GIS 6

PATHOLOGY

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In this lecture, we will continue with the second part of small and large intestinal pathology and discuss inflammation of the intestines. However, the infectious causes of inflammation will be discussed in microbiology. Please note that in some cases the professor used pictures in the video that were not in the slides. All pictures are included in the sheet. However, pictures from the slides that were not a part of the video (and therefore not discussed) will have a blue triangle in the bottom right-hand corner.

Inflammatory Intestinal Diseases

We will be discussing two inflammatory conditions of the intestines:

1. Sigmoid Diverticulitis – A disease that is limited to the rectum and sigmoid.
2. Chronic Inflammatory Bowel Diseases (CIBD) – A group of immune-mediated conditions that are subdivided into Crohn disease and ulcerative colitis.

1. Sigmoid Diverticulitis

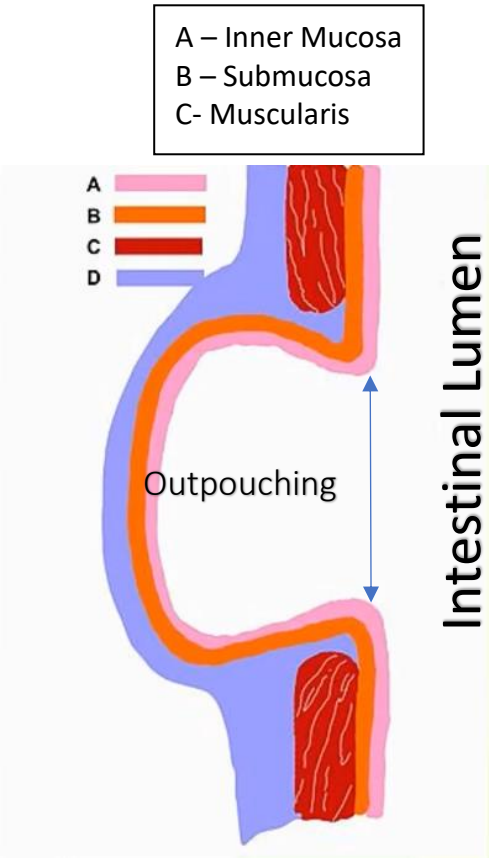
- Acquired – It affects older adults.

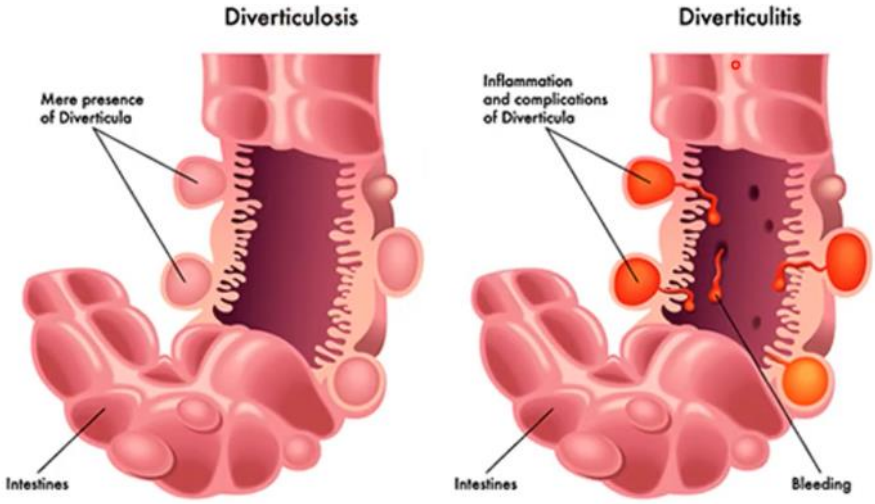
The underlying cause for diverticulosis (this name refers to the condition without inflammation, with inflammation it is called diverticulitis) is **constipation**, which is usually caused by a **low fiber diet**. This constipation will lead to **exaggerated peristaltic contractions in the bowel wall**, which will lead to **elevated intraluminal pressure in the sigmoid colon**. This leads to **outpouchings of colonic mucosa and submucosa**, which are called **diverticula**. This outpouching is usually composed of a thin wall of the colonic mucosa and submucosa. This is why it's called pseudodiverticulae, as it lacks the four layers of the bowel wall.

Morphology

- Flasklike outpouchings
- Most common location: Sigmoid colon
- Thin wall (atrophic mucosa, compressed submucosa)
- Attenuated or absent muscularis (See how Layer C {red} is not a part of the wall of the diverticula).
- Obstruction by a fecalith material leads to inflammation resulting in diverticulitis.
- Risk of stricture formation and stenosis in the wall of the bowel, and perforation of inflamed diverticulum. With perforation, the fecal material will go out into the peritoneal cavity with resultant peritonitis and severe abdominal pain.
- Recurrent diverticulitis leads to strictures and possible stenosis.

*The double sided arrow indicates the neck of the diverticulum.

