De Novo Diagnosis of Lymphocytic Colitis After SARS-CoV-2 Vaccination

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ABSTRACT
SARS-CoV-2 mRNA vaccines are safe and effective for most patients. Gastrointestinal complications reported after vaccination have included gastroparesis and inflammatory bowel disease flares. In this study, we present a unique case of lymphocytic colitis that occurred in a healthy middle-aged man after Moderna SARS-CoV-2 mRNA vaccination. This reveals an unexpected complication of a mRNA vaccine that presented as worsening diarrhea after vaccination in a dose-dependent pattern. Caregivers should be aware of lymphocytic colitis as a possible complication of the Moderna vaccine and monitor those patients closely for symptom resolution.

INTRODUCTION
The coronavirus disease 2019 (COVID-19) pandemic to date has cost the United States over 1 million lives.1 In December 2020, the Food and Drug Administration issued an emergency use authorization for the use of the BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) COVID-19 mRNA vaccines. The landmark trial by Baden et al2 demonstrated that mRNA-1273 prevented COVID-19 illness with 94.1% efficacy. However, the vaccines have been found to have adverse reactions including gastrointestinal complaints such as mild diarrhea, nausea, and vomiting. In addition, rare cases of gastroparesis, inflammatory bowel disease (IBD) flare, autoimmune hepatitis, and pancreatitis have been reported after vaccine administration.3-7 We report the first diagnosis of lymphocytic colitis after SARS-CoV-2 vaccination.

CASE REPORT
A 71-year-old man with a history of prediabetes and renal insufficiency presented initially in early 2021 to his primary care clinic complaining of blood with wiping and anal pain for 1 week. He was having 3 loose stools a day for the past 2 weeks, beginning 3 days after receiving his first dose of the mRNA-1273 Moderna mRNA vaccine. He had normal bowel habits before the vaccine. On physical examination, an anal fissure was noted. His anal pain resolved with topical rectal therapies, but he continued to have occasional rectal bleeding. After his second dose of the mRNA vaccine (18 days after the first dose), he began having up to 12 watery bowel movements a day, including 4 bowel movements at night.

One week after his second vaccination, he was seen in a gastroenterology clinic. On further evaluation, he denied recent antibiotic use, travel, sick contacts, or other exposures. The patient endorsed rare use of a nonsteroidal anti-inflammatory drug (1–2 tablets every 3 months). He denied any family history of colon cancer or IBD. On laboratory evaluation, his complete blood count and complete metabolic panel were within normal limits, except for creatinine 1.22 mg/dL (normal reference 0.67–1.17 mg/dL). The patient had a markedly elevated fecal calprotectin of 2,634 mg/kg (<50 mg/kg), negative TTG-IgA (with normal IgA), and a negative C. diff and gastroenteritis PCR.
An urgent outpatient colonoscopy performed 5 days after the clinic visit demonstrated continuous significantly edematous, erythematous, and granular mucosa in the sigmoid colon. The tortuosity and edema in the colon precluded advancement of the pediatric colonoscope. After changing to a thinner 9 mm diameter endoscope, the cecum was reached. The terminal ileum was normal. There was mild mucosal edema and erythema extending from the cecum to the descending colon (Figure 1). Biopsies were obtained throughout. After completion of the colonoscopy, given suspicion for ulcerative colitis, the patient was started on 1.5 g/d of extended-release mesalamine. A histologic evaluation of his colonic and rectal biopsies (Figure 1), which were reviewed by the gastrointestinal consensus group at Stanford, revealed expansion of the lamina propria by dense lymphocytic infiltrates and conspicuous infiltration of the surface and crypt epithelium by CD3+ T cells. Rare crypt abscesses were scattered in the distal colon, but architectural distortion and other findings of IBD were absent. Trichrome staining did not demonstrate increased collagen deposition at the surface, lending no support for involvement by collagenous colitis. CD3 and CD20 immunohistochemical stains showed normal distribution of T and B cells (predominantly T cells) in the transverse colon biopsies. Cytomegalovirus immunostain was negative. Overall, these findings were consistent with lymphocytic colitis. On follow-up 3 weeks later, his bowel movements had normalized, although he still had occasional bloating and fecal urgency. Repeat fecal calprotectin was 565 mg/kg.

The patient underwent follow-up colonoscopy 6 weeks later, which demonstrated improving sigmoid colitis with remainder of the colon appearing normal (Figure 2). Repeat biopsies again demonstrated lymphocytic colitis throughout the colon with infrequent crypt abscesses in the sigmoid colon and rectum without architectural distortion (Figure 2). Although consideration was made to switch the patient to budesonide, given how much the patient had improved, he was continued on oral mesalamine. On follow-up 6 months later, he remained asymptomatic with normal bowel habits.

**DISCUSSION**

In a phase 3 trial of the mRNA-1273 vaccine, developed by Moderna, gastrointestinal adverse reactions related to the vaccine have included nausea, vomiting, and diarrhea. However, additional studies have found added reactions to COVID-19 vaccinations not limited to mRNA-1273, including pancreatitis, gastroparesis, autoimmune hepatitis, and IBD flare. To the best of our knowledge, this is the first case of lymphocytic...
colitis that developed after COVID-19 vaccination. In this presentation, our patient at baseline had no gastrointestinal symptoms but after vaccination, developed loose stools that worsened to diarrhea with the second dose and was diagnosed with lymphocytic colitis. Although we cannot establish a causal relationship from this isolated case, the timing of the patient’s symptoms to the 2 doses of the vaccine makes mRNA-1273 a highly suspected reason. The significant endoscopic findings in our patient were atypical for microscopic (lymphocytic) colitis. IBD was on our differential diagnosis; however, after 2 colonoscopies 6 weeks apart, biopsies showed lymphocytic infiltration without any evidence of crypt architectural distortion suggestive of IBD. Given there were extensive biopsies from inflamed areas in 2 independent colonoscopies, it was very unlikely that chronicity was missed based on patchy distribution. Our case was reviewed by expert pathologists at our institution who agreed that the histologic findings were consistent with lymphocytic colitis and not IBD. We acknowledge the possibility that this may represent acute colitis that may evolve into IBD at a later point. A future colonoscopy in our patient will help clarify this possibility.

The mRNA-1273 vaccine is shown to have a strong CD4 T-cell response leading to Th1 cytokine expression. In microscopic colitis, mucosal inflammation involves a Th1 cytokine upregulation of interferon gamma, interleukin-15, and tumor necrosis factor alpha. Similar to McShane et al, we speculate that mRNA vaccination, by activating the innate immune system, may inadvertently trigger autoreactive lymphocytes, leading to autoimmune conditions such as flare of IBD, autoimmune hepatitis, and in our case, lymphocytic colitis.

Our case report recognizes lymphocytic colitis as a potential clinically important sequela of SARS-CoV-2 vaccination. Given the rarity of this case, it remains vital that patients receive SARS-CoV-2 vaccination. The natural history, long-term outcomes, and treatment of SARS-CoV-2 vaccine-related lymphocytic colitis warrant longitudinal studies.

**DISCLOSURES**

Author contributions: Study concept and study supervision: S. Friedland. Drafting of the manuscript: P. Lee, MT Wei, and S. Friedland. Data collection, data interpretation, critical review/revision of the manuscript: All authors. P. Lee is the article guarantor.

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Informed consent was obtained for this case report.
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