Armstrong



Ulcerative Colitis



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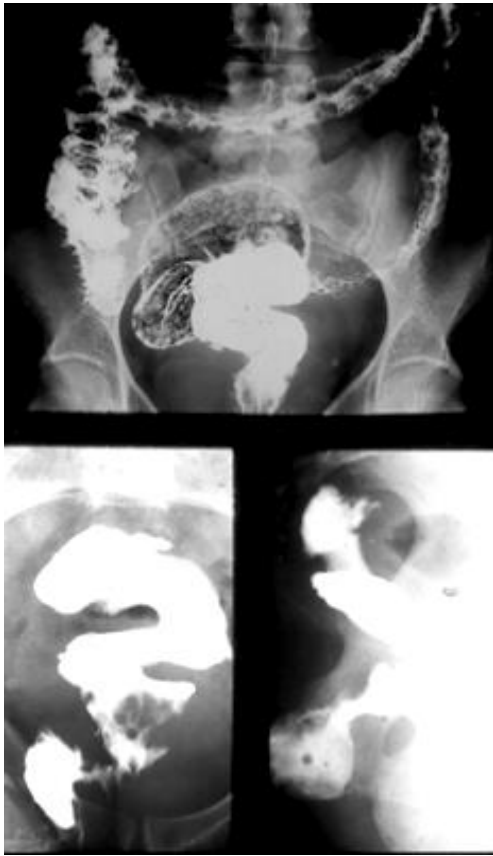
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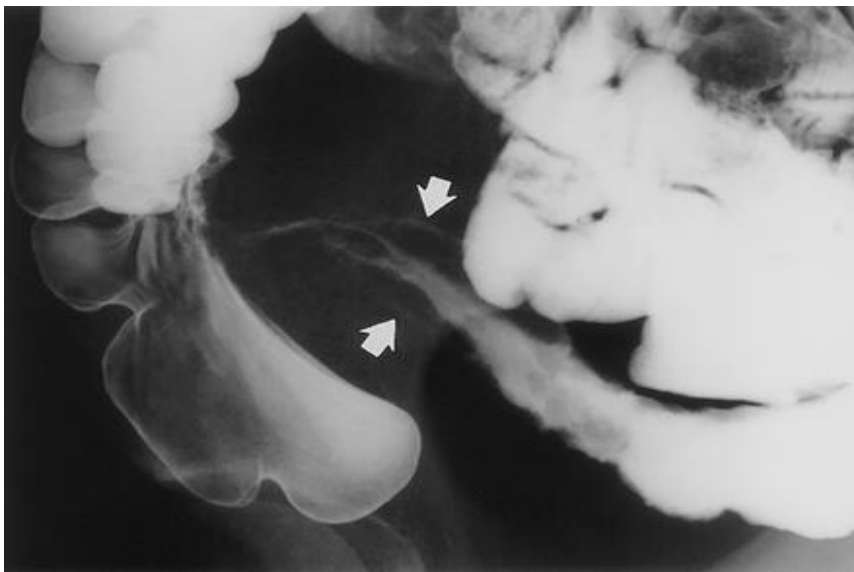


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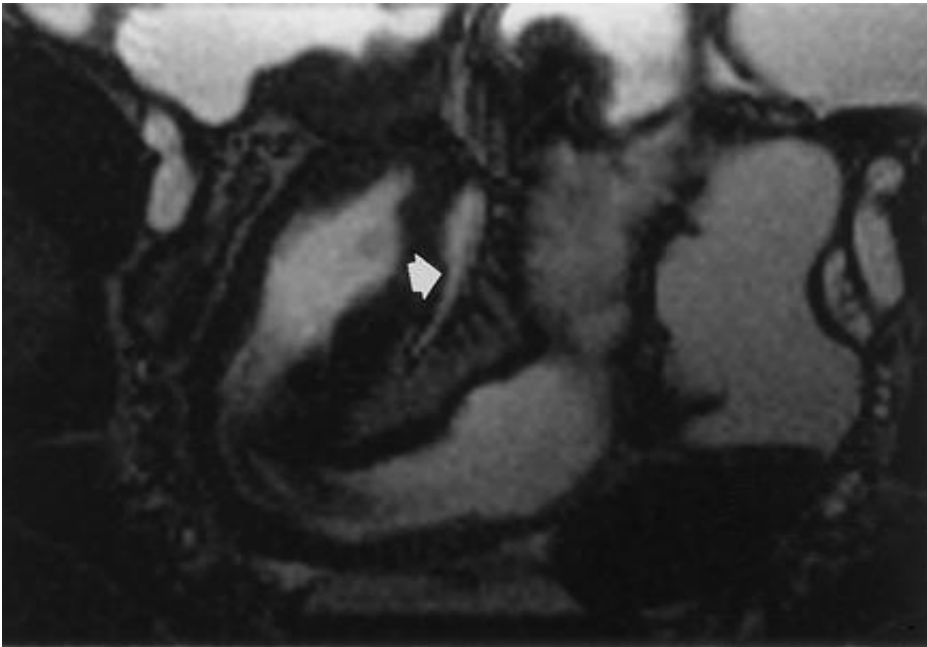
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Continuous,
circumferential

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Ulcerative Colitis



- “Stove/lead pipe” burned out appearance of ulcerative colitis

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Ulcerative Colitis



Narrowing,
possible UC-
associated
colonic
carcinoma
(CRC in UC)

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➤ Diagnostic imaging distinctions: chronic vs acute colitis

	Chronic	Acute
○ Featureless mucosa	+	-
○ Lead-pipe mucosa	+	-
○ Narrow lumen (hypertrophy of circular and longitudinal muscularis propria)	+	-
○ CT: fat attenuation (darker) in thickened colonic wall	+	-



➤ Endoscopy

- Rectal involvement (no rectal sparing except when treated, such as with 5-ASA therapy [enemas])
 - Mucosal ulcerations affect bowel wall in a symmetrical manner
 - Ulcers are linear, fine, stippled (“sandpaper” – like)
 - Normal smoothness (non-granular)
 - Wet and shiny
- Involvement extends proximally
- No skip lesions (continuous, symmetrical thickening of bowel wall)
- Mucosa is granular
- Symmetry of bowel wall is normal
- Polyps
 - Pseudopolyps, areas of normal mucosa surrounded by denuded inflamed mucosa
 - Seen with severe UC
 - Inflammatory polyps
- Loss of haustral pattern (“lead-pipe” appearance)
- Diffuse shortening
- Narrow lumen
- Area of normal mucosa surrounded by granulation tissue
 - Sessile / pedunculated
 - Seen with milder UC
- Megacolon
 - Associated with pseudopolyps
 - Bowel wall thickening
 - Haustral thickening
 - Dilation normal diameter ranges: sigmoid colon 3 to 6 cm; transverse colon 6 to 9 cm; cecum 9 to 12 cm)
- Perforation
 - Air in
 - Bowel wall (intramural air [aka pneumatosis])
 - Peritoneum (pneumoperitoneum)
- Strictures
 - R/O colitis-associated adenocarcinoma
 - Benign ulcers from
 - Muscle hypertrophy
 - Severe inflammation
- “Backwash ileitis”
- Nodules / dysplastic plaques
 - Single / multiple
 - Clusters, with opposed flat edge (in ½)



- Superficial ramifying blood vessels normal throughout, patchy, none
- Spontaneous bleeding ahead of instrument: none; present
- Valves: normal thin sharp crescent; swollen; absent
- Colitis-associated adenocarcinoma
 - Often associated with narrowing of colonic lumen (annular, constricting lesion)
 - Strictures (in ¼)
 - Multiple

❖ Scoring of Endoscopic Severity

- There are several systems to score the endoscopic severity of UC; the Mayo score is the used scoring system
 0. Normal mucosa, ramifying vascular pattern clearly visible throughout, no spontaneous bleeding, no bleeding to light touch
 1. Abnormal but not hemorrhagic appearance (between 0–2)
 2. Moderately hemorrhagic-bleeding to light touch but no spontaneous bleeding seen ahead of instrument on initial inspection
 3. Severely hemorrhagic – spontaneous bleeding seen ahead of instrument of initial inspection and bleeding to light touch
 4. Spontaneous bleeding and spotty ulceration

	0	1	2
○ Colour	Normal	Red	Deeply red
○ Vascular pattern	Normal	Partially absent	Totally absent
○ Friability	normal	Slight	Severe
○ Granularity	Absent	Fine	Coarse
○ Rectal valves	Sharp	Swollen	Absent
○ Ulcers	Absent	Few	Multiple
○ Spontaneous bleed	Absent	Discrete	Severe
○ Mucopurulent exudate	Absent	Little	Much

Useful background: **Mayo Score** for mucosal severity in ulcerative colitis

Mayo Index	0	1	2	3
○ Stool frequency	Normal	1-2 / day >normal	3-4 / day >normal	5 / day >normal
○ Rectal Bleeding	None	Streaks	Obvious	Mostly blood
○ Mucosa	Normal	Mild friability	Moderate friability	Spontaneous bleeding
○ Physician's global assessment	Normal	Mild	Moderate	Severe



Variable	Clinical disease activity	
	Mild	Severe
○ Stool frequency	Minimal	> 6 / d
○ Blood in stool	Absent	Continuous
○ Fever	Mild	Mean evening T > 37.5 °C or > 37.7°C for at least 2/4 days (any time of day)
○ Pulse	Mean rate < 90 bpm	> 90 bpm
○ Anemia		Hgb 7.5 mg/dL (compared) with normal values
○ Erythrocyte sedimentation rate	<30 mm/hr	> 30 mm/hr

Abbreviation: bpm, beats per minute; Hgb, hemoglobin T, temperature;

Adapted from: Truelove SC, Witts LJ. Br Med J. 1955;2:1041-1048

- Give the **endoscopic differentiation** between UC and Crohn colitis.

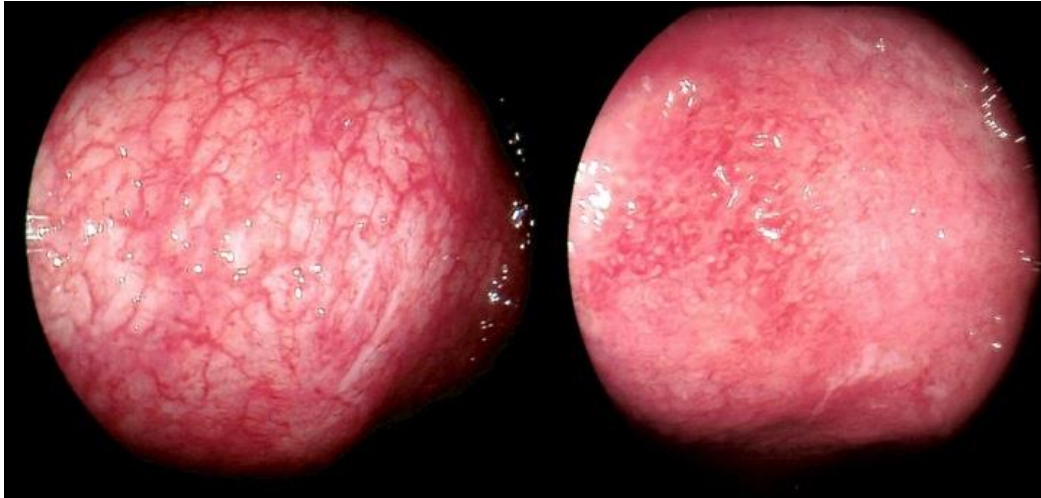
Variable	Ulcerative Colitis	Crohn Disease
○ Distribution	- Diffuse inflammation - Extends proximally in continuity from the anorectal junction	▪ Rectal sparing ▪ "skip" lesions
○ Rectal involvement	- Present	▪ May be absent
○ Skip areas / symmetry	- Absent always, symmetrical and continuous	▪ Common; asymmetric and discontinuous disease common
○ Inflammation	- Diffuse erythema - Loss of vascular markings - Mucosal granularity or friability	▪ Focal /asymmetric, "cobblestoning" ▪ Granularity and friability
○ Ulceration	- Small ulcers in a diffusely inflamed mucosa; deep, ragged ulcers in severe disease - Always in areas of mucosal inflammation - Large (>1cm) ulcers in severe disease	▪ Aphthoid ulcers ▪ Linear/serpiginous ulceration ▪ Intervening mucosa is often normal ▪ Discrete ulcers in normal mucosa; aphthous and linear ulcers pathognomonic ▪ Large and serpiginous ulcers and deep, longitudinal ulcers are common
○ Cobblestoning	- Absent	▪ Pathognomonic
○ Mucosal Bridging	- Occasional	▪ Occasional
○ Vascular pattern	- Blurred or lost	▪ Often normal
○ Granularity	- Common	▪ Less common
○ Mucosal friability	- Frequent in early UC	▪ Unusual
○ Colonic lumen	- Narrowed in long-standing chronic disease - Strictures are rare	▪ Strictures are common

Adapted from: Su C and Lichtenstien GR. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2514.



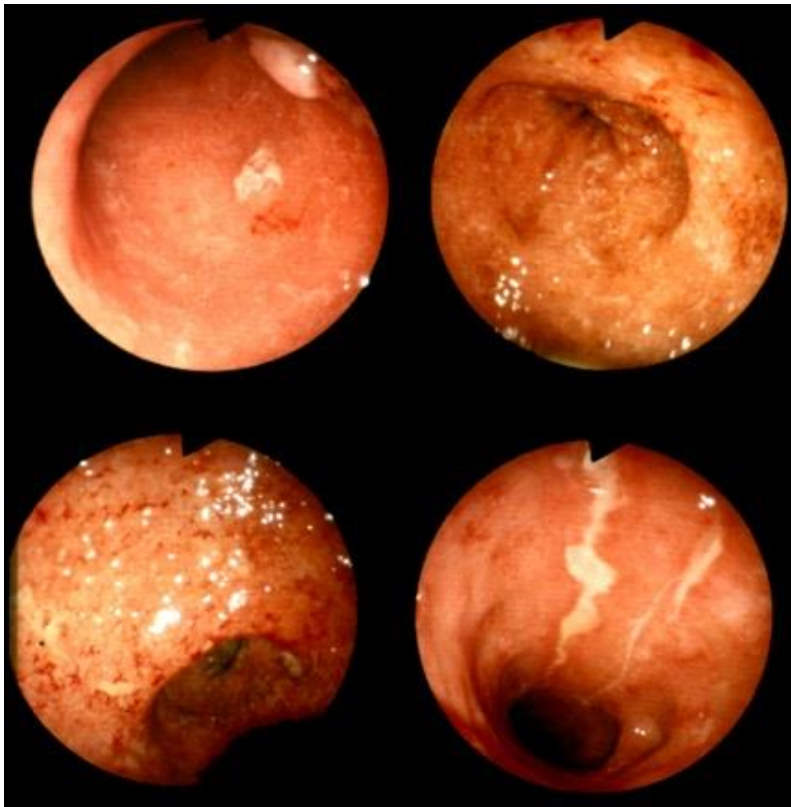
❖ Colonoscopy

Colonic Mucosal Vasculature in Ulcerative Colitis



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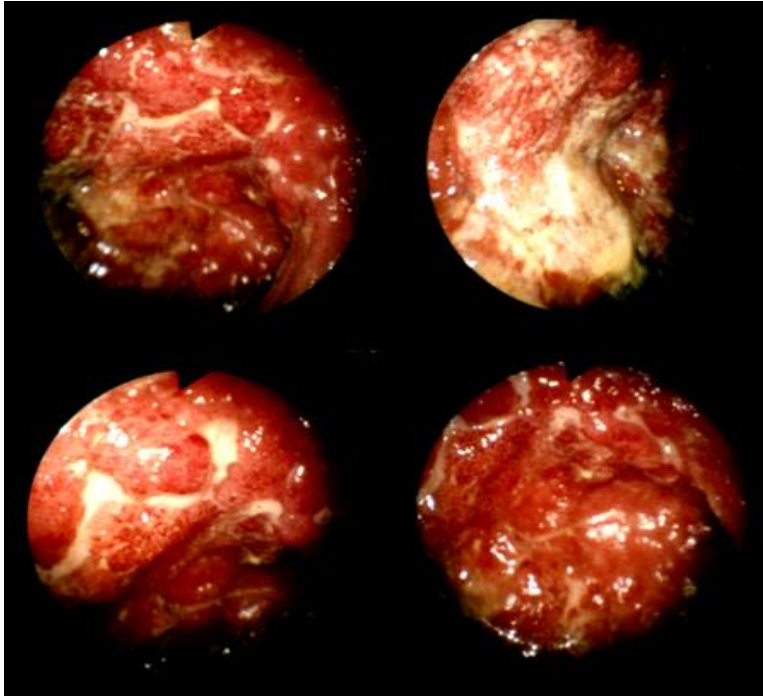
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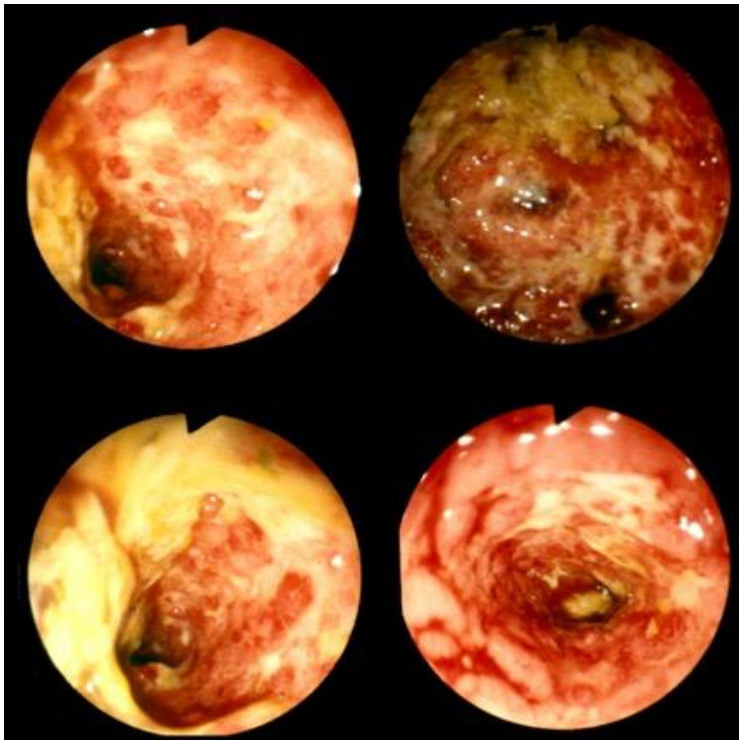


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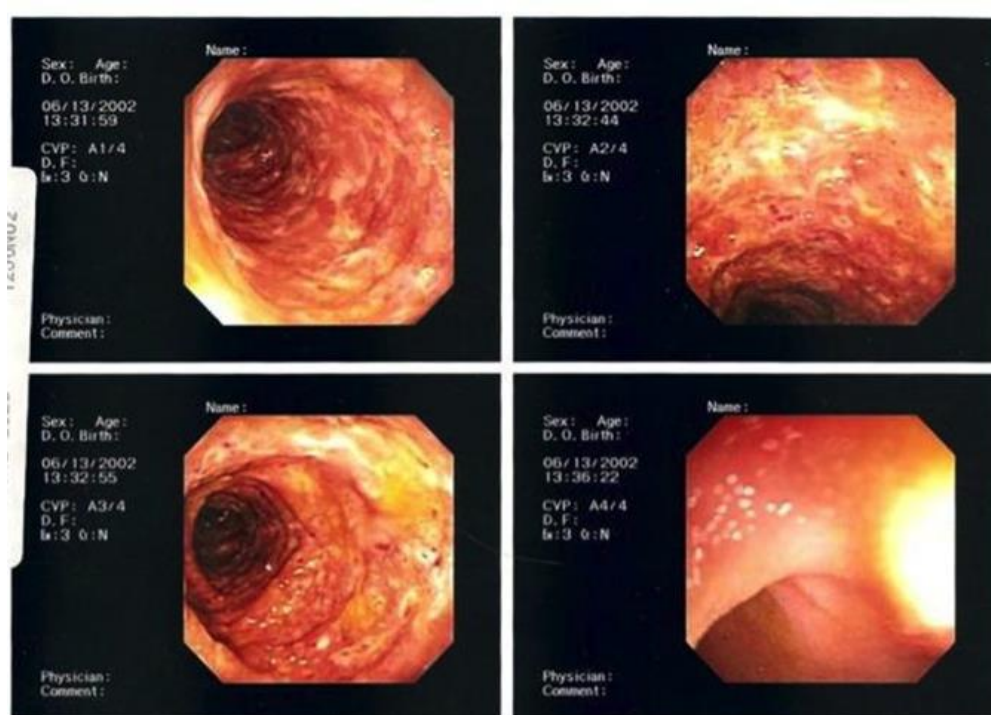
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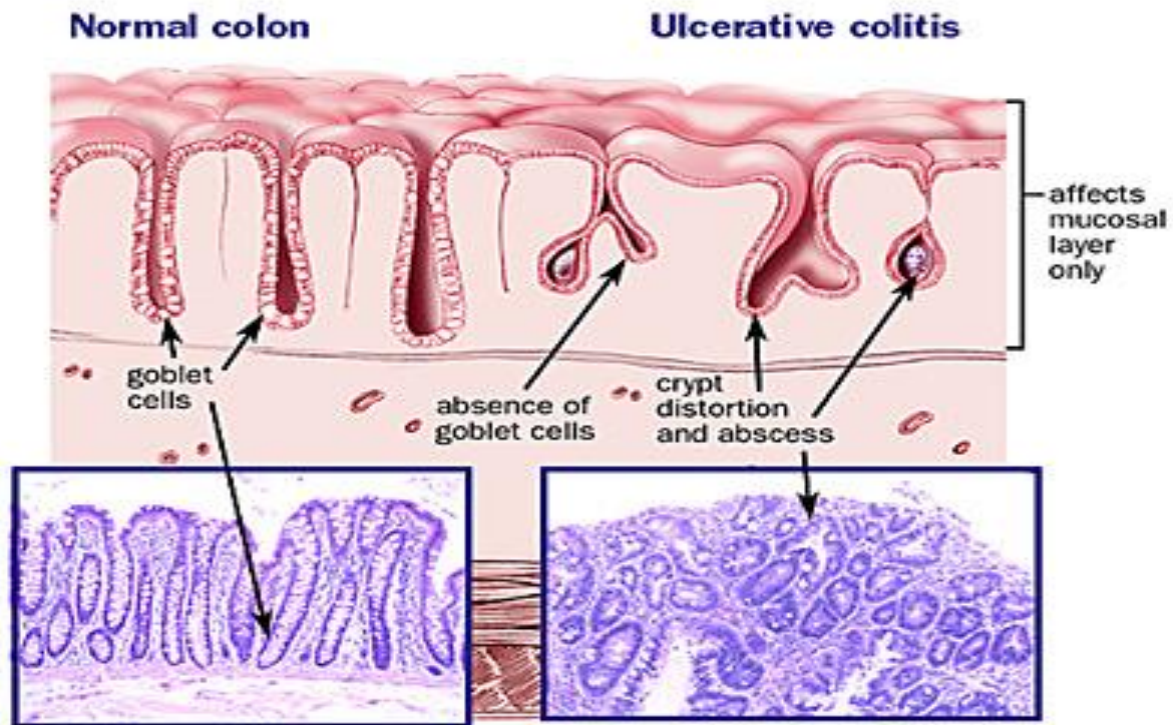
➤ Histopathology

- $\frac{1}{2}$ to $\frac{3}{4}$ of persons with UC on the left side have inflammation in the cecum and around the appendix
- Characteristics of chronic quiescent UC
 - Mucosa
 - Paneth cell metaplasia distal to hepatic flexure
 - Drop out of glands
 - Distortion of architecture of glands
 - Branching
 - Shortening
 - Muscularis mucosae
 - Hyperplasia
 - Submucosa
 - Fibromuscular hyperplasia (suggests previous ulceration and healing)

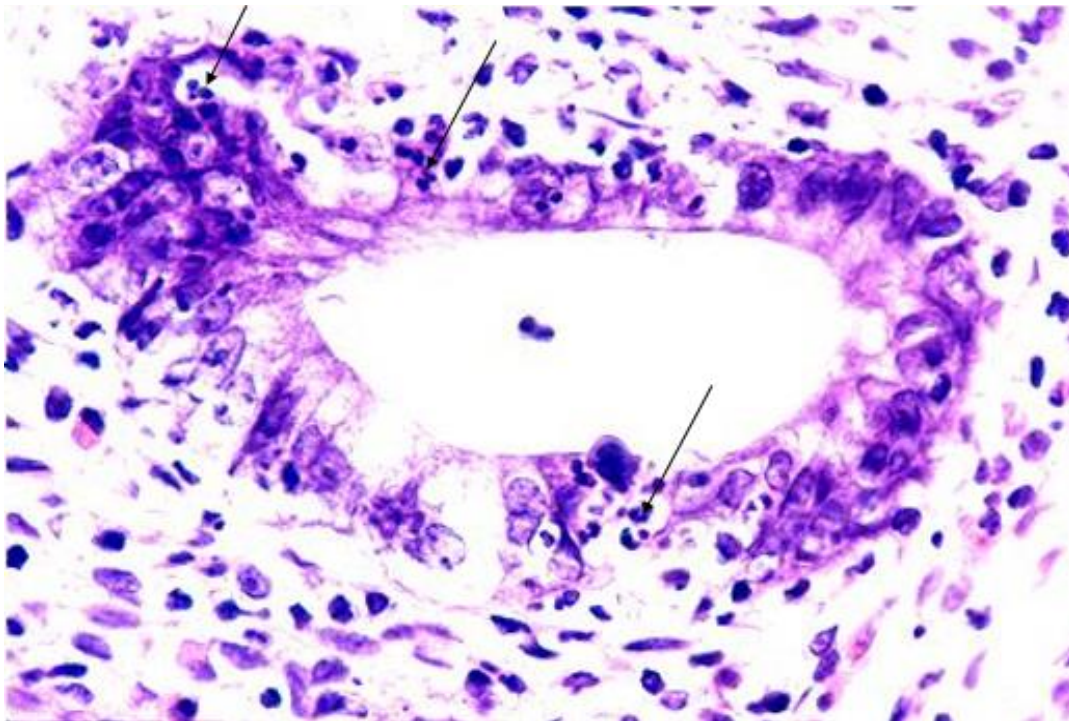
“Buzzwords” which suggest the type of IBD

UC	CD
○ Diffuse	○ Patchy
	○ Granulomas
	○ Perianal disease
	○ Rectal sparing
	○ Skip lesions
	○ Fistulae





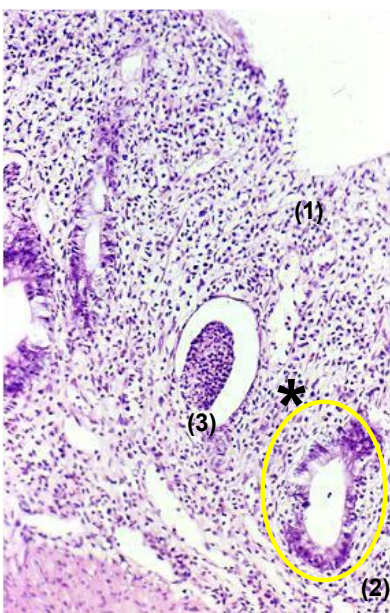
Ulcerative Colitis – cryptitis



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Ulcerative Colitis



- (1) Expanded lamina propria
- (2) Cryptitis
- (3) Crypt abscess

Courtesy of Professor Guito Tytgat, Netherlands

- Give the biopsy features of **acute self-limiting colitis (AC)** which help to distinguish it from chronic idiopathic ulcerative colitis (UC).
 - Crypts are straight, parallel, close
 - PML are abundant, and scattered in the lamina propria (LP)
 - No lymphoplasmacytosis at base of crypts

Abbreviations: AC, acute self-limiting colitis; LP, lamina propria; PML, polymorphonuclear leucocytes; UC, ulcerative colitis

- Give the histopathological differences between ulcerative colitis (UC) and Crohn disease(CD).

UC	CD
○ All samples inflamed	- May be some normal samples
○ Distal biopsy specimens most severe	- No pattern of inflammation
○ Mucosal disease	- Transmural disease
○ Capillary and venule engorgement	- Mononuclear infiltrate
○ No granulomata except those associated with crypt rupture	- Lymphangiectasia
	- Granulomata

Adapted from: Geller SA. In: Inflammatory Bowel Disease. From Bench to Bedside. 1994:336-351.



Pyoderma Gangrenosum (PG)

➤ Definition

- An ulcerative skin condition associated with accumulation of neutrophils in the skin lesions.
- Symptoms may be out of proportion to size / appearance of PG lesion
- May be severe

➤ Clinical

- Variable or absent parallelism with IBD activity
- Often associated with other EIMS (eye, arthritis)
- Recurrence is infrequent

Pyoderma Gangrenosum



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Pyoderma Gangrenosum



- Pyoderma adjacent to ileostomy
 - may reoccur at relocated stoma
 - medical therapy preferable
- Pyoderma of head and face common in children

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Pyoderma Gangrenosum



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- Differential
 - Tuberculosis
 - Herpetic infections
 - Fungal infections
 - Squamous cell cancer

Pouchitis

- Demography
 - The likelihood of developing chronic pouchitis in a UC patient having an IAPP is over 80% if serological testing shows high levels of pANCA (Fleshner P, et al. *Clin Gastroenterol Hepatol* 2008:561-8.)
 - Complications may develop in the pouch after proctocolectomy and IPAA (ileal pouch-anal anastomosis)
 - Prevalence
 - When IPAA is done for UC
 - Year 1 ~ 20%
 - Year 5 ~ 50%
 - When done for FAP
 - < 1%
- Differential
 - A patient has an ileoanal pelvic pouch (IAPP) after proctocolectomy for UC. Give the differential diagnoses for late pouch-related symptoms.
 - Pouch
 - Cuffitis
 - Irritable pouch syndrome
 - Adhesions
 - Stricture
 - Abscess
 - Pelvic floor dysfunction
 - Late anastomotic leak
 - Malignancy (squamous cell cancer) of anus, small bowel cancer
 - Small intestine
 - Crohn disease
 - NSAID-induced damage (especially with isolated afferent limb ulcers)
 - Poor reservoir capacity
 - Small intestinal bacterial overgrowth syndrome (SIBO)
 - Unmasked celiac disease
 - Unrelated conditions, including infections



➤ Pathology

- Multiple biopsies (6) must be taken from the mucosa of the reservoir (pouch)
- Abnormalities present in 95%
- Inflammation degree
 - Mild, 56%
 - Chronic, 39%

Dysplasia in the Patient with Inflammatory Bowel Disease (IBD)

➤ Terminology

- DALM (dysplasia-associated lesion or mass) is raised, and comes in several shapes: plaque, polyp, mass, stricture (this term, DALM, is losing favour)
- About half of patients with UC plus a DALM with high-grade dysplasia already have colon cancer
- In UC plus low-grade dysplasia (LGD) on biopsy, the risk of future development of colon cancer is 1% to 3% per person per year after diagnosis of LGD
- Multifocal LGD has an even higher risk of colon cancer, and colectomy is usually recommended.
- An unequivocally neoplastic proliferation
- Essentially equivalent to an adenoma
- Excludes all equivocal or regenerative lesions
- May be the superficial part of a carcinoma
- Often multifocal
- May occasionally be visible to endoscopist

Please see (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, Table 112.19, page 2007, "algorithm for the management of dysplasia-associated lesion or mass (DALM), flat dysplasia, indefinite dysplasia, or no dysplasia found on surveillance colonoscopy in patients with ulcerative colitis", and Figure 112.20, page 2008, "Recommended Algorithm for Management of Polypoid lesions [in chronic UC]. Biopsies of the colon taken for dysplasia / CRC surveillance in a patient in the UC ideally should be taken when the UC is inactive (i.e., in remission).

A recent consensus statement has shifted the emphasis and terminology surrounding these lesions to whether they are endoscopically visible and endoscopically resectable to determine management.

Please see (SCENIC International Consensus Statement on Surveillance and Management of Dysplasia in Inflammatory Bowel Disease. Gastroenterology 2015;148:639–651).



➤ Diagnostic imaging

Dysplasia in IBD



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Dysplasia in IBD



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➤ Endoscopy

- Give the endoscopic features of five types of dysplasia in patients with IBD.

Lesion	Endoscopy	Approximate Risk for CRC
○ Sporadic adenoma	– Circumscribed polypoid lesion, pedunculated or sessile – Typically outside the actively or previously inflamed colonic mucosa	5%
○ DALM, adenoma like	– Circumscribed polypoid lesion – Mostly sessile – In (previously) inflamed areas of the colonic mucosa. – Often undistinguishable from sporadic adenomas	5%
○ DALM, nonadenoma like	– Irregular – Diffuse – Masses or plaque like lesions in actively or previously inflamed areas of the colonic mucosa	60%
○ LGD in flat mucosa	– No gross abnormality	18%
○ HGD in flat mucosa	– No gross abnormality	36%

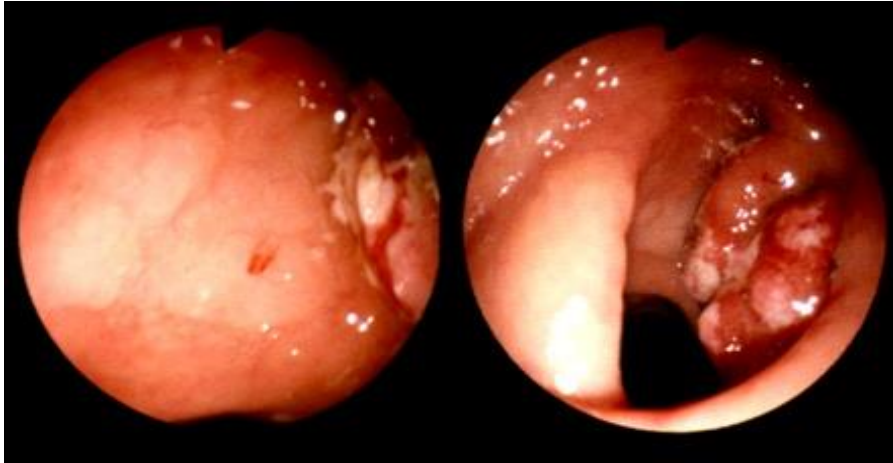
Abbreviation: CRC, colorectal cancer; DALM, dysplasia associated lesion or mass; HGD, high grade dysplasia; LGD, low grade dysplasia

Adapted from: van Schaik FD, et al. *Nature Review Gastroenterology and Hepatology* 2009; 11:671-8, page 674.

- Direct special attention to any mass lesion (additional biopsies should be obtained)
- Dysplasia associated lesion or mass (DALM) has a high incidence of cancer
- No need to routinely biopsy pseudopolyps unless:
 - Greater than 1 cm in diameter
 - Friable
 - Different coloration than other pseudopolyps
 - Have surface irregularities
- Multiple biopsies of all strictures
- Flat dysplasia
 - Endoscopically undetectable
 - Endoscopically visible suspicious alterations
 - Discoloration
 - Velvety / villous appearance
 - Irregular fine nodularity
- Raised dysplasia
 - Discrete polypoid lesion or nodular mass
 - Irregular plaque-like lesion / wart-like thickening
 - Conglomerate of polypoid lesions in a finite colonic segment

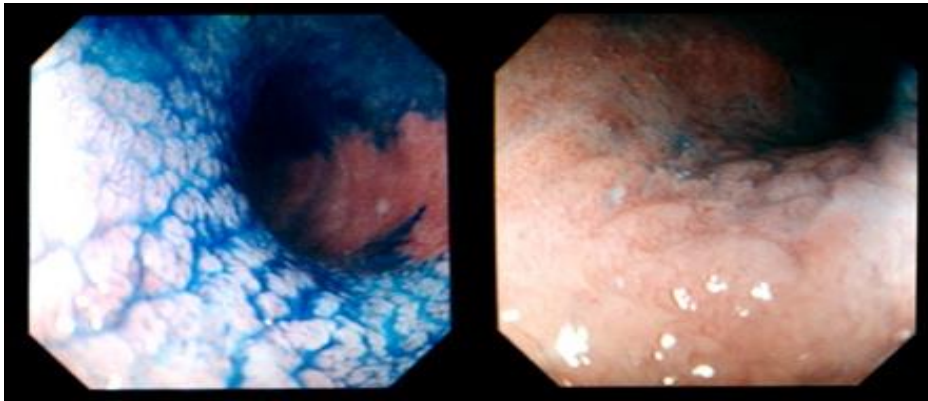


Dysplasia in UC



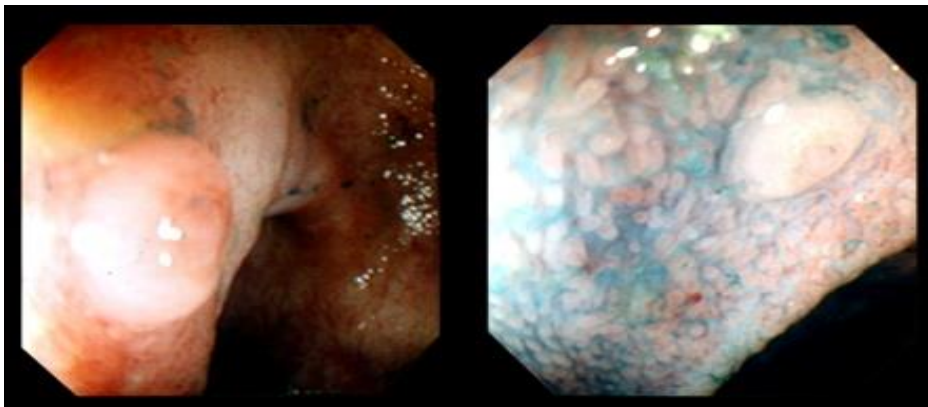
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Dysplasia in UC



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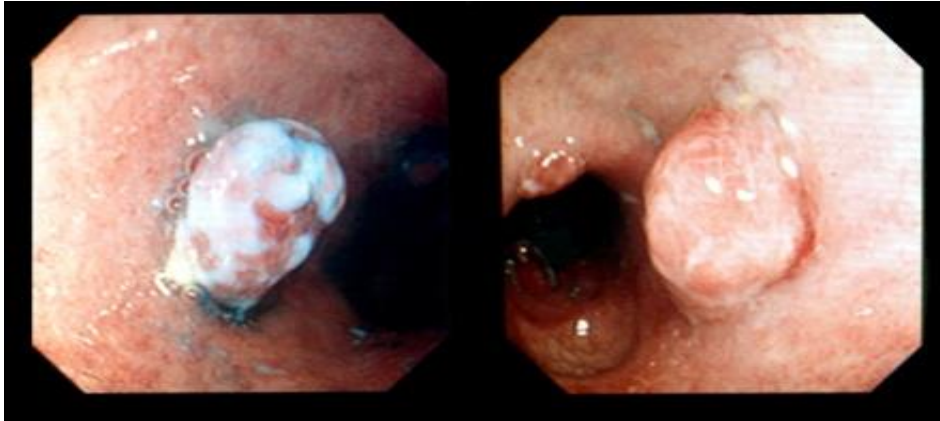
Dysplasia in UC



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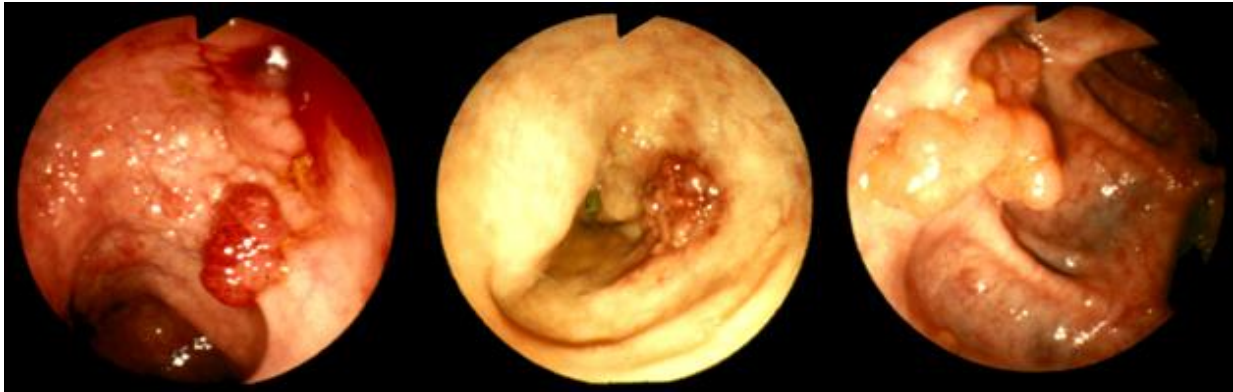


Dysplasia in UC



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Dysplasia in UC

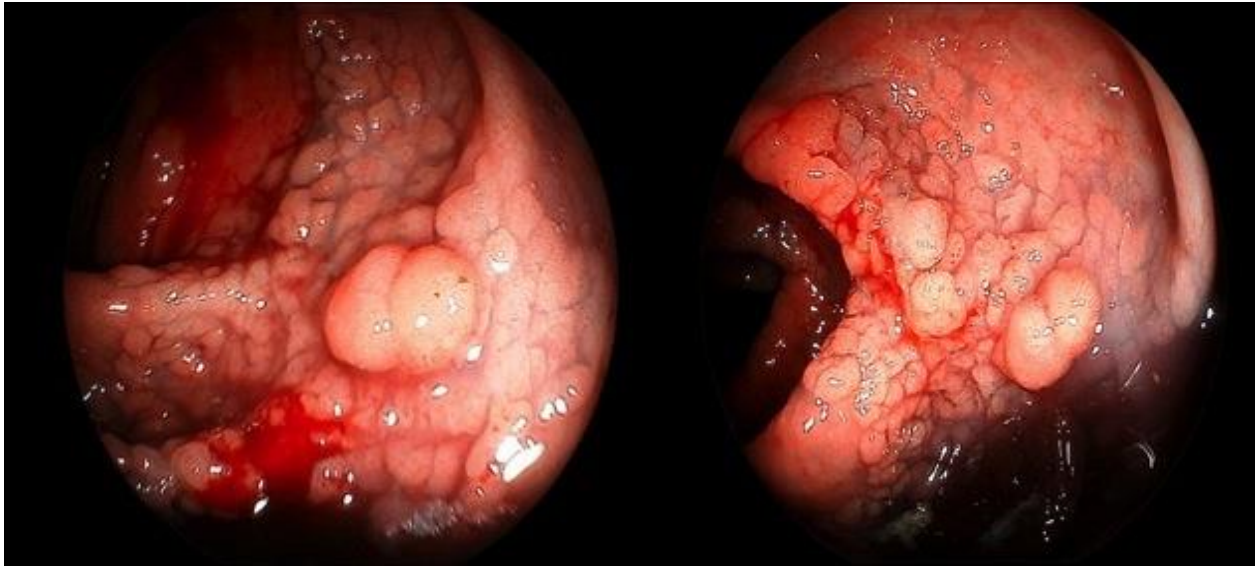


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- The problems of DALM (dysplasia-associated lesion or mass)
 - DALM lesions are uncommon
 - Difficult / impossible to distinguish from 'ordinary' (sporadic) sessile adenoma
 - Occasionally difficult to distinguish from bizarre pseudopolyps
 - Occasionally difficult to distinguish from early cancer
 - DALM may be of larger size, irregular shape, conspicuous discoloration and firmer consistency
 - May occur in uninvolved colon
 - May have same significance as (high grade) dysplasia

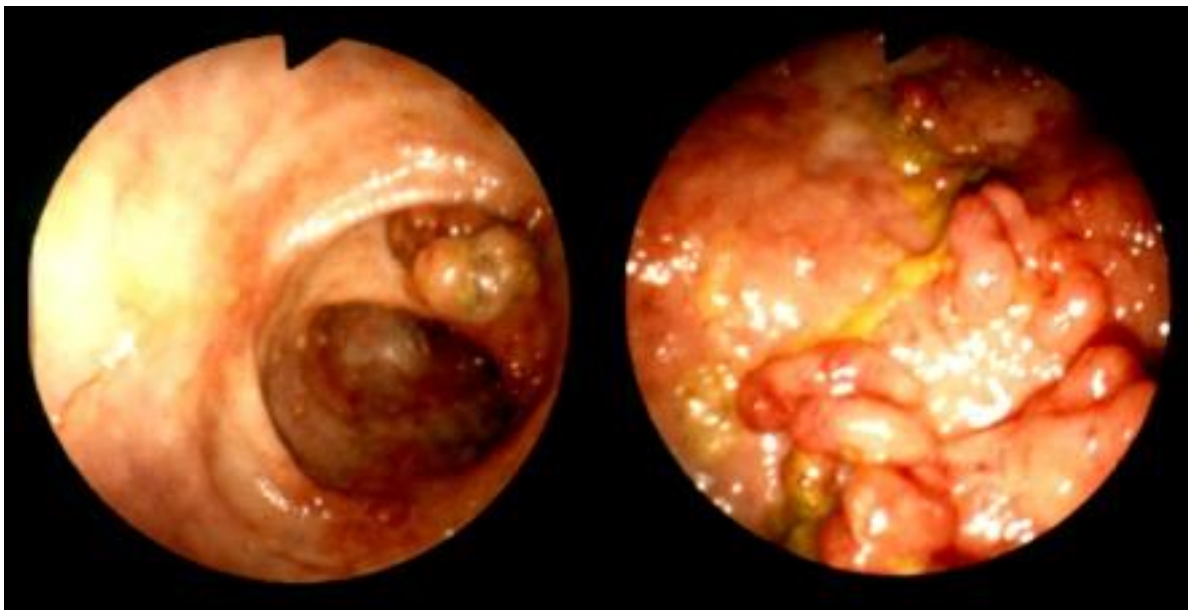


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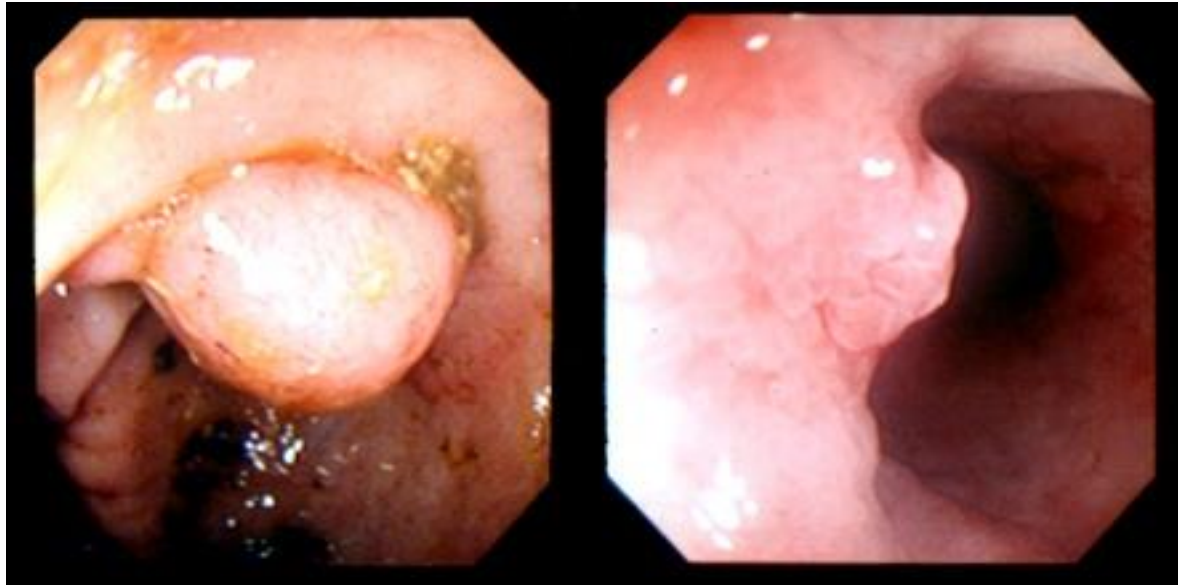
Dysplasia in UC



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Dysplasia in UC



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A patient with chronic distal UC for 30 years is found to have a polypoid lesion at the junction of the UC and non-UC mucosa.

- Give features which helps to distinguish a non-adenoma-like DALM (dysplasia-associated lesion or mass) from a sporadic adenoma (SPO-Ad).

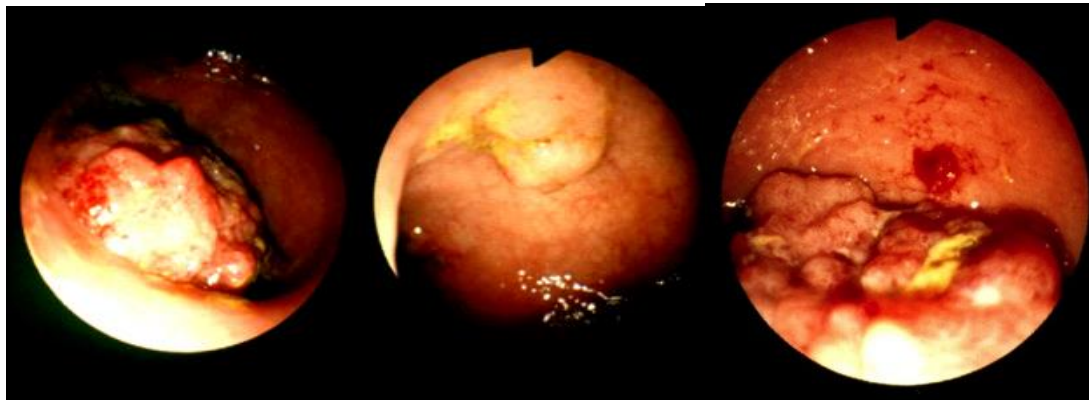
Feature	DALM	SPO-Ad
○ Age of patient	– Younger	▪ Older
○ Duration of UC	– Longer	▪ Shorter
○ Extensive	– More	▪ Less
○ Size of lesion	– Larger (~ 18 mm)	▪ Smaller (~ 5 mm)
○ Endoscopic appearance	– Large – Plaque – Ulcerated	▪ Pedunculated ▪ Sessile
○ Molecular markers		
– Beta catenin	– 8%	▪ 40%
– P53	– 29%	▪ 5%
○ Treatment		
– HGD	– Prompt colectomy	▪ Polypectomy, plus post polypectomy surveillance
– LGD	– Controversial	

Abbreviation: HGD, high grade dysplasia



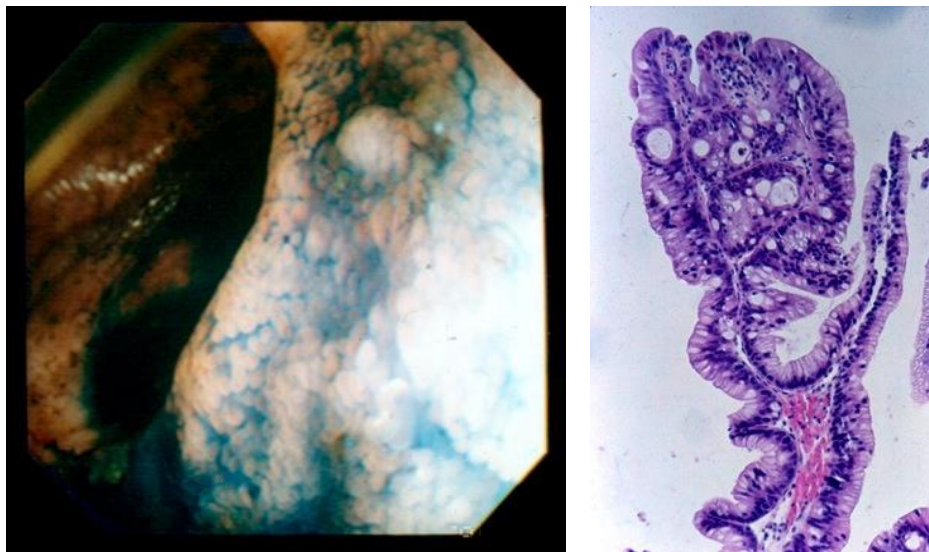
- When given the following statistics (M. A. Peppercorn and RD Odze, UpToDate May 2012), many patients will choose to have colectomy, rather than colonoscopy plus biopsy performed at least once per year with quadrant biopsies every 10 cm from cecum to rectum:
- 70% of UC and 30% of CC (crohn colitis) already have dysplasia at portion of the colon.
 - 19% to 33% already have CRC
 - 34% will have CRC in 1 year
- Progression
 - 50% LGD → HGD / CRC
 - 10% within 32 months LGD → HGD / CRC within 10 years
 - 15% LGD → CRC in 10 years

Dysplasia in UC



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Dysplasia in UC



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➤ Histopathology

- Give the pathological features of five types of dysplasia in patients with IBD.

Lesion	Pathological Features	Approximate Risk for CRC
○ Sporadic adenoma	– Circumscribed lesion – Tubular, tubulovillous or villous architecture – Biopsies from background mucosa (if submitted) are not inflamed	5%
○ DALM, adenoma like	– Tubular, tubulovillous or villous architecture – Biopsies from background mucosa (if submitted) show chronic +/- active colitis	5%
○ DALM, nonadenoma like	– Poorly circumscribed / non-polypoid appearing lesion with similar features to those described above	60%
○ LGD in flat mucosa	– Crypts lined with dysplastic epithelium but no polyp/mass – High ratio of nucleus to cytoplasm – Nuclei remain confined to the basal half of the cell	18%
○ HGD in flat mucosa	– Crypts lined with dysplastic epithelium but no polyp/mass – More crypt architectural complexity (fusion, cribriforming) – Nuclei extend into the luminal half of the cell ("loss of polarity") and may appear rounder / more atypical	36%

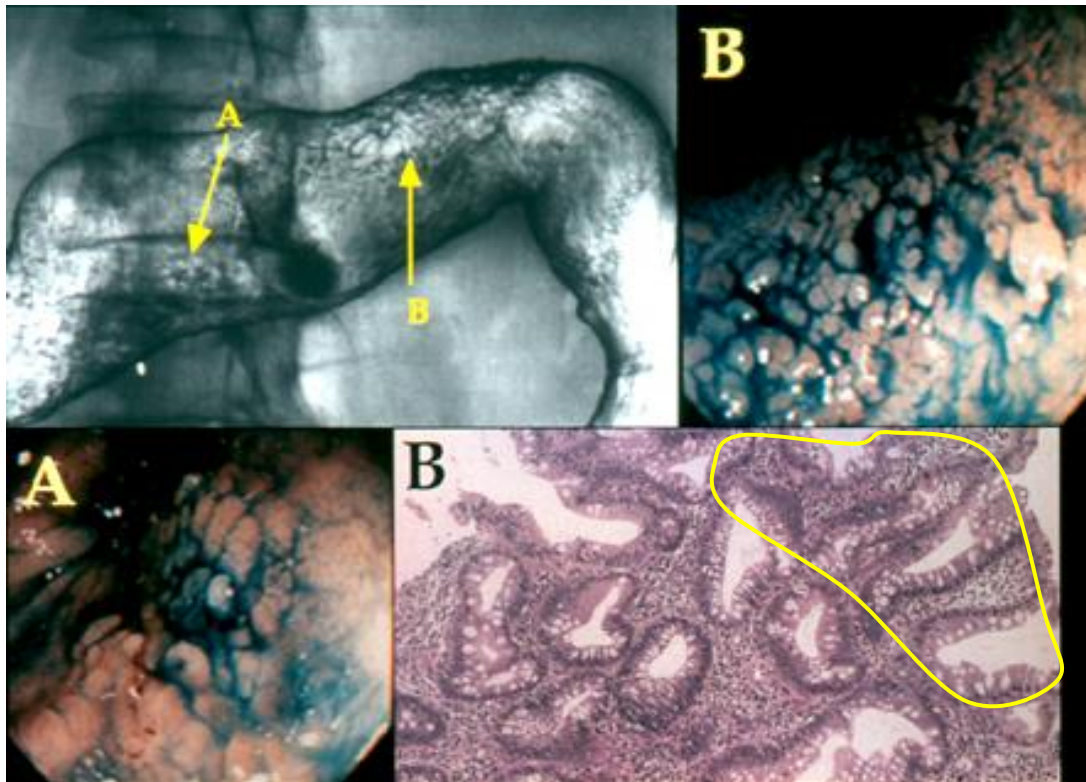
Abbreviation: CRC, colorectal cancer; DALM, dysplasia associated lesions or masses; HGD, high grade dysplasia; LGD, low grade dysplasia

Adapted from: van Schaik FD, et al. *Nature Review Gastroenterology and Hepatology* 2009; 11:671-8, page 674

Because of the significant overlap in the histologic findings, management should be based on the endoscopic visibility / resectability.



Low Grade Dysplasia (LGD) in UC



Courtesy of Professor Guito Tytgat, Netherlands

- Give histopathological features which help to **distinguish dysplasia from regenerative changes** in active UC.

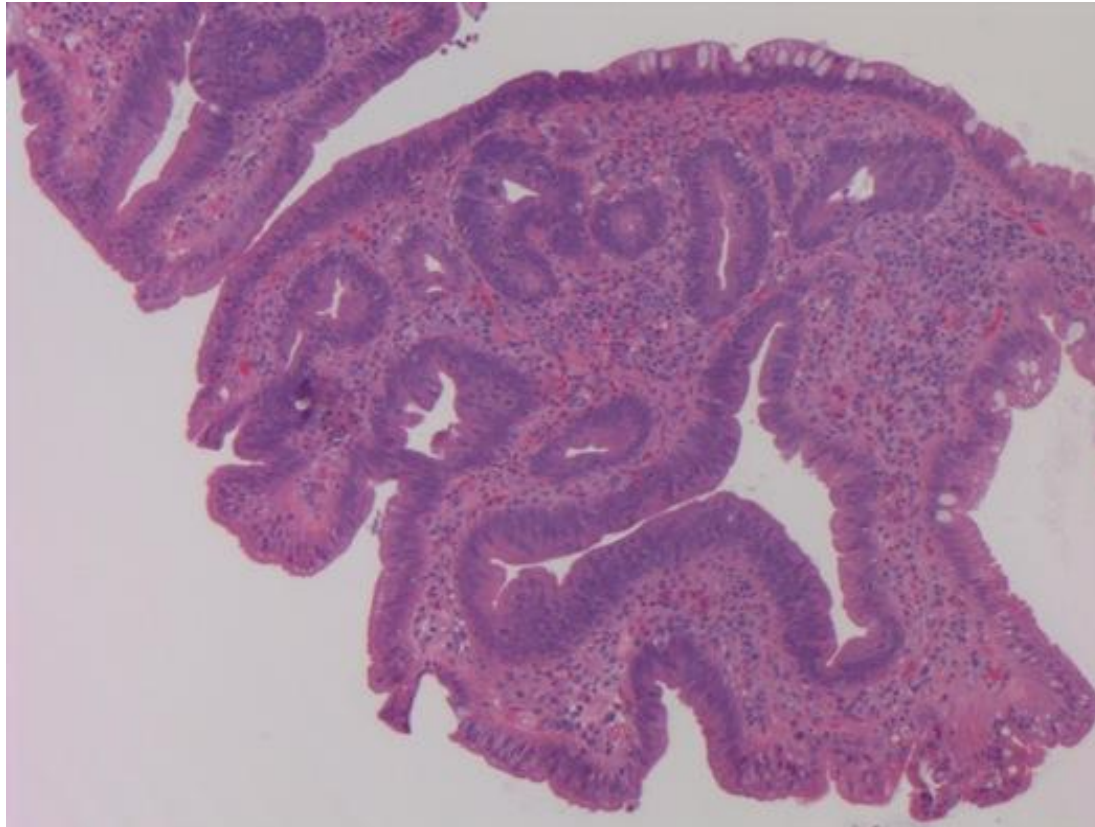
The following are histopathological features which suggest dysplasia

- Architectural
 - Back-to-back / cribriform gland pattern
 - Luminal necrosis
- Cytological
 - ↑ stratification of nuclei
 - ↑ nuclear size
 - ↑ pleomorphism (variation in size and shape)
 - ↑ ratio of nuclei / cytoplasm
 - ↑ mitoses (typical and atypical)
 - Loss of nuclear polarity
 - ↑ chromaticity (hyperchromaticity)
 - Involvement of the surface epithelium



Features	Dysplasia	Regenerative Changes
○ Changes in		
- Crypts	Yes	Yes
- Surface epithelium	Yes	No

Dysplasia-associated Lesion or Mass (DALM)



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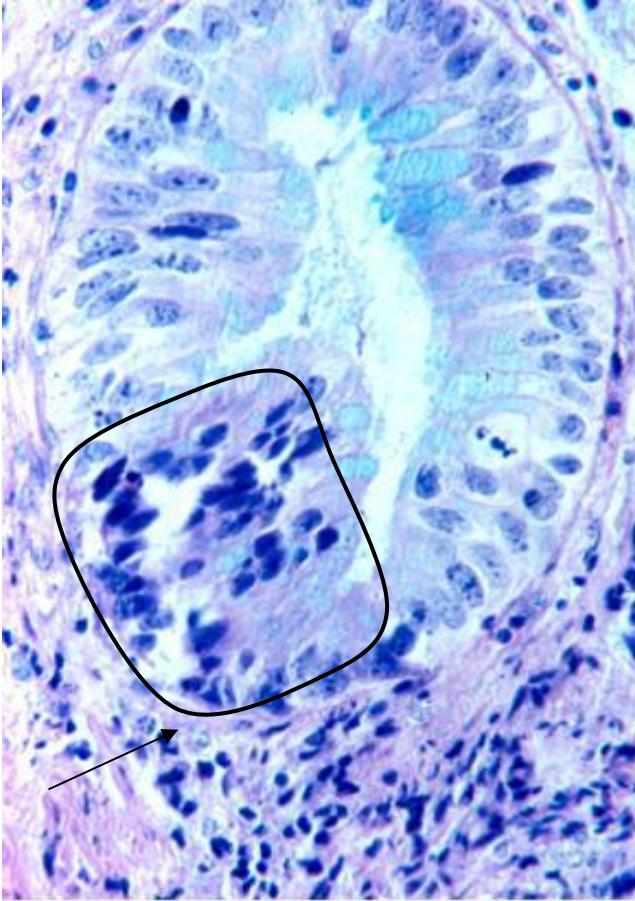
UC or Crohn colitis and mucosal biopsy findings at screening or colonoscopic surveillance

- HGD in flat mucosa → colectomy
- HGD or LGD in polypoid lesion → colectomy if
 - Polyp is not completely removed
 - There is adjacent dysplasia
 - There is invasive cancer

Abbreviations: HGD, high grade dysplasia; LGD, low grade dysplasia



Focal Dysplasia in UC



Courtesy of Professor Guito Tytgat, Netherlands

- Flat dysplasia
 - Endoscopically undetectable
 - Endoscopically visible suspicious alterations
 - Discoloration
 - Velvety / villous appearance
 - Irregular fine nodularity
- Raised dysplasia
 - Discrete polypoid lesion or nodular mass
 - Irregular plaque-like lesion / wart-like thickening
 - Conglomerate of polypoid lesions in a finite colonic segment

Colorectal Cancer (CRC) in IBD

- Colorectal cancer in chronic ulcerative colitis
 - Develops at younger age
 - Tends to be more advanced at diagnosis
 - Tends to be less differentiated
 - Tends to be more in the proximal colon
 - More frequently multiple



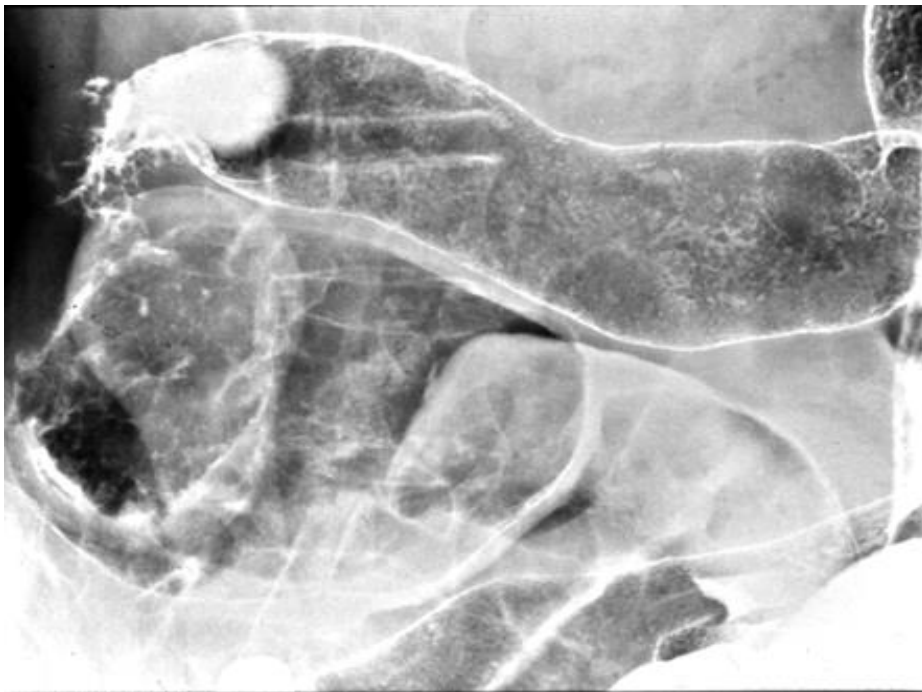
➤ Diagnostic imaging

CRC in UC



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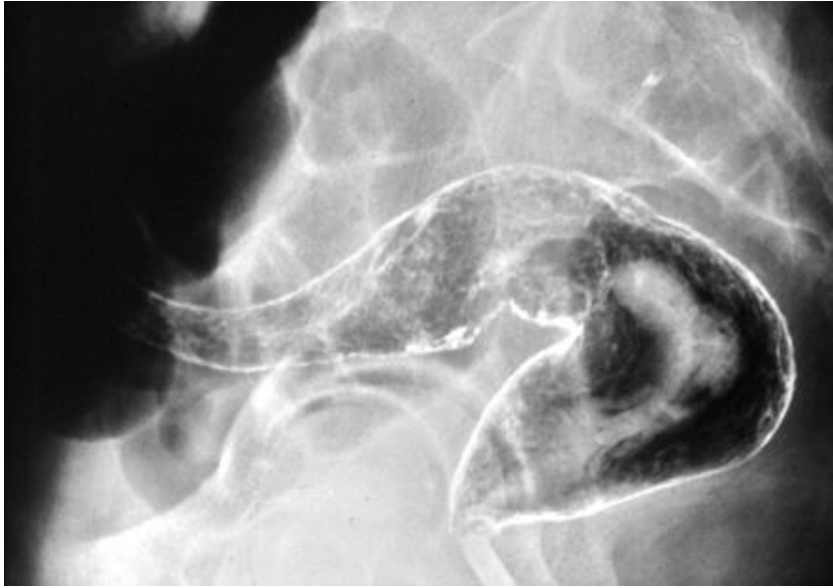
CRC in UC



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CRC in UC



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CRC in UC

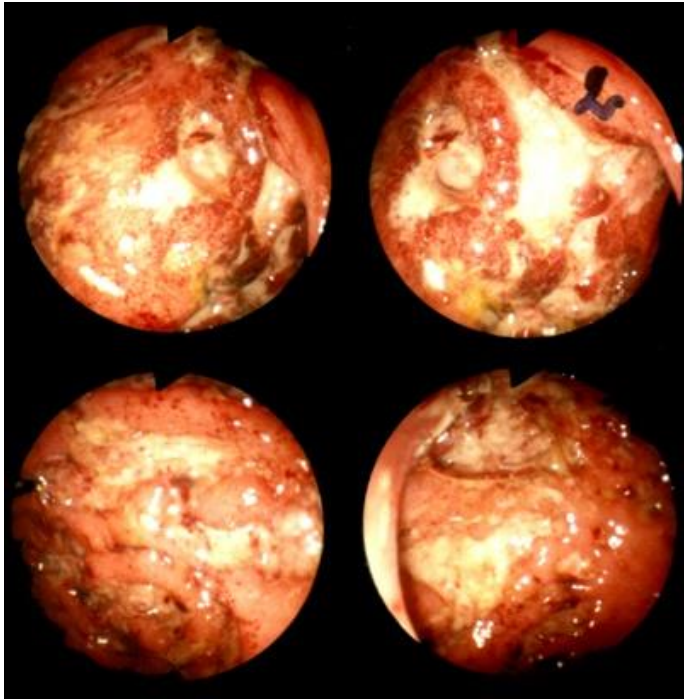


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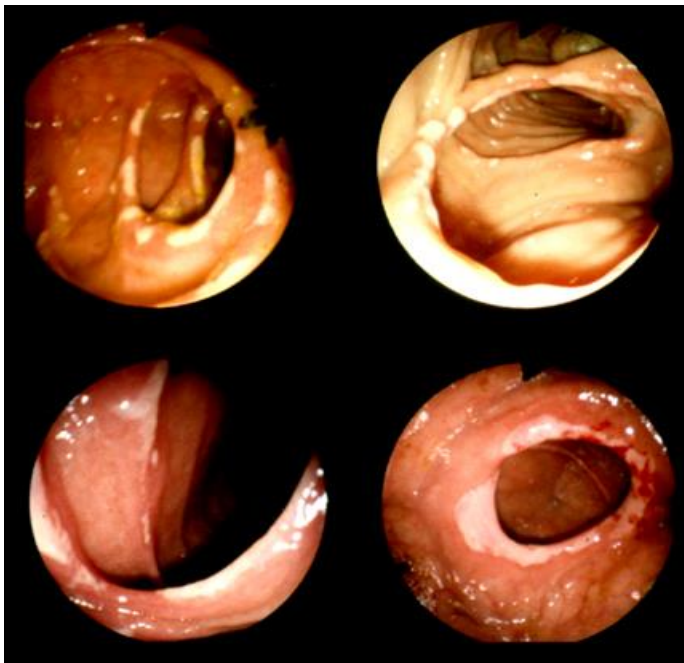
➤ Endoscopy

CRC in UC



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CRC in UC



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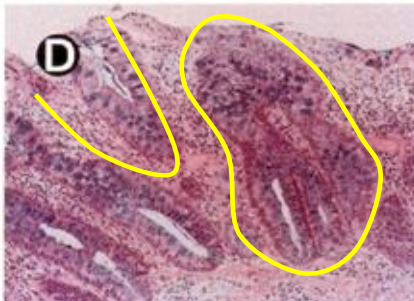
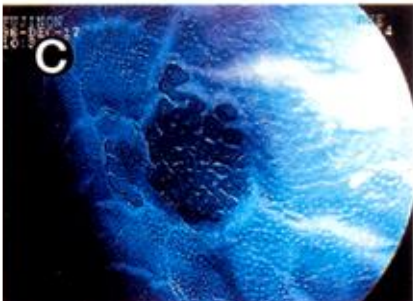


➤ Histopathology

Dysplasia in UC



Normal



Dysplasia

Courtesy of Professor Guito Tytgat, Netherlands

Focal High Grade Dysplasia (HGD) in UC



- Focal HGD
- Architectural complexity
- Nuclear hyperchromasia
- High NC ratio

Courtesy of Professor Guito Tytgat, Netherlands



➤ Differential

- Give features which help to **distinguish UC-CRC** from sporadic CRC (SPO-CRC).

Features	UC-CRC	SPO-CRC
○ Age of diagnosis of CRC, years	40	60
○ Location of dysplasia	CRC may be distant from UC CC (30%)	Associated with polyp
○ Location of CRC	R~ = LC CC 23% to 70%	LC > RC
○ Mutation		
– RAS protooncogene		
▪ %	~ 20%	50%
▪ Timing	Late	Early
– LOH for p53		
▪ Timing	Early	Late
▪ In non-dysplastic tissue	Yes	No
– Small SRC activation		
▪ Timing	Early	Late
▪ Correlate with degree of dysplasia	Yes	No
○ Pathology		
– Anaplastic	Often	Less often
– Mucinous	Often	Less often
○ Synchronous	more common in UC-CRC than in SPO-Ca	

Abbreviations: CC, Crohn colitis; CRC-CC, colorectal cancer in a patient with UC; CRC-UC, colorectal cancer in a patient with UC; LOH, loss of heterogeneity; RC, right colon; LC, left colon

In addition, there is a rare type of IBD-CRC which is a very well differentiated adenocarcinoma called tubuloglandular carcinoma.

Note:

- CRC screening in CD should be undertaken when $\geq 1/3$ of the colon is involved with CD.
- It is possible that 5-ASA, folic acid, calcium, ASA, or NSAIDs may reduce the risk of sporadic CRC, as well as CRC associated with IBD.
- There is no evidence that azathioprine, 6-MP or anti-TNF therapy reduce the rate of development of IBD-associated dysplasia / CRC.



OTHER FORMS OF COLITIS

Crohn Colitis (CC)

➤ Diagnostic imaging

- MRI in CC
 - T₁- weighted
 - Thickening of wall
 - Stranding of soft tissue
 - T₂- weighted
 - High-signal intensity in pericolonic fat
 - Abscess, fistula (best test)

To Paraphrase

- Give the three EIM of UC / CD which do not reflect the activity of the associated IBD.
 - AS / SI
 - PSC
 - PG

Abbreviations: AS, ankylosing spondylitis; CD, Crohn disease; EIM, extraintestinal manifestations; PG, pyoderma gangrenosum; PSC, primary sclerosing cholangitis; SI, sacroilitis; UC, ulcerative colitis;

- Multiple discrete areas of barium (barium rests) from colonic Crohn disease
 - Differential: amebiasis, Behcet disease, Crohn colitis, HSV, TB, Yersinia infection,.

Crohn Colitis



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Ileal Crohn disease



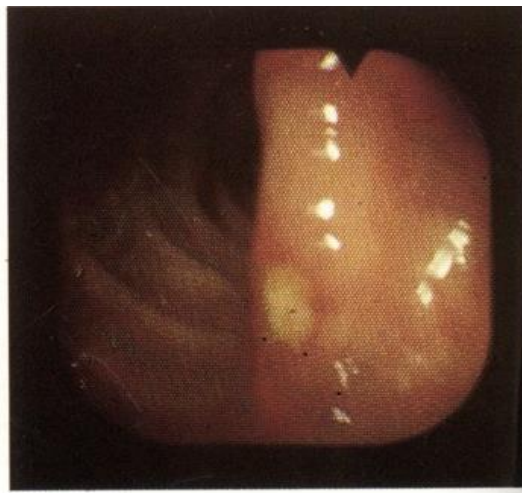
Multiple, discrete, asymmetric areas of (barium rests) filling from colonic Crohn disease.

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➤ Endoscopy

- Crohn Colitis
 - Long – usually 10 cm or longer
 - Abscesses frequently have a triangular configuration, but may at times be undistinguishable from the coexistent diverticula
 - This is an ulcerating mucosal process; folds are straightened, perpendicular, picket-fence-like & associated with a thick wall & secretions
 - Transverse fissures with marked edema of mucosa produce a step-ladder configuration
 - If a tract is seen, it is long, linear & located in the submucosa or muscular layers

Crohn Colitis

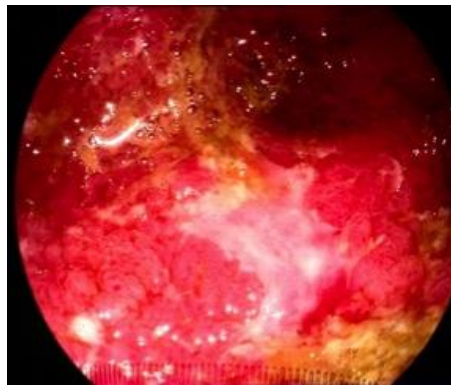
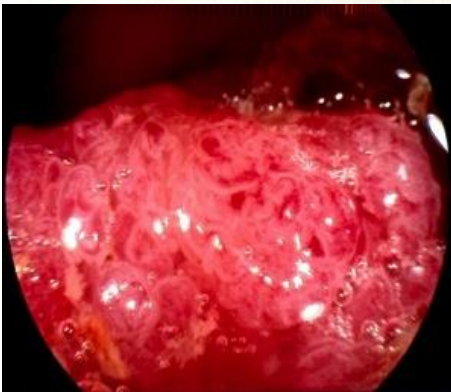
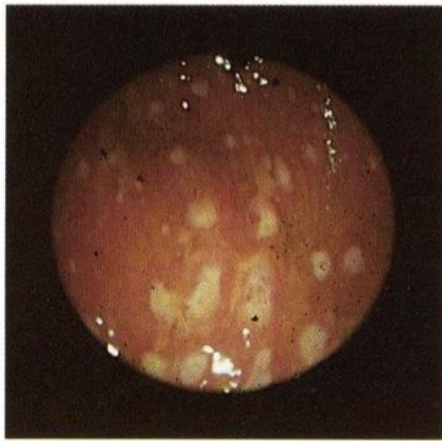


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➤ Colonoscopy

Crohn Colitis: Aphthous Ulcers



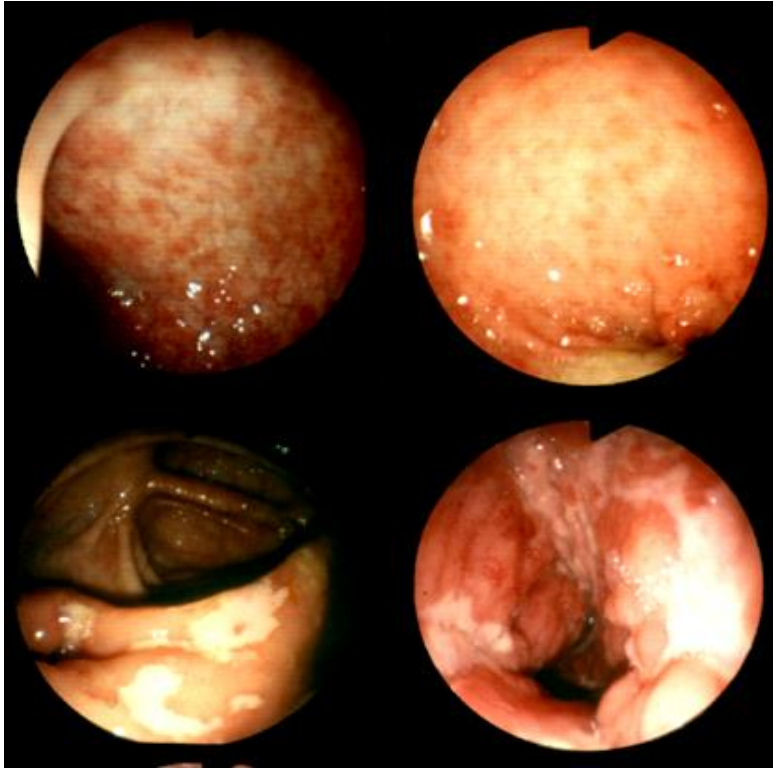
- Aphthous ulcers coalesce → deep, serpiginous, linear ulcers
- Ulcers are circumferentially asymmetric

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- Other features of Crohn disease
 - Discontinuous disease
 - May see solitary deep ulcers
 - Segmental narrowing
 - Inflammatory polyps
 - Fistulae
 - Rectal sparing
 - Cobblestone appearance of mucosa (longitudinal and transverse collections of barium from deep ulcers)
 - Large lymphoid follicles → small nodules
 - Ulcers surrounded by “halo” of edema (“aphthous” ulcers; central “umbilication”)
 - Poorly defined borders
 - Variation in size of central umbilication



Crohn Colitis



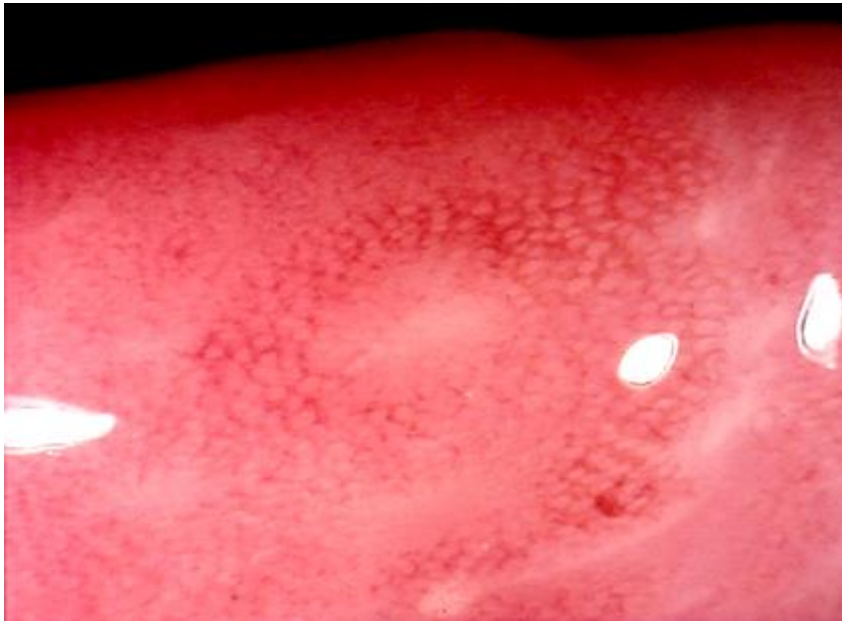
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SO YOU WANT TO BE A GASTROENTEROLOGIST!

- A patient with colitis (Crohn colitis or Ulcerative colitis) has a polypoid mucosa on endoscopy, with the appearance of inflammatory pseudo polyps.
- Mucosal biopsies are taken to confirm the histopathology of the suspected inflammatory polyps.
- As expected the biopsies show long crypts, and in the lamina propria there is a mixed inflammatory infiltrate.
- Give the additional histological findings you would search for which would diagnosis a second type of recurrent, inflammatory pseudopolyp.
 - “Cap polyposis” appears just like inflammatory pseudopolyp, but is likely due to repeated mucosal prolapse, and has a surface cap of fibropurulent exudate.

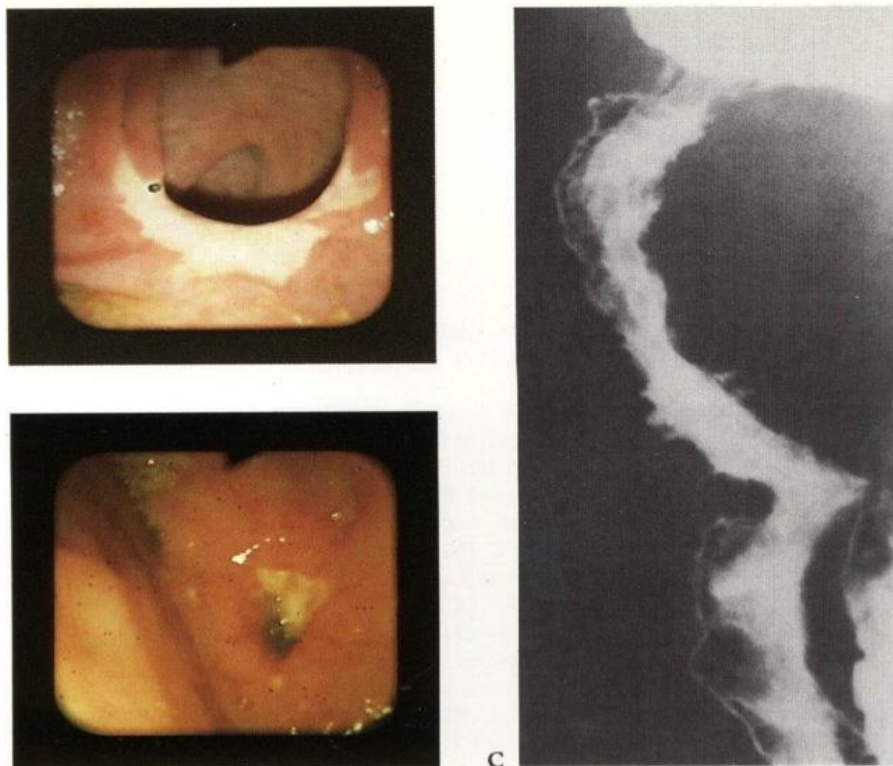


Post-resection for Crohn disease



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Post-resection for Crohn disease



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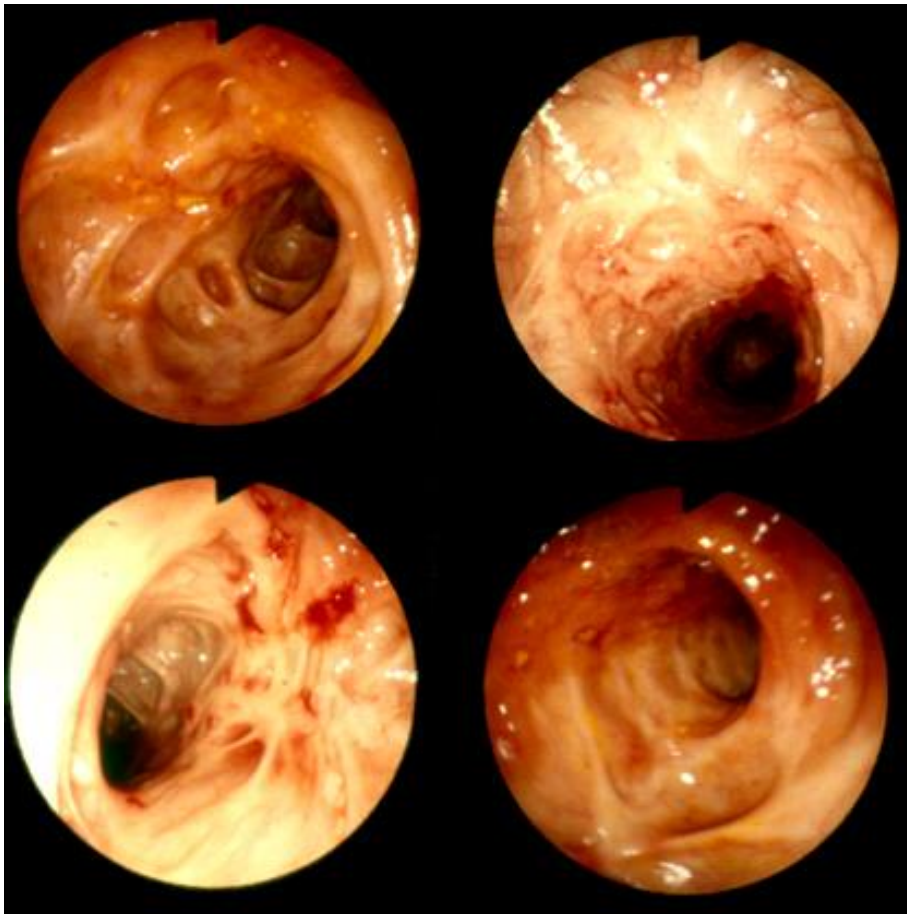


Post-resection Crohn disease



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Post-resection Crohn disease



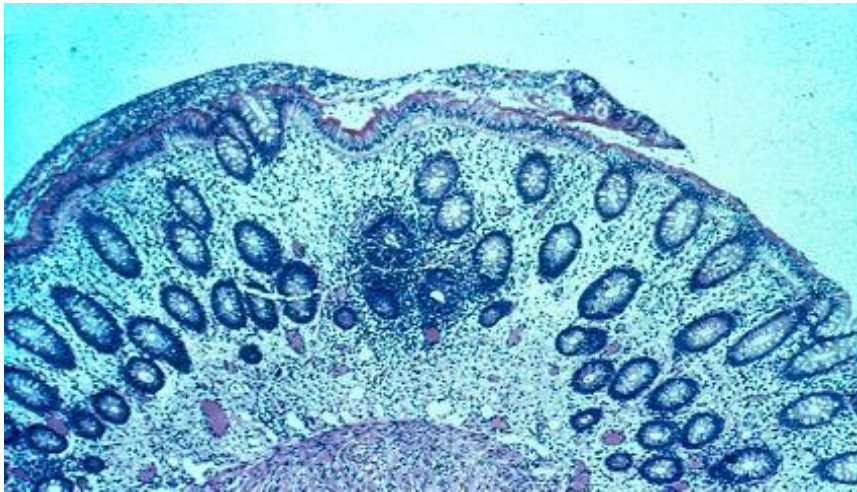
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➤ Histopathology

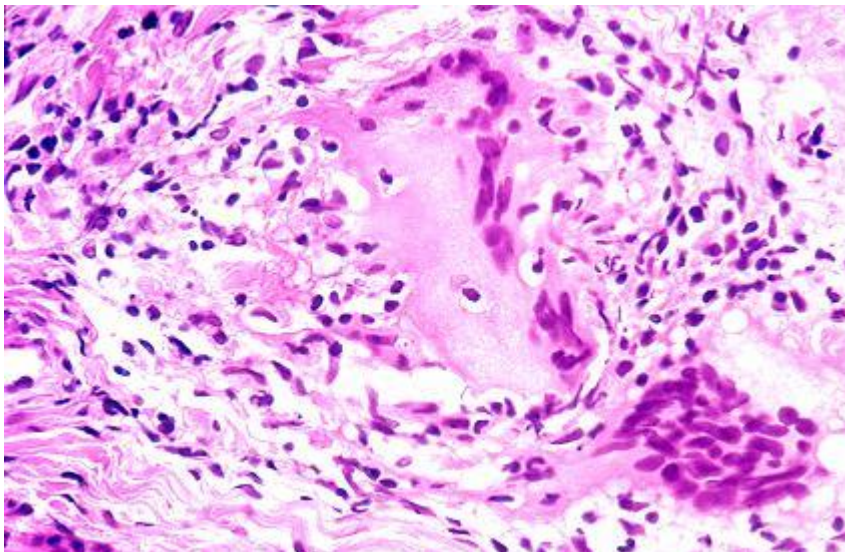
- Patchy chronic (architectural distortion, basal plasmacytosis) and active (cryptitis, crypt abscesses) inflammation
- Transmural inflammation, usually lymphocytic with transmural lymphoid aggregates
- Non-necrotizing granulomas, may be transmural
- Deep, fissuring ulcers
- Aphthous lesions (active epithelial inflammation overlying a lymphoid follicle)

Crohn Disease – patchy inflammation



Courtesy of Professor Guito Tytgat, Netherlands

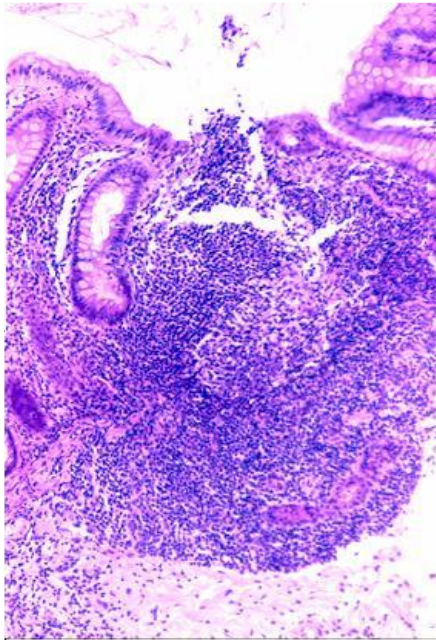
Crohn Disease – non-necrotizing granuloma



Courtesy of Professor Guito Tytgat, Netherlands

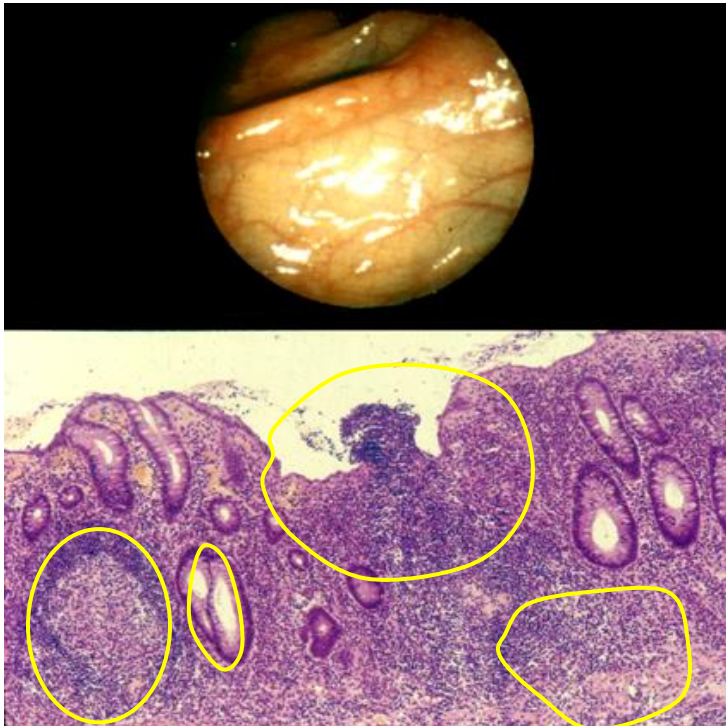


Crohn Disease



Courtesy of Professor Guito Tytgat, Netherlands

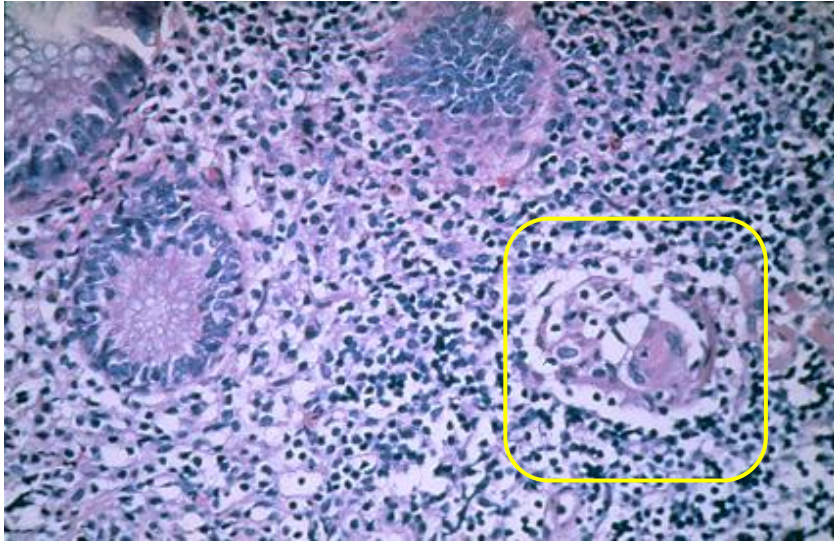
Crohn Disease



Courtesy of Professor Guito Tytgat, Netherlands

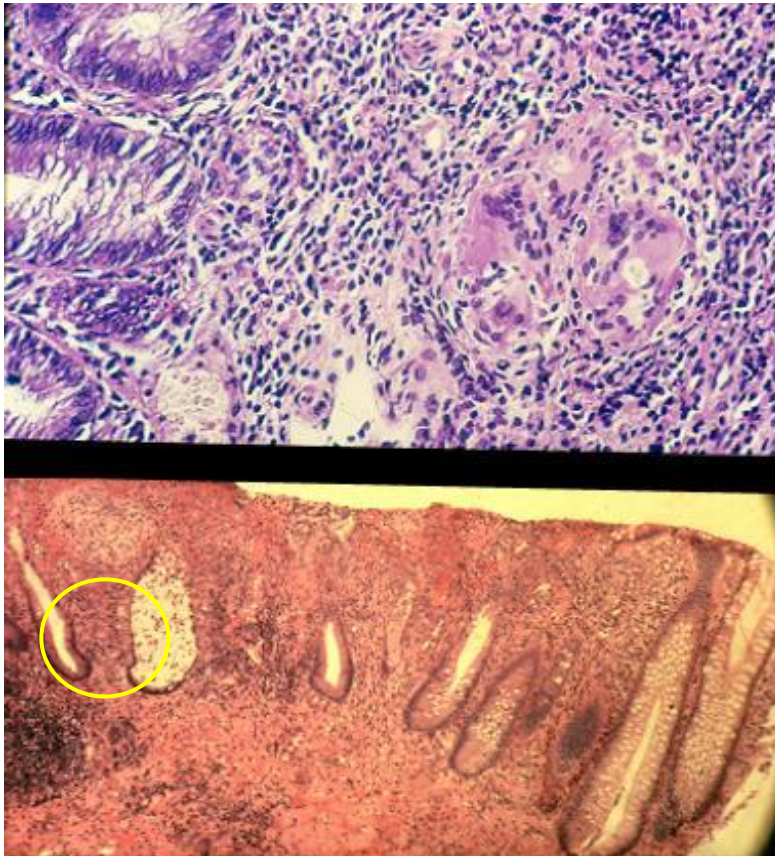


Crohn Disease: Granuloma



Courtesy of Professor Guito Tytgat, Netherlands

Crohn Disease Granuloma



- ↑ Inflammation within lamina propria with lymphocytes, plasma cells, eosinophils, and neutrophils
- Crypt destruction

Courtesy of Professor Guito Tytgat, Netherlands



Crohn Disease – Aphthoid lesions

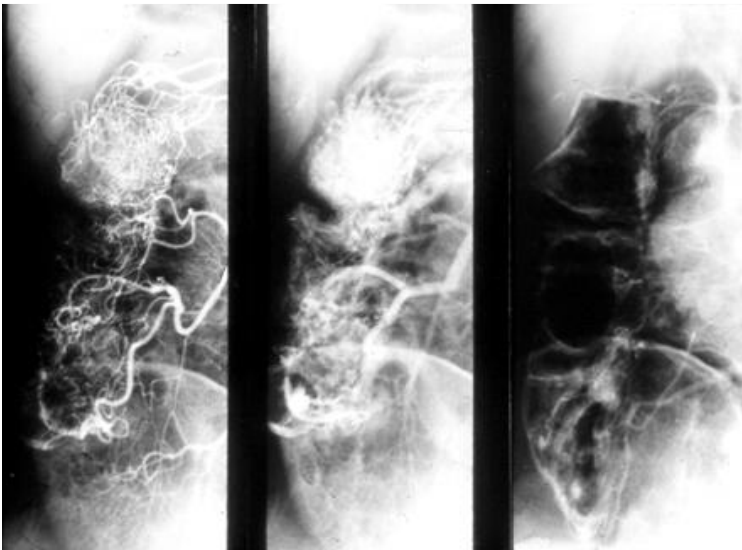


Courtesy of Professor Guito Tytgat, Netherlands

Radiation Colitis

- Diagnostic imaging
 - Angiographic features of angiodysplasia
 - Dilated tortuous slowly emptying intramural veins with prolonged opacification
 - Vascular tuft
 - Early filling vein
 - Dilated feeding artery or arterial feeder to antimesenteric border
 - Intraluminal extravasation

Angiography – Angiodysplasia



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➤ Endoscopy

• Endoscopic findings*

- Telangiectasia (51%)
- Friable mucosa (30%)
- Luminal narrowing (81%)
- Solitary ulcer (25%)
- Diffuse ulceration (18%)
- Fistula (19%)
- Gradual narrowing of lumen
- Narrow sigmoid colon wall (and sometimes proximal colon)
- Thick wall (“thumbprinting”)
- Haustral loss (loss of normal colonic folds)
- Strictures

* The numbers in brackets represent the approximate frequency of patients with radiation colopathy who have these symptoms and these endoscopic findings.

Angiodysplasia



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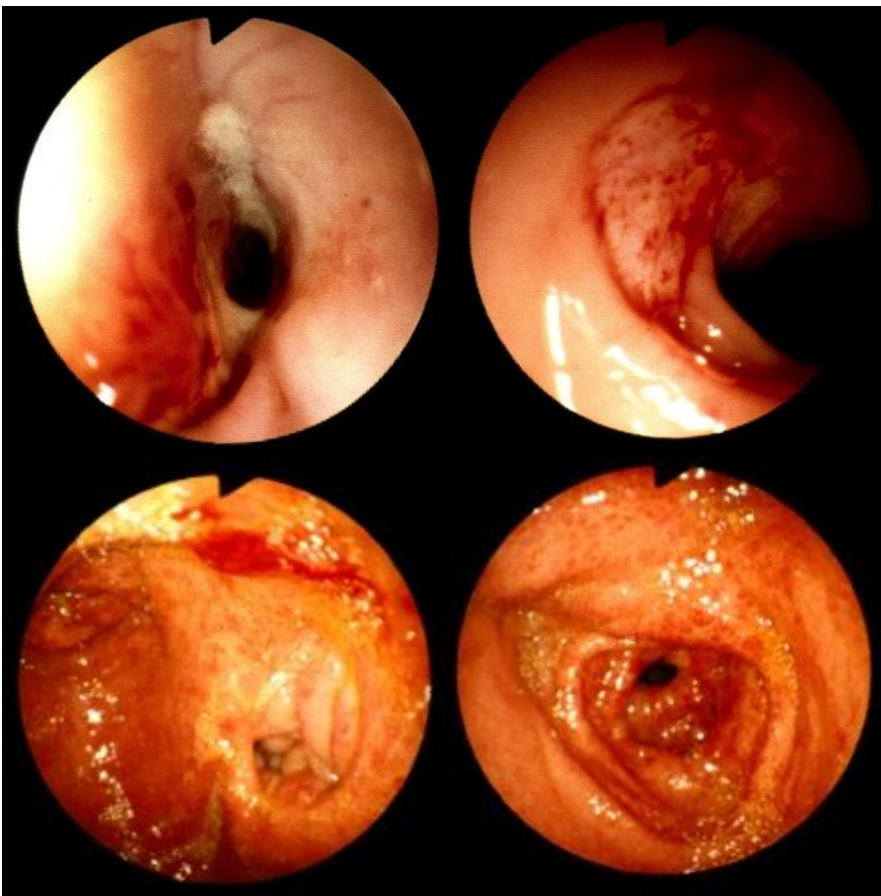


Radiation Colitis: Angiography



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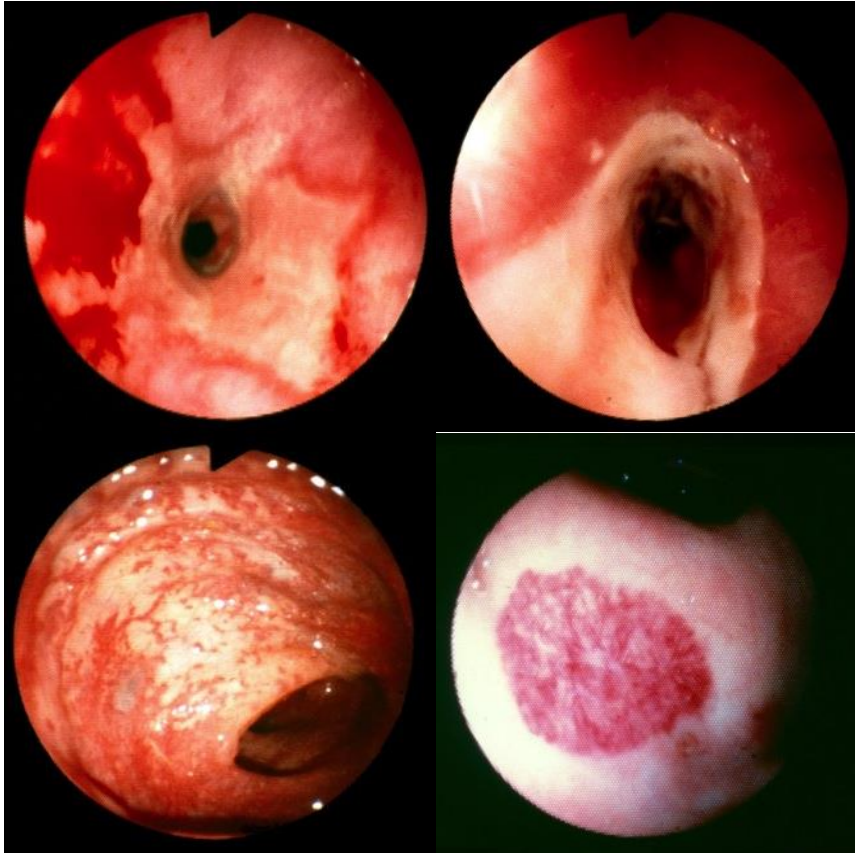
Radiation Colitis



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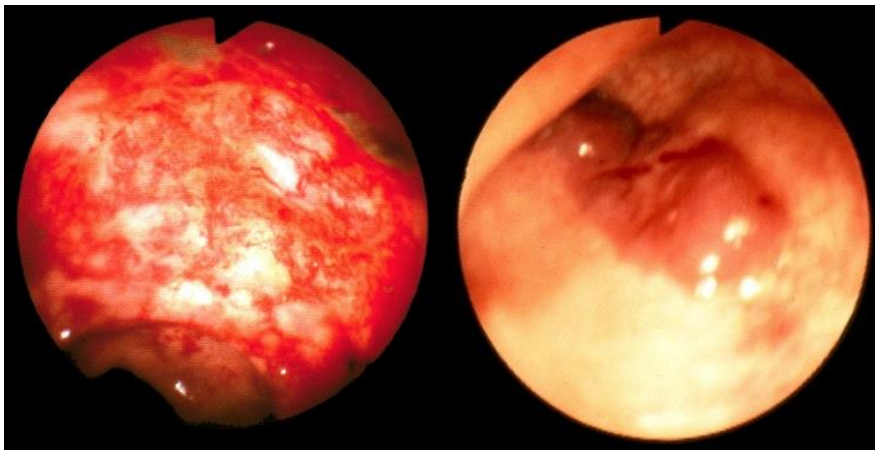


Radiation Colitis



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Radiation Colitis



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➤ Histopathology

- Give the histopathological features seen on small bowel biopsy which accompany chronic radiation damage.
 - Arterioles; (intima vasculopathy, only seen if submucosa is present in biopsy)
 - Obliterative endarteritis
 - Foam cells
 - Loss of vessel wall → ischemia
 - Mucosa
 - Atrophy/ischemic type changes
 - May be continuous or patchy (i.e., skip lesions)
 - Telangiectasias
 - Atypia of stromal, endothelial or epithelial cells with no increase in N:C ratio
 - Ulceration / necrosis
 - Submucosa (if present in biopsy)
 - Thickening
 - Hyaline
 - Collagen
 - Fibrosis
 - Telangiectasias
 - Lymphatics
 - Constriction
 - ↓ flow → edema
 - ↑ inflammation

Microscopic Colitis

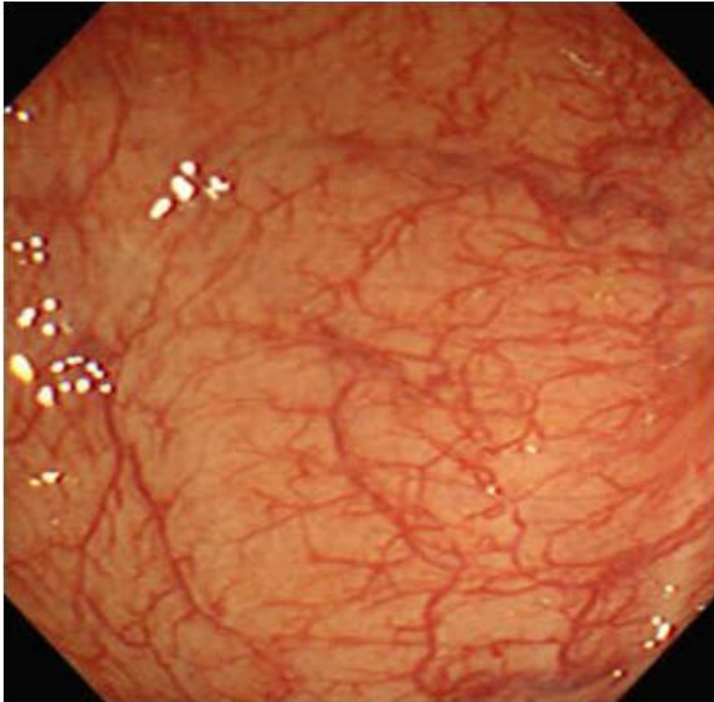
➤ Definition

- A chronic inflammatory condition causing chronic watery diarrhea, typically seen in middle-aged women, whose colonoscopy shows apparently normal mucosa but the mucosal biopsies are histologically abnormal
- The spectrum of microscopic colitis (MC) includes LC (lymphocytic colitis) and CC (collagenous colitis).
- MC occurs in a bowel which is endoscopically normal (implication; mucosal biopsies must be taken from endoscopically normal-appearing mucosa)



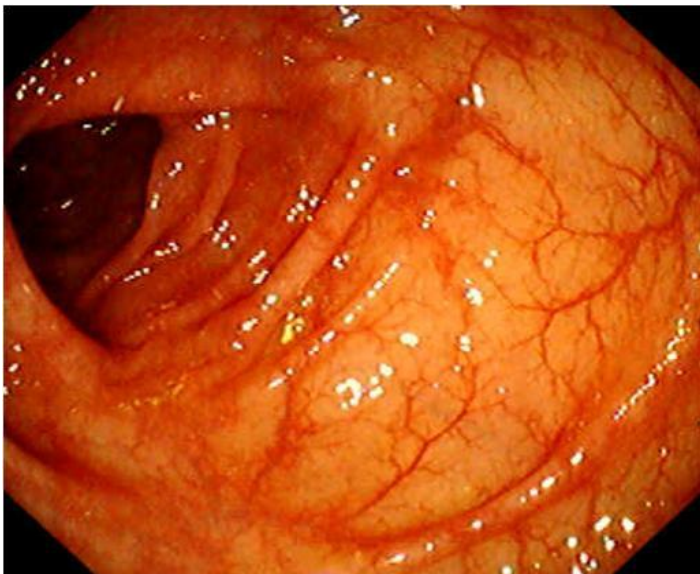
➤ Endoscopy

Collagenous Colitis



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Lymphocytic Colitis

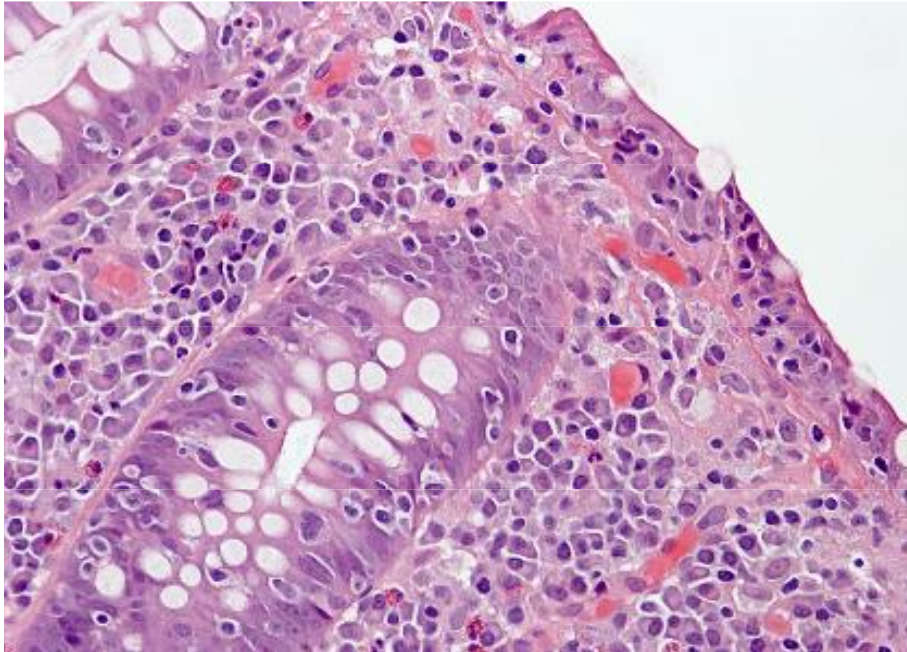


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The colonic mucosa appears normal on endoscopy in persons with biopsy proven microscopic colitis (collagenous colitis and lymphocytic colitis)

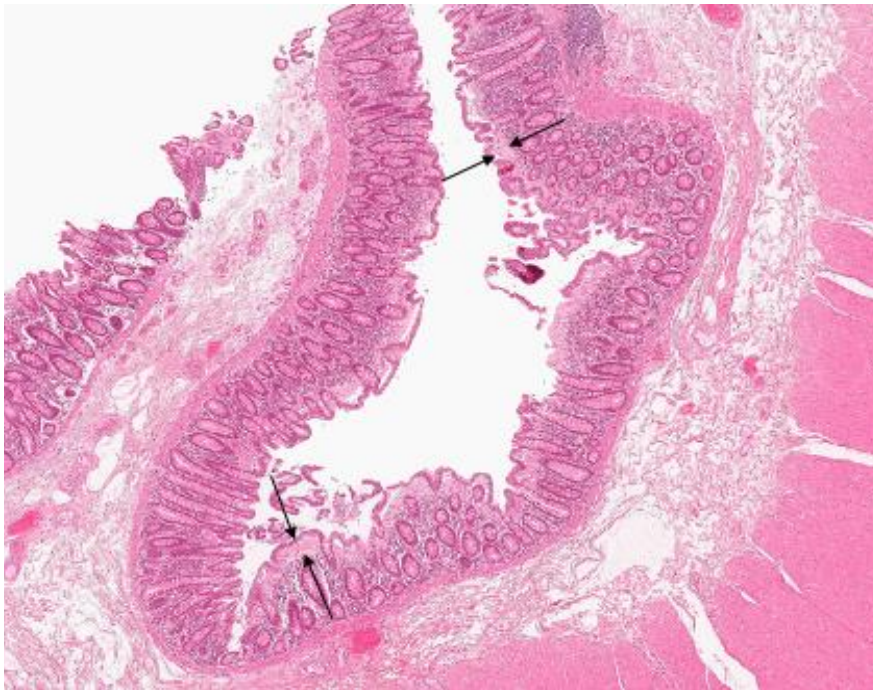


➤ Histopathology
Lymphocytic Colitis



Courtesy of Dr. Aducio Thiesen, University of Alberta, Edmonton

Collagenous Colitis

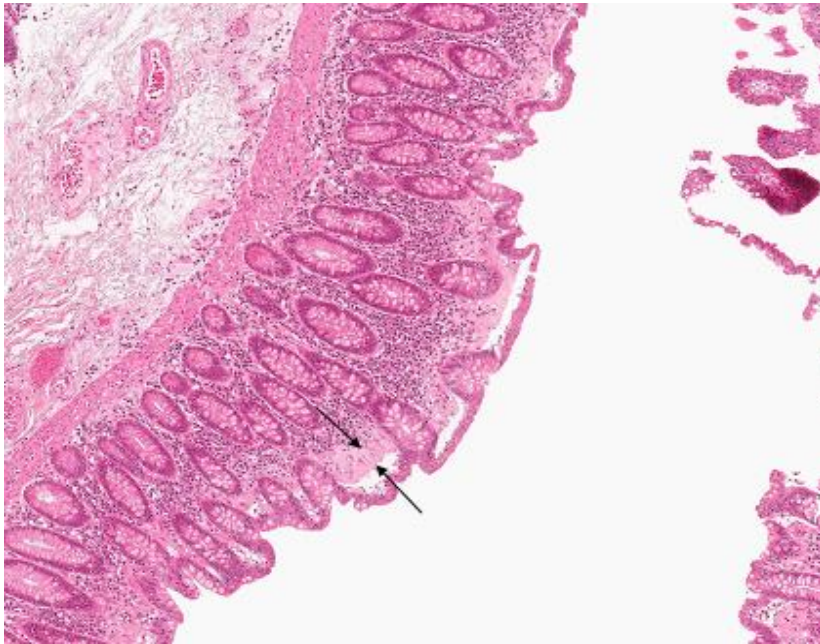


Large bowel wall showing a thickened subepithelial collagen band (arrows) with patchy separation of the surface epithelium indicative of collagenous colitis(H&E 40X)

Courtesy of Dr. Aducio Thiesen, University of Alberta, Edmonton

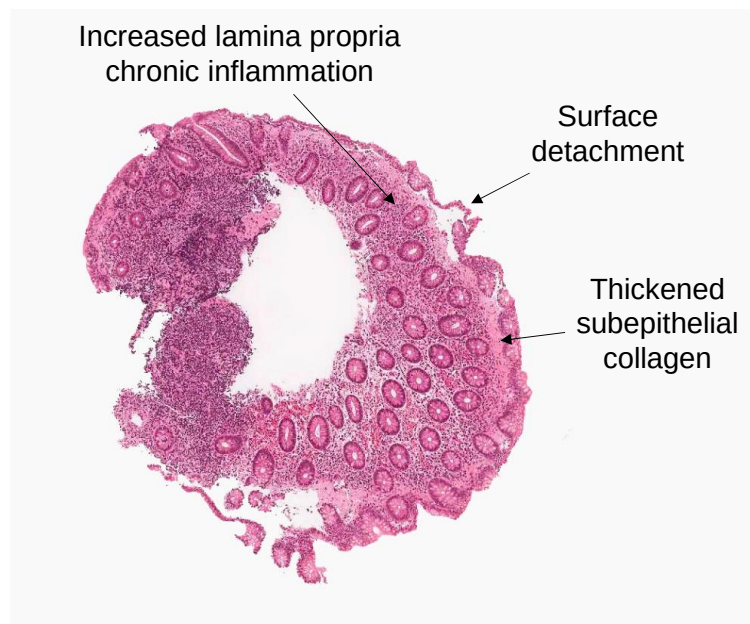


Collagenous colitis (H&E 100X)



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Collagenous colitis (H&E, 40X)



This low power view shows increased chronic inflammation within the lamina propria and a thickened subepithelial collagen band (pale pink), easily visible at this low magnification. There is focal surface epithelial detachment, typical of this condition.

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Collagenous colitis (H&E, 100X)



This higher power view highlights the thickened subepithelial collagen band (arrows), containing entrapped capillaries and inflammatory cells.

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Lymphocytic colitis

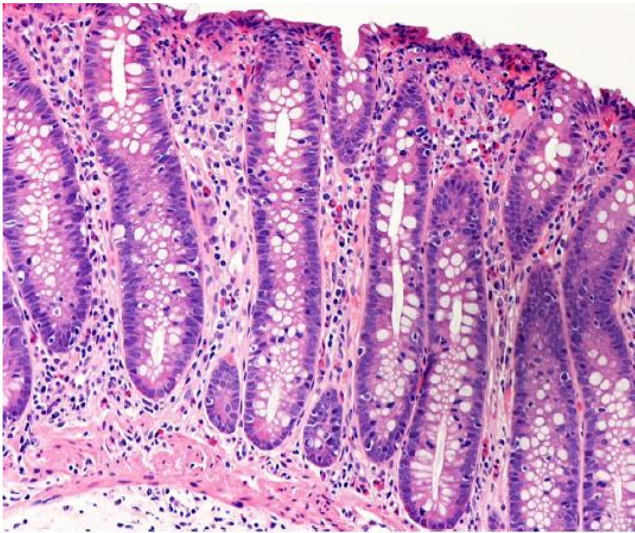


Large bowel biopsy showing surface epithelial attenuation and increased intraepithelial lymphocytes, predominantly in the crypts in this case (H&E 100X)

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Lymphocytic Colitis

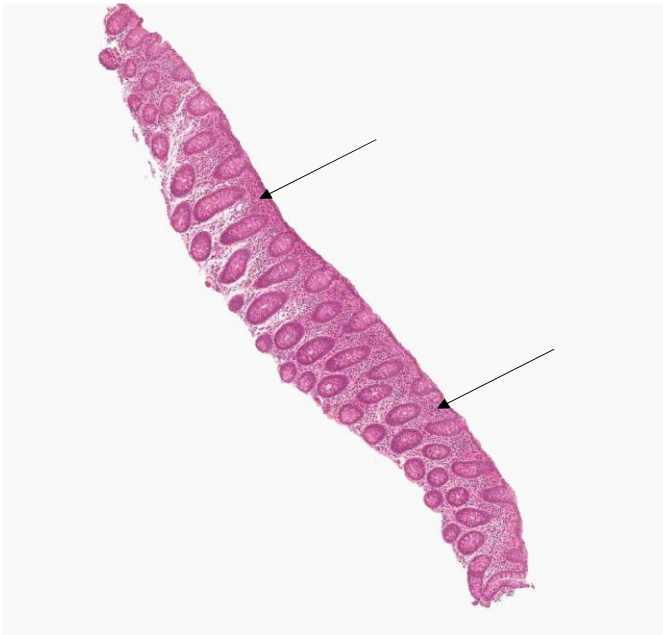


- ↑ numbers of intraepithelial lymphocytes (IELs) and increased superficial lamina propria lymphoplasmacytic infiltrate
- Epithelial damage common
- Crypt abnormalities are unusual
- Histologic changes variable throughout colon (80% cecum and transverse; 30% in rectum)
- Multiple biopsies above rectosigmoid in left colon are diagnostic in 90% of cases

- Lymphocytic / collagenous colitis
 - Normal crypt architecture
 - Surface epithelial damage
 - ↑ intraepithelial lymphocytes
 - ↑ (usually superficial) chronic inflammatory infiltrate in lamina propria
 - More severe in right vs left colon

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Lymphocytic colitis (H&E, 40X)

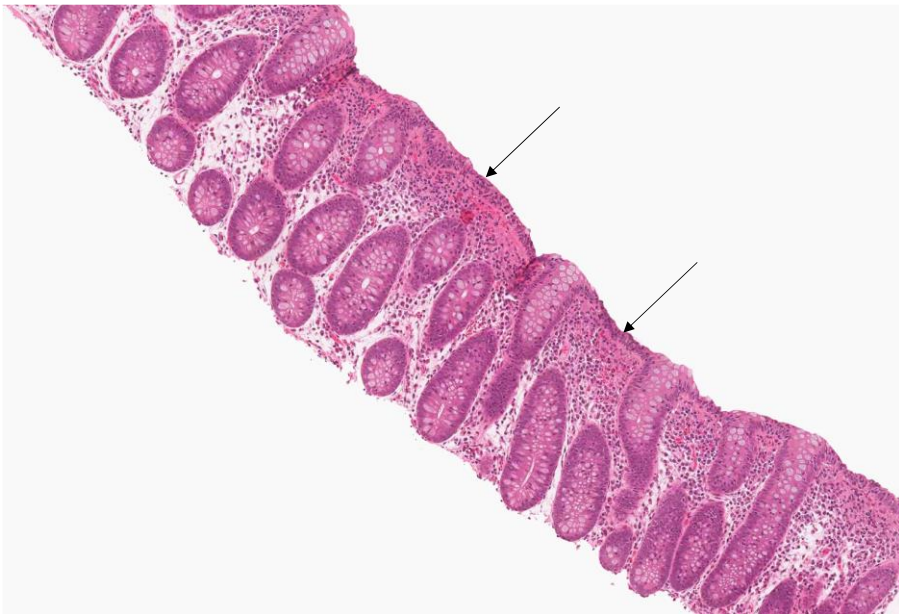


This low power view shows increased chronic inflammation within the lamina propria, predominantly affecting the more superficial part of the epithelium (arrows). This is an excellent low power clue that the diagnosis may be microscopic colitis (lymphocytic or collagenous).

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Lymphocytic colitis (H&E, 100X)



This higher power view shows attenuated surface epithelium (arrows) with numerous intraepithelial lymphocytes

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Diversion Colitis

➤ Definition

- “..... an inflammatory process that occurs in the diverted segment of colon and rectum after surgical diversion of the fecal stream” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 2242).

➤ Demography

- 3x more frequent after surgery for IBD than for non-IBD colonic disorders (87% versus 28%)
- “an inflammatory process that occurs in segments of the colorectum that are diverted from the fecal stream by surgery”

➤ Endoscopy

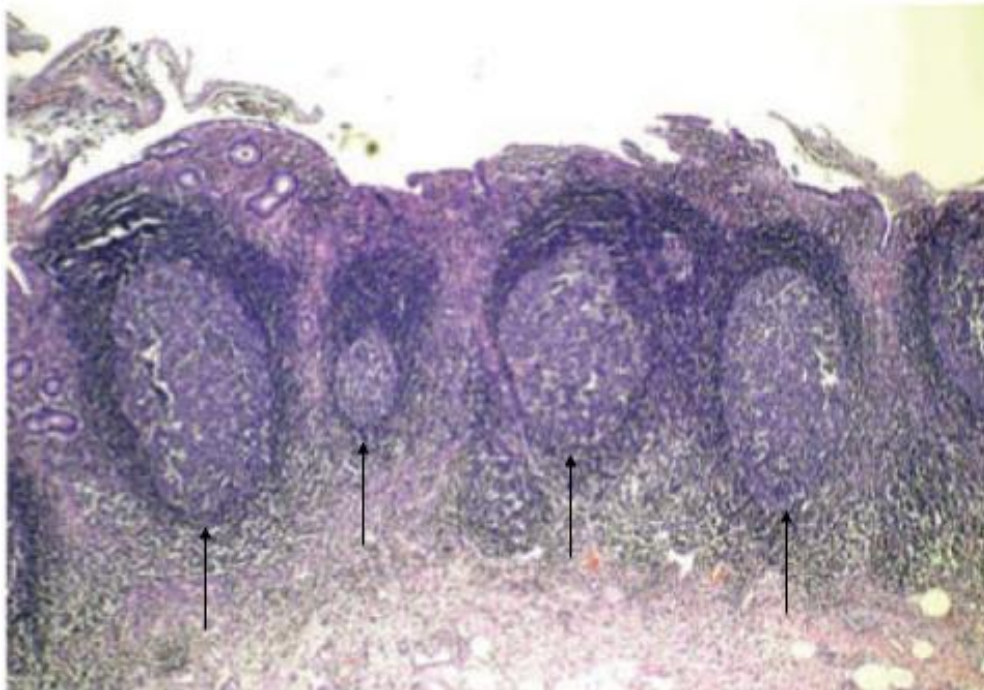
- Severity of diversion colitis
 - Mild 52%
 - Moderate 44%
 - Severe 4%
- Colitis in non-bypassed (“in continuity”) colon 0%
(Note: there are case reports of symptomatic UC developing in the “in continuity” colon in persons with established diversion colitis)



➤ Histopathology

- Inflammatory cells
 - Neutrophils, diffuse infiltration
 - Lymphocytes
 - Mononuclear cells
- Aggregates
 - Neutrophils
 - Lymphoid follicular hyperplasia
- Crypts
 - Cryptitis
 - Abscesses
- Paneth cells
 - Metaplasia
- Prominent lymphoid follicular hyperplasia in mucosa and submucosa
- Aphthous ulcers (erosions over lymphoid follicles)
- If the diversion was for Crohn disease, granulomas may occur in the bypassed bowel.
- May be difficult to distinguish from acute UC; prominent lymphoid follicles are the clue that this is likely diversion colitis

Diversion Colitis (arrows indicate lymphoid follicles)



Printed with permission: Nielsen OH, et al. Nat Clin Pract Gastroenterol Hepatol. 2008;5(1):28-39.

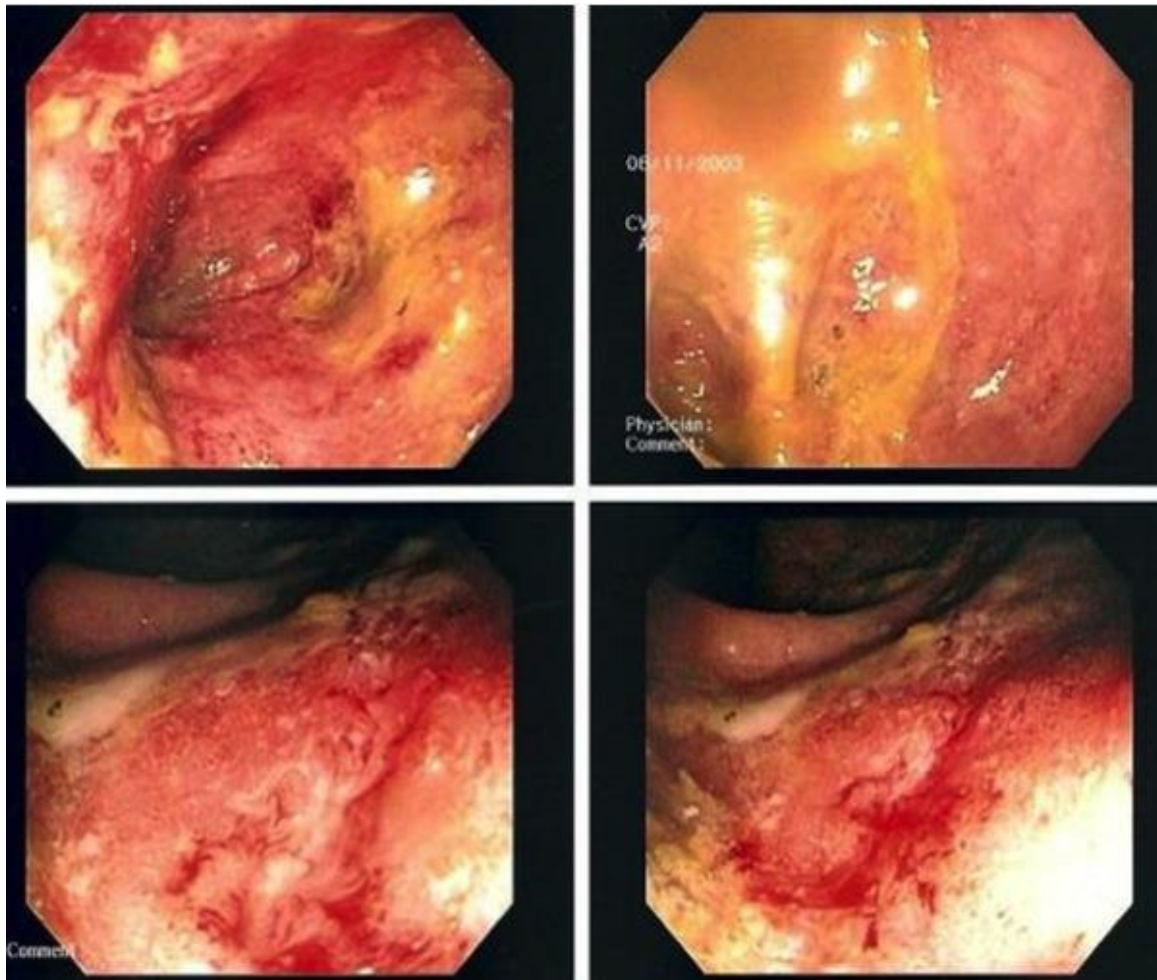


Infectious Colitis

➤ Endoscopy

- The mucosal biopsy may be normal or may show a spectrum of findings in infectious colitis, depending upon the micro-organisms,
 - None of the findings are sufficient to make a diagnosis without histopathology of mucosa
- The endoscopic pattern of redness / friability may be diffuse or patchy
- There may be erosions, ulcerations, pseudopolyps, or pseudomembranes
- The mucosa must be biopsied, and the stools or the mucosa must be cultured

Infectious Colitis



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Infectious Colitis



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➤ Histopathology

- Architecture
 - Normal, except with severe infection with *Salmonella typhimurium* or *Shigella* infections when there may be distortion of the crypts
- Crypts
 - Infiltration (cryptitis)
 - No WBC infiltration if patient is severely immunosuppressed
 - Crypt abscesses
- Patterns
 - Look for specific histological pattern which may help to narrow the differential for the infectious causes of infectious colitis, or the type of colitis other than acute infectious colitis
 - Minimal inflammation
 - Acute self-limited colitis (ASLC)
 - Focal active colitis (FAC)



- Pseudomembranes
- Granulomas
- Histiocytes
- Lymphohistiocytes
- Ischemic pattern
- Vacuolization
- Minimal change inflammatory (MIC)
 - Enteropathic Escherichia coli (EPEC)
 - Enteroadherent Escherichia coli
 - Neisseria
- Acute self-limited colitis (ALSC) / Focal Active Colitis (FAC)
 - Aeromonas
 - Campylobacter
 - Chlamydia trachomatis
 - Salmonella (non-typhoid)
 - Shigella
 - Syphilis (+/-↑ plasma cells)
 - Occasionally Clostridium difficile
- Pseudomembranes
 - Candida
 - Clostridium difficile
 - CMV
 - Enterohemorrhagic E. coli (EHEC)
 - Shigella (sometimes)
- Granulomas
 - Actinomycosis
 - Cryptococcus
 - Mycobacterium avium intracellular complex (MAI)
 - Mycobacterium tuberculosis
 - Syphilis
 - Yersinia
- Diffuse histiocytic
 - MAI
 - Rhodococcus
- Lymphatic involvement
 - Cryptococcus
- Lymphohistiocytic
 - Lymphogranuloma venereum
 - Salmonella typhimurium



- Ischemic (hemorrhagic) pattern
 - CMV
 - Enterohemorrhagic E. coli (EHEC)
 - Yersinia
- Inclusion body
- Infections with > 1 pattern
 - Spirochetosis including syphilis
 - Minimal inflammatory change (MIC)
 - Acute self-limited colitis (ASLC)
 - Granulomatous
 - C. difficile
 - Pseudomembranes
 - ASLC
 - Salmonella non-typhoid
 - ASLC
 - S. typhimurium
 - Lymphohistiocytic
 - Marked change in architecture
 - Shigella
 - ASLC
 - Pseudomembranes
 - Marked change in architecture
 - Mycobacterium avium-intracellulare (MAI)
 - Immunocompetent
 - Granulomatous
 - Immunocompromised
 - Diffuse histiocytic
 - Escherichia coli
 - EPEC
 - EAEC
 - EHEC

}

- MIC

 - Pseudomembranes
 - C. difficile
 - Pseudomembranes
 - ASLC
 - Acid fast staining
 - TB
 - MAI
 - Isospora belli
 - Cryptosporidium

Note: Tropheryma whipplei macrophages in Whipple disease are not acid fast.

Abbreviations: ASLC, acute self-limiting colitis; FAC, focal active colitis; MAI, mycobacterium avium-intracellulare; MIC, minimal inflammatory change



Neutropenic Colitis (aka Typhlitis)

- Diagnostic imaging
 - Typhlitis (inflammation of cecum)
 - Adynamic ileus
 - Wall-thickening
 - Fascia-thickening
 - Pericolonic soft tissue stranding

Neutropenic Colitis



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Neutropenic Colitis



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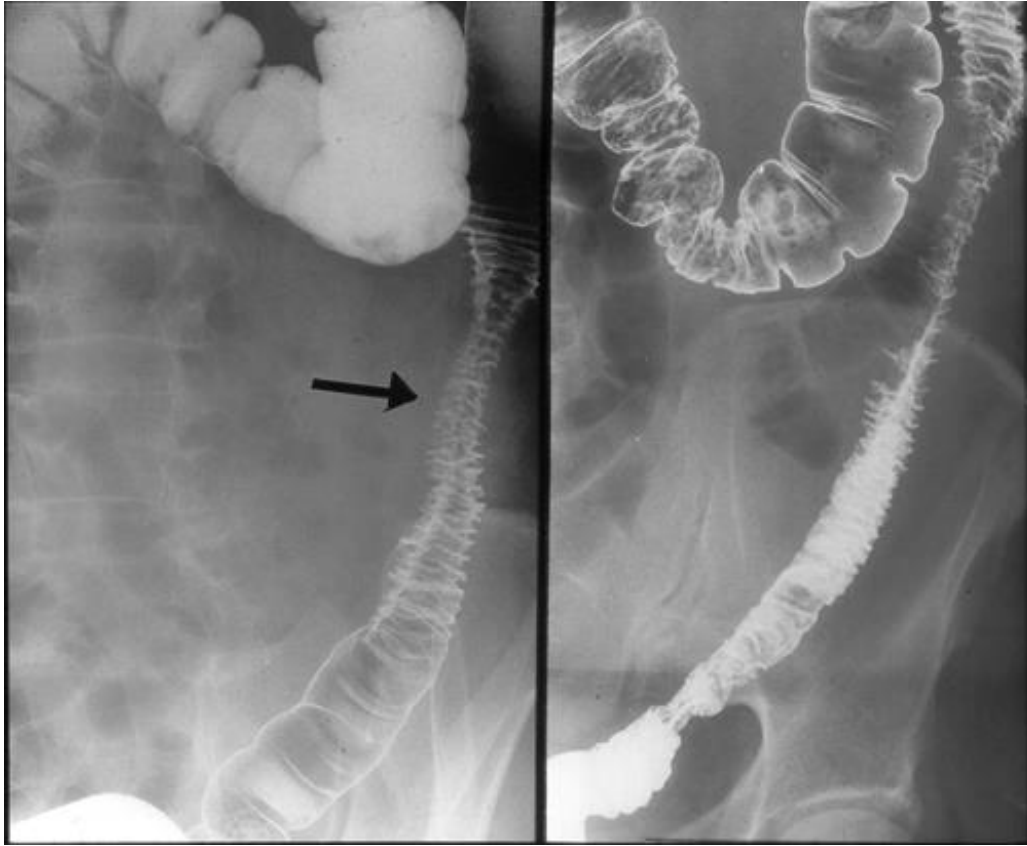
Neutropenic Colitis



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Neutropenic Colitis



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➤ Histopathology

- Histology of affected mucosa shows hemorrhage, often with necrosis. Minimal neutrophils are present.
- Acute necrotizing serositis with abundant neutrophilic polymorphonuclear leukocytes in the serosal adipose tissue

“A pessimist sees the difficulty in every opportunity;
and an optimist sees the opportunity in every
difficulty.”

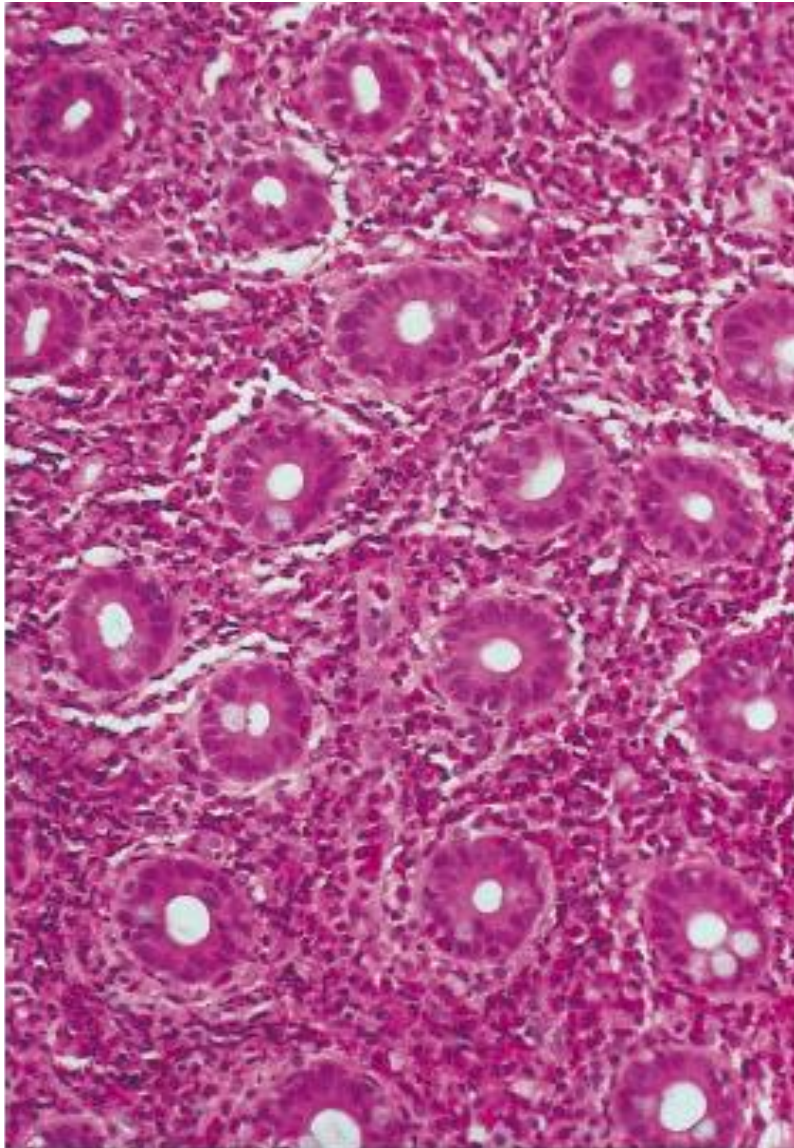
Sir Winston Churchill



Eosinophilic Colitis

➤ Histopathology

Eosinophilic Colitis



Numerous eosinophils fill the lamina propria, not destroying crypts.

Printed with permission: Carpenter HA and Talley NJ.
Am J Gastroenterol. 2000;95(4):878-96.



VIRAL INFECTIONS

➤ Endoscopy

CMV	HSV	HIV / AIDS	Adenovirus
○ Ulcers - Shallow/deep - Segmental/multiple Large ○ Pattern - Pseudomembranous - Hemorrhagic ▪ CMV in vessels	Erosions, multiple		○ Focal Acute

➤ Histopathology

	CMV	HSV	HIV/ AIDS	Adenovirus
○ Inclusion bodies	- Eosinophilic owl's eye in nucleus - Basophilic granules in cytoplasm - Usually in endothelial or stromal cells in colon - May be in epithelial cells in upper GI tract	▪ In epithelial cells ▪ Ground glass, nuclear ▪ Dark periphery ▪ Chromatin at margin ▪ Clear halo ▪ Cowdry type-A margination		- Enterocyte, goblet cells - Eosinophilic in nucleus, crescent shaped
○ Apoptosis enterocytes	↑		↑	↑
○ Mitotic bodies	↓		↓	
○ Crypts	↓			
○ Other	- Microthrombi - Inflammation - Necrosis			



Herpes Simplex Virus (HSV) Colitis

- Clinical
 - May cause an “attack” of UC recurrence
 - “Saddle” distribution of S2-S4 neuropathy (almost pathognomonic)
- Endoscopy
 - Usually left-sided only
 - Multiple small round ulcers
 - Raised borders central exudates
 - Found at the edge (“rim”) of the ulcers

CMV Colitis

- Clinical
 - May complicate UC and cause a recurrence of symptoms / inflammation
 - May cause severe colitis
- Endoscopy
 - Redness
 - Friability
 - Ulcers
 - Long
 - Deep
 - Serpiginous
 - Discrete, clean-based

Endoscopic Tip:

When dealing with possible viral infection of GI tract (e.g., esophagitis or colitis), take targeted biopsies.

- Centre of lesions CMV
- High on the rim (at edge) HSV



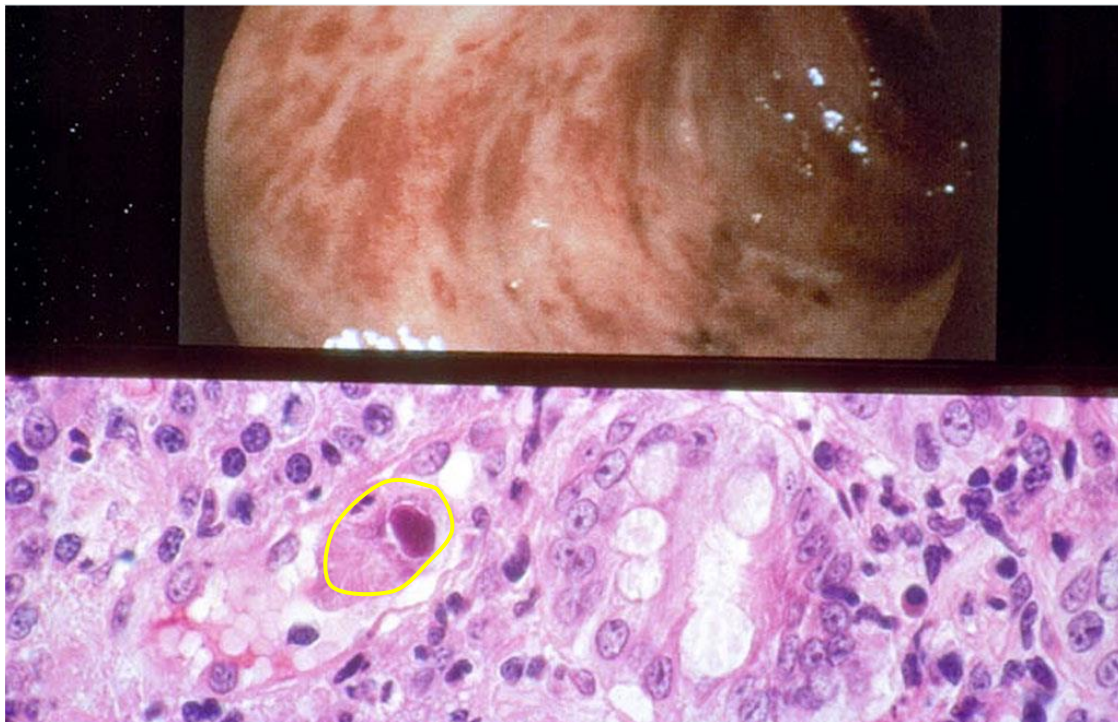
CLINICAL GEMS

- CMV colitis is often left sided (may misdiagnose if only doing a flexible sigmoidoscopy)
- Biopsies are taken in centre of lesions in an attempt to obtain granulation tissue which may show inclusions in endothelial cells.
- Take biopsies from both abnormal and normal appearing mucosa (CMV may be detected in both)
- Always check the retina to exclude CMV retinitis.