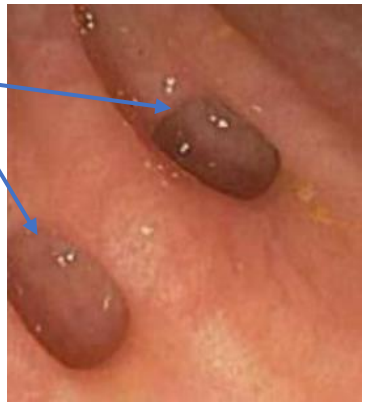


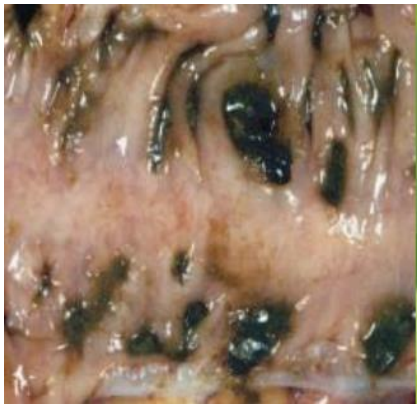


This figure illustrates the difference between diverticulosis and diverticulitis.
When there is an obstruction of the neck of these diverticula, usually by fecalith material, there will be diverticulitis (red diverticula). The main complaint of diverticulitis is abdominal pain. Recurrent bouts of diverticulitis will eventually lead to narrowing of the lumen of the bowel and stricture formation with resultant stenosis. The patient will then come complaining of intestinal obstruction.
*Notice that there are multiple diverticula (outpouches). This is usually the case due to the increased luminal pressure.

Colonoscopy:

These are the outpouches. This indicates the neck of the diverticula and is where fecal material enters.



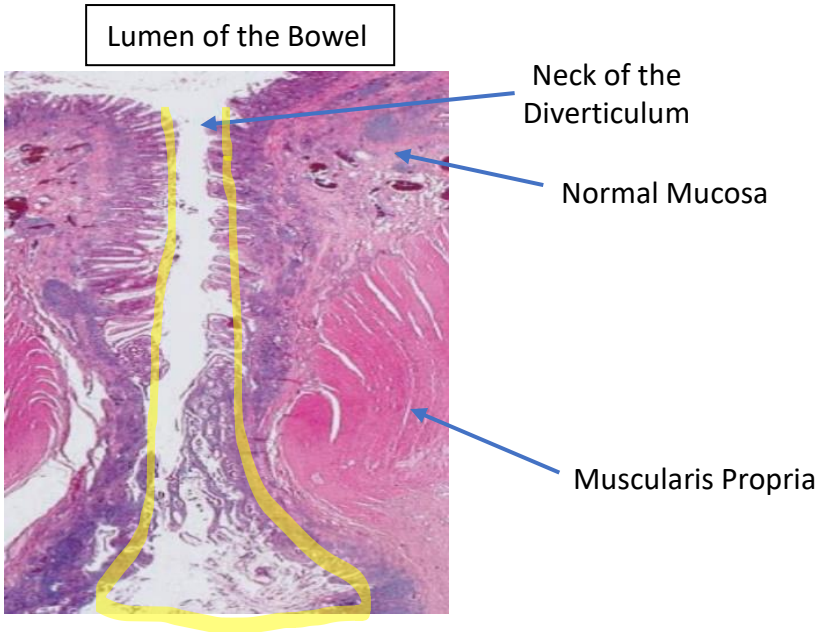


This image shows numerous diverticula with fecal material impacted at their necks. This is a typical morphological appearance seen during colonoscopy.

Microscopy:

If the patient underwent surgery, we'd be able to see the microscopic appearance.

The highlighted area outlines the diverticulum. Notice that the muscular propria is not a part of the wall. Therefore, the wall is thin and is exposed to perforation if diverticulitis takes place.



Clinical Features

- Mostly asymptomatic (other than the symptoms of constipation)
- Some patients may have intermittent lower abdominal pain.
- Digging into the patient's history shows constipation or sometimes diarrhea during bouts of diverticulitis.

With constipation the main complaint, and sometimes lower abdominal pain, these symptoms are nonspecific. However, you can suspect this condition if the patient is elderly, presents with these symptoms, and you were able to exclude other causes of constipation. The diagnosis can be reached through colonoscopy and seeing the diverticula.

Treatment

- The focus is to treat the cause: constipation. Therefore, a **high fiber diet** is best to counteract the constipation. Through this, the disease will not worsen.
- If there is a bout of diverticulitis and concurrent, ongoing inflammation then **antibiotics** are needed.
- If the symptoms are very severe with resultant stenosis and stricture formation, then **surgery** is offered (sigmoidectomy).

2. Inflammatory Bowel Disease (IBD)

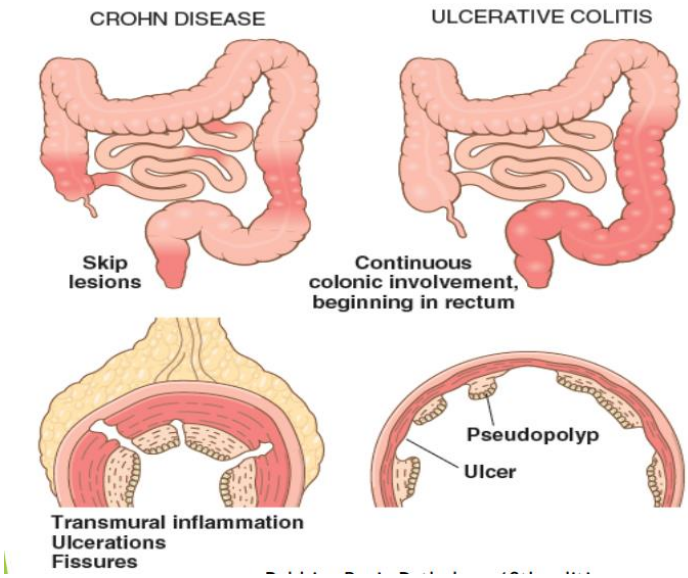
- These are known as chronic inflammatory bowel diseases.
- These are a group of diseases with genetic predisposition. Family history is very important to take because usually there is another relative complaining of the same disease.
- The main problem in IBDs is the inappropriate mucosal damage. This means that there is damage to the mucosa and sometimes bowel wall that is inappropriate to the antigenic stimuli. It is an **aggravated immune response** (the main pathology of the disease).

