

Problematic Issues in the Biopsy Diagnosis of Inflammatory Bowel Disease
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Introduction

The diagnosis of ulcerative colitis or Crohn's disease cannot be made reliably without pathologic examination of biopsy and/or surgical specimens. On the other hand, there are no histologic features that are by themselves diagnostically specific for these diseases. Therefore, optimal patient management requires close interaction between the treating clinician and the surgical pathologist. Nevertheless, in day-to-day practice, communication between these parties is often minimal, often only a few terse words jotted on a requisition form accompanying the specimen to be interpreted. This commonly produces frustration and dissatisfaction on both sides, and can hinder the diagnostic process.

Every standard surgical pathology textbook covers the characteristic histologic features of ulcerative colitis and Crohn's disease. However, there are instances in which atypical histologic patterns of disease involvement can make proper pathologic diagnosis difficult, particularly when only endoscopic biopsy specimens are being evaluated. This review centers on the problematic areas of histologic evaluation of IBD biopsies.

Characteristic Histologic Features of IBD in Biopsy Specimens

The histologic hallmarks of IBD in biopsy specimens are distortion of the normal crypt architecture and the presence of mixed inflammatory cell infiltrates in the lamina propria. The presence of both of these features, in the proper clinical context, is almost always a result of either ulcerative colitis or Crohn's disease. However, the possibility of another etiology must constantly be kept in mind of the surgical pathologist, particularly if some aspects of the clinical history, radiographic studies, or endoscopic findings are not supportive of a diagnosis of IBD. The histologic features supportive of a diagnosis of IBD are described in the following discussion.

Mucosal Architectural Changes

In normal colonic mucosa the crypts are arranged in straight and evenly spaced rows. Even at the time of the initial presentation of IBD, with symptoms of short duration, biopsies of involved segments will usually exhibit distortion of this normal crypt architecture (12-14). This is typically manifested by scattered branched and irregularly shaped crypts, as well as crypts that no longer extend all the way down to the muscularis mucosae. Assessment of crypt architecture is much easier in well-oriented biopsies. In poorly oriented biopsies the crypts are usually seen in cross section as doughnut-shaped profiles, which makes it difficult to evaluate branching and foreshortening. However, irregular spacing and variation in crypt diameter may still be observed in tangential sections.

A feature often associated with crypt architectural distortion is the presence of Paneth cell metaplasia. Paneth cells are normally present in the mucosa throughout the small intestine but in

the colon are limited to crypts of the cecum and ascending colon. In IBD Paneth cells may be present more distally, and their presence is a good marker of chronic colitis. In patients with inactive disease of very long duration crypt architectural distortion may become very subtle, to the point where the histologic (and endoscopic) appearance may be indistinguishable from normal. In this situation review of biopsies obtained during previous colonoscopic procedures may be necessary to confirm a diagnosis of IBD.

Crypt architectural distortion, while required for a histologic diagnosis of IBD, merely reflects the effect of long-standing mucosal inflammation and damage, and therefore can be present in any disorder causing chronic mucosal injury. For instance, biopsies from patients with chronic ischemic or radiation colitis typically exhibit crypt architectural distortion indistinguishable from that seen in IBD. Chronic infections, such as chronic *Clostridium difficile* colitis, may also produce crypt architectural distortion. Biopsies from the edge of a chronic ulcer of any etiology will demonstrate crypt distortion. Ulceration associated with *Entamoeba histolytica* is a classic example, but ulceration due to NSAID toxicity or stool impaction (stercoral ulcer) are more common in daily practice.

Inflammatory Changes

Normal colonic mucosa consists of surface and crypt epithelium between which lies a mixture of inflammatory cells, including lymphocytes, plasma cells, eosinophils and macrophages. In IBD there is an increase in lymphocytes and plasma cells in the lamina propria, often present as a band along the muscularis mucosae. This basal lymphoplasmacytosis is an important feature in the diagnosis of IBD because it is not prominent in bacterial colitis. Neutrophils, on the other hand, are present in both active IBD and bacterial colitis, and therefore have no discriminatory diagnostic value. However, the degree of neutrophilic inflammation is an indication of disease activity in IBD patients. Infiltration of neutrophils between crypt epithelial cells is known as “cryptitis”. When neutrophils completely transverse the crypt epithelium and accumulate within a crypt lumen, the term “crypt abscess” is applied. When effective medical therapy is instituted, the neutrophilic inflammation resolves first, followed by the lymphoplasmacytic infiltrates. During periods of inactive disease there may be no discernible increase in the number of lamina propria inflammatory cells, and the only residual histologic evidence of disease would be the distorted crypt architecture and Paneth cell metaplasia. A diagnosis of quiescent IBD is appropriate in such circumstances.

