Non-neoplastic Colorectal Pathology

Back to basics and some new things
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Colon Biopsies, Whirlwind Tour

Be proud to diagnose normal
Be ready to think outside the box
Have fun!

Diagnosis of Colitis

Requires evidence of injury to the epithelium
Normal to have more lymphoplasmacytic cells in the lamina propria of the cecum than the distal colon.

Right v Left Colon

Diagnostic Criteria for Ulcerative Colitis

Major Criteria: Diffuse mucosal inflammatory infiltrate; basal plasmacytosis; neutrophils overrunning mucosa; crypt abscesses; crypt distortion; villiform surface

Minor Criteria: decreased goblet cells; Paneth cell metaplasia

Clinical Characteristics: Chronic relapsing and remitting course; bloody diarrhea, diffuse colonic involvement; rectal involvement; pseudopolyps.
Untreated ulcerative colitis generally shows continuous mucosal involvement save for the occasional periappendiceal skip area (cecal patch), as illustrated in this image.

Ulcerative colitis. Quiescent disease may appear granular with areas of punctuate erythema.

Pseudopolyps in ulcerative colitis. These are mucosal remnants associated with intervening areas of ulceration.

Italian Crypt Distortion

Ulcerative Colitis
Ulcerative Colitis

Extraintestinal Manifestations
Arthritis, uveitis, dermatitis (pyoderma gangrenosum, erythema nodosum)
Sclerosing cholangitis
Ankylosing spondylitis
Many of these resolve with colectomy BUT sclerosing cholangitis and ankylosing spondylitis do not
Filiform (post-inflammatory) polyps. Note the finger-like appearance with two protruding layers of mucosa plastered together with one or no intervening layer of muscularis mucosae.

This post-inflammatory polyp has an interesting shape.

Pyloric metaplasia seen in the left side of the colon of a patient with long-standing ulcerative colitis.

Ulcerative colitis. Biopsy fragments from the same topographic area typically show similar findings with the same degree of inflammation and injury.

Focal gastritis. This highly nonspecific finding can be seen in both ulcerative and Crohn colitis. Note active inflammation on the left hand-side of the field with relative sparing of the mucosa on the right.
Diagnostic Criteria for Crohn’s Disease

Major Criteria: Patchy mucosal inflammatory infiltrate; often histiocyte-rich; submucosal inflammation; microscopic skip areas; crypt abscesses; cryptitis; granulomas.

Minor Criteria: Crypt distortion usually milder than in ulcerative colitis; normal goblet cell population; Paneth cell metaplasia; pyloric metaplasia; lymphangiectasia.

Clinical Characteristics: Progressive course; loose stool; affects terminal ileum/right colon; frequent sparing of rectum; skip areas; “cobblestone” mucosa; anal/perianal fissures & fistulas; aphthous ulcers. Anti Saccharomyces cerevisiae antibodies are of some diagnostic value.
Crohn’s Disease

Aphthous Ulcer

Transmural Inflammation

Granulomas

Granulomas, Foreign Body

Granulomas
Crohn disease. Often times, when several tissue fragments from the same general site are received in a single container, low magnification exam reveals different degrees of inflammation.

Crohn disease. Aphthous ulcer. It is spot-like and is overlying a lymphoid aggregate. This is an early subtle lesion of Crohn. The differential diagnosis is with a non-steroidal anti-inflammatory drug (NSAID) erosion, but an NSAID erosion would be expected to have less chronic inflammation.

Crohn disease. There is minimal acute inflammation in this biopsy, but note the granuloma in the superficial submucosa.

Crohn disease, low magnification, showing a fissure.
Finding prominent, well-formed, or necrotizing granulomas should prompt a search for microorganisms rather before suggesting the possibility of Crohn disease. This patient had gastrointestinal histoplasmosis.
Histoplasmosis

Extraintestinal Crohn disease, also known as "metastatic Crohn disease", can be encountered at any site as in this pulmonary example. Note granulomatous inflammation.

