The Differential Diagnosis of Colitis in Endoscopic Biopsy Specimens

A Review Article

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Context.—A variety of inflammatory disorders may affect the colon, with widely differing clinical outcomes and management. These conditions encompass a spectrum of acute and chronic conditions.

Objective.—Review the pathology of the major colitides and highlight the most diagnostically useful features.

Data Sources.—Review of recent literature supplemented with personal experience in the field of gastrointestinal pathology.

Conclusions.—The etiologies associated with the various types of colitis are diverse and the range of histologic changes is somewhat limited. Nevertheless, the combination of clinical and endoscopic data coupled with histopathology allows for accurate classification in the majority of cases.


Interpretation of inflammatory colorectal biopsies has become more challenging as newer and more subtle forms of colitis have been described. This review focuses on key diagnostic features that will hopefully allow the surgical pathologist to differentiate normal from abnormal and acute from chronic colitis as well as to identify new forms of colitis and unusual presentations of classic diseases such as ulcerative colitis (UC) and Crohn disease (CD).

HISTOLOGY OF NORMAL COLONIC MUCOSA

The colonic mucosa is made up of tubular crypts aligned perpendicular to the muscularis mucosae. The distance between the crypts and the internal diameter of the crypts is constant. A slight variation in crypt architecture, intercryptal spacing, and occasional crypt branching may occur in normal biopsies and is no cause for concern. The epithelium lining the crypts resembles that of the small intestine except for a higher proportion of goblet cells interspersed among the absorptive cells.

The lamina propria that surrounds the crypts normally contains eosinophils, lymphocytes, plasma cells, and a few histiocytes. It is important to know where the biopsy came from in the colon to determine if the cellularity is within normal range. Relative to the left colon and rectum, the right colon contains greater numbers of inflammatory cells in the lamina propria. Normally there are many more plasma cells and eosinophils in the lamina propria of the right colon. The closer one gets to the ileocecal valve, the more inflamed the lamina propria looks. The left side of the colon contains significantly fewer cells within the lamina propria, and the surface epithelium contains more goblet cells and fewer absorptive cells relative to the right colon (Figure 1, A and B).

Eosinophils are a normal constituent in the lamina propria, and their quantity and distribution have been the source of several investigations. One study quantified the number of mucosal eosinophils regarded as a normal finding in the right and left colon in 198 colon mucosal biopsies from those with normal endoscopic exams. Fifty-five percent of biopsies from the ascending colon contained eosinophils in the crypt epithelium, compared with only 5% of biopsy specimens from the descending colon. Lamina propria eosinophils were, on average, 3 times more numerous in the ascending relative to the descending colon. Interestingly, mesocolic eosinophils were slightly more numerous in samples obtained in April and May, corresponding to periods of highest pollen counts, but this relationship did not attain statistically significance. One can conclude that intramucosal eosinophils are more numerous normally in the proximal colon, but show only mild fluctuations with ambient allergen exposure. Another study examined the variability in colonic eosinophils depending upon where in the United States patients lived. This review of 256 mucosal biopsies from patients without symptoms found that the mean number of eosinophils per intercryptal space was highest in the southern United States, a 35-fold difference between the mean eosinophil concentrations of patients in New Orleans compared with Boston. It remains elusive why individuals residing in the southern parts of the...
United States harbor greater numbers of eosinophils in their lamina propria.

In the right colon, Paneth cells are a normal constituent, and in children they may be even be present in the normal transverse colon. When Paneth cells are encountered in the left colon and rectum, their presence provides a useful marker of previous mucosal injury. Most of the time, left-sided Paneth cells are associated with UC, but they are not specific to this condition. It is simply that UC is the condition that most commonly results in chronic damage in this segment of the colon.

Occasional intraepithelial lymphocytes, typically T cells, are a normal finding. There should be approximately 1 lymphocyte for every 20 epithelial cells. There tend to be a few extras on the right side as compared with the left side, and one should not count intraepithelial lymphocytes overlying a lymphoid aggregate (where they are normally present in large numbers).

