

Inflammatory Bowel Disease

Normal 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.

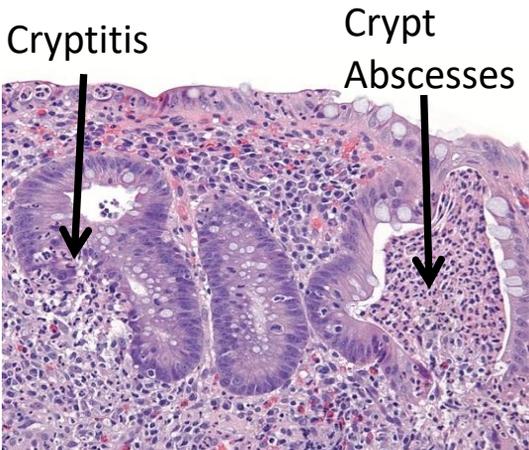
Intraepithelial lymphocytes (and even rare neutrophils) over lymphoid follicles is also normal.

Patterns of Damage in IBD

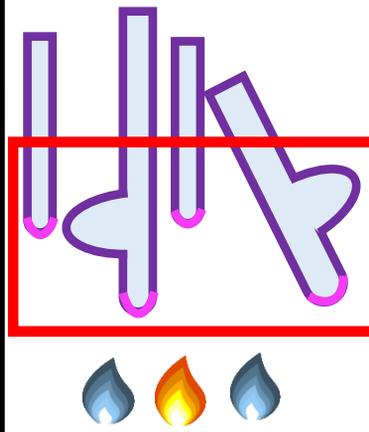
The inflammation in IBD is characterized by the presence/absence of "Activity," defined as neutrophilic inflammation of the epithelium with epithelial damage, and "Chronicity," including architectural distortion, a basal lymphoplasmacytosis, and Paneth cell metaplasia.

These words are combined such that you can have an "Active colitis," a "Chronic active colitis," or a "Chronic inactive colitis," which is also sometimes called "Quiescent colitis."

Activity = PMNs



Chronicity



Crypt architectural distortion

- Crypt shortening
- Crypt branching
- Crypt dropout
- Loss of crypt parallelism
- Villiform surface

Basal lymphoplasmacytosis

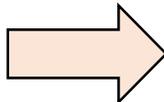
- Paneth cell metaplasia and hyperplasia
- Pyloric gland metaplasia
- Lamina propria and submucosal fibrosis



New onset, untreated IBD

Active Colitis

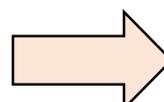
~ 1 month untreated



Typical appearance of active disease

Chronic Active Colitis

Treatment

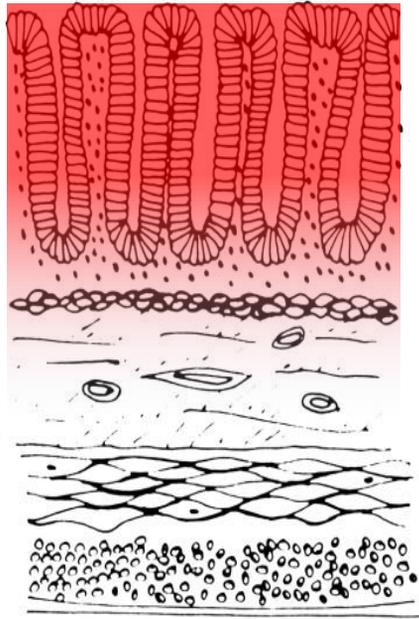
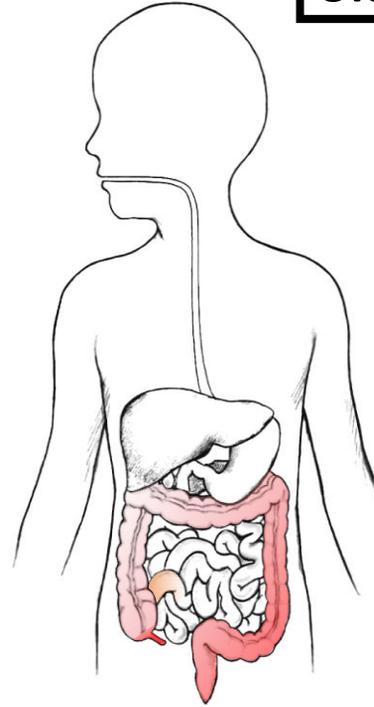