- IBDs are subdivided into two groups:
  i. **Ulcerative colitis (UC):** Limited to the colon and rectum and extends only into the mucosa and submucosa. Usually it starts in the rectum, then extends proximally to affect the colon up to the level of the ileocecal valve. So, there are variable degrees of severity between patients.

  ii. **Crohn disease (CD):**
    - Regional enteritis - It does not involve the bowel in a continuous fashion (as ulcerative colitis does), but instead it is regional. So, some areas may be involved, while adjacent areas are skipped, and then another area is involved.
    - Frequent ileal involvement.
    - Can affect any area in GIT (from the mouth to the anus).
    - Frequently transmural – This means not only the mucosa and submucosa are affected, but also the muscularis and serosa are affected.

In ulcerative colitis, there are no "skip lesions". In a transverse section (lower image), you can see the inflamed mucosa, ulcerations, and resultant pseudopolyps. The un-ulcerated mucosa can look like polypoid regions, and are called pseudopolyps.

In Crohn disease, in a transverse section, you can see deep ulcers that look like fissures of the abdominal wall. There is also a pseudopolypoid appearance and inflammation is transmural (all 4 layers are inflamed in the image).



Epidemiology

- Adolescence & young adults (patients in second or third decade)
- 2nd peak in fifth decade
- The disease is not usually diagnosed in elderly patients, like those sixty or older.
- Geographic variation
- The underlying cause is not well established but there is the hygiene hypothesis: childhood exposure to environmental microbes prevents excessive immune system reactions later on. Firm evidence is lacking! This hypothesis also applies to allergies.

Pathogenesis

- The exact mechanism of disease is not well understood.
- However, there is an agreement that it is multifactorial and due to a number of combined effects:
  - Genetic factors
  - Alterations in host interactions with intestinal microbiota
  - Intestinal epithelial dysfunction.
  - Aberrant (or exaggerated) mucosal immune responses
  - Altered composition of the gut microbiome

a. *Genetics:*
   - Family history – This is important evidence to indicate genetics plays a role.
   - Concordance rate for monozygotic twins is 20% for CD and 16% for UC. This also indicates that genetics plays a role.
   - 200 genes are associated with IBD, and all with CD (not UC, which is strange). Carriers of these genes display an exaggerated immune response to bacteria entering their bowel.
   - One gene is **NOD2** (nucleotide oligomerization binding domain 2): A susceptibility gene in Crohn disease.

- The presence of disease-associated (mutated) NOD-2: Ineffective defense against intestinal bacteria. The result is that bacteria are able to enter through the epithelium & trigger inappropriate inflammatory reactions.
- Autophagy genes are also involved.

b. Exaggerated Mucosal Immune Responses

- Immunosuppressive and immunomodulatory agents are main stays of IBD therapy.
- This proves that exaggerated immune responses are part of the pathogenesis.
- There is excessive immune activation by intestinal microbes.
- Defective immune regulation of T cells:
    - TH1 (mainly in CD) and TH2 (mainly in UC)

c. *Epithelial Defects*

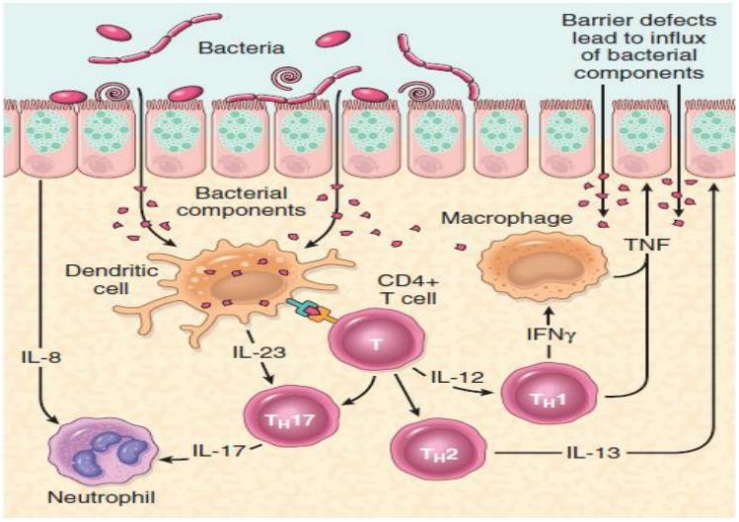
- Defects in intestinal epithelial tight junction barrier function >>>> in Crohn disease
- Barrier dysfunction >>> activates innate and adaptive mucosal immunity >>> sensitizes subjects to disease.
- Defects in Paneth cell (anti-microbial) granules.

d. Microbiota

- Quantity of microbes in gastrointestinal lumen is enormous (50% of stool mass)
- Inter-individual variation in microbial composition.
- Probiotic (or beneficial) bacteria may benefit IBD patients.

