Non-Neoplastic Disorders of the Intestines

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**Table of Contents**

**Introduction**  

**Case 1.** Diversion colitis  

**Case 2.** Diverticular disease-associated segmental colitis  

**Case 3.** Collagenous colitis  

**Case 4.** Non-steroidal anti-inflammatory drug-related injury  

**Case 5.** Kayexelate-sorbitol-induced necrosis  

**Case 6.** Prolapse injury  

**Case 7.** Ischemic colitis occurring in a young patient  

**Case 8.** Yersiniosis  

**Case 9.** Fungal infection in an immunocompromised patient  

**Case 10.** Duodenal ulcerative colitis  

**Legends for 35mm projection slides**  
*(see CD-ROM to be mailed later)*
Introduction

Classically, we have divided the inflammatory bowel diseases into chronic and acute forms, with ulcerative colitis and Crohn's disease predominantly comprising the chronic category. However, pathobiology rarely conforms to our attempts at neat categorization. Numerous other forms of chronic colitis have been described, such as collagenous colitis and lymphocytic colitis; in addition, we now recognize an increasing number of variations of ischemic colitis and drug or chemical-related colitis.

This course will address some of the so-called “atypical” colitides, that is, forms of colitis other than ulcerative colitis or Crohn's, often lacking constitutional symptoms, and often with nonspecific laboratory data. In addition, some variants of ischemic and drug/chemical-related colitis will be addressed, as will examples of interesting infectious diseases and changing patterns of distribution in ulcerative colitis.

General Approach to Evaluation of Intestinal Mucosal Biopsies for Inflammatory Disease

The "question-oriented approach" to inflammatory bowel diseases can facilitate both our diagnostic endeavors and our ability to communicate with our gastroenterology colleagues. Unless the following questions are answered in the course of the evaluation of a colonic mucosal biopsy, our interpretations may be limited, if not downright wrong. The responsibility is born equally between the gastroenterologist and the pathologist to pose and answer these questions:

1. Why was the biopsy done? [diagnosis, response to therapy, dysplasia surveillance, etc.]
2. What are the duration and nature of the patient's symptoms? [weeks, months, bloody diarrhea, watery diarrhea]
3. From where EXACTLY in the bowel is the biopsy taken?
4. What were the endoscopic findings?

Following this exercise, our goals should be to:

Provide a useful, reproducible diagnostic report
Provide feedback regarding adequacy and artifacts [e.g. cautery, size of biopsy, etc.]
Be aware of the clinical implications of our diagnosis
Choose direct communication over "clinical correlation recommended."
Case #1
DIVERSION COLITIS

Clinical Presentation: These rectal biopsies are from a 38 year old man with Crohn’s disease, status post resection of his terminal ileum and right colon. He has an ileostomy and a Hartmann’s pouch.

Endoscopic Findings: The endoscopist described streaky erythema without ulcers in the Hartmann’s pouch

Diagnosis: Diversion colitis

General Comments: Diversion colitis is an inflammatory process that occurs in segments of the large bowel that are excluded from the fecal stream, as in patients with an ileostomy or colostomy. It is found in 50-100% of patients following colonic bypass, and is cured by surgical reversal of this condition.

While this is often an incidental finding in asymptomatic patients, some may present with mucoid or bloody discharge and/or abdominal pain. The condition occurs 3 –36 months following colonic exclusion and completely regresses within 3 months of re-establishment of the fecal stream. Symptoms occur more frequently with increased duration of diversion.

Pathologic features: The gross and endoscopic features of diversion colitis include erythema, friability, edema, and nodularity with apthous ulcers. Histologically, the nodularity corresponds to large lymphoid aggregates with prominent germinal centers. The histologic features of diversion colitis are quite variable. Typically, one sees lamina propria plasmacytosis with prominent lymphoid follicles, often accompanied by cryptitis, crypt abscesses, and neutrophils within the lamina propria. Crypt architecture generally remains intact. In some instances, however, the inflammation may mimic severe ulcerative colitis, complete with crypt distortion and marked chronic inflammation of the lamina propria. In other cases, patchy cryptitis and aphthous lesions may mimic Crohn’s disease.

Pathogenesis: The cause of diversion colitis is thought to be a deficiency of short-chain fatty acids, which are usually derived from fermentation of dietary starches by normal colonic bacterial flora. Short-chain fatty acids are the main source of energy for colonocytes. Once the fecal stream is diverted, dietary starches are no longer present. Somehow this lack of colonocyte nutrition leads to an inflammatory disorder. If re-anastomosis and restoration of the fecal stream is not possible, the inflammation can be reversed by giving short-chain fatty acids via enemas several times a week.
Differential diagnosis: Because the histology is so variable, the key to making this diagnosis rests in knowing that the biopsies come from a diverted segment of colon. Pathologists should remember that a Hartmann’s pouch is a diverted segment of colon that virtually always shows some element of diversion colitis (not pouchitis). Even in patients with Crohn’s disease, the presence of a focally active colitis with aphthous ulcers should be considered to be diversion colitis, as previous studies have shown that these changes will quickly regress once the fecal stream is re-established.

Biopsies of a diverted segment are often taken prior to re-establishing the fecal stream, at which time it is critical that the pathologist make the correct diagnosis. If the pathologist is not told that the biopsies in question are from a diverted segment of colon, he or she will probably diagnose some form of chronic inflammatory bowel disease. This errant diagnosis will likely delay the patients’ surgery and lead to unnecessary anti-inflammatory therapy.

References:
Case #2
DIVERTICULAR DISEASE ASSOCIATED SEGMENTAL COLITIS

Clinical Presentation: These biopsies are from the sigmoid colon of a 67 year old man with abdominal pain and occasional diarrhea.

Endoscopic Findings: The endoscopist noted mild erythema in the sigmoid colon that seemed to spare the rectum. Scattered diverticula were also noted.

Diagnosis: Diverticular disease-associated segmental colitis

General Comments: Diverticular disease is common among patients over the age of 60, particularly in the sigmoid colon. Recently, several reports of diverticular disease associated colitis have been published that describe a chronic segmental colitis that is present in the distribution of the diverticula, mimicking ulcerative colitis. This colitis is restricted to the mucosa and is not related to diverticulitis. Patients typically present with hematochezia.

Another form of diverticular disease associated colitis mimics Crohn’s disease. This form of colitis occurs in patients with diverticulitis who do not have evidence of Crohn’s disease elsewhere in the gastrointestinal tract. The resection specimens demonstrate a Crohn’s-like reaction to the diverticulitis.

Pathologic features: Colonoscopic evaluation generally reveals patchy or confluent hyperemia, often accentuated on the crests of mucosal folds. The mucosa may appear granular, and an exudate is variably present. The distribution is predominantly descending colon and sigmoid, in the region of diverticular disease; the rectum is often spared.

