

The Differential Diagnosis of Colitis in Endoscopic Biopsy Specimens

Joel K. Greenson, M.D.

Professor of Pathology

University of Michigan Medical School

Ann Arbor, Michigan, USA 48109-0054

facjkgmd@umich.edu

Normal Histology:

The histology of the colon varies from right to left. The cecum and ileo-cecal valve have the largest number of inflammatory cells in the lamina propria while the left colon and rectum have the fewest. Plasma cells, lymphocytes, eosinophils and histocytes are all part of a normal lamina propria. Pathologists need to recognize this and not call this “mild non-specific colitis”.

Preparation artifacts:

In order to accurately assess colorectal biopsy specimens the pathologists must always be aware of what type of preparation is used prior to endoscopy. Sodium phosphate enema preparations are hyperosmolar solutions that set off an acute inflammatory response in the distal rectum. As most patients receive this preparation within a short time of endoscopy, the major findings are only those of edema with margination of neutrophils in vessel walls. There is also hemorrhage into the lamina propria with lysis of red blood cells. To the endoscopist this reaction will appear as a localized area of erythema that looks inflamed and hence these areas are often biopsied.

Histologically, 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. In some cases the surface epithelium may be completely stripped away. This can be particularly frustrating when trying to evaluate the surface epithelium for the changes of lymphocytic or collagenous colitis. 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, one may even find neutrophils 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 had some endoscope trauma. This can occur in patients undergoing colonoscopy when the entire colon is visually inspected first and rectal biopsies are preformed last.

Oral sodium phosphate solutions have also been associated with histologic changes in the colon. Small aphthous lesions have been seen endoscopically which histologically show foci of cryptitis and apoptosis centered on lymphoid aggregates. These changes can easily be misinterpreted as smoldering Crohn’s disease, infectious colitis or graft versus host disease.

Infectious Colitis:

Acute infectious-type colitis or acute self-limited colitis (ASLC) may be caused by a variety of infectious agents. While 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. ASLC is defined as a transient, presumably infectious colonic inflammation, which presents with the acute onset of bloody diarrhea. The patients generally recover in 10 to 14 days without residual inflammation or recurrent symptoms. ASLC usually has a constellation of generic histologic findings such that (with the exception of some viral and parasitic infections) there are no specific findings, which allow for a diagnosis of a specific pathogen. The majority of infectious colitides are never biopsied, as the patient's symptoms often resolve before the patient has time to see a gastroenterologist (particularly in our current managed care environment!). If the patient's symptoms persist, then (from a clinical prospective) it may be very difficult to determine if the patient's acute onset bloody diarrhea is due to acute onset ulcerative colitis 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.

Histopathology:

The most reliable histologic criteria for distinguishing ASLC from acute onset ulcerative colitis are the lack of crypt distortion and the lack of a basal plasmacytosis in ASLC. Patients with acute onset ulcerative colitis typically have histologic evidence of a chronic colitis despite the clinical history of acute onset bloody diarrhea. During the earliest phase of ASLC (peak activity) one may see edema, cryptitis, crypt abscesses, and surface damage with ulcers or erosions. As the illness resolves, there are 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 Crohn's disease and/or ischemia. According to Greenson and colleagues, the presence of focal active colitis in a patient that does not have a history of chronic inflammatory bowel disease should be interpreted conservatively, as the vast majority of cases turn out to be resolving ASLC. 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

Bacteria:

Bacterial infections may affect the colon in a number of ways. While 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. *C. difficile* infection can often be identified by its characteristic pseudomembrane formation. It should be pointed out, however, that *C. difficile* infection does not always have pseudomembranes, as some cases have biopsy findings identical to any other generic ASLC. Pseudomembranes may also be seen in ischemia and enterohemorrhagic *E. coli* infections (see below). Many bacteria have specific surface epithelial adherence factors which 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 (*Yersinia* and *Salmonella*) and systemic involvement may occur. Some of these bacterial infections cause histologic changes, which 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's patches. The biopsy findings in such cases can show aggregates of macrophages stuffed with cellular debris. **Mycobacterial infections** can also show specific histologic changes, as TB will have caseating granulomas while MAI will have aggregates of foamy macrophages in the lamina propria. **Chlamydia** and **Syphilis** can also infect the colorectum causing a granulomatous proctitis that may mimic Crohn's disease.