Skin involvement in Crohn's disease

Pouchitis. Chronic inflammation, architectural distortion, and villous atrophy are seen in this low power magnification.
Cuffitis. This image shows relatively uninflamed small bowel mucosa.

Cuffitis. Inflamed rectal mucosa was seen in the same biopsy as small bowel mucosa seen in the previous image.

**Inflammatory Conditions Likely to Result in Misdiagnosis Based on Features of Chronicity**

- Diverticular disease associated colitis
- Diversion colitis

**Diverticular disease-associated colitis**

Segmental chronic colitis in region of diverticula, usually sigmoid colon

Patients present with rectal bleeding, crampy lower abdominal pain, constipation or intermittent diarrhea

**Diverticular disease-associated colitis**

Diffuse or patchy colitis in area of diverticula

Erythema, friability, granularity

Sigmoid colon biopsy
Biopsies of involved segment have a chronic colitis:
- Hypercellular lamina propria
- Plasma cells
- Eosinophils

Diverticular disease-associated colitis. The pseudopolyps in this case are so striking as to suggest Crohn’s disease. However, Crohn’s disease restricted to the sigmoid colon would be very unusual.

Diverticular associated colitis. Notice the diverticulum is associated with an inflammatory response reminiscent of Crohn disease. In this case the surface epithelium lacks features of chronicity.
This patient had a resection of the diverticular diseased area. Note the granuloma in an adjacent lymph node. This patient has not manifested Crohn disease.

**Diverticular disease-associated colitis**

Differential diagnosis is left sided ulcerative colitis with rectal sparing or left sided Crohn’s disease.

Think of this when sigmoid biopsies have chronic colitis and rectum is normal in patient in the right age range for diverticula.

**Diversion Colitis**

A colitis that occurs in the bypassed segment after surgical diversion of the fecal stream.

Patients may present with bloody discharge or pain, but may also be asymptomatic.

**Diversion Colitis**

- Erythema
- Friability
- Edema
- Nodularity
- Aphthous ulcers

**Diversion colitis with prominent lymphoid aggregates**

**Lamina propria hypercellularity**

**Regenerative epithelium**
Lymphoid aggregates and lymphoid follicles are common and found in 2/3 of cases.

**Diversion Colitis**
- Loss of luminal short chain fatty acids that are produced by colonic bacteria
- Major energy source for colonic epithelial cells
- Treatment with instillation of solutions containing short chain fatty acids
- Resolves with restoration of bowel continuity

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**If it’s not IBD, then what is it?**

- There are many colitides other than Ulcerative colitis and Crohn’s disease
- Most of these can be grouped into one of three categories:
  1. Chronic nonbloody diarrhea, normal endoscopy
  2. Diarrhea with endoscopic colitis
  3. Abdominal pain, bloody diarrhea, histologic acute mucosal necrosis

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**Chronic Non-Bloody Diarrhea**

Endoscopic and histologic differential is:
- Normal
- Irritable bowel syndrome (normal histology)
- Microscopic colitis

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**Diarrhea, may be bloody**

Endoscopic and histologic differential is:
- Inflammatory Bowel Disease (IBD)
- something that looks like IBD

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**Abdominal Pain and Bloody Diarrhea**

Endoscopic and histologic differential is:
- causes of mucosal necrosis with or without pseudomembranes
Clinical History #1:

Patient with Chronic Non-Bloody Diarrhea

In this case, the diagnosis is some form of microscopic colitis

Microscopic Colitis

A category of chronic colitis in which there is no gross disease (normal endoscopy) but there is microscopic disease

Three known forms:
• Collagenous colitis
• Lymphocytic colitis
• Other

Collagenous Colitis

Chronic watery diarrhea
Abdominal pain, fatigue, weight loss
Insidious or abrupt onset
F:M = 6-8:1, median age 55 years
Associations: rheumatoid arthritis, thyroid disorders, celiac disease, NSAIDs use
Surface epithelial injury and surface lymphocytosis

