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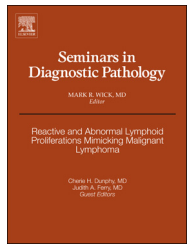

Histologic mimics of inflammatory bowel disease

*Lei Zhao, MD, PhD, John Hart, MD**

Department of Pathology, University of Chicago Medical Center, 5840 S. Maryland Ave., MC6101 Chicago, Illinois 60637

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ABSTRACT

This review summarizes a variety of clinical and histologic mimics of idiopathic inflammatory bowel disease. All the entities that are included demonstrate one or more histologic features typical of idiopathic inflammatory bowel disease that may lead to potential diagnostic confusion and misinterpretation by the pathologist. The elements of the clinical history, laboratory test results, and endoscopic findings that are helpful to the surgical pathologist in considering a diagnosis other than idiopathic inflammatory bowel disease are emphasized. On occasion, a poor response to standard treatment for idiopathic inflammatory bowel disease is the clue that prompts reconsideration of the initial diagnosis. Subtle histologic features, special stains, or other diagnostic methodologies that can aid in proper diagnosis are also discussed.

Introduction

Chronic mucosal injury is characterized by crypt architectural distortion, basal lymphoplasmacytosis, pyloric metaplasia, and Paneth cell metaplasia in the left colon. Most cases of chronic colitis in the United States represent idiopathic inflammatory bowel disease, the most common types of which are ulcerative colitis and Crohn disease. Rectal involvement, diffuse and continuous involvement of the colon, and ileal sparing are characteristic of ulcerative colitis; whereas granulomata, transmural inflammation, fissuring ulcers, aphthous erosions, skip areas composed of normal mucosa, and frequent small bowel involvement are typical features of Crohn disease. None of these findings are pathognomonic for idiopathic inflammatory bowel disease and, thus, extensive differential diagnoses should be considered when one, or more, of the aforementioned findings is present in endoscopic biopsy specimens (Table). This review focuses on conditions that simulate ulcerative colitis and Crohn disease in pathology specimens.

Infectious colitis

Bacterial pathogens

Most bacterial pathogens produce an acute self-limited colitis histologic pattern that is rarely confused with that of idiopathic inflammatory bowel disease (Fig. 1A). However, some organisms routinely produce endoscopic abnormalities that raise the possibility of idiopathic inflammatory bowel disease and persistent infection with any organism can cause histologic changes of chronic colitis.[1] *Campylobacter jejuni* is the most common bacterial pathogen causing colitis. Infections with this agent generally do not produce endoscopically evident mucosal changes, but severe disease may cause mucosal erythema, edema, and scattered aphthous ulcers in the distal colon that resemble features of ulcerative colitis.[2] *Shigella* and shiga-like toxin-producing *Escherichia coli* strains, including O157:H7, cause segmental injury that clinically mimics Crohn disease. The toxin damages vascular endothelium, leading to reduced production of anticoagulant factors

* *Corresponding author*.
E-mail address: john.hart@uchospitals.edu (J. Hart).

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Table – Conditions to consider in the differential diagnosis of idiopathic inflammatory bowel disease.

Differential diagnosis based on endoscopic findings
Proctitis
Sexually transmitted diseases
Severe *Campylobacter* infection
Mechanical trauma
Pancolitis
Common variable immunodeficiency
Henoch–Schönlein purpura
Eosinophilic gastroenteritis (hypereosinophilic syndrome)
Aphthous erosions or discrete ulcers
Infections
Medications
Ischemia due to any cause
Patchy involvement of gastrointestinal tract
Medications
Ischemia
Diverticular disease-associated colitis
Cryptogenic multifocal ulcerous stenosing small bowel disease
Terminal ileitis
Infectious enterocolitis (*Yersinia*, *Salmonella*, and tuberculosis)
Non-steroidal anti-inflammatory drugs
Isolated terminal ileal ulcers
Cryptogenic multifocal ulcerous stenosing small bowel disease
Inflammatory changes associated with specific etiologies
Crypt and cellular changes of chronic injury
Infectious enterocolitis
Medications
Vasculitis
Diverticular disease-associated colitis
Common variable immune deficiency
Lymphoplasmacytic infiltrates without prominent neutrophils
Infectious colitis (lymphogranuloma venereum, syphilis, and *Salmonella*)
Medications
Systemic mastocytosis
Eosinophilic gastroenteritis (hypereosinophilic syndrome)
Langerhans cell histiocytosis
Granulomata or granulomatous inflammation
Infections (tuberculosis, *Yersinia*, *Salmonella*, and *Histoplasma*)
Medications
Cord colitis
Chronic granulomatous disease
Sarcoidosis
Hermansky–Pudlak syndrome
Common variable immune deficiency

