Diagnostic Problems and Advances in Inflammatory Bowel Disease

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This review summarizes current diagnostic problems and advances with regard to patterns of inflammation and dysplasia in ulcerative colitis and Crohn's disease. Ulcerative colitis and Crohn's disease have a variety of characteristic but non-specific pathologic features. In approximately 5% of inflammatory bowel disease cases, a definite diagnosis of ulcerative colitis or Crohn's disease cannot be established, in which case the term "indeterminate" colitis is used. Most cases of indeterminate colitis are related to fulminant colitis, a condition in which the classic features of ulcerative colitis or Crohn's disease may be obscured by severe ulceration with early superficial fissuring ulceration, transmural lymphoid aggregates, and relative rectal sparing. Approximately 20% of patients with indeterminate colitis develop severe pouch complications, which is intermediate in frequency between ulcerative colitis (8–10%) and Crohn's disease (30–40%). In order to establish a diagnosis of ulcerative colitis or Crohn's disease, it is important to evaluate pathologic material in conjunction with clinical, laboratory, radiologic, and endoscopic features and to recognize the variety of changes that may be seen in fulminant ulcerative colitis.There are a number of exceptions to the classic principles of inflammatory bowel disease pathology that may lead to diagnostic confusion. For instance, apparent skip lesions on biopsy analysis may occur in patients with ulcerative colitis in the following settings; long term oral or topical therapy, focal ascending colon, cecum and/or appendiceal involvement in patients with left sided ulcerative colitis, upper gastrointestinal involvement in patients with ulcerative colitis, and at initial presentation of ulcerative colitis in pediatric patients. In all of these circumstances, the finding of patchy disease and/or rectal sparing should not be misinterpreted as either evidence against a diagnosis of ulcerative colitis, or as representing skip areas characteristic of Crohn's disease.Patients with ulcerative colitis and Crohn's disease are at increased risk for the development of dysplasia and carcinoma. Recent studies suggest that given a similar duration and extent of disease, patients with Crohn's disease have a similar risk of dysplasia and cancer as patients with ulcerative colitis. Dysplasia in ulcerative colitis may be classified as flat or elevated (dysplasia associated lesion or mass [DALM]). Patients with flat high grade dysplasia are generally treated with colectomy. However, there is recent evidence to suggest that patients with flat low grade dysplasia, particularly if detected at the time of initial endoscopic exam, or if its multifocal or synchronous, should also be treated with colectomy. Elevated lesions in ulcerative colitis (DALM) are subdivided into "adenoma-like" and "non-adenoma-like" lesions based on their endoscopic appearance. Recent data suggests that adenoma-like lesions, regardless of the grade of dysplasia, or the location of the lesion (*i.e.,* inside or outside areas of established colitis) may be treated adequately by polypectomy if there are no other areas of flat dysplasia in the patient. Although there are some histologic and molecular features that can help differentiate sporadic adenomas from adenoma-like polypoid dysplastic lesions related to ulcerative colitis, none of these adjunctive techniques can help distinguish these lesions definitively in any single patient. Patients with a non-adenoma-like DALM, (irregular, broad based, or strictured lesion) should be treated with colectomy because of the high probability of adenocarcinoma. The surveillance and treatment options for patients with flat and elevated dysplasia in ulcerative colitis are reviewed in detail.

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Ulcerative colitis (UC) and Crohn's disease (CD) are the two most common forms of chronic inflammatory bowel disease (IBD). Unfortunately, the pathogenesis of these disorders is unknown (1–4). As a result, there are no specific clinical or laboratory features that may help establish a diagnosis. Thus, diagnosis of UC and CD relies heavily on pathologic in-

terpretation of biopsy and resection specimens (1, 4). Since both UC and CD have a variety of characteristic, but non-specific (non-pathognomonic) pathologic features, it is important to evaluate pathologic material in conjunction with clinical, laboratory, radiologic and endoscopic features (1, 2). A summary of the classic microscopic features of UC and CD is noted in Table 1. Important features of untreated UC in biopsy specimens include diffuse involvement of the colorectum without skip lesions, lack of submucosal involvement, lack of granulomas (except those related to mucin or foreign bodies), and lack of terminal ileum involvement (with the exception of a minor degree of inflammation associated with backwash ileitis). In resection specimens, diffuse continuous mucosal disease (including the rectum), in the absence of deep fissuring ulceration, sinus tract formation, transmural lymphoid aggregates (away from areas of ulceration), small intestinal involvement (except in backwash ileitis) or granulomas, in the appropriate clinical, radiologic, and endoscopic setting, are findings normally considered consistent with UC. Typical features of CD include segmental involvement, less severe disease in the distal colon compared to the proximal colon, rectal sparing, submucosal inflammation, patchiness of inflammation, granulomas unrelated to mucin or foreign bodies, terminal ileum involvement, upper GI involvement, and a less pronounced degree of mucosal architectural changes, and mucin depletion, compared to UC. Under normal circumstances, any of these features should be considered sufficient for a diagnosis of CD (Fig. 1). However, in some cases, a definite diagnosis of UC or CD cannot be made due to overlapping features ("Indeterminate colitis"). Furthermore, several exceptions to the "classic" pathologic features outlined above (and in Table 1) do exist and may cause diagnostic confusion. These issues are discussed further below

Indeterminate Colitis

Definition

In approximately 5% of IBD cases, a definite diagnosis of UC or CD cannot be established due, most commonly, to either insufficient clinical, radiologic, endoscopic or pathologic data, or because of prominent overlapping features between these two disorders (5–8). Under these circumstances, the term "indeterminate" colitis (IC) has been used. However IC is not a disease entity and has no diagnostic criteria. Rather, it represents a provisional descriptive term to be used by pathologists' only when he or she is unable to establish a definite diagnosis given the information available at the time of surgical sign out. In fact, in up to 80% of cases, the true nature of the patient's underlying IBD usually becomes apparent within a few years (9).