➤ Histopathology

- Top
 - Ischemic changes
- Bottom
 - Intracellular inclusion bodies (“owl’s eye” appearance)

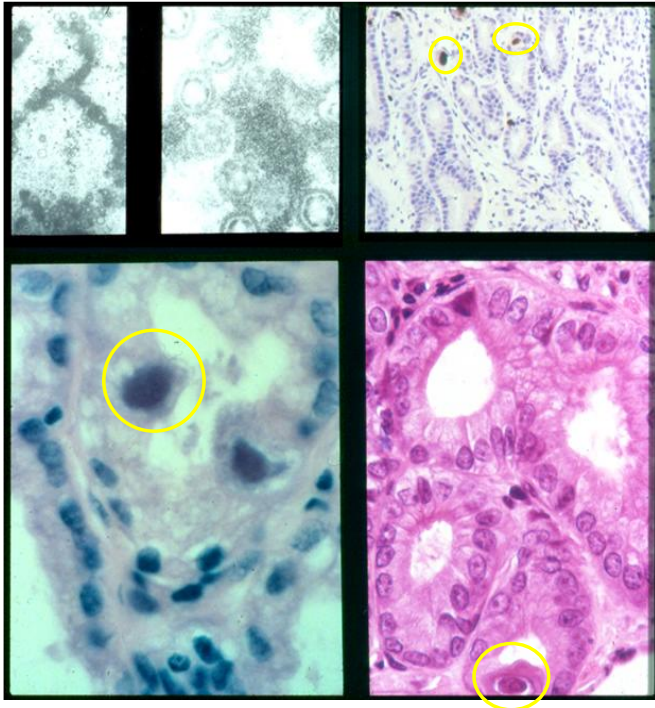
CMV Colitis



Courtesy of Professor Guito Tytgat, Netherlands

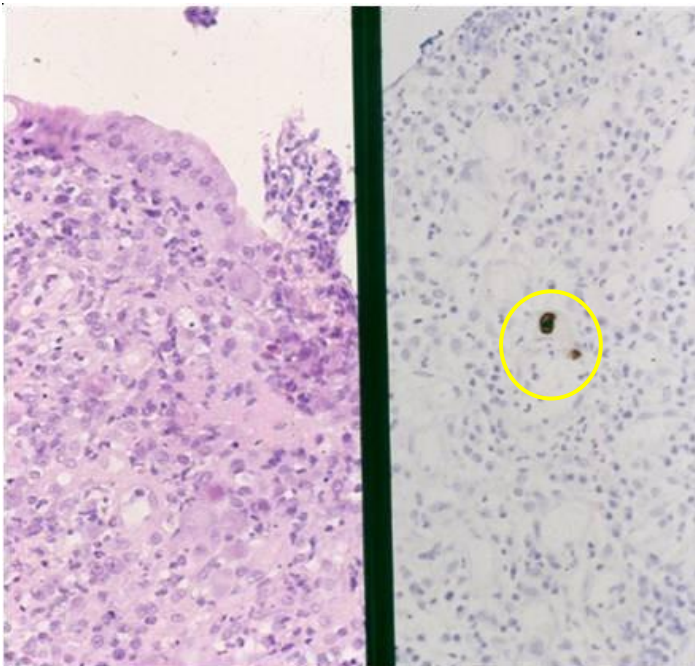


CMV Colitis



Courtesy of Professor Guito Tytgat, Netherlands

CMV Colitis



Courtesy of Dr. Aducio Thiesen, University of Alberta, Edmonton



BACTERIAL INFECTION

Clostridial Diseases

➤ Types

Presentation	Organism
○ Pseudomembranous colitis (PMC)	– C. difficile
○ Botulism	– C. botulinum
○ Necrotizing jejunitis	– C. perfringes
○ Neutropenic enterocolitis (NE, aka typhlitis) – Associated with adenocarcinoma of the terminal ileum and colon	– C. septicum
○ Note – Pseudomembranes are associated with infection with C. difficile and C. septicum, as well as Enterohemorrhagic E. coli (EHEC), Shigella, CMV, Candida	

Clostridium Difficile Infection (CDI)

➤ Terminology

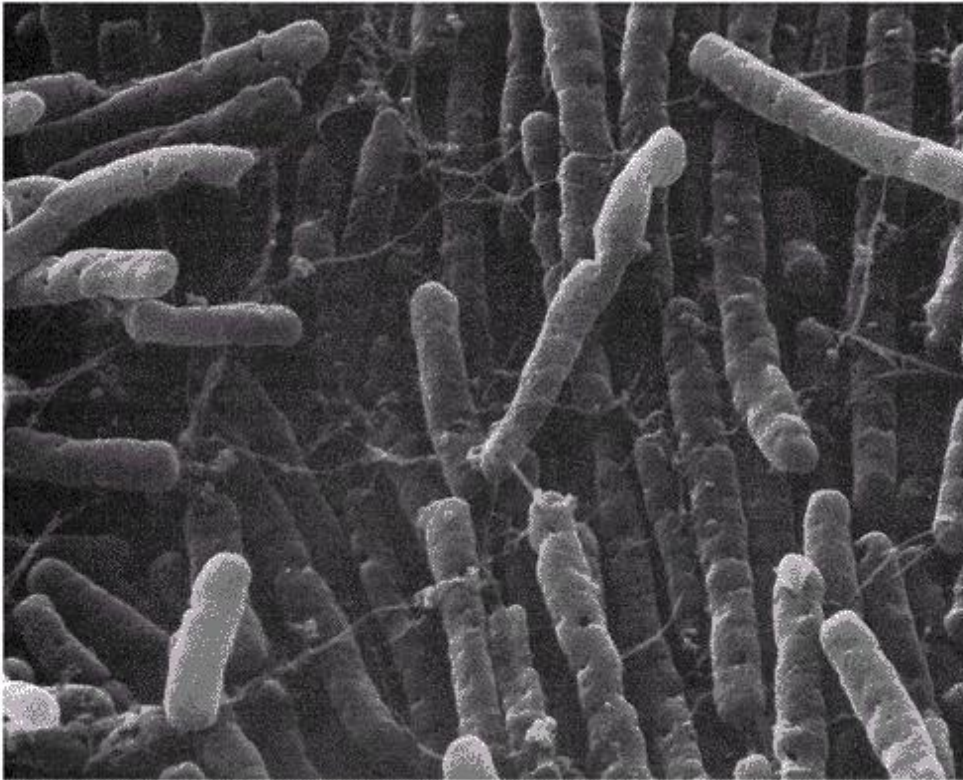
- Antibiotic-Associated Diarrhea (AAD)
- Pseudomembranous Enterocolitis (PMEC)
- Clostridium difficile-Associated Diarrhea and Colitis (CDADC).

➤ Microbiology

- A gram-positive, cytotoxin-producing, anaerobic, spore-forming bacterium
- NAP1 / B1 / 027 strain, a new, hypervirulent strain, responsible for multiple C difficile outbreaks since the early 2000s.
 - Characteristics
 - Production of binary toxin
 - Larger quantities of toxins A and B than other strains
 - Resistant to fluoroquinolones
- PMEC (PMC and PME) is caused by non-invasive C. difficile, S. aureus, and non-infectious conditions such as the seriously ill ICU patient.



Clostridium Difficile Infection (CDI)



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➤ Diagnostic imaging

- Thick haustral markings
- Diffuse, or local L/R – sided
- CT
 - Wall: circumferential thickening
 - Pericolonic: soft tissue stranding

➤ Endoscopy

- Non-specific colitis
 - Patchy, whitish-yellow plaques, with underlying bleeding when plaques removed (pseudomembranes; pseudomembranous colitis [PMC])
- May spare the rectum or left colon (i.e., may be only in the right colon)



Mind Teasers

- *C. difficile* infection causes endoscopic and histological changes in the colon, including pseudomembranes and pseudomembranous colitis (PMC)
- Pseudomembranous colitis has several (?) causes, including *C. difficile* infection (CDI)
 - CDI may cause pseudomembranes and pseudomembranous colitis
 - However, the finding of pseudomembranes and pseudomembranous colitis does not prove that the cause is *C. difficile*
 - Only a positive culture proves that PMC is caused by CDI
 - However, in the appropriate clinical setting, the endoscopic finding of pseudomembranes may be a sufficient suggestion of possible / likely CDI to begin antibiotic treatment empirically.

Pseudomembranous Colitis (PMC)



Source: Aljawad M (2015). *Clostridium Difficile* Infection. In Thomson ABR and Chande N (Eds). Medical Mini Review Series in Gastroenterology and Hepatology: Efficient Refresher for the Busy Clinical Gastroenterologist (volume 1), page 342.

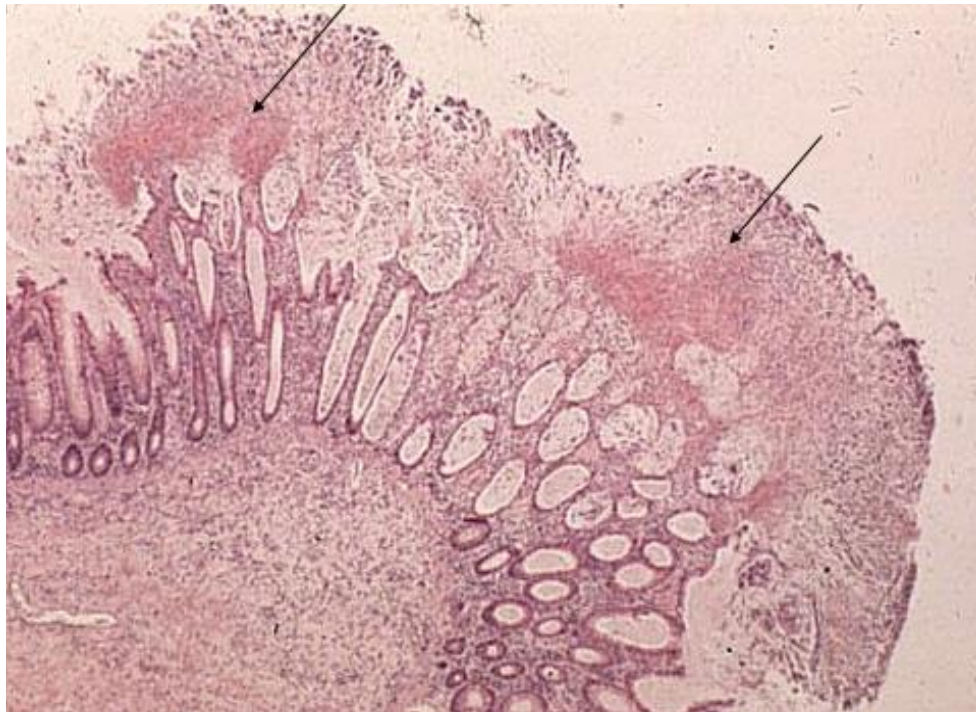


➤ Histopathology

- There is overlap between AAD, PMEC and CDADC
- Pseudomembraneous colitis (PMC) or pseudomembraneous enteritis (PME): the pseudomembrane is comprised of fibrin, inflammatory and cellular debris, may be seen only on biopsy and not on colonoscopy, and may be associated with underlying erosion / ulceration.
- Pseudomembranes may be seen histologically even when biopsies are taken from endoscopically normal-appearing mucosa
- Spectrum of changes
 - Focal active colitis
 - Crypt colitis
 - ↓
 - Ballooned
 - Necrosis
 - Filled with
 - PMNs
 - Mucin
 - Crypts
 - PMNs
 - Mucin
 - Fibrin
 - Epithelial cell loss
 - ↓ Severe prolonged
 - Necrosis of mucosa

} Pseudomembranes
("volcano" lesions)

Pseudomembraneous Colitis (PMC)



Arrows indicate
inflammatory
pseudomembrane

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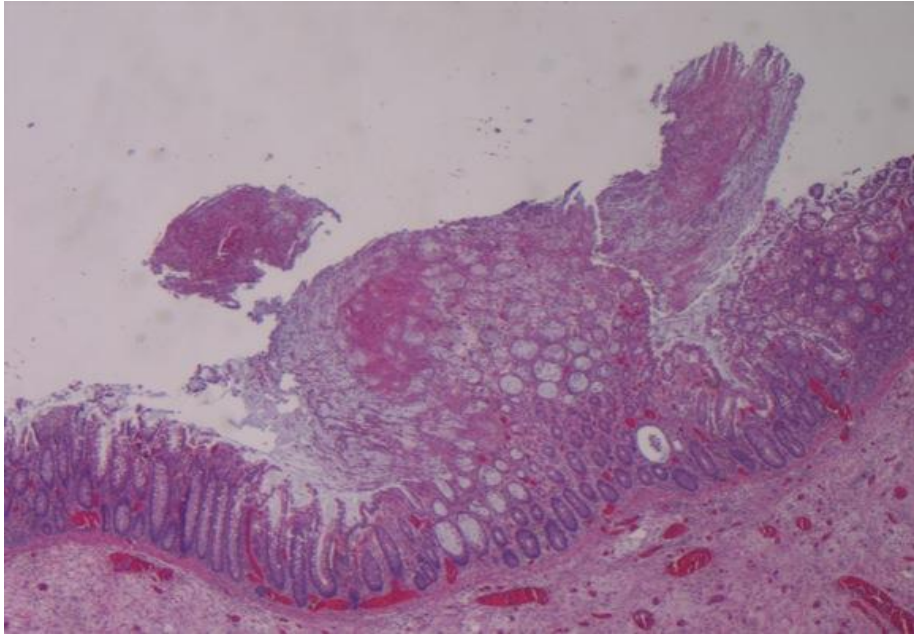
Colon

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MCQ Trick

- Remember: PMC does not always mean CDI, and CDI does not always cause PMC.

Pseudomembranous Colitis (PMC)



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MCQ Pearl

- *C. septicum* infection may result in an histological picture similar to *C. difficile*-associated colitis (pseudomembranous colitis, PMC)
- The neutrophils (polymorphonuclear leukocytes [PMNs]) in PMC are layered in the pseudomembrane, whereas in NEC, there are usually few PMNs, or a few PMNs despite the neutropenia in the peripheral blood

Yersinia enterocolitica and Pseudotuberculosis

➤ Histopathology

- Nodular inflammatory masses around Peyer patches ↑ Peyer patches
- Mesenteric lymph nodes frequently enlarged / involved
- Pattern of colitis
 - Granulomatous
 - Suppurative

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Aeromonas hydrophilia and A. sobria

- Endoscopy
 - Gram-negative bacterium which may be diffuse or segmental
 - Non-specific appearance, similar to acute ulcerative colitis
- Histopathology
 - Acute self-limiting colitis (ASLC)
 - May be associated with non-caseating granulomas

Mycobacterial Infections

- Endoscopy

Features	Mycobacterium Tuberculosis	Mycobacterium Avium-Intracellulare Complex (MAC)
○ Site	Ileum, Cecum, Jejunum > Appendix, R colon	SB > Colon
○ Multiple skip lesions	+	
○ Inflammatory nodules	+	+ (small)
○ Strictures	+	
○ Large inflammatory masses	+	
○ Ulcers	+	+

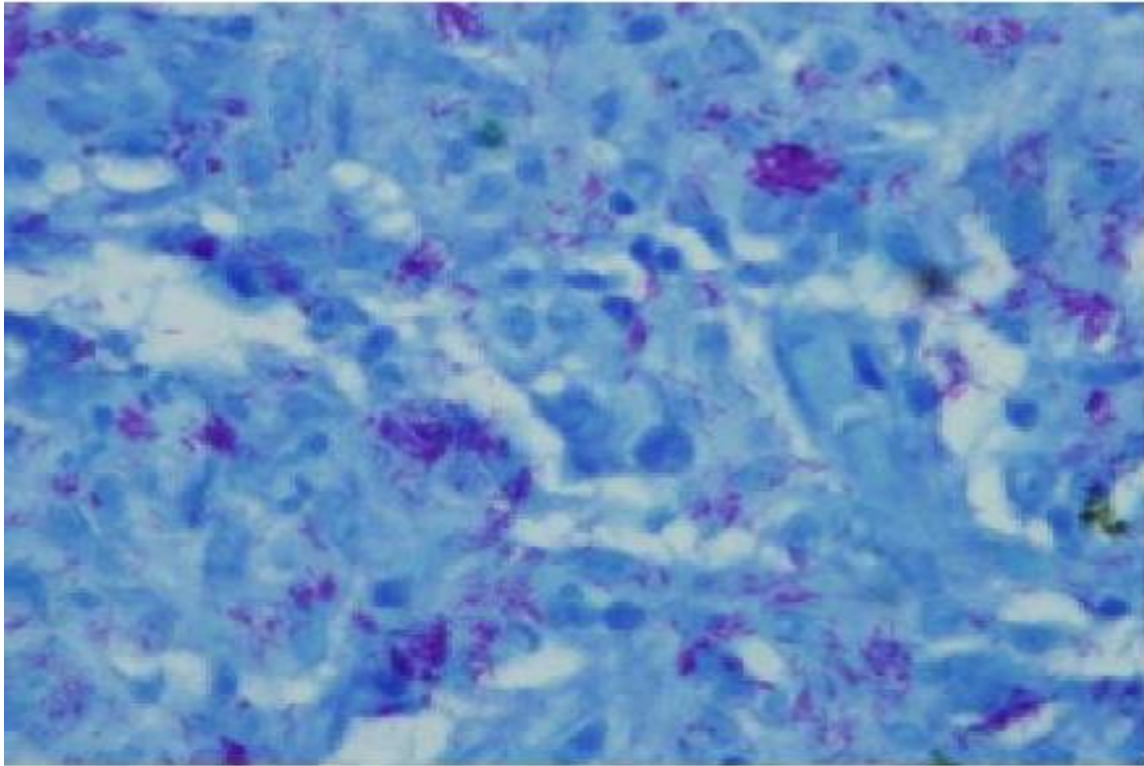
- Histopathology

Features	Mycobacterium Tuberculosis	Avium-Intracellular Complex (MAC)
○ Granulomas		
- Caseating	+	+ (may also be non-necrotizing)
- Confluent	+	These granulomas would likely look the same
- Rim of lymphocytes	+	
- Hyaline	+	
- Calcification	+	
○ Acid-fast bacilli, ZN+)	+	+
- Histiocytes, diffuse infiltration		+

Abbreviations: ZN, Ziehl-Neelsen stain



Mycobacterium avium-intracellulare (pink on acid fast stain) on Colon



Printed with permission: Bhaijee F, et al. Pathology Research International 2011; vol. 2011, Article ID 247923, 8 pages.

➤ Differential

- Caseating (necrotic) and non-caseating (non-necrotic) granulomas may be seen in Mycobacterial infections of the GI tract
- Non-infectious / autoimmune causes of GI tract granulomas include Crohn disease and sarcoidosis
- Give other infectious causes of granuloma in the GI tract
 - Actinomycosis
 - Chlamydia trachomatis
 - Syphilis
 - Yersinia



Treponema pallidum (Syphilis)

- Endoscopy
 - Site
 - Anorectal
 - Chancres (1°)
 - Condylomata (2°)
 - Rectum
 - Proctitis (1°)
- Histopathology
 - Crypts
 - Cryptitis with dense plasma cell infiltration
 - Abscess
 - Glands
 - Destruction
 - Epithelium
 - Reactive changes
 - Capillary endothelial cells
 - Proliferation (proliferative end arteriolitis)
 - Special stains
 - Warthin-Starry positive

Actinomycosis (Actinomyces)

- Endoscopy
 - Single large mass +/- ulceration
 - May extend / infiltrate the adjoining gut wall
- Histopathology
 - Anaerobic filamentous gram-positive bacterium in irregular round clusters
 - “Sulphur” granules
 - Surrounded by eosinophilic club-like projectors
 - Splendore-Hoeppli material
 - This in turn may be surrounded by
 - Neutrophils
 - Granulomas
 - Histiocytes
 - Giant cells
 - Fibrosis



FUNGAL INFECTIONS

- Aspergillus
- Candida
- Cryptococcus
- Histoplasmosis
- Mucormycosis

Aspergillus

- Endoscopy
 - Diffuse or segmental enterocolitis
 - Inflammatory masses, pseudomembranes
 - Ischemia / infarction in severe disease (vascular invasion)
- Histopathology
 - Vascular invasion
 - Nodular ischemic infarction around blood vessel and extending outwards
 - Neutrophils, granulomas
 - Hyphae
 - Septae, 45° angle branching

Candida

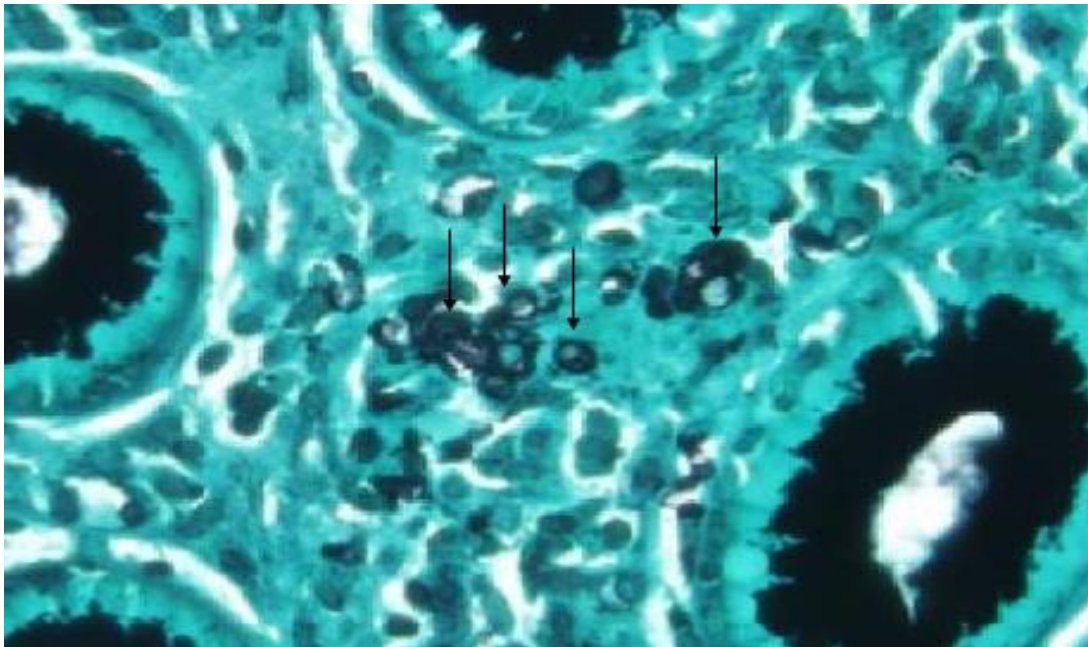
- Endoscopy
 - Diffuse or segmental enterocolitis
 - Inflammatory masses, pseudomembranes
 - Ischemia / infarction in severe disease (vascular invasion)
- Histopathology
 - Erosion / ulceration
 - Neutrophils / abscesses
 - Necrosis / infarction
 - Small round spores and pseudohyphae



Cryptococcus

- Endoscopy
 - Spectrum of normal mucosa to ulceration +/- white exudate
- Histopathology
 - Inflammation
 - Spectrum from normal to
 - Suppuration
 - Necrosis
 - Granulomas
 - Organisms
 - Round / oval
 - Budding, narrow base
 - Variable size
 - Capsule → halo of mucopolysaccharide material
 - Alcian blue
 - Colloidal iron
 - Fontana Masson
 - Mucicarmine
 - GMS
 - Lymphatic involvement
 - Special stains (for mucopolysaccharides)

Cryptococcosis of Colon (GMS stain)



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Histoplasmosis

- Endoscopy
 - Spectrum from normal mucosa to non-specific colitis

Histoplasmosis on Colon



Colonoscopy showed strictures, edematous mucosa and diffuse aphthoid ulcers measuring 0.5-1.0 cm in diameter scattered throughout the mucous membrane of the colon

Printed with permission: Yang B, et al. BMC Infect Dis. 2013; 13: 143.

- Histopathology
 - Lymphohistiocytic infiltration in mucosa and submucosa
 - Ulceration of mucosa
 - Small ovoid intracellular organisms with small buds

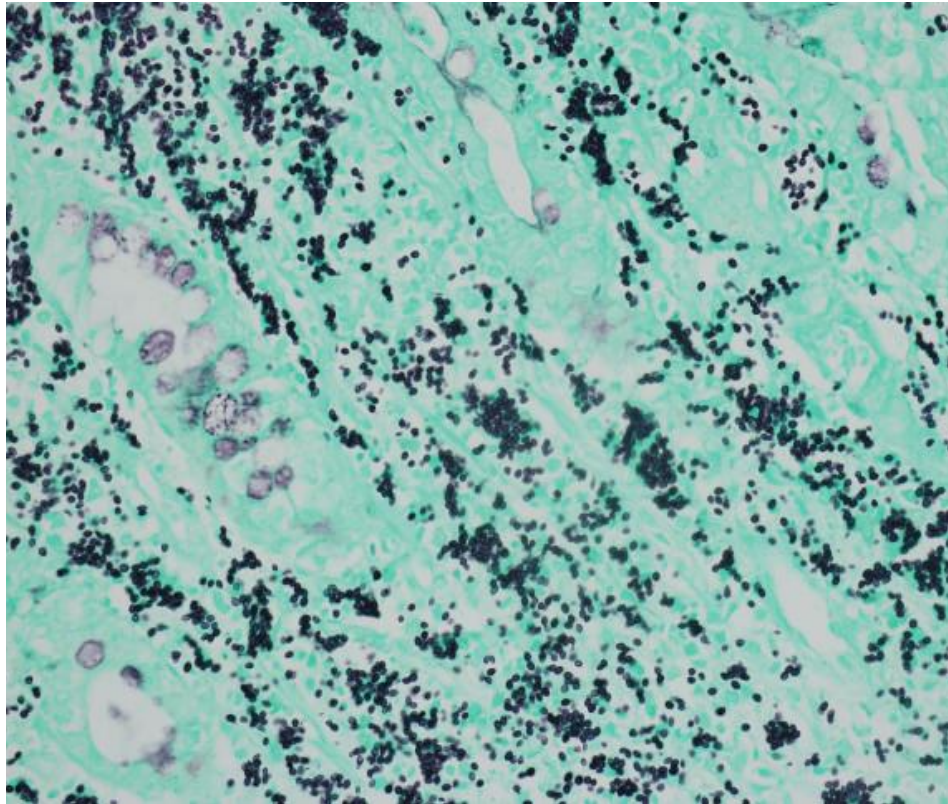
MCQ Trick: Backwards thinking

Disseminated histiocytosis will occur in the immunocompromised patient.

- Give the influence of the infected patient's immune status on the severity of the histological lesions in the GI tract.
 - The tissue reaction (histological changes) in the immunosuppressed patient may be minimal, even though they have a high risk for infection with Histoplasmosis, and even if they have disseminated Histoplasmosis



Histoplasmosis of Colon



Gomori methenamine silver (GMS) stained colon biopsy specimen (magnification $\times 40$) indicating granulomatous inflammation induced by mycotic infection, which was consistent with histoplasmosis

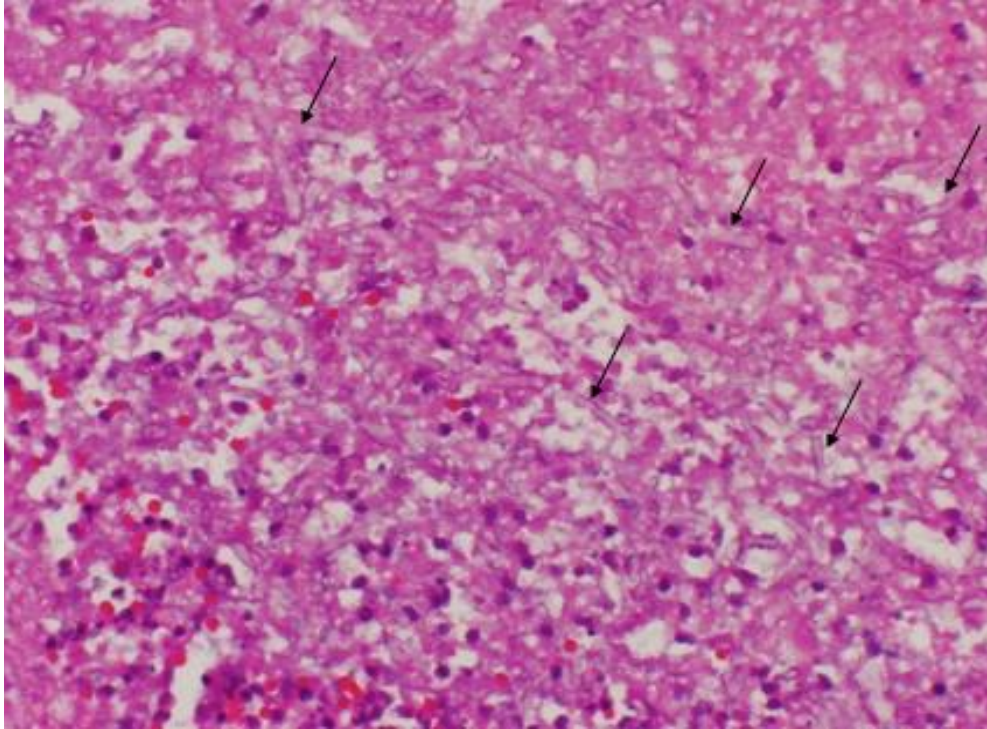
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Mucormycosis

- Endoscopy
 - Diffuse or segmental enterocolitis
 - Inflammatory masses, pseudomembranes
 - Ischemia / infarction in severe disease (vascular invasion)
- Histopathology
 - Vascular invasion
 - Nodular ischemic infarction around blood vessel and extending outwards
 - Neutrophils, granulomas
 - Hyphae
 - White, ribbon-like
 - Clear centre
 - Few septa, 90° angle branching



Mucormycosis of Colon



Operatively obtained jejunal tissue section from patient, showing multiple broad hyphae (please see arrows; hematoxylin and eosin, original magnification)

Printed with permission: Abidi MZ, et al. Case Rep Med. 2014; 2014: 637492.

"Creativity is intelligence having fun."

Albert Einstein



PARASITIC INFECTION

Entamoeba Histolytica-Associated Colitis

- Endoscopy
 - Spectrum of normal mucosa to
 - Small → large, serpiginous ulcers
 - Normal intervening mucosa

Amebic Colitis

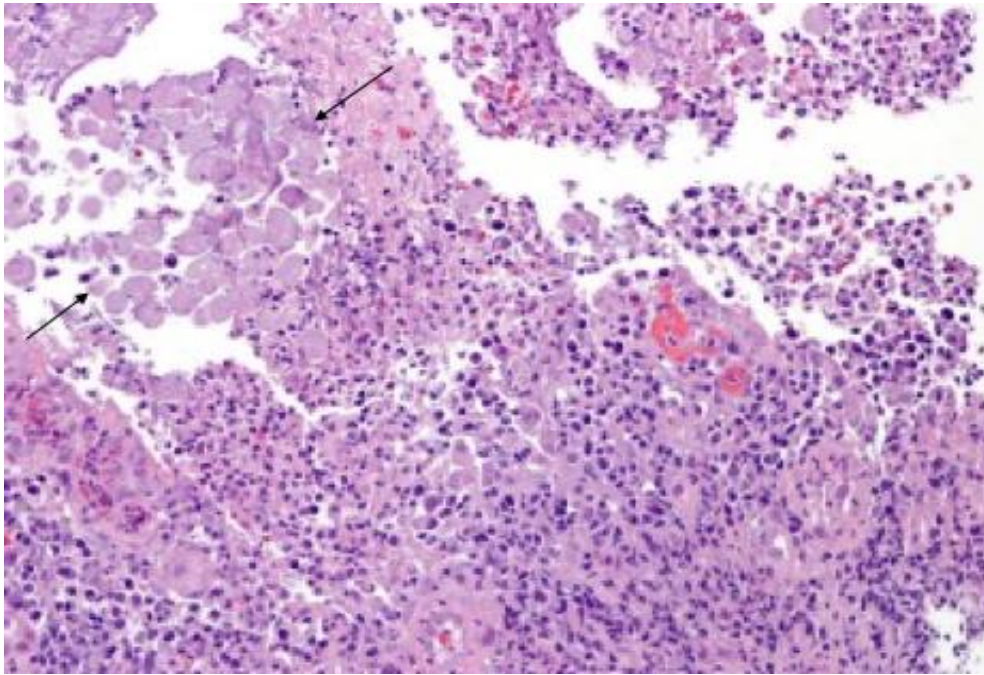


Printed with permission: Fleming R, et al. BMC Res Notes. 2015; 8: 781.

- Histopathology
 - Neutrophilic infiltration → deep “flask-shaped” ulcers from undermining of mucosa
 - Necroinflammatory debris
 - Inflammation and distortion of architecture with intervening / adjacent endoscopically normal mucosa
 - Entamoeba histolytica
 - Present in sheets
 - Macrophage-like structure
 - Foamy cytoplasm
 - Round, eccentric nucleus
 - Red blood cells ingested and visible within organisms
 - Architecture / inflammation may be indistinguishable from UC

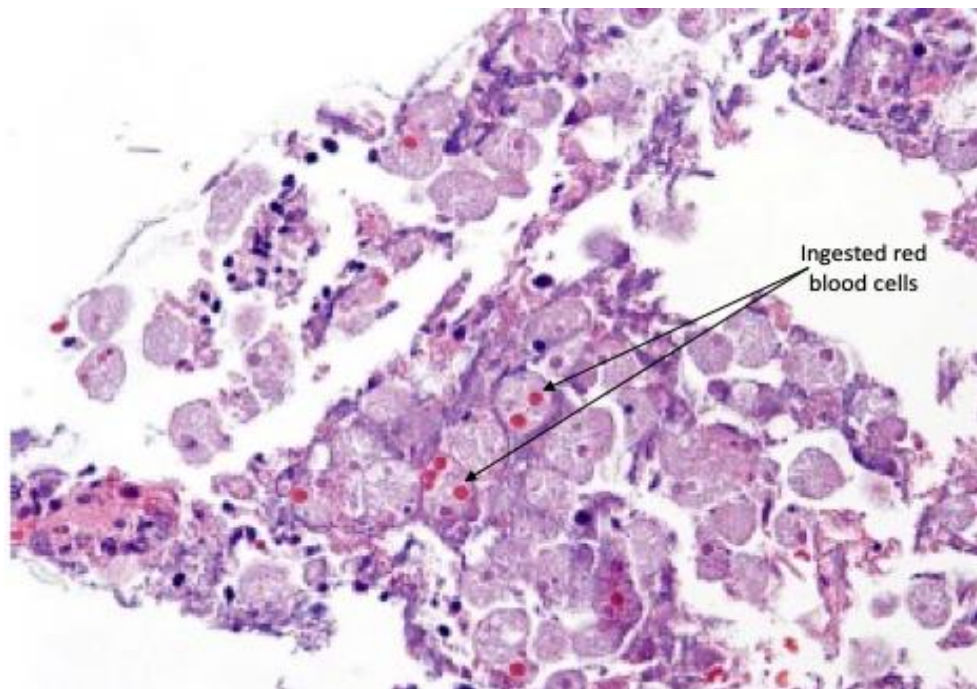


Amebic Colitis



Courtesy of Dr. Aducio Thiesen, University of Alberta, Edmonton

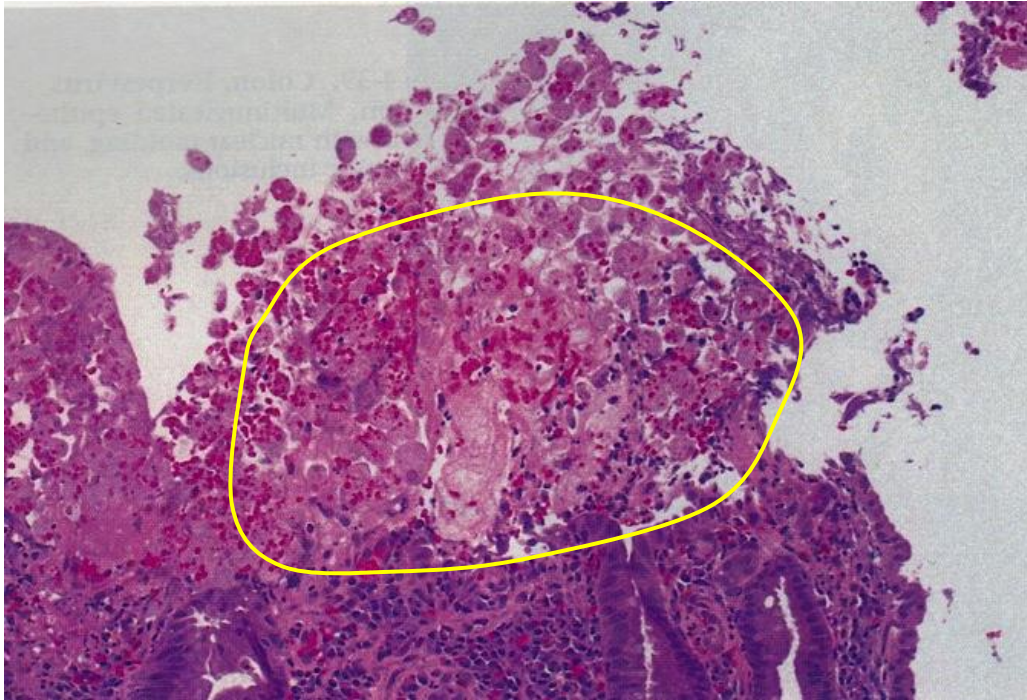
Amebic Colitis



Courtesy of Dr. Aducio Thiesen, University of Alberta, Edmonton



Amebic Colitis



Amebae
overlying
eroded
mucosa

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Cryptosporidium

Cryptosporidium is the most common parasitic infection in HIV / AIDs, but it can be easily confused with *Isospora belli*, both of which are acid fast, and are localized to the luminal membrane.

- Give features which help to distinguish between *Isospora belli* versus cryptosporidial infection of the GI tract.

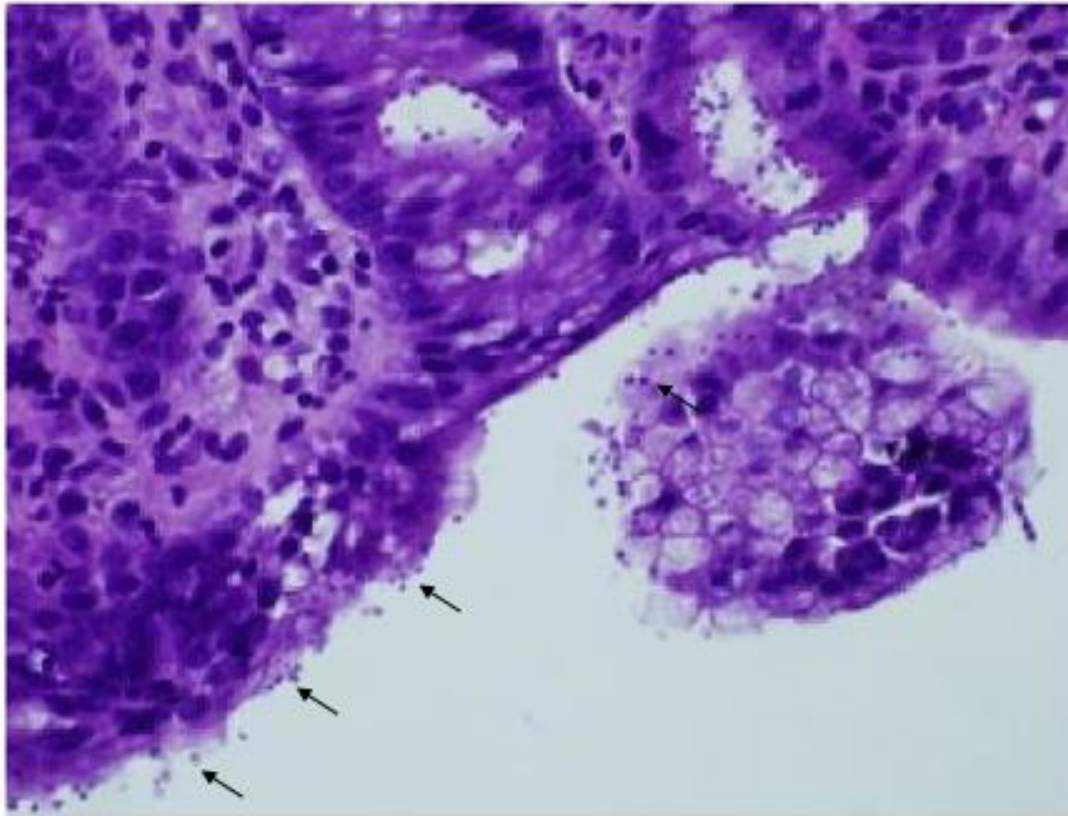
Feature	<i>Isospora belli</i>	<i>Cryptosporidium</i>
○ Geographical location (recent travel)	Haiti, Africa	World-wide
○ Acid-fast staining of stools	+	+
○ Charcot-Leyden crystals in stool	+	-
○ Localization of organism on mucosal biopsy		
- LM	+	+
- ICV	+	-
○ Sensitivity to TMP-SMX	+	+

Abbreviations: LM, luminal membrane; ICV, intracytoplasmic vacuoles; TMP-SMX, trimethoprim-sulfamethoxazole



➤ Endoscopy

Cryptosporidium of Colon



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Leishmania Donovanii (Leishmaniasis, Kala-Azar)

➤ Endoscopy

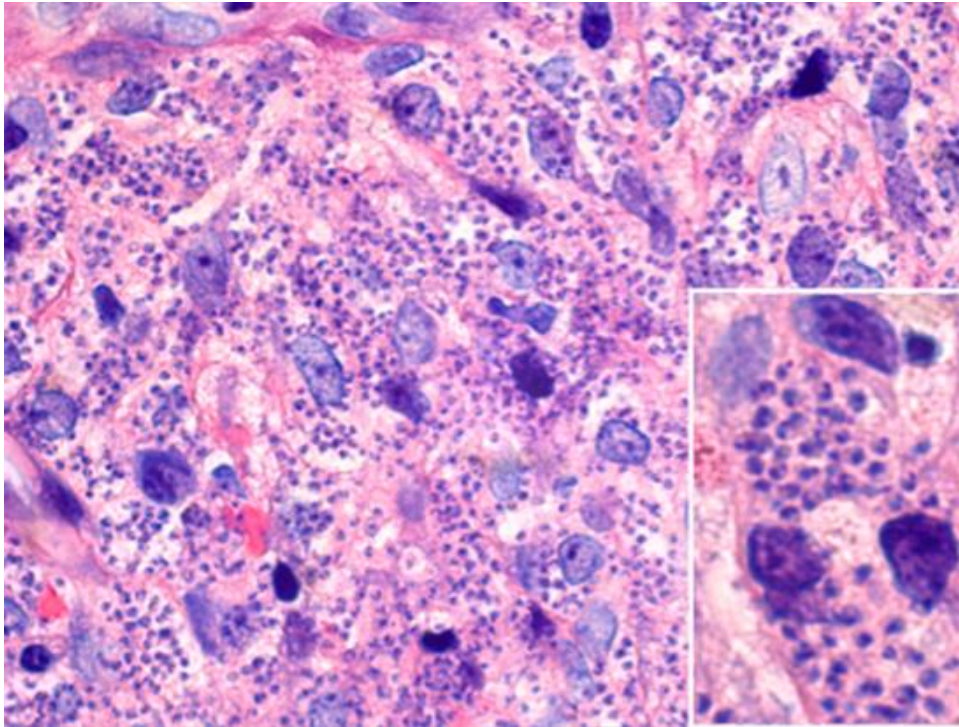
- Normal to non-specific changes

➤ Histopathology

- Macrophages in lamina propria containing organisms
- Organisms
 - Round / oval
 - Nucleus “double-knot” configuration
- Inflammatory infiltration
 - Minimal to absent



Leishmania Donovan of Colon



- Numerous intracellular amastigotes in lamina propria macrophages (Giemsa staining, x500)
 - Magnified section showing three enlarged macrophages (x1000)

Printed with permission: Eichenberger A, et al. BMC Infectious Diseases 2017;17:81

"A journey of a thousand miles begins with a single step."

Lao Tzu



COLONIC POLYPS AND CANCER: NON-FAMILIAL FORMS

Adenomatous Polyps

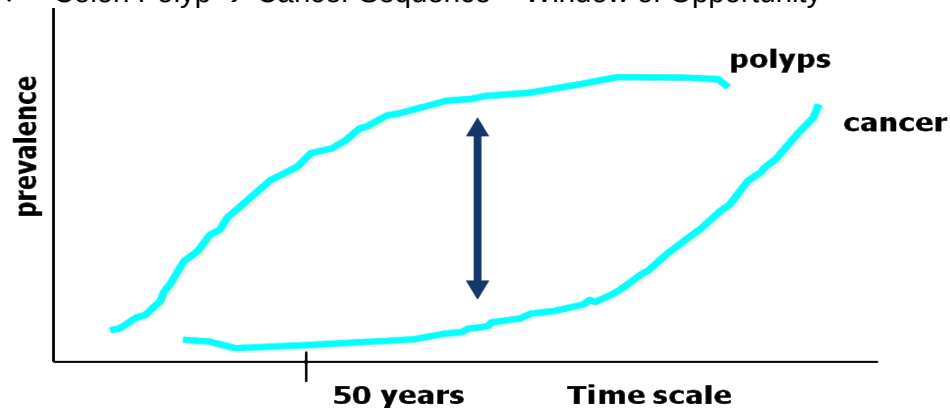
➤ Definition

- “A gastrointestinal polyp is a discrete mass of tissue that protrudes into the lumen of the bowel” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 2155).

➤ Demography

- Age 50, asymptomatic, average risk
 - Likelihood of finding
 - Adenomatous polyp, ~30% (5:3 M to F)
 - Advanced adenoma (adenoma with advanced pathology, ~8%)
 - Greater risk of large or right-sided adenoma in African Americans > 60 yr
 - Adenoma recurrence, 19% per year
 - Incidence
 - Adenomas, 5% per year
 - AAP, 0.4% per year

❖ Colon Polyp → Cancer Sequence = Window of Opportunity



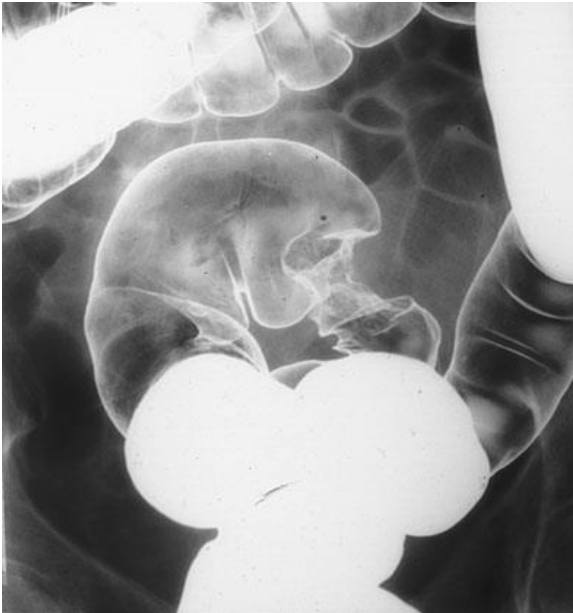
➤ Diagnostic imaging

- Barium
 - For any adenomatous polyp, the risk for malignancy goes up with an increase in size, and a transition from tubular (to tubulovillous) to villous histological type
 - Sessile or pedunculated
 - Left side > right side colon (~ 50% rectosigmoid)
 - Single or multiple (in 25 to 50%)
 - Homogenous adenoma
 - Small / large



- CT colonography (CTC)
 - Mass
 - Irregular shape
 - Flat (RC > LC) / lobulated filling defect (LC > RC)

Colonic Polyps



Double-contrast (air contrast")
barium enema: apple core"
lesion in sigmoid colon

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Colonic Polyps



Circumferential tumour of
cecum / ascending colon

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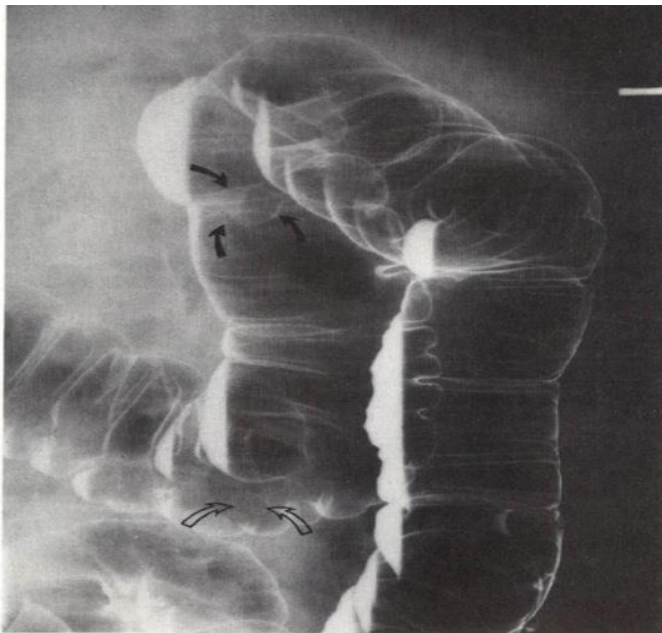
Filiform Inflammatory Polyps of Colon



- Air-contrast barium enema
- Filiform inflammatory polyp, descending colon

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Colonic Polyps

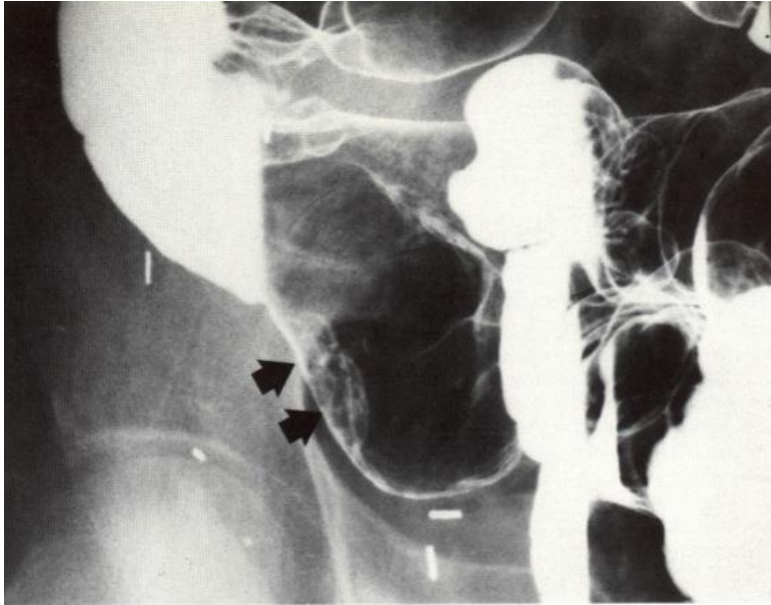


- Air contrast barium enema
- Splenic flexure and transverse colon polyps

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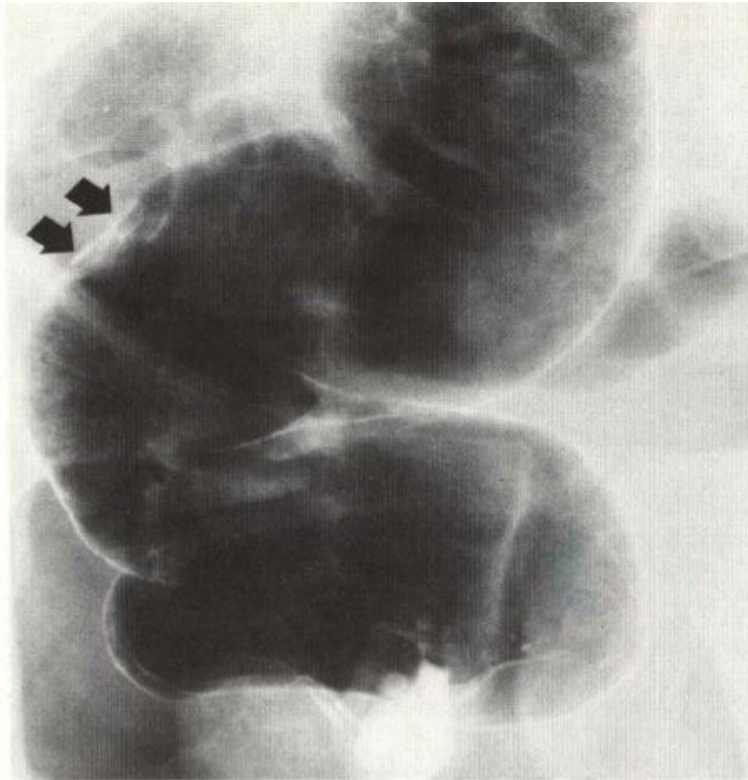
Colonic Polyp



- Air contrast barium enema
- Cecal lesion in profile

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Colonic Polyp



- Cecal lesion: posterior cecal wall neoplastic lesion

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- On the basis of performance characteristics, give the reasons why air contrast barium enemas (ACBE) are being used less and CTC (CT colonography) are being used more than standard white-light optical colonoscopy (WLOC) for the detection of colonic adenomatous and polyps.

❖ Approximate detection rate and polyp size

	Small < 6 mm	Medium 6 to 10 mm	Large > 10 mm
○ ACBE False positive, 10% False negative, 10%	32%	53%	48%
○ WLOC	80%	88%	95%
○ CTC	45%	78%	90%
○ Human DNA in stool			
	Sensitivity	Specificity	
– Adenoma > 1 cm	59%	-	
– Carcinoma	83%	82%	

Abbreviations: ACBE, air-contrast barium enema; CTC, CT colonography; WLO, white light optical enema

- Annual FOBT (slide guaiac test for pseudoperoxidase activity of hemoglobin) results in 33% ↓ CRC mortality as compared with non-tested control group
- Fecal immunochemical tests (FIT) are preferred over guaiac-based fecal occult blood tests for CRC screening
- In a validation experiment performed at room temperature, conversion of test outcomes only occurred 10 days or longer after fecal sampling

Source: Van Roon AHC, et al. Am J Gastroenterol 2012; 107: 99-107.

CT-Scan Staging in Rectal Malignancy

- Overall tumour detection 65–70%
- Perirectal fat infiltration 50–60%
- Absent perirectal fat infiltration ~80%
- Lymph node involvement ~20%
- Absent lymph node involvement ~100%
- Overall staging accuracy of invasiveness 35–95%

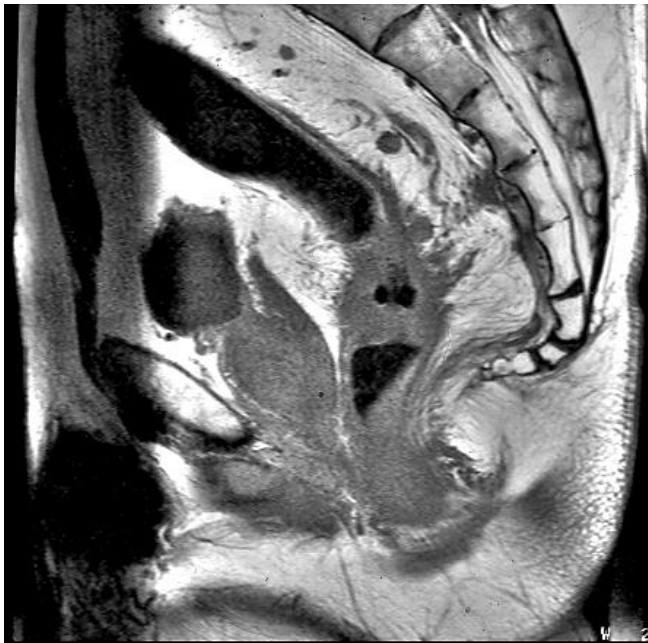


CTC Scan and CRC



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CT Scan and CRC



Abbreviations: CRC, colorectal cancer; CTC, CT colonoscopy

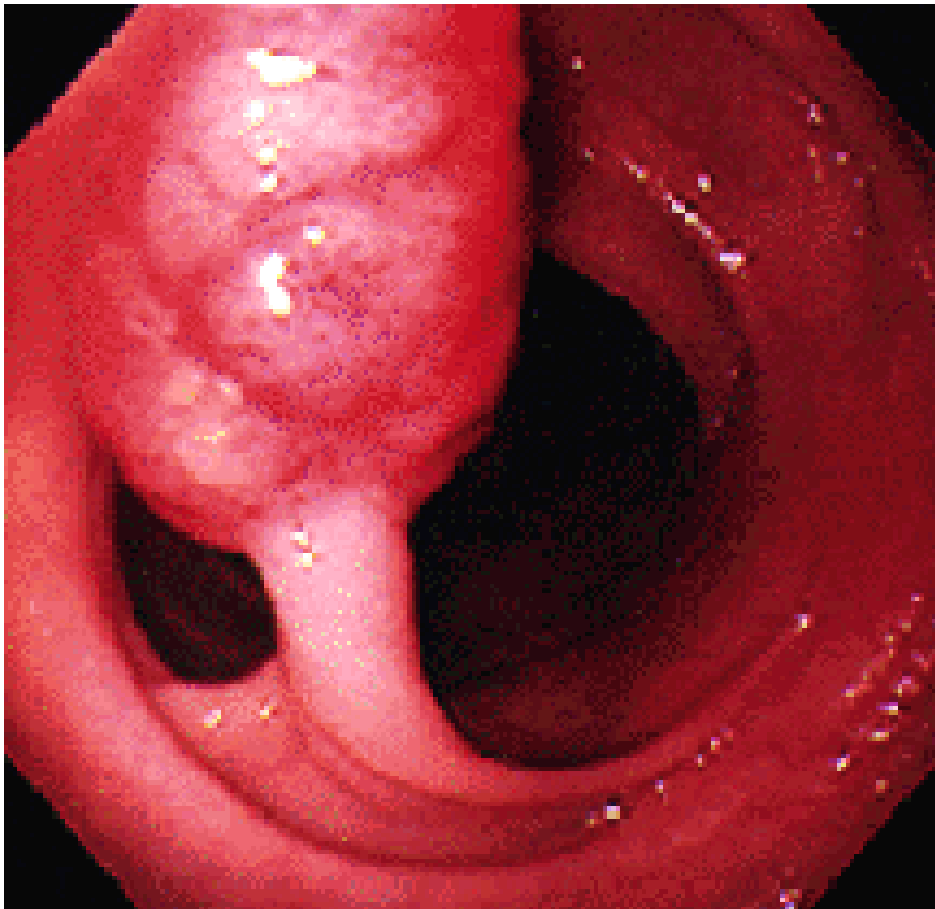
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➤ Endoscopy

- Size: colonic polyps come in all sizes, but for purposes of considering their malignant potential, they are categorized as
 - Diminutive < 5 mm
 - Small > 0.5 < 1 cm
 - Medium 1 to 2 cm
 - Large > 2 cm

Colonic Polyp



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Colorectal Cancer (CRC)



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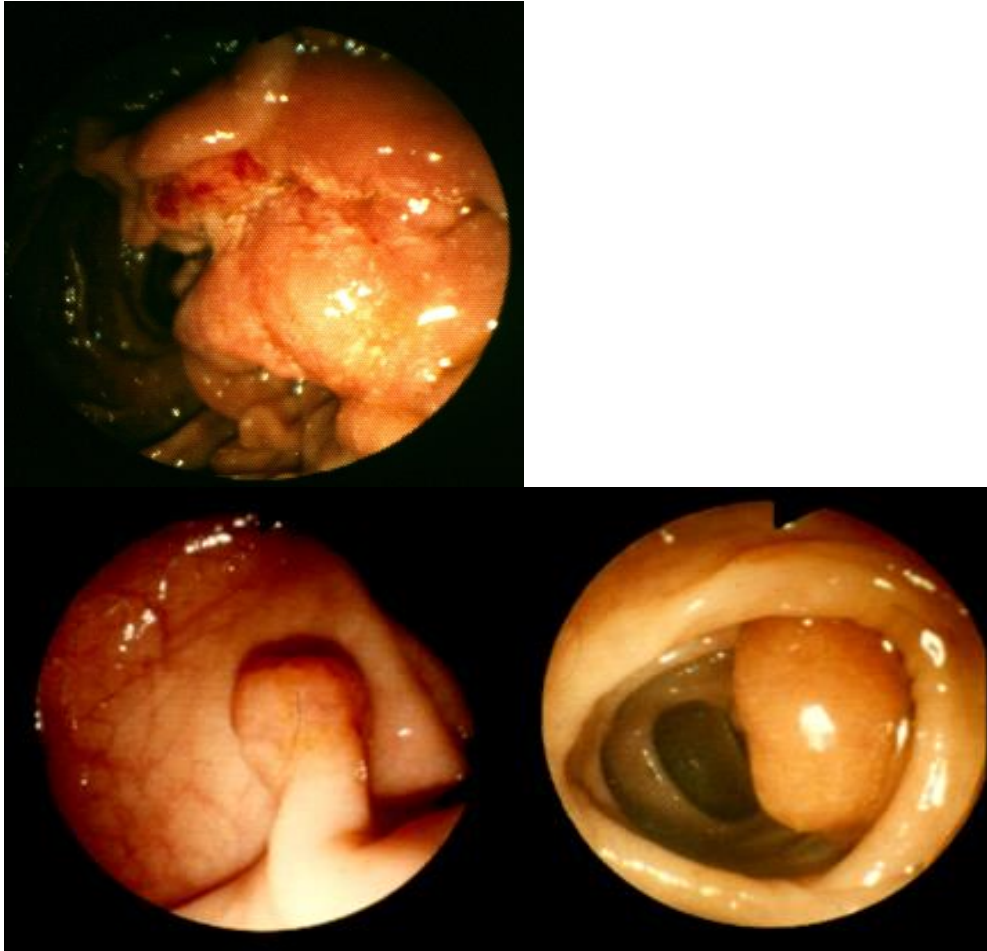
Colorectal Cancer (CRC)



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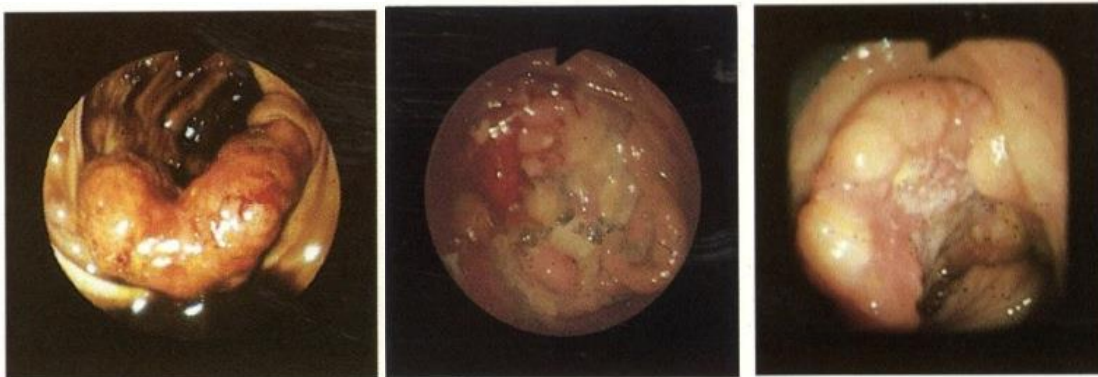


Colorectal Cancer (CRC)



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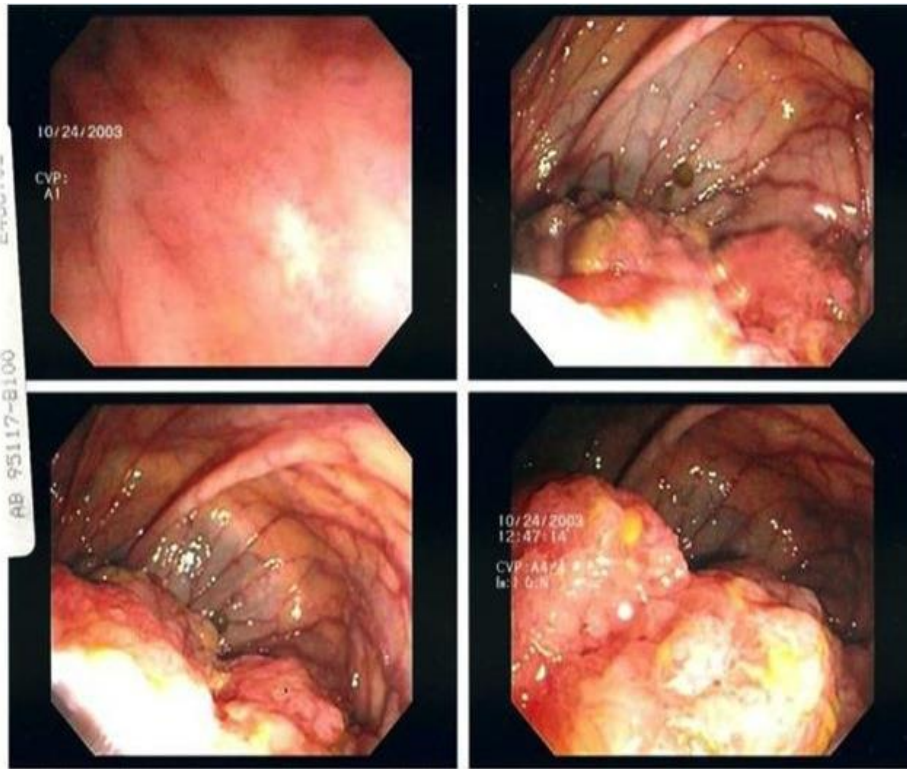
Cecal Lesion: Posterior cecal wall neoplastic lesion



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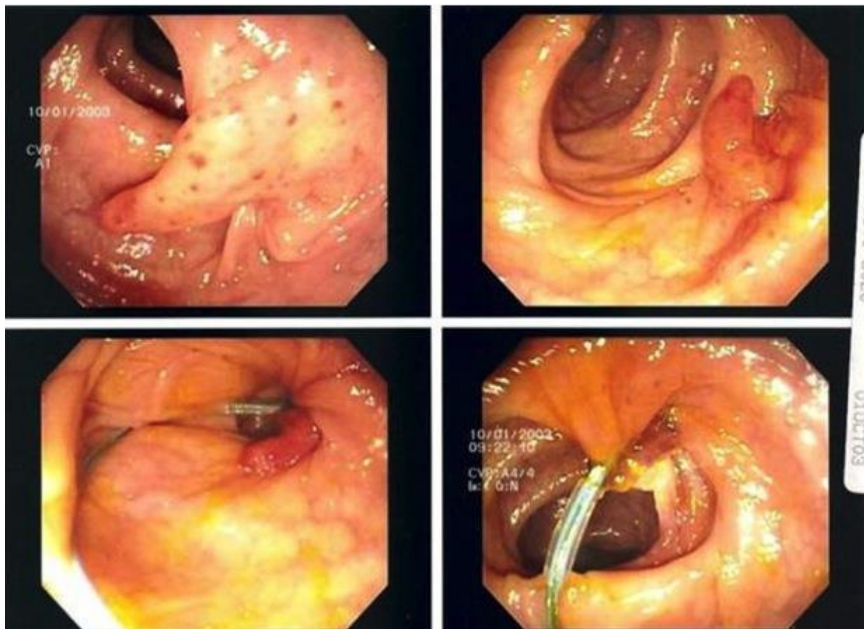


Colonic Villous Adenoma



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Adenomatous Polyp on Long Stalk



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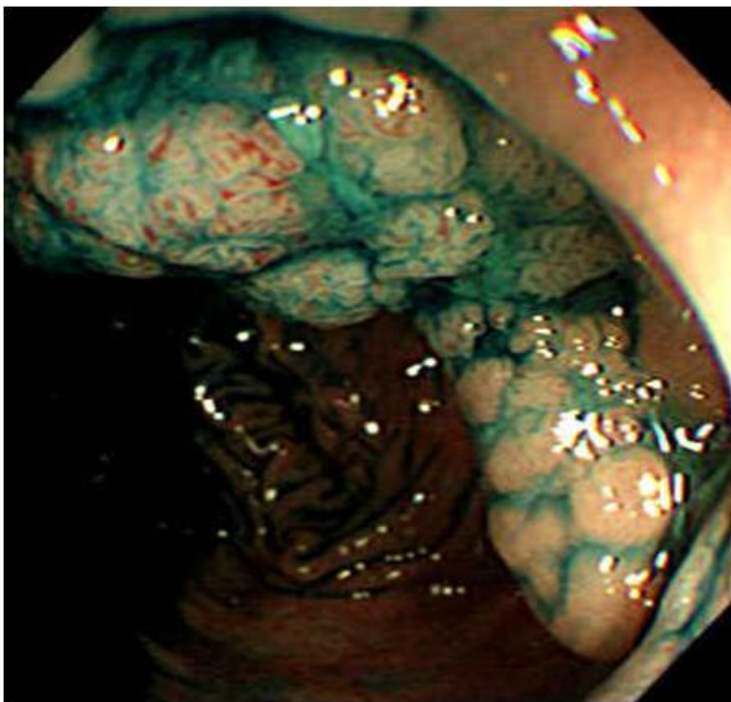


Colonic Mass-like CRC



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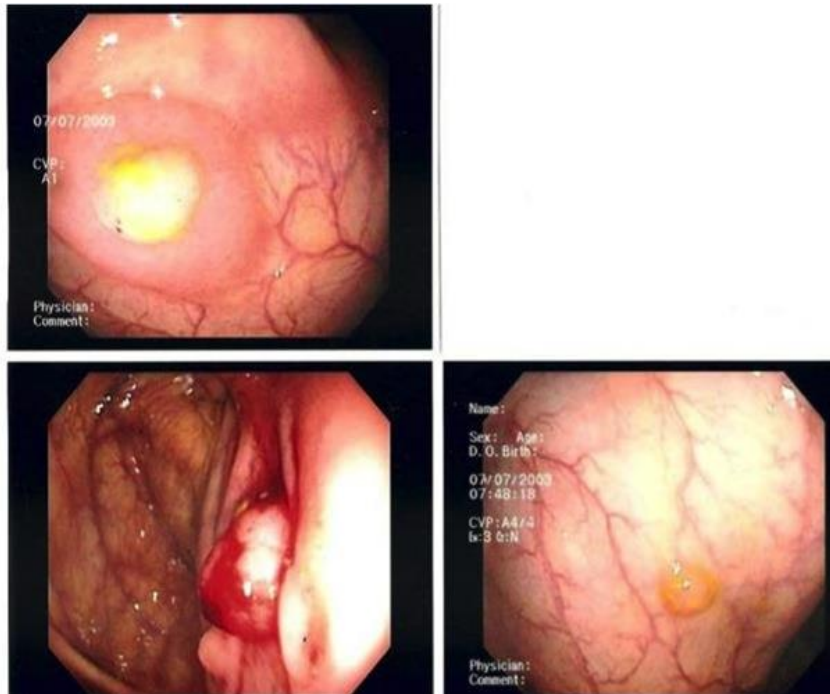
Villous Adenoma



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Colonic Villous Adenoma



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Clinical recommendation:

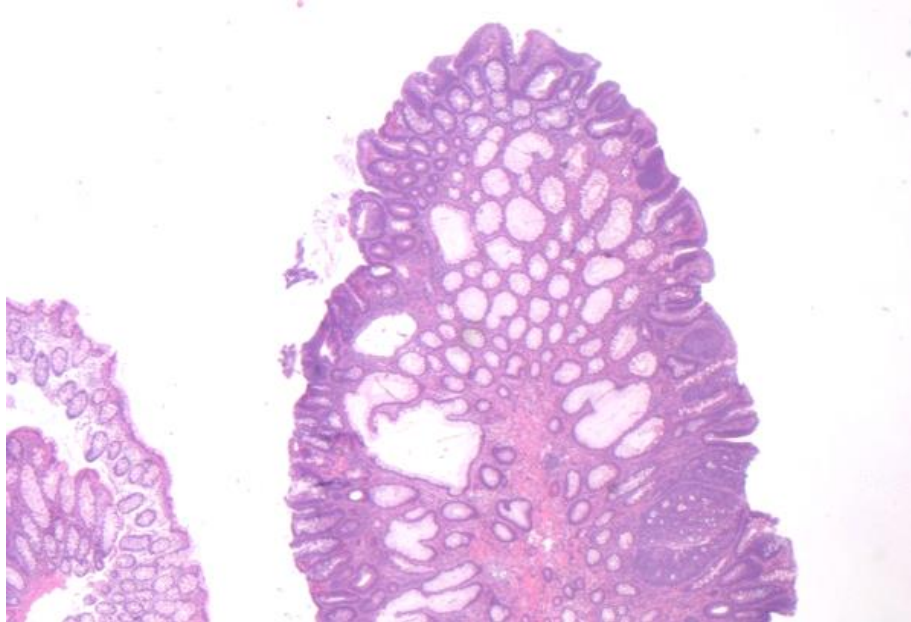
- Rather than using an adjective to describe the size of a polyp in a colonoscopy dictation (e.g., small, medium, large), give the actual estimated size, based on a reference object such as the endoscope or open biopsy forceps.
- Give the practical use of all of this information.
 - If you do sigmoidoscopy for CRC screening and an adenomatous polyp is found, you have an estimate of the likelihood of finding a second and more proximal lesion, were a colonoscopy to be now performed.
 - But because many proximal lesions do not have a distal marker, you really should be arranging for your patient to have colonoscopy, regardless of what the distal colon shows.
 - Histopathology
 - Adenoma
 - Immature goblet or columnar cell
 - ↑ cellularity of crypts
 - ↑ hyperchromasia (↑ basophilia)
 - Elongated nuclei
 - “Picket fence” pattern of nuclei

Often shows the appearance of “top down” dysplasia where the most marked histologic changes are at the surface and the base of the crypts may appear normal

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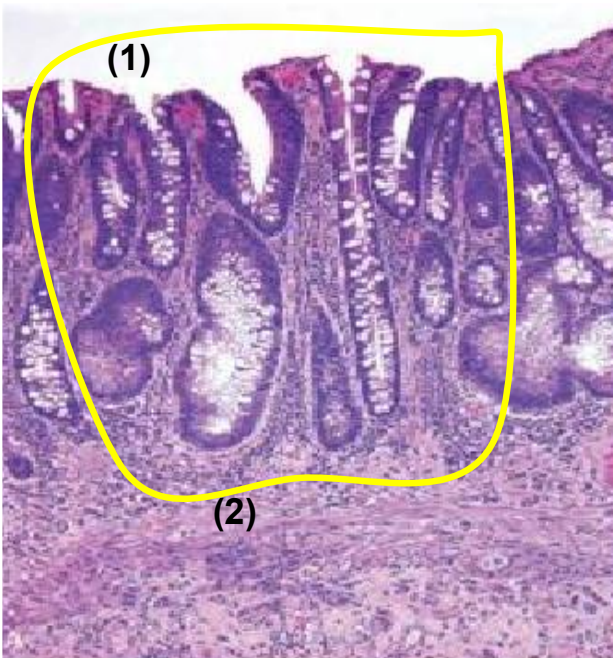


Colonic Tubular Adenoma



Courtesy of Dr. Aducio Thiesen, University of Alberta, Edmonton

Colonic Tubular Adenoma

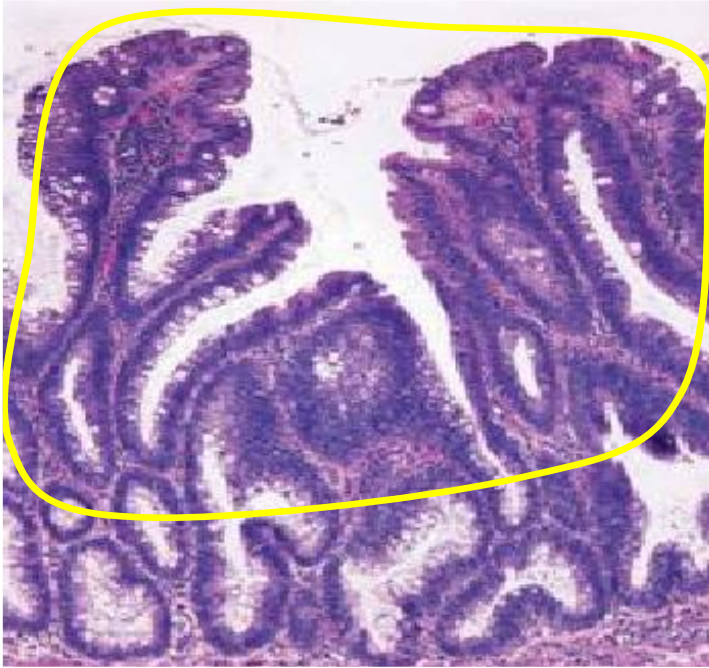


Tubular appearance (tubules point in, away from the lumen), smooth surface

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Colonic Tubulovillous Adenoma



Villi point out into the lumen and tubules point in, away from the lumen

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Colonic Villous Adenoma

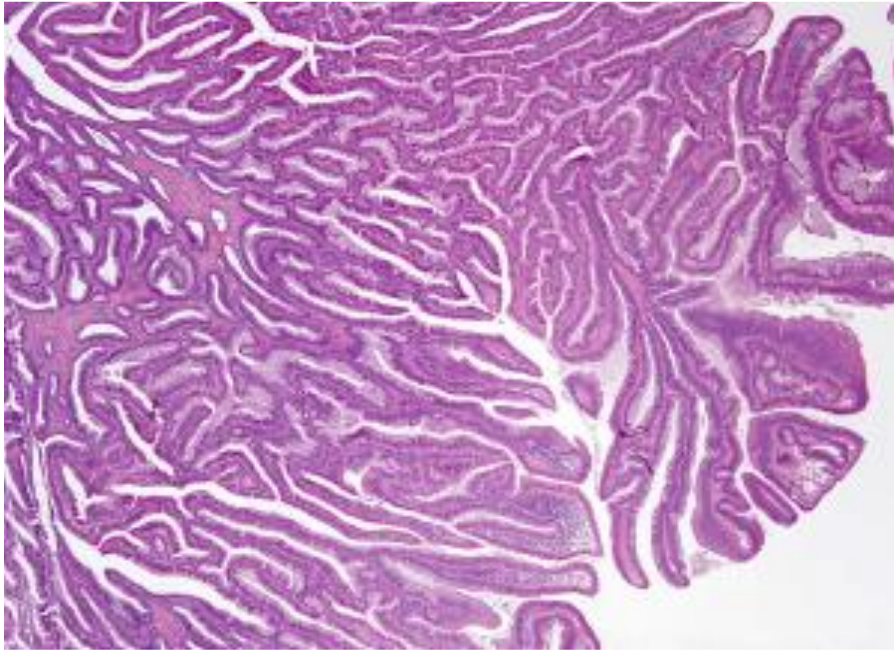


Villi point out into the lumen

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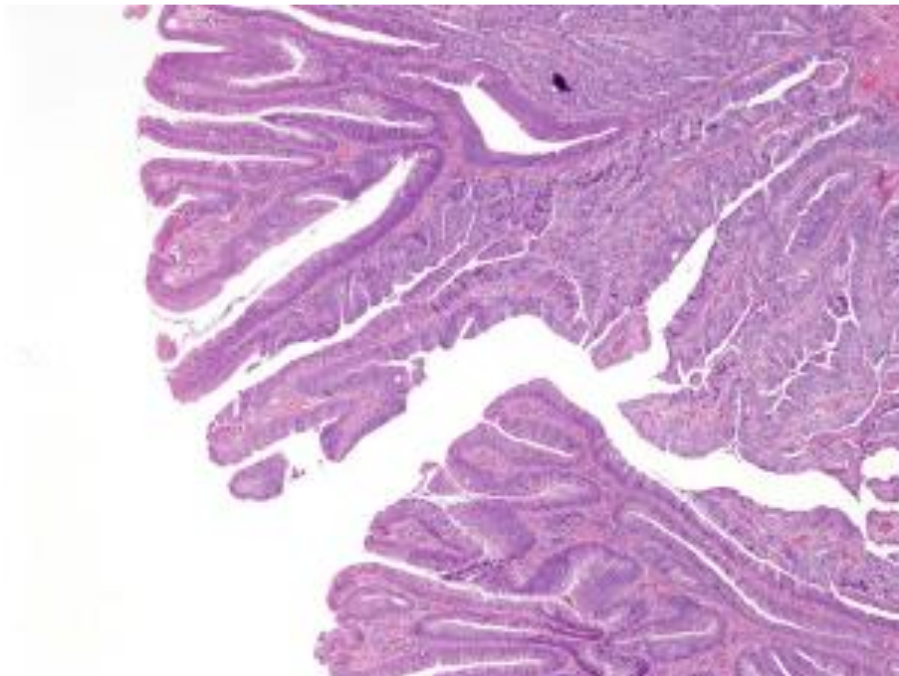


Colonic Tubulovillous Adenoma



Courtesy of Dr. Aducio Thiesen, University of Alberta, Edmonton

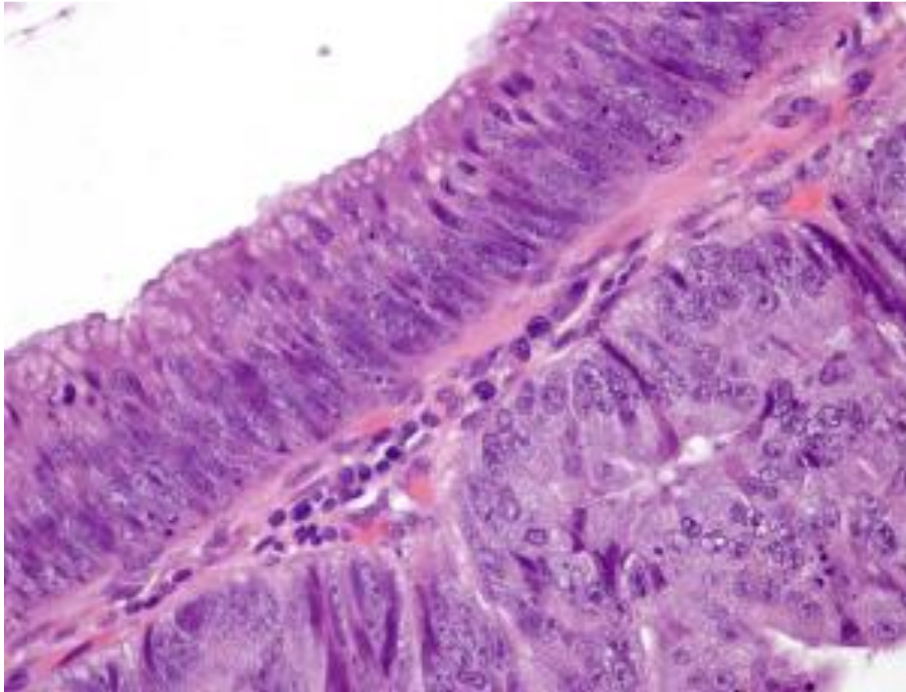
Colonic Tubulovillous Adenoma



Courtesy of Dr. Aducio Thiesen, University of Alberta, Edmonton

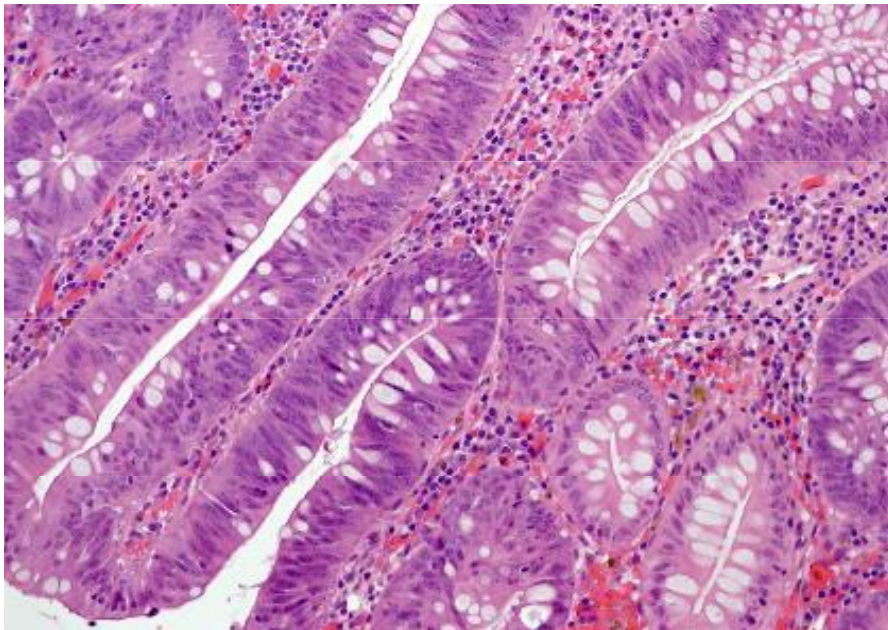


Colonic Tubular Adenoma – low grade dysplasia



Courtesy of Dr. Aduccio Thiesen, University of Alberta, Edmonton

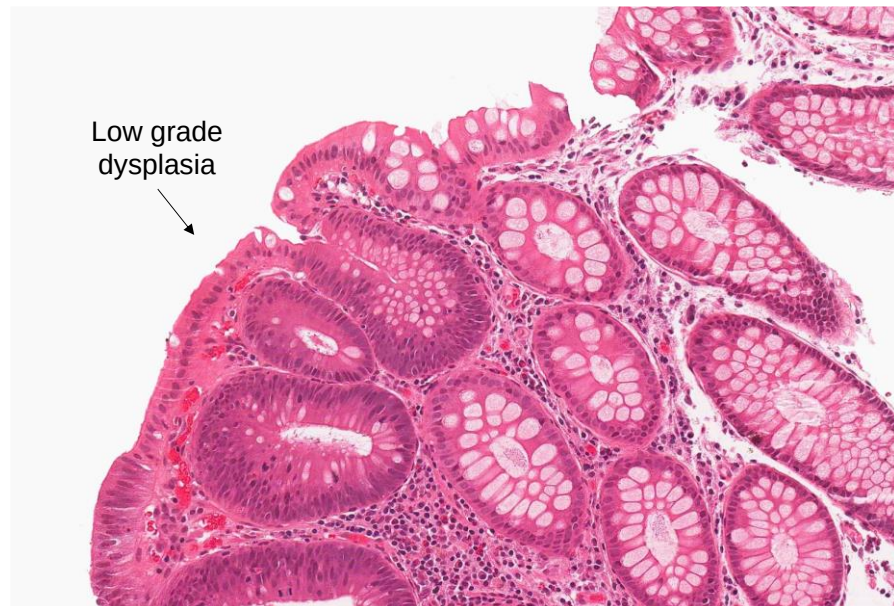
Colonic Tubular Adenoma



Courtesy of Dr. Aduccio Thiesen, University of Alberta, Edmonton



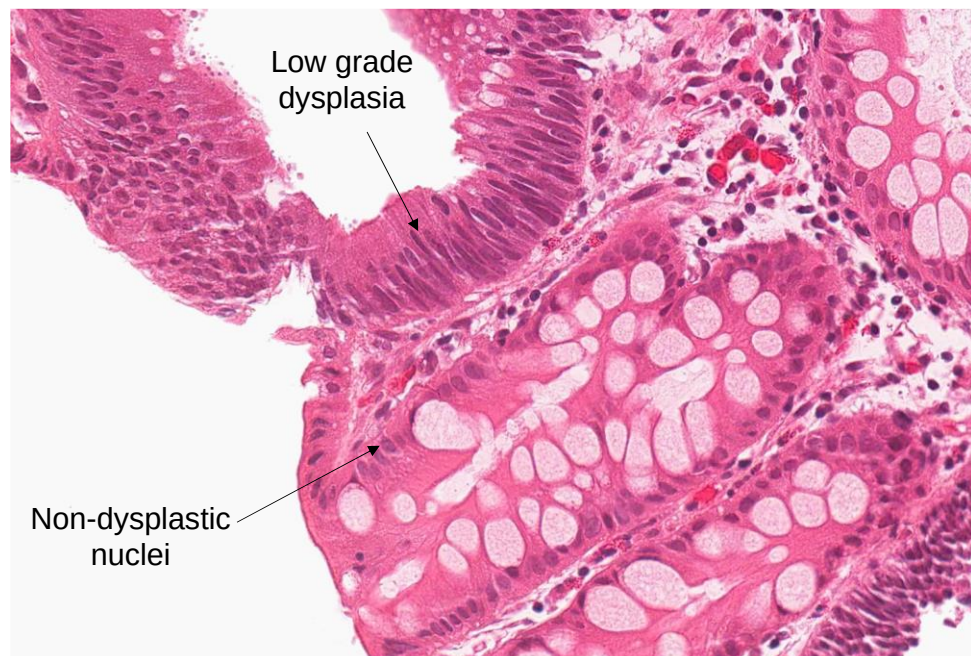
Tubular adenoma (H&E, 20X)



The dysplastic epithelium in the left side of the image has a tubular growth pattern (i.e., pointing in, away from the surface)

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Low grade dysplasia (H&E, 400X)



There is a sharp junction between the non-dysplastic epithelium (lower) and low grade dysplastic epithelium (upper). The low grade dysplasia is characterized by crowded, hyperchromatic, elongated nuclei.

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- Give the histopathological findings of low and high grade dysplasia.

Feature	Low Grade	High Grade
○ Nuclei	- Basal position - Hyperchromatic - Elongated - Uniform size	Stratified Pleomorphic (often show a more rounded appearance than LGD)↑↑
○ N/C ratio	↑ -	↑
○ Nucleoli	- Normal	May be present
○ Complex / cribriform architecture	-	+/-
○ Note:	- Common practice > LGD -- has replaced the previous categories of mild and moderate dysplasia > HGD -- includes severe dysplasia and “carcinoma <i>in situ</i>” - Recall that if an adenomatous polyp is ≥1 cm, has HGD, cancer, or a villous architecture, it is considered to meet the criteria for being called an AAP (adenoma with advanced pathology, or advanced adenoma [AA])	

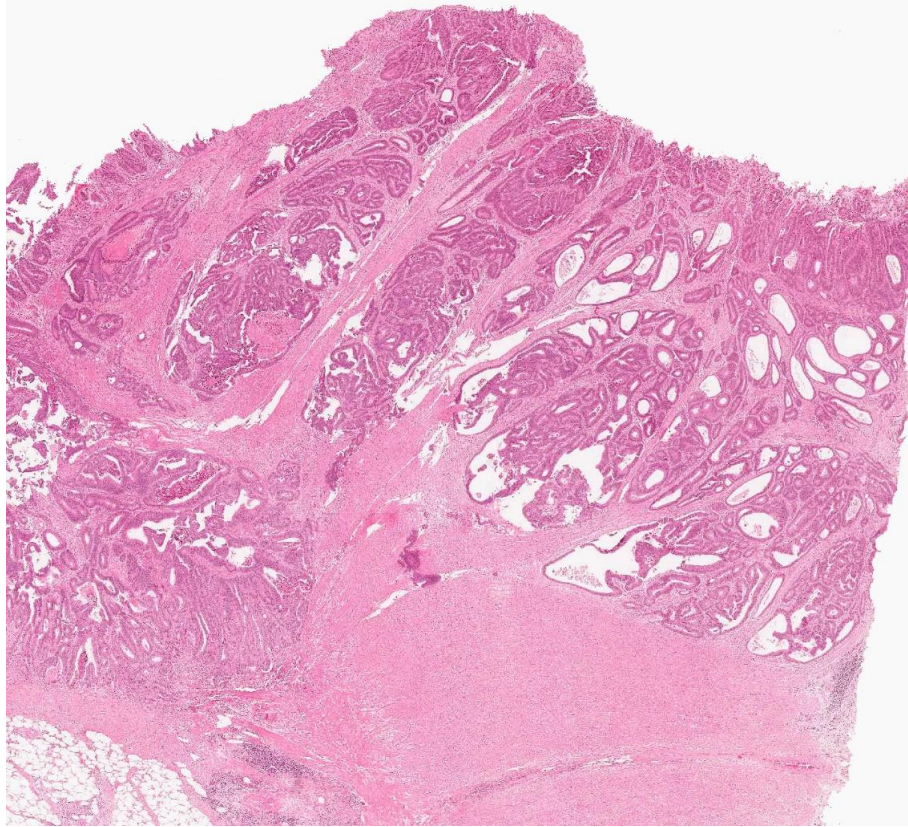
Abbreviations: HGD, high grade dysplasia; LGD, low grade dysplasia; N/C ratio, ratio of nucleus to cytoplasm

- Give the histopathological terms used to describe non-invasive and invasive colonic cancer.

Name	Through Basement Membrane	Into Lamina Propria	Through Muscularis Mucosae
○ Non invasive			
- Carcinoma in situ	-	-	-
- Intramucosal cancer	+	+	-
- Note that these 2 terms are now included in the category of “high grade dysplasia”			
○ Invasive			
- Malignant polyp	+	+	+



Colorectal carcinoma (H&E 20X)



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SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the anatomical reason why **carcinoma in situ** and intramucosal carcinoma are considered to be non-invasive lesions, with minimal potential to metastasize.
 - Carcinoma in situ and intramucosal cancer of the colon are contained in the mucosa, which lacks large lymphatics, and thus there is minimal potential to metastasize.
- Give the histopathological characteristics of an **AAP** (adenoma with advanced pathology):
 - AAP are adenomatous polyps which have one or more of the following:
 - Size ≥ 1 cm
 - Villous architecture
 - Presence of high grade dysplasia (HGD)
 - Carcinoma



INTESTINAL POLYPOSIS SYNDROMES

➤ Classification

- Give the classification of multiple colonic polyps, based upon inheritance.

- Inherited

- Adenomas

- FAP (familial adenomatous polyps)
 - Variants of FAP
 - Gardner
 - Turcot
 - AFAP (attenuated FAP)
 - MUTYH
 - Bloom syndrome
 - Familial tooth agenesis syndrome

MCQ ALERT

- In gastroenterology literature, HNPCC Lynch syndrome is inherited but is **not** a polyposis syndrome

Abbreviation: HNPCC, hereditary non-polyposis colon cancer

- Hamartomas

- PJS (Peutz-Jeghers Syndrome)
 - JPS (Juvenile polyposis syndrome)
 - PTEN hamartomas
 - Cowden disease
 - BRR (Bannayan-Ruvalcaba-Riley) syndrome
 - Neurofibromatosis and ganglioneuromatosis
 - Tuberous sclerosis

- Non-inherited

- Inflammatory (pseudopolyps)
 - Cap polyposis
 - Serrated polyposis syndrome
 - Lymphomatous polyposis
 - Usually caused by mantle cell lymphoma (a type of non-Hodgkin lymphoma)
 - NLH (nodular lymphoid hyperplasia)
 - May be associated with Gardner syndrome
 - Cronkite-Canada syndrome



- Give the **polyposis syndromes**, based upon the adenomatous and hamartomatous subtypes.

Syndrome	Inheritance Pattern	Polyp Type	Commercial Gene Mutation Testing
○ FAP	AD	Adenomatous	APC
○ AFAP	AD	Adenomatous	APC
○ MAP	AR (AD)	Adenomatous	MYH
○ PJS	AD	Hamartomatous: Peutz-Jeghers polyps	STK11
○ JPS	AD	Hamartomatous: Hamartomatous: juvenile	SMAD4 or BMPR1A
○ CS	AD	Hamartomatous:juvenile, ganglioneuroma, lipoma, hyperplastic	PTEN

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; AFAP, attenuated familial adenomatous polyposis; CS, Cowden syndrome; FAP, familial adenomatous polyposis; JPS, juvenile polyposis; MAP, modified adenomatous polyposis; PJS, Peutz-Jeghers syndrome

➤ Diagnostic imaging

Pancolonic Filling Defects (Polyposis), air contrast barium enema

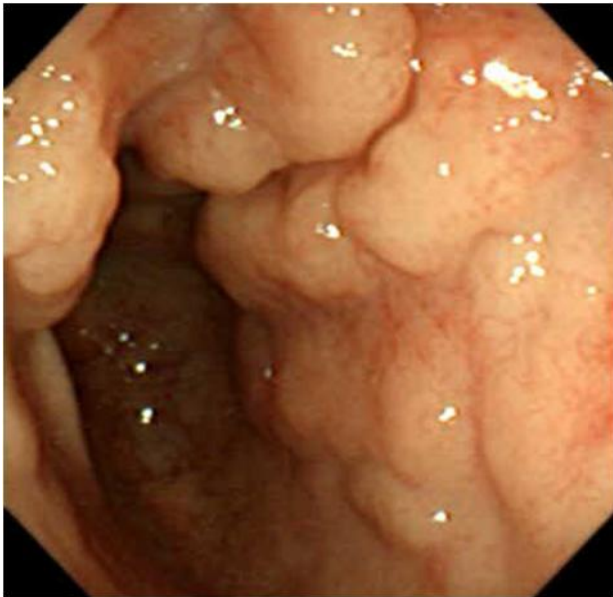


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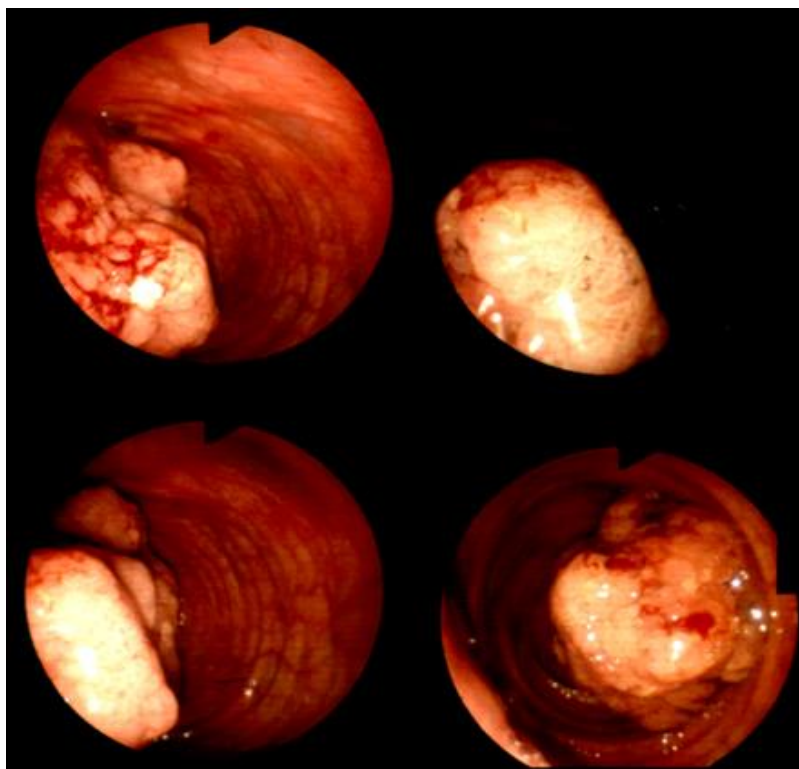
➤ Endoscopy

Colonic Lymphoma



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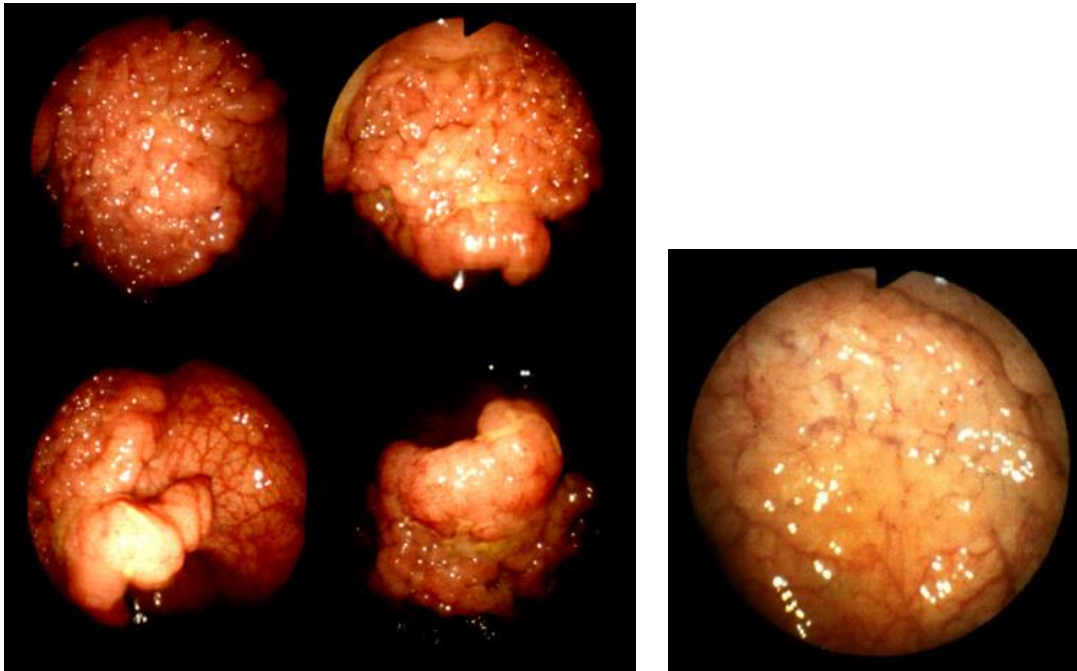
Giant Villous Adenoma of Colon



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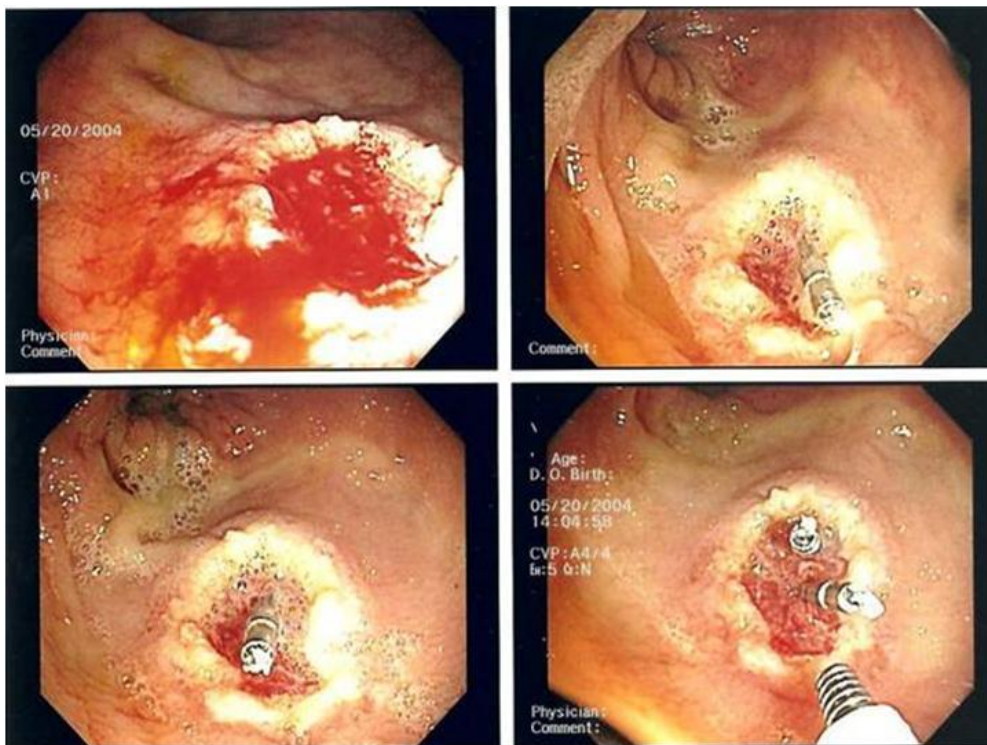


Rectal Villous Adenoma



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Colonic Adenoma



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Colon



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Familial Adenomatous Polyposis (FAP) Syndrome

➤ Demography

- Prevalence and Penetrance
 - FAP 20/10⁵, 80% prevalence of CRC
 - Represents ~ 1% of all CRCs
- Give the median age of onset of CRC in the 4 phenotypes of FAP.

Phenotype	Age, yrs
○ Profuse	39
○ Intermediate	39-50
○ Attenuated (AFAP)	>50 (R colon)
○ MYH (MAP)	>60 (recessive)

➤ Diagnostic imaging

Left-Sided Colon, Multiple Filling Defects,
air contrast barium enema

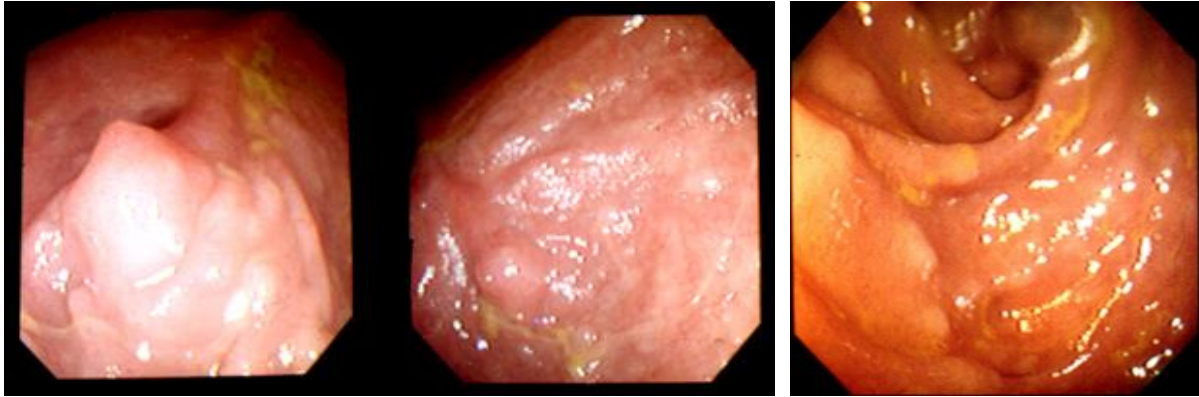


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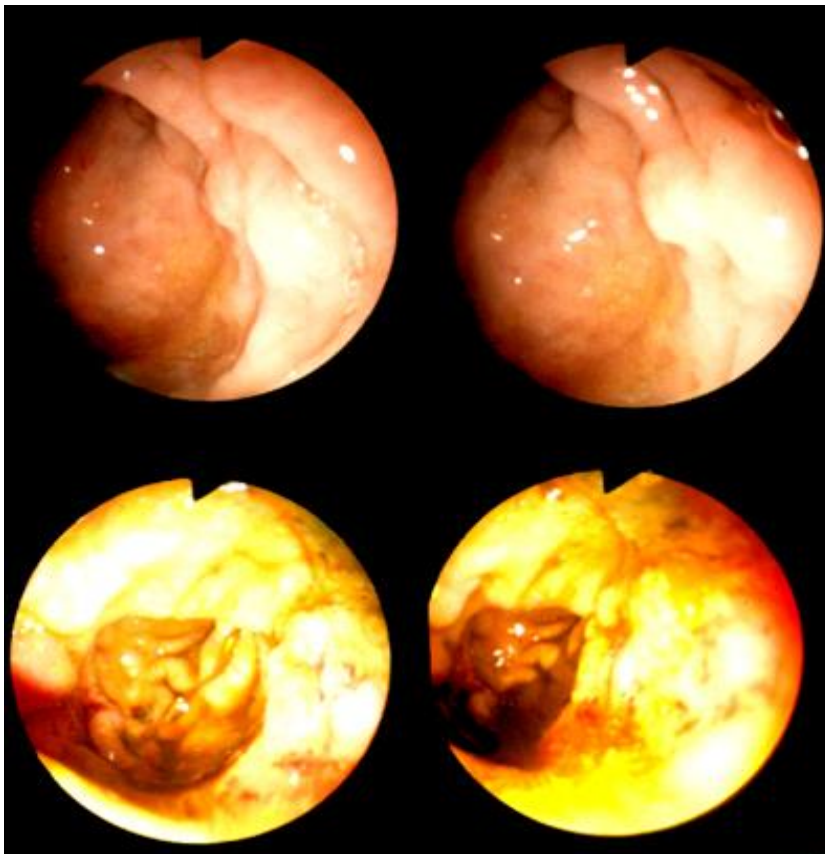
➤ Endoscopy

Multiple Small Colonic Sessile Polypoid Lesions



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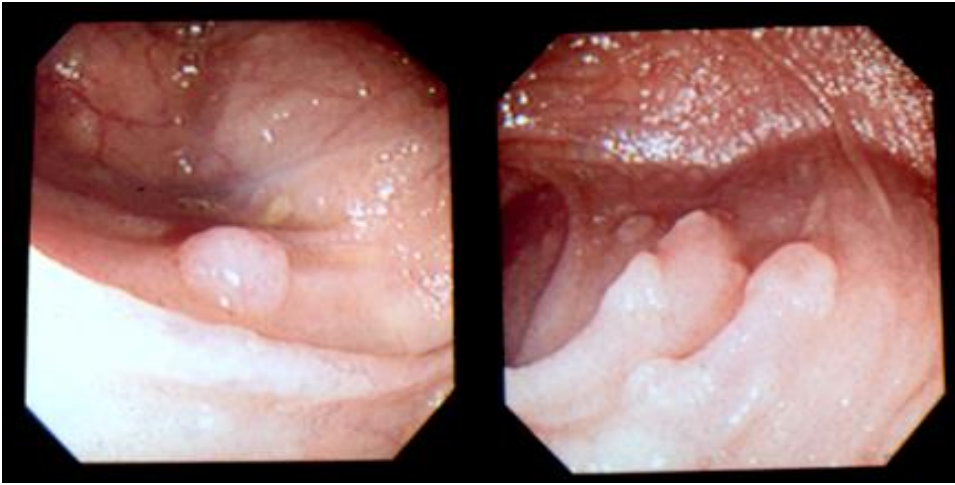
Multiple Small Colonic Filling Defects



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Multiple Small Colonic Filling Defects



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SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the names, genetic mutations, and recommended frequency of surveillance colonoscopy in three **attenuated syndromes** of colonic adenomatous polyps.
 - AFAP (attenuated form of FAP)
 - < 100 adenomas, often in proximal colon
 - Same duodenal and gastric polyp associations as classic FAP
 - Loss of the 5' and 3' regions of FAP
 - CRC develops later than in FAP, ~5 years rather than 32 years -
 - Surveillance colonoscopy every 2 years
 - APC gene pathway mutations
 - B-catenin
 - Axin
 - MUTYH (aka MYH) gene
 - 15-100 colonic adenomas
 - Defective MUTYH gene causes G:C → T:A translocation
 - Autosomal recessive
 - ↑ risk of CRC with biallelic MUTYH mutations
 - Colonoscopic screening age 18 to 20 with surveillance of 2 years
 - May be associated with CHRPE



Hereditary Non-polyposis Colon Cancer (HNPCC, aka Lynch Syndrome)

➤ Definition

- HNPCC is a familial / inherited cause of colorectal cancer. Although multiple adenomas may be observed in Lynch syndrome, it is not associated with large numbers of colonic polyps

Clinical Reminder

- Lynch syndrome is an inherited polyp disorder, like familial adenomatous polyposis (FAP), but Lynch syndrome is **not** a Hereditary Polyposis syndrome (that's why Lynch syndrome is also known as HNPCC, Hereditary non-polyposis colon cancer).
- Note that in the pathology literature, HNPCC is considered to be a polyposis syndrome.

➤ Genetics

- Autosomal dominant, high penetrance
- Germline mutation in DNR MMR (mismatch repair) genes in 80%
- The most common germline mutations in these DNA MMR genes are
 - Chromosomes 2
 - hMSH2 (40% to 50%)
- Chromosome 3
 - hMLH1 (20% to 30%)

➤ Causes / associations

- Give the characteristics, associated cancers and genetic testing of Lynch syndrome.

Genes	Genetic Testing	Lifetime Cancer Risks	Other Features Reported in Some Cases
○ MLH1	– Full sequencing	▪ Colon	50-80% ▪ Sebaceous adenomas, epitheliomas and kerato-xanthomas
○ MSH2	– Regions of MLH1, MSH2, and MSH6	▪ Endometrium	20-60% ▪ Café-au-lait spots (not confined to MSH2 mutations)
○ MSH6		▪ Stomach	11-19% ▪ Brain tumours (confined to MSH6 mutations)

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- Increasingly, screening for MMR genes is being performed in all persons diagnosed with colorectal cancer (CRC).
 - The Amsterdam and the Bethesda Criteria were developed to justify the screening for MMR gene justified from ↑ risk stratification based on these guidelines.



➤ Diagnosis

Amsterdam criteria I

There should be at least three relatives with CRC; all the following criteria should be present:

1. One should be a first-degree relative of the other two
2. At least two successive generations should be affected
3. At least one CRC should be diagnosed before the age of 50 years
4. Familial adenomatous polyposis should be excluded
5. Tumours should be verified by pathological examination

Amsterdam criteria II

There should be at least three relatives with a Lynch syndrome-associated cancer (CRC, cancer of the endometrium, small bowel, ureter or renal pelvis); all of the following criteria should be present:

1. One should be a first-degree relative of the other two
2. At least two successive generations should be affected
3. At least one should be diagnosed before the age of 50 years
4. Familial adenomatous polyposis should be excluded in the CRC case(s) if any
5. Tumours should be verified by pathological examination

Revised Bethesda criteria

1. CRC diagnosed in a patient of less than 50 years of age
2. Presence of synchronous, metachronous colorectal, or other Lynch syndrome-related tumours, regardless of age
3. CRC with MSI-H phenotype diagnosed at less than 60 years of age
4. Patient with CRC and a first-degree relative with a Lynch syndrome-related tumour, with one of the cancers diagnosed before the age of 50 years
5. Patient with CRC with two or more first-degree or second-degree relatives with a Lynch syndrome related tumour, regardless of age



Amsterdam Criteria (3-2-1)

- ≥ 3 first degree relatives with CRC
- 2 generations affected with CRC
- $\geq 1 < 50$ yr old
- ≥ 1 first degree relative of the other family members
- Approaches
 - In families not meeting the Amsterdam criteria, three approaches have been suggested:
 - approaches missing
 - The frequent presence of micro-satellite errors in tumour tissue is called micro-satellite instability (MSI)
- MSI is present in $>90\%$ of colon cancers in HNPCC. MSI is present in only about 15% of sporadic colon cancers, and occurs usually by a different mechanism.
- Abnormalities in mismatch repair MMR are easily detected in tumour tissue by immunohistochemistry and this testing is used as a surrogate marker for MSI
- It has been suggested that MMR / MSI testing be done on tumours when one of the “Bethesda criteria” are met. They are as follows:
 - Individuals with cancer in families that meet the Amsterdam criteria
 - Individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers*

Apply MMR / MSI testing to the colon cancer tissue in the following situations:

- CRC diagnosis <70 yrs (in Canada, allcomers in USA)
- CRC plus one first-degree relative with colon or endometrial cancer
- CRC plus a previous colon or endometrial cancer
- With this method, 24% of colon cancer cases will undergo MSI testing of the tumour, and 4% of colon cancer cases will have mutation finding in the MMR gene

Use a specific logistic model applied to an extended family that includes kindred structure and known cancer cases

- If the model predicts $>20\%$ chance of HNPCC, go directly to mutation finding.
- If the model predicts $<20\%$ chance of HNPCC, first do MSI and if positive, go to mutation finding



Bethesda Criteria (for testing tumour tissue)

❖ Original

- Persons who have had 2 Lynch tumours
- Persons with a Lynch tumour with a first degree relative under 50
- Persons with a Lynch tumour in at least 2 first- or second-degree relatives at any age
- CRC diagnosed before age 50
- CRC with MSI-related histological features diagnosed before age 60

❖ Revised Bethesda guidelines

- Colorectal cancer under 50 years of age
- Synchronous or metachronous Lynch syndrome related cancers¹ regardless of the age at diagnosis
- Colorectal cancer that exhibits histological features associated with the MSI² prior to age 60 years
- Individuals with colorectal cancer and a first-degree relative with a Lynch syndrome-related tumour¹, and at least one of the two diagnosed under age 50 years
- Individuals with colorectal cancer who have two or more first- or second-degree relatives affected with Lynch syndrome related cancers¹, regardless of age

¹Lynch syndrome related cancers for these guidelines include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma), sebaceous gland adenomas, and keratoacanthomas.

²**MSI associated histologic features** include tumour infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous / signet-ring differentiation, or “medullary” growth pattern.

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Please also see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, Table 123.5, page 2206.

❖ Sequence of testing for HNPCC

- Diagnosis of CRC
- Although multiple colonic tumours occur in HNPCC (~35%), only about 10% of persons with sporadic (non-HNPCC) CRC may have multiple polyps.
- Although the mean average of development of CRC is younger in HNPCC than in sporadic tumours (64 versus 67 years, respectively) in the individual patient it may be difficult to distinguish the two conditions.



- Give the cancer risk and the **screening recommendations** for Lynch syndrome (HNPCC) tumours.

Cancer	Cancer Risk	Screening Recommendations
○ Colon	80%	- Colonoscopy, every 1-2 years, beginning at age 20-25 yrs or 10 yrs younger than the earliest case in the family, whichever comes first
○ Endometrial*	43-60%	- Pelvic exam, transvaginal ultrasound and / or endometrial aspirate every 1-2 years, starting at age 25-30 yrs
○ Ovarian	9-12%	- Uncertain
○ Gastric	13-19%	- Upper GI endoscopy every 1-2 years, start at 30-35 yrs
○ Urinary tract	4-10%	- Ultrasound and urinalysis (urine cytology) every 1-2 yrs, starting at age 30-35 yrs
○ Renal cell adenocarcinoma	3.3%	- Same as above
○ Biliary tract and gallbladder	2.0-18%	- Uncertain, possible LFTs annually after age 30 yrs
○ Central nervous system, usually glioblastoma (Turcot syndrome)	4%	- Uncertain, possibly annual exam and periodic head CT in affected families
○ Small bowel	1-4%	- Uncertain, at least small bowel X-ray if symptoms occur

*Guidelines are empiric, except for colon

Adapted from: Burt RW. 2007 AGA Institute Postgraduate Course:240.

- Endoscopy
 - Multiple
 - Synchronous
 - Metachronous
 - Right-sided
- Histopathology “classic” features
 - Lymphocytes infiltrating the tumour epithelium
 - Mucinous or signet ring morphology
 - Poor differentiation
 - Crohn-like inflammatory reaction



Muir-Torre Syndrome

➤ Definition

- Extracolonic cancer in HNPCC is known as the Muir-Torre variant
- A rare subset of HNPCC associated genetically with
 - MSI
 - Loss of expression
 - hMLH1
 - hMSH2
- Associated cancers
 - Skin
 - Keratoacanthomas
 - Sebaceous adenomas
 - Carcinomas
 - Basal cell
 - Squamous
- GI tract
 - Stomach
 - Small intestine
 - Biliary tree
- GU
 - Ovary
 - Uterus
 - Ureter
- CNS
 - Brain

"We are what we repeated do.
Excellence then, is not an act, but a habit."

Will Durant



SERRATED POLYPOSIS SYNDROME

Definitions include:

1. At least five serrated polyps proximal to the sigmoid colon with two or more of these being > 10 mm
2. Any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis
3. > 20 serrated polyps of any size, but distributed throughout the colon

Two clinical variants are recognized, although overlap may be present:

- Type 1: Multiple SSA/Ps that can be larger and often more proximal. There is a significant risk of cancer.
- Type 2: Numerous small classical hyperplastic polyps are present throughout the colon. There may be a slightly increased risk of cancer.

➤ Demography

- During screening colonoscopy, hyperplastic polyps occur in 10% of persons (please remember that in screening colonoscopies for average risk persons, 25% of males and 15% of females over age 50 years will have adenomatous polyps).
- Smoking is a risk factor for both adenomatous and for hyperplastic polyps.

➤ Surveillance

- Give the surveillance recommendations after resection of serrated polyps.

Resected Polyp	Recommended Surveillance Interval
○ Typical hyperplastic polyp	- No surveillance recommended, unless multiple, large and proximally located
○ Sessile serrated adenoma (SSA; non dysplastic)	- 5 years if < 3 lesions, all < 1 cm size; - 3 years if ≥ 3 lesions, or any ≥ 1 cm size
○ Sessile serrated adenoma with dysplasia (SSAD)	- 1-3 years after ensuring complete resection
○ Traditional serrated adenoma (TSA)	
○ Suspected type I serrated polyposis	- 1-3 years, with resection of polyps > 5 mm

Adapted from: Huang C.S. Am J Gastroenterol 2011;106:229-240,page 237.



Colonic Mass, Air Contrast Barium Enema



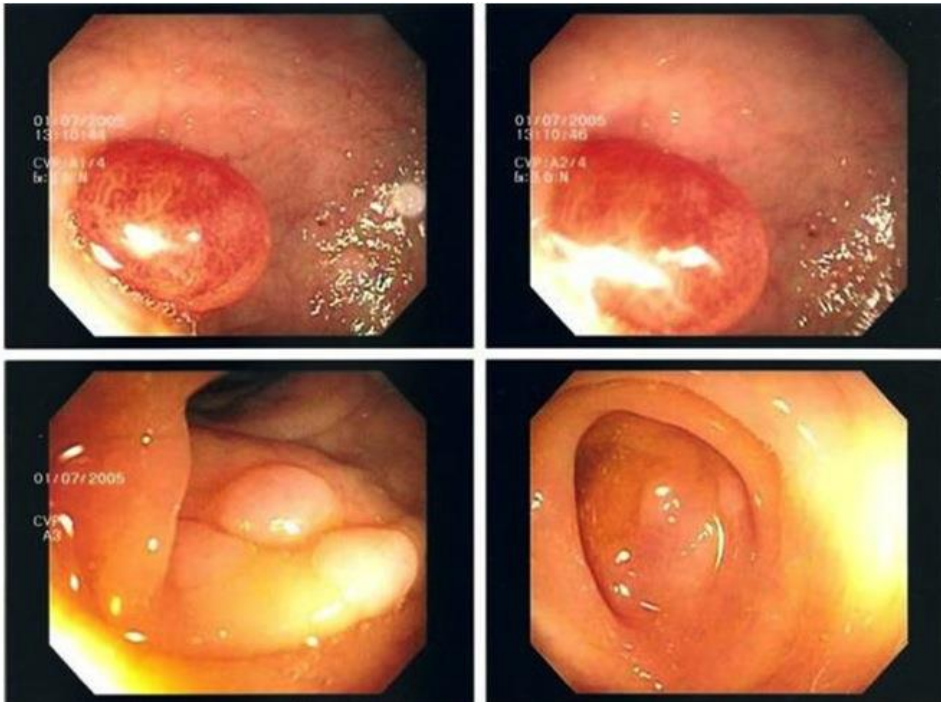
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➤ Endoscopy

- Both adenomatous and hyperplastic polyps may occur in the same colon, especially if there is a family history of CRC or HNPCC.
- If the patient has a hyperplastic polyp identified on sigmoidoscopy (usually small [< 5 mm]). They need to have a full colonoscopy, since a distal hyperplastic polyp is a marker for a proximal lesion (approximate risks):
 - Proximal neoplasia, 25%
 - Proximal advanced neoplasia, 5%
- Flat or sessile
- Mucus cap
- Pale
- Abnormal vascular pattern
- Fuzzy edges

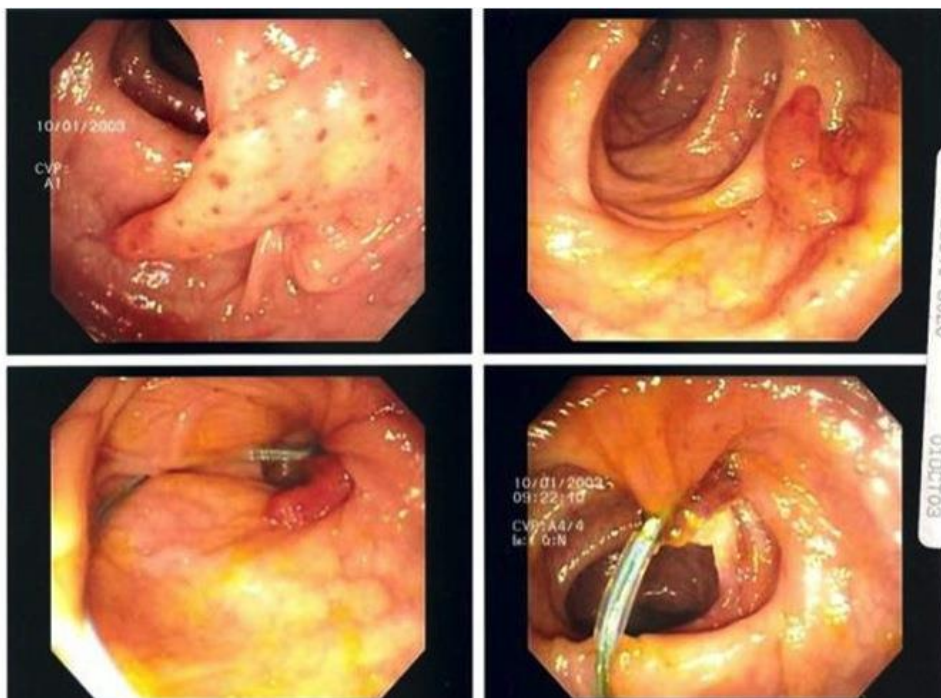


Serrated Hyperplastic Polyp



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Serrated Hyperplastic Polyp



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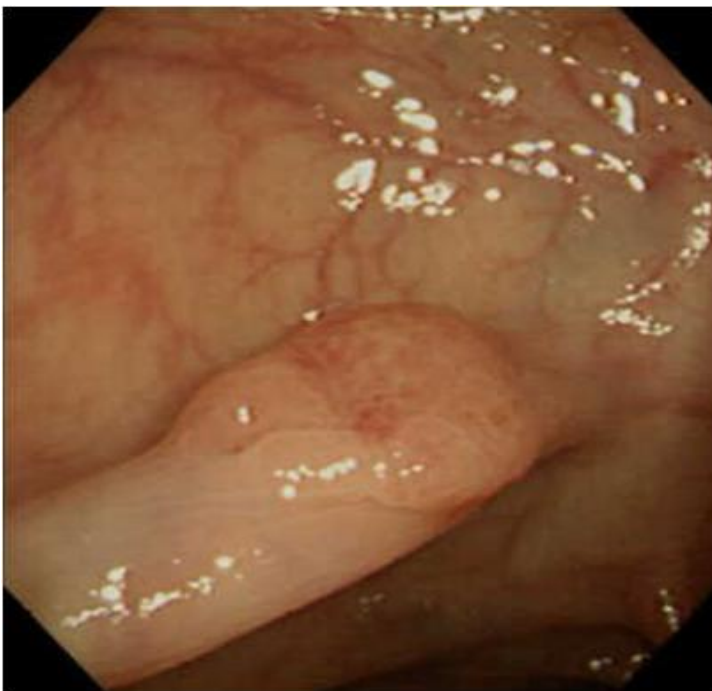


Colonic Hyperplastic Polyp



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Colonic Serrated Adenoma



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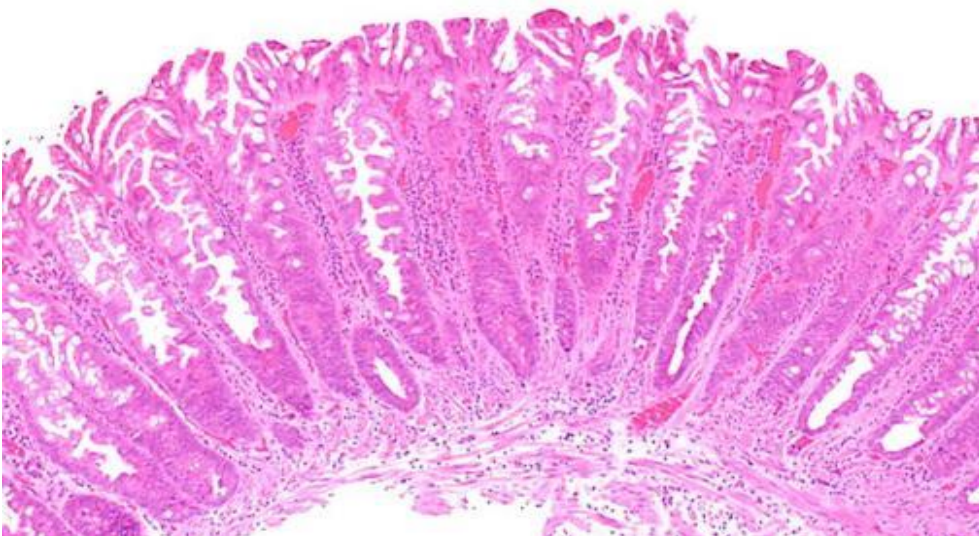
➤ Histopathology

- Give the features which help to distinguish hyperplastic polyps (HP), TSA (traditional serrated adenoma) from SSA (sessile serrated adenoma).

Features	Hyperplastic Polyps (HP)	Traditional Serrated Adenomas (TSA)	Sessile Serrated Lesion / Polyp / Adenomas (SSL / P / A)
○ Site	LC	LC	RC
○ Sessile	+/-	-	+
○ Size, mm	< 5	> 5	> 5
○ Mucus cap	-	-	+?
○ Crypts base irregular	-	-	+
○ High grade dysplasia	-	+/-	+/- (10%)
○ Premalignant	-	+	+
○ Molecular changes			
- APC		+	
- KRas	+/-	+	
- TP53		+	
- MSI		+	+
- BRAF	+/-	-	+
- DNA methylation		-	+
- Cp G island		-	+
Methylator phenotype			

❖ Hyperplastic Colonic Polyp

Hyperplastic Polyp

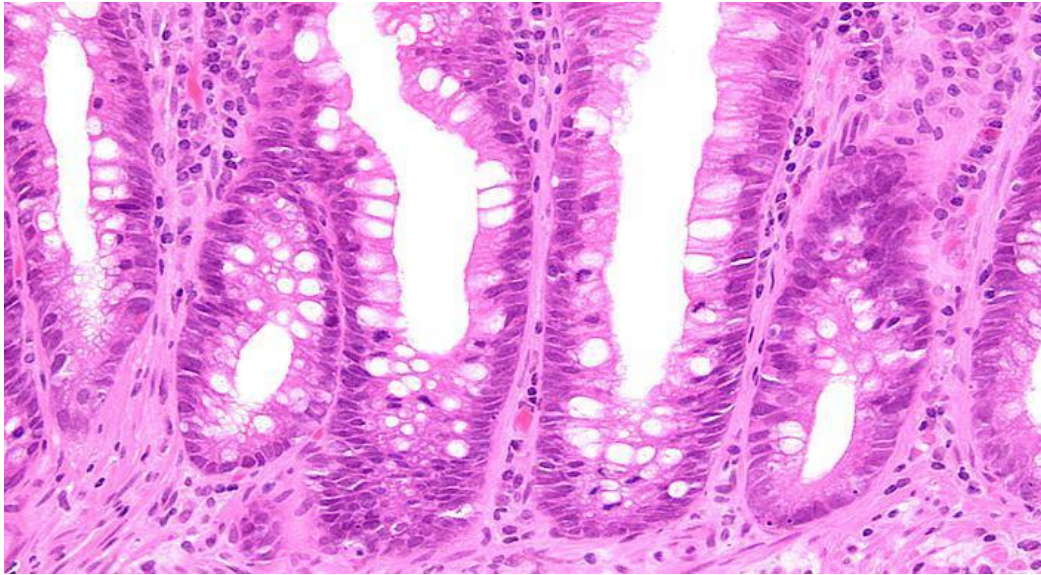


- Serrations in the luminal half
- Straight crypts with narrow bases
- Immature proliferative cells in the lower crypts

Source: Driman D (2015). GI Biopsy Crash Course: Normal Histology, Classical Entities and Common Issues. In Thomson ABR and Chande N (Eds). *Medical Mini Review Series in Gastroenterology and Hepatology: Efficient Refresher for the Busy Clinical Gastroenterologist* (volume 3), page 381.



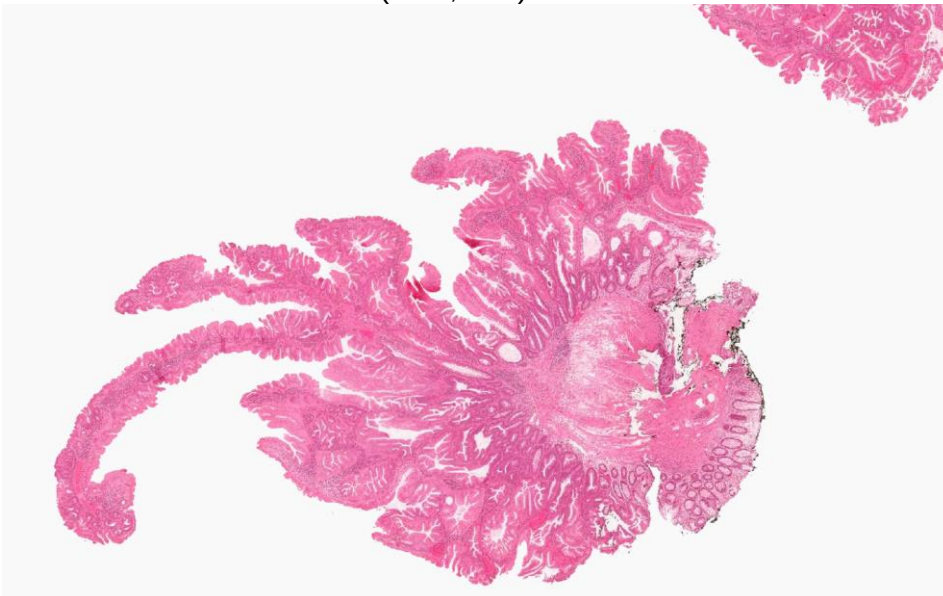
Hyperplastic Polyp



Source: Driman D (2015). GI Biopsy Crash Course: Normal Histology, Classical Entities and Common Issues. In Thomson ABR and Chande N (Eds). *Medical Mini Review Series in Gastroenterology and Hepatology: Efficient Refresher for the Busy Clinical Gastroenterologist* (volume 3), page 381.

❖ Traditional Serrated Adenomas (TSA)

Traditional serrated adenoma (H&E, 20X)

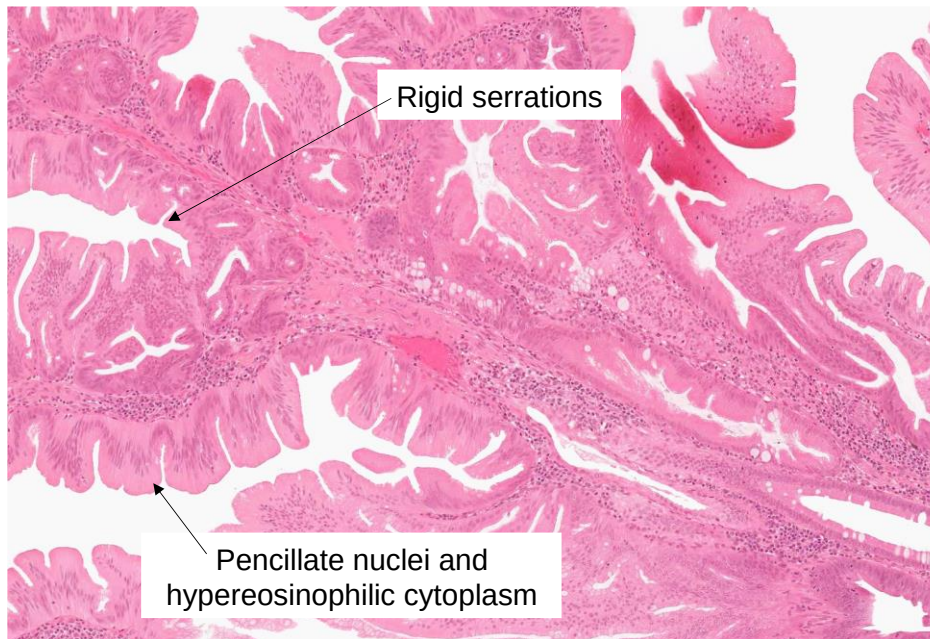


This polypoid lesion has the hypereosinophilic (pink) appearance typical of TSAs. Diffuse serrations can be seen at low power.

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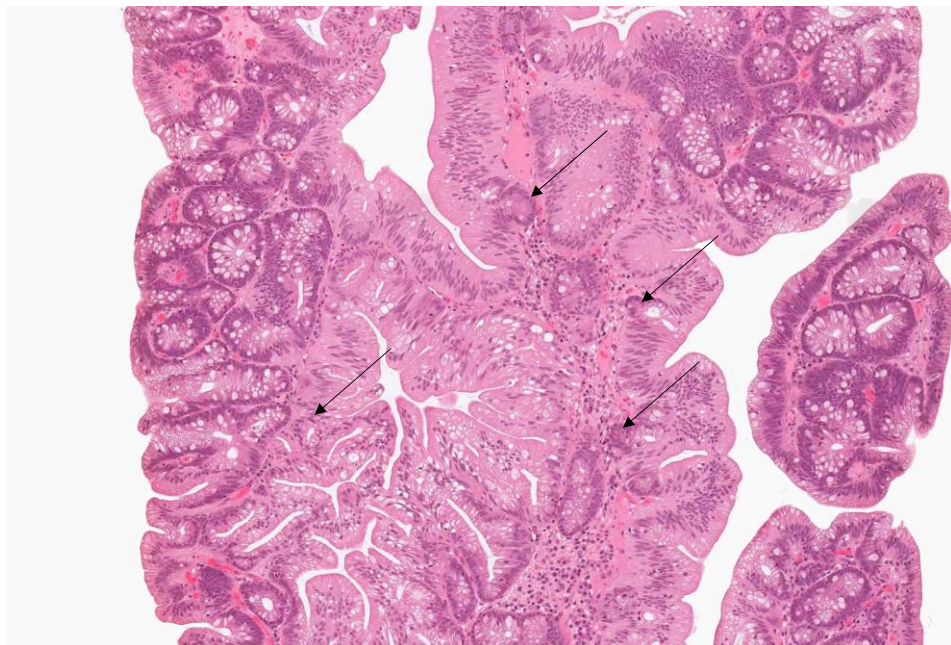
Traditional serrated adenoma (H&E, 100X)



The serrations in a TSA are "rigid" as opposed to the "softer" serrations seen in an SSA. In this case, the typical pencillate nuclei and hyper-eosinophilic cytoplasm can be seen.

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Traditional serrated adenoma (H&E, 100X)



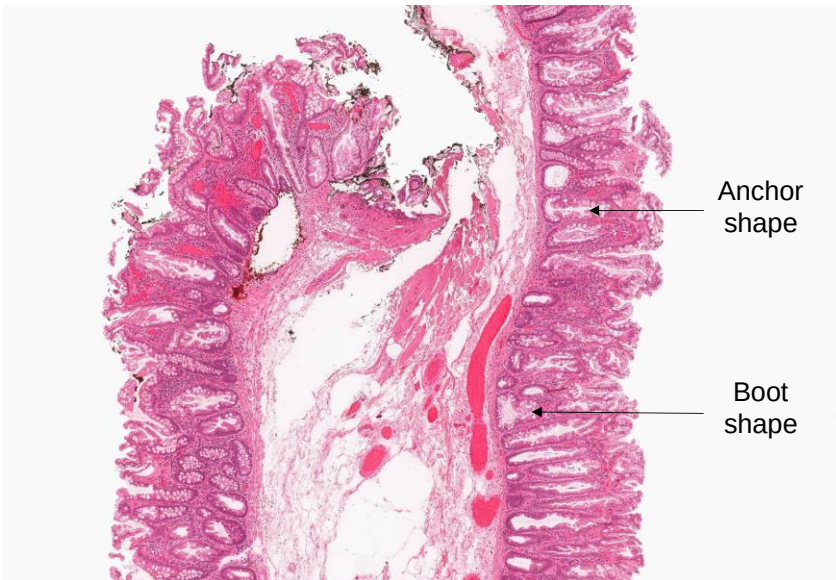
In this TSA, we see crypt budding (arrows), where smaller crypts appear to "bud" from larger ones.

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❖ Sessile Serrated Adenomas (SSA)

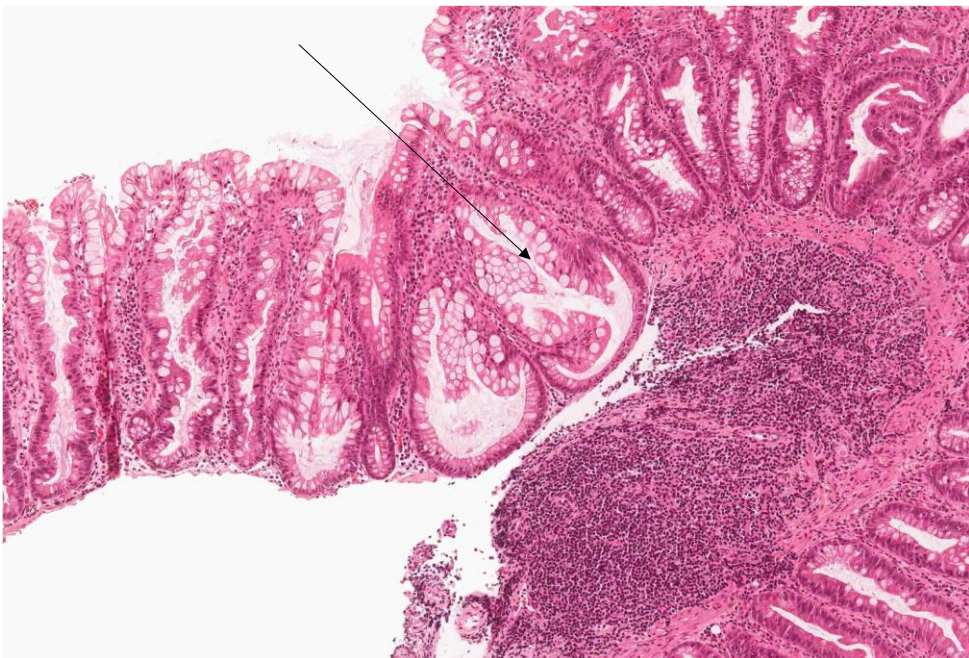
Sessile serrated adenoma (H&E, 40X)



This sessile lesion shows classic dilated crypt bases with abnormal shapes.