Sometimes focal neutrophilic cryptitis is present

Lymphocytic Colitis

Chronic watery diarrhea
Abdominal pain, weight loss in some patients
Males and females equally affected (or sight F predominance)
Broad age range, but mean in 6th and 7th decades

Abnormal collagen layer beneath surface epithelium

Sloughing of Surface Epithelium

A Trichrome stain highlights the abnormal collagen layer

Trichrome Stain
Lymphocytic Colitis

Stronger association with celiac disease than for collagenous colitis

- Of patients with celiac disease, a third will also have lymphocytic colitis on biopsy
- Of patients with lymphocytic colitis, a quarter may also have celiac disease

Cellular lamina propria
Plasma Cells
Fewer Eosinophils than for CC
Nondistorted crypts

Crypt lymphocytosis

Surface epithelial injury and surface lymphocytosis

Normal delicate basement membrane

Sometimes focal neutrophilic cryptitis is present
Frequently asked Questions about Collagenous and Lymphocytic Colitis

How thick must the collagen band be to diagnose collagenous colitis?
How many lymphocytes are needed in the surface epithelium to diagnose lymphocytic colitis?
Can I diagnose either of these without knowing the history and/or endoscopic findings?

How thick must the collagen band be to diagnose collagenous colitis?

With a trichrome stain, the subsurface blue band includes the basement membrane and any collagen beneath it.
Normal thickness (basement membrane): 2.5 to 3 microns, up to 3.5 in rectum.
In collagenous colitis, reported thickness ranges from 7 to 80 microns, averaging around 25.

But....

The thickness of the collagen band matters less than its structure, particularly the lower border.
In collagenous colitis, the lower border of the collagen band is irregular, with wisps of collagen extending into the lamina propria, encircling capillaries and myofibroblasts.

Thickness of Collagen in Collagenous Colitis by Location

How many surface lymphocytes are needed to diagnose lymphocytic colitis?

There is no defined threshold. When counted, the lymphocytes generally number greater than 15 per 100 epithelial cells, often 30 or more.

**BUT.....**

The subjective impression of “too many” is what most people really use, recognizing the patchiness of this finding.

**The Bottom Line**

Neither feature alone (collagen thickness or lymphocyte number) is sufficient for a diagnosis. They must be present together with other histologic features in the appropriate clinical setting.
Can I diagnose collagenous or lymphocytic colitis without knowing the history and/or endoscopic findings?

NO!

Lymphocytic colitis look-alikes

There are other circumstances in which the histologic features of either lymphocytic or collagenous colitis may be present.

Cleveland Clinic:
- only 70% of patients with biopsies that look like lymphocytic had full clinical pictures
- Others had constipation, hematochezia, abnormal colonoscopy, or this was incidental finding

Lymphocytic colitis look-alikes

Drug-induced colitis looking like lymphocytic colitis: ticlopidine, herbal preparations
Hashimoto's thyroiditis: 40% colon biopsies have features of lymphocytic colitis but only 25% of these have diarrhea
Viral enteritis
Patches of lymphocytic-like colitis in some patients with Crohn's

Collagenous colitis look-alikes

Healed mucosal injuries may result in superficial lamina propria fibrosis
- Ischemia
- Radiation
- Ulcerative colitis
- Prolapse
- Other features of collagenous colitis are not present.

Other Questions about Collagenous and Lymphocytic Colitis

What is the distribution of abnormalities?
What are the clinical implications of my diagnosis?
Are there unusual presentations that may confuse the picture?
**What are the clinical implications of my diagnosis?**

The treatments are similar.
- First line treatment with antidiarrheal agents
- Next 5-ASA compounds
- Steroids effective for most who fail above

Most achieve remission, but relapse common in those with collagenous colitis. Fewer patients with lymphocytic colitis have long-term symptoms, and many spontaneously resolve.

