

# Endoscopic, Imaging, and Histologic Evaluation of Crohn's Disease and Ulcerative Colitis

Bo Shen, M.D.

*Department of Gastroenterology and Hepatology, Desk A31, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195*

(Am J Gastroenterol 2007;102:S41-S45)

Distinguishing Crohn's disease (CD) of the colon from ulcerative colitis (UC) can challenge the clinician. A variety of diagnostic tools exist, but each method has its own strengths and weaknesses. The best diagnostic modality is a combination of laboratory, endoscopic, imaging, and histologic assessments.

## DIFFERENCES BETWEEN CROHN'S DISEASE AND ULCERATIVE COLITIS

The distinction between Crohn's colitis and UC is important as the two disease entities involve different medical management and surgical treatment strategies, especially the application of ileal pouch-anal anastomosis (IPAA) after total proctocolectomy. The two diseases also differ in prognosis and socioeconomic perspectives. For example, after restorative proctocolectomy with IPAA, the majority of patients do well with improved quality of life and daily function. In contrast, patients with Crohn's colitis or indeterminate colitis (IC) have a higher risk for disease recurrence after IPAA. Therefore, an accurate preoperative definition of CD vs. UC is important. The dilemma is in further defining IC.

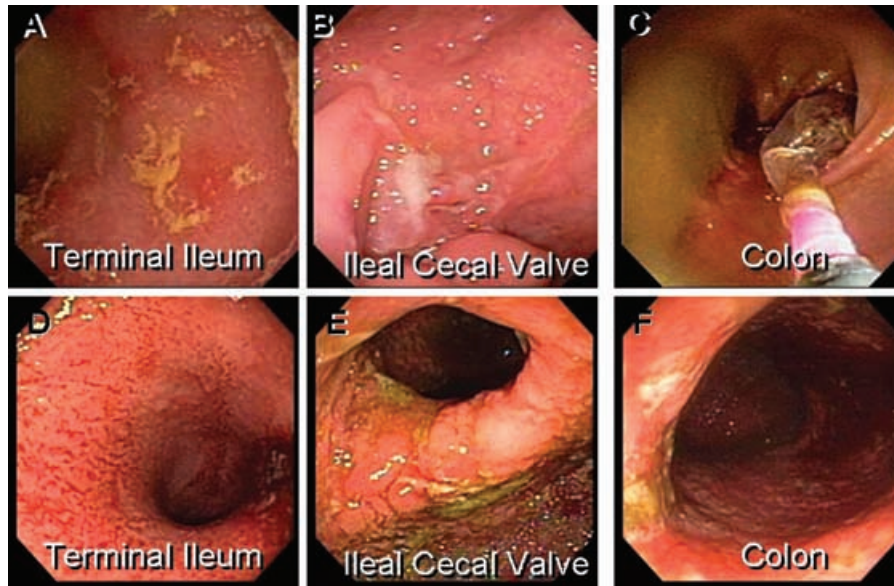
Ten percent to 15% of patients with CD have only colonic involvement, namely, Crohn's colitis (1). CD can occur in patients with restorative proctocolectomy with IPAA in patients with a pre-colectomy diagnosis of UC, IC, or CD. The true incidence of CD of the pouch in patients who initially undergo surgery for UC is not known. Reported cumulative frequencies range from 2.7% to 13% (2-9). Patients often say, "No one told me I had Crohn's disease. I had ulcerative colitis." This is troublesome. Clinicians should make every effort to differentiate CD from UC before the surgery by searching for features that suggest CD, such as segmental colitis or patchiness of the disease, rectal sparing, small bowel lesions, fistulae, transmural inflammation, granulomas, and pyloric gland metaplasia on histology. A combined assessment with endoscopy, radiography, and histology is often needed for accurate diagnosis and differential diagnosis.

## ENDOSCOPIC EVALUATION

Unless contraindicated due to severe colitis, a full colonoscopy with intubation of the terminal ileum should be performed during the initial evaluation of patients suspected of having inflammatory bowel disease (IBD). Since sodium phosphate-based bowel preparations (10, 11) and nonsteroidal anti-inflammatory drugs (12) can cause mucosal changes mimicking IBD, these agents should be avoided before the index colonoscopy. During the colonoscopy, special attention should be paid to the rectum and terminal ileum. Careful evaluation during the index colonoscopy is important for the differential diagnosis of CD and UC as the initiation of medical therapy may obscure discriminating features of CD from UC such as segmental colitis (patchiness) and rectal sparing (13, 14). In a study of 39 patients with treated UC, 44% of patients had endoscopic patchiness and 13% had endoscopic rectal sparing; 33% had histologic evidence of patchiness and 15% had histologic sparing. For example, a 35-yr-old female patient presented at the hospital with rectal-sparing colitis. She was diagnosed as having CD. However, after reviewing the index colonoscopy and histology taken 6 months prior, she was found to have diffuse colitis starting from the anal verge. The "pseudo"-rectal sparing was caused by previous topical mesalamine and topical corticosteroid therapy. She underwent colectomy with IPAA for medically refractory UC.