Diagnosis

Historically, the term IC was originally applied to cases of fulminant colitis (*i.e.*, severe colitis with systemic toxicity and often associated with colonic dilatation), a disease in which the classical features of UC may be obscured by severe ulceration with early superficial fissuring ulceration, transmural lymphoid aggregates, and relative rectal sparing, features normally associated with CD (10) (Fig. 2). However, more recently, the term has been used to describe any IBD case in which a definite diagnosis cannot be established. Naturally, the prevalence of establishing a "diagnosis" of IC is highly dependent on the level of awareness of the reviewing pathologist regarding the wide range of morphologic features that can be seen in IBD. For instance, in a recent study by Farmer *et al.*, 84 IBD colectomy specimens were reviewed by 24 university pathologists and the diagnostic accuracy was compared to a single GI pathologist who has a particular interest in IBD (7). Not unexpectedly, the GI pathologist rendered a diagnosis that was different from the others in 45% of specimens, and in most cases, it resulted in a change of diagnosis from UC to CD. In most instances, cases termed IC are usually UC, but a variable proportion (10–40%) turn out to be CD. Rarely, other pathologic mimics of IBD, such as NSAIDs colitis, diverticular disease-associated colitis, radiation or ischemic colitis, or infectious colitis may be interpreted as IC (4). Unfortunately, there is a strong clinical need to classify IBD patients definitively as CD or UC (or other), since an ileal pouch-anal anastomosis (IPAA) "pouch" procedure is generally contradicted in CD due to a high risk of morbidity related to pouchitis, fistulas, incontinence or anastomosis leaks (6, 7, 11, 12). In 1998, Swan *et al.* evaluated 95 cases of "fulminant colitis" (IC) with the aim of identifying features that can help separate UC from CD (10). After a comprehensive review of all pathologic material and clinical follow up information, microscopic examination correctly diagnosed UC or CD in 91% of cases. Interestingly, granulomas and transmural lymphoid aggregates away from areas of ulceration were the most specific indicators of CD.

TABLE 1. Classic Microscopic Features in Untreated Ulcerative Colitis and Crohn's Colitis (Hard Criteria)

Ulcerative Colitis	Crohn's Disease
Diffuse, continuous disease	Segmental disease
Rectal involvement	Variable rectal involvement
Disease worse distally	Variable disease severity
No fissures	Fissures, sinus, fistula
No transmural aggregates	Transmural lymphoid aggregates
No ileal involvement (exception: "backwash")	Ileal involvement
	Upper GI involvement
No granulomas	Granulomas

The most common reasons for rendering a diagnosis of IC are noted in Table 2. In addition to those discussed above, pathologists often fall back on a diagnosis of IC when a definite diagnosis of UC or CD cannot be made on biopsy analysis, a practice which is highly discouraged. In other instances, the diagnosis is used because of a lack of awareness regarding unusual variants of UC that can lead to apparent "skip" lesions in UC, or because of the unwillingness of pathologists to accept certain hard core criteria, such as segmental disease, granulomatous inflammation, transmural lymphoid aggregates, or deep fissuring ulceration as solitary criterion for CD.

Outcome

There have been many studies that have evaluated the pathologic features, natural history, and outcome of ileo-anal pouches in patients with IC (6, 8–18). However, the results vary considerably due to the fact that most of these studies are retrospec-
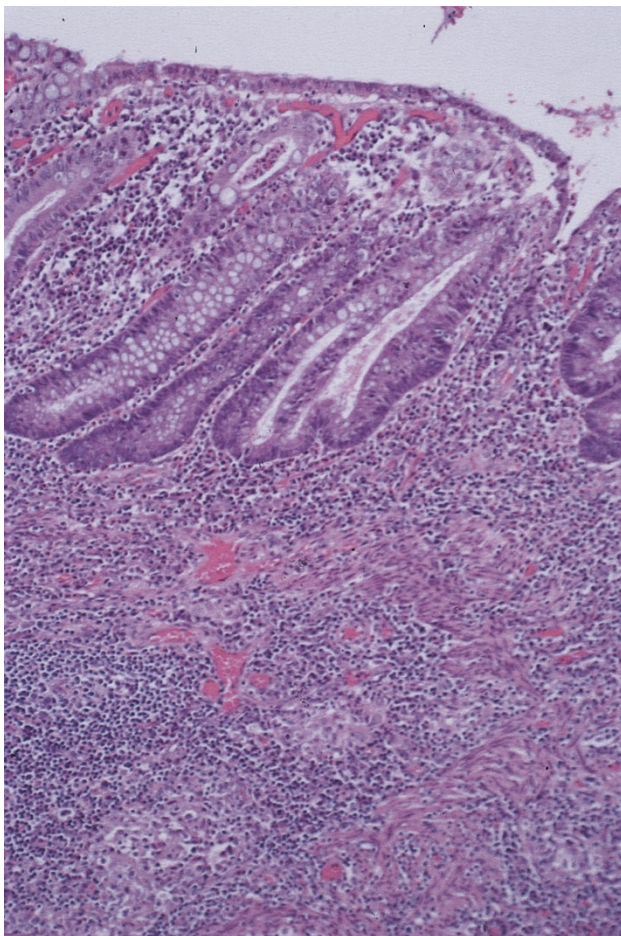

