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QUESTION

HOW DO YOU APPROACH POLYPOID LESIONS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE?

Francis A. Farraye, MD, MSc, FACG, FASGE

Patients with long-standing ulcerative colitis (UC) are at an increased risk for developing dysplasia and colorectal carcinoma (CRC). This risk approaches 8% by 20 years, and 18% by 30 years.¹ More recent data suggests that the risk of CRC in patients with UC may be lower than previously reported.^{2,3} Patients with extensive Crohn's colitis also have an increased risk of CRC and should undergo regular surveillance.⁴ At present, despite a lack of evidence from randomized controlled trials,⁵ surveillance colonoscopy is the best and most widely used method to detect dysplasia and cancer in inflammatory bowel disease (IBD) patients.⁶⁻⁹ However, there are several limitations to surveillance colonoscopy and colonoscopy practices that are not uniform.¹⁰ Multiple biopsies are needed, which is time-consuming. It has been estimated that 33 biopsies are needed to achieve 90% confidence to detect dysplasia if it is present.¹¹ Colonoscopic biopsies should be characterized pathologically as negative, indefinite for dysplasia, or positive for low-grade dysplasia (LGD), high-grade dysplasia (HGD), or carcinoma.¹² There are only moderate levels of agreement among pathologists on the diagnosis of dysplasia with better agreement for HGD versus negative than LGD versus indefinite. An expert gastrointestinal (GI) pathologist should confirm all cases of dysplasia. Of utmost importance, the success of any surveillance program depends on patient compliance with regular colonoscopy.

Dysplasia in IBD may occur in flat mucosa (endoscopically invisible) or as an elevated lesion on endoscopy. The finding of flat HGD or carcinoma (confirmed by 2 expert GI pathologists) in endoscopic biopsy samples is an indication for colectomy.¹³ There is accumulating evidence to suggest that flat LGD is also an indication for colectomy because of the relatively high rate of progression to HGD or cancer.^{3,13-15} The approach to the patient with flat dysplasia is discussed in Question 16 on page 67.

Recent studies by Rutter and Rubin suggest that most dysplasia found in patients with IBD is elevated.^{16,17} Blackstone and colleagues first described the term DALM (dysplasia-associated lesion or mass) in 1981. In Blackstone's study of 12 patients with DALMs, 7

were malignant,¹⁸ and, consequently, any raised dysplastic lesion was felt to be an indication for colectomy. However, it is now apparent that DALMs actually represent a heterogeneous population of tumors in which the cancer risk is not equal among these various subtypes. Raised dysplastic lesions with the appearance of sporadic adenomas have been termed adenoma-like DALMs.¹⁹ Adenoma-like DALMs are well circumscribed, sessile, or pedunculated lesions without hemorrhage, ulceration, or necrosis that resemble sporadic adenomas in patients who do not have IBD (Figure 14-1). In contrast, non-adenoma-like DALMs are defined as irregular, broad-based, or poorly circumscribed lesions that often contain foci of ulceration, necrosis, or hemorrhage (Figure 14-2). Inflammatory polyps have a typical endoscopic appearance (typically small, multiple, glistening, and filiform), have no malignant potential, and, thus, do not mandate removal (Figure 14-3 A, B).

Several reports have described the conservative management of small polypoid dysplastic lesions in patients with IBD. Recent studies have demonstrated that patients with adenoma-like DALMs may be treated adequately by polypectomy and continued surveillance because of their low association with cancer. However, non-adenoma-like DALMs still remain an indication for colectomy because of their high association with cancer.²⁰⁻²³ In one study, polypoid dysplastic lesions with the appearance of adenomas could be identified and removed by standard endoscopic techniques. In the absence of flat dysplasia surrounding the lesion or elsewhere in the colon, the risk of the development of dysplasia or colorectal cancer was low over an 82-month follow-up period.²¹ Rubin and colleagues demonstrated similar results in a cohort of patients followed for a mean of 49 months.²² Close follow-up endoscopic surveillance is required for patients in which a polypoid dysplastic lesion is removed. In general, the initial surveillance colonoscopy is in 3 months, and if no dysplasia is identified, the next procedure can be in 12 months.

