Atypical Presentation of Cytomegalovirus Infection in a Liver Transplant Patient

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Cytomegalovirus (CMV) is the most common viral infection in solid organ transplant recipients. Symptomatic infection usually presents with fever, pneumonia, colitis, or cytopenia. We describe a case of symptomatic CMV infection in a liver transplant recipient presenting with atypical symptoms of only persistent nausea and vomiting, in the absence of classical symptoms and signs; thus, highlighting the importance of high index of suspicion of CMV in immunocompromised patients, keeping in mind the high morbidity and mortality associated with this disease. (J CLIN EXP HEPATOL 2011;1:207–209)

Cytomegalovirus (CMV) is a double-stranded deoxyribonucleic acid (DNA) virus and is a member of the Herpesviridae family. It is the most common viral pathogen affecting solid organ transplant recipients.^{1–4} Although the incidence of CMV disease is decreasing due to the availability of better prophylactic and pre-emptive strategies, it still remains an important cause of morbidity and mortality for the immunocompromised transplant recipient population.^{5–7} It is estimated that 60–90% of all transplant candidates have latent CMV infections, but symptomatic CMV infection occurs in only 20–60% of cases.⁸ The CMV infection presents during the first 6 months after organ transplantation but delayed or late presentation is getting increasingly common due to pre-emptive therapy.⁹ The incidence of CMV infection varies according to the CMV serostatus of the donor and recipient, and the type of immunosuppression used. Risk is high if the recipient is seronegative and the donor is seropositive (CMV D+/R–) or muromonab-CD3 ortho kung t3 (OKT3) is used for immunosuppression.¹⁰ A prolonged prothrombin time at the time of liver transplantation and the diagnosis of acute liver failure as the underlying liver disease have also been associated with an increased rate of CMV infection.¹¹

Besides the common presentations of symptomatic CMV disease, such as viral syndrome, colitis, and pneumonia, CMV disease in liver transplant recipients often presents as hepatitis.¹² Fever, which is usually included in the case definition of CMV disease, is the most common symptom.¹³ Laboratory abnormalities include leucopenia, thrombocytopenia, and slightly elevated transaminases.¹⁴

We describe a case of CMV infection in a liver transplant recipient presenting with only atypical features of persistent nausea and vomiting as the only symptoms of CMV disease. This case highlights the importance of high index of suspicion for CMV infection in liver transplant patients presenting with atypical features and may represent an example of the changing clinical presentation of CMV-associated illnesses in a liver transplant recipient.

CASE REPORT

A 45-year-old woman was suspected to have endometrial tuberculosis in December 2010, and was started empirically on anti-tubercular treatment by a treating physician. Her baseline liver function tests were normal. She was given isoniazid, rifampicin, ethambutol, and pyrazinamide for 2 months. While on therapy, she developed deep jaundice followed by altered sensorium in January 2011, and was referred to the Gastroenterology and Hepatology Department of Sir Ganga Ram Hospital, New Delhi. At the time of admission, she was in grade III hepatic encephalopathy and her total serum bilirubin was 29.1 mg/dL with an international normalized ratio (INR) of 4.95. Her aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 967 and 1014 IU/L, respectively. Her markers for viral serology [IgM hepatitis E virus (HEV), IgM antibody-hepatitis A virus (anti-HAV), hepatitis B surface antigen (HBsAg), IgM antibody-hepatitis B core (anti-HBc), and antibody-hepatitis C virus (anti-HCV)] and autoimmune hepatitis markers [anti-nuclear antibody (ANA), antibody-smooth muscle antigen (ASMA), and