**PREPARATION ARTIFACT**

Histology of the enema effect is typified by an edematous lamina propria with extravasated red blood cells, some of which may be lysed. In addition, there is often mucin extravasation and flattening of the surface epithelium (Figure 2). In some cases the surface epithelium may be completed stripped away. This can be particularly frustrating when trying to evaluate the surface epithelium for the changes of lymphocytic colitis (LC) or collagenous colitis (CC). The longer the time interval between the enema and the endoscopy, the more pronounced these changes can become. If the patient has an enema the night before a procedure, neutrophils may reside in the epithelium, mimicking acute colitis. Occasionally some of these changes will be seen in patients who have not had an enema but instead have some endoscopy trauma. This can occur in patients undergoing colonoscopy when the entire colon is visually inspected first and rectal biopsies are performed last.

Oral sodium phosphate bowel preparations have also been associated with histologic changes in the colon.\(^3\) Endoscopically, aphthous lesions similar to those of CD may be seen, but the lesions are not friable and biopsy results do not show features of chronicity. Oral sodium phosphate bowel preparations should be avoided in patients with suspected graft-versus-host disease, as the apoptosis caused by the preparation can mimic mild GVHD.

**INFECTIOUS COLITIS**

Acute infectious-type colitis or acute self-limited colitis (ASLC) may be caused by a variety of infectious agents. Although some cases of ASLC may be caused by known bacterial pathogens such as *Campylobacter*, *Shigella*, or *Salmonella*, in the majority of cases, the exact pathogen is not identified. Acute self-limited colitis is defined as a transient, presumably infectious colonic inflammation that presents with the acute onset of bloody diarrhea. Patients generally recover in 10 to 14 days without residual inflammation or recurrent symptoms. Acute self-limited colitis usually has a constellation of generic histologic changes that do not allow differentiation from the other causes of diarrheal illness.

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**Differential Diagnosis of Colitis—Cerilli & Greenson**

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findings such that, with the exception of some viral and parasitic infections, specific findings that allow for a diagnosis of a particular pathogen are lacking.

The majority of infectious colitides are never biopsied, as the patient’s symptoms often resolve before the patient has time to see a gastroenterologist. If the patient’s symptoms persist, then (from a clinical perspective) it may be difficult to determine if the patient’s acute-onset bloody diarrhea is due to acute onset UC or acute infectious colitis. Colorectal biopsies are then used to help make this distinction. Hence, the diagnosis of ASLC on such biopsies can have a profound effect on patient management.

**Pathology**

Within the first 4 days of onset of bloody diarrhea, there are mucosal edema, acute cryptitis, crypt ulcers, and abscesses. About a week to 9 days later following the onset of bloody diarrhea, clinical resolution begins, heralded by histologic regenerative changes in the epithelium with mucus depletion and increased mitotic figures in crypt epithelial cells. There may also be a few persistent foci of cryptitis. This later finding, which we term focal active colitis, can be confused with smoldering CD and/or ischemia. The most reliable histologic criteria for distinguishing ASLC from acute-onset UC are the preservation of crypt architecture and the lack of plasmacytosis in the lamina propria in ASLC (Figure 3, A and B). The presence of either or both of these features should make one think of a chronic colitis and not ASLC. Small granulomas, usually secondary to crypt rupture, may be encountered in ASLC and should not lead one to an automatic diagnosis of CD.

The presence of focal active colitis in a patient who does not have a history of chronic inflammatory bowel disease should be interpreted conservatively, as the vast majority of cases turn out to be self-limited. Focal active colitis is more likely to be secondary to CD in pediatric patients, especially those who are teenagers. Focal active colitis can be seen not only in CD, but also in association with nonsteroidal anti-inflammatory drug (NSAID) use, ischemia, infections, partially treated UC, and as an isolated (incidental) finding in patients undergoing endoscopy to exclude neoplasia. Unfortunately, there are no particular histologic parameters of focal active colitis, such as amount, location, or distribution of the inflammation, that correlate with outcome or allow for selection of those at higher risk for inflammatory bowel disease.

Resolving ASLC can have a hypercellular lamina propria with increased lymphocytes, neutrophils, eosinophils, and a few plasma cells. This finding may fool the pathologist into
making the diagnosis of chronic colitis; however, on close inspection, basal plasma cells and crypt distortion will not be present. In some instances of resolving ASLC, a modest increase in intraepithelial lymphocytes may be seen. The presence of some residual surface epithelial damage and increased intraepithelial lymphocytes can sometimes be confused with lymphocytic colitis; however, the clinical context is different enough to usually prevent confusion.

