CASE STUDY SERIES IN IBD

Cytomegalovirus Colitis in a Patient With Ulcerative Colitis With Loss of Corticosteroid Response Upon Upadacitinib Initiation

Jonathan A. Salazar, MD,[1] Jeffrey D. Goldsmith, MD,[2] Athos Bousvaros, MD, MPH,[1] and Michaela Tracy, MD, MPH[1]

[1]Division of Gastroenterology, Hepatology and Nutrition, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts

[2]Division of Pathology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts

Cytomegalovirus (CMV), a member of the *Herpesviridae* family, affects 60% to 90% of individuals worldwide.[1] Primary infection often occurs in childhood or adolescence, characterized by mild symptoms followed by a prolonged period of viral latency. Immunocompromised hosts with greater T-cell dysfunction are at a higher risk of viral reactivation and development of systemic disease.[2] The risk and sequelae of CMV infection in immunocompromised patients such as transplant recipients are well documented in the literature and are characterized by a diverse range of symptoms, including CMV colitis. In contrast, several meta-analyses have shown that CMV disease in immunocompetent individuals is rare, potentially self-resolving, and not well understood.[3,4]

CMV colitis is a common manifestation of CMV disease in immunocompromised individuals.[3] Although CMV colitis requires antiviral therapy in severely immunocompromised patients, the effect of CMV infection in patients with ulcerative colitis (UC) and the role of antiviral treatment remain unclear. Individuals with UC who are female (assigned at birth), with pancolitis, shorter disease course (<60 months), and on chronic immunosuppressive regimens (eg, corticosteroids) appear to be at higher risk for CMV reactivation, and thus CMV colitis.[5] Current data suggest that patients with UC and CMV have greater rates of corticosteroid-resistant disease[6] and potentially higher rates of colectomy.[5] With the development of new immunomodulators such as Janus kinase (JAK) inhibitors for management of immune-mediated disease, it is increasingly imperative that clinicians understand the risk associated with CMV reactivation as well as the treatment protocol and long-term outcomes for patients with UC.

The current case report presents a teenage male with UC who was previously corticosteroid responsive and developed corticosteroid resistance with concurrent upadacitinib (Rinvoq, AbbVie) initiation and was subsequently found to have CMV colitis. The patient was treated with antiviral therapy and achieved clinical remission of his UC with upadacitinib monotherapy.

Corresponding author:
Dr Michaela Tracy, Division of Gastroenterology, Hepatology and Nutrition, Boston Children's Hospital, Harvard Medical School, 333 Longwood Avenue, Boston, MA 02115; Tel: (617) 355-6058;
E-mail: Michaela.tracy@childrens.harvard.edu

Case Report

A 15-year-old male was diagnosed with ulcerative pancolitis at age 14 years and achieved clinical remission with corticosteroid and aminosalicylate therapy. Within 10 months of weaning off corticosteroid therapy, he developed hematochezia and underwent a colonoscopy showing right-sided colitis with biopsies showing chronic moderately active colitis to the distal transverse colon. He achieved clinical remission with corticosteroid therapy initiation and was transitioned to anti–tumor necrosis factor (anti-TNF) therapy. After induction with anti-TNF therapy, he was unable to wean from corticosteroid therapy and required hospitalization owing to severity of his symptoms and extreme anemia. His laboratory workup showed a therapeutic anti-TNF level without evidence of anti-TNF antibodies.

He was reinitiated with corticosteroid therapy and transitioned to upadacitinib. Immediately after initiation of upadacitinib, the patient had a sustained 5-day improvement in his symptoms with a decrease in his daily Pediatric Ulcerative Colitis Activity Index (PUCAI) score from 60 to 20. After 5 days, however, his symptoms recurred (hematochezia, abdominal pain, tenesmus) and

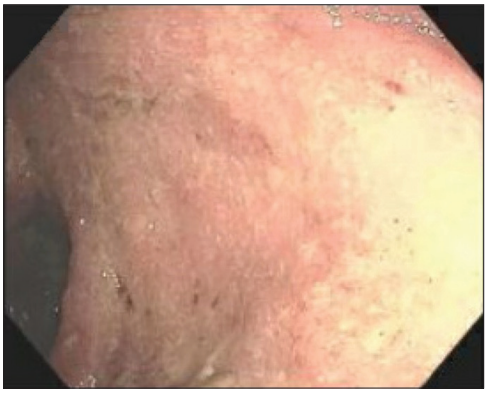

Figure 1. Colonoscopy of a 15-year-old male with ulcerative colitis and cytomegalovirus colitis receiving upadacitinib. Macroscopic findings in the descending colon show edematous and granular mucosa with decreased vascular pattern, increased exudate, and contact bleeding.