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Sessile serrated adenoma (H&E, 100X)

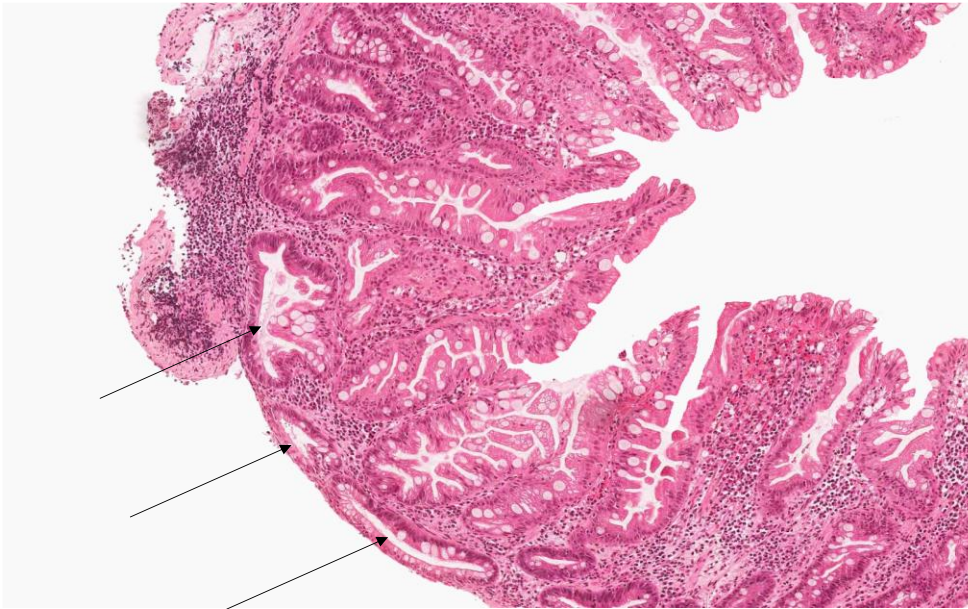


Dilated crypt bases, one with an anchor shape (arrow).

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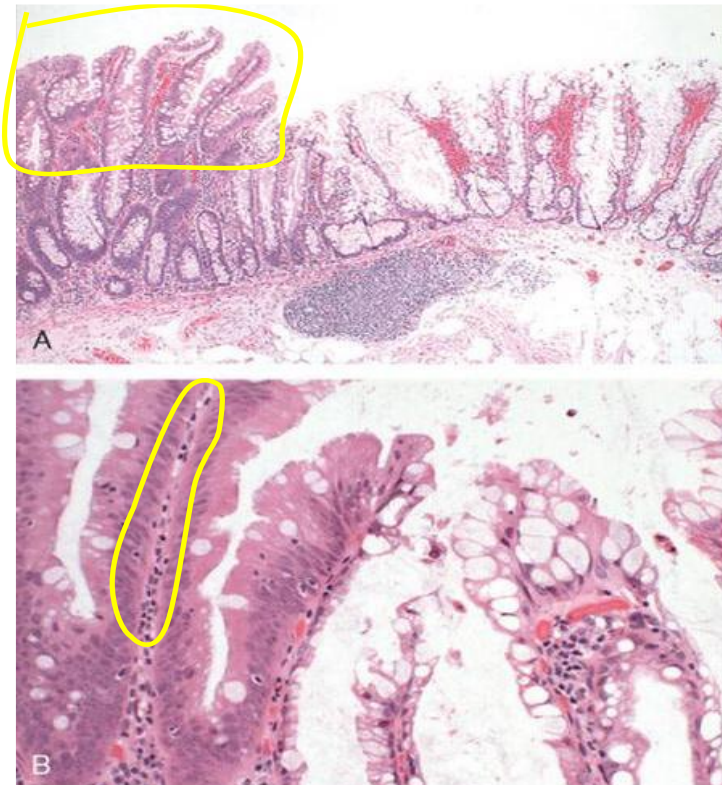
Sessile serrated adenoma (H&E, 100X)



Dilated crypt
bases (arrows).

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Sessile Serrated Adenoma (SSA) of Colon with low grade dysplasia



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Hamartomatous Polyposis Syndromes (HPS)

➤ Classification

- Give a classification of hamartomatous polyposis syndromes.
 - PJS (Peutz-Jeghers syndrome)
 - JPS (Juvenile polyposis syndrome, aka familial juvenile polyposis)
 - PTEN tumour syndrome
 - Cowden disease
 - BRR (Bannayan-Ruvalcaba-Riley) syndrome
 - Neurofibromatosis (mutation in NF1 gene), and ganglioneuromatosis ↑ with MEN 2B
 - Tuberous sclerosis
 - GI PEComas (mesenchymal tumours) plus:
 - Angiofibromas (face) or forehead plaque
 - Ungual or periungual fibromas
 - Multiple retinal nodular hamartomas
 - Cardiac rhabdomyoma
 - Subependymal giant cell astrocytoma
 - Subependymal nodule
 - Cortical tuber
 - Lymphangiomyomatosis
 - Multiple renal cysts
 - Ganglioneuroblastoma
 - PEComa family tumours
 - Shagreen patches
 - Hypomelanotic macules

Note: JPS, when associated with multiple polyps, is a diagnosis of exclusion (e.g., exclude PJS, CS, BRR, NFTA)



- Give the responsible gene risk of PJS, JPS and CS, as well as their associated clinical features.

Syndrome	Gene (% Chance of Finding a Mutation in Proband)	Lifetime Cancer Risk	Other Features
○ Peutz-Jeghers syndrome (PJS)	STK11 (30-70%)	- Breast 54% - Colon / rectum 39% - Pancreas 36% - Stomach 29% - Ovarian¹ 21% - Small bowel 13% - Lung 15% - Uterus / cervix² 9% - Testicle Rare	▪ Mucocutaneous pigmentation ▪ Histologically characteristic gastrointestinal hamartomas, mostly small bowel, but in all areas
○ Juvenile polyposis syndrome (JPS)	SMAD4 (20%) BMPR1A (20%) ENG (rare)	- Colon 68% - Upper GI cancers including stomach, pancreas and small bowel 21%	▪ GI juvenile polyps ▪ Features of HHT³ ▪ Digital clubbing ▪ Congenital defects
○ Cowden syndrome (CS)	PTEN (80-90%)	- Breast 25-50% - Thyroid 10% (especially follicular) - Endometrium 5% - Kidney ↑ - Colon and upper GI tract CRC may be ↑	▪ Mucocutaneous papules ▪ Macrocephaly ▪ Hamartomas of the gastrointestinal tract, thyroid, and breast ▪ Lhermitte-Duclos disease

¹Sex cord tumours with annular tubules; ²Adenoma malignum, ³Hereditary hemorrhagic telangiectasia

Printed with permission: Burt RW. 2007 AGA Institute Postgraduate Course. pg. 241.

➤ Histopathology

- Surface epithelium is tufted and free of basophilia.
- Nuclei are small, regular, and evenly spaced.
- Star-shaped crypts on cross section due to piling-up of mature epithelium
- No evidence of dysplasia.



Peutz-Jeghers Syndrome (PJS)

➤ Definition

- Autosomal dominantly inherited syndrome of histologically specific hamartomatous polyps together with characteristic mucocutaneous pigmentation
- Arises from mutations of the STK II (serine threonine kinase II, also called LKB I) gene on chromosome 19p13.3

➤ Demography

- Occurrence estimated to be 1 in 150,000 live births
- 50% of mutations are inherited, and 50% are spontaneous, appearing de novo
- Autosomal dominant germline mutation in the STK II (LKB I) gene, with mutations seen in 90% of persons with PJS

➤ Clinical

Pigmentation in PJS



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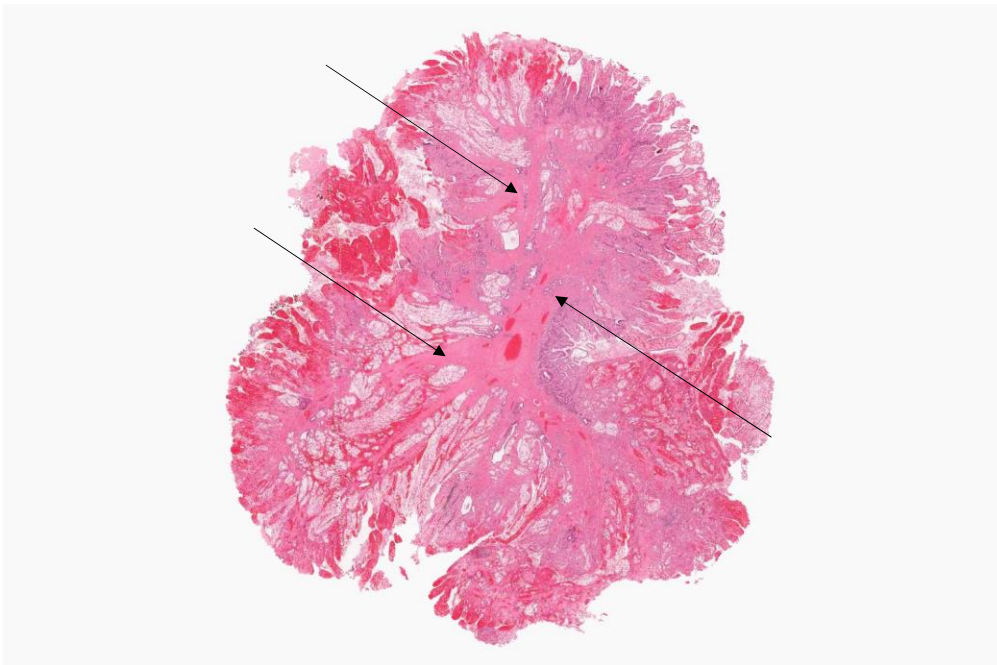


➤ Endoscopy

- Cerebriform polyps on EGD; microscopically, smooth muscle arborization
- Adenomatous changes occur in ~25% of PJS hamartomas, accounting for the development of adenocarcinomas
- Cancer risk (hamartoma-carcinoma sequence) is 90% by age 65

➤ Histopathology

Peutz-Jehgers Polyp (H&E, 6X)



The arborizing smooth muscle can be easily seen at low power (arrows).

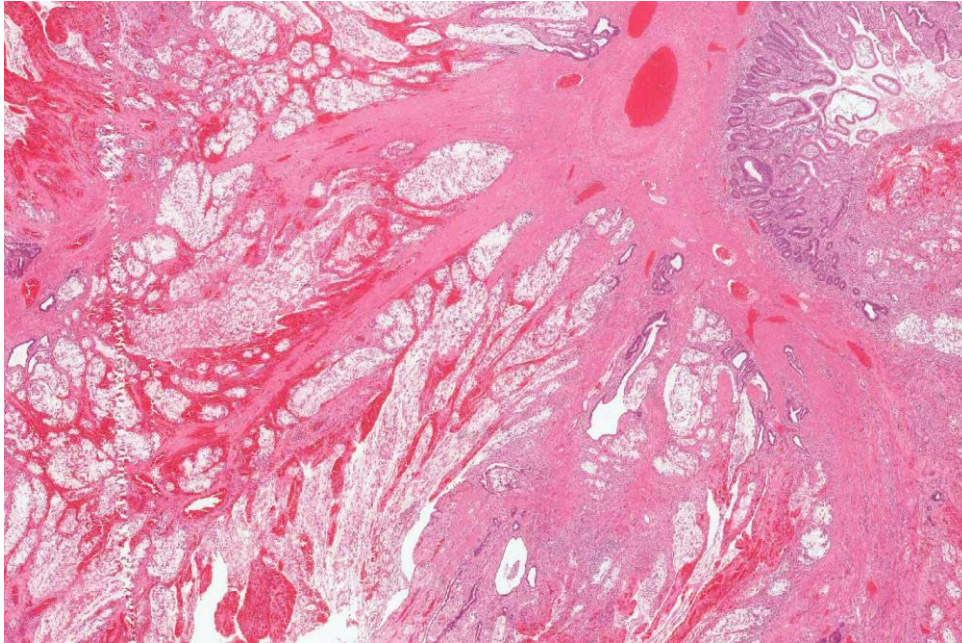
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“Challenges are what make life interesting and overcoming them is what makes life meaningful.”

Joshua J. Marine



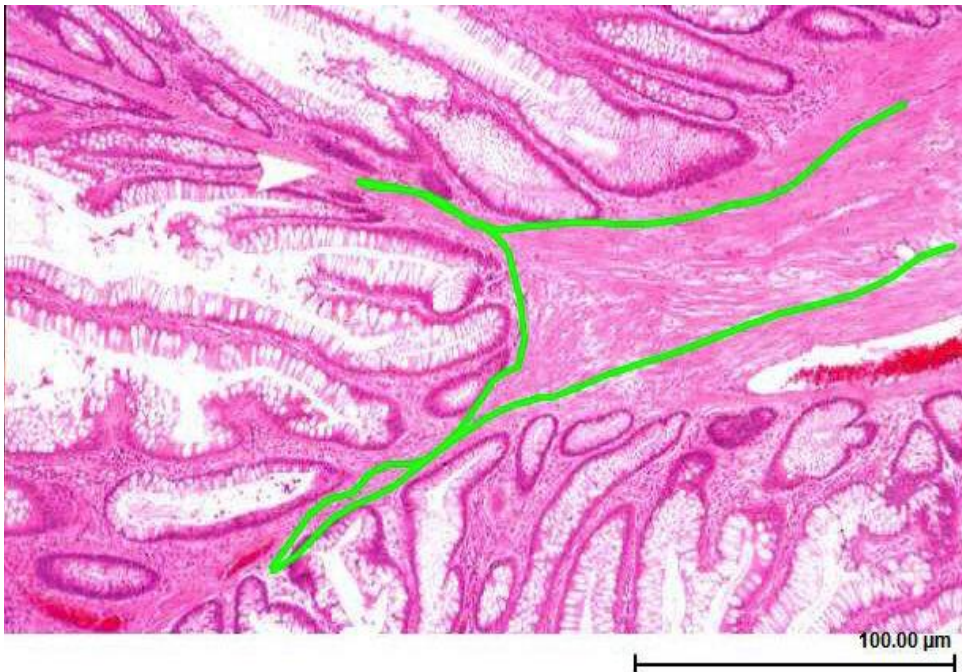
Peutz-Jehgers Polyp (H&E, 20X)



Pink bands of smooth muscle resemble tree branches ("arborizing").

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Peutz-Jehgers Polyp



Arborizing tracts of smooth muscle

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Juvenile Polyposis Syndrome (JPS)

➤ Demography

- The incidence of inherited JP is approx. 1 in 100,000 individuals
- 20-60% have a family history, and the remainder appear de novo
- Juvenile polyps occur in 2% of children. The diagnosis of JP is made with the presence of 10 or more juvenile polyps in the GI tract.

➤ Genetics

- At least a third of these will be found to have the autosomal dominantly inherited syndrome
 - Germline mutation in either the SMAD4 (MADH4) gene (in 35%) on chromosome 18q21.1 or in the BMPR1A (bone morphogenetic protein receptor 1A) gene (in 25%)
 - At least half of the affected families are found to have a disease from mutation of the SMAD4 gene.
 - Other genes may be involved (BMPRIA on chromosome 10)
- Give the gene and chromosome involved in PJS, JPS, and CS.
 - Distinguish from PJS and CS

Syndrome	Gene	Chromosome
– PJS	STK II	19p13.3
– JPS	SMAD4	18q21.1
– CS	BMPR1A PTEN	10

Abbreviations: BMPR1A, bone morphogenetic protein receptor type 1A); CS, Cowden Syndrome; PTEN, phosphate and tensin homologue

➤ Clinical

These juvenile type polyps may be seen sporadically or in JPS, CS, and BRRS or Gorlin syndrome.

- The polyps are most commonly found in the colon, but may occur anywhere throughout the GI tract.
- Multiple juvenile polyps in colon (98%), stomach (14%), duodenum (2%), jejunum and ileum (7%)
- The full-blown syndrome may be characterized by hundreds of polyps.
- Polyps in JP differ from sporadic juvenile polyps in that new polyps almost always recur after polyps are removed and polyps always occur in adults
- JP polyps have a smooth surface, are often covered by exudate, may be sessile or pedunculated and range in size from mms to cms
- Colorectal cancer (CRC) risk in JPS
 - 20% by age 25 years
 - 68% by age 60
- With the SMAD4 mutation, 23% have AVMs in brain, lung, and liver, consistent with HHT (hereditary hemorrhagic telangiectasia), and are more likely to have gastric polyps, massive gastric polyps, or gastric cancer



➤ Histopathology

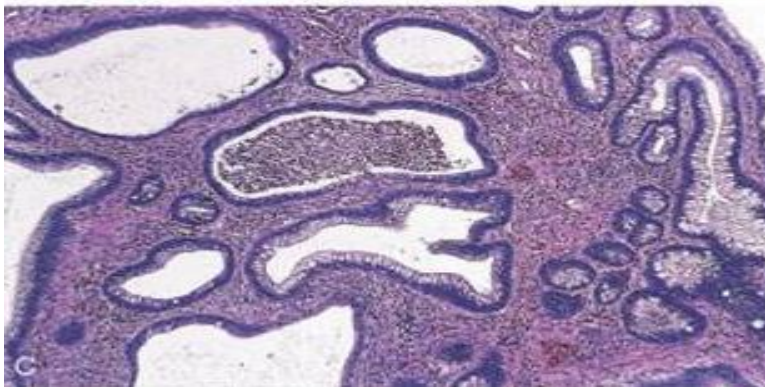
- The juvenile hamartomatous polyps demonstrate dilated cystic glands, columnar lining, abundant lamina propria which may contain an inflammatory infiltrate
- Expanded, inflamed lamina propria with cystic glandular dilatation, epithelial hyperplasia, regenerative epithelial atypia, surface erosion, and granulation tissue.
- The dilated basophilic gland is atypical, but its location in the basal proliferative zone and its association with an overlying erosion make regenerative atypia more likely than dysplasia.
- Round polyp with expanded lamina propria, cystic glandular dilatation, and erosion of the surface epithelium.

SO YOU WANT TO BE A GI PATHOLOGIST!

Juvenile polyps are hamartomas, and ordinarily should not be neoplastic. However, about 1/3 of JPS develop CRC, and a few even develop gastric cancer.

- Give a pathological explanation for this apparent contradiction.
 - JP and adenomatous polyps may occur in the same person
 - Hamartomatous plus adenomatous tissue may occur in the same polyp.

Juvenile Polyp of Colon



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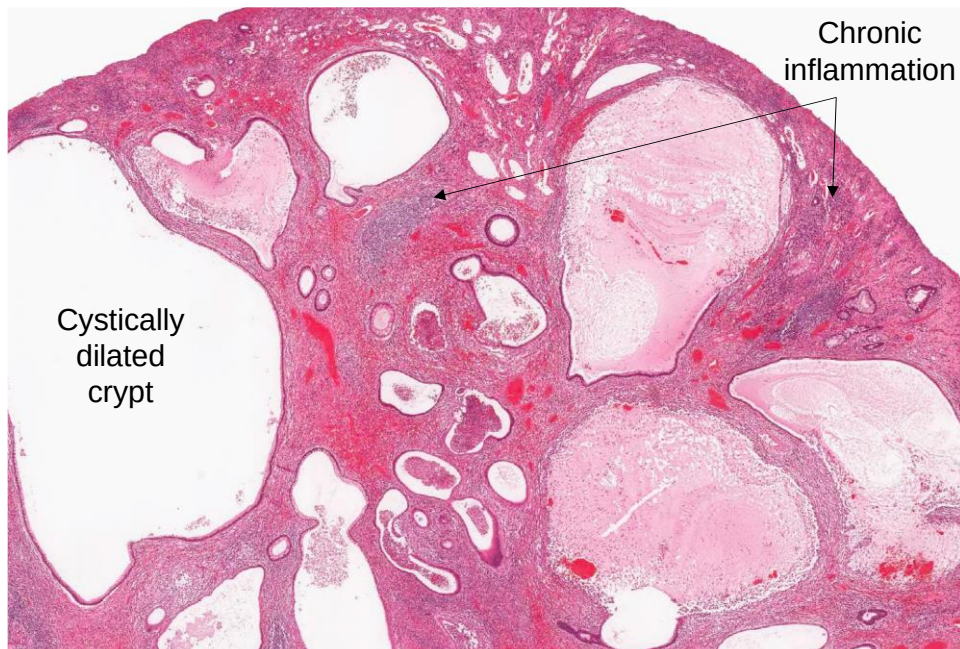
Juvenile polyp (H&E, 5X)



This juvenile polyp has a rounded surface contour and cystically dilated crypts.

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Juvenile polyp (H&E, 5X)



Higher power view of this juvenile polyp shows a chronic inflammatory cell infiltrate in the lamina propria.

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Cowden Syndrome (CS)

➤ Definition

- A juvenile-like polyp which contains neural components is characteristic for CS (Jass JR. *Pathol Res Pract* 2008:431-447).
- Autosomal dominant
- Mutations of the PTEN gene on chromosome 10

➤ Demography

- CS occurs in about 1 in 200,000
- Germline mutations in PTEN gene seen in 85% of CS affected persons
- Skin lesions (99%)
- Colon cancer risk is estimated at 17%. Additionally, this condition must be distinguished from other hamartomatous diseases

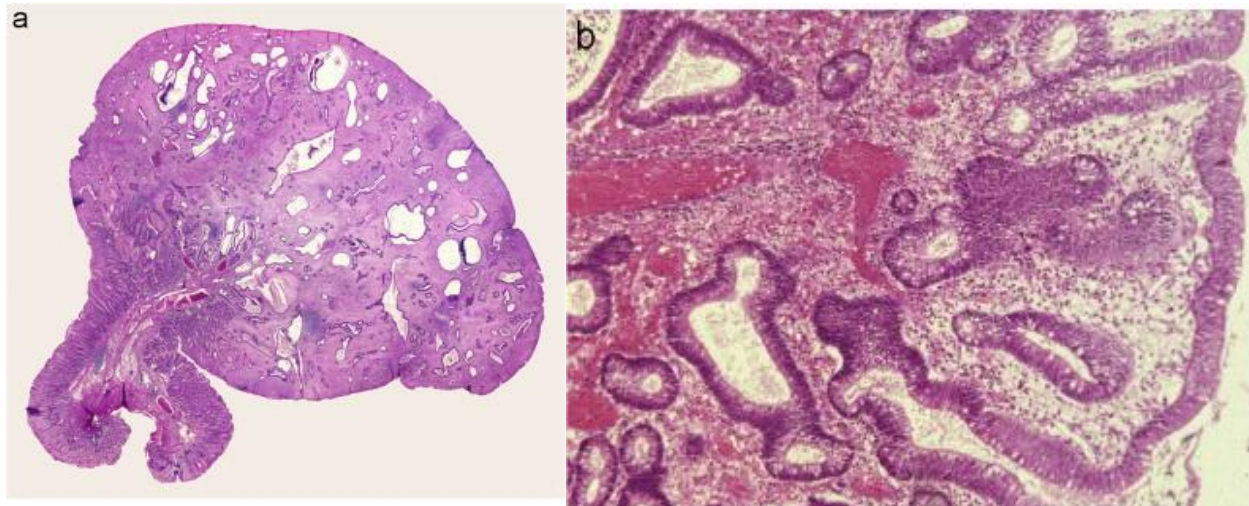
➤ Clinical (criteria for phenotypic diagnosis)

- 90% of affected persons have mucocutaneous papillomatous papules (hamartomas), as well as hamartomas of the infundibulum of the hair follicles (trichilemmomas)
- Other important features of CS include hamartomas of GI tract, tumours of breast and thyroid, macrocephaly, and mental impairment
- 40% have involvement of esophagus (glycogenic acanthosis), stomach and colon (hamartomas)
- Any part of GI tract from stomach to rectum may have hamartomas, juvenile polyps, adenomas, lipomas, inflammatory polyps, ganglioneuromas, or lymphoid hyperplasia
- Multiple hamartomatous polyps occur in the colon and throughout the GI tract.
- A number of different lesions occur:
 - Juvenile type polyps (by far the most common)
 - Lipomas
 - Esophageal glycogenic acanthosis
 - Inflammatory polyps
 - Ganglioneuromas
 - Lymphoid hyperplasia
- Thyroid abnormalities:
 - Two-thirds of patients have multinodular goiter, histologically arising from nodular hyperplasia or follicular adenomas
 - There is an approximate 3-10% risk of thyroid papillary carcinoma
- Cowden syndrome is the presence of multiple facial trichilemmomas (the hallmark sign, most commonly around the mouth, nose and eyes)
- Other skin features:
 - Café-au-lait spots
 - Vitiligo
 - Papillomatous papules
 - Acral keratoses
 - Cysts, as well as squamous cell and basal cell carcinomas



- Oral mucosal lesions
 - These are histologically similar to the trichilemmomas
 - They develop a few years after the skin growths and are present in approximately 85% of patients
 - They include pinpoint, red, flat-topped papules on the outer lips and small, flat, papillomatous or verrucous papules of the oral mucosa, gingiva and tongue
 - Cobblestone-like pattern in mouth from coalesced trichilemmomas in 40%
- Breast lesions:
 - 75% of affected females have breast lesions, including fibrocystic disease and fibroadenomas
 - There is a 30-50% incidence of breast carcinoma, with frequent bilateral occurrence, and a median age at diagnosis of 41 yrs
 - Genitourinary abnormalities (44% of affected women)
 - Multiple uterine leiomyomas (fibroids) and / or bicornuate uterus
- ↑ risk of endometrial cancer
- Additional benign soft tissue and visceral tumours have been observed:
 - Hemangiomas
 - Lipomas
 - Lymphangiomas
 - Neurofibromas
 - Uterine leiomyomas
 - Meningiomas
- Developmental or congenital abnormalities also occur:
 - Hypoplastic mandible
 - A prominent forehead
 - A high-arched palate

Cowden Syndrome



http://www.hereditarypathology.org/categories.php?parent_id=2170Diagnosis



CROHKHITE – CANADA SYNDROME (CCS)

➤ Clinical

- Give the clinical features which might make you suspect CCS (Cronkhite-Canada Syndrome).
 - Skin and hair changes
 - Alopecia
 - Dystrophic nails
 - Protein – losing enteropathy
 - No family history of similar condition (CCS is not inherited)
 - GI hamartomatous polyps with prominent lamina propria edema
 - Colon
 - Small intestine
 - Stomach
 - No ↑ risk of CRC (colorectal cancer)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

For the Canadian GIs – CCS (Cronkhite-Canada Syndrome): There are more than 5 inherited hamartomatous polyposis syndromes (e.g., PJS, JPS, Cowden disease, Bannayan-Ruvalcaba-Riley (BRR) syndrome, neurofibromatosis, ganglioneuromatosis, hereditary mixed (hamartomatous) polyposis syndrome, not to mention Devon family syndrome, and the **Cronkhite-Canada Syndrome (CCS)**).

- Give the typical clinical features of Cronkhite-Canada Syndrome (CCS), the histopathological differentiation from juvenile polyps, and the approximate risk of associated adenomatous changes and CRC.
 - Half of CCS patients have polyps from stomach to rectum. Their clinical characteristics are:
 - Colon
 - Multiple hamartomatous colonic polyps
 - Associated adenomatous tissue in 40%, risk of CRC 9%
 - Small bowel
 - Diffuse mucosal damage
 - SIBO (small intestinal bacterial overgrowth)
 - Stomach
 - ↑ risk of gastric cancer



SO YOU WANT TO BE A GASTROENTEROLOGIST!

There are numerous types of inherited adenomatous and hamartomatous polyposis syndromes, as well as non-inherited colonic polyposis comprised of hamartomatous, hyperplastic, lymphomatous or lymphoid tissue (NLH, nodular lymphoid hyperplasia).

One extremely rare inherited adenomatous polyposis syndrome associated with risk of CRC is the **Bloom Syndrome**.

- Give the features of the Bloom syndrome.
 - Clinical inspection
 - Short
 - Red face / telangiectasia
 - Hematology
 - Leukemia
 - Lymphoma
 - Genitourinary
 - Male sterility
 - Gene mutation
 - BLM

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the **extracolonic manifestations of** Tuberous sclerosis.
 - Skin
 - Angiofibromas and many others
 - Brain
 - Epilepsy
 - Intellectual disability
 - Heart
 - Cardiac rhabdomyomas
 - Bone
 - Bone cysts
 - Kidney
 - Renal cysts
 - Angiomyolipoma
 - Colon
 - Ganglioneuromas
 - Hamartomas



NEUROENDOCRINE TUMOURS (NET)

➤ Size and metastases

- Appendix and rectum
 - <1 cm: rarely metastasize
 - >2 cm: often metastasize
- Rectal NET
 - Lymph node metastases <1 cm 1.7%
 - Lymph node metastases 1.0-2 cm 10%
 - Lymph node metastases >2 cm 80%

➤ Classification

- Give the clinicopathologic classification of neuroendocrine tumours (NET) of the colon, rectum and appendix.

- Recommended Grading System for Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors (<https://whobluebooks.iarc.fr/>, WHO 5th edition, 2019)

Grade (well-differentiated)	Mitotic rate (per 2mm ²)	Ki67 index (%)
- Neuroendocrine tumor, G1	<2	<3
- Neuroendocrine tumor, G2	2-20	3-20
- Neuroendocrine tumor, G3	>20	>2

- For neuroendocrine tumors in any part of the gastrointestinal tract, size greater than 2.0 cm is associated with a higher risk of lymph node metastasis.
 - Rectal carcinoids smaller than 1.0 cm are almost always clinically indolent, and local excision is generally considered sufficient for tumors 1.0 cm or smaller, as well as many tumors between 1.0 cm and 2.0 cm.
 - More extensive procedures are usually reserved for patients with rectal tumors larger than 2.0 cm, rectal tumors with regional metastasis, and most colonic neuroendocrine tumors.
- The World Health Organization (WHO) classifies neuroendocrine neoplasms as well-differentiated neuroendocrine tumors (either the primary tumor or metastasis) and poorly differentiated neuroendocrine carcinomas (a morphologic distinction).
- Historically, well-differentiated neuroendocrine tumors have been referred to as “carcinoid” tumors, a term which may cause confusion because clinically a carcinoid tumor is a serotonin-producing tumor associated with functional manifestations of carcinoid syndrome. The use of the term “carcinoid” for neuroendocrine tumor reporting is therefore discouraged for these reasons.

Adapted from the College of American Pathologists Protocol for the Examination of Specimens From Patients With Neuroendocrine Tumors (Carcinoid Tumors) of the Colon and Rectum
Version: ColonRectumNET 4.0.0.1 Protocol Posting Date: June 2017.



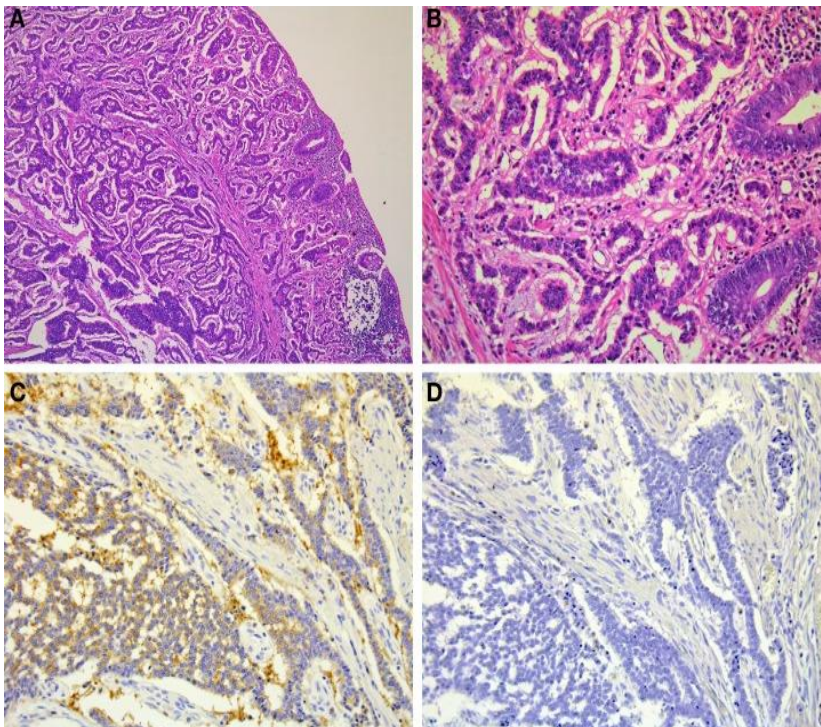
Rectal Neuroendocrine Tumour (NET)



Solitary sessile mass with slight ulceration

Printed with permission: Hirabayashi K, et al. Frontiers in Oncology 2013; 3: 2.

Colonic Neuroendocrine Tumour



- Microscopic findings of rectal NET. This rectal NET shows a trabecular proliferating pattern
 - A: low power view
 - B: high power view
 - C: Immunohistochemically, tumour cells of rectal NET are positive for synaptophysin
 - D: L cell NETS (typically occurring in the rectum) are negative for chromogranin A

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Neuroendocrine Carcinoma (NEC)

These are high grade malignant tumours, morphologically similar to small cell and large cell neuroendocrine carcinomas of the lung

Staging of NETs and NECs is via a site specific TNM system

MINENS

- Mixed neuroendocrine-non-neuroendocrine neoplasms are epithelial neoplasms comprising at least 30% each of a neuroendocrine component and a non neuroendocrine component, each morphologically and immunohistochemically recognizable as a discrete component.

Neuroendocrine Lesions of the Appendix

- NETs and NECs follow the same rules as the rest of the GIT.
- Goblet cell adenocarcinoma was redefined in the 2019 WHO classification of digestive system tumours. It is a malignant neoplasm, specific to the appendix. It is an amphicrine tumour composed of goblet-like mucinous cells, with some endocrine and Paneth-like cells, infiltrating the appendiceal wall.
- Prognosis depends on grade (1-3) and TNM stage.
- Common metastatic sites include peritoneum, omentum, abdominal wall, ovaries.

SUBMUCOSAL LESIONS

Colitis Cystica Profunda (CCP)

➤ Definition

- “..... dilated, mucus filled glands in the submucosa that can [protrude through the mucosa to] form solitary or multiple polyps” (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 2176).

➤ Endoscopy

- Mucus-filled cyst(s)
 - Usually on anterior wall of rectum
 - Usually about 6 cm from anal verge
- Filling defects limited to colon
- Multiple
- Round
- Mucosal / submucosal
- Filled with mucin
- May sometimes resemble a large villous adenoma / carcinoma

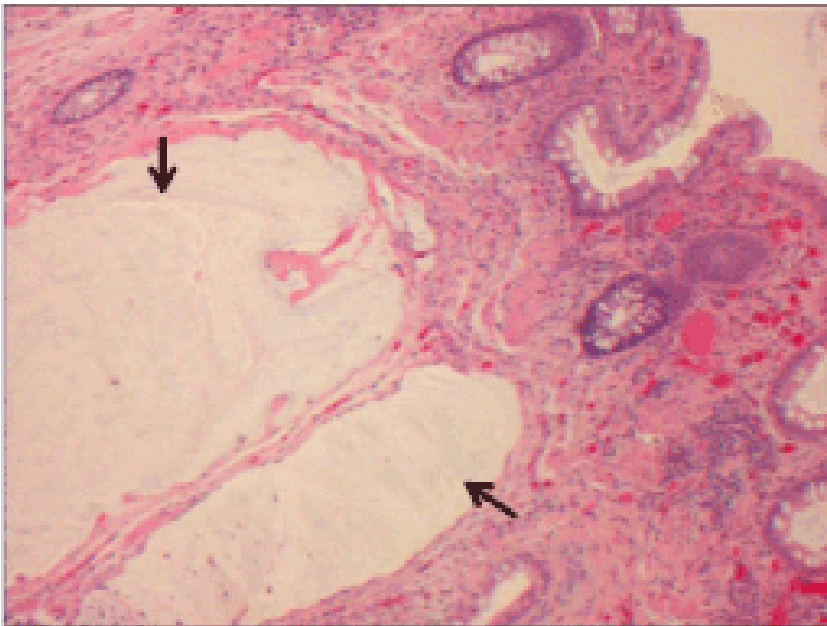


Colitis Cystica Profunda



Source: Bismar MM et al (2017). A case of colitis cystica profunda in a patient with diverticulosis. Clin Case Rep Rev 3: doi: 10.15761/CCRR.1000313

➤ Histopathology



Submucosal mucin filled cysts (arrows) lined by bland epithelial cells (occasionally lacking associated epithelia) surrounded by a fibrous stroma.

Source: Bismar MM et al (2017). A case of colitis cystica profunda in a patient with diverticulosis. Clin Case Rep Rev 3: doi: 10.15761/CCRR.1000313.



Pneumatosis Cystoides Intestinalis (PCI)

➤ Definition

- Gas-filled cysts in the wall of the bowel, thought to arise from idiopathic $\uparrow$ H₂ in the bowel lumen
- “..... multiple gas-filled cysts located in the submucosa and subserosa of the intestine” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 2248).
- Mostly in small intestine
- Note
 - When PCI involves only the colon (only 5% of all PCIs), then it is called **pneumatosis coli**

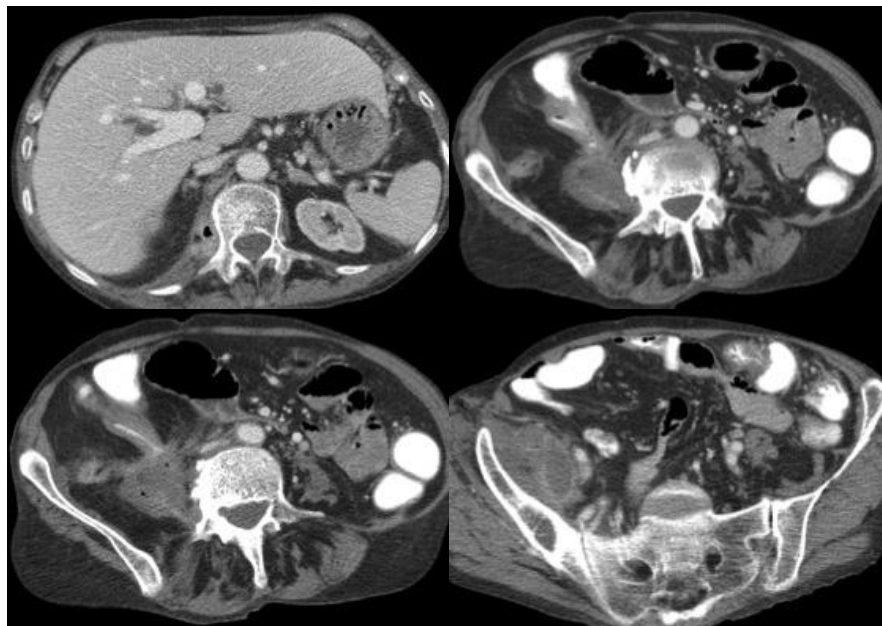
➤ Types

	Pneumatosis Cystoides Intestinalis (PCI)	Pneumatosis Linearis
○ Age of patient	– Adult	▪ May be a child
○ Predisposition	– COPD – Scleroderma	▪ Severe colitis (e.g., NEC)
○ Pathogenesis	– Diffusion of gas in bowel lumen into cyst	▪ Complication of severe mucosal inflammation by gas forming bacteria

Abbreviations: COPD, chronic obstructive pulmonary disease; NEC, necrotizing enterocolitis

➤ Diagnostic imaging

Pneumatosis Coli

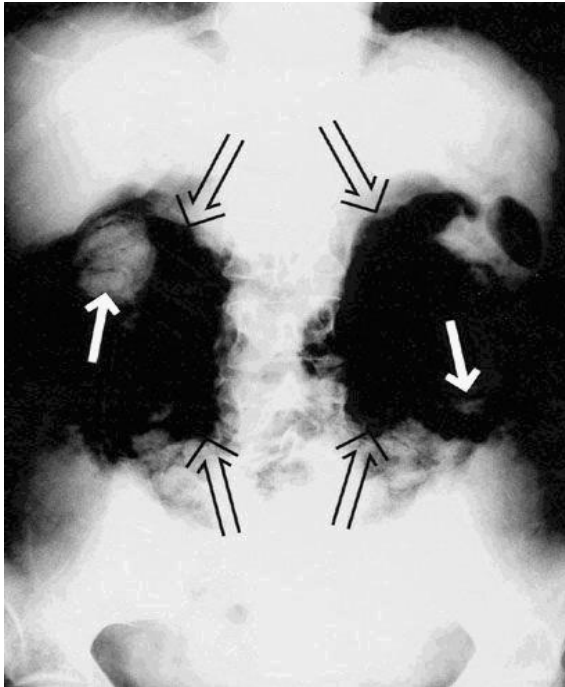


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Pneumatosis Cystoides Intestinalis



- Plain abdominal roentgenogram following admission
 - Extensive pericolic gas accumulation (open arrows) surrounding the ascending and transverse colon (closed arrows).

Printed with permission: Zülke C, et al. Bone Marrow Transplantation 2002; 29, 795-798.

➤ Endoscopy

Pneumatosis Cystoides



Multiple polypoid protrusions

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➤ Histopathology

- Thin walled “cystic” spaces lined by macrophages and giant cells, unilocular, or in clusters
- Do not communicate with lumen of bowel



COLORECTAL CANCER (CRC)

➤ Demography

- The age-standardized incidence of CRC (colorectal cancer) in Canada is approximately 25/10⁵ persons per year (26.9 for men, 21.3 in women) which means about 6% of the population will develop CRC in their lifetime.
- Half CRCs are distal to the splenic flexure, but the proportion of right-sided tumours may be increasing.
- Useful comparison: Approximate incidence of GI cancers (10⁵/year)

Years of Age	<49	50-74	>75
Esophagus	<1	12	28
Stomach	<1	22	78
Colon	<1	150	400

Source: Canadian Cancer Surveillance, Health Canada, 2018

- Average age of CRC diagnosis in syndrome / genetically based CRC
 - FAP ▪ 39 years of age
 - HNPCC ▪ 44 years of age

Funding Alert: The Billion Dollar cost of reducing death from CRC

➤ Colorectal Cancer (CRC)

- Lifetime risk of CRC 6%
- Lifetime risk of dying from CRC
 - Screening / surveillance
 - No 2.5%
 - Yes 1.6%
- Annual CRC mortality
 - Risk reduction
 - Absolute ~ **0.9%**
 - Relative ~36%
- Conversion rate (CR) to CRC
 - Adenoma, 30%
 - Villous, 17%
 - Dysplasia, 37%
- Synchronous CRC ~5%
- Metachronous CRC ~5%

➤ The Dilemma

- CRC screening results in
 - Relatively small risk of CRC mortality, with no reduction in all cause mortality
 - The quality of the data to date for evidence of benefit of CRC screening has been challenged in some constituencies.



➤ Diagnostic imaging

- Barium study
 - Mass
 - Annular mass may resemble a “napkin ring” or an “apple core”
 - Lobulated mass
 - Edge of mass may suddenly stop or produce a “shoulder”
 - May narrow (obstruct) colon
 - Signs of colitis proximal to obstructing CRC mass
 - If ileocecal valve does not open to relieve pressure of obstruction, venous outflow may fall and there may be associated ischemic changes usually < 6 cm in size
 - CT
 - Perforation
 - Fluid
 - Soft tissue mass
 - Extraluminal air
- Give the radiologic differentiation between colorectal cancer and diverticulitis.

	Diverticulitis	Cancer
○ Segment length	- Long	▪ Short
○ Mucosa	- Intact	▪ Destroyed
○ Contour	- Bizarre, “picket fence”	▪ Irregular, nodular
○ Bowel spasm	- Present	▪ Absent
○ Presence of diverticula in remainder of colon	- Usual	▪ Sometimes
○ Appearance of ends of deformity	- Tapered or cone	▪ Sudden, shelf-like, transition



Colonic Stricture, Air Contrast Barium Enema



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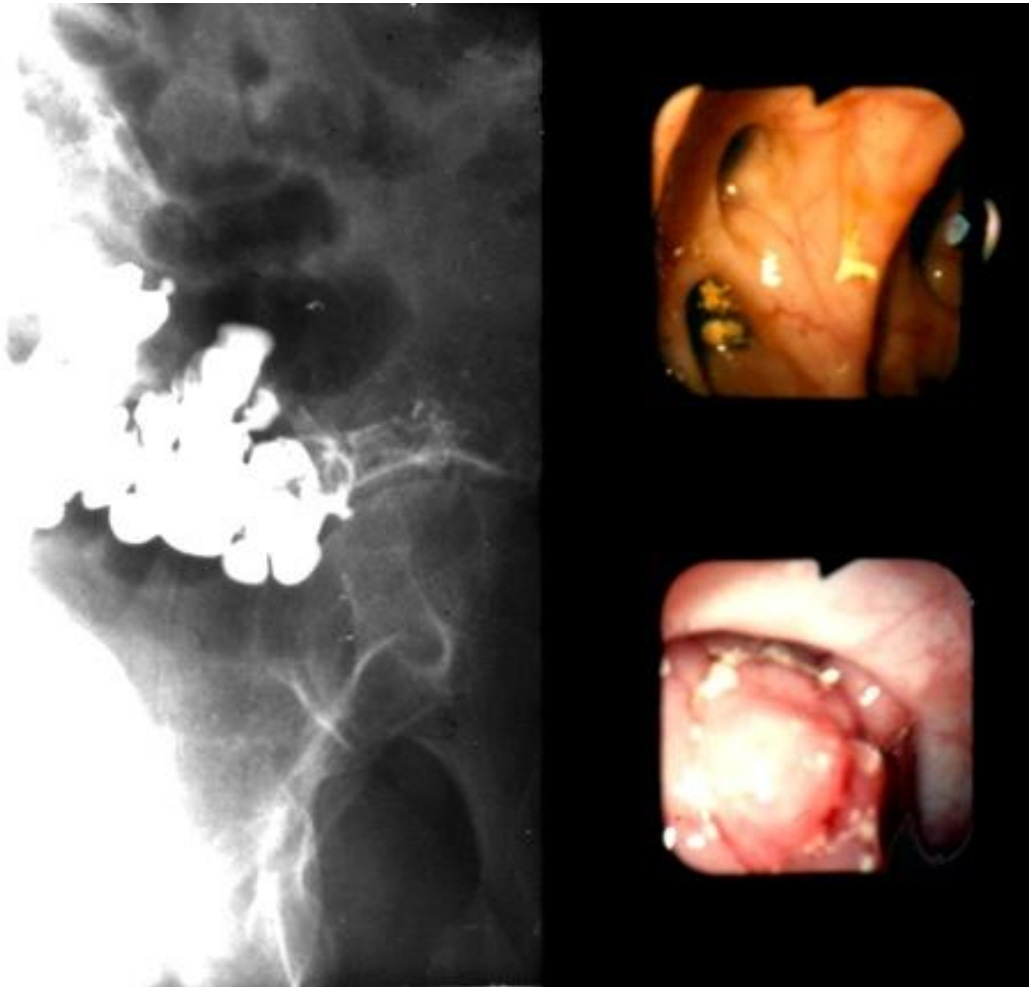
Colonic Filling Defect, Air Contrast Barium Enema



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Colorectal Cancer, air contrast barium enema (L), and colonoscopy (R)



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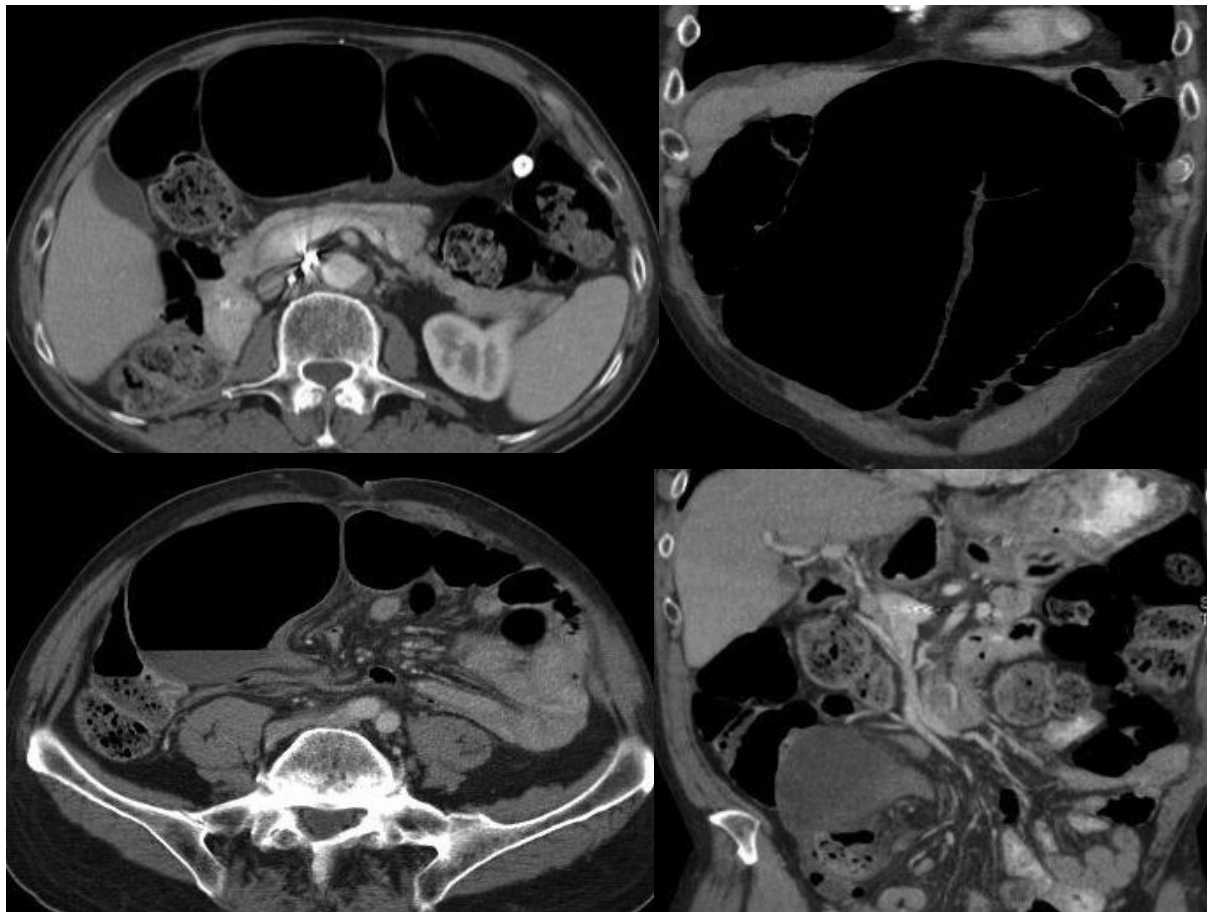
- CT colonography (CTC)
 - Mass
 - Mass may have irregular surface
 - Obstruction
 - Fold (haustral) thickening
 - Wall
 - Thickening
 - Circumferential wall thickening and perirectal fat stranding?
 - Caution rectal cancer may look like a region of normal collapse of the colonic wall
 - Intussusception
 - Shortened colon
 - Sausage-shaped filling defect
 - Proximal end of filling defect looks like “coiled spring”

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- Detecting CRC recurrence
 - Local
 - Barium enema / CTC
 - Lumen
 - Mass
 - Lumen: eccentric narrowing
 - Widened presacral space, with fuzzy margins
 - Lymphadenopathy
 - Extraluminal / distant
 - CT
 - Retroperitoneum
 - Liver
 - Lung

CT Scan: Perforated Carcinoma, Transverse Colon



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Colorectal Cancer, Air Contrast Barium Enema



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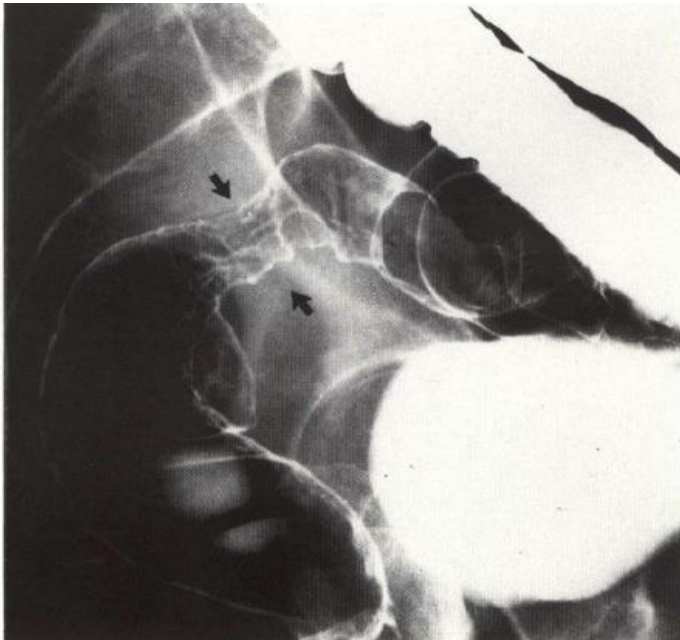
Double Contrast Barium Enema, localized area of colonic lumen, suggestive of "apple-core" colon cancer



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Metastasis to Colon, air contrast barium enema



- Inability to advance sigmoidoscope
- Narrowing of rectosigmoid area on double-contrast barium enema
- Intact mucosal pattern, suggestive of extrinsic lesion

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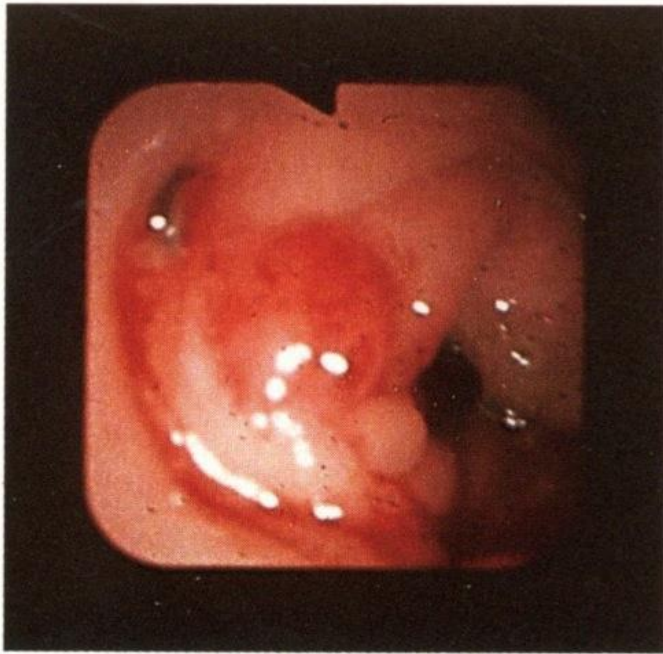
Post-Surgical Filling Defect: Recurrent Carcinoma at Colonic Anastomosis, air contrast barium enema



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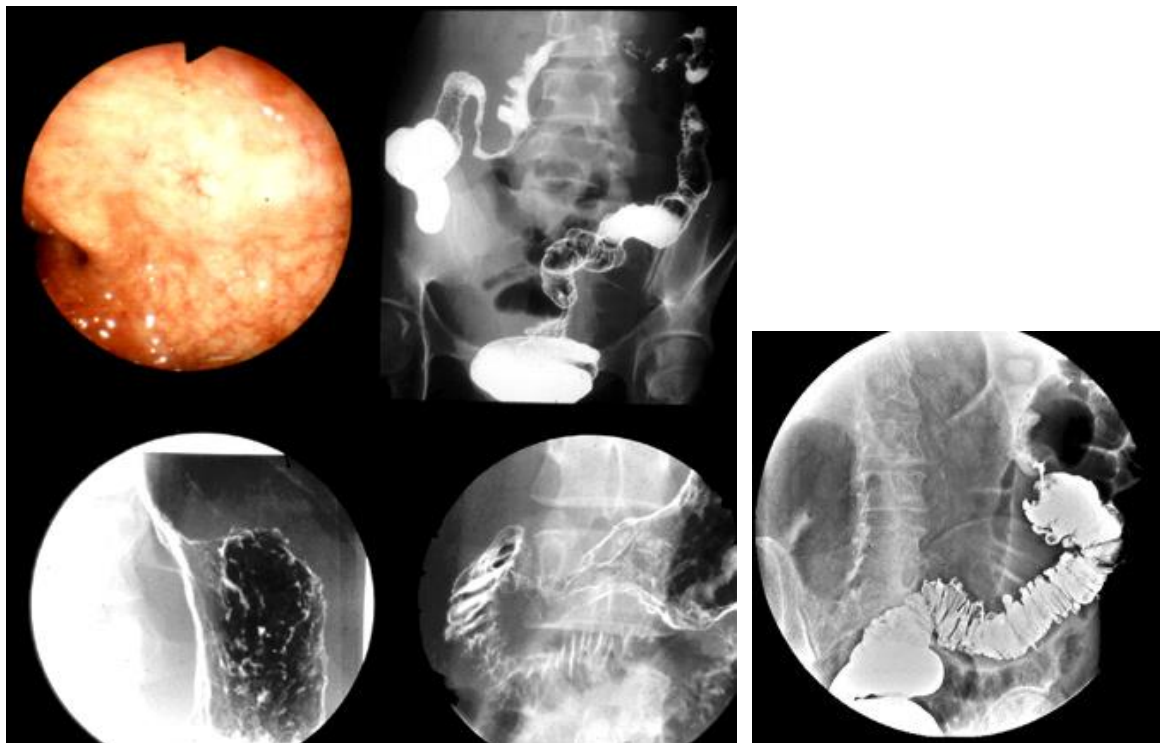


Recurrent Carcinoma at Site of Colonic Resection



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Colorectal Cancer



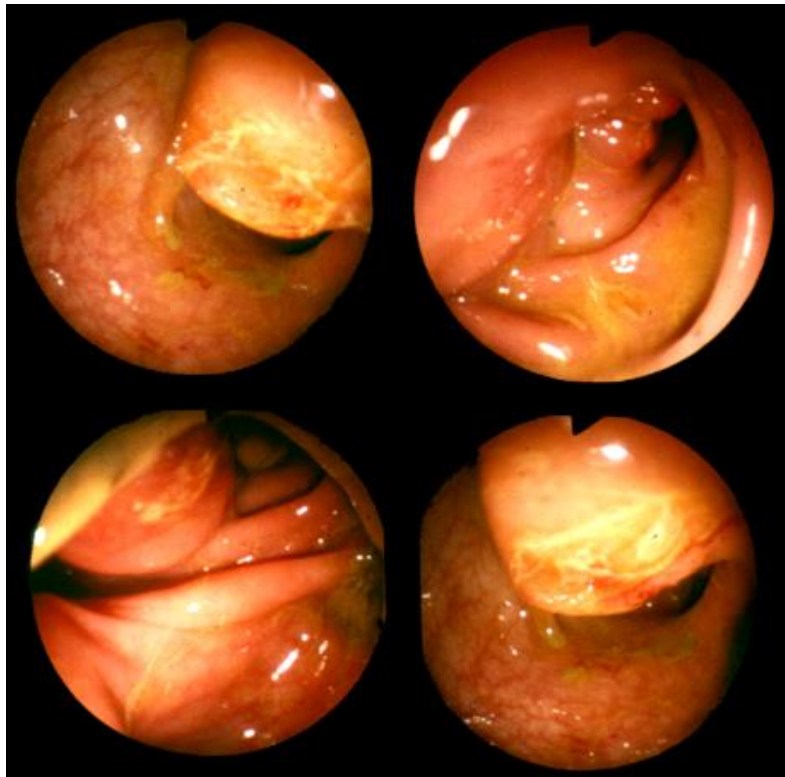
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➤ Endoscopy

- Give the endoscopic techniques or technical improvements which enhance the colonoscopic sensitivity for CRC screening (**quality improvement**).
 - Improve performance skills of colonoscopist
 - Documented intubation of cecum > 90%
 - Withdrawal time > 7 min
 - Personal detection rate of adenomatous polyps on screening colonoscopy of average risk persons > 50 years of age
 - Males 25%
 - Females 15%
 - Bowel cleansing
 - Insertion
 - Cap-fitted colonoscopy
 - Overtubes
 - Imaging
 - Wide-angle colonoscopy
 - Narrow-band imaging
 - Chromoendoscopy
 - Confocal laser microscopy

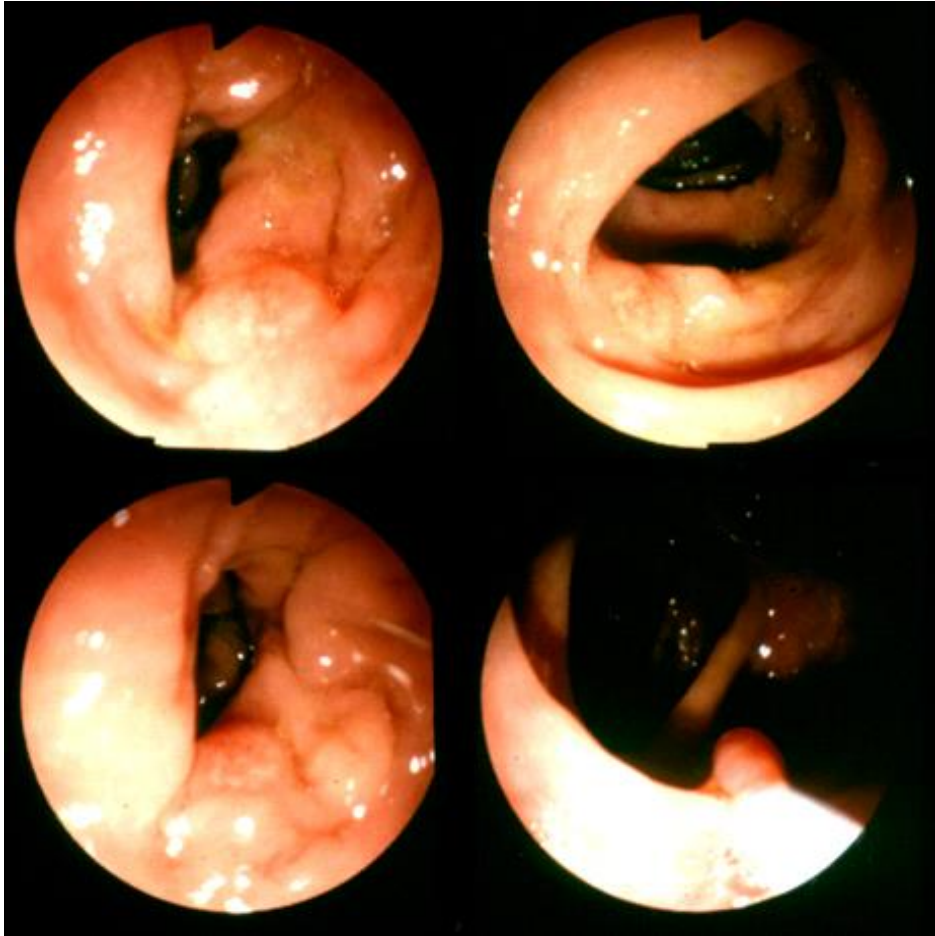
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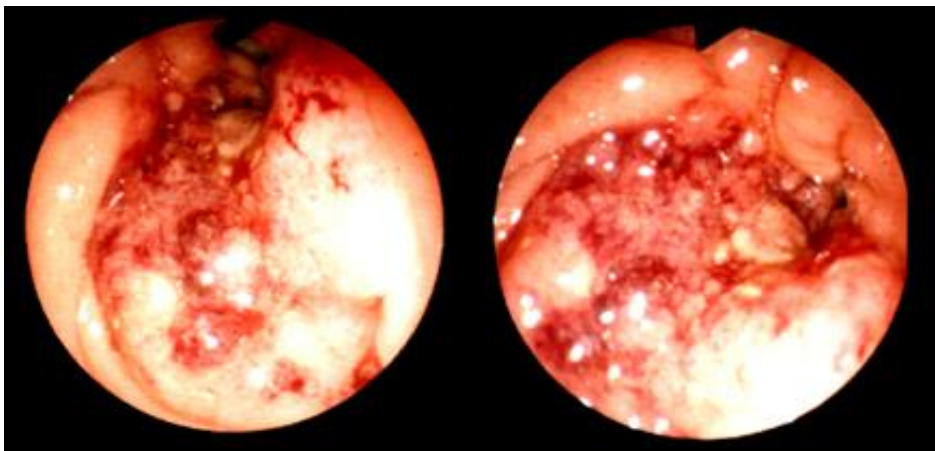


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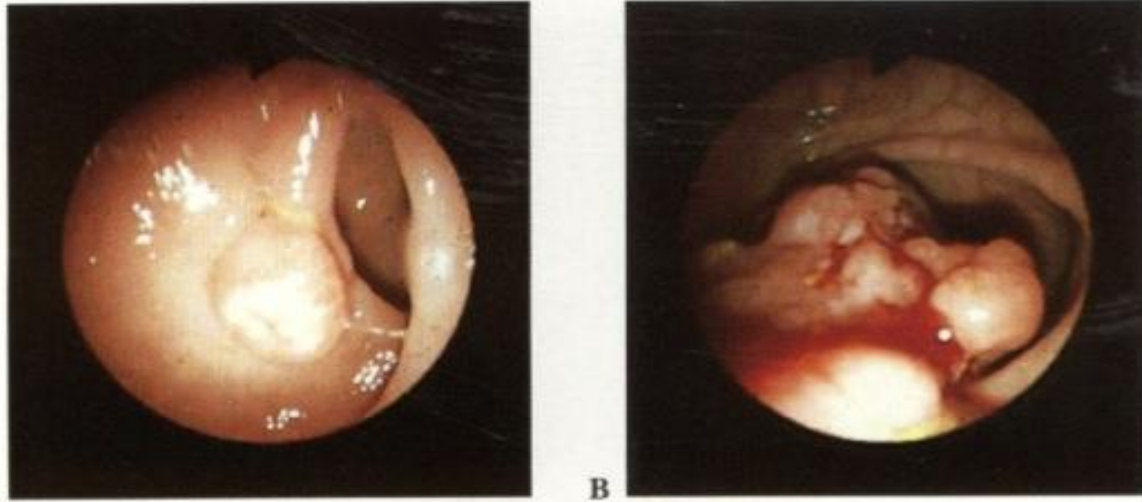
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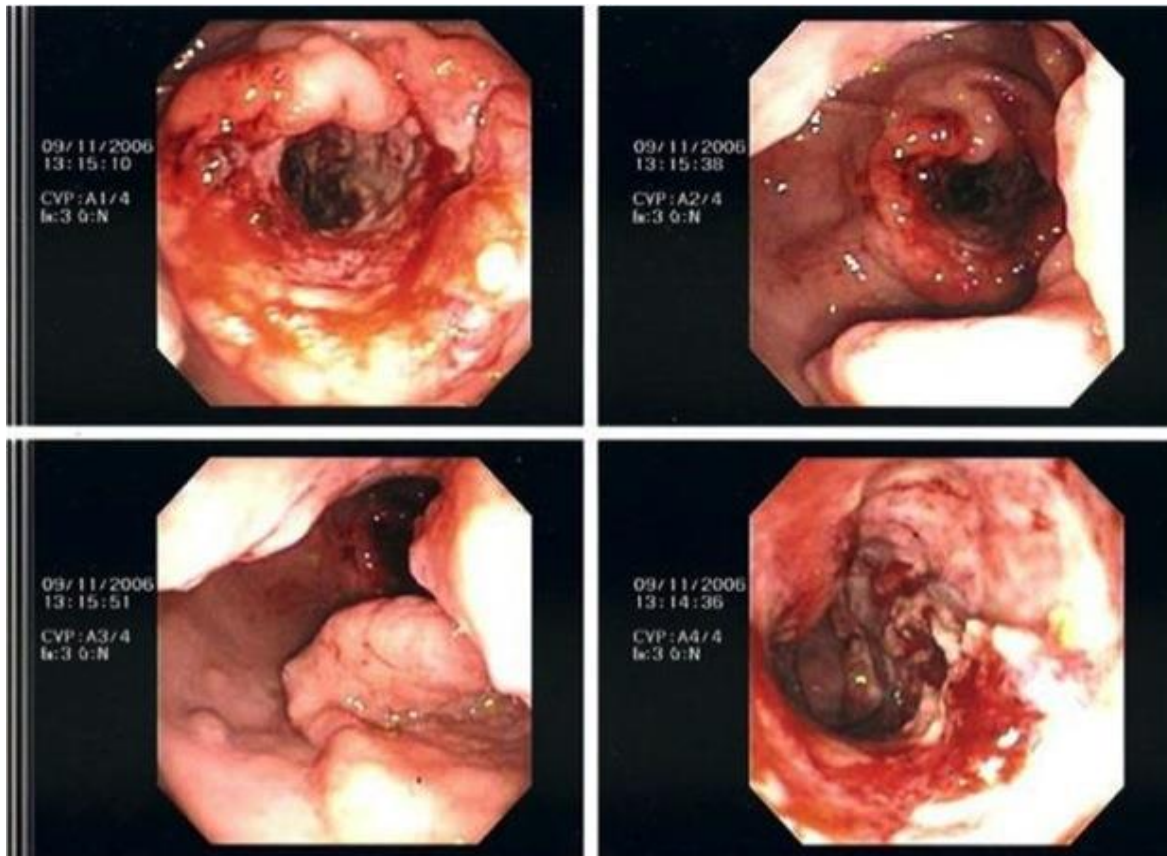


Colorectal Cancer



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Colonic Adenomatous Polyp on Stalk



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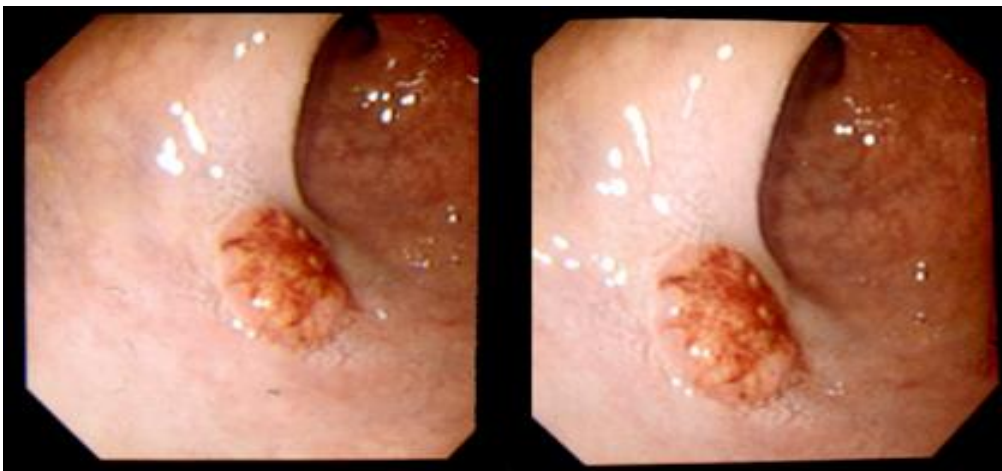


Colonic Lipoma and Leiomyoma



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Colonic Polyp Resection



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Endoscopic ultrasonography (EUS)

- Inner echogenic changes
 - Balloon mucosa
- Hypoechoic (HE)
 - Muscularis mucosae
- Middle E
 - Submucosa
- HE
 - Muscularis propria (MP)
- Outer E
 - Perirectal fat
 - Staging accuracy ~ 90%
 - Sensitive to find recurrent tumour near resection anastomosis
 - Sensitive to distinguish between metastatic inflammatory nodes

➤ Pathology

- The overwhelming majority of colorectal cancers are adenocarcinomas.
- These are graded as well / moderately / poorly differentiated according to the amount of gland formation, and staged according to the TNM system.
- In addition to grade and stage, important prognostic indicators include:
 - Lymphovascular space invasion (small vessels) and intra/extramural venous invasion
 - Perineural invasion
 - High grade tumour budding at the advancing edge of the tumour
- Sometimes, invasive adenocarcinoma is identified unexpectedly in a polypectomy.
 - The presence of a large invasive component (accepted measurements vary between studies but width >4 mm and depth >1-2 mm are considered “high risk”), lymphovascular space invasion, high grade tumour budding or poorly differentiated tumour component increase the risk of lymph node metastases and consideration of surgical resection with lymph nodes is warranted in these cases.
- Large polyps, usually those in the sigmoid / cecum can twist on their stalks causing artefactual misplacement of epithelium into the submucosa / stalk.
 - This is often associated with mucin extravasation or stromal hemosiderin, allowing its recognition as epithelial misplacement / “pseudoinvasion” rather than malignancy.



ENDOMETRIOSIS

➤ Definition

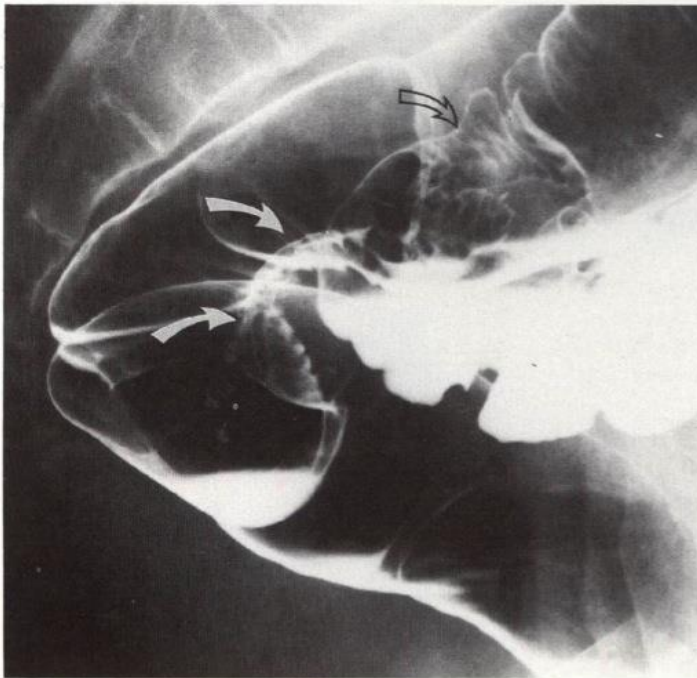
- o "... the presence of endometrial tissue outside the uterine cavity and musculature (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 2253).

➤ Demography (occurrence in women)

- o Menstruating, 15%
- o Infertile, 30%

➤ Diagnostic imaging

Endometriosis of Colon



Long linear indentations of colonic mucosa.

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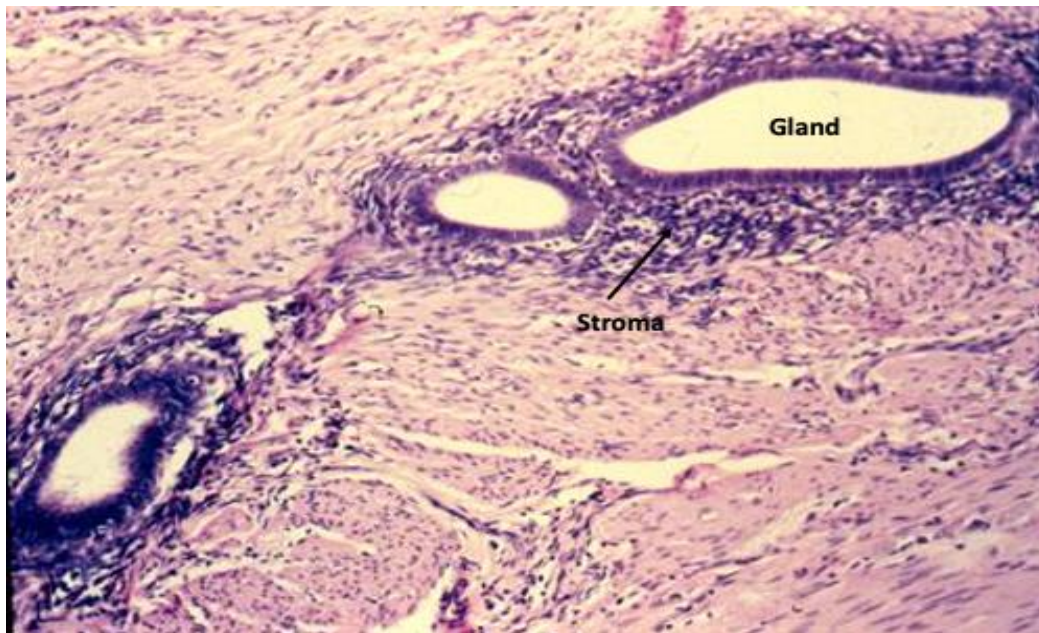
➤ Endoscopy

- o Site
 - Rectosigmoid (96%)
 - Appendix (10%)
 - Ileum (5%)
- o Colonoscopy
 - Compression by endometrial mass
 - Strictures (submucosal mass or partial narrowing, with intact mucosa)
 - Mucosa rarely abnormal → hematochezia



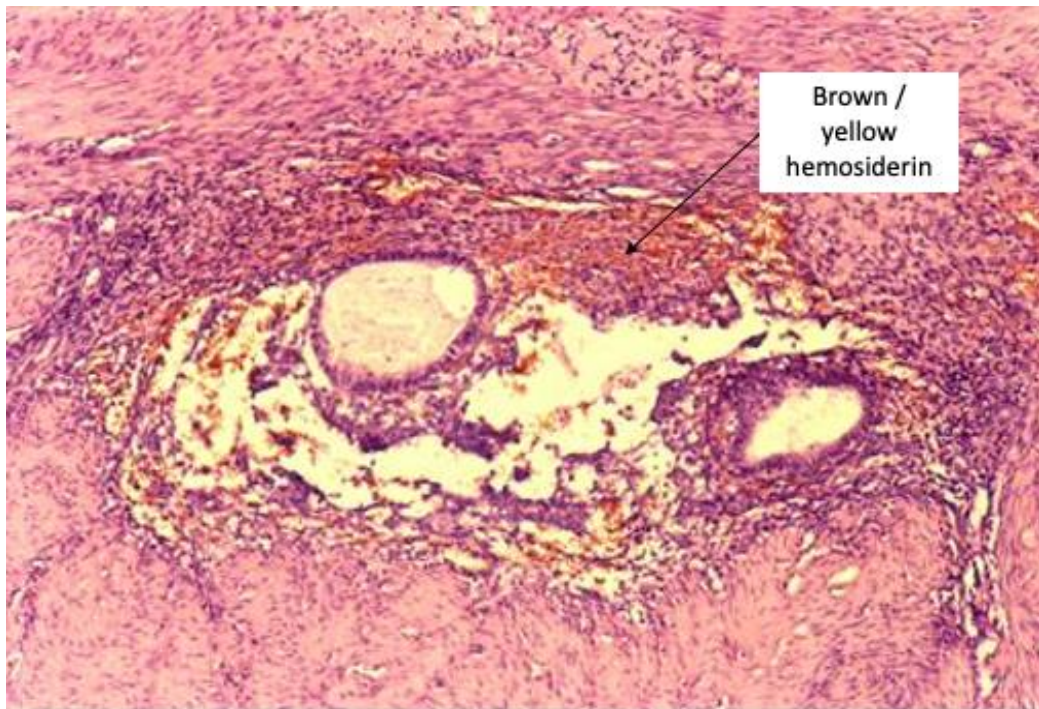
➤ Histopathology

Endometriosis of Colon – endometrial glands with surrounding endometrial stroma



Courtesy of Professor Guito Tytgat, Netherlands

Endometriosis of Colon – old hemorrhage present within the endometrial stroma



Courtesy of Professor Guito Tytgat, Netherlands



COLONIC OBSTRUCTION

➤ Mechanical Obstruction

- Distention to level of obstruction
- No distal contents of
 - Air
 - Fluid
 - Stool
- Ileum
 - Gaseous distention if ileocecal valve is open
- Causes of acute obstruction
 - Carcinoma
 - Diverticulitis
 - Extramural compression (metastases, other)
 - Impaction
 - Hernia
 - Adhesion
- Chronic obstruction
 - Haustra thickened
 - Luminal contents “grey, “granular”-appearing fluid
- Causes of large bowel obstruction (LBO)
 - CRC, 50%
 - Volvulus 10% - 15% (sigmoid, 75%; cecum, ~25%)
 - Diverticular disease, benign strictures 10%

➤ Diagnostic imaging

- Abdominal x-ray
 - Small intestine: megaduodenum, obstruction, diverticulosis



Colonic Obstruction, air contrast barium enema



- Marked distension usually of both large and small bowel with air-fluid levels throughout the abdomen
- Massive duodenal dilatation with abnormal motility
- Hypomotility or disorganized ineffective peristaltic activity
- Extensive dilution of contrast material
- Occasional abnormalities of the fold pattern depending on the underlying cause

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Colonic Obstruction, air contrast barium enema



- Dilation of cecum, ascending and transverse colon (70–90%)
- Paucity of gas in the left colon
- Preservation of haustral markings (vs mechanical obstruction)

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Colonic Obstruction, abdominal plain film



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Polypoid Tumour Intussusception (colon air contrast barium enema)



- Retrograde flow of barium and air
 - Lack of proximal gas suggests this is not an anterograde obstruction

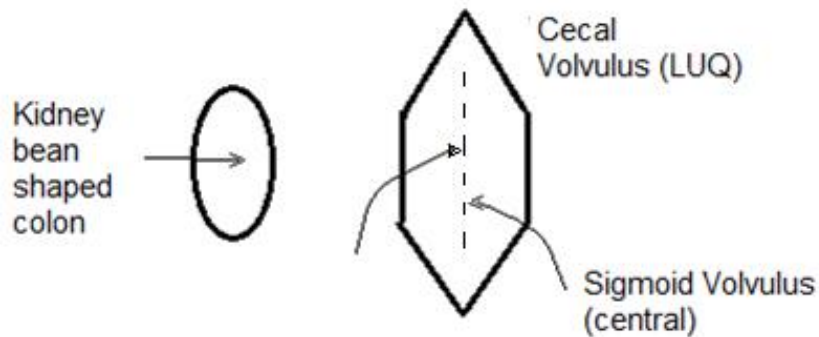
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Volvulus of the Colon

➤ Sites

- Sigmoid colon
 - On diagnostic imaging
 - Distention of sigmoid colon
 - No haustra
 - Apex points to right shoulder



- Torsion 180° to 360° clockwise or counter-clockwise orientation (50:50)
- Cecal volvulus
 - Less common (22%, vs sigmoid volvulus 75%)
 - More frequently is complicated by ischemia (large diameter [large radius, R], high wall tension [T] [Laplace law, $T = PR$], so the bowel becomes ischemic because of ↓ capillary perfusion.
 - On diagnostic imaging
 - Distention of cecum into the epigastric area or left upper quadrant
 - “bean-shaped”
 - Collapse of colon distal to cecum
 - Small bowel obstruction, single air-fluid level
 - Cecum in LUQ
 - Coffee-bean appearance
 - Dilated small bowel



➤ Diagnostic imaging

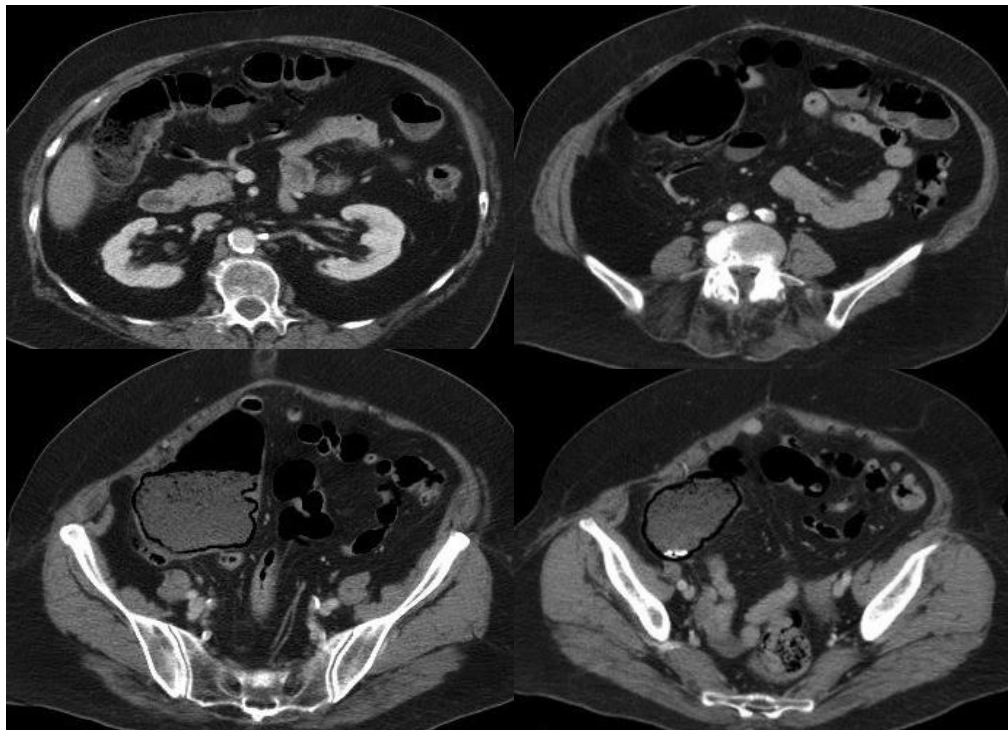
CT Scan: Sigmoid Volvulus



- A typical sigmoid volvulus (SV) in a 51-year-old woman. Coronal CT slice showing a typical SV
- Severity signs
 - Dilated loop (*)
 - Rectum filled with contrast enema (+)
 - Fully infiltrated mesosigmoid (arrowhead, which can be compared with normal mesentery [double arrowhead]).

Printed with permission: Vandendries C, et al.
British Journal of Radiology 2010; 83(995): 983-90.

CT Scan: Sigmoid Volvulus

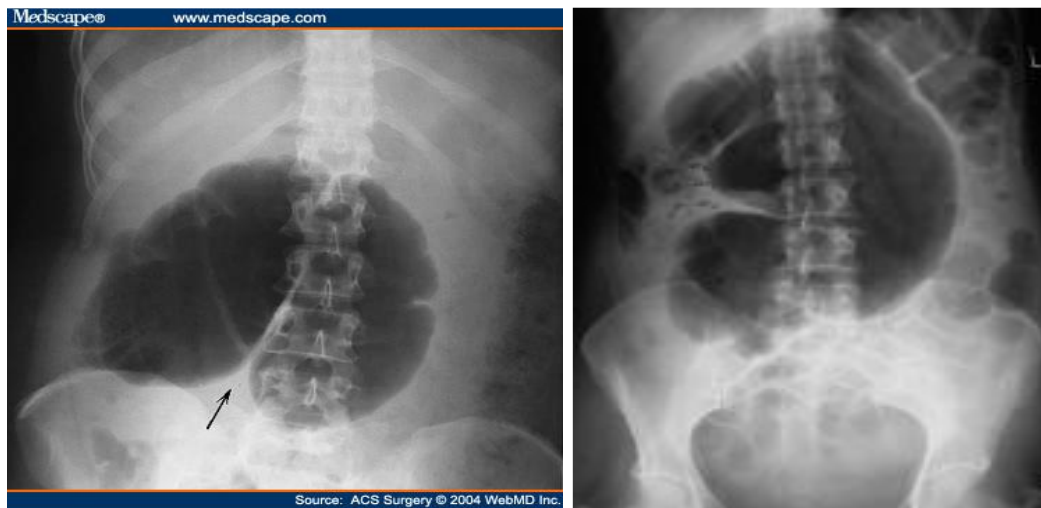


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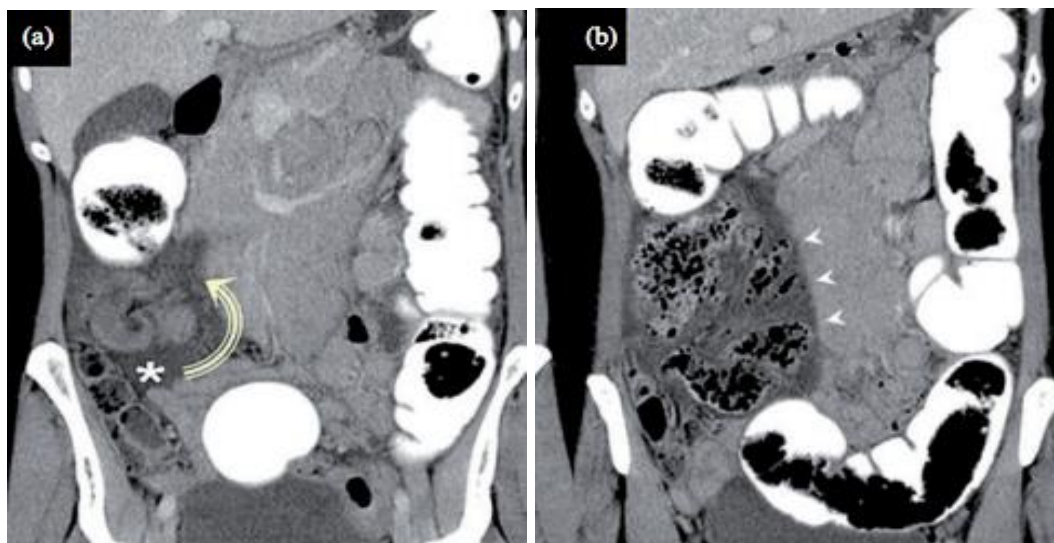


Cecal Volvulus



- Kidney bean sign

Cecal Volvulus



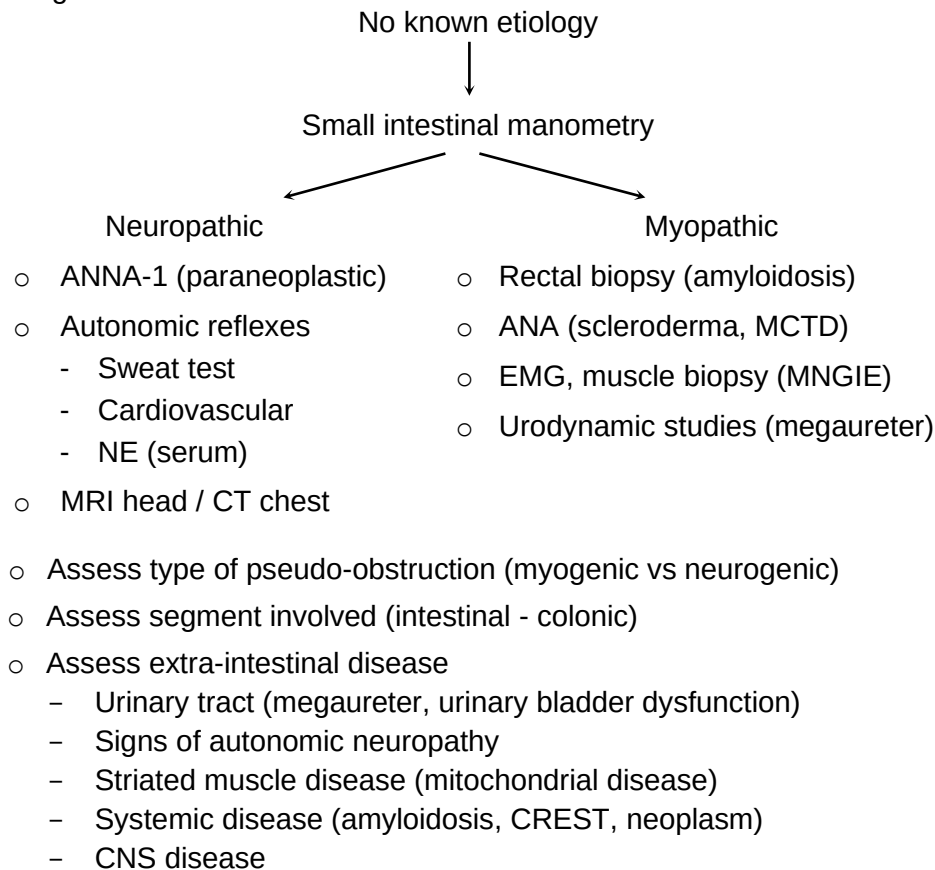
- An axial-type volvulus of the cecum in a 56-year-old woman who presented with signs of shock on admission (a,b).
- Coronal CT slices at the fulcrum point demonstrate a tight whirl sign (anteroposterior axis).
 - The cecum remains in the lower part of the abdomen, on the right side.
 - The ileo-cecal region is not involved. There is no free air in the abdominal cavity
 - Severity signs is significant thickening of the cecal wall (white arrowheads) that shows no enhancement and ascites (*) are present.
- A cecal perforation was present at laparotomy.

Printed with permission: Vandendries C, et al. Brit J Radiol 2010; 83(995): 983-990.



COLONIC PSEUDO-OBSTRUCTION

➤ Diagnostic evaluation



Acute Colonic Pseudo-Obstruction (ACPO; aka Ogilvie syndrome)

➤ Demography

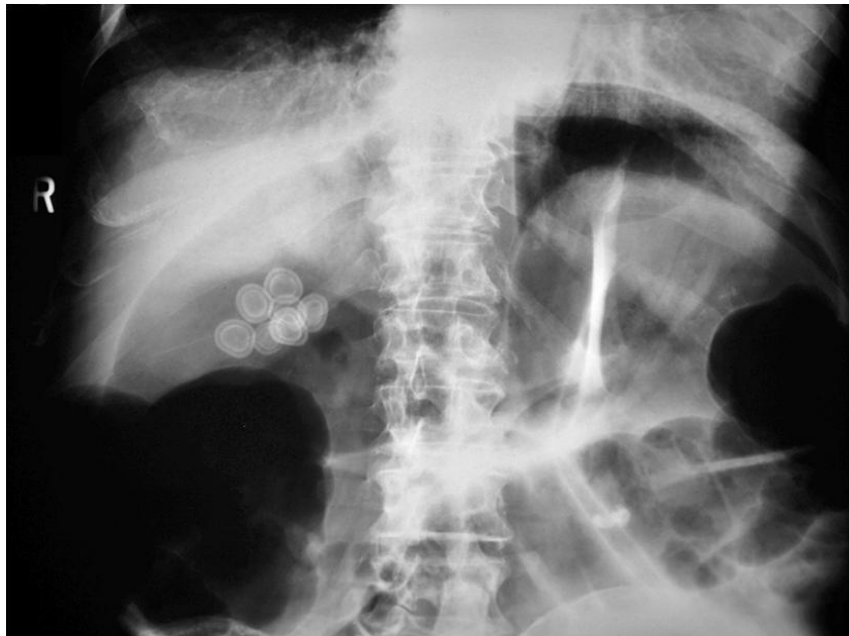
- ↑ age
- Males
- ↑ BMI

➤ Diagnostic Imaging

- Plain abdominal films
 - Sensitivity of plain abdominal films for SBO is poor, only about 75% (this means that you miss the diagnosis of SBO in 25%!)
 - It may be difficult to distinguish small bowel obstruction (SBO) from colonic obstruction (CO).



Acute Colonic Pseudo-Obstruction, abdominal plain film

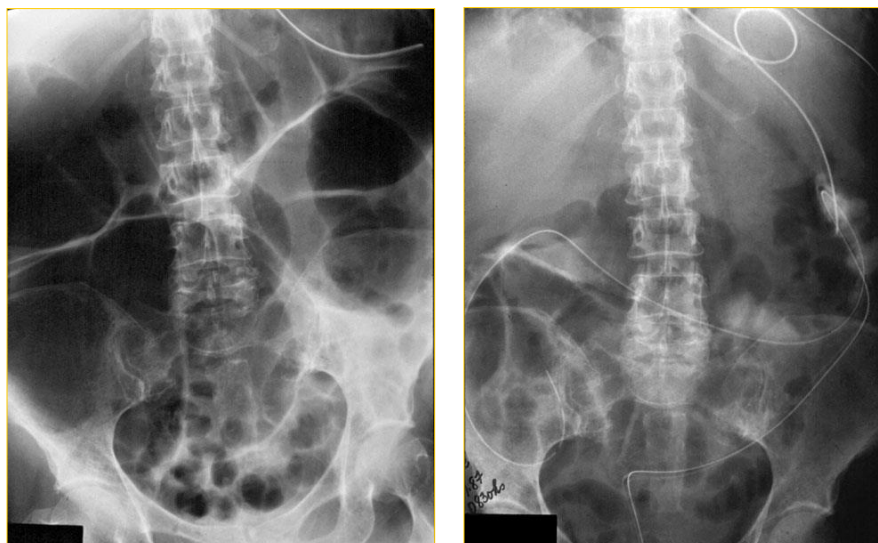


- Dilated colon, rectal involvement
- Incidental gallstones

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	SBO	CO
○ Air in the rectum	Yes	No
○ Dilation of both small and large intestinal		Yes (if ileocecal valve is incompetent)

Acute Colonic Pseudo-Obstruction, abdominal plain film



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Acute Colonic Pseudo-Obstruction



Abdominal plain film

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Acute Colonic Pseudo-Obstruction of Colon

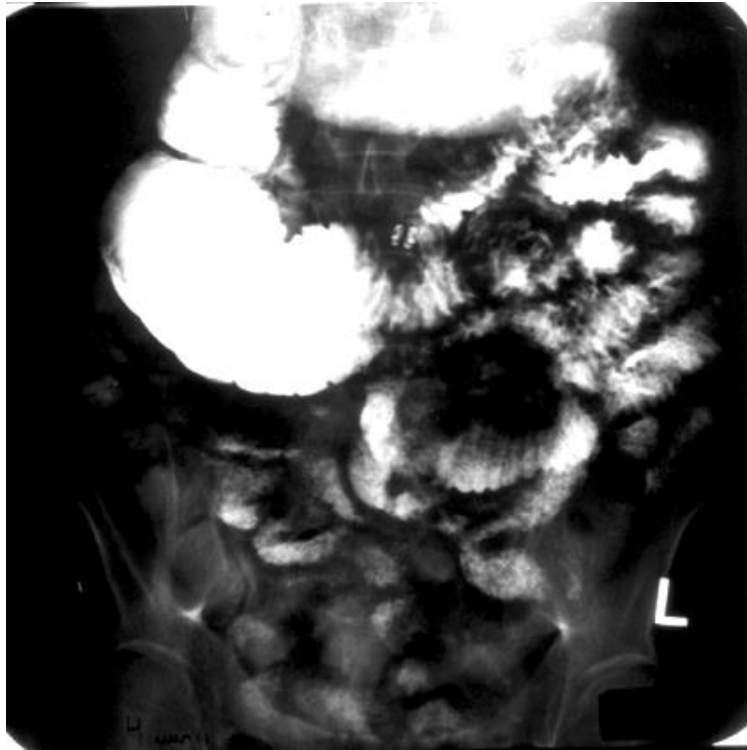


Abdominal plain film

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Colonic-Pseudo-Obstruction, air contrast barium enema



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➤ Pathology

- Predereentially affects cecum > AC > TC
- Presence of pain may herald ischemia / perforation
- Risk of perforation
 - < 12 cm, 2%
 - 12-14 cm, 7%
 - > 14 cm, 23%

Abbreviations: AC, ascending colon; TC, transverse colon

➤ Differential Diagnosis

- Mechanical obstruction
 - More pronounced abdominal pain
 - Often constipation, less common diarrhea
 - Rarely chronic or intermittent



Chronic Intestinal Pseudo-Obstruction (CIPO)

➤ Definition

- Acute, recurrent or chronic symptoms suggestive of obstruction of small or large intestine without any radiological, surgical or endoscopic evidence of mechanical obstruction
- Disordered GI motility
 - Muscle - ICC – neuron

➤ Causes / associations

Type	Myopathic	Neuropathic
○ Idiopathic	– Non-familial hollow visceral myopathy	▪ Hirschsprung disease ▪ Chronic idiopathic intestinal pseudo-obstruction ▪ Neurofibromatosis ▪ Myenteric ganglionitis
○ Infiltrative	– Scleroderma – Amyloidosis – Paraneoplastic visceral neuropathies	▪ Early scleroderma ▪ Amyloidosis
○ Neurologic Disease	– Myotonic and other dystrophies, mitochondrial myopathy (MNGIE) – Parkinson disease – Spinal cord injury ▪ Spinal cord injury → “spinal shock” → paralytic ileus → 40% have persistent constipation ▪ Constipation is due to – ↓ postprandial response in descending colon – ↓ resting anal pressure	▪ Diabetes ▪ Porphyria ▪ Brain stem tumour ▪ Multiple sclerosis (MS) ▪ Spinal cord transection ▪ Dysautonomias (Shy Drager)
○ Neoplastic		▪ Paraneoplastic (small cell lung tumour), mammary cancer, pancreas cancer
○ Endocrine	– Hypothyroidism – Diabetes – Hypoparathyroidism – Pheochromocytoma (MEN IIB)	
○ Drug-induced		▪ Anti-depressants ▪ Analgesics (narcotics) ▪ Anti-cholinergics ▪ Laxative abuse ▪ Smooth muscle relaxants ▪ Vincristine



Type	Myopathic	Neuropathic
○ Infectious		▪ Chaga disease, viral (CMV, EBV, HSV) infection
○ Familial	– Familial visceral myopathies	▪ Familial visceral neuropathies ▪ von Recklinghausen disease
○ Rheumatological (MSK) conditions		
– Amyloidosis		
– Sclerodermaq4q4q		
– Dermatomyositis		
– Polymyositis		
– SLE (systemic lupus erythematosus)		
○ Muscle		
– Myotonic dystrophy		
– Duchenne muscular dystrophy		
○ Gastrointestinal		
– Celiac disease		
– Jejunal diverticulosis		
– Radiation damage		
– Enteric		
▪ Neuropathies		
▪ Myopathies		

➤ Diagnostic imaging

Chronic intestinal pseudo-obstruction



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Chronic intestinal pseudo-obstruction



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➤ Histopathology

- Give the histopathology of the colon in persons with chronic intestinal pseudo-obstruction associated with small cell carcinoma of the lung.
 - Visceral neuropathy of the myenteric plexus (esophagus-stomach-bowel)
 - Neuron and axon degeneration
 - May be mild lymphoplasmacytic infiltration
 - Glial cell proliferation
 - Smaller number of neurons sometimes

“Try to be a rainbow in someone's cloud.”

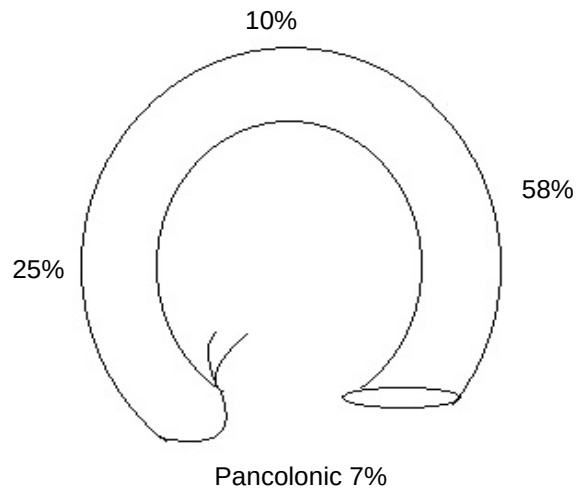
Maya Angelou



VASCULAR DISORDERS

Ischemic Colitis

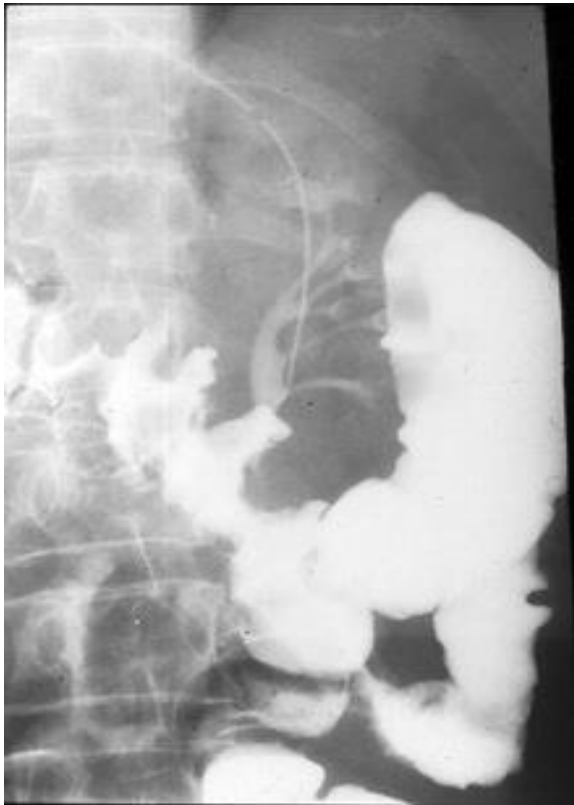
- Definition
 - o “..... the condition that results when blood flow to the colon is reduced to a level insufficient to maintain [colonic] cellular metabolic function”
- Demography
 - o Incidence $16/10^5$
 - o Women > men
 - o Mortality rate ~ 10%
 - o Site of ischemic colitis
 - Often occurs at “watershed” area of splenic flexure



- Diagnostic Imaging
 - o Abdominal radiograph
 - Dilation of colon
 - Thick wall
 - Edema
 - “thumb printing” (pseudotumours)
 - Pneumatosis coli (circumferential intramural air)
 - Venous gas in portomesenteric system (36%)

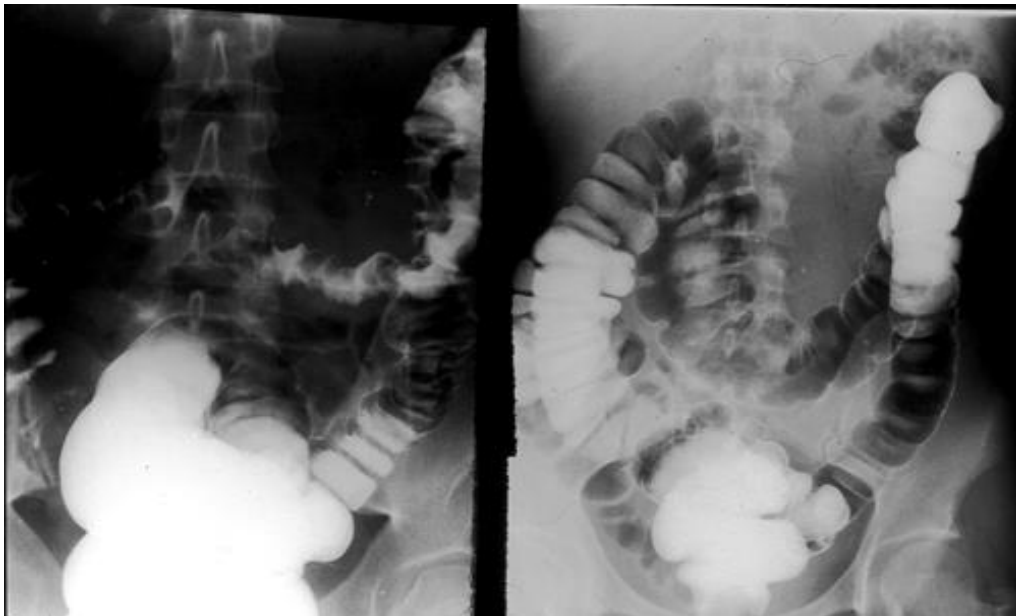


Ischemic Colitis, air contrast barium enema



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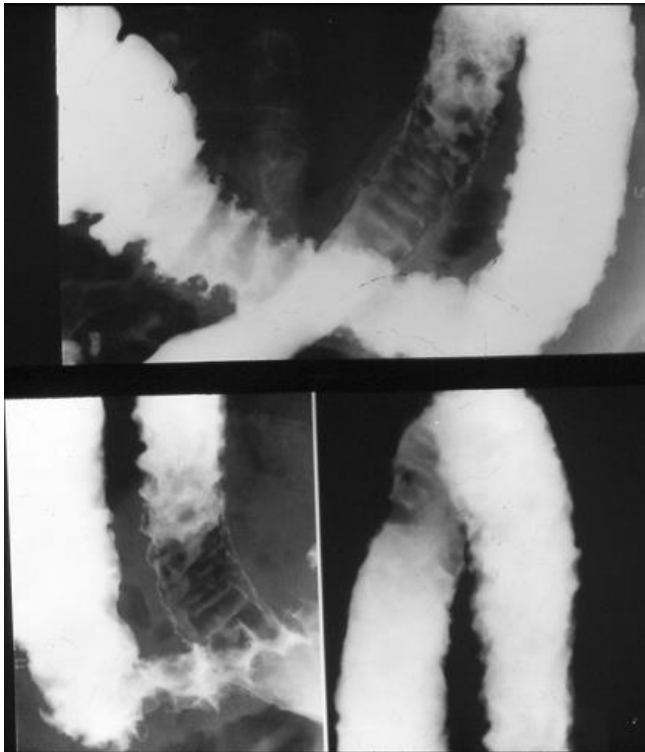
Ischemic Colitis, air contrast barium enema



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Ischemic Colitis, air contrast barium enema



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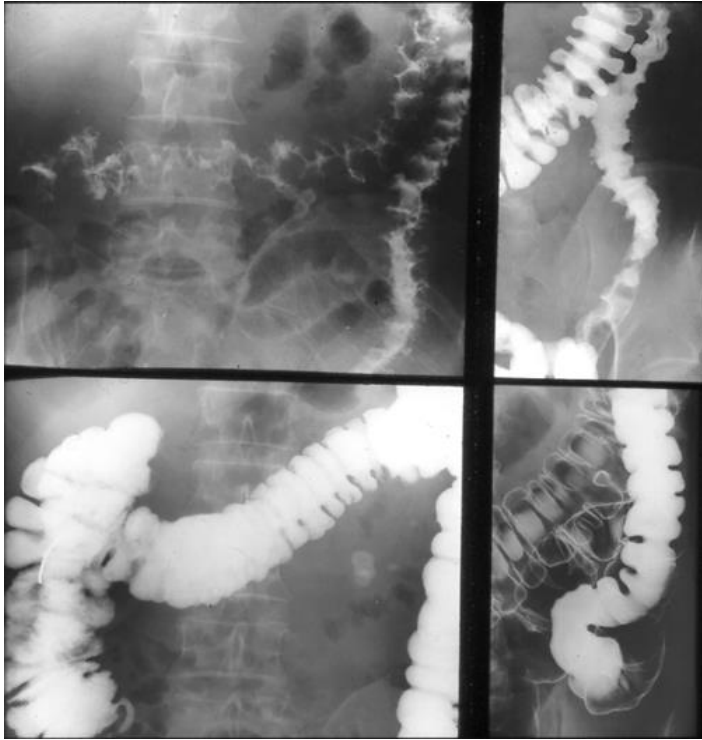
Ischemic Colitis, air contrast barium enema



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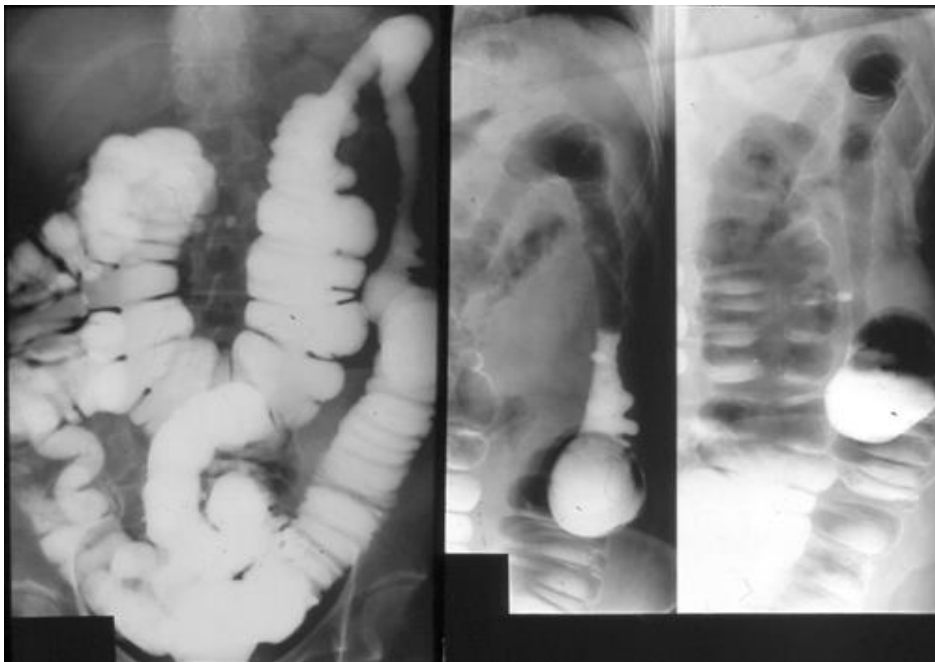


Ischemic Colitis



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Ischemic Colitis



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- o CT with contrast
 - Superior performance characteristics for
 - Gangrene
 - Pneumatosis coli
 - Also
 - Ascites ~ 1/3
 - Target sign / halo sign ~ 25%
 - Fat stranding (100% in one study)
- o CTA (multiphase CT angiography)
 - For suspected
 - AMI (acute mesenteric ischemia)
 - IRCI (isolated right-colonic ischemia)
- o Angiography
 - CTA negative (but diagnosis suspected clinically)
 - AMI (acute mesenteric ischemia)
 - IRCI (isolated right-colonic ischemia)

Ischemic Colitis: Angiography

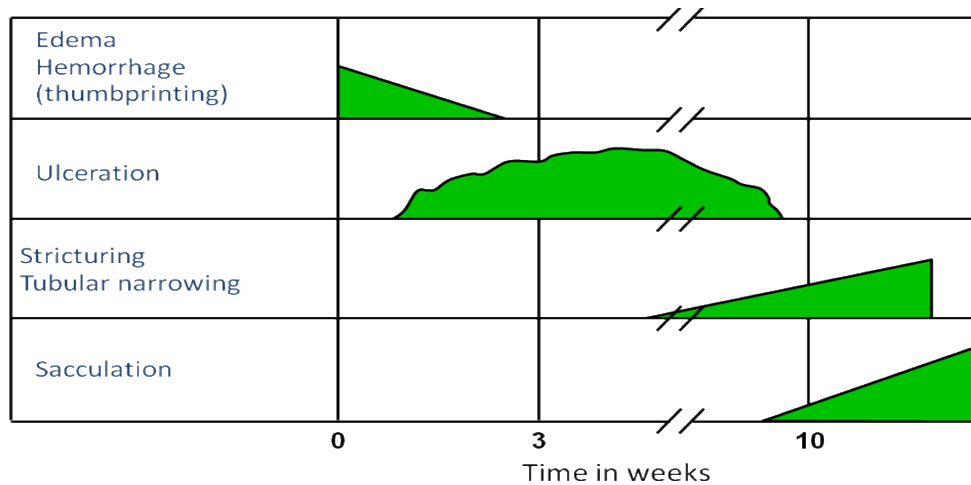


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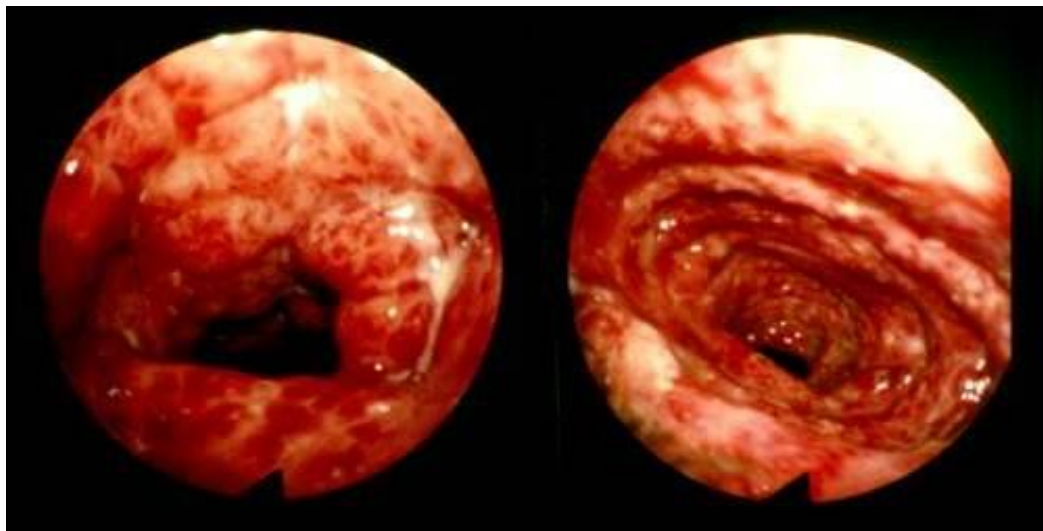
- o Colonoscopy
 - Within 48 h, using minimal air insufflation
 - Severe disease
 - ☐ Confirm localization of CI seen on CT
 - Biopsy
 - ☐ Except with severe disease / possible gangrene (peritoneal signs)

- Radiological Evolution



➤ Endoscopy

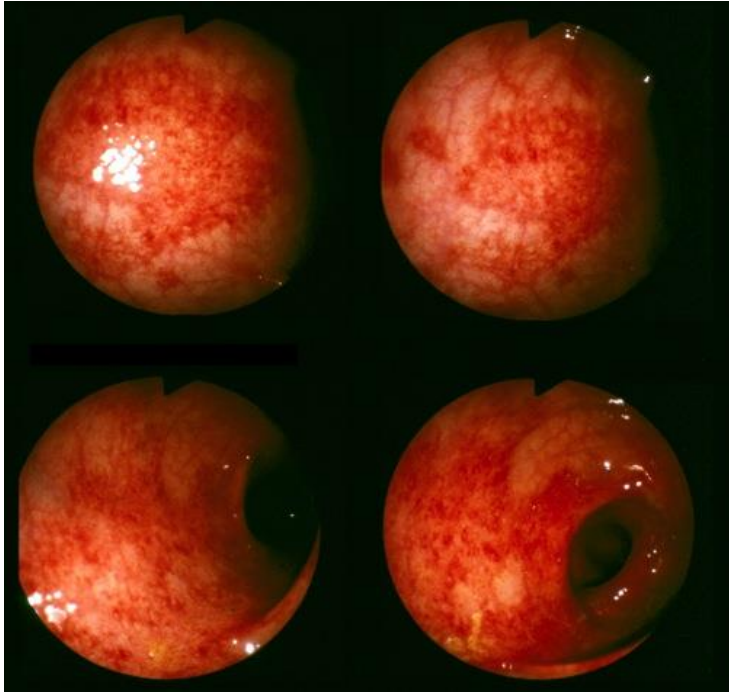
Ischemic Colitis



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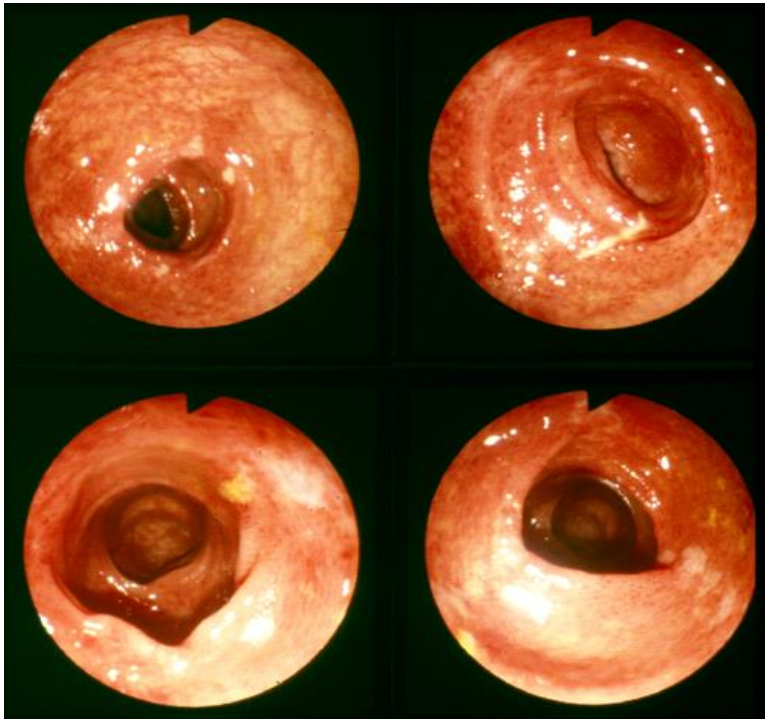


Ischemic Colitis



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Ischemic Colitis



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➤ Histopathology

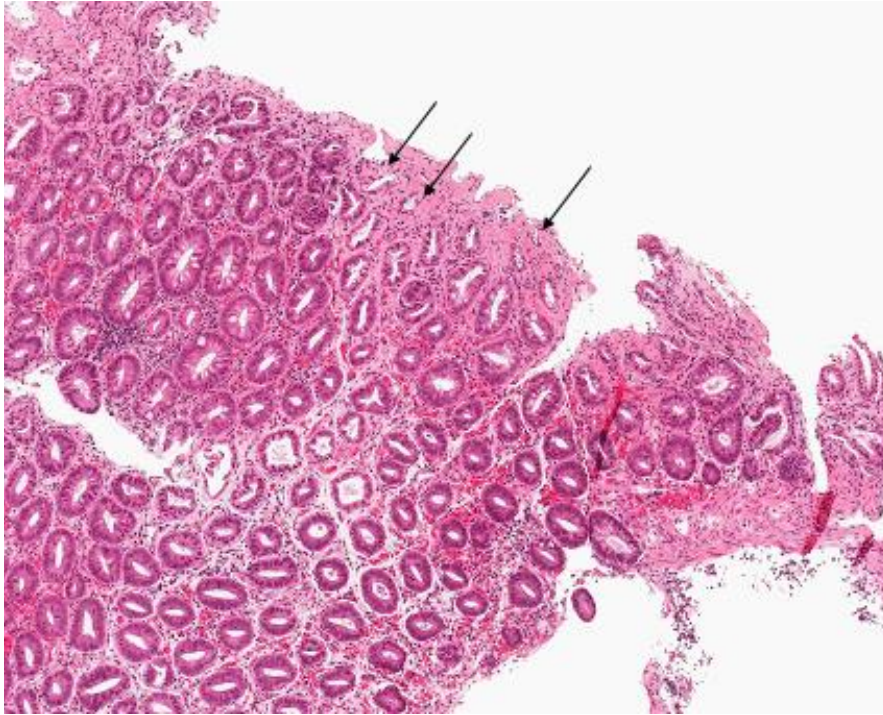
- o Reversible changes
 - Subepithelial bleeding
 - Edema
 - Colitis
 - Ulceration
- o Irreversible changes
 - Infarcted mucosa
 - Preceded by crypt withering with superficial crypt infarction and loss which later extends to involve full thickness mucosa
 - Early
 - Fulminant colitis (5%)
 - Stricture (14%)
 - Gangrene
 - Late
 - Chronic ischemic colitis
 - hyalinization of the lamina propria
- o Pathognomonic changes of “ischemic pattern colitis”
 - Infarction (60%)
 - Ghost cells (in 20%)
- o Non-specific changes
 - Bleeding
 - Mucosal
 - Submucosal
 - Edema
 - Inflammation
 - ↑ PMNs (↑ neutrophils)
- o Fibrin thrombi

CLINICAL CAUTION

- o The mortality rate is higher for isolated, right-sided CI (IRCI).



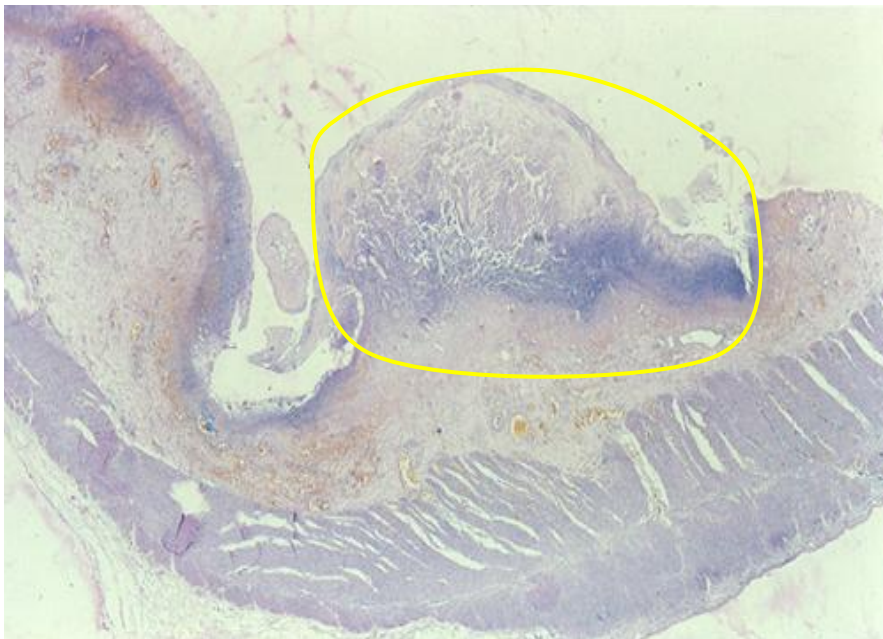
Ischemic Colitis



The superficial crypts are withered (arrows) and the intervening lamina propria appears mildly hyalinised (H&E 100X)

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Ischemic Colitis



Necrotic mucosa

Courtesy of Professor Guito Tytgat, Netherlands



Acute Mesenteric Ischemia (AMI)

➤ Demography

- Incidence of
 - CI in general population $7/10^5$ person-years
 - IBS $\sim 24/10^5$ person-years

Please see Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, Table 114.5, page 2039, "Cause of Colon Ischemia".

➤ Diagnostic imaging

- Give the diagnostic imaging tests used to diagnose acute mesenteric ischemia.
 - Abdominal film
 - Colonoscopy or flexible sigmoidoscopy, with mucosal biopsy
 - 'Doppler' ultrasound (shows only proximal vessels)
 - CT angiography
 - MRI
 - Angiography
- Give the diagnostic imaging findings suggestive of intestinal ischemia.
 - Bowel lumen
 - Caliber
 - Content
 - Transition point if associated obstruction
 - Intraluminal hemorrhage
 - Small bowel feces sign
 - Bowel wall
 - Thickness
 - Homogeneity
 - Enhancement pattern
 - Length of involvement
 - Pneumatosis
 - Mesentery
 - Edema
 - Hemorrhage
 - Patency of mesenteric vessels
 - Mesenteric vascular engorgement
 - Ascites
 - Volvulus
 - Intussusception



- X-ray
 - Flat plate
 - Edematous narrowing
 - Distension of gas-filled colon segment
 - Contrast barium enema
 - Severe spasm
 - Thumbprinting
 - Ulceration
 - Strictureing
 - Sacculation

Printed with permission: Gore, et al. *Clin Gastroenterol Hepatol* 2008; 6: 849-59.

Acute Mesenteric Ischemia



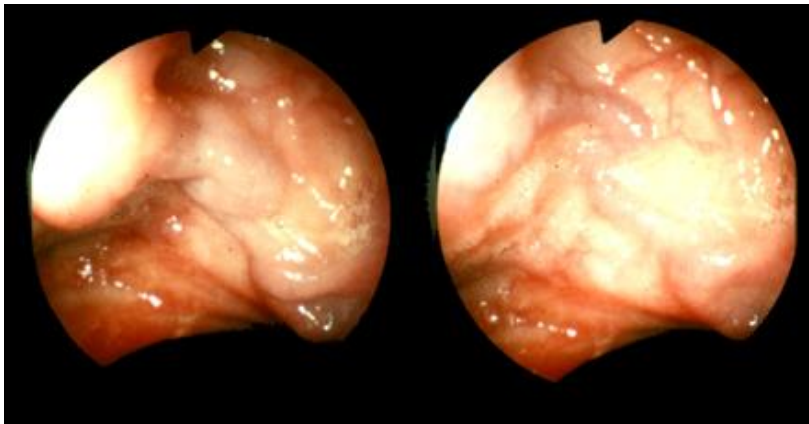
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➤ Endoscopy

- Give the colonoscopic changes in acute mesenteric ischemia.
 - Segmental disease
 - Rectal sparing
 - All parts of the colon may be affected by CI (~23% sigmoid colon, 23% right side of the colon [IRC]), both pancolitis and right sided colitis (IRCI) are common in persons with sepsis.
 - IRC has
 - 2x ↑ risk of needing surgery
 - 5x ↑ mortality rate
 - Swelling, edema
 - Superficial half of colonic mucosa preferentially affected
 - Hemorrhagic streaking (mucosal and submucosal redness and hemorrhage)
 - Superficial ulceration, slough
 - The presence of a circumferential ulcer has a worse prognosis than an ulcer in the longitudinal axis ("single-stripe" sign)
 - Deep ulcers
 - UC-like colitis
 - Liquefactive necrosis, perforation
 - Stricture (reversible, irreversible, saccular stricture)
 - Pneumatosis linearis (colonic gangrene, HIV disease)
 - Carcinoma (pressure of CRC produces local ischemia)
 - Diverticulosis-associated ischemia
 - Isolated R-colon ischemia (IRCI) may herald a SMA occlusion

Acute Mesenteric Ischemia



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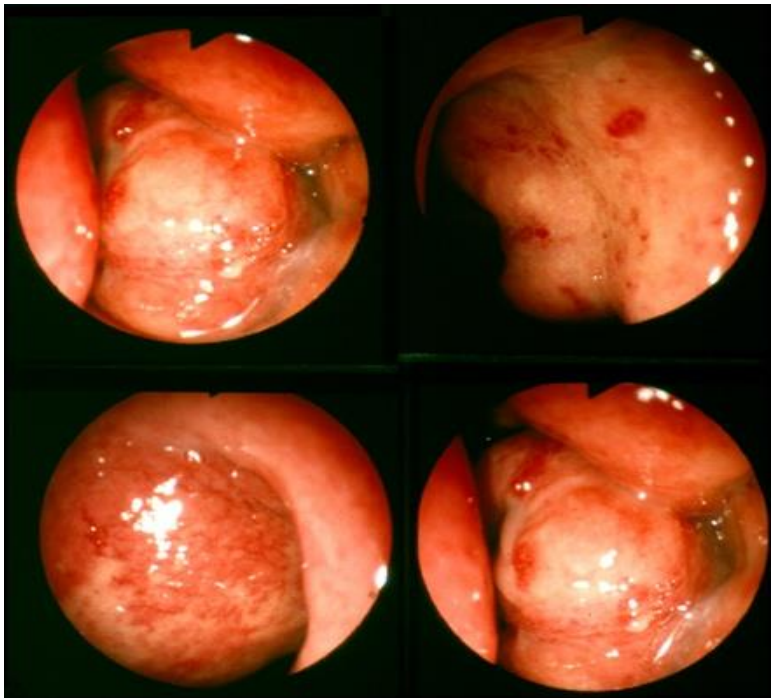


Acute Mesenteric Ischemia



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Acute Mesenteric Ischemia



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- Histopathology
 - Identical to ischemia from other causes
 - In isolated R-colon ischemia (IRC; but not other forms of CI), evaluation of vasculature is important
 - CI is associated with vascular surgery
 - Urgent surgery for ruptured AAA (~60%)
 - Elective surgery on aortic valve (~7%)

Adapted from: Brandt L. Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology / Diagnosis / Management 2006: pg. 2566.; Sreenarasimhaiah J. Best Pract Res Clin Gastroenterol 2005;19(2): 285-286.

Hemangiomas

- Definition
 - Hemangiomas are well circumscribed, non-encapsulated hamartomas, single or multiple, involving just the colon or diffuse along the GI tract (GIT), with or without non-GIT tissues.
- Diagnostic imaging
 - Hemangiomas may be cavernous, capillary or mixed
 - Plain film
 - Multiple foci of calcification (phleboliths) in abnormal vascular channels
 - Soft tissue mass distorting / displacing rectal air column
 - Barium enema
 - The vascular lesion distorts / displaces external surface of colon
 - Wall of rectum is thickened, causing a widened presacral space
 - Lumen of colon
 - Narrow
 - Rigid
 - Scalloped



Congenital Arteriovenous Malformations (AVMs)

➤ Definition

- Congenital AVMs are "...congenital communications between arteries and veins, located primarily in the submucosa". (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 606).

➤ Pathology

- Veins
 - Dilated
 - Tortuous
 - Thick walled
 - Hypertrophy of smooth muscle
 - Intima thick / sclerotic
- Arteries
 - Dilated
 - Wall atrophic
 - Sclerotic degeneration

GASTROINTESTINAL STROMAL TUMOURS (GISTs)

- GIST (gastrointestinal stromal tumours)
- Often "dumbbell" shaped (intra- and extramural growth)
- Site
 - Stomach ~70%
 - Small bowel ~25%
- Malignant potential
 - Risk of progressive disease is determined using site, size (≤ 2 cm, >2 - ≤ 5 cm, >5 - ≤ 10 cm, >10 cm), and mitotic rate (≤ 5 per 5 mm², >5 per 5 mm²).
 - Risk is assessed as none, low, intermediate or high
 - In the rectum, all GISTs >10 cm or with a mitotic rate >5 per 5 mm² are considered high risk
- Genetic mutations
 - Mutational activation of genes: KIT, PDGFRA, DC117
 - Medical treatment
 - TK (tyrosine kinase) inhibitors, e.g., imatinib, used as adjuvant or no adjuvant therapy (before surgical resection)



➤ Marker for GIST

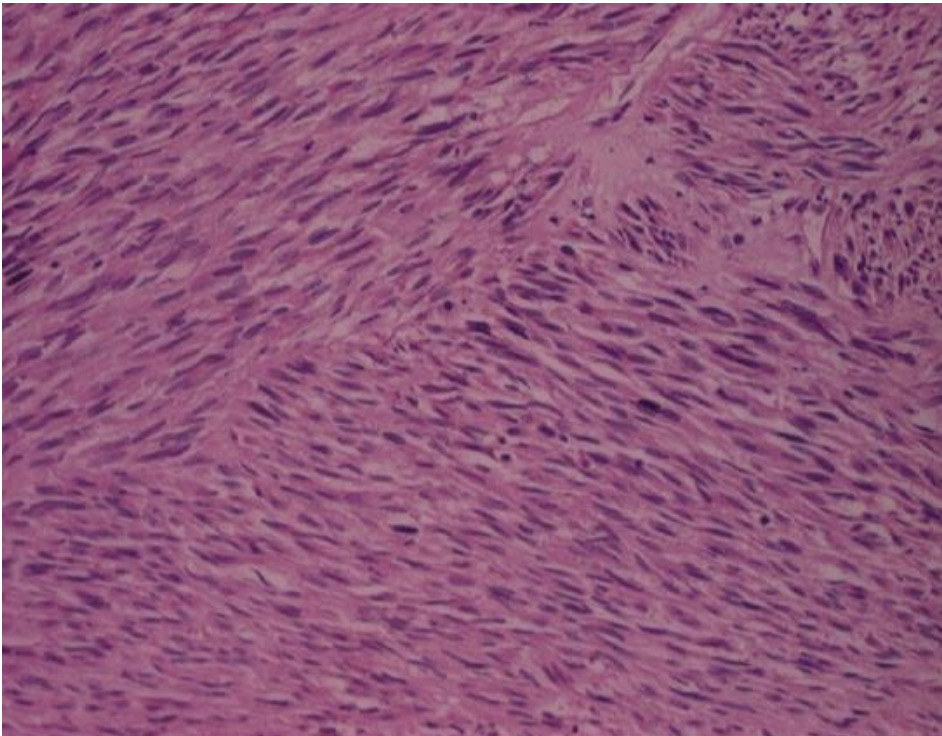
- C-kit (a stem cell factor receptor) (93%) DOG-1 ("discovered on GIST" 1) (92%)
- CD34 (a hematopoietic cell progenitor cell antigen) (71%)
- Potential confounding positive stains:
 - Smooth muscle markers
 - Smooth muscle actin (30%)
 - Desmin (8%)
- Potential confounding neural marker
 - S100 (10%)
- Other mesenchymal colonic tumours
 - Fat: Lipoma, Liposarcoma
 - Muscle: Leiomyoma, Leiomyosarcoma (leiomyomas multiple in ~25%)
 - Nerve: Schwannoma
 - Desmoid tumour

➤ Diagnosis

- EUS plus FNA

➤ Histopathology

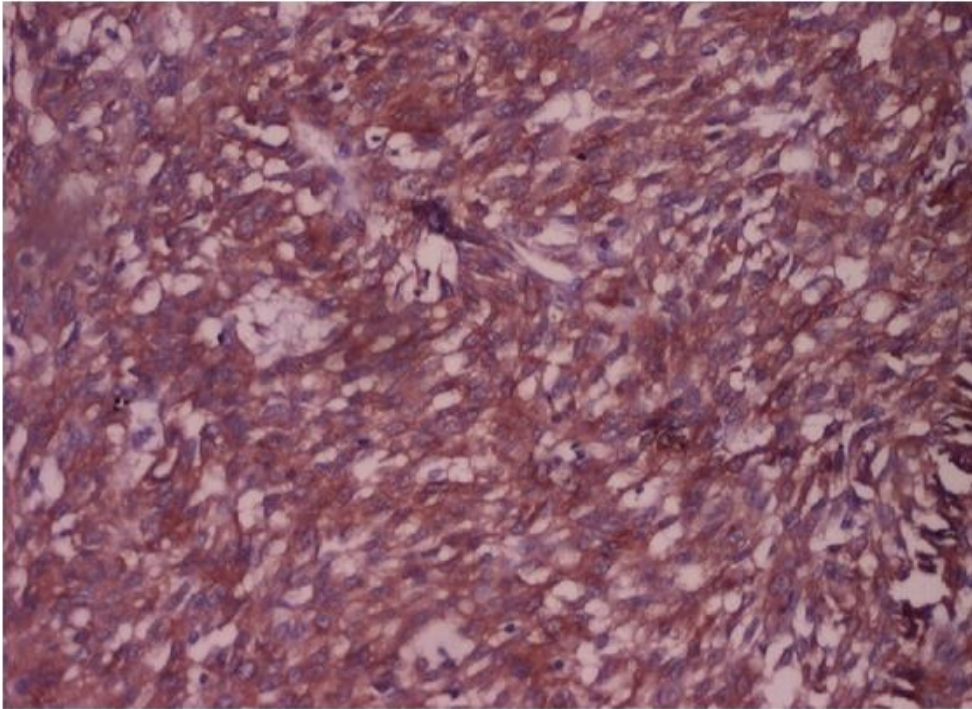
GIST



Source: Singhal S, et al. Case Reports in Gastrointestinal Medicine, vol. 2013, Article ID 934875, 4 pages, 2013.



GIST



Source: Singhal S, et al. Case Reports in Gastrointestinal Medicine, vol. 2013, Article ID 934875, 4 pages, 2013.

DIVERTICULAR DISEASE (DDC)

➤ Demography

- Diverticular disease is a significant contributor to morbidity and health-care expenditures.
- Affects ~ 25% of persons in “westernized” countries
- DDC ↑ prevalence with age
- May be more common with ↑ intake of red meat and ↓ fibre
- Associated with connective tissue disease, e.g., scleroderma, Ehlers-Danlos and Marfan syndrome
- Overweight, obesity, and physical inactivity among women increase
 - Diverticular disease requiring hospital admission
 - Risk for serious complications
- Prevalence by age:
 - Age 40 5%
 - Age 60 30%
 - Age 85 65%



- Prevalence by gender
 - Age<50 males more common
 - Age 50–70 slight female increase
 - Age >70 females more common
- Diverticular disease in the young (<40 years)
 - 2–5% of diverticular disease <40 years
 - Occurs more in males
 - Obesity is major risk factor
 - Location of diverticula usually in sigmoid and descending colon
 - Surgery necessary in 50% of patients

Source: Hjern F, et al. Am J Gastroenterol 2012; 107: 296-302.

➤ Pathology

- 90% of DDC is in the sigmoid
- ~15% of DDC are in the right-side of the colon, with or without co-existing left-sided DDC (Right sided DDC much more frequent in Asian countries)
- 2x ↑ elastin deposits in muscle cells in taenia as well as ↑ type III collagen and ↑ tissue inhibitor of metalloproteinases, but no muscle hypertrophy
- ↑ ICC (interstitial cells of Cajal)

○ Acute diverticulitis

- Uncomplicated
 - Accounts for 75%
 - About 30% require surgery (success rate of antibiotics and no surgery, 70% to 100%)
 - Localized infection
- Complicated
 - Accounts for 25%
 - > 95% require surgery
 - Complications
 - Hemorrhage
 - Obstruction
 - Perforation
 - Fistula
 - Abscess
 - Peritonitis



➤ Anatomy

- Pseudodiverticula where vasa recta perforate the colonic wall between the mesenteric taenia and the two anti-mesenteric taeniae (but not between the two anti-mesenteric taeniae)

Exam Tip

Diverticulosis is simply the harmless and common presence of uncomplicated diverticula in the colon. However, when a perforation occurs, local as well as systemic complications may develop.