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Abbreviations: ALT: alanine aminotransferase; ANA: anti-nuclear antibody; anti-HBc: antibody-hepatitis B core; anti-HCV: antibody-hepatitis C virus; anti-LKM: antibody-liver-kidney-microsomal antigen; ASMA: antibody smooth muscle antigen; AST: aspartate aminotransferase; CMV: cytomegalovirus; EBV: Epstein-Barr virus; HBsAg: hepatitis B surface antigen; HEV: hepatitis E virus; INR: international normalized ratio; i.v.: intravenous
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antibody-liver-kidney-microsomal antigen (anti-LKM)] were negative. Serum ceruloplasmin and serum ferritin were also normal. She was diagnosed as a case of drug (anti-tubercular)-induced acute liver failure. As she did not improve with conservative management and her bilirubin and INR continued to rise, she was advised liver transplantation. She underwent live-related right lobe liver transplantation in February 2011. The liver was donated by her adopted son. She was positive for IgG CMV and negative for IgM CMV antibody at the time of transplantation, as was her donor. She was given tacrolimus, mycophenolate mofetil, and oral prednisolone as per standard protocol for immunosuppression. At the time of discharge (on 21st day of transplantation), she was comfortable and her bilirubin was 1.9 mg/dL.

Two weeks later, she was re-admitted with complaints of nausea and vomiting for the past 3 days. There was no history of pain abdomen, fever, diarrhea, abdominal distension, or bleeding. At the time of admission, she was afebrile and her physical examination was unremarkable. Her blood counts, renal function tests, serum electrolytes, blood sugar levels, and urine examination were unremarkable. Liver function tests were normal except for mild elevation of AST (132 IU/L) and ALT (55 IU/L). Ultrasonography of abdomen did not reveal anything specific. Findings of chest and abdomen X-rays were within normal limits. The results of blood cultures, urine cultures, stool cultures, *Clostridium difficile* toxin assays, and hepatitis A, B, C, and E serology testing were negative. Tests for Epstein-Barr virus (EBV), and herpes simplex virus (HSV) had negative results. A flexible upper gastrointestinal (GI) endoscopy was noncontributory. She was treated with intravenous (i.v.) fluids, metoclopramide, ondansetron, and prochlorperazine. In spite of all anti-emetic medications, her symptoms did not improve. Her testing of CMV viral load showed a viral load of 9640 copies/mL. Hence, the patient was started on intravenous ganciclovir 250 mg twice daily. She started improving over the next 3–4 days and her symptoms resolved completely after completing 2 weeks of therapy. Two weeks after treatment with ganciclovir, CMV virus became undetectable in blood.

DISCUSSION

Cytomegalovirus is the most common and single-most important viral infection in solid organ transplant recipients. The patient at highest risk for symptomatic disease is the CMV-seropositive donor/CMV-seronegative recipient (D+/R-) who develops a primary infection after transplantation. The CMV infection usually develops during the first few months after transplantation and is associated with clinical manifestations of fever, pneumonia, GI ulcers, and hepatitis. These manifestations are associated with acute and/or chronic graft injury and dysfunction. Most cases of symptomatic CMV infection can be characterized

by a self-limiting syndrome of episodic fever spikes for a period of 3–4 weeks, arthralgias, fatigue, anorexia, abdominal pain, and diarrhea. However, CMV infection can disseminate to the lungs, liver, pancreas, kidneys, stomach, intestine, brain, and parathyroid glands, and can cause death. The CMV retinitis, manifested by decreased visual acuity and peripheral blindness, can occur and lead to retinal detachment and blindness. Thus, CMV disease in immunocompromised individuals can affect almost every organ of the body.

The most striking feature of the index case is the presentation of CMV disease with symptoms of persistent nausea and vomiting only. There was no history of abdominal pain, diarrhea, fever, or jaundice. Blood investigations did not show any cytopenia. Her upper gastrointestinal endoscopic examination did not reveal any morphological lesion in the stomach. Her symptoms started improving with the initiation of anti-viral therapy. The absence of detectable CMV-DNA in the blood paralleled the complete resolution of symptoms; thus, further supporting our contention that her atypical symptoms of nausea and vomiting were due to CMV infection only. Other reported atypical presentations of CMV infection in different settings include the presentation as voluminous diarrhea, inflammatory polyps, hemorrhoids, vascular thrombosis, and laryngitis.^{15–19}

In conclusion, CMV infection can present with only atypical symptoms in liver transplant patients. Early and timely high index of suspicion of the disease is warranted in view of high morbidity and mortality associated with CMV infection if diagnosis and treatment are delayed.

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