**Specific Pathogens in Infectious Colitis**

Bacterial infections may affect the colon in a number of ways. Although some pathogens damage the bowel through direct mucosal invasion, others produce toxins, which in turn cause tissue injury and symptoms. *Clostridium difficile* infection is a good example of the latter mechanism, as the toxins produced by the bacteria cause direct tissue damage. The diagnosis should be suspected in anyone who develops diarrhea during a course of antibiotics or within 6–8 weeks of completing treatment. The diagnosis can be confirmed by the detection of *C difficile* toxin in stool, and a subset of patients undergo sigmoidoscopy or colonoscopy with biopsy. *Clostridium difficile* infection can often be identified endoscopically and histologically by its characteristic pseudomembrane formation (Figure 4). It should be pointed out that *C difficile* infection does not always have pseudomembranes, as some cases have biopsy findings identical to those of any other generic ASLC. If severe mucosal damage occurs, with coagulative necrosis and pseudomembranes, the histologic features may overlap with those of ischemic colitis or enterohemorrhagic *Escherichia coli* infections.

Many bacteria have specific surface epithelial adherence factors that help the organisms invade and damage the mucosa. *Shigella, Salmonella, Campylobacter, Yersinia,* and some strains of *E coli* all adhere to the epithelium and induce an acute colitis. Infection may spread to mesenteric lymph nodes with either *Yersinia* or *Salmonella,* and systemic involvement may occur. Some of these bacterial infections cause histologic changes that are characteristic of a given organism. *Yersinia* may show stellate foci of necrosis within lymphoid aggregates and aphthous lesions in the area of the appendix and ileocecal valve. The reactive lymphoid tissue in this region may lead to intussusception. *Salmonella* (typhoid fever) may have a characteristic gross appearance with raised longitudinal folds with ulcerated mucosa overlying hyperplastic Peyer patches. The biopsy findings in such cases can show aggregates of macrophages filled with cellular debris.

The enterohemorrhagic strain of *E coli,* O157:H7, is associated with a spectrum of clinical presentations, the most unusual of which is that of an afibrile illness. Often despite a high volume of diarrhea, only a few leukocytes are present in the stool, and the bacteria cannot be grown on routine culture. Therefore, a high index of suspicion is necessary clinically. Patients may develop nonbloody diarrhea, hemolytic uremic syndrome, an acute abdomen, and thrombotic thrombocytopenic purpura, and may even die from the infection. This strain is highly virulent, and only a very small number of viable bacteria are required to produce symptomatic infection. The histologic features of enterohemorrhagic *E coli* are typically similar to the pattern of injury associated with acute ischemic colitis. The presence of fibrin thrombi within lamina propria capillaries may be a clue to the diagnosis. Imaging may also suggest ischemic colitis, with thumbprinting on plain films, and edematous thickening of the colonic wall. Although any segment or the entire colon may be involved, the presence of right-sided injury should raise the question of *E coli* rather than ischemic colitis or inflammatory bowel disease. Inflammation and injury are usually contiguous rather than segmental with *E coli*.

Mycobacterial infection often manifests specific histologic changes, as *Mycobacterium tuberculosis* infection induces caseating granulomas whereas *Mycobacterium avium-intracellulare* generates aggregates of foamy macrophages. Patients with inflammatory bowel disease who are treated with strong immunomodulatory therapy are at increased risk of these infections, so one must have a low threshold for ordering acid-fast stains if one encounters lots of granulomas in such a patient.

**MICROSCOPIC COLITIS**

**Collagenous Colitis**

Patients with CC present with a history of chronic watery diarrhea, and a significant minority of patients also have abdominal pain and weight loss. Middle-aged to elderly women are most often affected, although even children have been reported with CC. As many as 40% of patients have a concomitant autoimmune disease such as celiac sprue, thyroiditis, rheumatoid arthritis, or Sjögren syndrome. There also appears to be a strong association with NSAID use.

Colonoscopy yields normal or near normal mucosa, although there are a few reports of linear mucosal tears that were thought to occur upon insufflation during endoscopy. In addition, there are rare reports of CC with pseudomembranes.

It appears as though some luminal antigen or antigens are important in the pathogenesis. Diversion of the fecal stream will cause the histologic changes of CC to regress, whereas reestablishing the fecal stream will induce a relapse of both the abnormal collagen layer and clinical symptoms.

