

Patterns of GI Tract Injury

Esophagus

Benign Incidental Findings:

Gastric "Inlet Patch" - Heterotopic gastric mucosa in esophagus

Pancreatic Heterotopia/Metaplasia

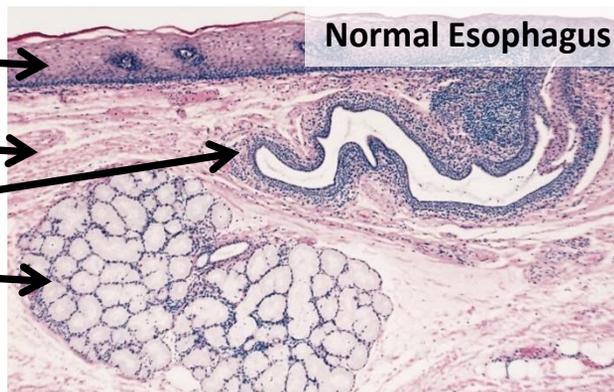
Glycogenic Acanthosis – Epithelial hyperplasia with abundant, enlarged superficial glycogenated cells; clinically appears white

Non-keratinizing stratified squamous mucosa

Muscularis mucosae

Esophageal duct

Submucosal glands



(Muscularis propria: distal = smooth muscle; proximal = skeletal muscle)

Acute Esophagitis

Intraepithelial Neutrophils with Erosion/Ulceration

GERD Often scattered Eos (usu. < 15/HPF), Intercellular edema, Basal cell hyperplasia, Elongation of vascular papilla. Worse distally (near GEJ).

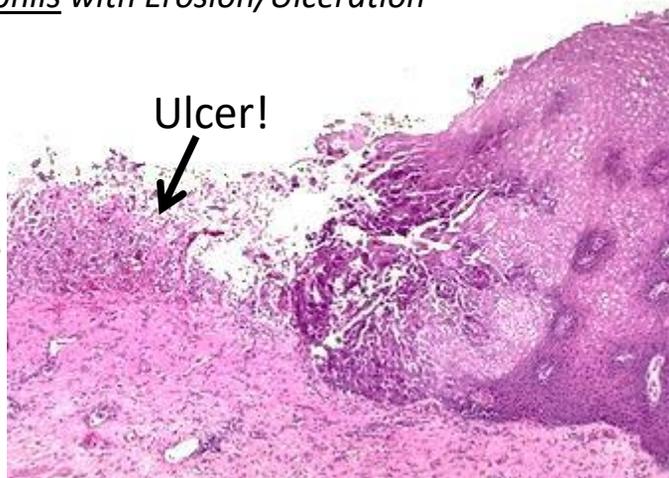
Infections

Candida - Look for fungal hyphae, Get PAS-D/GMS

HSV - Look for Molding, Multinucleation, Margination in epithelial cells.

CMV – Look for inclusions in mesenchymal cells.

Medications ("*Pill esophagitis*") Look for crystals, resins, and pill fragments; Polarize to help looking for foreign material.



Eosinophilic Esophagitis

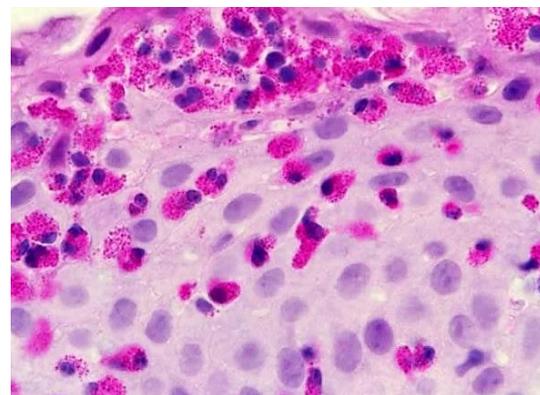
Increased intraepithelial Eosinophils (report per HPF)

GERD

Eos typically < 15/HPF, Intraepithelial T lymphocytes ("squiggle cells"), Intercellular edema, Basal cell hyperplasia, Elongation of vascular papilla. Worse distally (near GEJ).

Eosinophilic Esophagitis

Typically >20 Eos/HPF. Often eosinophilic microabscesses with degranulation. Often diffuse or worse proximally. Associated with "Atopic Triad" (Allergies, Asthma, Eczema). Presents with dysphagia, chest pain, food impaction, which may cause a food aversion. Endoscopically can appear as rings or furrows ("*Trachealization/felinization*")



Note: As EoE and GERD can appear identical on a single bx, close clinical and endoscopic correlation is often necessary to distinguish between the them!

Allergies/Systemic autoimmune disorders

Medication Reaction

Parakeratosis Pattern

Superficial squamous cells with retained nuclei

GERD

Eos typically < 15/HPF, Intraepithelial T lymphocytes (“squiggle cells”), Interstitial edema, Basal cell hyperplasia, Elongation of vascular papilla. Worse distally (near GEJ).

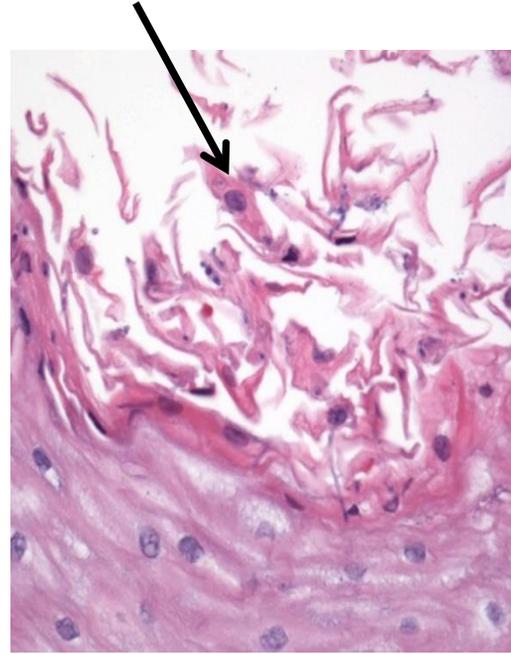
Candida Esophagitis

Look for fungal hyphae at surface and get PAS-D or GMS, particularly in immunosuppressed individuals. Budding yeast are NOT good enough!

Esophagitis Dissecans Superficialis (“*Sloughing Esophagitis*”) Superficial “mummified” layer (with ghost nuclei) with variable necrosis and minimal inflammation. Clinically can be quite dramatic with extensive peeling and fissuring. Has been associated with thermal injury, medications, and some autoimmune conditions.

Esophageal Leukoplakia/Epidermoid Metaplasia

Looks like skin with keratinization and a granular layer. Associated with motility disorders and oral leukoplakia. Possible increased risk of squamous dysplasia/carcinoma.