Careful endoscopic and histologic evaluations are important for the distinction of backwash ileitis from UC and Crohn's ileitis (Fig. 1). Ileoscopy via colonoscopy is useful to distinguish true CD ileitis from backwash ileitis, which occurs in up to 10% of active pancolitis in UC (15). Features that favor CD ileitis include discrete ulcers and/or strictures of the terminal ileum or ileocecal valve (15-17).

A patch of cecal inflammation around the appendiceal orifice can occasionally be seen in patients with left-sided UC. That is not an indication of segmental disease of CD, rather it is a feature of UC (18, 19). The clinical implication of cecal patch is not clear, and a recent controlled study revealed that UC patients with cecal patch had a similar rate of remission,



**Figure 1.** Distinction between Crohn’s ileitis (A–C) and backwash ileitis from diffuse pan-ulcerative colitis (D–F). Crohn’s ileitis is characterized by patchy erythema and ulcers at the terminal ileum (A) and ulcerated stricture at the ileocecal valve (B) with endoscopic balloon dilation (C, D). Backwash ileitis is featured with contiguous mucosal inflammation from the colon (F) to the terminal ileum (D) with a widely patent ileocecal valve (E).

relapse, and proximal extension as compared with UC patients with no cecal patch (19).

**IMAGING**

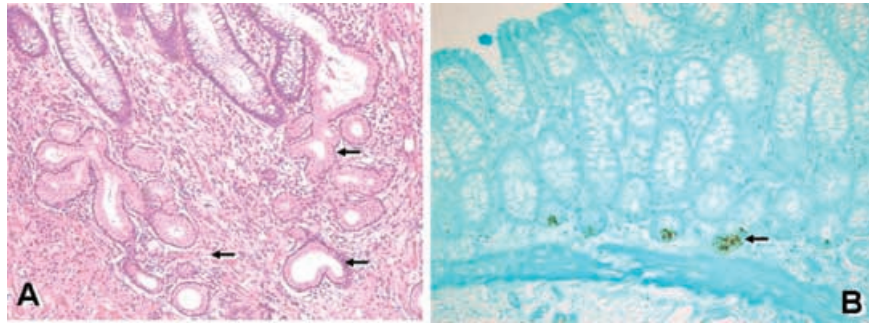
Transmural disease is a unique feature of CD. Transmural disease cannot be assessed by conventional colonoscopy with mucosal biopsy. However, this feature can sometimes be evaluated with a computed tomography (CT) scan or magnetic resonance imaging (MRI) for disrupted layered structure of bowel wall. Additionally, endoscopic ultrasound (EUS) has been used to assess transmural disease (20–22). CD causes asymmetric wall thickening, and in UC it is defined as a thickened third layer consistent with the muscularis mucosa (20, 21). However, EUS has not become a standard of care to assess the patient with Crohn’s colitis *versus* UC.

**OPTICAL COHERENCE TOMOGRAPHY**

Optical coherence tomography (OCT) has an advantage over EUS because it is higher resolution. OCT has a 10–25 times higher spatial resolution than currently available high-frequency EUS (23–25). But OCT has limitations. It can penetrate an image of about 3 mm—about the thickness of the colonic wall in uninflamed condition (26, 27)—compared with EUS, which has deeper image penetration. The layered structure of colon wall was intact. In contrast, the layer structure was disrupted in CD corresponding to transmural disease (26, 27). In the histology-correlated *ex vivo* study, the sensitivity and specificity for OCT to detect transmural disease were 86% and 91%, respectively (26). Using the clinical diagnosis of CD or UC as the gold standard in an *in vivo* via-colonoscopy study, the disrupted layered structure on OCT indicative of transmural inflammation had a diagnostic



**Figure 2.** Wireless capsule endoscopy in the detection of fibrostenotic Crohn’s disease of small bowel (A–C).



**Figure 3.** Pyloric gland metaplasia (A) in small bowel Crohn's disease (H&E stain) and Paneth cell metaplasia (B) in rectal mucosa biopsy detected by human defensin-5 immunohistochemistry in ulcerative colitis.

sensitivity and specificity of 90% and 83% (95% CI 67.3–93.3%) for CD, respectively (27).