In the ulcerative colitis-like variant, histologically one will find a range of chronic changes in the lamina propria, from a mild plasmacytosis and mild crypt distortion to a full-blown ulcerative colitis-like appearance. Cryptitis and crypt abscesses are also seen. If the pathologist is not informed of the presence of diverticula he or she will have a hard time classifying this form of inflammatory bowel disease. The key to making the correct diagnosis rests with recognizing that the colitis is present only in the distribution of the diverticula.

In the Crohn’s like variant, there is segmental thickening of the bowel wall with fat wrapping, a cobblestone pattern of the mucosa and bear-claw-like ulcers. Serosal exudates and transmural sinuses are usually seen. Microscopically, nearly all the histologic features of Crohn’s disease may be seen, complete with non-necrotizing granulomas. Of note, in one study, there was an absence of neural hyperplasia, gastric antral-gland type metaplasia and villiform mucosal surface changes. Pathologists must
recognize this reaction pattern and not rush to make the diagnosis of Crohn’s disease in a patient with no other history or risk factors for the disease.

**Pathogenesis and Natural History:** The pathogenesis of this condition is uncertain. The ulcerative colitis-like variant resembles mild ulcerative colitis in both clinical course and histologic features. Some patients have, however, developed classic ulcerative colitis. Follow-up studies on the Crohn’s-like variant have found that the vast majority of patients do not go on to develop Crohn’s disease (much like isolated granulomatous appendicitis cases).

**Differential diagnosis:** It can be very challenging to differentiate diverticular disease-associated colitis from Crohn's, ulcerative proctitis, or ulcerative colitis with rectal sparing. Patients with ulcerative colitis and rectal sparing tend to be younger and lack diverticula. In addition, even in ulcerative colitis with rectal sparing, the rectal mucosa is usually not absolutely normal (shows some features of quiescent colitis). Patients with Crohn's and ulcerative colitis tend to have involvement of other segments of the bowel.

**Treatment:** The treatment of diverticular disease associated colitis varies from therapies aimed at diverticulitis (fiber and antibiotics) to anti-inflammatory therapies similar to those used for ulcerative colitis. Some patients are refractory to medical management and require surgical resection.

**References:**
Case #3
COLLAGENOUS COLITIS

Clinical Presentation: This 47 year old woman had an eight month history of diarrhea, nausea, vomiting, and peripheral eosinophilia of 11%.

Endoscopic Findings: Colonoscopy was essentially normal.

Diagnosis: Collagenous colitis with increased eosinophils.

General Comments: Collagenous colitis (CC) is a disease primarily of women, with a female to male ratio of 9:1. This disorder is seen primarily in middle aged females with a mean age of 59 years at diagnosis, but a wide age range at presentation. No well documented cases have been described in children.

Chronic watery diarrhea is the main symptom, and in most patients has been present for months to years. Nocturnal diarrhea is not uncommon. The patients often have crampy diffuse abdominal pain, which may cause confusion and misdiagnosis as irritable bowel syndrome. A nondestructive, seronegative, enteropathic arthritis is seen in about 7% of CC patients. A variety of other immunologic disorders have been noted in these patients, with 17-40% having other autoimmune illnesses.

Routine laboratory studies are usually normal. However, antineutrophilic cytoplasmic antibodies have been reported. Radiographic and endoscopic studies are also usually normal. Thus, it is essential for clinicians to biopsy grossly normal mucosa to establish this diagnosis.

CC is a clinicopathologic syndrome characterized by (1) chronic watery diarrhea and crampy abdominal pain and (2) distinctive colorectal histopathology that includes a thickened subepithelial collagen band, prominent chronic inflammation in the lamina propria, and increased intraepithelial lymphocytes. In 1976, Lindstrom described the first case. Lindstrom coined the term “collagenous colitis” because of the histopathologic similarity to collagenous sprue, in which a collagen deposit is seen in a similar subepithelial location but in jejunal mucosa. Several studies have addressed the prevalence of CC. In persons with chronic diarrhea, the frequency of CC ranges from 0.3% to 5.0%. The incidence of this disorder has been estimated to range from 1.8 to 5.2 cases per 100,000 population. This disease is found mainly in “western” countries in Europe, Australia, and North America, but rare cases have been reported from Japan and Africa.

Pathologic features: As the name implies, there are 2 main histologic components to CC: increased collagen deposition and colitis. A main histologic component is the presence of increased subepithelial collagen. The collagenous band is actually beneath the epithelial basement membrane; it is not a thickened basement membrane. The increased collagen
can be recognized on conventional H&E stains as an eosinophilic band localized beneath the surface epithelium. On H&E and trichrome stains the basement membrane and the abnormal collagen band blend together visually. By immunoperoxidase stains, however, the subepithelial collagen band stains for a variety of collagens, primarily types I, III, and VI collagen, as well as tenascin. Stains for basement membrane components (type IV collagen and laminin) do not stain the abnormal collagen band. In normal patients, the subepithelial basement membrane is no greater than 3µm, but can be thicker in hyperplastic polyps and with tangential sectioning. In CC, the width of the band averaged 15µm in one series. In many patients, band thickness varies throughout the colon with the transverse colon usually having the thickest bands. The rectum can lack the subepithelial collagen band in up to 25% of cases, and in a small percentage, the rectum can be normal with no increase in inflammation. Consequently, multiple biopsy specimens should be taken in areas proximal to the rectosigmoid. In rare cases, subepithelial collagen has been noted to involve the duodenum and stomach in patients with CC.

The increased subepithelial collagen has qualitative and quantitative differences from normal colon. In normal colonic mucosa, the basement membrane has sharp, well defined borders. In CC, the increased collagen imparts a shaggy appearance to the lower border of the basement membrane with tendrils of collagen extending down into the upper lamina propria. To delineate mild increases in subepithelial collagen, a trichrome stain is helpful. Immunoperoxidase stains for tenascin have also been touted as a sensitive and specific marker for the subepithelial collagen band. Any increase in subepithelial collagen, in the proper inflammatory and clinical context, is diagnostic of CC. Hence, measurement of the thickness of subepithelial collagen layer is not necessary to diagnose CC.

The second histologic component in CC involves increases in inflammation both in the lamina propria and within the epithelium. The lamina propria is expanded by a mixture of inflammatory cells, including plasma cells, lymphocytes, eosinophils, and mast cells. Increased eosinophils can be striking in some cases. Eosinophil granule component as well as TGF-β produces by eosinophils may be involved in the pathophysiology of the disease. Crypt distortion is rare, but Paneth cell metaplasia is not uncommon, and a sprinkling of neutrophils can be seen in up to 25% of cases. Extensive neutrophils and pseudomembranes are rare, but have been described in a few cases, potentially in acute or early stages of the illness or in concomitant C. difficile infection.

A distinctive component of CC is increased intraepithelial lymphocytes. An increase in these cells is present in the majority, but not all, cases of CC. Prominent intraepithelial lymphocytes are not a feature of other forms of colitis or enteritis except for celiac disease and lymphocytic colitis. The intraepithelial lymphocytes of CC are predominantly CD8+ T cells and express the alpha/beta form of T cell receptor. Surface epithelial damage (flattening, detachment) may also be present.