IBD in recent remission

Chronic inactive (Quiescent) Colitis

IBD is subclassified as either *Ulcerative colitis (UC)* or *Crohn's disease (CD)*:

Ulcerative Colitis



Chronic active inflammation in the **rectum** proceeding proximally in **continuous, diffuse** pattern

Typical findings:

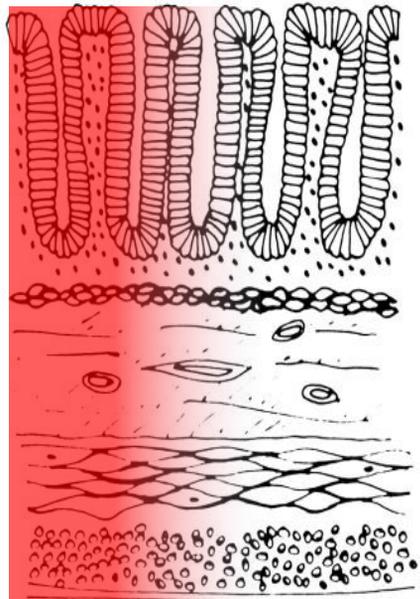
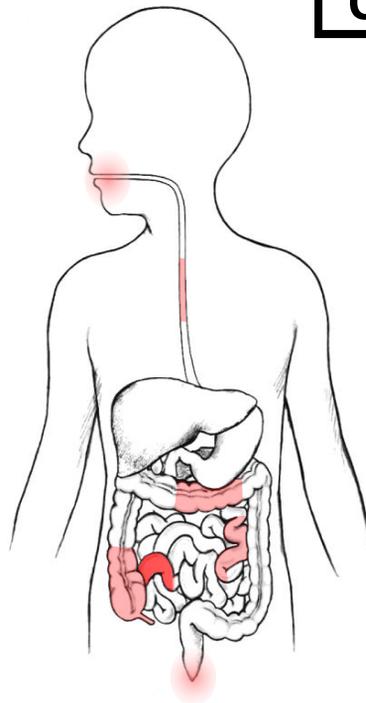
Chronic Active Colitis limited to mucosa and superficial submucosa with ulceration

Can see deeper inflammation with severe "fulminant" colitis

Can have increased inflammation in cecum near appendiceal orifice ("cecal patch")

Can have inflammation in terminal ileum ("backwash ileitis")

Crohn's Disease



Patchy Transmural chronic active inflammation in **any** part of the GI tract

Typical findings:

Transmural inflammation

Skip areas and **patchy** inflammation

Granulomas

Ulcers: superficial aphthous to fissuring

Muscle and nerve hypertrophy

Pyloric gland metaplasia (esp. in TI)

Fibrosis and strictures

Fistulas

Indeterminate Colitis

aka: IBD, type unclassified

Approximately 10% of patients unclassifiable, often due to the extensive pathologic and clinical overlap between UC and CD. Placeholder term--this is *NOT* a specific entity. Often due to insufficient data or fulminant colitis.