### RADIOLOGIC IMAGING AND CAPSULE ENDOSCOPY

MRI or CT enterography has been used to assess CD of small bowel (28). Wireless capsule endoscopy (WCE) is also available (Fig. 2). Data from retrospective studies, case series, and prospective studies have shown that WCE is useful for the diagnoses of CD when small bowel follow through (SBFT) and ileoscopy are negative or unsuccessful (28–39). The diagnostic yield of WCE ranges from 10% to 71% depending on the clinical setting. WCE has been shown to be more sensitive in the detection of small bowel CD than CT enterography (35, 36), SBFT (35, 36), and enteroclysis (39). A recent 4-way study of 42 patients compared SBFT, CT enterography, colonoscopy with ileoscopy, and WCE in the assessment of small bowel CD. Of these four modalities, WCE had the highest sensitivity (83%) with the lowest specificity (53%) and colonoscopy with ileoscopy had the highest specificity (100%) with a sensitivity of 74% (40). WCE is a useful tool for the detection of small erosions or ulcers in patients with suspected CD and a negative SBFT or colonoscopic examination. The previous studies showed that small-bowel erosions can be detected in patients who clearly have UC (41). UC does occasionally affect the small bowel (41). However, the precise role of WCE in the clinical management of patients with CD is yet to be defined (42).

### HISTOLOGIC EVALUATION

When some patients are evaluated for IBD—either CD or UC—the pathologist is looking for histologic signs of chronicity, such as basal plasmacytosis, expanding of the lamina propria with mononuclear cells, and distorted crypt structure. Noncaseating granulomas, a histopathologic hallmark of CD, are only detected in 15–36% of the patients (43, 44). Granulomas can be present in the submucosa, muscularis propria, or serosa, which could be missed with endoscopic mucosal biopsy. Biopsies from the edge of ulcers and

aphthous erosions may yield a high detection rate of granuloma (44). Granulomas are not pathognomonic for CD and they can be found in other disease conditions such as tuberculosis, fungal and bacterial infections, diversion colitis, sarcoidosis (45), and foreign body reaction (particularly from the suture line in patients with prior bowel surgery). When granulomas are next to the disrupted crypt or crypt abscess, they are generally “pseudogranulomas,” not a sign of CD.

The presence of pyloric gland metaplasia in the small bowel or colon biopsy specimens indicates chronic mucosal inflammation and may be suggestive of CD (Fig. 3A) (46). Paneth cell metaplasia of colon mucosa, particular at the left-side colon or rectum, can be considered as a histologic sign of chronic inflammation seen mainly in IBD (47, 48). Immunohistochemistry of human defensin 5 (HD5), a Paneth-cell-specific antimicrobial peptide, can be useful to distinguish CD from UC (Fig. 3B). HD5 immunohistochemistry is more sensitive for the detection of Paneth cell metaplasia than routine H&E histology. The presence of HD5 in the rectal mucosa biopsy indicative of chronic inflammation and exclusion of rectal sparing had a sensitivity of 73% and specificity of 87% in the distinction between CD and UC (49).

### CONCLUSION

In summary, the distinction between Crohn's disease and ulcerative colitis is important, but it can be challenging. Each diagnostic modality has its own pros and cons. Combining endoscopic evaluation, imaging, and histologic evaluation is often necessary.

### REFERENCES

- Farmer RG, Hawk WA, Turnbull RB Jr. Clinical patterns in Crohn's disease: A statistical study of 615 cases. *Gastroenterology* 1975;68:627–35.
- Fazio VW, Tekkis PP, Remzi F, et al. Quantification of risk for pouch failure after ileal pouch anal anastomosis surgery. *Ann Surg* 2003;238:605–14.
- Keighley MR. The final diagnosis in pouch patients for presumed ulcerative colitis may change to Crohn's disease:

