

## **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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## **Inflammatory Bowel Disease: Evolving Issues in Diagnostic pathology**

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### **Introduction**

Ulcerative colitis (UC) and Crohn's disease (CD) are the two most common forms of chronic inflammatory bowel disease (IBD). Tremendous strides have been made in recent years in the understanding of genetic factors underlying IBD. Unfortunately, the pathogenesis of these disorders still remains poorly understood and there is no single clinical, laboratory or molecular test that helps to establish a diagnosis. In current practice diagnosis of UC and CD heavily relies on clinico-pathologic correlation of pattern of inflammation and distribution of disease. Typical untreated UC is characterized by diffuse and continuous involvement of the distal colon without skip lesions, predominant mucosal involvement, lack of granulomata and lack of terminal ileum involvement. Typical features of typical CD include segmental or patchy involvement, more severe disease in the proximal colon, rectal sparing, transmural inflammation, granulomata and terminal ileum involvement. Involvement of upper GI tract is more common with CD and often the degree of mucosal architectural changes and mucin depletion are less pronounced as compared to UC. Many exceptions to the classic pathologic features outlined above have been recognized, especially with UC and remain a potential source of confusion in routine practice. These include mucin granulomata related to ruptured crypts or foreign bodies, minor degree of ileal inflammation (backwash ileitis), isolated involvement of appendix and cecal patch. In the last decade increasing experience has further widened the spectrum of findings expected in UC and CD, and the list of exceptions to the classic rules continues to grow. Some of these issues are discussed below.

### **I. Indeterminate colitis and ileo-anal pouch complications.**

Even in the most experienced hands in about 5-10% of cases a definite diagnosis of UC or CD cannot be made due to either insufficient clinico-pathologic data or overlapping features. Such cases are deemed "Indeterminate colitis" (IC)<sup>1,2</sup>. However, IC is not a disease entity and has no diagnostic criteria. In fact, in about 80% of cases, the true nature of the patient's underlying IBD becomes apparent within a few years<sup>3</sup>. It also appears in most instances, cases initially termed IC are actually UC however, a variable proportion also turn out to be CD. Unfortunately, sometimes there is a strong clinical need to classify IBD patients definitively as CD or UC, since an ileal pouch-anal anastomosis (IPAA) or "pouch" procedure is generally contradicted in CD due to increased complications. Recent studies have evaluated the pathologic features, natural history, and outcome of ileo-anal pouches in patients with IC<sup>4-6</sup>. Although, the results vary considerably, in general, approximately 20% of IC patients develop severe pouch complications. This frequency is intermediate between that seen in UC (8-10%) and CD (30-40%). Although the failure rate in IC is higher than UC, overall, IC patients have a similar outcome as UC, suggesting again that most IC cases probably represents UC. Interestingly, some recent studies suggest that despite pouch failure in a substantial proportion of CD patients (30-45%), there is quite acceptable pouch function in CD patients whose pouches can be retained in situ<sup>6</sup>.

### **II. Patchiness and skip lesions in UC**

#### **a) Skip lesions in UC**

Patchiness or skip lesions in UC have been recognized in certain settings. It is recognized that while the demarcation between the normal and involved segment may be sharp in some cases, it may be gradual in others creating a false impression of skip lesions. It has also been recognized

that some cases of left sided UC show a discontinuous area of inflammation in the cecum (“cecal patch”), primarily in the periappendiceal mucosa or involvement of appendix itself as a skip lesion<sup>7-9</sup>. It has been shown that such cases are very similar to classic UC with regards to demographic features, extra-intestinal manifestations, severity of disease and disease progression. In summary, patchy right-sided inflammation in patients with left-sided colitis has little clinical significance, but should be recognized by pathologists as a potential "skip" lesion in UC to prevent a false diagnosis of CD.

#### **b) Effect of oral and topical therapy on pathology**

It was initially shown by Odze et al that chronic features in UC may revert to normal in the natural course of the patient's illness, and that this phenomenon may be enhanced by topical therapy<sup>10</sup>. Subsequent studies have further shown that 30-59% of patients, some of whom are treated with oral sulfasalazine and/or steroids, show patchiness of disease or rectal sparing in their follow-up biopsies<sup>11,12</sup>. Awareness of these data should prevent the finding of a normal rectal biopsy, or patchiness of disease, in treated UC patients from being misinterpreted as representing CD. In addition, patients in clinical and pathologic remission, may also show minimal architectural features of chronicity, or even a completely normal biopsy. However, it is important to realize that these data relate primarily to biopsies from treated patients and one needs to be very careful while evaluating resection specimens. Large portions of mucosa from resected specimens that appear histologically completely normal probably indicate a true segmental disease i.e. CD. Thus, all potential IBD patients should be staged by colonoscopy with multiple biopsy specimens before institution of therapy as this is the best opportunity to properly classify the underlying disease as UC or CD.