he was unable to achieve clinical remission despite high-dose corticosteroid therapy. He then underwent repeat colonoscopy. His endoscopic workup revealed Mayo score 2 to 3 pancolitis (Figure 1) with cecal sparing, and biopsies were consistent with chronically moderately active colitis. There were no histologic signs concerning for CMV on initial hematoxylin and eosin (H&E) examination (Figure 2). Per clinical request, immunostaining for CMV was performed, which showed positive CMV staining in the sigmoid and descending colon (Figure 3); retrospectively, definitive viral cytopathic effect was not seen on H&E stain. Subsequently, quantitative CMV polymerase chain reaction resulted in 4.8 $\log_{10}$ copies of the CMV genome per mL. In consultation with the infectious disease service, he was initiated on enteral valganciclovir and weaned off corticosteroid therapy.

At a 6-week follow-up visit, the patient had achieved clinical remission of his UC with an undetectable CMV viral load. Valganciclovir was discontinued and he completed an 8-week induction course of 45 mg upadacitinib. He is currently in clinical remission on 30 mg upadacitinib monotherapy with a PUCAI score of 0. Repeat colonoscopy has not yet been performed.

Discussion

CMV disease in immunocompetent patients remains exceedingly rare. Patients with UC, however, have varying degrees of immunocompromise owing to the pathophysiology of inflammatory bowel disease (IBD) as well as the immunomodulator therapies used to treat this condition. Notably, patients with UC have an aberrant T-cell response mediated by natural killer lymphocytes that result in increased cytotoxic cytokines and impaired mucosal immunity, perhaps predisposing them to opportunistic infections such as CMV.[7] In addition, chronic corticosteroid therapy (>1 month) has been associated with greater risk of CMV reactivation,[8] which was supported by in vitro studies showing stimulatory effects of corticosteroids on CMV replication.[9] One study showed an almost 3-fold (odds ratio, 2.951; P<.001) increase in CMV disease in patients with IBD treated with corticosteroids and a near 2-fold (odds ratio, 1.86; P=.030) increase in those treated with immunomodulators. Notably, there was no association with TNF antagonist use.[10]

An additional risk factor for CMV disease in this patient may have been the addition of upadacitinib. The development of JAK inhibitor therapies has further

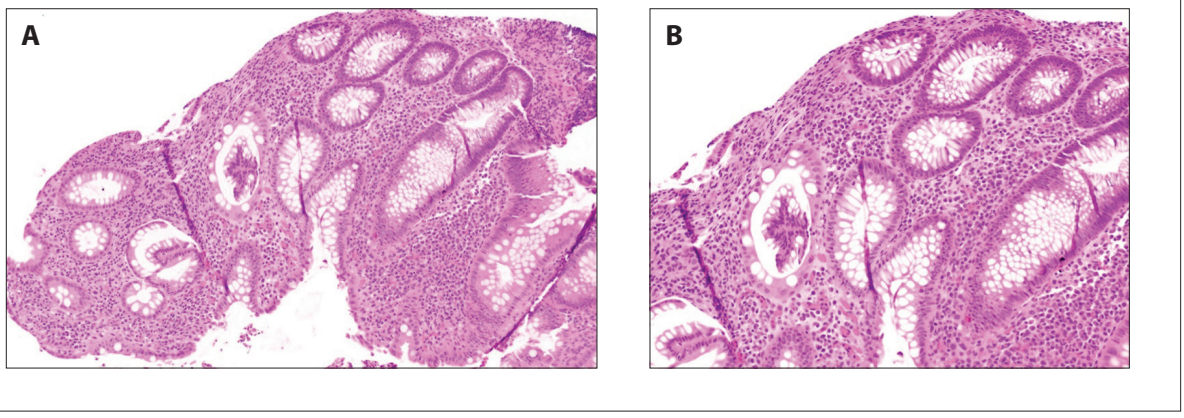

Figure 2. Hematoxylin and eosin examination (40× [**A**] and 100× [**B**] magnifications) of biopsies obtained from the descending colon show increased lamina propria inflammation and modest basal plasmacytosis consistent with chronic colitis; neutrophilic inflammation was seen in other areas. Viral cytopathic effect is not identified; Figure 2B is from the same area as Figure 3A.

