Infectious mimics of inflammatory bowel disease

Feriyl Bhaijee
Christina Arnold
Dora Lam-Himlin
Elizabeth A Montgomery
Lysandra Voltaggio

Abstract

Given the considerable overlap between the clinical, endoscopic, and histologic features of infectious colitides and inflammatory bowel disease (IBD), correct classification of chronic colitis requires thorough clinical and pathologic evaluation of affected patients. Herein, we discuss a pattern-based approach to colitis, classification of IBD, and infectious mimics of IBD. Infectious mimics of IBD include bacterial pathogens (*Shigella*, *Campylobacter*, *Salmonella*, shiga toxin-producing *Escherichia coli*, *Yersinia*, *Aeromonas*), tuberculous and non-tuberculous mycobacterial infections, sexually transmitted proctocolitis (syphilis, lymphogranuloma venereum), amoebiasis, and the recently described cord colitis syndrome. The histologic finding of chronic active colitis should be considered *infectious until proven otherwise* in order to detect treatable, curable conditions and prevent exacerbation by inappropriate immunomodulatory therapy. Family and medical histories, signs and symptoms, radiologic and endoscopic features (especially disease distribution), and serologic/ancillary studies for markers of infection are invaluable tools that aid in the distinction between infectious colitis and IBD.

Keywords Crohn; histopathology; infection; inflammatory bowel disease; mimics; ulcerative colitis

Introduction

A pattern-based approach to colitis (Table 1, Figure 1)

Focal active colitis (FAC): this histologic pattern is characterized by focal neutrophilic cryptitis without features of chronicity (Figure 2). FAC may be identified as a single crypt abscess, isolated cryptitis or multifocal cryptitis. By definition, segmental distribution and crypt architectural distortion are absent. Aetiologic considerations for this pattern include acute self-limited colitis which may be due to infection, medications like non-steroidal anti-inflammatory drugs (NSAIDs), chemicals/irritants, and bowel preparation artifact.

Acute colitis: this histologic pattern is similar to FAC but more severe or diffuse. Features include cryptitis, crypt abscesses, erosions, and ulcerations in the absence of crypt architectural distortion (Figure 3). While non-specific, this pattern of injury may be associated with acute viral and bacterial infections (cytomegalovirus, *Salmonella*, *Shigella*, *Campylobacter*, *Clostridium difficile*), medications (NSAIDs, Kayexalate, sevelamer, ipilimumab), and emerging or partially treated inflammatory bowel disease (IBD).

Chronic colitis: histologic changes of chronicity include lymphoplasmacytic lamina propria expansion, Paneth cell metaplasia, pyloric gland metaplasia, basal lymphoplasmacytosis, and architectural distortion (villonodular surface, abnormal crypt configuration, crypt dropout, crypt shortfall). In the authors' experience, cases of IBD are characterized by marked architectural distortion wherein glands bear no resemblance to normal colonic crypts (Figure 4). While some architectural distortion may be seen in other settings (e.g. diverticular associated colitis, diversion-associated colitis, sexually transmitted proctocolitis, cord colitis syndrome), dramatic architectural distortion is more often associated with IBD.

When confronted with a case of colitis, the process should be (i) classified as acute colitis vs. active chronic colitis vs. inactive chronic colitis, and then (ii) graded as mild, moderate, or severe. The first step is facilitated by identifying and categorizing features of acute and chronic colitis, as detailed above. The second step, while purely morphologic, is somewhat more subjective, especially in cases of acute or active chronic colitis. As there is currently no universally accepted, consistent and reproducible method of grading the degree of activity in mucosal biopsies, most pathologists use a 3-tiered descriptive classification (mild, moderate, and severe). In an attempt to move toward a unifying grading scheme, we recommend the Histologic Activity Index (HAI) for grading the severity of inflammation in IBD, which was developed by Noam Harpaz and has been routinely used at The Mount Sinai Hospital since 1988.[1] These relatively simple histologic criteria result in the following scores for each colonic mucosal biopsy: 0, inactive/quiescent/normal (no epithelial infiltration by neutrophils); 1, mildly active (neutrophilic infiltration of $<50\%$ of sampled crypts or cross section, no ulcers or erosions); 2, moderately active (neutrophilic infiltration of $>50\%$ of sampled crypts or cross section, no ulcers or erosions); and 3, severely active (erosion or ulceration, irrespective of other features).

Clinicopathologic correlation is attempted for every case and is intended to share the pathologist's perspective on the particular mucosal injury pattern. It addresses the unique features of the case in question and often requires communication with the clinical team or interaction with the electronic health record. These endeavours often add great value by providing a context for our descriptive diagnoses and offer guidance on clinical management.

Feriyl Bhaijee *MD Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA. Conflicts of interest: none.*

Christina Arnold *MD Department of Pathology, The Ohio State University Wexner Medical Center, Columbus, OH, USA. Conflicts of interest: none.*

Dora Lam-Himlin *MD Department of Laboratory Medicine and Pathology, Mayo Clinic, Scottsdale, AZ, USA. Conflicts of interest: none.*

Elizabeth A Montgomery *MD Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA. Conflicts of interest: none.*

Lysandra Voltaggio *MD Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA. Conflicts of interest: none.*

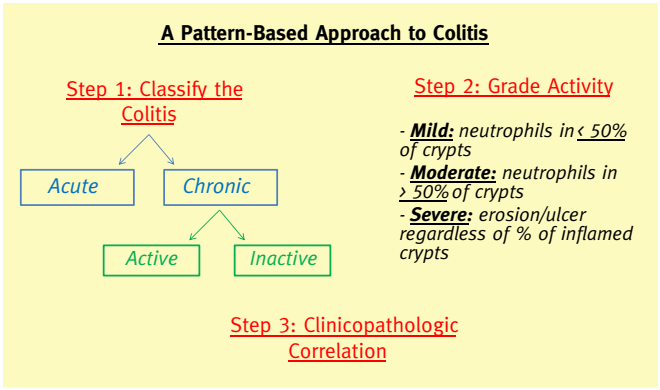

Figure 1 A pattern-based approach to colitis diagram. Adapted from Arnold, Lam-Himlin, and Montgomery. Atlas of Gastrointestinal Pathology. A Pattern Based Approach to Non-Neoplastic Biopsies. (2015) Philadelphia, USA. Wolters Kluwer.