Lymphocytic Pattern

Intraepithelial Lymphocytes

GERD

Lichen Planus

Band-like (“lichenoid”) infiltrate at junction between epithelium and submucosa. Dyskeratotic keratinocytes (“Civatte bodies”) are common. Associated with cutaneous LP, certain medications, and viral infections. Often older women. Risk of dysplasia → SCC

Graft Versus Host Disease

Donor T lymphocytes attack host tissue. Typically present with Rash, Diarrhea, elevated LFT's. Intraepithelial lymphocytes with dyskeratotic keratinocytes and scattered apoptotic bodies. Make sure CMV IHC is neg.

Crohn's Disease

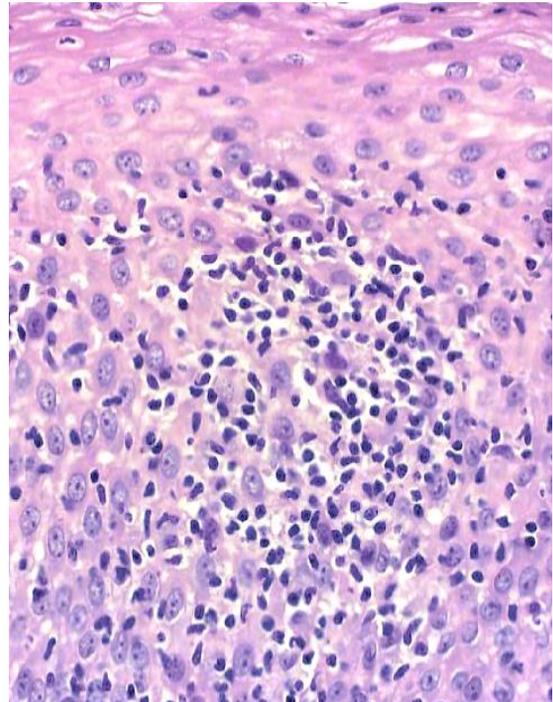
Look in lamina propria for granulomas

“Contact Mucositis”

May be a generalized response to mucosal injury, for example to an allergy to a medication or food.

Other

CVID, Celiac disease, Dysmotility, Etc...



Stomach

Oxyntic Mucosa (90% of stomach)

Present in body/fundus

Pink parietal cells make acid and intrinsic factor (B12 uptake)

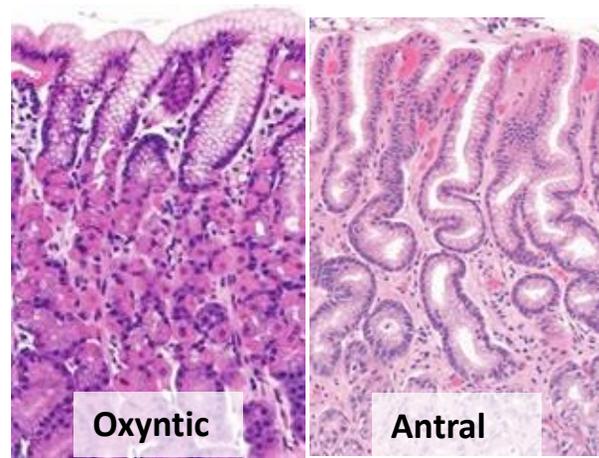
Purple chief cells make pepsinogen

Antral Mucosa

Present in distal antrum and cardia

Gastrin-secreting G cells are found ONLY in antrum

Usu. extremely few inflammatory cells, except at the gastric cardia, which commonly has some chronic inflammation.



Reactive (Chemical) Gastritis/Gastropathy

Foveolar hyperplasia (“corkscrew glands”),
Mucin depletion, *Edema*, *Minimal inflammation*,
Extension of smooth muscle bands between glands

Often caused by **chemical irritation** by bile reflux,
Medications (particularly NSAIDs), or alcohol.

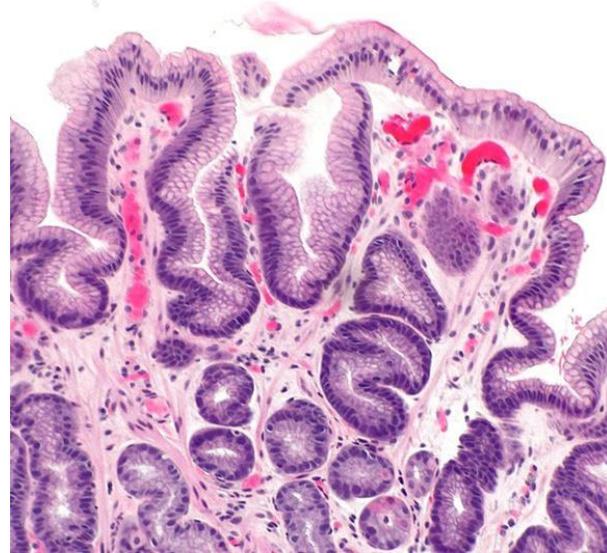
Portal Hypertensive Gastropathy

Above findings, plus dilated vessels in lamina propria. Seen
in patients with portal hypertension.

Endoscopically like “snake skin”

Gastric Antral Vascular Ectasia (“GAVE”)

Endoscopically looks like a watermelon. Above findings, plus
fibrin thrombi present in lamina propria capillaries.



Acute Gastritis *Intraepithelial Neutrophils often with Erosion/Ulceration*

Helicobacter pylori

Acute gastritis with characteristic superficial lymphoplasmacytic
inflammation and prominent lymphoid aggregates. Most common in
Antrum. Look hard in pits and consider getting Helicobacter IHC.
Risk of MALT and dysplasia/carcinoma.

Helicobacter heilmannii

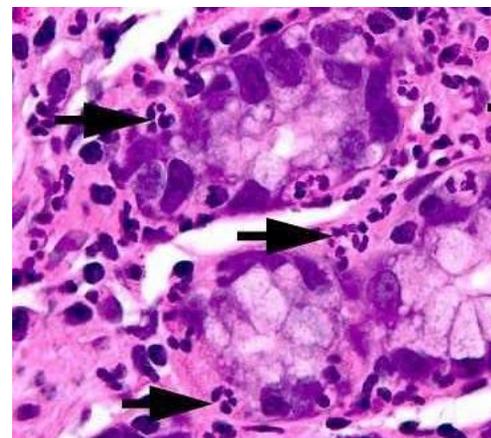
Less acute inflammation. More common in kids. Organisms are
longer, more tightly spiraled, and less numerous

Medications

Esp. NSAIDs. Often associated ischemic or reactive changes.

“Focally Enhanced Gastritis”

Focally injured glands surrounded by inflammation. Associated in kids with IBD, particularly Crohn’s
disease.



CMV

Chronic Gastritis

Chronic inflammation in the Lamina propria

Helicobacter pylori

Acute gastritis with characteristic superficial lymphoplasmacytic inflammation and prominent lymphoid aggregates. Most common in Antrum.

Autoimmune Metaplastic Atrophic Gastritis (AMAG)

Also known as autoimmune gastritis. Autoantibodies destroy parietal cells/oxyntic mucosa → No intrinsic factor → B12 deficiency → Pernicious anemia.

