REVIEW

Different forms of colitis: Determinate or indeterminate?

Kolitin değişik formları: Determinant veya indeterminant?

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The diagnosis of different forms of colitis involves differentiation from a variety of diseases, all causing gastrointestinal inflammation (1). Interpretation of colorectal biopsies, therefore, can be very difficult even for the experienced gastrointestinal pathologist (2). In the best of circumstances, analysis of the biopsy specimen, in conjunction with an interpretation of the clinical data, will yield a definitive diagnosis. More often, however, because of the limitation on the patterns of tissue response to a varied range of insults, the biopsy serves to narrow down the differential diagnosis instead of providing a specific diagnosis (2).

Despite the use of many sophisticated means of diagnosis, less than 50% of the cases will prove to have a microbiological cause. A proportion of the remaining cases will have or eventually develop a spectrum of changes that will substantiate a diagnosis definitive for ulcerative colitis (UC) or Crohn's disease (CD). The rest will continue to pose a significant problem, even though within this group there are many well-defined entities, such as collagenous colitis (3), lymphocytic colitis (4,5), diversion colitis (1), mucosal prolapse syndrome (6), eosinophilic colitis (7), colitis in diverticular disease (8), obstructive colitis (8), and ischemic colitis (3). There remains a group of cases of colitis with features suggestive of idiopathic inflammatory bowel disease (IIBD), but not specific for either UC or CD: the indeterminate colitis (IC) category (6,7,9).

IDIOPATHIC INFLAMMATORY BOWEL DISEASE (IIBD)

Patients with UC and CD share many similarities, but there are also many significant differences that make a distinction necessary. Different surgical approaches are being used for their treatment, and as a result, the pathologists are under great pressure when making a diagnosis of IIBD (2,4,10). When fully developed, the two diseases have distinguishing features: crypt architectural distortion, increased number of mononuclear cells and neutrophils in the lamina propria, a villous surface, crypt atrophy, and basal plasmacytosis are suggestive of UC, whereas presence of granulomas, focal active inflammation in one piece of the biopsy and normal mucosa in the other, and preservation of colonic mucin in the epithelium may suggest a diagnosis of CD (11). It is also important for the pathologist to decide whether the inflammation is acute or chronic, together with the extent of the disease and its severity (12,13). Obvious acute or active changes in IIBD include surface erosions or ulcers accompanied by neutrophilic infiltrates of the crypts or lamina propria. Cryptitis and crypt abscesses are common findings in the active stages of IIBD. In chronic IIBD, colitis mononuclear infiltration predominates with crypt architectural distortion and branching. There is usually goblet cell depletion in UC, though they are well preserved in CD. However, all the above features lack specificity for either disease and make the differential diagnosis a very difficult one for the pathologist (11,14,15).

In order to overcome the difficulty in the differential diagnosis of various forms of colitis with overlapping features, it might be useful to analyze the different patterns of inflammation and classify the diseases accordingly. In chronic colitis, for instance, one can observe mucosal atrophy with architectural distortion and irregular luminal surface. These changes may suggest a diagnosis of chronic UC, but similar changes can also be seen in CD, ischemia, chronic radiation injury, and tuberculosis. When an active colitis is encountered in a biopsy specimen, UC, CD and infectious/acute self-limited colitis should all be included in the differential diagnosis. A diffuse active colitis pattern is consistent with untreated, active UC when accompanied by crypt distortion and basal plasmacytosis

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to differentiate from infectious/acute self-limited colitis. However, CD and colitis associated with diverticular disease can also show diffuse active colitis sparing the rectum. A focal active colitis pattern, on the other hand, is suggestive of CD or infectious/acute self-limited colitis. However, it may also be seen in UC under medical treatment. Focal crypt injury as cryptitis and crypt abscesses occur commonly in several diseases, including ischemia, infections, UC, and obstructive colitis, and in patients on non-steroidal antiinflammatory drugs (NSAIDs). More subtle changes include mild surface damage, red cell extravasation into the lamina propria and mucosal edema, which accompany early ischemia, toxic injury such as drugs and radiation, and some infections (11,16-19).

INDETERMINATE COLITIS (IC)

Despite several classification systems and sophisticated diagnostic tools, the differentiation between UC and CD can still be difficult. In approximately 10% of cases, no differentiation can be made, and these cases are classified as IC. IC is even more marked in children than in adults, and further complicated by the fact that upper gastrointestinal disease (gastric or duodenal disease, or both, but lacking granulomas on biopsy) can be seen in patients in whom UC seems to be the most likely diagnosis clinically. However, the upper gastrointestinal pathology tends to resolve, though less commonly in adults (6%–12%) compared with children (20%–75%) (20,21).