**Pathologic Features**

At low power, biopsies of CC will often show a pink subepithelial stripe with an intact crypt architecture and an increase in superficial lamina propria mononuclear cells. Importantly, the lamina propria contains increased plasma cells and eosinophils and the surface epithelium often contains patchy numbers of intraepithelial lymphocytes with surface damage and entrapped cellular elements (Figure 5, A). The surface epithelium is not infrequently stripped off of the thickened collagen table. The subepithelial collagen generally blends imperceptibly with the basement membrane to form a hypocellular pink band that often entraps small capillaries. The entrapment of capillaries, along with chronic inflammatory cells, is a useful clue to the diagnosis.

The thickness of the collagen often varies from site to site in individual patients and should be evaluated only in well-oriented sections. The normal basement membrane of the colon measures 2 to 5 μm, whereas in CC the thickness of the collagen usually ranges from 10 to 30 μm. More important than the thickness of the subepithelial collagen is its irregularity. One should not be dissuaded from the diagnosis just because the collagen is less than 10 μm thick. Although it may seem intuitive that the intensity of symptoms correlates with the thickness of the collagen layer, this is in fact not the case. Biopsies obtained from the rectum and sigmoid colon may show less thickening and
may be in the normal range. When in doubt, particularly in those cases with only minimal or very patchy subepithelial collagen, a trichrome stain can be helpful to highlight the collagenous band and the irregular strands of collagen along its lower border (Figure 5, B and C).

Care should be taken not to overinterpret a thickened basement membrane as CC. Surface epithelial damage and increased lamina propria inflammation should always be present in cases of CC. Intraepithelial neutrophils may be seen, but they are usually less prominent than the intraepithelial lymphocytes. Large numbers of crypt abscesses are probably indicative of either superimposed infection or a separate diagnosis such as UC. Paneth cell metaplasia may be a marker of CC that is more refractory to therapy.18

Differential Diagnosis

A number of lesions may mimic some of the histologic changes of CC, including LC, chronic inflammatory bowel disease, solitary rectal ulcer/mucosal prolapse, enema effect, ischemia, and radiation colitis. Lymphocytic colitis looks identical to CC except for the absence of subepithelial collagen. Chronic inflammatory bowel disease typically shows more architectural distortion and the fibrosis involves deeper aspects of the lamina propria than is seen in CC. Mucosal prolapse also shows fibrosis in deeper portions of the lamina propria as well as muscular proliferation and crypt distortion. Enema effect may mimic some of the surface epithelial damage seen in CC as well as making it difficult to evaluate the surface epithelium. Ischemia often has fibrosis and hyalinization of the lamina propria that may be misdiagnosed as CC; however, the increased plasma cells in the lamina propria and the increased intraepithelial lymphocytes seen in CC will be absent. Radiation colitis also shows hyalinization of the lamina propria, usually with telangiectatic blood vessels and atypical endothelial cells and fibroblasts. The hyaline material does not stain as intensely on the trichrome stain as does the collagen in CC.
Prognosis and Therapy

Some patients with CC will have a spontaneous remission, and others will respond to simple over-the-counter antidiarrheal agents. Most patients, however, will require some form of therapy, and several trials have confirmed the effectiveness of budesonide over placebo in CC.20-22 The histologic response to therapy is variable, but a decrease in the subepithelial collagen layer as well as the lymphoplasmacytic infiltrate in the lamina propria is found in about half of the patients.23 The usual response requires approximately 2 weeks, but relapse is frequent when budesonide is discontinued.22 In one study, patients who were taking NSAIDs were more likely to require corticosteroid therapy, presumably reflecting more severe disease, but this association requires additional data to substantiate.23 Rarely, patients with refractory disease may require a diverting ileostomy. The overall course of the disease tends to wax and wane, but it is generally not as severe as UC or CD.

LYMPHOCYTIC COLITIS

Clinical Features

There is considerable overlap of both the clinical and pathologic features of LC and CC. Patients typically have chronic watery diarrhea with normal or near normal endoscopic findings. There tends to be less of a female predominance in LC as compared with CC, but the age range is quite similar.