#### **c) Diverticulitis associated chronic colitis**

Segmental chronic colitis limited to area of diverticulosis in the sigmoid colon is known to occur which clinically mimics CD<sup>13-15</sup>. The histologic changes may vary from mild increase in lamina propria lymphoplasmacytic infiltrate to full-blown chronic colitis with marked architectural distortion. Some cases have gross and histologic features that mimic CD that include fat wrapping and transmural lymphoid aggregates, without any other clinical or pathologic evidence supportive of CD. While some cases respond to diverticulitis type treatment (antibiotics and high fiber diet), some respond to IBD-type treatment. Some cases are refractory and need surgical resection of the involved segment. The exact nature of this colitis remains unclear. While initial reports suggested that this may represent a unique entity distinct from IBD, long term follow-up suggests some cases may represent true IBD<sup>15</sup>.

#### **d) Rectal sparing in UC and pediatric UC**

While rectal sparing in untreated UC in adults has been an area of debate and controversy, it has been shown in several recent studies that untreated pediatric patients may present initially with relative or complete rectal sparing or even patchy disease<sup>16-18</sup>. In addition the pediatric UC patients often show less prominent features of chronicity on biopsy as compared to adults. Thus, the absence of features of chronicity, milder disease, and microscopic skip areas at initial presentation in pediatric patients do not exclude the possibility of UC.

### **III. Ileal involvement in UC (“Backwash Ileitis”)**

It is commonly recognized that patients with severe pancolitis may show a mild degree of active inflammation in the distal few centimeters of the terminal ileum that is termed "backwash" ileitis<sup>19</sup>. Unfortunately, strict histopathologic criteria for backwash ileitis have not been defined. Generally the involvement is limited to few centimeters of distal ileum in cases of pancolitis, and the histology reveals mild non-specific inflammatory changes limited to the mucosa. This condition should be differentiated from CD of the terminal ileum, which typically shows longer lengths of involvement and is normally associated with other features of CD such as fissuring ulceration, granulomas, and transmural lymphoid aggregates. Although backwash ileitis has not

been shown to be a significant risk factor for the development of pouchitis, rarely adenocarcinoma has been shown to develop in this setting<sup>20</sup>.

#### **IV. Upper gastrointestinal involvement in UC**

Upper GI involvement is more commonly seen with CD than UC and any segment of GI tract may be involved<sup>21</sup>. The histologic changes are often non-specific and granulomatous inflammation is seldom seen. The typical finding in stomach is focal/ patchy gastritis (focally enhanced gastritis). However, a recent study shows that majority of such focal gastritis cases do not represent CD<sup>21</sup>. On a similar note, many of granulomatous gastritis cases also do not represent CD<sup>22</sup>. As a result, the histopathologic diagnosis of IBD in upper GI is often difficult and sometimes impossible. Gastric and/or duodenal involvement has rarely been also reported in association with UC however, pathologic features on biopsies are often non-specific<sup>23</sup>. More precise characterization of cases with long-term follow up is needed to help establish specific criteria for upper GI involvement in patients with IBD.

#### **V. Effects of newer therapies on pathology**

Newer forms of immunomodulatory therapy (Azathioprine, 6 Mercaptopurine and Remicade) are increasingly been used in the treatment of IBD however, studies looking at their impact on histopathologic changes of IBD are currently lacking. Occasional reports of opportunistic infections with use of these newer agents exist in literature, although it is unclear if the risk is higher as compared to other conventional treatment modalities<sup>24</sup>. A recent report suggested an increase in the incidence of EBV-associated lymphoproliferative disorder with the use of Azathioprine or 6-Mercaptopurine, however other large studies fail to substantiate this observation<sup>24,25</sup>.

## **VI. IBD vs NSAID induced mucosal injury and Incidental ileitis**

Non-steroidal anti-inflammatory drugs (NSAID) induced mucosal injury is increasingly recognized these days and virtually any segment of the GI tract may be affected. The histologic changes in the bowel range from superficial erosions with mild non-specific inflammation to deep ulcers and chronic inflammatory changes mimicking IBD<sup>26,27</sup>. Ulcers are frequently seen in terminal ileum or jejunum and can be multiple in some cases. While distinction from IBD may be relatively easier on resection specimens, it could be difficult to impossible on biopsies. Increasing use of capsule videoscopy and biopsies performed of terminal ileum in asymptomatic individuals for routine screening colonoscopy has resulted in rise in case of incidental ileitis. The clinical significance of this finding is unclear at present. While this could represent manifestation of NSAID induced mucosal injury, some cases possibly represent sub-clinical CD. Long-term follow-up studies are needed to clarify this issue.