Disease Model

- Starts by trans-epithelial flux of bacteria. Bacteria that is present in the lumen of the bowel enters through the epithelium into the underlying lamina propria and submucosa to meet with the inflammatory cells normally present there.
- Then there is activation of innate and adaptive (represented by T lymphocytes mainly) immune responses (takes place only in genetically susceptible hosts). (see the cells in the figure)
- The exaggerated immune response leads to the release of TNF and immune signals (or mediators such as INFs and other cytokines).
- The effect of the cytokines leads to increased tight junction permeability. Therefore, the barrier between the lumen and submucosa is lost.
- This leads to more flux of luminal bacteria and more amplification of the inflammatory response.
- It is a self-amplifying cycle: stimulus at any site is sufficient to initiate IBD.



In normal individuals, the normal flora and mucosal immunity prevents overgrowth of pathogenic bacteria. In genetically susceptible individuals, they may have an abnormality in the epithelial or immune system. Here, the disease model explained above may occur.

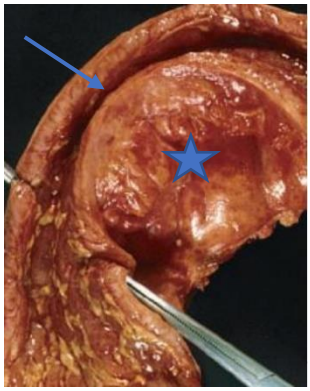
i. Crohn Disease

Macroscopic Morphology

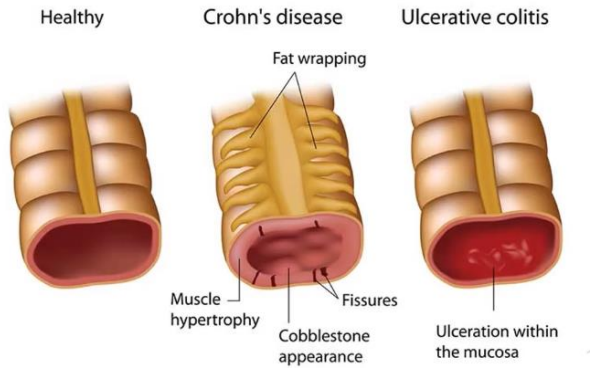
- Regional enteritis
- **Any area of the GIT**
- Most common sites: terminal ileum, ileocecal valve, and cecum.
- Affected Organs:
  - Small intestine alone: 40% of cases
  - Small intestine and colon: 30%
  - Colon only: 30%

- When the rectum is spared, it is unlikely to be UC and more likely to be CD.
- When only the colon is affected, the differential diagnosis includes both CD and UC. In this case, it is difficult to make a diagnosis, and later testing may be needed. The presence of a skip lesion or another area of the GIT affected would indicate CD.

- **Skip lesions**
- Strictures are common - There is transmural inflammation and when it subsides, fibrosis takes place resulting in strictures. In the image to the right is the small bowel. See how the bowel wall (star) is thickened and fibrotic and therefore the lumen (arrow) is smaller.



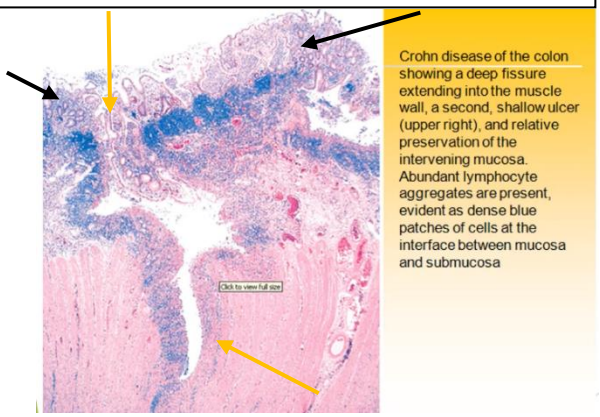
- Earliest lesion: aphthous, shallow ulcer
- With progression of the disease, there are elongated, serpentine, deep ulcers.
- Edema leads to loss of bowel folds. During an endoscopy, the bowel mucosa is flat as there are no folds due to the edema.
- **Cobblestone appearance**
- **Fissures, fistulas, perforations.**
  - Fissures are deep ulcerations that span the mucosa, submucosa, and can even reach the muscular propria.
  - A fistula is a connection between two lumens. In the case of CD, it may be between two loops of the small intestine or between the small intestine and large intestine. It may also be between the intestines and the urinary bladder, vagina, or urethra. Basically, it may be between any two organs in the abdomen and pelvis. The fistula may even connect between the bowel and the skin in the perianal area. Overall, this complication is known to happen in CD and **not** UC.
  - Perforation – The fissure has travelled to the serosa and there is an opening of the bowel to the peritoneum. This is considered an emergency and the patient may complain of peritonitis.
- **Thick bowel wall (due to transmural inflammation, edema, fibrosis, and hypertrophic muscularis propria)** This can lead to narrowing of the lumen.
- Creeping fat – Mesenteric fat will go and attach to the area of transmural inflammation.