If a dysplastic-appearing polyp is encountered (Figure 14-4) and felt to be endoscopically amenable to resection, it should be removed by standard snare cautery techniques. Additional biopsies need to be taken around the polypectomy site as well as throughout the colon. Dysplastic polyps located proximal to an area of colitis can be managed as a sporadic adenoma. Finally, classic-appearing pseudopolyps do not require endoscopic resection or biopsy, though there should be a low threshold to do so if there are any atypical features present. A recent internet-based study determined that academic and private practice gastroenterologists have more difficulty than IBD experts in distinguishing between and managing polypoid dysplastic lesions in patients with UC.²⁴

Newer techniques are needed to facilitate the identification of neoplastic lesions in patients with IBD. Chromoendoscopy may be the technique most readily applicable in clinical practice.^{25,26} Chromoendoscopy can improve the detection of subtle colonic lesions, raising the sensitivity of the endoscopic examination, and it can improve lesion characterization, increasing the specificity of the examination. Additionally, crypt architecture can be categorized using the pit pattern, aiding differentiation between neoplastic and non-neoplastic changes, and enabling the performance of targeted biopsies. Several different stains have been used, including contrast stains (indigo carmine) and vital stains (methylene blue). We await additional studies to determine if chromoendoscopy with targeted biopsies will replace our standard procedure of multiple random biopsies. Finally, a recent study demonstrated that confocal chromoscopic endomicroscopy was superior to standard chromoendoscopy with methylene blue for the detection of dysplasia in patients with UC.²⁷

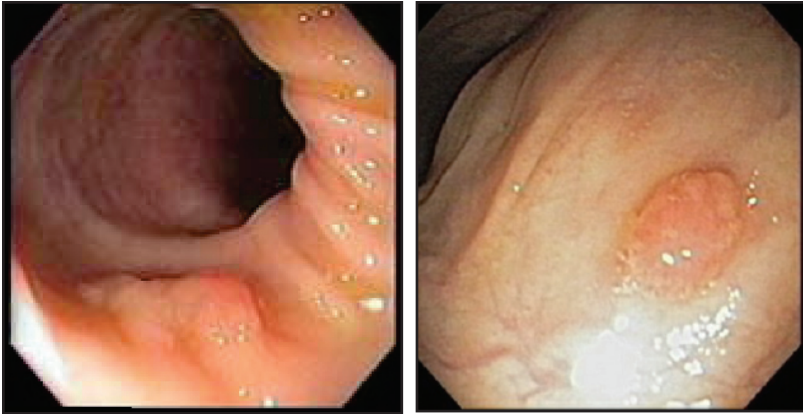


Figure 14-1. Adenoma-like DALM.

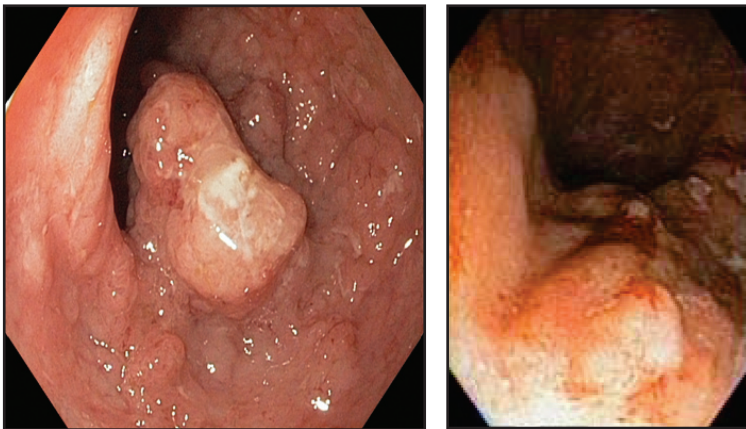


Figure 14-2. Non-adenoma-like DALM.