- Patients should be warned of the consequences. *Acta Chir Jugosl* 2000;47(Suppl 4):27–31.
4. Peyregne V, Francois Y, Gilly FN, et al. Outcome of ileal pouch after secondary diagnosis of Crohn's disease. *Int J Colorectal Dis* 2000;15:49–53.
  5. Goldstein NS, Sanford WW, Bodzin JH. Crohn's-like complications in patients with ulcerative colitis after total proctocolectomy and ileal pouch-anal anastomosis. *Am J Surg Pathol* 1997;21:1343–53.
  6. Deutsch AA, McLeod RS, Cullen J, et al. Results of the pelvic-pouch procedure in patients with Crohn's disease. *Dis Colon Rectum* 1991;34:475–7.
  7. Yu CS, Pemberton JH, Larson D. Ileal pouch-anal anastomosis in patients with indeterminate colitis: Long-term results. *Dis Colon Rectum* 2000;43:1487–96.
  8. Neilly P, Neill ME, Hill GL. Restorative proctocolectomy with ileal pouch-anal anastomosis in 203 patients: The Auckland experience. *Aust N Z J Surg* 1999;69:22–7.
  9. Gemlo B, Wong D, Rothenberger DA, et al. Ileal pouch-anal anastomosis. Patterns of failure. *Arch Surg* 1992;127:784–6.
  10. Zwas FR, Cirillo NW, el-Serag HB, et al. Colonic mucosal abnormalities associated with oral sodium phosphate solution. *Gastrointest Endosc* 1996;43:463–6.
  11. Rejchrt S, Bures J, Siroky M, et al. A prospective, observational study of colonic mucosal abnormalities associated with orally administered sodium phosphate for colon cleansing before colonoscopy. *Gastrointest Endosc* 2004;59:651–4.
  12. Lengeling RW, Mitros FA, Brennan JA, et al. Ulcerative ileitis encountered at ileo-colonoscopy: Likely role of non-steroidal agents. *Clin Gastroenterol Hepatol* 2003;1:160–9.
  13. Kim B, Barnett JL, Kleer CG, et al. Endoscopic and histological patchiness in treated ulcerative colitis. *Am J Gastroenterol* 1999;94:3258–62.
  14. Bernstein CN, Shanahan F, Anton PA, et al. Patchiness of mucosal inflammation in treated ulcerative colitis: A prospective study. *Gastrointest Endosc* 1995;42:232–7.
  15. Chutkan RK, Wayne JD. Endoscopy in inflammatory bowel disease. In: Kirsner JB, ed. *Inflammatory bowel disease*, 5th Ed. Philadelphia, PA: W.B. Saunders Company, 2000:453–77.
  16. Moum B, Ekblom A, Vatn MH, et al. Change in the extent of colonoscopic and histological involvement in ulcerative colitis over time. *Am J Gastroenterol* 1999;94:1564–9.
  17. Rutgeerts P. Strategies in the prevention of post-operative recurrence in Crohn's disease. *Best Pract Res Clin Gastroenterol* 2003;17:63–73.
  18. Okawa K, Aoki T, Sano K, et al. Ulcerative colitis with skip lesions at the mouth of the appendix: A clinical study. *Am J Gastroenterol* 1998;93:2405–10.
  19. Byeon J-S, Yan SK, Myung SJ, et al. Clinical course of distal ulcerative colitis in relation to appendiceal orifice inflammation status. *Inflamm Bowel Dis* 2005;11:366–71.
  20. Hildebrandt U, Kraus J, Ecker KW, et al. Endosonographic differentiation of mucosal and transmural nonspecific inflammatory bowel disease. *Endoscopy* 1992;24(Suppl 1):359–63.
  21. Shimizu S, Tada M, Kawai K. Value of endoscopic ultrasonography in the assessment of inflammatory bowel disease. *Endoscopy* 1992;24(Suppl 1):354–8.
  22. Shimizu S, Tada M, Kawai K. Endoscopic ultrasonography in inflammatory bowel diseases. *Gastrointest Endosc Clin North Am* 1995;5:851–9.
  23. Das A, Sivak MV Jr, Chak A, et al. High-resolution endoscopic imaging of the GI tract: A comparative study of optical coherence tomography versus high-frequency catheter probe EUS. *Gastrointest Endosc* 2001;54:219–24.
  24. Brezinski ME, Tearney GJ, Boppart SA, et al. Optical biopsy with optical coherence tomography: Feasibility for surgical diagnostics. *J Surg Res* 1997;71:32–40.
  25. Fujimoto JG, Brezinski ME, Tearney GJ, et al. Optical biopsy and imaging using optical coherence tomography. *Nat Med* 1995;1:970–2.
