Case Report

Unusual Lymphocytic and Granulomatous Pattern in Inflammatory Bowel Disease: A Case Report and Review of the Literature

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The interpretation of colonic biopsies can be challenging if the histologic presentation is not characteristic. The association between microscopic colitis and inflammatory bowel disease is weak and unclear. Collagenous colitis has been most frequently reported in association with ulcerative colitis either before or many years after ulcerative colitis is established. There are few reports of Lymphocytic colitis in association with Crohn's disease. To the best of our knowledge however Crohn's disease presenting as lymphocytic pattern colitis with granulomas has rarely if ever been reported. We present a case of a 34 year old male who presented initially with perianal abscess and fistula-in-ano and subsequent colonoscopic biopsies demonstrated minimal active chronic colitis with granulomas that progressed to lymphocytic colitis pattern inflammation with granulomas within a period of 6-8 months of suboptimal compliance with therapy.
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INTRODUCTION

Our knowledge of histopathologic changes associated with inflammatory bowel conditions has greatly expanded due to the increasing use of endoscopic biopsy in patients presenting with gastrointestinal complaints.[1] In daily practice, there are few commonly encountered inflammatory colitides such as microscopic colitis (MC), inflammatory bowel disease (IBD), infectious colitis, and drug induced colitis.[2]

There are two subtypes of IBD, ulcerative colitis (UC) and Crohn's disease (CD). Patients with IBD especially with UC present with rectal bleeding. UC involves more often the rectum extending proximally in a contiguous pattern to the rest of the colon. It causes superficial lesions affecting mucosa and superficial submucosa. CD typically causes transmural lesions in a segmental pattern with skipped areas of normal bowel. It often involves the terminal ileum and proximal colon but can involve the entire gastrointestinal tract. CD is distinct from UC by its characteristic complication of fistula and granuloma formation, besides the differences of its distribution and depth of lesions. While the diagnosis can be straightforward if the histopathologic findings are typical, it can be difficult if the diagnostic histologic features are absent and clinical information is lacking. This can also occur when the biopsies are acquired at either earlier stage of the disease or later stages of disease especially after treatment, under both circumstances, the microscopic findings of these lesions are not pathognomonic. In most cases diagnosis of IBD as UC or CD is based on the combination of clinical, endoscopic, radiological, and histological investigations.

Lymphocytic colitis (LC) and collagenous colitis (CC) are two entities under the umbrella term of microscopic colitis. As its name indicates patients with MC usually present with chronic watery, non-bloody diarrhea, have no significant endoscopic abnormalities but have distinct histological findings. LC is characterized by increased intraepithelial lymphocytic (IELs) infiltration, and CC is featured by a thickened subepithelial collagen band. In both entities, there are also increased inflammatory cells infiltration in the lamina propria but without prominent distortion of cryptic architecture.[3]

IBD and MC are clearly different entities. They have different epidemiology with IBD occurring at 20-40 years of age, and MC having a later age of onset at 60-70 years of age.[4-6] They also have different clinical presentation, endoscopic findings, and histopathological features.

While differentiating IBD and MC histologically is straightforward in most cases, it may be challenging when the histologic presentation is atypical with overlapping features. Here we present a case with a lymphocytic and granulomatous pattern colitis, suspected to be an unusual presentation of idiopathic inflammatory bowel disease.

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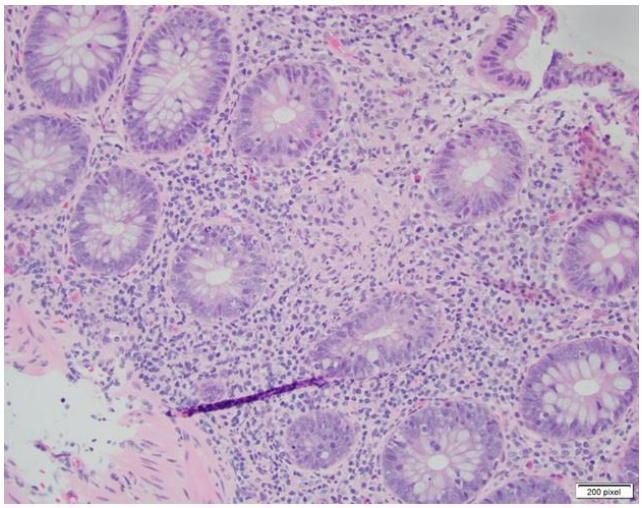

Figure 1. First colonoscopy; Focal active proctitis (rectosigmoid colon biopsy) with associated granuloma (H&E x200).