Misdiagnosis of CC can occur by focusing exclusively on the thickness of the subepithelial collagen band. CC is an inflammatory disorder of the colon, and thus increased mucosal inflammation is a prerequisite to the diagnosis. The basement
membrane can appear artificially increased in size. For example, tangential sectioning of
the basement membrane creates a thicker basement membrane than when correctly
oriented.

Pathogenesis: The cause of CC is unknown, and thus it can be considered a type of
chronic idiopathic IBD, albeit of a “gentler and more subtle form.” Hypotheses for the
etiology of CC include immune dysregulation, abnormalities in pericryptal fibroblasts,
intraluminal bacterial agents or toxins, plasmatic vasculosis, and drug induced damage.

Some of the most intriguing recent findings relate to the possible role of infectious agents
in CC. Swedish investigators found that diverting the fecal stream caused clinical and
histologic remission in 9 patients and that clinical symptoms and an abnormal collagen
table returned after ostomy takedown. This, of course, suggests that some luminal agent
or toxin is involved. Some investigators have found clinical improvement in patients
treated with antibiotics or with bismuth subsalicylate, an agent thought to work via an
antibacterial mechanism. Also, antibodies against Yersinia virulence factors are more
common in CC than in controls. The pattern of inflammation, with increased
intraepithelial lymphocytes, suggests polarization of the immune system toward a luminal
agent. One hypothesis is that a foreign luminal agent, possibly bacteria, initiates
colorectal inflammation that leads to an immunologic cross reactivity with an
endogenous antigen in luminal epithelial cells, leading to self sustaining inflammatory
condition.

CC has also been linked in rare cases to lansoprazole administration (although this
association is actually more common with lymphocytic colitis). In these cases, the drug
was clearly associated with the onset of symptoms, and resolved when it was stopped.
NSAIDs have also been linked to CC by a few investigators.

The mechanisms of diarrhea are variable. Fasting improves, but does not totally abate,
diarrhea in most patients, suggesting both an osmotic and a secretory component.
Reduced sodium and chloride absorption are the main mechanisms of diarrhea in CC, but
there is also an active component of chloride secretion. Down regulation of tight junction
molecules, particularly occludin, is thought to contribute to diarrhea. While the diarrhea
is felt to be mainly of colonic origin, some studies have also shown abnormal small
bowel wall permeability.

Differential diagnosis:

**Lymphocytic colitis.** This disease is the most similar to CC. Histologic similarities
include increased intraepithelial lymphocytes, increased chronic inflammation in the
lamina propria, and minimal architectural distortion. The major difference is the absence
of a thickened subepithelial collagen band in lymphocytic colitis.

**Celiac disease.** Celiac disease has histologic similarities to both CC and lymphocytic
colitis, as all of these entities have a striking increase in subepithelial lymphocytes.
Furthermore, collagenous sprue has a prominent subepithelial collagen band in the small
bowel. Although some patients have been reported with both celiac disease and CC, the majority of CC patients have microscopically normal duodenal and jejunal biopsies (although ileal biopsies may show a slight excess of intraepithelial lymphocytes).

**Crohn’s disease and ulcerative colitis.** In CC, the epithelium contains numerous lymphocytes but few neutrophils. The reverse is true for UC and CD, which feature few intraepithelial lymphocytes but prominent neutrophils in the epithelium accompanied by crypt abscesses, cryptitis, erosions, and ulcers. Moreover, crypt distortion is rare in CC but a prominent feature of CD and UC. Finally, CC has a distinctive thickened subepithelial collagen table, whereas CD has more diffuse transmural fibrosis.

**Treatment and Natural History:** CC is usually a chronic process, but patients can have spontaneous remissions. This complicates evaluation of drug effectiveness. While dietary modification (elimination of caffeine, lactose, or NSAIDs) may help some individuals, most require medication of some sort. In the past, first line therapy was sulfasalazine or other 5-ASA derivatives. If that failed, patients were treated with steroids or immunosuppressive regimens. Currently, the two main therapeutic regimens are non-absorbable steroid preparations (such as budesonide) or high dose bismuth preparations. While patients usually respond to these, they frequently have flares of diarrhea once medication is stopped.

**References:**

Case #4
NON-STEROIDAL ANTI-INFLAMMATORY DRUG-RELATED INJURY

Clinical Presentation: This 54 year old Jewish physician underwent screening colonoscopy for polyps.

Endoscopic Findings: He was found to have ulcers in the terminal ileum.

Diagnosis: Non-steroidal anti-inflammatory drug-related injury

General Comments: It has been well recognized that NSAIDs cause "peptic" ulcers in the duodenum, albeit at a lower rate than in the stomach. These ulcers are usually bland with "nonspecific" histology. This duodenal injury has been well recognized because of the ease of examination of the duodenum with the upper endoscope. The fate of the distal small bowel in patients taking NSAIDs has been less well researched because of the relative inaccessibility of the jejunum and ileum to endoscopic examination (except for the distal terminal ileum.) However, in the past decade or two, studies focusing on the small bowel have shown that NSAID damage to the distal small bowel is not uncommon.

A recent endoscopic study of 1,900 consecutive colonoscopies in which the terminal ileum was entered showed that 2% of the patients had lesions of the terminal ileum. These lesions ranged from erythema to erosions to ulcers. On follow up, 85% of the patients with these small bowel lesions were found to be taking NSAIDs up to one week before the endoscopic examination. Most of these patients had been endoscoped for a personal or family history of colorectal dysplasia and were asymptomatic. These patients had no history of symptoms of any primary small bowel disease and none developed small bowel disease on follow up for up to 60 months. The most common NSAID used in these patients was enteric coated aspirin, which was taken at low dose (235 mg/d) for health maintenance reasons.

When a greater length of the small bowel is studied, even more evidence of damage is seen in the distal small bowel of NSAID users. One careful study by Allison, et al, from the UK, looked for evidence of NSAID damage to the upper GI tract at post mortem. A single investigator examined the small bowel and stomach of all autopsies over a 22 month period. A drug history of NSAID usage was studied for each patient by reviewing hospital records as well as personal physician records. Of the 713 patients included in the study, 249 had some type of NSAID prescribed during the six months before death. Nonspecific ulcers were found in the jejunum or ileum of 21 (8.4%) of the NSAID group, while ulcers were seen in only 3 patients (0.6%) in the control group. Looking at just the long-term users of NSAIDS, the prevalence of ulcers was up to 13.5%. The pathology of the lesions in the NSAID usage group ranged from single to multiple tiny punched out ulcers to confluent areas of deep ulceration and stricture formation.

