

Use of ileocolonic biopsies in the evaluation of diarrhea in infants and children

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Pediatric inflammatory bowel disease: ulcerative colitis (UC) and Crohn's disease (CD)

A. Pathologic findings

The pathologic features of UC and CD are identical in children and adults and have been codified in many recent reviews. Classic UC begins in the rectum and, if it progresses, does so in a continuous retrograde fashion. Although by definition UC is confined to the colon, it may be accompanied by superficial mild non-specific mucosal inflammation in the terminal ileum ("backwash ileitis"). At microscopy, the inflammatory process in UC is superficial (confined to the mucosa and submucosa) and is diffuse within the mucosa of the involved segment (1, 2).

In contrast, colonic CD typically begins as localized right-sided or multifocal disease and progresses in a patchy fashion, with "skip areas" of uninvolved mucosa. Characteristic histologic findings include granulomas, deep or transmural inflammation (often characterized by the presence of lymphoid aggregates in the muscularis propria and/or at the muscularis/serosal interface), deep mural fissures or fistulas, and, in a minority of patients, a necrotizing or giant cell vasculitis. In the mucosa, the inflammatory lesions are often focal rather than diffuse (1, 2).

Although diagnostically important, granulomas are not invariably present in otherwise typical cases of Crohn's colitis. Even with serial sectioning, granulomas are detected in only approximately one-third of mucosal biopsy specimens from patients with Crohn's colitis. However, granulomas have been found in 56% to 82% of CD colonic resections. This higher yield is related to the greater amount of tissue available for examination and to the fact that the submucosa is the most common site for granuloma formation. In children with Crohn's colitis, granulomas tend to be more common in the rectosigmoid than elsewhere in the colon. Also, prospective data suggest that the prevalence of granulomas decreases with increasing duration of disease, perhaps due to the effects of medical therapy; thus, granulomas may be more often detected in children than in adults (3).

The sarcoid-like granulomas characteristic of CD must be distinguished from foreign body-type granulomas and from the non-specific mucin granulomas that may be present in both UC and CD. Mucin granulomas are typically adjacent to or in direct contact with inflamed or ruptured crypts, tend to be poorly formed and often contain giant cells (1, 2). Their true nature can be determined by detection of intracytoplasmic mucin using stains such as the alcian blue-PAS with diastase pretreatment.

In mucosal biopsy specimens from untreated patients, the presence of non-mucin granulomas or microgranulomas and focality of colitis are the best discriminators for CD (4). Focality of colitis in the rectosigmoid in children, however, should be interpreted with caution since it may be present at the onset of UC in this population (see later discussion). The pathologist can offer the largest amount of useful information if, at the onset of pediatric IBD, colonoscopy (rather than flexible sigmoidoscopy) with protocol sampling of even endoscopically unremarkable mucosa is performed. Of 42 pediatric patients ultimately proven to have IBD in one recent study, 10 had normal rectosigmoid biopsy specimens. Additional, more proximal, sampling confirmed a diagnosis of CD in 60%; the remaining four patients were later classified as either UC or indeterminate colitis (5).

B. Unusual features in rectosigmoid mucosal biopsies at the onset of pediatric UC

At first presentation and before therapy, the majority of adult patients with UC (>90%) will have diffuse active colitis, usually with features of chronicity, in rectosigmoid mucosal specimens. Initial rectosigmoid specimens in children ultimately shown to have UC, however, demonstrate focal colitis and/or the absence of chronic changes in approximately one-third of patients and are completely normal in 4% to 8% (6-8).

These atypical findings are not specifically related to the patients' ages at the onset of colitis (although they are predominantly found in patients younger than 10 years), the duration of symptoms before endoscopy, the symptoms themselves, or the ultimate evolution of UC (i.e., development of diffuse distal disease, proximal progression over time). The reasons for these findings are unknown. One suggestion is that children may be evaluated earlier in the course of UC than adults; however, it is also clear that changes of chronicity may develop within a few weeks or months of symptom onset (9, 10).

This presentation of UC with focal disease and a paucity or lack of features of chronicity in pediatric patients raises several diagnostic possibilities and stresses the need for a complete evaluation of the patient. First, it should be recognized that ulcerative colitis is not excluded by these findings. Second, they may represent a non-relapsing, infectious-type colitis, which often is patchy and may have rectal sparing. Crohn's disease also enters the differential diagnosis; detection of focal proximal colitis, granulomas, ileal disease or perianal disease would support that diagnosis.

