

Lymphocytic Colitis Diagnosis 40 Years after Onset of Ulcerative Colitis

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ABSTRACT

Lymphocytic colitis is a subtype of microscopic colitis characterized by normal colonoscopy findings and microscopic evidence of lymphocytic infiltration of colonic epithelial cells. The concomitant diagnosis of lymphocytic colitis and ulcerative colitis has been rarely reported. We present a 68-year-old man with a 40-year history of ulcerative colitis who was referred to our hospital for 3–4 weeks of non-bloody diarrhea with subsequent colonoscopy and biopsies confirming lymphocytic colitis.

INTRODUCTION

Microscopic colitis (MC) is an inflammatory disease of the colon characterized by chronic non-bloody diarrhea, fecal urgency, and abdominal pain, and it has two subtypes: lymphocytic colitis (LC) and collagenous colitis (CC).^{1–6} The etiology of MC and its association with inflammatory bowel disease (IBD) is uncertain; however, recent reports indicate a possible common pathophysiology between MC and IBD and suggest that MC may be part of a spectrum of IBD.^{1,3–5,7} Albeit rare, previous case reports have documented the diagnosis of LC up to 30 years after a diagnosis of ulcerative colitis (UC).^{1,3–5,8}

CASE REPORT

A 68-year-old man with a history of ankylosing spondylitis (AS) and UC presented for an outpatient colonoscopy in 1975 after an acute presentation of bloody diarrhea. Proctoscopy showed active inflammation, and he was diagnosed with UC, which improved with cortisone treatment without maintenance therapy. In the late 1970s, he was diagnosed with AS and was started on sulfasalazine. Approximately 10 years later, the patient had an acute episode of bloody diarrhea, with colonoscopy indicating diffuse colonic inflammation (Montreal Classification E3). Stool studies were negative. He was treated with prednisone and mesalamine; symptoms resolved, and he stopped mesalamine after a few months. The patient was started on methotrexate at this time for his AS. In 2009, he started adalimumab for his AS but switched to infliximab in 2014 for insurance reasons. The patient lost clinical response to infliximab in 2017 and was transitioned back to adalimumab and methotrexate. The patient denied any gastrointestinal (GI) symptoms from the 1980s up until 2017, and routine surveillance colonoscopies over that time revealed no active inflammation or dysplasia.

In May 2017, the patient was referred for colonoscopy due to 3–4 weeks of non-bloody diarrhea. He denied fecal urgency, nighttime symptoms, weight loss, or any other symptoms. GI pathogen analysis including stool culture, *Clostridium difficile* toxin, ova, and parasites was negative. The colonoscopy revealed no endoscopic evidence of active and chronic small or large bowel inflammation with a Ulcerative Colitis Endoscopic Index of Severity (UCEIS) of [0,0,0] and a Mayo endoscopic score of 0. Dysplasia surveillance biopsies throughout the colon

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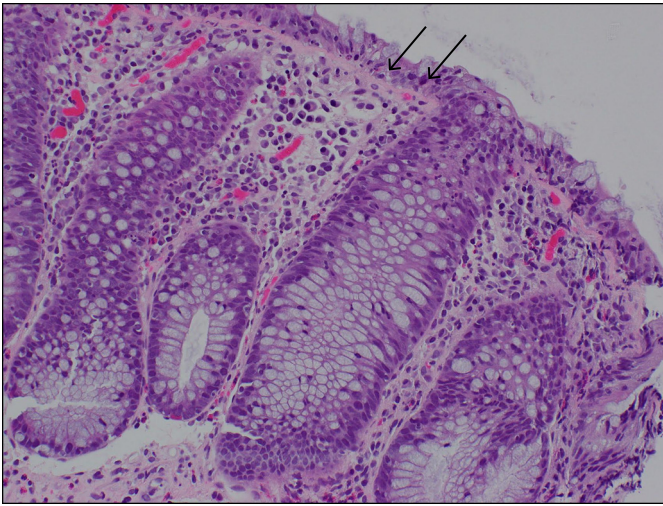


Figure 1. Hematoxylin and eosin (H&E) stain of a 10-cm colon biopsy (20×) showing mild active colitis with occasional intraepithelial neutrophils in a background of intraepithelial lymphocytosis (arrows) and chronic interstitial inflammation.

revealed mild active colitis at 10 cm (Figure 1). Biopsies at 30 cm and 70 cm showed LC (considered an active colitis) with chronicity, lymphocytes, and plasma cells; the presence of lymphocytes and plasma cells indicated chronic inflammation (Figure 2). During this time, he was also on aspirin and simvastatin for coronary artery disease and hyperlipidemia. At IBD clinic 4 months later, the patient reported that his diarrhea had resolved 3–4 weeks after the colonoscopy without further intervention from his regimen of adalimumab and methotrexate for AS. Patient has been asymptomatic from UC and LC at 14 months of follow-up since his diagnosis of LC.