With even more sensitive detection methods, subclinical damage to the distal small bowel can be seen in a majority of patients taking NSAIDs even at a low dose. Bjarnson and
colleagues have used radiolabeled RBCs and leukocytes followed by scintigrams and have found 60% to 70% of patients taking NSAIDs to have accumulations of RBCs and leukocytes in the distal small bowel, indicating increased small bowel inflammation. These same investigators have also found increased fecal excretion of labeled RBCs and leukocytes as well as increased intestinal permeability in patients taking NSAIDs. The pathology of the small bowel in most of the patients in the Bjarnson studies has not been investigated. However, in one of the Bjarnson studies, 18 patients with the highest fecal excretion of radionuclide had barium studies of the distal small bowel. Three of these patients had terminal ileal ulcers and two of these had strictures as well. Thus, much of the damage detected by these very sensitive radionuclide scans is likely very small or superficial erosions. Nonetheless, these tiny lesions spread over a long length of distal small bowel may contribute to clinically significant blood loss. Other studies have shown that up to 50% of NSAIDs users, with iron deficiency anemia, have no detectable lesions on gastroscopy or colonoscopy, suggesting the blood loss comes from the small bowel.

While most of the NSAID intestinal lesions are nonexciting, bland ulcers, there is one distinctive and striking small bowel lesion associated with NSAID use. A small percentage of patients taking NSAIDs develop "diaphragm disease" in which concentric luminal protrusions of fibrotic mucosa and submucosa occlude the lumen. These occlusions range from thin, delicate structures that appear to be only exaggerations of the plicae circulares to thicker, more rigid structures. These diaphragms can lead to a markedly narrowed lumen, leaving only a few millimeter opening in the center of the bowel. Most of diaphragm disease cases have been associated with slow release NSAIDs and most are in the terminal ileum. However, "diaphragm disease" has more recently been described in the jejunum and proximal colon as well. While the diaphragms have a very dramatic gross appearance, by histology they consist only of bland fibrosis, demonstrating a column of fibrotic tissue extending from the mucosa into deeper regions.

Pathogenesis: The pathogenesis is uncertain, but it is hypothesized that NSAIDs have a direct effect on enterocytes causing damage to mitochondria and other subcellular changes that ultimately translate into increased intestinal permeability. This increase in permeability makes enterocytes more susceptible to injury by other forces such as ingested foods, bacteria, and particularly bile acids. The fibrotic changes of diaphragm disease may be a further reaction to tissue injury by the abovementioned factors.

Natural History and Treatment: Most patients' symptoms resolve with cessation of NSAID administration. However, cessation of NSAIDs may be impractical in many patients. Therapeutic trials of drugs that may prevent NSAID damage (nabumetone, sulindac) or actually treat it (sulfasalazine, metronidazole) are ongoing.

Differential diagnosis: Since the ulcers seen in NSAID usage have no distinctive pathologic features, the main problem is in attributing the ulcers to some other disease process, most notably Crohn's disease. Crohn's induced ulcers are more likely to show signs of chronic injury, including increased chronic inflammation, scarring, or pyloric metaplasia, and, if one is lucky, a granuloma. In reality, however, it may not be possible to reliably distinguish aphthous ulcers of Crohn's disease from NSAID ulcers. Thus
clinical history and clinical context may be of great import in arriving at the correct diagnosis. In asymptomatic patients, being endoscoped for cancer screening, with only the findings of small ulcers in the terminal ileum, the most likely diagnosis is NSAID damage. Other causes of small erosions or ulcers in the terminal ileum include trauma (bones or toothpicks,) radiation injury, vasculitis, or potassium related injury.

References:
Clinical Presentation: This 74 year old man was status post right lung lobectomy, with acute decompensation on post-operative day 4.

Surgical Findings: Grossly necrotic-appearing bowel was resected.

Diagnosis: Kayexelate sorbitol -induced bowel necrosis

General Comments: One small series and several case reports have documented colonic infarction following the administration of kayexalate-sorbitol enemas. All of the patients had some underlying renal disease, and several were renal transplant patients. The colonic infarction usually presented as the abrupt onset of severe abdominal pain within hours after the administration of the enema. Upon laparatomy and resection, long segments of bowel, and even the entire colon and rectum, were found to be necrotic.

Kayexelate is the brand name for sodium polystyrene sulfonate, which is used in the treatment of hyperkalemia. It is a cation-exchange resin with action primarily in the large intestine where the sodium ions are partially released and replaced by potassium. The excess potassium is then evacuated along with the stool. Because kayexalate can cause constipation or even impaction, it is often administered along with an osmotic laxative, usually sorbitol. Sorbitol is a poorly absorbed sugar that is not degraded in the small bowel because the human small intestine lacks enzymes capable of splitting sorbitol into its component monosaccharides. In the colon, however, sorbitol is degraded by colonic bacteria into metabolic products that are acidic and osmotically active. Thus, sorbitol is simply given as an osmotic agent to help expel the kayexalate. Kayexalate and sorbitol are usually administered orally, but for speedier action, both may also be administered as an enema preparation.

Pathologic Features: A variety of necro-inflammatory changes have been described including ulcers, pseudomembranes, and transmural necrosis. The necrosis in these cases is bland and maybe mistaken for autolysis save for some hemorrhage and neutrophilic infiltrates. While Kayexalate itself is not known to cause damage, the dark purple crystals of Kayexalate are a useful histologic clue to the possibility that the patient received a sorbitol or other osmotic enema. Thus, in an autopsy or surgically resected specimen with bland colonic infarction and Kayexalate crystals, a phone call to the clinician is warranted, with a discussion of the patient's history. Through such a discussion, the etiology and pathogenesis of a particular patient's colonic ischemia may be elucidated. Most documented cases of Kayexalate-sorbitol injury occur in the colorectum following enemas. Less frequently, damage has been repeated in the upper GI tract following oral administration.

Pathogenesis: Following the recognition of these clinical cases, Lillemoe et al investigated the effects of kayexalate-sorbitol enemas in an experimental model using
both normal and uremic rats. The results of these experiments are summarized in the following tables.

Table 1. Results after enemas in normal (nonuremic) rats

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>Colonic pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>No enemas</td>
<td>normal</td>
</tr>
<tr>
<td>Saline enemas</td>
<td>normal</td>
</tr>
<tr>
<td>Kayexalate enemas*</td>
<td>normal</td>
</tr>
<tr>
<td>Sorbitol enemas</td>
<td>7/10 extensive transmural infarction</td>
</tr>
<tr>
<td>Kayexalate-sorbitol enemas*</td>
<td>6/10 mucosal infarction &amp; focal transmural necrosis</td>
</tr>
</tbody>
</table>

Table 2. Results after enemas in uremic rats

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>Colonic pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>No enemas</td>
<td>normal</td>
</tr>
<tr>
<td>Saline enemas</td>
<td>normal</td>
</tr>
<tr>
<td>Kayexalate enemas*</td>
<td>1/10 mucosal erythema</td>
</tr>
<tr>
<td>Sorbitol enemas</td>
<td>9/9 massive dilatation, extensive transmural necrosis</td>
</tr>
<tr>
<td>Kayexalate-sorbitol enemas*</td>
<td>all had massive dilatation, extensive transmural necrosis</td>
</tr>
</tbody>
</table>

*dark purple crystals of kayexalate noted

Two facts are apparent from these experiments: 1) The sorbitol (not the Kayexalate) is responsible for the colonic damage. 2) The damage from sorbitol enemas is potentiated in uremic rats. The detailed pathogenesis of the damage is not known, but it may be speculated that the osmotic load from the sorbitol enemas causes vascular shunting resulting in colonic ischemia. Alternatively, concentrated doses of sorbitol may cause directed toxic damage. Worsening of colonic pathology in the uremic rats is especially interesting, since all of the reported clinical cases have been in patients with severe renal disease. In renal disease, the renin-angiotensin system is disordered with mesenteric vascular instability, and thus the intestinal vasculature of the patients may be particularly vulnerable to an osmotic load.