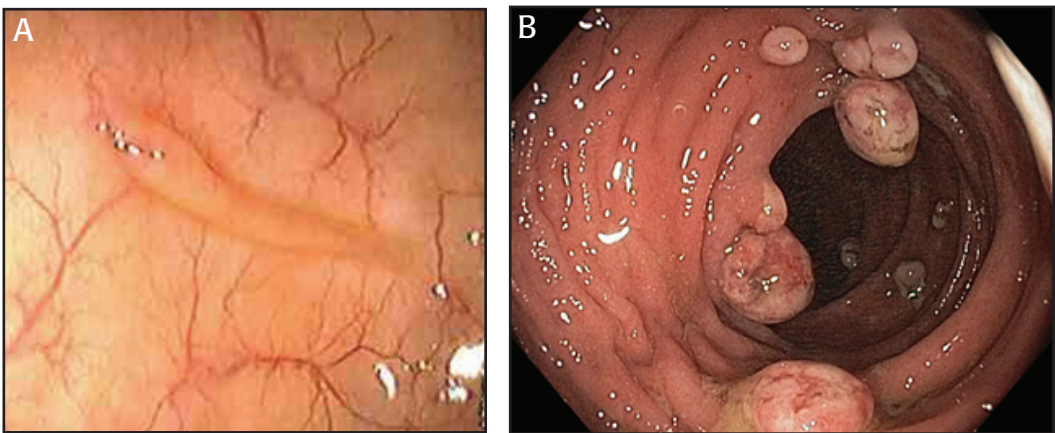


Figure 14-3. Pseudopolyp (A) and multiple pseudopolyps (B).

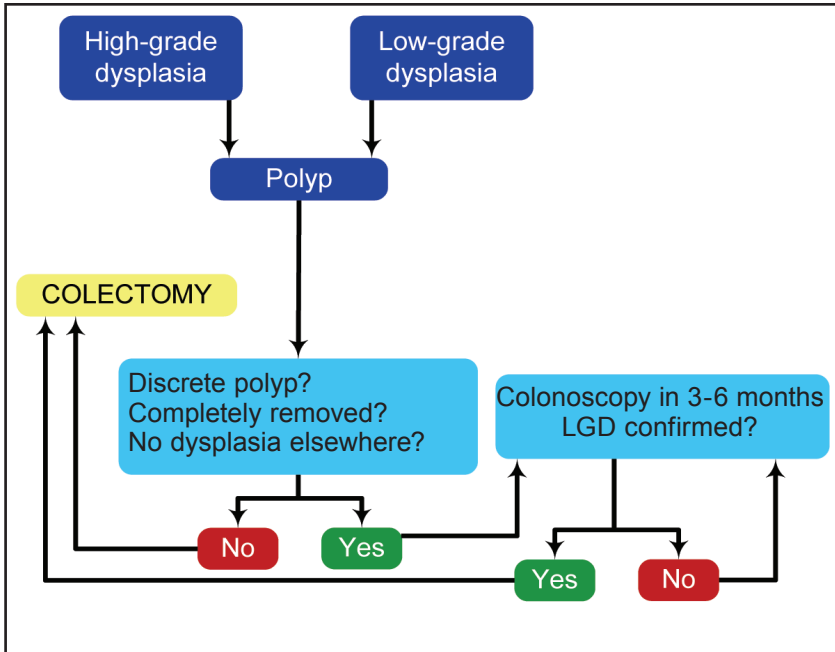


Figure 14-4. Management of polypoid dysplasia in patients with inflammatory bowel disease. Reprinted from *Gastroenterology*, 126(6), Itzkowitz SH, Harpaz N, Diagnosis and management of dysplasia in patients with inflammatory bowel diseases, 1634-1648, Copyright 2004, with permission from Elsevier.

In summary, dysplasia in patients with IBD may be flat or polypoid. Polypoid dysplasia that is completely excised and unassociated with flat dysplasia surrounding the polyp or elsewhere in the colon can be managed by polypectomy alone and continued surveillance.

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23 QUESTION

WHAT IS THE ROLE OF COMPUTED TOMOGRAPHIC ENTEROGRAPHY IN THE DIAGNOSIS AND MANAGEMENT OF INFLAMMATORY BOWEL DISEASE? HAS IT REPLACED BARIUM RADIOGRAPHY?

