

Unusual Presentation of Cytomegalovirus Infection in Patients After Organ Transplant

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Abstract

Objectives: Cytomegalovirus (CMV) infection has an enormous impact in solid-organ transplant patients. In immunocompromised patients, CMV is associated with well-known direct effects. We herein describe 3 unusual patterns occurring in the setting of tissue-invasive CMV associated with high viral load.

Materials and Methods: Of our 3 cases, the first patient after kidney transplant presented with cholestasis related to radiological cholangitis; the second patient after heart transplant presented with erythema nodosum with CMV infection as the sole cause; and the third patient after kidney transplant presented with acute renal failure related to mild interstitial nephritis with acute tubular necrosis and tubulitis.

Results: The first patient's cholestasis resolved with antiviral therapy, as did the erythema nodosum and CMV infection of the heart transplant patient. The third patient's acute renal failure resolved by increased steroid dosage, plasma exchanges, and ganciclovir therapy.

Conclusions: These 3 unusual presentations of tissue-invasive CMV had favorable outcomes with antiviral therapy.

Key words: Cholangitis, Glomerulopathy, Erythema nodosa, Ganciclovir, Kidney transplant

Cytomegalovirus (CMV) is a herpes virus. After initial infection, which resolves spontaneously in the normal host, the virus establishes life-long latency or persistence within the infected individual. Immunosuppression can result in virus reactivation (1). Infection with CMV has an enormous impact in solid-organ transplant patients, by directly causing systemic and tissue-invasive diseases, and by indirectly influencing various clinical outcomes (2-4). The direct effects are correlated with the peak of viremia, and include CMV syndrome (flu-like syndrome with sustained fever), mononucleosis syndrome, and tissue-invasive diseases such as hepatitis, myocarditis, pneumopathy, pancreatitis, colitis, and retinitis. In organ-transplant patients, the greatest virological-related pathology tends to occur in the transplanted organ; for example, liver-transplant patients have hepatitis, and lung-transplant patients have pneumonitis.

The indirect effects of CMV are independent of a high level of CMV viremia and result, in part, from the effect of the virus on the host's immune response in the setting of long periods of low-level CMV replication. This translates into organ allograft injuries, for example, acute or chronic rejection, and suppression of the systemic immune response, thereby leading to opportunistic infections or facilitated replication of viruses such as Epstein-Barr virus (5) and hepatitis C virus (6). CMV-related indirect effects can be decreased or prevented by CMV prophylaxis (5), but probably not by CMV preemptive therapies in humans (7).

Classic CMV-related invasive tissue diseases are common manifestations, while others are exceptional. Herein, we report 3 cases, one of CMV-induced cholangitis in a kidney transplant patient, CMV-

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associated erythema nodosum in a heart-transplant patient, and CMV-associated acute renal failure in a kidney transplant patient.

Case 1

A 19-year-old man underwent a kidney transplant from a living related donor in February 2007 for end-stage kidney disease related to chronic glomerulonephritis. His immunosuppression was based on daclizumab-induction therapy, mycophenolate mofetil, steroids, and cyclosporine. At posttransplant day 60, cyclosporine was converted to tacrolimus due to cyclosporine adverse effects. He experienced no acute rejections within the first year posttransplant. Because he was at high risk for CMV infection (the donor was CMV seropositive [D+] and he was CMV seronegative [R-]), valganciclovir prophylaxis was started on posttransplant day 5 at 900 mg per day; the dosage was adjusted based on renal function for calculated creatinine clearance was $> 1.002 \text{ mL/s/m}^2$. Valganciclovir was stopped on posttransplant day 100 due to neutropenia of $0.11 \times 10^9/\text{L}$. At that time, we assessed CMV infection by polymerase chain reaction (PCR) in specimens of blood and bone marrow aspiration; the results were negative.

At 5 months posttransplant, he was admitted to the hospital because of elevated temperature of 39°C , epigastralgia, tonsil ulcerations, and pancytopenia (neutropenia of $0.11 \times 10^9/\text{L}$, thrombocytopenia of $86.9 \times 10^9/\text{L}$, and hemoglobin of 115 g/L). Immunosuppression was based on tacrolimus at 9 mg per day (trough level of 6 ng/mL) and mycophenolate mofetil at 2 g per day. Serum creatinine was $150 \mu\text{mol/L}$ (baseline of $130 \mu\text{mol/L}$); liver function tests showed increased alanine aminotransferase (ALT) levels of $1.105 \mu\text{kat/L}$ (normal $< 0.765 \mu\text{kat/L}$), and anicteric cholestasis, that is, total bilirubin of $17 \mu\text{mol/L}$ (normal $< 21 \mu\text{mol/L}$), aspartate aminotransferase (AST) of $5.59 \mu\text{kat/L}$ (normal $< 1.02 \mu\text{kat/L}$), and alkaline phosphatase of $17.12 \mu\text{kat/L}$ (normal $< 4.76 \mu\text{kat/L}$).