FIGURE 1. Medium power view of a section of colon from a patient with Crohn's disease. The mucosa shows crypt architectural distortion and an increased amount of acute and chronic inflammation in the lamina propria. The inflammation extends into the deep mucosa and superficial submucosa. Non-necrotizing granulomas are present both in the superficial mucosa and in the submucosa.
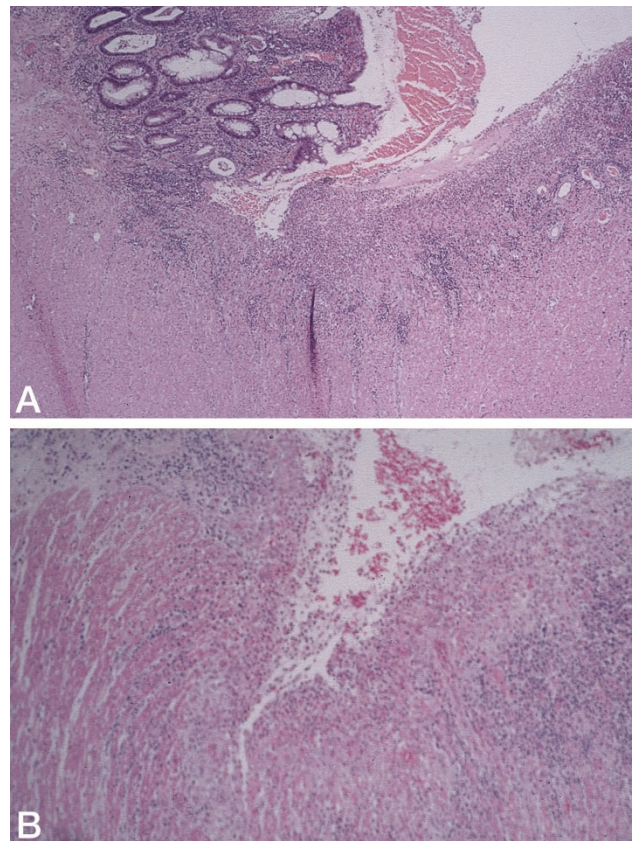

FIGURE 2. **A**, Low power view of a section of colon from a patient with fulminant ulcerative colitis. The mucosa shows severe chronic active inflammation and ulceration extending into the deep portions of the mucosa and superficial muscularis propria. **B**, In a patient with fulminant colitis, early superficial fissuring ulceration, as seen in this photograph, may occur rarely.

tive, have varying and undefined criteria for IC, and lack sufficient follow-up information. Nevertheless, in general, approximately 20% of IC patients develop severe pouch complications, which is intermediate in frequency between that seen in UC (8–10%) or CD (30–40%) (6, 8, 11, 14, 16). This is expected given that in most studies, the IC study group is composed of a mixture of true UC and CD patients. In a recent study by Yu *et al.* of 82 cases of IC and 1,437 cases of UC, all of whom had an IPAA operation, patients with IC had a higher incidence of pelvic sepsis, pouch fistulas and pouch failure in comparison to UC patients (6). However, ultimately, 15% of IC patients had their diagnosis changed to CD, and when the CD patients were removed from the analysis, the rate of pouch complications in IC and UC patients was similar. Similarly, in another study by McIntyre *et al.* in 1995, 71 cases of IC and 1,232 UC patients were compared for frequency of bowel movements, incontinence or prevalence of pouchitis and pouch failure (14). Although the failure rate in IC was higher than UC (19 vs. 8%), overall, the IC patients had a similar outcome as UC, suggesting again that most patients

TABLE 2. Common Reasons for Making a Diagnosis of Indeterminate Colitis

1. Fulminant colitis (fissures, transmural inflammation, rectal sparing in UC)
2. Insufficient clinical, radiologic, pathologic information
3. Interpretation of mucosal biopsy specimens
4. Failure to recognize unusual variants of UC and CD
   UC with
     Relative rectal sparing
     Superficial fissure
     Granulomas related to ruptured crypts
     Right sided involvement in left sided colitis
     Appendiceal involvement
     Backwash ileitis
     Therapy effect
   CD with diffuse mucosal involvement
5. Failure to utilize hard criteria for CD
     Transmural inflammation
     Granulomas
     Deep fissuring ulceration
     Ileal involvement
     Segmental disease
6. Presence of secondary disease (for example, pseudomembranous colitis, ischemic colitis, infection)

TABLE 3. Summary of Causes of Unusual Patterns of Disease in UC

1. Treatment effect
2. Low grade disease in remission
3. Appendiceal involvement
4. Cecum/ascending colon inflammation in left-sided colitis
5. Pediatric UC (initial presentation)
6. "Backwash" ileitis
7. Rare UGI involvement (*i.e.,* duodenitis)
8. Fulminant colitis

with IC probably have UC. Interestingly, although a substantial proportion of CD patients who receive an IPAA operation develop pouch failure (30–45%), some recent studies suggest that there is quite acceptable pouch function in CD patients whose pouches can be retained *in situ* (11, 13).