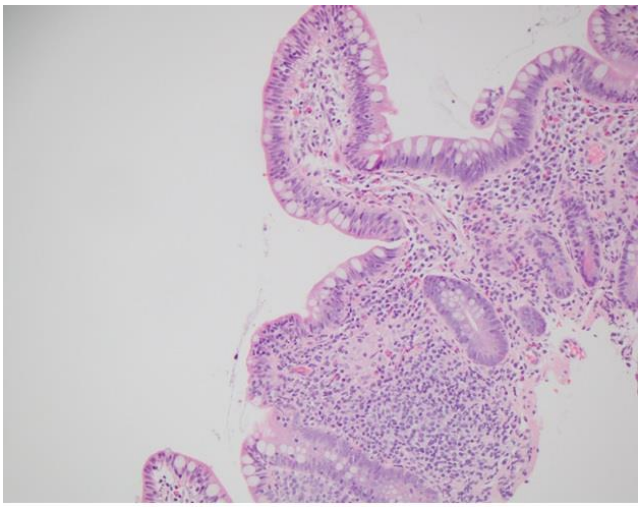

Figure 2. First colonoscopy; Terminal Ileum with granuloma (H&E x100).

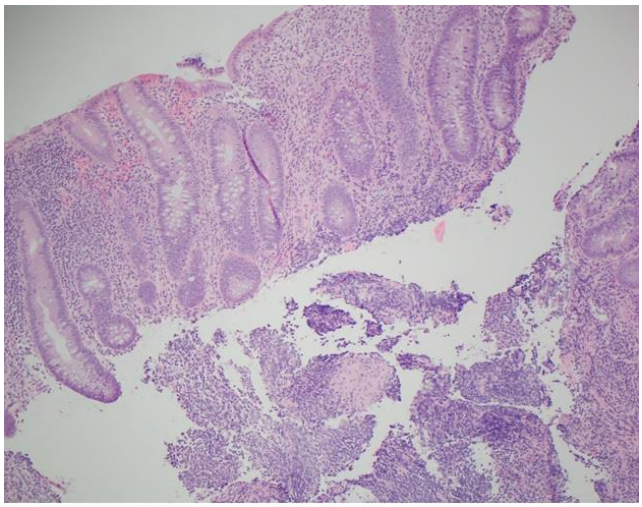

Figure 3. First Colonoscopy; Rectosigmoid colon with deep mural granulomatous inflammation suggestive of communicating fistula tract (H&E x100).

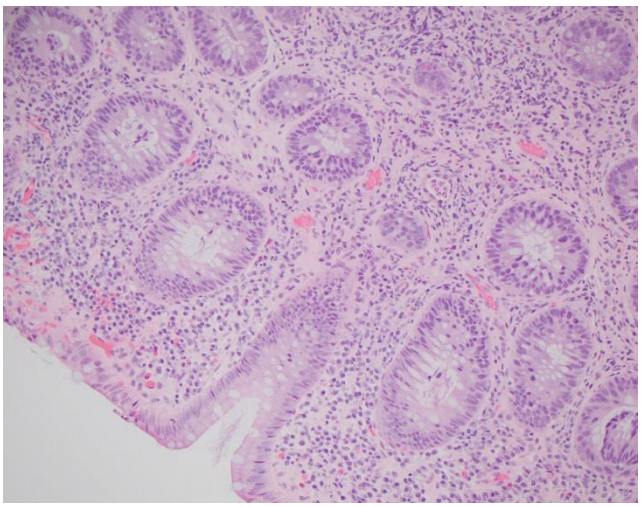

Figure 4. Second Colonoscopy; Persistent chronic active proctitis, rectosigmoid colon biopsy (H&E x200).