Collagenous Colitis

Clinical Features:

Patients with collagenous colitis (CC) present with a history of chronic watery diarrhea. Colonoscopy typically shows normal or near normal mucosa, although there are a few reports of linear mucosal tears which were thought to occur upon insufflation during endoscopy. In addition, there are rare reports of collagenous colitis with pseudomembranes. Females largely outnumber males and most patients are middle-aged or older.

It appears as though some luminal antigen or antigens are important in the pathogenesis of CC. Diversion of the fecal stream will cause the histologic changes of CC to regress, while reestablishing the fecal stream will induce a relapse. Studies have shown a strong association of CC with NSAID use and with celiac disease.

Pathologic Features:

At low power, biopsies of collagenous colitis will often show a pink subepithelial "stripe" with intact crypt architecture and an increase in superficial lamina propria mononuclear cells. At higher magnification the lamina propria will show increased plasma cells and eosinophils and the surface epithelium will have a patchy infiltrate of intraepithelial lymphocytes with areas of surface damage. The surface epithelium may also be stripped off of the thickened collagen table, making it harder to make the diagnosis. The subepithelial collagen usually blends imperceptibly with the basement membrane to form a hypocellular pink band that often entraps small capillaries. The thickness of the collagen often varies from site to site in individual patients and should

only be evaluated in well-oriented sections. The normal basement membrane of the colon measures 2 to 5 microns, while in collagenous colitis the collagen typically has a thickness of 10 to 30 microns. Biopsies from the rectum and sigmoid colon may show less thickening and may be in the normal range. When in doubt a trichrome stain can be used to highlight the collagenous band and show the irregular nature of its lower border (a feature not seen with normal basement membrane). Care should be taken not to over interpret a thickened basement membrane, as CC. Surface epithelial damage with increased intraepithelial lymphocytes should always be present in cases of collagenous colitis. 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 ulcerative colitis. Paneth cell metaplasia may be a marker of collagenous colitis that is more refractory to therapy. Differential Diagnosis:

A number of lesions may mimic some of the histologic changes of collagenous colitis including lymphocytic colitis, chronic inflammatory bowel disease, solitary rectal ulcer/mucosal prolapse, and enema effect, ischemia and radiation colitis. Lymphocytic colitis looks identical to collagenous colitis 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 collagenous colitis. 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 collagenous colitis 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 collagenous colitis, 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 collagenous colitis.

Prognosis and Therapy:

Some patients with collagenous colitis will have a spontaneous remission while others will respond to simple over the counter anti-diarrheal agents. Most patients, however, will require some form of anti-inflammatory therapy (steroids and or 5-aminosalicylic acid compounds). Rarely, patients with refractory disease may require a diverting ileostomy. Spontaneous remission without any therapy has also been reported. The overall course of the disease tends to wax and wane, but it is generally not as severe as ulcerative colitis or Crohn's disease.

Lymphocytic Colitis

Clinical Features:

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

The medications ranitidine and Cyclol 3 Fort have been reported to cause lymphocytic colitis. In each report the colitis recurred with a re-challenge of the drug. The association between LC and celiac disease is even stronger than the association between CC and celiac disease. These findings again support the notion that luminal antigens induce this colitis. In addition, HLA studies have shown an increased incidence of HLA A1, DQ2 and DQ1, 3 in lymphocytic colitis patients as well as other autoimmune processes.