Differential diagnosis: It must be remembered that other resins besides Kayexalate are used clinically. For instance, Questran (cholestyramine) is an orally-administered resin which binds to bile acids in the intestine and is then excreted. It is used in the treatment of hypercholesterolemia, bile-acid induced diarrhea, and C. difficile toxin-induced colitis. The histology of Questran (cholestyramine) is very similar to that of Kayexalate (polystyrene), except that Questran tends to be more opaque. With acid fast stains, Kayexalate crystals are more maroon while Questran is more pink.
References:


Clinical Presentation: This 22 year old woman presented with diarrhea, occasionally alternating with constipation, and bleeding per rectum.

Endoscopic Findings: Diagnosis: The endoscopist noted a beefy, friable 1cm polyp in the rectum.

Diagnosis: Prolapse injury

General Comments: Mucosal prolapse polyps present in a variety of clinical scenarios, including those of diverticular disease, the solitary rectal ulcer syndrome (SRUS), and at ostomy sites. Clinically, they are often a feature of SRUS, which usually occurs in young women with alternating diarrhea and constipation, rectal prolapse, and bleeding. When prolapse occurs at the anal verge and forms a polyp it is also known as the inflammatory cloacogenic polyp.

Pathologic features: Grossly, prolapse polyps are friable, ulcerated polyps with an irregular shape and a beefy, red appearance. The surface may be granular and ulcerated, and occasionally the polyps have an unusual brown color if they contain abundant hemosiderin. These lesions are most common in the distal colon and anorectum, but may appear anywhere in the lower GI tract (and rarely in the small bowel and stomach). They are usually solitary, but may be multiple.

The histologic features are similar regardless of the underlying disorder. Histologically, the appearance depends on the stage of development of the polyp. In general, the mucosa is inflamed, and the glands have a reactive appearance with crypt elongation and dilatation. There may be significant crypt architectural distortion. The surface mucosa may be serrated and tufted with goblet cell hypertrophy. Often there is superficial ulceration with a “fibrin cap” of fibrinopurulent debris.

The lamina propria is often very vascular, with numerous congested capillaries and hemosiderin deposition. The characteristic finding in mucosal prolapse at any site is the presence of fibromuscular hyperplasia of the lamina propria. The presence of strands of smooth muscle growing perpendicular to the muscularis mucosa is diagnostic of prolapse. Occasionally, the amount of fibrosis can overshadow the smooth muscle proliferation.

Pathogenesis: In SRUS, The process is thought to be due to malfunction of the puborectalis muscle such that excessive straining upon defecation results. This leads to mucosal prolapse that ultimately may ulcerate and form polypoid masses. Prolapse polyps at any site are therefore caused by prolapse of the intestinal mucosa into the lumen with subsequent ischemia, mucosal damage, inflammation, and repair.
**Differential diagnosis:** Prolapse polyps may mimic many other types of polyps, including juvenile polyps, inflammatory polyps of idiopathic inflammatory bowel disease, hyperplastic polyps, and adenomatous polyps. The presence of smooth muscle proliferation may mimic a Peughtz-Jehgers polyp, however, the branching or arborizing architecture of these lesions will be absent.

In some cases glands may become trapped in the submucosa forming what is know as colitis cystica profunda. Care should be taken to avoid diagnosing this process as a neoplasm; generally speaking the epithelium lining the cysts in colitis cystica profunda is cytologically bland. It is important to remember that prolapse polyps may contain significant reactive atypia, as well as serrated epithelium at the surface, that mimics neoplastic polyps.

Finally, as prolapse lesions contain distorted and inflamed mucosa, it is also possible to misinterpret these findings as representing inflammatory bowel disease, especially when ulcers dominate the picture. The presence of smooth muscle growing between the crypts is the best clue that one is dealing with mucosal prolapse rather than chronic inflammatory bowel disease. In general, the presence of the fibrinopurulent debris at the surface, as well as the perpendicular splaying of the muscularis mucosa, may help in resolving the differential. A clinical history of prolapse or an associated condition may be of invaluable assistance.

**Natural History and Treatment:** In the intestine, the polyps themselves are completely benign and the patient outcome is determined by the underlying disorder. If the polyps cause problematic bleeding they may be excised. Ultimately, however, patients with prolapse problems respond better to nonsurgical management such as bulk laxatives and stool softeners.

**References:**

Case #7
ISCHEMIC INJURY

Clinical Presentation: This 38 year old female presented with hematochezia.

Endoscopic Findings: Diagnosis: At endoscopy, an edematous mass was seen at the splenic flexure.

Diagnosis: Ischemic colitis

General Comments: "Ischemic colitis" is a histologic description of a pattern of injury for which there is a host of etiologies. Ischemia can give rise to a wide range of clinical presentations and pathologic changes. While many cases of ischemia occur in older patients with known cardiovascular disease, ischemic colitis can also be seen in younger people such as long distance runners and women taking oral contraceptives. Rendering this diagnosis should not be the end point of the biopsy evaluation, but rather should initiate a thorough search for potential etiologic factors.

Pathologic features: Pathologic features are similar regardless of underlying cause of ischemia. Grossly, ischemia tends to show geographic areas of ulceration with pseudomembranes. This is often accompanied by marked submucosal edema, a finding that gives rise to the “thumbprinting” seen on barium enemas. Endoscopically this submucosal edema can be prominent enough to appear mass-like. The watershed areas around the splenic flexure are the most common sites for ischemic lesions of the colon, however, nearly any site can be ischemic, even the proximal rectum.

Acute ischemic lesions of the colon show necrosis of the superficial portion of the mucosa that often spare the deeper portion of the colonic crypts. The remaining crypts usually have an atrophic or withered appearance which may show striking cytologic atypia. Care should be taken to avoid overcalling these reactive changes dysplastic. Other findings in ischemia include pseudomembranes, hemorrhage into the lamina propria, and hyalinization of the lamina propria. A trichrome stain can be used to highlight the hyalinization of the lamina propria. Cryptitis and crypt abscesses can be seen, but these are usually not prominent. These lesions may regress on their own or lead to perforation and/or stricture formation. The chronic phase of ischemia may be much harder to diagnose, as the only histologic finding may be areas of submucosal fibrosis and stricture that is rather non-specific.