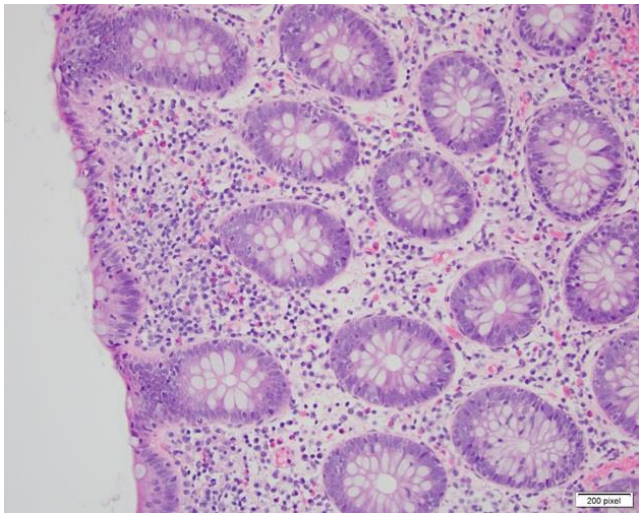

Figure 5. Second Colonoscopy with increased intraepithelial lymphocytes (H&E x200).

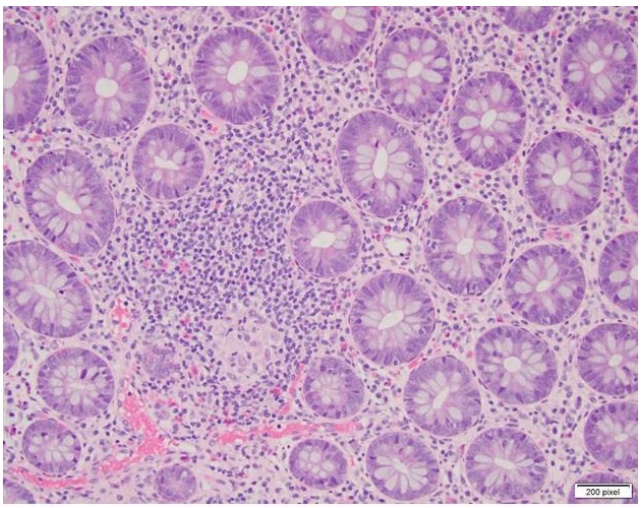

Figure 6. Second colonoscopy with persistent granulomas and increased intraepithelial lymphocytes (H&E x200).

CASE REPORT

This patient with a history of chronic low back and cervical pain, migraines, and depression on polypharmacy, initially presented at 31-year-old age with a perianal abscess and fistula-in-ano. He was treated surgically. He subsequently reported passing bright red blood through rectum since childhood, however he had never disclosed this to his medical providers previously and he had never been evaluated or treated for any gastrointestinal issues. His initial colonoscopy was performed at 33-year-old age and mild loss of vascularity and superficial small ulcerations in the sigmoid colon were noted.

Histologic evaluation of the biopsies showed predominantly chronic inactive granulomatous ileo-colitis and minimal active disease in the sigmoid colon and rectum (**Figures 1** and **Figure 2**). In addition, a rectal polyp was identified endoscopically and biopsied, which revealed chronic mildly active proctitis with inflammation associated with resolving fistulous tract on histology (**Figure 3**). The granulomas were predominantly non cryptolytic and located superficially as well as deep in the mucosa. The final interpretation favored minimally active/quiescent Crohn's ileo-colitis. He was started on mesalamine pills/enema. On 3 months follow-up he reported regular bowel movements without much bleeding, however he was not regular with use of the enema. He adamantly refused to take biologic therapy for treatment. Due to complaints of mid abdominal pain, esophagogastroduodenoscopy was performed which revealed a small erosion at the prepyloric part of stomach. On histologic evaluations, the duodenal biopsy was found to be unremarkable with mild chronic inflammation of the stomach noted without evidence of H. pylori microorganisms. He was again seen at the GI clinic 3 months after this procedure and reportedly had stopped taking mesalamine due to flulike symptoms and fatigue, however he did not complain of renewed diarrhea or bleeding per rectum. Repeat colonoscopy was performed 7 months after the first procedure. The exam revealed only mild loss of vascularity in a portion of the sigmoid colon and distal rectum with no other abnormalities noted. Histologic evaluation of the terminal ileum and colonic biopsies revealed increased IEL's (lymphocytic colitis like pattern) with scattered mucosal granulomas and only minimal crypt architectural distortion with mild chronic active inflammation in the rectosigmoid colon biopsy (**Figures 4-6**) and interpretation was made that these findings could be seen with chronic minimally active idiopathic inflammatory bowel disease (suspected Crohn's disease), however unusual infections such as brucellosis and syphilis as well as sarcoidosis could not be excluded. A Pas-ab special stain was reported negative for fungal micro-organisms. The patient continued to have no hematochezia or diarrhea with only nonspecific complaints of abdominal pain. A capsule endoscopy was performed which was unremarkable. The patient was noncompliant with mesalamine; however, no significant active disease was seen with current procedures, and no biologic agent was prescribed to the patient at the time of this case report.