Diagnostic Tests

In certain circumstances, serologic testing for anti-neutrophil cytoplasmic antibodies (ANCA) and anti-saccharomyces cerevisiae (ASCA) antibodies may be helpful in classifying IC cases into UC or CD (19). For instance, ANCA are detected in the serum of 60–70% of UC patients, but in only 10–40% of CD patients. Interestingly, of the CD patients who are ANCA positive, most have left-sided colitis with clinical, endoscopic and/or histologic features of UC. ASCA are present in 50–60% of CD patients, and has a sensitivity of 67% and a specificity of 92% as a serum marker for CD. Unfortunately, the use of ANCA and ASCA in IC has not been extensively studied, and needs further investigation.

Unusual Morphologic Variants of Ulcerative Colitis and Crohn's Colitis

There are a number of exceptions to the "classic" principles of IBD pathology that my lead to diagnostic confusion. A summary of the causes of unusual morphologic patterns of disease in UC is noted in Table 3. It is important for pathologists to recognize these variants in order to avoid falling into a diagnostic trap.

1. Effect of Oral and Topical Therapy

Classic teaching emphasizes that chronic UC is characterized morphologically by the presence of diffuse fixed architectural and/or cellular mucosal changes that categorize the process as chronic. However, in 1993, Odze *et al.* prospectively evaluated 123 rectal mucosal biopsies from 14 patients with pathologically confirmed UC treated with either 5 ASA or placebo enemas (20). Overall, over the course of treatment, 29% of rectal biopsies from 64% of patients were histologically normal showing no evidence of chronic or active disease. In fact, patients treated with 5 ASA showed a significantly higher percentage of normal biopsies (obtained from areas of mucosa previously shown to be involved with chronic-active disease) in comparison to the placebo group (Fig. 3). This was the first report to demonstrate that "fixed" 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. Subsequent studies by Kleer *et al.*, Bernstein *et al.* and Kim *et al.*, all of whom evaluated patchiness of disease and patterns of involvement in UC colorectal biopsies with time, confirmed and expanded the initial findings by Odze *et al.* (21–23). In these studies, 30–59% of patients, some of whom were treated with oral sulfasalazine and/or steroids, showed either patchiness of disease or rectal sparing in their follow-up biopsies. For instance, in a study by Kim *et al.*, 27% of follow-up endoscopies in 59% of patients showed either patchy (microscopic areas of skip lesions) disease, rectal sparing, or both during the follow up interval (23). 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 either evidence against this diagnosis or as representing focal skip areas characteristic of CD. In addition, patients with low-grade indolent disease, particularly those in clinical and pathologic remission, may also show minimal architectural features of chronicity, or perhaps even a completely normal biopsy appearance, during the natural waxing and waning course of their illness. However, it is important to realize that these data relate primarily to biopsy material from treated patients. It does not apply to patients who present initially before treatment, or in whom a diagnosis is being considered from evaluation of a resection specimen. Large portions of mucosa from a resection specimen that show a normal histologic ap-

pearance is an indication of true segmental disease and would normally provide reliable evidence in support of an alternative diagnosis such as CD.

2. Ascending Colon, Cecum, and Appendiceal Involvement as "Skip" Lesions in UC

Some patients with either subtotal or left-sided colitis may show patchy, mild, cecum and/or ascending colon chronic-active inflammation which may be falsely interpreted as CD due to the impression of segmental involvement (24–27). In fact, up to 65% of UC patients present initially with limited left-sided involvement, which may spread to involve more proximal portions of the colon in 29–58% of cases (24, 28, 29). In one study by D'Haens et al. of 20 patients with established left-sided UC, 6 showed a sharp demarcation between affected and unaffected portions of colon, whereas 14 showed a more gradual transition (24). The area of transition may appear somewhat patchy and give the false impression of skip lesions. Furthermore, 75% of the latter group of patients showed an area of inflammation in the cecum, primarily in the periappendiceal mucosa, that was separate in space from the distal inflamed segment. In a previous study by our group, 14 patients with both left-sided UC and pathologically confirmed patchy right-sided chronic inflammation were compared to 35 control patients with limited left-sided UC only (27). These two groups of patients showed similar demographic features, extra-intestinal manifestations, severity of disease, prevalence of extension to pancolitis, and natural history which suggests that patchy right-sided inflammation in patients with left-sided colitis has little clinical significance but should be recognized by pathologists to prevent a false diagnosis of CD in this setting.

Similarly, since the original description by Davison et al. in 1990 of discontinuous involvement of the appendix in 21% of 62 cases of UC (30), several other studies have shown that the appendix may be involved as a "skip" lesion in this disease (31, 32), although at least one other study has failed to confirm this finding (33). In another study by Groisman et al., ulcerative appendicitis was present in 86% and 87% of patients with non-universal and universal UC, respectively (31). In fact, this study contained two cases with limited left sided involvement combined with appendiceal involvement. In summary, both appendiceal and/or cecum/ascending colon involvement may occur in patients with subtotal colitis and should be recognized as a potential "skip" lesion in UC.