The concept of IC, first introduced by Mahadeva (14),

Inflammation patterns in different forms of colitis

Inflammation pattern	Diagnostic features	Disease/Clinical condition
Diffuse active colitis	Neutrophils predominate	Acute self-limited colitis
	Cryptitis, crypt abscesses	Infectious colitis (Yersinia, Shigella, Salmonella, Campylobacter, amoebic colitis)
	Surface epithelial damage	NSAIDs
	No architectural distortion	Hypertonic enemas
		CD
	Crypt distortion	Untreated UC
	Basal plasmacytosis	
	Pseudomembrane	Ischemic colitis
		Antibiotic-associated colitis
Focal active colitis	Focal cryptitis	CD
	Discontinuous inflammation of lamina propria	Acute self-limited colitis
		Infectious colitis (Yersinia, Shigella, Salmonella, Campylobacter, amoebic colitis)
		UC under medical treatment
		Ischemic colitis
		Obstructive colitis
		NSAIDs
Acute colitis with mucosal injury	Neutrophils predominate	Ischemic colitis
	Edema	Antibiotic-associated colitis
	Focal surface epithelial necrosis	Drug reaction
		Vasculitis
	Preservation of crypt outlines	Behçet's colitis
	Pseudomembranes	
Mild colitis	Mild surface destruction	Early ischemia
	Mild lamina propria infiltration of lymphocytes and neutrophils	Drug reaction (NSAIDs)
	Edema	Radiation colitis
	Red cell extravasation	Infectious colitis
	Increased intraepithelial lymphocytes	Lymphocytic colitis
	Subepithelial collagen band	Collagenous colitis

CD: Crohn's disease, UC: Ulcerative colitis, NSAIDs: Nonsteroid antiinflammatory drugs

was based on surgical specimens in which features of both CD and UC were detected, but the cases were neither typical UC nor CD. Patients in this group have common features: they require urgent surgery, and have total colitis with rectal sparing. The ulceration is severe, deep and histologically nonspecific. The intervening mucosa is well preserved. Since its first description, there have been many cases in the literature presenting with milder forms of colitis. Since there is very little information concerning the long-term outcome of patients diagnosed as IC, the diagnosis is often considered as temporary (6,15). There are several studies showing that a varying number of cases with a diagnosis of IC have eventually been classified as either CD or UC. Patients with IC require colectomy, and their pouch failure rates are much higher than in UC patients, with a higher frequency of relapse and increa-

Inflammation patterns in different forms of colitis

Inflammation pattern	Diagnostic features	Disease/Clinical condition
Chronic active colitis	Surface irregularity	UC
	Predominantly mononuclear inflammatory infiltrates with basal plasmacytosis	CD
	Cryptitis, crypt abscesses	IC
	Crypt branching and distortion	Diversion colitis
	Lymphoid hyperplasia	Prolonged infectious colitis (Campylobacter, Shigella, Yersinia, amoebic colitis)
	Epithelial mucus depletion	Drug reaction (NSAIDs)
		Diverticular disease-associated colitis
		Ischemia
		Radiation colitis
	Lamina propria fibrosis	Mucosal prolapse syndrome
	Smooth muscle fibers in the lamina propria	Chronic ischemia
		Radiation colitis
Chronic inactive colitis	Minimal inflammation	Inactive UC
	Edema, fibrosis in lamina propria	Inactive CD
		Mucosal prolapse syndrome
	Crypt distortion	Chronic ischemia
Chronic colitis with crypt regeneration	Mononuclear cells predominate	Graft-versus-host disease
	Lymphocytic infiltration of crypt epithelium	Immunosuppressive agents
	Crypt apoptosis	Viral infections
	Hyalinosis and fibrosis of lamina propria	Ischemic colitis
		Radiation colitis
Eosinophilic colitis	Eosinophilic infiltrates with or without crypt destruction	Food allergy
		Drug allergy
		Parasitic infections
		Idiopathic eosinophilic enteritis
		Hypereosinophilic syndrome
		Vasculitis
		CD
		UC
Colitis with a nonspecific ulcer	Isolated ulcer with granulation tissue base	NSAIDs
	Mild colitis in the surrounding mucosa	Oral contraceptives
		Vasculitis
		Cytomegalovirus
		Behçet's colitis
		Obstructive colitis

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sed risk of cancer (7,22). Technological advances based on genetic markers and a better knowledge of immune responses have allowed a better characterization. The latter has led to the development of serologic tests that are used for diagnostic purposes. Overall, perinuclear antineutrophil cytoplasmic antibodies (pANCA) are associated with UC, while anti-Saccharomyces cerevisiae antibodies (ASCA) and outer membrane protein C (Ompc) are more commonly positive in CD. The combinations ASCA+/pANCA- and ASCA-/pANCA+ are strongly associated with CD and UC, respectively. In a prospective study of 97 patients with clinical IC, a 48% positive predictability of ASCA-/pANCA- was found for sustained IC (23). In the population-based IBSEN study, however, no substantial number of IC patients with the pattern of pANCA-/ASCA- was found (24). Further data are needed to assess the value of serologic testing in adults and in children, where they may be less useful (25).

A practical approach to the differential diagnosis of various forms of colitis is presented below (see Table). The success of this approach depends on pattern recognition. Determining the pattern of inflammation in the colonic biopsy will then help to classify the colitis into a specific diagnostic category.

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