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## INFLAMMATORY AND INFECTIOUS DISEASES IN ADULT ILEOCOLONIC BIOPSIES

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**One of the advantages of flexible colonoscopy is that the terminal ileum can easily be reached and biopsied by an experienced colonoscopist during endoscopy. Thus, the pathologist will, with increasing frequency, receive ileal biopsies of patients whose ileum may or may not be diseased. Good knowledge of the normal ileal mucosal histology and pathology, of its normal function, and of pathological changes seen in different conditions is necessary for adequate reporting of these biopsies. In addition, it is also desirable to be aware of ileal diseases that occur less frequently.**

The microscopic features of terminal ileal mucosa are related to its absorptive function on the one hand, and to non-specific and specific defense mechanisms of the gut against potential hazardous components on the other hand. As a consequence the mucosa is under constant physiological and controlled inflammation. A consistent proportion of the ileal mucosal structure is determined by the presence of the gut-associated lymphoid tissue (GALT) which plays a key role in discriminating harmless nutrients and harmful pathogens.

It is important to distinguish this normal situation from alterations seen in infectious or inflammatory pathology. Further on, because of the therapeutic implications, it is necessary to recognize acute infectious and chronic -idiopathic or infectious- inflammation. This will in general be possible by evaluating the composition of luminal components, the inflammatory infiltrate and the occurrence of epithelial and mucosal architectural changes.

Often, while the histological findings in ileal biopsies alone will not suffice for a definite diagnosis, they will allow the confirmation of existing pathology or point to possible etiology.

The presence of focal active inflammation can indicate acute infectious ileitis, resolving infectious enteritis and early chronic inflammatory bowel disease - especially when eosinophilic cryptitis and crypt abscesses occur. It can also be related to the use of some drugs (e.g. NSAID's).

Small intestinal infections are, together with colonic infections, amongst the most frequent occurring diseases worldwide and they harass mankind. Especially among young children there are enormous numbers of deaths due to diarrheal disease. They can be caused by a great diversity of pathogens and their pathological and epidemiological features as well as their incidence can often differ in different areas of the world.

Amongst the infective causes of ileitis, only some stages of Yersinia enteritis are distinctive, as can be the case with tuberculosis. The most common causes of small intestinal infections are reviewed and some characteristics of their clinical and histological aspects are described. Moreover, the different infectious diseases are classified into acute and chronic as the recognition of the type of inflammatory infiltrate may be helpful to make a correct diagnosis. Here we will focus on diseases that occur more or less frequently and that are most typical in their small intestinal localization and,

they will be classified according to their clinical presentation, namely, whether they are generally accompanied by acute or persistent and chronic infections.

In patients suspected of having inflammatory bowel disease ileoscopy with biopsies is useful and the diagnosis can be made on histological grounds alone, even in the absence of macroscopic endoscopic lesions. One study in patients with inflammatory bowel disease found ileal disease without colonic involvement in 44/123 patients and microscopic lesions in 49% of patients with diarrhea. It was concluded that ileoscopy with biopsy is useful in selected patients with symptoms of inflammatory bowel disease. The main indications were the diagnosis of isolated ileal disease in the presence of a normal colon and the differential diagnosis in patients with pancolitis and predominantly left-sided colitis. From that group of patients approximately half had pathology in their ileal biopsies.

For the diagnosis of Crohn's disease the presence of sarcoid-like granulomas and isolated giant cells are fairly specific but uncommon and moreover, these features may also be seen in infectious diseases like tuberculosis and Yersiniosis. Other structural alterations like crypt architectural changes, villous abnormalities and the occurrence of the ulcer-associated cell lineage are suggestive of Crohn's disease, but again are not specific. The ulcer-associated cell lineage is a sign of chronic ulceration and regeneration and architectural mucosal changes can be seen in the vicinity of tumours, adhesions and endometriosis, and after cancer surgery.

The few available data from literature on the value of ileocoloscopy with biopsy in the clinical management of inflammation show convincingly that the examination of ileal biopsies may be of great help in the evaluation of small intestinal inflammatory processes, more particular in the working-out of inflammatory bowel diseases. Thorough knowledge of the normal histological spectrum and correct interpretation of ileal biopsies will allow to make a diagnosis of Crohn's disease rather than ulcerative colitis when features of chronic ileal inflammation are present. Likewise, in cases of chronic diarrhea and normal colonic findings, ileal biopsies will permit to distinguish between a variety of protracted acute infectious pathology and idiopathic inflammatory bowel disease.

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