The predictive value of focal active colitis for development or recognition of CD once the confounding conditions discussed in the preceding paragraph have been eliminated has recently been examined. In a cohort of 29 pediatric patients with focal active colitis, 8 (28%) developed CD; most of the remainder had either infectious colitis or remained idiopathic (11). In contrast, focal active colitis in adults evolved into a diagnosis of CD over time in fewer than 15% of patients (12, 13). One possible reason for the difference in outcome between the two populations is that unlike the case in adults, colonoscopy in children is typically performed for evaluation of abdominal pain, diarrhea or hematochezia rather than cancer surveillance, thus creating a bias towards detection of inflammatory diseases.

C. Effects of medical therapy on the histology of UC in colonic mucosal biopsy specimens

The classic teaching has been that quiescent UC heals with fixed morphologic changes that permit continued recognition of the colonic mucosa as injured. In 1993, however, Odze and colleagues demonstrated that medical therapy of left-sided UC with topical 5-aminosalicylic acid caused reversion of colonic mucosa to a normal appearance in 64% of patients (14). Since that time, several authors have confirmed and extended this observation. The results of these studies document that in patients with established extensive or pancolitis receiving contemporary medical therapy, histologic diffuse disease has become focal within the colon in up to 54% of patients and the rectum has become unremarkable in up to 34% on one or more occasions during follow-up (summarized in reference 15). These results were not related to the duration of disease or the type of therapy employed (systemic, topical, et cetera).

Rectal sparing and focal colitis are typical of CD. Thus, to avoid diagnostic confusion, it is important to know the medication history of patients with presumed UC in whom such findings are documented. In both children and adults with chronic IBD, unfortunately, such information is often not available at the time of biopsy specimen interpretation. In this situation and in the absence of granulomas, focality and rectal sparing should be described but not interpreted, with the comment that prior medical therapy may have affected the histologic findings.

D. Upper gastrointestinal tract involvement in pediatric inflammatory bowel disease

In contemporary medical practice, upper gastrointestinal endoscopy with biopsy is often performed before the institution of therapy in pediatric patients with newly diagnosed colonic IBD (both UC and CD). This procedure has led to some interesting findings. The protocols and the extent of histologic sampling have not been uniform in these studies, but most are prospective in nature.

Although the gross and microscopic abnormalities are not always described in detail, an intriguing finding in these studies is that the overall prevalence of endoscopic and histologic inflammatory lesions in the esophagus, stomach and duodenum is roughly equal in patients with newly diagnosed and typical colonic UC and CD. When known causes of such inflammation (such as reflux esophagitis and *Helicobacter pylori*-associated gastritis) are excluded, there still remains a high prevalence of non-specific lesions, particularly *H. pylori*-negative diffuse gastritis, in both conditions (16-19). Whether this gastritis is incidental or related to IBD is unknown, but the important point is that the mere presence of upper gastrointestinal inflammatory lesions can no longer be used to automatically categorize a patient as having CD.

The presence of granulomas in upper intestinal mucosal biopsies is highly specific for a diagnosis of CD. Their prevalence has varied from 25% to 60% in recent pediatric series, and they are most often found in gastric mucosa (16-19). In contrast, they are much less common in the stomach of adults with CD (a prevalence of only 5% in the study of Parente and colleagues) (20). In children, they are often detected in gastric and duodenal specimens even when synchronous colonic mucosal biopsies are negative for this finding (15, 17, 18).

Although focal gastritis can be seen in a minority of UC patients (8% to 12%) and non-IBD controls (19%), it is more common in patients with CD (43% to 52%) with a calculated positive predictive value for colonic CD of 70% to 80% (16, 20). All examples of gastritis, whether focal or diffuse, should be carefully evaluated to exclude *Helicobacter* infections as well as allergic and chemical-type injuries. As in the colon, "IBD-associated gastritis" is a diagnosis of exclusion.

In summary, upper endoscopy can be helpful in classifying colonic IBD. Biopsy specimens should be obtained from grossly normal as well as abnormal mucosa to detect treatable localized conditions, such as *H. pylori*-associated gastritis, and to detect granulomas and focal gastritis (17, 19, 20). In one recent pediatric study of the stomach in IBD, 87% of patients had various inflammatory changes in antral biopsies despite the fact that only 38% had endoscopically detectable mucosal changes (chiefly erythema and small ulcers) (16). The recent recognition that diffuse, non-*Helicobacter* chronic gastritis is common in patients with classic UC raises an interesting question: Is it a manifestation of UC? Additional prospective studies are necessary to clarify this issue.

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