Differential Diagnosis:

Active Colitis

(aka Acute Self-limited Colitis)

Causes: E. Coli, Salmonella, Shigella, Campylobacter, Viruses

E. coli O157:H7 → ischemic changes

Looks similar: Some medications (e.g., NSAIDs, Checkpoint inhibitors), New onset IBD

Neutrophilic Cryptitis
But, Chronicity ABSENT

Neutrophils in superficial lamina propria

Crypt abscesses

Hemorrhage, edema

Possible erosions

Focal Active Colitis

FOCAL Neutrophilic Cryptitis
Chronicity ABSENT

Causes:

NSAIDs → + Increased apoptoses, ischemic-like changes

Bowel preparation artifact → + Increased apoptoses, edema, mucin depletion

Early infection → Days 0-4 after onset

Ischemic changes → often with lamina propria hyalinization, crypt withering

Microscopic Colitis

Increased Intraepithelial Lymphocytes (IELs)
Neutrophils rare to absent

Lymphocytic Colitis

IEL $\geq 20/100$ surface epithelial cells

Normal architecture

Chronic inflammation in lamina propria
(usu. superficial)

Collagenous Colitis

IEL $>10-20/100$ surface epithelial cells

Increased Subepithelial Collagen

Entraps capillaries and lymphocytes
Highlighted by Trichrome stain

Additional DDX:

Ischemic colitis → Hyalinized lamina propria, withered crypts, minimal inflammation

Radiation colitis → Ischemic changes, Atypical stromal cells, Telangiectatic blood vessels

Diverticular disease-associated colitis → In colonic segment with diverticulosis

Diversion colitis → Colon isolated from fecal stream, Follicular lymphoid hyperplasia

Prolapse → Fibromuscular hyperplasia, Angulated diamond-shaped crypts

Vasculitis → Inflammatory destruction of vessels, Fibrinoid necrosis

Eosinophilic/Allergic Colitis → >60 Eos/10 HPF, Few PMNs, Absent chronicity

STD Proctitis → Often chlamydia or syphilis due to anal receptive intercourse. Lots of ulceration, plasma cells, and histiocytes. Confined to rectum.

Medical Management

Usually 2 phases: 1) **Induction** (to induce remission) and 2) **Maintenance** (to maintain remission)
These may use same or different medications/dosages.

Typical management previously involved “**Step-up** therapy,” where you start with a mild drug (e.g., mesalamine) and only move up to a more powerful drug if they “fail” that drug. However, recent clinical trials have shown better complication-free survival with a “**Top down**” model where you start with a more powerful medication (e.g., monoclonal antibody).

Mesalamine (5-ASA) – mechanisms of action unknown. Low activity. Usually used orally or rectally for mild UC.

Sulfasalazine – like 5-ASA (mechanism of action unknown). Usually used for mild ileocolic CD.

Budesonide – steroid taken orally with little system effect (mainly works on GI tract).

Prednisone – oral steroid often used to induce remission in active IBD. Long-term use limited due to side effects. Use in both CD and UC.

Azathioprine/6-Mercaptopurine – Thiopurines, inhibit DNA synthesis, thereby reducing WBC production and inflammation. Risk of lymphoma. Used in both CD and UC.

Tofacitinib (Xeljanz) – janus kinase (JAK) inhibitor. Currently only used in UC. Oral pill. Powerful.

Monoclonal antibodies:

Adalimumab (Humira) – recognizes TNF α . Used in both CD and UC.

Infliximab (Remicade) – recognizes TNF α . Used in both CD and UC.

Vedolizumab (Entyvio) – recognizes $\alpha 4\beta 7$ (gut-specific) integrin, inhibiting diapedesis. Used in both CD and UC, but likely better for UC. Very few side-effects as gut-specific.

Ustekinumab (Stelara) – recognizes interleukin (IL) 12 and 23. Used in CD.

Cancer Risk and Screening

Cancer Risk:

Ulcerative colitis = ~2.4 fold risk (**~ 2x risk**)
Crohn's Disease = ~1.9 fold risk

Inflammation \rightarrow DNA oxidation/damage \rightarrow Cancer
Risk proportional to severity/duration of inflammation.

Screening recommendations:

First 8-10 yrs after diagnosis \rightarrow No increased screening (not enough time for carcinogenesis)

Years 10-20 \rightarrow Every 1-3 yrs (shorter interval with worse, esp. if PSC)

Years 20 onward \rightarrow 1-2 yrs

Treatment of Dysplasia

With modern techniques, including high-definition and chromoendoscopy, most dysplasia is visible. As such, it can be completely resected endoscopically.

