SHORT REPORT

Cytomegalovirus ileitis in a patient after liver transplantation-differentiating from de novo IBD

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Abstract
Cytomegalovirus (CMV) infection of the gastrointestinal (GI) tract has been reported in immunocompromised patients and is seen following liver transplantation. Although CMV infection can affect any part of the GI tract, involvement of the terminal ileum is rarely encountered after liver transplantation. We report a case of a 32-year-old male who developed CMV infection of the terminal ileum while receiving immunosuppression for liver transplantation. Initial ganciclovir treatment did not improve the patient's symptoms and therapy was then switched to foscarnet which ultimately resulted in resolution of infection. However the patient continued to have symptoms because of intermittent small bowel obstruction because of ulcerations and fibrosis ultimately requiring surgical resection. CMV DNA polymerase chain reaction (PCR) was negative throughout the course of infection. Surgical resected specimen revealed no evidence of inflammatory bowel disease (IBD). Follow up colonoscopy up to a year after infection also did not reveal any evidence of IBD. Compartmentalization in the clinical presentation of CMV involving GI tract can be seen with a negative blood DNA PCR. Histological diagnosis thus forms an important part in the clinical follow-up of liver transplant patients undergoing intense immunosuppression and should be aggressively pursued in patients with GI symptoms. De novo IBD should be considered in the differential diagnosis in these patients who do not improve with anti-viral treatment.

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Abbreviations: CMV, Cytomegalovirus; GI, gastrointestinal; IBD, inflammatory bowel disease; OLT, orthotopic liver transplantation; LFTs, liver function tests; PCR, polymerase chain reaction.

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1. Introduction

Cytomegalovirus (CMV) belongs to the herpes virus family and approximately 50–80% of adults in the US are affected by the age of forty, most of who have had asymptomatic infection. CMV affects both immunocompromised and immunocompetent individuals. Although infections are usually asymptomatic in immunocompetent individuals, it may occasionally manifest as a mild mononucleosis like syndrome. However, CMV has emerged as a significant opportunistic pathogen in immunosuppressed patients and is associated with increased morbidity. Gastrointestinal CMV disease is primarily associated with organ transplantation, acquired immune deficiency syndrome, malignancy, cancer patients receiving chemotherapy, patients treated with steroids and inflammatory bowel disease.

Patients who have undergone orthotopic liver transplantation (OLT) are at increased risk of CMV infection. Before the introduction of ganciclovir prophylaxis in liver transplant recipients, the reported incidence of CMV disease varied from 18 to 29%. However, this incidence varies widely depending upon donor and recipient CMV serological status with incidence as high as 44%–65% in CMV D+/R− and as low as 8%–19% in CMV-seropositive liver transplant recipients (CMV R+). The incidence has come down to 12%–30% in CMV D+/R−, and <10% in CMV R+ liver transplant recipients with 3 months of prophylaxis with valganciclovir and oral ganciclovir recently. In fact, most patients present with delayed onset CMV disease (>3 months) after OLT. CMV disease can occur anywhere in the gastrointestinal tract from the mouth to the anus; colitis is the most commonly described manifestation. Isolated CMV infection of the small bowel, though reported, is distinctly rare. CMV ileitis has been reported in patients with liver transplant; however involvement of ileum with histological evidence of CMV in the absence of CMV antigenemia and/or a negative polymerase chain reaction for CMV DNA is uncommon. CMV ileitis usually presents with abdominal pain, tenesmus, intestinal bleeding, and rarely perforation. Very rarely, does it present with small bowel obstruction. Lack of response to ganciclovir is also very uncommon in OLT with incidence of less than 19% in CMV-seropositive liver transplant recipients receiving organs from seropositive donors.

Physical examination demonstrated mild diffuse abdominal tenderness with involuntary guarding in the right iliac region. A complete blood count and comprehensive chemistry profile revealed a white blood cell count of 4200/mm³, hematocrit 36.3% and platelets 113,000/mm³. The LFTs and the coagulation parameters were normal. Computed tomography revealed diffuse inflammatory changes in the terminal ileum with hyperenhancement of the wall suspicious for graft-versus-host disease or post transplantation lymphoproliferative disorder or infectious enterocolitis. There was also dilatation of the proximal ileum with loops containing gas and stool representing a focal ileus versus a small bowel obstruction. Stool testing was performed for C. difficile toxin, ova and parasite exam, bacterial, and viral culture, all of which were negative. Blood and urine cultures were also sent and were negative.