The medications ranitidine, Cyclo 3 Fort (Pierre Fabre Medicament, Castres, France), and ticlopidine have been reported to cause lymphocytic colitis.24-26 For each of these drugs, the colitis resolved upon drug withdrawal and recurred with a rechallenge. To date, there is compelling evidence to suggest a high or intermediate probability of causality for 17 drugs with the development of LC.27

The association between LC and celiac disease is even stronger than the association between CC and celiac disease.28 In a study of 29 celiac sprue patients, nearly one-third had colonic lymphocytosis that was histologically, quantitatively, and immunohistochemically indistinguishable from LC, and a smaller subset also manifested features of lymphocytic gastritis.29 Possible clues to make one suspicious that the lymphocytosis is possibly celiac sprue related include the lack of surface epithelial abnormalities, the lack of increased cellularity of the lamina propria, and the lack of ongoing watery diarrhea after treatment with a gluten-free diet.30 In addition, studies have shown an increased incidence of HLA A1, DQ2 and DQ1, 3; a decrease in HLA-A3; and increased rates of carriage of the tumor necrosis factor α gene polymorphism (308) in LC patients relative to control patients.31-33 These findings suggest that gastrointestinal epithelial T-cell infiltration may be an immunologic response common in genetically susceptible individuals sensitized to absorbed luminal antigens, and that colonic lymphocytosis may occur as a response to a number of antigens, including gluten.

Pathologic Features

In general, LC resembles CC, but lacks the abnormal increase in the subepithelial collagen table (Figure 5, C). Because of the shared histopathologic features apart from this, and the highly similar clinical features between CC and LC, it has been suggested that these are the same disease in different stages of evolution, but in fact these are more accurately regarded as 2 separate but related entities.

Additional requisite histologic abnormalities include surface epithelial damage with increased intraepithelial lymphocytes, which is often more prominent in LC (Figure 6). Just as in CC, there is generally a superficial plasmacytosis without crypt distortion in LC. There may be fewer lamina propria eosinophils in LC than are encountered in CC. The surface damage and lymphocytosis may be patchy and the lamina propria plasmacytosis tends to be diffuse. The pathologist must avoid evaluating the number of intraepithelial lymphocytes overlaying a lymphoid follicle, as one should see numerous intraepithelial lymphocytes in these areas normally. It is important to remember that there are more intraepithelial lymphocytes in the right colon as compared with the left colon, to avoid misinterpretation of the right colon as hypercellular. A few foci of cryptitis or a rare crypt abscess may be seen in LC, but more neutrophil inflammation than this suggests another diagnosis.

Recently it has been recognized that some cases of lymphocytic colitis have less surface damage and more intraepithelial lymphocytes in the deeper crypt epithelium. Another variation of LC has been described with collections of histiocytes and poorly formed granulomas underneath the surface epithelium.34

Differential Diagnosis

The differential diagnosis of lymphocytic colitis is somewhat narrower than that of CC. The resolving phase of infectious colitis can mimic LC, as there can be surface damage and a modest increase in intraepithelial lymphocytes. Lymphocytic colitis–like changes have also been described in an outbreak of chronic diarrhea linked to the water supply of a cruise ship.35 This so-called colonic epithelial lymphocytosis seemed to have less surface damage as compared with lymphocytic colitis. There are also reports of lymphocytic colitis–like histology in patients with constipation as well as in patients with endoscopic abnormalities.36,37 Hence, it is important for the pathologist to make sure the clinical history is consistent with LC before making this diagnosis.

Be aware that some histologic features normally associated with inflammatory bowel disease, including crypt irregularity and neutrophilic cryptitis and even crypt abscesses, may be encountered in a minority of those with LC, and that the presence of one or more of these features should not necessarily be interpreted as evidence incompatible with LC.38 And lastly, CC may be confused with lymphocytic colitis in cases for which only rectal biopsies are obtained or when the subepithelial collagen table in CC is patchy and fairly thin. In the latter, a Mason trichrome stain is particularly helpful to help identify small patches of subepithelial collagen that are not apparent on routine hematoxylin–eosin staining.

Prognosis and Therapy

Therapy for LC is quite variable and is largely identical to that for CC. Some patients’ symptoms will resolve spontaneously, whereas others may require over-the-counter antidiarrheal medications such as bismuth subsalicylate, or in other cases, 5-aminosalicylic acid compounds or immunosuppressants. Overall, LC is associated with a benign course, with resolution of diarrhea and abnormal
Enterohemorrhagic strains of E coli. Diagnostic distinction of symptoms may be crucial. This medium-power view of mycophenolate colitis shows dilated and distorted crypts lined by regenerative epithelium. Note the rather empty lamina propria and the eosinophil-rich debris within the crypts (hematoxylin-eosin, original magnification ×100).