Body-predominant injury with loss of oxyntic mucosa and Deep chronic inflammation → Intestinal and pyloric metaplasia & ECL cell hyperplasia → Can make neuroendocrine tumors (type I)

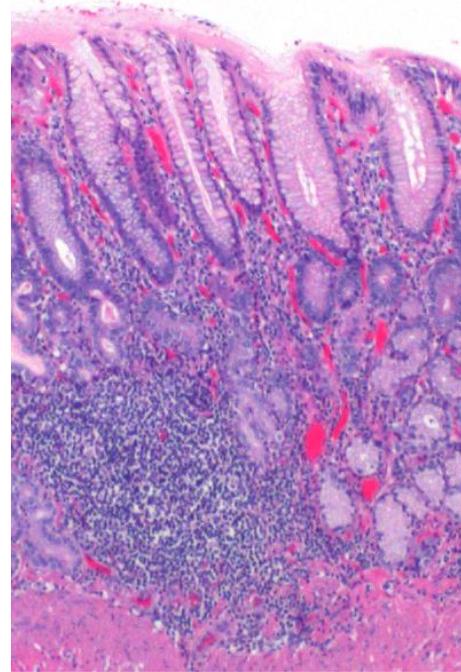
Gastrin stain can help confirm sample came from body (negative) and not antrum (positive).

Medications

Esp. NSAIDs. Often associated ischemic or reactive changes.

Other

CVID, Celiac disease



Lymphocytic Gastritis

Intraepithelial Lymphocytes

Helicobacter pylori

Celiac Disease

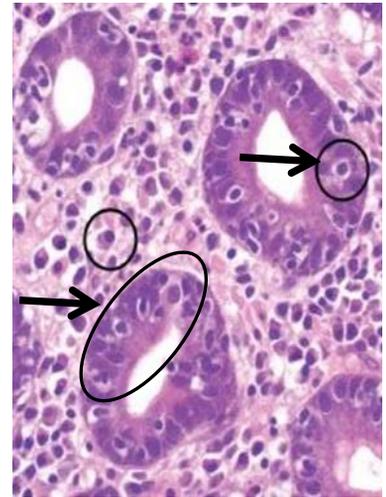
Medications (E.g., Ticlopidine, Olmesartan)

HIV

Other Immune-mediated Disorders

CVID, Crohn's Disease, Lymphocytic colitis, etc...

Lymphoma



Collagenous Gastritis

Increased subepithelial collagen band with Intraepithelial Lymphocytes (can highlight with trichrome stain)

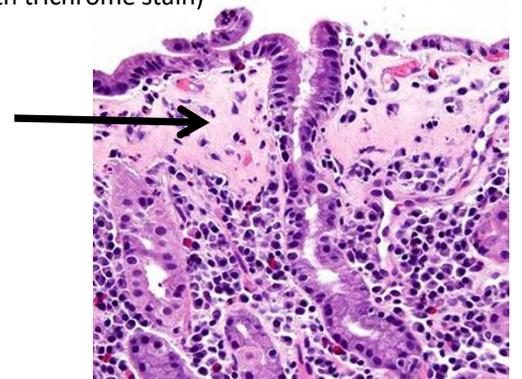
Collagenous colitis/enteritis

Celiac Disease

Medications (E.g., Olmesartan)

Helicobacter

Other Immune-mediated Disorders



Eosinophilic Gastritis

Increased Eosinophils

Although there is no strict cut-off, >30/HPF is likely too many and any in the epithelium, submucosa, or muscle is abnormal

Eosinophilic Gastritis/Gastroenteritis

Diagnosis of exclusion. Can be associated with Eosinophil-rich inflammation in other organs (e.g., esophagus and/or small bowel). Layer of bowel involved determines symptoms.

Helicobacter

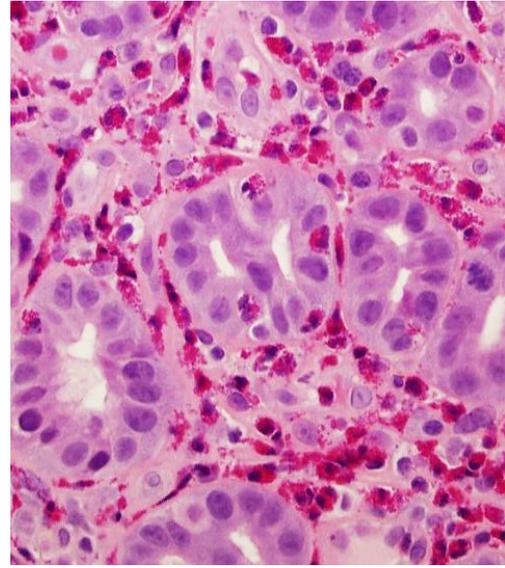
Parasites

Connective tissue diseases/Vasculitis

Food Allergies

Medications

Inflammatory bowel disease (particularly Crohn's)



Oxyntic Gland Hyperplasia

Dilated oxyntic glands with hypertrophic parietal cells with "snouts"

Single/Sporadic Polyp → Fundic Gland Polyp

Associated with Proton Pump Inhibitor use (increases gastrin levels through feedback, causing parietal cell hypertrophy). Extremely low risk of dysplasia/progression

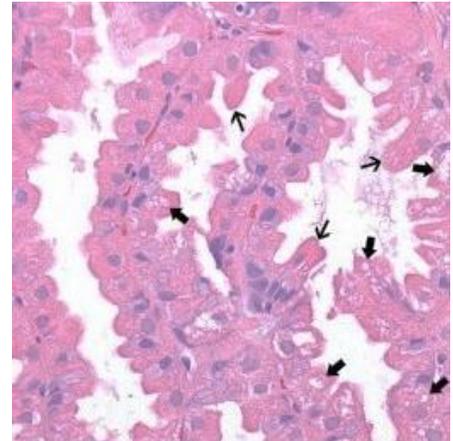
Innumerable or Dysplastic? Consider a Syndrome:

Familial Adenomatous Polyposis Can become dysplastic, but still low rate of progression to carcinoma

MutYH-Associated Polyposis

Zollinger-Ellison Syndrome

Gastrinoma (usu. in small bowel) causes increased acid secretion and ulcers. Associated with MEN1.



Foveolar Hyperplasia

"Corkscrew glands," Mucin depletion, Edema

Single/Sporadic Polyp → Hyperplastic Polyp

Associated with background inflammatory injury. Extremely low risk of dysplasia/progression

Innumerable or Dysplastic? Consider a Syndrome:

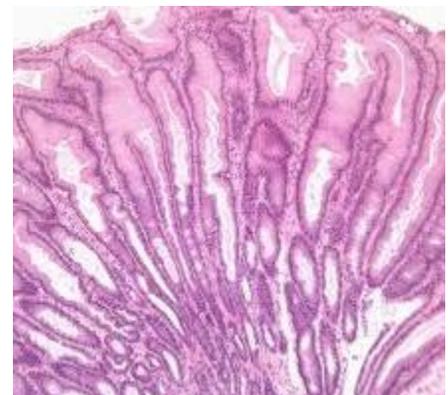
Ménétrier's Disease Whole stomach, protein-losing enteropathy

PTEN Syndromes (Cowden's, etc...)