Pathogenesis: While lack of blood flow to the mucosa is the underlying mechanism of disease, there is a long list of possible causes. Anything from occlusion of a major blood vessel to low-flow states secondary to hypovolemia may cause colonic necrosis (see table below). Many drugs have been associated with ischemic appearing lesions, including oral contraceptives, cocaine, narcotics, and amphetamines. In some instances the drug may induce vasospasm (i.e. cocaine) while in other cases the medication may lead to
thrombosis. Enterohemorrhagic strains of E. coli (such as E. coli O157:H7) also cause an ischemic type colitis, presumably due to the numerous fibrin thrombi that develop during this toxin-mediated infection. Mechanical obstruction may also lead to ischemia secondary to compression/obstruction of blood vessels. Vasculitis due to collagen vascular disease or CMV may also cause ischemia. Ischemic colitis is well described following even moderately strenuous long distance running or cycling. It is thought that visceral blood flow falls to 20-50% of baseline during exercise, and that these effects may be exacerbated by the ingestion of large quantities of NSAIDS as many athletes do.

CAUSES OF COLONIC ISCHEMIA (table adapted from Pat Dean M.D.)

I. Arterial Occlusion
   a. Superior mesenteric artery (usually due to atherosclerosis with thrombosis)
   b. Inferior mesenteric artery (often following surgical intervention)

II. Small vessel disease
   a. Diabetes mellitus
   b. Amyloidosis
   c. Radiation vasculopathy
   d. Vasculitides
   e. Infectious causes

III. Venous occlusion
   A. Thrombogenic factors
      1. Hypercoagulability
      2. Portal hypertension
      3. Idiopathic states (e.g. idiopathic myointimal hyperplasia)
   B. Mechanical conditions
      1. Direct extrinsic pressure (e.g., tumor compression)
      2. Prolapse
   C. Non-occlusive factors
      1. Shock
      2. Dehydration/hypovolemia
      3. Exercise-related diversion of blood flow
      4. Drugs and medications
      5. Diverticular disease
      6. Hirschsprung’s disease

Differential diagnosis: Ischemic colitis may mimic pseudomembranous colitis, ulcerative colitis, Crohn's disease, and other acute self limited colitides. Differentiating ischemia from C. difficile colitis can be difficult, as both may present with pseudomembranous colitis. The presence of a hyalinized lamina propria and atrophic crypts are specific
findings in ischemia that are not seen in C. difficile colitis. In addition the pseudomembranes tend to be diffuse in C. difficile and patchy in ischemia. The presence of an ischemic appearing lesion with pseudomembranes in the right colon should also make one think of enterohemorrhagic E. coli, especially if fibrin thrombi are present. Marked architectural distortion, cryptitis, aphthoid ulcers, and pseudomembranes may all be features of ischemia. Focality of the injury mitigates against ulcerative colitis, which is, of course, usually diffuse. Healed ischemic lesions may form strictures that mimic Crohn’s disease. Clinical and radiographic features may prove invaluable in sorting out the differential.

Natural History and Treatment: Disease course and therapeutic intervention are dependent on the underlying cause of ischemia. The sequelae of ischemic injury are very variable, ranging from focal areas of acute mucosal necrosis that may be transient and only require supportive care to full-blown gangrene of the gut that may be fatal despite emergency surgery.

References:

Case #8
YERSINIOSIS

Clinical Presentation: This case is a compilation of features from two patients. In the first case a 24 year old man presented with diarrhea and abdominal pain. The second case is that of a 50 year old man with abdominal pain and fever.

Endoscopic Findings: In the first case, the endoscopist saw a friable, nodular mass in the ileocecum. In the second case, the endoscopist saw patchy areas of ulceration and mucosal nodularity in the ileum and right colon, with intervening areas of normal mucosa.

Diagnosis: Yersinia infection

General Comments: Yersinia is one of the most common causes of bacterial enteritis in Western and Northern Europe, and numerous cases have been documented in North America and Australia. Y. enterocolitica (YE) and Y. pseudotuberculosis (YP) are the two Yersinia species pertinent to human gastrointestinal disease. The reported incidence of Yersinia infection is rising rapidly within both Europe and the United States. These Gram-negative coccobacilli are causative agents in appendicitis (primarily granulomatous), ileitis, colitis, and mesenteric lymphadenitis. Infection with either species may cause symptoms and signs of an acute abdomen, chronic abdominal pain, and diarrhea. Although yersiniosis is usually a self-limited process, chronic infections (including chronic colitis) and persistent abdominal pain have been well documented. Immunocompromised and debilitated patients, as well as patients on deferoxamine or with iron overload, are at particular risk of serious disease.

Pathologic features: Yersinia preferentially involves the ileum, right colon, and appendix. It is responsible for many cases of isolated granulomatous appendicitis. Grossly, involved bowel has a thickened, edematous wall with nodular inflammatory masses centered around Peyer's patches. Apthoid and linear ulcers may be seen. Involved appendices are enlarged and mimic suppurative granulomatous appendicitis; perforation is often seen. Involved lymph nodes may show gross foci of necrosis.

The inflammatory pattern in yersiniosis is variable. Both suppurative and granulomatous patterns of inflammation may be seen, and a mixture of the two is common. Infection with YE has not typically been associated with discrete granulomas, but has been characterized hyperplastic Peyer's patches with overlying ulceration and accompanying acute inflammation, hemorrhagic necrosis, and palisading histiocytes. Gastrointestinal infection with YP has characteristically been described as a granulomatous process with central microabscesses, almost always accompanied by mesenteric adenopathy. Recent studies have shown that there is significant overlap between the histological features of YE and YP infection, and that either species may show lymphoid hyperplasia, epithelioid granulomas with prominent lymphoid cuffing, transmural lymphoid aggregates, giant
cells, mucosal ulceration, cryptitis, and concomitant lymph node involvement. Some patients show only an “acute self-limited/infectious colitis” type pattern.

Special stains are often not helpful in the diagnosis of *Yersinia*, for the organisms are small, may be present in low numbers, and are difficult to distinguish from normal nonpathogenic colonic flora. Cultures, serologic studies, and PCR assays may be helpful in confirming the diagnosis.

**Pathogenesis:** Yersinia is harbored in meats, poultry, milk, eggs, and water, and colonizes many domestic pets and farm animals. Pathogenic *Yersinia* strains are thought to invade the mucosa of the intestine and multiply within Peyer’s patches and the regional nodes to which they drain. Further spread is hematogenous. It is postulated that in some patients organisms can survive for extended periods of time within Peyer’s patches, leading to chronic yersiniosis.

**Differential diagnosis:** The major differential diagnoses include other infectious processes, particularly Mycobacteria and Salmonella. Acid fast stains and culture results should help to distinguish mycobacterial infection; clinical features and the presence of greater numbers of neutrophils, microabscesses, and granulomas may help to distinguish yersiniosis from salmonellosis.