Characteristic Histologic Features of Bacterial Colitis in Biopsy Specimens

Many bacterial species can produce colitis, but most do not cause histologic changes that allow for a specific diagnosis. The term “acute self limited colitis” has been used to describe bacterial colitis in this situation. Biopsies are usually not performed unless the infection has been prolonged or has not resolved promptly to empiric antibiotic therapy. The infection is often waning by the time biopsies are obtained. Typically there is a mild neutrophilic infiltrate in the superficial lamina propria. Foci of cryptitis and crypt abscess may be present. Importantly, normal crypt architecture is well maintained, and basal lymphoplasmacytic infiltrates are not present. These features allow for distinction from idiopathic inflammatory bowel disease, which may have an initial clinical presentation indistinguishable from bacterial colitis. *Shigella*,

Salmonella, *Campylobacter*, *Yersinia* and *Aeromonas* species are the most common agents responsible for non-specific appearance of acute self limited colitis. As the name implies, these infectious usually resolve spontaneously or quickly respond to antibiotic therapy in immunocompetent hosts. Infection with any of these organisms can also occur in patients with pre-existing idiopathic inflammatory bowel disease. Unfortunately superimposed infection cannot be diagnosed by histologic examination, so cultures are necessary to exclude this possibility in any patient with sudden and unexplained relapse.

Some forms of bacterial colitis are more severe and produce characteristic histologic features. Colectomy may occasionally be necessary, usually because of uncontrollable bleeding or the threat of impending perforation. *Salmonella typhimurium* infection typically produces ulceration and necrosis of hyperplastic Peyer's patches in the terminal ileum and colon. Neutrophilic inflammation is inconspicuous but lymphohistiocytic infiltrates are prominent. Transmural necrosis may develop and is often associated with mesenteric lymphadenitis. *Yersinia enterocolitica* and *pseudotuberculosis* also exhibit a predilection for Peyer's patches and lymphoid follicles of the terminal ileum and right colon. Infection is characterized by necrosis of these structures, often with a striking element of granulomatous inflammation. Many cases of granulomatous appendicitis unrelated to Crohn's disease are due to *Yersinia* infection. *Campylobacter* infection is a very common cause of bacterial enterocolitis in the United States. Most often the appearance is non-specific, falling into the acute self limited colitis pattern. However, it is documented to produce toxic megacolon as well.

Histologic Distinction between IBD and Bacterial Colitis in Biopsies

The histologic features of bacterial colitis can overlap with those described previously for IBD. Definite distinction usually requires correlation with the clinical history, laboratory test results and colonoscopic features. Depending on the amount of this clinical data made available to the pathologist, a firm histologic diagnosis of IBD may be possible in some cases, while in others only a differential diagnosis can be given.

Most enteric bacteria (e.g. *E. coli*, *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*) produce a non-specific form of colitis, which in the past has been termed "acute self-limited colitis". Histologically there are neutrophilic infiltrates in the lamina propria, and in more severe cases there may be foci of cryptitis and crypt abscesses. These features are quite similar to those of IBD, although in infectious colitis the neutrophilic infiltrates tend to be more superficial. The key features in terms of distinction from IBD are the maintenance of normal crypt architecture and the lack of a basal lymphoplasmacytic infiltrate. However, these two histologic findings are difficult to assess in poorly oriented biopsies. The inflammatory changes in infectious colitis may be patchy or diffuse, so overlap with both ulcerative colitis and Crohn's colitis is possible. Gram stains performed on biopsy specimens are not useful since luminal bacteria are abundant in health. Instead, confirmation of the diagnosis requires a positive stool culture, which is obtained in only a minority of cases. Without a positive stool culture presumptive diagnosis rests on the self-limited clinical course or the resolution of symptoms with antibiotic therapy.

Skip Areas of Normal Mucosa and Rectal Sparing in Ulcerative Colitis

In the past the presence of skip areas of normal mucosa was considered to be a specific feature of Crohn's disease. This could take the form of a segment of normal colon between two affected portions, or the presence of normal epithelium adjacent to inflamed epithelium exhibiting crypt distortion in a single biopsy (microscopic skip area). Aphthous erosion or ulceration occurring in a background of normal mucosa represents the prototypic example of a skip lesion. It should be noted that the optical resolution of the latest generation of colonoscopes is such that normal lymphoid aggregates may be confused with small aphthous erosions, leading to an apparent discrepancy between endoscopic and histologic findings.