Edward V. Loftus, Jr., MD

Inflammatory bowel disease (IBD) remains a collection of idiopathic syndromes that are diagnosed by the clinician. There is no one single test that is pathognomonic for IBD, and the clinician must integrate the results of multiple streams of information to produce a diagnosis. In addition to the history and physical examination, the diagnosis typically has rested on the results of colonoscopy and/or ileoscopy with biopsy and barium examination of the small bowel, also known as small bowel follow-through (SBFT). At many centers, however, SBFT has been largely replaced by an examination known as computed tomography enterography (CTE). The hallmarks of this procedure include oral ingestion of a large volume (ie, at least 1400 mL) of a neutral oral contrast agent to optimize small bowel distension and provide a contrast between the lumen and the wall of the small intestine, intravenous (IV) administration of iodinated contrast, and acquisition of thin slices of images throughout the abdomen and pelvis.¹ In Crohn's disease (CD), the typical findings on CTE include mural hyperenhancement, mural stratification, increased mural thickness or asymmetry, fibrofatty proliferation, increased mesenteric fat density, and the "comb sign" (ie, engorged vasa recta) (Figure 23-1).

Some studies suggest an increased sensitivity of CTE for active small bowel inflammation relative to SBFT, and this is not surprising considering that CD is a transmural, not merely mucosal, process.² The aforementioned radiographic findings track well with other measures of CD activity such as ileal erosions on endoscopy or elevated serum C-reactive protein (CRP) concentrations.^{3,4} One prospective blinded study of diagnostic

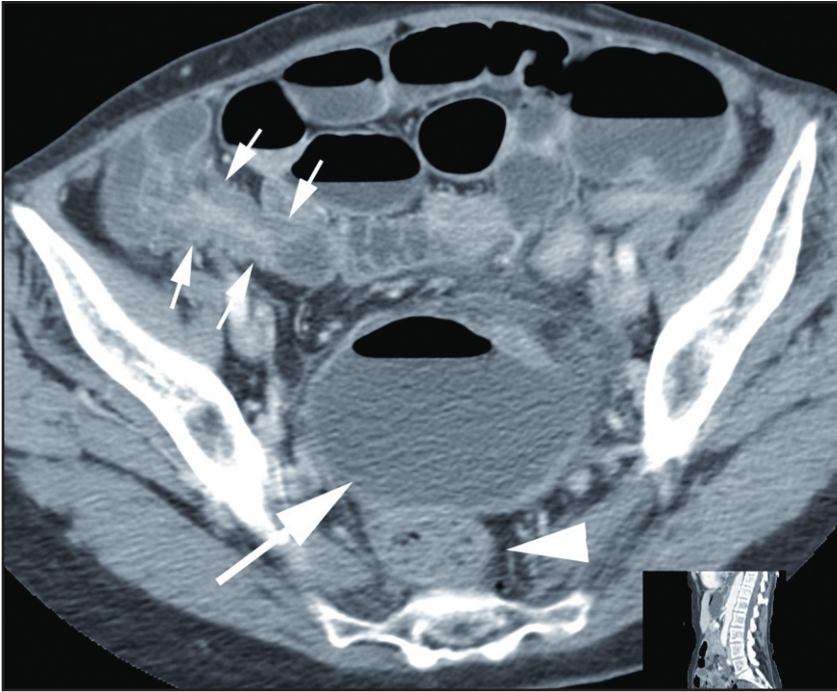


Figure 23-1. CTE of the abdomen and pelvis in a patient with Crohn's disease, which reveals mural thickening, hyperenhancement, and luminal narrowing of the terminal ileum (small arrows), and marked proximal small bowel dilation (large arrow) indicating significant partial small bowel obstruction. Arrowhead indicates rectum. Image courtesy of JG Fletcher, MD.

modalities in patients with known or suspected CD suggested that CTE was more sensitive in detecting active small bowel CD than ileoscopy or SBFT, although these differences were not statistically significant.⁵ Furthermore, CTE was found to be more specific than capsule endoscopy. CTE also has the advantage of detecting occult small bowel strictures that might have resulted in the impaction of an endoscopy capsule. One retrospective study suggested that the prevalence of penetrating disease in 357 consecutive patients with known CD who underwent CTE was over 20%, and that the penetrating complication was a new finding in over half of these.⁶ Moreover, almost 20% of these patients had evidence of extraintestinal manifestations or complications of IBD, and approximately two-thirds of these findings were new.