Once a dysplastic lesion has been resected, in the absence of surrounding dysplasia, ongoing meticulous colonoscopic surveillance is appropriate.

Proctocolectomy is only recommended for dysplasia if endoscopic resection is not possible, or if nonvisible high-grade dysplasia or adenocarcinoma is found.

Pre-malignant and Malignant lesions in IBD:

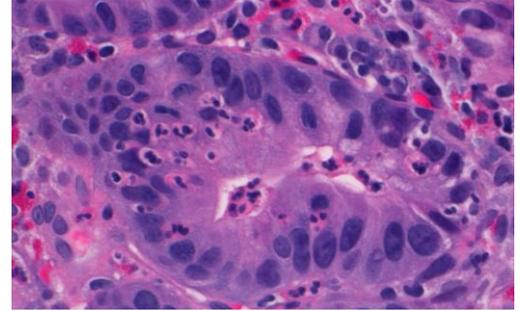
Generally, follows stepwise progression of: Non-neoplastic → Low-grade dysplasia → High-grade dysplasia → Adenocarcinoma. However, there are cases where it appears to go from low-grade (or even normal appearing) to adenocarcinoma very quickly or directly.

Conventional Dysplasia (look like usual adenomas):

Indefinite for Dysplasia

Unable to classify as definitely reactive or dysplastic.
Often atypia in setting of severe inflammation or ulceration.
Sometimes surface not present for evaluation.

Management: Treat active disease and repeat biopsy in 3-12 months.

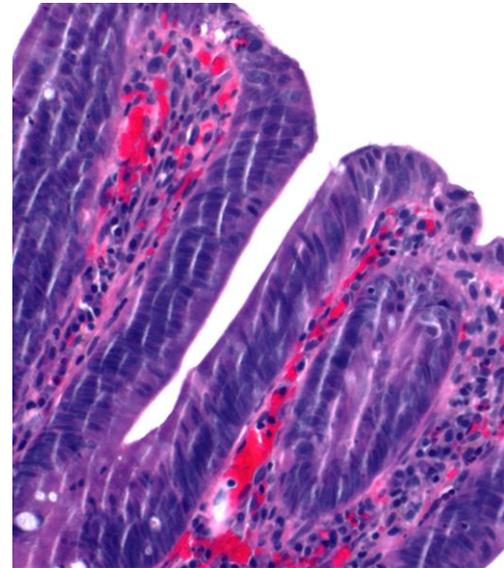


Low-Grade Dysplasia

Looks like a sporadic **Adenoma**.
Enlarged, hyperchromatic, smooth, "pencil-like" nuclei.
Pseudostratified nuclei with maintained basal orientation.
Higher N:C ratios; **Little to no surface maturation.**
Often abrupt transition (corresponding with clone)
Prominent apoptoses.

Molecular: IBD-associated dysplasia show more copy number aberrations and aneuploidy than sporadic adenomas. TP53 mutations are very frequently present early. Possibly reflecting a faster progression toward cancer.

Management: Complete endoscopic resection if visible.
Otherwise proctocolectomy ± IPAA to exclude cancer.



Hint: Try using a lymphocyte as what is "normochromatic"