He was taking no other medications apart from those for immunosuppression. Results of liver echography were normal. Results of magnetic resonance imaging (MRI) of the biliary tree displayed cholangitis with slight dilation of intrahepatic and extrahepatic bile ducts and hydrocholecystitis. Results of PCR testing for CMV were positive in specimens

of both blood ($5.86 \text{ log copies/mL}$) and bone marrow aspiration. Intravenous (IV) ganciclovir was started at 300 mg twice a day, and mycophenolate mofetil was reduced to 1 g per day. Despite 15 days of IV ganciclovir therapy, results of his liver function tests were still abnormal; that is, ALT was $2.08 \mu\text{kat/L}$, AST was $6.78 \mu\text{kat/L}$, and alkaline phosphatase was $10.08 \mu\text{kat/L}$.

After 4 weeks of IV ganciclovir therapy, results of liver function tests showed normal ALT levels but mild cholestasis with AST of $2.7 \mu\text{kat/L}$ and alkaline phosphatase of $5.28 \mu\text{kat/L}$. The level of CMV viremia had decreased to $2.87 \text{ log copies/mL}$; CMV serology was positive for both IgG and IgM. Lymphocytes were $1.87 \times 10^9/\text{L}$; the CD4 to CD8 ratio was 0.9. At this point, the patient was placed on valganciclovir therapy at 450 mg per day for 4 months. Cholestasis resolved in October 2007, three months after the onset of CMV disease. Biliary tree MRI was repeated in November 2007, four months after the diagnosis of CMV disease, and the results were normal.

Case 2

A 25-year-old man underwent a heart transplant in May 2006 for end-stage heart failure related to dilated cardiomyopathy. His immunosuppression was based on induction therapy with antithymocyte globulins, mycophenolate mofetil, steroids, and cyclosporine A. He did not experience any episodes of acute rejection. Because he was at risk for CMV reactivation (CMV seropositive [R+]), he underwent CMV prophylaxis of valganciclovir (450 mg/d) adjusted to calculated creatinine clearance until posttransplant day 180. At this point, 6 months posttransplant, asymptomatic CMV viremia was found at a level of $3.68 \text{ log copies/mL}$. His immunosuppression included cyclosporine 300 mg per day (2 hours concentration level of 900 ng/mL), mycophenolate mofetil at 2.5 g per day, and prednisolone at 10 mg per day. Because of the CMV viremia, valganciclovir was stopped, and he was placed on IV ganciclovir for 2 weeks; after this time, valganciclovir was resumed at 900 mg per day for 7 additional months, until June 2007. By this time, serum creatinine was $119 \mu\text{mol/L}$, and results of liver function tests had become normal.

However, 40 days later, he was hospitalized for severe fatigue. Findings on physical examination were unremarkable except for the presence of large

(3-cm diameter), erythematous, indurated, warm, painful plaques over his legs, suggesting erythema nodosum. His temperature was between 36.4°C and 36.8°C. His immunosuppression was unchanged over the previous 7 months; there was a C2 level of 1000 ng/mL. Results of laboratory tests showed hemoglobin of 102 g/L, without leucopenia or thrombocytopenia. Total lymphocytes were $0.98 \times 10^9/L$, and the CD4 to CD8 ratio was 0.85. The level of ALT had increased to 1.94 $\mu\text{kat}/L$, AST to 2.55 $\mu\text{kat}/L$, and alkaline phosphatase to 9.35 $\mu\text{kKat}/L$. Blood PCR tests were negative for types 1 and 2 herpes simplex viruses and for Epstein-Barr virus. Results of serologic tests were negative for hydatidosis, brucella, *Campylobacter jejuni*, hepatitis B, C, and E, histoplasmosis, toxoplasmosis, *Borrelia burgdorferi*, *Rickettsia connori*, *Yersinia enterocolitica* 09 and 03, *Yersinia pseudotuberculosis*, *Bartonella quintana*, and *Bartonella henselae*. However, results of CMV testing by PCR showed a level of 4.31 log copies/mL (although results had been negative 1 month earlier). Results of blood cultures were negative for bacteria and fungi. Because the results of liver function tests were slightly abnormal, he underwent a liver echogram, which had normal results. He was then placed on IV ganciclovir at 300 mg twice a day. The erythema nodosum lesions disappeared within 2 weeks of starting ganciclovir therapy. The level of CMV viremia decreased to 2.95 log copies/mL after 2 weeks and was negative 1 month later. Results of liver function tests progressively decreased to normal within 3 months. After 3 weeks of IV ganciclovir treatment, the patient was placed on valganciclovir at 900 mg per day for 5 months.