  26. Shen B, Zuccaro G, Gramlich TL, et al. Ex vivo histology-correlated optical coherence tomography in the detection of transmural inflammation in Crohn's disease. *Clin Gastroenterol Hepatol* 2004;2:754–60.
  27. Shen B, Zuccaro G Jr, Gramlich TL, et al. In vivo colonoscopic optical coherence tomography for transmural inflammation in inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2004;2:1080–7.
  28. Scapa E, Jacob H, Lewkowicz S, et al. Initial experience of wireless-capsule endoscopy for evaluating occult gastrointestinal bleeding and suspected small bowel pathology. *Am J Gastroenterol* 2002;97:2776–9.
  29. Hara AK, Leighton JA, Sharma VK, et al. Small bowel: Preliminary comparison of capsule endoscopy with barium study and CT. *Radiology* 2004;230:260–5.
  30. Herreras JM, Caunedo A, Rodriguez-Tellez M, et al. Capsule endoscopy in patients with suspected Crohn's disease and negative endoscopy. *Endoscopy* 2003;35:564–8.
  31. Mow WS, Lo SK, Targan SR, et al. Initial experience with wireless capsule enteroscopy in the diagnosis and management of inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2004;2:31–40.
  32. Fireman Z, Mahajna E, Broide E, et al. Diagnosing small bowel Crohn's disease with wireless capsule endoscopy. *Gut* 2003;52:390–2.
  33. Arguelles-Arias F, Caunedo A, Romero J, et al. The value of capsule endoscopy in pediatric patients with a suspicion of Crohn's disease. *Endoscopy* 2004;36:869–73.
  34. Costamagna G, Shah SK, Riccioni ME, et al. A prospective trial comparing small bowel radiographs and video capsule endoscopy for suspected small bowel disease. *Gastroenterology* 2002;123:999–1005.
  35. Eliakim R, Fischer D, Suissa A, et al. Wireless capsule video endoscopy is a superior diagnostic tool in comparison to barium follow-through and computerized tomography in patients with suspected Crohn's disease. *Eur J Gastroenterol Hepatol* 2003;15:363–7.
  37. Eliakim R, Suissa A, Yassin K, et al. Wireless capsule video endoscopy compared to barium follow-through and computerized tomography in patients with suspected Crohn's disease—final report. *Dig Liver Dis* 2004;36:519–22.
  38. Voderholzer WA, Ortner M, Rogalla P, et al. Diagnostic yield of wireless capsule enteroscopy in comparison with computed tomography enteroclysis. *Endoscopy* 2003;35:1009–14.
  39. Voderholzer WA, Beinhoelzl J, Rogalla P, et al. Small bowel involvement in Crohn's disease: A prospective comparison of wireless capsule endoscopy and computed tomography enteroclysis. *Gut* 2005;54:369–73.
  40. Chong AK, Taylor A, Miller A, et al. Capsule endoscopy vs. push enteroscopy and enteroclysis in suspected small-bowel Crohn's disease. *Gastrointest Endosc* 2005;61:255–61.
  41. Solem CA, Loftus EV Jr, Fletcher JG, et al. Small bowel (SB) imaging in Crohn's disease (CD): A prospective, blinded, 4-way comparison trial. *Gastroenterology* 2005;128(Suppl):A74.
  42. Valdez R, Appelman HD, Bronner MP, et al. Diffuse duodenitis associated with ulcerative colitis. *Am J Surg Pathol* 2000;24:1407–13.

43. Leighton JA, Shen B, Baron TH, et al. ASGE guideline: Endoscopy in the diagnosis and treatment of inflammatory bowel disease. *Gastrointest Endosc* 2006;63:558–65.
44. Ramzan NN, Leighton JA, Heigh RI, et al. Clinical significance of granuloma in Crohn's disease. *Inflamm Bowel Dis* 2002;8:168–73.
45. Potzi R, Walgram M, Lochs H, et al. Diagnostic significance of endoscopic biopsy in Crohn's disease. *Endoscopy* 1989;21:60–2.
46. Sands BE. From symptom to diagnosis: Clinical distinctions among various forms of intestinal inflammation. *Gastroenterology* 2004;126:1518–32.
47. Doumit J, Shen B, Goldblum J, et al. Pyloric gland metaplasia: A specific histopathologic marker for Crohn's disease. *Am J Gastroenterol* 2003;98:A781.
48. Wehkamp J, Schwind B, Herrlinger KR, et al. Innate immunity and colonic inflammation: Enhanced expression of epithelial alpha-defensins. *Dig Dis Sci* 2002;47:1349–55.
49. Lewin K. The Paneth cell in disease. *Gut* 1969;10:804–11.