Histopathology in more than 80% of patients within 38 months in one study, which is commensurate with most other studies with follow-up data. There is a small subset of patients who have LC and sprue-like changes in their small-bowel biopsies that remain refractory to therapy. One recent study showed a benefit with the tumor necrosis factor α antagonists infliximab or adalimumab for those with severe refractory LC, but the data are too limited to determine its utility among these patients overall.

**DRUG-INDUCED COLITIS**

Mycophenolate mofetil, an immunosuppressive agent, was Food and Drug Administration–approved in early 1995 for organ rejection prophylaxis in renal or cardiac transplant patients, and in 2000 to manage liver transplant rejection. Colonic biopsies from patients with mycophenolate mofetil–related diarrhea are altered by prominent crypt cell apoptosis and marked regenerative epithelial changes, often with increased eosinophils, crypt dilatation, and crypt distortion (Figure 7). The changes are similar and sometimes indistinguishable from intestinal graft-versus-host disease in bone marrow transplant patients. Diagnostic distinction is clinically relevant, because the treatment for mycophenolate mofetil toxicity is dosage reduction of mycophenolate mofetil and subsequent clinical evaluation of the diarrhea, whereas treatment for graft-versus-host disease is often mycophenolate mofetil. Crypt abscesses and Paneth metaplasia may be present as well, which may cause confusion with inflammatory bowel disease. Rare cases may mimic ischemia.

Nonsteroidal anti-inflammatory medications are nearly ubiquitous in our society and have the potential to damage any segment of the gastrointestinal tract. In the lower tract, nonspecific ulcers and erosions are often seen, and changes resembling ischemia have also been described. Nonsteroidal anti-inflammatory medications may cause perforation or bleeding of colonic diverticula, have been implicated in relapse to inflammatory bowel disease and the development of CC, and may exacerbate bleeding of colonic angiodysplasia.

**ISCHEMIC COLITIS**

**Clinical Features**

The etiology of ischemic colitis is multifactorial, giving rise to a wide range of clinical presentations depending on the duration and severity of the underlying pathology. Whereas approximately 90% of cases of ischemic colitis occur in patients older than age 60, often with comorbidities such as cardiovascular disease, ischemic colitis can also affect younger, seemingly healthy people secondary to medications or previous abdominal surgery. Symptoms may range from transient bloody diarrhea or abdominal pain to a full-blown surgical emergency due to an infarcted bowel. The incidence of ischemic colitis is thought to have been underestimated because it often has a mild and transient nature.

Although lack of blood flow to the mucosa is the ultimate cause of ischemic colitis, there is a long list of conditions that can lead to this. Ischemic necrosis may be due to atherosclerosis, low-flow states secondary to hypovolemia, vasculitis, adhesions, various drugs such as pseudoephedrine, and even long-distance running. In some instances, drugs may induce nonocclusive vasospasm (catecholamines, estrogen, toxemia). Whereas in other cases, medication such as estrogen replacement therapy causes occlusive thrombosis. Enterohemorrhagic strains of *E coli* (such as *E coli* O157:H7) can also cause an ischemic-type colitis, presumably because of fibrin thrombi that develop during this toxin-mediated infection.

**Pathologic Features**

Gross examination in mild cases may show only patches of pale edematous mucosa with admixed areas of petechial hemorrhage or superficial ulceration. More involved cases of ischemia show geographic areas of ulceration, sometimes accompanied by pseudomembranes and marked submucosal edema. Endoscopically this submucosal edema can be prominent enough to mimic a tumor or mass lesion. The watershed areas around the splenic flexure are the most common sites for ischemia, but nearly any site can be involved, including the proximal rectum. In chronic stages, stricture, mucosal atrophy and granularity, or a segmental mucosal pattern of distribution may ensue that resembles CD. Apart from the overall clinical impression, rectal sparing and rapid resolution on serial examinations helps distinguish ischemia from inflammatory bowel disease.