Case 3

A 57-year-old man underwent kidney transplant from a deceased donor in October 2005 for end-stage kidney disease related to reflux nephropathy. His immunosuppression was based on mycophenolate mofetil, steroids, and tacrolimus. He experienced no acute rejections within the first 6 months posttransplant. Because he was at high risk for CMV infection (the donor was CMV seropositive [D+] and he was CMV seronegative [R-]), valganciclovir prophylaxis was started on posttransplant day 5 at 450 mg per day, adjusted to renal function for serum creatinine of 130-150 $\mu\text{mol}/L$. Calculated creatinine clearance was $< 1.002 \text{ mL}/s/m^2$. Valganciclovir was

stopped by the fifth posttransplant month. At that time, CMV levels in blood by PCR were negative, and results of testing for CMV serology were also negative. Serum creatinine was 120 $\mu\text{mol}/L$. Immunosuppression included tacrolimus (1 mg/d, with trough levels of 8 to 13 ng/mL), mycophenolate mofetil at 1 g per day, and prednisolone at 2.5 mg per day. By the sixth and seventh months (1 and 2 months later), serum creatinine had become stable at 140-160 $\mu\text{mol}/L$ with no proteinuria.

After 7.5 months, he was admitted to the hospital because of edema and water weight gain of 5 kg. His serum creatinine was 450 $\mu\text{mol}/L$ (it had been 163 $\mu\text{mol}/L$ 2 weeks previously), although his urine output was normal ($> 2 L/d$) and proteinuria was 4.6 g per day; natriuresis was 90 mmol/day. His body temperature was normal. Results of kidney echogram were normal. Results of hematological tests showed mild thrombocytopenia of $115 \times 10^9/L$, whereas leukocyte count and hemoglobin levels were normal. Results of liver function tests were normal. Level of CMV in blood samples by PCR was 5.38 log copies/mL. Total lymphocytes were $0.91 \times 10^9/L$, and the CD4 to CD8 ratio was 1.32. Results of testing for antinuclear, anticytoplasmic nuclear, and anticardiolipin autoantibodies were negative, as was cryoglobulin. Complement subfractions were within the normal ranges. The C-reactive protein was 304 nmol/L (normal $< 28.6 \text{ nmol}/L$). On admission, because the patient was thought to have CMV disease with possible associated acute rejection, he was placed on IV ganciclovir (200 mg/d) and IV methylprednisolone (750 mg/d for 3 consecutive days, then 40 mg/d thereafter) before the CMV viremia result was available and a kidney biopsy was feasible. Mycophenolate mofetil was stopped and tacrolimus was maintained at 1.5 mg per day, aiming for trough levels of approximately 10 ng/mL.

By 48 hours later, the kidney biopsy was performed, and results showed mild interstitial nephritis with acute tubular necrosis and tubulitis (grade t1). Polymorphonuclear, T, and B lymphocytes were present in the interstitium associated with mild edema. Medullar hemorrhage without vasculitis was present. Two CMV inclusions in medullar tubular cells were identified by immunohistochemistry in entire specimens, examined at multiple levels. Staining for C4d was negative. Results of testing for donor-specific alloantibodies, as assessed by the Luminex technique, were negative.