and formation of microthrombi. Histologic features include crypt withering, fibrin deposits in the lamina propria, extensive ulcers, and hemorrhage. Thus, the differential diagnosis of colitis due to enterohemorrhagic *E. coli* and similar pathogens includes other causes of ischemic colitis, rather than idiopathic inflammatory bowel disease. On the other hand, *Salmonella typhi*, *Yersinia enterocolitica*, and *Yersinia pseudotuberculosis* can all cause endoscopic and histologic changes that simulate idiopathic inflammatory bowel disease, especially Crohn disease. All three pathogens produce punched-out or longitudinal ulcers in the ileum and right colon, and all may elicit crypt architectural abnormalities of chronic injury.[1,3–7] *Y. enterocolitica* and *Y. pseudotuberculosis* elicit prominent lymphoid hyperplasia and epithelioid granulomas that simulate Crohn disease. However, granulomatous inflammation due to these organisms also contains centrally located, neutrophil-rich microabscesses that are not typical of Crohn disease and represent a helpful diagnostic clue.[8] Routine stool cultures can identify *Shigella*, *Salmonella*, and *Campylobacter* infections and often include a shiga toxin assay to detect toxin-producing enterohemorrhagic *E. coli*. Detection of *Yersinia* and *Aeromonas* requires special culture methods.[9]

Mycobacterial infection

Intestinal tuberculosis shows a predilection for the ileum, either in isolation or with concomitant cecal colitis. Only 30% of affected patients have primary pulmonary infections.[10] Endoscopic findings include ulcers, nodular inflammation, intestinal wall thickening, and strictures, all of which can be easily mistaken for Crohn disease and lead to inappropriate treatment with corticosteroids or anti-tumor necrosis factor-alpha preparations that exacerbate infection.[11] Biopsies exhibit crypt architectural distortion, basal lymphoplasmacytic infiltrates, and both necrotic and non-necrotic granulomata. The presence of necrotic granulomata is atypical in Crohn disease cases and should alert the pathologist to the possibility of an infectious etiology (Fig. 1B). Acid-fast stains performed on formalin-fixed biopsy sections may have a low yield in cases with scant granulomatous inflammation, so additional diagnostic testing is often required for the diagnosis.

Sexually transmitted diseases

Sexually transmitted diseases should be considered in the differential diagnosis when patients present with isolated proctitis, particularly in the appropriate clinical context. Most of these infections occur in immunocompetent patients, but they also affect patients with immunodeficiency, including those with acquired immunodeficiency syndrome. It is important to remember that immunodeficient patients rarely develop *de novo* immune-mediated diseases, such as idiopathic inflammatory bowel disease and, thus, one should always be suspicious of infection when chronic colitis is encountered in such individuals. The most common causative agents of infectious proctitis are *Neisseria gonorrhea*, *Treponema pallidum*, and *Chlamydia trachomatis*.[12]

Patients with syphilitic proctitis are usually men who have receptive anal intercourse with other men. They present with tenesmus, diarrhea, and bloody stools. Biopsies reveal mucosal and submucosal lymphoplasmacytic infiltrates associated with variable crypt architectural distortion. Inflammatory infiltrates are most prominent around the vessels (Fig. 1C).[13] Features that should lead one to suspect an infectious etiology, rather than idiopathic inflammatory bowel disease, include the disparity between intensity of inflammation and crypt architectural abnormalities, as well as a tendency for infections to elicit perivascular inflammation with endothelial cell activation. An immunostain for *T. pallidum* is more sensitive and easier to interpret than silver stains (Fig. 1D).

Lymphogranuloma venereum (LGV) proctitis is caused by *C. trachomatis* L1, L2, and L3 and develops when the rectum is