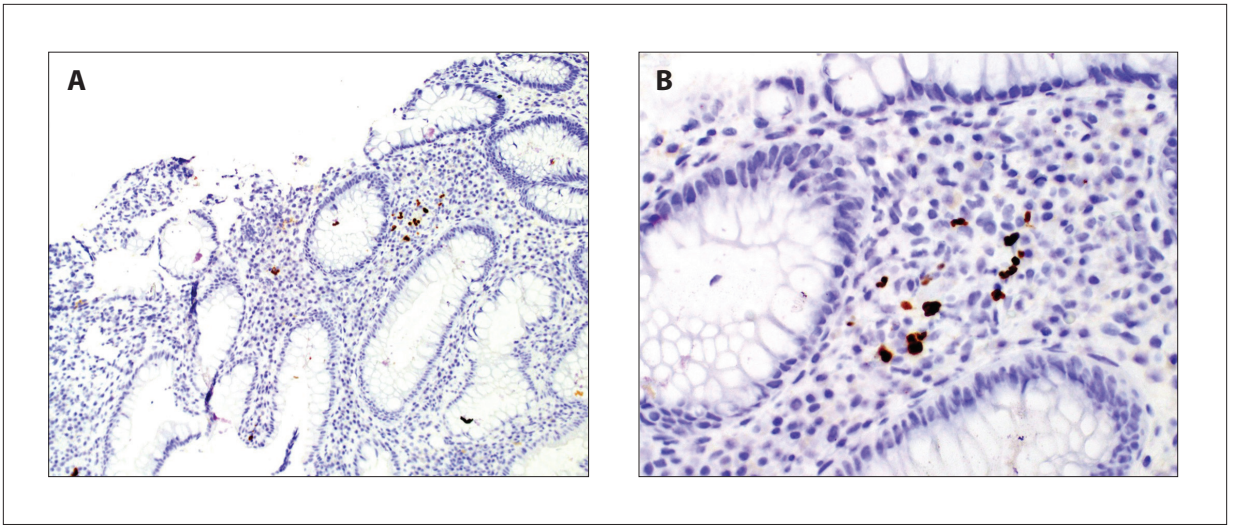

Figure 3. Immunohistochemical staining (100× [**A**] and 600× [**B**] magnifications) for cytomegalovirus on biopsies obtained from the descending colon show scattered positive nuclear staining in lamina propria cells that is diagnostic of cytomegalovirus infection. Figure 3B shows unequivocal nuclear staining.

diversified treatment modalities for these complex immune-mediated diseases. With their advent, however, new pathways exist for opportunistic pathogens to cause systemic disease. JAK proteins are important enzymes in intracellular signaling pathways associated with immune-mediated inflammatory responses. Inhibition of these proteins has shown efficacy in the management of various autoimmune diseases, including IBD. The development of varicella zoster virus in patients treated with nonselective JAK inhibitors (eg, tofacitinib [Xeljanz, Pfizer]) has now been well documented.[11] Current studies suggest that inhibition of the JAK proteins may lead to decreased efficacy of varicella zoster virus–specific effector T cells.[12]

Upadacitinib, a selective JAK1 inhibitor, has also shown great efficacy in the treatment of IBD.[13] The role of JAK1 inhibition in patients with UC and CMV infection, however, is not understood. In the initial safety and efficacy studies, CMV colitis and viremia were reported as rare adverse events.[13] More recent case reports include a similar case of CMV colitis in a pediatric patient receiving upadacitinib[14] as well as CMV retinitis in an adult patient treated with upadacitinib for rheumatoid arthritis.[15] Given that JAK1 activity leads to robust downstream signaling, the precise connection between JAK1 inhibition and higher rates of CMV colitis remains unclear.

