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CASE REPORT | LIVER

Refractory Cytomegalovirus Colitis Followed by *De Novo* Inflammatory Bowel Disease Post-Orthotopic Liver Transplantation

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ABSTRACT

Cytomegalovirus (CMV) and inflammatory bowel disease (IBD) are both immune-mediated complications that affect orthotopic liver transplantation patients. In this report, we present a 60-year-old man who underwent orthotopic liver transplantation for cryptogenic cirrhosis with serologies notable for CMV-seropositive donor and seronegative recipient. His post-transplant course was initially complicated by probable refractory CMV colitis. However, his gastrointestinal symptoms persisted, eventually leading to a diagnosis of post-transplant *de novo* IBD. The discussion highlights theories regarding the association between CMV and IBD, a topic that has been widely debated for decades.

KEYWORDS: cytomegalovirus; inflammatory bowel disease; liver transplantation

INTRODUCTION

Immune-mediated complications after orthotopic liver transplantation (OLT) range from infection to, less commonly, inflammatory bowel disease (IBD). One of the more common infectious complications is cytomegalovirus (CMV) infection, a herpesvirus that can reactivate after transplant and lead to devastating morbidity.[1] IBD, another immune-mediated complication after OLT, can occur as a recurrence of pretransplant disease or *de novo*. *De novo* IBD after OLT has primarily been described in patients with sclerosing cholangitis (PSC) or autoimmune hepatitis (AIH).[2–7] There are few case reports of *de novo* IBD diagnosis after OLT for conditions other than PSC or AIH,[8–10] although most were published decades ago. Our case is notable as a diagnosis of

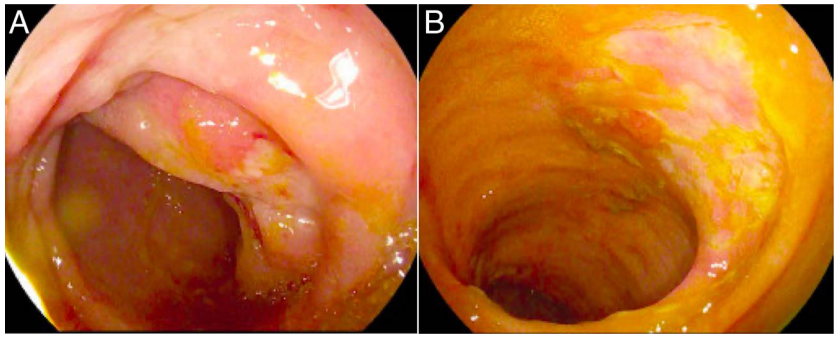

Figure 1. Erythematous mucosa and ulcerations within the sigmoid colon (A) and descending colon (B), visualized on flexible sigmoidoscopy performed 11 months after transplant.

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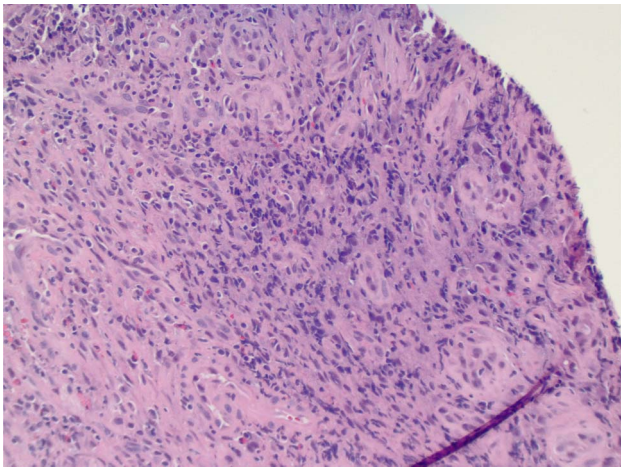

Figure 2. Image of a colonic ulcer in the colon (biopsy site not specified) at 200× magnification hematoxylin and eosin stain from flexible sigmoidoscopy performed 11 months after transplant.