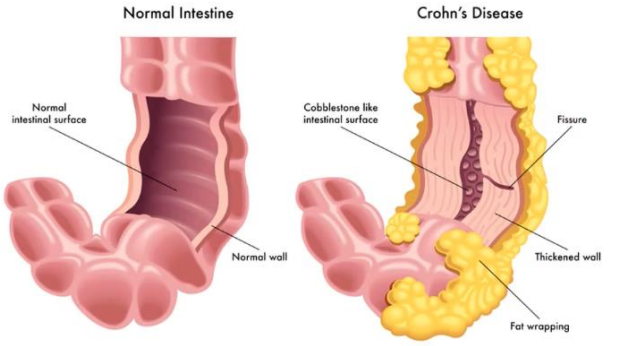
Compare the images between the healthy bowel and that of CD. Notice how in Crohn's the wall is thicker. The fissures have varying depths but do not cross the serosa. Fat wrapping is another name for creeping fat.

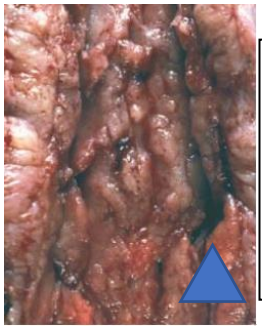
Notice that the wall is thin in UC because there is no transmural inflammation in and there is no fat wrapping.

Here you can see the microscopic appearance of a fissure.
Black Arrows: Normal mucosa
Yellow Arrows: Affected mucosa on top with the fissure deep to it reaching the muscularis propria.



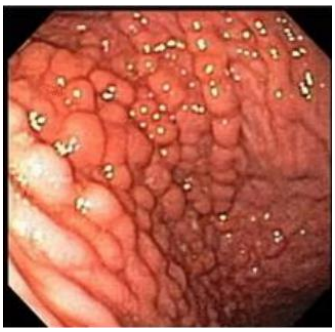
Creeping Fat:





This image indicates linear ulcers.

Cobblestone Appearance:



The right image shows what cobblestones look like, which is similar to how the bowel wall looks. The depressions "between stones" are the ulcerations and affected areas. The "stones" are the unaffected (or slightly affected) mucosa.

Microscopic Morphology

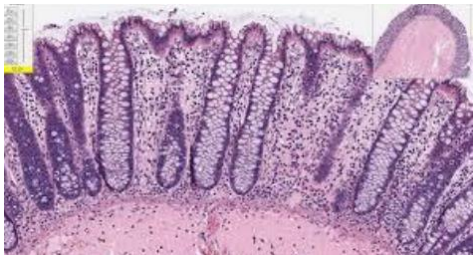
When examining a biopsy under the microscope, the appearance is characterized by different changes whether the disease is in the active or chronic phase.

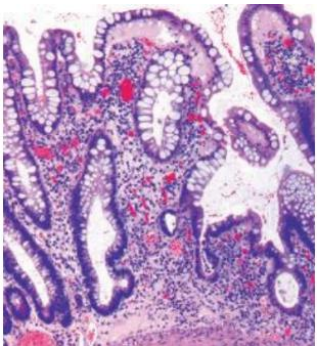
- Neutrophils are present in active disease. (main cell present in this phase)
- Crypt abscesses – The crypts are the glands seen in the colon and small bowel. Abscesses are present when neutrophils collect within the lumen of these glands.
- Ulceration – Mucosa and submucosa are sloughed and lost.

The chronic features are the mainstay of diagnosis of CIBDs, as the three points above can be seen in any infection affecting the bowel. The chronic changes (below) are needed to diagnose the case as CIBD.

- Distortion of mucosal architecture – Architecture and organization of the glands is lost and they are haphazardly arranged.
- In the long run, paneth cell metaplasia in the left colon may occur – Paneth cells are normally not seen in the left colon. However, when they start appearing in the rectum, sigmoid, and descending colon, this is considered a metaplastic change due to chronic inflammation.
- Mucosal atrophy – With time mucosal atrophy and dropping of the crypts occurs.
- **Noncaseating granulomas** (hallmark of the disease, diagnostic when seen along with other features) occur only in 35% of cases. You should look for these granulomas in any area of the bowel, regardless of whether it is affected by inflammation or not. They can be seen in any of the four bowel layers (mucosa, submucosa, muscularis propria, and serosa).
    - When you see granulomas, you need to exclude other causes of granulomas to diagnose it as CIBD.

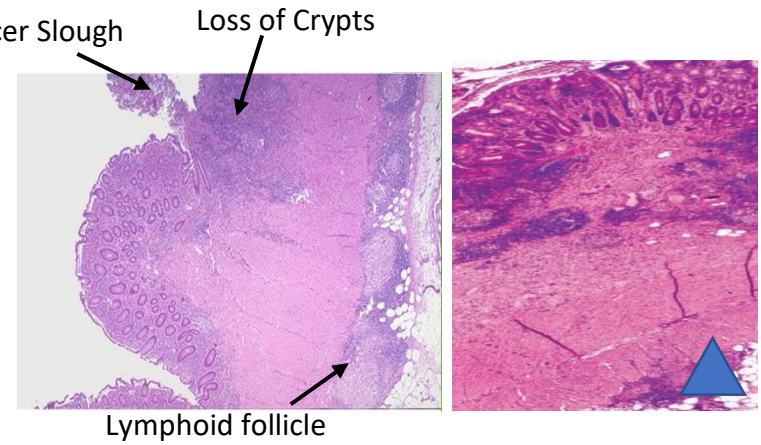
Normal Colonic Mucosa:
No active inflammation, the crypts are organized and aligned. In a transverse section, the glands would be circular.