Pathologic Features:

In general, lymphocytic colitis looks just like collagenous colitis without the subepithelial collagen table. The surface epithelial damage with increased intraepithelial lymphocytes is often more prominent/intense in lymphocytic colitis. 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 seen in CC. The surface damage and lymphocytosis may be patchy while the lamina propria plasmacytosis tends to be diffuse. The pathologist must avoid evaluating the number of intraepithelial lymphocytes overlying a lymphoid follicle, as one should normally see numerous intraepithelial lymphocytes there. One should also recognize that normally there are more intraepithelial lymphocytes in the right colon as compared to the left colon. A few foci of cryptitis or a rare crypt abscess may be seen in LC, but more neutrophilic 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.

Differential Diagnosis:

The differential diagnosis of lymphocytic colitis is somewhat narrower than collagenous colitis. 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 cruise ship. This so-called “colonic epithelial lymphocytosis” seemed to have less surface damage as compared to lymphocytic colitis. Reports have also been made of lymphocytic colitis-like histology in patients with constipation as well as in patients with endoscopic abnormalities. Hence, it is important for the pathologist to make sure the clinical history is consistent with LC before making this diagnosis. There are also reported cases of Crohn’s disease with patchy areas showing a lymphocytic colitis-like pattern. Collagenous colitis may be confused with lymphocytic cases when only rectal biopsies are obtained or when the subepithelial collagen table in collagenous colitis is patchy and fairly thin.

Prognosis and Therapy:

Therapy for lymphocytic colitis is quite variable and is largely identical to that used for collagenous colitis. Some patients’ symptoms will resolve spontaneously while others may require over the counter diarrheals, bismuth subsalicylate, 5-aminosalicylic acid compounds or immunosuppressants. Overall the prognosis is good, as eventually most patients respond to some form of therapy. However, there is a small subset of patients who have lymphocytic colitis and sprue-like changes in their small bowel biopsies that seems refractory to all therapy. These patients have been classified as having

lymphocytic enterocolitis, although some authors have raised the possibility that these patients have a lymphoproliferative disorder.

Ischemic Colitis

Clinical Features:

Ischemia can give rise to a wide range of clinical presentations depending on the duration and severity of the underlying pathology. While many cases of ischemia occur in older patients with known cardiovascular disease, ischemic colitis can also be seen in 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.

While 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 and even long distance running. In some instances the drug may induce vasospasm (catecholamines, cocaine) while in other cases the medication may lead to thrombosis (estrogens). Enterohemorrhagic strains of *E. coli* (such as *E. coli* O157:H7) can also cause ischemic-type colitis, presumably due to fibrin thrombi that develop during this toxin-mediated infection.

Radiologic Features:

The classic radiologic finding of ischemia on a barium enema study is that of “thumbprinting”. This finding is produced by marked submucosal edema. CT findings of circumferential bowel wall thickening may also be a marker for ischemia.

Pathologic Features:

Gross Findings:

Ischemia typically shows geographic areas of ulceration, which may have pseudomembranes. This is often accompanied by 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. Chronic or healed ischemic lesions may form isolated strictures that resemble Crohn’s disease.

Microscopic Findings:

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. 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 employed to highlight the hyalinization of the lamina propria. While cryptitis and crypt abscesses may be seen, these are usually not prominent. Depending on the severity of the decreased blood flow, these ischemic lesions may regress on their own or lead to perforation and/or stricture formation. 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 collagenous colitis, radiation colitis and Crohn's disease. Since pseudomembranes may be seen in both ischemia and *C. difficile* colitis it may be particularly difficult to differentiate these two. The presence of a hyalinized lamina propria and withered or atrophic appearing crypts are specific findings in ischemia that are not seen in *C. difficile* colitis. In addition the pseudomembranes tend to be more diffuse in *C. difficile* and patchy in ischemia. 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 ulcers from NSAID-induced damage or Crohn's disease 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 collagenous colitis 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, while 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.

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. Ischemia in a long distance runner is likely to be transient and self-limited, while severe thromboembolic disease may lead to a life threatening bowel infarct with perforation and peritonitis. Overall, 35% of cases will resolve with simple supportive care, while 15-20% may require surgery.