It must be noted that no causal relationship has been shown between JAK inhibition and CMV viremia. In pediatrics, the use of JAK inhibitors is usually reserved for treatment-refractory IBD. Furthermore, greater disease severity has been shown to be an independent risk factor for development of CMV disease. As such, the occurrence of CMV in patients receiving JAK inhibitors may reflect their disease severity rather than exposure to these medications.

The gold standard method for diagnosis of CMV colitis has also been widely studied without a consensus protocol.[16,17] The current standard of practice, including at Boston Children's Hospital, is immunohistochemical staining for CMV if viral cytopathic effect suggestive of CMV infection is noted on H&E or if the requesting clinician indicates high suspicion for CMV based on clinical and/or endoscopic findings. Notably, however, multiple studies have now shown that standard H&E staining lacks adequate sensitivity to accurately diagnose CMV colitis. Rather, immunohistochemical staining and viral load polymerase chain reaction have been shown to be more accurate in the diagnosis of CMV colitis.[18,19]

In this case report, the clinical suspicion for CMV was high, owing to various factors. First, this patient had previously been responsive to corticosteroid therapy. Shortly before diagnosis of CMV colitis, his disease became refractory to those high-dose corticosteroids. CMV infection has been associated with corticosteroid resistance, perhaps because of changes in specific glucocorticoid receptors.[20] Second, this patient had a 5-day response to upadacitinib, which was subsequently lost. As such, the clinical index of suspicion was high for a potential superimposed infection. Ultimately, in this case, his CMV colitis was likely a combination of his prolonged corticosteroid use (>6 months), exposure to upadacitinib, short duration of illness (<60 months), and presence of pancolitis that allowed for CMV reactivation and development of significant disease. His viral load was elevated in his blood, which also points to systemic disease. As such,

the decision was made to treat this patient with antiviral therapy, understanding that his underlying UC was being exacerbated by concurrent CMV infection. Upon treatment completion for CMV, he achieved clinical remission on upadacitinib monotherapy.

As the use of JAK inhibitors increases in pediatrics, more work is needed to understand the specific risk factors associated with these medications in the pediatric population. This case report highlights a potential association with CMV infection. More importantly, it underscores the importance of future work focusing on incorporating patient-specific factors to adequately risk-stratify patients with IBD on JAK inhibitors. In addition, a focus on better understanding when and how to evaluate for CMV disease, as well as the development of clear treatment parameters for patients with UC and CMV, remain important areas of research, especially if the incidence of CMV colitis increases with the introduction of new immunomodulatory therapies.

Summary

Patients with UC demonstrate varying degrees of immunocompromise owing largely to immunomodulator medication used to treat this disease. Known risk factors for the development of CMV colitis in patients with UC include prolonged corticosteroid use. With the advent of therapies such as JAK inhibitors (eg, upadacitinib), however, these new forms of immunomodulation may increase the risk of certain opportunistic infections in patients with UC. This case report presents a 15-year-old male with UC who was refractory to aminosalicylate and anti-TNF therapies and ultimately transitioned to upadacitinib with good response. After 5 days of upadacitinib therapy, however, he developed signs and symptoms of worsening colitis and was unable to improve on high-dose corticosteroid therapy. Although his prolonged corticosteroid use was likely the strongest risk factor for developing CMV colitis, the initial response to upadacitinib suggests that he developed CMV colitis after addition of this JAK inhibitor. Further work is necessary to understand the relationship between CMV reactivation and use of JAK inhibitor medications, yet this case reinforces several case reports that suggest an increased risk of CMV disease in patients treated with upadacitinib.

Disclosures

Dr Bousvaros has received research support from Janssen, AbbVie, Takeda, Buhlmann, Arena/Pfizer, Eli Lilly, Bristol Myers Squibb, and ProciseDx; has done consulting for Takeda, Best Doctors, Eli Lilly, Fresenius Kabi, Alivio Therapeutics, and the Blue Cross Blue Shield formulary committee; has received royalties from UpToDate; and has received honorarium from Boston University. The other authors have no relevant conflicts of interest to disclose.