Acute ischemic lesions of the colon show superficial mucosal necrosis that may spare the deeper portions of the colonic crypts. The remaining crypts typically have a withered or an atrophic appearance. There may be striking cytologic atypia, to the point where care should be taken to avoid overcalling these reactive changes dysplastic (Figure 8, A and B). Ischemic colitis may often have pseudomembranes as well as hemorrhage into the lamina propria, and hyalinization of the lamina propria. A trichrome stain can be evaluated in some cases if necessary to highlight the hyalinization of the lamina propria. Although cryptitis and crypt abscesses may be encountered, these are usually not prominent. Some vessels may be affected by platelet thrombi and necrosis. Depending on the severity of the decreased blood flow, these ischemic lesions may regress on their own or lead to perforation or strictures. The chronic phase of ischemia is often more difficult to diagnose, as the only histologic findings may be strictures and areas of submucosal fibrosis.
Differential Diagnosis

The differential diagnosis of ischemic colitis includes infectious lesions such as *C. difficile* colitis and enterohemorrhagic *E. coli* as well as drug-induced lesions such as NSAIDs and even some chronic colitides such as CC, radiation colitis, and CD. Because pseudomembranes may be seen in both ischemia and *C. difficile* colitis, it may be particularly difficult to differentiate these two. The presence of atrophic or withered-appearing microcrypts, lamina propria hemorrhage, full-thickness mucosal necrosis, and the endoscopic impression of a localized process, polyp, or mass are markers of ischemia, whereas the endoscopic identification of diffuse pseudomembranes favors the diagnosis of *C. difficile*. The presence of a hyalinized lamina propria is a rather specific and sensitive marker for ischemia in colon biopsies with pseudomembranes. The presence of an ischemic-appearing lesion in the right colon should also make one think of enterohemorrhagic *E. coli*, especially if fibrin thrombi are present.

Differentiating chronic ischemic ulcer from NSAID-induced damage or CD may be impossible, especially on biopsy material. Radiation exposure often causes arterial damage that can manifest itself as ischemia in the gut. In some instances the hyalinized appearance of the lamina propria in radiation colitis and the subepithelial collagen in CC can mimic the hyalinized lamina propria one sees in ischemia. The presence of telangiectatic vessels and atypical endothelial cells and fibroblasts should help identify radiation colitis, whereas the inflammatory component of CC should help with its identification.

Lastly, the regenerative epithelial changes in ischemia may mimic dysplasia. Recognition of the surrounding ischemic changes is the key to avoiding this pitfall. In summary, because the differential diagnosis includes a variety of other entities, an accurate diagnosis of ischemic colitis requires a combination of clinical suspicion and radiographic, endoscopic and histologic findings.

Prognosis and Therapy

The prognosis for ischemic colitis depends entirely on the underlying etiology of the ischemia as well as the severity of the process. Overall, about a third of cases are mild and transient, and will resolve with simple supportive care, whereas 15–20% may require surgery. In more severe cases, decompression of a distended colon may be required, and empiric broad-spectrum antibiotics are important to minimize bacterial translocation and sepsis that may occur with the loss of mucosal integrity. Ischemia in a long-distance runner is likely to be transient and self-limited, whereas severe thromboembolic disease may lead to a life-threatening bowel infarct with perforation and peritonitis.

Treatment is entirely dependent on the acuteness and severity of the condition. For the unfortunate 15% to 20% of patients who require surgery, there is an associated mortality rate of up to 60% in some series. As would be expected, those with total colonic ischemia have a worse prognosis than those with segmental involvement.54

DIVERSION COLITIS

Clinical Features

Defunctioning of the large bowel by ileostomy or colostomy is performed for a number of conditions, including CD, fecal incontinence, idiopathic constipation, and sphincter-saving operations for large-bowel neoplasia. Diversion colitis is the colitis that develops in the bypassed or excluded segments of the colon. Although diversion colitis is often an incidental finding in asymptomatic patients, some patients may present with mucoid or bloody discharge or abdominal pain. The colitis occurs 3 to 36 months following bypass and completely regresses within 3 months of reestablishment of the fecal stream.55,56

A deficiency of short-chain fatty acids is thought to be the cause of diversion colitis. Short-chain fatty acids are the main source of energy for colonocytes, and they are usually derived from fermentation of dietary starches by normal colonic bacterial flora. Once the fecal stream is diverted, dietary starches are no longer present. This lack of colonocyte nutrition leads to an inflammatory reaction. The inflammation can be reversed by giving short-chain