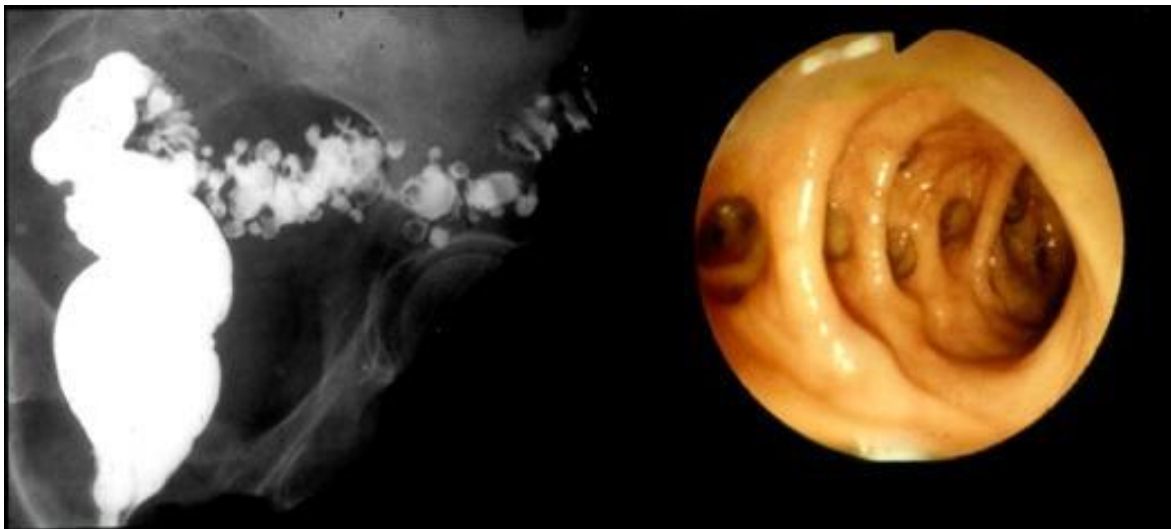
- Look for additional information in the MCQ stem, that might suggest microperforation (e.g., rebound, guarding, fever, leucocytosis, “shift-to-the-left”) which would prompt 2 choices
- Treat with bowel-directed antibiotics
- Don’t – that is, do not – do colonoscopy for fear of causing a perforation ,which may be deadly in this setting

➤ Diagnostic imaging

❖ Uncomplicated

- Barium enema

Colonic Diverticulosis, barium enema and colonoscopy



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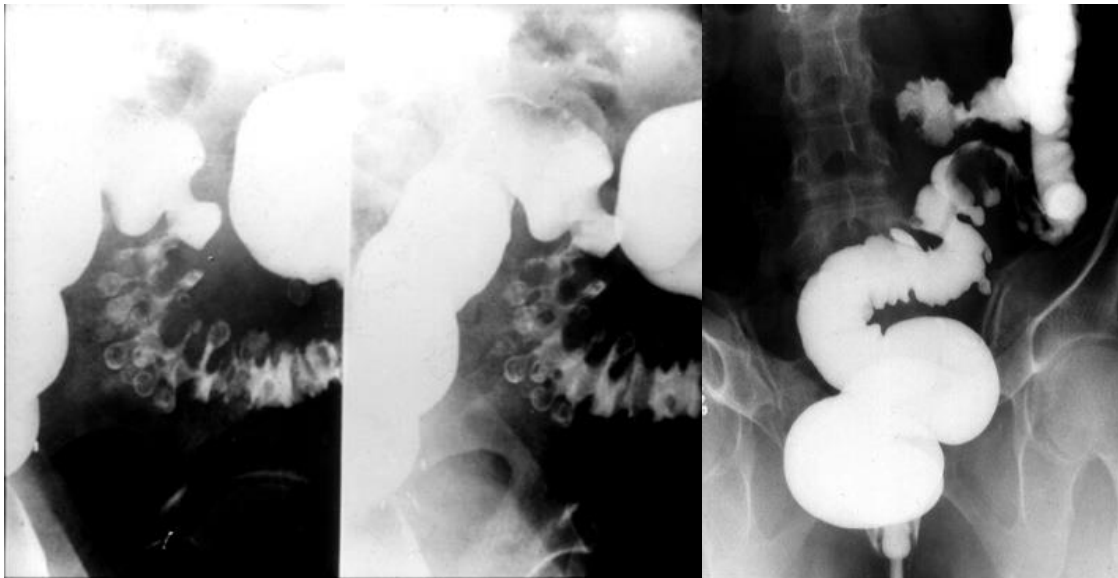


Colonic Diverticulosis, air contrast barium enema



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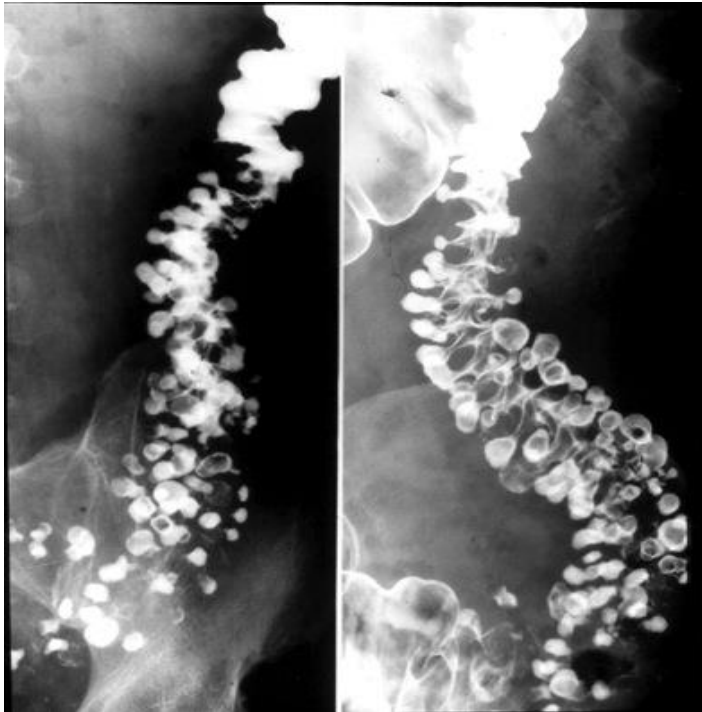
Colonic Diverticulosis, air contrast barium enema



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Colonic Diverticulosis, air contrast enema



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Colonic Diverticulosis, air contrast barium enema



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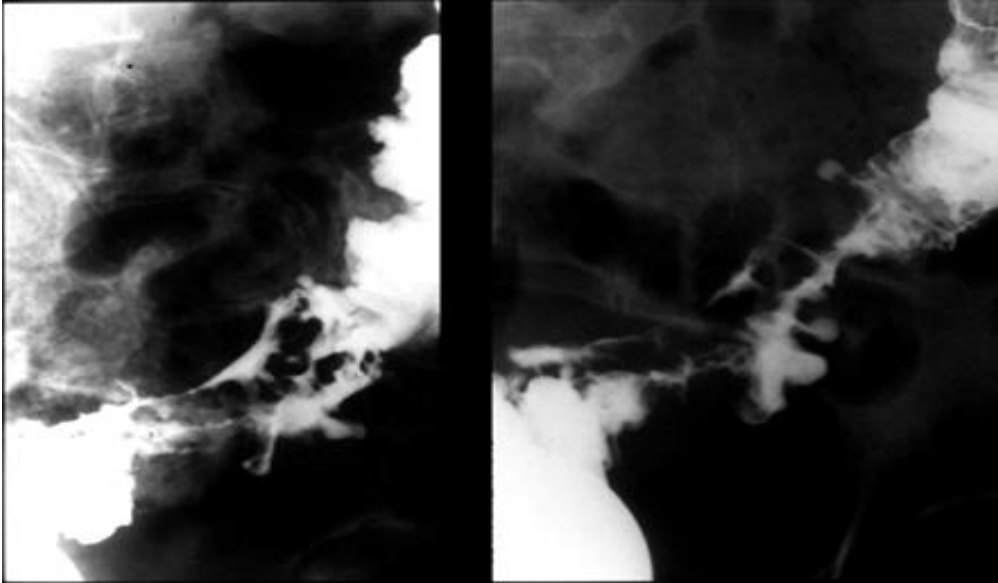
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Colon



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Colonic Diverticulosis, air contrast barium enema



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Pancolonic Diverticulosis, air contrast barium enema

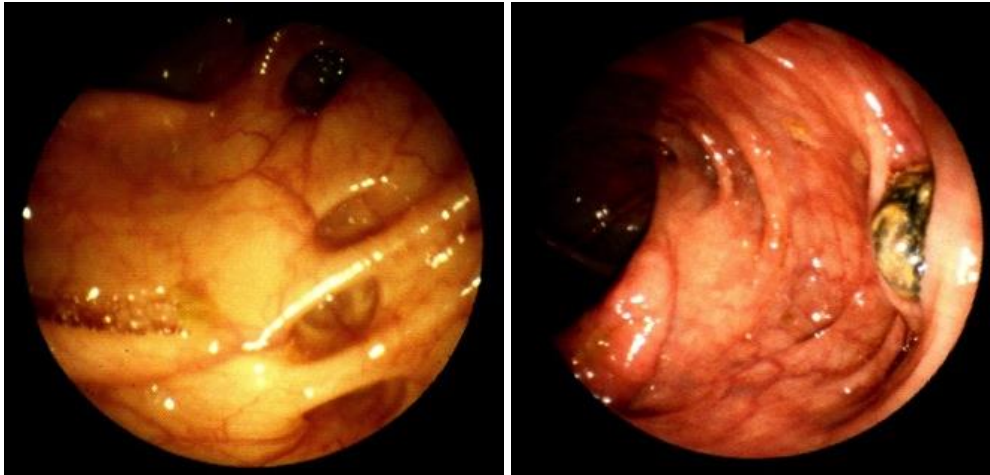


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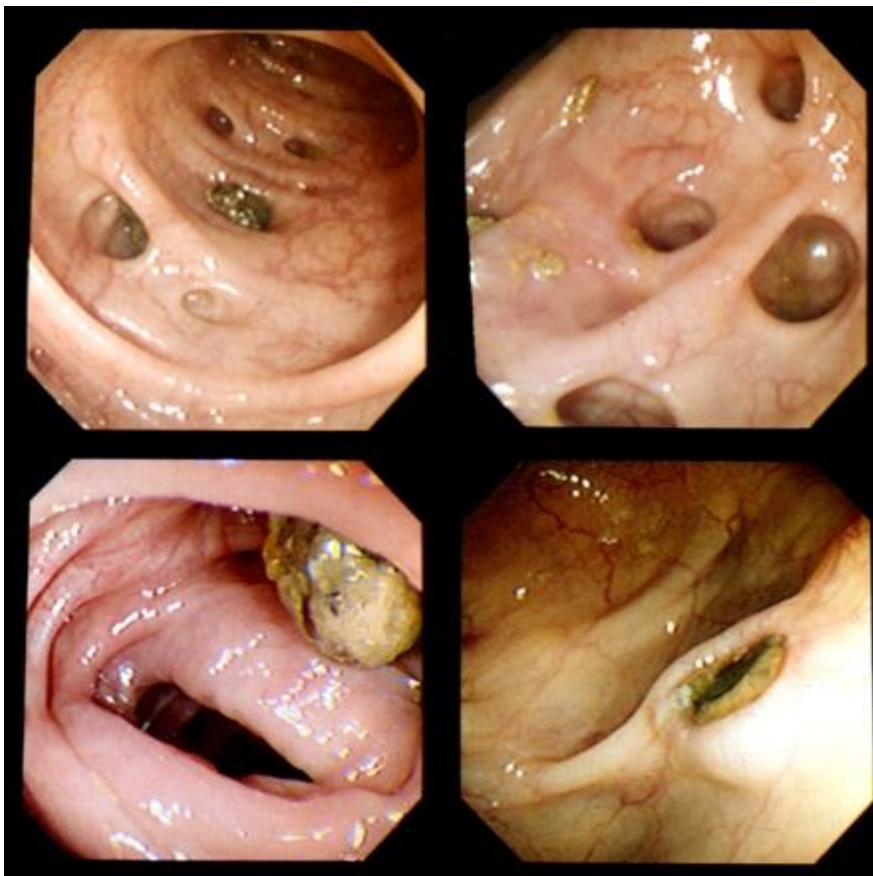
➤ Endoscopy

Colonic Diverticulosis



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Colonic Diverticulosis



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❖ Complicated

- Barium studies
 - Presence of diverticula
 - Thickened colonic wall
 - Mass
 - Overlying mucosa is normal
 - Narrowing of lumen
 - Abscess
 - Penetration / local perforation / walled off abscess
 - Extravasation of barium into the abscess
 - Intramural collection of barium which communicates with colonic lumen (“tracking” of barium)
 - Gas-filled cavity

Acute Diverticulitis, air contrast barium enema



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- CT scanning
 - Presence of diverticula
 - Thickened colonic wall
 - Stranding of soft tissue (from perforation and extravasation of contrast into pericolic tissues)
 - Intramural sinus tract
 - Mass / abscess in colonic wall or mesentery
 - Giant sigmoid diverticulum, which develops from enlargement of sinus tract from lumen of diverticulum to the cavity of an abscess



➤ CT Classification

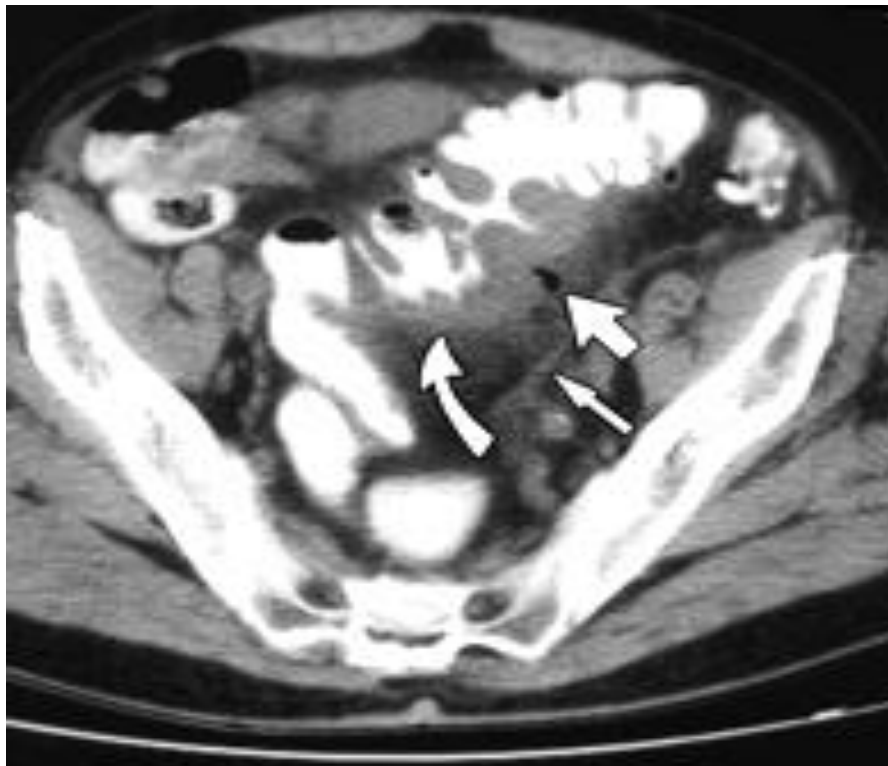
- Give CT classifications of diverticulitis (e.g., Hinchey and Buckley)
- Buckley Classification

CT Findings	
○ Mild	– Bowel wall < 3 mm, fat stranding
○ Moderate	– Bowel wall thickening >3 mm, phlegmon or small abscess
○ Severe	– Bowel wall thickening > 5 mm, frank perforation with subdiaphragmatic free air, abscess > 5 cm

Hinchey classification of diverticular penetration / perforation (Stages)

- I
 - Pericolic abscess, Mesenteric abscess
- II
 - Walled-off pelvic abscess
- III
 - Generalized, purulent peritonitis
- IV
 - Generalized, fecal peritonitis

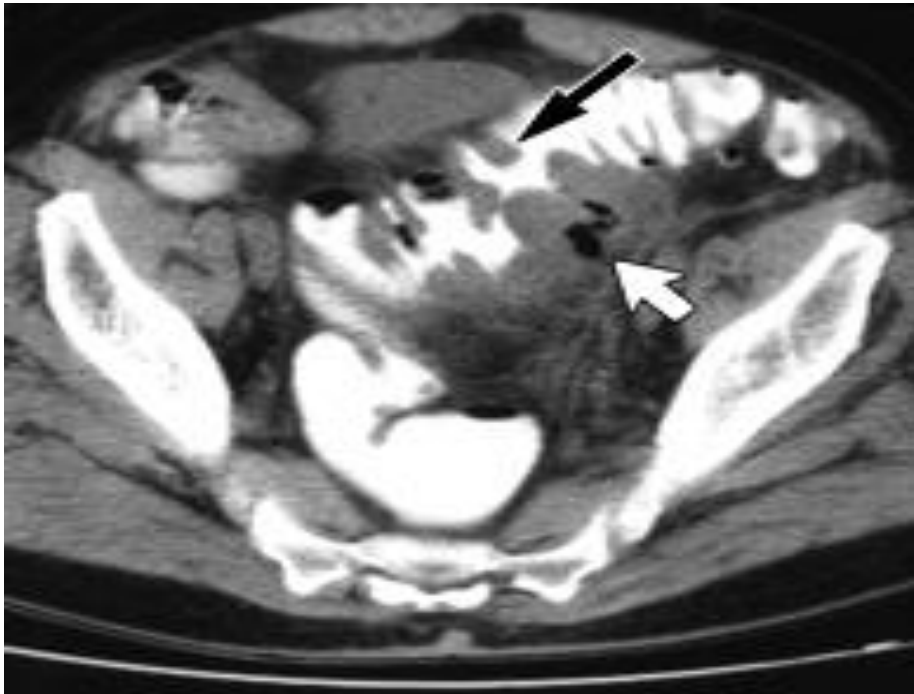
Diverticular Disease with Abscess, CT scan



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Diverticular Disease with Abscess, CT scan



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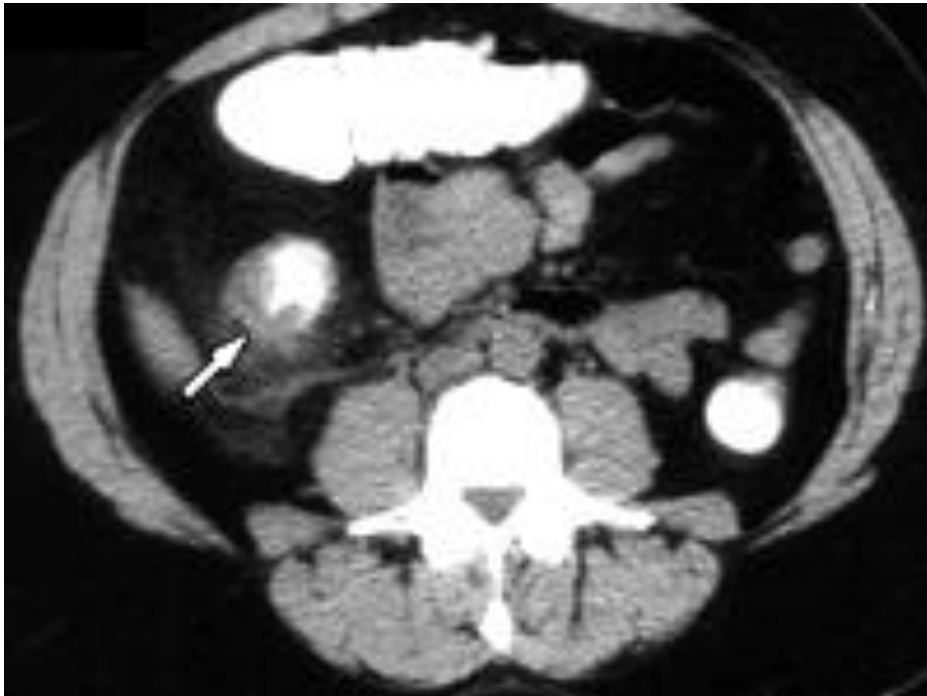
Diverticular Disease Perforation, CT scan



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Diverticular Disease Perforation, CT scan



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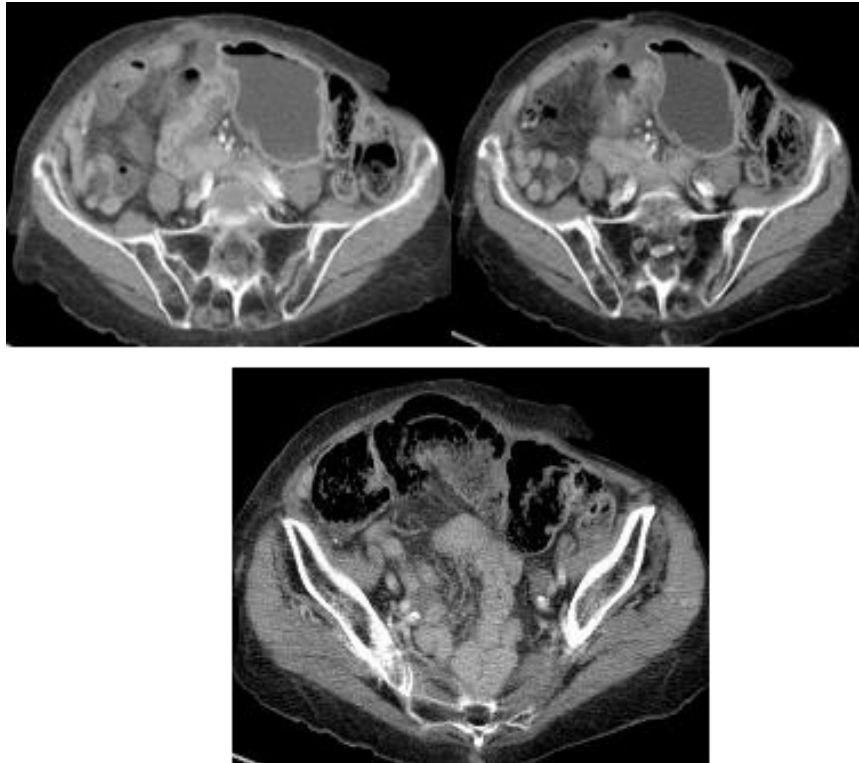
Acute Diverticulitis, CT scan



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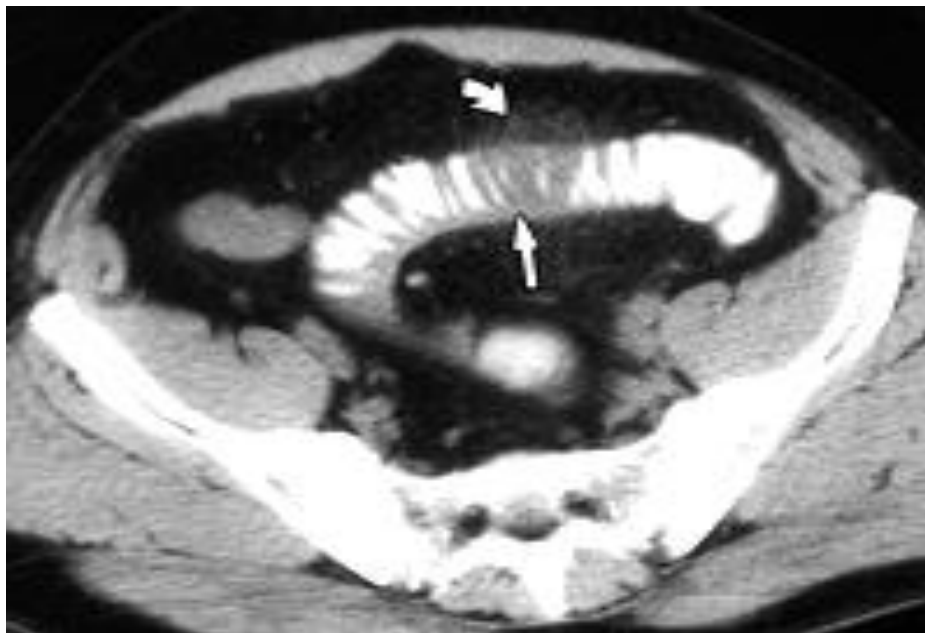


Acute Diverticulitis, CT scan



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Acute Diverticulitis, CT scan



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Acute Diverticulitis, CT scan



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- Give the diagnostic imaging (DI) changes of acute diverticulitis.
 - Plain film
 - Dilation
 - Abscess (soft tissue density)
 - Pneumoperitoneum (~10%)
 - Ultrasonography
 - Typical findings
 - Diverticula
 - Colonic wall, hyperechogenic
 - Abscess(es)
 - Performance characteristics (equivalent to CT)
 - Sensitivity, 84% to 98%
 - Specificity, 80% to 93%
 - Gastrografin enema
 - Diverticulosis
 - Extravasation (Extraluminal mass)
 - Sinus tract
 - Fistula
 - Performance characteristics
 - Sensitivity, ~75%
 - False-negative, ~30%

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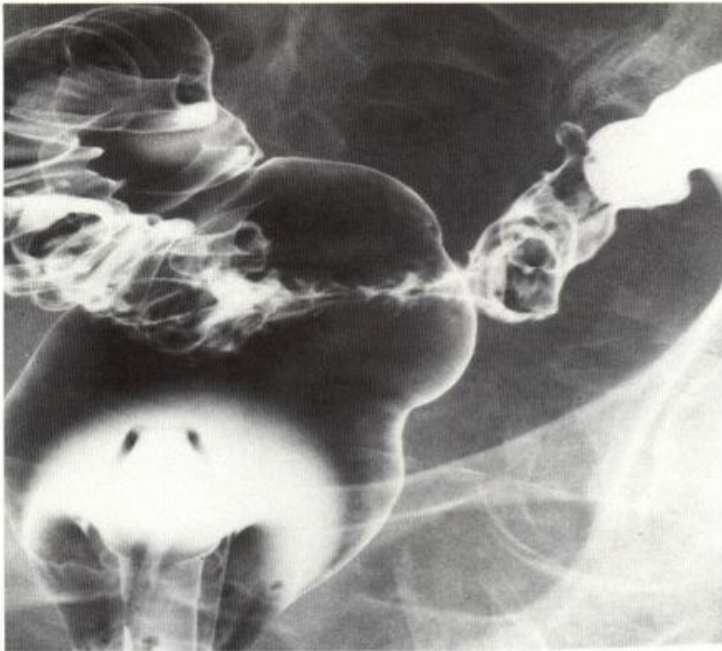


- CT scanning with contrast
 - Gold standard
 - Typical findings
 - Diverticula
 - Periodic infiltration of fatty tissue (fat stranding)
 - Colonic wall thickened (> 4 mm)
 - Abscess(es)
 - Performance characteristics
 - Sensitivity, 75% to 100%
 - Specificity, 93% to 98%

There are some radiologic features of diverticulitis the descending and sigmoid colon which help to differentiate it from Crohn disease

- Diverticulitis
 - Short process 3–6 cm in length
 - Diverticula sharply defined & frequently contain fecaliths, but may on occasion simulate abscesses.
 - When a diverticulum perforates, the abscess creates an extramural defect or an arcuate configuration of folds that stretch over the abscess
 - No transverse fissures; folds may be straightened but more commonly have an arcuate configuration
 - A short paracolic tract may be seen occasionally in diverticulitis (usually associated with an extramural defect); on rare occasions a perforation may run parallel to the bowel wall

CRC plus diverticular disease, ACBE



- Narrowing of colonic lumen
 - Intact mucosa of area of narrowing
 - Associated diverticular disease seen on air contrast barium enema.
- Colorectal cancer screening in patient with known diverticular disease

Abbreviation: ACBE, air contrast barium enema; CRC, colorectal cancer

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Diverticular Disease, Narrow Lumen



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Diverticular Disease, Narrow Lumen

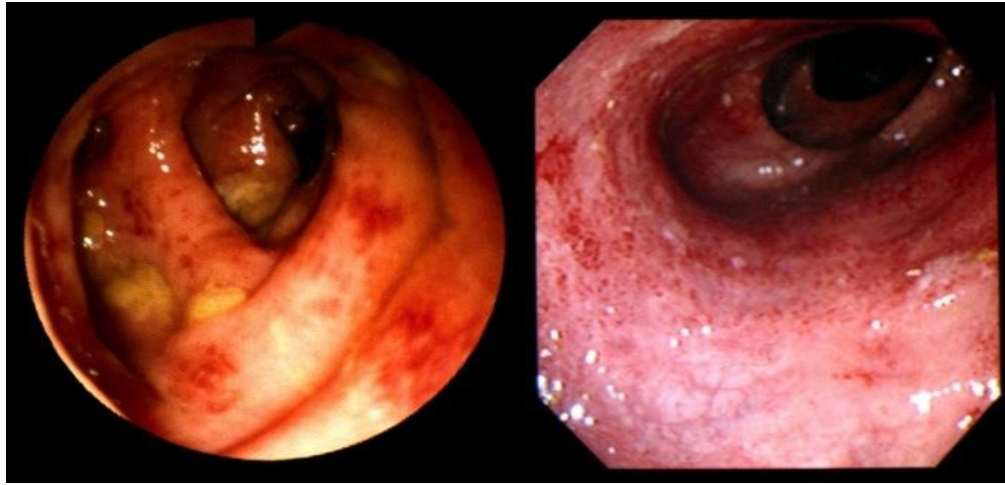


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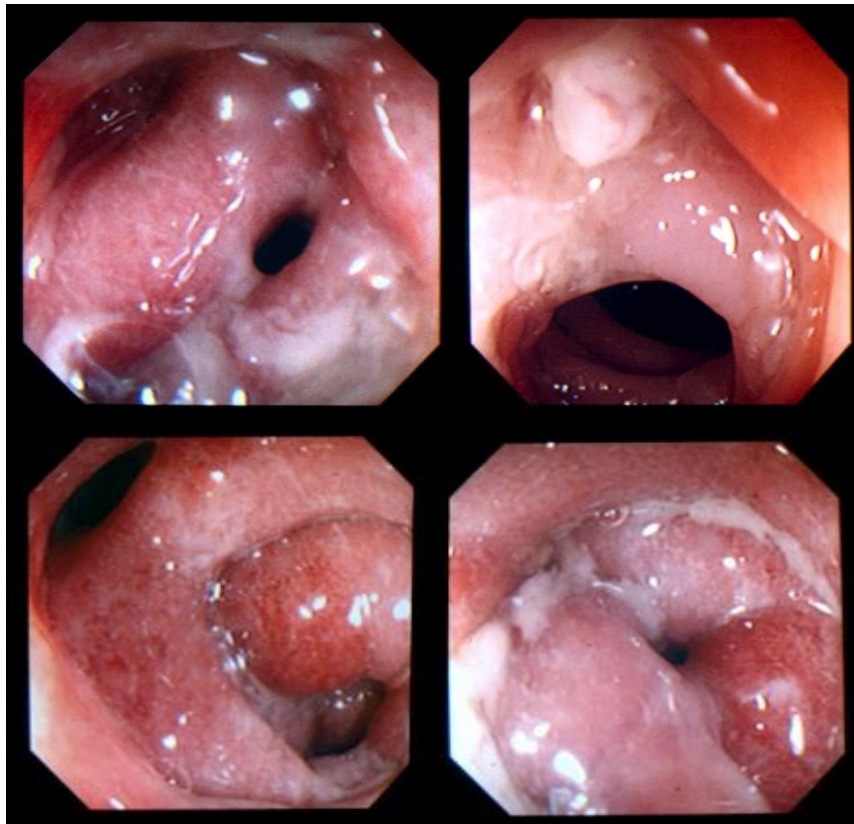
➤ Endoscopy

Acute Diverticulitis



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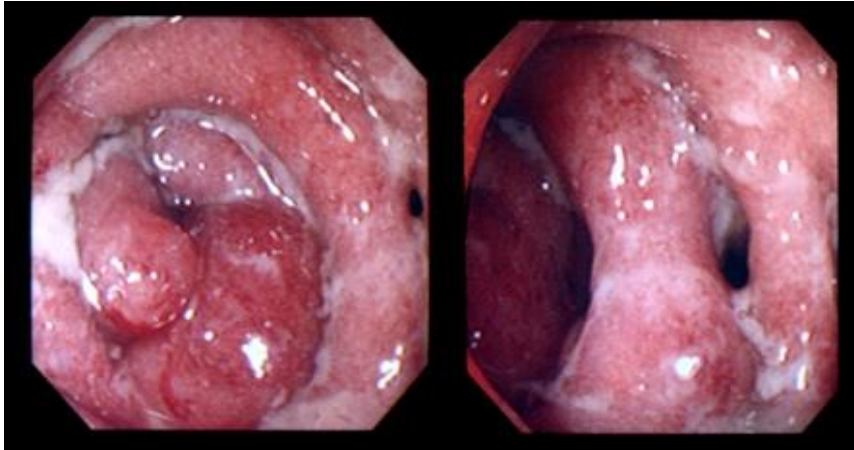
Acute Diverticulitis



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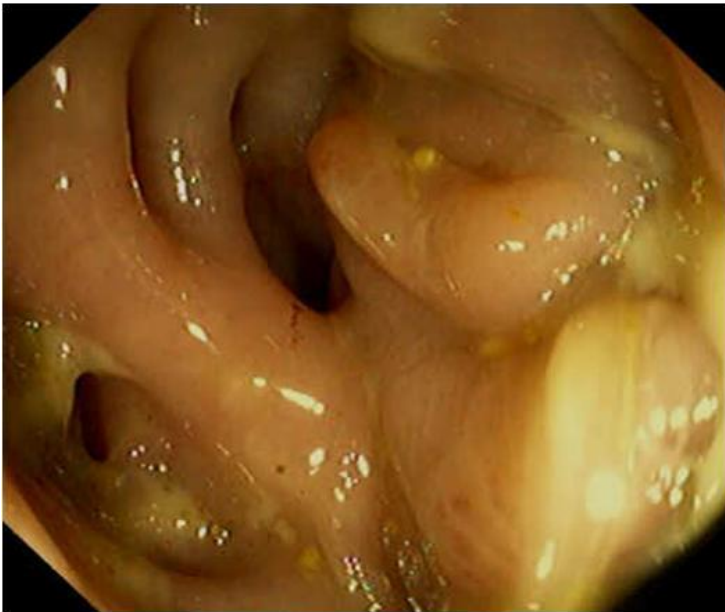


Acute Diverticulitis



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Diverticulitis



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- Non-specific inflammation
- Lymphocytes, PMN
- Granulomas
- Rectal sparing
- Diverticula Associated Colitis (DAC; aka SCAD [segmental colitis associated with diverticula])
 - Note: not typical of IBD



- Multiple openings into diverticula
 - Sparing of orifices of diverticula
 - Erythema on crest of fold
 - Sparing of rectum (diverticula are usually in sigmoid colon)
 - Usually mild disease
- Scleroderma-associated colonic diverticula
 - Sacculations – wide mouthed pseudodiverticula on antimesenteric border
 - Haustral markings: lost
 - Dilation
 - Localized narrowing
 - Elongation

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the earliest signs of inflammation in colonic diverticula.
 - Hyperplasia of the lymphoid tissue at the apex of the obstructed diverticulum.
- A colonic biopsy is shown to you blindly, without any clinical information. The biopsy shows
- Cryptitis
 - Chronic lymphocytic infiltration
 - Crypt abscesses
 - Granulomas
- Give the piece of information needed about the site of the biopsy before making the diagnosis of IBD.
 - SCAD (segmental colitis associated with diverticulosis) may be histologically indistinguishable from IBD, so determine if the biopsy was taken from a colonic diverticulum!

➤ Differential

- Give the differential diagnosis of acute diverticulitis.
 - Acute appendicitis – Suspect if RLQ symptoms or non-resolution with medical therapy
 - Crohn disease – Suspect if aphthous ulcers, perianal involvement, or chronic diarrhea
 - Colonic carcinoma – Suspect if weight loss, bleeding. Diagnose with colonic evaluation after acute inflammation resolved
 - Ischemic colitis – Suspect if high-risk patient, bloody diarrhea, or thumbprinting.
 - Pseudo-membranous colitis – Suspect with antibiotic use or diarrhea.
 – Diagnose with stool toxin
 - Complicated ulcer – Suspect if pneumoperitoneum or peritonitis, or with clinical disease history, NSAID use, or dyspepsia



- Ovarian cyst – Suspect in female patient with unilateral abdominal pain.
- Abscess, torsion – Diagnose with pelvic or transvaginal ultrasound
- Ectopic pregnancy – Suspect in female patient of childbearing age.
- Diagnose with pregnancy test and ultrasound

Diverticulosis and Hemorrhage

➤ Demography

- ~5% of persons with colonic diverticula will have an arterial bleed
- Just because a person with known diverticulosis has a LGIB does not prove that the LGIB is a diverticular bleed (may just as well be bleeding from angiodysplasia).
- The right colon is the source of bleeding in 49-90% of patients
- The source is not identified in 30-40% of cases. Bleeding is usually abrupt, painless and in large volume (33% are massive). Bleeding stops spontaneously in 70-80% of cases
- In those with bleeding, 30% go on to have a 2nd bleed and of those, 50% will have a 3rd bleed

LOWER GI BLEEDING (LGIB)

➤ Endoscopy

Entity	Age at Clinical Presentation	Size	Endoscopic Manifestation
○ Hemangiomas	Any age	> 5.0 mm	Nodular capillary
○ Cavernous	Any age	>1.0 cm	Frequently Polypoid lesions that protrude into the bowel lumen
○ Blue rubber BLEB	Younger age	in cms	Massive; Polypoid; seen by conventional X-ray
○ Kaposi sarcoma	Any age	mm to 2 cm	Nodules, grouped, or irregular
○ Idiopathic angiodysplasia			
– <i>Early lesion</i>	Usually over age 60	> 3.0 mm	Flattened, not above mucosa
– <i>Late lesion</i>	Usually over age 60	< 5.0 mm	Red puncta/irregular patches
○ Hereditary hemorrhagic telangiectasia	Childhood	Up to few mm	Multiple, red pinpoint, nodular lesions
○ Telangiectasia	Often after 4-5th decade	2-3 cm	GI bleeding (spider)
○ Congenital Arteriovenous Malformation	Any age, but often bleed in adolescence	Variable	Variable, large clots often present

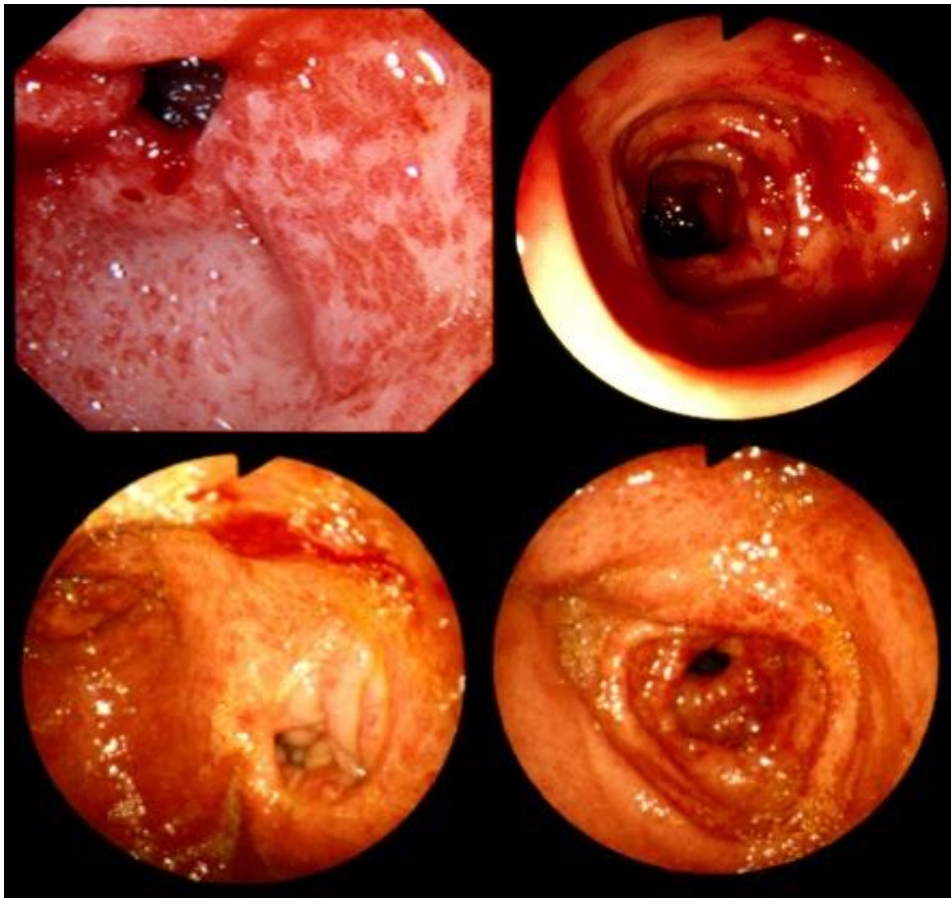


Colonic Bleeding, Telangiectasia



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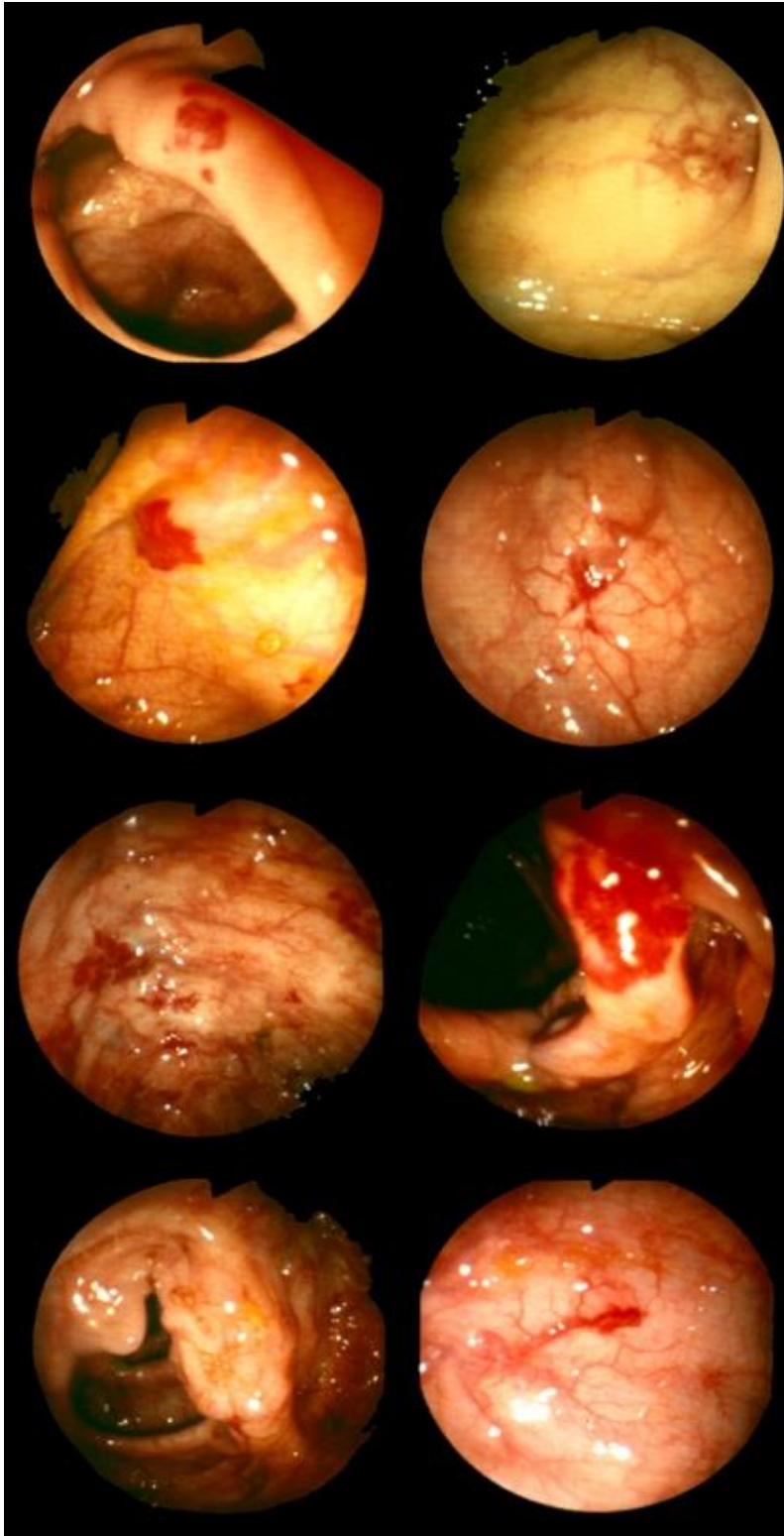
Colonic Bleeding, Telangiectasia



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Colonic Bleeding, Telangiectasia



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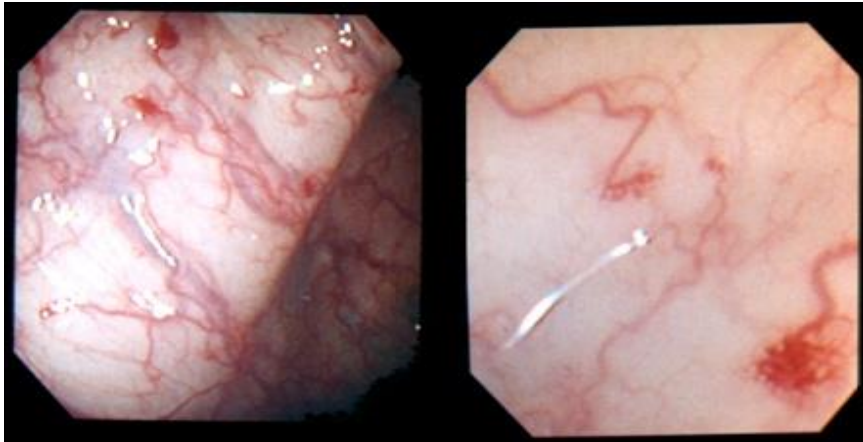
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Colon



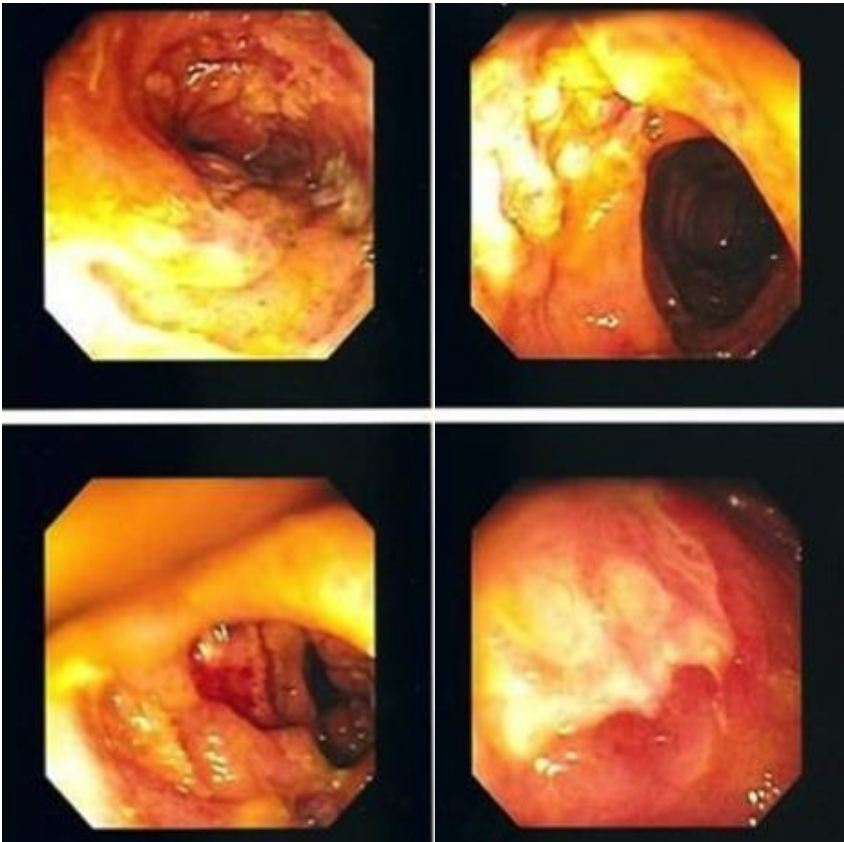
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Rectal Bleeding, Telangiectasias



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NSAIDs Colopathy, Rectal Bleeding

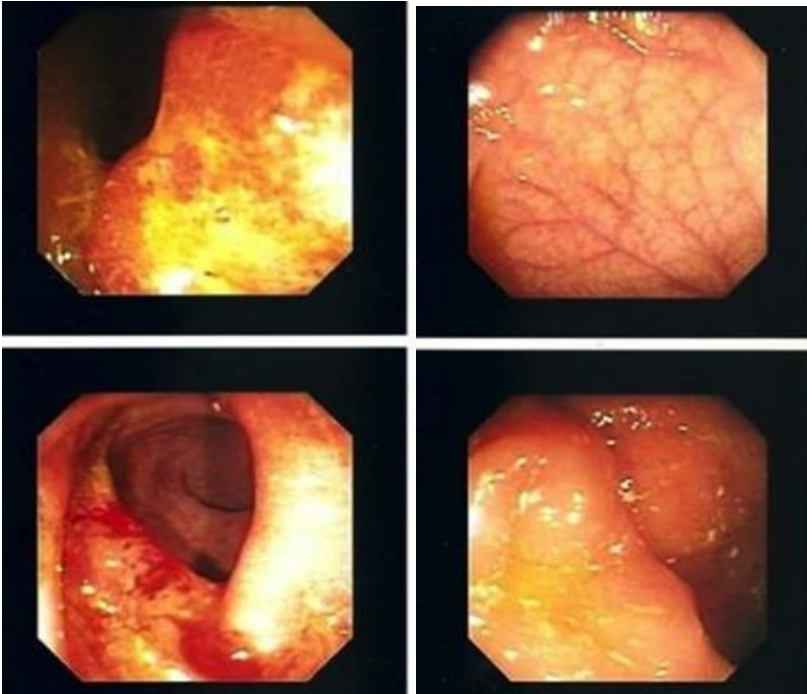


- Multiple different sized, aphthous ulcers
- Normal intervening mucosa
- Ileal ulceration

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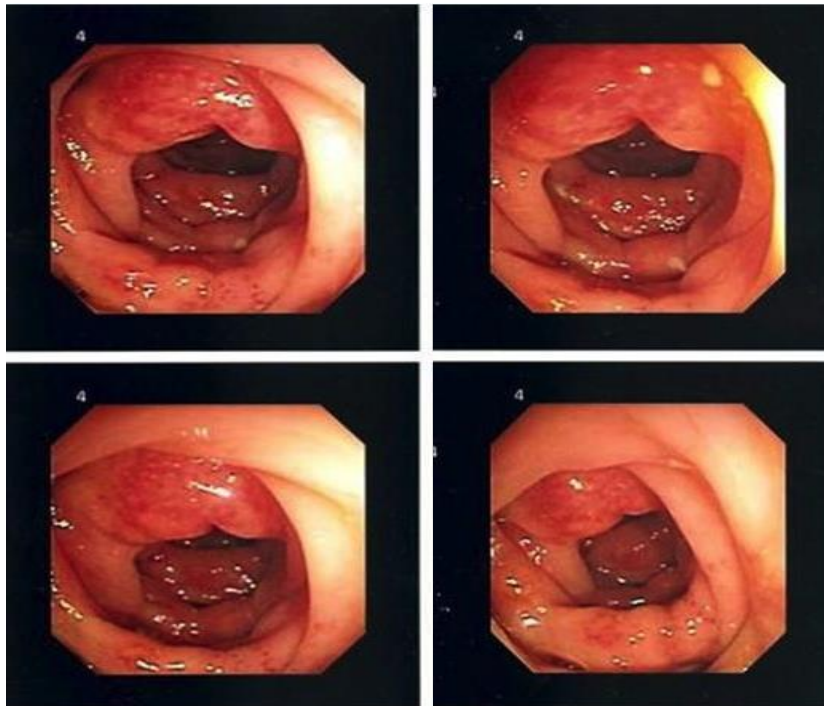
NSAID Colopathy, Lower, GI Bleeding



- Multiple different sized, aphthous ulcers
- Normal intervening mucosa
- Ileal ulceration

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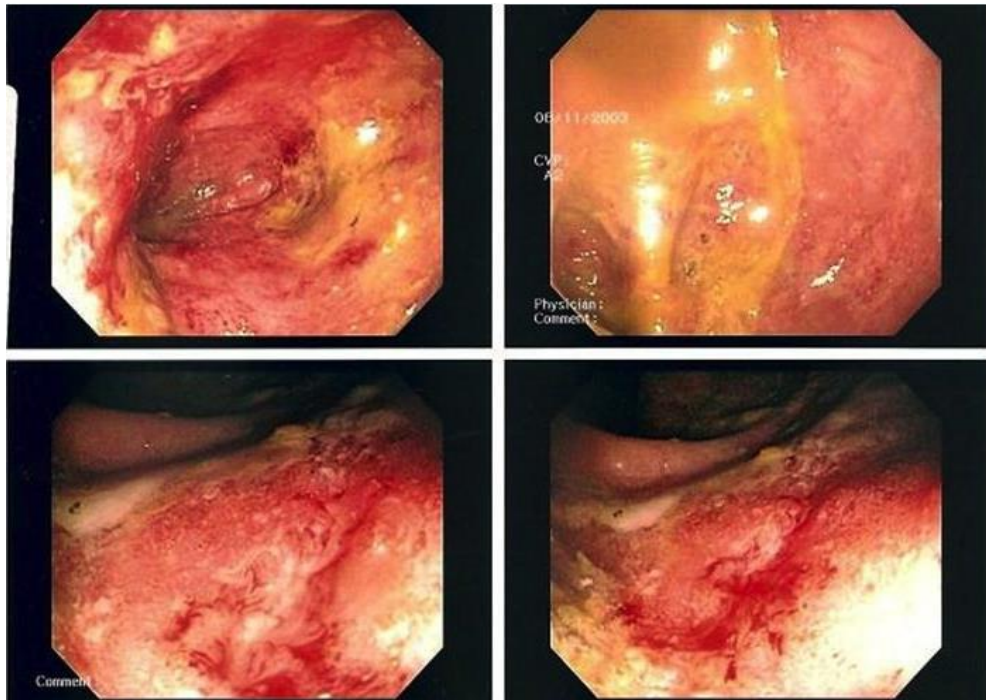
Rectal Bleeding, post-polypectomy (Adenoma 3 cm, removed-bleeding: injection, clips)



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Rectal Bleeding, Proctosigmoiditis



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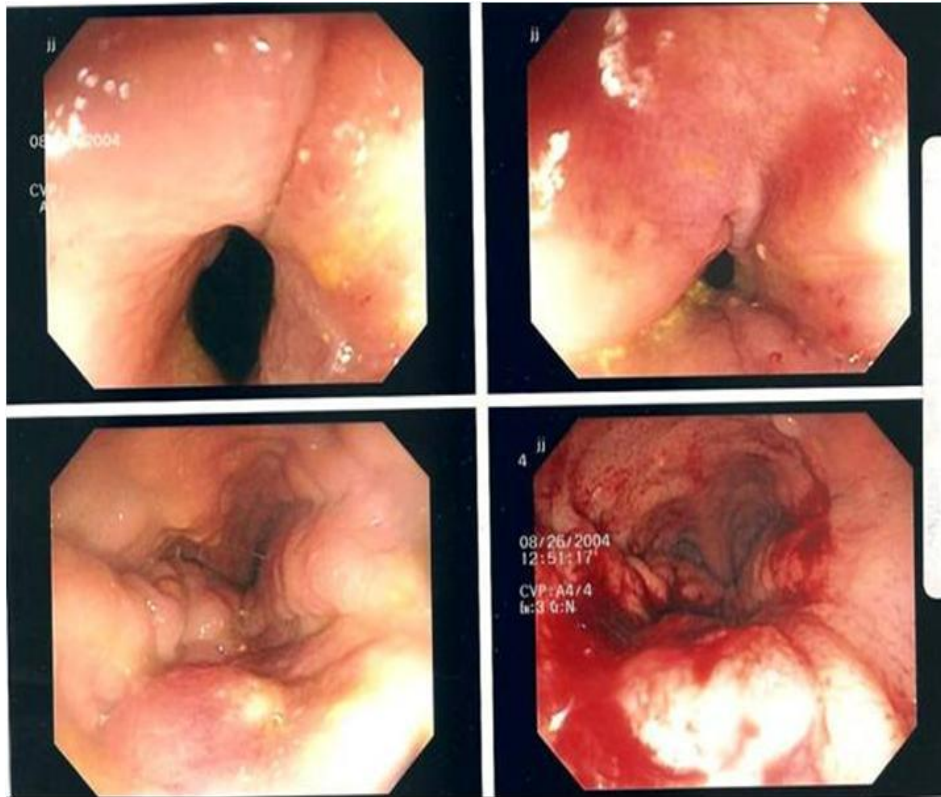
Rectal Bleeding after Balloon Dilation of Stricture



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Rectal Bleeding, Colitis



- Patchy redness in rectum and sigmoid colon
- Diffuse redness to splenic flexure

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"Belief in oneself is one of the most important bricks in building any successful venture"

Lydia M. Child



APPENDICITIS

➤ Diagnostic Imaging

- Barium studies
 - Filling defect at base of the cecum
 - Non-filling of the appendix (if fecolith present)
 - Folds
 - Thick
 - Tethered
 - Appendicolith
 - Laminated
 - Calcific densities
- Sonography (ultrasound)
 - Distention (≥ 6 mm diameter)
 - Fluid-filled appendix
 - Thickened wall (> 2 mm)
 - Appendicolith
- CT scan
 - Mass
 - Thick wall
 - Wall enhancement
 - Distention of appendix (by fluid)
 - Fluid in appendix (stranding attenuation)
 - Soft tissue stranding (fluid in surrounding fat) [periappendiceal]
 - Appendicolith
 - Periappendiceal fluid (abscess)
 - Types of appendiceal abscesses
 - Phlegmon
 - Abscess
 - Multicompartmentalized abscess
- Limitations of abdominal sonography
 - ↑ abdominal
 - Fat
 - Gas
 - Tenderness

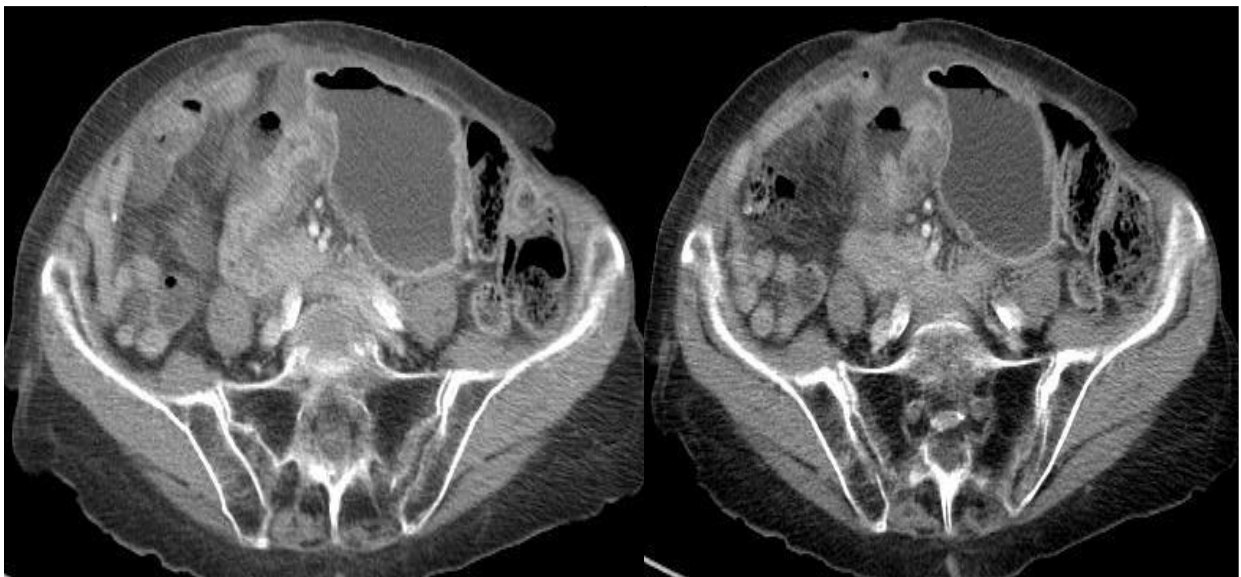


Appendicitis, CT scan



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Appendicitis, CT scan



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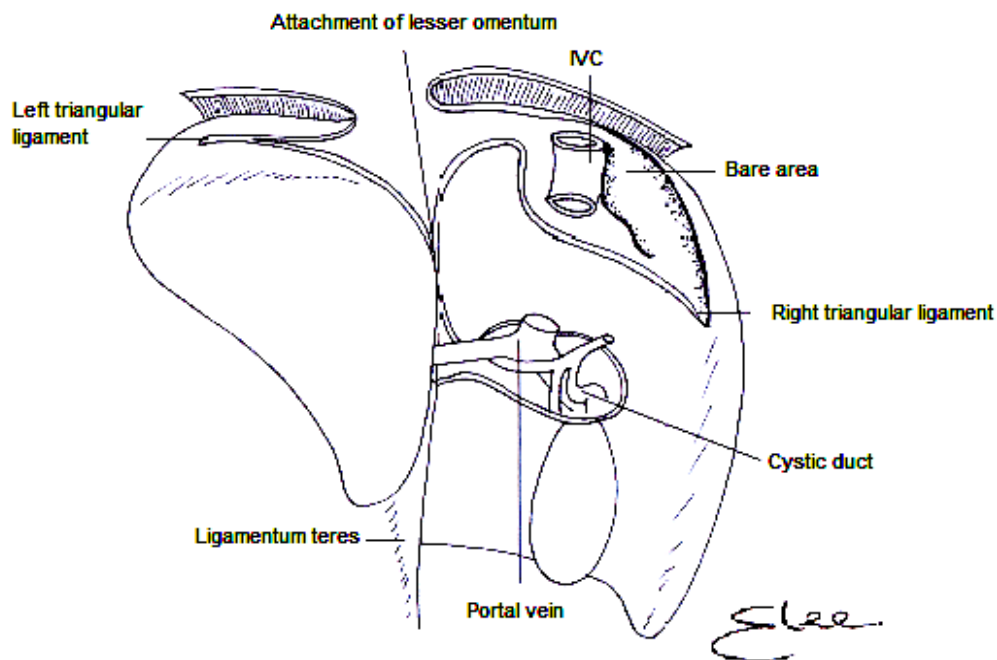
LIVER



GENERAL

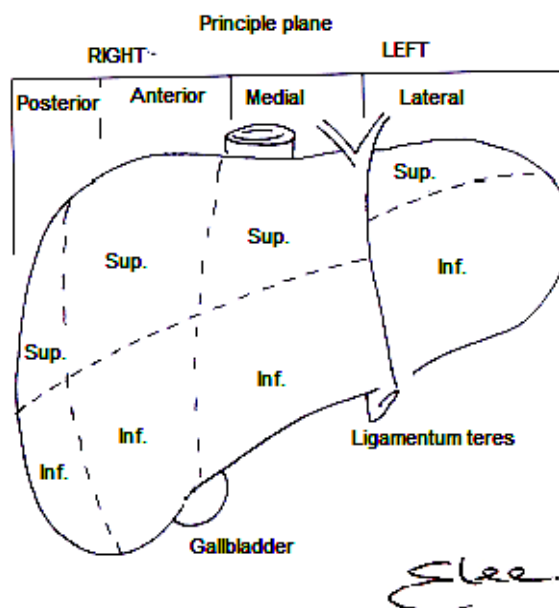
Anatomy of the Liver

- Posterior view of the liver, showing the right and left

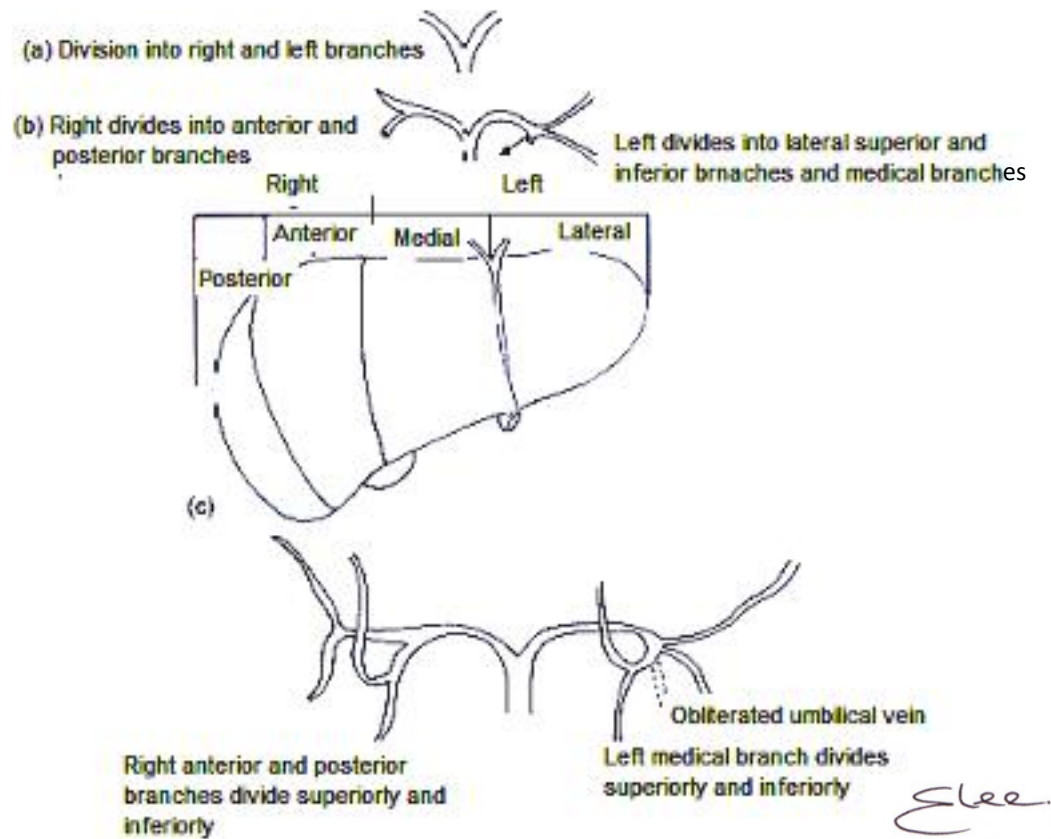


Triangular Ligaments

- Anterior view of the segments of the liver



➤ Intrahepatic branches of the portal vein



➤ Diagnostic imaging, CT

Normal CT Scan of Abdomen

- Size
- Attenuation
- Enhancement
- Lesions
- Capsule, surface
- Portal veins
- Hepatic veins
- Hepatic arteries

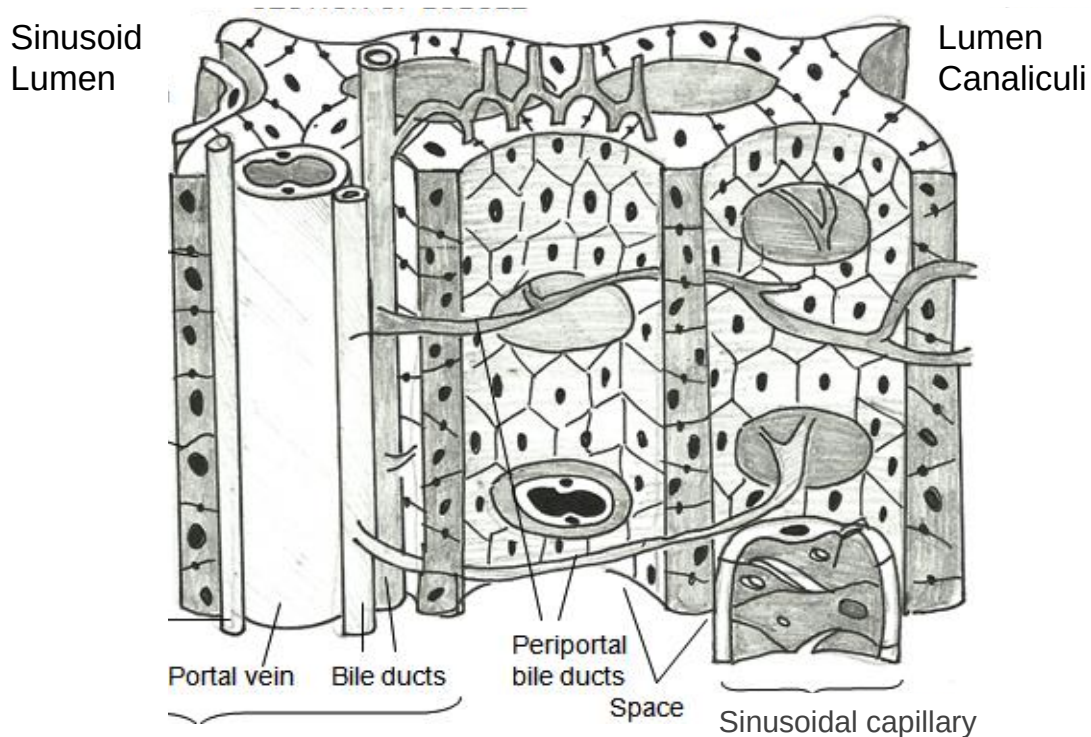


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Hepatocytes, Sinusoids, and the Intrahepatic Bile System

HEPATOCYTES, SINUSOIDS, AND THE INTRAHEPATIC BILE SYSTEM



Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 46-1, page 981.

Structure

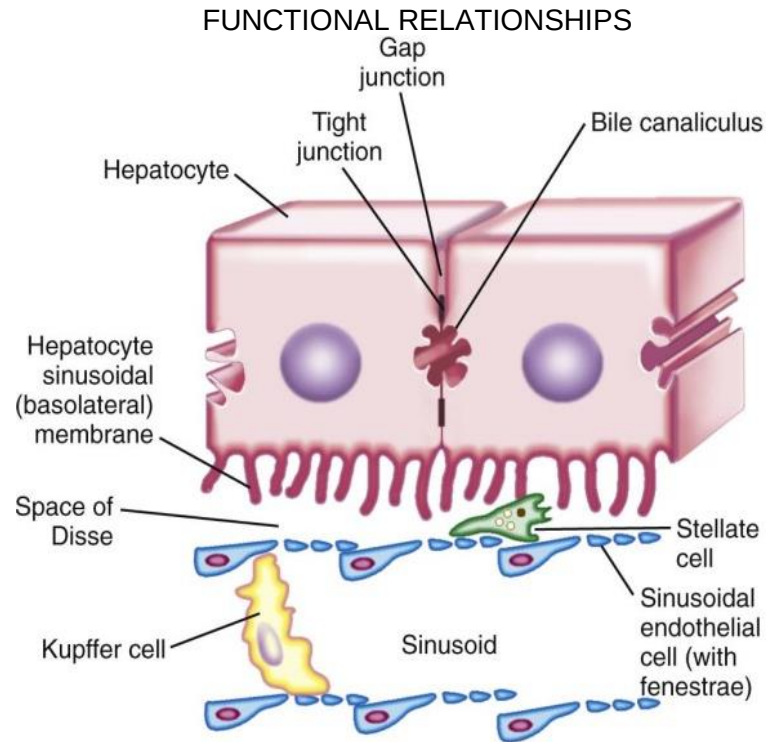
➤ Triad

- The portal triad consists of connective tissue containing a branch (or branches) of the hepatic artery (HA), portal vein (PV) and bile duct (BD)
- The hepatocyte plasma membrane is divided into 3 specialised domains, each covered by varying amounts of microvilli:
 - Sinusoidalal – faces the sinusoids
 - Lateral – faces the rest of the intercellular space between hepatocytes (the sinusoidal and lateral domains constitute the “basolateral” plasma membrane)
 - Bile canalicular – bounds part of the bile canaliculus
- Gap junctions allow some leakiness of the membrane, and thereby some passive movement of solutes.



- The extracellular matrix in the sinusoidal spaces of Disse contains the support structure or scaffolding for the liver lobules.
- Kupffer cells (fixed monocytes in the reticuloendothelial system [RES]) are in the sinusoidal spaces (of Disse), where they are in direct contact with the sinusoidal endothelial cells and portal blood.
- Stellate (fat-storing or “Ito”) cells also are in the space of Disse.
- These Ito or stellate cells store fat, and also act both as myofibroblasts, and as the source of the fibrotic reaction which leads to cirrhosis.
 - Stellate cells are not usually visible by light microscopy but may become hyperplastic and visible in hypervitaminosis A.
- At each corner of the hexagonal hepatic lobule is a triad, and in the center is a central vein (CV).
- Hepatic lobule represents the hepatocytes which drain into a central vein
- The Rappaport acinus represents the hepatocytes which drain into a bile duct in the hepatic triad.
- Plasma in the sinusoidal space comes into direct contact with hepatocytes in the space of Disse.
- The endothelial cells are fenestrated and lack a basement membrane. Thus, these endothelial cells are highly permeable.
- Stellate cells are between the endothelial cells and the hepatocytes.
- Two adjacent hepatocytes form a canaliculus, with the cells joined by tight junctions and the communicating gap junctions.
- The canalicular domain of the plasma membrane of two adjacent hepatocytes encloses and forms the bile canaliculus.
- Thus, there may be as few as three or as many as six portal tracts seen around any one lobule.
- Three conducting portal tracts (Cpt) here each split into three terminal portal tracts (TPT).
- The parenchyma has been diagrammatically represented as three zones which do not have a morphologically visible counterpart in routine histology.
- Zone 1 (Z1) is immediately around the terminal portal tract. Zone 2 (Z2) surrounds zone 1, and zone 3 (Z3), drawn in as hepatocytes and sinusoids, fills in the spaces between the Z2 down to the central efferent vein (CV).
- Each terminal portal tract is surrounded by zoned parenchyma and constitutes an acinus.
- Each group of three acini with their conducting portal tract form a complex acinus.
- Nine potential acini are illustrated, of which six are more fully detailed to include zone 3 hepatocytes.
- No acinus is complete because each will drain to more than one central vein.





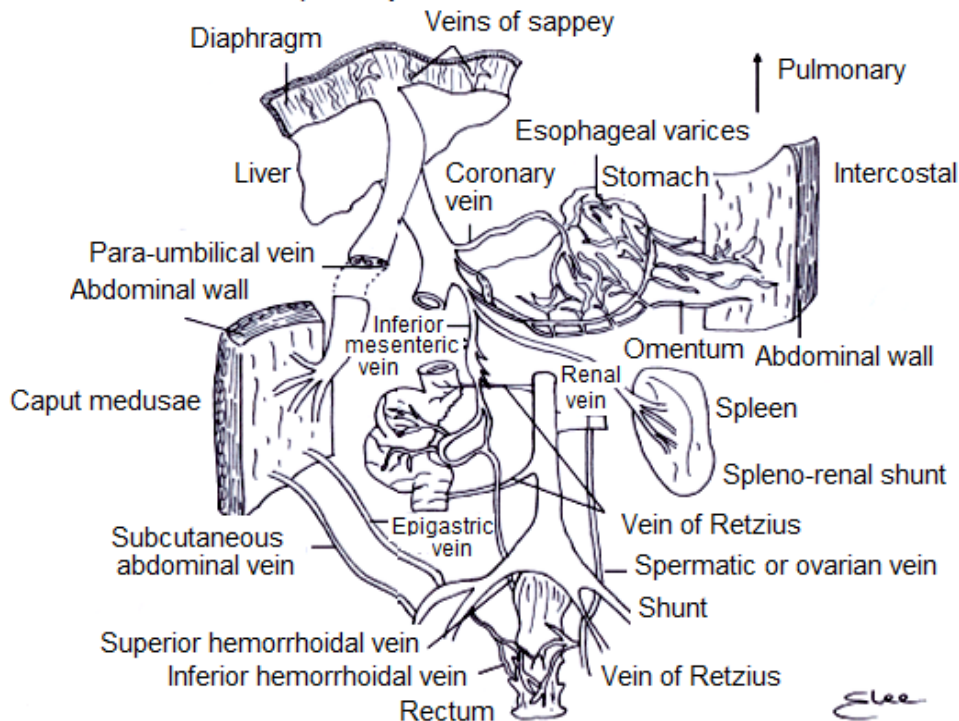
Adapted from: Roy-Chowdhury N and Roy-Chowdhury J. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 10th Edition. Saunders / Elsevier, Philadelphia, 2016; Figure 72-1, page 1224.

- The portal circulation is important for
 - The delivery to the liver of nutrients and other substances absorbed into or secreted by the intestine.
 - Progressive branching division into the right and left branches of the intrahepatic portal vein and its distribution to the lobes of the liver.
 - The development of increased pressure in the portal circulation leads to PHT (portal hypertension), which may be associated with the development of serious conditions such as bleeding esophageal varices, ascites, renal dysfunction, and hepatic encephalopathy.
 - Blood vessels that constitute the portal circulation and hepatic outflow tracts become distended as a result of increased blood flow and / or increased resistance, causing portal hypertension.



Portal Circulation

The sites of the portal systemic collateral in cirrhosis of the liver



Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, page 149, 9th Edition, 2010; and *Sherlock and Dooley*, page 61, 11th Edition, 2002.

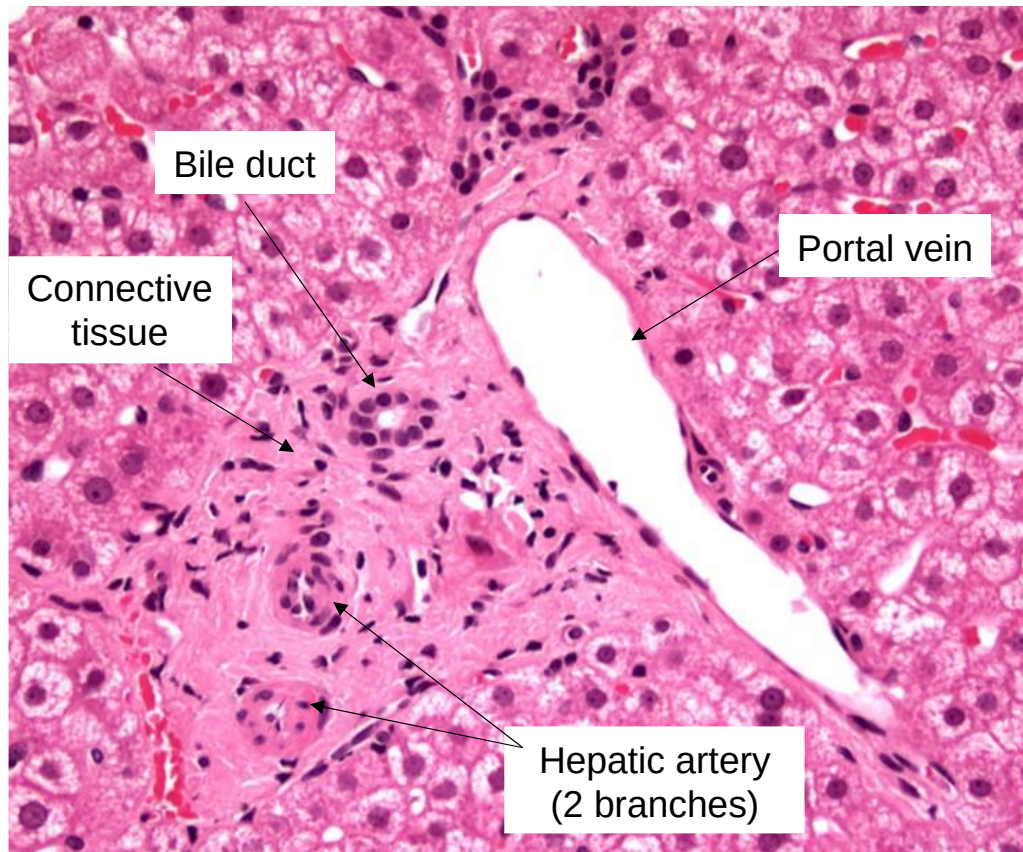
- Portal vein is posterior to the pancreas
- Division of the right branch into the anterior and posterior branches divide superiorly and inferiorly.
- Four segments of liver are supplied by the right anterior and posterior and the left lateral and medial branches
- Flows and pressures in hepatic vein (HV), portal vein (PV) and hepatic artery (HA):

	Flow, mL/min	Pressure, mmHg
- HV	1600	4
- PV	1200	7
- HA	400	100

- Inferior mesenteric vein
 - Superior mesenteric vein



Normal Liver Portal Triad



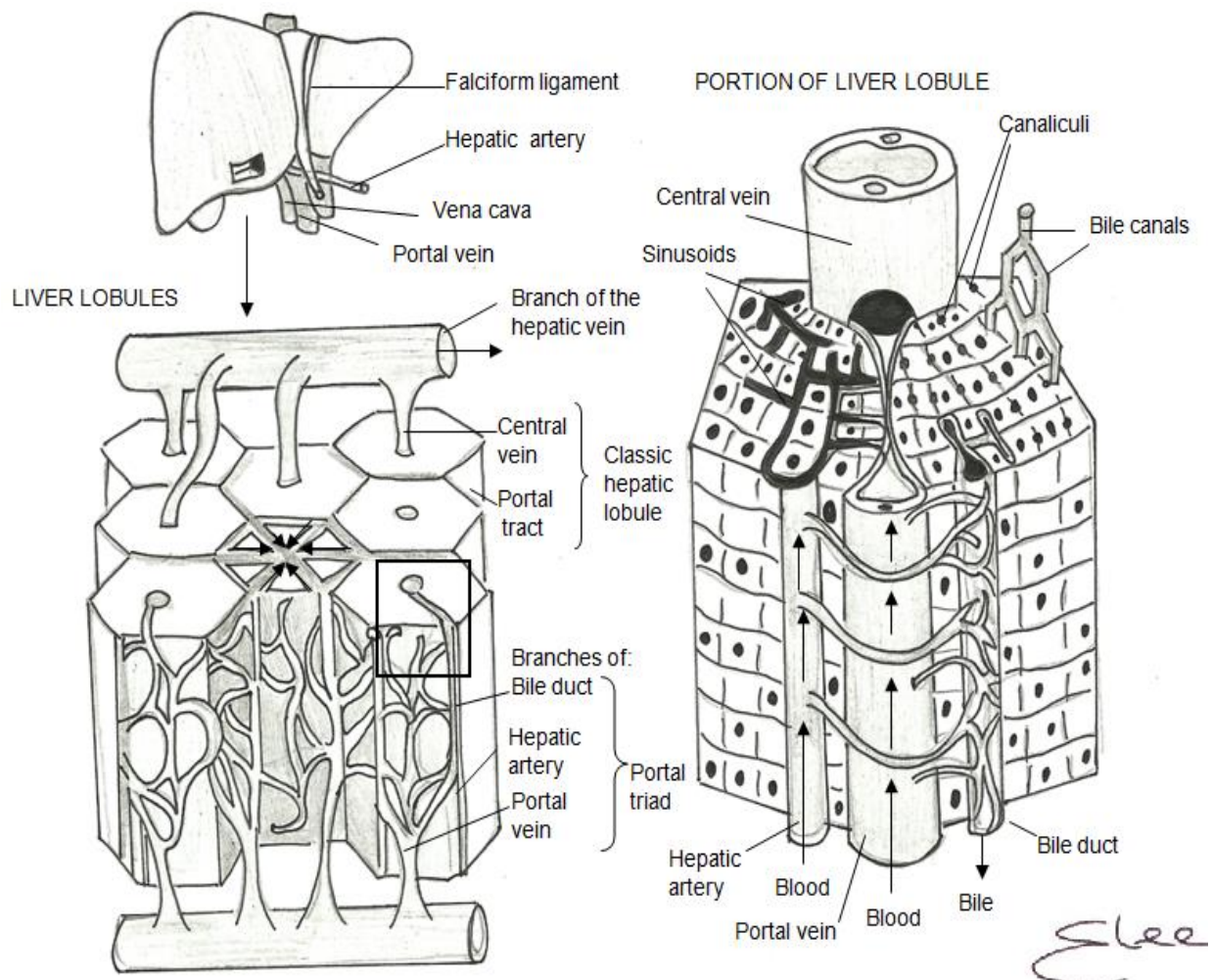
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Blood Supply and Flow to the Liver

- Blood to the liver flows in the portal vein (PV) and the hepatic artery (HA) (75% and 25%, respectively).
- Blood from the PV mixes with blood from the HA, flows to the central vein (CV), and then to the hepatic vein (HV).
- Blood from the HA flows into the sinusoidal capillaries, through the space of Disse (parasinusoidal space), between the microvilli of the hepatocyte basolateral membrane facing the sinusoid, and then into the hexagonally-shaped hepatocytes.
- The sinusoidal lumen is lined by fenestrated sinusoidal endothelial cells that allow the transport of macromolecules out of the space of Disse.
- Quiescent hepatic stellate cells reside within this space of Disse, adjacent to hepatocytes and endothelial cells.
- Hepatocytes which are close to the terminal portal vein (PV) and the terminal hepatic arteriole in the portal triad (zone I) have the richest blood supply.
- There is heterogeneity of hepatic function in zones I and III



- Zone I hepatocytes in the portal acinae are relatively resistant to toxic damage.
- The type and amount of substrate or xenobiotic presented to zone I hepatocytes is different from zone III.
- Zone I hepatocytes specialize in oxidative metabolism, whereas zone III hepatocytes specialize in biotransformation and drug detoxification.
- Hepatocytes in zone III near the central vein (CV) have a comparatively poor blood supply, and are more vulnerable to damage, especially ischemic injury.
- In cirrhosis, a number of changes occur in the hepatic microcirculation, including loss of fenestrae in endothelial cells (defenestration), constriction of sinusoids, and activation of hepatic stellate cells.
- Activation of the stellate cells with transformation to a myofibroblast like phenotype stimulates the formation of fibrosis.



Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 46-2, page 983.



➤ Histopathology

❖ Hepatocytes

- Polygonal cells, 20 to 30 µm in diameter
- Organized into “plates” of cells, 1-2 hepatocytes thick
- The nuclei of the hepatocytes are round
- The nuclei vary in size, and in adults 30% of hepatocytes may have 2 nuclei.
- These vesicles move from cis, to medial- and then to trans Golgi stacks (trans- Golgi network), and then to the cell membrane for exocytosis.
- Protein synthesized from the RER traffic to Golgi complex the cis side of outer membrane of nucleus is in continuity with the ER (endoplasmic reticulum).
- The ER contains cisternae
 - Rough ER (RER)
 - Attached ribosomes
 - Protein synthesis
 - Smooth ER (SER)
 - Lipid synthesis
 - Detoxification
 - Calcium regulation
- The endothelial cells of the sinusoids have fenestrae (pores).
- The size of the fenestrae can be changed
- The individual hepatocytes are joined by desmosomes (“..... specialized membrane structures that anchor intermediate filaments to the plasma membrane and link cells in the tight junctions”).
- Ca^{2+} and calmodulin act on filaments of actin to change the size of the fenestrae

❖ Kupffer cells

- Kupffer cells are tissue macrophages present in the lumen of the hepatic sinusoids
 - Tissue macrophages arise from monocytes and bone marrow stem cells
- Kupffer cell functions include:
 - Removing old red blood cells
 - Secreting lymphokine mediators
 - The Kupffer cell lymphokine mediators influence the hepatocytes to synthesize
 - Proteins
 - Mediators of inflammation
 - Prostaglandins
 - Low-density lipoproteins (LDL)

❖ Stellate cells (HSC, hepatic stellate cells; aka Ito cells) surround the wall of the sinusoids (perisinusoidal)



- Give the functions of the hepatic stellate cells.
 - Control the diameter of the lumen of the sinusoids
 - May become activated and express desmin and actin – transformation to a myofibroblast like phenotype
 - HSCs are activated by
 - Pro-inflammatory cytokines
 - Angiotensin
 - Oxidative stress (reactive oxygen species [ROS])
 - Growth factors
 - Extracellular matrix
 - Platelet-derived growth factor (PDGF)
 - Connective tissue growth factor
 - Leptin-associated production of TGF- β by Kupffer cells
 - Signals from Kupffer and endothelial cells
 - $\uparrow$ apoptosis, ROS $\rightarrow$ ROS paracrine stimulation of HSC
 - Altered ATP homeostasis
 - Mechanical stiffness of extracellular matrix (ECM)
 - Downregulation of Bambi-sensitized HSCs to TGF-B
 - HSCs alter cytoskeleton assembly increase extracellular matrix proteins (collagenous and non-collagenous glycoproteins, proteoglycans and glycosaminoglycans).
 - Receptors for vitamin A
 - Store vitamin A
- Give the regulated changes in gene expression which occur during activation of HSCs.
 - Transcription factors (modulation of the activity of transcription factors)
 - Transcription factors which activate the transcriptional targets of HSCs: Ets-1, Mef 2, CREB, EGR-1, vitamin D receptor, Foxf1, Jun D, and C / ERPB
 - HSC activation: α_1 and α_2 chains of type I collagen – α – SMA, TGFB1, TGF receptors MMP-2, and TIMPs I and 2
 - HSC inactivation (anti-fibrotic) – Lhx2 (LIM homeobox gene 2) - FoxO1 (forkhead box gene, group O)
 - Dominant – positive
 - b HLH (basic helix-loop-helix transcription factors)
 - E box DNA hexanucleotide sequence for b HLH binding
 - Myo D, SREBP-1c, C-Myb and C-Myc
 - Nuclear receptors
 - FXR (farnesoid X receptor)
 - RXR and FXR dimerize after “sensing” bile acids.
 - The dimerized RXR and FXR activate SHP.
 - SHP suppresses the expression of the collagen gene PXR (pregnane X receptor)
 - PXR is activated by steroids, certain drugs, xenobiotics and antibiotics.
 - PXR dimerizes with RXR and induces cytochrome P450 enzymes.



- PPARs (peroxisome proliferators-activated nuclear receptors)
 - ↓ HSC activation – expression of collagen gene.
- Retinoid responsive RXR and RAR
- Epigenetic regulation (methylation of promoters)
 - “Epigenetics refers to changes in DNA methylation and associated histone modifications that influence the chromatin states and impact gene expression patterns, without affecting the sequence of the target DNA.”
 - Activation of HSC leads to “global” reduction in methylation.
 - ↑ CBF1 and MeCP2 result in ↓ IKB by way of promoter methylation.
 - IKB repression results in de-repression of NFκB activity.
 - ↑ NFκB increases the survival of HSCs.
- Micro RNA
 - “micro RNAs (mi RNAs) represent a family of small non-coding RNAs controlling translation and transcription of many genes”
 - TGFβ, LPS and NF-κB down-regulate the miR-29 family of miRNAs
 - ↓ miR-29 enhances hepatic fibrosis (i.e., miR-29 is anti-fibrotic)
 - Post-translational regulation of transcription factors
 - Phosphorylation
 - Sumoylation
 - Prenylation
 - Acetylation
 - Glycosylation
- Pancreas
 - Insulin resistance
 - Obesity
 - Hyperinsulinemia
 - Increased serum leptin levels
 - ↑ β cell apoptosis
 - ↓ Insulin secretion
 - ↑ T2DM
- Muscle tissue
 - ↓ Mitochondrial function
 - ↓ VO₂ max
 - ↑ Insulin resistance

Abbreviations: ATP, adenosine triphosphate; ROS, reactive oxygen species; TNF-α, tumour necrosis factor-α; TGF-β, transforming growth factor-β.

Adapted from: Torres Dm and Harrison SA. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders / Elsevier, Philadelphia, 2010, Figure 87-5, page 1434; Lee UE et al., Best Practice & Research Clinical Gastroenterology 2011;25:195-206.



- ❖ Sinusoidal cells
 - Sinusoidal cells (aka HSECs [hepatic sinusoidal endothelial cells])
 - HSECs overlap, and form fenestrae by having
 - No junctions
 - No basement membrane
- ❖ The space of Disse
 - Is between the lining of the sinusoids and the hepatocytes
 - Contains plasma and collagen
 - This collagen in the space of Disse (type I, III and V) forms the scaffolding (skeleton) of the liver.
 - “There is bidirectional exchange of liquids and solutes between the plasma [in the portal venous blood] and hepatocytes at the sinusoidal surface [of the hepatocytes] (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 1207).
 - The skeleton is comprised of
 - Microfilaments
 - Polymers of G-actin
 - Act as highways for trafficking of intracellular proteins
 - α / β polymerized dimers of tubulin
 - ATP-driven motor proteins
 - Intermediate filaments
 - Laminins
 - Cytokeratins
 - Hepatocytes: CK8, CK18
 - Bile duct epithelium: CK8, CK18, CK19
 - Vimentin
 - Plectin
- ❖ Pit cells (aka liver NK [natural killer] cells)
 - Give the functions of the hepatic pit cells.
 - Express Ox-8 antigen
 - Kill tumour cells
 - Remove hepatocytes infected by virus
 - Intracytoplasmic membrane-bound sacs that contain protein kinase for protein degradation (autophagic lysosomal pathway)
 - CMA (chaperone-mediate autophagy). “..... is a selective mechanism for the degradation of altered cytosolic proteins in lysosomes” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 10th Edition. Saunders / Elsevier, Philadelphia, 2016, page 1231).



- ❖ The ubiquitin / proteasome pathway
 - Binds to misfolded proteins and directs proteasome-dependent proteolysis.
 - Regulate cytoplasmic protein trafficking
- ❖ Cell membrane
 - Dynamic polarization due to exo- / endocytosis
 - Endocytosis is non-selective, or selective by way of RME (receptor-mediated endocytosis).
 - Molecules, ligands bind to their membrane receptor and are taken up into the membrane.
 - Clathrin coated vesicles enter the cytoplasm and, lose the clathrin coat.
- ❖ The canalicular membrane of the hepatocytes
 - Secrets products into the bile canaliculus.
 - Flow across the canalicular membrane is unidirectional.
 - Bile flows into the terminal canals of Hering which are lined and formed by hepatocytes and cholangiocytes.
 - All membranes of the hepatocyte have microvilli in varying density.
- ❖ The central vein (aka terminal hepatic venule) is at the periphery of the acinus or centre of the lobule
 - Between the portal tract and the central vein are 3 zones of hepatocytes
 1. Periportal
 2. Intermediate
 3. Perivenular
- Terminology
 - Riedel lobe
 - A incidental variant of normal development, leading to a tongue like downwards projection of the anterior right lobe of the liver.

“No act of kindness, no matter how small, is ever
wasted.”

Aesop



CIRRHOSIS

➤ Diagnostic imaging

❖ CT

- Small (≤ 3 mm) and large (> 3 mm) liver nodules
 - Heterogeneous
- Nodules
 - Multiple
 - Small / large
- Lobe L $>$ R
- Spleen – enlarged
- Esophageal varices
- Recanalized “umbilical veins” (enlarged collateral veins (i.e., a paraumbilical vein); when large, are called “caput medusae”)

❖ MRI T₁

- Weighted
- Multiple nodules
 - Small / large
- Low-signal intensity on T₁
 - Varying signal intensity
 - High signal intensity on T₁

❖ MRI T₂

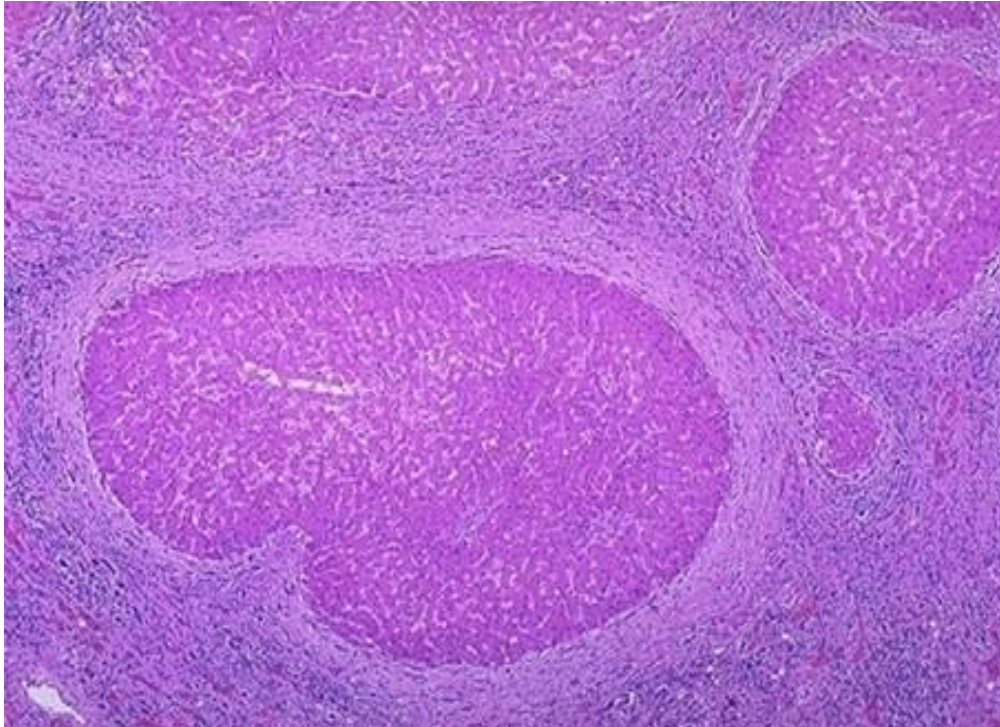
- Weighted, unenhanced
- High signal intensity mass

➤ Pathology

- Give the typical pathological features of Cirrhosis.
 - Disruption in architecture of entire liver
 - Bridging fibrous septa
 - Rounded parenchymal nodules of regenerating hepatocytes without central veins

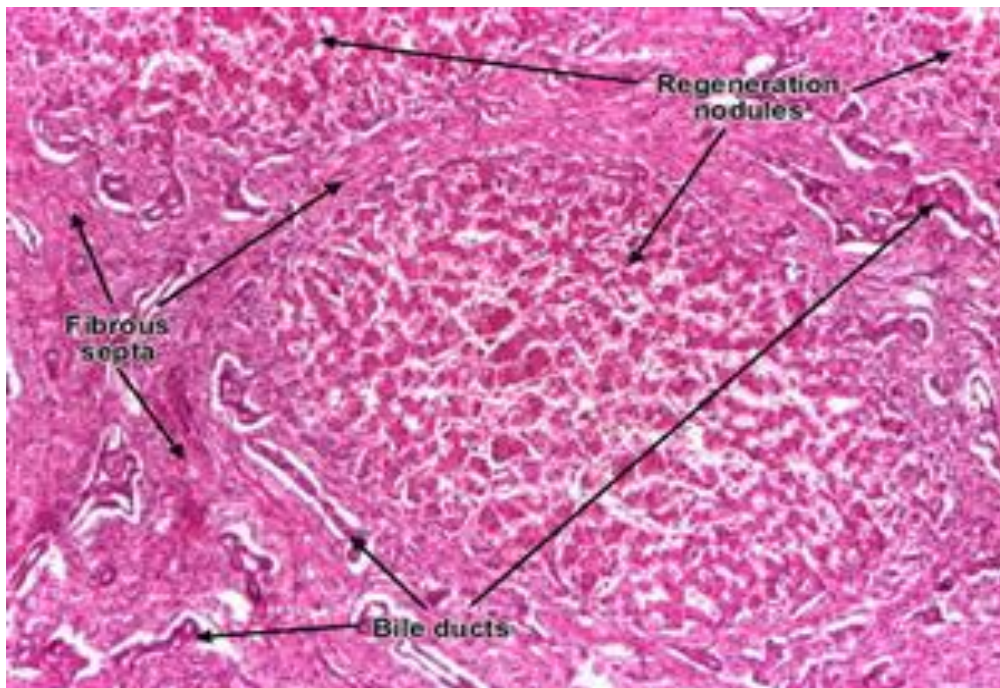


Hepatic Cirrhosis



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Hepatic Cirrhosis



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HEREDITARY HEMOCHROMATOSIS (HH)

➤ Definition

- HH is an autosomal recessive disorder in the HFE gene on chromosome 6, leading to either the C282Y or the H63D mutation, low expression of hepcidin (the hepatic iron-regulatory protein), and iron loading of the hepatocytes as well as some other tissues (skin, joints, pancreas, heart).

➤ Demography

SO YOU WANT TO BE A HEPATOLOGIST!

- Give the reason why the prevalence of HH associated with celiac disease may be underestimated.
 - Risk of CD (celiac disease) in HH (hereditary hemochromatosis), OR (odd ratio) ~ 2.2
 - The clinical expression of HH may have been reduced by CD, due to malabsorption of iron.
 - So the OR of CD + HH may be even higher

➤ Diagnostic imaging

- T₂ – weighted MRI liver: diffuse, low-signal intensity (↑ attenuation)
If focal high-signal intensity, possible HCC
Spleen: high-signal intensity
- Give the typical MRI findings in early HH, without cirrhosis or HCC.
 - ↓ Signal intensity of liver (darker) as compared with spleen, on T-2 weighted image
- Give the radiological features of the arthropathy of HFE-related HH.

The arthropathy of HFE-related HH has the following characteristics

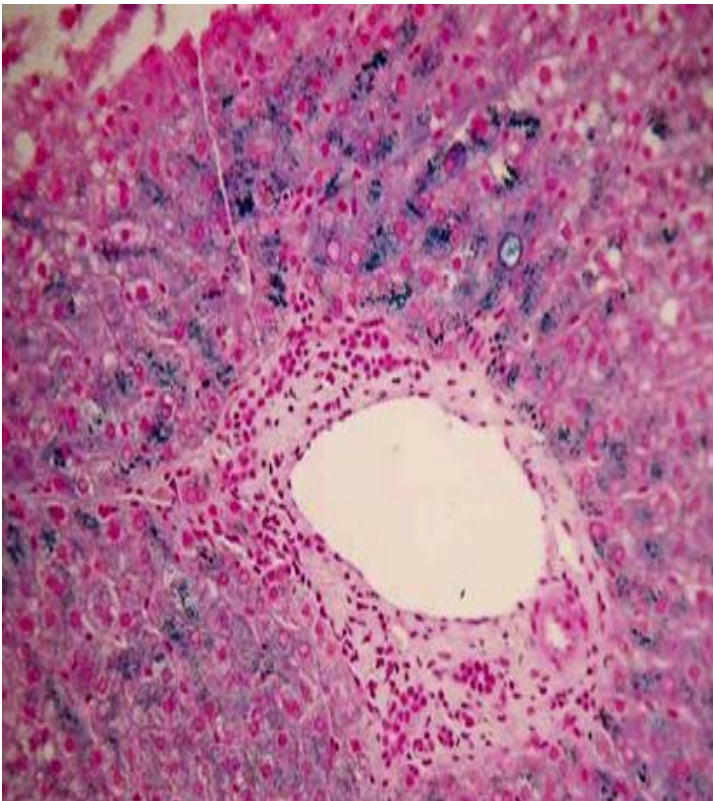
- Second and third metacarpophalangeal joints, or knees
- Joint space – narrow
- Joint swelling
- Chondrocalcinosis
- Subchondral cysts
- Osteopenia



➤ Pathology

- Liver biopsy in the person with HH is not necessary if
 - They are young (< 40 years)
 - Liver enzymes are normal, and if serum ferritin concentration is < 1000 mg/mL.
 - Otherwise, fibrosis or cirrhosis might be suspected, and liver biopsy would be indicated
- Perl's Prussian blue stain shows excess iron in the hepatocytes in HH, +/- fibrosis around the portal area, especially when the hepatic iron concentration is > 16,000 µg/g liver dry weight
 - Maximal iron loading of hepatocytes eventually results in positive iron staining in bile duct epithelial cells – this finding is highly suggestive of HH
- Cirrhosis
- ↑ risk of HCC, even without cirrhosis
 - It is important to treat patients with HH, to prevent the 20x ↑ risk of HCC.
 - Even when the HH cirrhosis patient has a liver transplantation, they remain at ↑ risk of cardiac disease.

Hemosiderin in Zone 1 hepatocytes in Type 1 HH

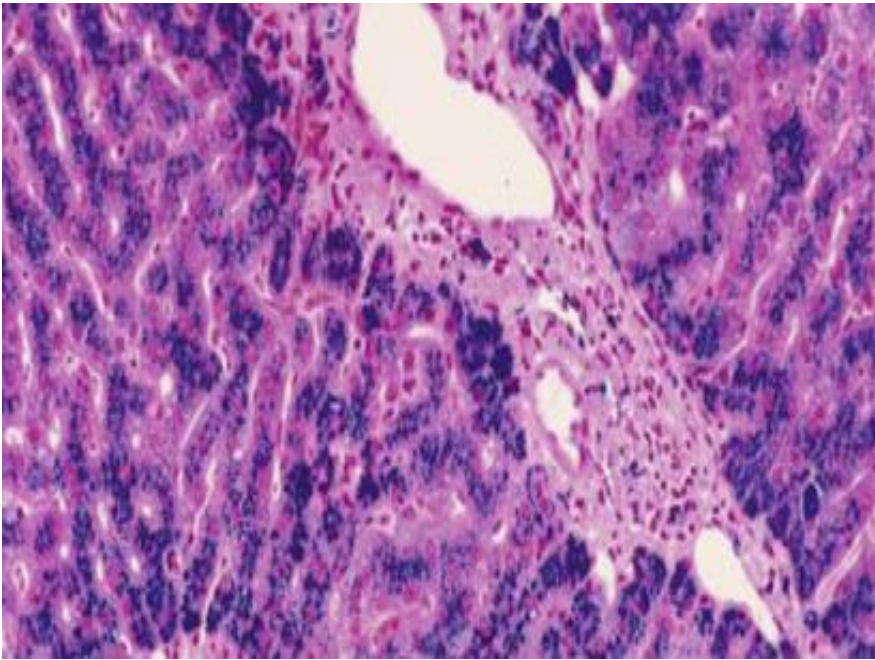


- In HFE-related Type 1 HH, iron accumulation begins as hemosiderin in periportal ('zone 1') hepatocytes.
 - The clinical significance will be related to rate of iron accumulation.
 - The calculated iron content for this biopsy was 7633 µg/g dry weight liver and the patient's age was 24, resulting in a calculated hepatic iron index of 5.7.
 - At this rate of accumulation, fibrotic-range iron accumulation (approximately 15000 or greater) will occur eventually. In contrast.
 - If the patient had been 84 years old, the hepatic iron index would have been 1.63, reflecting relatively mild gene penetrance and little risk of significant iron-related symptoms.

Printed with permission: Batts KP. Modern Pathology 2007; 20: S31-S39.



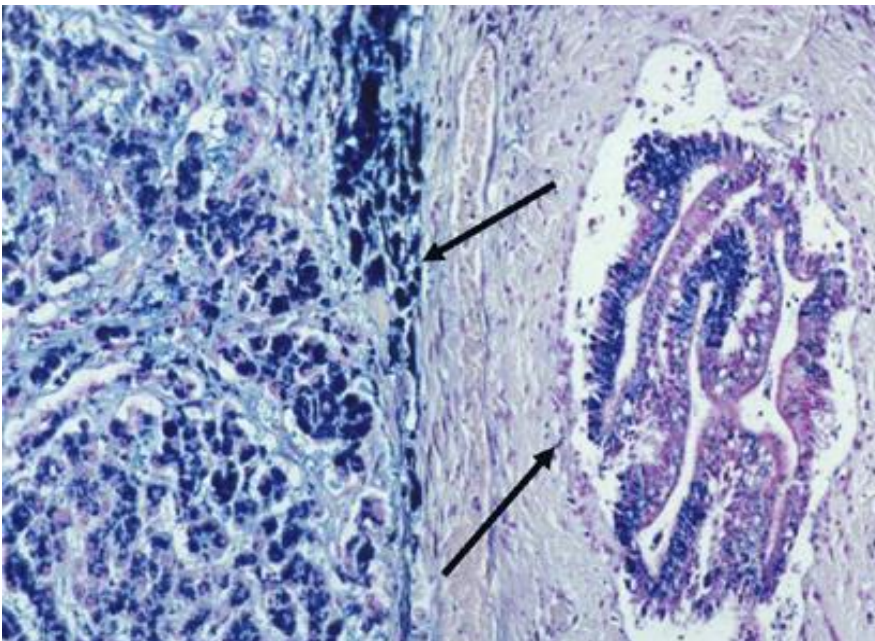
Panlobular Hemosiderin Accumulation in Type 1 HH



- The entire lobule has accumulated iron ('grade 4') and the measured iron content was 23000 µg/g dry weight liver.
- This represents highly penetrant HH regardless of age
 - High risk of developing significant fibrosis in the near-term
 - The likelihood of extrahepatic manifestations of HH is high as well.

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Marked Iron Accumulation in Cirrhosis due to Type 1 HH



- In addition to grade 4 iron accumulation in hepatocytes, many iron-laden macrophages are present (upper arrow)
 - This is a reflection of prior hepatocyte sideronecrosis and redistribution of iron into macrophages.
- Accumulation of iron in biliary epithelium is sometimes seen in severe disease when hepatocytes are maximally loaded with iron (lower arrow).

Printed with permission: Batts KP. Modern Pathology 2007; 20: S31–9.



BUDD CHIARI SYNDROME (BCS)

➤ Definition

- Obstruction of the hepatic venous outflow occurring anywhere from the right atrium to the small hepatic venules.

➤ Diagnostic imaging / histology

- MRI (contrast enhanced)
- Doppler ultrasound
- CT
 - Liver-heterogeneous diffuse, enhancement (hyperattenuation) of hepatic parenchyma
 - Hepatomegaly
 - Ascites
 - Chronic B-CS: parts of liver:
 - Peripheral – atrophy
 - Candidate lobe, hypertrophy
 - Portal vein thrombosis
 - Compression of IVC
 - Thombus (↑ density)
- Wedge hepatic venogram
 - “spider-web” pattern of intrahepatic collaterals (pathognomonic for sublobular venous occlusion) Liver biopsy (zone 3 congestion)
- Primary BCS – membranous obstruction of hepatic veins
- 2° BCS – obstruction of
 - Central and sublobular venous flow to liver, or
 - Obstruction of major hepatic veins

➤ Histopathology

- Give the acute and chronic histopathological changes of Budd-Chiari Syndrome.
 - Acute centrilobular
 - Wide subendothelium surrounding central veins
 - Congestion
 - Distention
 - Hemorrhage
 - Necrosis; may be central-central bridging necrosis
 - Hepatocyte dropout
 - Little inflammation
 - Chronic
 - Patchy, asymmetrical involvement
 - Perivenular sclerosis
 - Hepatocellular necrosis
 - Regenerative nodules
 - Cirrhosis



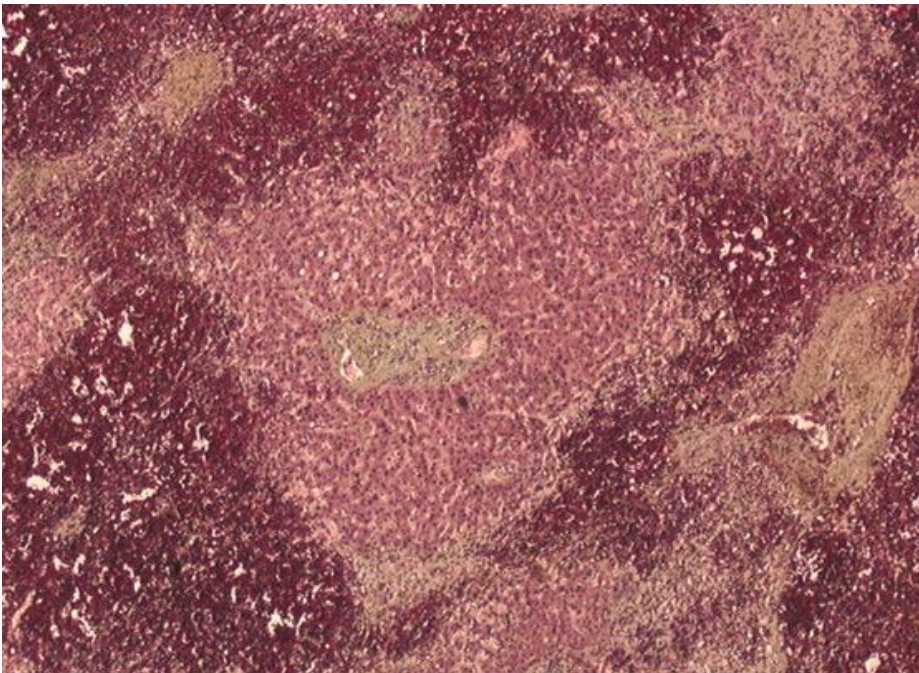
➤ Treatment

- Treat any esophageal varices
- Cause
 - Anticoagulants, thrombolysis, venesection
 - Cytotoxic drugs
- Surgical
 - Porta-caval shunt
 - TIPS (if incomplete obstruction)
 - Embolectomy (selected cases)
 - Liver transplantation
 - Note: the “uncorrected” MELD score does not take into account the refractory ascites which is common in BCS

Abbreviations: HV, hepatic vein; IVC, inferior vena cava; PV, portal vein

Adapted from: Stevens WE. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology / Diagnosis / Management* 2006: pg. 1756.; and Printed with permission: Kamath PS. *Clinic Gastroenterology and Hepatology Board Review* 2008: pg. 343; and 2010, pg. 1372.

Acute Budd-Chiari Syndrome

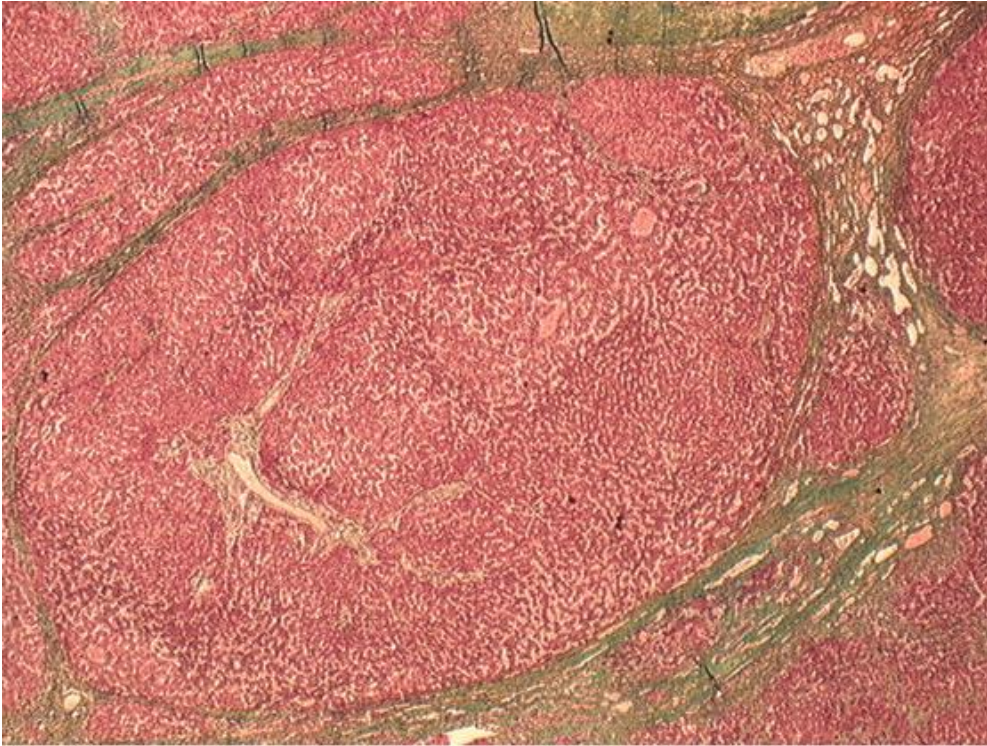


Extensive ischemic and congestive necrosis of centrolobular areas without fibrosis.

Printed with permission: Paradis V, et al. *Gut* 2005;54:1776-81.



Chronic Budd-Chiari Syndrome



- Extensive fibrosis (score 4), termed “venoportal cirrhosis”.
- Note the portal tract included in the nodule

Printed with permission Paradis V, et al. Gut 2005;54:1776-81.

“Health is the greatest gift, contentment the
greatest wealth, faithfulness the best
relationship.”

Buddha



WILSON DISEASE (WD)

➤ Definition

- An autosomal recessive condition caused by a mutation in ATP1B WD gene on chromosome 13, resulting in reduced secretion of copper from the liver into the bile, and accumulation of excessive copper in numerous tissues such as CNS, eye, liver, red blood cells, kidney.

Exam alert

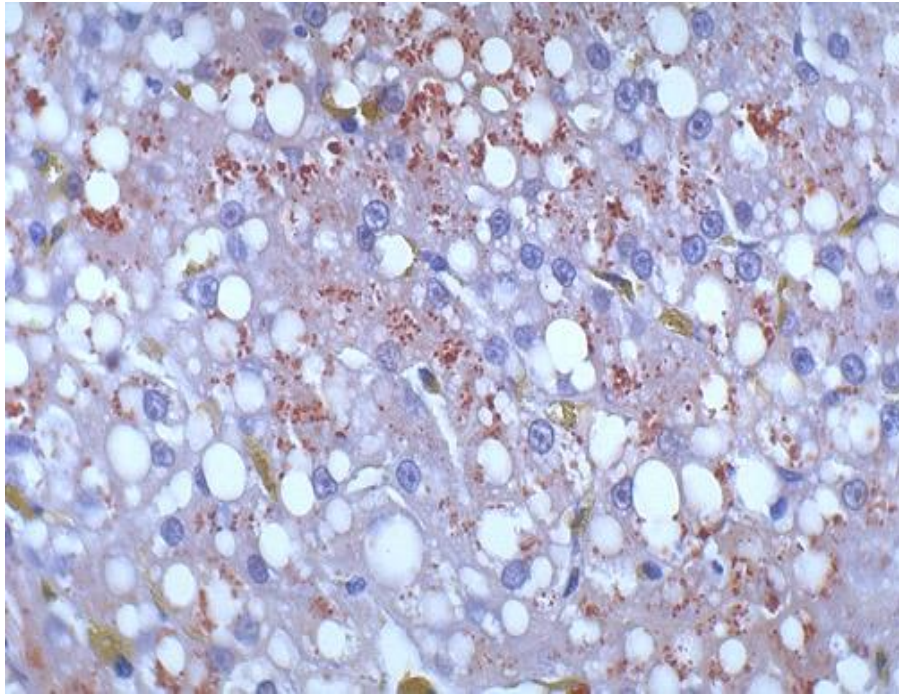
- Curiosity and Caution: WD is very rare, but is frequently tested (or over-tested) in written and clinical examinations.
- Watch out: NAFLD may occur in WD, which you should suspect from
 - Neurological symptoms / signs
 - ↓ serum alkaline phosphatase (AP), ↓ uric acid
 - Hemolytic anemia
 - Kayser-Fleisher (KF) rings
- Be sure to associate WD with liver disease plus neuropsychiatric symptoms (and especially Parkinsonian symptoms), Kayser-Fleisher rings from a copper-sulfur granular complex in Descemet membrane of the cornea, and sunflower cataracts from copper deposited in the lens of the eye.
- Caution: NAFLD is common and WD is rare; fatty liver is common in WD. So when you see MCQ of a person with NAFLD, always ask yourself-could this be a WD, especially if they have cirrhosis with bland steatosis (rather than steatohepatitis)?

➤ Histopathology

- Give the histopathological changes in the liver in WD.
 - Lysosomal deposits of Cu-metallothionein (orcein stains), initially in periportal hepatocytes but becoming panlobular
 - Inflammation, including parenchymal and portal inflammatory cell infiltrates
 - Mallory bodies
 - Patchy involvement of cystic dilation of mitochondrial cristae on EM



Wilson Disease



- The red-brown granular material is excessive lysosomal copper in a patient with the rare autosomal recessive disorder Wilson disease.
- Hepatic copper accumulation results in fatty change, cholestasis, acute / chronic hepatitis, and eventual cirrhosis.

Source: <https://library.med.utah.edu/WebPath/HISTHTML/STAINS/STAIN037.html>

➤ Scoring systems

❖ Scoring system developed at the 8th International Meeting on Wilson disease.

Findings	Score	Findings	Score
○ Coombs-negative hemolytic anemia		○ Mutation analysis detected	
– Present	1	– On both chromosomes	4
– Absent	0	– On 1 chromosome	1
		– No mutations detected	0

TOTAL SCORE	Evaluation
≥ 4	Diagnosis of WD established
3	Diagnosis possible, more tests needed
≤ 2	Diagnosis very unlikely

Printed with permission: European Association for Study of Liver. EASL Clinical Practice Guidelines: Wilson's disease. J Hepatol. 2012;56(3):671-85, Table 5.



❖ Scoring system developed at the 8th International Meeting on Wilson disease.

Findings	Score	Findings	Score
○ KF rings		○ Liver copper	
- Present	2	- > 5x ULN (> 4 µmol/g)	2
- Absent	0	- 0.8-4 µmol/kg	1
		- Normal (< 0.8 µmol/g)	-1
○ Mallory bodies		- Rhodamine-positive granules	1
- Severe	2		
- Mild	1	○ Urinary copper (in the absence)	
- Absent	0	- Normal	0
		- 1.2x ULN	1
○ Serum ceruloplasmin		- > 2x ULN	2
- Normal (> 2 g/L)	0	- Normal but > 5x ULN	3
- 0.1- 0.2 g/L	1		
- < 0.1 g/L	2		

A1- TRYPSIN (A1-AT) DEFICIENCY

➤ Genetics

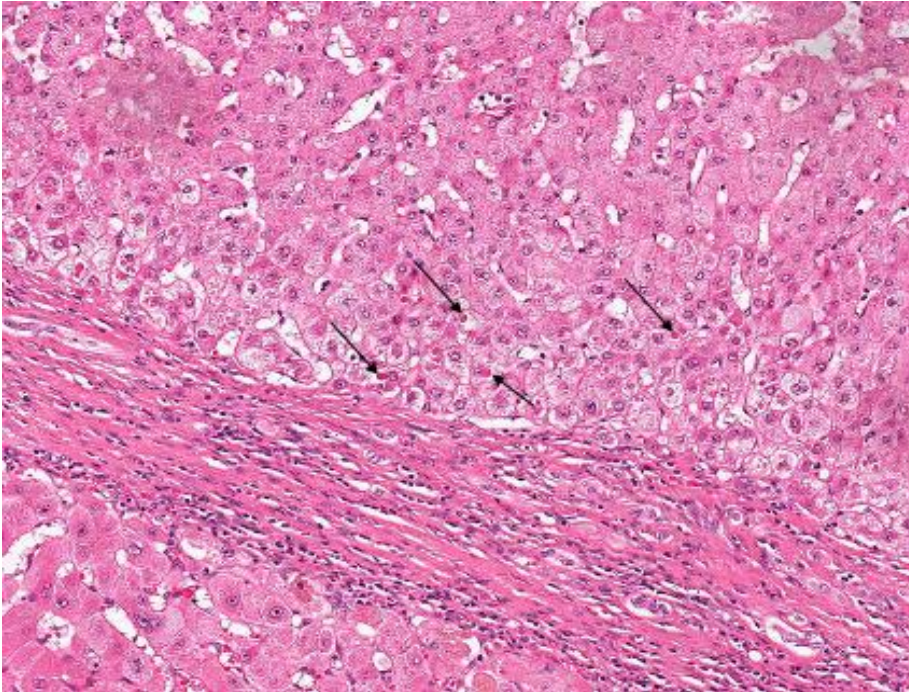
- Autosomal recessive disorder associated autosomal co-dominant mutation in A1AT (serine protease inhibitors) on chromosome 14
- Leading to chronic disease of lungs (emphysema) and liver (cirrhosis)

➤ Histopathology

- Give the histopathology of α1-AT deficiency.
 - Findings in pediatric patients may be of cholestatic hepatitis mimicking neonatal hepatitis or biliary atresia
 - ↓ bile ducts
 - Intracellular cholestasis
 - Inflammation – usually minimal
 - PAS (periodic acid-Schiff) – positive, diastase-resistant globular inclusions of polymers of α1-ATZ protein in periportal hepatocytes
 - IHC (immunohistochemistry)
 - Staining with monoclonal antibody to α1-ATZ confirms α1-ATZ proteins in the globular inclusions.



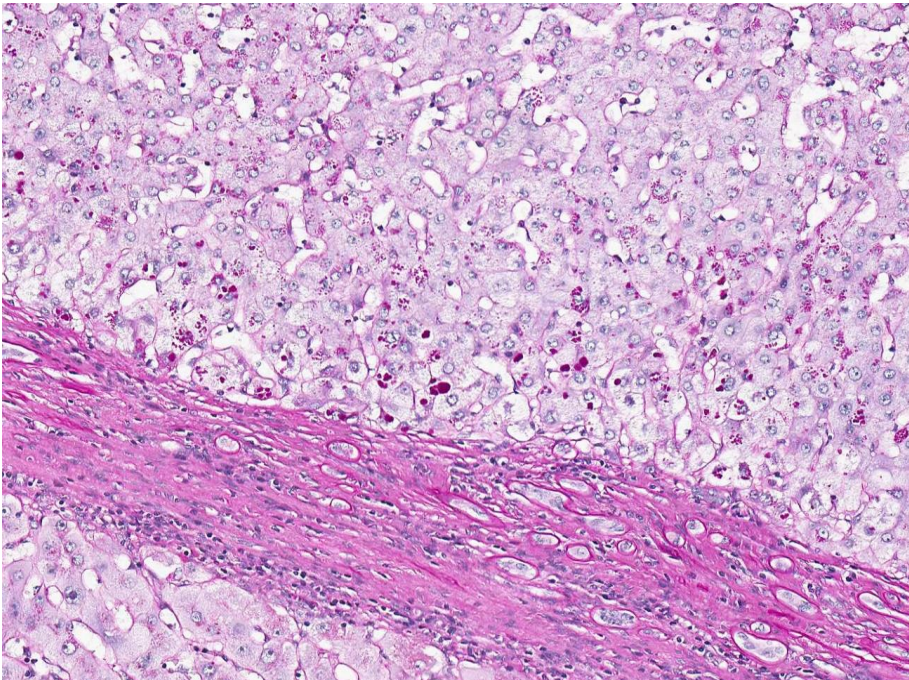
Alpha-1 Antitrypsin Deficiency (A1AT)



Liver containing brightly eosinophilic alpha-1-antitrypsin globules (arrows, H&E 200X)

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Alpha-1 Antitrypsin Deficiency (A1AT)

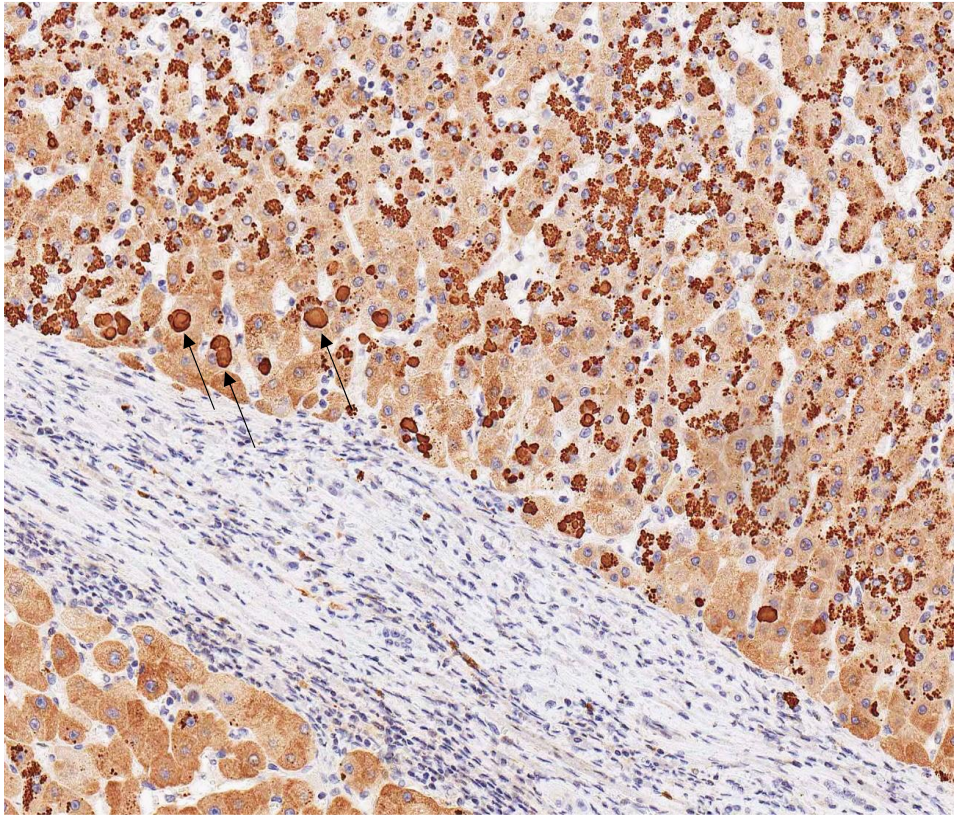


Liver containing alpha-1-antitrypsin globules (PASD 200X)

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Alpha-1 Antitrypsin Deficiency (A1AT)



Liver containing alpha-1-antitrypsin globules (arrows, A1AT immunohistochemistry 200X)

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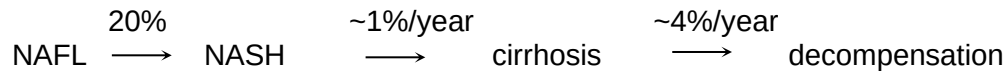
"Knowledge speaks, but wisdom listens."

Jimi Hendrix



NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

➤ Demography



- About 2/3 of NAFLD are simple steatosis and 1/3 are non-alcoholic steatohepatitis (NASH)
- Only 10-15% weight reduction reduces hepatic fat (Harrison SA, Day CP. *Gut* 2007;1760-9)

➤ Diagnosis

- High risk groups
- Unsuspected fatty liver on abdominal ultrasound → assess for causes of fatty liver:
 - Diabetes Type 2 / glucose intolerance
 - Obesity
 - Dyslipidemia
 - Drugs/Alcohol intake
 - HCV, genotype 3
 - HH (hereditary hemochromatosis)
 - WD (Wilson disease)
 - High titres of autoantibodies
 - Anti-tTG (tissue transglutaminase, suggestive of celiac disease)
- NAFLD fibrosis score / FibroScan®
- Liver biopsy for
 - Metabolic syndrome, ↑ Fibrosis score / FibroScan®
 - Other causes of hepatic steatosis have been excluded
- NAFLD and NASH may be distinguished using the Kleiner scoring system, also known as “NAS” (NASH activity score) (Kleiner DE, et al. *Hepatology* 2005;41:1313-21.)
- Based on:
 - Simple steatosis
 - Steatosis plus inflammation alone
 - Steatosis plus ballooning
 - Steatosis plus fibrosis (Matteoni CA, et al. *Gastroenterology* 1999;1413-1419.)
- Insulin resistance is easily measured using homeostatic model assessment)

Diagnostic Tip

“In NAFLD-associated cirrhosis, the typical histological features of NAFLD may be minimal or absent, potentially leading to the misdiagnosis of cryptogenic cirrhosis” (Feldman M., et al. *Sleisenger and Fordtran’s Gastrointestinal and Liver Disease*. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 1407).

- Approximately 1/3 of NAFLD patients have the same histology (over 1 to 14 years), 1/3 improve and one third worsen; however
- There may be sampling error and misclassification of histological grade
- Because NAFLD is a diffuse process, it is not clear how important an effect this sampling error would have



➤ Diagnostic Imaging

- Ultrasound (US) ↑ echogenicity
- CT liver density = spleen
- MRI bright T1 – weighted imaging of liver
 - Detection of > 33%, fat in liver; sensitivity
 - Sensitivity
 - US, 100%
 - CT, 93%
 - PPV
 - US, 62%
 - CT, 76%
- Support the diagnosis of NAFLD
- US, CT, MRI do not predict severity: do not distinguish simple steatosis from NASH

Abbreviations: PPV, positive predictive value; NASH, non-alcoholic steatohepatitis

- FibroScan® (aka TE [transient elastography])
 - Useful to identify advanced but not early cirrhosis from
 - HCV
 - PBC (primary biliary cholangitis)
 - HH (hereditary hemochromatosis)
 - NAFLD
 - Recurrent chronic hepatitis after liver transplantation
- MRE (magnetic resonance elastography)
 - “...superior to TE for staging liver fibrosis in patients with a variety of chronic liver disease” (Feldman M., et al. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 1235)
- Liver biopsy
 - “Gold standard”, but is actually only the “bronze standard” because of considerable sampling variation (patchy changes)
 - Severe steatosis (often centrilobular, macrovesicular)
 - ↑ Stainable iron more common with alcohol associated fatty liver
 - Signs of cirrhosis
 - Performance characteristics for fibrosis, cut-off value
 - High cut-off (0.70)
 - PPV, 73%
 - Specificity, 98%
 - Low cut-off (0.30)
 - NPV, 90%
 - 0.30 to 0.70, inaccurate (range includes 1/3 of NAFLD patients tested with Fibro Test)

Abbreviations: NPV, negative predictive value; PPV, positive predictive value

Adapted from: Pinzani, et al. *Nat Clin Pract Gastroenterol Hepatol* 2008; 5(2): pg 102; and Reid AE. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology / Diagnosis / Management* 2010, pg 1408.



SO YOU WANT TO BE A HEPATOLOGIST!

Bariatric surgery may improve NASH, give how useful is dieting for persons with NASH.

- o There is an inverse linear relationship between increasing weight loss and a decline in NAS (NAFLD activity score; even just a 5% loss of body weight has a clinically meaningful decline in NAS).

➤ Histopathology

- Give the liver biopsy criteria for NASH.
 - o Present in all or most cases
 - Diffuse or centrilobular steatosis, predominantly macrovesicular; degree may correlate with BMI
 - Parenchymal (lobular) and portal inflammation (+/- focal necrosis), neutrophils, lymphocytes
 - Ballooning hepatocyte degeneration
 - o Features observed with varying frequency
 - Lobular necrosis
 - Pericellular fibrosis ("chicken wire fibrosis" on trichrome stain) – perivenular* (zone 3), perisinusoidal or periportal (37%-84%)
 - Mallory bodies
 - Cirrhosis (7%-16% on index biopsy)
 - Glycogenated nuclei
 - Lipogranulomas
 - Stainable iron
- Give the pros and cons of performing a percutaneous liver biopsy in a patient with NAFLD and abnormal liver enzymes.

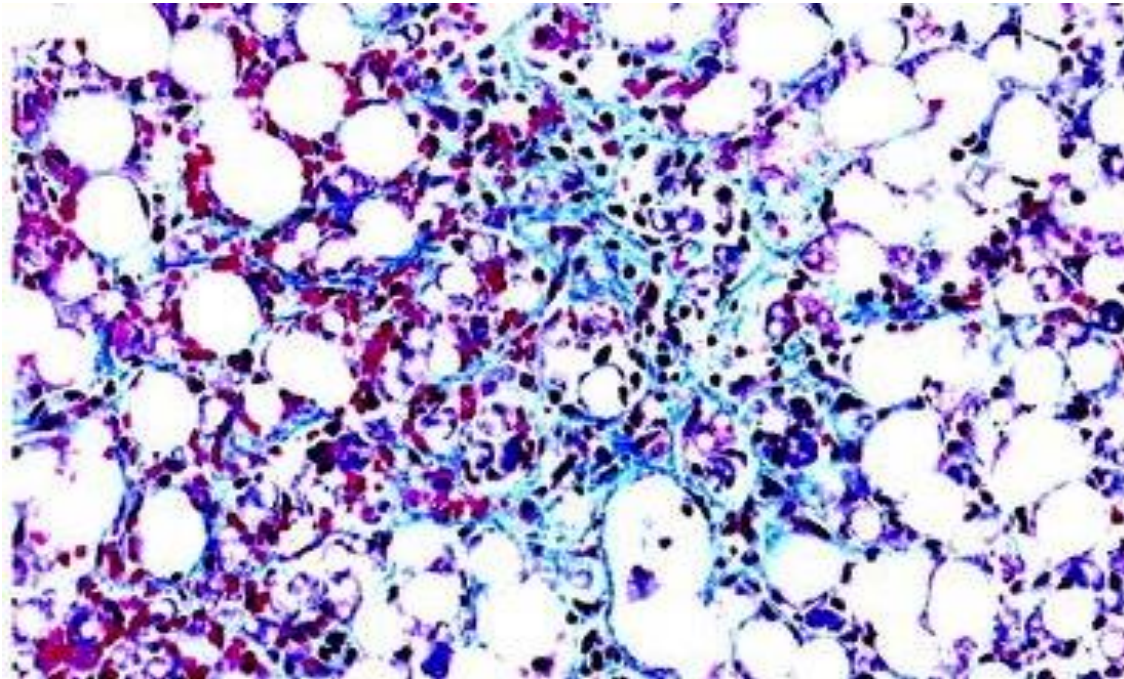
Issues	Argument in Favor of Biopsy with Acceptable Risk	Reasons for not Performing a Biopsy
Abnormal hepatic biochemical tests and NAFLD		
o Elevated ALT	- Confirm diagnosis	- Cause accurately identified clinically in > 90% cases without biopsy
o Diagnosis of NAFLD	- Patients may not have classic NAFLD risk factors	- Accurate diagnosis of NAFLD generally possible without biopsy
o Identify severity of NAFLD	- Only biopsy can distinguish simple steatosis from steatohepatitis	- Non-invasive markers may be developed to distinguish the two
o Treatment of NAFLD	- Presence of steatohepatitis or fibrosis may motivate some to undertake risk factor modification	- There is no proven therapy for NAFLD. Absence of steatohepatitis or fibrosis may remove motivation for some to undertake risk factor modification

Printed with permission: Reddy K R. 2006 AGA Institute Postgraduate Course Syllabus: pg. 81.



- Focal Fatty Liver (FFL)
 - Patchy process of fat accumulation which may look like a hepatic mass on diagnostic imaging
 - Typical appearance on CT scan which helps to distinguish FFL from metastatic lesion:
 - Density close to water
 - Not spherical in shape
 - No mass effect
 - The FFL may regress without treatment
- Give the typical histopathological features of non-alcoholic steatohepatitis.
 - Macrovesicular (+/- microvesicular) steatosis, zone 3 (or panlobular)
 - Lobular neutrophil and lymphocyte infiltrate
 - Ballooning degeneration of hepatocytes
 - "Chicken-wire" fibrosis

Non-alcoholic Steatohepatitis



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➤ Grading

- A detailed grading and staging of the biopsy lesions of NASH.
 - Grade 1. Mild
 - Steatosis: predominantly macrovesicular, involves <33% or up to 66% of the lobules; increased BMI may correlate with BMI
 - Ballooning: occasionally observed; zone 3 hepatocytes
 - Lobular inflammation: scattered and mild acute (polymorphs) and chronic (mononuclear cells) inflammation
 - Portal inflammation: none or mild
 - Grade 2. Moderate
 - Steatosis: any degree and usually mixed macrovesicular and microvesicular
 - Ballooning: present in zone 3
 - Lobular inflammation: polymorphs may be noted associated with ballooned hepatocytes, pericellular fibrosis; mild chronic inflammation
 - Portal inflammation: Mild to moderate
 - Grade 3. Severe
 - Steatosis: typically > 66% (panacinar): commonly mixed steatosis
 - Lobular inflammation: scattered acute and chronic inflammation; polymorphs may appear concentrated in zone 3 areas of ballooning and perisinusoidal fibrosis
 - Portal inflammation: Mild to moderate
 - Staging (fibrosis)
 - Stage 1: zone 3 perivenular perisinusoidal fibrosis, focal or extensive
 - Stage 2: as above plus focal or extensive periportal fibrosis
 - Stage 3: bridging fibrosis, focal or extensive
 - Stage 4: cirrhosis



Brunt grading system for steatohepatitis

Lesion	Grade	Significant Histologic Variable			
		Steatosis*	Ballooning	Inflammation	
				Lobular**	Portal***
Mild	1	1-2	Minimal	1-2	0-1
Moderate	2	2-3	Mild	1-2	1-2
Severe		2-3	Marked	3	1-2

*Extent of steatosis	1 2 3	$\leq 33\%$ 33 – 66% $\geq 66\%$
**Extent of Lobular Infammation	0 1 2 3	None < 2 foci/20 x field 2-4 foci/20 x field > 4 foci/20 x field
***Extent of Portal Inflammation	0 1 2 3	None Mild Moderate Marked

Adapted from: Brunt EM, et al. Am J Gastroenterol 1999; 94(9):2467-74.

Brunt staging system for steatohepatitis

Stage	Perisinusoidal Fibrosis	Periportal Fibrosis	Bridging Fibrosis	Cirrhosis
1	Focal/Extensive	-	-	-
2	Focal/Extensive	Focal/Extensive	-	-
3	+/-	+/-	+	
4	+/-	+/-	Extensive	+

+, present

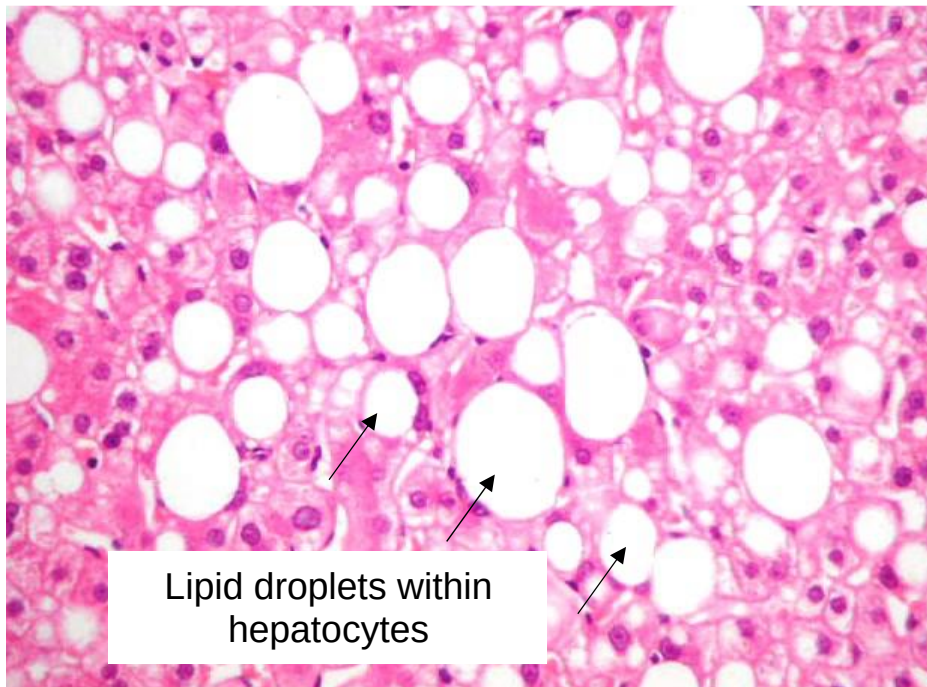
+/-, present or absent

-, absent

Adapted from: Brunt EM, et al. Am J Gastroenterol 1999; 94(9):2467-74.

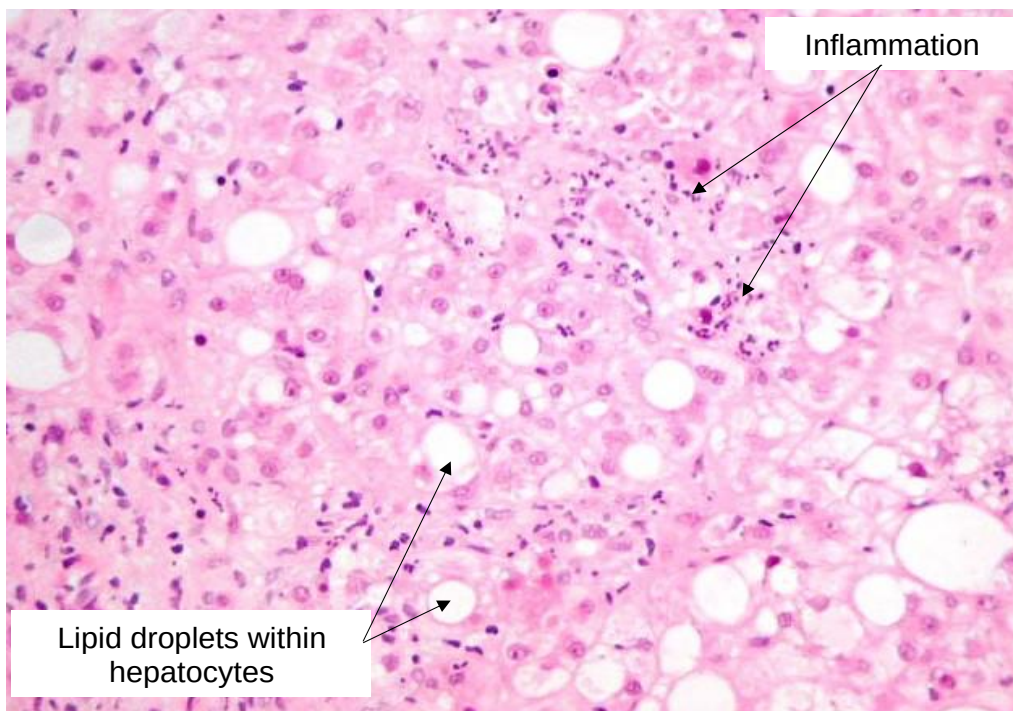


Steatohepatitis



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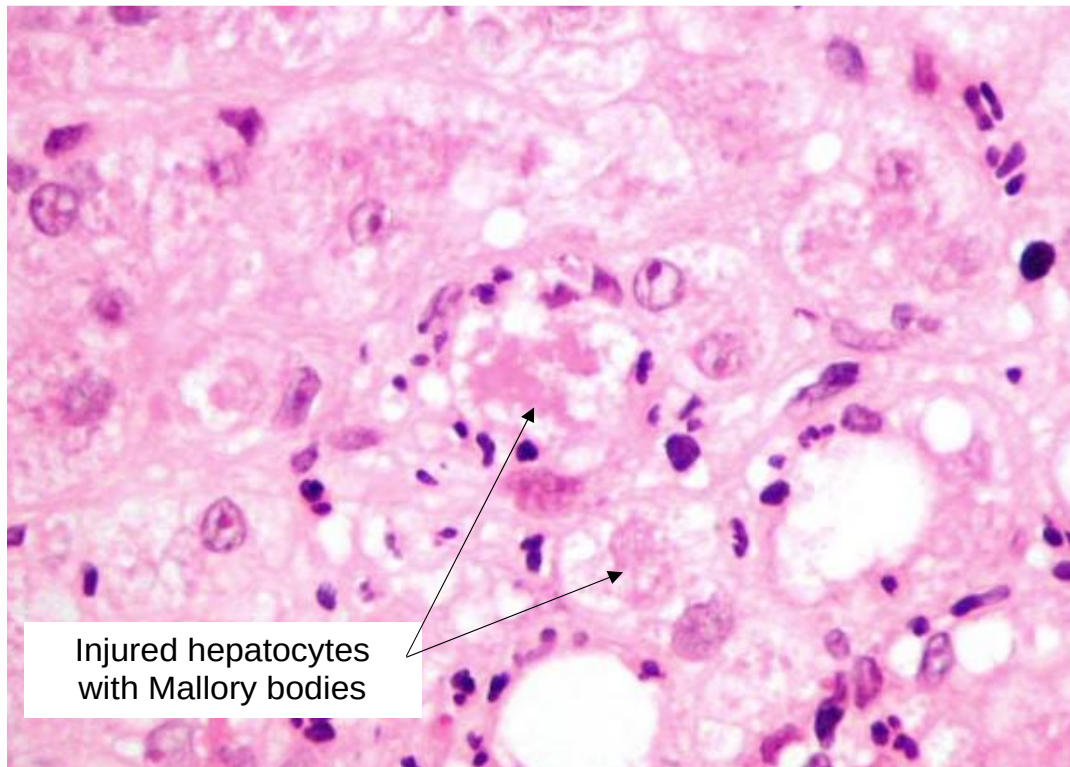
Steatohepatitis



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Steatohepatitis



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ALCOHOLIC LIVER DISEASE (ALD)

- Definition
 - ALD is a disorder associated with the intake of excessive amounts of alcohol over prolonged periods of time, leading to acute and / or chronic compensated / decompensated liver disease.
- Histopathology
 - Give the typical histopathological features of ALD.
 - Hepatocyte swelling and necrosis
 - Macrovesicular fatty change in centrilobular area
 - Lobular neutrophils, portal lymphocytes and macrophages
 - “Chicken Wire” fibrosis



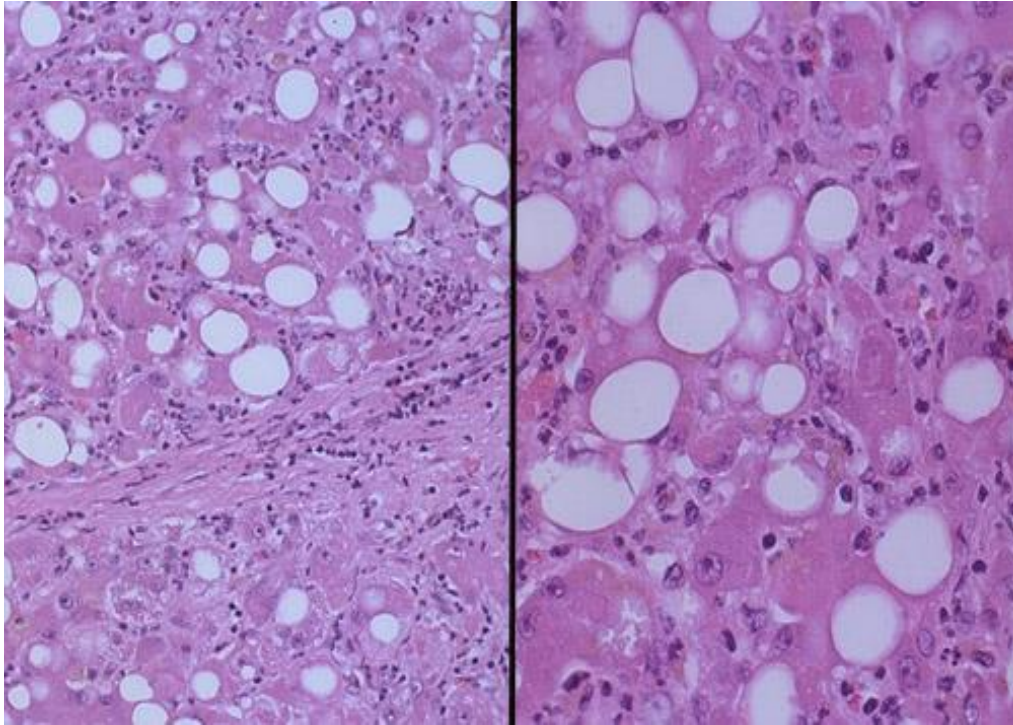
- Steatosis
 - Centrilobular
 - Perivenular
 - Macrovesicular +/- microvesicular If combination of macro plus microvesicular, then there is an ↑ risk of cirrhosis
- Ballooning degeneration
- Mallory bodies in damaged hepatocytes
- Necroinflammatory reaction around damaged hepatocytes
 - Polymorphonuclear leukocytes (neutrophils)
- Central vein
 - Perivenular sclerosis / fibrosis
- Macronodular cirrhosis
- Hepatic siderosis occurs in ~20% of ALD patients
- Conditions which may mimic ALD
 - NAFLD (non-alcoholic fatty liver disease)
 - HH (hereditary hemochromatosis)
 - BCS (Budd-Chiari syndrome)
 - Amiodarone hepatotoxicity

Compare and contrast viral hepatitis and alcoholic hepatitis based on histology, history and physical, laboratory tests and liver histology.