Colonoscopy subsequently revealed moderately diffuse erythematous mucosal erosions in the distal ileum and a small ulcer in the ileum (Fig. 1). The colonic mucosa was normal. Multiple biopsies were obtained. Terminal ileal biopsies clearly revealed intranuclear eosinophilic inclusions consistent with CMV infection which was confirmed by immunocytochemical staining (Fig. 2). CMV polymerase chain reaction (PCR) was undetectable by PCR. Mycophenolate was stopped because of the concern of worsening CMV infection in patients with mycophenolate and steroids were substituted. The patient was started on intravenous ganciclovir 5 mg/kg twice daily. Ganciclovir was started and continued for 1 week. We switched to valganciclovir for 3 more weeks. After treatment for 4 weeks, the patient had persistent symptoms and continued

2. Case report

A 32-year-old white male with history of OLT 3 years prior secondary to alcohol induced end-stage liver disease presented with a 2-week history of increasing abdominal pain, nausea, vomiting and 1 episode of hematochezia. His past medical history was significant for OLT and diabetes post transplantation. He was on mycophenolate 500 mg post transplantation. Serologic testing of the donor and recipient indicated previous CMV infection in both. Antiviral prophylaxis against CMV was not administered based on the practice in our institution where prophylaxis is given only to CMV-seronegative transplant recipients receiving organs from seropositive donors.

We report here a case of a 32-year-old male who developed CMV infection of the terminal ileum presenting as partial small bowel obstruction while receiving immunosuppression for liver transplantation. Initial ganciclovir treatment did not improve the patient’s symptoms and therapy was then switched to foscarnet. Although patient cleared his CMV infection, he continued to have symptoms of intermittent partial small bowel obstruction because of fibrosis and ulcerations ultimately requiring surgical resection. We describe the literature and bring in arguments to differentiate from de novo inflammatory bowel disease (IBD) arising in the setting of post liver transplant.
to have abdominal pain and diarrhea. Stool testing was performed for *C. difficile* toxin, ova and parasite exam, bacterial, and viral culture, all of which were negative. CMV PCR was negative again. Hence fosfomycin was started intravenously and continued for 3 weeks. Although his diarrhea and abdominal pain improved a little, his symptoms did not improve markedly and hence a repeat colonoscopy was done. Colonoscopy revealed stenosis in the distal ileum 5 cm proximal to the ileocecal valve (Fig. 3). The mucosa in the distal ileum was also congested and nodular and the mucosa of the cecum appeared friable (Fig. 4). However CMV immunohistochemical staining was negative (Fig. 5). The patient was switched to prophylactic dose of valacyclovir and a decision was made to do surgical intervention. However the patient was not able to tolerate an oral diet and had repeated hospital admissions for partial small bowel obstruction. The patient was started on total parenteral nutrition (TPN) given his inability to take oral diet for improving the nutrition before surgery. The patient’s nutritional status improved after being on TPN for 4 weeks. The patient was taken to the operating room for ileocecal resection. Laparotomy revealed thick and dilated small bowel with extensive scar formation. Patient underwent the procedure without any complications. Pathology revealed evidence of chronic active ileitis with ulcerations, granulation tissue and fibrosis (Fig. 6). CMV immunostaining was negative in the resected specimen (Fig. 7). Patient did well following the procedure and on follow-up. The patient was followed after a year with a repeat colonoscopy and the repeat examination was normal with no evidence of IBD.

![Figure 2](image1.png)  
**Figure 2** Positive immunohistochemical staining for CMV.

![Figure 3](image2.png)  
**Figure 3** Colonoscopy revealing stenosis in the distal ileum 5 cm proximal to the ileocecal valve.

![Figure 4](image3.png)  
**Figure 4** Mucosa in the distal ileum with congestion and nodularity and friable cecal mucosa.

![Figure 5](image4.png)  
**Figure 5** Negative immunohistochemical staining for CMV.
3. Discussion

Gastrointestinal CMV disease is the most common site of tissue-invasive CMV and is primarily associated with organ transplantation, acquired immune deficiency syndrome, malignancy, cancer patients receiving chemotherapy, patients treated with steroids and inflammatory bowel disease. Among immunosuppressed patients, there appears to be an organ predilection for CMV infection; bone marrow transplant recipients are at increased risk for CMV pneumonitis, whereas in patients with the acquired immunodeficiency syndrome, retinitis and GI disease are more likely.

Tissue invasive CMV disease most commonly affects the GI tract, while involvement of the liver (CMV hepatitis) is much more commonly seen in OLT recipients. Symptomatic GI involvement with CMV has been reported in 2–16% of solid organ transplant patients. The segment of GI involvement in transplant recipients may also be influenced by the type of transplant, with, for example, esophageal involvement is seen with hematopoietic stem cell transplant recipients, colon involvement in renal transplant recipients, and stomach involvement in heart and heart/lung transplant recipients. The high rate of GI involvement with tissue-invasive CMV disease is unclear, although recent evidence points towards CMV as a primary pathogen in the gut.