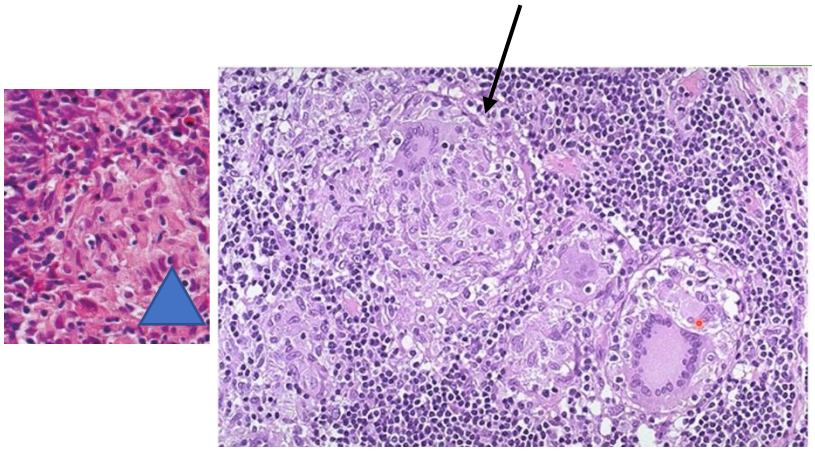




Abnormal Colonic Mucosa:
The chronic changes are characterized by the haphazard arrangement of crypts. The glands are abnormally orientated and distributed. This image is typical for the chronic changes.

Inflammation can be chronic or active. Inflammation starts in the mucosa with ulceration. In the area adjacent to the ulceration is normal mucosa, which is consistent with skip lesions of CD. There is transmural inflammation and loss of crypts/gland.





The most important hallmark of CD is non-caseating granulomas. They are composed of discrete regions, with no caseating center, and combinations of multi-nucleated giant cells and epithelioid macrophages. Finally, it is surrounded by lymphocytes.

Clinical Features

- Most common complaint: Intermittent attacks ("on and off" disease) of mild diarrhea, low-grade fever, and abdominal pain.
- Acute right lower-quadrant pain and fever (20%) – Due to terminal ileitis or ileocecal valve inflammation. It may be the first manifestation of the disease and may be misdiagnosed as acute appendicitis. If the surgeon were to try to remove the appendix, they would find it normal but the terminal ileum is inflamed.
- Bloody diarrhea and abdominal pain (colonic involvement)
- Asymptomatic intervals (weeks to months of no symptoms) between attacks.
- Triggers of the attacks: physical or emotional stress, specific dietary items, NSAID use, and cigarette smoking. (they are not causes of the disease!)

Long-Term Complications

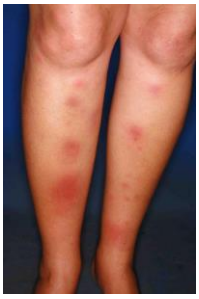
- Iron-deficiency anemia – Accompanied with a long history of bloody diarrhea.
- Hypoproteinemia and hypoalbuminemia, malabsorption of nutrients, vitamin B12 and bile salts (as the disease affects the small bowel in 70% of cases).
    - Most prominently is malabsorption of vitamin B12 and bile salts as they are absorbed in the terminal ileum, which is what's most commonly affected by the disease.
- Fistulas, peritoneal abscesses (complication of rupture and resultant peritonitis), and strictures due to fibrosis. The patient may come complaining of constipation as a new symptom.
- Most feared complication: **Risk of colonic adenocarcinoma** – The risk is increased when the disease continues for many years. It would not appear after only a year, but as the disease is sometimes diagnosed late, you should always suspect this risk and follow up with the patient with multiple colonoscopies. This should be done even if the patient is being treated and does not complain of symptoms.

*Sometimes the disease is diagnosed late with the emergence of long-term complications as the patient will not seek treatment with intermittent abdominal pain.

Extra-Intestinal Manifestations

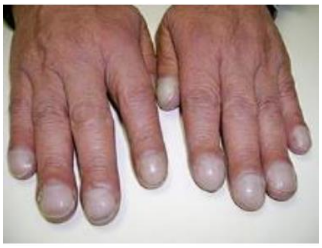
The patient will not complain only of gastric problems because it is an immune-mediated, multi-system disease.

- Uveitis – Inflammation of the iris.
- Migratory polyarthritis – Multiple joints at the same time or one after the other. The joint is affected by immune-mediated arthritis: swelling, redness, and pain.
- Sacroiliitis – Inflammation of the sacroiliac joint.
- Ankylosing spondylitis – Immune-mediated disease of the spine.
- Erythema nodosum
- Clubbing of the fingertips
- Primary sclerosing cholangitis (more with UC) – A disease affecting the bile ducts in the liver, causing fibrosis and narrowing of the duct. This leads to elevated levels of bilirubin and jaundice.