	Viral Hepatitis	Alcoholic Hepatitis
○ History	– Risk factors	▪ Significant alcoholic intake
○ Physical examination	– Mild hepatomegaly, extrahepatic stigmata not prominent	▪ Moderate to marked hepatomegaly ▪ Florid extrahepatic stigmata
○ Laboratory tests	– AST variable	▪ AST < 300
○ Liver histology	– Mononuclear cells – Portal tract centered – Ground glass cells (HBV) – Special stains (HBV) – Fat, esp. HCV	▪ Polymorphs ▪ Mallory hyaline ▪ Macrovesicular fat



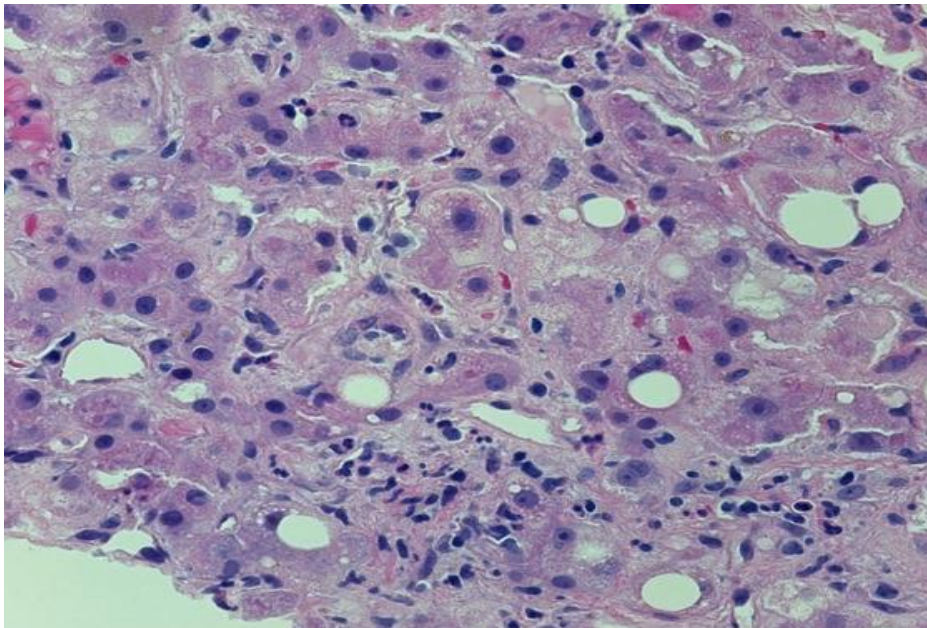
Alcoholic Liver Disease



Neutrophils present
in the lobule and
fibrous septa

Reference: Colombat M, et al. Portal lymphocytic infiltrate in alcoholic liver disease. *Hum Pathol.* 2002;33;1170-4.

Alcoholic Liver Disease

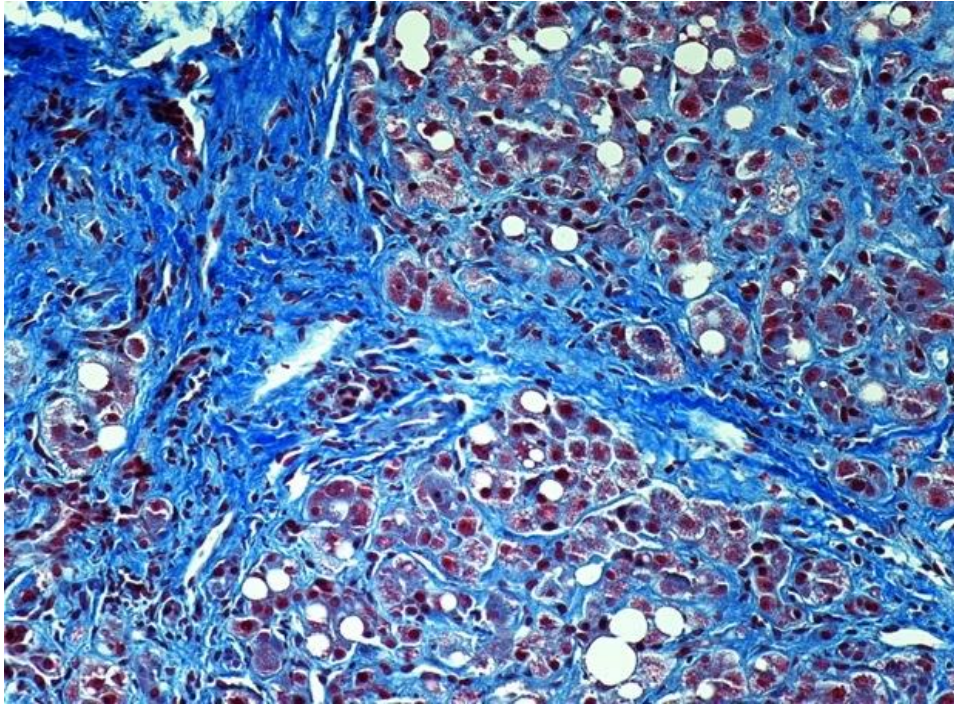


- H&E stain
 - Neutrophilic infiltrates
 - Mallory-Denk bodies
 - Steatosis

Courtesy Isabel Fiel, Mount Sinai, New York



Alcoholic Liver Disease



- Trichrome
 - Chicken-wire fibrosis

Courtesy Isabel Fiel, Mount Sinai, New York

"We can't help everyone, but everyone can help someone."

Ronald Reagan



AUTOIMMUNE HEPATITIS (AIH)

➤ Definition

- “AIH is a disorder of unknown cause characterized by unresolving inflammation of the liver and by the presence of interface hepatitis [limiting plate of the portal tract is disrupted by a lymphoplasmacytic infiltrate] on histologic examination, ... hypergammaglobulinemia” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 1461), and autoantibodies”.

➤ Demography

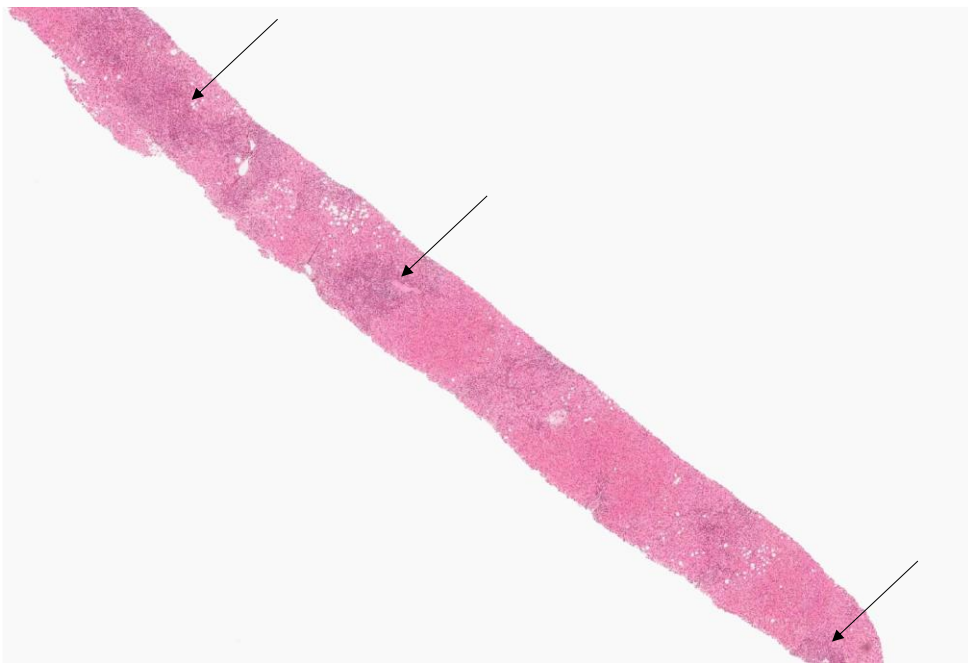
- Varies world-wide
- In North America, incidence ~ 2/10⁵ / year; prevalence ~ 17/10⁵

➤ Histopathology

Case: Clinical vignette: A 45-year-old high school principal from Trois-Riviera, QC, with treated hypertension presents with a 6 month history of pruritus. The GGT and AP are increased twice normal. You suspect Autoimmune Hepatitis.

- Give the typical histopathological features of Autoimmune Hepatitis.
 - Portal and interface infiltrate with abundance of plasma cells
 - Bridging necrosis
 - Central necrosis with plasma cells

Autoimmune hepatitis (H&E, 20X)



Low power view shows chronic inflammation centred on portal tracts (arrows).

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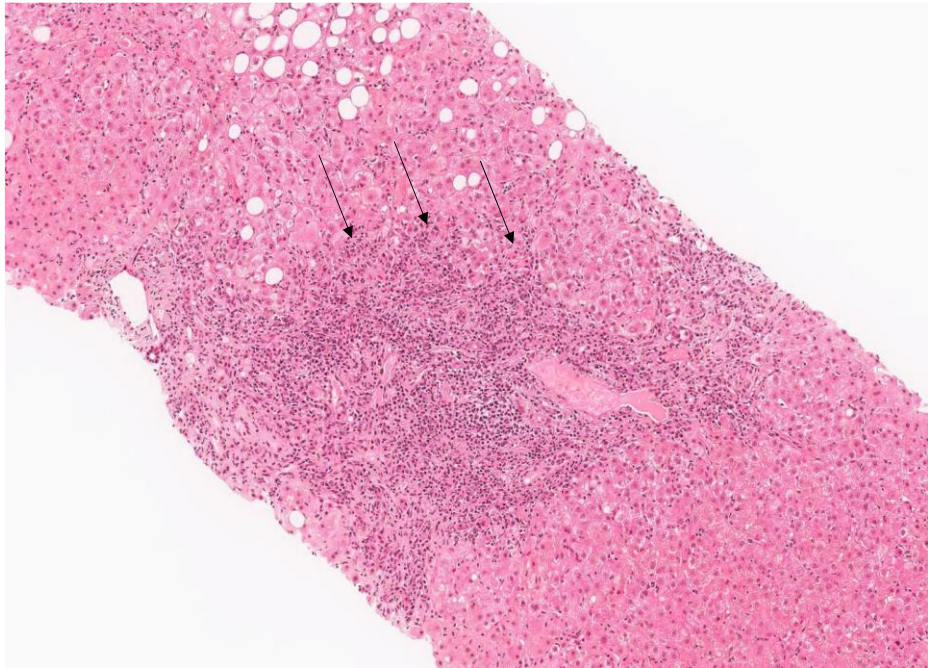
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Liver

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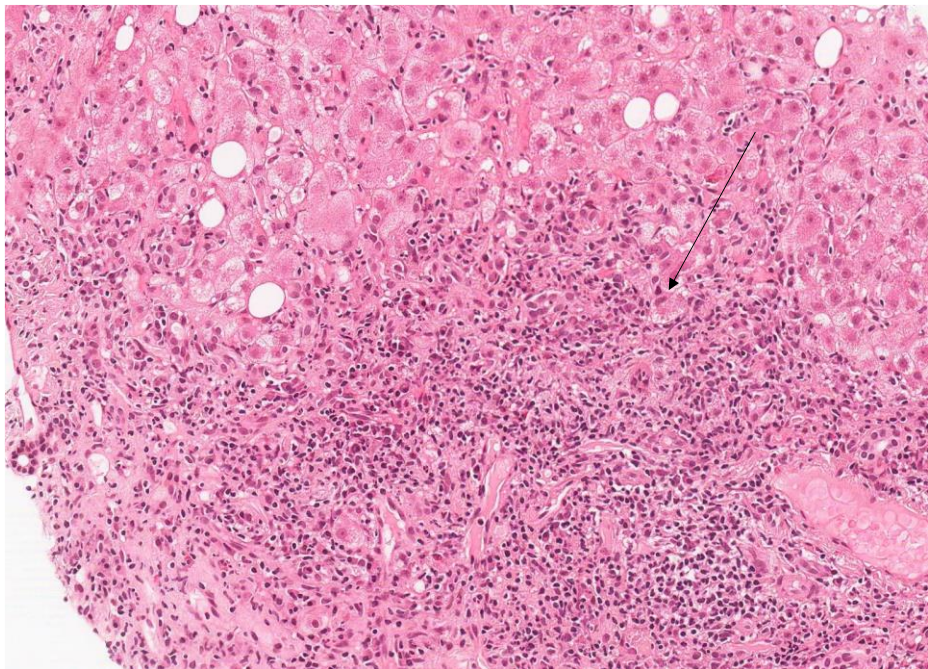
Autoimmune hepatitis (H&E, 100X)



Chronic inflammation centred on portal tracts with interface hepatitis involving the adjacent liver parenchyma (arrows).

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Autoimmune hepatitis (H&E, 200X)

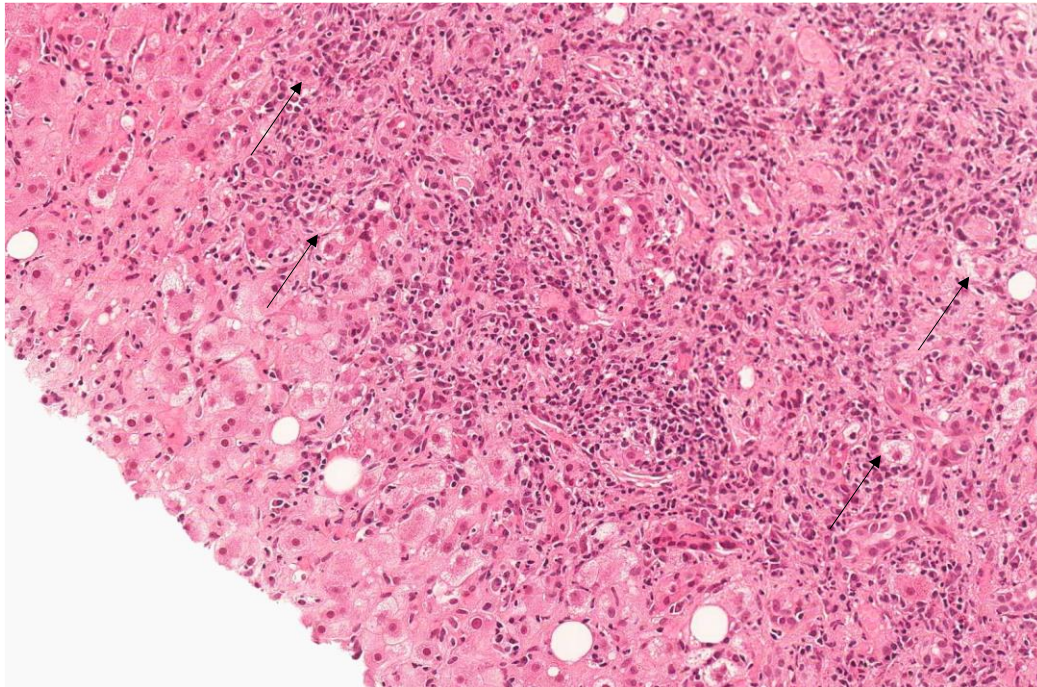


The inflammatory infiltrate surrounds and injures periportal hepatocytes (interface hepatitis, arrow).

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Autoimmune hepatitis (H&E, 200X)



The inflammatory infiltrate surrounds and injures periportal hepatocytes (interface hepatitis, arrows).

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PRIMARY BILIARY CHOLANGITIS (PBC)

➤ Definition

- PBC is an autoimmune liver disease characterized by specific antibodies, a characteristic liver biopsy (inflammatory destruction of the interlobular bile ducts), and progression to chronic cholestasis, biliary cirrhosis, and complications related to portal hypertension and liver failure.
 - Note: the former name was “primary biliary cirrhosis”

➤ Demography

- F >> M, 9:1
- Age of diagnosis
 - Usually 30 to 60 years
- Incidence
 - $3/10^5$
- Prevalence
 - $40/10^5$



➤ Differential diagnosis

- Give examples of chronic benign biliary disorders involving the intrahepatic, extrahepatic, and combined intra- and extrahepatic ducts (big duct abnormalities), which may **mimic PBC**.
 - Congenital
 - Alagille syndrome (and nonsyndromatic paucity of the intrahepatic bile ducts)
 - Cystic fibrosis
 - Duct plate abnormalities
 - Choledochal cysts
 - Infectious
 - Cytomegalovirus
 - Biliary sepsis
 - Parasites
 - HIV (intrahepatic), AIDS cholangiopathy (extrahepatic)
 - Infiltrative
 - Cholangiocarcinoma
 - Histiocytosis X
 - Lymphoma
 - Mastocytosis
 - Ischemic
 - Thrombosis of hepatic artery
 - Paroxysmal nocturnal hemoglobinuria (PNH)
 - Vasculitis
 - Henoch-Schönlein
 - Ischemic strictures (post liver transplantation)
 - Immune
 - PSC, secondary sclerosing cholangitis
 - Sarcoid autoimmune cholangiopathy
 - Graft vs host disease
 - Allograft rejection
 - Drugs and toxins
 - Drugs
 - Floxuridine
 - TPN-associated cholestasis
 - Idiopathic
 - Caroli syndrome

Abbreviation: PNH, paroxysmal nocturnal hemoglobinuria; TPN, total parenteral nutrition

AMA-Negative PBC

- Symptoms, biochemistry, liver histology, clinical course, therapy and indications for liver transplantation are similar to AMA+ PBC
- Human leukocyte antigen (HLA) alleles may be different in AMA- versus AMA+ PBC, with possible loss of protective allele
- No difference in Treg (regulatory T cells or t cell subgroups)
- Serology
 - Most have ANA or anti-smooth muscle antibodies
 - 50% have anti-gp 210



- Compare and contrast PBC and AIH under the following headings.

Finding	PBC	AIH
○ Gender	F>M	F>M
○ Prominent symptoms	Pruritus	Fatigue
○ Laboratory	AMA+, ↑ IgM (if associated autoimmune syndromes)	AMA-, ↑ IgG, ASA+, Anti-DNA+
○ Pathology		
– Ducts	Florid duct damage	Minimal duct damage
– Hepatocytes	Intact lobules	Interface hepatitis (zone 1)
– Infiltration	Lymphoid aggregates	Lymphocytes and plasma cells

Abbreviation: ASA, anti-smooth muscle antibody

- Give the diagnostic criteria for recurrent PBC after liver transplantation (LT) for PBC, as well as the important differential diagnostic considerations.

Diagnostic Criteria for Recurrent PBC	Differential Diagnostic Considerations
○ LT for confirmed diagnosis of PBC	▪ HCV infection with lymphocytic cholangitis
○ Persistence of serum AMA	▪ Drug-induced liver injury (DILI)
○ Compatible Histopathology	▪ Acute cellular rejection
– Portal inflammation	▪ Biliary obstruction
– Lymphocytic inflammatory infiltrates	▪ Graft-vs-Host Disease (GVHD)
– Lymphocytic cholangitis	
– Epithelioid granulomas	
○ Exclusion of differential diagnostic considerations	

Interpretation: 2 of 4 diagnostic criteria = probable; 3 of 4 = definite

Printed with permission: Ilyas JA, et al. Liver transplantation in autoimmune liver diseases. Best Pract Res Clin Gastroenterol. 2011;25(6):765-82.

➤ Histopathology

- Give the typical histopathological features of PBC.
 - Dense lymphocytic infiltrate in portal tracts
 - Granulomatous destruction and loss of medium-sized interlobular bile ducts
 - Portal (or sometimes lobular) non-necrotizing granulomas



- Give the histopathology used to determine the Ludwig 4 stage classification of PBC.
 - Stage I
 - Focal areas of inflammation (lymphocytes) confined to the portal space
 - Florid duct lesion
 - Inflammatory destruction of the small (< 100 µm diameter) intrahepatic interlobular and septal bile ducts
 - Development of ductopenia
 - Reactive proliferation of bile ductules (“ductular reaction”)
 - Stage II
 - Interface hepatitis (aka piecemeal necrosis):
 - Inflammation extends from portal tract into hepatic parenchyma
 - Some destruction of the limiting plate
 - Stage III
 - Fibrosis, with no regenerating nodules
 - Stage IV
 - Fibrosis
 - With regenerating nodules (cirrhosis)
 - Fibrous septa

Scheur staging for PBC

- Stage 1
 - Florid duct lesion; portal hepatitis
- Stage 2
 - Ductular reaction and periportal hepatitis
- Stage 3
 - Scarring; bridging necrosis; septal fibrosis
- Stage 4
 - Cirrhosis

MCQ Alert

You are asked a multiple choice question about which has the higher “mortality rate”, those PBC patients who have symptoms at the time of diagnosis, or those who are asymptomatic. Watch carefully the wording, whether mortality is liver-related or non-liver related:

Symptoms at diagnosis	Cause of higher mortality
○ None	– Non-liver related
○ Fatigue, pruritis, jaundice	– Liver-related
○ For PBC patients who are symptomatic (fatigue, pruritus, jaundice) at the time of diagnosis, the liver-related mortality rate (MR) is higher than in the PBC patients who were asymptomatic at the time of diagnosis.	
○ However, the initially asymptomatic PBC patients have a high MR from non-liver related conditions, than do the initially symptomatic PBC patients.	
○ The trick is whether the question addresses liver-related mortality rates in a- / symptomatic PBC patients.	



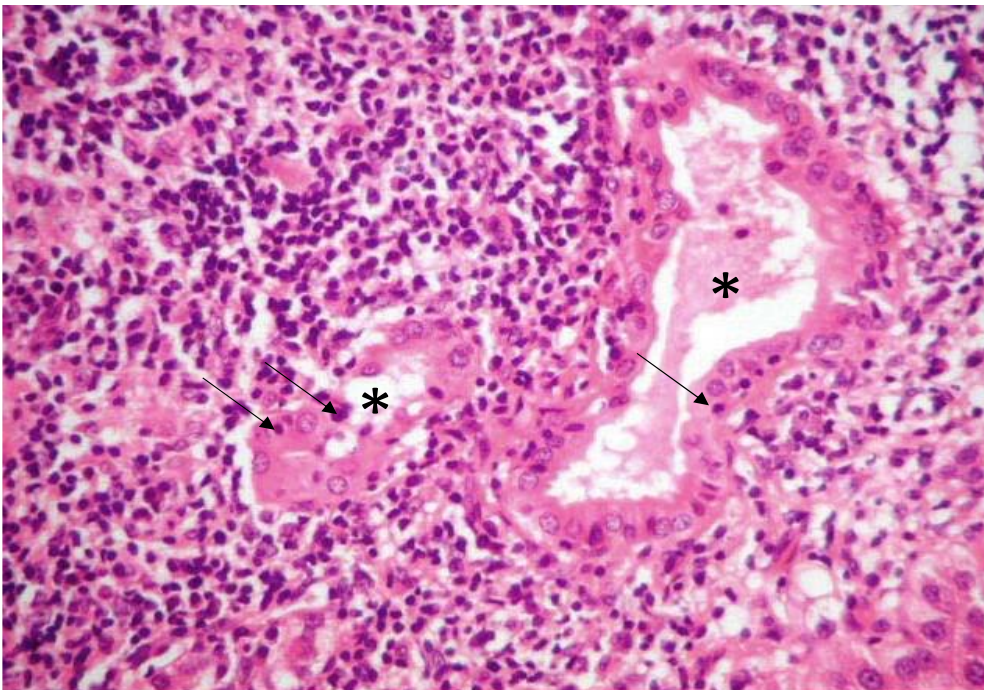
Clinical Tip: Liver Biopsy in PBC

- “In a patient with AMA in serum, the combination of a serum alkaline phosphatase [AP] level greater than 1.5 times the upper limit of normal [ULN] plus a serum AST level less than 5 times the upper limit of normal yields a 98.2% positive predictive value for a diagnosis of PBC”.
- 98% PPV for PBC: AMA+, $\uparrow$ AP $> 1.5 \times$ ULN + $\uparrow$ AST $< 5 \times$ ULN
- “....a liver biopsy is not necessary to confirm the diagnosis in most patients with PBC and should be performed in only the minority of AMA+ patients with a serum alkaline phosphatase level less than 1.5 times normal or a serum AST level greater than 5 times normal” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 1481).

Case: Clinical vignette: A 50-year-old woman from Halifax, NS, presents with an asymptomatic elevation in her GGT and AP at the time of routine follow up of her dyslipoproteinemia. You suspect Primary Biliary Cholangitis (PBC).

- Give the typical pathological features of PBC.
 - Dense lymphocytic infiltrate in portal tracts
 - Granulomatous destruction and loss of medium-sized interlobular bile ducts

Primary Biliary Cholangitis (PBC)

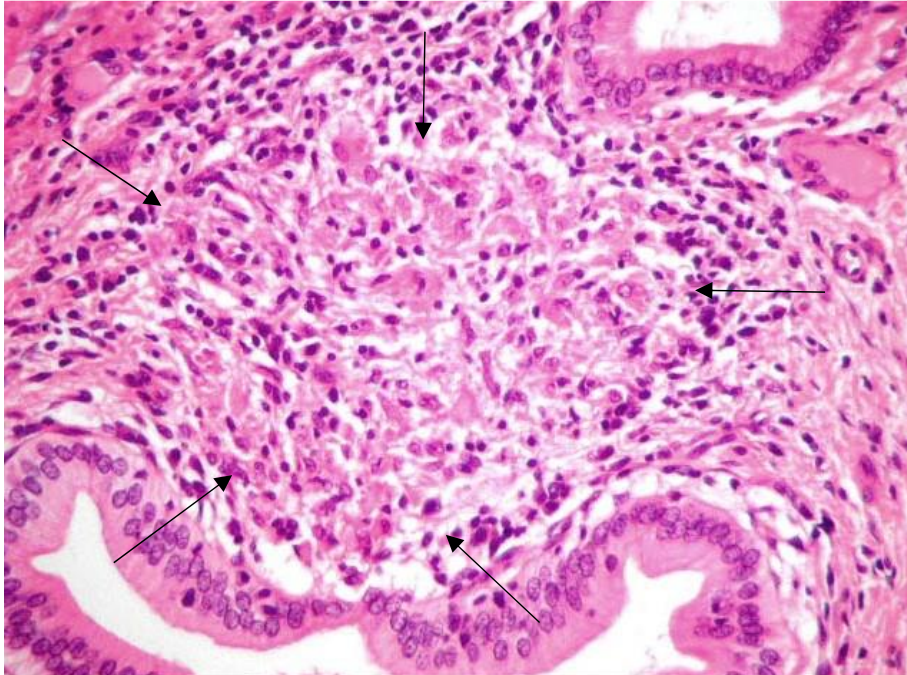


“Florid duct lesion”. Bile ducts (*) are abnormally shaped and show epithelial attenuation and intraepithelial lymphocytes (arrows).

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Primary Biliary Cholangitis (PBC)



Granulomatous portal inflammation. A loose aggregate of histiocytes (arrows) is present in this portal tract. Intraepithelial lymphocytes can also be seen in the bile ducts epithelium (lower left) and there is a multinucleate giant cell in the upper right.

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"Things work out best for those who make the best
of how things work out."

John Wooden



PRIMARY SCLEROSING CHOLANGITIS (PSC)

➤ Definition

- PSC is a chronic cholestatic liver disease characterized by inflammation and fibrosis of the extrahepatic and intrahepatic bile ducts than can progress to cirrhosis.

➤ Demography

- Incidence – $1/10^5$ per year
- Prevalence – $10/10^5$
- The prevalence of PSC is 20.9 and 6.3 per 100,000 men and women, respectively.

➤ Diagnostic Imaging

- Give the features on diagnostic imaging that distinguish between the cholestatic conditions PSC and PBC (primary biliary cholangitis).

PSC	PBC
○ Usually intra- and extrahepatic ducts tapered and narrow ○ Diffuse segmental strictures ○ Dominant strictures ○ Intrahepatic duct “pruning” (↓ arborisation) → “beading”	– Intrahepatic ducts smoothly tapered and narrow – Lymphocytic interface inflammation may be hard to distinguish from AIH (autoimmune hepatitis) – Diffusely thickened, fibrotic wall – Inflammation of duct epithelium – Atrophy / attenuation of interlobular epithelium

➤ Differential diagnosis

- Give a classification of the secondary causes / associations of **secondary sclerosing cholangitis (SSC)**, and provide examples.
 - GI disease associations
 - Colon
 - Ulcerative Colitis
 - Crohn colitis or ileocolitis
 - Liver
 - Hepatic allograft rejection
 - Hepatic graft-versus-host disease (after bone marrow transplantation)
 - Cystic fibrosis
 - Overlap with PBC
 - May be difficult to distinguish from AIH (PSC may have lymphocytic interface hepatitis)
 - Post-liver transplantation (fibro-intimal hyperplasia)
 - Bile ducts
 - Cholangiocarcinoma
 - Choledocholithiasis
 - Stricture
 - Biliary parasites
 - Recurrent pyogenic cholangitis
 - Fungal infection
 - Cholangitis



- Pancreas
 - Chronic pancreatitis
 - IgG4-associated cholangitis (IAC), with or without IgG4-associated pancreatitis
- Systemic diseases with fibrosis
 - Retroperitoneal fibrosis
 - Riedel's thyroiditis
 - Mediastinal Fibrosis
 - Pseudotumour of the orbit
 - Inflammatory pseudotumour
 - Peyronie disease
 - Chronic sclerosing sialadenitis
- Autoimmune or collagen vascular disorders
 - Systemic lupus erythematosus
 - Systemic sclerosis
 - Type I diabetes mellitus
 - Rheumatoid arthritis
 - Sjögren's syndrome
 - Autoimmune hemolytic anemia
- Kidney
 - Membranous nephropathy
 - Rapidly progressive glomerulonephritis
- Infections
 - Biliary TB
 - HIV (CD4+ T lymphocytes < 100/mm³)
 - AIDS cholangiopathy
 - Cryptosporidium
 - Microsporidium
 - CMV
- Inflammation
 - Sarcoidosis
 - Hypereosinophilic syndrome
- Immunodeficiency diseases
 - Congenital immunodeficiency
 - Combined immunodeficiency
 - Dysgammaglobulinemia
 - X-linked agammaglobulinemia
 - Acquired immunodeficiency
 - Selective immunoglobulin A deficiency
 - Acquired immunodeficiency syndrome
 - Angioimmunoblastic lymphadenopathy
- Congenital abnormalities
 - Caroli disease
 - Choledochal cyst
- Iatrogenic (drugs)
 - Hepatic arterial infusion of chemotherapy, intraductal formaldehyde or hypertonic saline (used for echinococcal cyst removal)
 - Intra-arterial floxuridine (FUDR, causing ischemia and toxic vasculitis)
- Ischemic
 - Vascular injury from liver surgery
 - Hepatic allograft arterial occlusion
 - Paroxysmal nocturnal hemoglobinuria
 - Prolonged circulatory failure (shock)
 - Systemic vasculitis
- Infiltration
 - Benign
 - Mastocytosis
 - Histiocytosis X
 - Biliary papillomatosis



- Malignant
 - Cholangiocarcinoma
 - Hepatocellular carcinoma (HCC)
 - Metastatic cancer
 - Lymphoma

Adapted from: Ross AS and Kowdley KV. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology / Diagnosis / Management* 10th Edition. Saunders / Elsevier, Philadelphia, 2016; Box 68-1, page 1167.

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An Asian Canadian with no previous biliary tract surgery, presents with recurrent episodes of fever, RUQ pain and jaundice (Charcot triad). He is negative for AMA, ANA, ASA, pANCA and HIV, and ERCP shows multiple filling defects and a stricture / dilation of the left hepatic duct.

- Give the likely diagnosis.
 - RPC (recurrent pyogenic cholangitis) may be confused with PSC, but the demography, negative serology, and the findings of ERCP defects in the left rather than the right hepatic duct make this diagnosis likely.

In the context of investigating a person with PSC and possible cholangiocarcinoma, give reasons for false-negative and false-positive CA 19-9 elevations, an false-positive PET scans.

- | | |
|---------------------------------|--------------------------------|
| ○ CA19-9 | ○ PET scan |
| - False negative | - False positive |
| ▪ Negative Lewis antigen status | - Bacterial tract inflammation |
| - False positive | |
| ▪ Choledocholithiasis | |
| ▪ Bacterial cholangitis | |

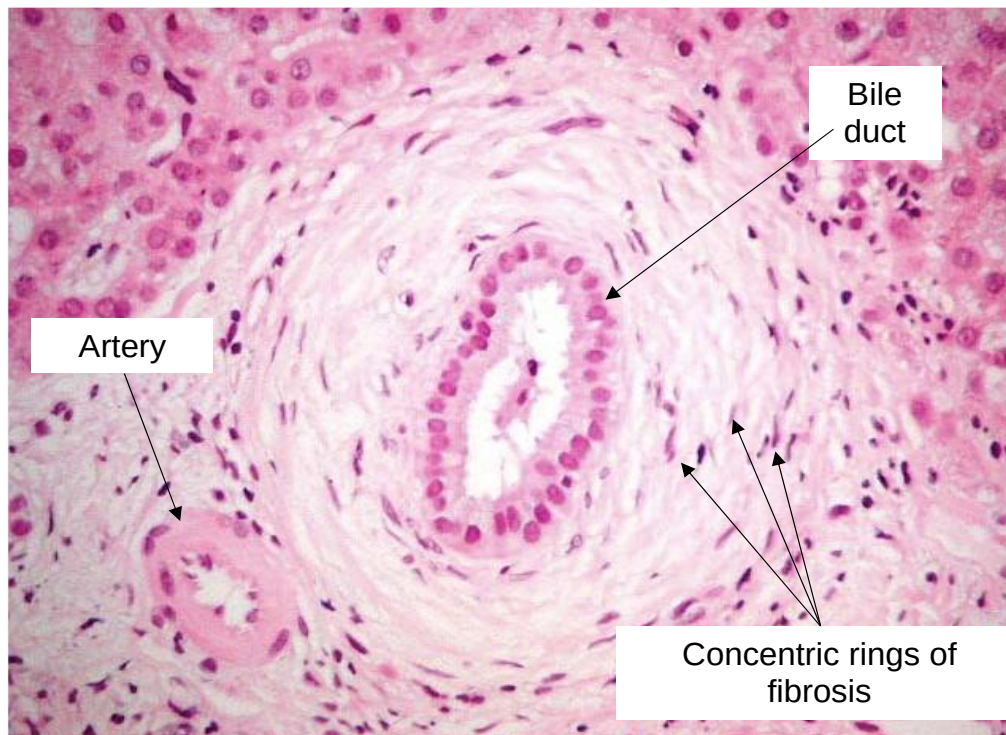
➤ Histopathology

- Give the typical histopathological features of PSC.
 - "Onion skin" fibrosis around interlobular bile ducts
 - Types
 - Large-duct PSC (95%) 80% are associated with IBD.
 - If large-duct PSC not associated with IBD, test for ↑ IgG4 to diagnose autoimmune cholangitis.
 - Diagnosis may be made by ERCP / MRCP.
 - Small-duct PSC (5%)
 - Small-duct PSC is a variant in which only the intrahepatic ducts are involved
 - Liver biopsy necessary to make diagnosis because ERCP likely normal
 - "onion-skin" fibrosis
 - Destruction of the bile duct
 - Replacement of destroyed duct with fibrous tissue
- Small-duct PSC $\xrightarrow{20\%}$ large-duct PSC $\xrightarrow{10\%}$ cholangiocarcinoma



- PSC + gallbladder polyps → elective cholecystectomy for high risk of malignant transformation of even small gallbladder polyps
- Findings
 - Medium-sized bile ducts:
 - “onion skin” lesion: (fibro-obliterative process)
 - Small interlobular / septal bile duct branches: fibro-obliterative cholangitis
 - Periductular inflammation
 - Obliteration of bile duct by fibrosis
 - Atrophy
 - Ductopenia
 - Ductular proliferation

Primary Sclerosing Cholangitis



The bile duct is surrounded by concentric rings of fibrosis.

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INFECTIOUS HEPATITIS

Bacterial Hepatitis

➤ Diagnosis

There are certain “buzz words” which are meant to signal a likely diagnosis.

- Give buzzwords which when applied to the patient with acute hepatitis, suggest typhal fever from infection with either *Salmonella typhi* or *Salmonella paratyphi*.
 - Hepatitis plus
 - “Stepwise fever”
 - Stepwise increase in body temperature readings
 - “Temperature-pulse dissociation”
 - Pulse rate does not increase as much as expected for the temperature (i.e., relative bradycardia)
 - “Rose spots on skin”
 - Salmon-pink macules on skin of trunk
 - Other clues that acute hepatitis might represent typhoid fever.
 - RLQ tenderness (ileitis / cecitis)
 - ALT / LDH < 4 (↑ ALT, ↑↑ LDH)
 - ↑ AP (AP increased more than in most patients with hepatitis)
 - ↑↑ WBC, with “left shift”
 - Treatment
 - Fluoroquinolone

A young woman presents with RUQ pain and tenderness, fever and abnormal liver enzymes. The CT of the upper abdomen shows only non-specific hepatic changes.

- In this context, give the meaning of the “**Fitz-Hugh Curtis (FHC) syndrome**” and “violin string” perihepatic adhesions on laparoscopy.
 - Fitz Hugh Curtis syndrome is a gonococcal or chlamydial infection of the female pelvic organs which involves the surface of the peritoneum, causing perihepatic fibrinous exudate (violin string adhesions).
 - This diagnosis would be suspected in a sexually active women with a painful pelvic examination.
- Give the mechanisms responsible for the common finding of cholestasis on liver biopsy from a person with sepsis.

Sepsis releases

- Exotoxins and endotoxins
 - Inhibits transport across hepatocyte sinusoidal and canalicular membrane
- TNF-α
 - Same effect as exo- / endotoxins



Viral Hepatitis

➤ Types

- Give the name of common viral infections of the liver.
 - The “viral alphabet soup” (HAV, HBV, HCV, HDV, HEV*)
 - EBV (Epstein-Barr virus)
 - CMV (cytomegalovirus)
 - HSV* (herpes simplex virus)
- Give a comparison of viral hepatitis (A, B, C, D, E) under the headings - virus type, mode of transmission, incubation period, serological diagnosis, risk of fulminant hepatitis and risk of chronicity.

	Virus Type	Transmission	Incubation (days)	Serologic Diagnosis	Fulminant Hepatitis	Risk of Chronicity
○ Fecal / oral						
– HAV	RNA		20-35	HAV-IgM	0.1-2.0%	No
– HEV	RNA		10-50	Anti-HEV	1-2% 15-20% Pregnant	No
○ Percutaneous						
– HBV*	DNA	-IVDU	60-110	HBsAg	0.1-0.5%	Adults < 5% Preschoolers 25% Neonates >90%
– HCV**	RNA	-Sexual (MSM, prostitute services, multiple sexual partners)	35-70	Anti-HCV	<1%	> 80%
– HDV	RNA	-IVDR (IV drug use) (even once) -Pre-1990 blood transfusions -multiple sexual partners	60-110	Anti-HDV		Usual in a super-infection with HBV; rare by itself

* Also perinatal

** Pre-1990 blood transfusion

Abbreviation: MSM, men who have sex with men



- Give which of the viral causes of hepatitis have a higher mortality during pregnancy.
 - HEV
 - HSV

Hepatitis A Virus (HAV)

- Demography
 - Transmission is by fecal-oral route
 - Person-to-person
 - Contaminated food or water
 - Males >> females
 - Injection illicit drugs
 - Non-injection illicit drugs
 - MSM (men who have sex with men)
- Histopathology
 - Give the typical histopathological features of Hepatitis A (rarely biopsied).
 - Portal and periportal inflammation
 - Ballooning degeneration
 - Relative sparing of centrilobular hepatocytes
 - Acidophil bodies or cytolysis (hydropic degeneration)
 - Bridging necrosis
 - Interface hepatitis

Hepatitis B Virus (HBV)

- Demography
 - Give the geographic site for the most common distribution of Hepatitis B genotypes A-H.
 - A – Northwestern Europe, North America, Central Africa
 - B,C – Southeast Asia, including China, Japan, and Taiwan (prevalence is increasing in North America)
 - D – Southern Europe, Middle East, India
 - E – West Africa
 - F – Central and South America, United States Indigenous peoples, Polynesia
 - G – United States, France
 - H – Central and South America

Source: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology / Diagnosis / Management*. 2010, Table 78-1.



- HBV progression

Acute HBV → chronic HBV:

- Neonate 90% asymptomatic enteric disease
- Children 50%
- Adults 10% symptoms

Source: *Clin Liver Disease* 10; 14: 75-91; *Hepatology* 07; 45:1056-75

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- Give the rate of vertical transmission of HBV from their mothers.
 - HBeAg
 - Positive, transmission in 60% to 90%
 - Negative, transmission in 15% to 20%
- Give the risk of PCR-detectable HBV DNA in persons who are positive for anti-HBc.
 - 0% to 30%
- Give the clinical importance of the 0% to 30% of anti-HBc positive persons having HBV DNA in their serum.
 - Blood that is HBsAg negative but anti-HBV positive has up to a 30% risk of having HBV DNA, and therefore of being infectious.
- Give the explanation for the high rate of transmission of HBV from HBsAg-negative but HBc-positive blood donors.
 - HBV may replicate in many body tissues other than liver
 - These extrahepatic tissues act as reservoirs for HBV DNA

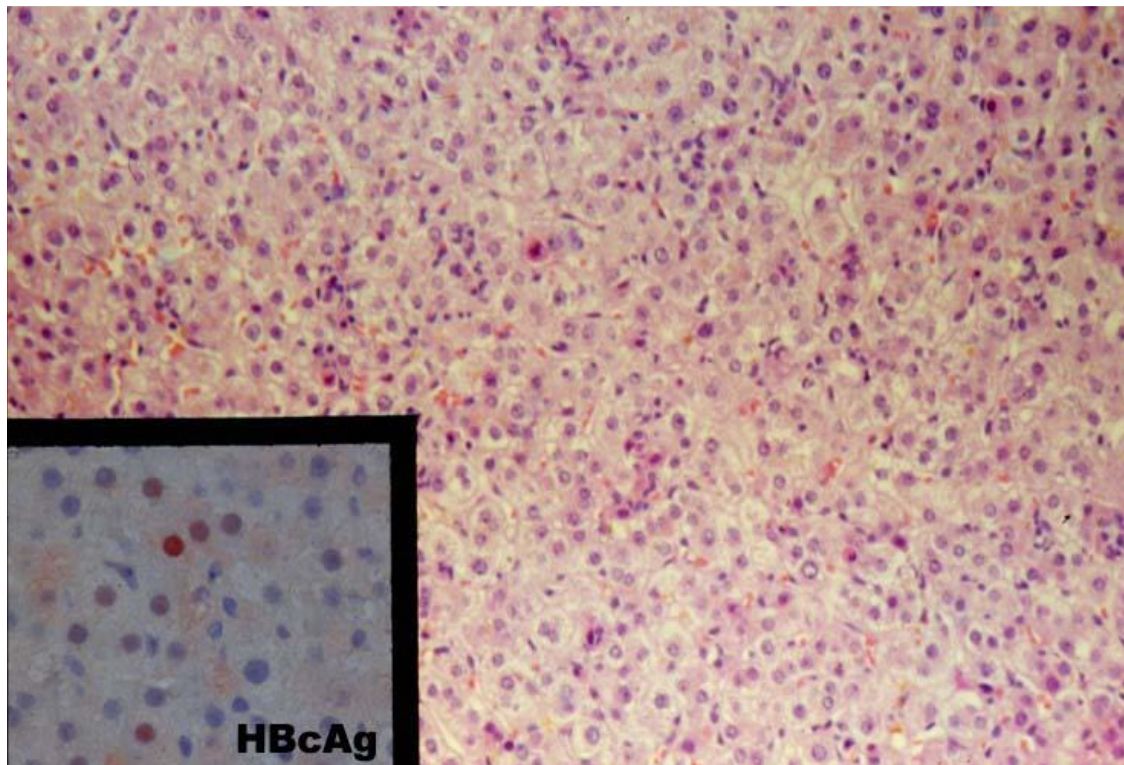
- Spontaneous HBeAg seroconversion, ~10%
- 5-year cumulative risk of progression of HBeAg-positive chronic hepatitis B to cirrhosis, ~10%
- HBV-associated compensated cirrhosis progressing to decompensation, 16%
- 5-year cumulative risk of developing HCC, 14%



➤ Histopathology

- Give the hepatic histopathological features of HBV infection.
 - Ground-glass hepatocytes
 - HBsAg in the ER of infected hepatocytes
 - Cysteine in HBsAg stained by orcein, Victoria blue, aldehyde fuchsin indicate viral replication
 - Also there may be core antigen in cytoplasm and hepatocyte nuclei
 - After treatment, cytoplasmic core antigen disappears, but persistence of nuclear core antigen indicates presence of HBV ccDNA template
 - Portal infiltration with mononuclear cells
 - Interface hepatitis (disruption of hepatocytes of the limiting plate)
 - Piecemeal necrosis
 - Fibrous tissue extending from portal areas
 - Fibrous septal mononuclear cells in bridges between portal tracts

Hepatitis B Viral Infection



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HBV Infection and Hepatocellular Cancer (HCC)

➤ Demography

- Give characteristics of healthy HBV carriers (no cirrhosis) who are candidates for HCC screening.
 - African males / females > 20 years
 - Asian males > 40 years
 - Asian females > 50 years
 - Caucasian (at age of diagnosis of cirrhosis, ultrasound every 6 mon)
 - Family history of HCC
 - Inactive or active disease with cirrhosis*
 - Co-infection with HCV, HIV
 - HBeAg negative

*Caucasians with inactive disease and no cirrhosis have a low risk of HCC development, and HCC screening is generally not recommended, but may be considered if there is a family history of HCC, or co-infection with HCV

Adapted from: Sherman M. *Best Practice & Research Clinical Gastroenterology* 2005;19(1): 105.

Please also see section section on Hepatocellular Cancer.

Hepatitis C Virus (HCV)

➤ Demography

- Perinatal exposure
 - Transmission rate
 - HCV ~ 5%
 - HCV + HIV ~ 15%
 - Breastfeeding dangerous when HCV > 10^8 copies / mL
- Percutaneous
 - Blood products ($1/2 \times 10^6$)
 - IV drug use (60% to 90% HCV infected)
 - Accidental pinpricks
 - Hemodialysis
- Non-percutaneous
 - Sexual contact
 - Intercourse
 - Per rectum
 - During menstruation



➤ Natural history of HCV

- Acute → chronic HCV 55% to 89%
- Chronic HCV → compensated cirrhosis ~1% per year after infection
- Compensated cirrhosis → HCC ~2% per year
- cirrhosis → decompensation ~3% per year

Adapted from: Berenguer M, and Wright TL. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology / Diagnosis / Management* 2006: pg. 1696.; and 2010: pg. 1325.

➤ Terminology

In the patient with HCV, define the terms RVR, EVR, ETR and SVR, as well as the definition and clinical implication of each of the 4 types of responses.

- RVR
 - Rapid virologic response
 - Undetectable HCV on a serum after 4 weeks of anti-HCV therapy
 - Higher chance of SVR; may respond as well with only 24 weeks of treatment
- EVR
 - Early virologic response
 - 2-log (100-fold) drop in HCV RNA load after 12 weeks of anti-HCV therapy
 - Failure to achieve EVR associated with almost no chance of SVR and treatment can usually be stopped
- Partial EVR (pEVR)
 - EVR at week 12, HCV RNA up to week 24, but no HCV RNA after week 24
 - Partial EVR
 - > 2-log (100-fold) decrease in HBV DNA after 12 weeks of anti-HBV therapy (residual HBV RNA still present)
- cEVR
 - Complete EVR
 - No HCV RNA in serum after 12 weeks of anti-HCV therapy
 - On treatment response. Observe for SVR.
- PVR
 - Partial viral response
 - HCV RNA present in serum at 12 weeks, but not at 24 weeks
- NR
 - No response
 - Failure to achieve EVR
- ETR
 - HCV RNA undetectable at end of treatment wk 48 – 1 genotype, wk 24 – 2,3
- SVR
 - Sustained viral response
 - Surrogate marker for eradication of SVR
 - No detectable HCV RNA in serum after 24 weeks of anti-HCV therapy

Printed with permission: Wedemeyer H. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders / Elsevier, Philadelphia, 2016, page 1343-4, as well as Table 80-2, page 1343.



➤ Diagnostic imaging

A pregnant woman with HCV cirrhosis presents in the 3rd trimester with sudden hypotension, tachycardia, diaphoresis and a known drop in her hemoglobin concentration by 40%. She gives no history of bleeding po/pr; she develops LUQ pain, pulsatile mass and bruit. Upper endoscopy does not show esophageal or gastric varices.

- Give the reason why Doppler abdominal ultrasound needs to be performed.
 - This woman has signs of acute blood loss, and ultrasound would be performed to look for an aneurysm of the splenic vein.
 - She's found to have a co-infection with HIV. Give the management.
 - There is a long duration between rupture of her membranes in the time of delivery, so fetal scalp monitoring was performed.
 - The splenic artery aneurysm is repaired.
 - Breast-feeding recommended, unless the nipples are cracked / bleeding.
 - The baby is assessed for HCV / HIV at one year of age (false positive HCV antibody in 1st year because of transfer of maternal anti-HCV across the placenta; ↑ risk of HCV due to HIV co-infection, and delayed delivery after membrane rupture).
 - The mothers HCV / HIV is treated along the usual guidelines.

➤ Histopathology

- Give the typical histopathological features of Hepatitis C.
 - Portal lymphocytic infiltrate
 - Sometimes macrovesicular steatosis +/- Mallory hyaline
 - No / minimal plasma cells or eosinophils
 - Liver biopsy grading of HCV is made by a scoring system (e.g., Knodell, Ishak or METAVIR)

- Give the pros and cons of performing a percutaneous liver biopsy in a patient with HCV.

Issues	Argument in Favor of Biopsy with Acceptable Risk	Reasons for Not Performing a Biopsy
○ Prognosis	– Extent of fibrosis and inflammation are best predictors of disease progression	▪ Non-invasive markers may accurately stage and grade disease
○ Decision to treat	– Genotype 1: Identify those most in need of therapy (therapy longer in duration and less likely to succeed)	▪ Genotypes 2 and 3: Patients motivated for therapy may forgo biopsy (therapy shorter in duration and more likely to succeed)
○ Treatment-related side effects	– Severity of liver disease helps in deciding whether to endure or stop therapy	▪ Commitment to therapy should be independent of disease severity
○ Previously treated	– Lower success with retreatment. Identify those most in need of therapy (advanced fibrosis)	▪ Motivated patients who are genotype 2 or 3, who were previously treated with interferon monotherapy, are candidates for re-treatment regardless of disease severity

Printed with permission: Reddy K R. 2006 AGA Institute Postgraduate Course Syllabus: pg. 81.

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- Give the circumstances when liver biopsy needs to be considered in HCV.
 - Genotype 1, 4 – perform liver biopsy when results will change treatment of HCV
 - Genotype 2,3 – perform liver biopsy when treatment of HCV may be postponed
 - Liver biopsy not necessary if clinical, laboratory or diagnostic imaging suggests that cirrhosis is already present

Clinical Alert!

❖ HCV and autoimmune conditions

- Because autoantibodies are common in HCV, and may not be associated with disease, be **cautious** making the diagnosis of an autoimmune condition in a person with HCV based just on seropositivity for autoantibodies.

❖ False-negative HCV serology

- Even though the EIAs (enzyme immunoassays) for HCV have excellent performance characteristics (sensitivity and specificity of ~ 99%), anti-HCV may be negative in some persons who have HCV replication in the liver.
 - This false-negative HCV serology is seen with
 - Hemodialysis
 - Immune suppression
 - If the person is not at high risk for a false negative HCV (e.g., hemodialysis, immune suppression), a negative anti-HCV on an EIA excludes HCV infection.
 - Anti-HCV positive is diagnostic of HCV infection if there is ↑ serum ALT
- Early diagnosis of HCV depends on the time after exposure when the test becomes positive:
 - HCV RNA 1 to 3 weeks
 - Anti-HCV 7 to 8 weeks

- Give reasons for biopsying the liver of persons with HCV, genotype 1, without obvious cirrhosis.
 - Determine stage of HCV
 - There is no correlation between ALT or viral load, and stage of fibrosis.
 - Surrogates for the presence of advanced fibrosis such as reversal of ALT / AST ratio, platelet count, pro time-INR are not sensitive.
 - Markers of fibrosis such as hydroxyl proline are not sufficiently specific.
 - Determine prognosis
 - Given the variable natural history and the complexity and cost of treatment, informed decision can only be made based on histology.



- Determine treatability
 - Patients who do not respond need further advice on what is next and histology may be essential in these persons.
 - Liver biopsy may be safer than treatment when you consider alternatives such as treating everyone.
- Post-liver transplantation (to distinguish between acute cellular rejection or HCV recurrence).

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Scoring systems have been used in HCV for the estimation of the extent of fibrosis and the presence of cirrhosis.

- Give reasons relating to the performance characteristics of one grading system (such as the METAVIR scoring system), which would shed light on possible limitations of liver biopsy as the test for standard of care.
 - Concordance (intra- and interobserver variation in reporting degree of fibrosis), 85% to 90%
 - Sampling error (biopsies < 2 cm in length and containing fewer than 11 portal tracts may underestimate fibrosis in chronic viral hepatitis)
 - False negative rate (for correct staging of cirrhosis), 15% difference in reported fibrosis
 - 1 stage, 33%
 - 2 stage, 2%

- Give the basis for the **Simple METAVIR** scoring system.
 - Inflammation
 - None, mild, moderate, severe
 - Fibrosis
 - None (0)
 - Portal (1)
 - Portal fibrosis with septa (2)
 - Bridging fibrosis (3)
 - Focal
 - Diffuse
 - Marked
 - Cirrhosis

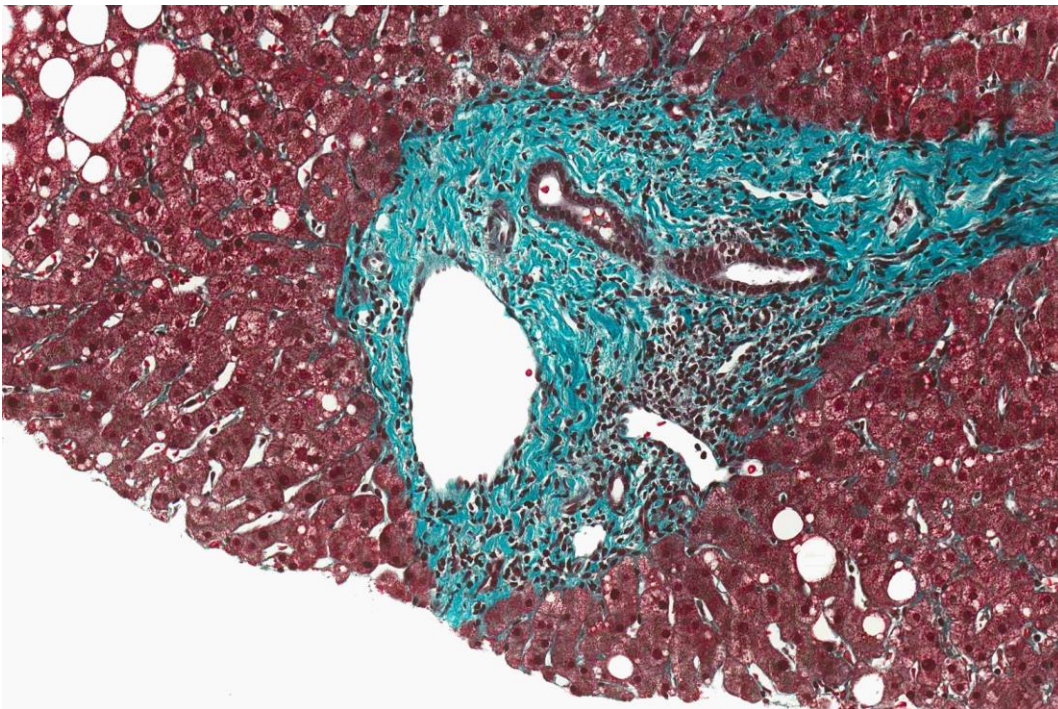


- Give the **METAVIR** system for staging / grading chronic hepatitis.

	Piecemeal and Lobular Necrosis *(A)	Fibrosis (F)
0	None	None
1	Mild activity	Portal fibrosis without septa
2	Moderate activity	Portal fibrosis with septa
3	Severe activity	Numerous septa (bridging fibrosis), without cirrhosis
4		Cirrhosis

Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 1323.

Fibrosis, Batts-Ludwig Stage 1/4 (Portal Fibrosis)

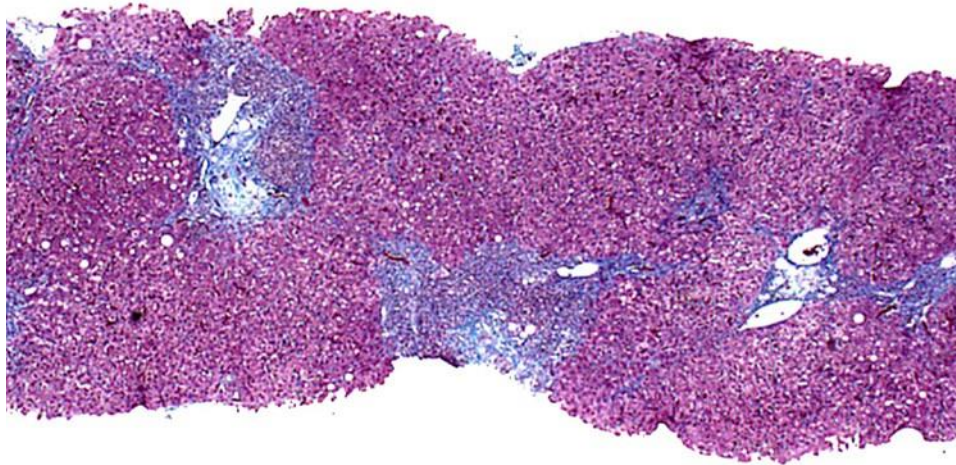


In this liver core, portal tracts are expanded by fibrosis (blue/green)

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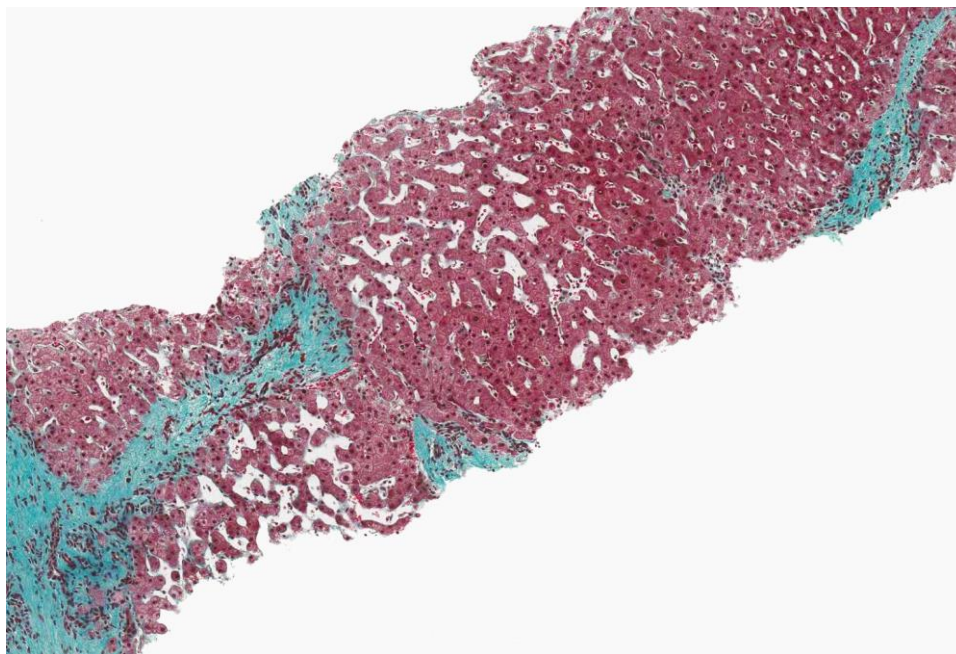
Fibrosis, Batts-Ludwig Stage 2/4 (Periportal Fibrosis)



In this liver core there is periportal fibrosis (blue) with short fibrous spurs but no complete fibrous bridges.

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Fibrosis, Batts-Ludwig Stage 3/4 (Bridging Fibrosis)

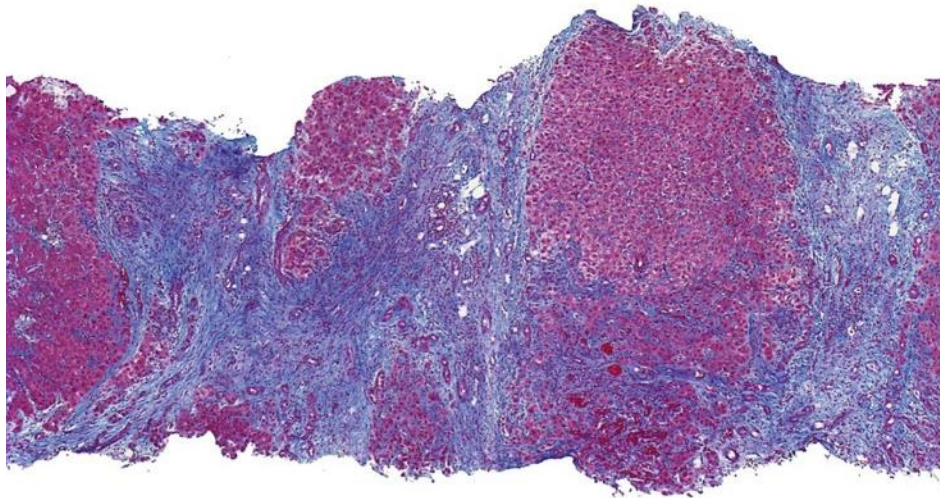


In this liver core there are fibrous bands (blue/green) joining adjacent portal tracts.

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Bridging Fibrosis, Batts-Ludwig Stage 4/4 (Cirrhosis)



In this liver core there is bridging fibrosis (blue) with complete nodule formation.

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- Give modifiable as well as non-modifiable factors which are associated with the **histological progression** of HCV infection.
 - Patient
 - Age (> 40 yrs)
 - Males
 - Caucasian
 - Life style
 - Obesity
 - Alcohol (> 50 g/day)
 - Smoking
 - Cannabis use (marijuana)
 - Co-morbidities
 - Steatosis
 - Insulin resistance
 - Diabetes (genotypes 1 and 4)
 - Iron overload
 - Co-infection
 - HBV
 - HIV
 - Immunosuppression
 - Schistosomiasis
 - Virus
 - Progression of HCV is not associated with HCV load or genotype
 - Laboratory/pathology
 - Elevated serum ALT levels
 - Histology - Moderate to marked necroinflammation



Other Hepatotropic Infections

Hepatitis D Virus (HDV)

- Nuclear antigen in hepatocytes of persons infected with HBV.
- 3 genotypes HDV RNA encodes HDag
- HBsAg protects the complex of HDV-RNA-HDag; hepatocyte injury is likely immune-mediated
- Serological markers
- HDV infection may occur
 - HBV DNA and HBsAg must be present for HDV replication
 - Associated with severe HBV
 - Severe chronic HBV (cirrhosis)
 - Fulminant HBV
 - HBV carriers (especially IV drug users [IVDU])
 - HBV: HBV DNA, HBsAg
 - Previously HBsAg⁺, now anti-HBc⁺
 - More common in IVDUs chronic HDV in ~ 5%
 - Usually HDV resolves as HBV resolves
 - With HBV (coprimary infection)
 - HDV replication inhibits HBV replication

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- The patient tests positive for HBV DNA⁺ / HBsAg⁺ and IgM anti-HDV⁺
- On the basis of their IgM anti-Hbc, determine if the HDV infection represents a coinfection of HBV, or if the person previously had HBV and the HDV was acquired afterwards (superinfection).

Type of Infection	Previous HBsAg	ALT	IgM anti-HBc ⁺	Clinical Course
○ Coinfection	Negative	Double peak [*]	Positive	Usually resolves as HBV improves
○ Superinfection	Positive	↑ from baseline ^{**}	Negative	Progresses to cirrhosis

^{*}first with HBV infection, then later with HDV

^{**}baseline may be increased because of initial HBV infection



Hepatitis E Virus (HEV)

- RNA virus
 - More common in adults and males
 - High attack and mortality rates in pregnant women (each trimester)
 - Increased spontaneous abortions
 - Stillbirths
 - Neonatal deaths
 - Transplacental transmission (“vertical”, mother-to-fetus)
 - Fecal-oral transmission (water contaminated with HEV)
 - Presentations
 - Acute icteric or non-icteric hepatitis
 - Fulminant hepatic failure (22%)
-
- Give the PRIM countries where HEV is endemic.
 - Pakistan
 - Russia
 - India
 - Mexico

“Optimism is the faith that leads to achievement. Nothing can be done without hope and confidence.”

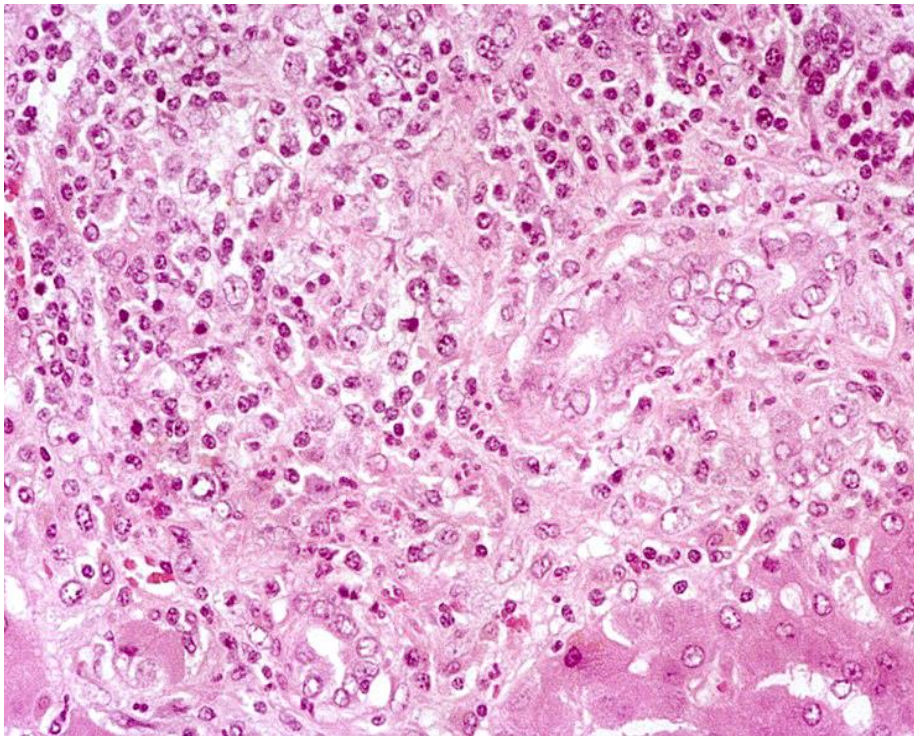
Helen Keller



Epstein-Barr Virus (EBV)

- Mononucleosis-like illness (IgM anti-EBV)
- Worse clinical course in persons > 30 years
- May cause
 - Chronic hepatitis
 - Granulomatous hepatitis
 - PTLD (post-transplantation lymphoproliferative disease)

Epstein-Barr Viral Hepatitis

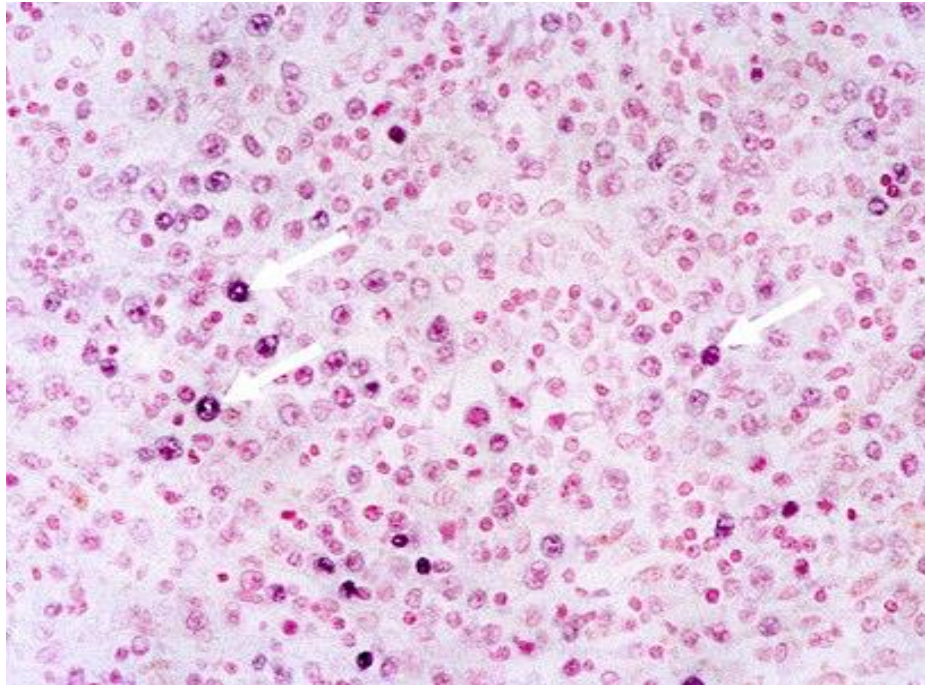


EBV positive post-transplant lymphoproliferative disorder with numerous lymphocytes (H&E 200X)

Courtesy of Dr. Subrata Chakrabarti, Western University



Epstein-Barr Viral Hepatitis



EBV positive post-transplant lymphoproliferative disorder with darkly staining EBV positive cells (in situ hybridization for EBER)

Courtesy of Dr. Subrata Chakrabarti, Western University (ON)

Cytomegalovirus (CMV)

- Give types of hepatobiliary disorders associated with CMV infection.
 - Transaminitis
 - Hepatitis
 - Acute
 - Granulomatous
 - Cholestatic
 - Fulminant hepatic failure
 - Post liver transplantation
 - Fibrosing cholestatic hepatitis
 - Graft rejection-like picture
 - Typical pathological changes on liver biopsy
 - Focal hepatocyte and bile duct damage
 - Lymphocytic sinusoidal infiltration
 - Giant cell transformation in neonatal hepatitis
 - +/- Owl's eye nuclear inclusions



Herpes Simplex Virus (HSV)

- Cutaneous (often orolabial) and genital HSV lesions
 - Transaminitis
 - Immune suppressed persons
 - Pregnant women
 - 3rd trimester
 - Fulminant hepatic failure
 - Acute HSV hepatitis from an infection with HSV-1 or HSV-2 may occur in immunocompetent as well as immunocompromised persons.
- Give laboratory features and which should alert the physician about the possibility of HSV hepatitis and the need to begin empiric therapy with acyclovir.
 - ↑↑ ALT, AST (> 1000)
 - ↓ WBC
 - Fever / abdominal pain
 - Associated HSV
 - Pneumonitis
 - Encephalopathy
- Histopathology
- Give the typical histopathological changes of HSV on liver biopsy.
 - Focal or extensive parenchymal:
 - Hemorrhage
 - Necrosis
 - Minimal lymphocytic portal inflammation
 - Hepatocytes

Cowdry A type nuclear inclusions in hepatocytes near the necrosis (ground glass nuclei with margination of chromatin = peripheral dark rim) Regenerative hepatocyte multinucleation

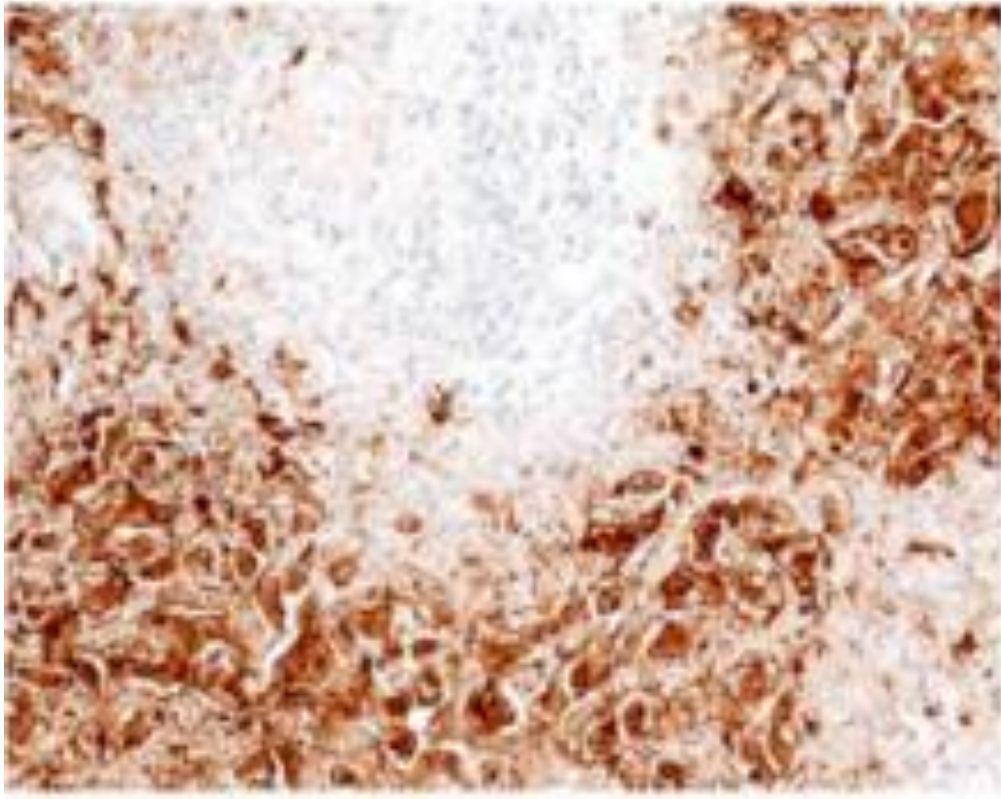
Please see: Peltekian KM, Hirsch G. Chapter 59. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 7: Drug used in viral hepatitis, page 799-800.

- The liver biopsy of the patient with acute viral hepatitis shows inclusions in the nuclei of the hepatocytes. Give the histopathological features which help to differentiate between CMV- vs HSV- associated hepatitis.
 - CMV hepatitis
 - Hepatocytes contain intra-nuclear inclusion with a surrounding halo
 - This halo is aka “owl’s eye” inclusion
 - Positive CMV immunohistochemistry



- HSV hepatitis
 - Focal or extensive
 - Hemorrhage
 - Necrosis, extensive
 - Hepatocytes
 - Cowdry A type inclusions in hepatocytes near the necrosis = ground glass nuclei with peripheral margination of chromatin
 - Regenerative multinucleated hepatocytes

HSV-associated Hepatitis



HSV1-infected hepatocytes detected with immunoperoxidase staining (×240)

Printed with permission: Honsig C, et al. BMJ Case Rep 2017; pii: bcr2016218310.



LEPTOSPIROSIS (aka Weil syndrome)

➤ Clinical

- General
 - Fever
 - Rigors
- Eyes
 - Conjunctival suffusion
- Heart
 - Temperature-pulse dissociation
- Lung
 - Cough, no sputum
- MSK
 - Myalgias
- Kidney
 - ↓ Na⁺, ↓ K⁺
 - Renal insufficiency
- Hematology
 - Lymphadenopathy
- Liver
 - ALF (acute liver failure; rare)

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- In the context of a “zoonosal infection”, give the clinical findings of **Weil syndrome**.
 - A severe infection (e.g., hepatitis)
 - Fever, jaundice
 - Conjunctivitis, myalgias
 - Bleeding

Clinical Gem

- Give infectious causes of liver disease which cause fever and **temperature-pulse dissociation**.
 - Amebiasis
 - Leptospirosis

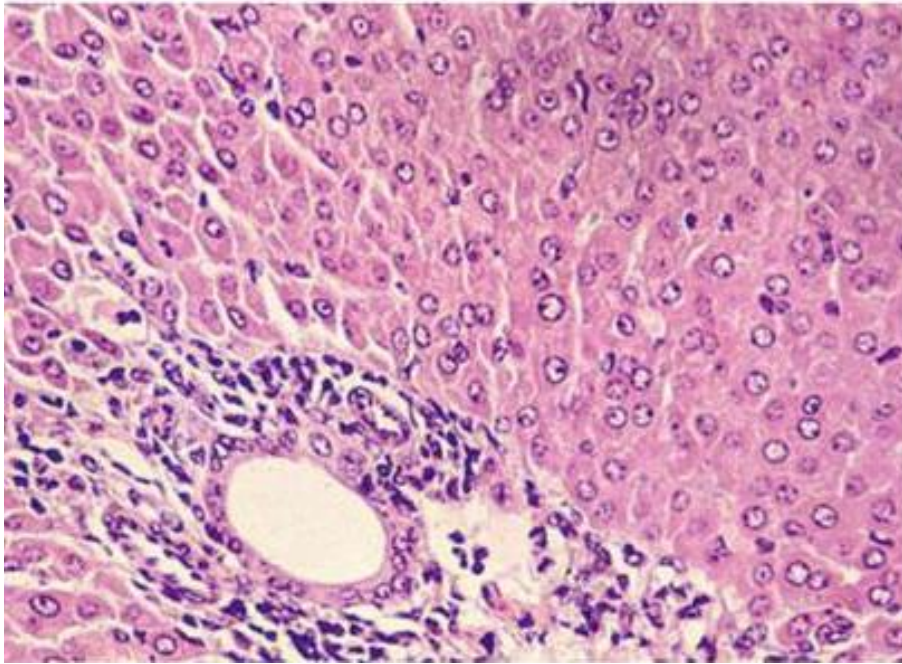
➤ Laboratory

- ↑ AST, ↑ bilirubin



➤ Histopathology

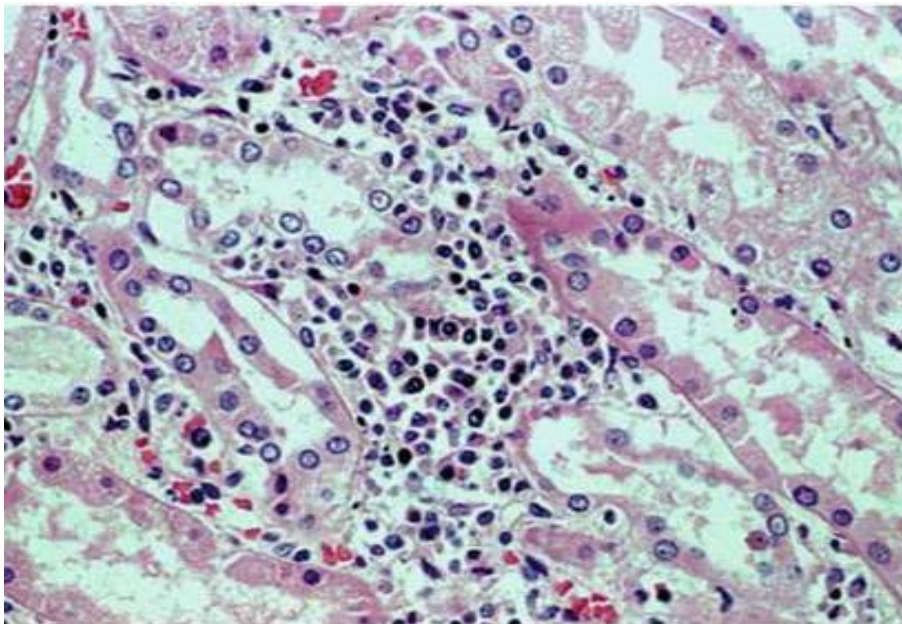
Leptospirosis



Liver typically shows dissociation and separation of liver cell plates, a hallmark of the disease

Printed with permission: Haake DA and Levett PN. Curr Top Microbiol Immunol 2015; 387: 65-97.

Leptospirosis



Kidney: Acute tubular necrosis and interstitial nephritis

Printed with permission: Haake DA and Levett PN. Curr Top Microbiol Immunol 2015; 387: 65-97.



AMEBIC LIVER DISEASE

➤ Diagnosis

- Serology positive in 95% (after only 1 week of infection)
- CT scan
 - Elevated right hemidiaphragm (50%)
 - Adhesions destroy the costophrenic angle
 - Solitary
 - Lesions
 - Large, round lesion
 - Usually right lobe of liver
 - Low attenuation (dark)
 - Enhancing rim of hepatic tissue
 - “anchovy paste” aspirate
- When to suspect amebic liver abscess
 - ↑ AP, leukocytes without eosinophilia
- When to suspect poor prognosis
 - ↑ bilirubin
 - ↓ albumin

Pyogenic Liver Abscess

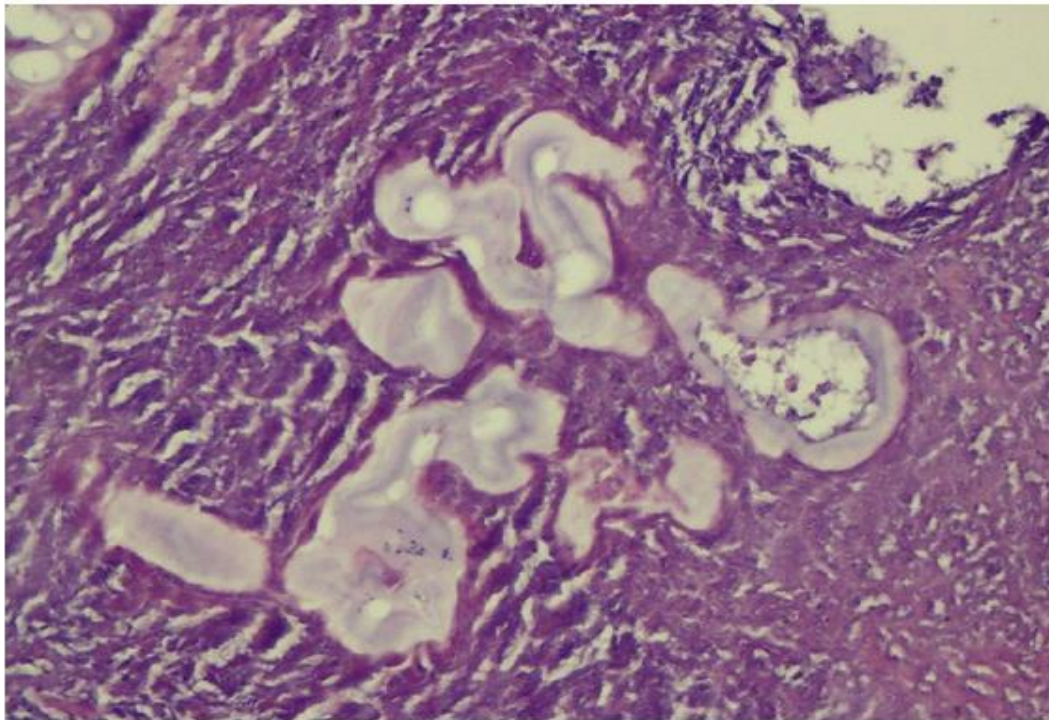
- Give sources of bacteremia which may result in a pyogenic liver abscess.
 - Luminal GI tract: perforated viscus e.g.,
 - Peptic ulcer disease
 - Appendicitis
 - Diverticulitis
 - Colon cancer
 - IBD
 - Peritonitis
 - Liver
 - HCC
 - Treatment of 1^o/2^o hepatic neoplasm
 - Chemoembolization
 - Percutaneous ablation
 - Biliary tree
 - Cholangitis
 - Cholecystitis
 - Sphincterotomy
 - Intrahepatic stones
 - Gallbladder cancer
 - Penetrating abdominal wound
 - Heart
 - Bacterial peritonitis



ECHINOCOCCAL (“HYDATID”) CYST OF THE LIVER

- Demography
 - Sheepherder (also think of fasciolosis)
- Diagnostic imaging
 - US / CT scan
 - Smooth cyst
 - Round
 - Daughter cysts
 - Internal septations
 - Calcification, especially “eggshell” calcification
 - Hydrated-sand (portions of the tapeworms)
- Histopathology
 - Anaphylaxis after cystic rupture
 - Cyst filled with “hydrated sand”
 - Cyst contains “daughter cysts”
 - Liver cysts with eggshell calcifications
 - Smooth, round cyst with internal septations
 - Solitary hepatic cyst of right lobe

Echinococcus Infection of the Liver

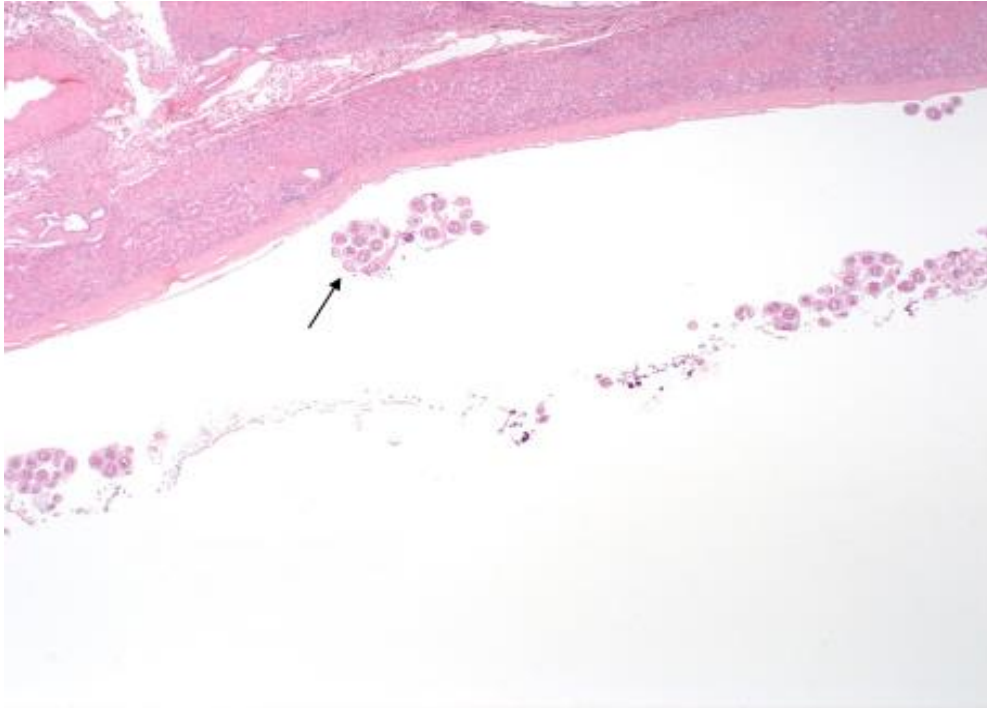


Germinative membranous structures of Echinococcus in the liver parenchyma

Printed with permission: Bulakci M, et al. Case Rep Radiol. 2014; 2014: 638375.

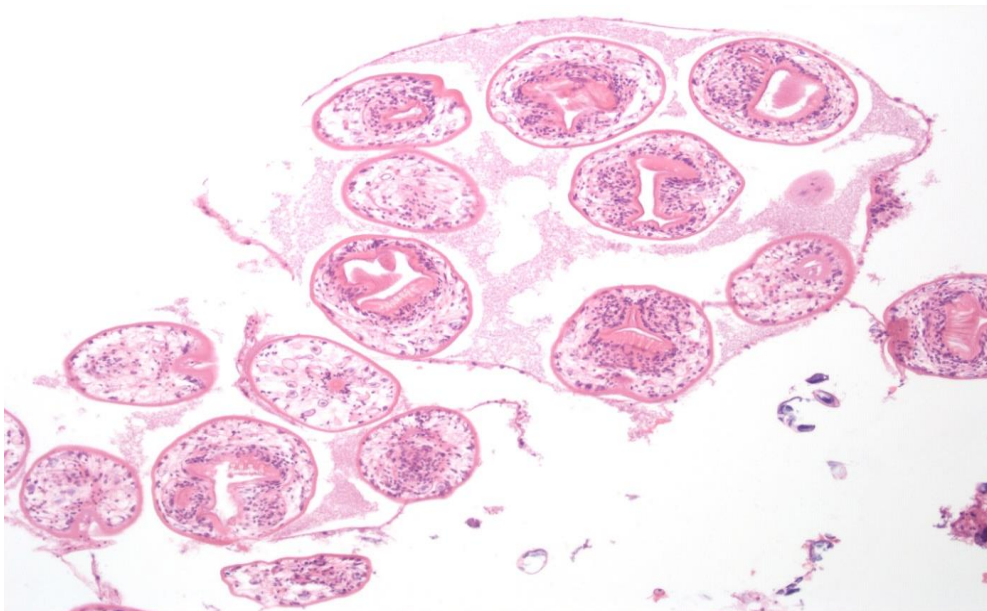


Echinococcal Cyst Containing Protoscolices (H&E, 20X)



Courtesy of Dr. Liena Zhao, Western University, London (ON)

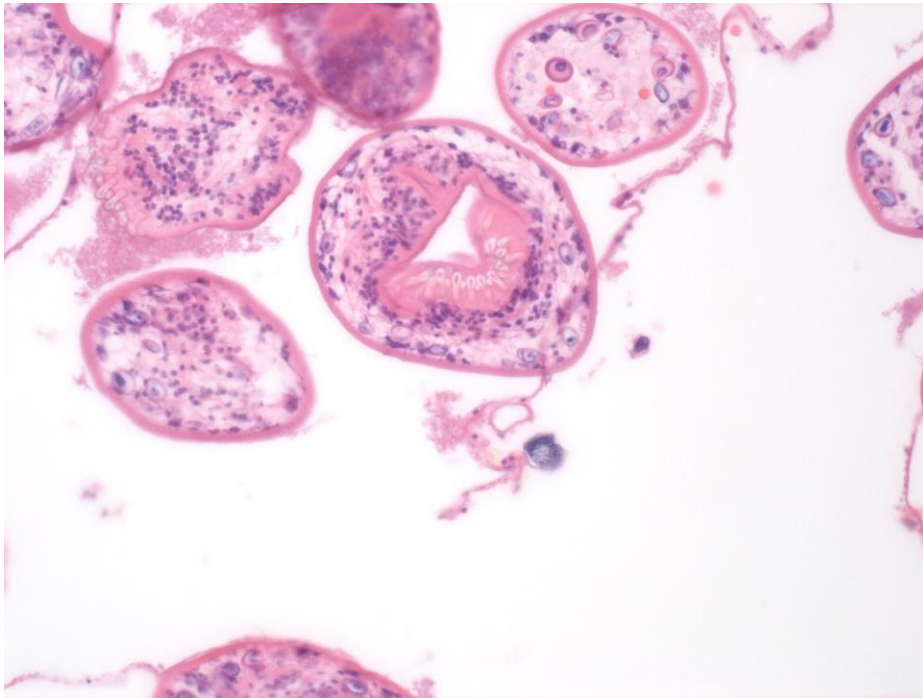
Protoscolices of Echinococcus granulosus in a Hydatid cyst (H&E, 200X)



Courtesy of Dr. Liena Zhao, Western University, London (ON)

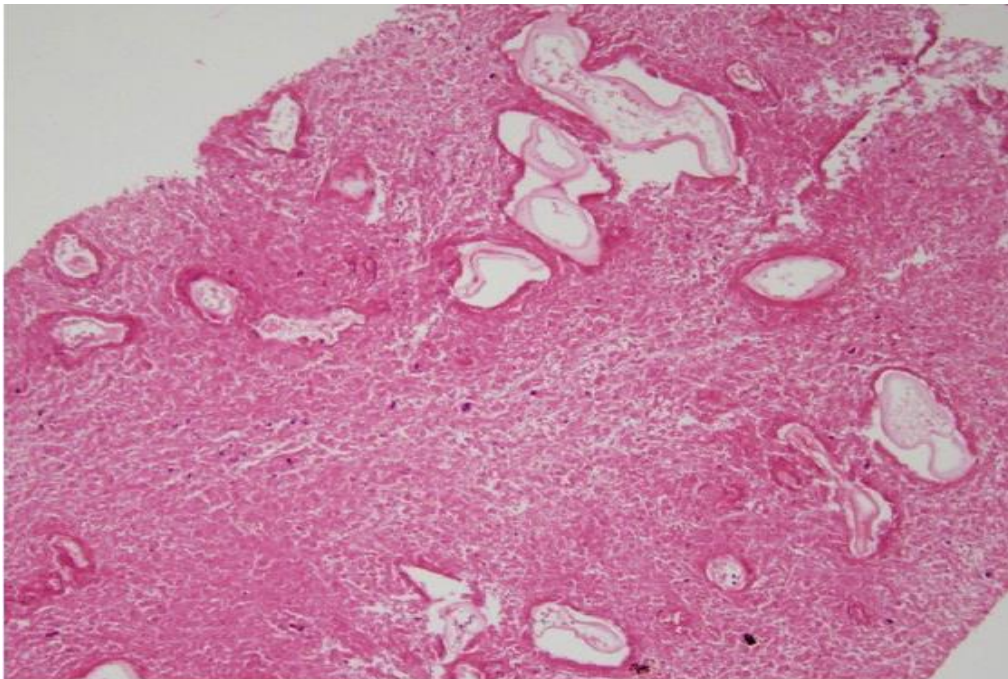


Protoscolices of Echinococcus granulosus in a Hydatid cyst (H&E, 400X)



Courtesy of Dr. Liena Zhao, Western University, London (ON)

Echinococcus Infection of the Liver



Laminated membrane fragments are seen within the necrotic liver parenchyma of second case

Printed with permission: Bulakci M, et al. Case Rep Radiol. 2014; 2014: 638375.



LIVER PARASITES

- Give the likely hepatic parasitic infection for 15 of the following “buzzwords” or associations for liver parasites.

Buzzword / Association	Parasitic Infection
Abscess filled with “anchovy paste”	Amebiasis
Anaphylaxis after cystic rupture	Echinococcosis
Biliary ductal fibrosis	Clonorchiasis
Contaminated freshwater plants	Fascioliasis
Cyst filled with “hydrated sand”	Echinococcosis
Cyst containing “daughter cysts”	Echinococcosis
Epilepsy	Schistosomiasis
Gallstones	Clonorchiasis
Hepatic abscess with elevation of right hemidiaphragm with adhesion obliterating the costophrenic angle	Amebiasis
Liver cysts with eggshell calcifications	Echinococcosis
Portal hypertension without stigmata of chronic liver disease	Schistosomiasis
Portal vein granulomas and fibrosis	Schistosomiasis
Reduviid bug (aka kissing bug)	American trypanosomiasis (aka Chagas disease)
Sandfly	Leishmaniasis (kala-azar)
Serum sickness (aka Katayama fever)	Schistosomiasis
Shepherd	Fascioliasis, echinococcosis
Smooth, round cyst with internal septations	Echinococcosis
Solitary hepatic cyst of right lobe	Echinococcosis, amebiasis
Strong male predominance	Amebiasis
Tortuous tract in liver on CT	Fascioliasis
Transverse myelitis	Schistosomiasis
Tsetse fly	African trypanosomiasis (aka sleeping sickness)
Undercooked fish	Anisakiasis

Printed with permission: Spiegel BM, Karsan AA. Acing the hepatology questions on the GI board exam. Slack Incorporated 2012, page 145-146.



- Give the likely associations for liver parasites for the following hepatic parasitic infection.
 - Amebiasis
 - Abscess filled with “anchovy paste”
 - Hepatic abscess with elevation of right hemidiaphragm with adhesion obliterating the costophrenic angle
 - Strong male predominance
 - Solitary hepatic cyst of right lobe
 - Anisakiasis
 - Home-made sushi
 - Clonorchiasis
 - Biliary ductal fibrosis
 - Gallstones
 - Undercooked fish
 - Echinococcosis
 - Anaphylaxis after cystic rupture
 - Cyst filled with “hydrated sand”
 - Cyst containing “daughter cysts”
 - Liver cysts with eggshell calcifications
 - Smooth, round cyst with internal septations
 - Solitary hepatic cyst of right lobe
 - Sheepherder
 - Fascioliasis
 - Contaminated freshwater plants
 - Tortuous tract in liver on CT
 - Sheepherder
 - Schistosomiasis
 - Epilepsy
 - Portal hypertension without stigmata of chronic liver disease
 - Portal vein granulomas and fibrosis
 - Serum sickness (aka Katayama fever)
 - Transverse myelitis
 - Leishmaniasis (kala-azar)
 - Sandfly
 - American trypanosomiasis (aka Chagas disease)
 - Reduviid bug (aka kissing bug)
 - Tsetse fly

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MCQ Tricky Terms

- In the context of liver disease, give the meaning of
 - Kala-azar
 - Grey pigmentation of the skin arising from infection with visceral leishmaniasis
 - Anchovy paste
 - Red / brown “pasty” aspirate from an amebic abscess



CIRRHOTIC CARDIOMYOPATHY

➤ Definition

- A cardiac dysfunction in patients with cirrhosis, characterized by impaired
 - Contractile responsiveness to stress, and / or
 - Altered diastolic relaxation with,
 - Electrophysiological abnormalities in the absence of other known cardiac disease.

➤ Diagnosis

❖ Diagnostic criteria

- Systolic dysfunction
 - Blunted increase in cardiac output on exercise, volume challenge or pharmacological stimuli
 - Resting ejection fraction <55%
- Diastolic dysfunction
 - E/A ratio <1.0 (age-corrected)
 - Prolonged deceleration time (>200 ms)
 - Prolonged isovolumetric relaxation time (>80 ms)

❖ Supportive criteria

- Electrophysiological abnormalities
- Abnormal chronotropic response
- Electromechanical uncoupling / dys-synchrony
- Prolonged Q-T_c interval
- Seen in 60% of persons with cirrhosis correlates with the severity of the liver disease, and predisposes the person to ventricular arrhythmias
- ↑ left atrium
- ↑ myocardial mass
- ↑ BNP and pro-BNP
- ↑ troponin I

Abbreviations: BNP, brain natriuretic peptide; E/A ratio, ratio of early to late (arterial) phases of ventricular filling

Printed with permission: Møller S, and Henriksen JH. *Gut* 2008; 58: 274.



- Give the diagnostic tools in the assessment of systolic and diastolic dysfunction in persons suspected of having cirrhotic cardiomyopathy.

❖ Systolic function

- Echocardiography / MRI:
 - Volumes
 - Fractional shortening
 - Velocity of fractional shortening
 - Ejection fraction (planimetry)
 - Response to stress (dobutamine)
 - Wall motion
- Exercise ECG
 - Exercise capacity
 - Oxygen consumption*
 - Pressure x heart rate product
- Radionuclide angiography (MUGA)
 - Ejection fraction
 - Cardiac volumes
 - Pattern of contractility
- Myocardial perfusion imaging with gating
 - Regional myocardial perfusion
 - Cardiac volumes
 - Ejection fraction
 - Wall motion and wall thickening

❖ Diastolic function

- Echocardiography / MRI / MUGA
 - E/A ratio
 - Deceleration time
 - A and E waves
 - Relaxation times

Printed with permission: Møller S, and Henriksen JH. *GUT* 2008; 58: pg. 276.
Training program in gastroenterology.



DRUG- INDUCED LIVER INJURY (DILI)

➤ Definition

- In the context of DILI, give the meaning of the Hy law
 - In DILI, the finding of clinical jaundice plus $\uparrow$ ALT or AST has a mortality rate of $\sim 10\%$.

Please see Chitturi S, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders / Elsevier, Philadelphia, 2016, Table 88-5, page 1458, for "Risk Factors for Acetaminophen Induced Hepatotoxicity".

➤ Diagnosis (factors to consider in the **diagnosis of DILI**)

- Time to onset
 - Variable range but usually < 12 months
- Clinical features at presentation
 - Can be asymptomatic
 - Rash and eosinophilia are found infrequently
 - Classification into hepatocellular versus mixed and/or cholestatic liver injury on the basis of R value

$R = (\text{initial ALT} / \text{ULN}) / (\text{AP} / \text{ULN})$: patient with an R value > 5 have hepatocellular liver injury, and $R < 2$ is indicative of cholestatic liver injury.

The R value helps the clinician to identify other etiologies of acute liver injury to consider and exclude (i.e., differential diagnosis)

➤ Histopathology

- Give histopathological changes of the spectrum of DILI.
 - Asymptomatic liver disease
 - Acute hepatitis
 - The ALT / AST or serum bilirubin may be increased Hy's law: when aminotransferases and serum bilirubin are increased, prognosis is poor (mortality rate $\sim 10\%$; zonal or nonzonal necrosis mortality rate $\sim 5\%$)
 - Acute / chronic steatosis $\downarrow$ beta-oxidation $\rightarrow$ microvesicular steatosis (acute) $\rightarrow$ macrovesicular (fat droplet occupies $> \frac{1}{2}$ of cytoplasm with eccentric compressed nucleus) steatosis (chronic) histologically resembles NAFLD, NASH and ALD (alcoholic liver disease)
 - Examples of causative drugs
 - Ibuprofen
 - Sulindac
 - Acute liver failure (ALF)
 - Mortality rate $\sim 50\%$, especially if serum bilirubin $> 3 \times \text{ULN}$



- Chronic hepatitis
 - Occurs in 5% to 10% of adverse drug reactions
 - More common with cholestatic / cholestatic than hepatocellular liver injury
 - Autoimmune-like chronic hepatitis (AIH)
 - Female > males
 - Positive ANA, anti-smooth muscle antibody
 - ↑ globulins in serum
 - Histopathologically identical to type 1 autoimmune hepatitis
 - Examples of causative drugs
 - Phenytoin
 - Diclofenac
 - Viral hepatitis-like
 - Serology negative
 - Histopathology similar to chronic viral hepatitis
 - Examples of causative drugs
 - Aspirin
 - Isoniazid
 - Granulomatous hepatitis
 - Non-caseating granulomas
 - Periportal hepatitis
 - Hepatocellular injury or cholestasis
 - Not associated with bile ducts
- Phospholipidosis
 - Phospholipid filled lysosomes, which make hepatocytes appear “foamy” (foamy hepatocytes)
 - Examples of causative drugs
 - Amiodarone
 - Chlorpromazine
- Bland cholestasis
 - Pure cholestasis
 - Bile plugs in zone 3
 - Minimal hepatocellular inflammation
 - Examples of causative drugs
 - OCA (oral contraceptive agents)
 - Anabolic steroids
 - Cholestatic hepatitis
 - Cholestasis surrounded by inflammation
 - Proliferation of bile ducts
 - ↑ ALT / AST, ↑ AP, ↑ GGT
 - Symptoms of hypersensitivity



- Typical causative drugs
 - NSAIDs
 - Erythromycin
- PBC-like
 - Histopathologically similar to PBC
 - Serologically AMA-negative
 - Typical causative drugs
 - Amitriptyline
 - Erythromycin
 - Ductopenic cholestasis
 - Examples of causative drugs
 - Amoxicillin
 - Clindamycin
- Sclerosing cholangitis
 - Diagnostic imaging (ERCP, MRCP) and histopathology similar to PSC (primary sclerosing cholangitis)
- Fibrosis / cirrhosis
- Vascular disease
- Endothelial damage → thrombosis
 - SOS (sinusoidal obstruction syndrome)
 - B-CS (Budd-Chiari syndrome)
- Hepatic vein (HV) thrombosis
 - B-CS (Budd-Chiari syndrome)
 - Obstruction of HV or IVC (inferior vena cava)
 - Associated with
 - Coagulation disorders
 - Myeloproliferative disorders
 - Use of OCA (oral contraceptive agents)

"Don't judge each day by the harvest you reap
but by the seeds you plant."

Robert Louis Stevenson



VASCULAR DISEASES

➤ Classification

- Classify, and give examples of the vascular diseases of the liver.
- Disorders of portal venous inflow
 - Acute mesenteric / portal vein thrombosis (PVT)
 - Chronic mesenteric / PVT
- Disorders of hepatic arterial (HA) inflow
 - Hepatic artery thrombosis
 - Hepatic arteriovenous fistula
 - Ischemic hepatitis
- Disorders of hepatic venous outflow
 - Veno-occlusive disease (VOD)
 - Budd-Chiari syndrome (BCS)

Printed with permission: Kamath PS. *Mayo Clinic Gastroenterology and Hepatology Board Review* 2008: pg. 337.

Portal Colopathy

➤ Definition

- Portal colopathy is the “...vascular manifestations of portal hypertension in the colon” (Feldman M., et al. *Sleisenger and Fordtran’s Gastrointestinal and Liver Disease*. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 602).
- Endoscopically – vascular ectasia, redness, “blue vein”

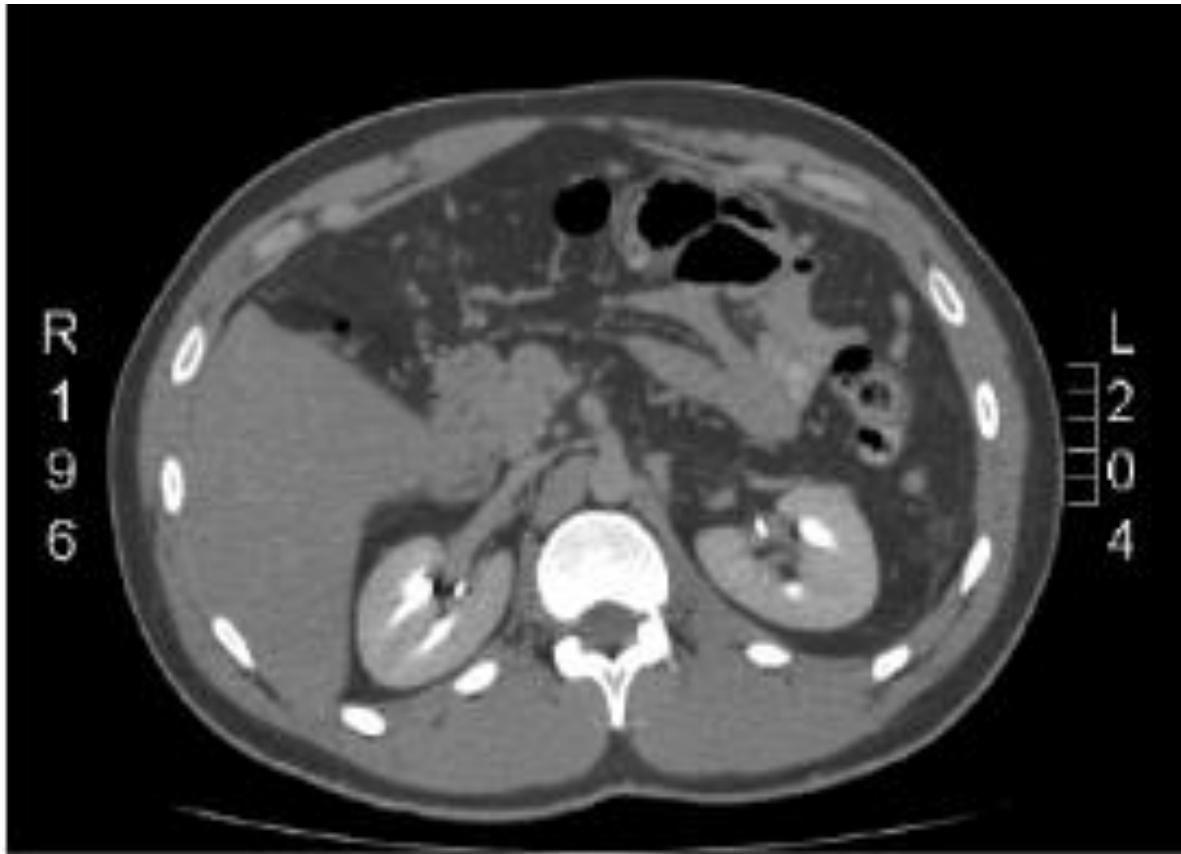
Portal Vein Thrombosis (PVT)

➤ Diagnostic imaging / histology

- Doppler ultrasound
- MRI (contrast enhanced); multiphasic CT
- Liver biopsy (zone 3 congestion, portal inflammation and fibrosis, generalised / localised atrophy)



Portal Vein Thrombosis



Printed with permission: Cohen R, et al. Portal Vein Thrombosis. Case Reports in Vascular Medicine, vol. 2015, Article ID 823063, 5 pages, 2015.

Sinusoidal Obstruction Syndrome (SOS, aka Veno-occlusive disease [VOD])

- Definition
 - SOS is diffuse, idiopathic endothelial injury causing non-thrombotic obstruction of central hepatic venules, leading to dilation of sinusoids and hepatic congestion.
- Differential
 - SOS develops after BMT on days 10 to 20
 - Distinguish from GVHD (graft-versus-host disease) which develops after day 15
 - Sepsis and drug toxicity do not usually cause painful hepatomegaly or ascites, as does SOS



➤ Diagnostic Imaging

- Give the non-specific changes seen on diagnostic imaging (abdominal ultrasound, CT or MRI) which suggest the diagnosis of SOS (Sinusoidal Obstruction Syndrome).
 - Liver, spleen
 - Hepatosplenomegaly
 - Portal vein (PV)
 - Dilated
 - Flow in PV slow or reversed
 - Umbilical vein
 - Recanalization
 - Gallbladder thick walled
- Give the timing and method of diagnosis of liver and biliary diseases following **stem cell transplantation**.

Disease	Timing	Diagnosis
○ Sinusoidal obstruction syndrome (SOS)	Onset before day 20	– Typical clinical features plus exclusion of other causes of jaundice and weight gain – Imaging (Doppler ultrasound or CT) – Transvenous measurement of wedged hepatic venous pressure gradient and liver biopsy – Note atypical presentations (acute hepatitis, anasarca)
○ Cholestasis of infection (cholangitis lenta)	Following sepsis or neutropenic fever (usually before day 30)	– Exclude other causes of cholestasis – Inferential diagnosis in a patient with cholestatic jaundice
○ Acute GVHD	Day 15-50	– Confirm GVHD in skin, gut – Exclude other causes of cholestasis – Liver biopsy
○ Acute viral hepatitis	HSV, day 20-50 Adenovirus, day 30-80 VZV, day 80-250 HBV and HCV, during immune reconstitution	– Pre-transplant blood test (antigen, antibodies, PCR results) – Isolation of virus from other sites (stool and urine for adenovirus) – PCR of serum for specific viruses
○ Fungal abscess	Day 10-60	– Liver biopsy histology / PCR / immunostains – Hepatic pain, fever – Liver imaging (MRI>CT) – Serum fungal antigen(s)



Disease	Timing	Diagnosis
○ Bacterial infection	Day 10-80	– Hepatic pain, fever – Liver imaging – Liver biopsy, culture
○ Drug-liver injury	Day 0-100	– Clinical evidence linking elevations of serum ALT or alkaline phosphatase to drugs known to cause liver injury
○ Ischemic liver disease	Day 0-30 Day 15-60	– Clinical evidence linking shock to subsequent rises in serum ALT
○ Biliary obstruction	Day 10-50	– History, examination – Biliary ultrasound
○ Idiopathic hyperammonemia	After day 80	– ERCP > magnetic resonance cholangiography – Unexplained confusion, coma – Blood ammonia
○ Chronic hepatitis C	Pre-transplant Long-term follow-up after transplant	– HCV RNA in serum – Elevation of serum ALT after immune reconstitution
○ Iron overload	After day 80	– Transferrin saturation – Marrow iron qualification – Liver iron quantification (Ferriscan MRI, liver biopsy quantification)
○ Chronic GVHD	Years after transplant	– Prior acute GVHD history – Chronic GVHD in other organs – Consistent elevations of serum ALT, alkaline phosphatase – Note hepatitis presentation
○ Nodular regenerative hyperplasia (NRH)		– Liver biopsy (reticulin stain) – Signs of portal hypertension but preserved liver function – Laparoscopic appearance of the liver

Printed with permission: McDonald, G.B., and Frieze, D. *Gut* 2008; 57:987-1003.



Splenic Vein Thrombosis (SVT)

- Give the anatomical reasons why thrombosis of the splenic vein (SV) may cause gastric fundal varices, but not esophageal varices.
 - Thrombosis of SV (SVT) causes $\uparrow$ pressure in short gastric veins.
 - Obstruction of SV is distant to the joining of the SV to the SMV (superior mesenteric vein), which form the portal vein and from there the esophageal veins.
 - Thus, EV do not form with SVT (but do form with PVT)
 - What is usual surgical treatment for isolated gastric fundal varices due to the splenic vein thrombosis (SVT)?

A Trick Question

The usual surgical treatment for isolated gastric fundal varices due to splenic vein thrombosis (SVT) is splenectomy.

- Give the circumstance where splenectomy would not be curative for SVT.
 - A SVT combined with a portal vein thrombosis (PVT) would not be cured by splenectomy.

Ischemic Hepatitis

➤ Terms

- Give reasons why “Ischemic” or “Hypoxic” hepatitis may not be a satisfactory term.
 - Reduced hepatic blood flow from any cause, i.e., congestive heart failure, respiratory failure, systemic hypotension, may cause the following pathological changes
 - Very little inflammatory infiltrate (i.e., no “hepatitis”)
 - Centrilobular necrosis
 - Loss of hepatocytes
 - RBCs in sinusoids
 - May progress to centrilobular fibrosis



Hepatic Artery Aneurysm (HAA)

- Causes / associations
 - Atherosclerosis (may also cause hepatic infarction)
 - Mycotic infection
 - Vasculitis
 - Pseudoaneurysms
 - Liver biopsy
 - Percutaneous transhepatic cholangiogram
 - Liver transplantation

SO YOU WANT TO BE A HEPATOLOGIST!

Atherosclerosis may involve the hepatic artery, and cause a HAA, which may rupture, and is associated with a 30% mortality rate.

- Give another but chronic hepatobiliary complication of atherosclerosis of the hepatic artery.
 - Slow obstruction of the hepatic artery may reduce the blood supply to the bile duct (especially the common bile duct), leading to
 - Ischemic cholangiopathy
 - CBD strictures
 - Obstruction

➤ Clinical

- Give the physical finding on the abdominal wall of the person with cirrhosis which suggests that the hepatic bruit is from recanalization of the umbilical vein.
 - The presence of a caput medusae suggests ↑ blood flow in the abdominal wall veins, arising from recanalization of the umbilical vein, producing the Cruveilhier – Baumgarten (CB) murmur.

HEPATIC FIBROSIS

➤ Diagnosis

❖ Gold standard

- Liver biopsy
- Only “bronze standard” because of considerable sampling variation (patchy changes)

❖ A panel of blood tests

- α₂-microglobulin
- Apolipoproteins A-1
- Haptoglobin
- Total bilirubin
- GGT
- ALT



- To estimate
 - Hepatic fibrosis
 - First 5 tests
 - Necroinflammatory activity
 - All 6 tests
- ❖ Fibro test (aka Fibrosure)
 - Performance characteristics
 - Sensitivity, 90%
 - Specificity, 36%
 - PPV, 88%
 - NPV, 40%
 - Validated in HBV, HCV, ALD, methotrexate in psoriasis
 - Low cut-off (0.30)
 - NPV, 90%
 - 0.30 to 0.70, inaccurate (this range includes 1/3 of NAFLD patients tested with Fibro Test)
- ❖ FIBROSpect II
 - A score derived from variably weighted values of the following:
 - Hyaluronate
 - Tissue inhibitor of metalloproteinase I
 - α 2-macroglobulin
 - Performance characteristics for advanced fibrosis in HCV
 - PPV, 88%
 - Sensitivity, 72%
 - Specificity, 74%
 - Severe steatosis (centrilobular, macrosteatosis)
 - ↑ Stainable iron
 - Signs of cirrhosis
- ❖ FibroScan®
- ❖ NAFLD Fibrosis Score
 - Age
 - BMI
 - Blood sugar
 - AST / ALT
 - Platelet count
 - Albumin
 - High cut-off
 - PPV, 82% to 90%
 - Low cut-off
 - NPV, 88% to 93%

Adapted from: Pinzani, et al. *Nature Clinical Practice Gastroenterology & Hepatology* February 2008; 5(2): pg 102; and Reid AE. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology / Diagnosis / Management* 2010, pg 1408.



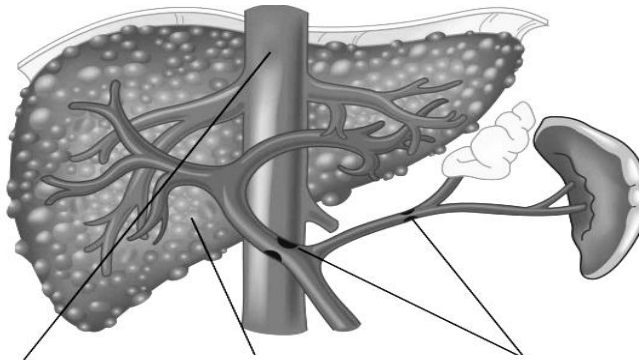
PORTAL HYPERTENSION (PHT)

➤ Definition

- Hepatic sinusoidal pressure ≥ 6 mm Hg

Classification of Causes of Portal Hypertension

- The different sites of increased resistance to portal flow (posthepatic, intrahepatic, and prehepatic) and associated diseases are shown.
- Many diseases have a mixed pattern.



Increased Portal Blood Flow

- Arteriovenous fistula
- Idiopathic tropical splenomegaly

Post hepatic

- Budd-Chiari syndrome
- Constrictive pericarditis
- Inferior vena cava obstruction
- Right-sided heart failure
 - Webs
 - Tumour
 - Invasion
 - Thrombosis
- Severe tricuspid regurgitation

Intrahepatic

- Pre-sinusoidal (non-cirrhotic)
 - Idiopathic portal hypertension
 - Primary biliary cholangitis
 - Sarcoidosis
 - Schistosomiasis
 - Chronic active hepatitis
 - Congenital hepatic fibrosis
 - Toxins: vinyl chloride, arsenic
 - Idiopathic portal hypertension
- Sinusoidal
 - Alcoholic cirrhosis
 - Alcoholic hepatitis
 - Cryptogenic cirrhosis
 - Post-necrotic cirrhosis
 - Sinusoidal obstruction syndrome
- Post-sinusoidal
 - Veno-occlusive disease
 - Central hyaline sclerosis (alcoholic liver disease)

Prehepatic

- Portal vein (PV) thrombosis
- Splenic vein (SV) thrombosis
- Wedge hepatic vein pressure may be high in patients with “presinusoidal” causes, especially as the disease progresses, indicating sinusoidal and / or collateral involvement
- Some “post sinusoidal” conditions may also have sinusoidal component

Adapted from: Shah VH and Kamath PS. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 10th Edition, Saunders / Elsevier, Philadelphia, 2016, Figure 92-5, page 1528; and Sherlock and Dooley, 11th Edition 2002, Figure 10.36, page 166; 10.40, and 10.41, pages 168-169.



- Give sites of portal vein-systemic circulation which develop in portal hypertension, and name the collateral blood vessels in this abnormal flow.

Site	Vessel(s)
○ Rectum	– Inferior mesenteric vein → pudendal vein
○ Umbilicus	– Umbilical vein → left portal vein
○ Retroperitoneum (in women)	– Ovarian vessels → iliac veins
○ Gastroesophageal area	– Hepatic venous pressure gradient ▪ 10 mm Hg for esophageal varices to develop ▪ > 12 mm Hg for esophageal varices to bleed ▪ > 16 mm Hg for gastric varices to bleed

Idiopathic Portal Hypertension (IPH) and Hepatoportal Sclerosis (HPS)

- IPH and HPS are associated with ↑PP (portal pressure) and no obstruction of the extrahepatic portion of the PV (portal vein).
- Give the distinctive hepatic histopathological feature of IPH versus HPS seen on liver biopsy.
 - IPH
 - Normal
 - HPS, intrahepatic portal veins show
 - Subendothelial thickening
 - Thrombosis
 - Recanalization

Hereditary Hemorrhagic Telangiectasia (HHT) / Osler-Weber-Rendu Disease (OWRD)

- Diagnosis
- Give the **diagnostic criteria** for HHT / OWRD.
 - Positive family history
 - Epistaxis
 - Telangiectasias
 - AV fistulas (lung, liver)



- Give the likely diagnosis, based on the location of the bruit.
 - A splanchnic artery which forms a fistula with a mesenteric vein causes a sudden and dramatic increase in portal pressure (from > 6 mm Hg to > 100 mm Hg), leading to sudden onset of ascites and varices, with bleeding from the varices.
 - The likely diagnosis is HHT (hereditary hemorrhagic telangiectasia)
 - AV fistulas to the lung or liver are common in HHT.

Hereditary Hemorrhagic Telangiectasia / Osler-Weber-Rendu Disease



Source: Sandhu A (2015). GI Endoscopy and Pathology. In Thomson ABR and Chande N (Eds). Medical Mini Review Series in Gastroenterology and Hepatology: Efficient Refresher for the Busy Clinical Gastroenterologist (volume 3), page 406.





Source: Sandhu A (2015). GI Endoscopy and Pathology. In Thomson ABR and Chande N (Eds). Medical Mini Review Series in Gastroenterology and Hepatology: Efficient Refresher for the Busy Clinical Gastroenterologist (volume 3), page 406.

Portopulmonary Hypertension (PPH)

- Definition
 - Portal hypertension associated with hepatic cirrhosis
- Demography
 - Occurs in 0.25-4.0% of persons with end-stage liver disease, and usually within 4-7 years of the diagnosis of portal hypertension (PHT) (even though there is not a direct correlation between the development of PPH and PHT)



➤ Differential

- Give an approach to distinguish between hepatopulmonary syndrome and portopulmonary hypertension.

Clinical	Hepatopulmonary Syndrome (HRS: AV shunts)	Portopulmonary Hypertension (constriction of pulmonary vessels)
○ Prevalence in cirrhotics evaluated for LT	~ 25%	~ 5%
○ Symptomatology	- Progressive dyspnea - SOB on sitting up	- Chest pain - SOB on lying down
○ Pathophysiology	- ↑ VEGF → ↑ angiogenesis - ↓ gas exchange → hypoxemia - Intrapulmonary vasodilation in precapillary and capillary PA circulation due to vasoactive mediators	- Vasoconstriction - Remodeling of resistance vessels - ↑ PAP ▪ Medial proliferation and hypertrophy ▪ Arteriopathy ▪ Thrombosis ▪ ↑ endothelin – 1
○ Production of NO and CO	- ↑ (↑ iNos, ↑ HO-1)	- Normal
○ Clinical examination	- Platypnea - Cyanosis - Finger clubbing - Spider angiomas	- No cyanosis - RV heave - Pronounced P2 component
○ ECG findings	- None	- RBBB, rightward axis - RV hypertrophy - No / mild hypoxemia
○ Arterial blood gas levels	- Moderate-to-severe hypoxemia	
○ Chest radiograph	- Normal	- Cardiomegaly - Hilar enlargement
○ CEE	- Tri-regurg; Always positive; left atria opacification for >3-6 cardiac cycles after right atrial opacification > 6%	- Usually negative. Positive for <3 cardiac cycles; if atrial septal defect or patent foramen ovale
○ ^{99m} TcMAA shunting index ("bubble study")	- Normal / low PVR	- < 6% roatrial opacification - Elevated PVR - Normal mPAOP - Large pulmonary arteries
○ Pulmonary hemodynamics	- Normal / 'spongy' appearance (type I)	- Distal arterial pruning



Clinical	Hepatopulmonary Syndrome (HRS: AV shunts)	Portopulmonary Hypertension (constriction of pulmonary vessels)
○ Pulmonary angiography	– Discrete arteriovenous communications (type II) (usually lower lobe)	– Only indicated in mild-to-moderate stages
○ OLT	– Always indicated in severe stages	– Late contraindication
○ MELD exception points	– Yes	– No
○ Role of LT	– Reverses HPS in 80%	– Nuclear

Abbreviations: ^{99m}TcMAA, technetium-99 m-labelled macroaggregated albumin; CEE, contrast enhanced echocardiography; ECG, electrocardiogram; HPS, hepatopulmonary syndrome; OLT, orthotopic liver transplantation; PAOP, mean pulmonary artery occlusion pressure; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; RBBB, right bundle branch block; SOB, shortness of breath (aka dyspnea)

Printed with permission: Herve P, et al. *Best Practice & Research Clinical Gastroenterology* 2007; 21(1): pg. 142.

ACUTE LIVER FAILURE (ALF)

➤ Definitions

- A sudden (usually < 24 weeks length of illness) loss of hepatic function in a patient without preexisting liver disease, with the development of coagulopathy (INR > 1.5) and hepatic encephalopathy (Ritt DJ, et al. *Medicine (Baltimore)* 1969:151-72.)
- ALF is defined as "...the rapid development of hepatocellular dysfunction, specifically coagulopathy and mental status changes (encephalopathy) [and often jaundice] in a patient without prior liver disease".
- Coagulopathy (INR ≥ 1.5) and encephalopathy in a patient without previous cirrhosis and with an illness of < 26 weeks duration
- ALF is "...a clinical syndrome that represents the final common pathway of severe liver injury resulting from numerous infections, immunologic, metabolic, vascular and infiltrative disorders", leading to severe cellular or mitochondrial dysfunction and hepatocellular necrosis".
- "Hepatic encephalopathy is a defining criteria" for ALF. (Feldman M., et al. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th Edition. *Saunders / Elsevier* 2010, page 1557).
- The time interval between the onset of illness and the development of ALF is < 8 weeks, although some authors suggest a range of different time intervals:
 - Hyperacute ≤ 1 week
 - Acute 1 to 4 weeks
 - Subacute 4 to 24 weeks

Note: since these subgroups have no prognostic significance, the use of these terms is no longer wide-spread



- Demography
 - $< 1/10^5$ per year
 - 1-year survival ~ 2/3
- Differential
 - The diagnosis of ALF is based on clinical findings, and must be differentiated from conditions with similar clinical findings
- Diagnostic Imaging
 - Liver US with Doppler
 - Chest x-ray
 - CT head
 - CT of the head in ALF is neither sensitive nor specific to detect early intracerebral hypertension, but can identify the advanced stages of intracerebral hypertension and brainstem herniation
 - Cardiopulmonary evaluation
 - ECG
 - 2-D surface echo with Doppler
 - Pulmonary function tests
 - Cancer Surveillance
 - Pelvic, prostate, breast, colon and HCC, as indicated

Adapted from: Gill RQ, and Sterling RK. *J Clin Gastroenterol* 2001;33:191-8.

ESOPHAGEAL VARICES (EV)

- Demography
 - The risk of any patient with compensated cirrhosis having EV (esophageal varices) is ~ 50%
 - The risk of these EV bleeding is ~ 30% in next 2 years
 - It is important to identify all those cirrhotic patients who might have EV and therefore would benefit from primary prophylaxis using EVBL (esophageal variceal band ligation)
 - Presence of varices at diagnosis of cirrhosis
 - Compensated
 - 30%
 - Decompensated
 - 60%
 - Risk of first esophageal variceal bleed (EVB) 12% per year



- Risk of esophageal varices bleeding
 - Frequency of EV
 - Cirrhosis 40%
 - Cirrhosis plus ascites 60%
 - Rates of development of EV
 - 2.5- 5% per year
 - Rate of progression of small to large EV
 - ~10% per year
 - Risk of new EV bleeding
 - Overall, ~25% in 2 years
 - Diameter < 5 mm, 7%
 - > 5 mm, 30%
 - EV bleeding stops spontaneously in ~ 50%
 - Within 5 days of initial bleeding, 40%
 - The mortality rate for each episode of variceal bleeding is 30%
 - Rebleeding of EV after initial EV bleeding 50% per year
 - Occult infection from spontaneous bacterial peritonitis (SBP) may increase the rate of early rebleeding
 - Antibiotics are used on an empirical basis in cirrhotic patients with a variceal bleed or ascites
 - In persons with hepatic cirrhosis, esophageal varices develop in 2.5% of persons per year
 - The risk of EV bleeding increases with:
 - Longer varices
 - The presence of red wale marks on the varices
 - More extensive liver dysfunction

Abbreviations: EVBL, endoscopic variceal band ligation; SBP, spontaneous bacterial peritonitis

➤ Classification

- F1
 - Small
 - Straight
 - Tortuous
 - < 1/3 of lumen of esophagus (< 5 mm diameter)
- F2
 - Large, tortuous, fill < 1/3 of lumen
- F3
 - Fill > 1/3 of lumen of esophagus (> 5 mm diameter)



- Give the **SARIN classification** of gastroesophageal varices (GEV) or isolated gastric varices (IGV).
 - o GEV1
 - GV in continuity with EV
 - Extend 2 to 5 cm below GE junction
 - Easiest to obliterate with cyanoacrylate
 - o GEV2
 - GV in continuity with EV
 - GV extend to cardia and fundus
 - o IGV1
 - No EV
 - GV in fundus
 - Most difficult to obliterate with cyanoacrylate
 - o IGV2
 - No EV
 - GV in gastric body, antrum, and pylorus
 - o Bleeding risk
 - GEV2 IGV1 > GEV1, IGV2 (unless patient is matched for CTP score, in which case the risk of bleeding is similar for each type of varix)
- Terminology
 - o Screening
 - Determine if there are EV (esophageal varices)
 - Screening for EV by EGD
 - Before 1st EVB in cirrhotic, compensated or decompensated
 - Consider: if ↑ ratio of platelet count / spleen size
 - o Pre-primary development of EV
 - o Primary prophylaxis
 - Prevent the first EVB (esophageal variceal bleeding)
 - Varices < 5 cm, Child A, B – continue EGD surveillance of size of EV
 - Child C – non-specific beta blocker (NSBB)
 - < 5 cm Child B -- NSBB, or EVL
 - o Secondary prophylaxis
 - Prevent recurrent EVB
 - o Acute bleeding
 - Stop EVB



- Diagnostic imaging
- Give findings seen on abdominal Doppler ultrasound which suggest the presence of portal hypertension.
 - o Portal vein
 - Reversed (hepatofugal) blood flow
 - Diameter > 13 mm
 - ↑ portal blood flow
 - o Splenic and mesenteric vein
 - Loss of changes on respiration
 - o Portosystemic collateral vessels
 - o Splenomegaly
- Give advantages of MDCT (multidetector row CT) venous EUS in the evaluation of the patient with portal hypertension and possible varices.
 - o MDCT is useful to
 - Detect varices in the gastric fundus
 - Distinguish submucosal from perigastric varices
- Give advantages of gadolinium-enhanced magnetic resonance imaging versus EUS in the evaluation of the patient with portal hypertension and possible varices.
 - o MRI is useful to measure
 - Portal and azygous blood flow
 - Stiffness of spleen
- Give advantages of EUS in the evaluation of the patient with portal hypertension and possible varices.

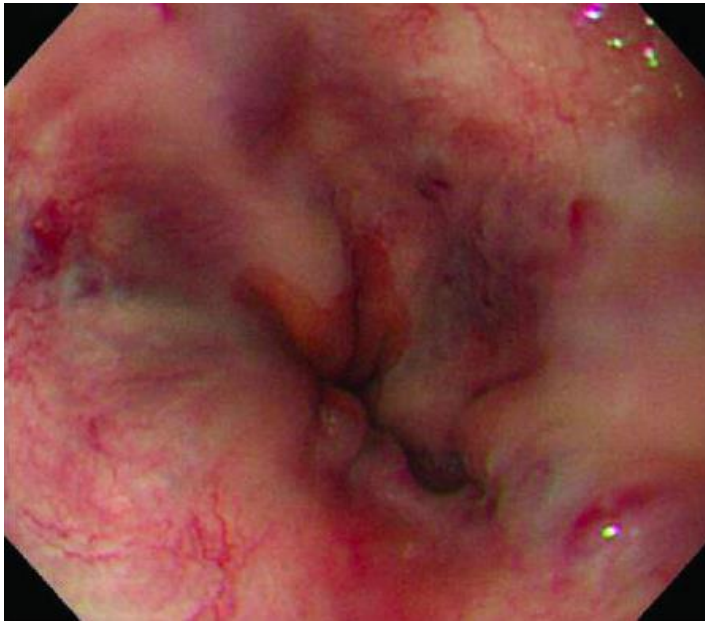
EUS is useful to measure:

 - o Cross-sectional area of varices
 - o Size and blood flow in
 - Left gastric vein
 - Azygous vein
 - Paraesophageal collaterals
 - o Transmural pressure in the varix
 - o Effectiveness of endoscopic therapy (including recurrence of varices after EVBL (esophageal variceal band ligation))



➤ Endoscopy

Esophageal Varices



Printed with permission: Ishiguro H, et al. Gastroenterology Research and Practice, vol. 2012, Article ID 946169, 6 pages, 2012.

Esophageal Varices



Printed with permission: Ishiguro H, et al. Gastroenterology Research and Practice, vol. 2012, Article ID 946169, 6 pages, 2012.



Junctional Varices and Fundic Varices

Useful background

- o Varices may appear in the esophagus, at the junction of the esophagus and stomach (junctional varices), or as isolated gastric fundic varices.
- o Fundic varices may occur in association with esophageal or junctional varices, when there is portal hypertension.
- o When there are isolated fundic varices, the HVP (hepatic venous pressure gradient) is normal (< 12 mm Hg).
- Give the anatomical basis for isolated fundic varices.
 - o The splenic vein joins the superior mesenteric vein to form the portal vein (PV).
 - o The esophageal vein (EV) comes from the PV, so any obstruction which is proximal to the take-off of the EV from the PV causes left-sided portal hypertension, without esophageal or junctional varices.
 - o Thrombosis of the splenic vein leads to congestion of spleen and distention of the short gastric veins (SGV).
 - o Distention of the SGV leading from the spleen to the gastric fundus will cause isolated gastric fundal varices.

The usual treatment of isolated gastric fundal varices arising from splenic vein thrombosis (SVT) is splenectomy.

- Give the anatomical circumstances when a splenectomy may not be therapeutically successful to treat SVT and its associated left-sided portal hypertension.
 - o Splenectomy for SVT would not be useful to treat left-sided portal hypertension if thrombosis of the splenic veins were also associated with thrombosis of the inferior and / or superior mesenteric veins.

"We make a living by what we get, but we
make a life by what we give."

Winston Churchill



ASCITES

➤ Definition

- o Free fluid in the peritoneal cavity
- o The laparoscopic appearance suggestive of peritoneal TB
 - “Millet-seed”
 - “Violin-string”
- o The peritoneal surface absorbs only up to 500 mL/day of ascitic fluid
- o Excessive use of diuretics above this physiological level of ascitic fluid mobilization of 500 mL/day
 - Does not ↑ removal of ascitic fluid
 - Causes depletion of fluid from intravascular spaces
 - Causes contraction alkalosis and prerenal azotemia
 - Spot urine Na^+ < 10 mmol/L

➤ Diagnosis

- o Cytology of ascitic fluid is ~ 100% sensitive to detect peritoneal carcinomatosis, but the sensitivity to detect 1°/2° liver tumour is lower.
Increased neutrophils, or fat (chylous ascites) makes ascitic fluid cloudy
- o Ascitic fluid becomes creamy coloured (chylous) when the concentration of triglyceride in ascites is > 200 mg/dL.
- o Chylous ascites occurs with
 - Cirrhosis
 - Rupture of the intra-abdominal lymphatics
- o Dark brown (not pink or red) ascitic fluid (bilirubin concentration in ascitic fluid > 6 mg/dL) suggests perforation of
 - Biliary tree
 - Duodenum/jejunum
- o In HIV / AIDs, TB and coccidiomycosis occur, and look the same on laparoscopy.
- o In a patient with chronic renal failure on hemodialysis, look hard for causes of ascites before diagnosing idiopathic (nephrogenic) ascites.

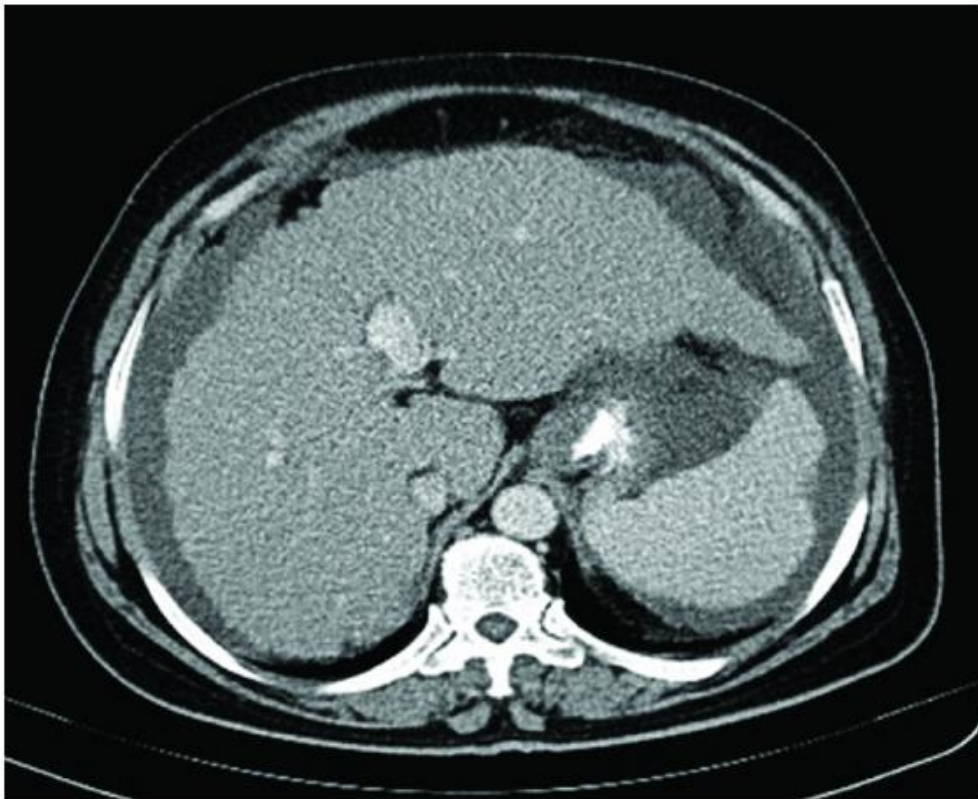


- Give the indications for **diagnostic paracentesis**.

- o Ascites, new onset
- o SBP, suspected
- o Admission to hospital
- o GI bleeding
- o Shock
- o Fever
- o HE (hepatic encephalopathy)
- o Systemic infection / sepsis
- o Non-specific GI symptoms
- o Worsening liver function
- o Worsening renal function

- Diagnostic imaging

Ascites, Abdominal CT scan



Source: Maleki N, et al. Case Reports in Gastrointestinal Medicine, vol. 2014, Article ID 928496, 4 pages, 2014.



Refractory Ascites

➤ Definition

- o “.....ascites unresponsive to a sodium-restricted diet [2 gm per day] and high-dose diuretic treatment [e.g., furosemide 10 mg/day and aldosterone 400 mg/day]) (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 1538).
- o The development of refractory ascites (“ascites that cannot be mobilized or the early recurrence of which [i.e, after LVP] cannot be satisfactorily prevented by medical therapy”; European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol. 2010;53(3):397-417)
- o Due to inappropriately high neurohumoral activation
- o Refractory ascites signals a poor prognosis and the need for assessment for possible liver transplant (LT).
- o Usually develops slowly over weeks to months.
- o Ascites that is not eliminated even with maximum and optimal diuretic therapy, or
- o Ascites that is not eliminated because maximum dosages of diuretics cannot be attained, given the development of diuretic induced complications (renal failure).
- o 1 year mortality rate for ascites refractory to medical care ~ 68%

Malignancy-Associated Ascites

➤ Pathogenesis

- Give mechanisms by which tumours may cause ascites.
 - o Peritoneal carcinomatosis
 - o Extraperitoneal carcinomatosis
 - Hepatic 1^o (HCC), 2^o (metastases)
 - o Lymph node obstruction
 - o Budd-Chiari syndrome ± IVC obstruction

Abbreviation: HCC, hepatocellular carcinoma; IVC, inferior vena cava



➤ Causes / associations

- Give the causes of malignancy-associated ascites.
 - o Peritoneal carcinoma (1°, 2°)
 - o Massive liver metastases
 - o Peritoneal carcinomatosis with massive liver metastases
 - o Hepatocellular carcinoma (HCC)
 - o Malignant lymph node obstruction
 - o Malignant Budd-Chiari syndrome (BCS, from tumour emboli in hepatic veins)

Source: Runyon BA. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology / Diagnosis / Management*, 10th Edition. Saunders / Elsevier, Philadelphia, 2016, Box 93-2, pg. 1563.