Crohn's disease and yersiniosis may be very difficult to distinguish from one another, and it is very important to keep this entity in the differential diagnosis of Crohn’s disease as it is usually a self limited process with no further sequelae for the patient. Both Crohn’s and yersiniosis may show very similar histologic features, including transmural lymphoid aggregates, skip lesions, and fissuring ulcers. In fact, isolated granulomatous appendicitis has in the past frequently been interpreted as primary Crohn's disease of the appendix. However, patients with granulomatous inflammation confined to the appendix rarely develop generalized inflammatory bowel disease. Features that may favor Crohn's include cobblestoning of mucosa and creeping fat grossly, and changes of chronicity microscopically including crypt distortion, thickening of the muscularis mucosa, and prominent neural hyperplasia. However, some cases are indistinguishable on histologic grounds.

**Treatment:** Most infections are either self-limited or resolve with a course of antibiotics. Debilitated patients, or those in whom the infection has disseminated, could require intensive supportive care and IV antibiotics.

**References:**
Case #9  
FUNGAL INFECTIONS OF IMMUNOCOMPROMISED PATIENTS

Clinical Presentation: This case represents a 66 year old woman who had chronic lymphocytic leukemia. She presented with diarrhea and occasional fever.

Endoscopic Findings: The endoscopist saw very mild erythema of the colonic mucosa, and random biopsies were taken from the left colon.

Diagnosis: Histoplasma infection in an immunocompromised patient.

General Comments: The importance of fungal infections of the gastrointestinal tract has increased as the numbers of patients with organ transplants, AIDS, and other immunodeficiency states have increased. Signs and symptoms of gastrointestinal fungal infections are in general similar regardless of etiologic agent, and include diarrhea, vomiting, melena, frank GI bleeding, abdominal pain, and fever. It is important to remember that although fungal infections of the GI tract are often a part of a disseminated disease process, gastrointestinal symptoms and signs may well be the presenting manifestations of disease.

Fungi can often be correctly classified in tissue sections based on morphologic criteria. Fungal organisms can often be appreciated in routine H&E sections in fulminant infections, but GMS and PAS stains remain invaluable diagnostic aids. It should be stressed, however, that fungal culture should be relied upon as the gold standard of speciation. Antifungal therapy may vary according to the type of fungus identified.

*H. capsulatum* is endemic to the central United States, but has been described in many nonendemic areas as well. It is most abundant in soil enriched with bat or avian droppings. Although disseminated infection occurs primarily in elderly patients, young children, and the immunocompromised, it can also occur in otherwise healthy individuals. Gastrointestinal involvement occurs in approximately 80% or more of patients with disseminated infection.

Pathologic features: Patients may initially present with signs and symptoms of gastrointestinal illness, and do not always have concomitant pulmonary involvement. Notable presenting signs and symptoms include diarrhea, GI bleeding, abdominal pain, dysphagia, nausea, and vomiting; most patients also have fever at presentation. The ileum is the most common site, but any level of the gastrointestinal tract may be involved. Gross lesions are very variable and include ulcers, nodules, obstructive mass lesions, and normal mucosa (particularly in immunocompromised patients). Often, a combination of these lesions is seen in a single patient.

Histologic findings include diffuse lymphohistiocytic infiltrates and nodules, usually involving the mucosa and submucosa, with associated ulceration. Often these lesions are
present overlying Peyer's patches. Discrete granulomas and giant cells are seen in only a minority of cases. In immunocompromised patients, large numbers of organisms may be seen with virtually no tissue reaction. *Histoplasma* organisms typically are small, ovoid, usually intracellular yeast forms with small buds at the more pointed pole. There is a “halo” effect around the organisms on H&E. In addition to special stains, culture may aid in diagnosis; serologies and skin tests are available, but there are problems with sensitivity and specificity.

**Morphologic Features of Fungi Involving the Gastrointestinal Tract**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Morphologic Features</th>
<th>Host Reaction</th>
<th>Major Differential Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspergillus species</strong></td>
<td>Hyphae-septate uniform width</td>
<td>Ischemic necrosis with angioinvasion</td>
<td>Zygomyctes</td>
</tr>
<tr>
<td></td>
<td>Branching-regular acute angles</td>
<td>Acute inflammation</td>
<td>Fusarium</td>
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<tr>
<td></td>
<td>Conidial head formation in cavitary lesions</td>
<td>Occasionally granulomatous</td>
<td>Pseudallescheria boydii</td>
</tr>
<tr>
<td><strong>Zygomycetes</strong></td>
<td>Hyphae-paucisepitate ribbon-like thin walls</td>
<td>Similar to Aspergillus</td>
<td>Similar to Aspergillus</td>
</tr>
<tr>
<td></td>
<td>Branching-Haphazard</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Candida albicans</strong></td>
<td>Mixture of budding yeast and pseudohyphae; occasional septate hyphae</td>
<td>Usually suppurative</td>
<td>Trichosporon</td>
</tr>
<tr>
<td><strong>Candida tropicalis</strong></td>
<td>Mixture of budding yeast and pseudohyphae; occasional septate hyphae</td>
<td>Usually suppurative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Occasionally granulomatous</td>
<td>May be necrotic and ulcerative</td>
<td></td>
</tr>
<tr>
<td><strong>Candida glabrata</strong></td>
<td>budding yeast</td>
<td>Similar to other Candida species</td>
<td>Histoplasmosis</td>
</tr>
<tr>
<td></td>
<td>no hyphae</td>
<td></td>
<td>Cryptococcus</td>
</tr>
<tr>
<td></td>
<td>no &quot;halo&quot; effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cryptococcus neoformans</strong></td>
<td>Pleomorphic narrow based buds</td>
<td>Usually suppurative</td>
<td>Histoplasmosis</td>
</tr>
<tr>
<td></td>
<td>Usually mucicarmine positive</td>
<td>may have extensive necrosis</td>
<td>Blastomycosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sometimes granulomatous</td>
<td>C. glabrata</td>
</tr>
<tr>
<td><strong>Histoplasma capsulatum</strong></td>
<td>Ovoid, narrow based buds</td>
<td>Lymphohistiocytic infiltrate with parasitized histiocytes</td>
<td>Cryptococcus</td>
</tr>
<tr>
<td></td>
<td>Intracellular</td>
<td>occasional granulomas</td>
<td>P. marneffei</td>
</tr>
<tr>
<td></td>
<td>&quot;halo&quot; effect around organism on H&amp;E</td>
<td></td>
<td>C. glabrata</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Intracellular parasites</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P. carinii</td>
</tr>
<tr>
<td><strong>Pneumocystis carinii</strong></td>
<td>ovoid internal enhancing detail foamy casts</td>
<td>Ranges from suppurative to granulomatous</td>
<td>Histoplasmosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Small Parasites</td>
</tr>
</tbody>
</table>
Pathogenesis: Most primary histoplasma infections are pulmonary; gastrointestinal involvement virtually always occurs in disseminated infections, although there are rare cases of primary inoculation of the GI tract by histoplasma. Dissemination occurs through the reticuloendothelial system, including the Kupffer cells of the liver and the histiocytes of the GI tract.