**Unusual presentations**

*Collagenous colitis with linear ulcers and perforation*

Patients with diarrhea and all the features of lymphocytic colitis except for surface lymphocytosis ("cryptal lymphocytic coloproctitis")
- Some of these may have gluten sensitivity

**The Normal biopsy in the patient with chronic diarrhea**

Important finding for some clinical diagnoses, for example irritable bowel syndrome (IBS)

May mean the cause of the diarrhea is due to an extracolonic factor

**Therefore…..**

The diagnosis of NORMAL is very important!

Requires recognition of trivial abnormalities that are best ignored!
- Focal active colitis
- Bowel preparation-induced abnormalities

**Bowel preparation effects**

*oral sodium phosphate*

Endoscopic aphthoid ulcers—-not true ulcers, but lymphoid aggregates that appear aphthous to endoscopist
True aphthous ulcers—less common
Focal active colitis
Scattered apoptotic bodies
**NaP induced colorectal aphthous ulcerations**

Incidence: 2.6% to 24.5%.
Targetoid appearance: pale centers and erythematous outer halos.
Measure about 2- to 3-mm.
Usually surrounded by a normal mucosa.

Can be observed throughout the colon.
+++ descending & rectosigmoid colon.
Single or clusters.
(2 / 3 up to > 30 lesions)
Disappear within a span of a few days to a few weeks.

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**Clinical History #2:**

Patient with diarrhea, sometimes bloody

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**Acute self-limited colitis (ASLC)**

Transient—sudden onset bloody diarrhea, spontaneous recovery within 10 to 14 days

Presumably infectious.

When culture is positive (40%), Campylobacter fetus ssp jejuni most common pathogen
Thus, the clinical differential diagnosis is

**Acute infectious colitis**

versus

**Ulcerative colitis at first presentation**

Endoscopy shows:

- Diffuse erythema
- Mucosal friability, focal hemorrhages and ulcers

**ASLC early phase:**

- Edema
- Superficial Ulcers
- Cryptitis, crypt abscesses
- Cellular lamina propria
- No distortion

**Resolving ASLC:**

- Less Edema
- Regenerative Epithelium
- Only focal cryptitis
Features to distinguish ASLC from Ulcerative Colitis

Lack of features that indicate chronicity
- No crypt distortion
- No significant plasmacytosis

HISTORY!!!

Biopsies from patients with infectious colitis show superficial lamina propria and epithelial inflammation. Note the lack of basal plasmacytosis.

Endoscopic appearance of cytomegalovirus (CMV) colitis.

Cytomegalovirus (CMV) colitis. Note the virocyte in the center of the field. CMV typically affects the endothelial cells in the colon and follows the rules of minimal crypt distortion.
Cytomegalovirus (CMV) colitis affecting epithelial cells. This is occasionally seen in CMV colitis.

Adenovirus colitis. There are Cowdry A inclusions (center) and Cowdry B (smudged) inclusions at the upper right.

Immunohistochemical preparation for adenovirus.

Colonic spirochetosis. Numerous spirochetes are seen here carpeting the epithelial surface.

Colonic spirochetosis. Some cases may go unnoticed unless the mucosa is examined at high power.
Colonic spirochetosis, Warthin Starry stain. The anaerobic intestinal spirochetes *Brachyspira aalborgi* and *Brachyspira pilosicoli* seem to be responsible for most cases of spirochetosis. *B. pilosicoli* colonizes the intestinal tract of many animal species, especially pigs, and can be found in approximately 30% of fecal samples from persons in developing countries.

Microsporidia

These biopsies are from a patient with a clinical course consistent with viral gastroenteritis. Numerous lymphoid aggregates were seen. These features are not wholly specific but in keeping with the clinical history.