Radiation Colitis

Clinical Features:

Acute radiation damage is often subclinical, while patients with chronic radiation damage may complain of diarrhea, abdominal pain and/or rectal bleeding. Patients receiving radiation therapy for cervical and prostate cancer have the highest risk of radiation damage.

Acute radiation injury occurs within hours to days of radiation exposure and is due to epithelial injury. This damage usually heals within two months. Chronic radiation colitis occurs secondary to damage to the mesenchymal tissues of the gut. These changes may remain clinically silent for long periods of time. Unfortunately these lesions can remain symptomatic for the life of the patient.

Pathologic Features

Gross Findings:

Acute: Endoscopy shows edema and a dusky appearing mucosa.

Chronic: As much of the damage induced by radiation is due to ischemic damage to mesenteric vessels; ulcers, strictures, fistulas and adhesions may be seen. Endoscopically, there is typically patchy erythema, which is secondary to telangiectasia of the mucosal capillaries.

Microscopic Findings:

Acute: Acute radiation damage is rarely seen, however, the changes are those of epithelial damage, increased apoptosis, decreased mitoses, and regenerative atypia. Increased numbers of eosinophils may also be seen.

Chronic: In addition to telangiectasia of the mucosal capillaries, Chronic radiation damage often has areas of hyalinization around these dilated vessels with atypical “radiation fibroblasts”. The endothelial cells may also show similar radiation induced atypia. Some degree of crypt distortion and even foci of cryptitis may be seen. Superimposed changes of ischemia may also be present.

Differential Diagnosis:

An accurate history is paramount if one is to make a diagnosis of radiation colitis. Chronic radiation damage can be very subtle in biopsy specimens, as the vascular changes in the capillaries are easily overlooked. These same vascular changes can mimic the telangiectasia seen in portal colopathy or angiodysplasia. One would not expect to see a hyalinized lamina propria or radiation fibroblasts in these conditions. Occasionally the hyalinized changes in the lamina propria can mimic collagenous colitis, however, these hyalinized areas do not stain as intensely as collagen on a trichrome stain. In addition, the characteristic inflammatory changes of collagenous colitis will be absent. The presence of crypt distortion may mimic quiescent ulcerative colitis/proctitis. Given that many of the changes of radiation colitis are secondary to ischemia, ischemic colitis is often in the differential diagnosis. The regenerative atypia seen in acute radiation damage may mimic dysplasia. Once again a history of radiation exposure is imperative to make the correct diagnosis.

Prognosis and Therapy:

Unfortunately the damage caused by radiation is permanent and hence symptomatic patients may require surgical resection. Steroid therapy may be of some benefit. Laser therapy may be useful to induce hemostasis in areas of active bleeding.

Diversion Colitis

Clinical Features:

Diversion colitis is usually a mild colitis that occurs in bypassed or excluded segments of the colon. This is most often seen in a Hartmann’s pouch. While diversion colitis is often an incidental finding in asymptomatic patients, some patients may present with mucoid or bloody discharge and/or abdominal pain. The colitis occurs 3 –36 months following bypass and completely regresses within 3 months of re-establishment of the fecal stream.

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 fatty acids via enemas several times a week, or by re-establishing the fecal stream.

Radiologic Features:

Double contrast barium enemas are able to detect the lymphoid follicular hyperplasia that is characteristic of diversion colitis.

Pathologic Features

Gross Findings:

The gross and endoscopic features of diversion colitis include; erythema, friability, edema, and nodularity with aphthous ulcers.

Microscopic Findings:

Histologically, the nodularity seen grossly corresponds to large lymphoid aggregates with prominent germinal centers. The remaining features of diversion colitis are quite variable. In some instances the inflammation may mimic severe ulcerative colitis with crypt distortion and marked chronic inflammation of the lamina propria. In other cases, patchy cryptitis and aphthous lesions may mimic Crohn's disease. Due to 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 usually a Hartmann's pouch).

