

Morphologic Features of Mild, Temporally-Early Crohn's Disease

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This discussion focuses on the morphologic features of mild, temporally-early Crohn's disease (CD). This topic suffers from large historical perspective biases. A short historical review is provided as a precis to this presentation.

History of Crohn's Disease

The first descriptions of Crohn's disease were published by Crohn, Ginzburg, and Oppenheimer and Crohn and Rosenak in 1932 and 1936, respectively ^{1,2}. They termed the disease regional enteritis to distinguish it from tuberculosis enteritis. The authors noted that regional enteritis was not confined to the ileum, proximal involvement of the cecum and right colon was typical. Rappaport published the first full, detailed pathologic study of Crohn's disease resection specimens using the archives of military hospitals in 1951 ³.

That CD could extensively involve the colon in a pattern similar to ulcerative colitis was first described in 1960 by Lockhart-Mummery ⁴. Up to this time, extensive involvement of the colon was considered ulcerative colitis with (*severe*) backwash ileitis. Simply put, before this study was published, Crohn's colitis did not exist.

The new technologic research tool of the 1960s and 70s, the electron microscope, sparked interest in identifying the early morphologic features of CD. Obtaining tissue for study was not a straightforward task. Although radiological studies had advanced to the point of being able to identify early mucosal fissures and wall thickening, CD was squarely a surgical disease. CD tissue only became available when complications of stenosis or fissures made surgery mandatory. Authors of the era used grossly normal ileum or colon proximal to CD stenotic or fistulous segments ⁵⁻⁷.

Small mucosal erosions of CD were termed "aphthoid ulcers" by Brooke based on their gross similarity to the oral lesions of aphthous stomatitis ⁸. Aphthoid ulcers or erosions were pinpoint to about 3 mm in diameter. They typically developed over a lymphoid follicle or aggregate. The aphthoid erosion proper consisted of a focal erosion and active surface epithelial proliferation along its periphery. Active inflammation with fibrin extended from erosion and the adjacent mucosa and subjacent submucosa was edematous ⁹⁻¹¹.

. Given the source of studied tissue (resection specimens with stenoses or fistulas) and the length of most patients CD symptoms preceding surgery (years), it was implicitly understood by authors of the day that the small size of the ulcers and mild histologic changes were not synonymous with temporally early CD ¹². In 1972, Morson commented that aphthoid erosions most likely took years to progress and cause sufficient structural damage (to the bowel) to produce clinical or radiological signs ¹³.

Technologic advances brought the functional hollow-lumen magnifying colonoscope into the clinic during the latter half of the 1970's. Endoscopic examination

of ileum as part of work up of CD was first described in 1975¹⁴. The first pathology publications related to endoscopically-procured mucosal biopsies of the rectum, colon, and distal ileum were published in the early 1980's¹⁵. The clinical utility of colonoscopy was not immediately recognized. Given the many decades of experience with radiologic studies and the monolithic view that CD was a surgical disease, many studies during the early 1980's debated the advantages and disadvantages of colonoscopy compared to radiology¹⁶. In 1984, Goldin et al. reported diagnosing recurrent CD via ileoscopy that also included a substantial number of ileoscopy first case reports.

Contemporary-era studies that broke with the previously held views of CD began being published in the mid-1980s. Borch et al. found 8% of endoscopically normal appearing ileal mucosa predominantly from patients with chronic diarrheal symptoms of inflammatory bowel disease had mild active ileitis¹⁷. The histologic features, in the absence of granulomas were considered nonspecific.

Mild, Temporally-Early Crohn's Disease

Mild, temporally-early CD frequently presents as altered bowel habits and mild abdominal pain that closely mimic those of irritable bowel disease and mild-watery diarrhea syndrome¹⁸⁻²². CD should be considered as one of the microscopic colitides, along with lymphocytic colitis, collagenous colitis, infectious colitis, and amyloid.

Histologically, focal lesions in endoscopically minimally abnormal or normal mucosa can be found in the ileum or colon. In children, ileal CD lesions are delayed compared with colonic lesions²³. Active ileal inflammation is more frequent in adults²⁴⁻²⁶. Microscopically, CD is frequently thought of as patchy and involving all levels of the bowel wall with crypt architectural distortion. Mild early-CD rarely has homogeneous dense lymphoplasmacytic inflammation that expands the lamina propria and diffuse crypt branching is almost as rare.

There is no single feature that definitively identifies or allows a pathologist to diagnose CD. The three main morphologic features of mild CD are *mild focal crypt disarray, focal lamina propria edema, and patchy abnormal lymphoplasmacytic lamina propria inflammation*. Individually, each morphologic feature of mild CD is nonspecific. However, when well-developed and together, this constellation of features is highly diagnostic of CD.

Crypt architectural distortion in mild CD is usually as crypt disarray; crypts that are irregularly arranged and vary in size and shape. Rarely in mild CD is there sufficient injury to the crypts to induce a regenerative response of branching due to crypt fission. Conceptually, crypt disarray appears to be due to edema and patchy inflammation "pushing" the crypts around in the lamina propria. This is in contrast to UC where there is direct, "cryptocentric" injury.

Lamina propria edema in mild CD is often focal, 1 - 4 crypts wide. Very often this level of focality can be seen as involving a portion of mucosa within a biopsy tissue fragment. The lamina propria often appears paler with a sparser density of lymphoplasmacytic

inflammatory cells in the edematous area than the adjacent non-edematous lamina propria. Crypt disarray is often most prominent in the focus of lamina propria edema.

Focal lamina propria lymphoplasmacytic inflammation most often appears to be a poorly formed lymphoplasmacytic aggregate or a slightly increased density of lymphocytes and plasma cells in which the normal gradient is lost (normal gradient is most dense beneath surface epithelium with increasing sparse density towards muscularis mucosa).

