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Severe Ocrelizumab-Induced Enterocolitis Treated Successfully With Ustekinumab

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ABSTRACT

As biologics have become the mainstay of treatment for many autoimmune diseases, their adverse effects are also being identified and described increasingly in the literature. Colitis associated with biologics is a previously described phenomenon in the literature with anti-CD20 (rituximab). The mechanism was thought to be related to B-lymphocyte depletion. We present a case of severe enterocolitis induced by another anti-CD20 monoclonal antibody (ocrelizumab), highlighting a potentially promising therapeutic approach. We performed an extensive literature review and found 4 similar cases. Our case is the first to be salvaged successfully with ustekinumab.

INTRODUCTION

The use of biologics in the treatment of autoimmune and malignant disease processes has been growing since the introduction of biologics.¹ As such, their adverse effects are increasingly recognized. Biologic-induced enteritis and colitis is a phenomenon that has been described in the literature and continues to be delineated.² Rituximab is an anti-CD20 monoclonal antibody used to treat many autoimmune diseases, and it has been linked to the exacerbation of inflammatory bowel disease (IBD) and de novo IBD.³⁻⁵ Ocrelizumab is a second-generation anti-CD20 monoclonal antibody. Unlike rituximab, ocrelizumab is mostly humanized, and it has now reportedly been linked to inducing colitis.⁶

CASE REPORT

A 42-year-old woman from South Asia with a history of multiple sclerosis (MS) presented with fever, abdominal pain, and watery diarrhea a week after receiving her first dose of ocrelizumab. An extensive workup including *Clostridium difficile*, stool ova and parasite, rotavirus, shiga toxin, stool cultures, tuberculosis, and coronavirus disease 2019 testing was all negative. Abdominal computed tomography showed signs of pancolitis. Empiric antibiotics did not help (given before stool cultures had been collected). The patient had diagnostic colonoscopy which revealed diffuse and circumferential erythema, ulcerations with spontaneous bleeding in the entire colon, and the examined part of the terminal ileum (Figure 1). Colonic biopsies showed severe active colitis and terminal ileitis with no signs of chronicity (Figure 2). Cytomegalovirus immunostain of the colonic biopsies was negative. The patient continued to be symptomatic with watery diarrhea, abdominal cramps, and recurrent fever.

Given the short time between the administration of ocrelizumab and her presentation, a diagnosis of ocrelizumab-induced enterocolitis was made. The patient was treated with intravenous methylprednisolone 60 mg daily for 3 days with minimal clinical response (persistent abdominal pain, diarrhea, and rising C-reactive protein). Ustekinumab 390 mg intravenous was then started as a salvage therapy. Three days after ustekinumab induction infusion, the patient had significant improvement of her symptoms with the resolution of fever, abdominal pain, and diarrhea. The patient was discharged with a prednisone-tapering regimen to avoid an MS flare, and she was scheduled to receive maintenance therapy with ustekinumab (90 mg subcutaneously every 8 weeks). Surveillance colonoscopy 8 weeks later showed complete mucosal remission. Twelve weeks later, the patient continued to be asymptomatic.

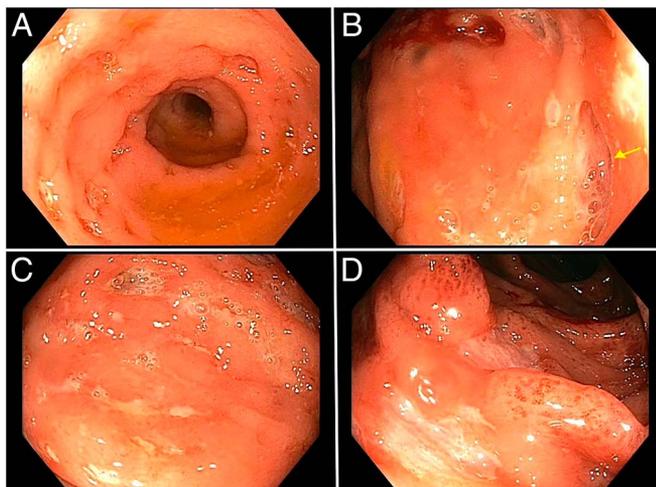


Figure 1. Diagnostic colonoscopy revealed (A) active terminal ileal erythema and punched-out ulcers and (B–D) diffuse and circumferential colonic erythema and ulcerations with spontaneous bleeding.

DISCUSSION

Drug-induced enteritis and colitis is a well-described phenomenon in the literature linked to many different classes of medications including biologics.² The number of cases of colitis and enteritis has been increasingly reported in alignment with the increasing use of biologics in many different clinical settings, such as autoimmune diseases and malignancies. For example, anti-CD20, rituximab, has been linked to many cases of new-onset colitis and worsening of IBD cases.^{3,5} Ocrelizumab is a humanized monoclonal antibody that binds to the CD20 antigen on B lymphocytes and has been approved to treat primary progressive MS and relapsing MS in 2017.⁷ The pathophysiology of colitis induced by anti-CD20 monoclonal antibodies is not fully understood, but it is believed to be related to B-lymphocyte depletion by these monoclonal antibodies.^{4,8} B cells produce interleukin-10, a regulatory cytokine that maintains immune equilibrium and provides an anti-inflammatory effect by inhibiting Th1-derived immune responses. Mouse models have shown that B-cell-depleted knockout mice lacking interleukin-10 developed severe colitis.^{9,10} It is important to note that ocrelizumab-induced B-cell suppression returns to pretreatment levels at a median of 72 weeks (27–175 weeks) after discontinuation of ocrelizumab.¹¹ This may explain the delayed onset of colitis in some cases.