In the relatively recent era of routine colonoscopy and effective medical therapy for IBD it has become clear that healing ulcerative colitis can appear quite patchy endoscopically, simulating the appearance of Crohn's colitis. Fortunately, microscopic examination of these apparent "skip areas" of endoscopically normal mucosa in patients with treated ulcerative colitis usually reveals evidence of quiescent disease, as indicated by the presence of (sometimes subtle) crypt architectural distortion. However, patchy areas of completely normal mucosa have been documented in longstanding ulcerative colitis. Often this is a result of intensive long-term medical therapy. There are also cases in which skip areas of normal mucosa are definitely present from the onset (typically a segment in the transverse or descending colon), and yet all other clinical and histologic features are consistent with the diagnosis of ulcerative colitis. The clinical course in such a patient is almost always that of typical ulcerative colitis.

Topical steroid therapy delivered via enema has been convincingly demonstrated to result in complete resolution of active inflammation and regression of crypt architectural distortion in rectal biopsies from ulcerative colitis patients. Histologically documented rectal sparing at the onset of symptoms has been documented to occur in a subset of pediatric patients with ulcerative colitis. These patients may also have histologically patchy disease at presentation (10 to 34% in various studies). No clinical feature appears to separate children who present with rectal sparing from those who don't, although atypical histology may be more common in the youngest children. Usually over time these patients develop a more classic diffuse pattern of disease.

IBD in Patients with Primary Sclerosing Cholangitis (PSC)

Any patient diagnosed with PSC should undergo full colonoscopy in order to rule out IBD, even if there is no history of G.I. symptoms. Biopsies should be obtained throughout the colon even if there is no endoscopic abnormality, as there still may be histologic evidence of quiescent IBD. The histologic features of IBD in patients with PSC can be atypical. The disease is often more prominent in the right colon, can be quite patchy, and the degree of crypt architectural distortion can be subtle. In addition, "backwash ileitis" is not uncommon. Although all of these features are suggestive of Crohn's disease, the clinical course of IBD in the vast majority of PSC patients is that of ulcerative colitis (i.e., no perianal disease, strictures, fistulas, or upper G.I. involvement). PSC is among the strongest predisposing clinical features for the development of dysplasia in IBD patients.

Cecal Red Patch (“cectitis”)

Some patients with typical left-sided ulcerative colitis exhibit endoscopic and histologic evidence of an additional isolated focus of disease in the cecum, usually taking the form of a patch of inflamed mucosa near the appendiceal orifice and/or ileocecal valve. This so-called “cecal red patch” may be regarded as a skip lesion and therefore a feature favoring Crohn’s disease by those not aware of its occurrence in ulcerative colitis. Histologic sections from these endoscopically abnormal patches reveal changes typical of mildly active ulcerative colitis, with crypt architectural distortion and mild mixed inflammatory cell infiltrates. It should be remembered, however, that cecal biopsies normally contain more intense lamina propria inflammatory cell infiltrates than are present in biopsies from other parts of the colon. In fact, rare neutrophils may even be present normally in cecal mucosa.

There is no known epidemiologic association to explain the development of a cecal red patch, and it appears to be clinically insignificant. In most patients the cecal red patch remains as a stable endoscopic feature. However, in a subset of patient pancolitis ultimately develops.

Terminal Ileal Biopsies in IBD

Crohn’s disease can affect any portion of the gastrointestinal tract; but involvement of the terminal ileum is most common. The histologic features of Crohn’s ileitis are essentially identical to those evident in colonic biopsies. There is usually clearcut distortion of normal villous architecture at least focally. Mucous (pyloric) gland metaplasia is a reliable marker of long-standing inflammation and is common in ileal biopsies from patients with Crohn’s disease. However, mucous gland metaplasia has also been documented in biopsies of ileal ulcers from patients taking non-steroidal anti-inflammatory drugs.

Although ulcerative colitis is classically limited to the colon, some patients with pancolitis may exhibit so-called “backwash ileitis”. “Backwash ileitis” generally consists only of scattered neutrophils in the lamina propria and surface epithelium, with relative preservation of the mucosal architecture. However, the spectrum of ileal mucosal damage in backwash ileitis has not been well defined in the current era of routine colonoscopic ileal biopsies.