3. Initial Presentation of Pediatric Patients with UC

Several recent studies have shown that pediatric patients who present initially with untreated UC may show evidence of relative, or complete, rectal sparing or even patchiness of disease (34–39). For instance, in one study by Markowitz et al. of 12 pediatric patients with untreated UC, 5 (42%) showed patchy, mild active inflammation and mild crypt changes in the rectum in comparison to more proximal colonic biopsies (33). In fact, one patient had a completely normal rectal biopsy. More recently, a large study by our group presented at the 2002 USCAP meeting by Glickman et al., compared the rectal mucosal biopsy appearance of 70 pediatric UC patients to 44 adult patients, all at initial presentation (35). In comparison to adults, the pediatric group showed significantly fewer cases with chronic active disease, and more patients with microscopic skip areas and relative rectal sparing in comparison to adults. Two of the 70 pediatric patients showed completely normal rectal biopsies at initial presentation in contrast to none of the adult patients. Thus, the absence of features of chronicity, mild active disease, and microscopic skip areas, at initial presentation in pediatric patients, does not exclude the possibility of UC.

4. 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 terminal ileum which is presumably related to reflux of colonic contents (40, 41) (Fig. 4). This is termed "backwash" ileitis. This condition should not be confused with CD of the terminal ileum which more typically shows longer lengths of involvement and is normally associated with chronic active inflammation, and other features of CD such as fissuring ulceration, granulomas, and transmural lymphoid aggregates (41). Unfortunately, strict histopathologic criteria for backwash ileitis have not been defined. In fact, studies regarding the morphology of backwash ileitis date back to the 1960s, and, thus, is a topic in need of re-evaluation. Although backwash ileitis has not been shown to be a significant risk factor for the development of pouchitis, rarely, premalignant dysplastic changes, and even adenocarcinoma, has been show to develop in this setting (42, 43). In fact, one recent study by Heuschen et al. showed a strong association of backwash ileitis with the development of colorectal cancer in patients with UC who have undergone proctocolectomy (44). In their study, colorectal cancer was found in 29% of 107 pancolitis patients with backwash ileitis, compared to 9% of patients without backwash ileitis and 1.8% of patients with limited left sided colitis. However, even in that study, discrete pathologic criteria for backwash ileitis were not defined.
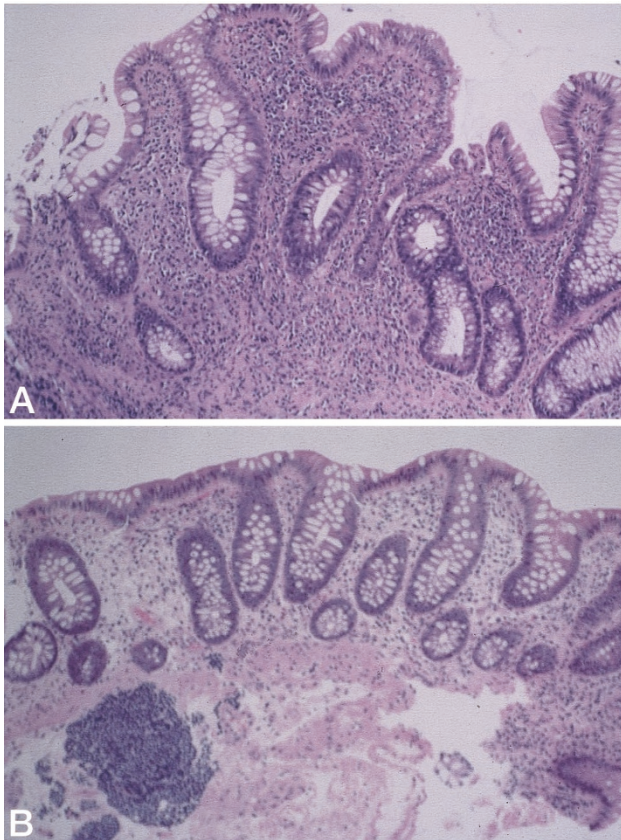
FIGURE 3. A, Biopsy of a patient with long standing ulcerative colitis showing chronic active colitis characterized by crypt architectural distortion and increased inflammation in the lamina propria. **B**, This biopsy is from the same area of the colon as in Figure 3A, obtained 6 months after the patient was treated with 5-ASA rectal enemas. This biopsy is essentially within normal limits, and shows a normal crypt architectural pattern and an absence of inflammation in the lamina propria.
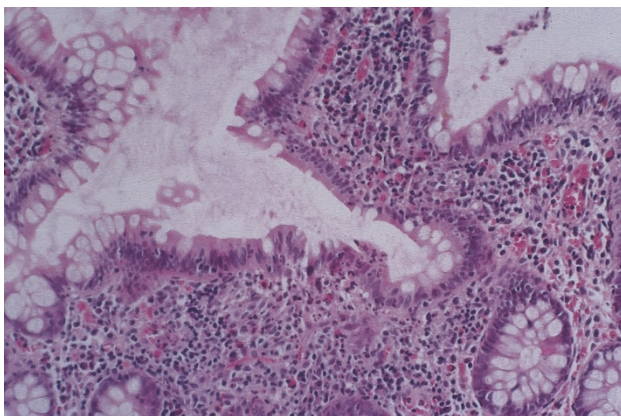

FIGURE 4. High power view of the distal terminal ileum in a patient with fulminant ulcerative colitis showing a mild degree of neutrophilic inflammation in the superficial lamina propria and superficial epithelium. This patient had no granulomas, fissuring ulceration, strictures or evidence of pyloric metaplasia in the ileum. The inflammation is focal and mild and only present in the distal few centimeters of ileum. In the appropriate clinical setting, these features have been interpreted as indicative of "backwash ileitis."

