## Title

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CASE REPORT | INFLAMMATORY BOWEL DISEASE

# Successful Treatment of Rituximab-Induced Crohn's Disease With Ustekinumab

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## ABSTRACT

Autoimmune optic papillitis is a rare disorder that causes progressive visual loss, often treated with rituximab (RTX). However, its use is not without risks. Here, we present a 51-year-old man who experienced vision loss because of autoimmune optic papillitis, which was well-controlled with RTX. Four years later, the patient developed abdominal pain and diarrhea and was found to have RTX-induced Crohn's disease (CD). The patient failed treatment with azathioprine, but was subsequently able to achieve clinical and endoscopic remission of his CD with ustekinumab, while continuing RTX therapy for autoimmune optic papillitis. This case report describes the efficacy of the anti-interleukin 12/23 monoclonal antibody in inducing remission of RTX-induced CD.

**KEYWORDS:** Crohn's disease; rituximab; ustekinumab

## INTRODUCTION

Rituximab (RTX) is a common therapy used to treat many autoimmune and lymphoproliferative diseases.[1] Development of RTX-induced Crohn's disease (CD) and ulcerative colitis has been reported previously[2–12]; however, the exact mechanism of pathogenesis is unclear. There are also limited data on treatment of this condition. In a review of the literature, we found only 1 case report where ustekinumab (UST) was successfully used in the treatment of fistulizing CD induced by RTX.[2] In this article, we present a case of RTX-induced CD successfully treated with UST with clinical and histologic remission while continuing RTX therapy.

## CASE REPORT

A 51-year-old man with a medical history notable for gastroesophageal reflux and chronic pain necessitating a spinal stimulator was diagnosed with autoimmune optic papillitis after presenting with several months of progressive vision loss. A lumbar puncture, brain magnetic resonance imaging, and autoimmune workup were not consistent with multiple sclerosis. He initially underwent 6 rounds of plasma exchange and corticosteroid therapy and was started on RTX by his neurologist and neuro-ophthalmologist with improvement in vision.

After 4 years of RTX therapy, he developed diffuse abdominal pain, nonbloody diarrhea with nocturnal urgency, and reported unintentional weight loss of 60 pounds, hypothesized to be due to decreased oral intake from pain. By the time he was evaluated by gastroenterology, symptoms had been ongoing for 6 months. Physical examination revealed diffuse periumbilical tenderness without peritoneal signs or abdominal distension and absence of oral ulcers or skin rashes. Laboratory results were significant for an elevated C-reactive protein (CRP) of 68 mg/L (reference: ≤4.9), low albumin 2.8 g/dL (reference: 3.6–5.1), and stool calprotectin 482 μg/g (reference: ≤49). An evaluation for infectious etiologies, including stool *Clostridioides difficile*, stool enteric pathogens panel by polymerase chain reaction, cytomegalovirus DNA, and coccidiomycosis, was all negative. Computed tomography enterography showed pancolitis without small bowel involvement.

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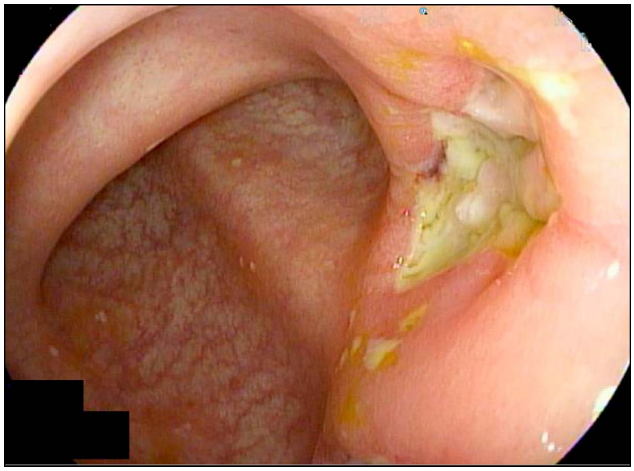

**Figure 1.** Segmental ulcerations in the proximal transverse colon on index colonoscopy.

With a differential diagnosis including infectious colitis, ischemic colitis, and inflammatory bowel disease (IBD), a decision was made to proceed with endoscopic evaluation with biopsies. An esophagogastroduodenoscopy was grossly normal. On colonoscopy, the patient was noted to have a normal terminal ileum, segmental ulcerations in the distal ascending colon and proximal transverse colon, and erythema in the distal descending and sigmoid colon (Figures 1 and 2). Pathology revealed focal active colitis, cryptitis, scattered crypt abscesses, and a few branching crypts consistent with CD.