Segmental Colitis (“Sigmoiditis”)

There is a small group of patients with chronic colitis limited to the sigmoid colon that shares many clinical and histologic features typical of IBD. These patients tend to be middle aged or older and often have coexistent diverticular disease. While mild inflammation is not uncommon near diverticular orifices, these patients exhibit a diffuse colitis, often with linear ulcerations. Biopsies from the affected segment in such patients reveal prominent crypt architectural distortion and basal lymphoplasmacytic infiltrates typical of IBD. The changes may be patchy, resembling Crohn’s disease (with granulomas in a small minority), or diffuse, resembling ulcerative colitis. The terms “sigmoiditis”, “diverticular disease-associated colitis” have been applied in these cases. Biopsies from the rectum, by definition, are completely normal. Some patients subsequently develop clear-cut evidence of Crohn’s disease elsewhere in the

gastrointestinal tract; others develop rectal involvement and therefore are regarded as having ulcerative colitis; a small number continue to exhibit isolated sigmoiditis.

Differential Diagnosis of Mucosal Granulomas

Epithelioid granulomas are highly characteristic of Crohn's disease. Unfortunately, granulomas can be identified in biopsy specimens in less than 50% of Crohn's disease patients, limiting the utility of this feature. The routine examination of serial sections increases the likelihood of the identification of granulomas. Poorly formed granulomas can occur in association with ruptured crypt abscesses in ulcerative colitis, presumably in response to extravasated mucin. Examination of serial sections may be necessary to demonstrate the relationship between the damaged crypt and the granuloma. Also, in a tangential section the pericryptal fibroblast sheath can resemble a small granuloma.

There are a number of intestinal infections that can produce granulomatous colitis.

Mycobacterial intestinal infection can occur in a number of settings. It can result from dissemination of a severe pulmonary infection, a primary infection (usually of the ileocecal region) due to consumption of unpasteurized dairy products, or an infection of an immunocompromised host. Granulomatous inflammation is the hallmark finding, and can be seen in any bowel layer. Fibrosis and lymphoid hyperplasia are common, and a mass-like effect may be produced. The histologic differential diagnosis is usually limited to Crohn's disease and Yersinia or fungal infection. Granulomas exhibiting caseating necrosis are highly suggestive of mycobacterial infection, but are not uniformly present. Intestinal **mycobacterium avium complex** infection is more common than pulmonary involvement. Histiocytes containing numerous organisms are present in the lamina propria, but the mucosa is otherwise normal (specifically, granulomas are not seen in this infection). Lamina propria muciphages have a similar light microscopic appearance, so a high index of suspicion must be maintained. The organisms are usually easily highlighted by AFB stains. Schistosomiasis can produce colitis, but more frequently the larval forms cause a granulomatous and eosinophilic response without a significant neutrophilic component.

Mimics of IBD

There are a number of diseases that can cause clinical and pathologic confusion with IBD. On occasion the alert pathologist is the first to raise the possibility of a mimic of IBD, but usually it takes input from a variety of sources (radiographic studies, laboratory evaluations, additional clinical history) to arrive at the proper diagnosis.

Entameba histolytica is an important cause of colitis worldwide, although it is rare in the United States. Infection is acquired by the ingestion of food or water contaminated by fecal material containing cysts. Classically infection produces deep flask-shaped ulcers which can raise the possibility of Crohn's disease. In the early stage of disease only a mild diffuse colitis may be present, which might cause confusion with ulcerative colitis. The trophozoites can be identified if biopsies are obtained from ulcer bases. They resemble histiocytes but are slightly larger and have an internal structure; occasionally ingested red blood cells may be evident. A PAS stain is

useful to highlight the organisms, which are most often found within necrotic debris. Diagnosis by examination of stool samples or by serologic testing is also possible.

Systemic vasculitis can present with gastrointestinal involvement and produce bloody diarrhea. Endoscopy may reveal isolated areas of ulceration and therefore be confused with Crohn's disease. Microscopic polyangiitis, polyarteritis nodosa, and Churg-Strauss syndrome are among the most common forms of vasculitis to involve the G.I. tract. The vessels involved by vasculitis are usually not sampled by endoscopic biopsies, and interestingly, mucosal ischemic changes are sometimes not prominent. Diagnosis is often delayed until involvement of another organ system becomes evident clinically (e.g., kidney, skin).

Hypereosinophilic syndrome is a multiorgan disorder that sometimes involves the G.I. tract and liver, producing histologic changes that resemble ulcerative colitis and primary sclerosing cholangitis respectively. The diagnosis requires a markedly elevated peripheral blood eosinophilia, and a bone marrow biopsy to exclude eosinophilic leukemia.

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