Further studies can help delineate whether it can also guide how long the patients with colitis need to be treated or monitored for. Because of the condition's rarity, there has been no consensus on guidelines on the treatment of this condition. The management of ocrelizumab-induced colitis requires meticulous and very close evaluation and monitoring. Ruling out infection and other potential causes of colitis is crucial in making the correct diagnosis. Colonoscopy is key to the diagnosis of these cases.

Treatment of patients with ocrelizumab-induced colitis is very challenging. Immunosuppression with glucocorticoids is the

most used medical therapy. There have only been 4 cases of ocrelizumab-induced colitis reported in the English literature (Table 1). Among those 4 cases, glucocorticoids were only successful in 2 cases.^{6,12,13} The rest eventually required surgical intervention. Using off-label biologic therapy in ocrelizumab-induced colitis has not been studied, and the outcome cannot be predicted.

Moreover, given that ocrelizumab is used primarily for the management of patients with MS makes the therapeutic options limited. For instance, antitumor necrosis factor agents are not preferred as a therapeutic option in patients with demyelinating diseases such as MS.¹⁴ Anti-integrin, vedolizumab, is known for its safety profile, but it cannot be used here as a salvage therapy because of its slow onset of action.¹⁵ Our case did not respond to glucocorticoids well. Given the limited choices of biologic therapy which are governed by the reasons detailed above, we opted to use ustekinumab as a salvage therapy. Fortunately, the patient responded very well after the induction dose. Ustekinumab has a fast onset of action. It also has a safer profile than antitumor necrosis factor agents in demyelinating diseases. Ustekinumab has also been previously used to treat rituximab-induced colitis with variable outcomes, and this has encouraged us to try it in our patient.¹⁶ We think that ustekinumab could be a great option to be used as a salvage therapy in ocrelizumab-induced colitis which does not respond to steroids. We do not have guidelines on the duration of treatment, but considering that B-cell depletion can last from 6 months to 3 years, this should be taken into account, and it may be wise to extend therapy beyond induction.¹¹ However, given that patients with MS need to be on alternative therapy for their disease, it is imperative to work with a neurologist to choose the right therapy that can potentially work for both MS and colitis. Natalizumab is one such medication approved for both diseases; however, it is rarely used, given its potential side effect of progressive multifocal leukoencephalopathy. S1P receptors modulator, ozanimod, was approved for the treatment of MS and ulcerative colitis. Therefore, it could be a promising therapy for these patients.¹⁷

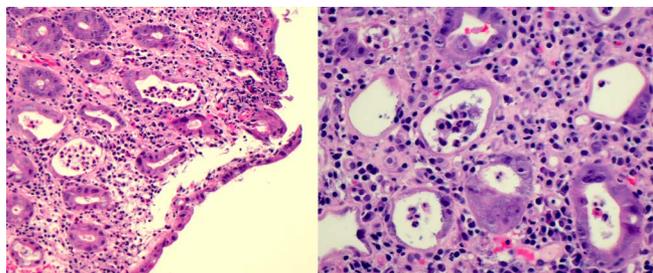


Figure 2. Random colon biopsies revealed diffuse active colitis with neutrophilic infiltration, crypt abscesses, and focal erosion/ulceration. No evidence of chronic inflammation (such as crypt architectural distortion, basal lymphoplasmacytosis, Paneth cell metaplasia, or duplicated muscularis mucosae), viral inclusions, amoeba, or other micro-organisms (hematoxylin and eosin stain).

Table 1. Cases of ocrelizumab-induced colitis

Case	Age (yr)	Sex	Onset of symptoms	Symptoms	Treatment used	Outcome
Patient 1 ⁶	43	Female	6 mo after the second dose	Abdominal pain and watery diarrhea	Glucocorticoid, no response	No response to steroids. Total colectomy
Patient 2 ¹²	62	Male	1 wk after the first dose	Abdominal pain and watery diarrhea	Glucocorticoid	Responded to glucocorticoids and required extended-release budesonide. The case evolved into collagenous colitis
Patient 3 ¹³	61	Female	2 mo after the third dose	Watery diarrhea	Budesonide and mesalamine	Recovered
Patient 4 ⁶	47	Male	Several weeks after initiating ocrelizumab	Watery diarrhea	Glucocorticoid	No response to steroids. Segmental sigmoid resection with an end colostomy

DISCLOSURES

Author contributions: All authors contributed equally to the manuscript. A. Gremida is the article guarantor.

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Patient consent was obtained for case.

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