➤ Diagnosis

- o Cytology of ascitic fluid is ~ 100% sensitive to detect peritoneal carcinomatosis, but the sensitivity to detect 1°/2° liver tumour is lower.

SPONTANEOUS BACTERIAL PERITONITIS (SBP)

➤ Definition

- o An ascitic fluid count of ≥ 250 PMN /mm³ makes the diagnosis of spontaneous bacterial peritonitis (SBP), and empiric antibiotic treatment must be started immediately, with adjustment of antibiotic when culture results come back – “do not wait for the cultures”
- o The causative organisms of SBP are E. Coli, Klebsiella, and e.g., less frequently Streptococcus and Staphylococcus.

➤ Demography

- o In the cirrhotic with ascites admitted to hospital
 - About 1/3 have bacterial peritonitis
 - 2/3 SBP, 1/3 non-neutrocytic bacterascites (MNB)
 - Commonest monomicrobial organisms: E. Coli, Streptococci (pneumococci), Klebsiella
- o In the cirrhotic patient who is hospitalized for GI bleeding, 40% develop SBP (that's why all cirrhotics with GI bleeding and ascites are given prophylactic antibiotics).
- o SBP is present in at least 20% of cirrhotics at the time they are admitted to the hospital
- o SBP worsens vasodilation, and thereby contributes to early variceal rebleeding and to the development of renal failure (HRS, hepatorenal syndrome)
- o Persons at risk of developing SBP include those with a previous episode of SBP, SBP occurring with variceal hemorrhage, or low protein ascites
- o Once SBP has occurred, the one year mortality rate is 50-70%



➤ Diagnosis

- o Consider SBP and perform diagnostic paracentesis if:
 - Symptoms / signs (abdominal pain, fever, chills)
 - Patient is in emergency room or admitted
 - Worsening renal function or encephalopathy
- o SBP is present if ascites PMN count >250 cells/uL (if fluid bloody, subtract 1PMN per 250 RBC/ μ L)
- o Cirrhosis with ascites
- o Serum creatinine >1.5 mg/dL (133 mol/L)
- o Absence of shock
- o Absence of hypovolemia as defined by no sustained improvement of renal function (creatinine decreasing to <133 mol/L) following at least 2 days of diuretic withdrawal (if on diuretics), and
- o Volume expansion with albumin at 1 g/kg/day up to a maximum of 100 g/day
- o No current or recent treatment with nephrotoxic drugs
- o Absence of parenchymal renal disease as defined by proteinuria < 0.5 g/day, no microhaematuria (<50 red cells / high powered field), and normal renal ultrasonography

Printed with permission: European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol. 2010;53(3):397-417, Table 8.

Please see: Swan MG. Chapter 58. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 1: Ascites, page 773.

Ascitic Fluid Neutrophils $\geq 250/\text{mm}^3$	Ascitic Fluid Culture Positive	Treatment for SBP
Yes	Yes	Yes
Yes	No	Yes
No	Yes	- o Repeat diagnostic paracentesis, and if – Neutrophils < 250 / mm^3 / no symptoms, follow patient – Neutrophils > 250 / mm^3 / treat symptoms – Remember ▪ In the cirrhotic patient who is hospitalized for GI bleeding, 40% develop SBP (that's why cirrhotics with GI bleeding and ascites are given prophylactic antibiotics).

Please see: Swan MG. Chapter 58. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 2: Spontaneous Bacterial Peritonitis, page 774.



➤ Treatment

The most common cause of SBP are gram-negative aerobes such as E.Coli, and these should be sensitive to first line use of quinolones such as ciprofloxacin.

- Give circumstances when you would avoid quinolones for an empiric diagnosis of SBP, and instead start with
 - 4 g/day IV for 5 days, or
 - Amoxicillin / clavulanic acid IV, then po
 - o Previously taking quinolones for prophylaxis of SBP
 - o High prevalence of quinolone-resistant bacteria in practice area
 - o SBP developing in hospital (nosocomial SBP)

Secondary Polymicrobial Bacterial Peritonitis (Non-Neutrocytic Polymicrobial)

➤ Diagnosis

- o Secondary bacterial peritonitis from bowel perforation is polymicrobial, but unless gene probes are used for rapid diagnosis, a serious time delay will ensue.
- o Measure the ascitic fluid total protein, glucose and LDH; if 2 or 3 of these are abnormal abdominal, exclude perforation rather than diagnosing neutrocytic spontaneous bacterial peritonitis (SBP).
 - Total protein > 1 g/dL
 - Glucose < 50 mg/dL
 - LDH > ULN for serum
- o PMNs contain LDH, so when PMNs increase in SBP, there is ↑ LDH; in secondary BP, there is ↑↑↑ PMNs, so ↑↑↑ LDH (LDH in ascites > serum LDH)
- o ↑ ascitic fluid amylase (> 2000 U/L, or 5x serum amylase) suggests
 - Acute pancreatitis
 - Intestinal perforation
- o If ascitic fluid contains ↑ lymphocytes (not PMNs), suspect
 - Tuberculous peritonitis
 - HCC / hepatic metastases
 - Pancreatitis

Clinical Pearls

- o If you think the patient might have ascites from secondary peritonitis
 - Don't "play around" with measuring ascitic fluid concentrations of glucose or LDH (lactate dehydrogenase)
 - Do diagnostic imaging (such as CT scan) to find the source of the suspected perforation.
- o Once SBP has developed, the patient's prognosis is poor, and they should be referred for consideration of liver transplantation
 - While awaiting LT, give prophylactic antibiotics to prevent recurrent SBP:
 - Cotrimoxazole (800 mg sulfamethoxazole and 160 mg trimethoprim po od)
 - If the total protein concentration of the ascitic fluid is < 15 g/L in the patient with severe liver disease, give norfloxacin 400 mg/day po to ↓ risk of SBP and death.



HEPATORENAL SYNDROME (HRS)

➤ Definition

- o A functional and potentially reversible form of prerenal azotemia with a cascade of events associated with intense splanchnic arterial vasodilation in the setting of cirrhosis or acute liver injury and resulting in profound renal arterial vasoconstriction and progressive renal failure” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier 2010, page 1546).
- o Functional renal failure in the person with cirrhosis and ascites
- o Type I, rapidly progressive; type II, slowly progressive
- o Another definition
 - In the presence of acute or chronic liver disease
 - ↓↓ urinary Na⁺
 - Baseline ↑ Cr (creatinine) > 1.5 mg/dL (133 μmol/L), or change in serum Cr concentration
 - No abnormal urinary sediment < 50 RBC/hpf (no catheter used); protein < 500 mg/day
 - Hyperbilirubinemia may be associated with granular and epithelial cell casts.
 - Oliguria (only premorbid)
 - Most have < 500 mL urine per day
 - May be precipitated by
 - Previous renal insufficiency
 - Bleeding
- Give the reason why a change in the serum creatinine (Cr) concentration may be a better indicator of the diagnosis of HRS than an integrated baseline Cr.
 - o The urinary Cr may be lower in the malnourished cirrhotic, so that an abnormal creatinine concentration (<1.5 mg/dL [$> 133 \mu\text{mol/L}$]) may be present, despite a ↓ CrC (creatinine clearance) < 20 mL/min.

➤ Demography

- o HRS occurs in cirrhotics with ascites, ~8% per year
 - Admitted for SBP or other infections, 30%
 - Needing large volume paracentesis, 10%
- o Severe alcoholic hepatitis, 25%
- o Reduces 3 yr survival from liver transplant to 60% vs ~75%, when no HRS
- o Cirrhosis, ascites, but no azotemia
 - HRS development

1-yr	5-yr
18%	39%
- o Acute severe alcoholic hepatitis, and no cirrhosis
 - HRS develops in 28%
 - Risk of HRS is less in PBC



- o Some useful figures
 - Cirrhosis plus ascites 2-yr survival rate, of only 50%
 - Diuretic-resistant ascites (develops in ~10%), 6-month survival rate of only 50%, and 1-yr survival rate, 25%
 - Ascites, spontaneous bacterial peritonitis and HRS are on different parts of the same pathophysiological spectrum
- Diagnosis
 - o Cirrhosis with ascites
 - o Consider HRS in a patient with cirrhosis and ascites, who has a serum creatinine level of >1.5 mg/dL (133 $\mu\text{mol/L}$)
 - o HRS is a diagnosis of exclusion. Before making the diagnosis of HRS, rule out and treat:
 - Sepsis
 - Shock
 - Vasodilators, NSAIDs
 - Organic renal failure (urine sediment, kidney ultrasound)
 - o Absence of parenchymal renal disease as defined by proteinuria < 0.5 g/day, no microhematuria (<50 red cells / high power field), and normal renal ultrasonography
 - o Diuretics should be discontinued and intravascular volume expanded with IV albumin
 - o If renal dysfunction persists despite above, diagnose HRS
 - o Absence of hypovolemia (from hemorrhage, diarrhea, overdiuresis) defined by
 - No sustained improvement of renal function (creatinine decreasing to <133 $\mu\text{mol/L}$) following at least 2 days of diuretic withdrawal (if on diuretics), and
 - Volume expansion with albumin at 1 g/kg/day up to a maximum of 100 g/day
 - o No current or recent treatment with nephrotoxic drugs
 - o No or insufficient improvement in serum creatinine level (remains > 1.5 mg/dL) 48 hr after
 - Diuretic withdrawal
 - Adequate volume expansion with intravenous albumin and 1.5 L of 0.9% saline

Printed with permission: EASL clinical practice guidelines J Hepatol. 2010;53(3):397-417, Table 8.



- Give the major and minor criteria for the diagnosis of the hepatorenal syndrome (HRS), and distinguish this from acute tubular necrosis (ATN).

❖ Major criteria

- o Presence of cirrhosis
 - Renal failure (creatinine >1.5mg/dL) if no previous renal impairment, or a serum a ↑ by 50% over baseline
- o Lack of improvement in serum creatinine after ≥48 hrs of diuretic withdrawal and volume expansion with 1.5 L of 0.9% saline
- o Absence of
 - Shock
 - Use of nephrotoxic drugs (eg: aminoglycosides)
 - Parenchymal renal disease (urine protein > 500 mg/day)
 - Granular or red cell casts
 - Hematuria
 - Urinary obstruction by sonography

❖ Minor criteria (suggests HRS, or prerenal failure)

Parameter	Osmolarity mOsm/Kg	Urine (Na) mmol/L	Sediment	Protein mg/day
o Prerenal				
– Hypovolemia	>500	<20	Normal	<500
o Renal				
– Acute tubular	<350	>40	Granular casts	500-1500
– Interstitial	<350	>40	WBC eosinophils	500-1500

Adapted from: Fitz GJ. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology / Diagnosis / Management* 2006: pg. 1979.

"Strong people don't put others down...
They lift them up."

Michael P. Watson



HEPATIC ENCEPHALOPATHY (HE; aka Portosystemic Encephalopathy)

- Demography
 - o HE occurs in $\frac{1}{2}$ to $\frac{3}{4}$ of cirrhotics
 - o HE non-transplanted mortality rate > 50% in 3 year
- Diagnosis
 - o Exclude other causes of metabolic encephalopathy
 - o Exclude possible precipitating factors of HE
 - o Altered neuropsychiatric testing
 - Number connection tests (Trail making)
 - Visuomotor skills
 - Mental tracking and concentration
 - Digit symbol test
 - Block design test
 - Standardized test battery, the psychometric HE score (PHES)
 - Digit span test (Weschler adult intelligence scale – passive auditory, working attention)
 - Critical flicker frequency (correlates with PHES [Psychometric hepatic encephalopathy score])
 - Quality of life measures: SE-36, chronic liver disease questionnaire (CLDQ)
 - o Clinical examination
 - Memory
 - Writing
 - Sleeping
 - Agitation
 - o Scoring systems
 - PSET (portosystemic encephalopathy syndrome test)
 - Psychometric tests
 - o Blood concentrations of NH_3
 - Arterial hyperammonemia in 90% of HE
 - Arterial $\text{NH}_3 \geq 200$ mg/L predict brain edema and herniation of the brain stem
 - o Critical flicker frequency test
 - o MR-based techniques
 - o EEG abnormalities
 - Bilateral slow wave activity
 - Neither sensitive nor specific
- The finding of an elevated serum ammonia concentration is not specific for the diagnosis of hepatic encephalopathy. Give causes of hyperammonemia.
 - o Liver / GI tract
 - Acute liver failure
 - Cirrhosis
 - Gastrointestinal bleeding



- o Renal
 - Chronic kidney disease
- o Inborn errors of metabolism
 - Proline metabolism disorders
 - Urea cycle disorders (e.g carbamyl phosphate synthetase I deficiency, ornithine transcarbamylase deficiency, argininosuccinate lyase deficiency, N-acetyl glutamate synthetase deficiency)
- o Medications
 - Alcohol
 - Diuretics (e.g., acetazolamide)
 - Narcotics
 - Valproic acid
- o Muscle exertion and ischemia
- o Blood sampling
 - Tourniquet use
 - High body temperature
 - High protein diet
- o Diet
 - Do not restrict dietary protein
 - May need to reduce salt intake to 2 g/day
 - May choose to ↑ intake of K⁺-containing foods depending on diuretic use and serum K⁺
 - Do not restrict water intake unless serum Na⁺ < 120 mEq/L
- o Cigarette smoking

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology / Diagnosis / Management*. Ninth edition, 2010, Table 92-1.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

A patient with cirrhosis develops HE (hepatic encephalopathy), and their MELD score rises when he / she is treated with antibiotics.

- Give the explanation for the rise in the MELD score when the patient with HE is treated with antibiotics
 - o Antibiotics given for HE reduce the intestinal microbiota
 - o This ↓ microbiota leads to ↓ bacterial synthesis of vitamin K
 - o With ↓ bacterial vitamin K available for absorption and production of coagulation factors (II, VII, IX, X, protein C), the INR rises
 - o ↑ INR contributes points to the MELD score, so there is ↑MELD score

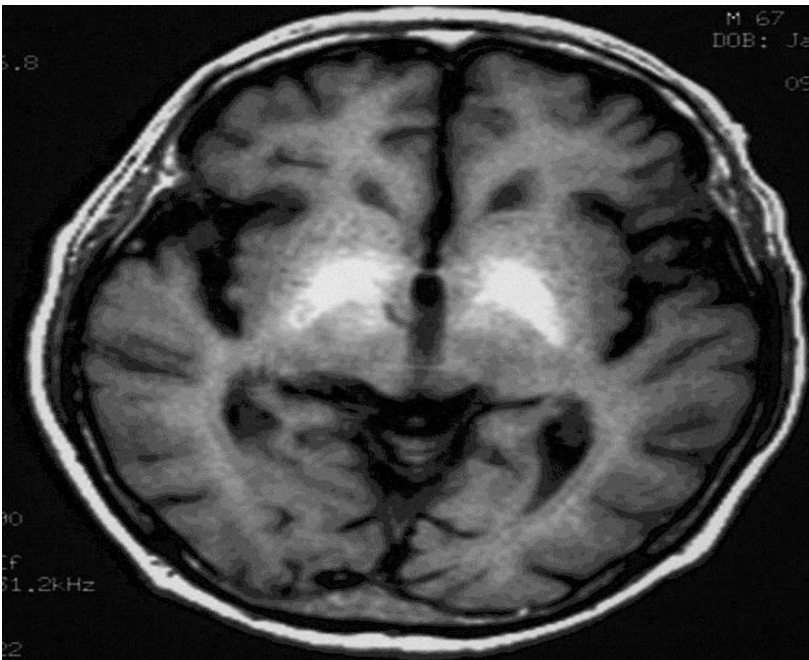


Patients with stage 0 to 2 HE will have tremor and asterixis. Patients with stage 3 or 4 may not be able to cooperate for the clinical testing for these signs.

- Give the upper motor neuron signs in stage 3 or 4 HE which can be demonstrated without the patient's cooperation.
 - o Clonus
 - o Hyperreflexia
 - o Hyperrigidity

➤ Diagnostic Imaging

Chronic Hepatic Encephalopathy



Brain MR imaging (T1WI) showed hyperintensity of basal nuclei indicating chronic hepatic encephalopathy

Source: Yamamoto T, et al. J Clin Med Res. 2012; 4(4): 295–298.

➤ Histopathology

SO YOU WANT TO BE A HEPATOLOGIST!

- Give the histopathological changes in the brain of persons dying from hepatic encephalopathy (HE).
 - o Capillaries
 - Vacuolization of basement membranes (↑ permeability of blood-brain barrier)
 - o Edema
 - Brain
 - Endothelial cells
 - Astroglial cells
 - o Herniation
 - Brainstem



Minimal Hepatic Encephalopathy (MHE)

- Causes / associations
- Give important areas of assessment of the patient with possible MHE.
 - o Exclude other causes of metabolic encephalopathy
 - o Exclude possible precipitating factors of HE
 - o Neuropsychiatric testing
 - o Number connection tests (Trail making)
 - o Visuomotor skills
 - o Mental tracking and concentration
 - o Digit symbol test
 - o Block design test
 - o Standardized test battery, the psychometric HE score (PHES)
 - o Digit span test (Wechsler adult intelligence scale – passive auditory, working attention)
 - o Critical flicker frequency (correlates with PHES [Psychometric hepatic encephalopathy score])
 - o Quality of life measures: SE-36, chronic liver disease questionnaire (CLDQ)

PULMONARY COMPLICATIONS OF CHRONIC LIVER DISEASE

Hepatopulmonary Syndrome (HPS)

- Definition
 - o $\uparrow$ Aa PO₂ (age-corrected alveolar-arterial oxygen) gradient (< 64 years, 15 mm Hg; > 64 years, 20 mm Hg) arising from intrapulmonary vasodilation
 - o Diagnostic approach if PO₂ from pulse oximeter is < 96, then there is likely moderate severe HPS (Pa O₂ < 70 mm Hg; sensitivity 100%, specificity 88%)
 - o Diagnosis made by transthoracic echocardiography with contrast (technetium-labeled macroaggregated albumin) to detect > 6% shunt fraction
 - o Delay of microbubbles reaching the left ventricle on V echo bubble study
 - o Intra-pulmonary vasodilation and shunting occurring in the presence of chronic liver disease or pulmonary hypertension, resulting in acute or alveolar-arterial O₂ gradient > 15 mmHg (> 20 mmHg for persons > 64 years)

Abbreviations: AaPO₂, alveolar-arterial O₂ pressure gradient for oxygen; PaO₂, partial pressure gradient for oxygen; ^{99m}Tc-MAA, perfusion body scan with ^{99m} Technetium-labeled macroaggregated albumin

Printed with permission: Pastor CM, and Schiffer E. *Nature Clinical Practice Gastroenterology & Hepatology* November 2007;4(11): pg 615.



- Diagnostic imaging
 - o Pulmonary vascular dilation at contrast-enhanced echocardiography or ^{99m}Tc -MAA
 - o Pulmonary vasodilation on chest CT
 - o Tests of pulmonary shunting
 - Using technetium macro-aggregated albumin

Spontaneous Bacterial Hydrothorax (SBH)

- Causes / associations
 - o SBH may develop in cirrhotic pleural effusion (hydrothorax) with / without ascites.
 - o Perform DP (diagnostic paracentesis) of hydrothorax
 - o If hydrothorax fluid
 - $> 250/\text{mm}^3$ neutrophils, plus positive culture $\rightarrow$ treat $> 500/\text{mm}^3$ but negative culture (in the absence of pneumonia)
- Laboratory
 - Give characteristics of pleural fluid in hepatic hydrothorax.
 - o Cell count < 250 polymorphonuclear cells mm^3 (uncomplicated)
 - o Protein < 2.5 g/dL
 - o Pleural fluid / serum total protein ratio < 0.5
 - o Pleural fluid / serum lactate dehydrogenase ratio > 0.6
 - o Pleural fluid / serum albumin gradient > 1.1
 - o Pleural fluid / serum bilirubin ratio < 0.6
 - o pH > 7.4
 - o Glucose level similar to that of serum

Printed with permission: Cárdenas A, and Arroyo V. *Best Practice & Research Clinical Gastroenterology* 2007; 21(1): pg. 69.



Portopulmonary Syndrome

- Definition
 - Pulmonary arterial hypertension (PAH) in a patient with portal hypertension (PHT)
- Diagnosis
 - Based upon evidence of PAH plus PHT
 - PAH
 - mPAP
 - At rest > 25 mm Hg
 - With exercise > 30 mm Hg
 - PCWP > 15 mm Hg
 - PVR > 240 dyne s cm⁻⁵
 - PHT
 - HVPg measurements, or
 - Clinical features
 - Thrombocytopenia
 - Splenomegaly
 - PS shunts
 - PV hemodynamic changes

Abbreviations: HVPg, hepatic venous pressure gradient; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PHT, portal hypertension; PS, portosystemic; PV, portal vein; PVR, pulmonary vascular resistance;

“The path to success is to take massive,
determined action”

Tony Robbins

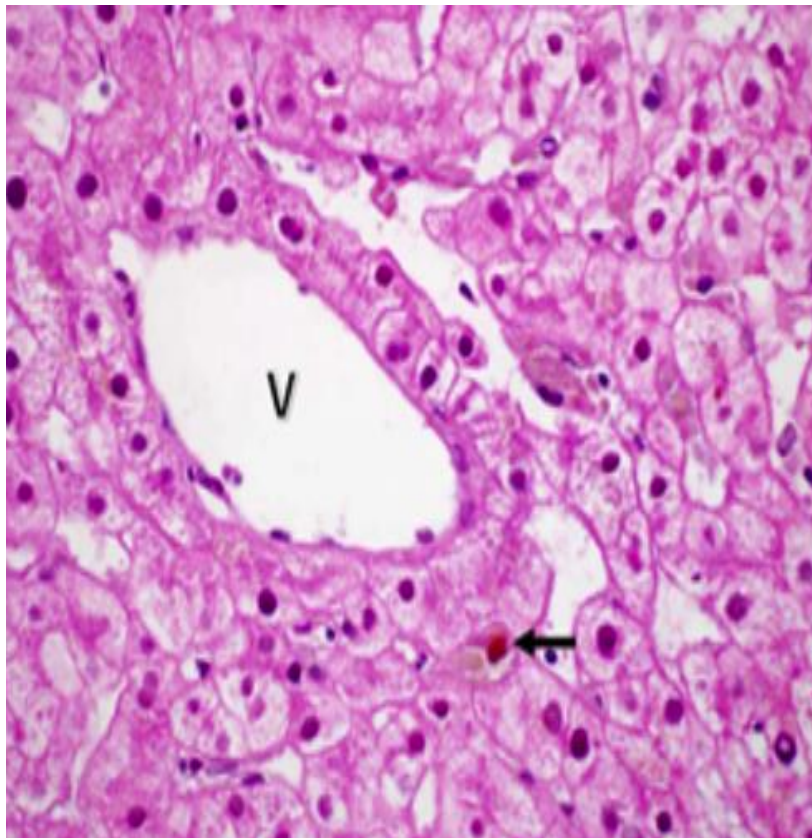


CHOLESTATIC LIVER DISEASE (aka Cholestasis Syndrome)

➤ Histopathology

- Give the histopathologic features of cholestasis:
 - o Bile plugs
 - o Canalicular cholestasis
 - o Ductular cholestasis
 - o Bile ductular proliferation
 - o Liver-cell rosettes (pseudoglandular formations around canalicular spaces)
 - o Feathery degeneration of hepatocyte cytoplasm

Cholestasis Syndrome

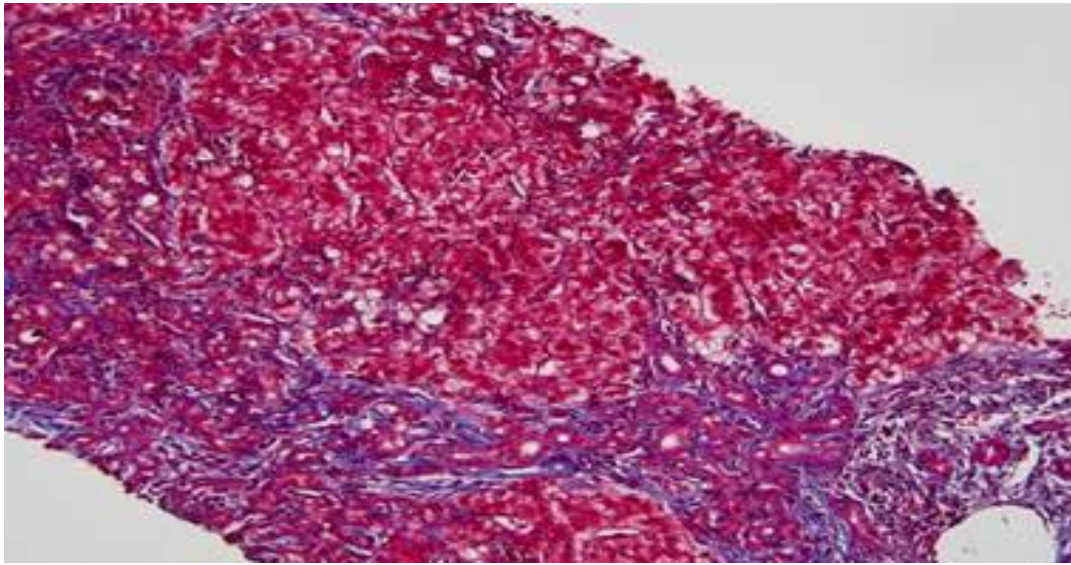


- o The portal areas showed a mild, predominantly lymphocytic infiltrate associated with mild bile duct injury
- o A large bile plug (arrow) can be seen near the central vein (V) in this photo

Courtesy of Drs. Karim Qumosani and Noor Al Yatama,
Western University, London (ON)

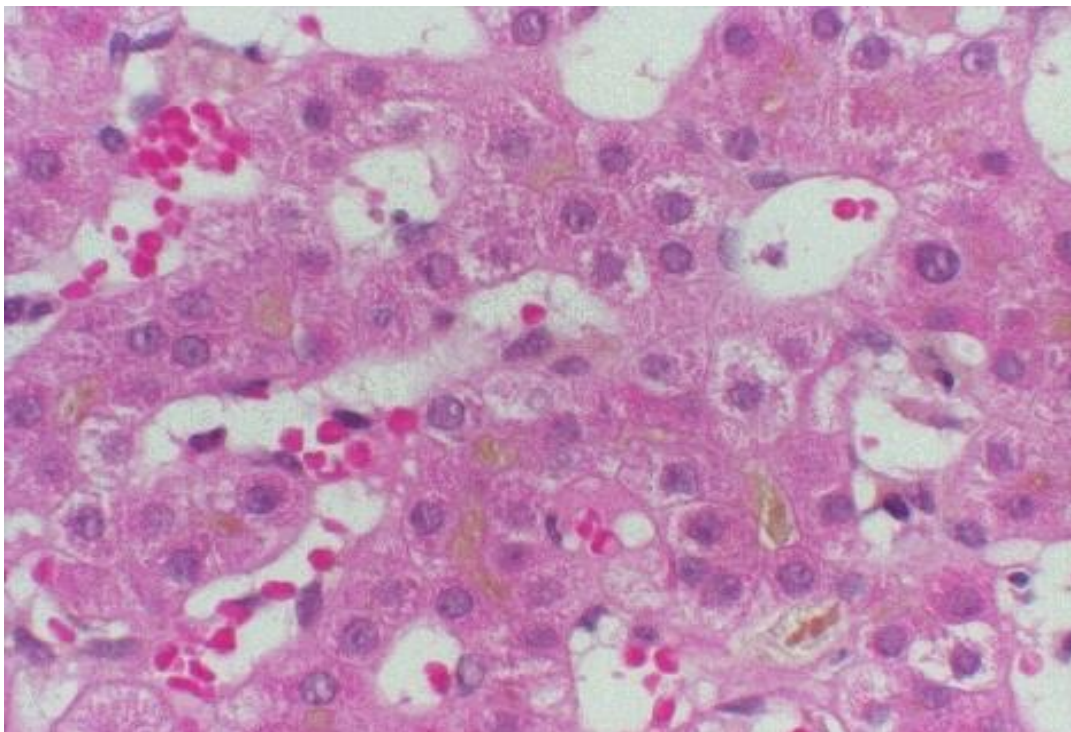


Cholestasis Syndrome



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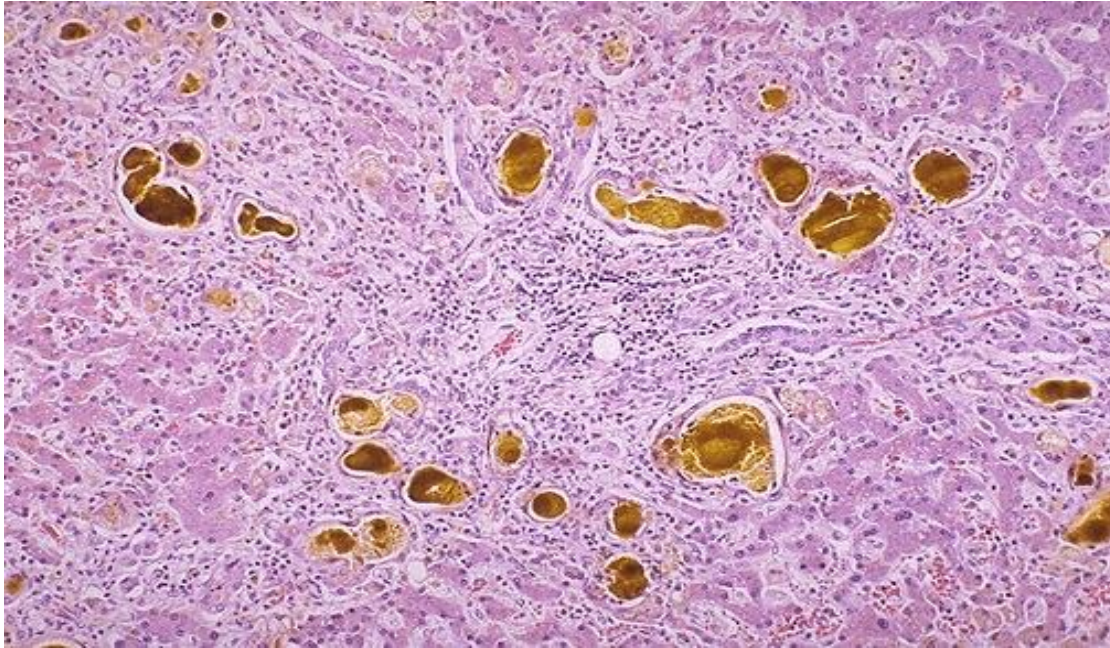
Cholestasis



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Cholestasis with Bile Plugs



Courtesy of Dr. Michael Sey, Western University, London (ON)

Alagille Syndrome (Familial Intrahepatic Cholestasis)

➤ Definition

- o Alagille syndrome is autosomal dominant familial intrahepatic cholestasis due to a decrease in the number of interlobular bile ducts (ratio of interlobular bile ducts to portal tracts < 0.4) due to mutations in the jagged 1 (JAG1) gene, resulting in periportal fibrosis and cirrhosis.
- o 94% of Alagille syndrome patients have mutations in the JAG1 gene, and the remainder have mutations in the gene coding for the NOTCH2 receptor.

Associated changes in

- o Face
 - Wide forehead
 - Deeply set and widely spaced eyes
 - Small chin
 - Triangular face
- o Ears
 - Large
- o Spine
 - Short
 - Butterfly vertebrae
- o Heart
 - Murmurs (commonly pulmonary stenosis)



Biliary Atresia

- Definition
 - o “biliary atresia is characterized by the complete obstruction of bile flow as a result of the destruction or absence of all or a portion of the extrahepatic bile ducts” (Feldman M., et al. *Sleisenger and Fordtran’s Gastrointestinal and Liver Disease*. 9th Edition. *Saunders / Elsevier*, Philadelphia, 2010, page 1052).
- Histopathology
 - o Edematous portal tracts
 - o Bile ductular proliferation
 - o Bile stasis in canaliculae and hepatocytes
 - o Bile plugs
 - o Fibrosis

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the sensitivity of a bile duct > 6 mm as a sign for choledocholithiasis.
 - o Only about 75%

Positive scintigraphy has a specificity of about 90%.

- Give the causes of a false-positive test.
 - o Fasting, or when dealing with a critically ill patient may give a false-positive hepatobiliary scan (i.e., non-visualization).
- Give the method used to overcome the false-positive HIDA scan results in the ICU setting.
 - o The patient is given IV morphine, causing ↑ sphincter of Oddi pressure, producing SOD, unless the cystic duct is truly blocked. The morphine-augmented cholescintigraphy reduces the likelihood of a false-positive test by about 50%.

Congenital abnormalities of the biliary tree include choledochal cysts, Caroli disease and Caroli syndrome.

- Explain why biliary atresia is sometimes not included in this list of congenital abnormalities of the biliary tree.
 - o Injury to biliary tract occurs after birth
 - o There is some evidence for an in utero infection (e.g., HSV, retrovirus, Rhesus rotavirus).



Choledochal Cyst

➤ Definition

- o Choledochal cysts are congenital anomalies of the biliary tract that are manifested by cystic dilation of the extrahepatic and/or intrahepatic bile ducts
- o Segmental, saccular, congenital dilation of bile ducts, without obstruction

➤ Diagnostic imaging

- o ERCP / MRCP multiple, marked dilations of bile ducts
- o MRI
 - T₁ – weighted
 - Multiple, marked dilations of intrahepatic bile ducts (dark)
 - T₂ – weighted
 - Same as T₁ – weighted, but white
 - Dynamic contrast
 - Enhanced MRI
 - Heterogeneous enhancement in early arterial phase of contrast enhancement (i.e., HCC)
 - Marked increase risk of cholangiocarcinoma / adenocarcinoma of the extrahepatic bile ducts

Trivia alert:

- Give the differences between Caroli disease and Caroli syndrome.

Caroli syndrome same as Caroli disease, plus

- o HF (heart failure)
- o Choledochal cysts

“What lies behind us and before us are tiny matters compared to what lies within us.”

Henry Stanley Haskins



PREGNANCY AND THE LIVER

- Demography
 - o 1/200
 - Hyperemesis gravidarum
 - HELLP (hemolysis, elevated LFTs, low platelets)
 - o 1/1000 ICP (intrahepatic cholestasis of pregnancy)
 - o 1/10,000 AFLP (acute fatty liver of pregnancy)
- Pathology
 - o Liver biopsy is not necessary in ICP, but would show bland cholestasis, , with bile plugs in canaliculi and hepatocytes

Acute Fatty Liver in Pregnancy

- Demography
 - o Seen in 1/1000 pregnancies
 - o AFLP accounts for 16-70% of severe liver disease as well as maternal and fetal deaths during pregnancy
- Differential

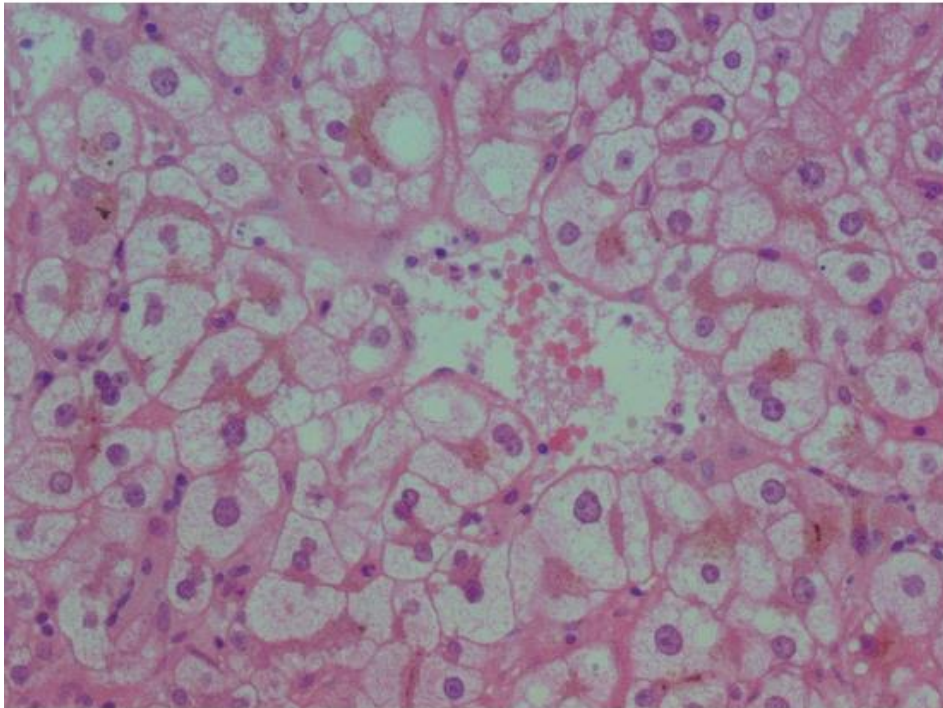
Ticks and Treats

- o Overlap - questions are often asked of candidates to distinguish between AFLP (acute fatty liver of pregnancy) and HELLP.
- o It is helpful that AFLP does not usually have thrombocytopenia.
- o In groups of patients, ALT / AST may be increased in AFLP; although this increase may not be as high as in HELLP, and in the individual patient this relative elevation of differences in ALT / AST is not useful.
- o Beware, AFLP is not considered to be a pre-eclamptic liver disease, but about 50% of AFLP may actively have associated pre-eclampsia.
- o Both HELLP and AFLP may be associated with inherited defects in the beta oxidation of fatty acids.
- o And don't forget: AFLP is associated with severe pericentral (zone 3) microvesicular fat, and HELLP may be associated with fatty liver, albeit not as severe as the pericentral microvesicular fat of AFLP.



➤ Histopathology

Acute Fatty Liver in Pregnancy



Source: Yassin A, et al. Case Reports in Obstetrics and Gynecology, vol. 2011, Article ID 402710, 3 pages, 2011. doi:10.1155/2011/402710

Hemolysis, Elevated LFTs, Low Platelets (HELLP) Syndrome

➤ Definition

- o The HELLP (hemolysis, elevated liver enzymes, low platelet) syndrome is a form of pre-eclampsia liver disease.

➤ Demography

- o Pre-eclampsia occurs in 5-10% of pregnancies, and accounts for 20% of maternal deaths
- o HELLP occurs with about 12% of women with severe eclampsia
- o Pre-eclampsia and the HELLP syndrome usually occur in the 3rd trimester, but in 28% HELLP occurs in the early post-partum period.



➤ Diagnosis

- o Required for diagnosis
 - Hypertension (sustained systolic blood pressure of $\geq 140/90$ after week 20 of pregnancy, in a women whose blood pressure was previously normal)
 - Hypertension-associated end organ damage (e.g., liver damage in HELLP syndrome)
- o Proteinuria (≥ 300 mg urinary protein per 24 hr, or 30 mg/dL urine [dipstick #1])
- o While abdominal ultrasound may be reliable to detect intrahepatic complications of HELLP, imaging is not reliable to prove the absence of AFLP (the liver must contain $> 30\%$ before the abdominal ultrasound becomes reliably positive for steatosis).

➤ Pathology

- o The usual patchy hepatic necrosis may lead to confluent necrosis, hepatic hematoma, and even hepatic rupture requiring surgical intervention or hepatic artery embolization.
- o Fibrin deposits in sinusoids $\rightarrow$ focal ischemic necrosis $\rightarrow$ periportal hemorrhage, subcapsular hematoma, hepatic rupture.
- o Maternal and fetal mortality from a free rupture is 50-100%.

JAUNDICE / HYPERBILIRUBINEMIA

➤ Differential diagnosis

- Give major intrahepatic and extrahepatic causes of cholestasis leading to jaundice.

- o Intrahepatic
 - Drugs
 - Alcoholic hepatitis $\pm$ cirrhosis
 - PBC
 - Viral hepatitis
 - Chronic hepatitis $\pm$ cirrhosis
 - Cholestasis of pregnancy
 - Sepsis
 - TPN
- o Extrahepatic
 - Common bile duct stone(s)
 - Pancreatic / periampullary cancer
 - Benign biliary stricture
 - PSC, SSC (secondary sclerosing cholangitis)
 - Bile duct carcinoma
 - Benign pancreatic disease
 - Extrinsic duct compression

Adapted from: Heathcote J. *First Principles of Gastroenterology* 2005: pg. 590.



- Give factors contributing to **physiological jaundice** in the neonate.
 - o Absence of placental bilirubin metabolism
 - o Reduced hepatic blood flow via ductus venosus shunting
 - o Decreased red blood cell survival
 - o Proportionally increased red blood cell mass
 - o Reduced enteric bacterial flora
 - o Presence of intestinal β -glucuronidase
 - o Immature liver function
 - o Delayed oral feeding

Printed with permission: Machida H. *First Principles of Gastroenterology* 2005: pg. 725.

- Give a comparison of congenital syndromes of conjugated **hyperbilirubinemia** (Gilbert, Crigler-Najjar types 1 & 2 [CN-T₁, CN-T₂], Dubin-Johnson (DJ), and Rotor's syndrome) in terms of their prevalence, autosomal inheritance, serum bilirubin concentration, diagnostic features, prognosis and treatment.

Name	Defects
o Gilbert syndrome	– “a mutation in the TATAA element in the 5' promoter region of the UDP glucuronyl transferase gene”¹ – Activity of UDP-GT is ~ 30% of normal.
o Crigler-Najjar – type II	– $\downarrow$ UDP-GT activity < 10% of normal
o Crigler-Najjar – type I	– UDP-GT is zero (risk of kernicterus)

Conjugated hyperbilirubinemias (> 15% of total bilirubin is conjugated)

- o Dubin – Johnson syndrome
 - Defect in MRP₂ gene
- o Rotor syndrome
 - Defect unknown

¹ Adapted from: Lidofsky SD. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders / Elsevier, Philadelphia, 2016, page 339.



- Give the variables to differentiate between Gilbert syndrome, Crigler-Najjar (CN) type-1 and -2, Dubin Johnson syndrome (DJS), and Rotor syndrome (RS).

❖ Gilbert Crigler-Najjar

Variables	Gilbert	CN-T1	CN-T2	DJS	RS
o Prevalence	7% of population	Very rare	Uncommon	Uncommon	Rare
o Inheritance (all autosomal)	Dominant	Recessive	Dominant	Recessive	Recessive
o Serum bilirubin concentration	<100 $\mu\text{mol/L}$ (all conjugated)	>400 $\mu\text{mol/L}$ (all conjugated)	<100 $\mu\text{mol/L}$ (about half conjugated)	<100 (about half conjugated)	<100 (about half conjugated)
o Diagnostic features	Bilirubin conc' $\uparrow$ with fasting $\downarrow$ with phenobarbital	Bilirubin conc'- no response to phenobarbital	Bilirubin conc' $\downarrow$ with phenobarbital	Coproporphyrin excretion (>80% isomer !) Pigment in centrolubular hepatocytes	Normal gallbladder visualization at oral cholecystography
o Prognosis	Normal	Early death from kernicterus	Usually normal	Normal	Normal
o Treatment	None needed	Liver graft	Phenobarbital	Avoid estrogen	None available

“Good actions give strength to ourselves and inspire good actions in others”

Plato



HEPATIC CYSTS

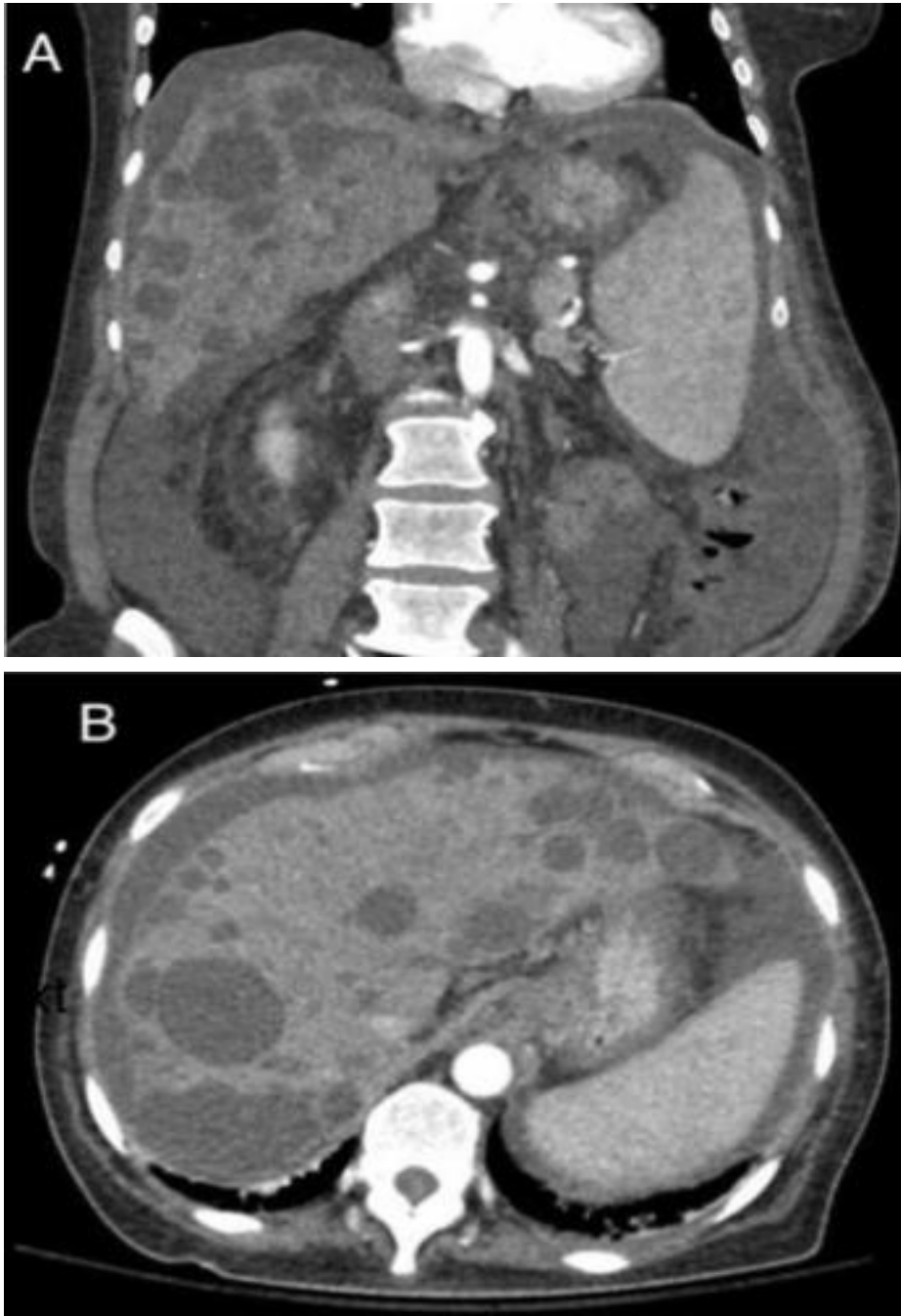
- Definition
 - o Epithelial-lined, fluid-filled space
- Diagnostic Imaging
 - o CT
 - Low-attenuation lesions (no enhancement, dark)
 - o MRI-unenhanced
 - T₂-weighted (white)
- Give features on diagnostic imaging which may help to differentiate the nature of the hepatic tumour / cyst.
 - o Cysts containing daughter cysts (hydatid)
 - o Partly cystic and partly solid
 - Biliary
 - Mucinous cystic neoplasms
 - o Hyperechoic lesion with interspersed hypoechoic areas
 - Areas of
 - Necrosis
 - Hemorrhage
 - o Vascular
 - Hemangiomas
 - Metastasis from NET (neuroendocrine tumour)

Polycystic Liver Disease

- Definition
 - o PCLD alone, or PCLD plus ADPKD (autosomal dominant polycystic kidney disease), or PCLD plus cysts in pancreas or spleen, arise from ductal plate malformation
- Diagnostic Imaging
 - o MRI
 - T₂ – weighted image – bright fluid-filled cysts



Polycystic Liver Disease



Computed tomography of abdomen and pelvis (coronal and axial scans) showing polycystic liver disease along with evidence of portal hypertension in form of splenomegaly and ascites.

Source: Khan MS, et al. Isolated polycystic liver disease: an unusual cause of recurrent variceal bleed. Case Reports in Gastrointestinal Medicine, vol. 2018, Article ID 2902709, 4 pages, 2018.



Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Compression	Sign
- PV (portal vein) - HV (hepatic vein) / IVC (inferior vena cava)	▪ EV (esophageal varices) ▪ Ascites
- o Pearl and Gem: remember that portal hypertension can occur in ADPKD in the absence of obstruction of PV, HV or IVC, due to the association of - ADPKD with CHF (congenital hepatic fibrosis) - o The large hepatic cysts may also cause gastric outlet obstruction	

Caroli Disease

Intrauterine malformation of ductal plate

- o Dilated ducts associated with
 - Congenital hepatic fibrosis
 - Medullary sponge kidney
 - Choledochal cysts, type V
- o Stones form in dilated ducts
 - Cholangitis (~33%)
 - Cholangiocarcinoma (10%)

➤ Diagnostic Imaging

Caroli Disease

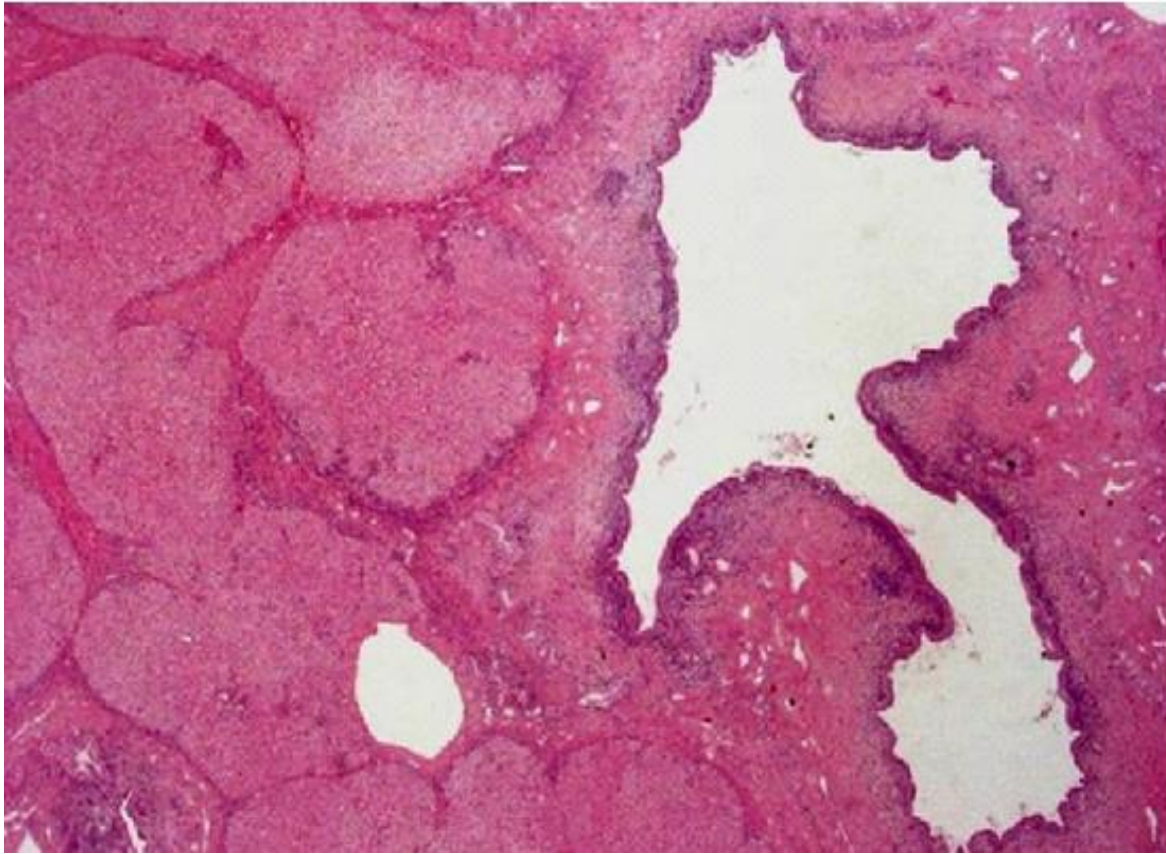


Source: Sato Y, et al. Int J Hepatol. 2012; 2012: 107945.



➤ Histopathology

Caroli Disease



Source: Sato Y, et al. Int J Hepatol. 2012; 2012: 107945.

"Optimism is the faith that leads to achievement.
Nothing can be done without hope and
confidence"

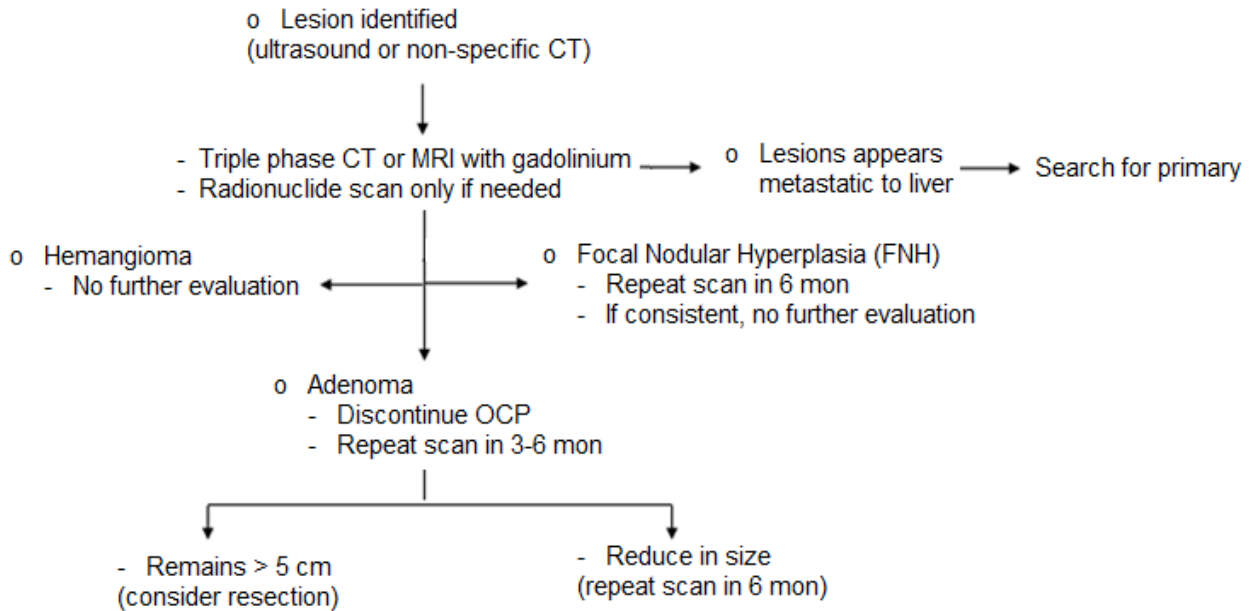
Helen Keller



HEPATIC MASSES

➤ Diagnosis

- Give an **algorithm** for evaluation of hepatic mass in a patient with no cirrhosis



- o Note – in the patient with cirrhosis, an hepatic mass is considered to be an HCC until proven otherwise

“Try not to become a man of success but a man of value.”

Albert Einstein



BENIGN LIVER TUMOURS

Hepatic Hemangioma

- Definition
 - o Vascular lesion with anastomosing vascular channels of varying size arising from vascular endothelial cells in fibrous septa
- Diagnostic imaging
 - o CT
 - Masses
 - Single (2/3) or multiple
 - Small (< 4 cm)
 - When > 4 cm, called "giant cavernous hemangioma"
 - Globular
 - Peripheral
 - Peripheral nodular enhancement (high attenuation; white)* on early phase of contrast enhancement
 - Low-attenuation (dark)
 - Progressive centripetal fill-in"* of peripheral enhancement after 5 to 30 min pathognomonic
 - Central area of fibrosis in larger tumour masses
 - Central enhancement
 - Early enhancement
 - Diffuse
 - Rapid washout
 - o CT-angiography
 - Cotton-wool pooling of contrast
 - Normal vessels without AV shunt
 - Persistent enhancement

Hepatic Hemangioma, CT Scan



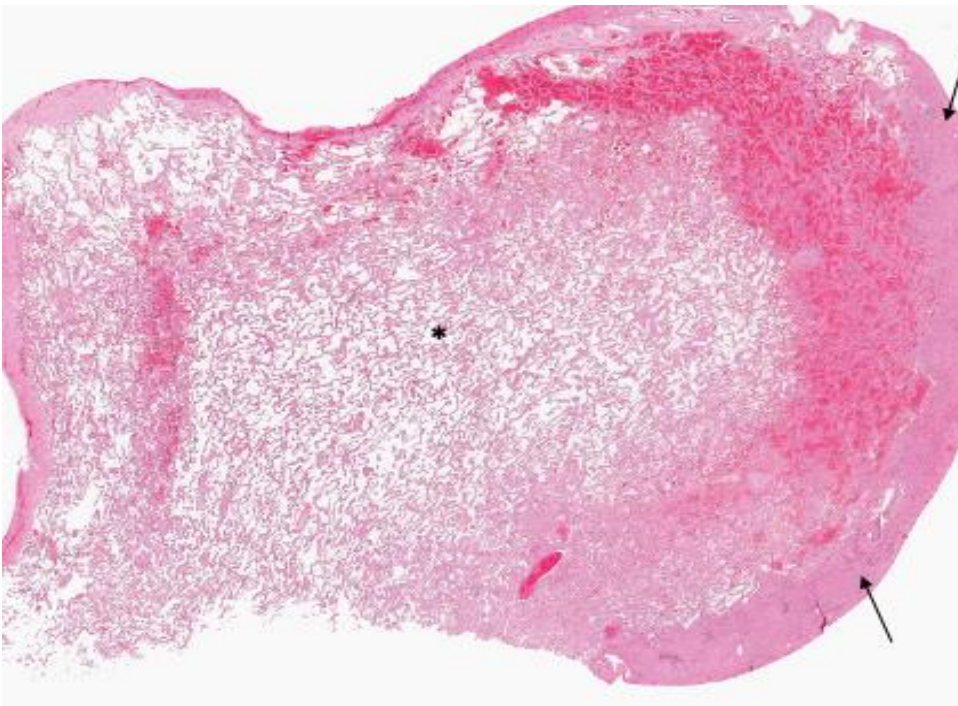
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- o MRI
 - T1-weighted sequence – low-signal intensity (dark)
 - T2-weighted sequence (suppresses signal from fat)
 - High signal intensity (white)
- o Nuclear medicine
 - Gadolinium scan
 - Peripheral nodular enhancement
 - Delayed filling (1 to 2 hours)
 - Progressive centripetal fill-in
 - Hepatic Tc-99m RBC scan
 - Diagnoses hemangiomas > 2.5 cm
- o Ultrasound
 - Mass
 - Homogeneous (in 2/3)
 - Hyperechoic (white; from numerous vascular channels)
 - Doppler ultrasound not helpful because of low flow in hemangioma
 - No hypoechoic halo (as is seen in echogenic tumour metastases)

➤ Histopathology

Hepatic Hemangioma

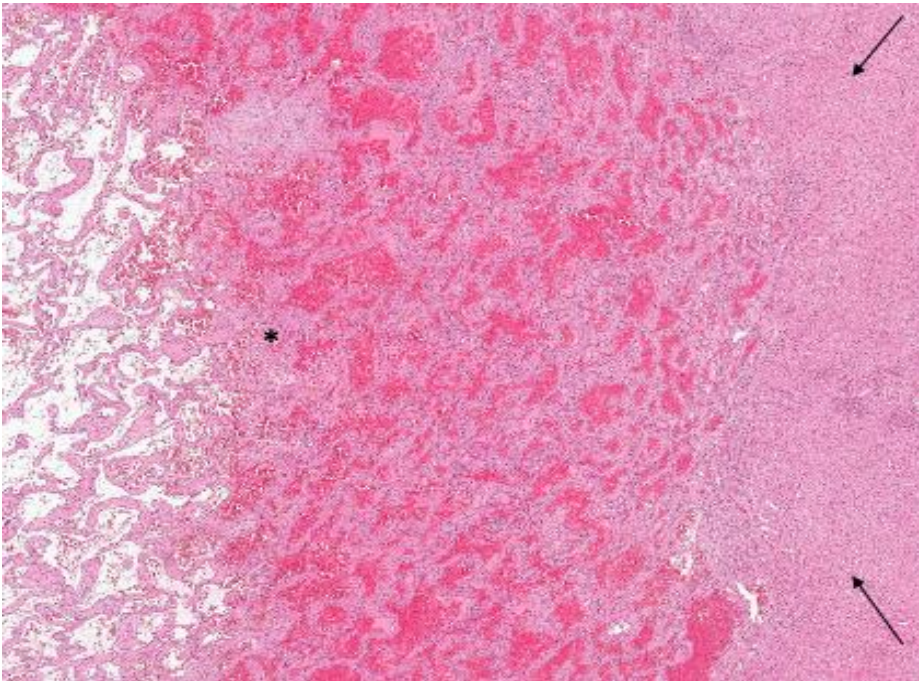


Liver containing a large cavernous hemangioma (*) with some normal liver at right (arrows, H&E 10X)

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Hepatic Hemangioma



Liver containing a large cavernous hemangioma (*) with some normal liver at right (arrows, H&E 40X)

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Cavernous Hemangioma

- Definition
 - o Common congenital malformation of the liver vasculature, with ectatic blood vessels with no malignant potential and not affected by oral contraceptive hormones. Because of tortuous vessels and stasis, thrombosis and pain may occur
- Diagnostic imaging
 - o Abdominal ultrasound echogenic
 - o Bolus-enhanced CT with sequential scans
 - These show
 - Periphery – enhanced
 - Margin – corrugated
 - Centre – hypodense
 - o SPECT (single photon emission computed tomography) with colloid ^{99m}Tc –labelled red blood cells
 - o Note:
 - Enhance slowly with dynamic studies because the increased vascularity is from capillaries
 - MRI may show pathognomonic changes
 - Ring – or C-shaped configuration
 - Centre – fibrous, with no uptake (avascular)



You do not want to perform a percutaneous biopsy in a patient with a large hypoechoic liver lesion on abdominal ultrasound which is suggestive of a cavernous hemangioma.

- Give the findings of diagnostic imaging tests which suggest that a hepatic mass is a cavernous hemangioma.
 - o CT or MRI contrast enhanced
 - Centipetal filling of contrast (from the periphery to the center)
 - Well circumscribed
 - o RBC nuclear scan with technetium
 - ↑ Uptake of labelled RBCs on the venous phase
 - ↑ retention on delayed films

SO YOU WANT TO BE A HEPATOLOGIST!

In the context of a large hemangioma, give the meaning of the **Kasabach-Merritt** syndrome (KMS).

- o The Kasabach-Merritt syndrome is a large hemangioma, DIC (disseminated intravascular coagulation) and thrombocytopenia resulting from platelets being sequestered and destroyed in the hemangioma.

Cavernous Hemangioma



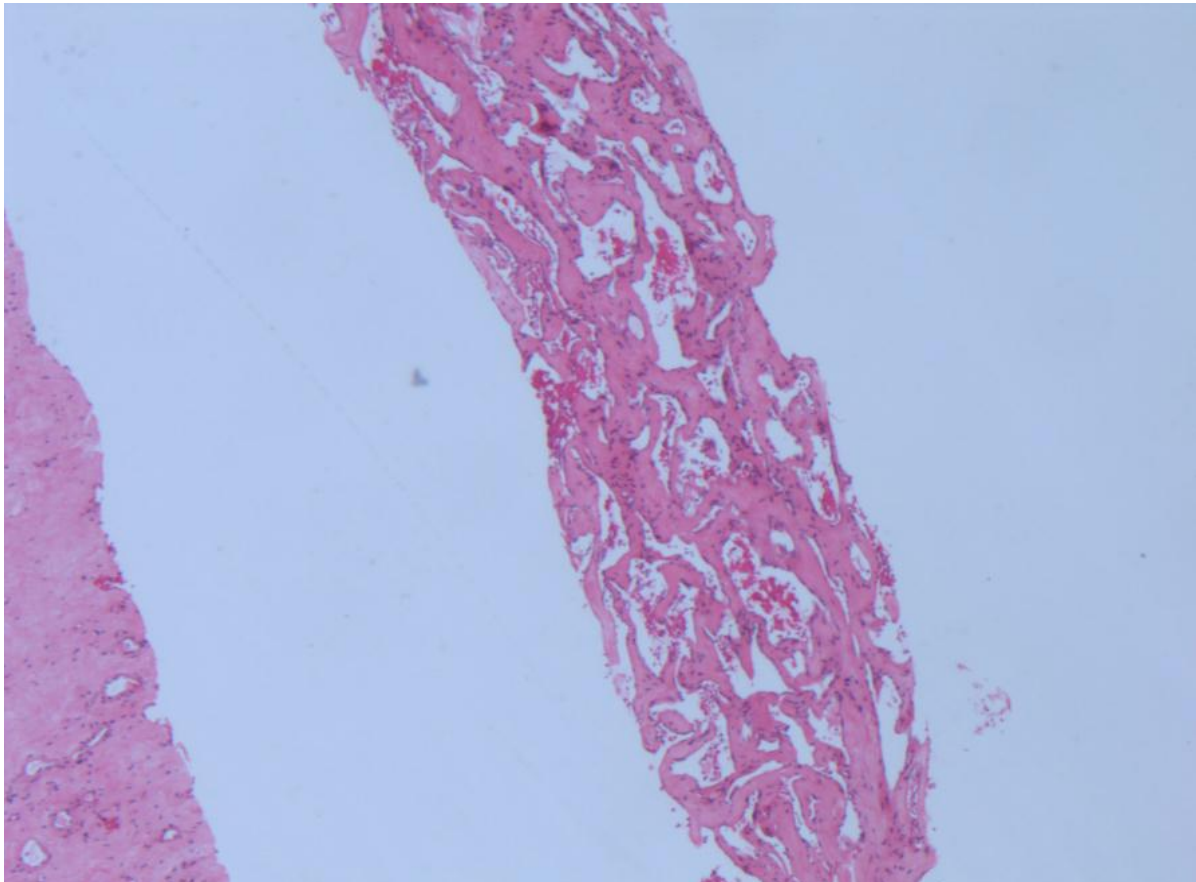
Courtesy of Dr. Mahmoud H Mosli, Western University, London (ON)



➤ Histopathology

- o Common congenital malformation of the liver vasculature, with
 - Ectatic blood vessels with
 - No malignant potential and
 - Not affected by oral contraceptive hormones (but does enlarge under influence of estrogens / pregnancy)
 - Because of tortuous vessels and stasis, thrombosis and pain may occur
- o The increased vascularity is of capillary origin

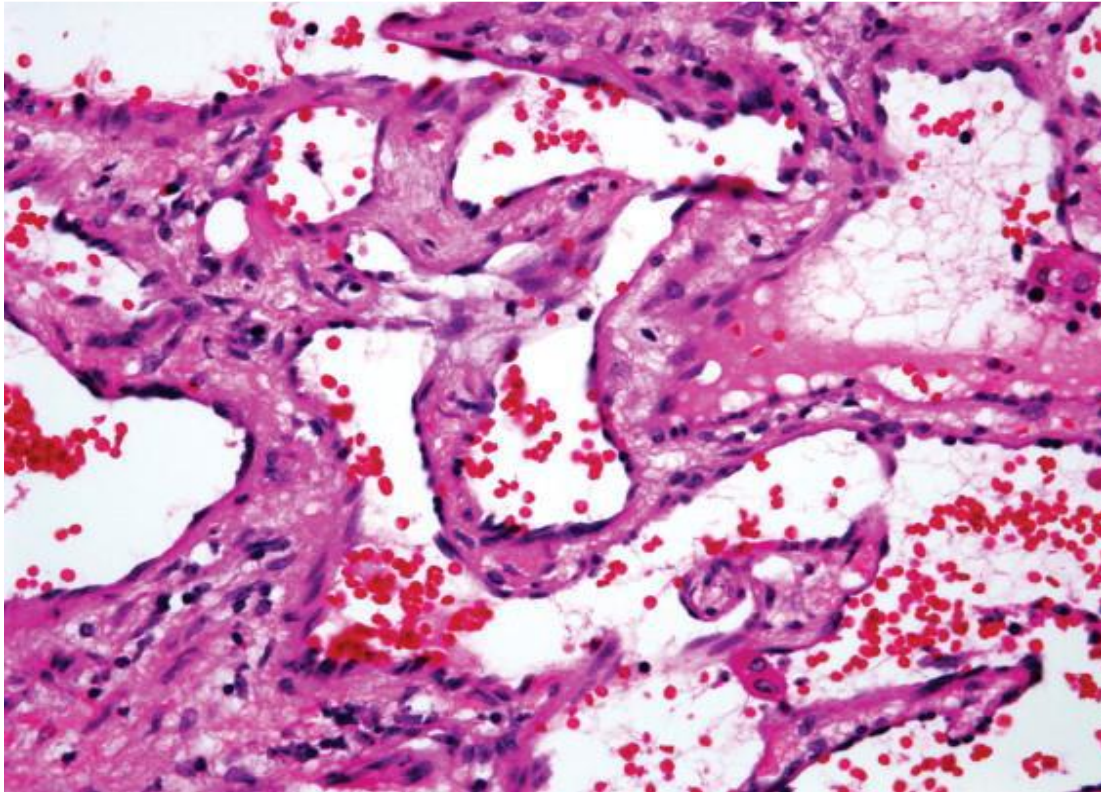
Cavernous Hemangioma



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Cavernous Hemangioma



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Focal Nodular Hyperplasia (FNH)

➤ Definition

- o Circumscribed, usually solitary lesion [of the liver] composed of nodules of benign hyperplastic hepatocytes surrounding a central stellate scar" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier 2010, page 1587).
- o Common congenital malformation of the liver vasculature, with hyperplasia of hepatocytes around the vascular abnormality, leading to a central scar
- o Solid mass of abnormally arranged hepatocytes, blood vessels, bile ducts and Kupffer cells (hamartoma)

➤ Demography

- o 2nd only to hemangiomas as a cause of a benign tumour of the liver
- o More common in females



➤ Diagnostic Imaging

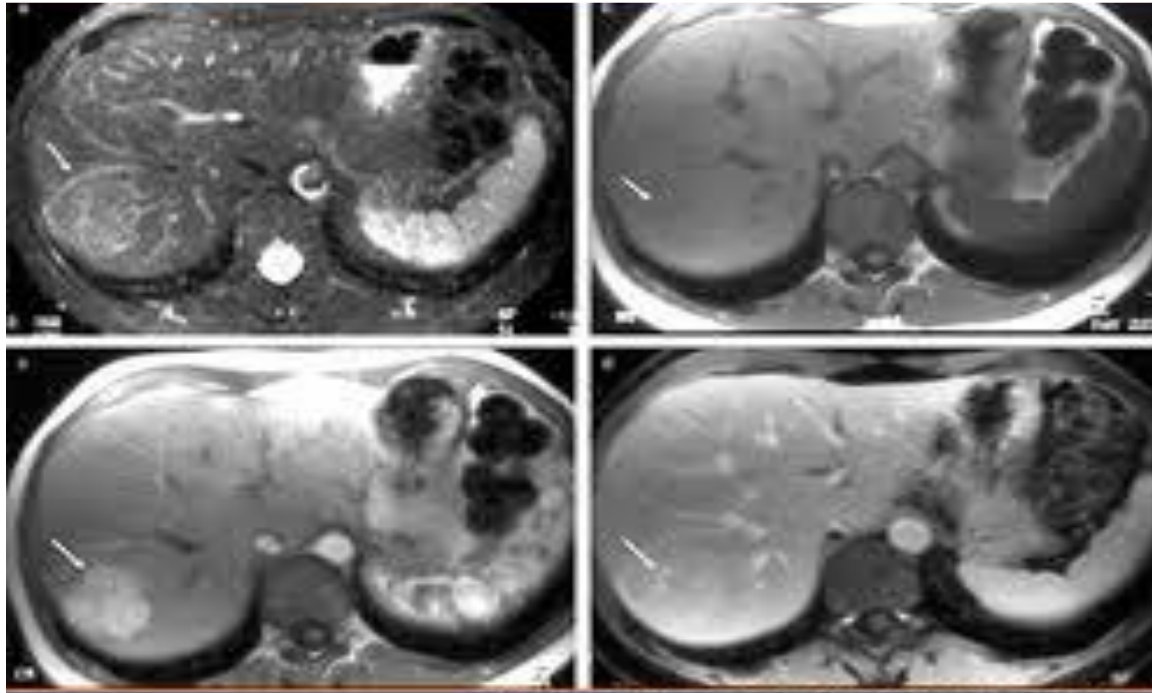
- o Ultrasound
 - Variable appearance
 - Well-defined borders
 - Difficult to see (isoechoic)
 - Central scar, hypoechoic
 - Subtle changes in contour
 - Subtle displacement of normal vessels
 - Hypervascular centrally
- o CT
 - Mass
 - Unenhanced, very difficult to see ("stealth")
 - Solitary (80%)
 - Homogeneous enhancement during arterial phase
 - Central stellate scar
 - No capsule
 - Peripheral enhancement (large peripheral veins)
 - Fibrous septa which divides tumour into lobules
- o Contrast-enhanced CT
 - Single lesion
 - Subcapsular
 - Hypodense or isodense
 - Hypodense central scar
 - Hypodense delayed imaging
 - Arterial phase
 - Homogenous enhancement
 - Enhancement of mass during arterial phase
 - Fibrous septa
 - Centre
 - No enhancement
 - Central stellate scar
 - Hemorrhage / necrosis

"Memories of our lives, of our works and our deeds
will continue in others."

Rosa Parks



Focal Nodular Hyperplasia, CT Scan



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- o MRI
 - T₁-weighted
 - Isointense mass, hypointense / low-signal intensity (white / dark)
 - T₂-weighted
 - Central stellate scar, hyperintense (white)
 - Mass, isointense / hypointense
 - Post-gadolinium
 - Arterial-phase
 - Mass
 - Homogeneous arterial enhancement
 - Central stellate scar
 - Hypointense
 - Central to peripheral septations (lobulation, segmentation)
 - Portal venous phase
 - Isointense
 - Homogenous enhancement in arterial phase of MRI enhancement, with no late-enhancing capsule
- o Sulphur colloid scintigraphy
 - Uptake of tracer into Kupffer (RE, reticuloendothelial) cells equal to or greater than that of normal surrounding liver-pathognomonic for FNH
 - When FNH is multiple (20%), then in 25% of the multiple FNH, there are hepatic hemangiomas



- Give an approach to **distinguish** between **focal nodular hyperplasia (FNH)** and **hepatic adenoma (HA)**.

Characteristic	FNH	Adenoma
o Gender	Female	Female
o Hormone therapy	-*	+++
o Symptoms	Rare	Occasional
o Multiple	About 30%	12-30%
o Pathological associations	Hemangiomas	Glycogenoses, androgens, peliosis
o Diagnostic Imaging	-Please see following table	
o Central arterial scar	Yes, static	No; If stimulated (estrogens, OCA)
o Treatment	Conservative	Resection if symptomatic
o Malignant potential	-	+

*the telangiectatic subtype of FNA is associated with estrogen use

- Give the diagnostic imaging characteristics on CT / MRI / PET scan / nuclear medicine of hemangioma, focal nodular hyperplasia (FNH), adenoma, HCC, and metastases.
 - o Hemangioma – nodular, no washout at periphery; RBC scan, triphasic CT scan (arterial phase); MRI
 - o Focal nodular hyperplasia
 - Central vessels
 - Stellate central scar
 - Homogenous
 - o Adenoma
 - Heterogeneous
 - Hemorrhage
 - Fat
 - Necrosis
 - Orphaned arteriole (no bile duct) “feeding” lesion
 - o HCC
 - Tumour thrombus in vessel
 - Fat
 - Cirrhosis
 - Capsule heterogeneous
 - Bile production
 - Extrahepatic involvement



- o Metastases
 - Washout at periphery
 - Ring enhancing
 - Fat
 - Blood
 - Calcification
 - New or increasing size – may be hyper / hypo-vascular

Adapted from: Hussain SM, and Semelka RC. *Magn Reson Imaging Clin N Am* 2005;13(2):255-75.

Distinguishing diagnosis: FNH, Adenoma, Fibrolamellar HCC			
	FNH	Hepatic adenoma	Fibrolamellar HCC
Enhancement	Homogenous	Heterogeneous	Homogeneous
Central stellate scar	+	-	+
Adenopathy, invasion of vessels	-	-	+

- Give clinical, laboratory and diagnostic imaging **differences** between **FNH** and **FLHCC** (fibrolamellar hepatocellular cancer).

Feature	FLHCC	FNH
o Associated with cirrhosis	-	-
o Normal hepatic synthetic function	+	-
o Treated by surgical resection	+	Depends
o Diagnostic imaging		
- Central scar	+	+
- Calcification	+	-
- ↓ Intensity (dark, hypointense) on T2-images of MRI	+	-
- Progressive enlargement	+	-
o Histology		
- Large, granular cells	+	-
- Pale bodies	+	-
- Bands of fibrosis	+	-
o Bile duct proliferation	-	+
o Malformed blood vessels in central scar	-	+



- Give the diagnostic features of types of diagnostic imaging, which help to distinguish between hepatic hemangioma, focal nodular hyperplasia (FNH), and adenoma.

	Hemangioma	FNH	Adenoma
o Ultrasound	- Hyperechoic - Well defined borders	- Variable appearance - Well defined borders	- Non diagnostic
o Triple phase CT	- Pre contrast: hypodense - Centripetal globular enhancement - Retained contrast in delayed images	- Pre contrast: Hypo or isodense - Homogenous arterial enhancement - Hypodense central scar - Isodense in delayed imaging	- Pre contrast: Hypo or isodense - Irregular enhancement - Delayed peripheral arterial enhancement during venous phase
o MRI	- T1: well circumscribed low signal - T2: Hyperintense signal	- T1: low signal - T2: Hyperintense signal with central scar	- T1: Low signal intensity with well defined capsule - T2: Heterogenous enhancement
o Gadolinium enhanced MRI	- Progressive enhancement - Delayed washout on venous phase	- Homogenous arterial enhancement - Hypodense central scar - Contrast accumulates in scar on delayed T1	- Irregular enhancement with delayed washout
o Radionuclide scan (tagged RBC)	- ↑ uptake during venous phase - Delayed emptying	- Equal or ↑ uptake compared to surrounding liver	- ↓ uptake compared to surrounding liver

Source: Shiffman ML. 2009 ACG Annual Postgraduate Course:167-171.

➤ Histopathology

- Give the typical histopathological features of FNH.
 - o Hyperplastic regenerative nodules separated by fibrosis septa.
 - o Usually single (multiple in 30%)
 - o Malformed blood vessels in central scar
 - o Bile ductular proliferation
 - o Hepatocyte nodules surrounded by fibrous septa
 - o Foci of intense lymphocytic infiltration



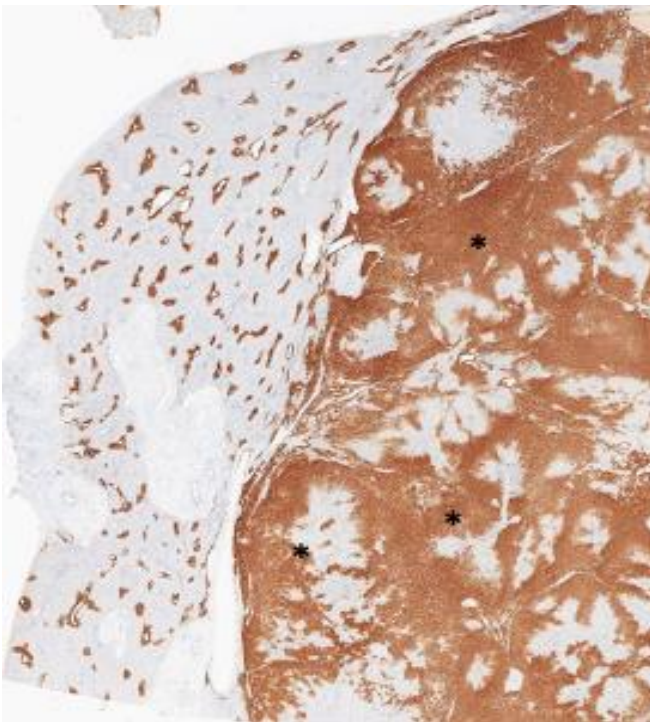
Focal Nodular Hyperplasia



Cluster of large vessels (circled) with adjacent nodular liver (H&E 20X)

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Focal Nodular Hyperplasia



Cluster of large vessels with adjacent nodular liver showing map like staining with Glutamine Synthetase (*, right) compared to the normal perivenular staining of the background liver (left) (Glutamine Synthetase 10X)

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Hepatic Adenoma

- Subtypes
 - HNF1A inactivated
 - B-catenin activated
 - Inflammatory
- Demography
 - About 85% occur in women of childbearing years
 - Usually seen in 1/10⁶ women in their childbearing years, and especially if they are on OCA (3 x increased risk)
 - Premalignant, with risk of malignancy increasing with size of adenoma
- Etiology
 - Oral contraceptive use (80%) of young women with HCA in North America and Europe
 - Anabolic steroids in males
 - Androgens for aplastic anemia
 - Various metabolic disorders
 - PCOS
 - FAP
 - B-thalassemia
 - Recent association with obesity / metabolic syndrome
- Diagnostic imaging
 - CT
 - Unenhanced
 - High attenuation mass
 - “whorled” appearance: hemorrhage into adenoma
 - Contrast enhanced
 - Mass
 - Large
 - Solitary
 - Pre contrast: Hypo or isodense
 - Irregular enhancement
 - Delayed peripheral arterial enhancement during venous phase
 - Irregular enhancement with delayed washout
 - ↓ uptake compared to surrounding liver
 - Heterogeneous, hemorrhage, fat, necrosis, orphaned arteriole (no bile duct) “feeding” lesion
 - Heterogeneously enhancement
 - Multiple compartments
 - Capsule

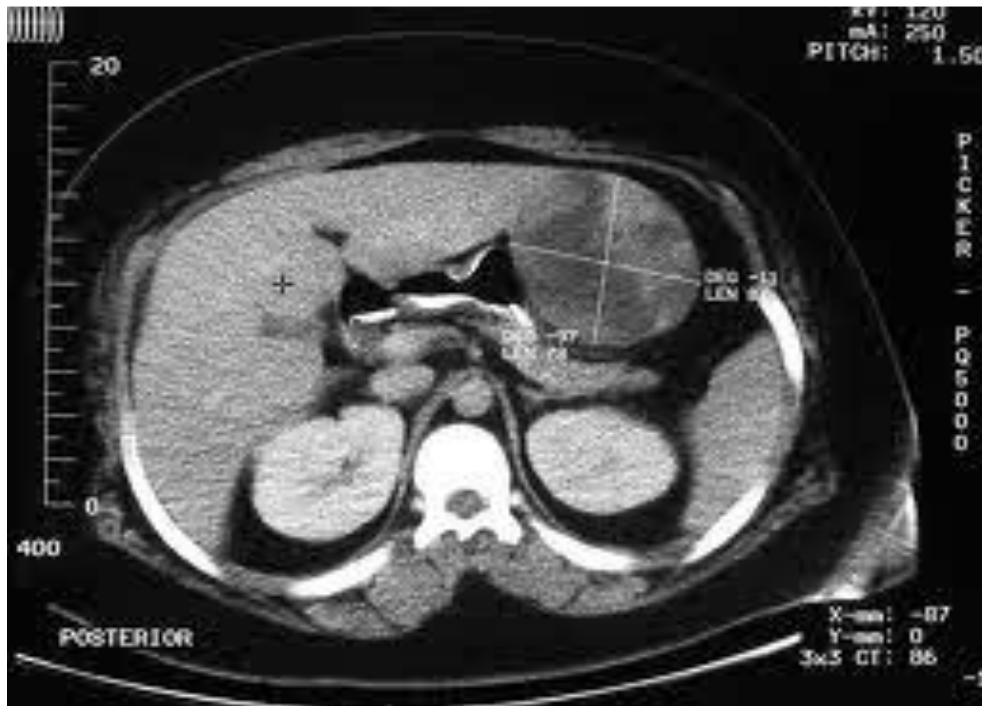


- o MRI
 - T1 weighted
 - HNF1A inactivated: diffuse and homogenous signal dropout in typical fat rich adenoma; usually moderate arterial enhancement, not persistent during delayed phase
 - T2 weighted
 - Inflammatory: Hyperintense; diffuse / predominantly at periphery; usually strong arterial enhancement, persistent during delayed phase

Note: cannot reliably distinguish between adenoma and HCC

Subcapsular hemorrhage (unenhanced CT, high attenuation mass with “whorled” appearance suggests bleeding into adenoma

Hepatic Adenoma, CT Scan



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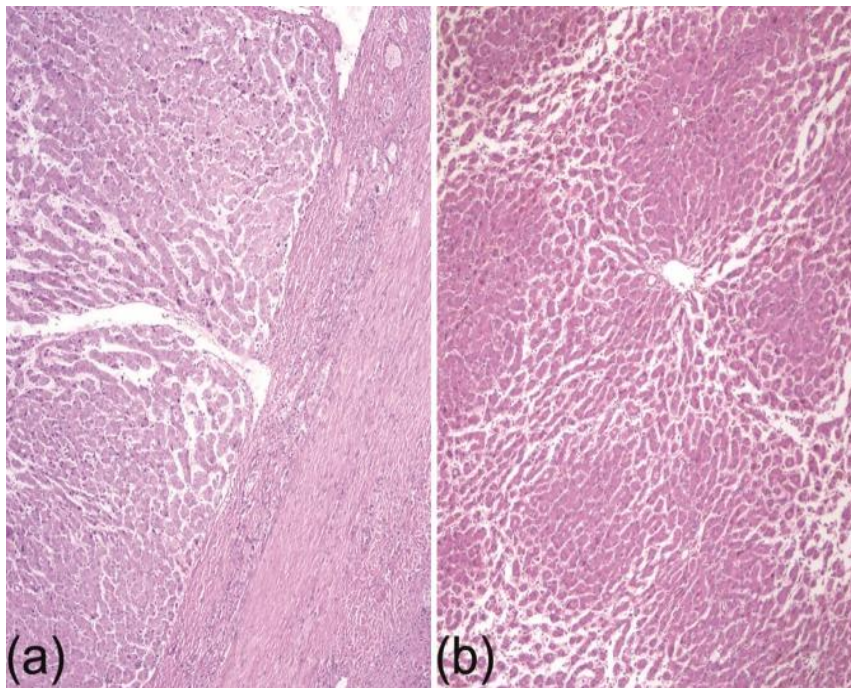
- o Multiphase, helical CT or MRI
 - Definite margin (pseudocapsule)
 - Vessels enter adenoma at the periphery and pass in a spoke-wheel manner to the centre
 - Focal avascular areas
- o Technitium sulfur colloid scan
 - Features on triphasic CT or gadolinium enhanced MRI may be difficult to distinguish from HCC
 - A technitium sulfur colloid scan may be needed to show the typical cold lesions (no sulfur colloid uptake)
 - Serum AFP may become positive when hepatic adenomas becomes malignant



➤ Histopathology

- o 90% single, 10% multiple
- o Circumscribed, but not encapsulated
- o No triads or central veins
- o Sheets of normal looking hepatocytes in plates 1-2 cells thick cytoplasm may be normal, clear or steatotic
- o May undergo malignant transformation
- o Specific features:
 - HNF1A inactivated
 - Lobulated
 - Diffuse steatosis
 - +/- few pseudoglands
 - B-catenin activated
 - May show more atypia
 - Often diffuse staining for glutamine synthetase (depending on specific exon mutation)
 - Inflammatory
 - Sinusoidal dilatation
 - Lymphocytic inflammation
 - Thick walled arteries
 - Ductular reaction

Adenoma



- o Solid lesion with fibrous pseudocapsule (A) constituted by
 - Hepatocytes arranged in cords; veins in between that resemble central veins, and
 - Occasionally dilated sinusoid spaces (B).

Printed with permission: Martinez-Mier G, et al. BMJ Case Rep. 2013; bcr2013202111.



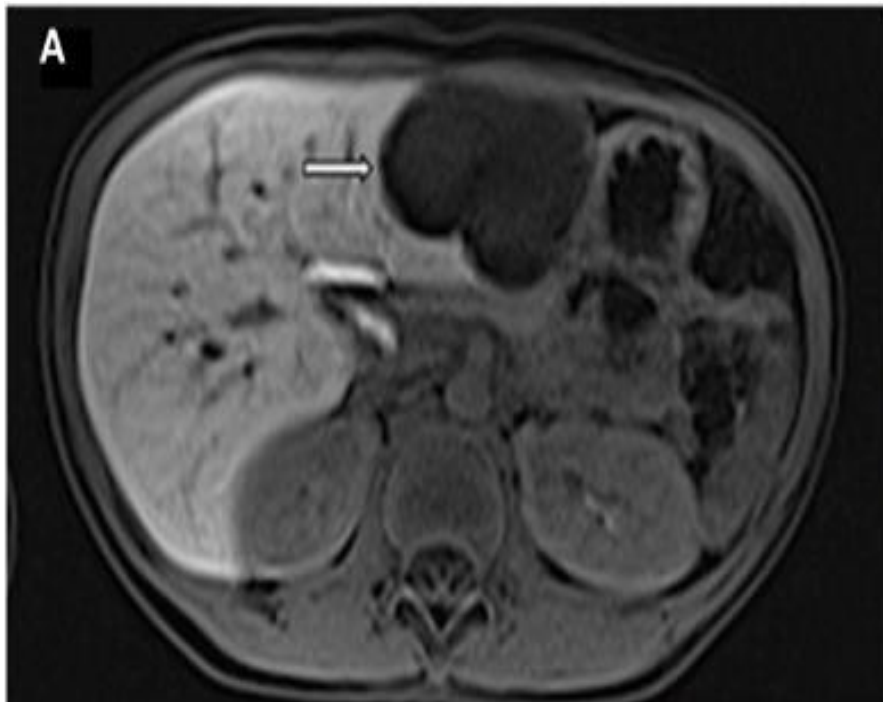
- Prognosis / management
 - Biopsies recommended to confirm diagnosis
 - Surgical resection for lesions > 5 cm or other high risk features for malignant transformation: male sex, androgen associated, B-catenin activation, borderline features for HCC
 - All subtypes have risk of hemorrhage if > 5 cm
 - Risk of progression to HCC
 - HNF1A inactivated – low
 - B-catenin activated – high for exon 3 mutation; low/no for exon 7/8 mutation
 - Inflammatory - low

Mucinous Cystic Neoplasm (MCN) (previous terminology: hepatobiliary cystadenoma)

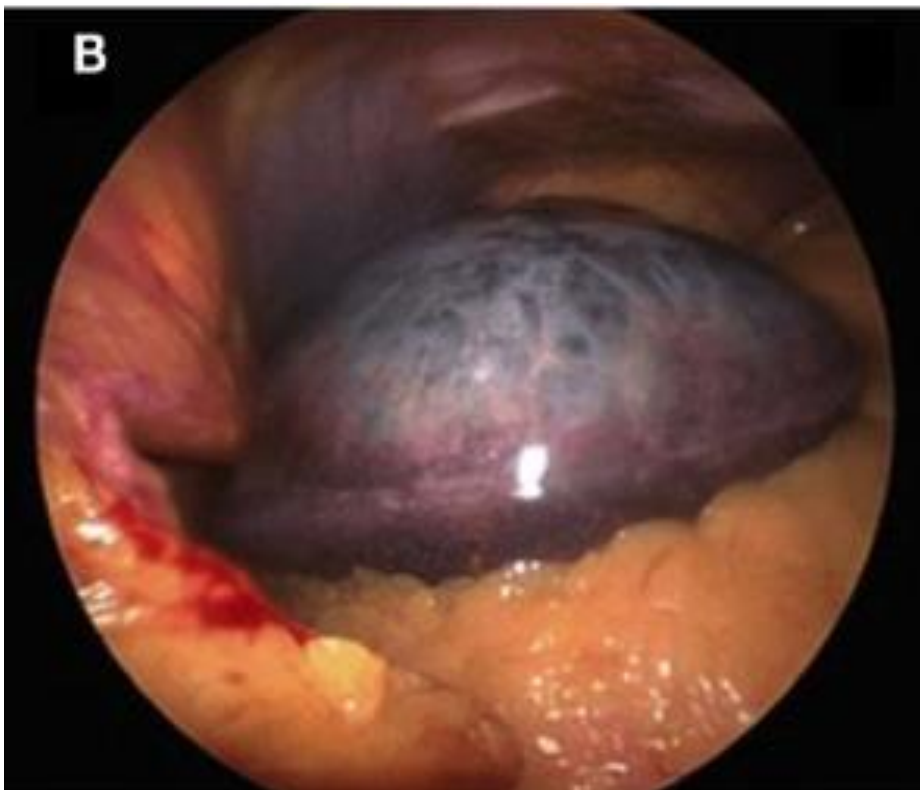
- Definition
 - Cyst forming epithelial neoplasm
 - Lined by cuboidal to columnar variably mucin producing epithelium
 - Associated ovarian type subepithelial stroma – prerequisite for diagnosis
 - Epithelium is categorized as having low / intermediate grade dysplasia vs high grade dysplasia
 - Invasive carcinoma may occur
- Diagnostic imaging
 - CT, contrast-enhanced
 - Cystic mass
 - Large
 - Multilocular (septations)
 - Thick capsule
 - No
 - Wall calcification
 - RIM of hyperenhancement



Mucinous Cystic Neoplasm



(A) Magnetic resonance imaging of the liver (with Eovist contrast) showing a cystic lesion in the left hepatic lobe measuring 6.0 cm × 6.1 cm × 3.8 cm. There is thin enhancement of septations seen within the lesion.



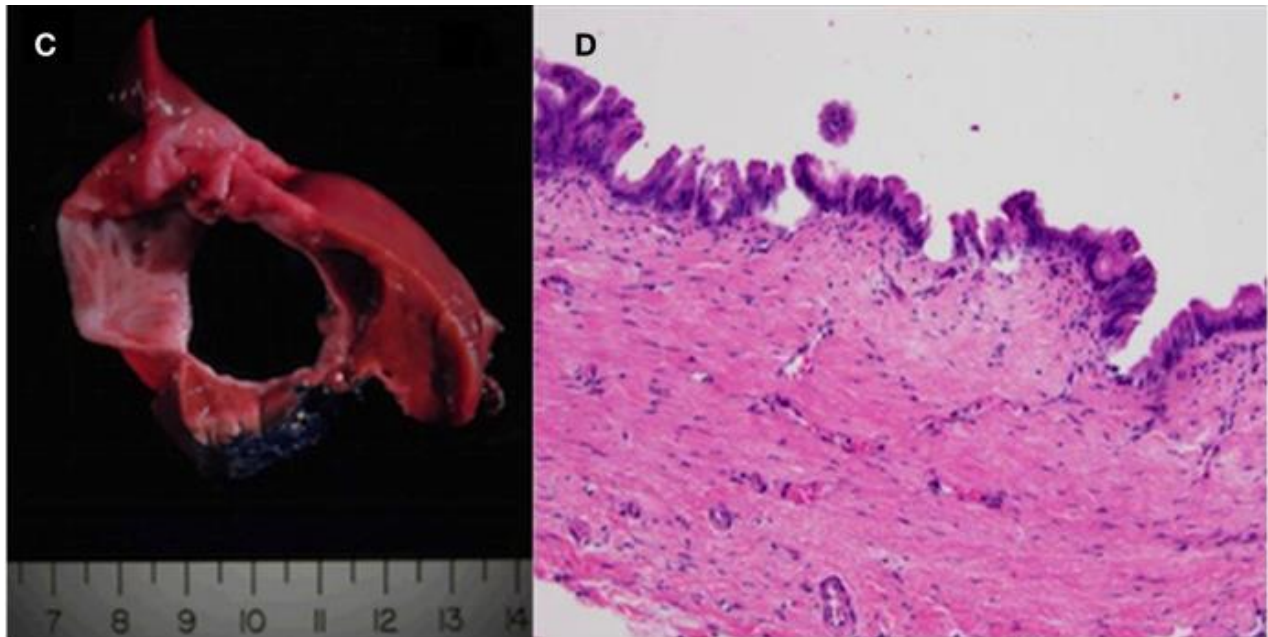
(B) Gross pathology showing a large, well-circumscribed mass with surrounding liver parenchyma.

Printed with permission: Ferraguti DA, et al. Front. Pediatr 2017; 5:215.



➤ Histopathology

Mucinous Cystic Neoplasm



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- o (C) Serial sectioning of the mass revealed a cyst-like appearance with clear serous fluid filling the central portion.
- o (D) The resected cyst is lined by mucin-type epithelium ranging from low cuboidal to stratified-columnar with frequent papillary tufting.
 - No significant nuclear pleomorphism or loss of nuclear polarity.
 - Best classified as mucinous cystic neoplasm with low-intermediate grade dysplasia (original magnification 20×, hematoxylin and eosin).

Printed with permission: Ferraguti DA, et al. Front Pediatr 2017; 5:215.

➤ Prognosis

- o Prognosis of MCNs without associated invasive carcinoma is excellent if complete resection is possible
- o Recurrences may occur after incomplete resection
- o Invasive adenocarcinoma arising in association with MCN may have a better prognosis than intrahepatic cholangiocarcinoma

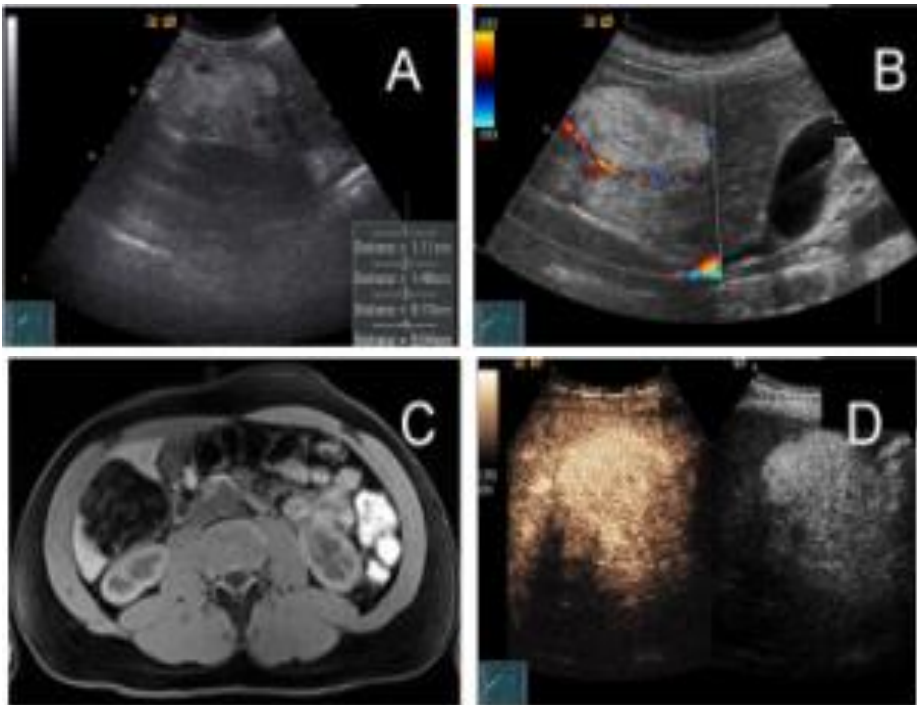


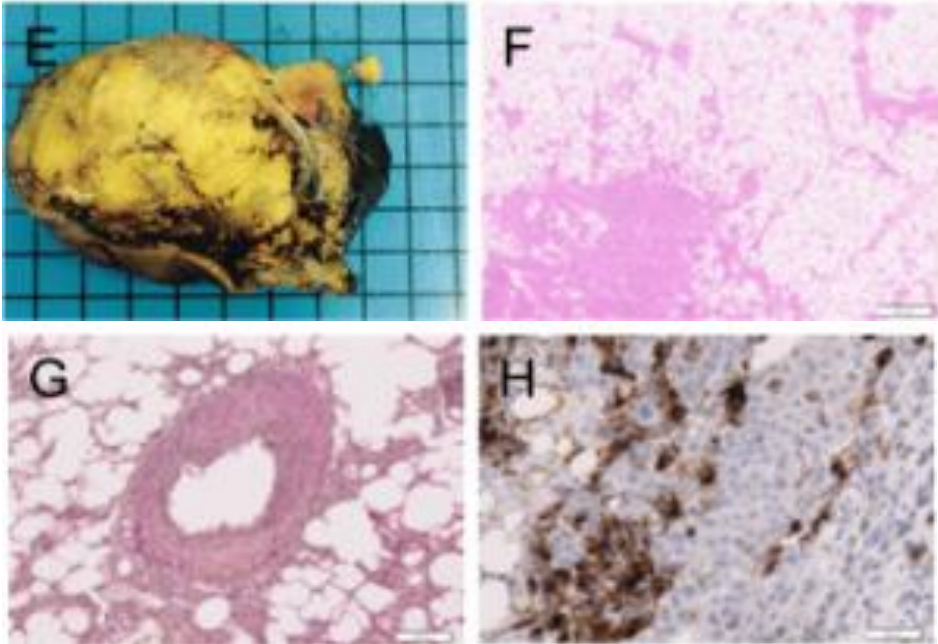
Hepatic Angiomyolipomas

- Definition
 - o A type of PEComa (group of perivascular epithelioid cell tumours)
 - o Rare in the liver
 - o Most are sporadic but may be associated with tuberous sclerosis
- Histopathology
 - o Recognized by a large fat (“lipo”) component with spindled (or sometimes epithelioid) smooth muscle type cells (“myo”) radiating out from large blood vessels (“angio”)
- Diagnostic Imaging
 - o Ultrasound
 - Hyperechoic mass
 - Single / multiple
 - o CT, contrast-enhanced
 - Focal hyperenhancement (fat; must have in mass to make diagnosis)

Note: Difficult to distinguish from HCC or metastatic liposarcoma (also may contain fat)

Hepatic Angiomyolipoma





Radiological and histopathological characterization of hepatic angiomyolipoma.

- (A) Detection of a hepatic lesion by abdominal ultrasonography
- (B) Color Doppler examination showing peripheral hypervascularization
- (C) Typical MRI aspects of hepatic angiomyolipoma
- (D) CEUS findings
- (E) Gross pathological findings after surgery
- (F) Histological demonstration of mostly adipose tissue
- (G) Demonstration of epithelioid cells typically arranged around blood vessels
- (H) Positive immunohistochemistry for the melanoma marker HMB-45

Printed with permission: Krebs S, et al. J Med Case Rep 2011; 5: 481.

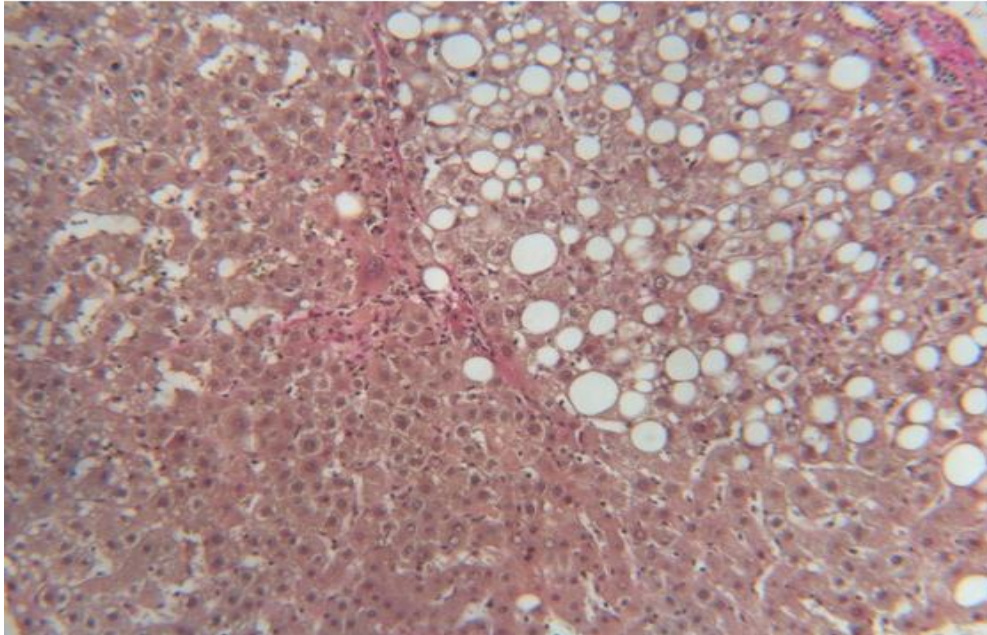
Nodular Regenerative Hyperplasia (NRH)

- Definition
 - o Regenerative nodules without fibrosis
- Causes / associations
 - o Injury to the hepatic vasculature from
 - Autoimmune disorders
 - Myeloproliferative syndromes
 - Antineoplastic medications → remodeling of surrounding liver tissue into a nodule around portal triads, which contains liver tissue and no fibrosis
- Diagnostic imaging
 - o MRI is the best diagnostic imaging test to distinguish HCC from a large cirrhotic nodule



➤ Histopathology

Nodular Regenerative Hyperplasia



Nodular regenerative hyperplasia of the liver with localised fatty degeneration.

Printed with permission: Biecker E, et al. Case Rep Gastrointest Med 2011; 938580.

Peliosis Hepatis (PH)

- Definition
 - o Blood-filled spaces in the liver resulting from focal rupture of sinusoidal walls
 - o Severe sinusoidal dilatation may resemble peliosis
- Types
 - o Parenchymal
 - Death of hepatocytes leads to sinusoidal dilation
 - o Phlebectatica
 - Weakness of reticulin framework leading to sinusoidal dilation
 - o May progress to
 - Cholestasis
 - Liver failure
 - Portal hypertension
 - Development of a mass lesion
 - Spontaneous rupture
 - Calcifications
 - Fibrosis
 - Regenerative nodules
 - Cirrhosis



- Give clinical and laboratory features which suggest the diagnosis of Peliosis hepatis (PH).

PH is characterized by multiple blood-filled spaces in the parenchyma of the liver.

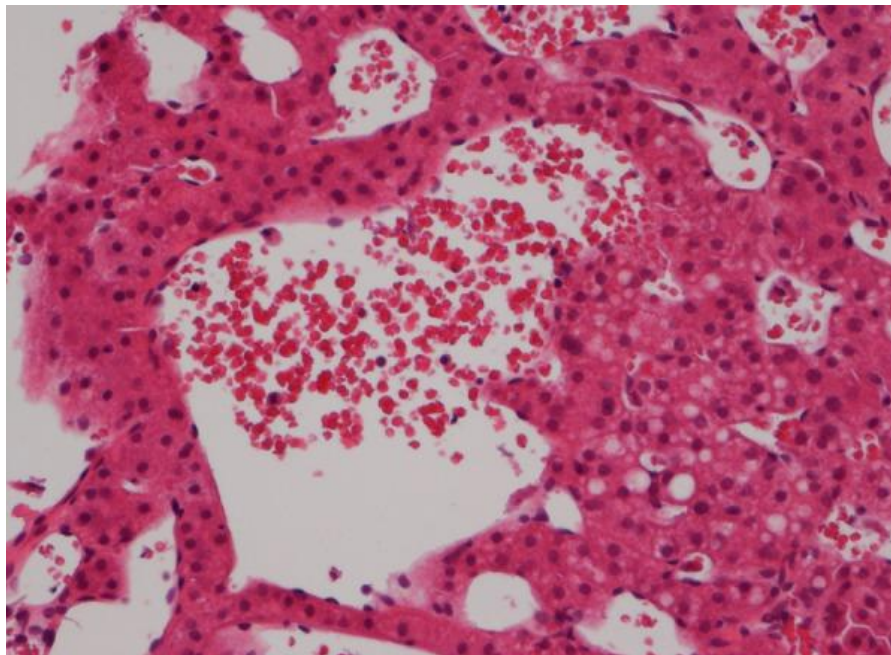
- o Causes / associations
 - Anabolic steroids
 - Bartonella infection in HIV-immunosuppressed patients
 - Azathioprine
 - OCA (oral contraceptive agent)
 - Tamoxifen
 - Vitamin A
 - Hydroxyurea
 - Hairy cell leukemia

➤ Laboratory

- o About 1/3 of patients with severe disease will have asymptomatic, harmless ↑ ALT.

➤ Histopathology

Peliosis Hepatis



Histological section of liver biopsy showing sinusoidal dilatation together with a central blood-filled microcyst. The biopsy contains numerous similar vascular lesions indicating peliosis hepatis (H&E).

Printed with permission: Grønlykke L, et al. BMJ Case Rep. 2013; bcr2013200539.

- o Peliosis-like change may occur in several tumours, including
 - Hepatic adenoma
 - HCC
 - Angiosarcoma
- o The adjacent liver parenchyma should be examined to exclude any associated tumour.

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MALIGNANT LIVER MASSES

- Diagnostic imaging
- Give the diagnostic imaging characteristics on CT / MRI / PET scan / nuclear medicine of hemangioma, focal nodular hyperplasia (FNH), adenoma, HCC, and hepatic metastases.
 - o Hemangioma – nodular, no washout at periphery; RBC scan, triphasic CT scan (arterial phase)
 - o Focal nodular hyperplasia
 - Central vessels
 - **Stellate central scar**
 - Homogenous
 - o Adenoma
 - Heterogeneous
 - Hemorrhage
 - Fat
 - Necrosis
 - Orphaned arteriole (no bile duct) “feeding” lesion
 - o HCC
 - May see tumour thrombus in vessel
 - Fat
 - Cirrhosis in background liver
 - Capsule heterogeneous
 - Bile production
 - +/- extrahepatic involvement
 - o Metastases
 - Washout at periphery
 - Ring enhancing
 - Fat
 - Blood
 - Calcification
 - New or increasing size – may be hyper/hypo-vascular

Clinical MCQ Alert

- o Any mass lesion in the liver of patient with cirrhosis is considered to be an hepatocellular carcinoma (HCC) until proven otherwise

Adapted from: Hussain SM, and Semelka RC. *Magn Reson Imaging Clin N Am* 2005;13(2):255-75.



Hepatocellular Carcinoma (HCC)

➤ Demography

- o Usually seen in
 - Cirrhosis
 - Non-cirrhotic or cirrhotic HBV infection
 - HCV with cirrhosis and non-cirrhotic HCV infection (in Japan)
 - Hemochromatosis
 - NAFLD (non-alcoholic fatty liver disease)
- o Hepatocellular carcinoma (HCC) is one of the most common malignant tumours worldwide and its incidence is increasing in industrialized countries
- o Distribution varies widely worldwide
- o About 80% of HCC worldwide are due to HBV and HCC, and most cases are associated with cirrhosis.
- o Because of the high mortality rate of HCC, the prevalence approximately equals the incidence
- o Overall median survival of HCC - 6 to 12 months
- o The epidemiology of HCC varies with the part of the world
- o M:F 2:1-4:1; increased BMI, androgenic hormones
- o 70-90% of HCC occur against the background of hepatic fibrosis grades 3 to 4, or cirrhosis, 1-4% per year (El-Serag HB, Rudolph KL. *Gastroenterology* 2007:2557-2576); the remainder are associated with HBV and hemochromatosis (HCV in Japan)
- o Ranks eighth in frequency among cancers worldwide
Sixth among men and eleventh among women
 - High incidence
 - 15/10⁵
 - Asia (except Thailand and Indonesia), sub – Saharan Africa
 - M > W 3.7 : 1
 - Medium incidence
 - Asia
 - Thailand
 - Indonesia
 - Australia
 - New Zealand First Nations people (Maori)
 - Alaskan Inuit
 - North America
 - Low incidence < 3/10⁵
 - North America*
 - South America
 - Europe
 - Middle East
 - Australia



➤ Types

o Focal

- Capsule
- Transient hepatic attenuation defects (THAD) (mass contains both hyper- and hypoattenuating areas; may also see a triangle-shaped area of hyperattenuation)
- Mosaic appearance

o Multifocal (multicompartmentalized, mosaic)

- Multiple discrete cystic / solid regions are central or peripheral

➤ Diagnostic Imaging

- Give the diagnostic workup and treatment of a liver mass in a patient with chronic liver disease.

o Mass <1 cm	- Diagnosis	▪ Low likelihood of being HCC, therefore no specific diagnostic tests		
	- Follow up	▪ Repeat imaging study every 3 months ▪ If no growth in 1-2 years, no HCC; continue screening every 6 months ▪ If growth, treat as HCC		
o Mass 1-2 cm	- Diagnosis	▪ Two dynamic imaging studies (US, CT scan, or MRI)	• Both with typical vascular pattern • One typical and the other atypical • Both atypical • Treat as HCC	- Treat as HCC - Consider biopsy of mass
	- Follow up after biopsy	▪ Biopsy confirms HCC ▪ Non diagnostic biopsy	• Repeat imaging study every 3 months: • If no growth in 1-2 years- no HCC • If growth, treat as HCC	- Consider re-biopsy of mass vs close follow up
o Mass >2 cm	- Diagnosis	▪ One dynamic imaging study (US, CT scan, or MRI)	• Typical vascular pattern • Atypical vascular pattern management	- Treat as HCC
	- Follow up after biopsy	▪ Biopsy confirms HCC ▪ Non diagnostic biopsy	• Repeat imaging study every 3 months: • If no growth in 1-2 years- no HCC • If growth, treat as HCC	

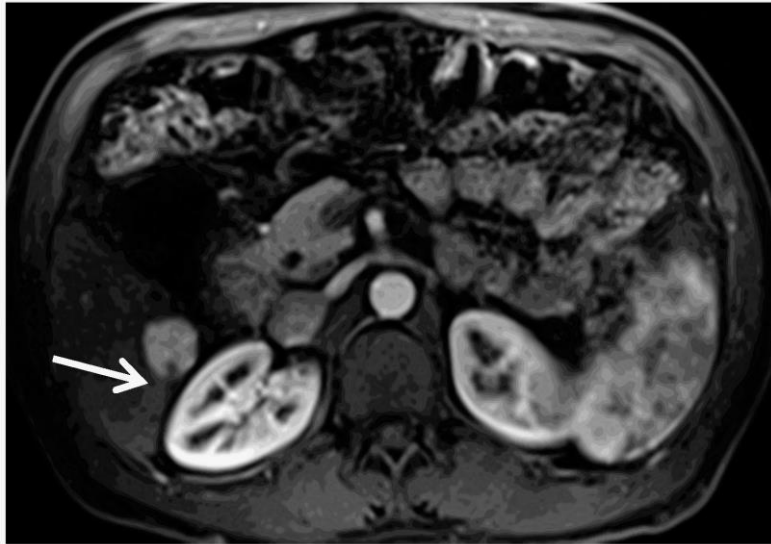


- o The contrast enhanced imaging studies of computed tomography (CT) and magnetic resonance imaging (MRI) use the unique dynamic radiological behaviour of hepatocellular carcinoma (hypervascular on the arterial phase and washout on the delayed venous phase).
- o The sequence of events needed to make the radiological diagnosis depends on the size.

Abbreviations: CT, computerized tomography; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; US, ultrasound

Printed with permission: Garcia Tsao, et al. *Am J Gastroenterol* 2009; 104:1822.

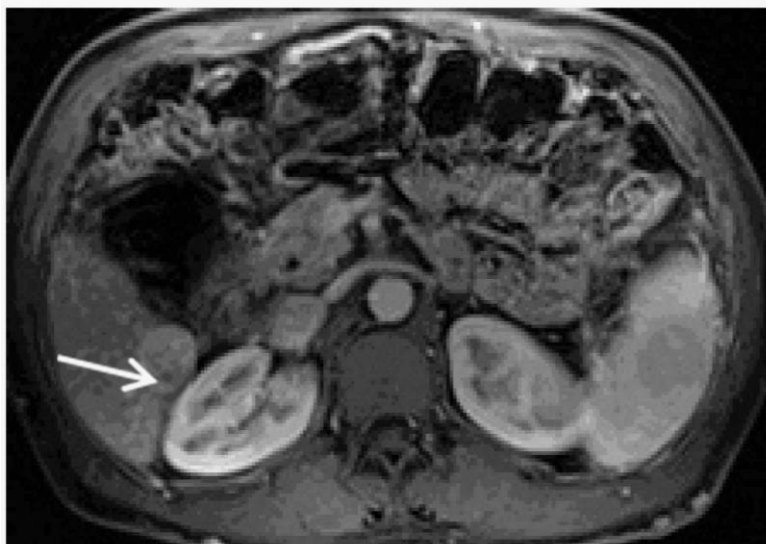
Hepatocellular Carcinoma, MRI contrast-enhanced



On a late arterial phase image, a 2.3 cm HCC (arrow) demonstrates unequivocal arterial enhancement relative to the surrounding liver

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Hepatocellular Carcinoma, MRI contrast-enhanced



On the portal venous phase of the same exam, the hepatocellular carcinoma (arrow) has decreased in enhancement relative to the earlier arterial phase, while the hepatic parenchyma has increased in signal intensity

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Hepatocellular Carcinoma, MRI contrast-enhanced



A coronal image obtained in the equilibrium phase demonstrates the hepatocellular carcinoma (arrow) as being of lower signal intensity than the adjacent cirrhotic parenchyma.

Printed with permission: Niendorf E, et al. *Diagnostics* 2015; 5(3): 383–398.

- o Hepatic nodules < 2 cm in diameter on imaging may still contain a focus of HCC.
- o Imaging techniques may show hypervascularization in the arterial phase, followed by washout in the venous phase, suggestive of malignancy.
- o Importance of DI in HCC
 - Non-invasive criteria have been established by American and European groups (AASLD and EASL), and provide a similar sensitivity of about 80% in making a diagnosis of what turns out to be HCC.
 - Hepatic regenerative activity → ↑AFP
 - Risk of seeding from tumour biopsy ~ 3%: this is why liver biopsy avoided if possible, and diagnosis of HCC may be from imaging studies.
- Give the non-histological (diagnostic imaging) criteria for HCC (hepatocellular cancer).
 - o Hepatic mass on ultrasound in cirrhotic liver
 - o Focal lesion > 2 cm with evidence of cirrhosis
 - o Arterial hypervascularization and venous washout; MRI (contrast enhanced ultrasound;
 - o Sulphur colloid scan – old (Kupffer cells positive in FNH)
 - o AFP > 200 ng/mL (normal AFP does not rule out HCC)

Adapted from: Talwalkar JA, and Gores GJ. *Gastroenterology* 2004;127(5 Suppl 1):S126-32.



- o In the presence of a liver mass in a person with cirrhosis and an AFP > 500 mg/mL, HCC is likely
Hepatic regenerative activity ↑AFP
- o Only 1/3 of HCC patients have AFP > 100 mg/mL, but values > 200 mg/mL are highly specific for HCC, 10.9 mg/mL, sensitivity 66%
- o Diagnosis in a cirrhotic is usually made by diagnostic imaging, without liver biopsy (risk of seeding of tumour)
- o Risk of seeding from tumour biopsy ~ 3%

* Note: Not necessary to biopsy liver to diagnose HCC, since dynamic imaging / CT / MRI are usually diagnostic

- o A non-invasive diagnosis of HCC in a cirrhotic
 - Nodule > 2 cm
 - AFP > 400 ng/mL
 - Diagnostic imaging
 - 1 of 2 tests, if AFP > 400 ng/mL
 - 2 of 2 tests, regardless of AFP
- o Hepatic nodules smaller than 2 cm in diameter may still represent / contain a focus of HCC.
- o Dynamic MRI
 - Dynamic MRI using gadolinium contrast agents may be used in association with dynamic CT if the hepatic mass is 1 to 2 cm in size. The findings on the arterial phase of high signal intensity on T2-weighted images, on the venous and delayed phases finding central washout if contrast and capsular enhancement, have a sensitivity and specificity for HCC of 81% and 85%.
- o MRI super-paramagnetic MRI
 - Iron oxide taken up by Kupffer cells, which are missing in HCC
 - Shows up as dark HCC on this test
 - Arterial phase is sensitive
 - Venous phase is specific
- o Screenign every 6 months with AFP (alpha-fetoprotein) and abdominal ultrasound over 5 years improves survival from HCC in HBV-positive patients in China (42-5). Most of the detected HCC in the screened group were detected at an early stage; with 3 year survival rates after HCC resection of 53% in the screened group versus none in the non-screened group
- o Improved survival from HCC screening depends of course on the availability of effective therapy for the early detected lesions
- o HCC screening in persons awaiting liver transplantation is cost-effective



- Give the differential of **hypervascularity** on ultrasound, in addition to HCC.
 - o Arterial portal shunts
 - o Atypical hemangiomas
 - o Aberrant venous drainage
 - o Dysplastic nodules
 - o Confluent fibrosis
- Give the imaging criteria applied for confirming HCC in patients with cirrhosis and a nodule detected by ultrasound.
- ❖ Ultrasound
 - o Lesion has nodular configuration
 - o Lesion is at least 1 cm in longest diameter*
 - o Lesion shows arterial hypervascularization:
 - o Hyper enhanced nodule in the arterial phase by two imaging techniques**
 - o In general terms, abdominal ultrasound has a sensitivity of 48% and a specificity of 97% for detection of HCC.
 - o Algorithm for mass / nodule in cirrhotic liver on abdominal ultrasound (US) in persons at risk for HCC

Size, diameter	Follow-up
< 1 cm	US every 4 mon for 1 year, then every 6 mon long-term
> 1 cm	4-phase CT / dynamic contrast enhanced MRI
 - o IOUS (intraoperative [including laparoscopic] ultrasound)
 - 16% of planned partial hepatectomies may be canceled because of IOUS showing inoperability
 - May help to guide segmental or non-anatomic resections
 - o Ideal for patients with good hepatic function (C-P class A)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the circumstances when an elevated AFP (alfa fetoprotein) > 200 mg/mL is considered by AASLD guidelines to be diagnostic of HCC.
 - o In the presence of cirrhosis in the liver (especially when > 2 cm)



SO YOU WANT TO BE A HEPATOLOGIST!

The AASLD recommends ultrasonic surveillance (US) for selected HBV infected persons every 6 months. This provides superior survival than when US is performed every 12 months. When US is performed at three month screening intervals more small (< 10 mm diameter) lesions are found.

- Give the reason why this 3 month rather than 6 month US screening interval is not recommended.
 - o Survival from HCC depends on several factors such as the size of the tumour and not the risk of having an HCC.
 - o Focal lesion < 1 cm may not be HCC; by performing US every 3 months, when > 1 cm, perform more sensitive diagnostic imaging for HCC characteristics of ↑ arterial vascularity; and venous phase washout.
 - o It is the larger tumour which is more likely to grow even larger, and to spread and worsen prognosis.
 - o There is no difference in
 - The quantitative incidence of the development of HCC if focal lesion were detected by US by 3 or 6 month screening intervals
 - Survival, decompensation or liver transplantation

Abbreviations: AASLD, American Association for the Study of Liver Diseases; HCC, hepatocellular carcinoma; US, ultrasound

❖ Importance of size of HCCs

- o Only when factors other than the size of HCC are considered, is the prognosis affected, e.g.,
 - Operative risks
 - Comorbidities
 - Hepatic reserve C-P stage (based on Child-Pugh / MELD score)
 - Vascular invasion
 - Metastases
 - Territorial local seeding
 - Multifocality
- o With HCC ≥ 10 cm, the overall survival rate is 27%

❖ MRI

- o T₁ – weighted
 - Hyperintense mass (white)
- o When HCC contains fat, MRI detects mass
 - Low-intensity internal focus (dark; nodule within a nodule)
 - Capsule



- o Low-intensity T₂-weighted
 - Isointense / hypointense mass
 - High-intensity internal focus (white)
- o Dynamic contrast-enhanced
 - High-intensity internal focus (white) becomes hyperenhancing (white)
- o Delayed contrast-enhanced
- o Internal focus becomes isointense
 - High intensity T₁ – weighted MRI images
 - HCC or dysplastic nodule
 - High intensity T₂ –weighted
 - Dysplastic nodule isotense
 - HCC hyperintense
- o Gad-MR (gadolinium magnetic resonance)
 - The most sensitive and specific imaging technique for the diagnosis of HCC

❖ Other methods

- o Contrast-enhanced ultrasonography
- o Helical-computed tomography
- o Superparamagnetic iron oxide magnetic resonance
- o Similar performance characteristics as CT, but size of HCC is a factor, with accuracy of > 90% for > 20 mm lesion seen on MRI, but 30% for lesion < 20 mm
- o Biopsy under radiological guidance

	Sensitivity	Specificity
- US	90%	91%
- CT	92%	98%

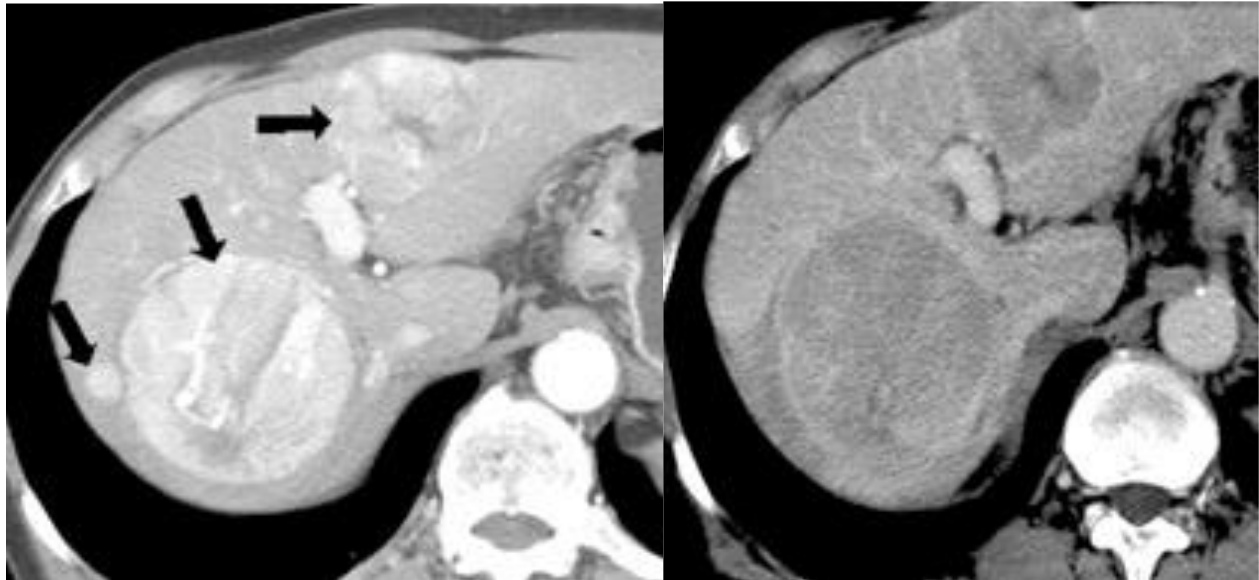
Distinguishing Diagnosis: HCC vs Dysplastic Nodule

	HCC	Dysplastic nodule
o High-intensity-weighted mass	+	+
o High intensity mass	+	(remains isointense)



- ❖ CT arteriogram (CTA)
 - o Hyper-vascular
 - o AV shunting
 - o Angiogenesis

Hepatocellular Hyperplasia, CT Scan



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- ❖ CT, contrast-enhanced, hypoattenuating mass if HCC contains blood / necrosis
 - o Arterial phase
 - Hyperenhancing (hyperattenuating) mass (white)
 - Slowly hypoenhancing (hypoattenuating) capsule
 - o Portal-venous phase “washout”; AV shunting)
 - Hyperenhancing disappears
 - o Arterial phase hypoattenuating
 - o Capsule becomes hyperattenuating on portal-venous phase (late)
 - o Dysplastic hepatic nodules also enhance in arterial phase; use MRI to distinguish HCC from dysplastic nodule
 - o Arterial enhancement (hypervascular, supplied by hepatic artery) and washout, for HCC, sensitivity is 90% and specificity is 95%
 - o HCC hallmark on diagnostic imaging
 - Based on the dynamics of the arterial enhancement and delayed venous washout
 - Some features may also occur in cholangiocarcinoma
 - o 4 phase hepatic tumour protocol for HCC



- o CT
 - Arterial neovascularization
 - ↓ HA, PV supply
- o Dynamic multiphase (dM) CT
 - Assess HA (hepatic artery) and PV (portal vein)
 - dM CT detects small HCC not found on conventional CT
 - Small HCCs may be iso-dense on conventional CT

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- o Multiphase, dynamic, helical CT is the imaging technique of choice for the diagnosis of HCC.
 - The most helpful features are
 - Enhanced arterial phase in the involved area
 - Washout (loss of central nodule enhancement with uninvolved liver), and
 - Enhancement of the capsule in the porto-venous and delayed phase. When the lesion is > 2 cm these diagnostic imaging changes are considered to be diagnostic for HCC.
- Give the reasons why the classical CT changes of HCC may disappear as the HCC enlarges
 - o Arterial enhancement (neoangiogenesis causing hypervascularity)
 - o Shift of blood from primarily portal artery

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CT scanning and performing serial AFP measurements increases sensitivity for finding HCC, but are **not** recommended for screening.

- Give the reason why:
 - o Combining ultrasonography (US) of the liver with AFP to detect a focal lesion is associated with an increased rate of false positives, as also is CT screening.
 - o If a focal lesion is identified on US, then contrast diagnostic imaging is recommended
 - 4-phase CT scan
 - Dynamic contrast enhanced MRI

Distinguishing Diagnosis: HCC, Lipoma and Hematoma

	HCC	Lipoma	Hematoma
o T1/2 – weighted hyperintense mass	+	-	
o Capsule	+	-	-



Distinguishing Diagnosis: HCC vs hepatic metastases

	HCC	Metastases
o Multifocal	+	+
o Dominant lesion	+	-
o Hyperattenuation on early phase contrast enhancement	+	-
o Late phase hypoattenuation	+	-

- o Surgical resection (partial hepatectomy) in carefully selected patients potentially curative (5-year survival rates > 90%)
- o % off newly diagnosed HCC patients eligible for resections ~ 15%
- o Ideal patients
 - 1 tumour
 - Confined to liver (not stage IIIB, IIIC, IVA, IVb)
 - No hepatic vascular invasion
 - No PHT (portal hypertension)
 - Good hepatic functional reserve (C-P class A)
- o "Shades of grey" - some hepatobiliary surgeons will operate for stages
 - IIIB Invasion of PV (portal vein) or HV (hepatic vein), or direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
 - IVA Node positive, any T stage, no metastases
 - IVB Distant metastases, any T stage, any N stage
 - C-P B Child-Pugh stage B
- o PVE (portal vein embolization) before partial hepatectomy for HCC (especially right sided HCC) may lead to physiological hepatic hypertrophy
- o Patients with cirrhosis may have benign lymphadenopathy at the porta hepatis, and in the portacaval space, so diagnostic imaging findings at these times does not necessarily signify nodal HCC
- o If the nodes have the same density as the HCC itself, biopsy the nodes to determine if they are involved (IVA), in which case partial hepatectomy might not be performed (please see above, "nodal metastases")
- o Fibrolamellar HCC can be resected together with lymph node resection



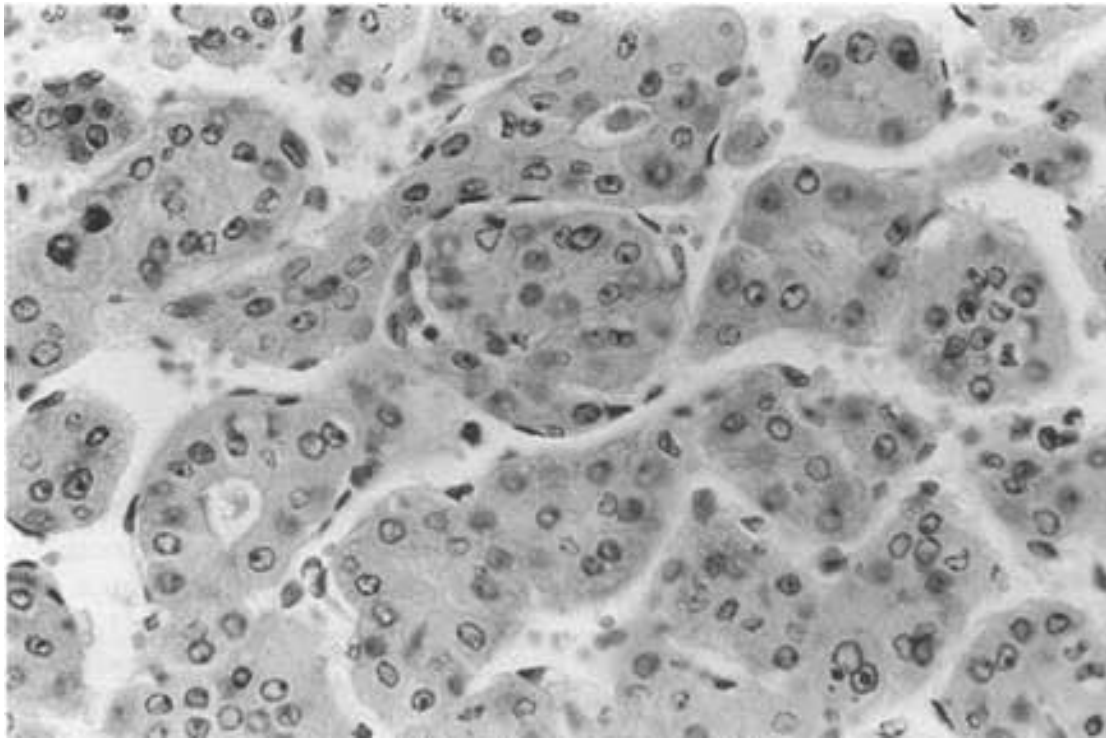
- Give what proportion of patients with HCC or pancreatic cancer in whom investigations suggest that the primary lesion is resectable will the tumour turn out to be non-resectable as defined by diagnostic laparoscopy and laparoscopic ultrasound?
 - o About one third of patients with HCC or pancreatic cancer will have their respectability status down-graded to non-resectable by diagnostic laparoscopy and laparoscopic ultrasonography.

➤ Histopathology

- Give the histopathology of hepatocellular (HCC).
 - o Gross
 - Nodules
 - Large circumscribed mass
 - Diffuse infiltration
 - o Microscopic
 - Architectural changes:
 - Thickened cell plates (trabecular pattern)
 - May be pseudoglandular arrangements with hepatocytes surrounding a bile canaliculus
 - Stromal invasion may be identifiable
 - Vascular invasion may be present
 - Cytology
 - Hepatocytes – polygonal cells with eosinophilic cytoplasm
 - Nuclei may be large and often contain prominent nucleoli
 - Cytoplasm may contain bile, especially in more well differentiated tumours
 - Sinusoids are “endothelialised” – lined by a visible layer of endothelial cells that stain strongly positive for vascular markers CD31 / CD34
 - Sarcomatoid and clear cell patterns exist
 - AJCC Cancer Staging Manual, 8th edition¹ advocates a 4-tier grading scheme:
 - G1: Well-differentiated – minimal to mild atypia, relatively thin cell plates, closely resemble normal liver
 - G2: Moderately differentiated - mild to moderate nuclear atypia, thicker cell plates
 - G3: Poorly differentiated - marked nuclear atypia and/or high mitotic activity, may be difficult to identify as hepatocellular morphologically
 - G4: Undifferentiated - rarely used, reserved for tumors that do not show obvious hepatocellular or other differentiation on morphology or immunohistochemistry

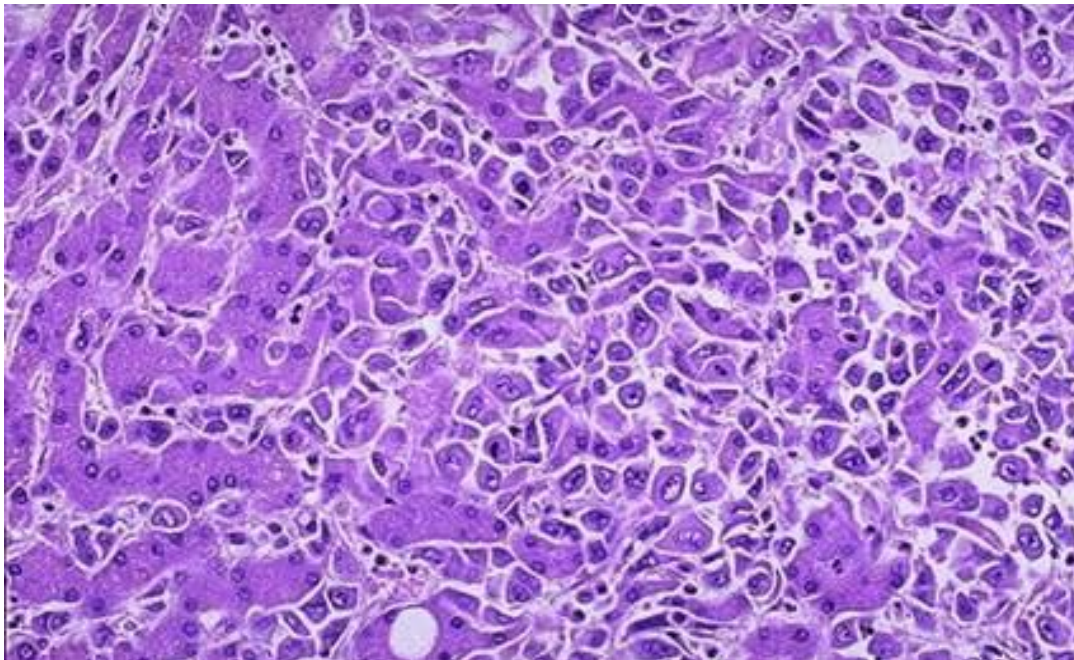


Hepatocellular Carcinoma



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Hepatocellular Cancer



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Liver



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HCC in HCV

- Demography
 - o Patient
 - Alcohol drinking (heavy > 50 g/d)
 - Male gender
 - Larger BMI
 - o Older age of HCV onset and diagnosis
 - o HCV infection for > 25 years
 - o Absence of previous HCV treatment
 - o Failure of HCV to respond to IFN (interferon)
- Pathology
 - o HCC in HCV may be associated with:
 - Greater degree of hepatic fibrosis
 - Iron overload

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The presence of active inflammation increases the risk of HCC in the patient with chronic HCV infection.

- Give the type of T cells as well as adjunct inflammatory markers which reflect a poor prognosis in HCV associated HCC
 - o CD68-positive T cells
 - o 8-OHdG (8-hydroxydeoxyguanosine) DNA adducts
 - o 4-HNE (hydroxynonenal) protein

"The difference between how a person treats the powerless versus the powerful is as good a measure of human character as I know."

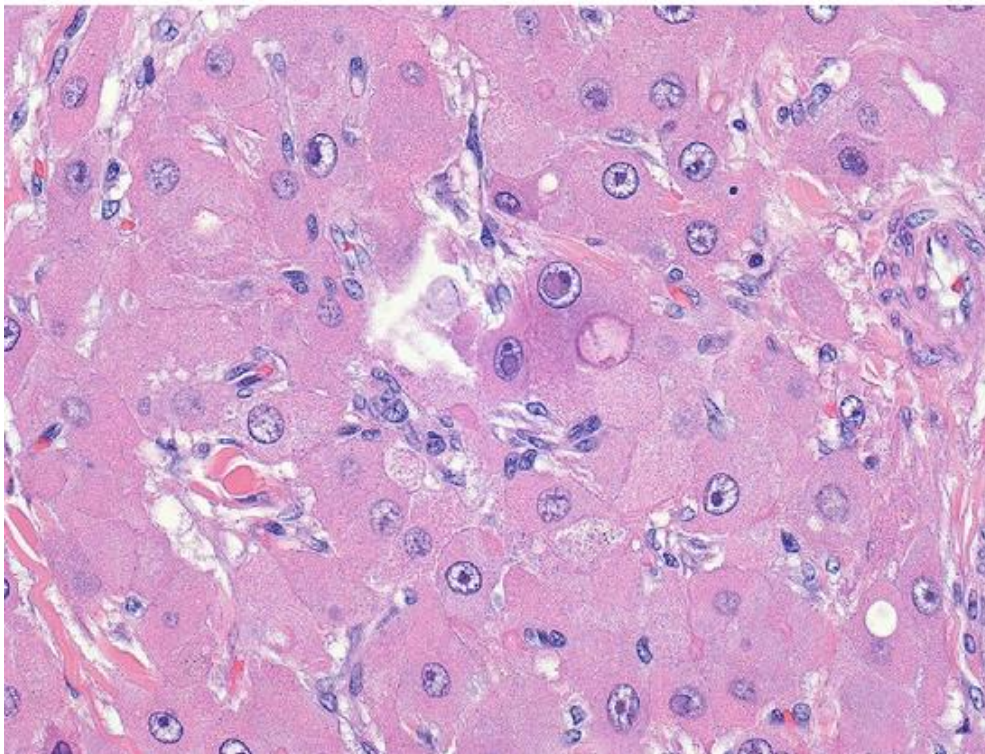
Robert Sutton



Fibrolamellar HCC

- Diagnostic imaging
 - o CT, contrast enhanced
 - Mass
 - Well-circumscribed
 - Central scar
 - Calcification
 - No underlying cirrhosis
- Histopathology
 - o Hepatocytes
 - Large
 - Eosinophilic
 - o Cytoplasm
 - Large mitochondria
 - Hyaline bodies
 - o Fibrous stroma
 - Lamellar fibrous tissue separates clusters of tumour cells

Fibrolamellar HCC

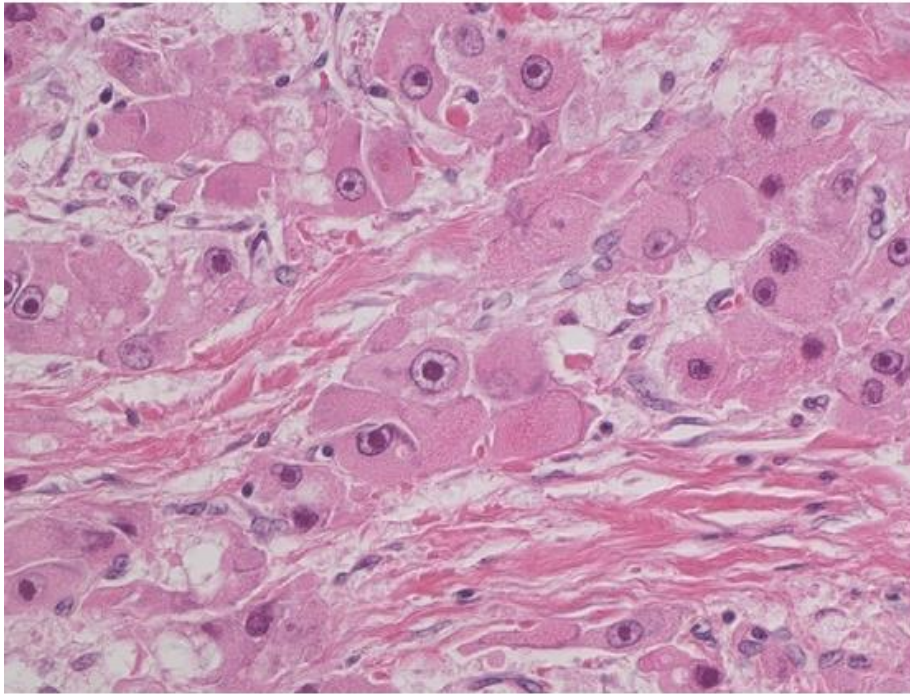


- o Large eosinophilic tumour cells
- o Large vesicular nuclei
- o Large nucleoli

Source: Torbenson M. Scientifica, vol. 2012, Article ID 743790, 15 pages, 2012.