References

1. Rowshani AT, Bemelman FJ, van Leeuwen EM, van Lier RA, ten Berge IJ. Clinical and immunologic aspects of cytomegalovirus infection in solid organ transplant recipients. *Transplantation*. 2005;79(4):381-386.
2. Kandiel A, Lashner B. Cytomegalovirus colitis complicating inflammatory bowel disease. *Am J Gastroenterol*. 2006;101(12):2857-2865.
3. Rafailidis PI, Mourtzoukou EG, Varbobitis IC, Falagas ME. Severe cytomegalovirus infection in apparently immunocompetent patients: a systematic review. *Virol J*. 2008;5:47.
4. Galiatsatos P, Shrier I, Lamoureux E, Szilagyi A. Meta-analysis of outcome of cytomegalovirus colitis in immunocompetent hosts. *Dig Dis Sci*. 2005;50(4):609-616.
5. Mourad FH, Hashash JG, Kariyawasam VC, Leong RW. Ulcerative colitis and cytomegalovirus infection: from A to Z. *J Crohns Colitis*. 2020;14(8):1162-1171.
6. Lv YL, Han FF, Jia YJ, et al. Is cytomegalovirus infection related to inflammatory bowel disease, especially steroid-resistant inflammatory bowel disease? A meta-analysis. *Infect Drug Resist*. 2017;10:511-519.
7. Targan SR, Karp LC. Defects in mucosal immunity leading to ulcerative colitis. *Immunol Rev*. 2005;206:296-305.
8. Hirayama Y, Ando T, Hirooka Y, et al. Characteristic endoscopic findings and risk factors for cytomegalovirus-associated colitis in patients with active ulcerative colitis. *World J Gastrointest Endosc*. 2016;8(6):301-309.
9. Forbes BA, Bonville CA, Dock NL. The effects of a promoter of cell differentiation and selected hormones on human cytomegalovirus infection using an in vitro cell system. *J Infect Dis*. 1990;162(1):39-45.
10. McCurdy JD, Jones A, Enders FT, et al. A model for identifying cytomegalovirus in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2015;13(1):131-137.
11. Sánchez González CO, Nieto González JC. JAK kinase inhibitors and varicella zoster virus infection in patients with rheumatoid arthritis. Systematic review of the literature. *Reumatol Clin (Engl Ed)*. 2022;18(8):453-458.
12. Sunzini F, McInnes I, Siebert S. JAK inhibitors and infections risk: focus on herpes zoster. *Ther Adv Musculoskelet Dis*. 2020;12:1759720X20936059.
13. Irani M, Fan C, Glassner K, Abraham BP. Clinical evaluation of upadacitinib in the treatment of adults with moderately to severely active ulcerative colitis (UC): patient selection and reported outcomes. *Clin Exp Gastroenterol*. 2023;16:21-28.
14. Bao MM, Kennedy JM, Dolinger MT, Dunkin D, Lai J, Dubinsky MC. Cytomegalovirus colitis in a patient with severe treatment refractory ulcerative colitis. *Crohns Colitis 360*. 2024;6(1):otae014.
15. Hirai H, Akai Y, Ogata N, Ueda T. Cytomegalovirus retinitis in a patient taking upadacitinib: a case report. *Cureus*. 2023;15(11):e48337.
16. Yang H, Zhou W, Lv H, et al. The association between CMV viremia or endoscopic features and histopathological characteristics of CMV colitis in patients with underlying ulcerative colitis. *Inflamm Bowel Dis*. 2017;23(5):814-821.
17. Tandon P, James P, Cordeiro E, Mallick R, Shukla T, McCurdy JD. Diagnostic accuracy of blood-based tests and histopathology for cytomegalovirus reactivation in inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis*. 2017;23(4):551-560.
18. Liao X, Reed SL, Lin GY. Immunostaining detection of cytomegalovirus in gastrointestinal biopsies: clinicopathological correlation at a large academic health system. *Gastroenterol Res*. 2016;9(6):92-98.
19. Gauss A, Rosenstiel S, Schnitzler P, et al. Intestinal cytomegalovirus infection in patients hospitalized for exacerbation of inflammatory bowel disease: a 10-year tertiary referral center experience. *Eur J Gastroenterol Hepatol*. 2015;27(6):712-720.
20. Wang S, Dou Y, Yang H, Ni A, Zhang R, Qian J. Alteration of glucocorticoid receptors and exacerbation of inflammation during lytic cytomegalovirus infection in THP-1 cells. *FEBS Open Bio*. 2017;7(12):1924-1931.