CTE is not for every patient with known or suspected CD. The lack of adequate bowel distension and the lack of IV contrast both severely limit CTE's utility, so patients who cannot ingest the relatively large volume of oral contrast or who cannot receive iodinated IV contrast (renal insufficiency, severe contrast dye allergy) should undergo alternative imaging. Some have raised concerns about the cost of CTE relative to SBFT. While it is true that CTE is significantly more expensive than SBFT, many believe that the increased amount of information it gleans and the resultant changes in patient management are well worth the increased cost. Indeed, one study suggested that CTE changed the ordering clinicians' perception of corticosteroid benefit in over half of patients with CD.⁷ Nevertheless, additional prospective studies that better quantify the added value of CTE

and how it changes patient management are required. A second concern that has been raised about CTE has been the increased exposure of the patient to ionizing radiation. The effective dose of radiation received by the patient during CTE is estimated to be 3 to 4 times higher than that received during SBFT. Indeed, we found in a population-based cohort that, although the average cumulative dose of ionizing radiation from diagnostic procedures was not much higher than what one would expect from background radiation, the doses received by the top quartile of patients was significantly higher, and much of this increase could be explained by the increasing use of CT.⁸ Hopefully, this issue will become less clinically relevant with the refinement of CT dose-reduction techniques, particularly in patients requiring serial imaging. Our radiologists have already been able to reduce the effective dose of radiation by approximately 30%, and it is expected that further dose reductions will occur in the near future. Advances in the spatial resolution of magnetic resonance imaging (MRI) have allowed us to offer MR enterography in selected patients.

To conclude, CTE is a significant advance in small bowel imaging over SBFT. At our center and many others, CTE has largely replaced SBFT as the first-line small bowel imaging modality in patients with known or suspected CD due to its increased sensitivity in the detection of active small bowel inflammation, ability to detect extraluminal complications, and superior specificity relative to capsule endoscopy.

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39

QUESTION

How Do You Dose 5-AMINOSALICYCLIC ACIDS? WHEN DO YOU USE TOPICAL THERAPY? HOW DO YOU MONITOR DURING THERAPY?

Russell D. Cohen, MD, FACG, AGAF

When I treat patients with Crohn's disease (CD) or ulcerative colitis (UC) and am planning to use a 5-aminosalicylic acid (5-ASA) agent, I consider the following issues:

The first is, "How sick is the patient?" Is this patient someone who really needs an agent that is more effective than a mesalamine agent, or perhaps combination therapy with an oral and topical mesalamine therapy?

The second question I ask is, "Where is the patient's inflammation located?" This is perhaps one of the most important issues when choosing to use mesalamine therapies in patients with inflammatory bowel disease (IBD). While all of the various therapies rely on the mesalamine component to be the anti-inflammatory, they all have different delivery mechanisms, and it is important to understand where the drug is supposed to release, and then target it appropriately to the patient (Figure 39-1).¹

For example, patients who have small bowel CD, regardless of whether they have colonic disease as well, are best served by using Pentasa. Pentasa releases by moisture, guaranteeing release within the small intestine. Pentasa does reach the colon, and it is effective in patients with Crohn's colitis and UC as well. Personally, I find Pentasa to be the best tolerated of the mesalamine agents, and, if a patient is having difficulty tolerating some of the other agents, they will often end up on Pentasa. While it used to be a rather large number of pills (16), the 500 mg formulation has allowed us to use 6 to 8 pills to give 3 to 4 g daily. While the labeling is for 4-times-a-day dosing, I typically dose it bid (twice a day), and have not found any difference in efficacy or tolerance.