Given concerns about immunosuppression in the setting of the recent COVID-19 pandemic, he was started on azathioprine 50 mg daily with plans for future uptitration. However, 7 months later, he presented with perianal pain and swelling. An abdominal and pelvic CT was suggestive of a perirectal abscess (Figure 3). Subsequent examination under anesthesia confirmed the diagnosis, leading to incision and drainage performed by colorectal surgery. The patient was also prescribed

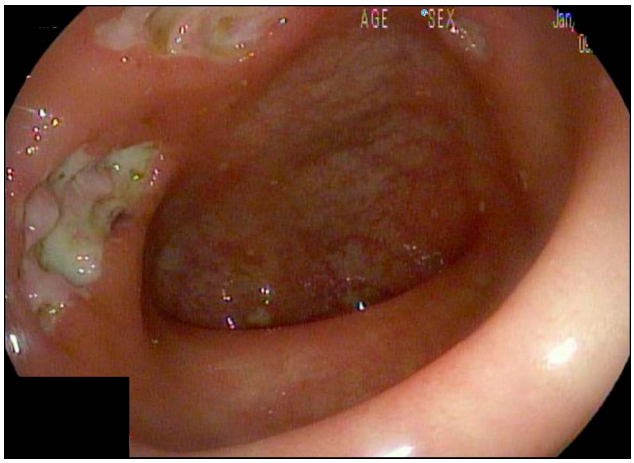


**Figure 2.** Segmental ulcerations in the proximal transverse colon on index colonoscopy.

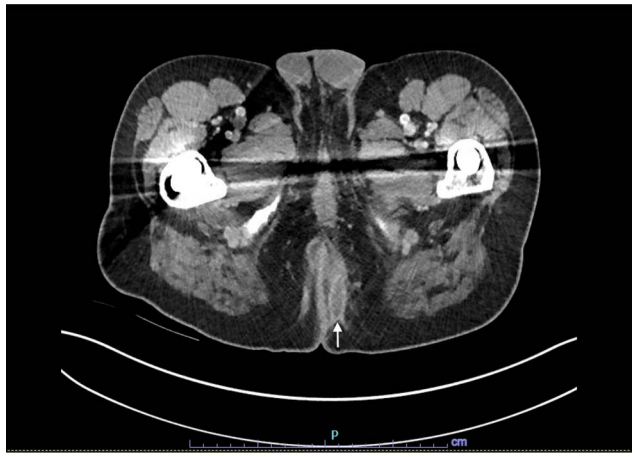


**Figure 3.** Perirectal abscess (white arrow) on computed tomography.

a 14-day course of levofloxacin and metronidazole with resolution of the perianal abscess.

With inadequate response to azathioprine and a continued need for maintenance therapy with RTX, he was started on UST 390-mg intravenous induction followed by maintenance therapy of 90 mg subcutaneously every 8 weeks for CD.

Three months after initiating UST therapy, the patient reported firmer stools, reduced fecal urgency, and fewer episodes of nocturnal awakening. However, it was noted that drug efficacy was waning 4 weeks after each injection (as well as a corresponding rise of fecal calprotectin and serum CRP). Thus, UST was increased to 90 mg subcutaneously every 4 weeks with good response as evidenced by a calprotectin of 75.1 μg/g, albumin of 4.7 g/dL, and CRP of 12.3 mg/L. A repeat colonoscopy 1 year later showed both endoscopic and histologic remission (Figure 4). By the 1-year mark, the patient regained the weight with a healthy body mass index of 23.91 and reported having 2 to 3 formed bowel movements daily. He also did not

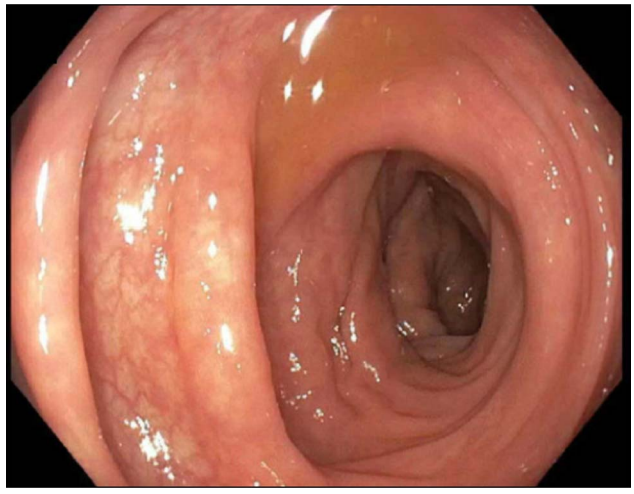

**Figure 4.** Follow-up colonoscopy after 1 year of ustekinumab demonstrates endoscopic remission.

experience any opportunistic infections. Furthermore, with continued RTX therapy every 6 months, the patient had no progression of optic papillitis.

