

## **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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