5. Upper Gastrointestinal Involvement in UC

Rarely, gastric and/or duodenal involvement, has been reported in association with clinically and pathologically confirmed UC (45–48). A recent study by Valdez *et al.* described 4 patients with chronic active inflammation in the duodenum similar in appearance to the patients' colonic disease (45). However, until these cases are followed up for longer intervals of time, it is difficult to know if the upper GI involvement actually represents a manifestation of UC, or simply an as yet unidentified associated disorder. More precise characterization of cases with long-term follow up is needed to help establish specific criteria for upper GI involvement in patients with UC.

6. Unusual Patterns of Disease in Crohn's Disease

Typical features of CD, such as granulomas, fissuring ulceration and transmural lymphoid aggregates, are seen less commonly in the colon compared to the small intestine. In fact, CD may involve the colon in a manner similar to UC, consisting of continuous mucosal inflammation of the colorectum, minimal or no submucosal inflammation, and an absence of upper GI involvement (49–52). In these cases, the diagnosis relies heavily on finding
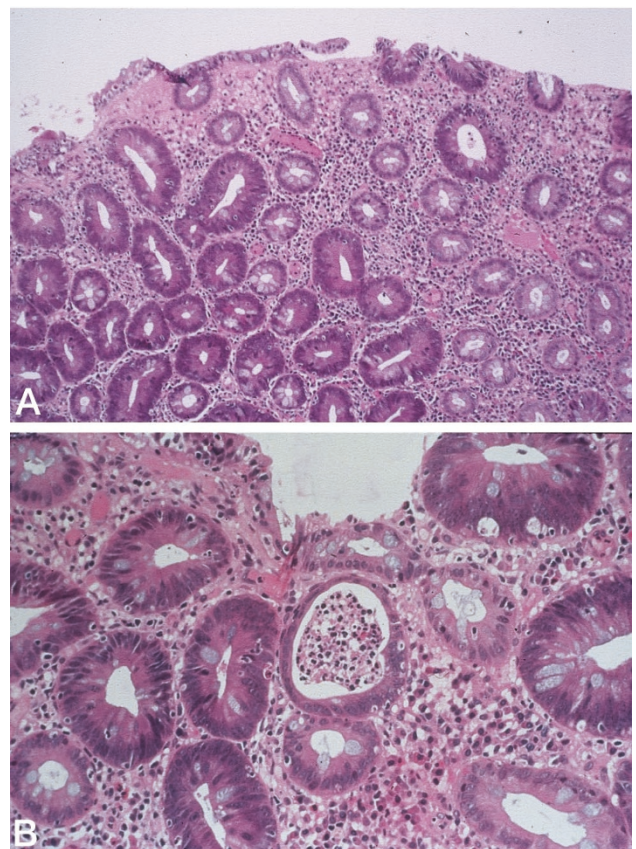
FIGURE 5. A, Medium power photograph of a polypoid dysplastic lesion arising in a patient with chronic ulcerative colitis. The polyp shows a mixture of low-grade dysplastic crypts and non-dysplastic crypts at the surface of the polyp. Note the increased inflammation in the lamina propria. **B**, High power view of a different area from the same polyp showing low-grade dysplastic crypts at the surface of the polyp with a crypt abscess.

granulomas or transmural lymphoid aggregates in the resection specimen. However, more often than not, these cases follow a clinical course typical of CD and may account for some of the cases of presumed UC which have CD-like complications (53).

Dysplasia in Ulcerative Colitis and Crohn's Disease

1. Dysplasia in Crohn's Disease

Patients with inflammatory bowel disease are well known to have an increased risk for the development of adenocarcinoma (54–59). Although this risk is well established in patients with UC, there is less data available in CD. Several studies suggest that given a similar duration and extent of disease, the risk of colon cancer is similar in CD and UC (60–63). In CD, there is also an increased risk of adenocarcinoma in excluded segments of bowel and in the small intestine (57). In one study by Bernstein et al., the relative risk of colon cancer in CD and UC was 2.64 and 2.75, respectively (54).

Most studies also support the dysplasia-carcinoma sequence in CD (55, 57). For instance, in a study by Freidman et al., a screening and surveillance program detected dysplasia, or cancer, in 16% of 259 patients who had follow-up for a median of 24 months (55). Furthermore, the reported frequency of dysplasia in Crohn's patients with colorectal carcinoma ranges from 40–100% (64, 65). In a review of Crohn's-related adenocarcinomas, 61% were found to have dysplasia in either the adjacent, or distant, colonic mucosa (57). Dysplasia in CD is morphologically similar to that seen in UC.

Overall, the survival benefit of endoscopic surveillance in CD is controversial, primarily due to the lack of prospective studies (55, 58, 66, 67). However, there is a growing trend toward endoscopic surveillance in patients with long standing CD (66). Unfortunately, surveillance is often difficult in this disorder due to the frequent presence of strictures. In CD, up to 12% of strictures are malignant (67). Thus, from the standpoint of surveillance, colonoscopic examination often requires the use of a pediatric endoscope.