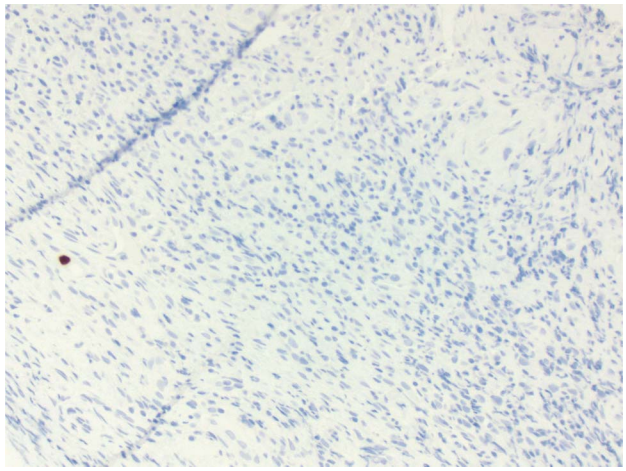

Figure 3. CMV immunohistochemistry from flexible sigmoidoscopy performed 11 months after transplant. The brown staining shows a CMV-positive enlarged endothelial cell in a capillary adjacent to the ulcer. 200X magnification. CMV, cytomegalovirus.

de novo IBD was made after the patient underwent OLT for cryptogenic cirrhosis, unrelated to PSC or AIH. To our knowledge, this is the first report of *de novo* IBD after a post-transplant course complicated by probable refractory CMV disease, defined as lack of improvement after 2 weeks of appropriately dosed induction therapy.[11]

CASE REPORT

A 60-year-old man presented to Duke University Hospital in December 2020 with acute-on-chronic liver failure due to cryptogenic cirrhosis. He underwent OLT in January 2021, with serologies notable for CMV-seropositive donor and seronegative recipient. Two months later, he was discharged on mycophenolic acid 720 mg every 24 hours because of diarrhea while taking mycophenolate 1,000 mg, tacrolimus with a goal trough of 6 to 8 ng/mL, and prednisone 20 mg daily. He completed 6 months of valganciclovir prophylaxis for CMV mismatch serostatus per institutional protocol.

Eight months after OLT, the patient was hospitalized for diarrhea and CMV DNAemia with a plasma CMV polymerase chain reaction of 2530 IU/mL. On admission, alanine transaminase was 242 U/L and aspartate transaminase was 120 U/L. Liver biopsy showed moderate lobular and focal interface hepatitis with no morphologic evidence of acute cellular rejection. Immunohistochemistry for CMV showed rare positive cells suggestive of a cytomegaloviral infectious etiology for the hepatitis. Colonoscopy was not performed because of a high degree of suspicion for CMV colitis. The patient was treated with 6 weeks of induction ganciclovir dosed 5 mg per kilogram every 12 hours, followed by maintenance valganciclovir 900 mg by mouth daily.

After hospital discharge, the patient endorsed symptoms of worsening abdominal pain and loose stools. CMV polymerase chain reaction at this time ranged from suppressed at <200 IU/mL to undetected. He was readmitted 11 months after OLT and underwent a flexible sigmoidoscopy, which revealed diffusely congested, erythematous mucosa with ulcerations within the sigmoid and descending colon. Biopsy demonstrated mucosa with active cryptitis and ulceration. Rare (endothelial) cells in the ulcer were positive on CMV immunohistochemistry (Figures 1–3). He was discharged on another course of induction ganciclovir, discontinued after 2 weeks because of recurrent neutropenia and lack of improvement in symptoms. He was then started on maribavir 400 mg every 12 hours for probable refractory CMV disease.

Despite the changes in CMV therapy, he continued to have gastrointestinal symptoms, and a flexible sigmoidoscopy was repeated 13 months after OLT. Although the colonic mucosa showed mucosal ulceration in the sigmoid colon that was worse from that earlier (Figure 4), no viral cytopathic effect was appreciated by evaluation of hematoxylin and eosin (H&E)-stained slides, and immunohistochemistry for CMV was negative. Stool

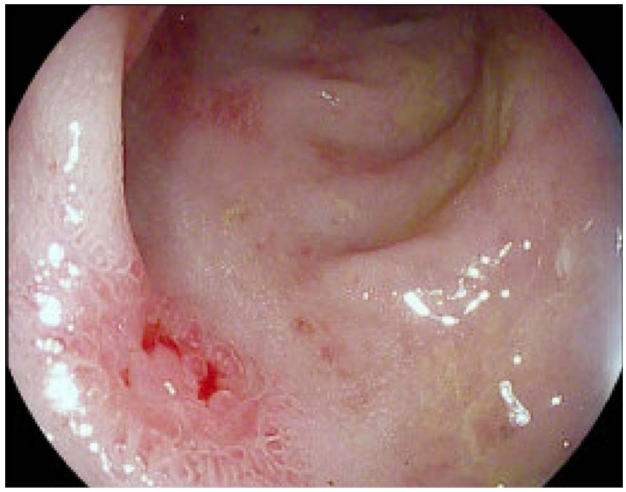

Figure 4. Ulcer in the sigmoid colon, visualized on flexible sigmoidoscopy completed 13 months after transplant.