Cronkhite-Candada Syndrome

Juvenile Polyposis

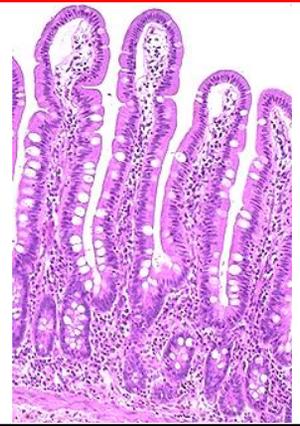
Peutz-Jeghers Syndrome



Small Intestine

Quick Checklist:

- Villi? Long and skinny? Go away or blunt with Celiac Disease
- Goblet Cells? Go away with autoimmune enteropathy
- Intraepithelial lymphocytes? Increased in Celiac (and others)
- Plasma cells? Go away with CVID
- Critters? Look between villi and on surface for Giardia, etc..
- Vessels ok? Look for amyloid and vasculitis
- Endocrine cells? Go away with endocrine dysgenesis



Acute Duodenitis

Neutrophils in duodenal epithelium

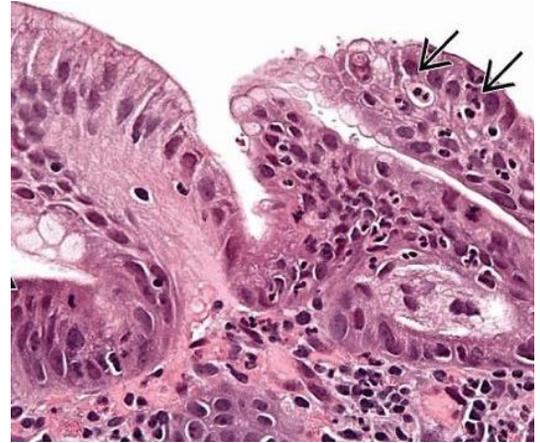
Peptic Duodenitis

Additionally see Gastric foveolar metaplasia and chronic inflammation. Associated with excess gastric acid and/or *Helicobacter*

Infection Most commonly *Helicobacter* (can lead to ulcers → Peptic Ulcer Disease). Sometimes Adenovirus, CMV, or other viruses.

Medications Most commonly NSAIDs

Inflammatory bowel disease (particularly Crohn's)



Acute Ileitis

Neutrophils in ileal epithelium

Medications Most commonly NSAIDs

Infection Including common stool pathogens (bacterial and viral)

Inflammatory bowel disease Crohn's disease is more likely to impact TI (so look for granulomas, and signs of chronicity, including pyloric gland metaplasia). In UC, there is typically inflammation in the nearby cecum (that is thought to "backwash")

Eosinophilic Gastroenteritis

Increased Eosinophils

Although there is no strict cut-off, >60/HPF is likely too many and any in the epithelium, submucosa, or muscle is abnormal

Eosinophilic Gastroenteritis

Diagnosis of exclusion. Can be associated with Eosinophil-rich inflammation in other organs (e.g., stomach or colon). Layer of bowel involved determines symptoms.

Parasites

Connective tissue diseases/Vasculitis

Food Allergies

Medications

Inflammatory bowel disease (particularly Crohn's)

Eosinophilic Gastroenteritis Symptoms	
Layer	Symptoms
Mucosa	Diarrhea, malabsorption
Muscle	Ileus
Serosa	Ileus and ascites

Chronic Injury

Architectural distortion: crypt branching, dropout, and pyloric gland metaplasia often with villous blunting and a basal lymphoplasmacytosis

Often starts to look like colon with IBD!

Inflammatory Bowel Disease

Chronic ACTIVE inflammation, with cryptitis and crypt abscesses. Particularly Crohn's in the TI (and small bowel in general). Look for granulomas and transmural inflammation in resections.

"Diaphragm Disease" Due to NSAIDS

Mild → erosions with associated acute inflammation
Severe → multiple episodes can cause scarring → stenosis
Usu. Less chronic inflammation than Crohn's

Medications

Mycophenolate – Immunosuppressant (often given after transplantation) that can cause epithelial/crypt damage with increased apoptosis → causes diarrhea

Ischemia Severe pain. Coagulative necrosis. Crypt withering. Lamina propria hyalinization and hemorrhage. Reperfusion brings acute inflammation.

Radiation Most sensitive to damage. Endothelial injury → edema, fibrin, and ischemic changes with enlarged/bizarre nuclei.

Graft vs. Host Disease (GVHD) Donor T-lymphocytes attack host bowel. First see apoptotic bodies in crypts. Severe damage shows crypt abscess, crypt distortion, and epithelial destruction.

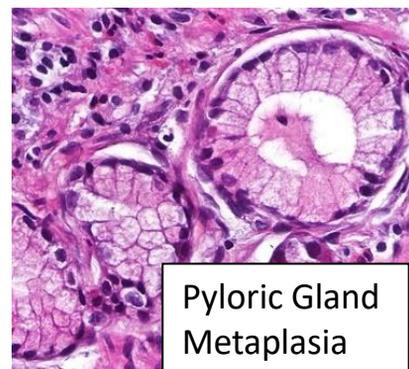
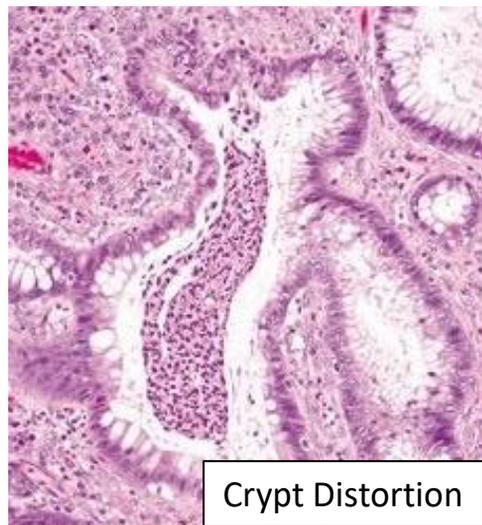
Graft Rejection Host T-lymphocytes attack donor bowel. Similar to GVHD: Inflammation (mostly lymphs) with crypt destruction and apoptosis.

"IPAA" findings (*given to patients with UC or FAP*)
Usu. NOT given to Crohn's patients as high risk of complications

Pouchitis Acute and chronic inflammation of ileal reservoir. Unclear etiology, but often treated with antibiotics/probiotics. If refractory, consider Crohn's, but clinical Dx based on strictures/fistulas.