Differential Diagnosis:

As many people with diverted segments of colon have inflammatory bowel disease, the main differential diagnosis is generally that of recurrent Crohn's disease or ulcerative colitis. 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:

Prognosis is excellent since diversion colitis will completely regress once the fecal stream is re-established. 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.

Diverticular Disease-Associated Colitis

Clinical Features:

Diverticular disease is common among patients over the age of 60, particularly in the sigmoid colon. Diverticular disease-associated colitis has been described as a chronic segmental colitis present in the distribution of the diverticula that mimics ulcerative colitis. This colitis is restricted to the mucosa and is not a manifestation of diverticulitis. Patients often present with hematochezia.

There is also a form of diverticulitis that 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:

Gross Findings:

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.

Microscopic Findings:

Histologically one can find a range of changes in the mucosa, from a mild plasmacytosis and mild crypt distortion to a full-blown ulcerative colitis-like appearance. Cryptitis and crypt abscesses are typically seen.

Differential Diagnosis:

The main differential diagnosis is between diverticular disease-associated colitis and ulcerative colitis. The key to the correct diagnosis is to recognize that the distribution of disease is identical to the distribution of the diverticula. Crohn's disease is also in the differential due to the presence of rectal sparing.

Prognosis and Therapy:

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.

Mucosal Prolapse/Solitary Rectal Ulcer Syndrome**Clinical Features:**

Mucosal prolapse presents in a variety of clinical scenarios including those of the solitary rectal ulcer syndrome (SRUS), diverticular disease (polypoid prolapsing mucosal folds), and at ostomy sites. The solitary rectal ulcer syndrome most often occurs in young women with alternating diarrhea and constipation, pain and/or difficulty defecating, and rectal bleeding. The etiology is thought to be 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 also occur in association with diverticular disease, at ostomy sites, and adjacent to other mass lesions; the common denominator being an abnormality that causes mucosal prolapse and resultant injury. When this process occurs at the anal verge and forms a polyp it is also known as the inflammatory cloacogenic polyp. These other forms of mucosal prolapse are typically asymptomatic but are important to recognize so as not to be confused with adenomas or chronic inflammatory bowel disease.

Radiologic Features:

Anal endosonography and defecography can be employed to make the diagnosis, with the later being the "gold standard". Prolapse polyps throughout the GI tract may be picked up on barium enemas.

Pathologic Features:**Gross Findings:**

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. Endoscopically these lesions can look quite threatening, as the mass lesions mimic carcinoma, and the ulcerative lesions mimic Crohn's disease. The solitary rectal ulcer syndrome is typically located on the anterior rectal wall between 4 and 10 cm, while prolapse polyps associated with diverticular disease are typically found in the sigmoid colon at the mouths of diverticula.

Microscopic Findings:

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 colonic crypts is diagnostic of prolapse. Occasionally, the amount of fibrosis can overshadow the smooth muscle proliferation. The epithelium is often

inflamed and ulcerated, and in some cases an ischemic appearance may be present complete with small pseudomembranes. There may be significant crypt architectural distortion. The lamina propria is often very vascular, with numerous congested capillaries and hemosiderin deposition. The surface mucosa may be serrated and tufted with goblet cell hypertrophy. In polypoid cases, the mucosa often takes on a villiform configuration that can mimic a villous adenoma. In some cases glands may become trapped in the submucosa forming what is known as colitis cystica profunda.

Differential Diagnosis:

Perhaps the most crucial differential diagnosis is between mucosal prolapse and colorectal neoplasia. SRUS can easily be misinterpreted as a villous adenoma or even an invasive carcinoma with disastrous consequences for the patient (particularly if an anterior-perineal resection is performed). It is important to evaluate the epithelium critically and notice that the changes are reactive/hyperplastic rather than dysplastic. Cases of SRUS with colitis cystica profunda may be confused for a well-differentiated mucinous carcinoma. Recognition that the lining epithelium in the cysts is not dysplastic is the key to an accurate diagnosis. Similarly, if the ulcerative component of SRUS is recognized without the characteristic fibromuscular hyperplasia of the lamina propria, an errant diagnosis of chronic inflammatory bowel disease may be rendered. A trichrome stain can be used to confirm the presence of fibromuscular hyperplasia, allowing one to avoid this diagnostic pitfall.