Although any part of the GI tract may be affected by CMV in OLT, colitis is the most common manifestation of GI involvement. CMV infection of the small bowel, though reported, is distinctly rare, only involves 4% of CMV infections of the GI tract. CMV ileitis usually presents with abdominal pain, tenesmus, intestinal bleeding, and rarely perforation. In a large series of 31 immunohistochemically proven CMV infection, GI involvement was seen in 22 patients and two patients with isolates small bowel involvement had presented with intestinal perforation. All of this is proposed to be secondary to CMV vasculitis as supported by the presence of CMV inclusions in the endothelial cells. Histology of the affected mucosa shows a nonspecific inflammatory reaction and giant cells with ovoid nuclei containing amphophilic “Cowdry” inclusion bodies with a peripheral halo termed as Owl’s eye inclusions. Mesenchymal cells are infected most frequently (97%) followed by endothelial cells (35%), smooth muscle cells (6%) and epithelial cells (3%). Very rarely, do patients present with small bowel obstruction. Recently CMV causing a diaphragm-like stricture of the small intestine was described requiring surgical resection. Our patient presented with features of intermittent small bowel obstruction in spite of treatment with ulcerations and fibrosis. Continued use of immunosuppressive drugs, including steroids may have lead to persistent CMV activation with ulcerations and fibrosis resulting in intermittent obstruction in the ileum.

The finding of terminal ileal thickening, which did not improve despite treatment for CMV, is of interest. A similar phenomenon was reported in a previous patient with CMV infection and a gastric mass. CMV infection can target fibroblasts, epithelial cell, and smooth muscle cells and infection may induce fibroblasts smooth cell proliferation, resulting in obstruction that persists even after treatment. After resection, CMV inclusions were not seen highlighting that the fibroblast response rather than persistent infection was responsible for the symptoms.

Most cases of CMV infection occur in the first year after transplant. In fact in the large series of 31 patients, only 5 patients had CMV infection after the first year. Late CMV disease has been reported particularly among OLT patients and has not been shown to relate to any specific risk factor. Our patient had the infection 3 years following OLT. Although drugs used for maintenance immunosuppression have been associated with CMV disease, particularly high doses of mycophenolate mofetil, net immunosuppression rather than the particular drug increases the risk of CMV disease after OLT. Our patient was on tacrolimus and steroids for immunosuppression and steroid free regimens have shown to decrease the risk of CMV infection.

Gastrointestinal CMV disease has been suggested to produce "compartmentalized" infection termed as the presence of tissue invasive disease without a positive PCR. Our patient...
also had a compartmentalized infection which made it very difficult to follow the patients clinical improvement based on PCR based viral assay. Our patient clearly demonstrated the importance of a histological diagnosis of CMV infection as PCR was negative throughout the course of infection.

CMV infection in OLT recipients responds well to ganciclovir. In contrast to high resistance to ganciclovir in lung and kidney–pancreas transplant recipients who have rates as high as 9% and 13%, respectively, ganciclovir resistance after OLT is <0.5%.14,15 Genotyping has been suggested in patients who do not respond to ganciclovir to decide on the appropriate treatment.29 Our patient did not respond clinically to ganciclovir and because of the compartmentalization with negative PCR, it was very difficult to assess the response to treatment without colonoscopy. We did not do genotyping, but pursued foscarnet for 3 weeks and repeat colonoscopy showed disappearance of CMV on immunohistochemistry. In a large series of 31 patients, foscarnet was used in 4 patients; however resistance requiring foscarnet therapy was seen only in 1 patient.12 Surgical resection has been reported in patients with CMV infection. In the large series by Fica et al.,12 partial resection of the small bowel was required in only two patients. Our patient had persistent intermittent small bowel obstruction which necessitated surgery.

There are also reports of de novo IBD occurring after solid organ transplantation, in particular after OLT.30 The argument can be made that this patient actually had CD with CMV superinfection and it may be the reason that the patient did not improve with anti-viral treatment and required surgery. Post-transplant de novo IBD although uncommon, it has an incidence that is an order of magnitude higher than that seen in the general population. It infrequently arises in the first year after transplanting, and manifests as ulcerative colitis (UC) more commonly than Crohn’s disease (CD). In fact, there are only approximately 10 patients with CD de novo after transplant.31 Rates are substantially higher following OLT relative to other solid organs. The only risk factor identified to date for de novo post-transplant IBD appears to be CMV serology mismatch.31 Although our patient did not respond to ganciclovir, switching to foscarnet resulted in disappearance of CMV inclusion bodies. The resected surgical specimen of the terminal ileum showed evidence of chronic active enteritis and fibrosis. However there was no pathological feature of CD. Also repeat colonoscopy up to 1 year following surgical resection did not show any evidence of IBD. The patient was back on his immunosuppressive regimen and off steroids within a month after surgery. Thus the argument of this episode being IBD can be ruled out most probably based on a normal colonoscopy a year after. However this patient can still develop de novo IBD years after CMV infection. Time alone can answer the question.

Thus the presence of isolated ileitis, lack of response to ganciclovir, and presentation with partial small bowel obstruction requiring surgical resection makes this case of CMV infection very unique.

5. Conclusion

To conclude, the above cases clearly illustrate the morbidity caused by CMV infection in an OLT recipient. The compartmentalization of GI CMV infection in OLT patients reinforces the importance of obtaining an accurate histological diagnosis even in the absence of a negative CMV PCR. Post-transplant de novo IBD should be considered in the differential diagnosis in these patients who do not improve with anti-viral treatment. Further research needs to be done to understand the morbidity of CMV infection and possible preemptive prevention and/or treatment in the future. Clinicians should till then carefully suspect CMV disease in patients at risk.

References


