**CASE 5**

**DIAGNOSIS: Active chronic colitis with granulomas.**

**CLINICAL HISTORY:**

A 56-year-old male has a history of primary biliary cholangitis and chronic diarrhea of 12 years.

**MICROSCOPIC DESCRIPTION:**

The terminal ileum has no significant histologic changes. The colon biopsies demonstrate a diffuse increase in chronic inflammation from the right colon to the left colon. The architecture is overall preserved with some irregularity. There is Paneth cell metaplasia in the left colon, and mild basal plasmacytosis is also present. There is an increase in lymphocytes within the epithelium as well as cryptitis and crypt abscesses. Granulomas are scattered through the colon, a few of which are associated with crypt rupture.

**DISCUSSION:**

Inflammatory bowel disease (IBD) encompasses ulcerative colitis (UC) and Crohn disease (CD). UC classically has a continuous pattern of injury that involves the rectum, and injury is predominantly limited to the mucosa. CD on the other hand is typically patchy, does not involve the rectum, and is a transmural disease. On biopsies, the primary histologic feature is evidence of chronic injury. This includes architectural distortion, such as crypt shortening, crypt branching, and irregular crypt spacing, as well as expansion of the lamina propria by chronic inflammation, basal lymphoplasmacytosis, and basal lymphoid aggregates. Metaplastic changes such as Paneth cell metaplasia in the left colon and pyloric metaplasia in the terminal ileum are also signs of chronic injury.

It is important to differentiate UC and CD for proper management. There are a few clues that may be helpful for biopsies. Because UC has a continuous pattern of injury, at low magnification, one can appreciate increased inflammation involving every biopsy fragment. Meanwhile, CD is a segmental disease so one will see interspersed fragments of normal appearing colon. The terminal ileum is frequently involved in CD and is less commonly inflamed in UC. Lastly, non-necrotizing epithelioid granulomas are commonly associated with CD.

Another consideration in the differential for chronic diarrhea is microscopic colitis (MC), which includes lymphocytic colitis (LC) and collagenous colitis (CC). MC is usually a pancolitis. Similarly to IBD, there is increase in chronic inflammation within the lamina propria, and there is surface epithelial damage. The most notable feature for LC is a marked increase in intraepithelial lymphocytes. Intraepithelial lymphocytosis may also be seen in CC, but it tends to be milder. CC is diagnosed based on the presence of a thickened subepithelial collagen band. Thickening of the collagen band may be patchy and can be better visualized with a trichrome stain. The most helpful distinction from IBD based on histology is the absence of significant architectural distortion. These are called MC because endoscopically, the colon appears normal in most cases.

Not all colitides follow these textbook distinctions. For example, this case raises many important points that pathologists should be aware of:

1. Granulomas do not necessarily make this case CD. While they are more commonly associated with CD, UC may also have granulomas, usually in association with crypt rupture. Crypt rupture results in extravasated mucin that then leads to development of granulomatous reaction. Crypts are more likely to rupture in the deeper portions of the mucosa. On the other hand, CD related granulomas have been described to be more sporadically located in the mucosa and often involve the superficial mucosa. Granulomas are also not limited to IBD. Infection, notably by mycobacteria, histoplasma, and yersinia, should be ruled out when encountering unexpected granulomas. Sarcoidosis may also rarely involve the colon. There are rare reports of granulomas associated with medications, such as ​immune modulators, TNF1a inhibitors, and diclofenac​.

2. There are IBD variants. Not only can CD result in a pancolitis, but it can also cause a superficial pattern that has injury limited to the mucosa; mimicking UC. On the other hand, UC may also have ileitis, usually in pancolitis and is described as “backwash ileitis.” UC can also appear patchy, often due to prior treatment with variable regional effect, but it is also not uncommon to have inflammation in the right colon in subtotal UC.

3. Microscopic colitis may have evidence of chronic injury. Metaplastic changes and even architectural irregularities have been described in MC. On the other hand, basal plasmacytosis and basal lymphoid aggregates are not routinely seen.

4. Microscopic colitis is not always microscopic. Endoscopic findings have been described for collagenous colitis, including mucosal abnormalities, pseudomembranes, and mucosal breaks.

5. Aside from histologic findings, clinical history can also aid in diagnosis. Watery diarrhea is the main symptom in MC, whereas stools tend to be bloody in IBD. A history of strictures and fistulas are highly suggestive of CD over UC. Medications, history of radiation, diverticular disease, recurrent infections, ischemia are also potential causes of chronic injury that may mimic IBD.

For challenging cases that have many overlapping features, the most important action is to discuss with the clinician and correlate clinically. Ultimately, this patient has been managed for UC for the past 12 years and is doing well.

**References**

1. Ayata, G. Prevalence and significance of inflammatory bowel disease-like morphologic features in collagenous and lymphocytic colitis. The American journal of surgical pathology. 2002;26(11). https://doi.org/10.1097/00000478-200211000-00003.

2. Baert, F. A case of diclofenac-induced colitis with focal granulomatous change. The American journal of gastroenterology. 1995;90(10).

3. Fiehn, AK. Distribution of histopathological features along the colon in microscopic colitis. International journal of colorectal disease. 2021;36(1). https://doi.org/10.1007/s00384-020-03747-z.

4. Ghrenassia, E. Digestive-tract sarcoidosis: French nationwide case-control study of 25 cases. Medicine. 2016;95(29). https://doi.org/10.1097/MD.0000000000004279.

5. Koulaozidis, A. Distinct colonoscopy findings of microscopic colitis: not so microscopic after all? World journal of gastroenterology. 2011;17(37). https://doi.org/10.3748/wjg.v17.i37.4157.

6. Langner, C. Histology of microscopic colitis-review with a practical approach for pathologists. Histopathology. 2015;66(5). https://doi.org/10.1111/his.12592.

7. Mahadeva, U. Granulomatous ulcerative colitis: a re-appraisal of the mucosal granuloma in the distinction of Crohn's disease from ulcerative colitis. Histopathology. 2002;41(1). https://doi.org/10.1046/j.1365-2559.2002.01416.x.

8. Odze, R. Diagnostic problems and advances in inflammatory bowel disease. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2003;16(4). https://doi.org/10.1097/01.MP.0000064746.82024.D1.

9. Odze, R. Surgical Pathology of the GI Tract, Liver, Biliary Tract, and Pancreas. 4 ed2023.

10. Saurine, TJ. Microscopic colitis with granulomatous inflammation. Histopathology. 2004;45(1). https://doi.org/10.1111/j.1365-2559.2004.01906.x.

11. Soucy, G. Clinical and pathological analysis of colonic Crohn's disease, including a subgroup with ulcerative colitis-like features. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2012;25(2). https://doi.org/10.1038/modpathol.2011.120.

12. Sumi, T. Sarcoidosis development during ulcerative colitis remission in a patient with a susceptible human leukocyte antigen serotype. Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG. 2021;38(1). https://doi.org/10.36141/svdld.v38i1.6722.

13. Tanaka, M. Distribution of collagenous colitis: utility of flexible sigmoidoscopy. Gut. 1992;33(1). https://doi.org/10.1136/gut.33.1.65.

14. Thijs, WJ. Microscopic colitis: prevalence and distribution throughout the colon in patients with chronic diarrhoea. The Netherlands journal of medicine. 2005;63(4).