## DISCUSSION

RTX is a chimeric monoclonal antibody against CD20 surface antigens on B lymphocytes.[1]

Recently, there have been several case reports of ischemic colitis,[3] CD,[2,4–7] and ulcerative colitis[9,10] that developed after initiation of RTX. Kristjánsson et al[11] found that patients on RTX have a 6-fold increased risk of developing IBD compared with the general population, and this risk was not associated with concurrent immune-mediated disease. Eckmann et al[13] also found that 5% of those treated with RTX presenting with new onset diarrhea had colitis; of those, 60.8% had IBD, and 39.2% had microscopic colitis. It has been previously hypothesized that B cells play a protective role at the mucosal barrier through production of interleukin-10, and that, RTX can induce colitis through depletion of B cells and stimulation of T lymphocytes, leading to immune disequilibrium.[14]

Although there are multiple studies showing increased risk of IBD among patients treated with RTX, there is no clear guideline on successful long-term treatment of these patients.[12] Historically, the management of RTX-induced IBD often entailed discontinuing RTX.[9,10,12,13] However, previous case reports have shown instances where patients experienced persistent CD, despite discontinuing RTX, requiring immunosuppressive therapies such as infliximab.[4,7] We chose UST because anti–tumor necrosis factor therapies have been associated with an increased risk of inflammatory demyelinating central nervous system disease.[15] To the best of our knowledge, there is only 1 case report where UST was successfully used in the treatment of fistulizing CD induced by RTX, although RTX was discontinued at the time of treatment.[2] In this article, we present a patient who was able to achieve endoscopic and histologic remission on UST while still continuing RTX treatment, highlighting the prospect of UST as a promising therapy for patients who are RTX-dependent.

## DISCLOSURES

Author contributions: XJ Li, BM Fung, and R. Kumar: wrote the manuscript. BM Fung: edited the manuscript. K. Rashmi: edited the manuscript and approved final manuscript. XJ Li is the article guarantor.

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Informed consent was obtained for this case report.

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## REFERENCES

1. Pierpont TM, Limper CB, Richards KL. Past, present, and future of rituximab—The world's first oncology monoclonal antibody therapy. *Front Oncol*. 2018;8:163.
2. Shankar U, Vijayasekar K, Bansal R, Walfish A. Treatment of rituximab-induced Crohn's disease with ustekinumab induction and long-term maintenance of remission. *Inflamm Bowel Dis*. 2020;26(1):e3.
3. Lipka S, Katz S, Crawford JM. Fulminant colitis following rituximab therapy. *Gastroenterol Hepatol*. 2016;12(1):58.
4. Fraser D, Boyle S, Amft N. Perianal Crohn disease after treatment with rituximab for active granulomatosis with polyangiitis. *J Rheumatol*. 2016;43(12):2199–200.
5. Varma P, Falconer J, Aga A, Prince HM, Pianko S. Rituximab-induced Crohn's disease. *Scand J Gastroenterol*. 2017;52(5):606–8.
6. Cavalcanti E, Armentano R, Lolli I. Crohn's disease following rituximab treatment for follicular lymphoma in a patient with synchronous gastric signet ring cells carcinoma: A case report and literature review. *Cancer Res Treat*. 2020;52(4):1291–5.
7. Morita K, Shibano T, Maekawa K, et al. Crohn's disease following rituximab treatment in a patient with refractory nephrotic syndrome. *CEN Case Rep*. 2019;8(1):55–60.
8. Barreiro Alonso E, Álvarez Álvarez A, Tojo González R, de la Coba Ortiz C. Rituximab-associated colitis. *Gastroenterol Hepatol*. 2019;42(4):251–2.
9. Ardelean DS, Gonska T, Wires S, et al. Severe ulcerative colitis after rituximab therapy. *Pediatrics*. 2010;126(1):e243–6.
10. Shahmohammadi S, Sahraian MA, Shahmohammadi A, Doosti R, Zare-Mirzaie A, Naser Moghadasi A. A presentation of ulcerative colitis after rituximab therapy in a patient with multiple sclerosis and literature review. *Mult Scler Relat Disord*. 2018;22:22–6.
11. Kristjánsson VB, Lund SH, Gröndal G, et al. Increased risk of inflammatory bowel disease among patients treated with rituximab in Iceland from 2001 to 2018. *Scand J Gastroenterol*. 2021;56(1):46–52.
12. Mallepally N, Abu-Sbeih H, Ahmed O, et al. Clinical features of rituximab-associated gastrointestinal toxicities. *Am J Clin Oncol*. 2019;42(6):539–45.
13. Eckmann JD, Chedid V, Quinn KP, Bonthu N, Nehra V, Raffals LE. De novo colitis associated with rituximab in 21 patients at a tertiary center. *Clin Gastroenterol Hepatol*. 2020;18(1):252–3.
14. Mizoguchi E, Mizoguchi A, Preffer FI, Bhan AK. Regulatory role of mature B cells in a murine model of inflammatory bowel disease. *Int Immunol*. 2000;12(5):597–605.
15. Kunchok A, Aksamit AJ, Davis JM, et al. Association between tumor necrosis factor inhibitor exposure and inflammatory central nervous system events. *JAMA Neurol*. 2020;77(8):1–11.