Differential diagnosis: The differential diagnosis for the inflammatory lesions includes ulcerative colitis, Crohn’s disease, as well as sarcoidosis and other infections. Once organisms have been identified, they must be differentiated from other infectious agents (see table below) such as P. carinii (PC lacks budding and has a characteristic internal structure); Candida glabrata (has more frequent buds, is slightly larger, and is often extracellular rather than intracellular); and cryptococcus (which has a mucicarmine positive capsule).

References:

Clinical Presentation: A 20 year old female underwent a subtotal colectomy with ileostomy for ulcerative colitis three years ago. Nine months after surgery, the patient became symptomatic again, prompting evaluation.

Endoscopic Findings: At endoscopy, the duodenum showed “diffuse enteritis.”

Diagnosis: Duodenal involvement by ulcerative colitis

General Comments: Traditionally, ulcerative colitis (UC) and Crohn's disease (CD) have been distinguished clinically and histologically by anatomic distribution as well as by patterns of inflammation associated with them. CD is classically regarded as a discontinuous disease with skip areas, whereas UC is characterized as a diffuse mucosal disease of the colon with continuous and symmetric involvement, virtually always involving the rectum. Other than “backwash ileitis,” UC has traditionally been regarded as sparing the small bowel completely.

Several recent publications have challenged these traditional views regarding the anatomic distribution of UC. Several studies based on colorectal biopsies from chronic UC patients have demonstrated rectal sparing, patchy rather than diffuse colitis, and even complete rectal healing during the course of chronic disease. Rare case reports of patients with histologically documented UC associated with small intestinal involvement also appear in the literature, further challenging the classic dogma relating to the anatomic distribution of UC.

Diffuse duodenitis has now been well described in patients with confirmed diagnoses of UC. Duodenal involvement is often diagnosed when there is persistent nausea, vomiting, and/or bloody diarrhea in patients who have already had their colons resected for UC.

Pathologic features: Endoscopically, findings are similar to colonic UC with diffusely erythematous, friable mucosa. Histologically, the features are similar to UC within the large bowel, showing diffuse mucosal inflammation with basal plasmacytosis of the lamina propria, neutrophilic cryptitis, crypt abscesses, and mucosal crypt distortion.

Differential diagnosis: The major item in the differential diagnosis, of course, is CD. No other clinical, radiographic, or endoscopic features of CD should be present, nor should gross or microscopic findings of CD exist in either the duodenal biopsy in question or in previous specimens. The recognition of duodenal involvement by UC suggests that rather than automatically diagnosing CD in all patients presenting with pancolitis and diffuse duodenitis, one should consider the possibility of UC with an aberrant anatomic distribution as these patients may be candidates for successful re-anastomosis or ERPT procedures.
It remains to be determined whether duodenal involvement by UC is a previously unrecognized complication of chronic UC, a component of a variant type of UC, or possibly a completely different concurrent disease entity. Although this type of small intestinal involvement is not typical of the natural history of UC, it is possible that it is a rare complication of UC. As traditional views regarding the distribution of UC are already changing, further studies are needed to better understand and characterize the issue of upper small intestinal inflammation in UC.

**Treatment:** Cases of duodenal involvement by UC in the literature have done well treated with medical therapy for UC.

**References:**

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Case 1. **Diversion colitis**
1. Low magnification view showing superficial mucosal erosion and prominent mucosal lymphoid aggregates, yet no significant architectural distortion.
2. Higher magnification of the prominent lymphoid aggregates typical of diversion colitis. Although some cases of diversion colitis have cryptitis and crypt abscesses, this case does not.

Case 2. **Diverticular disease-associated segmental colitis**
3-4. Note expansion of the lamina propria by a lymphoplasmacytic infiltrate, and moderate architectural distortion, resembling ulcerative colitis.
5. Cryptitis and prominent lymphoid aggregates may be present.

Case 3. **Collagenous colitis**
6. Low magnification shows thickened subepithelial collagen band as well as a mixed inflammatory infiltrate within the lamina propria and epithelium.
7. Higher magnification highlights the inflammatory infiltrate typical of collagenous colitis, sometimes including increased eosinophils.

Case 4. **Non-steroidal anti-inflammatory drug-related injury**
8. Low magnification of ileal biopsy shows superficial mucosal ulceration, mild villous blunting, and prominent lymphoid aggregates. Prominent lymphoid aggregates are normally present within ileal mucosa, but may confound the histologic evaluation of inflammatory processes.
9. Higher magnification shows villous edema and mixed inflammatory infiltrate in lamina propria, features that may be seen in the context of NSAID-related injury.

Case 5. **Kayexelate sorbitol-induced necrosis**
10-11. Mucosal and submucosal necrosis with the resin crystals typical of kayexelate induced bowel necrosis.

Case 6.  **Prolapse injury**
12. Low magnification view shows prolapse polyp with mushroom-like cap of fibrinopurulent exudates.
13. Architectural distortion, crypt abscesses, and reactive epithelial atypia within a prolapse polyp, accompanied by marked hemosiderin deposition.
14. Higher magnification emphasizes congested capillaries within lamina propria, as well as hypertrophic muscularis mucosa extending into the mucosa in a perpendicular fashion.

Case 7.  **Ischemic colitis occurring in a young patient**
15. Low magnification shows superficial mucosal erosion and hemorrhage, accompanied by gland withering and marked lamina propria fibrosis.
16. High magnification emphasizes gland withering and lamina propria fibrosis.

Case 8.  **Yersiniosis**
17. Note expansion of lamina propria by inflammatory infiltrate and mucosal edema at low magnification, yet preservation of architecture.
18. Higher magnification shows prominent neutrophils within the lamina propria, particularly within the upper half of the mucosa; there is also focal cryptitis. These features are typical of the “acute self-limited colitis” pattern of inflammation.
19. Marked lymphoid hyperplasia and epithelioid granulomas with giant cells are seen in this right colon section.
20. Higher magnification shows cryptitis, crypt abscesses, and mild architectural distortion.
Case 9. **Fungal infection in an immunocompromised patient**

21. Low magnification of this colon biopsy shows a mild lymphohistiocytic infiltrate within the mucosa and submucosa, focally. Note absence of discrete granulomas.
22. GMS stain shows clusters of intracellular yeast forms within the mucosa and superficial submucosa.
23. High magnification of GMS stain shows that the organisms are small and ovoid with a point at one end, consistent with *Histoplasma capsulatum*.

Case 10. **Duodenal ulcerative colitis**

24. Low magnification shows moderate blunting of duodenal villi and expansion of the lamina propria by a lymphoplasmacytic infiltrate.
25. Higher magnification emphasizes architectural distortion of the duodenal glands, and the dense lymphoplasmacytic infiltrate.
26. Focal cryptitis, crypt abscesses, and gland loss are noted.