**Yersinia enterocolitica.** Although granulomas may raise the possibility of Crohn disease, these tend to be necrotizing, bigger, and more prominent in the setting of *Yersinia* infection.

Clinical History #3:

Abdominal Pain and Bloody Diarrhea

Colonoscopy shows edema, erythema, and ulcers in the right colon.
**Acute Mucosal Necrosis**

Differential diagnosis:
- Ischemia
- C. difficile-associated pseudomembranous colitis
- Verotoxin-producing E. coli (serotype 0157:H7) colitis
- Others—NSAIDs induced erosions

**Ischemic injury**

Many causes, most related to cardiovascular disease or conditions leading to hypotension, thus most patients older

Abdominal pain, with or without bleeding, may be asymptomatic

Any part of the colon may be involved

**Colonoscopy:**
- Erythema
- Friability
- Edema
- Ulcers, with exudate

**Ischemic colitis**

Necrosis of epithelium, including surface and part of all of crypts
Ischemic colitis
Necrosis of epithelium, including surface and part of all of crypts.

Ischemic Colitis
The lamina propria has a hypocellular, pale eosinophilic appearance.

Ischemic Colitis
There may be mucosal hemorrhage, a little or a lot.

Ischemic Colitis
Small crypts ("microcrypts" lined by regenerative epithelium are typical.

Ischemic Colitis
Necrotic mucosa may mix with inflammation, blood and fibrin to form pseudomembranes.

E.coli 0157:H7 Colitis
E. coli serotype 0157:H7 is a noninvasive organism that produces Shiga-like toxins. Also called verotoxins because they are active against Vero cells.
**How is the infection acquired?**

E. coli 0157:H7 can live in the intestine of healthy cattle. During slaughter, the meat can become contaminated. Bacteria present on udders or equipment can get into milk.

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**E.coli 0157:H7 Colitis**

Routine stool cultures do not distinguish between 0157:H7 and other strains of *E. coli*.

BUT....

Most laboratories also use a culture medium that will screen for the organism based on its pattern of sorbitol fermentation OR a molecular test.

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**Endoscopic Findings:**
- Patchy edema
- Erythema
- Superficial Ulcers
- Most common in the cecum and right colon.

**Resembles Ischemia**
- Superficial mucosal necrosis
- Hemorrhage
- Regenerative epithelium

**Fibrin thrombi are sometimes found in mucosal capillaries**
Some biopsics may resemble an acute infectious colitis (ASLC pattern).

NSAIDs focal ischemic-type injury

Ischemic colitis

Abnormal mitosis in ischemic colitis
Pseudomembranous Colitis

Most cases caused by C. difficile
toxin production following
antibiotic therapy
Other less common causes
include CMV

Patients present with diarrhea,
often bloody, fever, pain
Rarely, extracolonic
manifestations develop, including
small intestinal involvement,
sepsis, splenic or pancreatic
abscess, pleuritis/empyema, or
reactive arthritis.

Plaques of adherent
pseudomembrane with
normal-appearing intervening
mucosa

Necrosis of surface and upper crypt
epithelium
Inflammatory pseudomembranes fills
dilated crypts and covers surface

Biopsies of intervening mucosa may look
normal, have features of ASLC, or may
have focal surface injury
Endoscopic images from a patient with radiation colitis.

Distinguishing between the causes of Acute Mucosal Necrosis

- Age
- Presentation
- Antibiotic history
- Stool cultures
- Toxin assays

WORTH LOOKING FOR!

Crypts may be more dilated in pseudomembranous colitis
Pseudomembranes less common in E. coli 0157:H7
Hyalinized (trichrome blue) lamina propria not a feature of pseudomembranous colitis
None of these is always true!

Distinguishing between the causes of Acute Mucosal Necrosis
With no antibiotic history, differential diagnosis is between E.coli and ischemia

Remember… Young women taking oral contraceptive pills may also develop colonic ischemia

Thank you