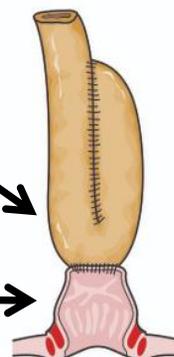
vs

Cuffitis Chronic active inflammation of rectal cuff, attributed often to residual/recurrent UC.



Lerner System for Grading GVHD

Grade	Findings
1	Isolated apoptotic bodies
2	Loss or damage of isolated crypts, w/ or w/o crypt abscesses
3	Loss of 2 or more contiguous crypts
4	Extensive crypt loss with epithelial destruction



Malabsorption

Villous atrophy with increased intraepithelial lymphocytes (IEL)

Causes Diarrhea clinically, often with weight loss.

Gluten Sensitive Enteropathy (Celiac Disease)

Gluten exposure triggers inflammation, primarily in duodenum. Positive serology for: Antigliaden, Tissue transglutaminase (TTG), and antiendomysial (EMA) (if not IgA deficient!). Associated with haplotypes HLA-DQ2 or DQ8 (absence both of these essentially excludes diagnosis). Number of IEL typically >20/100 enterocytes. "Crescendo" at tip of villi.

Other Protein Sensitives (e.g., cow milk, soy, eggs)

Often increased Eosinophils in mucosa

Peptic duodenitis

Medications (e.g., Olmesartan and NSAIDs)

Small Bowel Bacterial Overgrowth excess anaerobic bacteria (often caused by decreased acid and dysmotility) digest bile and carbohydrates → variable local damage and bloating

CVID Immunodeficiency with impaired B-cell differentiation. Usually plasma cells ABSENT → low serum Ig's → recurrent infections.

Tropical Sprue Unknown etiology, but likely infectious. After travel to Africa, Asia, or South America. Must exclude other infections.

Autoimmune Enteropathy Gut autoantibodies → often absent goblet or Paneth cells. Most common in infants. Can see similar pattern associated with thymoma.

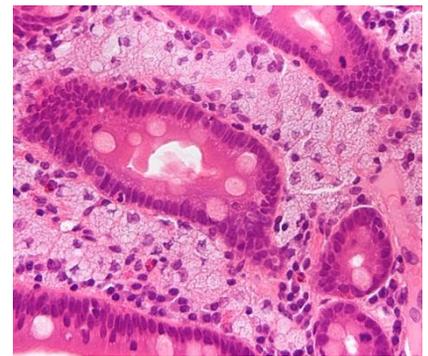


Foamy Macrophages *"Foamy" macrophages in mucosa*

Mycobacterium avium intracellulare (MAI) Get a FITE stain!
Immunocompromised/AIDS-defining opportunistic infection.

Whipple Disease Get a PAS/D stain! *Tropheryma whipplei* causes an infection often afflicting adult white men → arthralgias, weight loss, diarrhea. Treat with antibiotics.

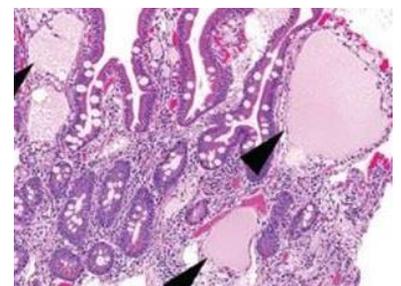
Nonspecific Macrophages



Dilated Lacteal *Engorged/dilated lymphatics*

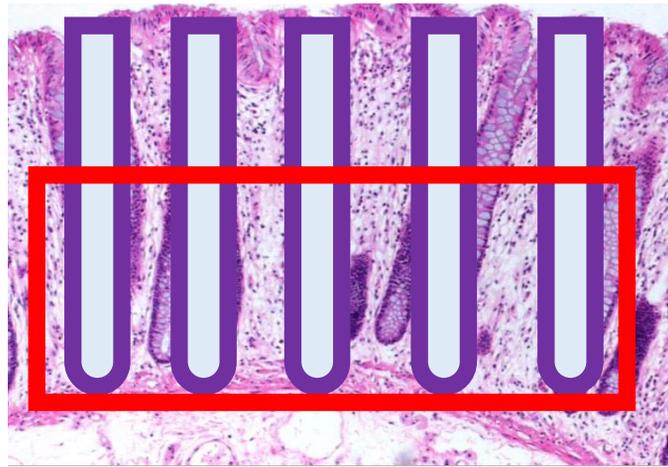
Primary Lymphangiectasia Poorly understood. Dilated lymphatics → lymph/albumin leakage into gut → diarrhea and protein-losing enteropathy.

Secondary Lymphangiectasia Similar manifestations as primary, but secondary to obstruction, tumor, adhesions, stricture, prior surgery, etc...



Colon

Crypts should be oriented parallel to one another, perpendicular to the surface (like test tubes), resting on the muscularis mucosae



Regional Variation

Right Colon	Left Colon
More lymphocytes	Less lymphocytes
Paneth cells normal	Paneth Cells abnormal
Fewer goblet cells	More goblet cells

Some architectural distortion and muciphages in the rectum is considered normal.

Focal Active Colitis

*Rare collections of neutrophils in crypt epithelium
(Otherwise normal)*

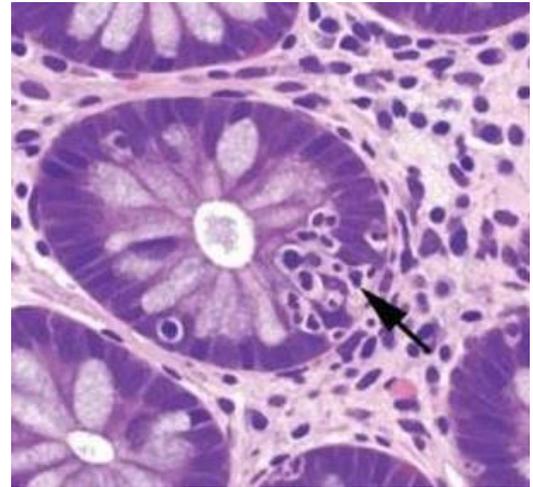
Medications (esp. NSAIDs)

Acute Self-limited Colitis Resolves in <4 weeks. Usually infectious (e.g., *Campylobacter*, *Salmonella*, *Shigella*, or *Yersinia*) with abrupt onset and coinciding fever.

Bowel preparation artifact

Ischemic Colitis

IBD Usu. More insidious onset.