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Figure 8. A, This medium-power view of ischemic colitis shows a hyalinized, smudgy-appearing lamina propria with markedly regenerative crypt epithelium. Note that there is very little inflammation yet the surface is sloughing. B, This high-power view shows atrophic or withering crypts with nuclear atypia. Although this atypia is regenerative, it can easily be misinterpreted as dysplasia if viewed out of context. The hyalinized lamina propria is a key to the correct diagnosis (hematoxylin-eosin, original magnifications ×100 [A] and ×200 [B]).
The treatment of Pathologists should be cautious about making the This diverted segment of colon contains strikingly enlarged lesions may also mimic infectious colitis. Definitive diagnosis is generally that of recurrent CD or UC. The aphthous mucosa undergoes changes that mimic full-blown inflammatory bowel disease, with increased lymphoplasmacytic lamina propria cellularity, basal lymphoid aggregates, acute cryptitis, and even crypt abscesses. Distorted crypt architecture is frequent, as is surface epithelial sloughing and Paneth cell metaplasia.

Prognosis and Therapy

Prognosis is excellent because diversion colitis will completely regress once the fecal stream is reestablished. If this is not possible, then the inflammation can be reversed by giving short-chain fatty acids via enemas. As diversion colitis is often asymptomatic, therapy is often not necessary.

Pathologic Features

The gross and endoscopic features of diversion colitis include erythema, friability, edema, and nodularity with aphthous ulcers. Histologically, diversion colitis has the potential to take on a wide spectrum of changes ranging from mild colitis to those reminiscent of severe active chronic UC. The hallmark of the condition relates to the grossly apparent nodularity, which corresponds to large lymphoid aggregates with prominent germinal centers (Figure 9). The remaining features of diversion colitis are much more variable. In some instances, the inflammation may mimic severe UC with crypt distortion and marked chronic inflammation of the lamina propria. In other cases, patchy cryptitis and aphthous lesions may mimic CD. Because of the nonspecific nature of these histologic changes, it is imperative that the pathologist knows that he or she is looking at material from a diverted segment of colon (most often a Hartmann pouch).

Differential Diagnosis

As many people with diverted segments of colon have inflammatory bowel disease, the main differential diagnosis is generally that of recurrent CD or UC. The aphthous lesions may also mimic infectious colitis. Definitive diagnosis requires the knowledge that the pathologic changes are occurring in a diverted segment.

Prognosis and Therapy

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ric 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.65–66 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.66,67 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. It is important to correctly separate inflammatory bowel disease patients definitively as CD or UC (or other), because an ileal pouch–anal anastomosis “pouch” procedure is generally contraindicated in CD because of a high risk of morbidity related to pouchitis, fistulas, incontinence, or Anastomotic leaks.

Diffuse duodenitis has now been well described in patients with confirmed diagnoses of UC.68,69 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 those of colonic UC, with diffusely erythematous, friable mucosa. Histologically, the features are similar to UC within the large bowel, showing diffuse mucosal inflammation with basal plasma-cytosis 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 reanastomosis 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.

Prognosis and Treatment

Patients with duodenal involvement by UC in the literature have done well when treated with medical therapy for UC.

CROHN COLITIS

It is very difficult to make a definitive diagnosis of Crohn colitis in endoscopic biopsy material. Without the presence of terminal ileal disease, one can really hang one’s hat on the presence of epithelioid granulomas. Care must be taken not to misinterpret crypt rupture or mucin granulomas, which can be found in any active colitis. Crypt rupture granulomas often have large multinucleated giant cells and/or eosinophils within the granuloma. It is helpful to examine multiple levels to make sure a granuloma is not associated with a ruptured crypt. In our experience it is common to find granulomas in biopsies of children with CD, but they are much less common in older adult patients.

Although patchy or focal inflammation is the hallmark of CD, UC is often patchy once therapy has been instituted. Skip lesions are another feature felt to be a hallmark of CD; however, one may have skip lesions in fulminant UC as well as in patients with left-sided UC who have a cecal patch.64,70 One may also have rectal sparing in UC because of therapy or longstanding burnt-out disease and even in acute-onset disease in children.70 Ultimately, when dealing with endoscopic biopsies, there is no substitute for clinical and endoscopic correlation. The more information one has, the more likely one can make a firm diagnosis. Even when one has all the appropriate information, there are still cases that defy classification. In such cases there is no shame in calling something active chronic colitis, unclassified type.

SUMMARY

Recognition of specific histologic features or a combination of features coupled with clinical and endoscopic data allows for accurate classification in the majority of cases. In some cases, the necessary clinical and/or endoscopic information may not be available and pathologists will have to do the best they can to describe the abnormalities seen.

References

15. Cerilli & Greenson

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