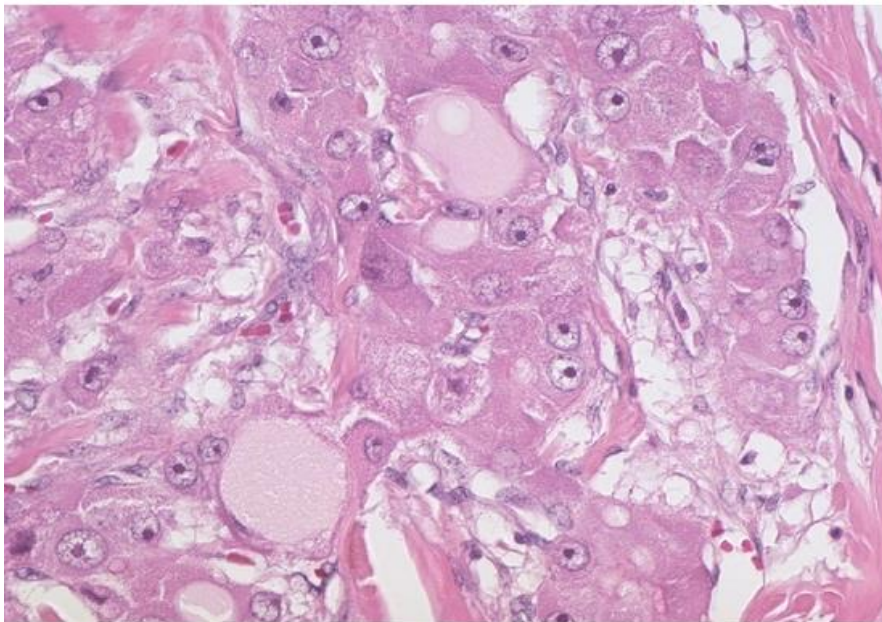
Fibrolamellar HCC



- o Intratumoral fibrosis is a typical finding in fibrolamellar carcinoma

Source: Torbenson M. Scientifica, vol. 2012, Article ID 743790, 15 pages, 2012.

Fibrolamellar HCC



- o Cytoplasmic inclusions with distinct borders
- o Typically a "pale" grey colour

Source: Torbenson M. Scientifica, vol. 2012, Article ID 743790, 15 pages, 2012.



- Give the non-pathological characteristics which differentiate FLM (fibrolamellar HCC) from conventional HCC.
 - o Younger persons, often female
 - o Not associated with
 - Cirrhosis
 - HBV, HCV
 - o No AFP secreted
 - o Better prognosis

Cholangiocarcinoma

- Demography
 - o Prevalence in North America, 1/10⁵
 - o Cholangiocarcinoma is the second most common hepatic malignant tumour.
- Diagnostic Imaging

Intrahepatic Cholangiocarcinoma (IHC)

- o Locations
 - Hepatic duct bifurcation (Klatskin tumour)
 - Distal CBD
 - Intrahepatic (5-15%)
- o IDUS high frequency intraductal ultrasound
- o Infiltrating or polypoid mass
- o Lobular atrophy hepatic segment
- o Metastases
 - Regional nodes
 - Portacaval area
 - Peri pancreatic regions
- o MRI
 - MRI "... is currently the imaging technique for cholangiocarcinoma" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 1174).
 - T₁ – weighted
 - Polypoid mass in bile duct lumen
 - Non-specific changes
 - Hypointense (low signal intensity)
 - Bile duct thickening
 - Mass may surround PV / HA
 - Lobular atrophy



- T₂ – weighted
 - Hyperintense (white) mass
 - Heterogeneous
 - Multiple dilated ducts may converge to central mass
- Mucin
 - Elongated filling defect
- o CT
 - MRCP is best exam for intrahepatic cholangiocarcinoma (IHC)
 - Hypoattenuating / isoattenuating
 - Delayed – hyperattenuating (from fibrotic [desmoplastic] reaction)

.....

Distinguishing Diagnosis: Intrahepatic cholangiocarcinoma (IHC)

- o HCC – hypervascular
 - o Mucinous cystic neoplasms – cystic, lobular (septated)
 - o Metastasis – cannot be distinguished from IHC
-

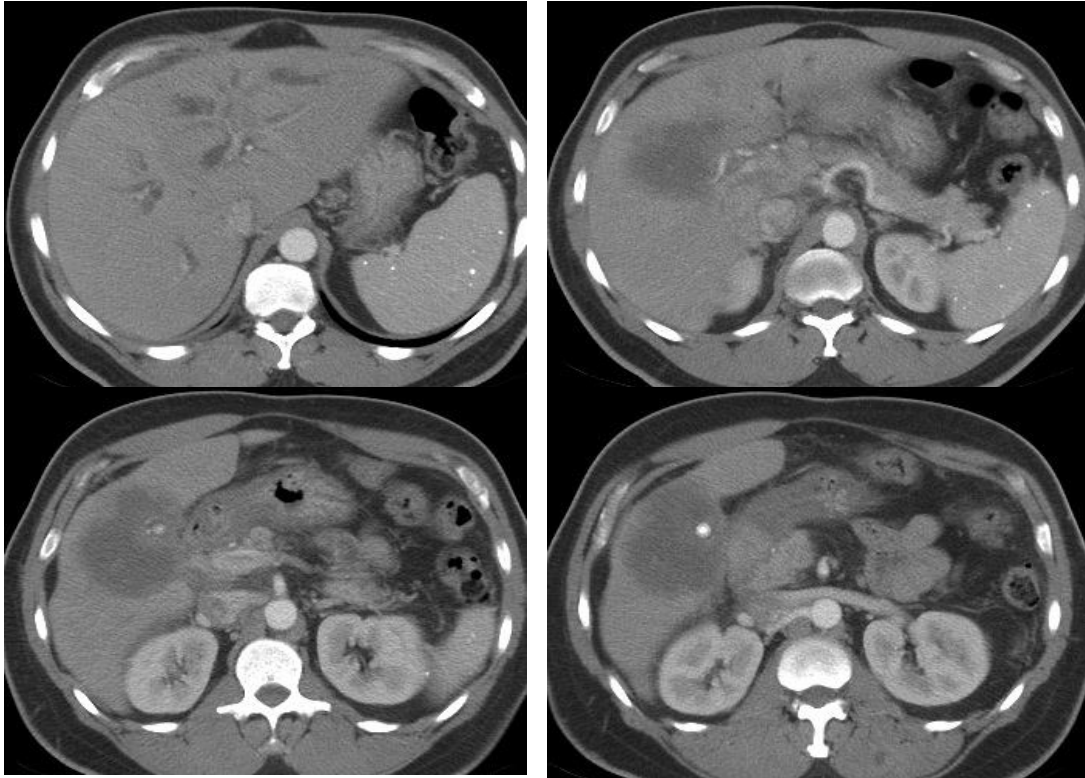
o Cytology

	Sensitivity
- Cytology alone	30%
- Cytology, brushings and biopsies	40% to 70%

- o PET
 - ↑ uptake (sensitivity 93%)
- o May be very subtle infiltrative pattern
- o Fibrous composition
- o Mat narrow other tubular structures
 - Portal vein – look for thrombus
 - Hepatic artery – “sawtooth” pattern
 - Biliary strictures
- o CT
 - Mild PV enhancement, may be more conspicuous on delayed images

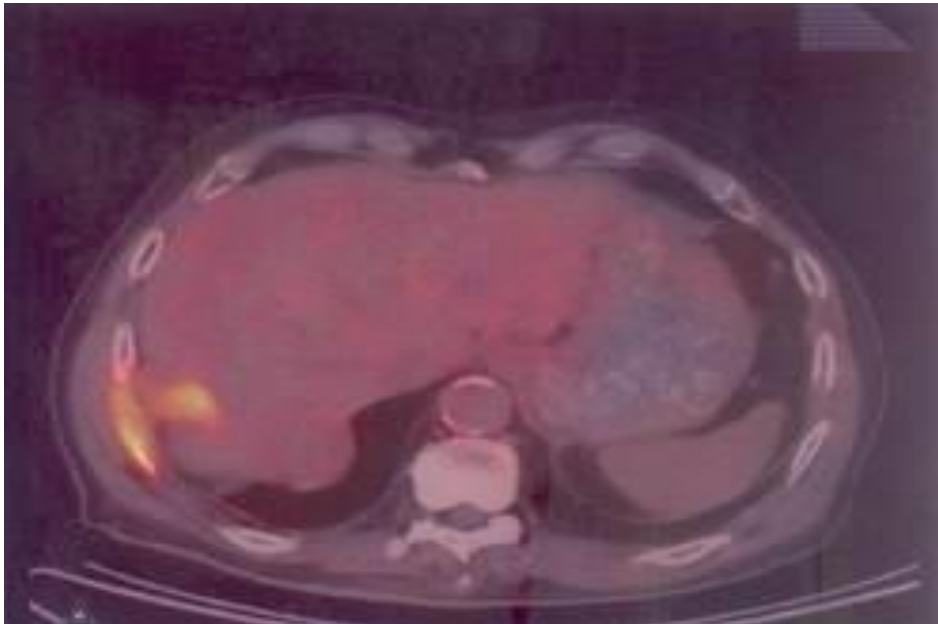


Cholangiocarcinoma



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Cholangiocarcinoma

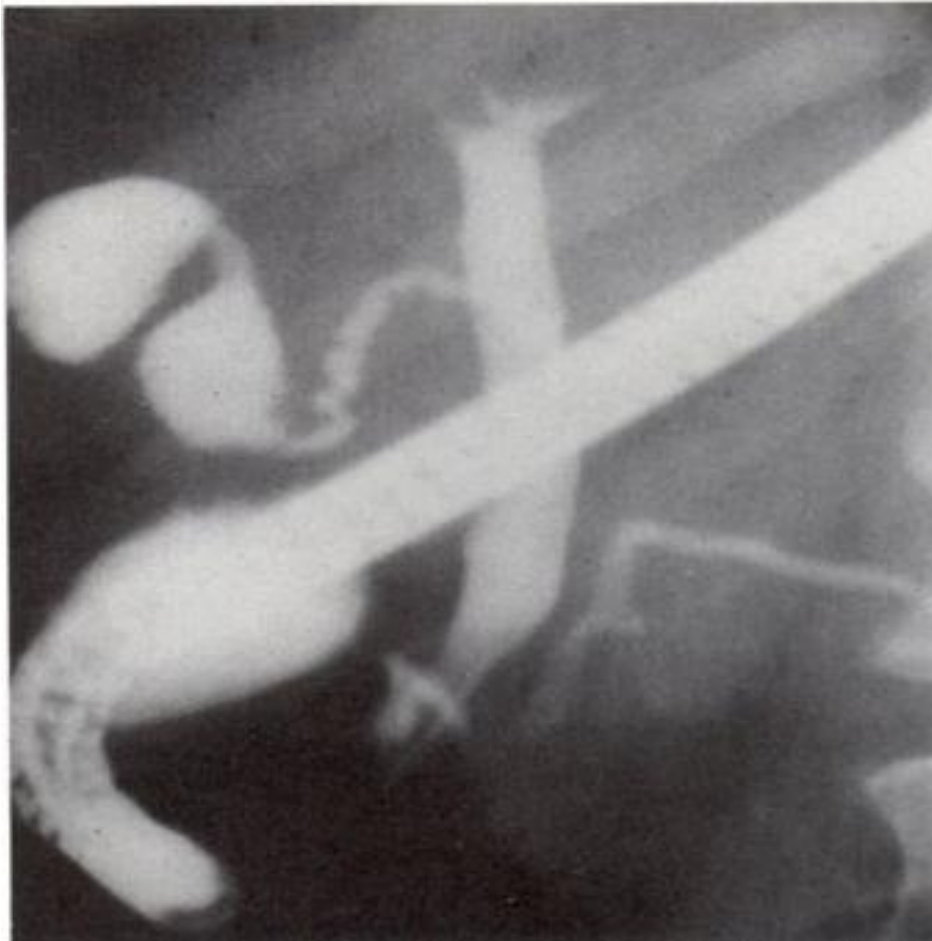


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- o ERCP, MRCP
 - Intraluminal filling defect
 - Infiltrating (thickening of duct wall)
 - Polypoid within duct lumina
 - Extension (along duct into liver, or into vessels)
 - Commonly at bifurcation of R/L hepatic ducts ("Klatskin" type)
 - When in peripheral ducts – proximal duct dilation

Cholangiocarcinoma



Source: Teriaky A (2017). Approach to Patients with Hepatic Mass. In Al-Judaibi B and Thomson ABR (Eds). Medical Mini Review Series in Hepatology: Efficient Refresher for the Busy Clinical Gastroenterologist (volume 4), page 251.



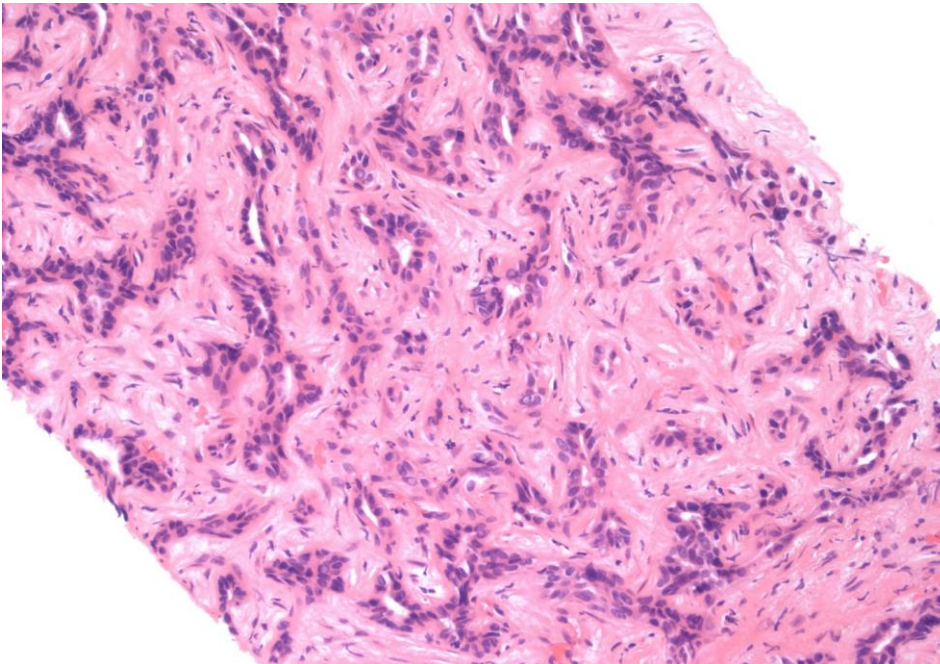
➤ Pathology

- o Subtypes
 - Intrahepatic
 - Extrahepatic
 - Hilar (Klatskin tumour)
 - Distal bile duct
 - Four types, by Bismuth - Corlette Classification (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 9th Edition. Saunders / Elsevier, Philadelphia, 2010, Table 69.3, page 1173 for details of Diagnostic Criteria for Cholangiocarcinoma.
- o Perihilar cholangiocarcinoma is extrahepatic in location, but the ICD classification considers that this an intrahepatic tumour
- o Sampling techniques
 - Brushings → cytology specimen
 - FNA (fine-needle aspiration) → cytology specimen
 - Percutaneous biopsy → histology specimen

➤ Cyto / histopathology

- o Cytology specimens may contain few cells (paucicellular) because much of the tumour may consist of the desmoplastic stromal reaction
 - May be difficult / impossible to distinguish from metastatic adenocarcinoma – biopsy report may read “adenocarcinoma, consistent with upper GI or pancreaticobiliary origin”. Pancreaticobiliary origin includes intrahepatic cholangiocarcinoma.

Cholangiocarcinoma

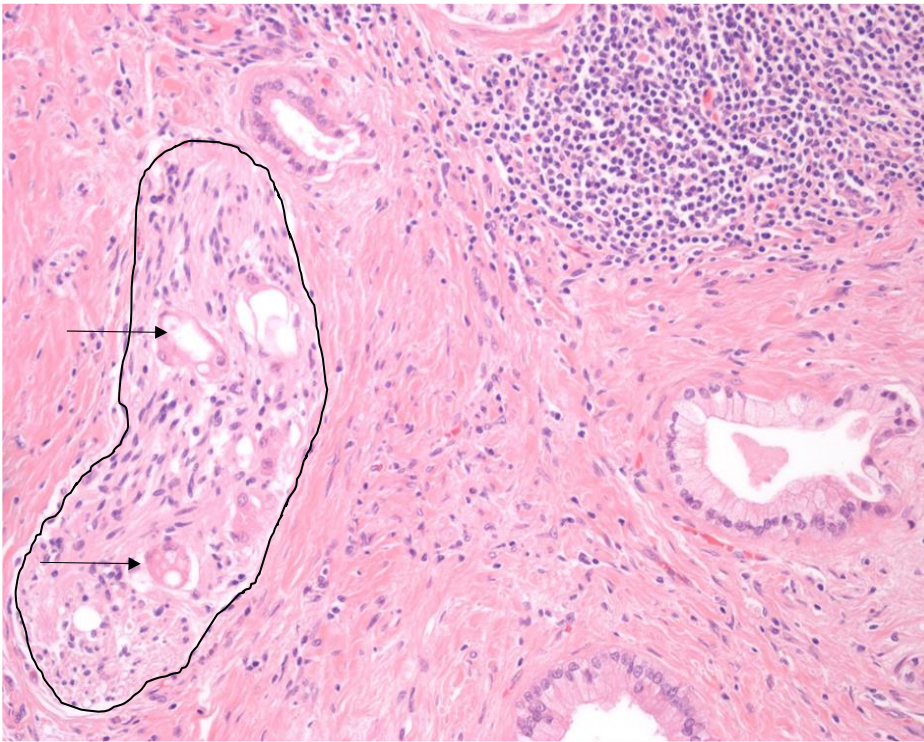


Characterized by irregular, infiltrating glands in a desmoplastic stroma (H&E 200X)

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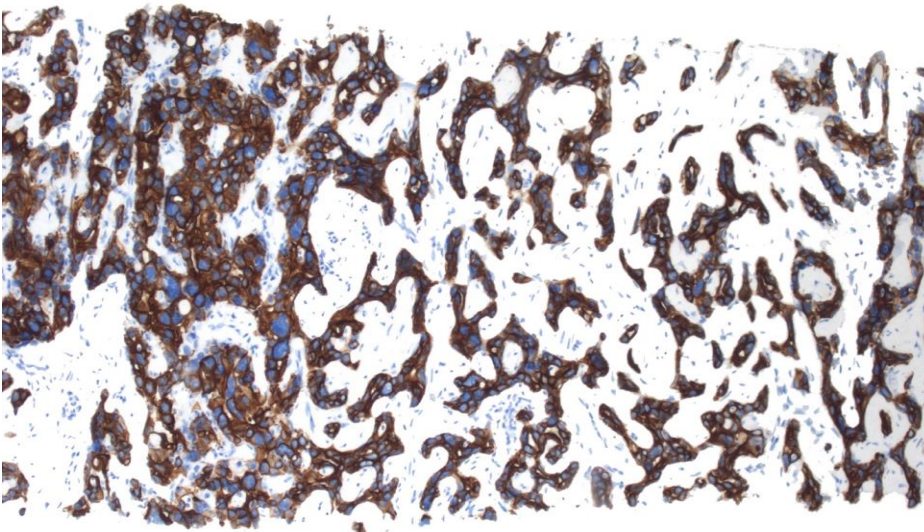
Cholangiocarcinoma



Malignant glands (arrows) infiltrate a nerve (outlined); perineural space invasion is a common feature of pancreaticobiliary carcinomas (H&E 200X)

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Cholangiocarcinoma



Diffuse, strong CK7 positivity (CK7 100X)

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Post-Transplant Lymphoproliferative Disorder (PTLD)

- Demography
 - o There is a 10-fold increased risk of non-Hodgkins lymphoma (B-cell, related to EBV) after liver transplantation, giving a relative risk of 3%
 - o Most commonly occur in first 18 months post LT
 - o More immune suppression in heart transplant patients, so more PTLD
 - o 5 year survival rate, 50%
- Pathology
 - o Posttransplant lymphoproliferative disorders (PTLDs) are characterized by abnormal , heterogeneous lymphoid proliferations (usually B-cells, and usually EBV-positive) Different types can occur in the liver, including monomorphous and polymorphous

Epithelioid Hemangioendothelioma

- ❖ Low grade vascular malignancy with behaviour / prognosis in between hemangioma and angiosarcoma
- ❖ Contrast-enhanced CT
 - o Masses
 - o Multiple
 - o Confluent
 - o Hypoattenuation (dark)
 - o Peripheral
 - o Capsule retraction
- ❖ Pathology
 - o Lesion composed of dendritic or epithelioid cells with intracytoplasmic vacuoles (capillary lumina) containing red blood cells
 - o Immunohistochemistry for vascular markers is positive

Angiosarcoma

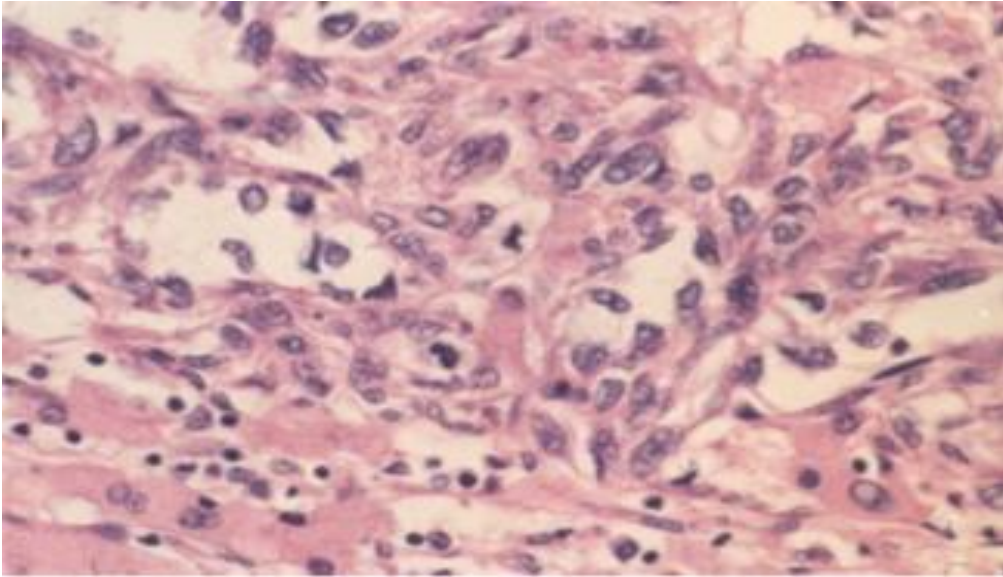
Useful Background: Angiosarcoma may be associated with

- o HCC
- o Cholangiocarcinoma
- o Lung cancer
- o Peritoneal tumours



- Diagnostic Imaging
 - o Unenhanced CT
 - High attenuation (white)
 - Heterogeneous

Angiosarcoma



- o Hematoxylin and eosin stain ($\times 400$); typical features of hepatic angiosarcoma
 - Sinusoidal and spindle-shape growth of the malignant endothelial cells
 - Atrophy of liver cells
 - Disruption of the hepatic plates (not shown here)

Printed with permission: Li Q, et al. Int Semin Surg Oncol 2007; 4: 3.

Hepatic Metastases

- ❖ Contrast – enhanced CT (portal-venous phase)
 - o Hypovascular
 - Masses
 - Often multiple
 - Hypoattenuating (dark)
 - Calcified
 - Primary site
 - Colon – large, calcified
 - Stomach, small bowel – less calcification
 - Breast, lung – small diffuse / infiltrative
 - o Hypervascular (CT, arterial phase)



- o Types
 - Adenocarcinoma
 - Colon
 - Pancreas
 - Upper GI tract
 - Lung
 - Breast
 - Prostate
 - Others less commonly
 - Neuroendocrine tumours
 - Melanoma

❖ Ultrasound

- o Mass – hyperchoic (white)
- o Halo – hypoechoic (dark)
- o Arterial phase hyperenhancing cystic
- o Portovenous phase hyper → isoattenuating

SO YOU WANT TO BE A HEPATOLOGIST!

- Give which is the better test to assess the size and fibrosis of the liver in a patient with suggested cirrhosis, abdominal ultrasound with doppler, or an ultrasound.
 - o Meta-analysis supports transient elastography to diagnose cirrhosis with a high diagnostic accuracy independent from the underlying liver disease (Friedrich-Rust, et al. *GE* 2008;134:960-974), and is not used to assess liver size.

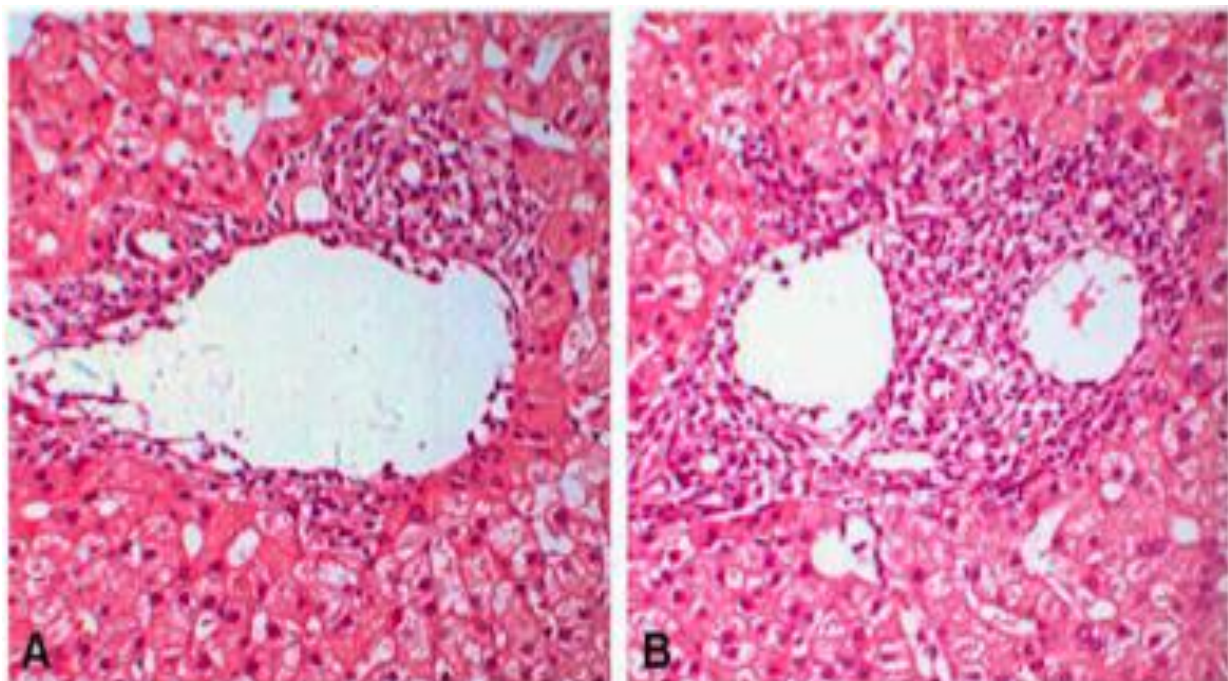


LIVER TRANSPLANTATION (LT)

➤ Histopathology

- Give the histopathological features of acute cellular rejection after Liver Transplantation (LT).
 - o Three features are required to make a diagnosis of acute cellular rejection:
 1. Rejection type portal inflammatory infiltrate
 2. Bile duct damage
 3. Endothelialitis (endotheliitis)

Liver Transplantation Rejection



The histopathological features of acute cellular rejection. Typical histopathological changes, including portal inflammation, bile duct inflammation / damage and venous endothelialitis, so called “triads,” appeared in mild (A, RAI = 4) and moderate (B, RAI = 7) acute cellular rejection (H&E, $\times 200$).

Printed with permission: Cheng L, et al. Diagnostic Pathology 2012; 7:148.

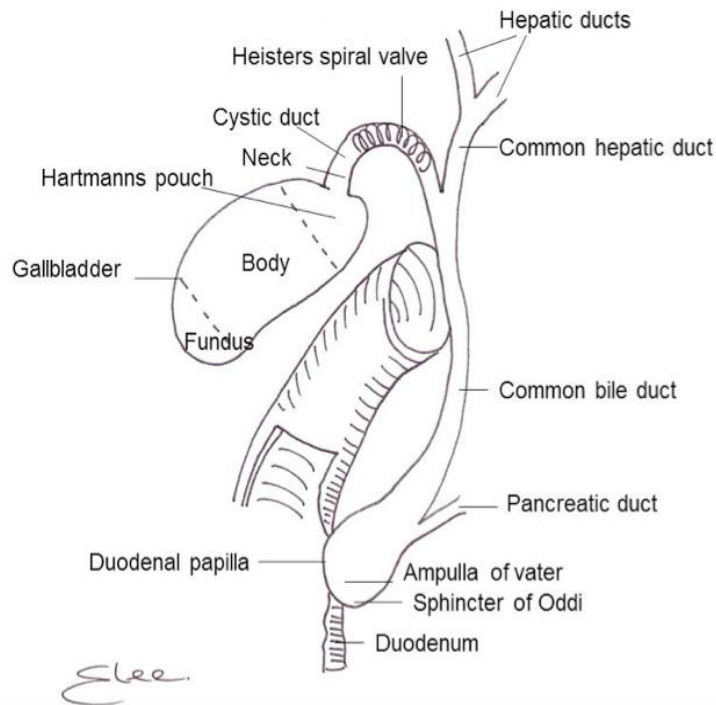




NORMAL

➤ Anatomy of Hepatobiliary Tree and Gallbladder

- o The function of the gallbladder is to concentrate and store bile, and to release the bile at appropriate stimulated intervals.



Adapted from: Sherlock and Dooley, Figure 1.6, page 3, 11th Edition, 2002

- o Bile ducts and Gallbladder (from small to large)
- o Canaliculus
- o Terminal channels (aka canals of Hering)
- o Bile ductules
- o Interlobular bile ducts
- o Hepatic ducts (right and left)
- o Common hepatic duct
- o Cystic duct (ends in gallbladder which can be roughly subdivided into neck, infundibulum, Hartmann pouch, body & fundus)
- o Common bile duct (joins with pancreatic duct before exiting the pancreas in 80% of people)
- o Ampulla of Vater

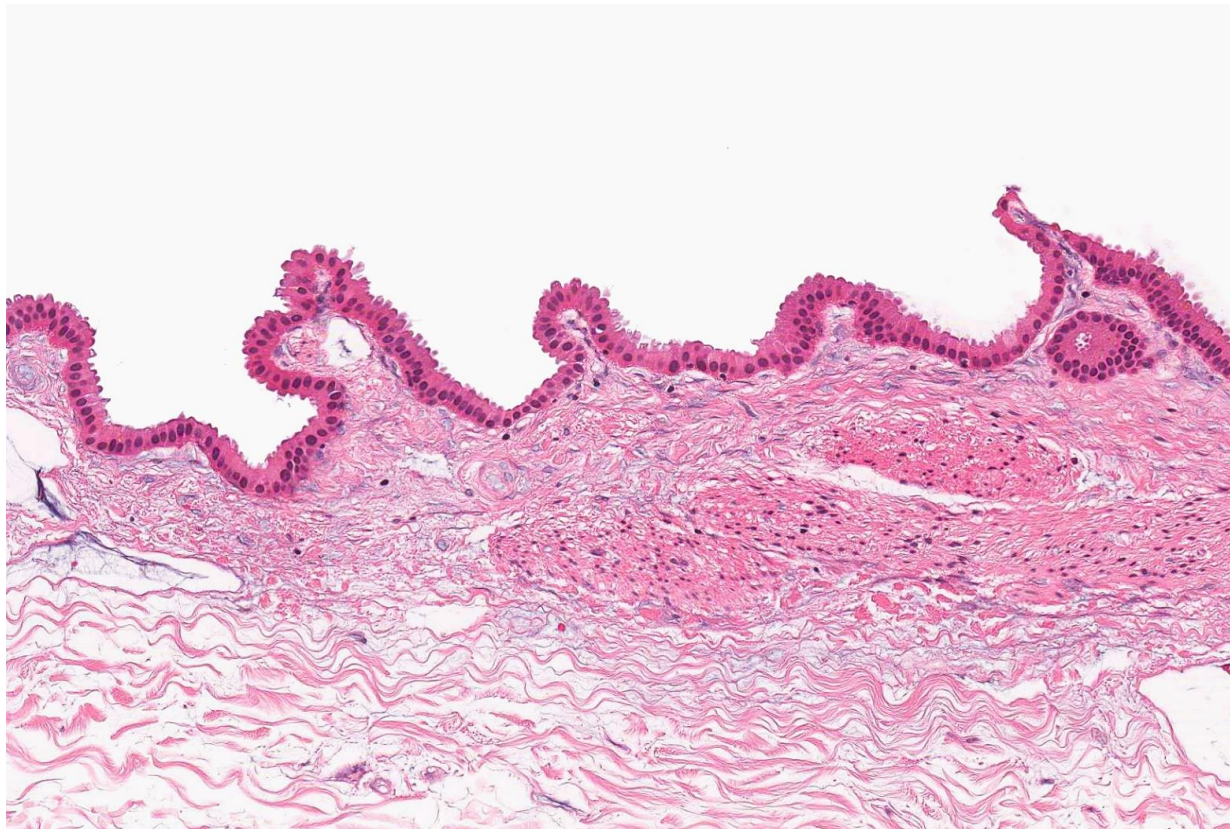


In the context of the anatomy of the gallbladder, give what is the **Hartmann pouch**, and what is its clinical significance?

- o “Hartmann pouch is a bulging of the inferior surface of the infundibulum that lies close to the neck of the gallbladder” (Feldman M., et al. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th Edition. *Saunders / Elsevier*, Philadelphia, 2010, page 1049).
- o Gallstones may become impacted in the Hartmann pouch, which blocks the cystic duct, and leads to cholecystitis.

➤ Histopathology

Normal gallbladder lined by biliary type epithelium (H&E, 200X)



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GALLSTONES (CHOLELITHIASIS)

➤ Definition

- o Stones in the biliary tree usually arise from cholelithiasis.
- o However, multiple stones in the biliary tree, especially in the left hepatic system, suggests recurrent pyogenic cholangitis (RPC), aka “oriental cholangitis”.
 - RPC may be caused by infections, such as *Clonorchis sinensis* and *Ascaris lumbricoides*, which lead to the formation of intraductal brown pigment stones
 - Because of the recurrent episodes of cholangitis, strictures may occur in the biliary tract

➤ Types

- | | | |
|---------------------------------|--|--|
| o Composition | <ul style="list-style-type: none">– Cholesterol– Black pigment– Brown pigment– Mixed– Rare | <ul style="list-style-type: none">▪ Crystals of cholesterol monohydrate▪ Calcium bilirubinate▪ Calcium carbonate / phosphate▪ Polymerised bilirubin▪ Bacterial degradation products of biliary lipids, calcium salts of fatty acids, unconjugated bilirubin and precipitated cholesterol▪ Calcium carbonate▪ Calcium-fatty acids |
| o Site | <ul style="list-style-type: none">– Intrahepatic– Gallbladder– Bile duct | <ul style="list-style-type: none">▪ Brown pigment▪ Cholesterol >> black pigment▪ Mixed |
| o Physical state of cholesterol | <ul style="list-style-type: none">– Low concentrations– Critical micellar concentration (CMC) | <ul style="list-style-type: none">▪ Simple micelles are spontaneously formed with BA monomers<ul style="list-style-type: none">– Small (~3 nm diameter)– Disk-like macromolecular aggregates– Solubilize and incorporate▪ Cholesterol▪ Phospholipids (mostly lecithin, with some phosphatidylethanolamines and sphingomyelin) to form mixed micelles |



- Biliary vesicles
 - Secreted by hepatocytes
 - Composed of cholesterol monohydrate crystals and phospholipids
 - Large (40-100 nm diameter)
 - Multilamellar spherical structures
 - As the gallbladder (GB) absorbs water, the GB bile becomes concentrated
 - The stability of the biliary vesicles determines the stability of bile molecular rearrangements such that in high concentrations of BA, the biliary vesicles may transform into mixed micelles
- Phase diagram and triangular co-ordinates
 - The maximal solubility of cholesterol is determined by the relative molar percentage of cholesterol, phospholipids and bile acids
 - This allows for the quantification of the degree of saturation of bile with cholesterol
 - This quantification of cholesterol saturation is CSI (cholesterol saturation index), aka the lithogenic index
 - Examples of CSI
 - < 1 unsaturated
 - 1 saturated
 - > 1 supersaturated (↑ risk of forming gallstones)

➤ Diagnostic imaging

- ERCP, MRCP, contrast-enhanced CT
 - Duct dilation (extra- / intrahepatic ducts)
 - Filling defects in ducts
 - May be fluid around stone
 - Target sign
 - Fluid all around stone
 - Crescent sign
 - Fluid around part of stone
 - Pseudocalculus
 - Only the superior part of the filling defect outlined in pseudocalculus (caused by spasm of Sphincter of Oddi), whereas both superior and inferior parts of the filling defects seen with stone

- Transhepatic cholangiogram
 - Narrowing of distal portion of common bile duct (CBD); dilation of intrahepatic bile ducts

Abdominal Ultrasound of Stones	Sensitivity
In GB	95-98%
In CBD	50%



- o It has been suggested that an abdominal ultrasound is the best test to exclude other intra-abdominal conditions which may give similar clinical findings of RUQ pain, fever, leucocytosis, hyperamylasemia (or elevated serum lipase concentration).
- o However, this approach can be challenged based on the performance characteristics of abdominal ultrasound, CT scan, and hepatobiliary scanning.
- o ERCP “gallstone pancreatitis” (GSP) – only 10% have stone in CBD
 - When to suspect GSP
 - Jaundice
 - LEs increasing

} ERCP + Stone removal

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Cholescintigraphy (aka hepatobiliary scintigraphy) has a sensitivity of about 95% and a specificity of about 90% for acute cholecystitis, and a normal scan virtually excludes acute cholecystitis.

- Give the names of the chemicals used for hepatobiliary scintigraphy.
 - o HIDA 99 m Tc-labelled hydroxyl iminodiacetic acid
 - o DISIDA (diisopropyl iminodiacetic acid)
- In the context of an abdominal ultrasound performed for cholelithiasis, give the meaning of the wall-echo shadow sign (aka “double-arc shadow”)
 - o The wall-echo shadow sign is the presence of echogenic stones and acoustic shadowing in a contracted gallbladder filled with stones.

Please see Feldman M, et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier 2010, Table 67.2, for details of the diagnostic criteria for acute acalculous cholecystitis.

Useful Quotes

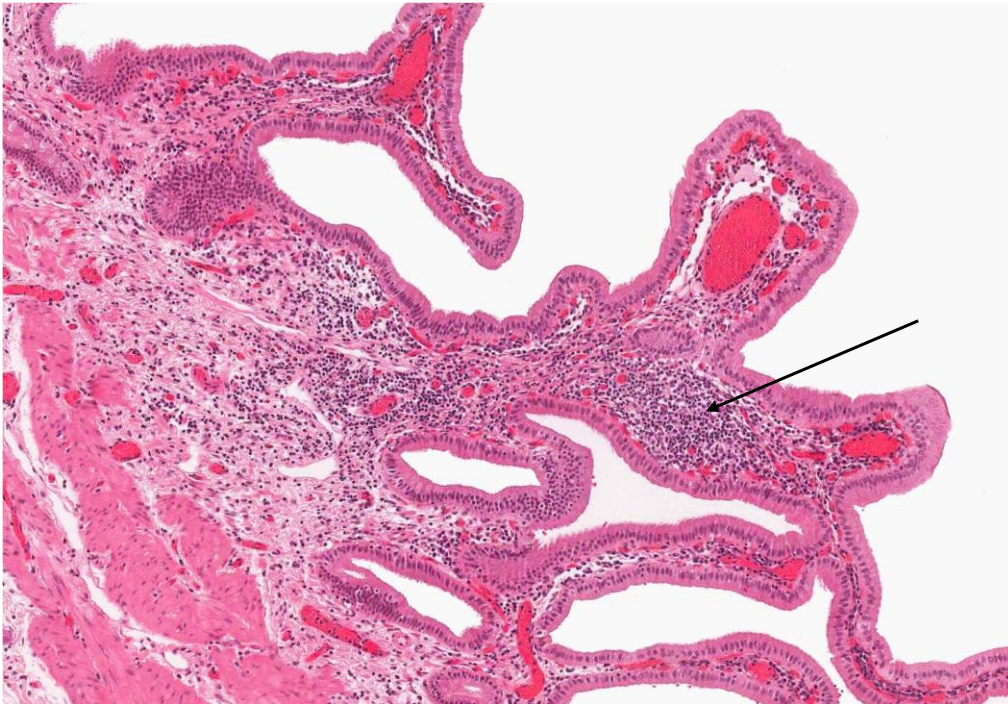
“..... for the average patient, early operation [for acute cholecystitis] is preferable because

- The total length of hospitalization [is] reduced
- Costs are reduced
- Morbidity is less, and
- Deaths related to progressive acute cholecystitis are prevented”

Feldman M, et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier 2010, page 1130.



➤ Histopathology



Gallbladder lined by biliary type epithelium with a chronic inflammatory cell infiltrate in the lamina propria (arrow) indicating chronic cholecystitis, in this case, secondary to gallstones (H&E, 100X)

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Recurrent Pyogenic Cholangitis (“Oriental Cholangiohepatitis”)

- o Percutaneous Cholangiogram, CT, Ultrasound
 - Intra- / extrahepatic duct pigmented stones
 - Duct dilation
 - Focal strictures
 - Straight, rigid IHDs
 - Tapering (pruning) of ducts
 - Decreased arborisation of ducts
 - Gallstones
- o MRI
 - T₁ – weighted
 - Dark tubular structures
 - T₂ – weighted
 - Dark tubular structures
 - Gadolinium – enhanced
 - Stones in dilated ducts



Mirizzi Syndrome

- Diagnostic imaging
 - o ERCP, CT, ultrasound
 - Filling defects (stones) impacted in cystic duct (CD) or head of gallbladder, secondary narrowing of common bile duct (CBD) or common hepatic duct (CHD) by inflammatory stricture.

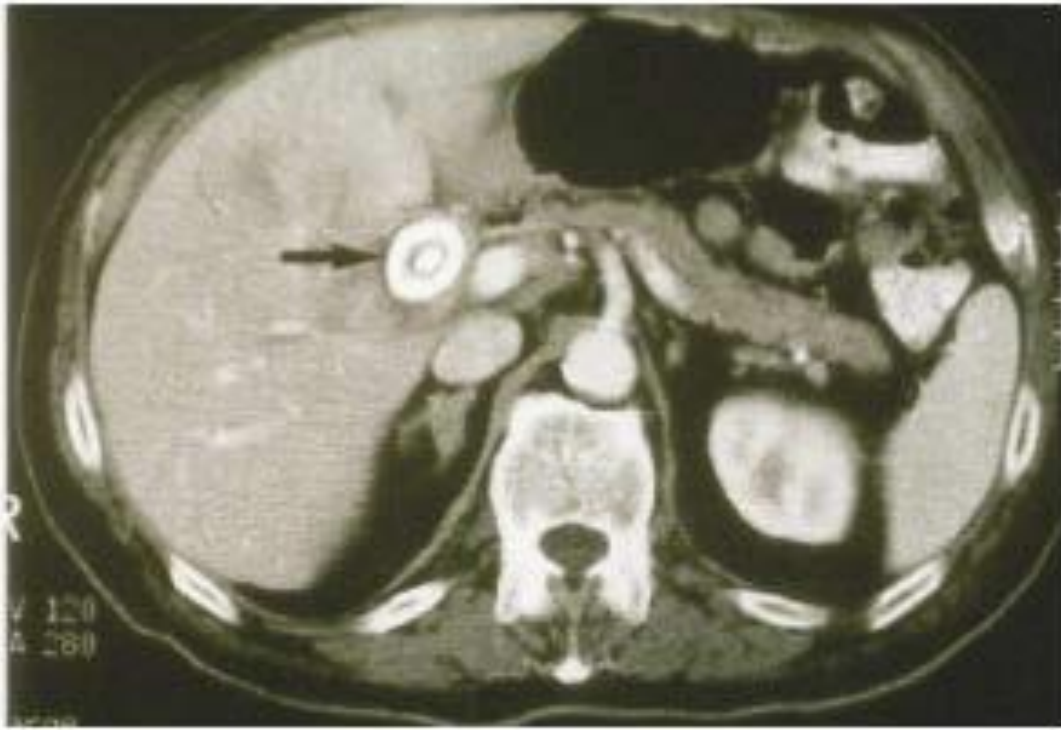
Mirizzi Syndrome: ERCP Findings



Courtesy of Dr. Terry Ponich, Western University, London (ON)



Mirizzi Syndrome: CT Findings



Courtesy of Dr. Terry Ponich, Western University, London (ON)

Acute Calculus Cholecystitis

- Definition
 - o Acute inflammation of the gallbladder wall due to obstruction of the cystic duct by gallstones
- Diagnostic imaging
 - o Ultrasound
 - Lumen-cholelithiasis or sludge
 - Wall-thickening / edema
 - Striations
 - Murphy sign positive when using ultrasound probe
 - Decreased hepatic echogenicity (dark) around gallbladder ("perihepatitis")
 - Pericholecystic fluid
 - o Cholescintigram
 - Non-visualization of gallbladder up to 4 hours
 - Enhanced uptake of tracer into the liver near the inflamed gallbladder (perihepatitis)



Gallstones and Pericholecystic Fluid (Suggestive of Acute Cholecystitis)



- o CT and ultrasound findings. Top figures, left and right: CT showing a distended gallbladder wall with decreased contrast enhancement of the wall and pericholecystic fluid
- o Bottom left: Ultrasound showing normal mild gallbladder wall thickening with irregular appearance of the gallbladder.

Printed with permission: Dhir T and Schiowitz R. Int J Surg Case Reports 2015;11:46-49.

“The Man Who Has Confidence In Himself Gains The
Confidence Of Others.”

Hasidic Proverb

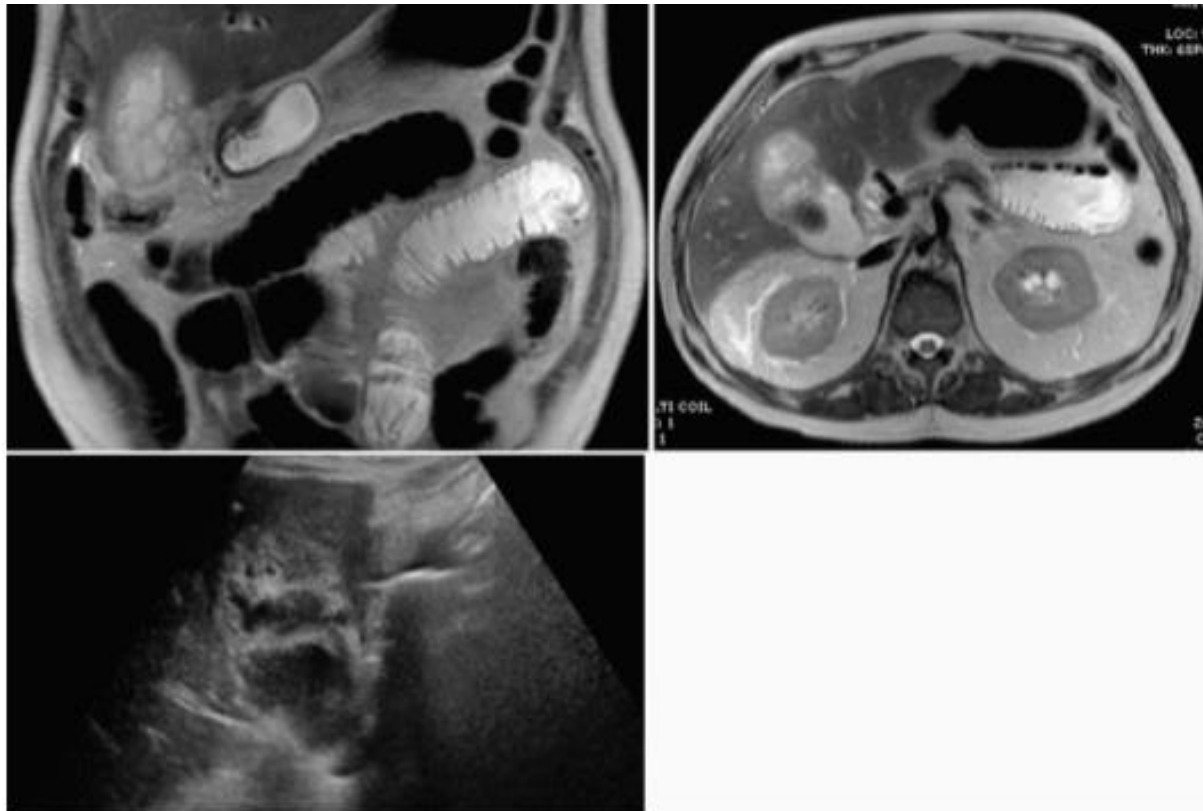


Gangrenous Cholecystitis

➤ Diagnostic imaging

- o Ultrasound contrast – enhanced CT
 - Wall – thickening (intramural edema; white [water attenuation])
 - Lumen
 - Striated appearance
 - Echogenic (light) filling defects (sloughed gangrenous mucosa)
 - Pericholecystic
 - Fluid collection (from perforation)
 - Fluid may collect in “Morrison pouch” (posterior subhepatic space)
 - May see associated gallstones

Gangrenous Gallbladder



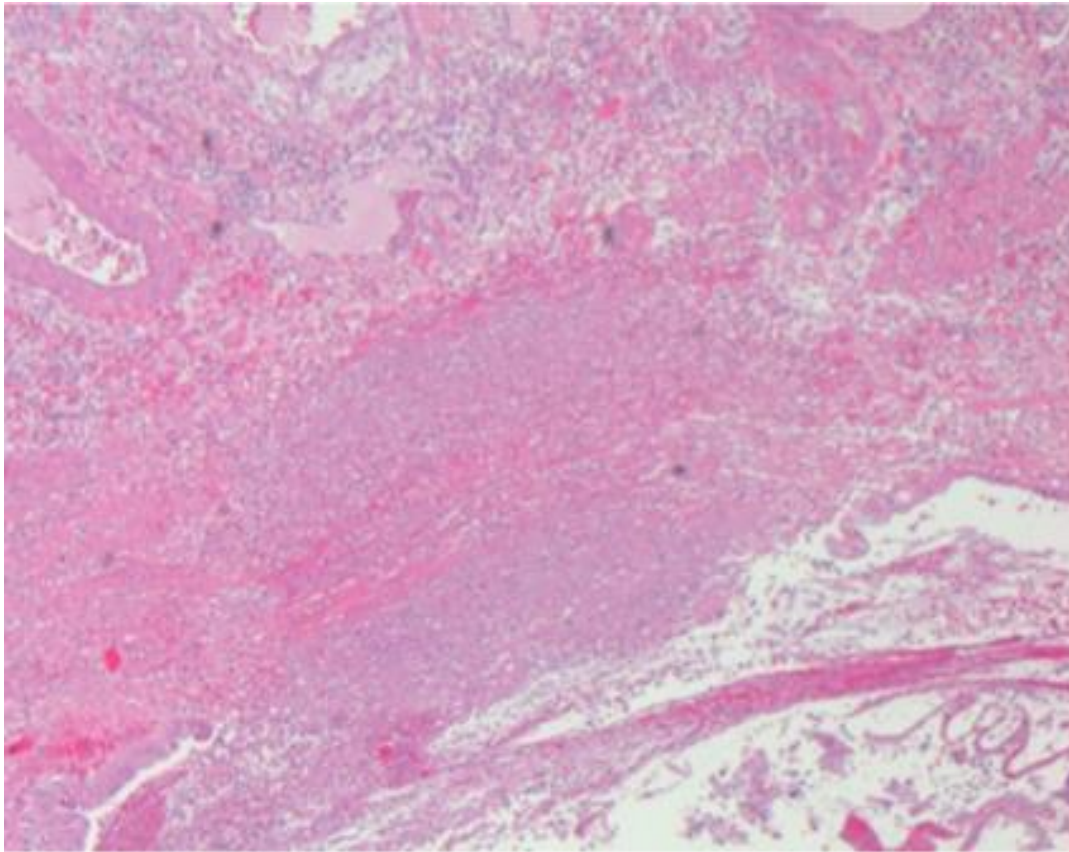
- o Left to right: MRCP and ultrasound imaging. Top left and right.
 - MRCP showing thickened gallbladder wall, lack of wall enhancement and septated surface with diffuse inflammation
 - Bottom left: Ultrasound showing thickened wall, maximally dilated at 1.2 cm with multiple septations.

Printed with permission: Dhir T and Schiowitz R. Int J Surg Case Reports 2015;11:46-49.



➤ Histopathology

Severe Acute Cholecystitis



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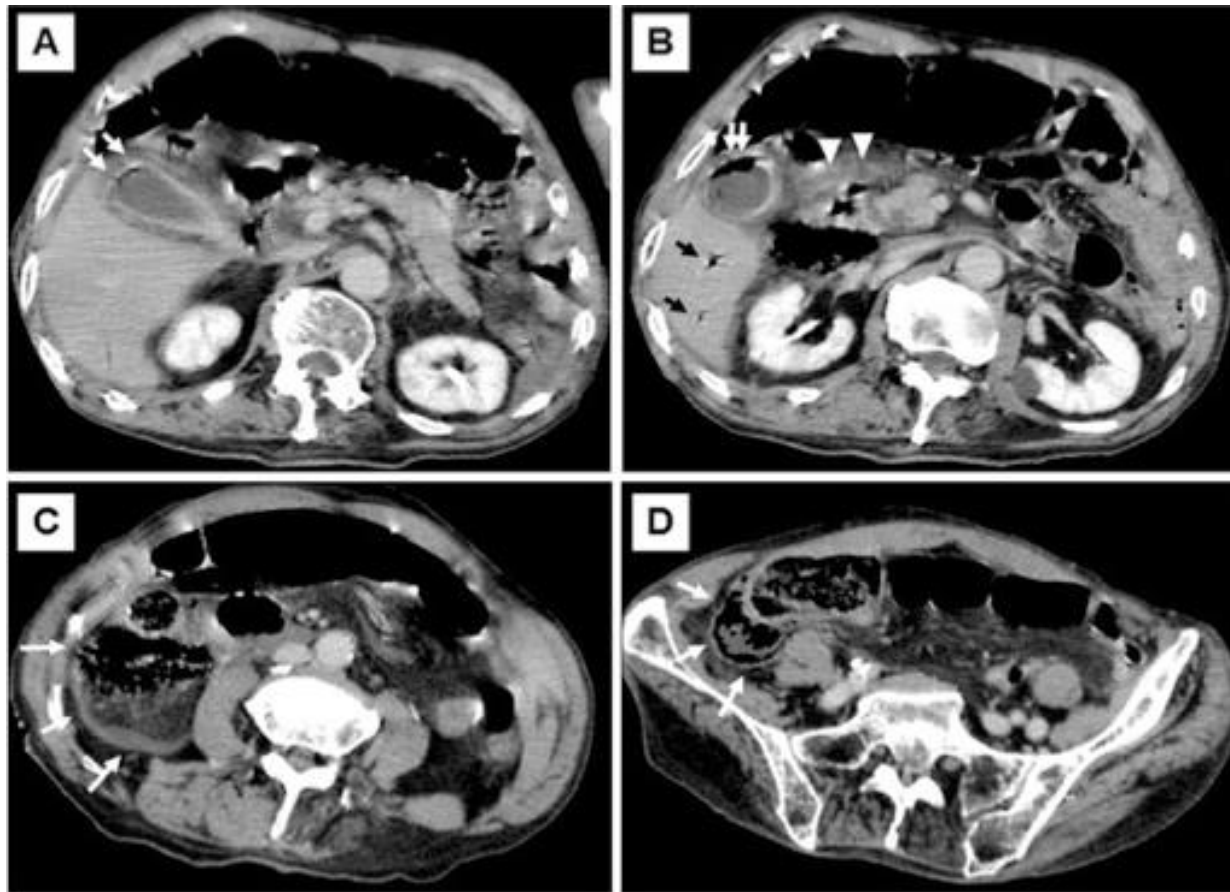
Emphysematous Cholecystitis

➤ Diagnostic imaging

- o Abdominal plain radiograph
 - Air
 - In gallbladder wall
 - In surrounding tissue (extraluminal air in pericholecystic tissue)
 - Produced from gas-forming *Clostridium perfringens*
- o Ultrasound
 - Air in gallbladder wall: posterior “dirty” shadowing, echogenic (white) rim



Emphysematous Cholecystitis



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Abdominal CT findings

- o A: CT shows a thickened wall and intramural air of the gallbladder, suggesting emphysematous cholecystitis (white arrows)
- o B: Pneumobilia was detected in the intrahepatic bile duct (black arrows). The gallbladder contained air within the lumen (white arrows). Subserosal free air was detected in the hepatoduodenal ligament and around the pancreas head (white arrowheads)
- o C: Massive pneumoretroperitoneum was observed behind the right-sided colon (white arrows)
- o D: Pneumoretroperitoneum extended to the retroperitoneal space behind the ascending mesocolon, bordered by the cecum and iliopsoas muscle (white arrows)

Printed with permission: Yagi Y, et al. BMC Gastroenterology 2015;15:114.



Acute Acalculous Cholecystitis

- Definition
 - o Acute inflammation of the gallbladder wall without obstruction of the cystic duct by gallstones
- Diagnostic imaging
 - o Ultrasound, CT, cholescintigraphy
 - Inflammatory changes in wall of gallbladder (similar to acute cholecystitis with stones)
 - Cystic duct is not obstructed by stones
- Give the findings on abdominal ultrasound, CT scanning and hepatobiliary scanning which suggest the diagnosis of acalculous cholecystitis.

Acalculous cholecystitis is suggested by the following findings on diagnostic imaging

Abdominal Ultrasound	CT Scan	Hepatobiliary Scan
- o Gallbladder (GB) wall > 4 mm* - o Positive US Murphy sign - o Collection of pericholecystic fluid	- o GB wall > 4 mm - o Sloughed GB mucosa - o Pericholecystic fluid - o Intramural air	o Lack of “hot spot”** (failure of filling of GB, with passage of radionuclide into duodenum)

- Give the performance characteristics of diagnostic imaging tests for acalculous cholecystitis.

Diagnostic Imaging Test	Sensitivity	Specificity
o Abdominal ultrasound	67% to 92%	90%
o CT scan	> 95%	> 95%
o Hepatobiliary scan ¹	> 90%	90%

¹The morphine-augmented cholescintigraphy increases specificity to about 95%

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- In the context of acalculous biliary pain and in the setting of apparently an idiopathic post-cholecystectomy syndrome, give the meaning of the Meltzer-Lyon test.
 - o The Meltzer-Lyon test is the collection and staining of the stool to establish the presence of microlithiasis as a possible cause of post-cholecystectomy syndrome.
- Give the microscopic appearance of the substance examined in the Meltzer-Lyon test.
 - o The Meltzer-Lyon test involves collecting and examining the stools for microlithiasis in the setting of the post-cholecystectomy syndrome.
 - o Microscopic examination may show rhomboidal cholesterol crystals or granules of calcium bilirubinate.



Acalculous Cholecystitis



Source: Koufakis T and Gabranis I. Case Reports in Hepatology, vol. 2016, Article ID 6080832, 3 pages, 2016.

➤ Histopathology

- Give the histopathological changes in the gallbladder in chronic cholecystitis due to gallstones, versus acalculous cholecystitis.

Histopathology	Gallstone-associated Cholecystitis	Acalculous Cholecystitis
o Inflammation	Lymphoplasmacytic	Lymphoplasmacytic
o Muscle layer	↑↑	-
o Rokitansky-Aschoff sinuses	+	-
o Explanation		
- Rokitansky Aschoff sinuses		
▪ Diverticula of gallbladder mucosa into the muscle layer		



STRICTURES AND STENTS

The commonest places for an injured biliary tract / duct are the cystic duct and ducts of Luschka.

- Give the features in favour of using a plastic versus a metal stent for the management of a hilar bile duct tumour.

	Feature	Plastic	Metal
o Stricture	– Size	3 mm	10 mm
	– Head	< 6 mon (temporary)	> 6 mon (“permanent”)
o Stent	– Cost	~ \$300	~ \$1500
	– Covered	No	Yes
o Plastic stent can be inserted through a larger metal stent (3mm → 10 mm)			

- Give the anatomical sites which favour the use of covered versus uncovered metal stents.
 - o Covered
 - Head of pancreas (HOP) (↑ risk of migration)
 - o Uncovered
 - Intrahepatic duct

ERCP showing sphincterotome inside the common bile duct



- o Abdominal radiograph obtained during bedside ERCP showing sphincterotome inside the common bile duct (red arrow)
 - The migrated stent (yellow arrow) is seen with the distal tip inside the bile duct.

Source: Shah R and Qayed E. Case Reports in Gastrointestinal Medicine, vol. 2018, Article ID 8763671, 3 pages, 2018.



Benign Biliary Strictures

- Types
- Give the **Bismuth classification** for benign biliary strictures.

Classification	Location
I	> 2 cm distal to hepatic confluence
II	< 2 cm distal to hepatic confluence
III	Hilar stricture, hepatic confluence is preserved
IV	Involves the hepatic confluence, bile ducts are separated

Source: Zepeda-Gomez S and Baron TH. Nat Rev Gastro Hep 2011; 8: 573-581.

SPHINCTER OF ODDI DYSFUNCTION (SOD)

- Basic mechanism
 - o Stenosis
 - o Dyskinesia
- Diagnosis
 - o Scintigraphy
 - o Fatty meal ultrasonography
 - o Morphine + neostigmine low sensitivity / specificity (Nardi test)
 - o SOM (sphincter of Oddi manometry) may show ↑ SOD (sphincter of Oddi dysfunction) (> 35 to 40 mm Hg)
- Sphincter of Oddi Manometry (SOM)
 - o SOM, done at time of ERCP
 - o The insertion of the manometry of catheter may cause spasm
 - o SOM - specific, not sensitive
 - o SOD patients have a high complication rate
 - Post-ERCP
 - Post-ERCP placement of the stent

Measurement of SOM (sphincter of Oddi manometry) is performed at the time of ERCP.

- Give non-invasive tests for biliary or pancreatic SOD, as well as their performance characteristics.
 - o Biliary scintigraphy (ultrasound) after
 - Fatty meal (stimulated ultrasound testing of diameter of biliary duct)
 - CCK injection (for biliary SOD)



ACUTE CHOLANGITIS

➤ Diagnostic imaging

- Give the pros and cons of imaging tests for the diagnosis of acute cholangitis.

Parameter	Abdominal Ultrasound	CT	MRCP	EUS	ERCP
o Availability	Widely available	Helical CT is rare	Available	Limited	Available
o Portability	Portable	No	No	Limited	Limited
o Invasiveness	Non-invasive	Non- invasive	Non-invasive	Invasive	Invasive
o Need for sedation	No	No	Some patients	Yes	Yes
o Sensitivity for detection of stones	Low	High (best for helical CT)	High	As good as, if not better than ERCP	Gold standard in most studies
o Sensitivity for detection of strictures	Low	Fair	Best non-invasive method	Good	Excellent
o Sensitivity for detection of tumours	Low	Good	Good	Excellent	Fair
o Advantages	Widely available and non invasive	Widely available and accurate	Accurate without radiation exposure	Excellent for small stones, can be done at same time as ERCP	Therapeutic capability
o Disadvantage	Low sensitivity	Effects on renal function, poor detection of small stones, not portable	Not compatible in patients with implanted metal devices, poor detection of small stones, not portable	Invasive, poor imaging of intrahepatic ducts	Invasive, possible worsening of condition owing to contrast injection

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; MRCP, magnetic resonance cholangiopancreatography

Printed with permission: John G. Lee. *Nature Reviews Gastroenterology and Hepatology* 2009;6:533-41

➤ Pathology

o Ascending cholangitis

– Interlobular ducts

- Neutrophils around ducts, in their walls, and in their lumens +/- rupture of wall, with formation of an abscess in the portal tract

– Sinusoids

- Neutrophil infiltration

– Hepatocytes

- Necrosis



COMMON BILE DUCT DISEASE

➤ Diagnostic imaging

- Give the advantages and limitations imaging modalities for detecting stones in the common bile duct.

Imaging Modality	Description	Advantages	Limitations
o Transabdominal ultrasonography	– Non-invasive procedure whereby high-frequency sound waves are converted into images	▪ 1st line imaging modality ▪ Noninvasive ▪ Widely available and inexpensive ▪ Sensitivity 22-65%* ▪ Specificity 70-98%*	▪ Artifacts may be caused by pneumobilia, surgical clips, biliary stents, duodenal diverticula, and calcifying pancreatitis
o Endoscopic ultrasonography	– Use of a duodenoscope with an ultrasound transducer at its tip; images are more accurate and detailed than ones obtained by traditional ultrasonography because of the proximity of the transducer to the organs of interest	▪ More cost-effective than ERCP as a diagnostic tool ▪ Sensitivity 85-97%* ▪ Specificity 90-95%*	▪ Not widely available; operator dependent; artifacts may be caused by pneumobilia, surgical clips, biliary stents, duodenal diverticula and calcifying pancreatitis
o Intraductal ultrasonography	– Imaging of the biliary tree with an ultrasound transducer mounted at the tip of a catheter inserted through duodenoscope	▪ Sensitivity 97-100%*	▪ Probes have limited durability; stones, sludge and air bubbles may be indistinguishable
o ERCP	– Injection of a contrast agent directly into the common bile duct and imaging at duodenoscopy; considered the “gold standard” against which other imaging modalities are compared	▪ Sensitivity 89-90%* ▪ Specificity 98-100%*	▪ Operator dependent; overall complication rate 4-6%; mortality associated with procedure 0.1-0.5%
o Helical computed tomography cholangiography	– Computed tomography of biliary system following intravenous administration of a contrast agent	▪ Sensitivity 71-85%* ▪ Specificity 88-97%*	▪ Similar drawbacks to those with intravenous cholangiography



Imaging Modality	Description	Advantages	Limitations
o Laparoscopic intraoperative ultrasonography	– Intraoperative use of a specialized laparoscopic probe with an ultrasound transducer at the tip that is positioned to visualize the biliary system	▪ Sensitivity 80-83%* ▪ Specificity 99-100%*	▪ Technically difficult to perform, especially in obese individuals; operator dependent; suboptimal visualization of the intrapancreatic portion of the common bile duct; artifacts may be caused by pneumobilia; detects sludge and small stones that are of limited clinical significance
o Intraoperative cholangiography	– Insertion of a catheter through the cystic duct at the time of surgery, followed by injection of a contrast agent into the common bile duct and fluoroscopic imaging	▪ Sensitivity 75-100%* ▪ Specificity 97-100%*	▪ Prolongs the duration of the surgical procedure; fluoroscopy use in the operating room
o Intravenous cholangiography	– Injection of a contrast agent intravenously, followed by radiographic imaging of the biliary system	▪ Relatively non-invasive; provides information on the biliary ductal system ▪ Sensitivity 48-50%* ▪ Specificity 95-97%*	▪ Risk of reaction to contrast agent (1%) or renal impairment ▪ Limited value in patients with elevated bilirubin level because of decreased excretion of dye into the biliary system
o Magnetic resonance cholangiopancreatography	– Magnetic resonance imaging whereby the hepatobiliary and pancreatic system are visualized using a specialized sequence	▪ Can be used when endoscopic ultrasonography and ERCP is not possible (e.g., after Roux-en-Y gastric or biliary procedures); diagnostic accuracy decreased if stones < 5 mm or common bile duct >10 mm ▪ Sensitivity 85-100%* ▪ Specificity 91-97%*	▪ Hard for patients with claustrophobia to tolerate ▪ May cause dysfunction of certain pacemakers or implantable cardiac defibrillators, or may dislodge metallic prostheses

Abbreviation: ERCP, endoscopic retrograde cholangiopancreatography.

*Using different reference standards across multiple studies.

Printed with permission: Almadi MA, et al. Management of suspected stones in the common bile duct. CMAJ. 2012;184(8):884-92. Table 2.



SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the differential diagnosis for the situation where abdominal ultrasound shows:
 - Dilated intrahepatic duct
 - Normal extrahepatic duct
 - Small (contracted gallbladder) filled with stones
- o These three features on abdominal ultrasound suggest compression of the common hepatic duct, such as from
 - Tumour (Klatskin tumour at bifurcation of R. & L. hepatic ducts)
 - Stone in neck of gallbladder or cystic duct (Mirizzi syndrome, Type I)

- Give the approximate values for the performance characteristics for diagnostic imaging studies of the biliary tree.

	Cholelithiasis (> 2 mm)		Acute Cholelithiasis		Choledocholithiasis	
	Sens	Spec	Sens	Spec	Sens	Spec
o Abdominal ultrasound with acoustic shadow	> 95%	> 95%	Murphy sign, PPV, > 90% (if cholelithiasis is present)		< 50% for stones ~ 75% for diameter > 6 mm (dilation)	
o Oral cholecystography	> 90%	> 90%	-	-	-	-
o Hepatobiliary scintigraphy	-	-	95%	90%	-	-
o ERCP	80%	-	-	-	95%	95%
o EUS	-	-	-	-	95%	97%
					PPV, 99%	
					NPV, 98%	
o MRCP					93%	94%

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; sens, sensitivity; spec, specificity

Clinical Gem: **Best Tests**

- o For cholelithiasis—abdominal ultrasound
- o For acute cholelithiasis—biliary scintigraphy
- o For choledocholithiasis—MRCP or EUS—for low-to-moderate pretest probability

Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier 2010, Table 65.6, page 1108.



SO YOU WANT TO BE A GASTROENTEROLOGIST!

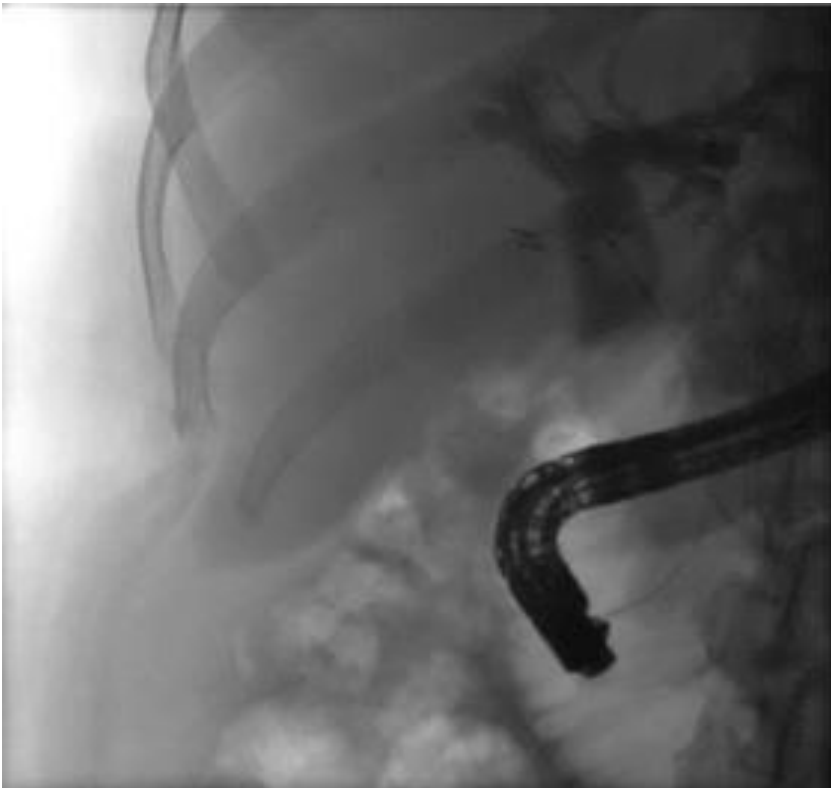
In the context of suspected gallbladder disease, give the meaning of the **Couvoisier sign**.

- o Painless jaundice plus a palpable gallbladder suggests a cancer obstructing the bile duct.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the anatomical reason why the gallbladder is at high risk for the development of **necrosis**.
 - o The gallbladder is at high-risk of developing necrosis because the blood supply to the gallbladder is the cystic artery, an end artery, thereby placing the gallbladder at risk of ischemic necrosis if the blood flow through the cystic artery becomes impaired.

Choledocholithiasis (ERCP)

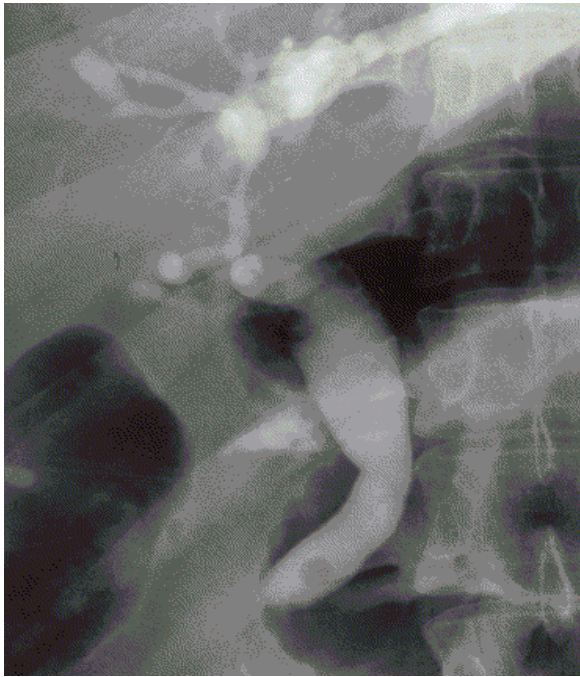


- o Dilation of left and right hepatic ducts and common bile duct
 - Consistent with choledocholithiasis

Printed with permission: Peters X, et al. Int J Surg Case Rep. 2017; 41: 80-82.



ERCP – distal CBD stone



Courtesy of Dr. Terry Ponich, Western University, London (ON)

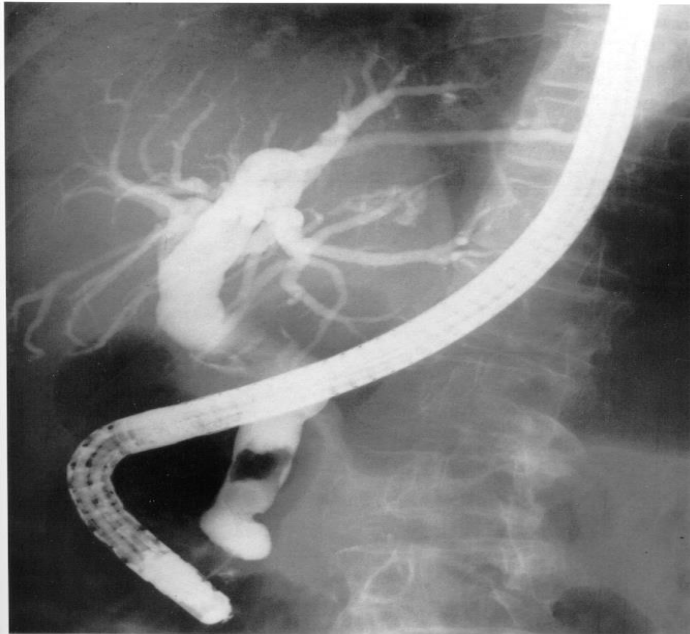
MRCP – Distal CBD Stone



Courtesy of Dr. Terry Ponich, Western University, London (ON)

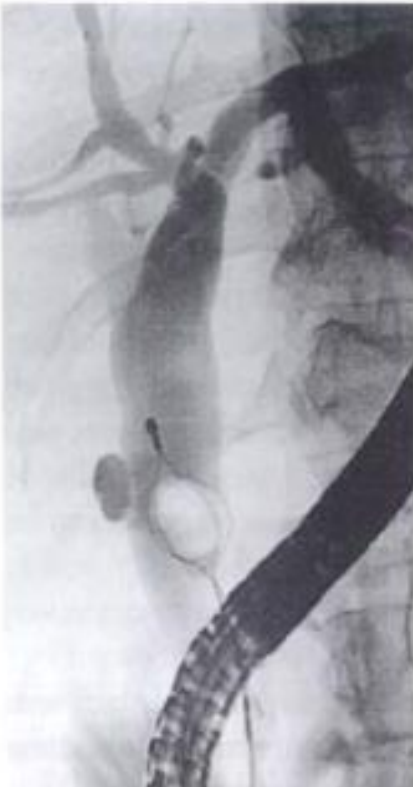


ERCP



Courtesy of Dr. Terry Ponich, Western University, London (ON)

Endoscopic Stone Removal



Courtesy of Dr. Terry Ponich, Western University, London (ON)

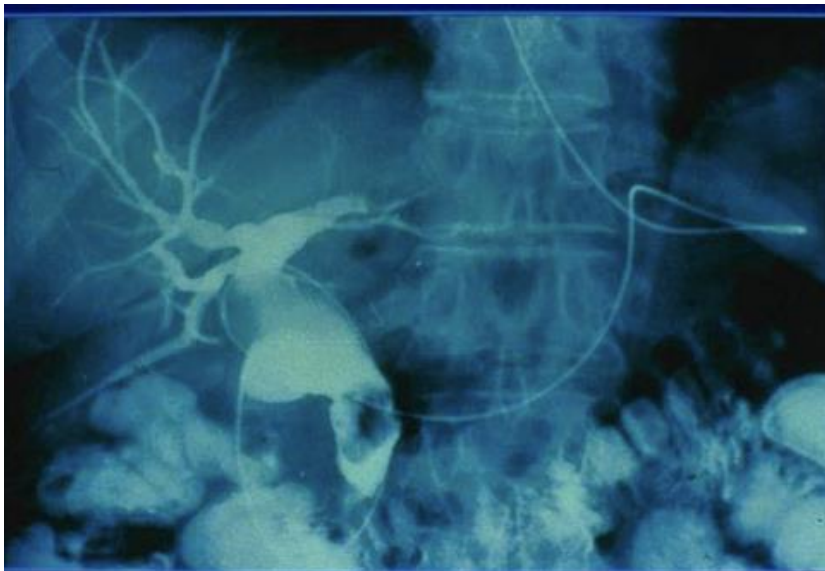


Stones In the Gallbladder and Dilated CBD



Courtesy of Dr. Terry Ponich, Western University, London (ON)

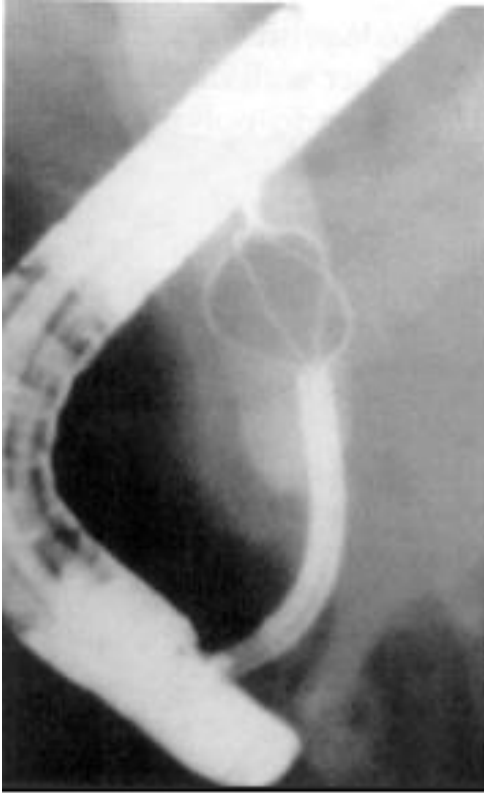
Nasobiliary Drainage



Courtesy of Dr. Terry Ponich, Western University, London (ON)



Lithotripsy



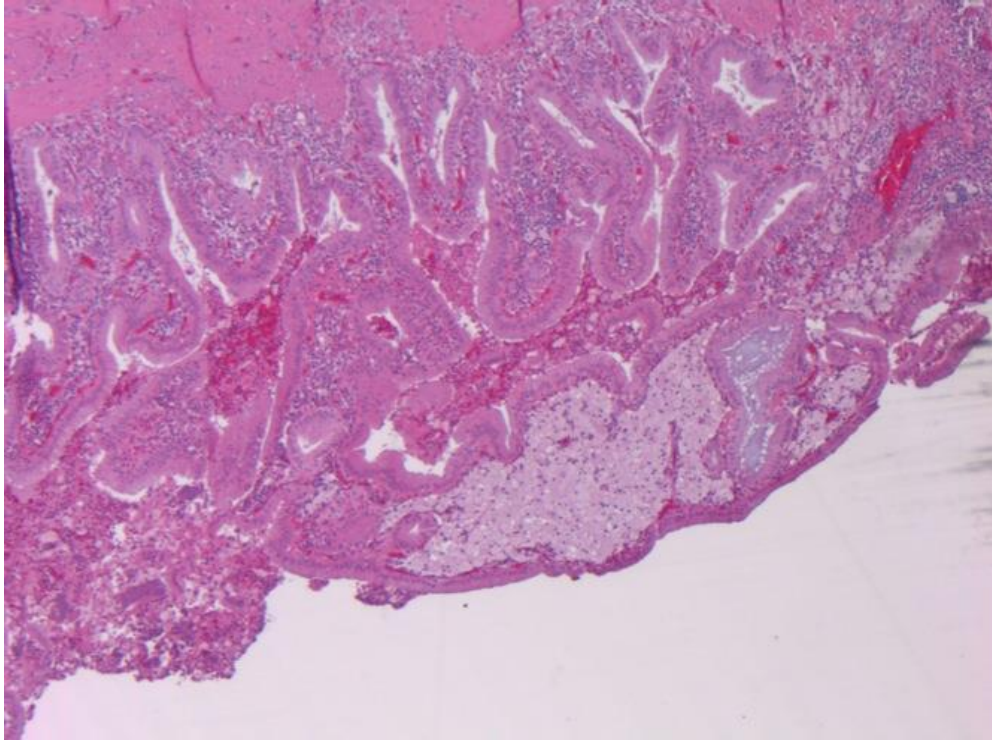
Courtesy of Dr. Terry Ponich, Western University, London (ON)

CHOLESTEROLOSIS

- Definition
 - o “Macrophages in the lamina propria of the gallbladder” appearing foamy from accumulation of cholesterol esters plus triglyceride.
- Types
 - o Diffuse collections of cholesterol in GB lamina propria, ending at cystic duct
 - o Focal collections of cholesterol
 - o Polyps (2 to 10 mm)
 - o Combined diffuse plus polypoid accumulations
- Histopathology
 - o Foamy macrophages of variable distribution (please see above)
 - o Hyperplasia of the mucosa
 - o Hyperplasia may be polypoid in appearance



Cholesterolosis of Gallbladder



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ADENOMYOSIS

- Definition
 - o “An acquired, hyperplastic lesion [of the gallbladder] characterized by excessive proliferation of surface epithelium with imagnations into the thickened muscularis (Rokitansky-Aschoff sinuses) or even more deeply” to produce tiny diverticula (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 1146).
 - o In adenomyosis, the **Rokitansky-Aschoff sinuses** are deep and branched and there is hyperplasia of the muscularis.
- Types
 - o Generalized
 - o Fundic
 - o Segmental (may produce a narrowing of the lumen of the gallbladder)

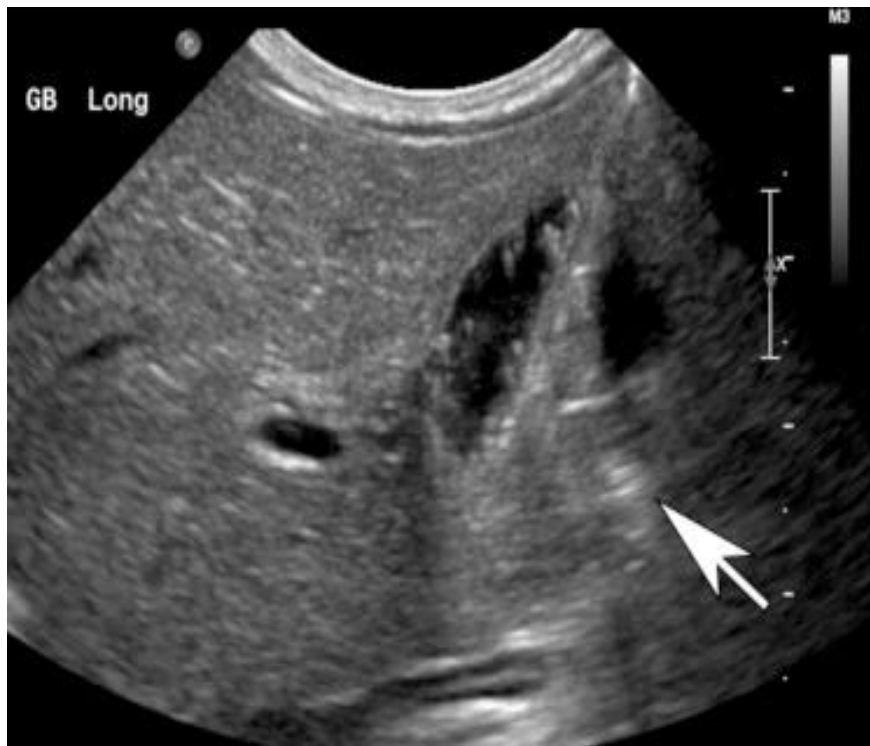


➤ Diagnostic imaging

o Ultrasound

- Multiple echogenic foci in wall
- “comet-tail” artifacts (crystals of cholesterol trapped in the Rokitansky – Aschoff sinuses [herniation of mucosa into the muscle layer of the wall of the gallbladder])
 - Pathognomonic for adenomyosis of gallbladder
- May be in non-dependent part of gallbladder
- Thickened wall
 - Diffuse (diffuse thickening of gallbladder wall mimics acute / chronic cholecystitis)
 - In the fundus / rest of gallbladder
 - Narrows lumen of gallbladder
 - Filling defects in lumen near fundus of gallbladder

Gallbladder Adenomyomatosis

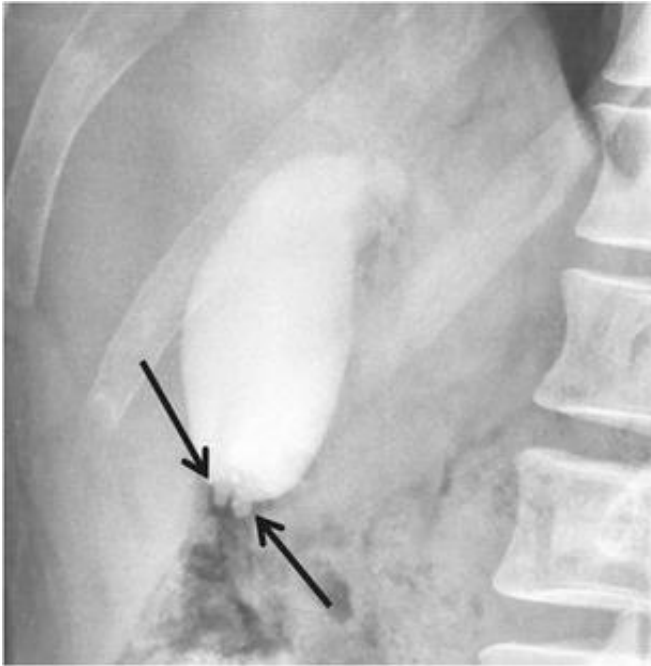


- o Ultrasound image shows gallbladder with comet-tail reverberation artifact (arrow), pathognomonic for adenomyomatosis of the gallbladder.

Printed with permission: Alapati S and Braswell LE. Radiology Case Reports 2014; 9(3), Article 859



Gallbladder Adenomyomatosis

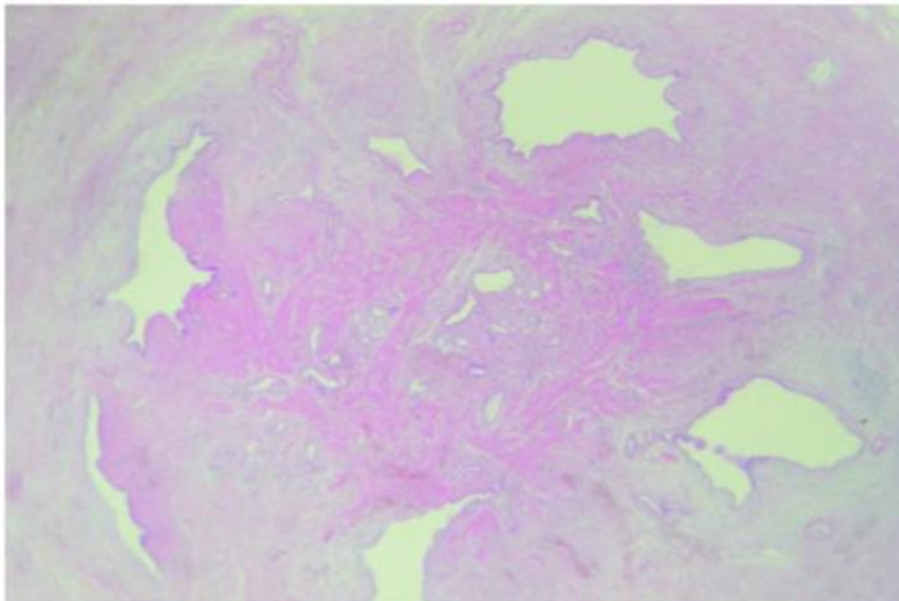


- o Typical cholecystography findings.
 - Fundal gallbladder adenomyomatosis
 - Rokitansky-Ashof sinuses (arrow)
 - Filled by contrast material as a consequence of their communication with the gallbladder lumen.

Printed with permission: Bonatti M, et al. Insights Imaging 2017;8(2):243–253.

➤ Histopathology

Gallbladder Adenomyosis

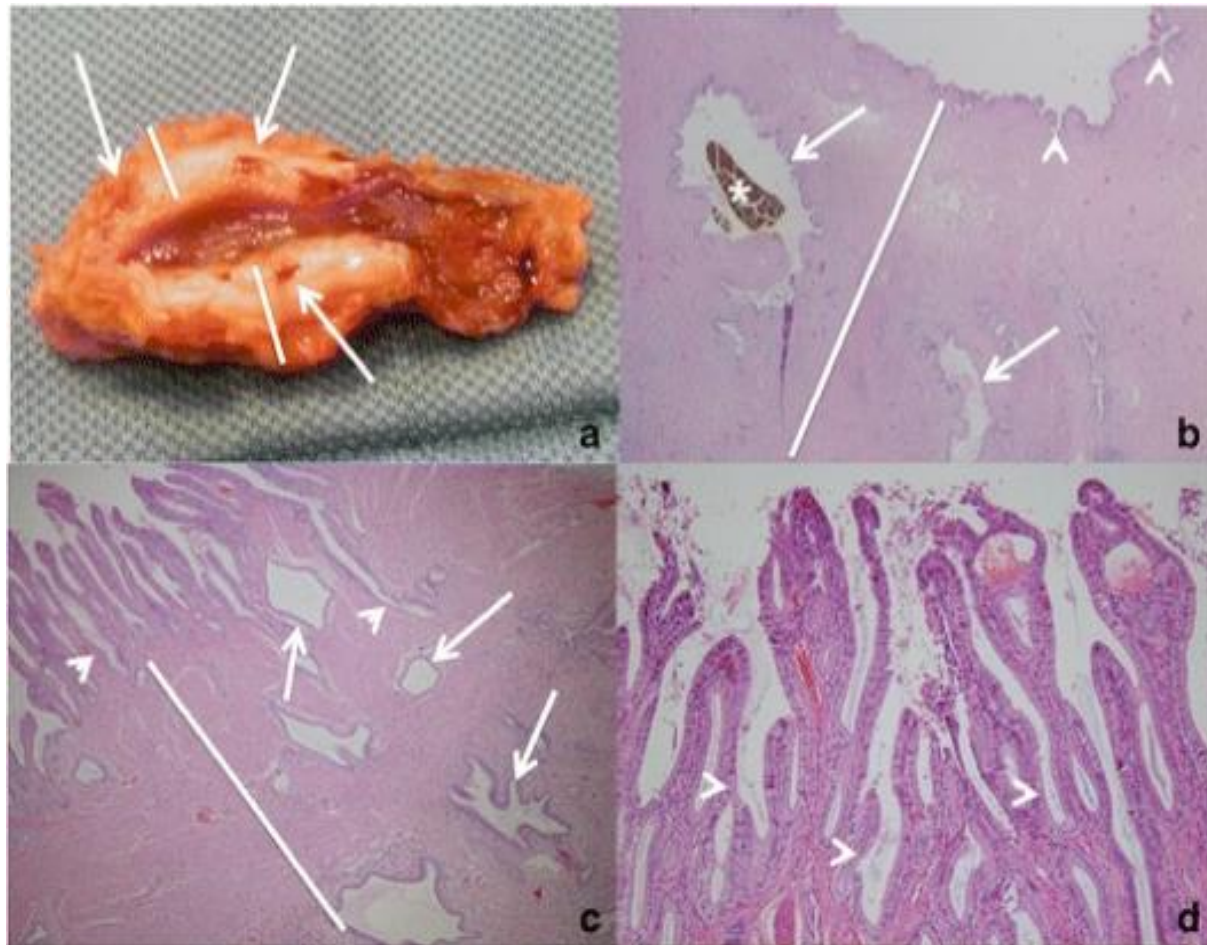


- o Histological examination of gallbladder fundus
 - A nodule of adenomyosis demonstrating
 - Invagination of mucosa into the muscularis layer (low power magnification)

Printed with permission: Mann CD, et al. Ann R Coll Surg Engl 2007; 89(6):W14–W16.



Gallbladder Adenomyosis



- o Macroscopically (a) GA is characterized by gallbladder wall thickening (lines) containing small cystic spaces (arrows) representing Rokitansky–Aschoff sinuses.
- o Microscopically, at low (2×) magnification (b and c), wall thickening is due to hyperplasia of the muscular layer (lines); a variable degree of epithelial proliferation (arrowheads) is also appreciable and epithelium-lined cystic spaces, representing RAS (arrows), can be observed within the muscular layer.
- o Biliary stones (star) may be present within RAS. At high (40×) magnification (d), the proliferative mucosal glandular component that leads to epithelial infolding (arrowheads) and RAS formation is better recognizable

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GALLBLADDER CARCINOMA

➤ Demography

- o $1/10^5$, with global incidence rates of GB-Ca parallel to incidence rates of cholelithiasis.
- o Very rare
- o F > M, 2:1
- o Highest prevalence in
 - Indigenous people of North America
 - Hispanics
 - Mexico
 - Chile
- o Mean age
 - 72 yr
- o Site
 - Fundus, 60%
 - Body, 30%
 - Neck, 10%

➤ Diagnostic imaging

Polyps

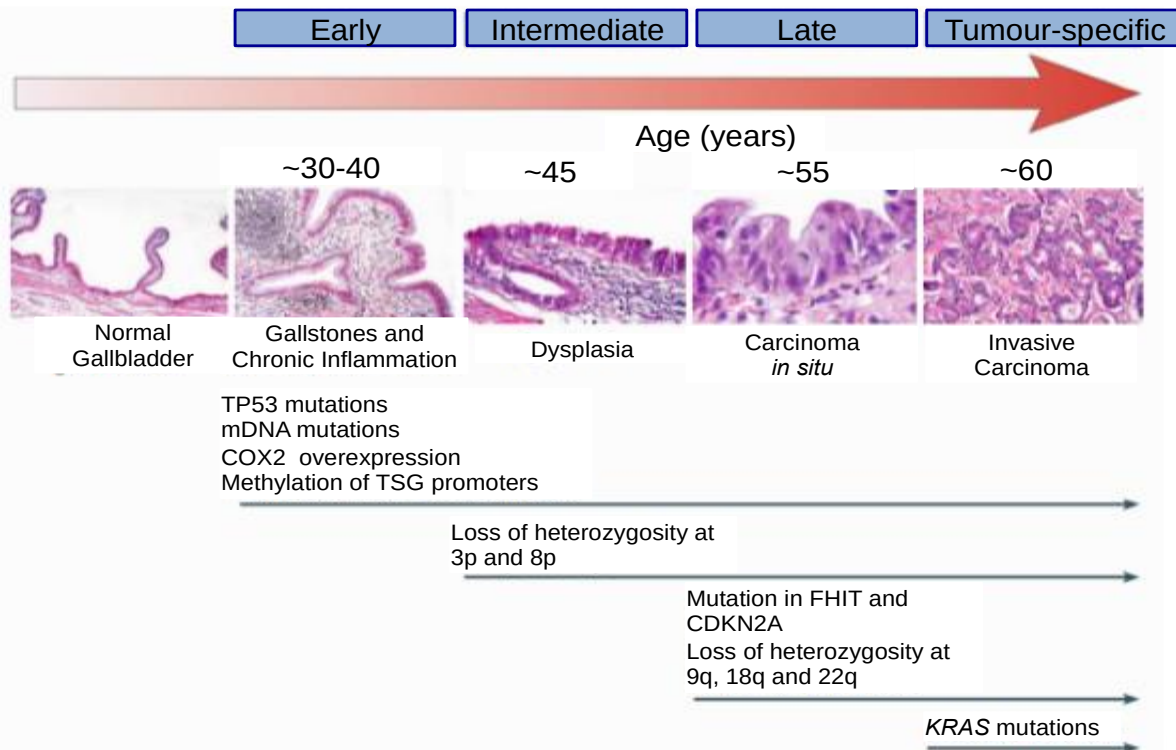
- o Ultrasound
 - Intramural filling defects
 - Multiple / single
 - Usually < 1 cm (when > 1 cm, suspect carcinoma)
 - Non-mobile
 - No posterior acoustic shadowing
 - Internal blood flow
 - Blood flow in mass
 - Melanoma metastatic to the gallbladder looks similar

Carcinoma

- o Ultrasound, contrast enhanced CT
 - Hypoechoic (white) mass
 - Infiltrating (scirrhous type, infiltrates into liver)
 - Polypoid type grows into lumen
 - Blood flows into mass
 - Usually > 1 cm
 - Distension of gallbladder



➤ Histopathology



- o Sequential histopathological and molecular changes in the pathogenesis of gallbladder carcinoma associated with gallstones and inflammation.
- o The multistage pathogenesis of the most common form of gallbladder cancer begins with gallstones and chronic cholecystitis, with retention of the normal gallbladder epithelium.
- o A relatively well- defined sequence of subsequent flat-epithelial, premalignant changes has been identified, which includes dysplasia and progression to carcinoma in situ, ultimately leading to the development of an invasive carcinoma.
- o The median age at diagnosis of each histopathological change is shown.
- o These histological changes are accompanied by progressive molecular abnormalities, which commence in the histologically normal appearing epithelium that is present in chronic cholecystitis. These early changes include TP53 mutations, COX2 overexpression, mitochondrial DNA mutations and abnormal hypermethylation of promoters of various tumour-suppressor genes (TSGs).
- o During the development of dysplasia, further changes (intermediate changes) take place, including allelic loss at several chromosomal sites (in particular on the p arms of chromosomes 3 and 8).
- o Late changes at the carcinoma in situ stage include inactivation of the fragile histidine triad (FHIT) and CDKN2A tumour-suppressor genes and losses at additional chromosomal regions, particularly on the q arms of chromosomes 9, 18 and 22.
- o Finally, later, tumour-specific changes occur, which are detected only in invasive tumours and include KRAS mutations.

Printed with permission: Wistuba II and Gazdar AF. Nature Reviews Cancer 2004;4:695-706



- Immunohistochemical changes (IHC)
 - o Positive for
 - Cytokeratin
 - AE1/AE3
 - Cam5.2
 - CEA
 - CK7
 - o Variably positive
 - CK20
 - CDX2

MCQ Gem

- o In many intestinal tissues, carcinoma is preceded by adenoma. This is not usually the case for carcinoma of the gallbladder.

There are a variety of adenoma types characterized by their morphology and immunohistochemistry. All of these may be associated with adenocarcinoma.

“There are little gems all around us that can hold
glimmers of inspiration.”

Richelle Mead



PANCREATICOBILIARY OBSTRUCTION AND ENDOSCOPIC STENTING FOR BILIARY DRAINAGE

- o Preoperative
 - Plastic stent
 - SEMS (self-expanding metal stent), using TTS (through-the-scope) delivery systems, +/- Argon plasma coagulation to trim / reposition stent
 - Preoperative endoscopic biliary drainage before pancreaticoduodenectomy
 - Reduced need for repeat surgery 4% vs 15%, but
 - Increases the rate of serious complications 74% vs 39%
- o Palliation
 - Stents
 - Median stent patency
 - Plastic 126 days
 - Metal 273 days
 - Adverse outcomes
 - Plastic 39%
 - Metal 12%
 - Surgery
 - Bypass
 - Percutaneous drainage
- o Regardless of estimated patient survival time, metal and not plastic stents should be used for cholangiocarcinomas and for malignant biliary strictures (e.g., Klatskin tumour at hilar bifurcation)
- o Obstruction of hilum
 - Use uncovered metal stents (SEMS) – Low rate of migration of stent – Difficult to remove
 - High rate of obstruction from ingrowth of tumour (diagnose tumour overgrowth with MRCP; sensitivity, 87%; specificity, 86%)
 - May also use plastic stents for both right and left hepatic duct systems
 - Note
 - Use uncovered rather than covered SEMS to reduce migration of stent (15 vs 7%)
 - Do not perform sphincterotomy before placement of covered SEMS in order to reduce migration (3% vs 16%)
 - Do not use a covered metal stent for a biliary tract obstruction in a patient with a gallbladder, to avoid stent blockage of the cystic duct, leading to cholecystitis



BILE LEAKS AFTER LAPAROSCOPIC CHOLECYSTECTOMY

- Demography
 - o Significant bile leaks ~1%
- Diagnostic imaging
 - o Detect on abdominal ultrasound
 - o If ultrasound is negative but clinical suspicion is high, perform cholescintigraphy (HIDA scan) or ERCP
 - ERCP gives identification of leaks ~ 95%
 - Other pathology detected, e.g.,
 - Stones
 - Strictures
 - T-tube

Bile Leak after Laparoscopic Cholecystectomy



Courtesy of Dr. Terry Ponich, Western University, London (ON)

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Bile Leak after Laparoscopic Cholecystectomy “



Courtesy of Dr. Terry Ponich, Western University, London (ON)

“How can I know who I am, until I see what I do?

How can I know what I value, until I see where I
walk?”

Karl Weic

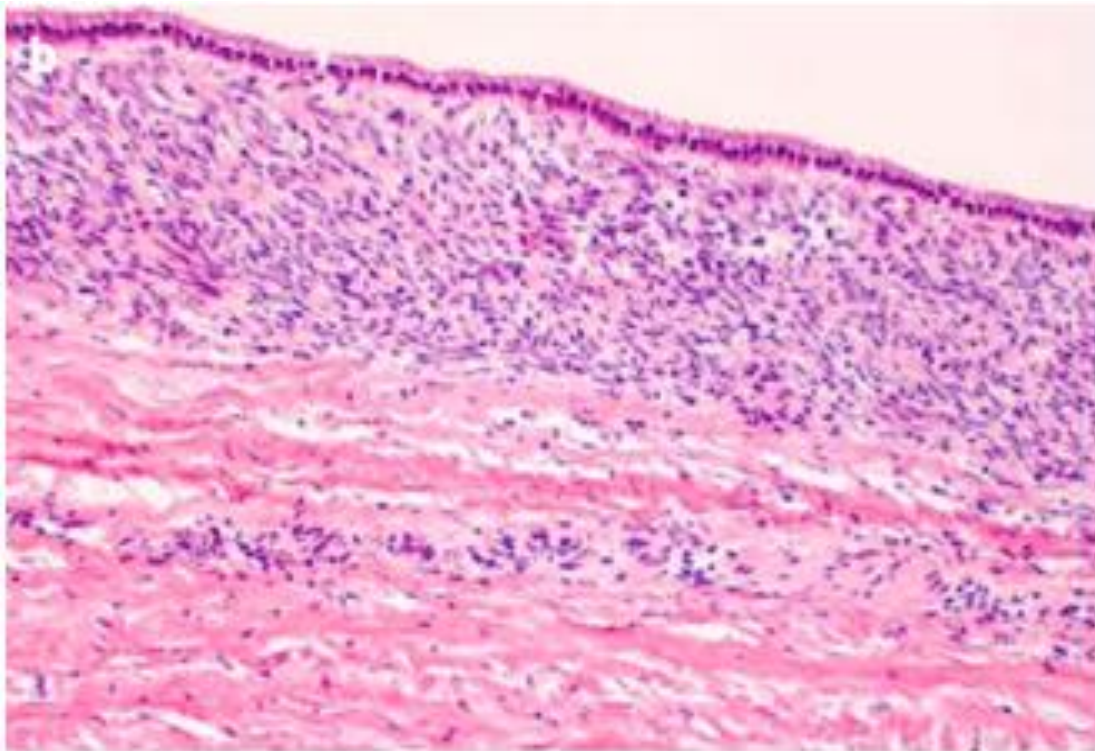


BILIARY CYSTS

Mucinous Cystic Neoplasm

- Definition
 - o A type of cystic lesion that occurs in the pancreas.
 - o These lesions are benign, though there is a high rate of progression to cancer.
- Histopathology

Mucinous Cystic Neoplasm



Printed with permission: Ryan CK, et al. (2013) Pathology of the Liver, Biliary System, and Exocrine Pancreas. In: Krueger G., Buja L. (eds) Atlas of Anatomic Pathology with Imaging. Springer, London



MISCELLANEOUS CONDITIONS

Phrygian Cap

- Definition
 - o A congenital abnormality of the fundus of the gallbladder causing folding of the wall
- Diagnostic imaging
 - o Ultrasound
 - Thin, white infolding of the wall of the fundus of the gallbladder
 - High attenuation (dark) line projecting into the lumen of the gallbladder
 - o Contrast enhanced CT
 - Focal narrowing in the wall of the fundus of the gallbladder

Useful background: Distinguishing features on ultrasound / contrast-enhanced CT

	Phrygian Cap	Focal Adenomyosis
– Fundus	+	Anywhere
– Membrane	Thin	Thick
– Annular	-	+

Phrygian Cap



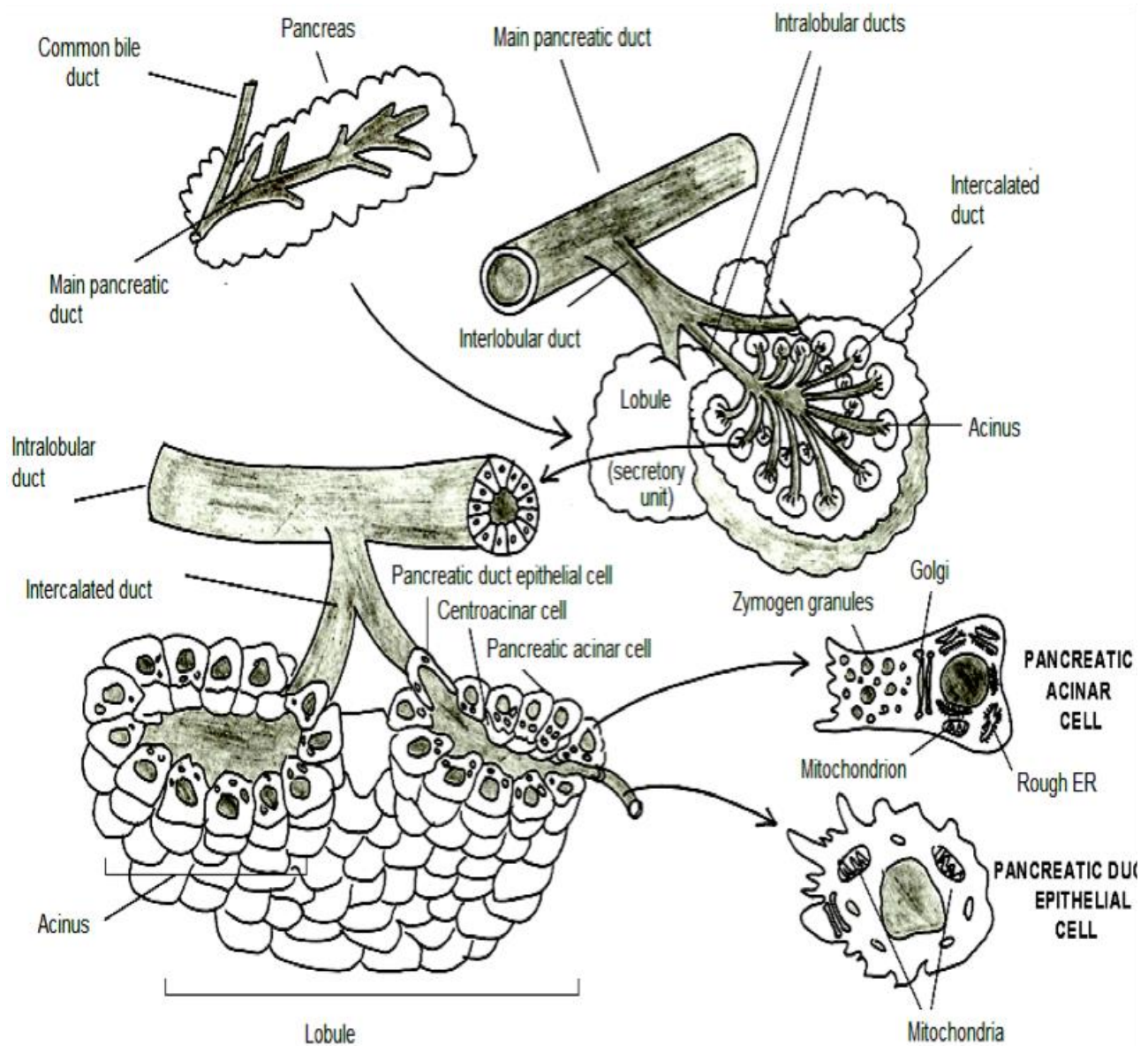
- o Long axis view of the gallbladder shows it extending from the hilum to the lateral border of the liver. We observed a folding of the fundus which is known as the “Phrygian cap” deformity.

Source: Rafailidis V, et al. Case Reports in Radiology, vol. 2014, Article ID 246476, 4 pages, 2014. doi:10.1155/2014/246476





FUNCTIONAL ANATOMY OF THE PANCREAS



Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 43-1, page 913.

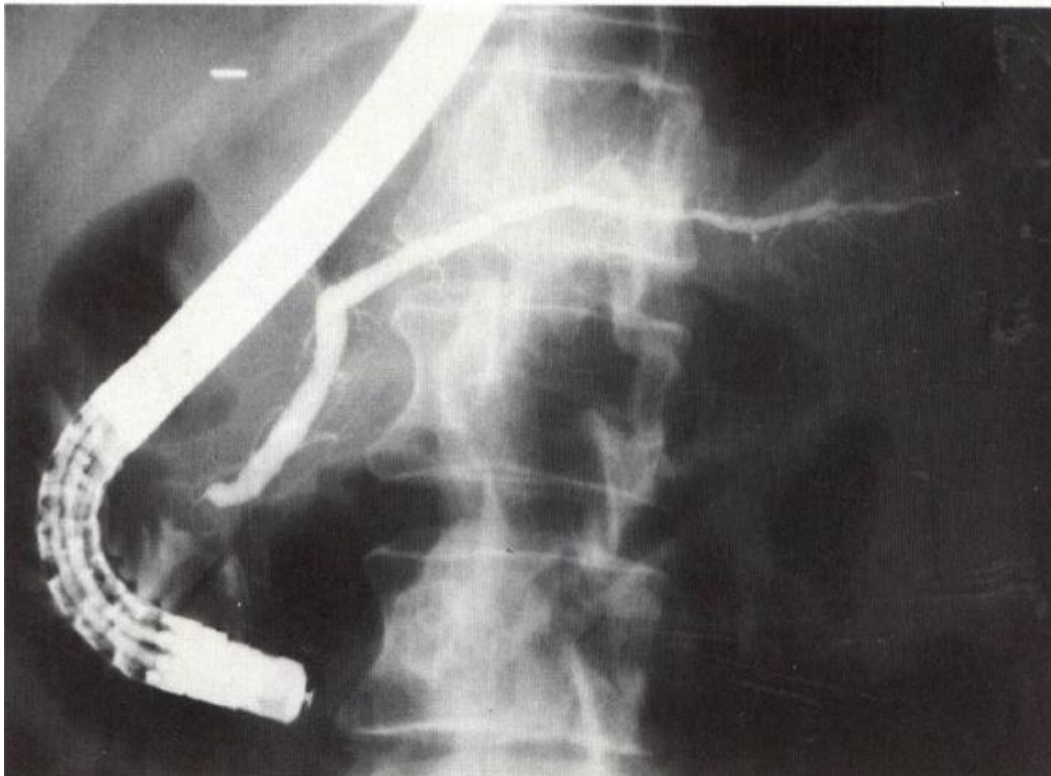
- o From 15 to 100 acinar cells form an acinar cluster.
- o Acinar cluster connects the acinar lumen to an intercalated duct. Multiple intercalated ducts join the intralobular ducts.
- o The intralobular ducts join the interlobular duct, and then the main pancreatic duct.



- o The cells at the junction of the acinus and the intercalated ducts are cuboidal centroacinar cells. These, as well as the proximal intercalated duct cells, have many mitochondria to facilitate salt and water secretion.
- o The more distal intercalated ducts are lined by larger cuboidal cells containing cytoplasmic vesicles and granules, which facilitate the secretion of both alkaline fluid and proteins.
- o The average amount of pancreatic juice produced daily contains 15-100 g of protein (in fact, the pancreas has the body's highest rate of daily protein synthesis and secretion).
- o Acinar cells secrete enzymes (protein), as well as isotonic NaCl-rich fluid.
- o This acinar fluid represents about a quarter of the total fluid secreted by the pancreas gland.
- o The other 75% of the fluid secreted is HCO_3^- rich fluid from the pancreatic duct cells.
- o The HCO_3^- in the duodenal lumen helps to neutralize the acidic "squirts" of the mixture of the 2 mm particles of food as well as gastric acid which leaves the stomach as the result of antral contraction and the coordinated relaxation of the pylorus.

➤ Diagnostic imaging

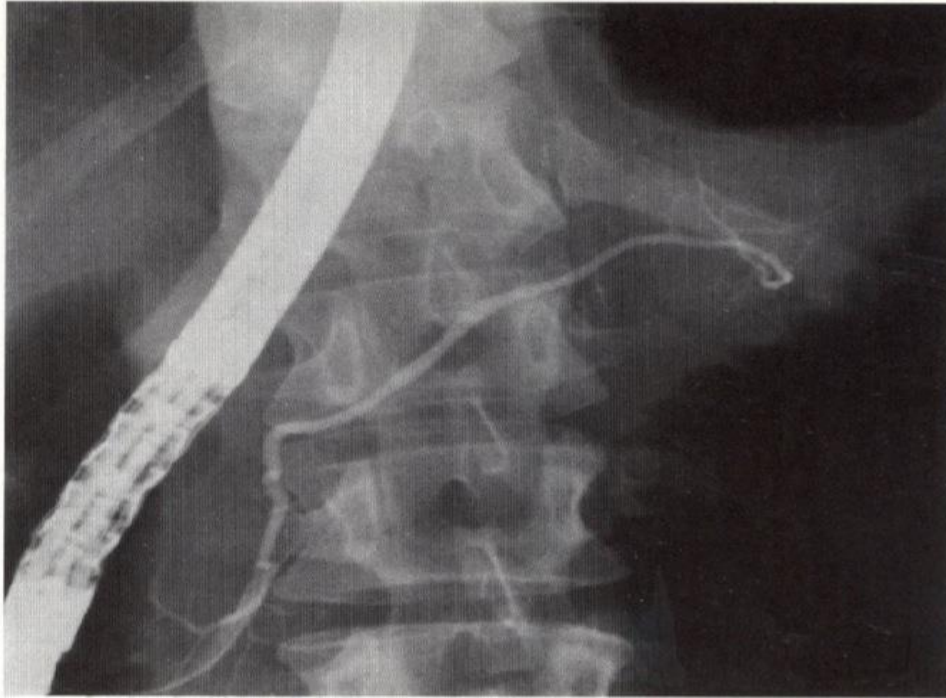
Normal Pancreatic Duct, ERCP



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Normal Pancreatic Duct, ERCP



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Normal Pancreatic Duct (< 5 mm), ERCP

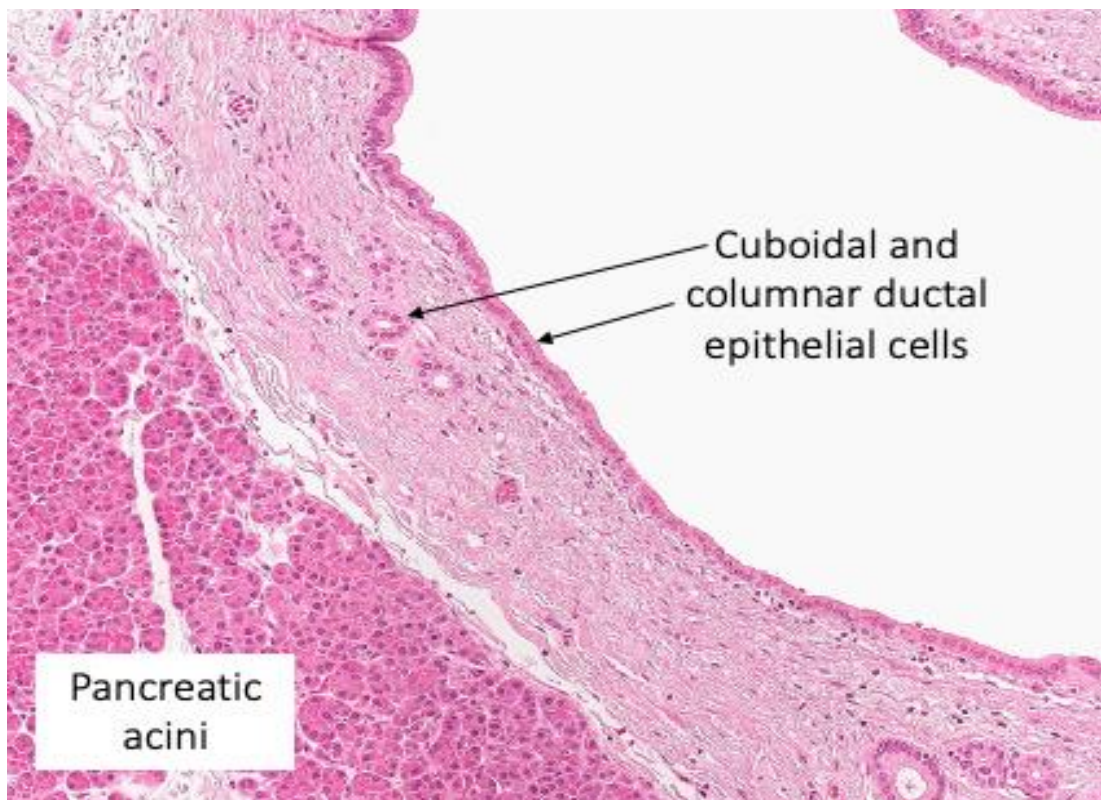


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- Histopathology
 - o Simple cuboidal epithelium of a pancreatic duct seen by light microscopy (LM). The duct is surrounded by connective tissue and pancreatic acini.
 - o High-magnification LM revealing the structure of the pancreatic acinus. Nuclei are located near the base of the cells. The Golgi apparatus lies in a supranuclear position but is not visible with this stain.

Pancreatic Ductal Epithelium (H&E 200X)



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PANCREATITIS

➤ Demography

	Acute	Chronic
o Incidence	20/10 ⁵ per year	5/10 ⁵ per year
o Gender	M > F	M > F
o Average age		52 yr

➤ Genetics

- o May be associated with mutation in PRSS1 (cationic trypsinogen gene)

➤ Diagnostic imaging

Acute	Chronic
o Diffuse edematous enlargement	o Dilation of ducts o Cysts o Calcification (alcohol association)

➤ Pathology

Acute	Chronic
o Acute inflammation o Necrosis → abscess o Bleeding	o Lymphoplasmacytic cell infiltration o ↓ acini o Ductal cells reactive o Fibrosis / fibroblast proliferation o Islet cells of Langerhans usually persist, despite loss of acini o Necrosis

Acute Pancreatitis

➤ Definitions

- o Acute pancreatitis is "...an event triggered by sudden pancreatic injury that is followed by sequential inflammatory responses" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders Elsevier, Philadelphia, 2010, page 901).
 - Alternate definitions:....an acute inflammatory process of the pancreas with variable involvement of other regional tissue or remote organ systems" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 931).
 - "...best defined clinically by a patient with [or all of the following criteria: (1) symptoms such as epigastric pain, consistent with the disease; (2) a serum amylase or lipase greater than three times the upper limit of normal; or (3) radiologic imaging consistent with the diagnosis, usually using computed tomography (CT) or magnetic resonance imaging (MRI) (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 960).



- o Chronic pancreatitis “.....is a process that usually begins with recurrent pancreatitis and ends with immune-related destruction of the pancreas and widespread glandular fibrosis” ((Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 931).
- Demography
 - o Wide variation in quoted incidence ~ 25/10⁵
 - o Incidence depends on causes
 - o Most common causes are alcohol excess and cholelithiasis
- Causes
 - o Gallstones
 - o CBD calculus
 - o Annular pancreas
- Diagnostic imaging
 - o Abdominal ultrasound may be hypoechoic in acute pancreatitis, but its usefulness may be limited by overlying bowel gas (in ~ 1/3), its poor sensitivity to detect CBD stones, and the challenge to differentiate hypoechoic areas from acute versus chronic pancreatitis versus malignancy.
 - o Sensitivity of detecting CBD stones: EUS = ERCP = MRCP > US or CT
 - o In the patient with suspected necrotizing pancreatitis, EUS is superior to ERCP because of the lack of risk of introducing infection.
 - o Abdominal ultrasound not sensitive to detect cholelithiasis / choledocholithiasis in acute pancreatitis; use MRI or EUS
 - o Early prognostic assessment of severity of pancreatitis (within first 24 hr)
 - o Microlithiasis occurs in 37-89% of persons with idiopathic acute pancreatitis, and some experts recommend cholecystectomy for associated symptoms
 - o Definitions
 - Microlithiasis, stones < 3 mm
 - Biliary sludge, a suspension of crystals, mucin, glycoproteins, cellular debris, and protein across material
 - Biliary crystals, crystals of calcium bilirubinate, calcium carbonate, or cholesterol monohydrate; the use of duodenal drainage to assess the presence of biliary crystals has a sensitivity of 65%, and a specificity of 94-100%
 - The risk of pancreatitis following ERCP is high in persons with IAP (idiopathic acute pancreatitis), sphincter of Oddi dysfunction (SOD), or a post history of pancreatitis (12.5% risk)

Abbreviations: IAP, ideopathic acute pancreatitis; SOD, Sphincter of Oddi dysfunction



- Give the way to distinguish on diagnostic imaging the possibilities of alcoholic pancreatitis versus biliary tract stones.
 - o Abdominal ultrasound
 - Not sensitive for bile duct (BD) stones
 - May show indirect evidence of
 - Stones
 - Dilated BD or cystic duct
 - Cholecystitis
 - Gallbladder wall > 4 mm
 - ↑ pericholecystic fluid

The **abdominal plain film** (APF) is useful to support the diagnosis of acute pancreatitis.

- Give findings on the APF which suggest acute pancreatitis, and distinguish between the “sentinel loop” and the “colon cut-off” signs.
 - o Stomach
 - Anterior displacement
 - Separation of the contours of the stomach and transverse colon
 - o Duodenum
 - Descending portion displaced and stretched by head of enlarged pancreas
 - o Jejunum / Ileum
 - “Sentinel loop” (localized dilated segment of small bowel)
 - Ileus
 - o Colon
 - “Colon cut-off” sign
 - Spasm of colon with
 - Proximal dilation
 - Distal lack of gas
 - Irregular haustral pattern
 - o Gallbladder
 - Calcified stones
 - o Pancreas
 - Stones
 - Calcification
 - Ascites
 - Retroperitoneal air (abscess)
 - Gas-forming organism
 - Microperforation of gut
 - Adjacent pseudocyst



Acute Pancreatitis, CT Scan



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Alcoholic Pancreatitis

➤ Definition

- o “About 60% ofpersons who present with their first attack of acute alcoholic pancreatitis have already developed histologic chronic pancreatitis” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 989).
- o In persons with acute alcoholic pancreatitis who have not yet developed obvious chronic pancreatitis, stopping alcohol;
 - ↓ rate of progression to chronic pancreatic insufficiency
 - Does not alter the frequency of recurrent attacks of acute pancreatitis



ERCP-Associated Pancreatitis

- Definition
 - o Pain + > 3x ↑ amylase within 24 hours requiring admission > 48 hrs
 - o Use prophylactic stents in high risk patients
- Diagnostic imaging

ERCP-Associated Pancreatitis



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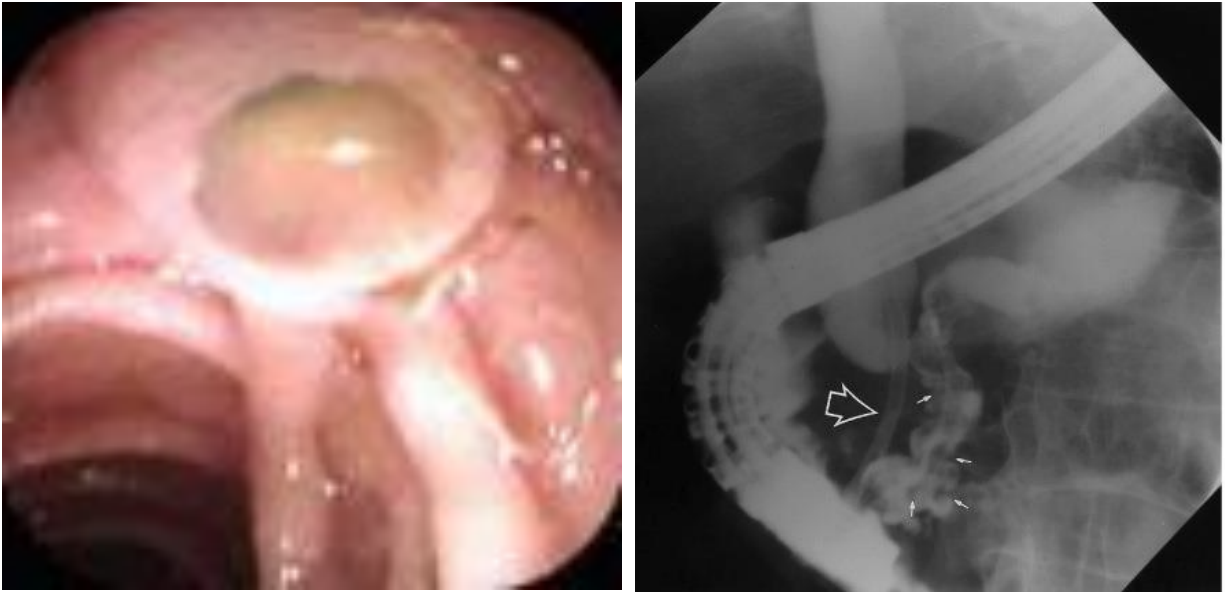
ERCP-Associated Pancreatitis



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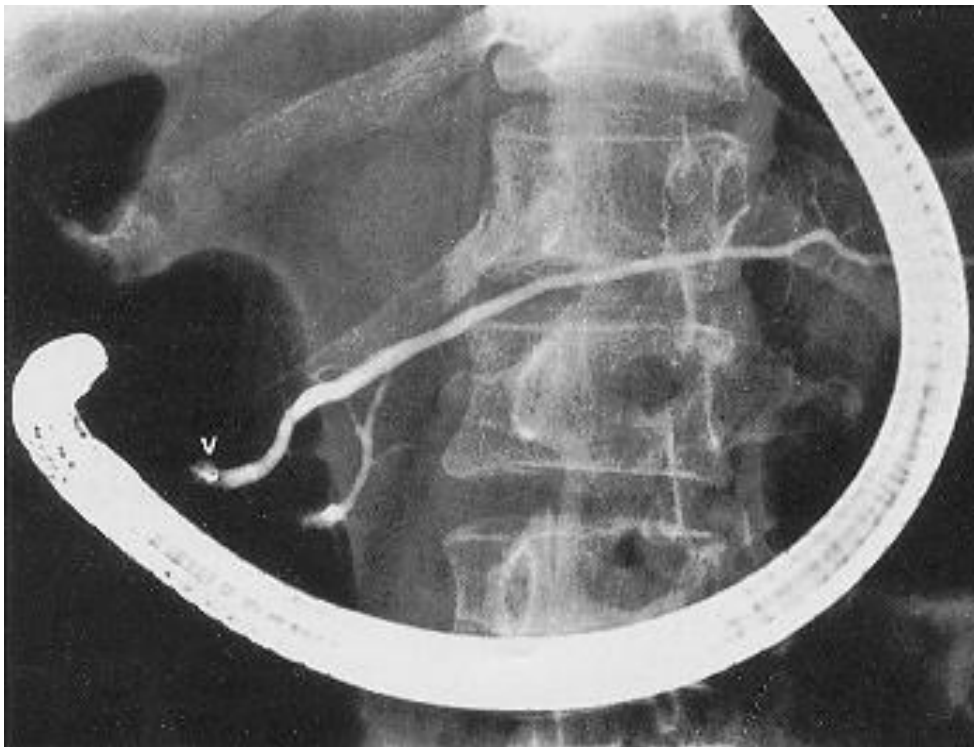


ERCP-Associated Pancreatitis



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ERCP-Associated Pancreatitis



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ERCP-Associated Pancreatitis



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An unusual cause of acute pancreatitis



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Necrotizing Pancreatitis and Abscess

➤ Definition

- o “Necrotizing pancreatitis is defined, in the absence of laparotomy or autopsy, by the presence of greater than 30% of non-enhancement of the pancreas on a contrast-enhanced CT scan” or MRI (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. *Saunders / Elsevier* 2010, page 981).

➤ Pathological types

- o Walled-off pancreatic necrosis (WOPN)
 - Several weeks after pancreatic necrosis and duct disruption, the cystic area contains liquid as well as solid material (non-enhancing pancreatic parenchyma on contrast-enhanced CT scan).
- o Pancreatic abscess
 - “.....infected pseudocyst or infected liquefied collections without significant solid debris (pancreatic necrosis” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. *Saunders / Elsevier*, Philadelphia, 2010, page 1038).
 - A pancreatic pseudocyst is not a cyst, because although there may be cystic spaces filled with pancreatic secretion fluid from a duct which has been disrupted by obstruction or inflammation, the cystic space does not have an epithelial lining, and so is not a true cyst.

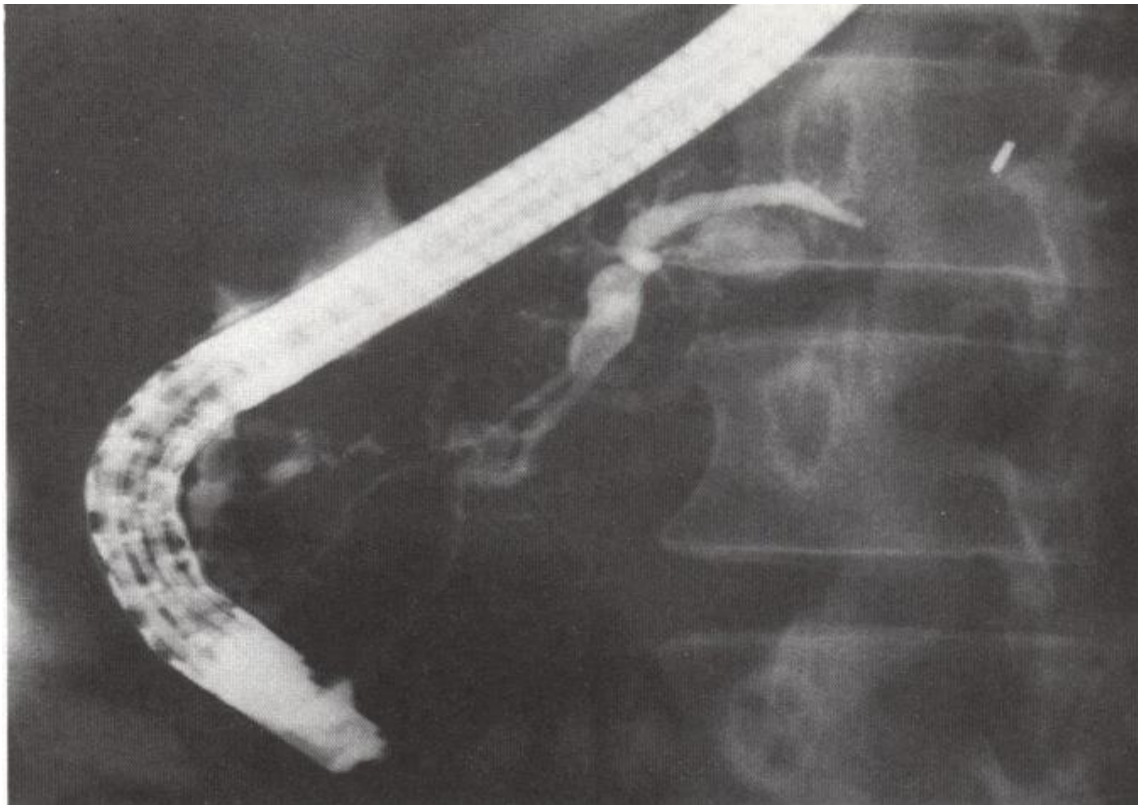
➤ Diagnostic imaging

- o Plain film (“abdominal radiograph”)
- o In the luminal GI tract
 - Mass effect on
 - Stomach: anterior displacement
 - Colon: inferior displacement
 - Inflammatory changes
 - Thick folds
 - Spasm
 - Narrowing
 - Often the splenic flexure
 - Distention
 - Proximal and transverse colon
 - Sharp cut-off distention at splenic flexure (colonic “cut off” sign)
- o In the pancreas
 - Signs of pancreatitis



- o CT scan
 - Peripancreatic fluid
 - Air in pancreas
 - Pancreatic – colonic fistula
 - Pancreatic abscess
- o Contrast – enhanced CT
 - Abnormal fluid collection
 - Air in lesion (20%)
- o Barium enema
 - Colon cut off sign if pancreatic abscess with inflammatory narrowing of colon
 - Dilation of colon proximal to the splenic flexure

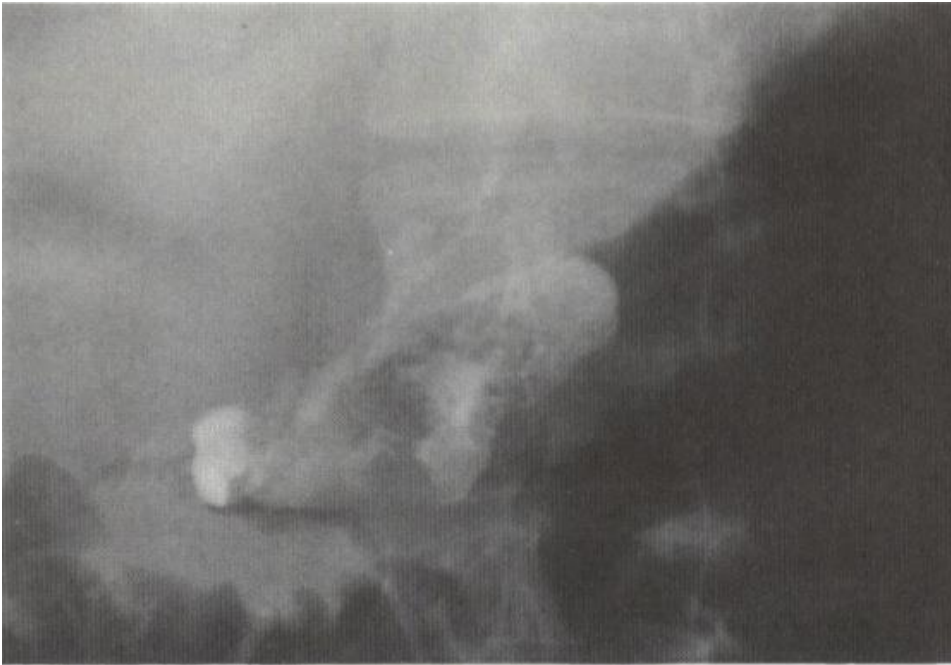
ERCP: Pancreatic Abscess



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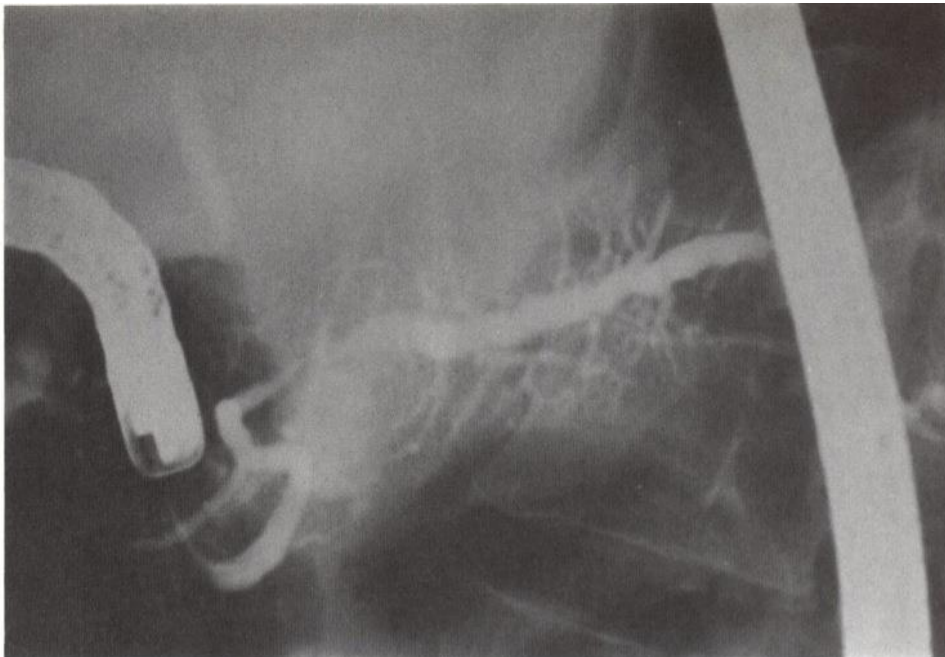
Pancreatic Abscess



- Post ERCP after drainage of pancreatic duct
 - After drainage of duct contrast material, there was persistence of extravasated material (abscess)

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Pancreatic Abscess



Narrowing of duct in pancreatic neck, distal ductular dilation, contrast outside duct at area of narrowing.

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➤ Pathology

- o Necrosis of pancreatic tissue, often with associated peripancreatic fat necrosis, and accompanied by disruptions in pancreatic ducts.
- o Necrotizing pancreatitis may be infected (1/3) or non-infected (2/3)

Gallstone Pancreatitis

➤ Diagnostic imaging

- o In the setting of ↑ suspicion of gallstone pancreatitis, don't be side-tracked if abdominal ultrasound is normal (pancreatitis → ileus → bowel air may obscure pancreas).

Drug-Associated Pancreatitis

Useful background: Classification and examples of drugs associated with induction of acute pancreatitis

➤ Class I: implicated in > 20 reports, at least one documented case following re-exposure

- | | |
|-------------------------|-----------------------------------|
| o Asparaginase | o Pentamidine |
| o Azathioprine | o Pentavalent antimonials |
| o Cytarabine | o Steroids |
| o Didanosine | o Sulfasalazine |
| o Estrogen preparations | o Sulindac |
| o Furosemide | o Tetracycline |
| o Mercaptopurine | o Trimethoprim / sulfamethoxazole |
| o Mesalamine | o Valproic acid |
| o Opiates | |

➤ Class II: implicated in > 10 reports

- | | |
|---------------------|-----------------------|
| o Acetaminophen | o Hydrochlorothiazide |
| o Carbamazepine | o Interferon Alfa-2b |
| o Cisplatin | o Lamivudine |
| o Cyclopenthiiazide | o Octreotide |
| o Enalapril | o Phenformin |
| o Erythromycin | o Rifampicin |

Printed with permission: Keller J, et al. *Best Pract Res Clin Gastroenterol* 2007;21(3):519-33.



Acute Recurrent Pancreatitis

Less common causes

- o Pancreas divisum
 - Symptoms may develop in those with acute recurrent pancreatitis arising from relative disruption to the flow of pancreatic juice through the minor papilla.
 - The presence of pancreas divisum is associated with a high risk of post-ERCP pancreatitis
- o Sphincter of Oddi dysfunction (SOD)
 - Postulated to be the cause of acute recurrent pancreatitis when the basal pressure in the pancreatic sphincter is > 40 mm Hg
- o IBD and drugs
 - The ↑ rate of acute pancreatitis in persons with inflammatory bowel disease (IBD, risk is ↑ 4x in Crohn disease and 1.5x in Ulcerative Colitis) may be due to drugs used to treat the conditions, such as 5-ASA / sulfasalazine or azathioprine / 6-mercaptopurine.
- o Celiac disease
- o Severe burns
- o Smoking (possibly making the effects of alcohol worse)
- o AIP (autoimmune pancreatitis)
 - ↑ IgG4
 - May be associated with
 - Acute pancreatitis
 - Chronic pancreatic insufficiency
 - Stricture of main pancreatic ducts
 - Diabetes

Chronic Pancreatitis

➤ Definition

- o Chronic pancreatitis “.....is a process that usually begins with recurrent pancreatitis and ends with immune-related destruction of the pancreas and widespread glandular fibrosis” ((Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 931).
- o Chronic pancreatitis is a spectrum which displays histologic changes of chronic inflammation, loss of acinar tissue.
- o The fibrosis of chronic pancreatitis results from immune-mediated process (e.g., TGF- β and IL-10) which activate the pancreatic stellate cells.