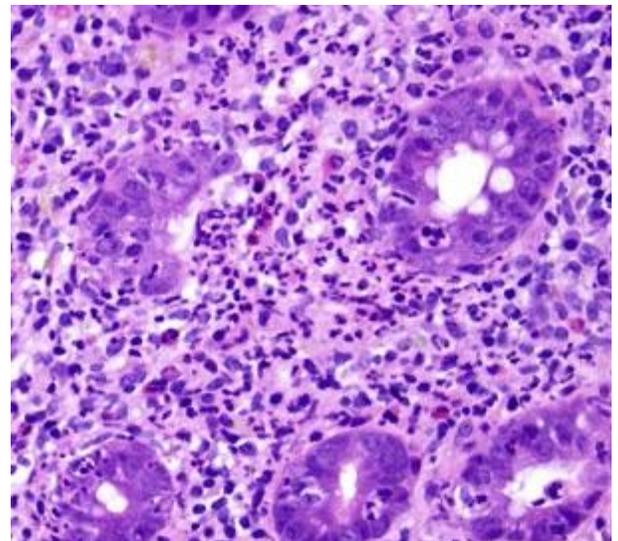
Acute Colitis

Extensive cryptitis and crypt abscesses, WITHOUT features of Chronicity

Infection Usu. acute bacterial or viral infections (e.g. CMV, *Salmonella*, *Shigella*, *Campylobacter*, etc...), so make sure this has been evaluated clinically. Often food contamination (fecal-oral). May see Pseudomembranes.

Medications Esp. NSAIDs. Also Resins (Kayexalate and Sevelamer) and Ipilimumab.

IBD Usually has features of chronicity, so would have to be emerging (very recent onset) or partially treated.



Chronic Active Colitis

Active colitis with features of Chronicity

Features of Chronicity include: Architectural distortion (crypt branching, loss, and shortening), basal lymphoplasmacytosis, and Paneth cell or pyloric metaplasia

Inflammatory Bowel Disease (IBD)

Chronic systemic autoimmune inflammatory disease.

On a mucosal colonic biopsy, can be impossible to distinguish Crohn's from UC and must rely on clinical/endoscopic impression.

Look for Granulomas and Dysplasia.

(See IBD handout for Crohn's vs UC)

Infection Always rule out CMV in refractory IBD (along with other causes clinically)

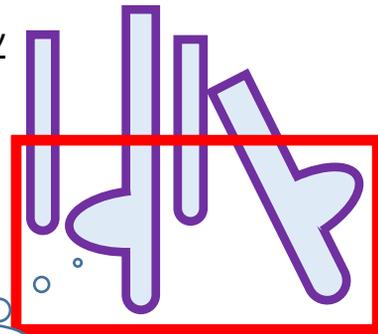
Diverticular Disease Most common in older patients in sigmoid colon. Can mimic IBD with Diverticulitis and Segmental Colitis Associated with Diverticulosis (SCAD).

Diversion-Associated Colitis In bowel diverted from fecal stream (causes short chain fatty acid deficiency).
Usu. see florid lymphoid hyperplasia with prominent germinal centers.

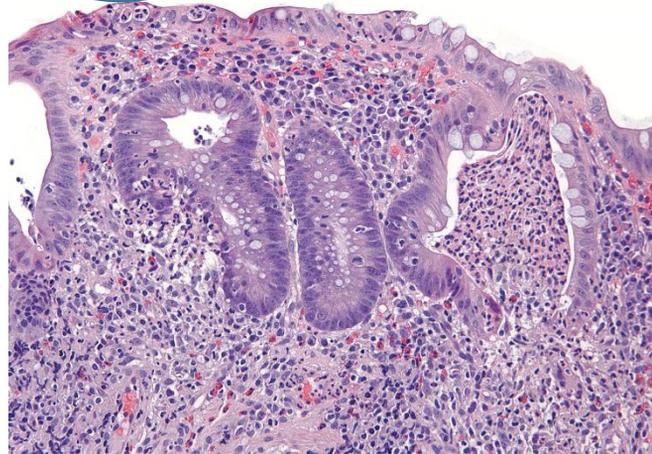
STD Proctocolitis Sexually Transmitted Diseases: Esp. Syphilis and lymphogranuloma venereum (Chlamydia). Often tons of plasma cells. Consider particularly with primarily rectal disease.

Cord Colitis Syndrome After Umbilical cord transplantation. Often see granulomas.

Medications NSAIDs, Ipilimumab, and resins



Think of those test tubes being melted!



Ischemic Colitis

Superficial epithelial damage, Crypt withering, Lamina propria hyalinization and hemorrhage.

Occasional pseudomembranes and acute inflammation (with reperfusion)

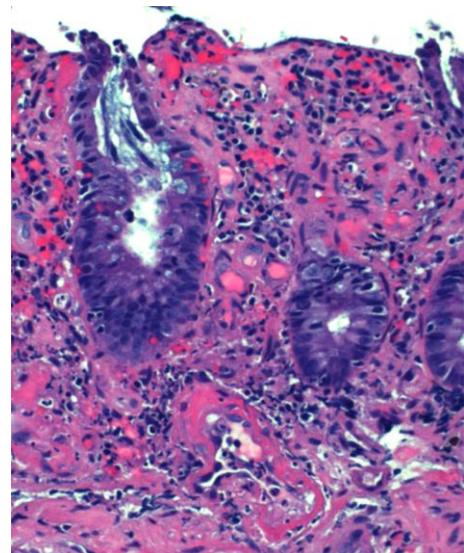
Ischemia Due to poor perfusion. Most common in “watershed” areas (splenic flexure, rectosigmoid, and ileocecal regions) in older patients with vascular occlusion or low-flow states.

Infection

E.coli 0157:H7 (EHEC)—Endothelial damage from toxin → Fibrin thrombi often seen. Associated with Hemolytic Uremic Syndrome (Anemia, low platelets, renal failure)

C. Difficile—Pseudomembranes, less hyalinization and crypt withering

Medications Esp. NSAIDs. Also Resins (Kayexalate and Sevelamer) and Ipilimumab.



Eosinophilic Colitis

Increased Eosinophils

Although there is no strict cut-off, >60/HPF is likely too many and any in the epithelium, submucosa, or muscle is abnormal

Eosinophilic Colitis/Gastroenteritis

Diagnosis of exclusion. Can be associated with Eosinophil-rich inflammation in other organs (e.g., esophagus and/or small bowel). Layer of bowel involved determines symptoms.

Parasites

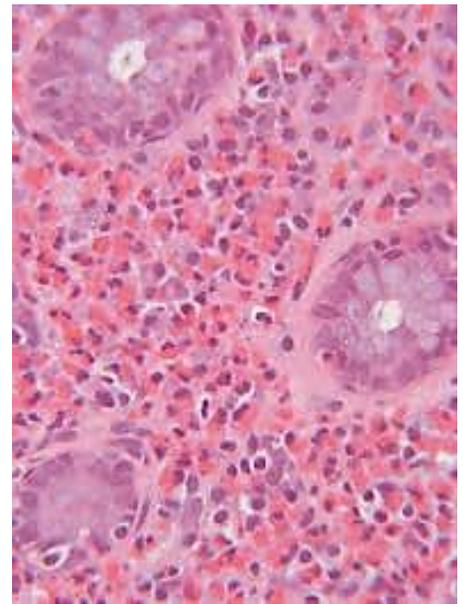
Connective tissue diseases/Vasculitis

Food Allergies

Medications

Systemic mastocytosis

Inflammatory bowel disease (particularly Crohn's)



Lymphocytic Colitis

Increased intraepithelial lymphocytes

Lymphocytic Colitis Watery diarrhea with normal endoscopic findings. Increased intraepithelial lymphocytes (>20 lymphs/100 epithelial cells). Classically older women.