Villous abnormalities in mild early-CD are most often minimal. Occasional there will be focal villous flattening and broadening due to edema.

Gastric-type mucus gland metaplasia in ileal biopsies occurs in approximately 25% of chronic CD patients. It is essentially diagnostic of CD in patients with mildly altered bowel habits and is not seen in backwash ileitis from UC²⁷. It is a specific form of healing response, related to trefoil peptides²⁷⁻³⁰

References

1. Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis: a pathologic and clinical entity. JAMA 1932;99:1323-1329.
2. Crohn BB, Rosenak BD. A combined form of ileitis and colitis. JAMA 1936;106:1-7.
3. Rappaport H, Burgoyne FH, Smetana HF. The pathology of regional enteritis. Military Surgeon 1951;109:463-502.
4. Lockhart-Mummery HE, Morson BC. Crohn's disease (regional enteritis) of the large intestine and its distinction from ulcerative colitis. Gut 1960;1:87-105.
5. Goodman MJ, Kirsner JB, Riddell RH. Usefulness of rectal biopsy in inflammatory bowel disease. Gastroenterology 1977;72:952-956.
6. Joffe N, Antonioli DA, Bettmann MA et al. Focal granulomatous (Crohn's) colitis: radiologic-pathologic correlation. Gastrointest Radiol 1978;3:73-80.
7. Nyhlin H, Stenling R. The small-intestinal mucosa in patients with Crohn's disease assessed by scanning electron and light microscopy. Scand J Gastroenterol 1984;19:433-440.
8. Brooke BN. What is ulcerative colitis? Lancet 1953;1:1220-1225.
9. McGovern VJ, Goulston SJ. Crohn's disease of the colon. Gut 1968;9:164-176.
10. Sankey EA, Dhillon AP, Anthony A et al. Early mucosal changes in Crohn's disease. Gut 1993;34:375-381.

11. Schattenfroh S, Bartels M, Nagel E. Early morphological changes in Crohn's disease. Transmission electron-microscopic findings and their interpretation: an overview. *Acta Anat (Basel)* 1994;149:237-246.
12. Rickert RR, Carter HW. The "early" ulcerative lesion of Crohn's disease: correlative light- and scanning electron- microscopic studies. *J Clin Gastroenterol* 1980;2:11-19.
13. Morson BC. The early histological lesion of Crohn's disease. *Proc R Soc Med* 1972;65:71-72.
14. Geboes K, Vantrappen G. The value of colonoscopy in the diagnosis of Crohn's disease. *Gastrointest Endosc* 1975;22:18-23.
15. Goldman H, Antonioli DA. Mucosal biopsy of the rectum, colon, and distal ileum. *Hum Pathol* 1982;13:981-1012.
16. Coremans G, Rutgeerts P, Geboes K et al. The value of ileoscopy with biopsy in the diagnosis of intestinal Crohn's disease. *Gastrointest Endosc* 1984;30:167-172.
17. Borsch G, Schmidt G. Endoscopy of the terminal ileum: diagnostic yield in 400 consecutive examinations. *Dis Colon Rectum* 1985;28:499-501.
18. Fry LC, Carey EJ, Shiff AD et al. The yield of capsule endoscopy in patients with abdominal pain or diarrhea. *Endoscopy* 2006;38:498-502.
19. Liszka L, Woszczyk D, Pajak J. Histopathological diagnosis of microscopic colitis. *J Gastroenterol Hepatol* 2006;21:792-797.
20. Beattie RM, Croft NM, Fell JM et al. Inflammatory bowel disease. *Arch Dis Child* 2006;91:426-432.
21. da Silva JG, De BT, Cintra Damiao AO et al. Histologic study of colonic mucosa in patients with chronic diarrhea and normal colonoscopic findings. *J Clin Gastroenterol* 2006;40:44-48.
22. O'Beirne JP, Ireland A. Progression of collagenous colitis to Crohn's disease. *Eur J Gastroenterol Hepatol* 2005;17:573-575.
23. Meinzer U, Idestrom M, Alberti C et al. Ileal involvement is age dependent in pediatric Crohn's disease. *Inflamm Bowel Dis* 2005;11:639-644.
24. Cuvelier C, Barbatis C, Mielants H et al. Histopathology of intestinal inflammation related to reactive arthritis. *Gut* 1987;28:394-401.
25. Mielants H, Veys EM, Cuvelier C et al. HLA-B27 related arthritis and bowel inflammation. Part 2. Ileocolonoscopy and bowel histology in patients with HLA-B27 related arthritis. *J Rheumatol* 1985;12:294-298.

26. Mielants H, Veys EM, Cuvelier C et al. Ileocolonosopic findings in seronegative spondylarthropathies. *Br J Rheumatol* 1988;27 Suppl 2:95-105.:95-105.
27. Goldstein NS. Isolated ileal erosions in patients with mildly altered bowel habits. A follow-up study of 28 patients. *Am J Clin Pathol* 2006;125:838-846.
28. Ahnen DJ, Poulsom R, Stamp GW et al. The ulceration-associated cell lineage (UACL) reiterates the Brunner's gland differentiation programme but acquires the proliferative organization of the gastric gland. *J Pathol* 1994;173:317-326.
29. Ming SC, Simon M, Tandon BN. Gross gastric metaplasia of ileum after regional enteritis. *Gastroenterology* 1963;44:63-68.
30. Koukoulis GK, Ke Y, Henley JD et al. Detection of pyloric metaplasia may improve the biopsy diagnosis of Crohn's ileitis. *J Clin Gastroenterol* 2002;34:141-143.