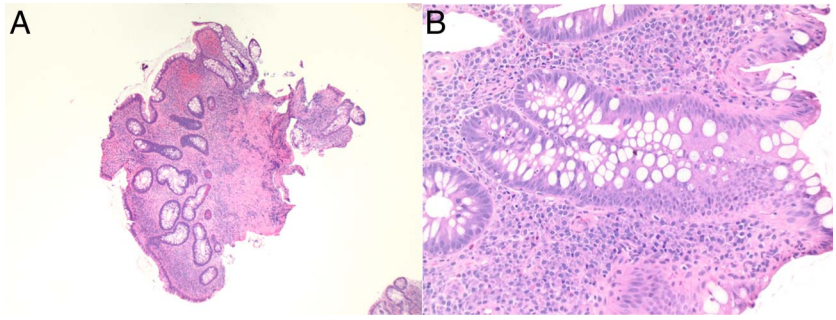

Figure 5. Chronic colitis in the transverse colon, characterized by crypt architecture disarray and increased lamina propria cellularity including basal plasmacytosis visualized on colonoscopy 1 year after vedolizumab infusions were initiated. H&E stain, magnification 40× (A). Area of active colitis in the right colon characterized by neutrophils in crypt H&E stain; magnification is 200× (B).

was negative for *Clostridioides difficile*, parasites, and viruses. Notably, fecal calprotectin returned positive at 1,391 ug/g. Based on these findings, a diagnosis of *de novo* IBD was favored. He was started on prednisone 40 mg daily and continued tacrolimus for immunosuppression. After 8 weeks of maribavir treatment, letermovir 480 mg daily was initiated for secondary prophylaxis. Owing to concerns for probable refractory CMV disease on ganciclovir and recurrent neutropenia with valganciclovir and ganciclovir, letermovir was chosen over valganciclovir.

For IBD, the patient was started on vedolizumab infusion (300 mg every 8 weeks). One year after the infusions were initiated, repeat colonoscopy demonstrated chronic active colitis (Figure 5) and the vedolizumab infusions were adjusted to every 4 weeks. His symptoms overall improved, although he continues to require intermittent adjustments to his prednisone dose because of increased diarrhea with taper attempts. He currently remains on prednisone 20 mg daily. In addition, he did not experience any further issues with CMV reactivation after treatment with maribavir. He ultimately completed 6 months of letermovir secondary prophylaxis.

DISCUSSION

In contrast to CMV infection, a well-documented complication of solid organ transplantation, *de novo* IBD is considered rare and mostly documented in the form of case reports typically focusing on patients transplanted for PSC or AIH.[2–7] It is not surprising that most prior studies demonstrated diagnosis of *de novo* IBD, an autoimmune disease, in patients transplanted for PSC and AIH, 2 other autoimmune conditions. Notably, CMV serostatus mismatch is a risk factor of *de novo* IBD in patients transplanted for either PSC or AIH.[12] While CMV serostatus mismatch may be associated with *de novo* IBD in patients transplanted for PSC and AIH, it is unclear whether CMV mismatch confers a similar risk in patients transplanted for other liver diseases.[12]

The relationship between CMV and IBD, even outside of the transplant setting, has been described in the literature since 1961.[13] However, the specific nature of the relationship is debated. One author proposed 3 theories: CMV as a cause of IBD, a pathogen that complicates IBD, or an innocent bystander.[14] Prior observational studies have shown an association between untreated CMV infection and steroid-refractory ulcerative colitis.[15–17] One study of patients with ulcerative colitis found an association between CMV infection and increased rates of inpatient mortality, longer length of hospital stay, and increased rates of colectomy.[18] In addition, treatment with ganciclovir improves outcomes in some patients with IBD.[19] These studies support the theory that CMV exacerbates IBD. However, other studies have found that steroids improved symptoms of acute colitis, even if CMV was observed on biopsy, implicating CMV as an innocent bystander.[20]

Existing literature about the association between CMV and IBD has largely focused on the nontransplant patient. Our case report raises the possibility that CMV mismatch and disease increase risk of another immune-mediated complication, IBD, in the post-transplant setting. We highlight the possibility that CMV may be an exacerbating factor rather than an innocent bystander in *de novo* IBD pathogenesis. CMV serostatus and disease are important factors to take note of when considering a patient's potential risk of *de novo* IBD.

DISCLOSURES

Author contributions: B. Selvan, JA Messina, MR Kappus: conception and design. B. Selvan: writing—original draft. All authors: writing—review and editing, final approval of manuscript, and accountable for all aspects of the work. B. Selvan is the article guarantor.

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