Prolapsing polypoid mucosal folds may be confused with Peutz Jeghers polyps due to the increase in smooth muscle associated with prolapse. One can usually differentiate the two based on the lack of an arborizing architecture in the smooth muscle of prolapse polyps.

Prognosis and Therapy:

Prolapse changes are completely benign and the patient outcome is determined by the underlying disorder. If diverticular disease associated polyps cause problematic bleeding they may be excised. Patients with SRUS may respond to nonsurgical management such as bulk laxatives and stool softeners. Patients with severe rectal prolapse may require surgical intervention.

Allergic Proctocolitis

Clinical Features:

Allergic proctocolitis is a disease of infants in the first year of life that develop an allergy to formula or breast milk. Occasionally the allergy will be to a food ingested by the mother that is passed to the child via breast milk rather than the breast milk itself. The children present with blood streaked stools, diarrhea, vomiting or anemia.

Pathologic Features:

Gross Findings:

Endoscopic features of allergic proctocolitis include focal erythema and friability as well as rare ulcers or erosions.

Microscopic Findings:

The histologic features of allergic proctitis are often focal and may be quite subtle. The major finding is that of increased eosinophils which can be in the lamina propria and within the epithelium and muscularis mucosae. Studies from the northern United States (Boston) have found that the presence of greater than 60 eosinophils per 10 high power

fields in the lamina propria correlates with allergic proctocolitis. Since the normal number of eosinophils in the lamina propria of the colon varies by geographic region, this number may be inappropriate in more southern climates where eosinophil counts are higher. The distribution of eosinophils is also important as their presence in the epithelium, muscularis mucosae and at the periphery of lymphoid aggregates correlates with allergy. One may also find foci of cryptitis in allergic proctocolitis.

Differential Diagnosis:

Allergic proctocolitis needs to be distinguished from infectious colitis, necrotizing enterocolitis and colitis associated with Hirschsprung's disease. As all of these conditions may show cryptitis, the diagnosis of allergy rests on finding abnormal numbers and distributions of eosinophils.

Prognosis and Therapy:

Treatment revolves around dietary manipulation to exclude whatever nutrient seems to be causing the symptoms. The prognosis is excellent, as most children outgrow this condition.

Ulcerative Colitis vs. Crohn's disease

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.

Dysplasia in IBD:

The risk of neoplasia in ulcerative colitis and Crohn's colitis increases with both the duration and the extent of disease. In patients with extensive or pancolitis, the cancer risk increases dramatically 8-10 years after the first onset of disease. Childhood onset of colitis and primary sclerosing cholangitis further increase the risk of developing colorectal carcinoma.

The performance of surveillance endoscopy to identify dysplastic precursor lesions via endoscopic biopsy specimens has become the main management strategy to combat this risk. Biopsies should be classified as negative for dysplasia, indefinite for dysplasia, low-grade dysplasia or high-grade dysplasia according to standard criteria. A prophylactic colectomy is the procedure of choice when high-grade dysplasia or low-grade dysplasia associated with a lesion or mass is present. Some centers also recommend a colectomy for the presence of low-grade dysplasia in flat mucosa. Given these management recommendations, care should be taken not to overcall reactive epithelial changes in the face of active colitis. All diagnoses of dysplasia should be confirmed, preferably by a pathologist experienced in interpreting gastrointestinal biopsies.

During the active phase of IBD there is often extensive mucosal damage. Repair of this damage leads to proliferative changes in the mucosa that often mimic dysplasia. The regenerative epithelium may show increased mitotic figures with nuclear stratification, prominent nucleoli, and mucin depletion. If these changes are worrisome enough, the diagnosis of indefinite for dysplasia should be used in this setting. There is a large combination of cytologic and architectural changes that can lead to the diagnosis of indefinite for dysplasia. Some of the more common findings include incomplete maturation and cytologic atypia that does not reach the surface. Pathologists need to recognize that in the background of active inflammation any diagnosis of dysplasia is suspect.