DISCUSSION

Microscopic colitis refers to forms of colitis with no significant radiology and endoscopy findings but exhibiting distinct histopathologic abnormalities.[7] Clinically, patients with MC may present with watery, non-bloody diarrhea, abdominal pain, weight loss and fecal urgency. Episodes of remission and relapse is observed during the course of the disease. In addition to the two major types of MC including collagenous colitis and lymphocytic colitis, other variants subtypes have been reported.[7,8] The median age at the time of diagnosis is 59 years. There is a slight female predilection with female: male ratio of 2.4:1.

Endoscopically, some MC may show edema or erythema, mucosal tearing, hemorrhagic, submucosal dissection, and pseudomembranes. However, by definition, MC has no endoscopic abnormality, which is different from IBD. Histologically, LC is characterized by diffusely increased IELs $\geq$ 20/100 surface epithelial cells, surface epithelial damage, and increased inflammatory cell infiltration in lamina propria. And CC features thickened subepithelial collagen layer $\geq$10μm.[3] A histopathological subtype of MC has been reported to have subepithelial multinucleated giant cells arising from fusion of macrophages.[9] It is uncommon to observe mucosal granulomas in MC. Saurine et al. however reported the presence of prominent granulomatous inflammation in four cases of MC. These four cases all share clinical and radiological pictures that are consistent with MC.[10] Granulomatous inflammation in colonic mucosa is most likely an immune mediated reaction to a multitude of pathogenic agents including infections, foreign body, sarcoidosis, drugs and IIBD, specifically CD.[10-12]

The etiology of MC is largely unknown and probably multifactorial. It is proposed that multiple mucosal insults may trigger immunological reactions in predisposed individuals. There are a couple of facts supporting this theory: 1. LC is frequently associated with other immune disorders including diabetes mellitus, rheumatoid arthritis, psoriasis, thyroid disease, and celiac disease. 2. Patients with LC respond to steroids therapy. 3. Studies have shown that the increased IELs and lymphocytes in lamina propria in the involved bowel are mainly composed of a mixed population of T helper cells, T cytotoxic cells, with T helper 17 and T cytotoxic 17 cytokine profiles.[11,13,14]

Although the incidence of MC is roughly similar to that of chronic idiopathic IBD,[15,16] IBD is a more severe chronic inflammatory bowel disease, both clinically and histologically. It has been reported that aberrant mucosal immune response plays an important role in pathogenesis of IBD, with an increased amount of T helper 17, T cytotoxic 17, regulatory T helper cells, and regulatory cytotoxic T cells in the lamina propria of the diseased colon in comparison with colon of healthy individuals. In addition, there are more T helper type 1 cells and type 1 CD8+ T cells in patients with CD, and more T helper type 2 cells in patients with UC.[13,14,17]

A possible association between MC and IBD has been studied and described. While some cases of MC may transform into IBD, IBD may regress and mimic or present histologically as MC. In addition, MC can coexist with IBD in different regions of the bowel. This may be interpreted as both MC and IBD sharing common mucosal immunological pathways as mentioned above. It is reported that approximately 1% of patients with MC may evolve into IBD, and this subset of patients with MC tend to have higher level of T help type 1/type 1 CD8+ T cells, T helper type 2/type 2 CD8+ T cells, and TNF- α producing lymphocytes than those who recover from MC.[13,14,17]

Our case report reveals a lymphocytic colitis pattern of chronic ileocolitis with granulomas. Considering the patient's past medical history of anal enterocutaneous fistula, involvement of terminal ileum and ascending colon, and the presence of non cryptolytic granulomas, the diagnosis of Crohn's disease was suggested.