For patients who have disease located only in the colon, or perhaps at the very end of the ileum and the colon, then it is appropriate to use one of the pH-release agents such as Asacol or Lialda. Asacol currently comes as 400 mg tablets, and, while the standard

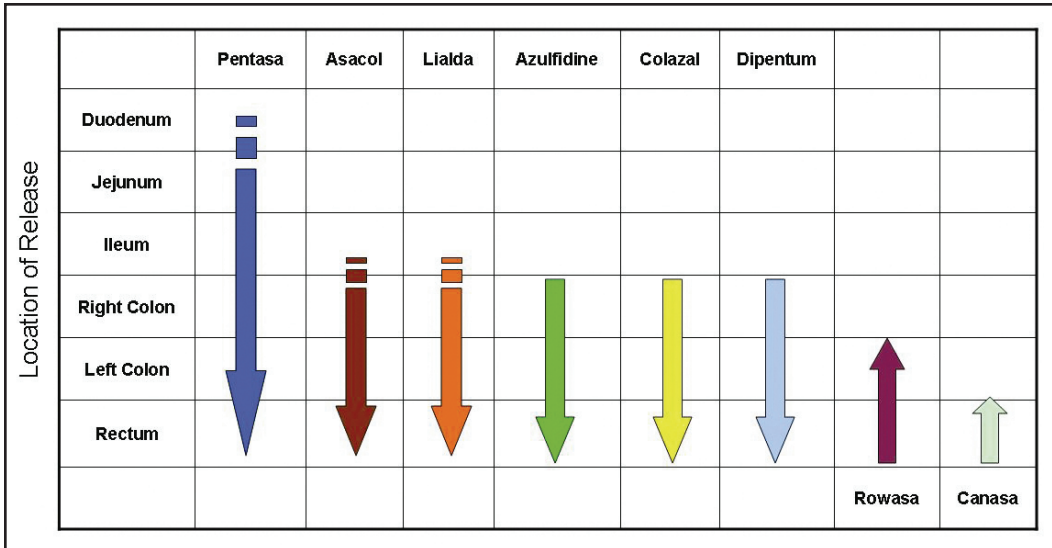


Figure 39-1. Location of medication release for mesalamine-based products.

dose is felt to be 6 pills a day, many of us use 8 to 12 pills for patients who have more aggressive disease. It is still unclear whether there is truly a dose response above 2.4 g, although sicker patients often will use higher doses of mesalamine to get better. Though the labeling is for tid (3 times a day), I usually dose Asacol bid as well to improve patient convenience and compliance.

Lialda is marketed as once-a-day dosing of 2 or 4 pills. Each pill contains 1.2 g of mesalamine. It has only been on the market for less than a year, but in my limited post-market experience with this agent, I find it to be effective at 2 to 3 pills daily. While it can be dosed bid, it is probably unnecessary to do so.² In the case of both Asacol and Lialda, there is the need for the bowel to reach a pH of 7 in order for the agent to release. If patients are passing tablets entirely whole or if the agent is ineffective, it is advisable to try switching to a different delivery system of mesalamine rather than just between these two agents, which have the same initial delivery. Some patients will develop diarrhea or other side effects to the coating on the Asacol or Lialda and not to some of the other delivery systems, so it is always wise to try switching between delivery systems if patients are not responding or perhaps having an adverse reaction. Obviously, a severe adverse reaction would limit the ability to use any mesalamine agents.

Colonic disease, whether the problem is ulcerative or Crohn's colitis, can be treated with any of the agents mentioned above, but the azo-bond drugs, such as Colazal (Salix Pharmaceuticals, Inc., Morrisville, NC), Dipentum (UCB, Inc., Brussels, Belgium), and Azulfidine (Pharmacia & Upjohn, Bridgewater, NJ) are specifically targeting the large intestine. Again, I dose these agents bid, although some patients prefer to use them 3 to 4 times a day due to the number of pills. In the case of Colazal, I typically give 4 pills bid and may back down to 3 pills bid when patients are in remission. Azulfidine is tricky to dose, as you have to start at a low dose (perhaps 1 g daily) and increase the dose slowly over the ensuing week or so. Dipentum also should initially be dose titrated to 1 to 2 g daily, as many patients get diarrhea with this medication. I prefer Dipentum in patients