Low-grade dysplasia has been defined as an unequivocal neoplastic change showing enlarged hyperchromatic nuclei that are stratified and which are arbitrarily confined to the basal half of the gland. These changes are identical to most adenomas of the colon. High-grade dysplasia is typified by more intense cytologic atypia in which the nuclear stratification extends higher than the basal half of the glands. In addition marked nuclear pleomorphism and loss of polarity of the cells are also markers of high-grade dysplasia. Drawing the line between low-grade and high-grade dysplasia can be problematic and probably should not be done on the basis of single crypt or two.

While many manuscripts including this one are replete with photomicrographs of reactive epithelial changes, changes indefinite for dysplasia, low-grade dysplasia and high-grade dysplasia, these images tend to be classic examples that few would argue with. In the real world, we are faced with the daunting challenge of placing a continuum of pathologic changes into one of these four diagnostic boxes. It is not surprising that even expert gastrointestinal pathologists struggle with this and that inter and intra-observer reproducibility is not as good as we would hope. Melville and colleagues reported that there was good agreement between pathologists when looking at high-grade dysplasia and no dysplasia, but rather poor agreement for low-grade dysplasia and indefinite for dysplasia. Reports by Eaden et al and Dixon and colleagues found rather poor inter-observer agreement across all grades even among gastrointestinal pathologists. These shortcomings have led many to look for better markers for the risk of CRC in IBD. To date, while flow cytometry and several molecular markers have been studied, none have replaced histopathology as the gold standard (yet).

Another major problem with dysplasia surveillance programs in IBD is the issue of appropriate sampling. Since many dysplastic lesions are grossly unapparent, clinicians must take numerous random biopsies throughout the colorectum to adequately sample the mucosa. Rubin and colleagues have estimated that a minimum of 33 biopsies per colonoscopy is needed to detect dysplasia with 90% confidence. Current management guidelines put forth by the American Society for Gastrointestinal Endoscopy recommend taking 2-4 random biopsies every 10 cm in addition to biopsying mucosal irregularities and polypoid lesions separately. My own experience with a large consult practice, however, is that outside of tertiary care medical centers, many gastroenterologists take only a handful of biopsies when performing surveillance endoscopy.

One more confounding factor in surveillance endoscopy that can have profound management implications is the issue of sporadic adenomas occurring in patients with IBD. From a purely morphologic prospective, adenomas and colitic dysplasias are often identical under the microscope. This places much of the burden on deciding whether a lesion is a sporadic adenoma or a DALM on the shoulders of the endoscopist, as the gross description of the lesion and whether it was from an area involved with colitis or not is of paramount importance. Most studies agree that pedunculated polyps that look like typical sporadic adenomas should be managed as such, unless they occur in younger patients (under age 40). Morphologically, the presence of dysplasia along the stalk of the polyp or in the adjacent non-polypoid mucosa favors a DALM over a sporadic adenoma. How to manage sessile lesions is a bit more complicated as sessile lesions arising in an area involved in colitis have often been interpreted as representing DALMs. A recent study by Torres and colleagues found that discrete adenoma-like areas of dysplasia arising in areas not involved with colitis could be treated conservatively as could similar lesions arising

in areas involved with colitis providing the flat mucosa adjacent to the lesion was not dysplastic. They also noted that compared to sporadic adenomas, DALMs had more mononuclear cells in the lamina propria and were more likely to show admixture of dysplastic and normal crypts at the surface of the lesion. As these morphologic changes are subtle and not absolute, many investigators have focused on molecular techniques to try and differentiate between colitis associated dysplasia and sporadic adenomas. For the time being, however, all hope of arriving at the correct diagnosis will be lost if the clinician puts all biopsies of flat and polypoid mucosa in one container which is not labeled as to site and fails to give the pathologist an endoscopic description.

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