This image depicts erythema nodosum. They are red, elevated, and tender lesions that appear mainly on the lower limbs.

This is another extra-intestinal manifestation that appears in long-standing Crohn's disease. It is a non-specific sign because it can be seen in other chronic conditions (cirrhosis and chronic pulmonary diseases).



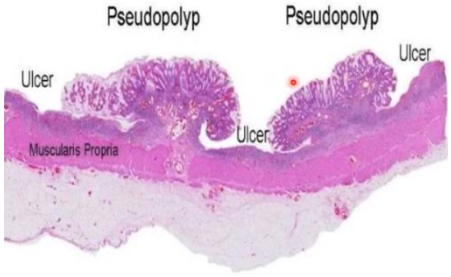
ii. Ulcerative Colitis

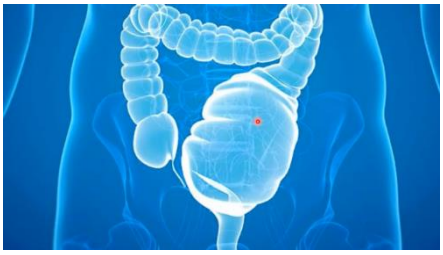
Morphology

- Always involves the rectum – Can check for involvement through colonoscopy or biopsy.
- Extends proximally in continuous pattern – No skip lesions.
- Pan colitis – The entire large intestine (up to the cecum) is affected. But this does not occur in all of the cases.
- *Occasionally* focal appendiceal or cecal inflammation – In a discontinuous fashion, a large area of the colon is skipped and there is only focal appendiceal or cecal inflammation. But this is not the typical scenario.
- It may be ulcerative proctitis (only the rectum is involved) or ulcerative proctosigmoiditis (rectum and sigmoid colon are the only involved segments).
- Small intestine is normal (except-in cases of pan colitis-in backwash ileitis, where a very small area {only a few cm} of the terminal ileum is affected by the regurge of inflammatory infiltrate through the ileocecal valve). In general, if we have small and large intestinal involvement we should think of Crohn's disease.

Macroscopic

- Broad-based ulcers – Not deep, serpentine, or linear. They are shallow ulcers that usually affect the mucosa and submucosa.
- Pseudopolyps – Elevated, unaffected area between ulcers (however, the mucosa is inflamed with no ulcer). Not true polyps.
- Mucosal atrophy occurs in long-standing disease.
- Mural thickening absent – The wall of the bowel is atrophic and thin
- Serosal surface normal – No transmural inflammation
- No strictures
- Complication: Toxic megacolon – Due to the thinning of the bowel wall. If the patient develops a concurrent infection, the gases produced by the bacteria may lead to dilation of the colon. This is known as toxic megacolon, which has the risk of rupture, sepsis, perforation and resultant peritoneal inflammation. Can also be seen in CD and other inflammatory conditions of the colon (like pseudomembranous colitis) so it's not specific.

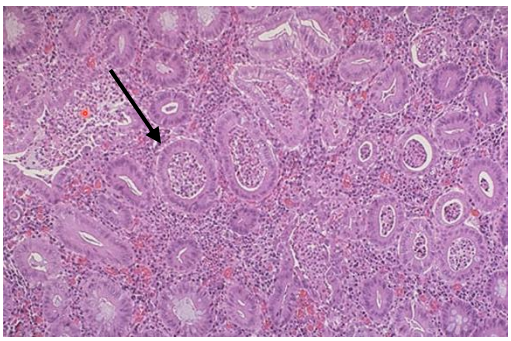




Microscopic

The microscopic changes in UC are not specific, as a similar appearance can be seen in CD.

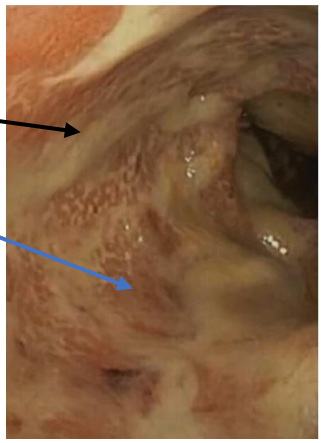
- Inflammatory infiltrate – Whether it is active or chronic inflammation.
- Crypt abscesses – Seen in the active phase.
- Crypt distortion - A chronic feature with haphazard arrangement of colonic crypts.
- Epithelial metaplasia – Another chronic feature
- Submucosal fibrosis – Can be seen due to inflammation, but thickening of the bowel wall is not seen in UC.
- Inflammation limited to mucosa and submucosa – No transmural inflammation
- No skip lesions – The disease is continuously spread from the rectum.
- No granulomas

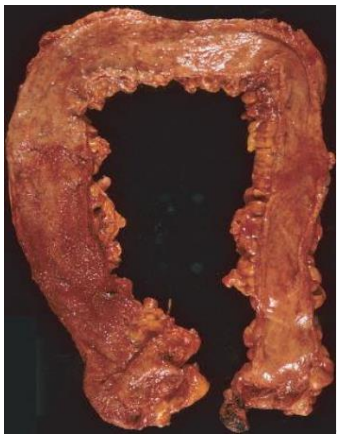


This image illustrates crypt abscesses. There are many neutrophils found in the lumen of the gland. Since there are many crypt abscesses, it indicates the disease is active. In addition, the glands are haphazardly arranged, which indicates a chronic disease.