Classification of IBD: ulcerative colitis vs. Crohn disease

There are many reasons why pathologists should attempt to establish a correct of diagnosis of UC or CD in affected patients.[2] Firstly, these distinct disease entities vary in their respective aetiology, natural history, need for surgical intervention, medical management, risk of other diseases (e.g. primary sclerosing cholangitis), and incidence of extra-colonic involvement. Secondly, rates of familial involvement differ between UC and CD. Finally, and most importantly, UC patients respond well to total colectomy with ileal pouch anal anastomosis while CD is a relative contraindication to this procedure because of the high risk of pouch complications.

The distinction between UC and CD is normally based on evaluation of various clinical, radiologic, endoscopic, and pathologic findings. Clinical features such as family history, symptoms/signs, serology, and perianal involvement often raise suspicion for either UC or CD, which is further buttressed by radiologic evidence of disease distribution and the presence or absence of strictures, fistulae, or creeping fat. Endoscopic evaluation of disease distribution and severity, as well as terminal ileal involvement, offers further diagnostic information prior to pathologic assessment of mucosal biopsies.

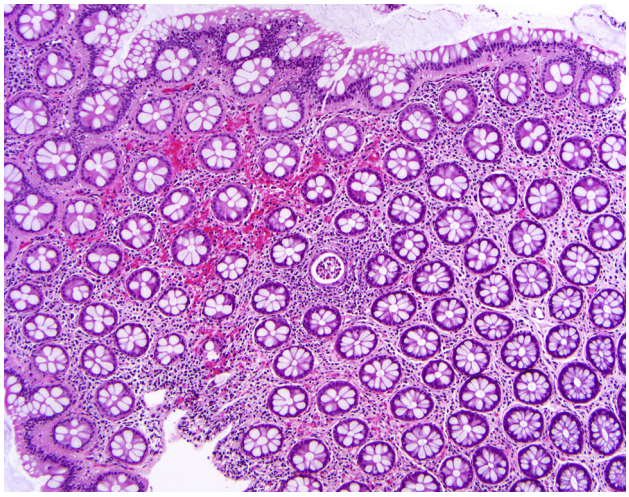

Figure 2 Focal active colitis. A single crypt abscess is seen here in the center of the field. Notice the intact architecture with crypts equidistant to one another. The lamina propria is not expanded.

The classic histologic features of UC vary between pre- and post-treatment specimens. At initial presentation, UC shows diffuse continuous disease with invariable proctitis in adults. Disease severity usually decreases from distal to proximal sites with only occasional terminal ileal involvement (distal 1–5 cm). Inflammatory activity is mostly superficial (i.e. mucosal) with only rare transmural lymphoid aggregates restricted to areas of ulceration. Fissures are likewise rare but can be seen in fulminant colitis, occasionally resulting in perforation. Sinuses and fistulae are absent and granulomata are only seen in relation to ruptured crypts (Figure 5). Following treatment, the disease distribution may become patchy or discontinuous with variable rectal involvement and variable severity from distal to proximal sites.

The classic histologic features of CD in both pre- and post-treatment specimens include patchy/segmental or continuous disease distribution with occasional rectal involvement, patchy and variable disease severity throughout the GI tract, and frequent terminal ileal involvement (>5–10 cm). Inflammatory activity may be superficial or transmural with scattered lymphoid aggregates. Deep fissures resulting in perforation are more common than in UC, and sinuses and fistulae are often present. Notably, non-necrotizing epithelioid granulomata, present in almost half of all CD cases, are usually scattered throughout the bowel wall and are not associated with ruptured crypts or extravasated mucin.

While mucosal biopsies are required to distinguish between acute (self-limited) colitis and chronic colitis, these specimens are typically superficial and thus unable to disclose important histologic features, such as the depth of disease activity, transmural lymphoid aggregates, fissuring ulcers, sinus tracts, and submucosal fibrosis. Moreover, the mucosal features of UC and CD are often indistinguishable, as active disease (e.g. cryptitis, crypt abscesses, erosion, ulceration) and features of chronic injury (e.g. basal plasmacytosis, lymphoplasmacytic expansion of the lamina propria, architectural distortion, and left-sided Paneth cell metaplasia) are seen in both entities. Thus, especially in treated patients, the mucosal features of UC and CD are often indistinguishable. Following treatment, only granulomata and ileitis not related to backwash, infection, medications, or bowel prep can be used to favour CD. In untreated patients, however, the following features are suggestive of (or consistent with) CD: patchy disease, deep fissures, transmural inflammation, rectal sparing (in adults), CD-like ileal or upper gastrointestinal tract involvement, granulomata, and anal/perianal disease. In the absence of these features, and in the presence of diffuse colonic involvement or continuous left-sided or sub-total colitis, UC is favoured.

In cases of diagnostic difficulty, when a pathologist is unable to definitively diagnose UC or CD due to overlapping histologic features, a diagnosis of “indeterminate colitis” or “IBD, unclassified” may be rendered. This interim diagnosis, which is used in 1–20% of IBD cases, exists until further information (clinical, radiologic, or pathologic) or follow-up data allow definite classification. Ultimately, the majority of indeterminate cases represent UC, thus most of these patients are candidates for a