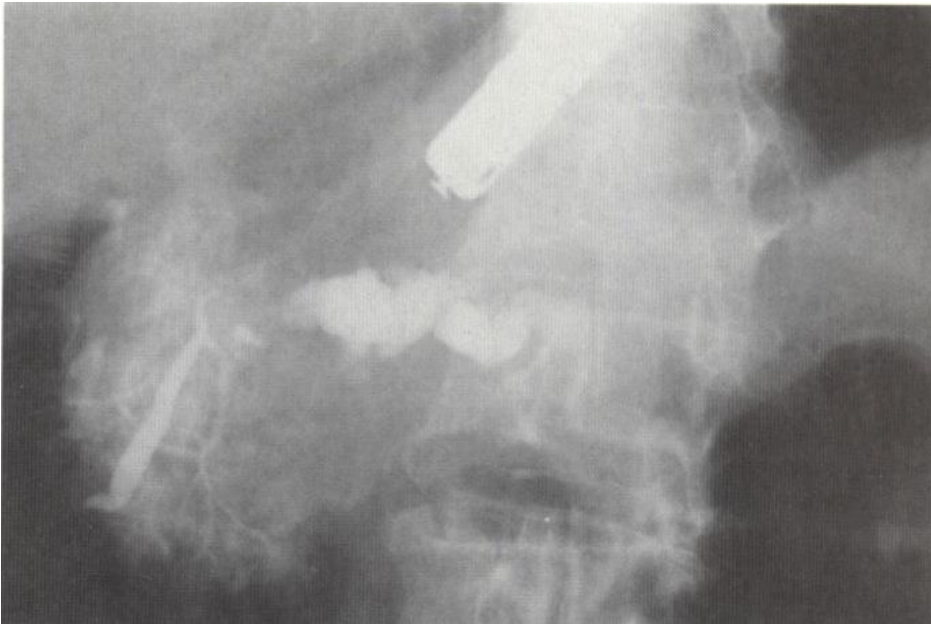
- Demography
 - o The incidence of chronic pancreatitis is approximately 8/10⁵ per year, and the prevalence is 27/10⁵.
 - o 10 year survival rate is 70%
 - o The standardized mortality ratio (SMR) is 3.6:1, with higher mortality rates associated with
 - Advanced age
 - Alcohol etiology
 - Continued alcohol use (↑ SMR by 60%)
 - Smoking (especially in alcoholics)
- Laboratory
 - o In situations where the results of pancreatic structure vary from the functional tests, it is suggested that “.....hormonal stimulation testing appears to be somewhat more sensitive and specific than ERCP” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 999).
- Diagnostic imaging
 - o Accuracy of detection on abdominal ultrasound: gallstones, > 90%; dilated CBD, 55-91%; CBD stones, 20-75%
 - o Contrast enhanced CT useful to grade pancreatitis, and to detect necrosis as well as neoplasm; equivalent to gadolinium-enhanced dynamic MRCP (but contrast-enhanced MRCP is superior to contrast enhanced CT to detect CBD stones) (Arvanitakis M, et al. *Gastroenterology* 2005:715-23).

There are numerous diagnostic imaging tests of pancreatic structure, and their performance characteristics for chronic pancreatitis vary widely:

Diagnostic Imaging Test	Sensitivity	Specificity
o Abdominal ultrasound	50% to 80%	80% to 90%
o CT	75% to 90%	> 85%
o Multidetector CT	> 80%	~100%
o ERCP	70% to 90%	80% to 100%
o EUS		
– > 3 diagnostic criteria, all comers	83%	57%
– Advanced disease	73%	81%
– > 4 criteria	90%	86%
o A caution about EUS to diagnose chronic pancreatitis: certain patient and disease related factors can mimic the EUS changes of pancreatitis, and lead to a false positive diagnosis.		



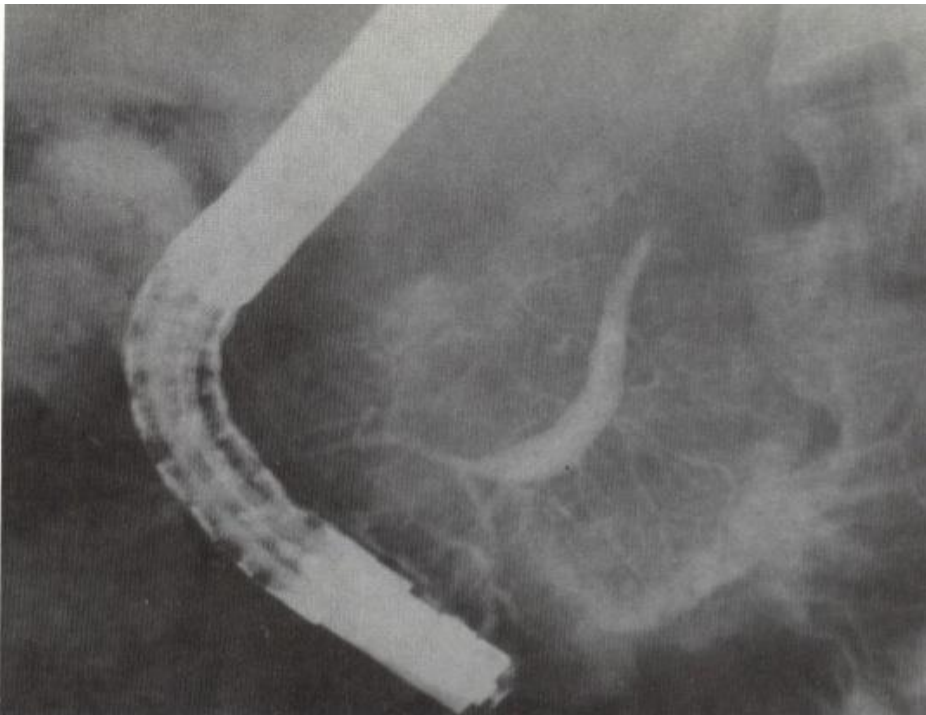
Narrowing of Pancreatic Duct, ERCP



Abrupt narrowing of pancreatic duct, but with distal dilation. The diagnosis was chronic pancreatitis, but there were no ductular changes in the head of the pancreas or calcification.

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Narrowing of Pancreatic Duct, ERCP

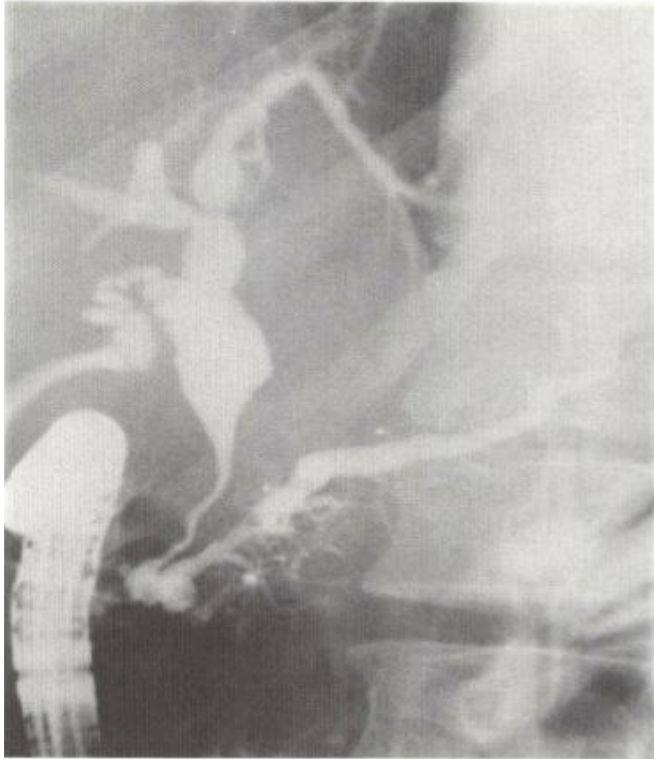


- o Abrupt narrowing and blockage of pancreatic duct, calcification, distal dilation, side branch changes)
 - Compare with pancreas divisum in which the opacified portion of the duct is usually narrower.

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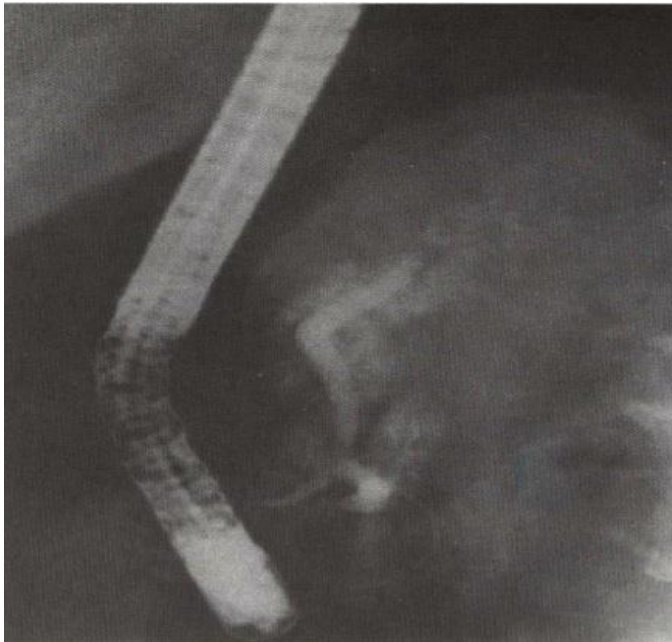
Narrowing of Biliary System



Narrowing of proximal pancreatic duct, with smooth narrowing of distal common bile duct from fibrosis of head of pancreas from chronic pancreatitis.

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Chronic Pancreatitis

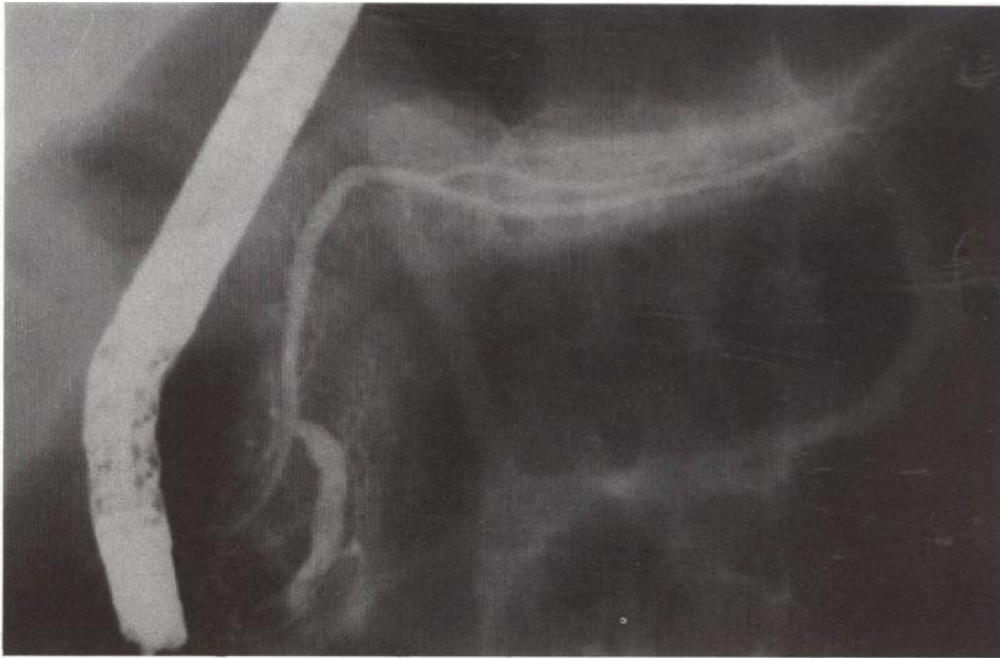


Normal calibre ducts stopping suddenly in body of pancreas, with acinar filling in head and distal calcification.

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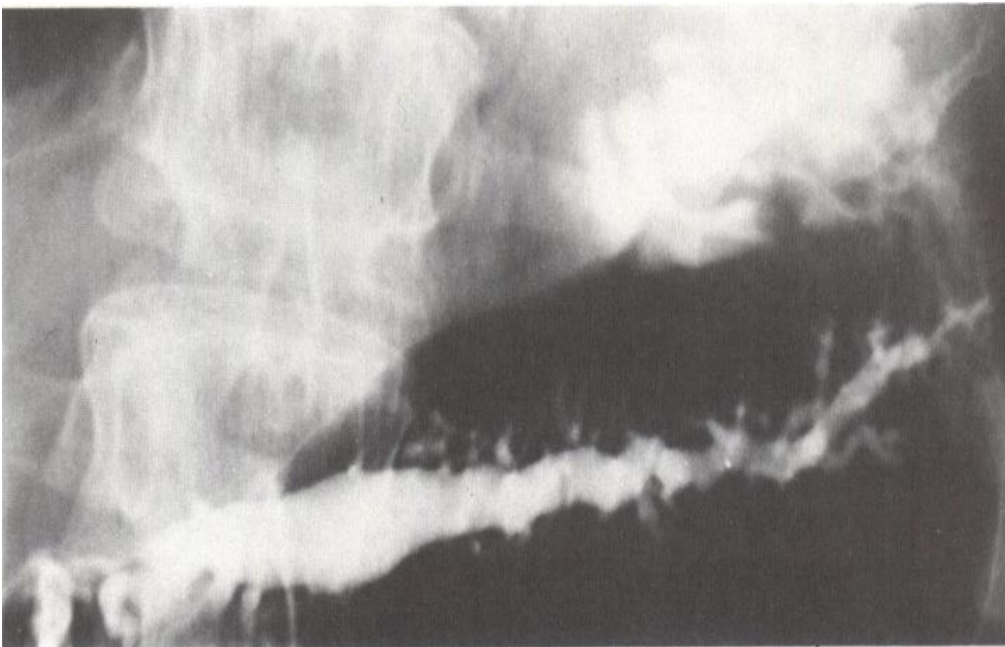
Chronic Pancreatitis



Bifurcation of main duct in body of pancreas, with calcification in parenchyma.

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Chronic Pancreatitis



Dilated main duct, disorganized and dilated branch ducts, small cystic areas in parenchyma.

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Grading of chronic pancreatitis by ERCP (Cambridge System)

Grade	Main Pancreatic Duct	Side Branches
o Normal	- Normal	Normal
o Equivocal	- Normal	< 3
o Mild	- Normal	≥ 3
o Moderate	- Abnormal	> 3
o Severe	- Abnormal, plus ≥ 1 of the following: ▪ Large cavity (> 10 mm) ▪ Duct obstruction ▪ Intraductal filling defects ▪ Severe dilation or irregularity	> 3

EUS Features (criteria for Chronic Pancreatitis)

Ductal Criteria	Parenchymal Criteria
o Dilated main pancreatic duct (MPD)	- Focal areas of reduced echogenicity
o Irregularity of MPD (strictures, dilations)	- Echogenic / hypoechoic foci
o Visualization of side branches	- Echogenic bands / strands
o Increase of echogenicity of MPD wall	- Enlarged gland
o Intraluminal echoes	- Accentuation of lobular architecture
o MPD disruption / cyst formation	- Cavities / cysts
	- Shadowing (parenchymal) calcifications

EUS Feature	Pathology Correlate
o Intraductal echogenic foci	- Stones, calcifications
o Echogenic duct wall	- Ductal fibrosis
o Side branch ectasia	- Periductal fibrosis causing dilated side ducts
o Inhomogeneous echo-pattern	- Edema
o Enhanced echogenic foci	- Calcifications
o Prominent interlobular septa	- Fibrosis
o Lobularity	- Fibrosis, glandular atrophy



A caution about EUS:

- o Certain patient- and disease-related factors can mimic the EUS changes of pancreatitis, and lead to a false positive diagnosis:

Patient-related	Disease-related
o Age	– Diabetes mellitus
o Tobacco	– Chronic renal disease
o Alcohol	

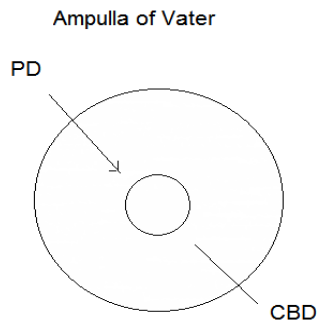
- For laboratory and / or diagnostic imaging tests for chronic pancreatitis, give the use for detecting major versus minor duct disease.

Diagnostic Test	Possible Findings in 'Big Duct' Disease	Possible Findings in 'Small Duct' Disease
o Fecal elastase	– Usually low (<100/g of stool)	▪ Usually normal
o Serum trypsin	– Usually low (< 20 ng/mL)	▪ Usually normal
o Abdominal ultrasonography	– Pancreatic atrophy – Pancreatic duct dilation – Pancreatic calcifications – Pseudocyst(s)	▪ Usually normal
o Computerized tomography	– Pancreatic atrophy – Pancreatic duct dilation – Pancreatic calcifications – Pseudocyst(s)	▪ Usually normal or equivocal
o MRCP	– Pancreatic atrophy – Pancreatic duct dilation – Irregularity or stricture – Pancreatic calcifications – Pseudocyst(s)	▪ Usually normal or equivocal
o Endoscopic ultrasonography	– Abnormal (> 4 features of chronic pancreatitis)	▪ May be abnormal
o ERCP	– Abnormal	▪ Normal or minimally abnormal
o Direct hormonal stimulation tests (e.g., secretin test)	– Abnormal	▪ Usually abnormal

Abbreviations: MRI, magnetic resonance imaging, MRCP, magnetic resonance cholangiopancreatography.

Source: Lieb JG II, and Forsmark CE. Aliment Pharmacol Ther. Review: Pain and Chronic Pancreatitis. *Journal Compilation* 2009;29:713.



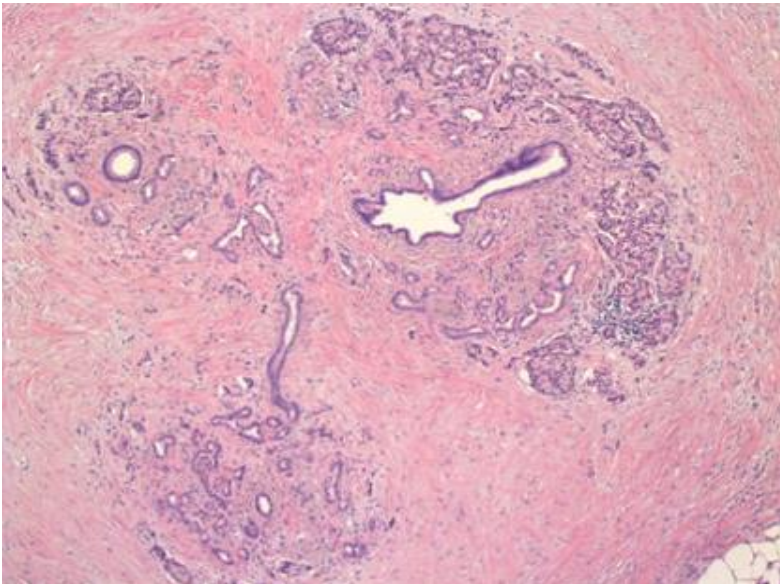


- o Estimate diameter of common bile duct (CBD) and pancreatic duct (PD) from the 11 mm diameter of the endoscope.
- o Normal diameter of values of CBD
- o Age
 - < 50, 6 mm
 - > 50, ↑ mm/10 yrs
- o After cholecystectomy – 11 mm

➤ Histopathology

- o Acute inflammation
 - Lymphocytes / Plasma cells
- o Chronic self-sustaining inflammation
 - Lymphocytes, plasma cells, macrophages
- o Fibrosis within and between lobules
- o Duct metaplasia
- o Eosinophilic protein plugs in duct
- o Destruction of acinar cells (islets of Langerhans usually preserved)
- o Similar histological changes to chronic pancreatitis may be seen in
 - Advanced age
 - Diabetes
 - Chronic kidney disease

Obstructive Chronic Pancreatitis



Advanced stage: dilated lobular ducts surrounded by remnants of acinar tissue embedded in fibrosis.

Printed with permission: Klöppel G. Modern Pathology 2007; 20, S113–S131.



SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Within the context of chronic pancreatitis, distinguish the histological features of AIP (autoimmune pancreatitis) from IDCCP (idiopathic duct centric chronic pancreatitis).

	Type 1 AIP	Type 2 AIP	IDCCP
o Cells	- Dense lymphoplasmacytic infiltrate - ↑ IgG4 positive plasma cells	- Dense periductal lymphocytes and plasma cells with: - Ductal / lobular abscesses and / or - Ductal alteration with neutrophils	- Significantly less inflammation; mostly lymphocytis; no periductal accentuation - Acinar atrophy (marked)
o Veins	- Obliterative thrombophlebitis		
o Fibrosis	- Storiform fibrosis		- Diffuse fibrosis (marked)

SO YOU HAVE NOT GIVEN UP WANTING TO BE A GI JOE/JILL

- Give the pathology of obstructive chronic pancreatitis.
 - o Obstructive chronic pancreatitis is
 - A distinct disease entity
 - Caused by a single dominant narrowing or stricture of the pancreatic duct
 - Characterised by diffuse interlobular and intralobular fibrosis
 - This fibrosis is “.....usually equally and symmetrically distributed in the affected area.”

(Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 993).

“Challenges are what make life interesting and overcoming them is what makes life meaningful.”

Joshua J. Marine



Hereditary Pancreatitis and Gene Mutations

➤ Definition

- o Hereditary pancreatitis is “.....recurrent acute or chronic pancreatitis in an individual from a family in which the pancreatitis phenotype appears to be inherited through a disease-causing gene mutation expressed in an autosomal dominant pattern.”
 - Usually caused by
 - Gain of function mutation in the PRSS1 gene
- o Familial pancreatitis is “....pancreatitis from any cause that occurs in a family with an incidence [of pancreatitis] that is greater than would be expected by chance alone, given the size of the family and incidence of pancreatitis within a defined population” (familial may or may not be caused by a genetic defect).
 - Usually caused by
 - SPINK1 mutations, or
 - CFTR – SPINK1 genotypes atypical (homozygous or atypical compound heterozygous).
- o Tropical pancreatitis is “.....a form of early age-onset, non-alcoholic chronic pancreatitis occurring in tropical regions that is often clustered among family members, and that has a complex genetic basis.”
 - SPINK1 N34S mutations are common

Autoimmune Pancreatitis (AIP)

➤ Definition

- o AIP is a mass forming, inflammatory lesion of the pancreas which shows usually diffuse involvement of the pancreas with irregular narrowing of the pancreatic duct and swelling of parenchyma.
- o There are 2 types;
 - Type 1 is the pancreatic manifestation of IgG4-related disease (which may also involve bile ducts, gallbladder, salivary glands, kidneys, retroperitoneum, and lymph nodes); “Lymphoplasmacytic sclerosing pancreatitis”
 - Type 2 is not related to IgG4; “Idiopathic duct centred pancreatitis”
- o Both types can be mistaken for pancreatic carcinoma and share some clinical and radiologic features

➤ Clinical features

- o Type 1:
 - Affected patients tend to be older (70s) and are more commonly male
 - Symptoms include fatigue, obstructive jaundice, weight loss, onset of diabetes mellitus
 - There may be painless swelling of the submandibular gland(s); in a patient with obstructive jaundice, this is highly suggestive of type 1 AIP

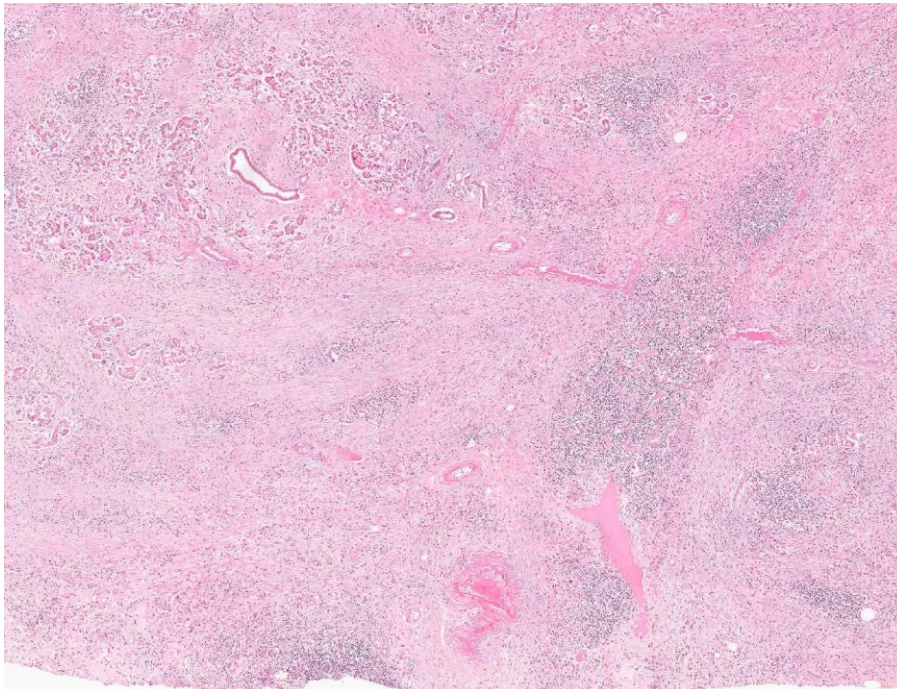


- o Type 2:
 - Affected patients tend to be in late middle age (50s)
 - M:F 1:1
 - May be demographic / clinical overlap with alcoholic pancreatitis
 - Accounts for almost 50% of cases in Europe and North America but is very rare in Asian countries
 - Symptoms include abdominal pain and are less likely to present with obstructive jaundice

➤ Histology

- o Type 1:
 - 3 features:
 - Lymphoplasmacytic inflammation
 - Storiform (whirling) fibrosis
 - Obliterative phlebitis
 - Immunohistochemistry shows increased IgG4+ plasma cells in the inflammatory infiltrate
 - Ductal epithelium is usually preserved
- o Type 2:
 - Dense *periductal* infiltrate of lymphocytes and plasma cells
 - Duct luminal neutrophils with microabscesses – “Granulocytic epithelial lesion”
 - +/- duct erosion, ulceration or destruction

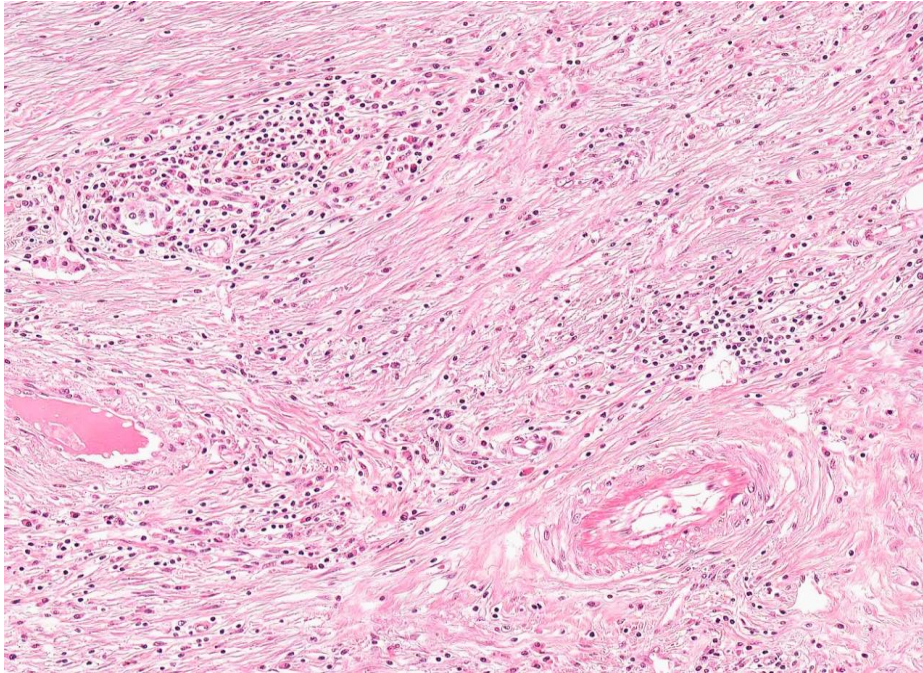
Autoimmune pancreatitis, type 1: Acinar loss and fibrosis with dense inflammatory infiltrates (H&E 40X)



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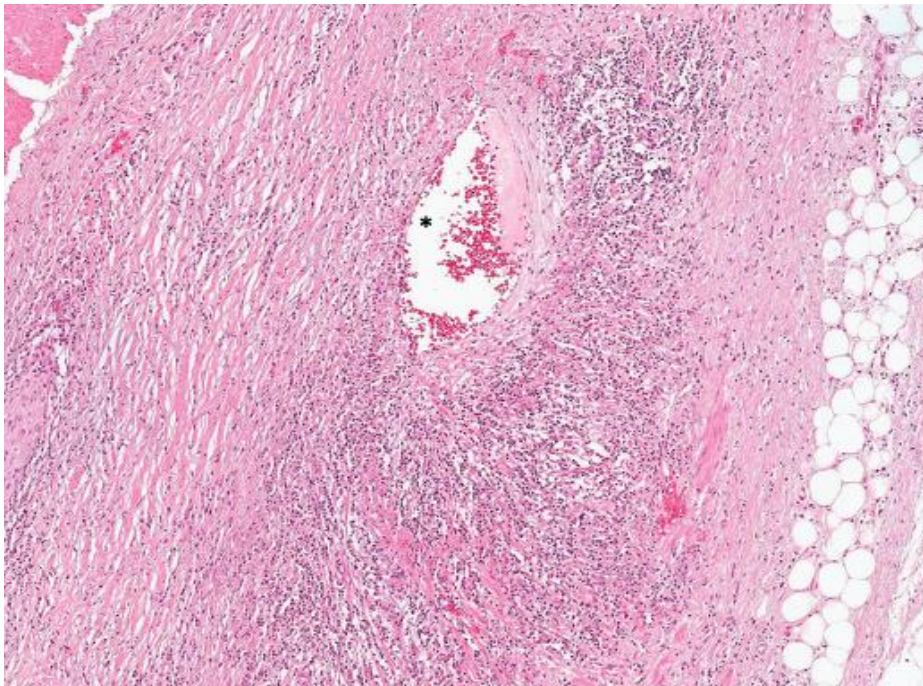


Autoimmune pancreatitis, type 1: Numerous plasma cells (H&E 200X)



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Autoimmune pancreatitis, type 1: Obliterative phlebitis with residual venous lumen (*, H&E 100X)



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Autoimmune pancreatitis, type 1: Obliterative phlebitis with residual venous lumen (*) and elastic lamina (arrows, MOVAT 100X)



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- Diagnostic imaging
 - o CT / MRI shows “sausage-shaped” enlargement of pancreas
 - o CT / MR: diffusely enlarged gland with delayed enhancement
 - o ERCP: diffusely irregular, attenuated main pancreatic duct
 - o Atypical imaging features
 - Pancreatitis
 - Focal pancreatic mass
 - Focal pancreatic duct stricture
 - Pancreatic atrophy



- Give diagnostic imaging manifestations of autoimmune pancreatitis.
 - o Abdominal ultrasound, EUS
 - Pancreas
 - Hypoechoic
 - Diffusely enlarged
 - o CT
 - Pancreas
 - Enlarged
 - “Sausage-shaped”
 - IV contrast
 - Delayed
 - Prolonged
 - No distal atrophy
 - Rim around the pancreas (delayed images)
 - Border
 - Peripheral (RIM) enhancement, and delayed enhancement; ERCP shows characteristic diffusely irregular and narrowed pancreatic duct
 - Rim-halo (hypoattenuation around the outside [rim] of pancreas)
 - Enhancement delayed
 - High density mass
 - Mass effect from focal swelling
 - Pancreatic duct
 - Diffuse or segmental narrowing (strictures)
 - Atypical imaging features:
 - Pancreatitis
 - Focal pancreatic mass / duct stricture
 - Pancreatic atrophy
 - Persistent distal biliary stricture
 - o MRI, MRCP
 - Pancreas
 - Diffusely enlarged ($\downarrow$ T₁ – and $\uparrow$ T₂ -weighted intensity)
 - Atrophy
 - Calcifications
 - Pancreatic duct
 - Attenuated main duct
 - Biliary strictures
 - o ERCP
 - Pancreatic duct
 - Diffuse or segmental narrowing from strictures
 - Narrowed main duct
 - No dilation
 - Irregular narrowing of intrahepatic ducts
 - No cut-off sign
 - Beaded (diffuse, irregular narrowing)
 - Focal stricture

See Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 993 for Diagnostic Criteria for Autoimmune Pancreatitis.



- Give diagnostic features on CT scanning in AIP which predict a favorable response to steroids.
 - o Diffuse swelling of pancreas
 - o Hypoattenuating halo around pancreas
 - o No focal mass in pancreas
 - o No strictures of ducts
- Compare and contrast the diagnostic imaging of autoimmune chronic pancreatitis (AIP) versus alcoholic chronic pancreatitis (ACP).

Site	ACP	AIP
o Duct	– Duct dilation	▪ Duct narrowing
o Pseudocyst	– Common	▪ Rare
o Calcification or stone	– Common	▪ Rare
o Pancreatic parenchyma	– Atrophy	▪ Enlargement

Printed with permission: Dite P, et al. *Best Practice & Research Clinical Gastroenterology* 2008; 22(1): pg. 136.

➤ Diagnosis

- Give the **Mayo Clinic HISOR diagnostic criteria** for the diagnosis of autoimmune pancreatitis (AIP), and the features characteristic for the diagnostic groups.
 - o Histology
 - At least one of the following:
 - Periductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis
 - Lymphoplasmacytic infiltrate with storiform fibrosis with abundant IgG4+ cells (>10 IgG4+ cells / HPF)
 - o Imaging
 - Typical: diffusely enlarged gland with delayed 'rim' enhancement, diffusely irregular, attenuated main pancreatic duct
 - Other: focal pancreatic mass / enlargement, focal pancreatic ductal stricture, pancreatic atrophy, calcification, pancreatitis
 - o Serology
 - Elevated serum IgG4 level (normal 8-140 mg/dL)
 - o Other organ involvement
 - Hilar / intrahepatic biliary strictures, persistent distal biliary stricture, parotid / lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis
 - o Response to steroid therapy
 - Resolution or marked improvement of pancreatic / extrapancreatic manifestation with corticosteroid therapy

Abbreviations: HPF, high power field; IgG4, immunoglobulin G4



➤ **Japan Pancreas Society** criteria for the diagnosis of AIP

Diagnostic criteria: for diagnosis, criterion I must be present together with criterion II and / or III

- I. Imaging criterion: diffuse narrowing of the main pancreatic duct with irregular wall (more than one third the length of the entire pancreas) and enlargement of the pancreas
- II. Laboratory criterion: abnormally elevated levels of serum gammaglobulin and / or IgG, or the presence of autoantibodies
- III. Histopathologic criterion: marked lymphoplasmacytic infiltrate and dense fibrosis

Abbreviations: AIP, autoimmune pancreatitis; IgG, immunoglobulin G

Printed with permission: Gardner, et al. *AM J Gastroenterol* 2009; 104: 1620-1623.

➤ Diagnostic groups of AIP

- o Group A: diagnostic pancreatic histology
 - Presence of one or more of the following criteria:
 - Specimen demonstrating the full spectrum of LPSP
 - >10 IgG4 + cells / HPF on immunostatin of pancreatic lymphoplasmacytic infiltrate
- o Group B: typical imaging and serology
 - Presence of all the following criteria:
 - CT or MRI scan showing diffusely enlarged pancreas with delayed and 'rim' enhancement
 - Pancreatogram showing diffusely irregular pancreatic duct
 - Elevated serum IgG4 levels
- o Group C: response to corticosteroids
 - Presence of all the following criteria:
 - Unexplained pancreatic disease after negative workup for other etiologies
 - Elevated serum IgG4 and / or other organ involvement confirmed by presence of abundant IgG4 positive cells
 - Resolution or marked improvement of pancreatic and / or extrapancreatic manifestations with corticosteroid therapy

Abbreviations: AIP, autoimmune pancreatitis; CT, computed tomography; HPF, high power field; IgG, immunoglobulin G; LPSP, lymphoplasmacytic sclerosing pancreatitis; MRI, magnetic resonance imaging

Printed with permission: Gardner, el. *AM J Gastroenterol* 2009; 104: 1620-1623.

- Give features of cholangiographic diagnostic imaging which suggest a biliary duct malignancy, rather than benign disease such as AIP or PSC.
 - o Length - > 10 mm
 - o Contour - Irregular
 - Ragged
 - o Filling defect - Fixed
 - o Shouldering - Sudden transition above stricture from normal to abnormal tissue
 - o Hilar region



- Give features on cholangiographic diagnostic imaging which help to distinguish PSC from AIC.

	AIC	PSC
o Stricture		
- Band-like	-	+
- Beaded	-	+
- Pruned-tree-like	-	+
- Segment	+	-
- Long	+	-
- Prestenotic dilation	+	-
- Bifurcation	-	-
- Distal CBD	+	-
o Diverticulum formation	-	+

- o Note: In AIC, about half of patients have:
 - Involvement of proximal intrahepatic or extrahepatic ducts
 - Intrahepatic strictures

➤ Histopathology

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Within the context of chronic pancreatitis, distinguish the histological features of Autoimmune chronic pancreatitis (ACP / AIP type 1) from Idiopathic duct centric chronic pancreatitis (IDCCP / AIP type 2).

	ACP	IDCCP
o Cells	- ↑ lymphocytes - ↑ plasma cells - IgG4 positive	▪ Neutrophils, as well as periductal lymphocytes and plasma cells
o Veins	- Obstructive phlebitis	
o Fibrosis	- "Whorled" = storiform (aka LPSP [lymphoplasmacytic sclerosing pancreatitis])	



- Give clinical and pathological features which distinguish between type 1 and 2 AIP.

Pathological types

Features	Type 1 AIP	Type 2 AIP
- Older age	+	-
- % ↑ serum IgG4 (≥ 280 mg/dL)	High%	Low%
- Idiopathic duct centric pancreatitis	-	+
- Granulocytic epithelial lesion	-	+
- > 10 IgG4-positive cells	+	-
- Predominantly periductal lymphoplasmacytic infiltrate	-	+
- Obliterative phlebitis	+	-
- Acinar fibrosis	+	-
- Systemic involvement	+	-
- Associated affected organs / conditions	Biliary tract Kidney Salivary glands Retroperitoneum	IBD
- High relapse rate	49%	0%

“Be an advocate, seek something good for everyone: seek justice and love.”
Grandad



SPLENIC VEIN THROMBOSIS (SVT)

➤ Demography

- o SVT develops in ~ 20% of persons with acute pancreatitis

Clinical Pearls

- o The patient has experienced repeated episodes of severe abdominal pain radiating to the back, in association with high levels of alcohol ingestion. On this occasion (s)he had similar pain and alcohol abuse, and the serum amylase or lipase is normal.
- o You are offered several plausible MCQ choices, as well as acute pancreatitis. Chronic pancreatitis is the answer – caution: normal serum amylase or lipase do not rule out chronic pancreatitis.
- o Alcoholics have an ↑ risk of having gallstones in the patient with acute pancreatitis. Suspect biliary tract gallstones if
 - Bilirubin > 4 mg/dL
 - ALT, AST > 1000 U/mL
- o If the patient with acute pancreatitis has also been drinking recently, the ALT, AST may be > 1000 U/mL, and the bilirubin may be increased (true, often > 15 mg/dL).

➤ Diagnostic imaging

Splenic Vein Thombosis



Printed with permission: Mujtaba G, Josmi J, Arya M, Anand S. Case Rep Gastroenterol. 2011 Apr;5(1):179-82. doi: 10.1159/000327215.



CYSTS AND TUMOURS

➤ Types

- Give the main types of pancreatic cysts.
 - o Pre-malignant / potential to harbour invasive adenocarcinoma
 - MCN (mucinous cystic neoplasm)
 - IPMN (intraductal papillary mucinous neoplasm)
 - Main duct (MD – IPMN)
 - Branch duct (BD – IPMN)
 - Malignant potential MD >> BD – IPMN
 - o Not pre-malignant
 - Serous cystadenoma (SCA)
 - Pseudocysts

The following features are useful when determining the most likely diagnosis of a cystic pancreatic neoplasm.

- o Patient
 - Age, gender
- o Pancreas
 - Site
 - Relation to large ducts
 - Contents
 - Serous
 - Mucinous
 - Necrotic debris
 - Lining cells
 - Columnar
 - Rich in mucin
 - Cuboidal
 - Rich in glycogen
 - Surrounding stroma
 - MCNs have a characteristic ovarian type stroma surrounding their lining epithelium
- o Types
 - Serous cystadenoma (SCA)
 - Mucinous cystic neoplasm (MCN)
 - Intraductal papillary mucinous neoplasm (IPMN)



- Give the differences of the characteristic features of SCA, MCN, IPMN.

➤ Demography

	SCA	MCN	IPMN
o Gender	F>M	F>>M(9:1)	M>F(6:4)
o Average age	65 yr	50 yr	64 yr
o Endoscopy	-	-	Wide-open ampulla Mucinous drainage

- Classify and give types of cystic and cystic-appearing lesions of the pancreas.
 - o Congenital true cysts
 - Polycystic disease
 - Von Hippel-Lindau disease
 - Cystic fibrosis
 - Dermoid cysts
 - o Inflammatory
 - Pseudocysts
 - Abscess with cystic degeneration
 - Hydatid cyst
 - o Cystic vascular lesions
 - o Cystic epithelial neoplasms
 - *Mucinous tumours*
 - Mucinous cystadenoma and cystadenocarcinoma
 - Intraductal papillary mucinous neoplasm– *Non-mucinous tumours* Serosus cystadenoma
 - Cystic degeneration in malignant neoplasm (adenocarcinoma, lymphoma, other)
 - o Misdiagnosed nonpancreatic lesions
 - Splenic artery aneurysm
 - Choledochal cyst
 - Mesenteric cyst
 - Duodenal duplication cyst or diverticulum
 - Lesser sac biloma
 - Lymphangioma
 - Hypoechoic solid tumour
 - o Metastases, with cystic component

Printed with permission: Degen L, et al. *Best Practice & Research Clinical Gastroenterology* 2008; 22(1): 92.



➤ Diagnosis

- Give a comparison of IPMN versus pancreatic pseudocyst.

	IPMN	Pseudocyst (PC)
o Sex	- Male (3-4:1)	Male
o Age	- 60s	Variable
o Ethanol abuse	- No association	Yes
o Pancreatitis history	- Yes uncommon	Yes uncommon
o Malignant potential	- Yes	No
o Location	- Head	Head
o Locularity	- Multilocular	Unilocular
o Calcifications	- No	No, unless associated with chronic pancreatitis

Adapted from: Scheiman JM. *AGA Institute Postgraduate Course* 2006: pg. 586.

	SCA	MCN	IPMN
➤ Diagnostic imaging			
o Uni-/multilocular	+	+	+
o Number	Equal or less than 6	Equal or greater than 6	Variable
o Size (cm)	Less than 2	Equal or greater than 2	Variable
o Calcification	Septum	Dystrophic	Variable
o Mural nodule	-	+	-
o Thick septations	-	+	-
o Central scar	+	-	-
o Honeycombed	+	-	-
o Dilated main/side ducts	-	+	+
o Filling defects	-	-	+
o Mucus coming out of papilla of Vater	-	-	+
➤ Laboratory (cyst fluid)	Watery	Mucus, blood	Mucus, blood
➤ Pathology			
o Site	Body, tail (50%)	Body, tail (> 80%)	Head - Main duct type - Branch duct type
o Communication of cysts and major ducts			+("bunch of grapes")



	SCA	MCN	IPMN
➤ Histopathology			
o Architecture	Usually numerous cystic spaces with central scar	Large, flat monolayer	Monolayer, or papillary
o Epithelial cells lining cysts			
– Shape	Cuboidal	Columnar	Columnar
– Nuclei	Small Central	Basal (unless high grade dysplasia present)	Basal (unless high grade dysplasia present)
– Cytoplasm	Clear / vacuolated Contains glycogen	Mucin Vacuoles	Mucin Vacuoles Granular / eosinophilic / oncocytic **
– Atypia of architecture, cells	-	+/-	+/-
o Stroma	Acellular	Ovarian type	No distinctive stroma
o Dysplasia	-	At least low grade dysplasia by definition	At least low grade dysplasia by definition
o Invasive adenocarcinoma	-	May be present	May be present (~1/3)
➤ Immunohistochemistry			
o PAS-positive diastase sensitive	+	-	-
o Cytokeratins			
– AE1 / AE3	+	+	+
– CAM5.2	+	+	+
– CK7,8,18,19	+	+	+
– CK20	-	+/-	+/-
o EMA	+	+	+
o mCEA	-	+	+
o Estrogen / progesterone receptors	-	+ in ovarian type stroma	-
o MUC2+ / MUC1-***	-	-	+ (2/3)*

* IPMN-gastric foveolar type of IPMN is MUC1- / MUC2-

** "IPMN" with prominent granular eosinophilic cytoplasm are called IOPN, intraductal oncocytic papillary neoplasm

*** IPMN types

Intestinal	MUC1-, MUC2+
Pancreaticobiliary or invasive	MUC1+, MUC2-
Gastric foveolar	MUC1+, MUC2-



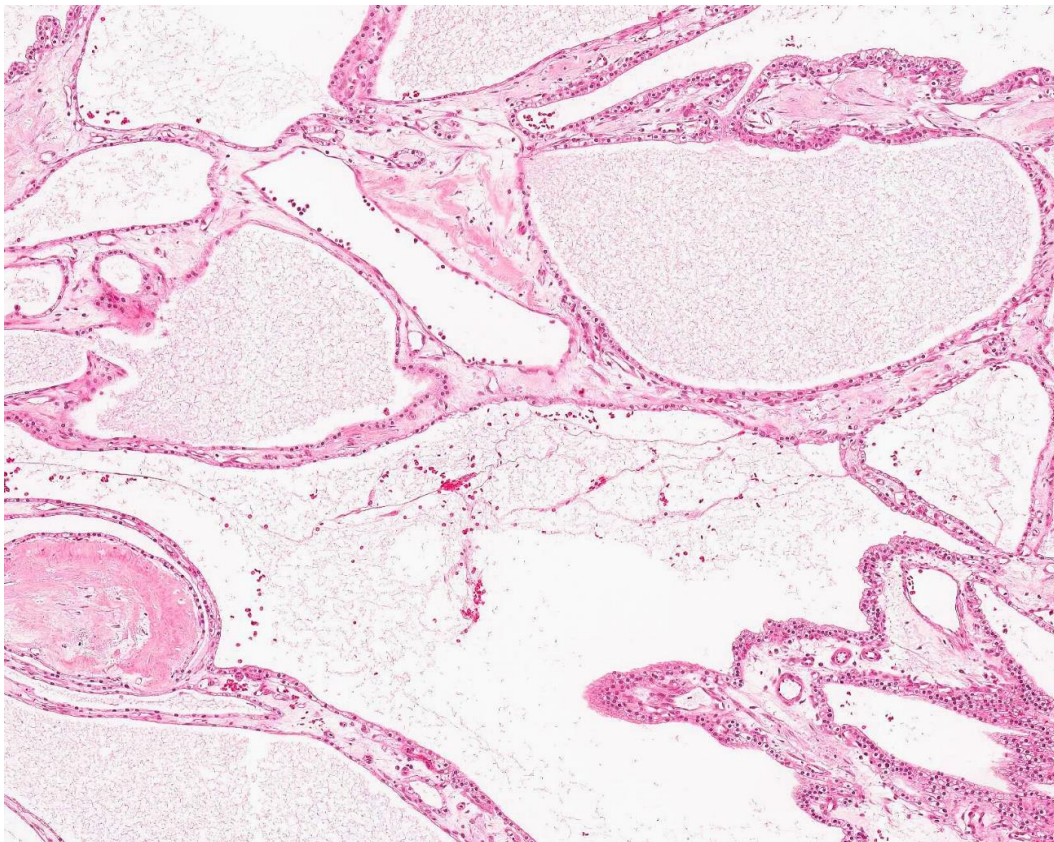
Serous Cystadenoma

- Definition
 - o “A benign epithelial neoplasm [of the pancreas] characterized by uniform glycogen-rich cuboidal cells lining numerous small cysts containing serous fluid”
 - o Well-circumscribed mass containing multiple tiny (<3 mm) cysts
 - o Honeycomb” gross appearance
 - o Cysts contain serous fluid
 - o Central stellate scar
 - o Scar may become calcified
- Diagnostic imaging
 - o Contrast – enhanced CT
 - Mass
 - Multiple (≥ 6), small (< 2 cm) cysts
 - Septal calcification
 - Central scar
 - Low attenuation (dark)
 - Circumscribed
 - Septa – thin (“honeycomb” – like)
 - Central “sunburst” calcification
 - o Ultrasound
 - Cysts, or solid appearance if multiple small cysts result in numerous acoustic interfaces
 - MRI without contrast
 - T_1 –weighted images
 - Low signal intensity (dark)
 - T_2 –weighted images
 - High signal intensity (white)
 - Duct dilation
- Histopathology
 - o Body or tail of pancreas
 - o Many tiny cysts lined by cuboidal cells with clear cytoplasm and uniform nuclei
 - o Fibrous septa
 - o Honeycomb appearance
 - o Scar with stellate appearance
 - o Stellate scar may be calcified
 - o Cysts filled with clear, watery fluid (no mucin)
 - o Cytology of fluid may show cuboidal cells with glycogen-rich cytoplasm



- o Rarely malignant (3%)
- o No communication with pancreatic duct
- o Cysts lined by single layer of cuboidal cells
- o Occasionally seen are intracystic epithelial papillae
- o Stroma may contain trapped ductular or acinar cells, or islets of Langerhans
- o When serous cystadenoma becomes “locally aggressive” and metastasizes, then called “serous cystadenocarcinoma”
- o FNA
 - Few cells, which are
 - Monomorphic
 - Cuboidal
 - Nuclei small
 - Cytoplasm clear / vacuolated
 - Proteinaceous cystic material

Serous Cystadenoma (H&E 100X)



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Mucinous Cystic Neoplasm (MCN)

- Definition
 - o Mucin-producing neoplasm of the pancreas
 - o No communication with pancreatic duct on ERCP / MRCP
 - o Usually (80%), in body or tail of pancreas
 - o May be benign, but in individual patient assume to be malignant
 - o Larger cysts with nodules in wall are more likely to be malignant
- Diagnosis
 - Give a comparison of pancreatic serous cystadenoma versus mucinous cystic neoplasm.

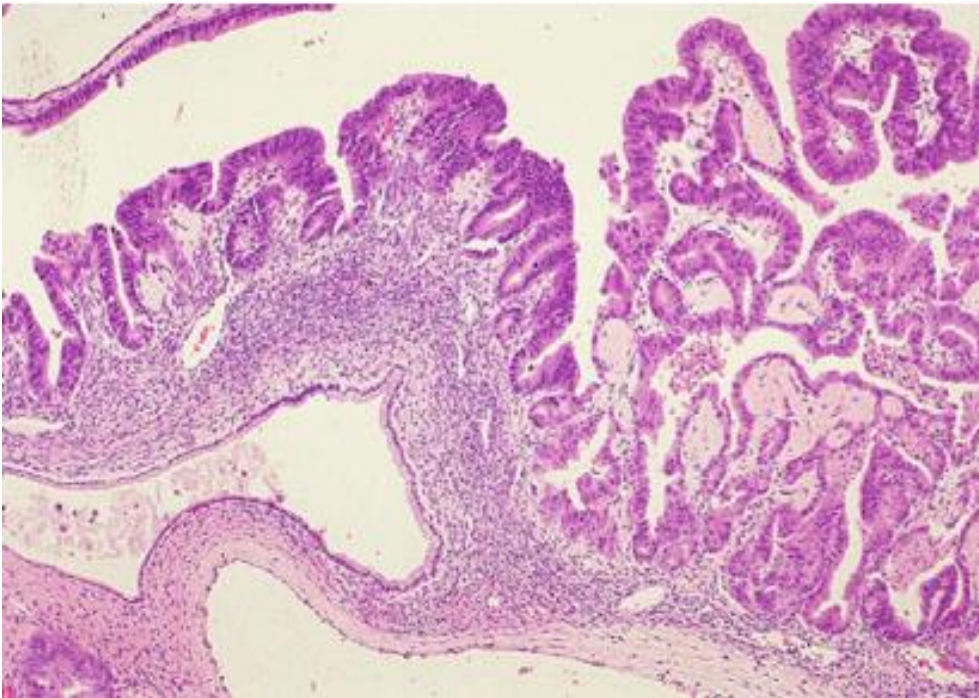
	Serous Cystadenoma (SCA)	Mucinous Cystic Neoplasm
o Sex	Female (2-3:1)	Female (>98%)
o Age	60s	Mean 48 yrs (Range 14-95)
o Ethanol abuse	No association	No association
o Pancreatitis history	Yes (uncommon)	Yes (uncommon)
o Malignant potential	No (exceedingly rare)	Yes (15%)
o Location	Usually body / tail	Body / tail
o Locularity	Multiple small	Unilocular or multilocular
o Calcifications	Yes (central sunburst or stellate)	Yes (peripheral, curvilinear)

Adapted from: Scheiman JM. *AGA Institute Postgraduate Course* 2006: pg. 586.

- Histopathology
 - o Thick wall
 - o Occasional septa
 - o Thick mucous material (+/or hemorrhagic necrotic material)
 - o Cysts lined by tall columnar mucin-producing epithelium
 - o Occasional goblet-type mucinous cells
 - o May contain activated multinucleated giant cells
 - o Rim of calcification in 20%
 - o Stroma (ovarian-like)
 - o Low (encompasses previous low grade and moderate dysplasia categories) or high grade dysplasia
 - o 15% associated with invasive pancreatic adenocarcinoma



Mucinous Cystic Neoplasm (with ovarian-type stroma) of Pancreas



The distinctive hypercellular stroma, which shows all the morphologic and immunophenotypic characteristics of ovarian stroma, has become a requirement for the diagnosis of this tumour type. The epithelium in mucinous cystic neoplasia may show various degrees of atypia, ranging from low grade (lower left) to high grade (upper).

Printed with permission: Volkan Adsay N. Mod Pathol. 2007; 20 Suppl 1:S71-93.

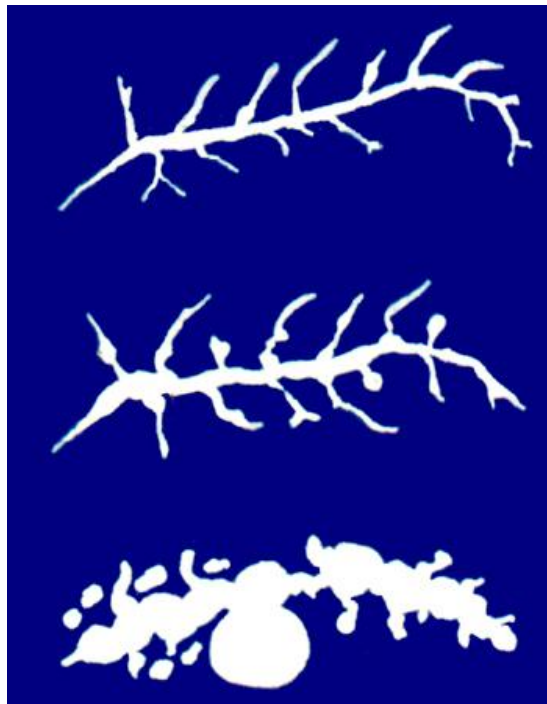
- Fluid in cyst
 - ↑ CEA suggests invasive adenocarcinoma
 - Cytology shows
 - Thick mucin and often few mucinous epithelial cells which may form sheets and small clusters
- Prognosis
 - If invasive carcinoma is not present the prognosis is excellent (5 year survival rate 100%)
 - Associated invasive carcinomas follow an aggressive clinical course which depends on TNM staging and resectability



Intraductal Papillary Mucinous Neoplasms (IPMN)

- Definition
 - o “.... Papillary neoplasms within the main pancreatic duct showing mucin hypersecretion that often leads to duct dilation and chronic obstructive pancreatitis.
 - o Lesions of main or branch pancreatic ducts, with proliferation of the mucinous epithelium leading to ductal and cystic dilation
 - o Papillary mucin-producing epithelial lesions that arise in the large pancreatic ducts and lack a distinctive ovarian stroma
 - o Thick (viscous) mucous with ↑ CEA, ↑ amylase
- Demography
 - o Male: female ratio: 1-2.4 (with significant geographic variation)
 - o Mean age of diagnosis: 65 years
 - o Up to 40% of IPMNs are multifocal, arising from a field defect in the entire pancreas that can cause multiple primary neoplasms (WHO classification of tumours 2019)
- Types
 - Three types of IPMN, including main, branch or main plus branch (mixed) pancreatic ducts

- Mild: Normal or only slightly dilated main pancreatic duct, mild ectasia of side branches. No pseudocyst, no concretions.
- Moderate: Dilatation, caliber fluctuations, mild tortuosity main pancreatic duct. Mild cystic dilation, stenosis or obstruction of side branches.
- Severe: Beading, stenosis, obstruction, cyst formation, calculi in main pancreatic duct or side branches.



- Diagnostic imaging
 - o MDCT (multidetector CT), MRCP, breath-hold MRCP, MRCP with secretin (S-MRCP), CT using pancreatic protocol (detects IPMN in 97% of cases), EUS, ERCP, MRI
 - o Contrast-enhanced CT
 - Mass arises either in pancreatic ducts
 - Uni- or multiocular
 - Dilated ducts (contain mucin)
 - Small villous IPMNs look like “frondlike enhancing filling defects within the dilated pancreatic duct”
 - Atrophy of parenchyma
 - Calcification
 - Solid tissue-like attenuation from mucin within ducts
 - o MRCP
 - MRCP is superior to CT to demonstrate communication between ducts, and cyst morphology
 - o ERCP
 - Standard for diagnosis
 - Filling defects in ducts
 - Duct dilation
 - Cyst may fill with contrast from a duct (communication)
 - Mucin seen dripping out of papilla of Vater
 - Mucin flowing out of patulous ampulla of Vater is highly suggestive of an IPMN
 - Papillary projections into the lumen of the duct
 - o PET scanning sensitivity, 57-90%; specificity, 85-97%
 - o Exclude pancreas divisum (MRCP, 100% accurate; CT, sensitivity 90%, specificity, 97%)

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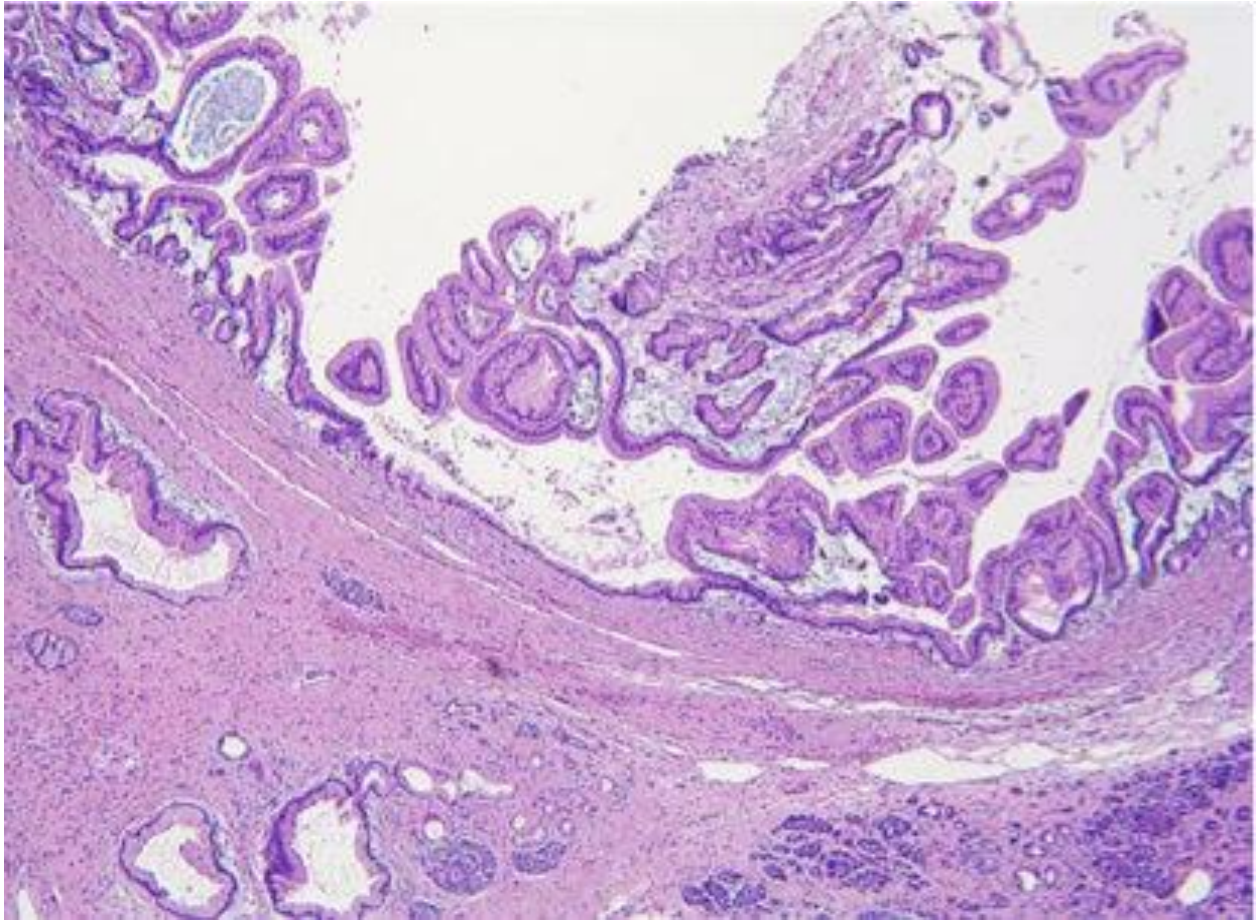
- Give “pathognomonic” findings which help to differentiate between the types of pancreatic cyst.
 - o ERCP-mucus dripping from ampulla of Vater → IPMN
 - o CT-central, sunburst calcification → serous cystadenoma



- Histopathology
 - o Cytology
 - Columnar mucinous epithelial cells with variable atypia
 - o Grape-like cluster of cysts, localized or diffuse dilation of main pancreatic duct, patulous ampulla of Vater
 - o Lesions of main or branch pancreatic ducts, with proliferation of mucinous epithelium leading to ductal and cystic dilation
 - o Microscopy
 - Papillae lined by tall columnar cells
 - Columnar cells produce mucin
 - Intracellular and extracellular mucin
 - Cuboidal cells with eosinophilic cytoplasm
 - 3 histologic types:
 - Gastric type (~70%)
 - Intestinal type (~20%)
 - Pancreaticobiliary type (least common)
 - Columnar cells may have granular, eosinophilic cytoplasm
 - When granular eosinophilic cytoplasm is present, these IPMNs are called IOPNs (intraductal oncocytic papillary neoplasms)
 - o Range histologically from low grade to high grade dysplasia
 - o Invasive carcinoma is found in association with up to 60% of main duct IPMNs. Concomitant adenocarcinomas (separate to the IPMN and not thought to be arising from it) are more commonly seen with branch duct IPMNs. Main duct IPMNs are more likely to become malignant and to grow faster: 63% develop HGD / cancer in 5 years, vs 15% for branch duct IPMNs
 - Grading
 - Low grade (incorporates previous categories of low and intermediate grade dysplasia)
 - High grade dysplasia irregular branching of papillae (architectural complexity)
 - Severe atypia
 - Loss of nuclear polarity
 - Stratification
 - Nuclear pleomorphism
 - Mitotic figures
 - o FNA
 - Epithelial atypia
 - Atypia focal or confluent
 - Nuclei round
 - Clear cytoplasm
 - Mucin



IPMN in Smaller Pancreatic Ducts



- These tumours can involve any component of the ductal system.
 - The larger cyst in this example is in fact a markedly dilated branch duct.
 - Smaller units are often involved (lower left) with what is presumed to be spread of the lesion.
 - It can be difficult, to distinguish these from incidental / independent PanINs.
 - This example also illustrates the gastric foveolar-type of papillae.

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“Give light and people will find the way.”

Ella Baker



- Give the diagnostic features of pancreatic cysts.

Cyst Type	EUS Features	Fluid Appearance	Cytology	Fluid CEA	Amylase
o SCA	Microcystic, honeycombed, 20% macrocystic	Thin, clear, sometimes bloody	Cuboidal cells, clear glycogen rich cytoplasm	Low	Low
o MCN	Macrocystic	Viscous, clear	Mucin-rich fluid, columnar mucinous cells with variable atypia	High	Low
o IPMN	Cystic main or branch duct dilation	Viscous, clear	Mucin-rich fluid, columnar mucin-positive cells (3 types), with variable atypia	High	High
o Pseudo-cyst	-Variable	Variable, typically non-mucinous	Small cells, scant cytoplasm, monomorphic nuclei	Unknown	Low
o SPT	Mixed solid and cystic	Bloody	Papillary structures, macrophages, myxoid stroma, monomorphic neoplastic cells	Low	Low
o LEC	- Solid, heterogeneous - Subtle posterior enhancement	Thick and milky, gray or frothy	Anucleated squamous cells, lymphocytes	Variable	Low
o PP	Macrocystic, thick wall, unilocular, internal debris	Thin, dark, non-mucinous	Inflammatory cells without evidence of mucin or epithelial cells	Variable	High

Abbreviations: EUS: Endoscopic ultrasound; IPMN, intraductal papillary mucinous neoplasm; LEC, lymphoepithelial cysts; MCN, mucinous cystic neoplasms; PD: Pancreatic duct; PET, pancreatic endocrine tumour; PP, pancreatic pseudocysts; SCA, serous cystadenoma; SPT, solid pseudopapillary tumours

Printed with permission: Fasanella KE, and McGrath K. *Best Practise and Research Clinical Gastroenterology* 2009; 23:35-48; Brugge WR. *2009 ACG Annual Postgraduate Course*:231-234.



Pseudocysts

➤ Definitions

- o A collection of pancreatic juice lined by fibrous and reactive granulation tissue, usually caused by pancreatitis or leakage of the pancreatic ducts, and usually communicating with the pancreatic ductal system
- o Small or large, single or multiple, inside or outside of the pancreas itself
- o Non-epithelialized fluid collection > 4 wk old, as a consequence of AP, CP, trauma from disruption of pancreatic duct (PD), acute pancreatitis (AP), chronic pancreatitis (CP)
- o Localized necrosis of pancreatic tissue, or pancreatic as well as peripancreatic fat necrosis, cause a leak in the pancreatic duct and a cystic space filled with amylase-rich fluid
- o The acute pseudocyst may become chronic “..... as a sequela of chronic pancreatitis and downstream pancreatic ductal obstruction with fibrotic strictures or stones” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 1039).
- o WOPN (walled-off pancreatic necrosis)
 - Internal debris in WOPN, rather than fluid in pseudocyst, is predictor of inferior outcome
 - Nasocystic or PEG-cystic cavity drain
 - Necrosectomy, 90% success rate within 4.1 month

➤ Demography

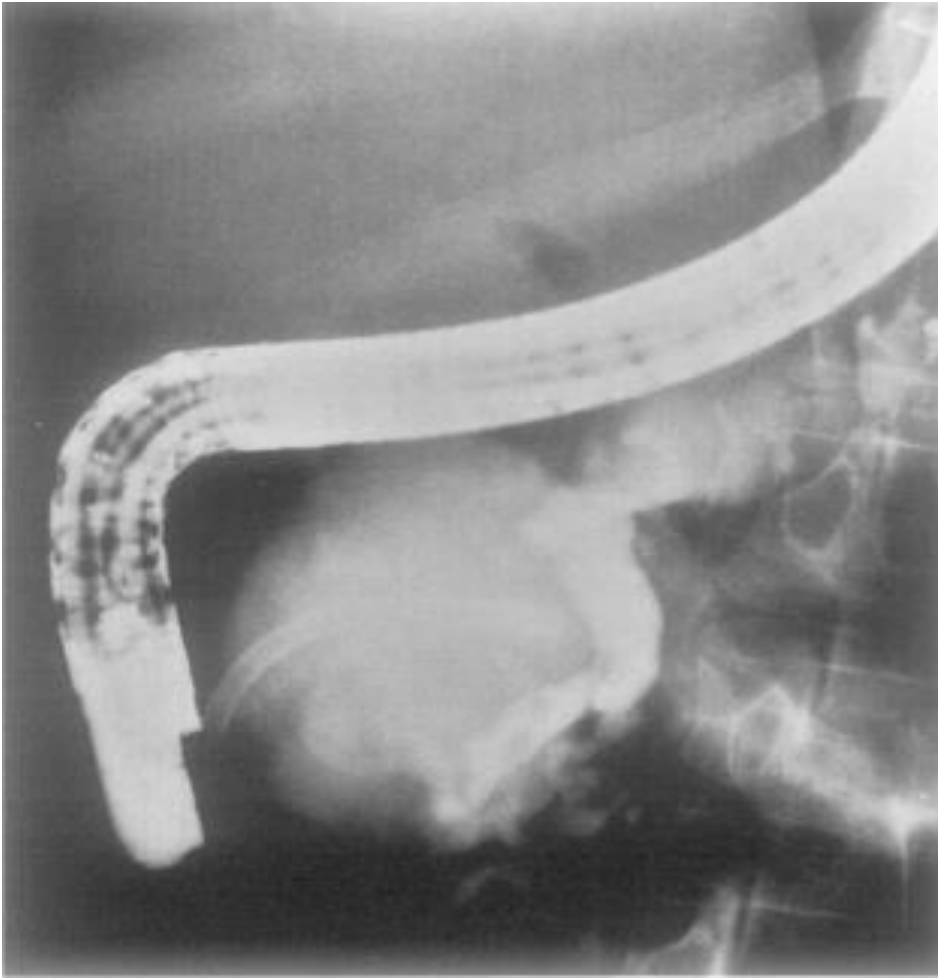
- o Gender M >> F
- o Age > 40 yr
- o Associated alcoholism / alcoholic pancreatitis

➤ Diagnostic imaging

- o Peripancreatic fluid collection
- o Lasts > 6 weeks
- o Thick fibrous wall
- o Contains distinct fat
- o Blurring (loss) of distinct tissue planes between mass and the retroperitoneal fat and peripancreatic tissue stranding
- o Thickening / stranding of soft tissue
- o Peripancreatic fluid collection
- o Communicates with pancreatic duct
- o Use EUS to
 - Perform FNA
 - Identify ideal drainage site
 - Identify gastric varices, pseudoaneurysms
- o Diagnostic imaging, with percutaneous catheter drainage
 - Especially successful for normal pancreatic ducts, or
 - Strictures which do not communicate to duct



Pancreatic Pseudocysts



ERCP. Patient with chronic pancreatitis and a large pseudocyst. Endoprosthesis inserted via duodenal wall in pseudocyst.

Printed with permission: Smits ME, et al. The efficacy of endoscopic treatment of pancreatic pseudocysts. *Gastrointest Endosc* 1995;42(3):202-7.

➤ Differential

- o Suspect that an encapsulated collection of fluid on diagnostic imaging is a pseudocyst rather than a cystic pancreatic cancer when
 - There is a history of
 - Pancreatitis
 - Pancreatic trauma
 - CT shows
 - Inflammatory changes
 - Simple cyst (i.e., no internal septa)
 - No echogenic mucin
 - No mass lesion
- o Ductal carcinoma



- o Other types
 - Pancreatic cysts
 - Serous
 - Mucinous
 - IPMN (intraductal papillary mucinous neoplasm)
 - Solid pancreatic neoplasms
 - Solid pseudopapillary neoplasm
 - Solid pancreatic adenocarcinoma with some cystic changes

Paraduodenal Wall Cyst

➤ Definition

- o Inflammatory infiltration of small pancreatic ducts in the “groove region” of the pancreas, causing dilated cysts lined by partially denuded ductal epithelium.

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- With respect to the location of paraduodenal wall cysts, give the “groove” region of the pancreas.
 - o The region demarcated by “...the superior aspect of the pancreas, the common bile duct and the minor papilla”, or
 - o “the superior aspect of the [head of] the pancreas, the common bile duct, and the duodenum” (Hruben RH and Ali SZ. Chapter 17. Gastrointestinal and Liver Pathology. Second Edition, page 522-3)

➤ Demography

- o M >> F
- o Onset > 50 yr
- o Often associated with alcohol

➤ Differential

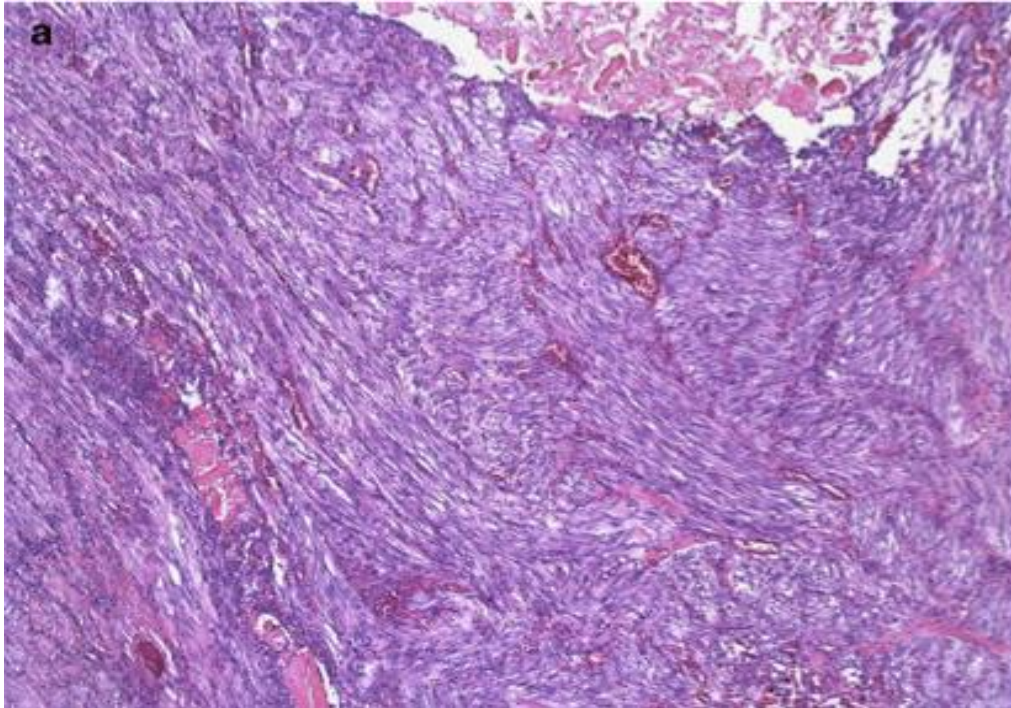
- o Pancreatic cyst / neoplasm
- o Other neoplasms with spindle cells

➤ Histopathology

- o Located to “groove” region of pancreas
- o Infiltration of inflammatory cells → dilation of small ducts → cysts
- o Cysts are lined by partially denuded epithelium of the small pancreatic ducts
- o There may be florid myofibroblastic proliferation (spindle cells)

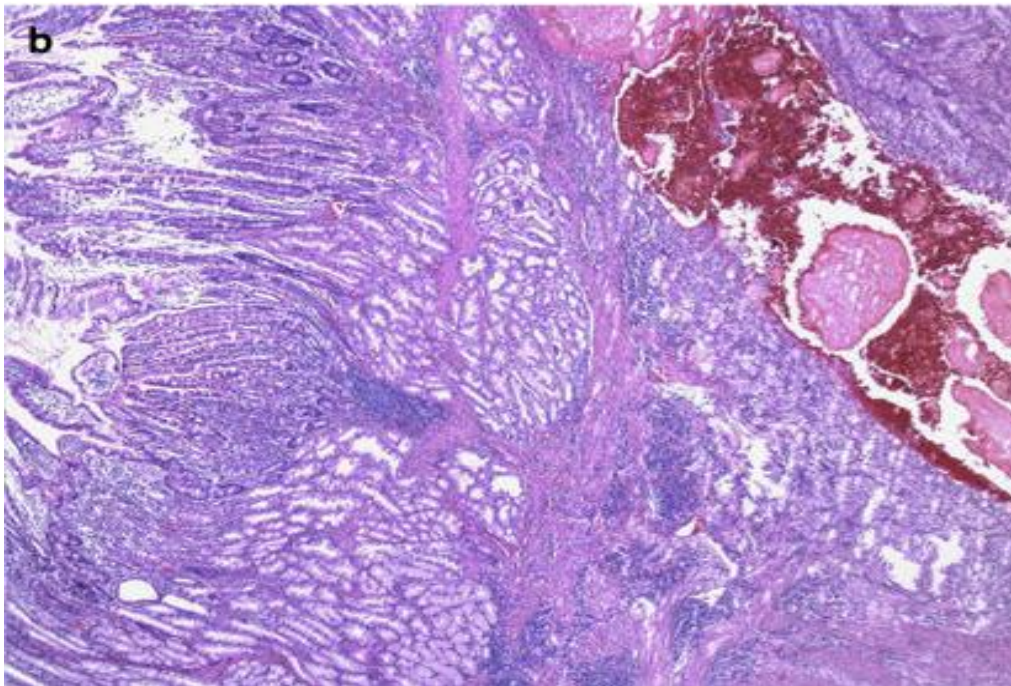


Paraduodenal Pancreatitis



Printed with permission: Klöppel G. Modern Pathology 2007; 20, S113–S131.

Paraduodenal Pancreatitis



Printed with permission: Klöppel G. Modern Pathology 2007; 20, S113–S131.



Solid Pseudopapillary Neoplasms

- Definition
 - o "... a low-grade malignant epithelial neoplasm composed of poorly cohesive cells with uniform nuclei and frequent nuclear grooves surrounding delicate blood vessels and [forming] solid masses that show cystic degeneration and intracystic hemorrhage".
- Demography
 - o Gender, F >> M (20:1)
 - o Average age at diagnosis ~ 25 yr
- Endoscopy
 - o Heterogenous areas
 - Solid
 - Cells uniform
 - Cytoplasm may contain eosinophilic globules
 - Nuclear grooves
 - Cystic
 - Loss of adhesion of cells
 - Necrosis
 - RBCs
 - Foam cells
 - Cholesterol crystals

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Papanicolaou staining of FNA (fine needle aspiration) of solid pseudopapillary neoplasm may show a characteristic configuration of the neoplastic cells in the aspirated fragments.

- Give the name of the configuration, and its composition.
 - o "Chinese characters" appearance arising from the neoplastic cells in the aspirated fragments aggregating around the finely branched capillaries.
- Give the histological features, which are characteristic of a pancreatic solid pseudopapillary neoplasm.
 - o Solid and pseudopapillary structures
 - o Hemorrhage and pseudocystic changes
 - o Neoplastic cells not cohesive but attach to and surround fibrovascular cores



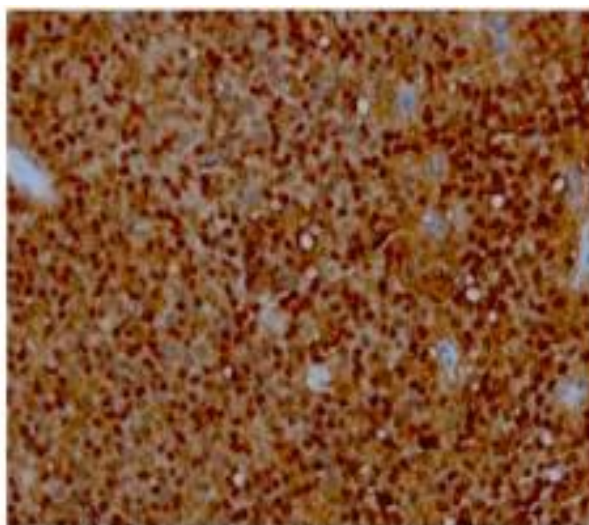
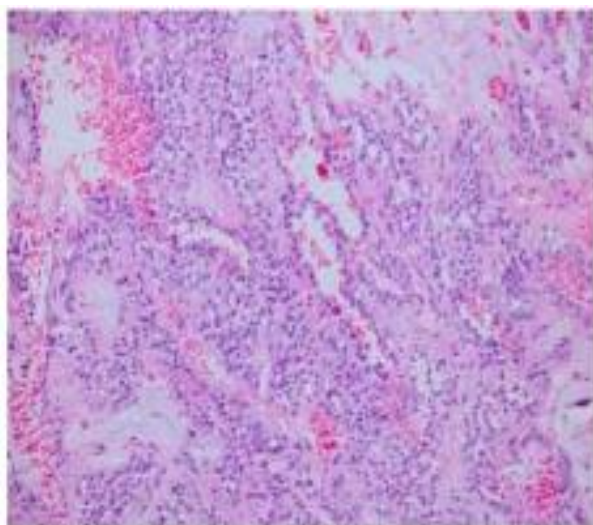
- Give the immunohistochemical positive features for pancreatic solid pseudopapillary neoplasms (PPN) versus infiltrating pancreatic ductal adenocarcinoma (PDA).

	Pseudopapillary Neoplasm (PPN)	Infiltrating Ductal Adenocarcinoma (PDA)
o Vimentin	+	-
o NSE	+/-	-
o CD10	+	-
o α 1-antitrypsin (in hyaline globules)	+	-
o β -catenin in abnormal position in nucleus	+	-
o Cytokeratin (CK7, 8, 19)	+/-	+
o CEA, CA19-9	-	+
o AE1 / AE3	+/-	+
o Synaptophysin	+/-	-
o CyclinD1	+	-
o PR	+	-
o CD99	+	-
o CD56	+	-

Abbreviations: NSE, neuron-specific enolase

Note: IHC staining with combination of CD10 and β -catenin is present in 90% of PPN

Solid Pseudopapillary Tumor of the Pancreas



H and E stain (L) and B-catenin stain (R) with prominent nuclear staining

Source: Punch C, et al. Case Reports in Oncological Medicine, vol. 2016, Article ID 7523742, 2 pages, 2016.



OTHER MALIGNANT TUMOURS OF THE PANCREAS

➤ Types

- Give types of other malignant tumours of the pancreas.
 - o Lymphoma
 - Flow cytometry needed to confirm subtype in many cases
 - Round
 - Discrete
 - More hypoattenuating
 - o NET (well differentiated neuroendocrine tumour)
 - Functioning
 - Gastrinoma
 - Insulinoma
 - Glucagonoma
 - VIPomas
 - Somatostatinoma
 - Non-functioning
 - Neuroendocrine carcinomas
 - Small cell or large cell type

Pancreatic Neuroendocrine Tumours

➤ Demography

- o Incidence < 1/ 100,000 person years
- o Wide age range, highest incidence 30-60 years
- o No sex predilection
- o Subdivided into
 - Well differentiated neuroendocrine tumours (NET)
 - Poorly differentiated neuroendocrine carcinomas (NEC)
- o NETs are graded as:
 - G1 (<2 mitoses per 2mm², Ki67 <3%)
 - G2 (2-20 mitoses per 2 mm², Ki67 3-20%)
 - G3 (>20 mitoses per 2 mm², Ki67 >20%)
- o NECs are high grade malignant tumours by definition

➤ Diagnostic imaging (NETs)

- o Ultrasound / endoscopic ultrasound
 - Hypoechoic mass (must have a water-filled stomach)
 - Intraoperative ultrasound is ~ 99% sensitive for islet cells tumour (ICT)



- Rim of hyperenhancing tissue
- Metastatic islet cell tumour
 - Echogenic (white), with posterior acoustic shadowing
- Rare cystic ICT
 - Septation
 - Nodule
- o Contrast – enhanced CT
 - Hyperenhancing (white) mass in arterial phase
 - Solid / cystic
 - Single / multiple
 - “gastrinoma triangle”

Distinguishing diagnosis: Islet cell tumour (ICT) metastasis to liver vs hepatic hemangioma on ultrasound

	Echogenic	Posterior Acoustic Shadowing
o Hemangioma	+	-
o ICT	+	+

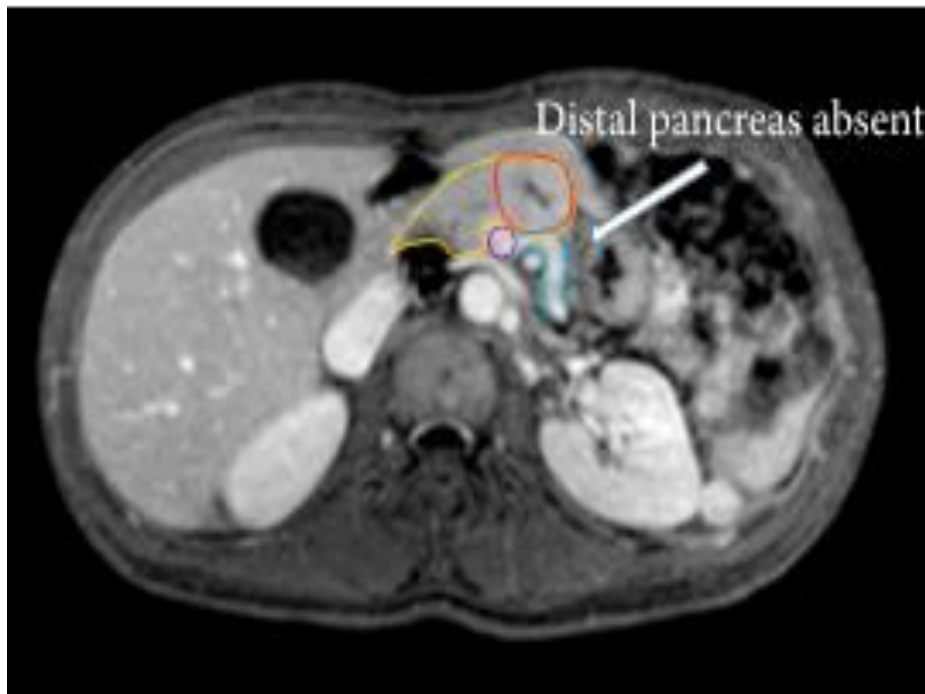
- Give the features of the octreotide scan uptake by somatostatin-receptor rich islet cell tumour.
 - o MRI
 - T₁ weighted
 - Masses – hypointense (dark)
 - T₂ weighted
 - Masses – hyperintense (white)
 - Liver metastases – fluid-filled layers

Distinguishing diagnosis: Ductal Adenocarcinoma vs Islet Cell Tumours

Features	Ductal Adenocarcinoma	Islet Cell Tumour
o Size	≤ 40 mm	0.5 mm to 100 mm
o Vascularity	↓	↑
o Vascular Encasement	++++	+
o Calcification	+	++++
o Duct dilation	++++	+



Pancreatic Neuroendocrine Tumours (MRCP)



- o Axial image of an MRCP demonstrating the relevant anatomy of the tumour, vessels, and proximal pancreas, with the absence of the dorsal pancreas (white arrow).
- Outlines represent the pancreatic head and neck (yellow), the pancreatic neuroendocrine tumour (red), the superior mesenteric vein (purple), and the splenic vein (blue).

Source: Nassif S, et al. Case Reports in Gastrointestinal Medicine, vol. 2016, Article ID 3801962, 4 pages, 2016.

Distinguishing Diagnosis

	Primary Lymphoma	Ductal Adenocarcinoma	Non-Functioning ICT
o Circumscribed	+		
o Vascular encasement		+	
o Pancreatic / Bile duct obstruction		+	
o Homogeneous	+		
o Hyperenhancement	+		+
o Calcification			+



Functioning Neuroendocrine Tumours (NET)

- Definition
 - o Well differentiated pancreatic neuroendocrine tumour (PanNET) associated with a clinical syndrome caused by abnormal secretion of hormones by the tumour

Gastrinoma

- Demography
 - o 1 per year / 10^6 population
 - o Malignant locally confirmed in 33%
 - o 20% associated with MEN 1
 - o > 50% of sporadic and >70% of hereditary gastrinomas occur in the duodenum

Insulinoma

- Demography
 - o 1 per year / 10^6 population
 - o Locally confirmed in 90%
 - o Solitary in 95%
 - o < 2 cm in 85-90 %
 - o 4% associated with MEN 1
 - o In MEN 1 patients insulinomas are multiple in 90%
 - o Enucleation if solitary; pancreatectomy if multiple

Glucagonoma

- Demography
 - o Occur in 10-15% of patients
 - o Frequently multiple (> 30%)
 - o Tumours > 3 cm tend to show aggressive behavior (metastases)



VIPoma

- Definition
 - o Neuroendocrine tumour, usually (> 80%) of the pancreatic tail, secreting ↑ PNM-27 (vasoactive intestinal peptide)
- Pathology
 - o Single tumour
 - o Large
 - o ~75% in tail of pancreas
 - o High rate of metastases

Somatostatinoma

- Diagnosis
 - Give the clinical and laboratory findings in patients with Pancreatic (Pan) and intestinal (Int) somatostatinomas (the approximate frequency of symptoms is shown).

	Somatostatinoma	
	Pancreatic	Intestinal
o Diabetes mellitus	95	20
o Gallbladder disease	94	40
o Steatorrhea	85	10
o Hypochlorhydria	85	15
o Diarrhea	75	25
o Weight loss	50	35

- Diagnostic imaging of functioning PanNETs
 - o CT
 - Masses
 - Well circumscribed
 - Enhancing
- Endoscopy
 - o Size
 - < 2cm
 - o Number
 - Single or multiple
 - o Shape
 - Well-outlined
 - Lobular / trabecular
 - o Consistency
 - Cystic or solid
 - Diffuse
 - “Checkerboard” appearance



- Histopathology
 - o Identical to non-functioning PanNETs
 - o Nuclei
 - Round
 - Uniform
 - o Chromatin
 - Salt and pepper
 - o Cytoplasm
 - Granular (neurosecretory granules)
 - Eosinophilic
 - o Stroma
 - Fibrovascular
 - Insulinoma
 - Psammoma bodies
 - Somatostatinoma
 - May contain amyloid
 - o ↑ N:C (nuclear to cytoplasm) ratio
- FNA cytology
 - o Single cells, or fragments
 - o Round, uniform cells
 - o Nuclei
 - Round
 - Eccentric
 - “Plasmacytoid”
 - o Binucleated / multinucleated cells may be present
 - Focal rosette formation
 - o ↑ N:C (nuclear-to-cytoplasmic) ratio
 - o May be “lymphocyte-like” morphology
 - o Fine, granular chromatin (spickled chromatin)
 - o Useful background
 - Often very large, and in head of pancreas → mass effect
 - Well demarcated and enhancing on CT scan
- Give the locations other than the head of the pancreas (extrapancreatic), where gastrinomas may occur.
 - o Duodenum
 - o Liver
 - o Lymph node



- Special studies
 - o Argyrophilic
 - o Immunohistochemistry (IHC): positive for
 - Chromogranin
 - Synaptophysin
 - NSE
 - Increasingly IHC is not performed to detect hormones other than perhaps for gastrin, since the specific hormone shown on IHC may not necessarily be functional, or causing any symptoms
- Demography
 - o Gender
 - M > F, 2:1
 - o Average age, 60 yr
 - o More common
 - Smokes
 - Family history
- Endoscopy
 - o Bleeding from sphincter of Oddi (major papilla and major duct) suggests pancreatic neoplasm
 - o Duct dilated “upstream” from cancer
 - o Areas of
 - Necrosis
 - Cystic changes
- Histopathology
 - o Architecture
 - Glandular differentiation of malignant epithelial cells
 - Atypia: haphazard growth pattern
 - Luminal necrosis
 - o Epithelial cells
 - Atypical
 - Single malignant cells
 - Formation of
 - Glands
 - Papillae
 - Cribriform structures



- Nuclei
 - Pleomorphic (size varies greatly)
 - Overlap
 - ↑ chromatin
 - Irregular shape / outline
 - Nucleoli
 - Present
- Mitosis
- Infiltration
- o Variants of infiltrating pancreatic ductal adenocarcinoma
- ❖ Fine Needle Aspiration (FNA) biopsy findings
 - o Usually head of pancreas
 - o Focal cystic degeneration
 - o Areas of necrosis
 - ↑ cellularity
 - Fragments, or single neoplastic cells with ductal features
 - o Acinar cells
 - Few, or none
 - o Nuclei
 - Enlarged
 - Overlapped
 - Irregular contour
 - Multinucleation
 - Lack of polarity
 - Haphazard arrangement
 - Hyperchromasia
 - “drunken honey comb” arrangement
 - o Cytoplasm
 - Vacuoles
 - Mucinous change
 - Cytokeratin CK₇, CK₈, CK₁₈, CK₁₉
 - CEA, CA 19-9
 - Dupan – 2
 - MUC 1, MUC 4, MUC 5 AC
 - o Infiltrating colloid adenocarcinoma
 - Neoplastic epithelial cells floating in pools of extracellular mucin (H&E).



- o Well- to moderately differentiated ductal adenocarcinoma, fine-needle aspiration
 - Multiple tissue fragments
 - Single discohesive pleomorphic neoplastic cells
 - Fragments of fibrous tissue and background mucin (Papanicolaou).
- o Poorly differentiated ductal adenocarcinoma, fine-needle aspiration.
 - Tumour fragment composed of haphazardly placed pleomorphic tumour cells
 - Prominent anisonucleosis
 - Occasional macronucleoli, and a
 - Total lack of glandular differentiation (Papanicolaou stain)

Pancreatic Duct Adenocarcinoma

➤ Demography

- o Incidence 10/10⁵
- o Prevalence features are meaningless because the mortality rate is so high.
- o 10% are metastatic
 - Pancreas supplied by splanchnic artery
 - Renal cell , especially late
- o 1% endocrine
- o 90% acinar / 10% ductal
- o 70-75% in head of pancreas
- o 60% originate around main pancreatic duct
- o 40% in upper dorsal part, adjacent to common bile duct – (may leave main pancreatic duct unaffected)
- o Variable figures for multifocality (0-25%) ~15%

A Curiosity!

- o Persons with annular pancreas have an increased risk of developing hepatopancreatic adenocarcinoma.

CLINICAL GEM

In the context of pancreatic cancer, give the meaning of the Trousseau syndrome.

- o The Trousseau is vascular thrombosis in a patient with pancreatic cancer



➤ Diagnosis

- o ↑ CA19-9 (tumour marker) occurs in
 - 70% to 80% of persons with pancreatic adenocarcinoma
 - Some persons with biliary obstruction and cholangitis
- o The tumour marker CA 19-9 has a sensitivity of 86% and a specificity of 87% to diagnose pancreatic ductal cancer (PDCA).
- o CA19-9 may be falsely positive in the presence of jaundice or cholangitis (-a-b).
- o Because CA 19-9 is not suitable for screening, the diagnosis of PDCA is usually made by diagnostic imaging of the abdomen.
- o Diagnostic imaging: “EUS is superior to CT for detection of co-existent [pancreatic] malignancy [in a pseudocyst] particularly when the lesion is small” *Saunders / Elsevier*,
- o EUS also has the substantial advantage of FNA.

Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Philadelphia, 2010, page 1014.

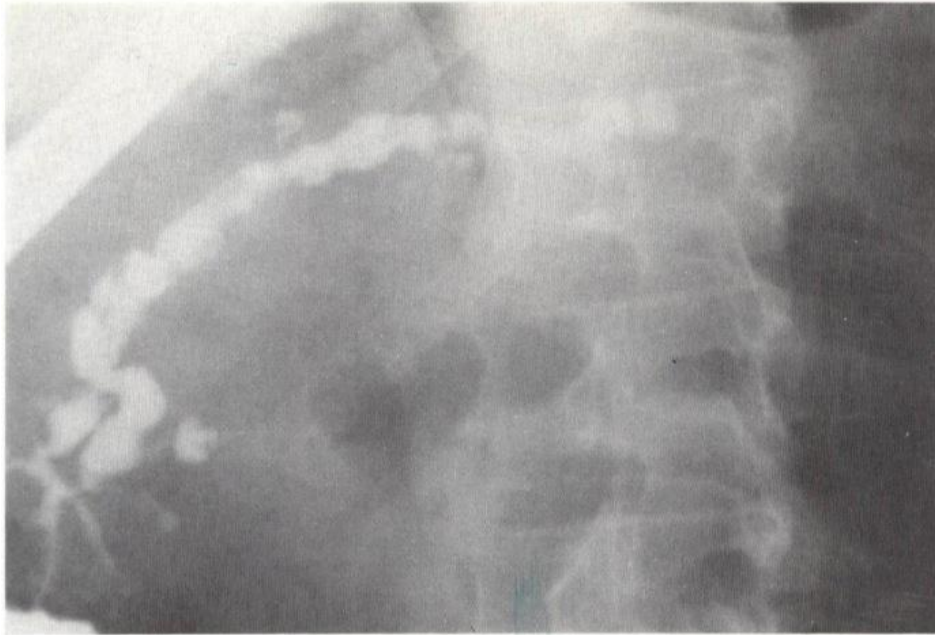
- Give the names of immunohistochemical markers which may be used to confirm that a tumour in the pancreas is mucus secreting, and is not derived from acinar or neuroendocrine cells of the pancreas.
 - o Markers for mucin
 - MUC1, MUC2, MUC4
 - o CEA (carcinoembryonic antigen)
 - o CA 19-9, Ca 125
 - o DuPan2
 - o Markers for cytokeratins should also be positive but do not help to differentiate
 - 7, 8, 18, 19
 - o Negative stains
 - Trypsin, alpha-1-antichymotrypsin
 - Neuroendocrine markers (synaptophysin, chromogranin)
- Give the possible techniques for screening of high risk individuals for pancreatic cancer.
 - o Non-invasive
 - Stool or blood analysis for gene mutations
 - Computed tomography (CT)
 - Positron emission tomography (PET)
 - Magnetic resonance imaging (MRI)
 - o Invasive
 - Endoscopic ultrasonography (EUS)
 - Endoscopic pancreatoscopy (ERP)
 - Endoscopic retrograde cholangiography (ERCP) for brush cytology or collection of pancreatic juice or bile for cytology & mutation analysis
 - Duodenal / pancreatic juice collection for mutation analysis



- Give the scientific rationale for screening / surveillance of pancreatic cancer.
 - o Mutational activation of KRAS is early event in 90% and detectable in plasma, stool, duodenal aspirate, pancreatic juice and brush cytology (false positive in hyperplastic lesions)
 - o Increased telomerase activity in pancreatic juice
 - o Loss of heterozygosity for tumour suppressor genes p16, p53 and MADH4
 - o Start screening at least a decade before the earliest age of onset in an affected family or at age 50 except for hereditary pancreatitis
 - o Molecular Markers to possibly Improve of Pancreatic Cancer.
 - Early Diagnosis
 - o Oncogenes:
 - K-ras 80–90%
 - o Tumour suppressor genes:
 - P16 80–100%
 - P53 50–70%
 - DPC4 50–70%
 - o The imaging modalities for pancreatic cancer
 - Site space
 - 10-20% : localized disease
 - 40% : locally advanced pancreatic cancer
 - 40% : metastatic disease
 - o US / Doppler
 - o Spiral CT
 - o Echoendoscopy
 - o MRI
 - o MCRP
 - o ERCP
 - o Angiography
- Diagnostic imaging
 - o Cystic neoplasms may mimic a pseudocyst, especially when there are nodules or internal septations.



Carcinoma of the head of the pancreas, ERCP



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- o Entire pancreatic duct dilated by cancer in head of pancreas.
- o Endoscopic
 - ERCP (endoscopic retrograde cholangiopancreatography)
 - Evaluation of recurrent pancreatitis (Avoid in chronic pain syndromes)
 - Pancreatic duct disruptions or leaks
 - Symptomatic pancreatic pseudocysts
 - Drainage of pancreatic necrosis
 - Palliative stenting
- o EUS (endoscopic ultrasound)
 - Diagnostic procedure in acute and chronic pancreatitis
 - Consider before transmural drainage of pancreatic fluid collection / necrosis / pseudocyst
 - Pancreatic mass < 2 cm
 - Sensitivity
 - EUS 98%
 - CT 91%
 - Usually used to complement CT for staging
 - More sensitivity than CT to determine if there is vascular invasion
 - Suitable to obtain biopsy (FNA, fine needle aspiration), as also is CT
 - Useful for celiac plexus block
 - Types of EUS
 - Radial (Olympus) 360° perspective
 - Linear (for sampling or injection) (Pentax)



- o Non-endoscopic
 - AbUS (abdominal ultrasound)
 - Mass
 - Hypoechoic
 - Poorly defined
 - Ducts
 - Dilated
 - Helical CT pancreatic protocol
 - Dual-phase scanning after PO / IV contrast, with pancreatic arterial phase at 40 sec and portal venous phase at 70 sec after IV contrast agent is given.
- o Pancreas protocol for h (helical) CT
 - Oral contrast, to distinguish between pancreas and duodenum
 - Hypoattenuating – adenocarcinoma
 - Hyperattenuating – neuroendocrine tumour
 - 10% are isoattenuating, so use indirect signs
 - Indirect signs
 - Dilated PD, CBD, double duct (PD+CBD)
 - Mass effects
 - Pancreatic atrophy
 - Abnormal pancreatic contour
 - 97% correct diagnosis of PDCA
 - 100% accurate in predicting unresectable disease
 - 85% of persons predicted to have resectable disease by CT turn out to actually have unresectable disease
- o Contrast – enhanced CT
 - Mass
 - Large
 - Hypoattenuating (dark) in pancreatic phase, but isoattenuating in portal venous phase
 - Some pancreatic adenocarcinomas are isoattenuating
 - Uncinate process
 - Rounded
 - Hypoattenuated
 - Staging
 - Local extension
 - Encasement of vessels
 - Occlusion of splenic vein
 - Deformity of superior mesenteric vein (SMV)
 - Multiple collaterals
 - Hepatic metastases
 - Lymphatic / peritoneal spread
 - CT superior to Doppler ultrasound for staging



SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the CT criteria for unresectable PDCA.
 - o The CT criteria for unresectable PDCA are
 - Distant metastases (does not include lymph nodes)
 - Encasement of celiac axis (e.g., SMA or aorta)
 - Occlusion of PV, SMV or VC

Abbreviations: PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein; VC, vena cava

- o MRI, MRA, MRV, MRCP
 - Magnetic resonance imaging
 - Gadolinium contrast used for MRA, MRV, MRCP
 - Use MRI to directly biopsy pancreatic mass
- o Staging sensitivity for PCa
 - MRI 84%
 - CT 91%
- o PET (positron emission tomography using radioactive fluorodeoxyglucose [FDG] F18)
 - Shows focal area of ↑ uptake of FDG in pancreas, and “hot spots” (↑ FDG uptake) of metastases in liver.
 - Does not show details of anatomy of pancreas, s do CT or MRI.
 - Performance characteristics: sensitivity of 95% to detect malignant pancreatic tumours.

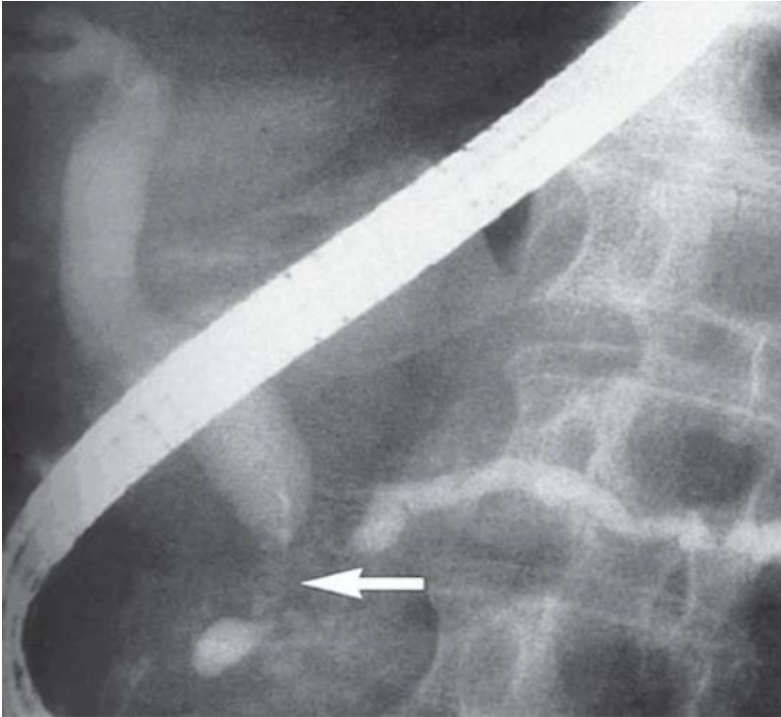
See Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, Table 60.8, page 1027.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give histopathological variants of invasive pancreatic ductal adenocarcinoma.

Variant type	Differentiation
o Adenosquamous	– Granular and squamous
o Hepatoid	– Hepatocellular
o Mucinous non-cystic	– “Mucin-producing cells floating in pools of mucin”
o Signet ring cell	– ↑ mucin in cytoplasm of single cells – ↑ mucin displaces nuclei to periphery of cells
o Mixed ductal-endocrine	– Endocrine component > 25%
o Metastatic	– Clear cell renal cell carcinoma – Breast – Stomach





Courtesy of Dr. Terry Ponich, Western University, London (ON)

SO YOU WANT TO BE A GASTROENTEROLOGIST!

There are numerous tests to diagnose and to stage PDca. It is important to establish whether the patient is a surgical candidate for pancreatic resection, or if they are **non-resectable**.

- Give a non-endoscopic and non-diagnostic imaging test for non-resectability of PDca.
 - o Staging laparoscopy with peritoneal lavage and cytology yields data rendering a patient to be declared non-resectable, despite lack of this evidence on CT/MRI.
 - Staging laparoscopy, 25%
 - Peritoneal cytology, 10%
- A patient with a predicted resectable PDca has a Whipple pancreaticoduodenectomy. The patient is hopeful for a 5-year mortality rate of 11% to 25%, and a median survival of 11 to 20 months. The patient asks, based on her/his case, what are the factors which predict that he/she will have a better outcome.
 - o Predictors of outcome in patients with resectable PDca:
 - Size, < 3 cm
 - Margins, negative
 - Metastases (to lymph nodes), none
 - Blood loss during surgery, < 750 mL



➤ Pathology

- o Most pancreatic carcinomas are from duct cells, and may secrete mucin.

- o Site

- Pancreas
 - 70% HOP (head of pancreas)
 - 15% BOP (body of pancreas)
 - 15% TOP (tail of pancreas)
- Wall of duodenum
- Ampulla of Vater
- Distal bile duct (aka common bile duct)

- o Biliary stricture → brush cytology

- Sensitivity 56%
- Specificity 90% to 100%
- PPV 59% to 100%
- NPV 43% to 89%
- False positive results with strictures from
 - Inflammation
 - PSC
 - Sphincterotomy

	Overall	Non-operated
Sensitivity	91%	96%
Specificity	100%	100%

➤ Histopathology

- o Brush cytology + biopsy

	Sensitivity	Specificity
– Biopsy demonstrated HGD / adenocarcinoma	43% to 88%	> 90%
– Positive biopsy plus cytological LGD	100%	84%

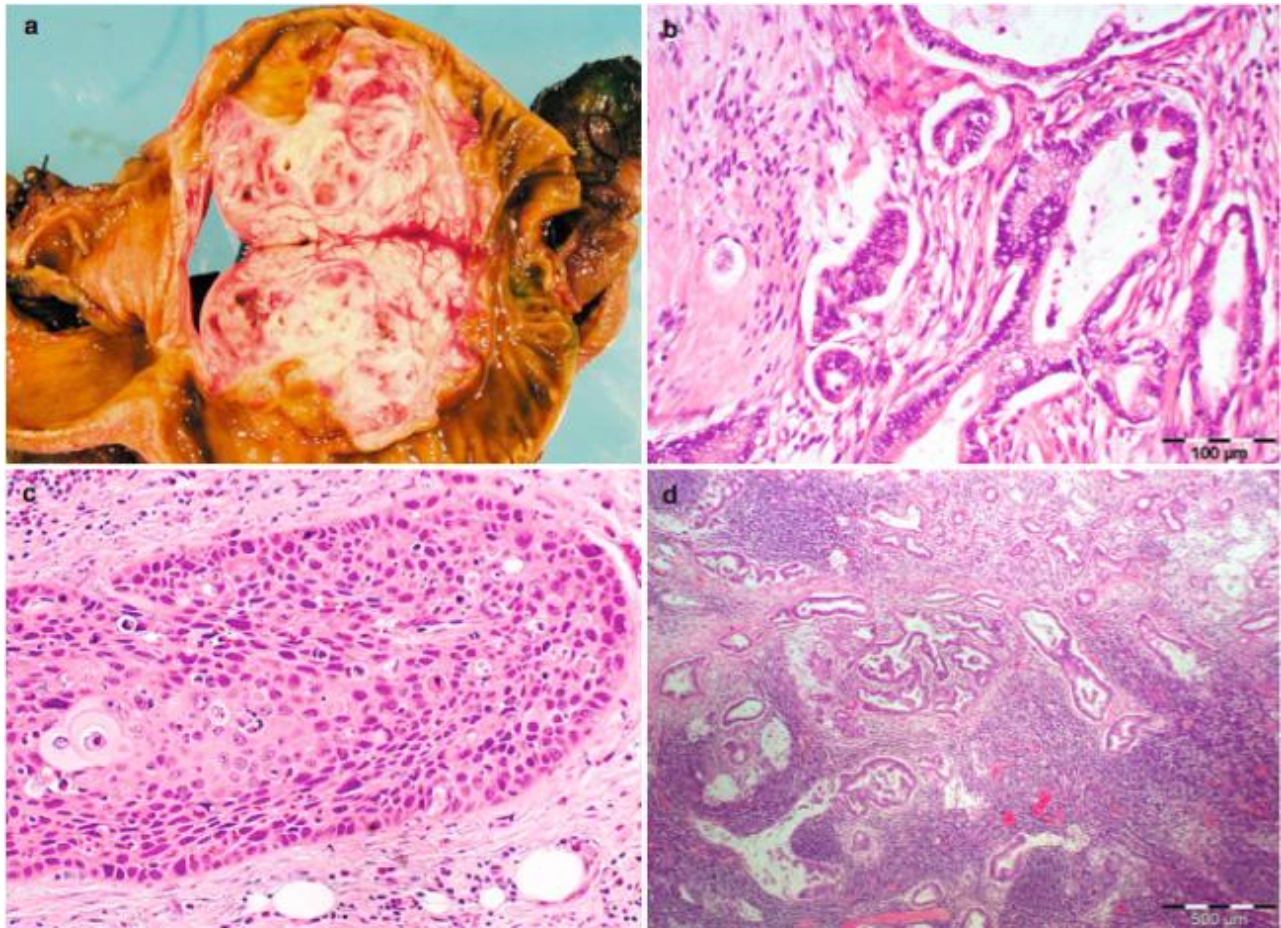
Abbreviation: HGD, high grade dysplasia; LGD, low grade dysplasia; PSC, primary sclerosing cholangitis

- Give the performance characteristics of EUS +FNA to establish a diagnosis of biliary tract malignancy.

- o Sensitivity 77%
- o Specificity 100%
- o PPV 100%
- o NPV 29%
- o Accuracy 79%



Pancreatic Carcinoma



- o Pancreatic ductal adenocarcinoma frequently presents as a solid, firm mass with necrosis and hemorrhage
 - (a), usually located in the head of the organ but less frequently occurring in the body and tail
- o Microscopically, the tumour consists of
 - Malignant glandular structures embedded in a fibrous stroma
 - (b). Tumour cells are pleomorphic and mitotically active
 - Frequent cellular apoptosis and atypical mitoses
- o In some areas, cells may form solid sheets with
 - Central necrosis, mimicking squamous cell carcinoma (c).
- o There are usually extensive lymph node metastases (d)

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SO YOU WANT TO BE A GI PATHOLOGIST!

- Give immunostains which are positive in infiltrating pancreatic ductal carcinoma.
 - o Usually positive
 - Cytokeratins
 - CK7
 - CK8
 - CK18
 - CK19
 - CEA (carcinoembryonic antigen)
 - CA19-9
 - Dupan-2
 - Mucins
 - MUC1
 - MUC4
 - MUC5AC
 - Mesothelin
 - Claudin 18
 - PSCA (prostate stem cell antigen)
 - Fascin
 - o Sometimes positive
 - Smad 4 proteins (~50%)
- Give variants of pancreatic carcinoma.
 - o Mucinous non-cystic
 - o Adenosquamous
 - o Mixed ductal endocrine carcinoma
- In the context of pancreatic carcinoma, give the meaning of the cytomorphological findings of “drunken honey comb appearance” and “Idaho potato appearance”
 - o Drunken honey comb
 - Flat sheets of cells with loss of nuclear polarity
 - o “Idaho potato”
 - Convoluted nuclear contours



Pancreatoblastoma

- Definition
 - o A very rare pediatric single solid, well-circumscribed and lobulated tumour of the pancreas comprised of acinar and endocrine differentiation plus squamous nests of large, uniform cells in the centers of epithelial lobules.
- Endoscopy
 - o Mass
 - Single
 - Well-circumscribed
 - Solid
 - Lobulated
- Histopathology
 - o Epithelial cell
 - Uniform cells
 - Necrosis
 - Hemorrhage
 - Cytoplasm
 - Stromal fragments with core of capillaries surrounded by malignant epithelial cells
 - Rarely
 - Glandular
 - Mesenchymal
 - Chondroid
 - Osteoid
 - Forming nests
 - Nuclei
 - ↑ chromatin
 - ↑ nucleoli
 - o Differentiation
 - o Epithelium lobules contain
 - o Spindle cells
 - Long
 - Triangular-shaped



- Special studies

Components	Immunostain
o Acinar	– Cytokeratins – Trypsin – Chymotrypsin – Lipase
o Endocrine	– Chromogranin – Synaptophysin
o Squamoid nests	– Nuclear-labeling (false positive)
o Ductular	– CEA
o Alpha-fetoprotein(AFP-positive in ~1/3)	

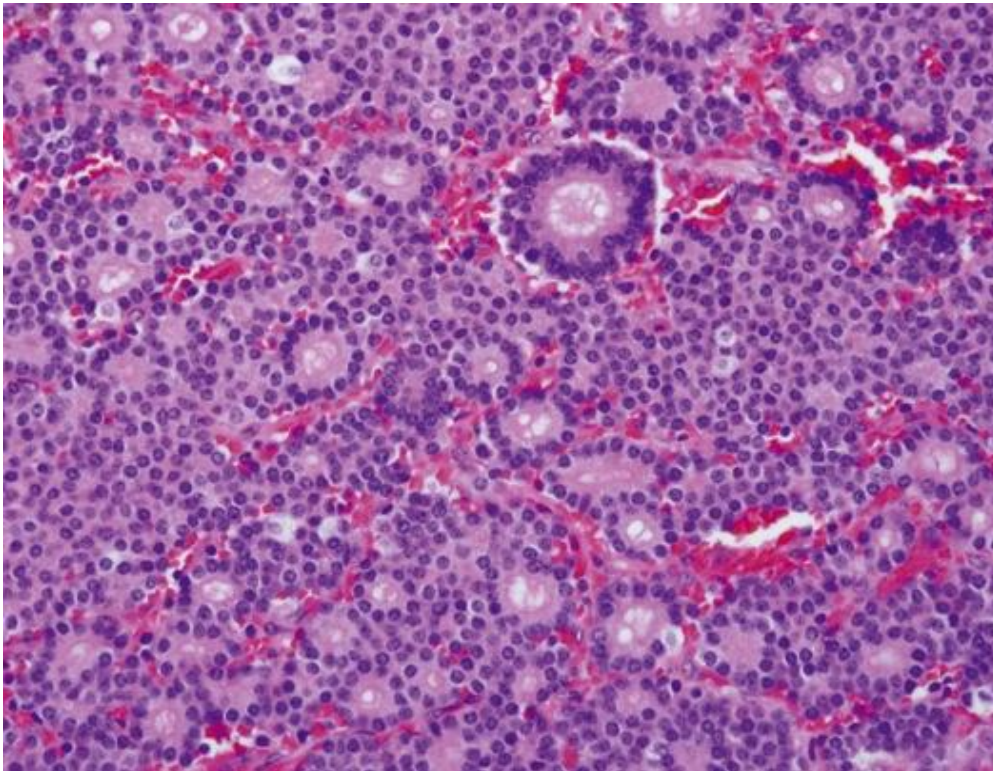
Acinar Cell Carcinoma

- Definition
 - o Large well-circumscribed malignant epithelial neoplasm of the pancreas comprised of a prominent production of exocrine enzymes, such as trypsin, chymotrypsin and lipase, and up to 25% of the tumour having an endocrine component.
- Demography
 - o Gender, M>F
 - o Age
 - Onset > 60 yr
- Histopathology
 - o Differentiated
 - Nests / trabeculae of cells
 - Pyramidal cells from acini (acinar formation)
 - Clustered around small lumen
 - Nuclei
 - Basal
 - Nucleoli
 - ↑ mitotic rate
 - Single
 - Cytoplasm granules
 - o Undifferentiated
 - Sheet of cells



- o Usually head of pancreas
- o Solid growth pattern (no cystic degeneration)
- o “nest or trabeculae of cells forming acini with pyramidal shapes clustered around small lumina”
- o Nuclei basally placed
- o Nuclei single, prominent
- o Granular cytoplasm
- o Neoplastic cells form small lumina, have granular cytoplasm, and often have a single prominent nucleolus.

Acinar Cell Carcinoma



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- Give the histopathological features which help differentiate acinar cell, pancreatic exocrine and pancreatoblastoma neoplasms.

Differential	Acinar Cell Carcinoma	Pancreatic Endocrine Neoplasms	Pancreatoblastoma
o Acinar formation	+	-	
o Basal nuclei	+	-	
o Granular cytoplasm	+	-	
o Chromatin "salt and pepper"	-	+	
o One prominent nucleoli		-	
o ↑ mitotic rate		-	
o Hyalinized stroma		+	
o Squamoid nests		-	+

- Special studies (immunochemistry)
 - o Pancreatic enzymes
 - o Cytokeratins
 - CK8
 - CAM5.2
 - AE1 / AE3
 - o Chromogranin, synaptophysin (in ~ 1/3)

SO YOU WANT TO BE A GI PATHOLOGIST!

An acinar cell carcinoma of the pancreas has a prominent production of exocrine enzymes and up to 25% of the tumour having an endocrine component.

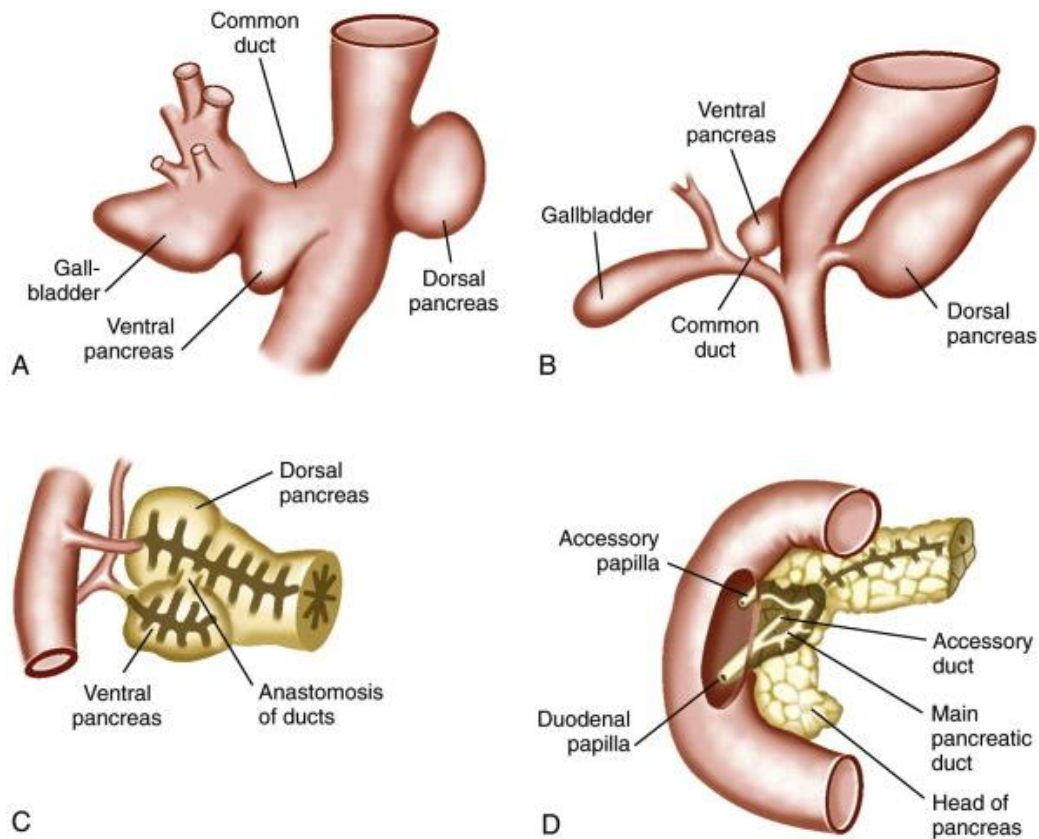
- Give the name of the pancreatic tumour when the endocrine component is > 25%.
 - o Mixed acinar-endocrine carcinoma



CONGENITAL ABNORMALITIES

Annular Pancreas

- Definition
 - o A developmental anomaly of the abnormal fusion of the dorsal and ventral pancreatic buds, forming a ring around the pancreas
- Demography
 - o Annular pancreas (AP) 100 / 10⁵
- Embryology



SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give the stages in the **embryonic development** of the pancreas.
 - o At about 4 weeks of gestation (A), dorsal and ventral buds are formed from the duodenum.
 - o At 6 weeks (B), the ventral pancreas extends toward the larger dorsal pancreas.
 - o By about 7 weeks (C), fusion of dorsal and ventral pancreas has occurred and ductular anastomosis is beginning.
 - o At birth (D), the pancreas is a single organ, and ductular anastomosis is complete.

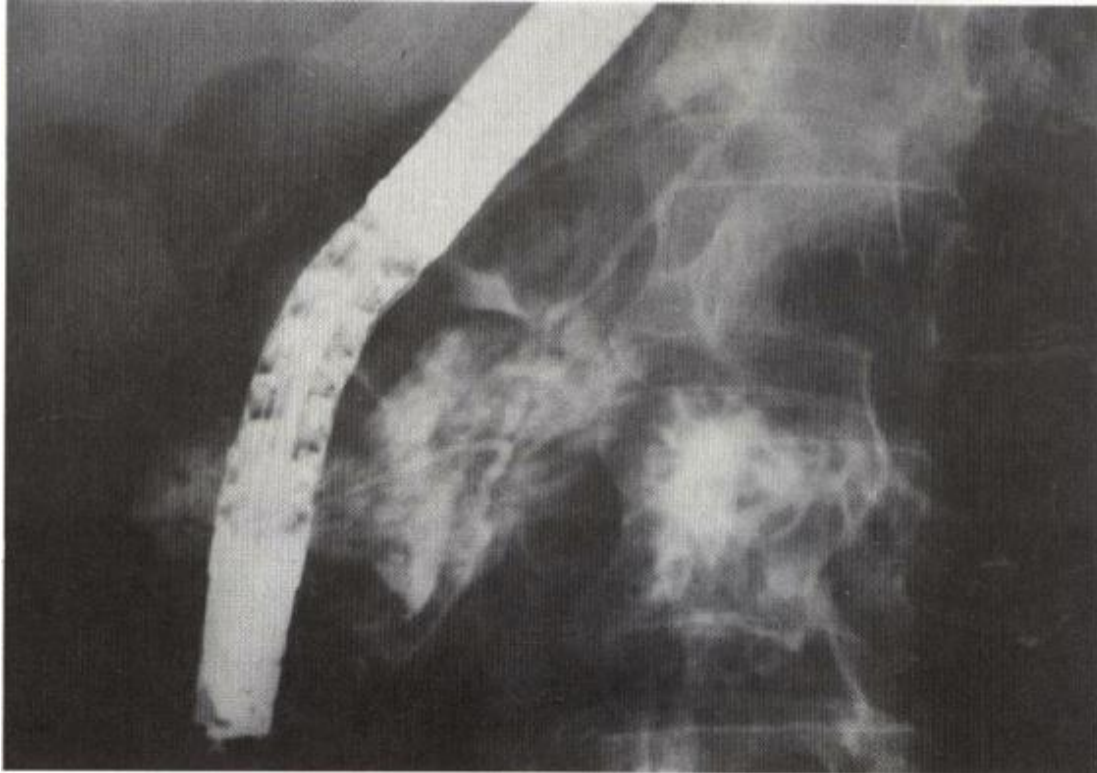
Printed with permission: Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Figure 55-10, page 915.

➤ Diagnostic imaging

- o Abdominal plain film may show “double-bubble” sign of duodenal obstruction, which may occur with any cause including annular pancreas.
- o CT
 - Enlarged head of pancreas
 - No focal mass
- o Contrast-enhanced CT
 - Low attenuation
 - Peripancreatic tissue stranding
- o MRCP
- o ERCP
 - “ring like” pancreatic duct surrounding the duodenum plus normal pancreatic duct (failure of the normal left ventral bud of the pancreas to fully rotate during normal embryological development)
 - Ventral pancreatic duct circles around the duodenum – Pancreatic tissue may encircle the duodenum
- o Laparotomy Source: Spiegel BM. Acing the GI board exam. Slack Incorporated 2009, page 79.



Annular Pancreas



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Ectopic Pancreas

- Definition
 - o A developmental anomaly of pancreatic tissue being located outside of (ectopic to) the usual location of the organ, such as in the small intestine or in a Meckel diverticulum
- Demography
 - o Affects ~2% of the population



Cystic Fibrosis (CF) Involving the Pancreas

➤ Genetics

Useful background: Characteristics of CFTR (Cystic Fibrosis Transmembrane Conductance Regulator)

- o CFTR is a peptide which functions as an anion channel.
- o Cl^- and HCO_3^- pass through this channel, causing alkaline pancreatic fluid secretion.
- o In the pancreas, CFTR is in the apical membrane of the pancreatic duct cell.
- o CFTR is regulated.
- o The regulation of CFTR is by way of three regulatory domains
 - NBD (nucleoside binding domain) 1 and 2.
 - R (regulatory) domain
 - R domain binds to cytoplasmic glutamine to stimulate Cl^- secretion.
 - $\text{NBD}_{1/2}$ binds to cytoplasmic ATP to stimulate HCO_3^- secretion.
 - The conformation of the CFTR protein changes depending upon whether it is bound to $\text{NBD}_{1/2}$.
- o The second messenger system regulates NBD_1 , NBD_2 and the R domain of CFTR.
- o For CFTR, second messenger system includes
 - ATP
 - PKA
 - Ca^{2+}
 - Glutamate (intra-acinar cell)
- o The second messenger system in turn is stimulated by secretin and VIP as well as Ach.
 - Secretin / VIP → receptors → $\uparrow$ cAMP → $\uparrow$ PKA (protein kinase A)-mediated phosphorylation of R domains of CFTR.
 - Ach → $\uparrow$ Ca_i^{2+} (intracellular Ca^{2+})
- o Numerous genetic mutations of CFTR have been described.
- o The commonest genetic mutation in CFTR is ΔF508 , a three-base pair deletion of the phenylalanine-coding codon 508.
- o When there are major mutations in CFTR alleles, function of CFTR is lost.
- o When CFTR no longer functions normally as a regulated anion channel in the apical membrane of the pancreatic duct cell, mucus is not hydrated, ducts are blocked and tissue atrophies.
- o There may be modifier genes, or environmental factors which influence the clinical features of CF (gastric fibrosis).
- o Many organs are affected in CF, and vary with the nature of the genetic changes e.g., alter the impact and environmental factor on causing pancreatitis, such as alcohol damage leading to pancreatitis.
- o The clinical impact of CFR, a susceptibility gene, may also be affected by an unidentified modifier gene.
- o A modifier gene interacts with a susceptibility gene to “increase the risk of developing a pathological outcome” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 937).

538



- Diagnostic imaging
- Give radiological features of **meconium ileus** / DIOS (distal intestinal obstruction syndrome).
 - o Proximal ileum
 - Hypertrophy of wall
 - o Distal ileum
 - Dilation, or
 - Narrowing from inspissated meconium
 - o Bead-like appearance from pellets of meconium
 - o Air / gas
 - Little air or air-fluid levels
 - Bubbles of gas in meconium
 - o Colon
 - Empty
 - Microcolon
 - o Associated
 - Volvulus
 - Atresia
 - Ascites
 - Calcification
 - Intussusception
 - Rectal prolapse
 - Cancer
 - Stomach
 - Small intestines
 - Pancreas
 - Biliary tree
- Histopathology
- Give the usual **phenotype changes** in CFTR involving the pancreas.
 - o Thick, inspissated macromolecules such as mucus.
 - o This blockage causes
 - Fibrosis
 - Dilated ducts
 - Pseudocysts
 - Chronic inflammation
 - Atrophy



- Give histopathological features of the pancreas in cystic fibrosis.
 - o Inspissated secretions in ducts
 - o Blockage extends to acinar cells
 - o Epithelial flattening and atrophy
 - o Dilation of acini with calcium-rich eosinophilic concretions
 - o Pseudocysts
 - o Hyperplasia and necrosis of ductular and acinar cells
 - o Inflammation (mild)
 - o Fibrosis
 - o Calcification
 - o Late loss of islet of Langerhans (glucose intolerance is common)
 - o However, CFRD [cystic fibrosis-related disease] is uncommon).

Pancreas Divisum (PD)

➤ Definition

- o Developmental features of the dorsal and ventral pancreatic ducts to fuse, resulting in the minor (Santorini) system becoming the major ductal drain through the small minor papilla, and the major papilla receiving the major duct which drains only a small portion of the pancreatic gland.
- o A congenital abnormality caused by: “failure of the dorsal and ventral pancreatic ducts to fuse”.
- o Most of the pancreatic secretions then drain “.....through the relatively small dorsal duct of Santorini and minor [accessory] papilla rather than the ventral duct of Wirsung and the major papilla” (Feldman M., et al. Sleisenger and Fordtran’s Gastrointestinal and Liver Disease. 9th Edition. Saunders / Elsevier, Philadelphia, 2010, page 918).

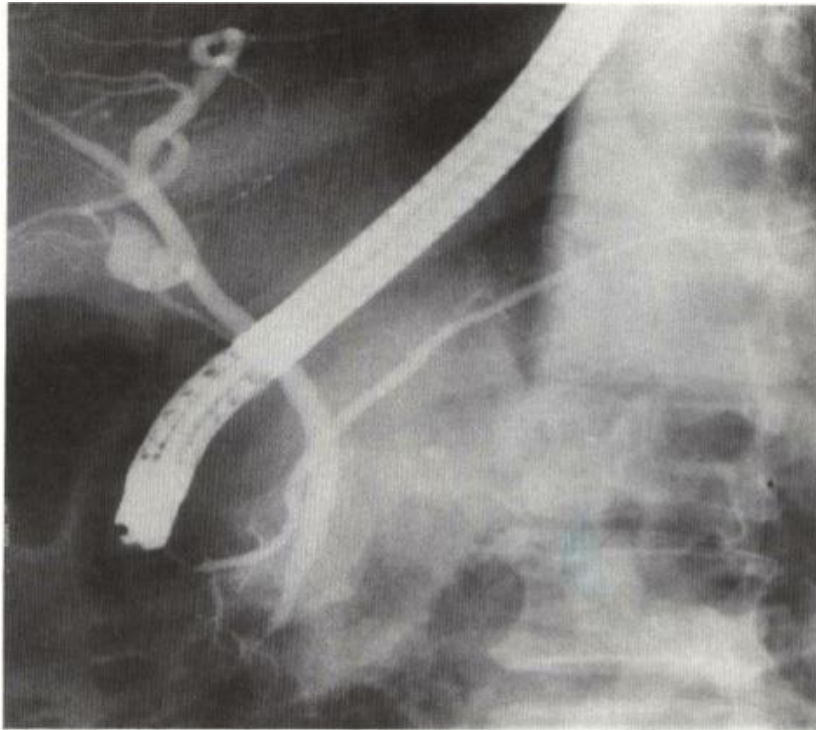
➤ Demography

- o Affects ~5% of the population, and only a small proportion develop symptoms.
- o In patients with CFTR gene mutations, pancreas divisum is found in 47%
- o The frequency of pancreas divisum is the same in patients with idiopathic pancreatitis, chronic alcoholic pancreatitis, and in controls without any pancreatic diseases (5-7%).



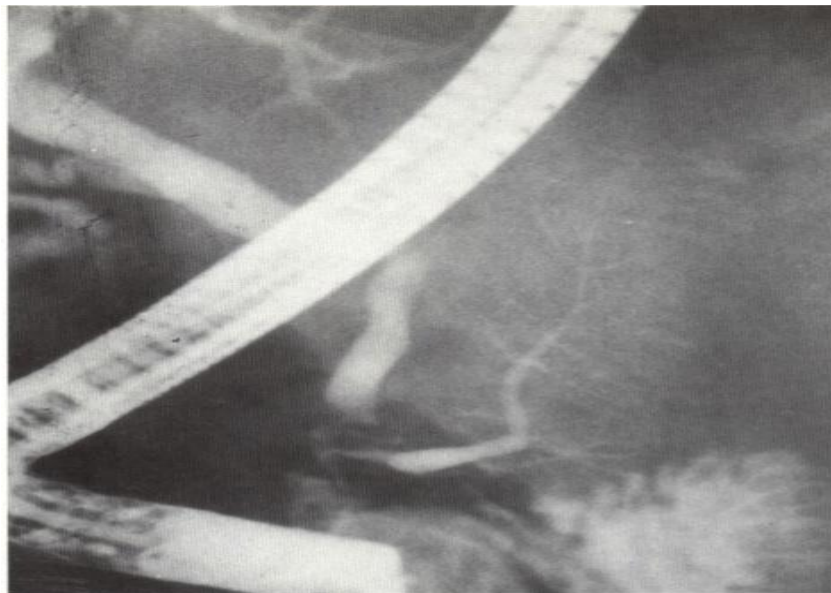
➤ Diagnostic imaging

Pancreas Divisum



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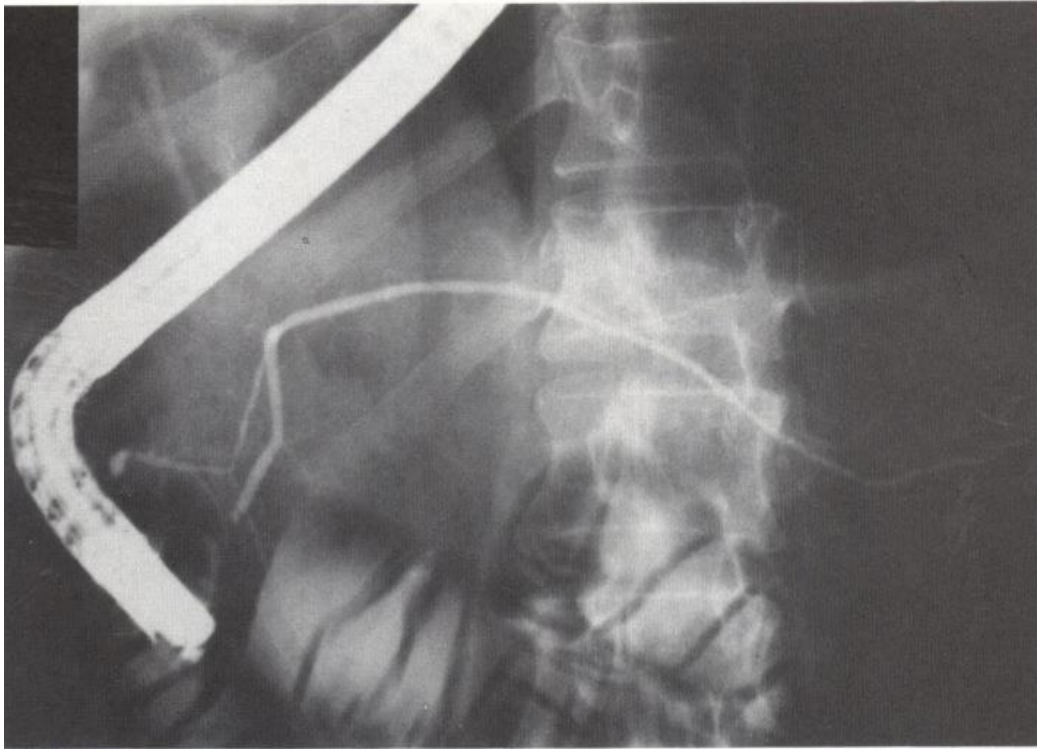
Pancreas Divisum



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Accessory Duct of Santorini



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➤ Pathology

o ERCP

– Drainage

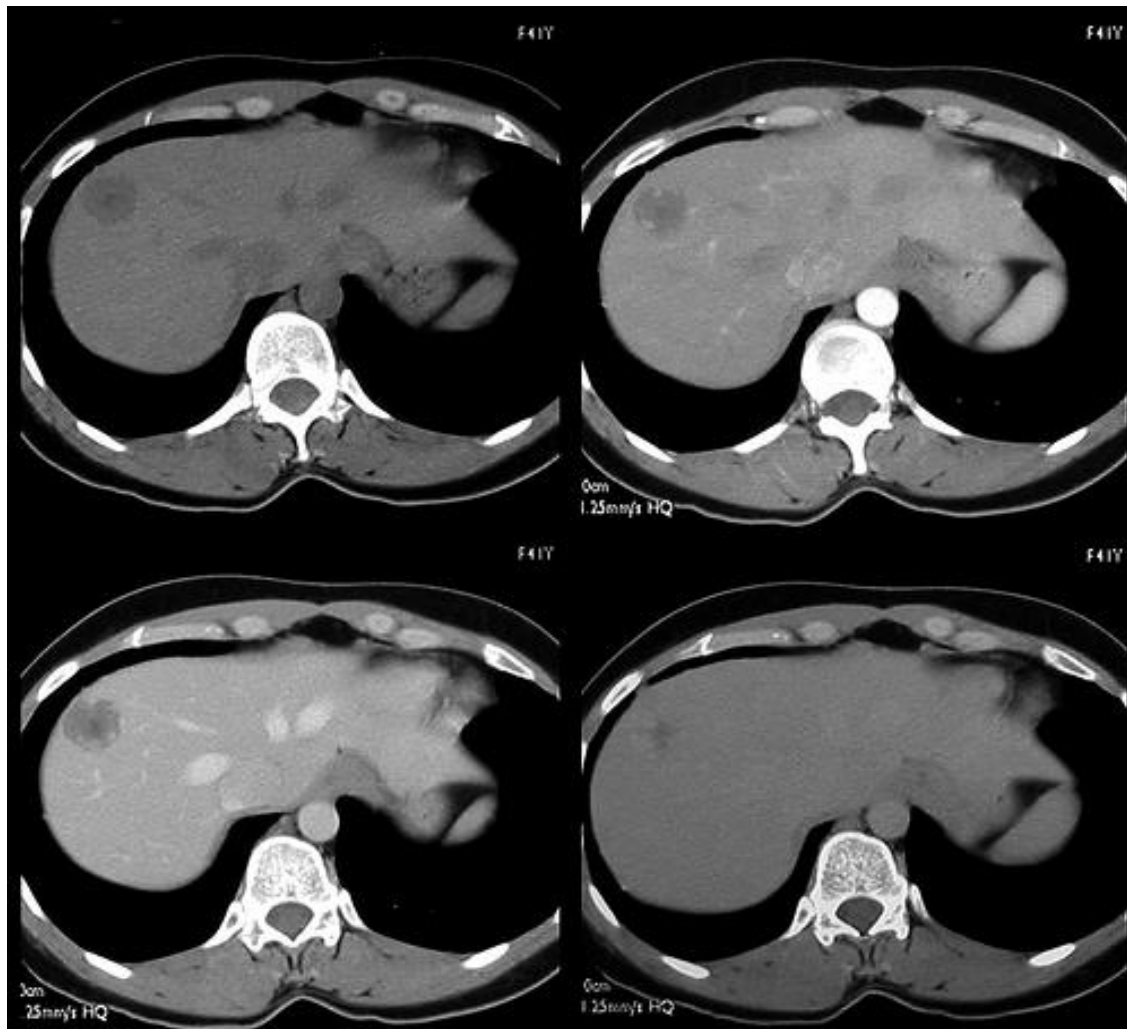
- Dorsal pancreas
- Duct of Santorini accessory papilla
- Duct of Wirsung major papilla
- Small, branching duct

“There is never a better measure of what a person is than what he does when he’s absolutely free to choose.”

William M Bulger



COMMON PROTOCOLS AND WHEN THEY ARE USED



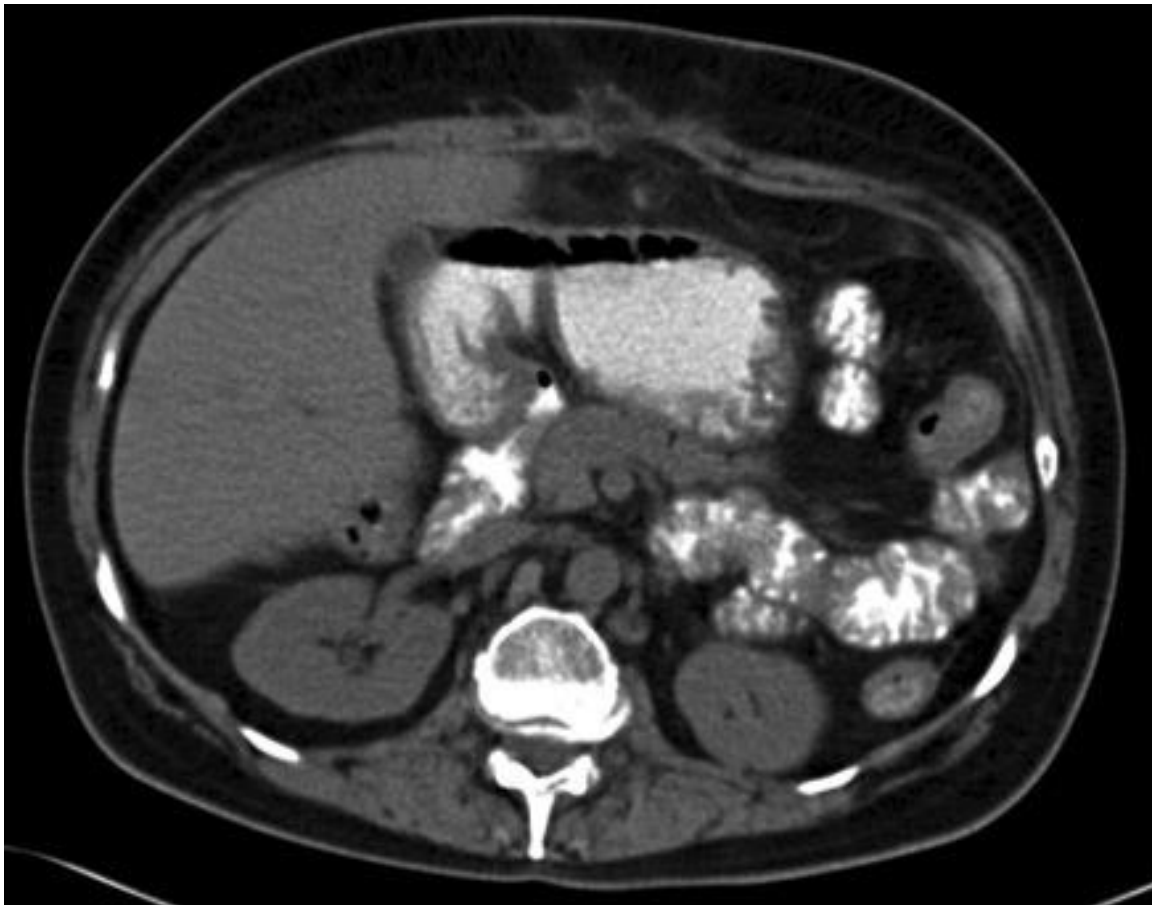
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- o Non-contrast CT:
 - Acute intraperitoneal or retroperitoneal hemorrhage
 - Calcification
 - Patient not suitable candidate for contrast
- o Single phase IV contrast
 - Most routine indications
- o Multiphasic IV contrast
 - Liver lesions
 - +/- non-contrast, arterial, portal venous, delay
 - Renal masses
 - Non-contrast, corticomedullary, nephrographic, excretory



Common Protocols – Oral Contrast

- o Positiveoralcontrast(hypaque)
 - Abscess (helps differentiate fluid-containing bowel from extraluminal fluid)
 - Certain cancers with peritoneal metastases
 - Other indications (variable)
- o Negativeoralcontrast(water / milk)
 - Bowel wall – mucosal abnormality
 - Crohn disease
 - Pancreatic masses
 - Distends duodenum and makes ampulla more visible
 - Bowel obstruction
 - Intrinsic negative oral contrast – bowel contents (no need to administer contrast)



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- o Size, position
 - Beware of anomalies
- o Enhancement
- o Pancreatic duct
- o Nodes
- o Fluid
- o Inflammation





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