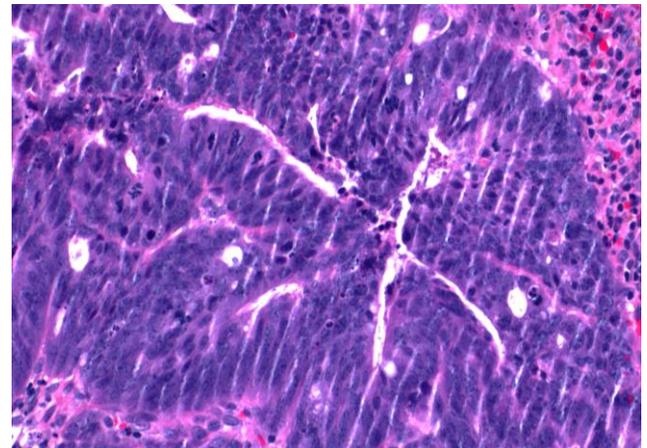
High-Grade Dysplasia

Enlarged, hyperchromatic, pleomorphic nuclei.
Often plumper than LGD.
Irregular nuclear contours. Prominent nucleoli.
Loss of nuclear polarity.
Complex architecture: Cribriforming, crypt branching/budding.

P53 staining often highlights both grades:
Dysplasia → Strong P53 staining (or null-type) at the surface in atypical areas.

Negative/Indefinite → weak staining at bottom of crypts (proliferative compartment), without strong staining at the surface.

H&E is still the gold standard though, so only do it on cases that are equivocal!



Nonconventional lesions:

Serrated Epithelial Change

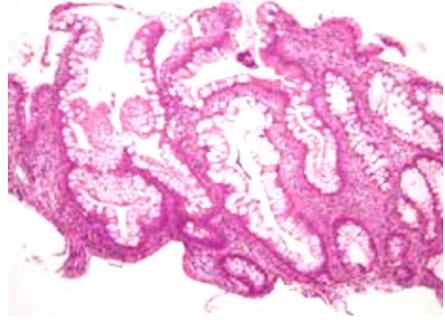
Serrations at top and bottom of crypts.

Distorted crypt architecture where some crypts do not reach the muscularis mucosae. (unlike SSL)

Normal nuclei. Goblet cell-rich epithelium.

Controversial risk of CRC. Many studies show increased risk of dysplasia/carcinoma.

Emerging genetics, likely TP53 mutations.



Note: The colon in IBD patients can frequently show surface serrations/hyperplasia, particularly in the distal colon, so strict criteria are necessary.

Non-Conventional Dysplasia

May be present with conventional dysplasia in ~50% of cases. More common on left side as polypoid mass.

Hypermucinous—Villous architecture with prominent cytoplasmic mucin.

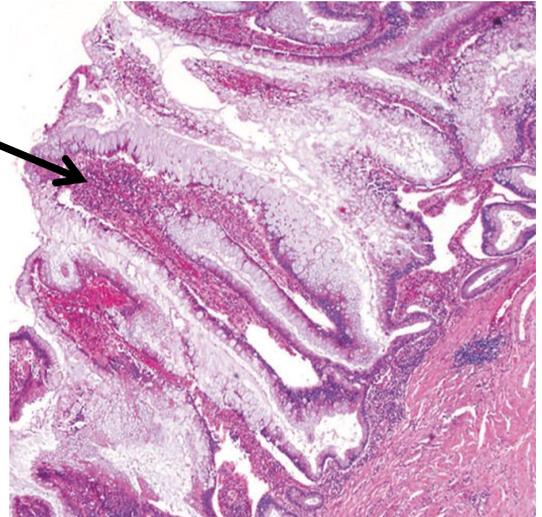
Traditional Serrated Adenoma (TSA)-like

Sessile serrated lesion (SSL)-like

Paneth cell differentiation

Goblet cell deficient—absence of goblet cells

“Terminal epithelial differentiation,” TED, or “Crypt cell dysplasia,” CCD –flat lesions, round to oval hyperchromatic nuclei. Can be just in crypts.



Adenocarcinoma

Invasive through basement membrane:

- Infiltrating glands/cells
- Broad, expansive confluent growth of glands

Compared to Sporadic, IBD-associated CRC is:

- More often multifocal (field defect)
- More often higher grade
- More often advances stage
- More often signet-ring or mucinous

Unique variant:

Low-grade tubuloglandular adenocarcinoma—very bland small to medium-sized round glands that invade with little desmosplastic stroma. Often CK7 (+). Frequent IDH1 mutations.