2. Dysplasia in Ulcerative Colitis

Incidence: The strongest risk factors for the development of carcinoma in UC are the extent and duration of disease (68–72). Some studies also suggest that sclerosing cholangitis represents a significant risk factor for cancer as well (73–75). Controversial risk factors include early age of onset, family history of colon cancer and folate deficiency (76–78). It is generally accepted that patients who have had UC for at least seven to eight years are at risk for developing carcinoma and should be entered into a colonoscopic surveillance program (58, 68,
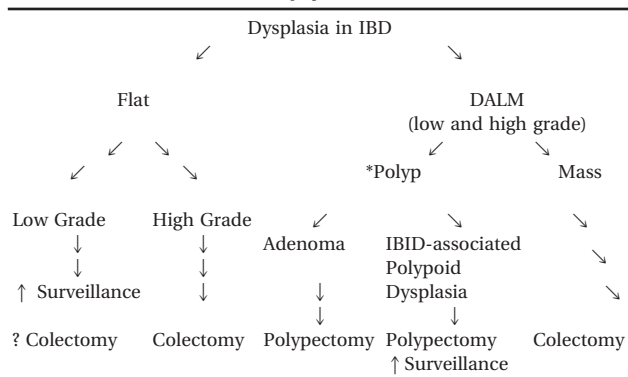
79–81). The incidence of dysplasia in UC is difficult to estimate; studies suggest a 5% incidence of dysplasia after ten years and a 25% incidence after 20 years (80, 82–85). The cumulative incidence of colorectal cancer after 25–35 years of UC ranges from 3.1% to 43%. A reasonable rule of thumb is that the risk of carcinoma increases approximately 1%-2% per year after the first ten years of disease.

Pathologic Features: It is widely accepted that cancer in UC progresses through a step-wise process from inflammation to dysplasia and carcinoma. Dysplasia, as defined by the inflammatory bowel disease-dysplasia morphology study group in 1983, is unequivocal neoplastic epithelium (86). Grossly, there are two general patterns; flat and raised (87, 88). Raised lesions, or dysplasia associated lesions or masses (DALMs), are graded similarly, but are treated differently from flat dysplasia, as discussed below. Atypical changes in UC are separated into three distinct categories: negative for dysplasia, indefinite for dysplasia, and positive for dysplasia. Epithelium that is considered dysplastic is further subclassified into low grade and high grade depending on the severity of the atypia. The morphologic criteria for dysplasia are reviewed by Riddell et al. (86).

Some of the problems encountered in the evaluation of dysplasia includes sampling error and interobserver variability in interpretation (86, 89–91). Since Riddell et al.'s study in 1983, several interobserver studies have shown only moderate levels of agreement (89–91). However, at this time, assessment of risk of malignancy in UC by other histochemical (mucins, sialosyn TN), immunohistochemical (PCNA, MIB-1, p53) or molecular (APC, p27, p16, aneuploidy) methods have not been shown to be more effective than histologic evaluation of dysplasia (92–97).

Natural History and Treatment: Dysplasia is broadly categorized as flat, or associated with an endoscopic (gross) lesion (DALM) (87, 98–100). This subdivision is important since it has direct ramifications as to the risk of malignancy and the treatment of the patient (see Table 4). In brief, low-grade flat dysplasia has a low incidence of associated carcinoma in patients who have had a colectomy (less than 20%). Furthermore, the natural history of low grade dysplasia is not fully understood and given that there is significant interobserver variability in interpretation of biopsies, most patients with flat low grade dysplasia are treated with increased surveillance (58, 68, 79–81, 101, 102). However, recent data suggests that the five-year predictive value of low-grade dysplasia for the development of either high-grade dysplasia or cancer may be as high as 54% (85). Thus, many institutions now recommend colectomy for patients with flat low-grade dysplasia, particularly if it is

TABLE 4. Treatment of Dysplasia in IBD

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                          Dysplasia in IBD
                         ↙              ↘
              Flat                          DALM
                                      (low and high grade)
           ↙      ↘                      ↙        ↘
        ↙            ↘           *Polyp              Mass
   Low Grade   High Grade    ↙        ↘                ↘
      ↓            ↓      Adenoma   IBID-associated      ↘
      ↓            ↓          ↓     Polypoid              ↘
   ↑ Surveillance  ↓          ↓     Dysplasia             ↘
      ↓            ↓          ↓        ↓
  ? Colectomy   Colectomy  Polypectomy  Polypectomy    Colectomy
                                       ↑ Surveillance
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* Polyp implies benign dysplastic epithelium, well circumscribed, completely excised, and not associated with either flat dysplasia or carcinoma.

found on initial exam, is multifocal, or synchronous (58, 85). In contrast, flat high-grade dysplasia has a higher probability of coexistent cancer at colectomy (40–67%) and of progression to carcinoma (40–90% 2–5 year predictive value) (85, 102). For these reasons, flat high-grade dysplasia is generally treated with colectomy. Patients with biopsies considered indefinite for dysplasia should have a repeat endoscopy in 6 months to 1 year, preferably at a time after the inflammation has subsided (58).

3. DALM in Ulcerative Colitis

General Comments: Any dysplastic lesion, either low or high grade, if associated with a polyp or mass (DALM), has traditionally been considered a strong indication for colectomy because of a high associated risk of carcinoma (40%-50%) (88, 98). However, this recommendation is based on some early studies that failed to recognize the different subtypes of DALMs that may be associated with UC (88, 98–100). In 1981, Blackstone *et al.* found 12 patients with macroscopic dysplastic lesions in a four year follow-up study of 112 UC patients (88). Seven of the 12 patients were found to have invasive carcinoma at the time of colectomy. These authors concluded that the gross finding of a dysplastic lesion on colonoscopy was an ominous sign that carried a high risk of cancer and, therefore,

constituted a strong indication for colectomy. Certainly, for patients who have a dysplasia-associated mass, or a large polyp which is incompletely excised, colectomy is the most suitable form of treatment. However, few studies have addressed the clinical significance of isolated polypoid dysplastic lesions (similar in appearance to a sporadic adenoma) that arise on a background of UC. As a result, the treatment of isolated "adenoma-like" polypoid dysplastic lesions which have been totally excised, and contain no invasive cancer, until recently, has been controversial (88, 103). Is a simple polypectomy adequate treatment for these patients? Until recently (87, 104), there has been no data to help separate a sporadic adenoma, which happens to develop in a patient with UC, from a polypoid dysplastic lesion related to the underlying IBD. Clearly, the former lesion can be treated by simple polypectomy, whereas the latter should probably be treated with a colectomy (see below) (87).