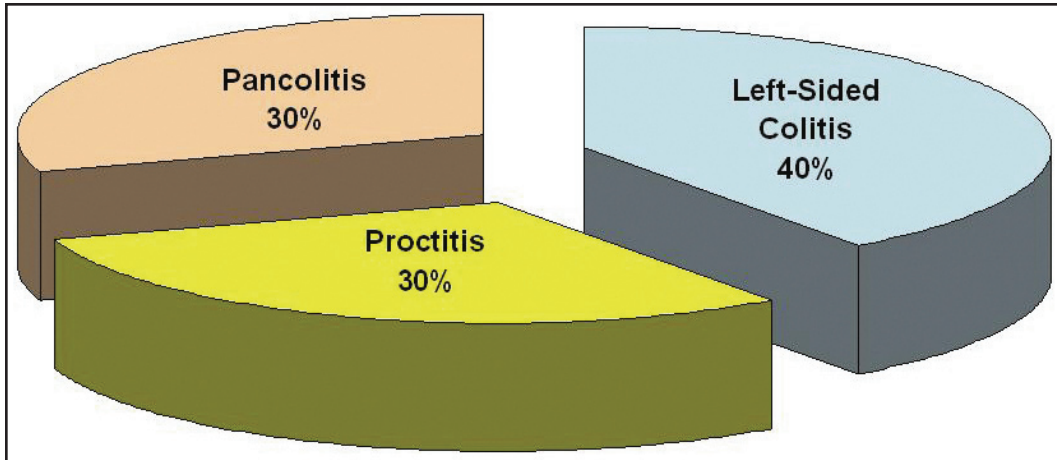


Figure 39-2. Location of disease at diagnosis in patients with ulcerative colitis.

with distal left-sided disease who have a constipation-predominant presentation. There is the thought that perhaps the diarrhea-inducing effect allows the mesalamine to reach the distal colon (or perhaps just relieves the feeling of constipation that the patient suffers from).

Topical therapies are perhaps the most overlooked agents in the approach to treating patients with UC, especially distal colitis, which can be the only location in up to 70% of patients (Figure 39-2). UC always starts in the rectum and works proximally, so one could argue that all patients should be on topical therapy. In reality, patients who just have proctitis are often most rapidly and effectively treated with mesalamine suppository (Canasa; Axcan Pharma US, Inc., Birmingham, AL).³ Dosed at bedtime or bid, these are very effective in getting symptoms down very quickly. Patients who have proctitis but then extend proximally will often still note a benefit from including Canasa as part of their regimen, both for induction and maintenance therapy.

In patients for whom the inflammation extends beyond the rectum, mesalamine enemas (Rowasa) are also very effective.⁴ These are usually dosed at bedtime, as patients may have trouble holding them during the day. Some patients find that they can use half a dose and hold the agent better. Again, these are very effective in induction and maintenance of remission. Some patients may be able to just use the enemas once or twice weekly to maintain their remission.

Luckily, the mesalamine agents are all extremely safe. Sulfasalazine has numerous safety concerns due to the sulfa moiety, and, as a result, the monitoring of blood counts, renal, and hepatic function needs to be more frequent with this agent. The non-sulfa-containing agents have very few serious adverse reactions other than idiosyncratic reactions. Patients who have a strange reaction such as a hepatitis, pericarditis, pleuritis, or pancreatitis would probably best be served without any of these agents.

There has been ongoing debate about whether there is an increased rate of interstitial nephritis in patients who are receiving mesalamine products. As the rates of interstitial nephritis are extraordinarily low, it may be difficult to know for sure whether this is

truly an instigating agent in the rare cases. Nevertheless, it is wise to check renal function within 6 months of starting therapy, and then perhaps yearly afterwards. Checking urine eosinophils and sediment in patients who have suspicion of renal dysfunction can be considered.

The agent that induces remission is often the one we use to maintain remission in patients with UC and CD. Some patients prefer not to use topical therapy long term, but there is an evidence base suggesting that they are effective in the maintenance of remission, even when used intermittently throughout the week. Unfortunately, many doctors seem to shy away from even prescribing these agents, which are highly effective in patients with difficult refractory cases.

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