Three days after admission, the serum level of creatinine peaked at 666 $\mu\text{mol/L}$, with proteinuria of 1 g per day. He required 1 hemodialysis session. Four days later, the serum level of creatinine was 579 $\mu\text{mol/L}$, proteinuria was 0.6 g per day, and the level of CMV viremia was still high at 4.8 log copies/mL. The kidney biopsy was repeated, and results showed glomerulitis (grade 2), capillaritis (ptc2), and mild interstitial inflammation. Staining for C4d was focally positive (grade C4d1). Because of the glomerulitis lesions, the lack of improvement in kidney function, and the persistently high CMV viremia load, the patient was treated with a plasma-exchange procedure for 5 consecutive days, followed by IV immunoglobulin at 40 g per day for 3 consecutive days, in addition to the previous treatments. At the end of these treatments, 15 days after admission, his serum level of creatinine was 270 $\mu\text{mol/L}$, proteinuria was 130 mg per day, and the level of CMV viremia was 5.56 log copies/mL. At this point, he was discharged on IV ganciclovir 300 mg per day for a total of 3 weeks, followed by valganciclovir at 450 mg three times a day. One month later, the serum level of creatinine was 195 $\mu\text{mol/L}$, proteinuria was 70 mg per day, the level of CMV viremia was 2.95 log copies/mL, and results of CMV serology had become positive.

Discussion

Infection with CMV can be associated with many clinical symptoms as a result of tissue invasion by the virus. Herein, we have reported on rare clinical manifestations of CMV disease in organ-transplant patients.

Viral cholangitis is less common than viral hepatitis. The effect of systemic viruses on the biliary tree is primarily dependent on the status of the host's immune system. Infants and immunocompetent patients are at risk of CMV cholangitis (8). The first case of CMV-associated jaundice in an immunocompetent patient was published in 1985 (9). Since then, only 2 cases of severe acute cholangitis have been reported (10, 11). One of these resolved with ganciclovir therapy (11), whereas the other had a fatal outcome (10). In immunocompromised patients, at least 3 other case reports have suggested that CMV infection may result in fibrosing cholestatic hepatitis (12-14), with fatal outcomes. Moreover, in 1 case, the patient underwent surgery for empyema of

the gallbladder. Histological examination showed CMV inclusions in the gallbladder wall (13). However, these 3 patients were receiving azathioprine therapy, which is associated with hepatic toxicity (15).

This case report is the first to describe CMV-associated cholestasis with overt radiological signs of cholangitis. Although the liver echogram was normal, MRI of the biliary tree displayed an aspect of cholangitis associated with slight dilation of intrahepatic and extrahepatic bile ducts and hydrocholecystis, suggesting CMV-induced lesions. At that time, the patient was receiving no known hepatotoxic drugs. Moreover, following effective anti-CMV therapy, repeat MRI of the biliary tree 4 months later was normal, suggesting a strong link between CMV disease and the occurrence of cholangitis.

Erythema nodosum has been linked with several infectious and noninfectious diseases. Its pathogenesis may be due to an immunologically mediated hypersensitivity reaction to an infectious agent. Inclusions of CMV have been observed in endothelial cells of blood vessels from immunocompromised patients with disseminated CMV infection and vasculitis (16), and with immunocompetent hosts with acute CMV syndrome (17). The development of erythema nodosum is rarely related to CMV, but has been reported (18, 19). In our patient, we had eliminated most of the classic infections associated with erythema nodosum. The only finding was CMV infection with high viral burden. Because the cutaneous lesions improved within 2 weeks of ganciclovir therapy, we inferred that erythema nodosum was caused by CMV infection.

Cytomegalovirus infection in kidney-transplant patients can occasionally cause kidney allograft infection or dysfunction (20). Interstitial nephritis can be caused by CMV, with CMV detected in tubular epithelial cells (21, 22). In addition, CMV-induced acute glomerulopathy has been described with characteristic lesions involving glomerular capillary endothelial cells and accumulation of mononuclear cells in glomerular capillaries (23-25); prominent podocytes (26); and positive staining with anti-CMV monoclonal antibody of endothelial cells (26). In some cases, these endothelial cell viral lesions have been associated with acute necrotizing and crescentic glomerulonephritis (27). Our third patient presented

with acute renal failure with normal urine output, normal natriuresis, and de novo proteinuria. This favored the diagnosis of interstitial nephritis instead of acute rejection, and this was confirmed by the results of the kidney biopsy. Because of continued renal dysfunction, he underwent a second kidney biopsy, results of which showed glomerulitis. Ultimately, the outcome was favorable although we cannot ascertain which therapy was ultimately responsible for this.

We conclude that, in addition to the classic CMV-related clinical manifestations, other rare presentations can be encountered, such as cholangitis, erythema nodosum, or acute renal failure.

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