Correlating our findings with the observations made in other studies,[14] we suspect that there is not only an association and overlap between MC and IBD, but also that MC histologic pattern may be an atypical presentation of early IBD or in post-therapy remission stages. In either of these stages, the distortion of crypts may be lacking in the presence of hypercellularity in the lamina propria. Inactive IBD may show feature of MCs, both LC and CC. Follow-up biopsies from patients with inactive IBD may show both lymphocytic colitis pattern or collagenous colitis pattern inflammatory changes. For example, microscopic findings include increased IEL, increased lymphocytic infiltration in lamina propria, crypt distortion, and Paneth cell metaplasia in the distal colon. These pathologic changes support the diagnosis of IBD. However, if the characteristic changes of IBD are not present, the diagnosis cannot be made based solely on histopathological findings.[20] And it should be put in a relevant clinical history (such as age, because IBD shows an early disease onset in 20-40 years of age), endoscopic, and histopathologic findings. In this present case, the patient is 34-year-old with past medial history of enterocutaneous fistula formation had endoscopic findings of mild loss of vascularity and small ulcerations in the sigmoid colon. Combination of these with histopathological changes, a diagnosis of unusual lymphocytic and granulomatous pattern in inflammatory bowel disease was rendered. A diagnosis of IBD favoring CD was made because of the presence of granulomas throughout the colon and involvement of the terminal ileum. A differential diagnosis including chronic infection with Syphilis and Brucella was also proposed due to the atypical presentation. While a Pas-ab special stain was negative for fungal micro-organisms, a diagnosis of Syphilis and Brucella would require culture or serologic testing which was recommended in the final report.

It has been reported that drug-induced colonic pathological changes resemble acute infectious-type colitis, ischemic colitis, microscopic colitis, and chronic idiopathic IBD. Several drugs including proton pump inhibitors (lansoprazole, esomeprazole, omeprazole, lansoprazole), H2 receptor antagonists (ranitidine, cimetidine), nonsteroidal anti-inflammatory drugs, carbamazepine, selective serotonin reuptake inhibitor, beta-blockers, statin, bisphosphonates, acarbose, and isotretinoin have been described to cause lymphocytic colitis.[18] The patient in this case report had a history of pantoprazole and ranitidine use for his gastric erosion and naproxen for chronic low back pain and migraine. While the latter usage started many years before the first colonoscopy, the former two medications were initiated after his first biopsy and used only temporarily. Thus, the contribution of the medications to the microscopic findings of the biopsies may be suggestive but inconclusive.

A variant of MC has been reported as focal active colitis. This may be seen in infections, ischemia, CD, or UC after partial treatment. However, whether focal active colitis should be interpreted as MC variant or an initial change of IBD is still unclear.

Studies have shown that patients with LC may have a family history of IBD. It has been reported that LC pattern may be seen in CD and CC in UC. Moreover, some patients have been diagnosed both IBD and MC at different time points in the course of disease and that either one may precede the other. A retrospective study has shown that six patients with UC subsequently transformed to CC or LC after 15 years of being diagnosed with UC. Three out of these six cases showed complete remission both clinically and histologically. The other three cases reverted back to UC.[8] However, the underlying mechanism of this transformation/evolvement is unclear. Transcriptional factor nuclear factor κB activation in epithelial cells has been shown in patients with CC. And the activation of this transcription factor has been found in both epithelial cells and macrophages in the lamina propria in UC patients.[19] Taken together, IBD may evolve into MC, and MC can transform back to IBD. In contrast to the study of complete remission of UC into LC or CC, our current report shows a granulomatous IBD progressing into mixed lymphocytic colitis and granuloma pattern of IBD. This, together with the study mentioned above, suggests that MC and IBD may represent a spectrum of the same disorder, in which the coexistence of both characteristic features IBD and MC may be identified at some point of the disease course. However, since the prognostic implication of this pathologic finding is unclear, following up these patients for the progression of IBD and dysplasia is recommended.

CONCLUSION

Inflammatory bowel disease must be differentiated from other conditions such as drug induced colonic change and microscopic colitis because the treatment strategies are different. The diagnosis of IBD might be straightforward if the case presents with characteristic pathological changes. However, the diagnosis can be challenging if there are coexistence of pathological changes seen in other colitides, in particular a subtype of microscopic colitis. A correlation with history and disease progression based on multiple colonoscopies and biopsies maybe necessary. Whether immunologic profile of the inflammatory cells can be used to predict if a microscopic colitis will eventually progress to a

more debilitating Idiopathic inflammatory bowel disease is still a subject that is being studied and in the future may help to identify a subset of microscopic colitis patients that need a different level of care to facilitate in their outcomes.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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