Differential Diagnosis of UC-associated Polypoid Dysplasia vs. Sporadic Adenoma: In 1998, our group published the results of a retrospective study of 59 IBD patients (51 UC, 8 CD), all of whom had at least one benign polypoid dysplastic lesion excised, and in whom the differential diagnosis with an incidental sporadic adenoma was entertained (87). On the basis of our follow-up data, several clinical, endoscopic and pathologic features were significantly different between probable IBD-associated polypoid dysplastic lesions and sporadic adenomas (see Table 5). Histologically, polypoid dysplastic lesions associated with IBD appear similar to sporadic adenomas in terms of their overall architectural and cytologic features. However, polypoid dysplastic lesions have a higher degree of inflammation within the lamina propria, and usually show a mixture of normal and dysplastic crypts at the surface of the polyp (Table 5) (Fig. 5). Stalk dysplasia, if present, should alert the pathologist that dysplasia may be present in the adjacent mucosa and that they are likely dealing with an IBD-associated dysplastic lesion rather than an adenoma. Features such as size, architectural type (tubular, tubulovillous, villous), degree of dysplasia, and nuclear chroma-

TABLE 5. Summary of Differentiating Features between IBD-Associated Polypoid Dysplasia and Sporadic Adenomas

Feature Dysplasia	Probable Adenoma	Probable Polypoid Dysplasia
Patient age	Older (>60 years)	Younger (<50 years)
Extent of disease	Usually subtotal	Usually total
Disease activity	Usually inactive	Usually active
Disease duration	Shorter (<10 yr)	Longer (>11 yrs)
Polyp location	Usually non-diseased area [↑ right colon]	Diseased area [↑ left colon]
Associated Flat Dysplasia	Never	Occasionally
Increased lamina propria inflammation	Usually absent	Usually present
Villous architecture	Usually absent	Occasionally present
Mixture of benign and dysplastic crypts at surface of polyp	Usually absent	Usually present
LOH of 3P	Uncommon	Common
LOH of P16	Rare	Common

tin pattern are not helpful in distinguishing these two groups of lesions.

IBD-associated polypoid dysplasia shows a different pattern of genotypic abnormalities (P53, β catenin, APC, P16, 3P) compared to sporadic adenomas, and, thus, may provide a valuable means of distinguishing these lesions (103, 105–112). For instance, by immunohistochemistry, we have recently described a significantly higher degree of P53, and a lower degree of nuclear β catenin immunostaining, in UC-associated polypoid dysplasia compared to sporadic adenomas (106). These techniques may be used in diagnostically difficult cases.

From a molecular point of view, a recent study of adenoma-like polypoid dysplastic lesions by Odze *et al.* strongly supports the concept that these lesions have a different molecular genotype than non adenoma-like DALMs (108). For instance, regardless of their location either within or outside (proximal) to areas of colitis, adenoma-like polypoid dysplastic lesions showed a similar prevalence of 3p, APC and p16 mutations as non UC-associated sporadic adenomas. However, non adenoma-like DALMs from UC patients showed a significantly higher prevalence of 3p and p16 mutations indicating a different timing of molecular events in these lesions. Based on these findings, we believe that adenoma-like polypoid dysplastic lesions in UC and "sporadic" adenomas represent the same pathobiologic entity.

Treatment of Adenoma-Like DALMS: There is compelling recent data to suggest that UC patients with an adenoma-like polypoid dysplastic lesion may be treated adequately by polypectomy and continued surveillance (113–115). In a recent study by our group (Engelsjerd *et al.*) the clinical outcome of 24 UC patients with an adenoma-like polypoid dysplastic lesion were compared to 10 UC patients with a coincidental sporadic adenoma (based on tumor location proximal to colitis) and 49 non-UC (control) patients with a sporadic adenoma (114). After more than 3 years of follow-up, 58% of UC patients with an adenoma-like lesion developed further adenoma-like polyps, which was statistically similar to the 50% of UC patients with sporadic adenomas and the 39% of control group patients who developed further adenomas. Only 1 UC patient with an adenoma-like polyp developed an isolated focus of low-grade dysplasia and none developed adenocarcinoma. Dramatically similar results were found by Rubin *et al.* in a study of 30 UC patients and 18 CD patients with 70 "dysplastic polyps" all of whom were treated with polypectomy (mean follow-up:4.1 years) (115). Most patients (52%) did not develop any further polyps and none developed either dysplasia or adenocarcinoma. As a result of these studies, a new proposal for the treatment of adenoma-like polypoid dysplastic lesions has been proposed and is outlined in Table 6.

TABLE 6. Treatment of DALM's in Ulcerative Colitis

	DALM	
	↙ ↘	
	Adenoma-like	Non Adenoma-like
↙ ↘		
Outside colitis	Inside colitis	↓
↓	↓	
● Polypectomy	● Polypectomy	Colectomy
● regular surveillance	● Confirm absence of flat dysplasia	
	● ? increased surveillance	

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