Collagenous Colitis Watery diarrhea with normal endoscopic findings. Increased intraepithelial lymphocytes with increased subepithelial collagen layer (irregularly thickened, trapping inflammatory cells, vessels, and fibroblasts). Highlight with trichrome stain.

Medications (e.g., NSAIDs, Olmesartan, SSRIs, etc...)

Viral Infections



Granulomatous Colitis

Granulomas! Rule out infection with FITE and GMS/PAS-D

Crohn's Disease Loose, non-necrotizing. Seen in less than 1/2 of cases. *Note:* In UC can see granulomatous reaction to crypt rupture!

Infections Esp. if Necrotizing! Rule out fungi and mycobacteria. Look around for parasites (e.g., Schistosomiasis)

Nonspecific mucosal injury

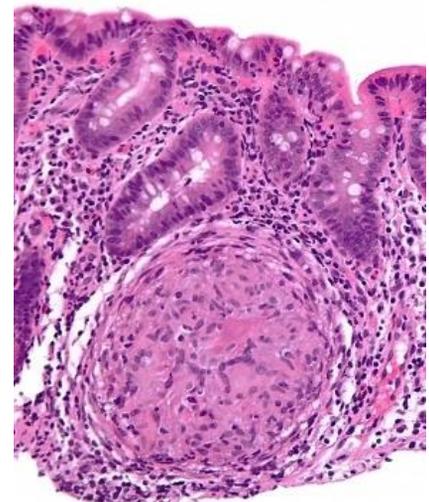
Medications

Sarcoidosis

Cord Colitis Syndrome

Diverticular disease

CVID and Chronic Granulomatous Disease

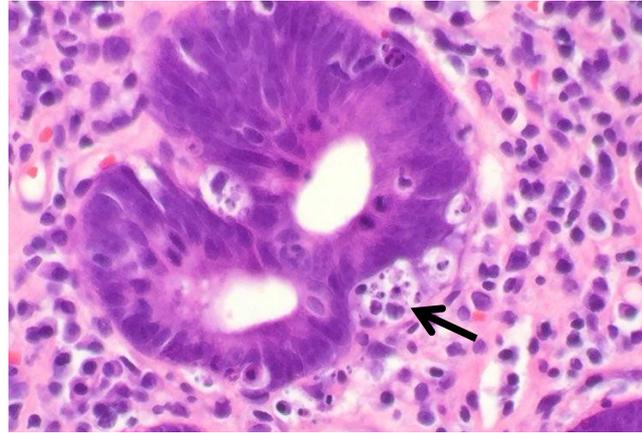


Apoptotic Colitis

Increased apoptoses in crypt epithelium

Graft vs. Host Disease (GVHD) Donor T-lymphocytes attack host bowel. First see apoptotic bodies in crypts. Severe damage shows crypt abscess, crypt distortion, and epithelial destruction.

Medication-effect Classic cause: Mycophenolate (MMF), which has a similar appearance to GVHD, but with more eosinophils



Pigments and Inorganic Material

Iron

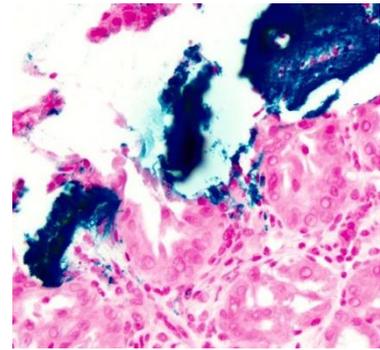
Appears brown and granular on H&E; Blue on Iron Stain

Deposition Patterns:

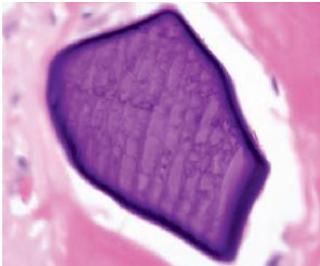
A: Deposition in lamina propria/macrophages → prior mucosal microhemorrhages

B: Coarse, crystals at surface → Iron pill

C: Subtle, uniform deposition in deep glands → Iron overload

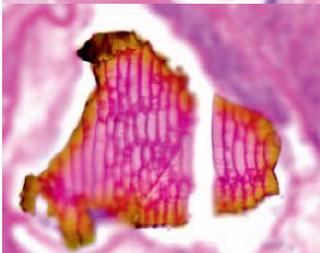


Resins



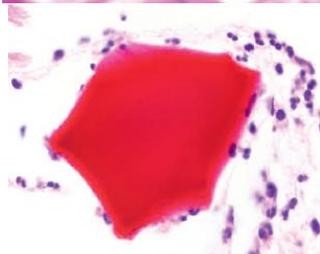
Kayexalate: Used to treat hyperkalemia in renal failure → causes ischemic and ulcerative changes. Linked to fatalities, so urgent dx.

Purple on H&E with narrow fish-scale pattern.



Sevelamer: Used to treat hyperphosphatemia in renal failure → Associated with mucosal injury.

Bright pink to rusty yellow on H&E with irregular fish-scale pattern.



Bile Acid Sequestrants: (e.g., cholestyramine) Binds bile acids (lowers cholesterol). NOT associated with injury

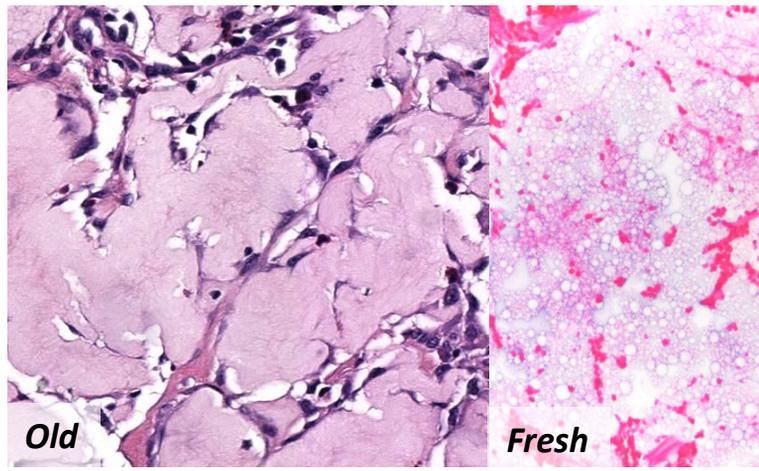
Bright pink/orange on H&E with smooth, glassy texture.

Lifting Agent

Appears homogeneous pink, often with a giant cell response (when fresh, more mucin-like)

Synthetic material injected during EMR/ESD. May resemble amyloidosis (but Congo Red negative) or Pulse granuloma.