Chronic + Active Changes are needed to call it a CIBD. However, if the patient is on treatment, or is between attacks, the active inflammation may not be present.

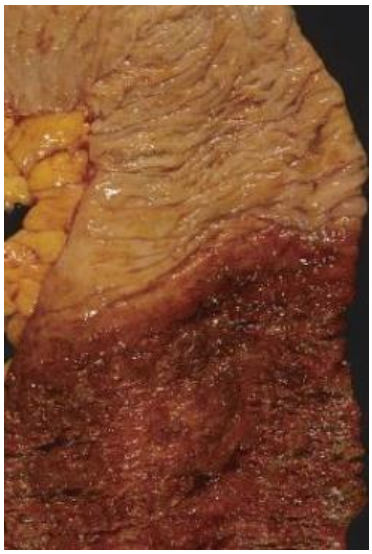
Mucopurulent membranes and shallow ulcers are present. This is typically seen in UC in a continuous fashion.

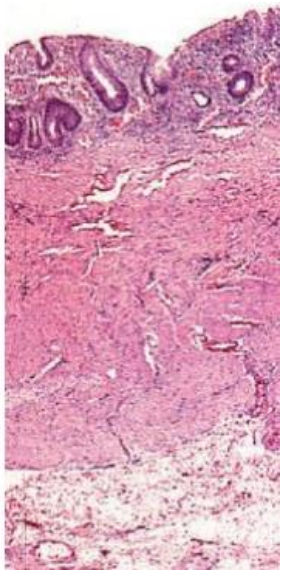




This is a case of pancolitis. The whole colon of this poor patient was removed. This is the most severe form of UC.

There is an abrupt transition between the normal and diseased segment. In the diseased segment (lower, red part), the inflammation is continuous.





The inflammation is limited to the mucosa and submucosa. In the mucosa the crypts are haphazardly arranged, indicating a chronic disease. The muscularis propria and serosa are normal.

Clinical Features

There is also overlap in the clinical features between UC and CD, so we can not only rely on clinical features for diagnosis (same for microscopy). Diagnosis requires the full picture, but extra-intestinal manifestations are usually more associated with CD.

- Relapsing remitting disorder – On and off disease.
- Attacks of bloody mucoid diarrhea + lower abdominal cramps followed by an asymptomatic interval and then another attack.
- Attacks of pain are temporarily relieved by defecation.
- Attacks last for days, weeks, or months before the patient enters an asymptomatic interval.
- Infectious enteritis may trigger disease onset. For unknown reasons, cessation of smoking may trigger the disease symptoms as well.
- Colectomy cures intestinal disease only. So extra-intestinal manifestations (which still can be seen in UC) are not cured by colectomy.
    - CD: Colectomy is not usually performed as a therapeutic measure in CD, because there are extra-colonic manifestations in other areas of the GIT. Surgery can be used in certain cases of CD, such as when there is stricture, stenosis, fistula, or perforation.

Feature	Crohn Disease	Ulcerative Colitis
Macroscopic		
Bowel region affected	Ileum ± colon	Colon only
Rectal involvement	Sometimes	Always
Distribution	Skip lesions	Diffuse
Stricture	Yes	Rare
Bowel wall appearance	Thick	Thin
Inflammation	Transmural	Limited to mucosa and submucosa
Pseudopolyps	Moderate	Marked (More prominent)
Ulcers	Deep, knifelike	Superficial, broad-based
Lymphoid reaction	Marked	Moderate
Fibrosis	Marked	Mild to none
Serositis	Marked	No
Granulomas	Yes (~35%)	No
Fistulas/sinuses	Yes	No
Clinical		
Perianal fistula	Yes (in colonic disease)	No (as there is no transmural inflammation)
Fat/vitamin malabsorption	Yes	No
Malignant potential	With colonic involvement	Yes
Recurrence after surgery	Common (as other areas of GIT affected)	No
Toxic megacolon	No	Yes

NOTE: Not all features may be present in a single case.

The last row regarding toxic megacolon is present in the slides but was crossed out in the video.

This is an important table that summarizes all the changes discussed and the differences between CD and UC. Remember that the differentiation is not easy nor straightforward. Even with all forms of information collected, a definitive diagnosis may still not be reached and it is just described as chronic inflammatory bowel disease.

Colitis-Associated Neoplasia (Very Important!)

- The risk of adenocarcinoma of the colon is increased in long standing UC and CD.
- Begins as dysplasia which can transform into carcinoma.
  - These patients should be followed up by regular check-up colonoscopies with random biopsies taken to check for the appearance of dysplasia.
- Risk (of dysplasia and subsequent carcinoma) depends on:
  - Duration of disease: Risk increases after 8-10 years.
  - Extent of involvement: More risk with pancolitis.
  - Inflammation: Risk increases with frequency & severity of active disease with neutrophils. Therefore, a patient compliant with their treatment, with a limited number of attacks, and their condition controlled by medication, will not have active inflammation and this lowers the risk of adenocarcinoma.

Two last points not included in the video but are in the slides:

- Early detection needs surveillance programs approximately 8 years after diagnosis.
- Exception is with PSC (primary sclerosing cholangitis) patients, screening at diagnosis.