DISCUSSION

LC is characterized by unremarkable endoscopic findings with histologic analysis indicating >20 intraepithelial lymphocytes per 100 surface epithelial cells on colonic biopsies.^{2-4,7}

The rare occurrence of LC in patients with UC in remission has been previously documented; however, the epidemiology of this concordance is not well described.^{1,4,5,9} A 2017 case-control study reports an increased frequency of UC history in LC patients (7% vs 1% in controls), and a 2016 cohort study reports that <2% of patients diagnosed with LC had a history of UC.^{1,9}

A review of the scientific literature indicates 58 confirmed cases in the past 30 years of MC diagnosed in patients before or after a diagnosis of IBD.^{4,5,13} Of these cases, only 11 were of patients diagnosed with LC and UC.^{4,5,13} One case series identified 4 patients with UC in remission who subsequently developed LC, while another case series reported 2 patients initially diagnosed with LC who later developed UC.^{4,5,13} A 2018 retrospective observational study and review reports 5 cases of LC in women previously diagnosed with UC; 4 of the 5 patients were diagnosed with extensive colitis.¹³ The time between diagnosis of LC and UC ranged from 1 to 30 years.

The etiologies of MC and IBD are still not fully elucidated and require further research.^{1,4,5} Smoking has been associated with the development of MC and Crohn's disease, but is protective against UC.^{1,2,5,10} Non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors, and statins have also been implicated in the development of MC; however, further research is required to prove causation.^{2,3,5-7,10}

Previous records indicate an increased prevalence of autoimmune disorders in patients diagnosed with MC (e.g., type 1 diabetes, thyroiditis, celiac disease), all of which (including MC) share the HLA-DQ2 allele.^{1-5,7,11} Furthermore, antecedent reports indicate that patients with MC and IBD may share similar genetics and that MC may share a common pathophysiology with IBD, namely a dysregulated immune response to the gut microbiome in genetically susceptible individuals.^{1-5,12} Finally, a recent review suggests patients originally diagnosed with extensive UC may be more prone to

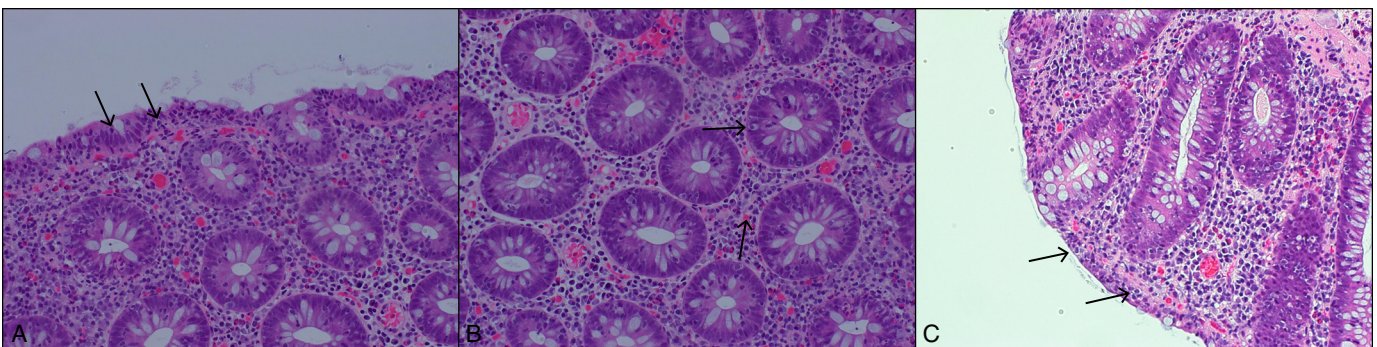


Figure 2. (A and B) H&E stain of a 70-cm colon biopsy (20×) showing lymphocytic colitis with surface epithelial injury associated with lymphocytic infiltration (arrows), loss of mucin, and scattered eosinophils. There is no thickened subepithelial collagen, which distinguishes lymphocytic colitis from collagenous colitis. (C) H&E stain of a 30-cm colon biopsy (20×) showing lymphocytic colitis with abundant subepithelial plasma cells. Arrows indicate intraepithelial lymphocytes.

developing LC compared to patients with limited left-sided and proctosigmoid involvement of UC.¹³

Our patient developed LC despite being treated with adalimumab and methotrexate for his AS, both of which have been used to treat MC.^{2,3} His exposure to NSAIDs and statin medications, in addition to the extent of his UC, may all have predisposed him to developing LC.^{2,3,5-7,13} However, a common genetic etiology between MC and IBD is unlikely in our case because there was a long interval (40 years) between the 2 diagnoses, which, to our knowledge, is the longest documented time period between the development of LC and UC. In addition, although nonspecific colonic lymphocytic infiltration may be seen in patients with AS, no definitive correlation has been established between LC and AS.¹⁴ In conclusion, identification of risk factors such as medications and the extent of disease in UC patients may help predict development of LC in the future.

DISCLOSURES

Author contributions: D. Stavrakis and S. Taleban wrote the manuscript, and K.M. Meiklejohn provided pathology slides. S. Taleban is article guarantor.

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Informed consent was obtained for this case report.

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