Common names: "ORISE" and "Eleview"



Crospovidone

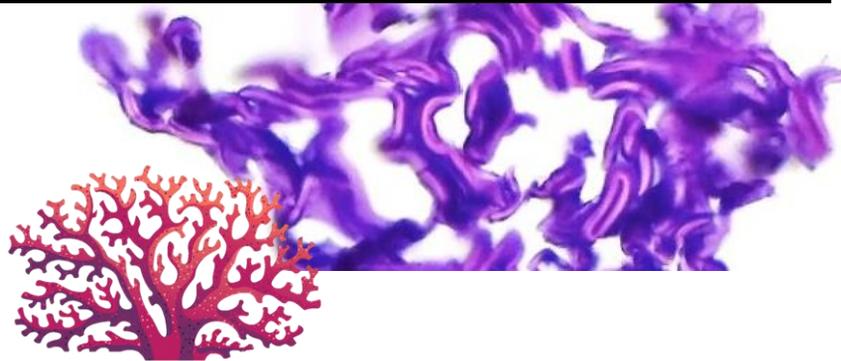
Coral shaped

"Pink center with a purple coat"

Incorporated into many medicines.

Biologically inert → incidental finding

Non-birefringent



Microcrystalline cellulose

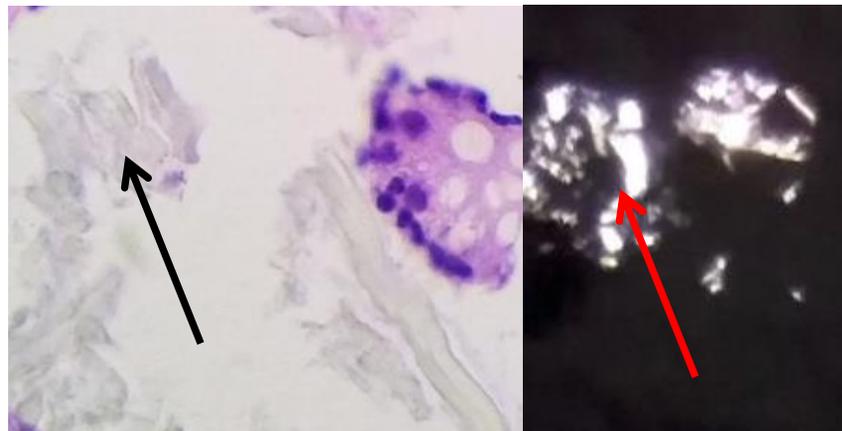
Appears transparent on H&E

Birefringent

Often rod-shaped

Incorporated into many medicines

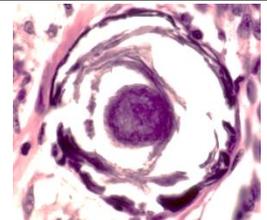
Biologically inert → incidental finding



Calcium

Appears dark purple and often cracked on H&E; Black on von Kossa

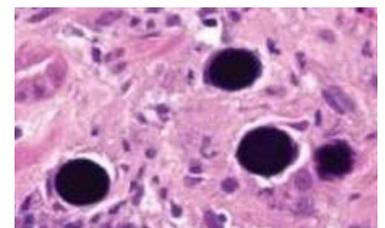
Can be: Metastatic (in normal tissue due to high serum calcium levels), dystrophic (in damaged tissue due to injury), or idiopathic



⁹⁰Yttrium-labeled Microspheres

Appear as uniform dark/opaque perfect circles.

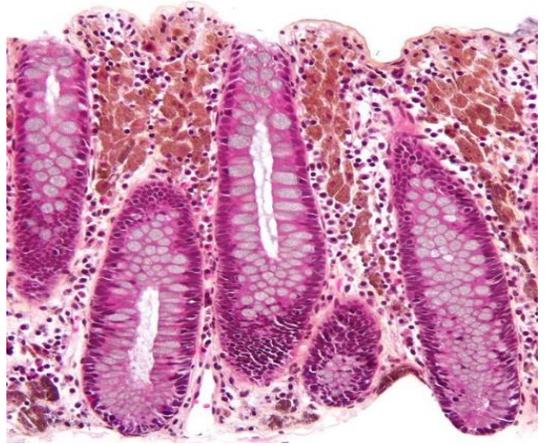
Given by interventional radiology as internal radiation therapy for hepatic malignancies. Often also see radiation injury.



Melanosis

Coarse, brownish black pigment in cytoplasm of macrophages.

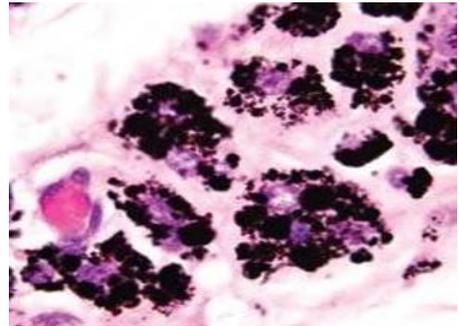
Consists of deposited Lipofuscin. Although classically associated with laxative use, can be seen in any disorder with increased epithelial cell turnover, including constipation.



Tattoo

Very black, coarse granules in macrophages, often with a foreign body giant cell reaction.

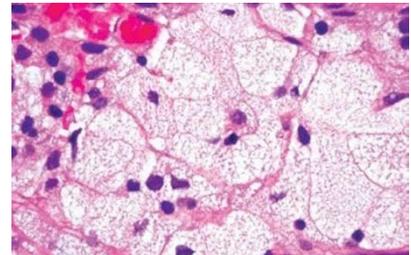
Used to mark lesions endoscopically for later identification.



Muciphages

Mucin-containing macrophages in lamina propria

Presumably cleaning up after epithelial injury and turnover. Very common, especially in rectum.

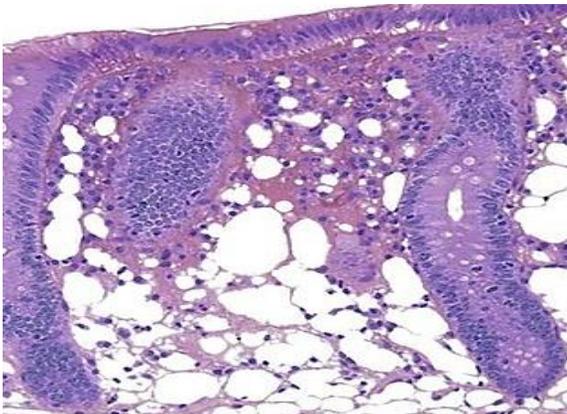


Air

“Pseudolipomatosis”

Empty spaces, irregular in size, without a foreign body reaction.

Attributed to insufflation artifact. No associated nuclei (not fat).



Pneumatosis Cystoides Intestinalis

Empty spaces, WITH a foreign body reaction.

(which means it happened in vivo!!)
Often iatrogenic or infectious cause.

