Late and Atypical Cytomegalovirus Disease in Solid-Organ Transplant Recipients

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Posttransplantation cytomegalovirus (CMV) disease typically occurs 1–4 months after solid-organ transplantation. The case definition invariably includes unexplained fever for ≥3 days, often with leukopenia. Late and atypical presentation of CMV disease has been rarely reported. Five cases of late and atypical CMV disease in heart (n = 1), liver (n = 1), and kidney (n = 3) transplant recipients occurred within a 4-month period in early 1999. These patients presented at a median of 25 months after organ transplantation (range, 6 months to 22 years). Atypical findings included absence of fever in 3 patients, elevated white blood cell counts in 4 patients, and normal platelet counts in 4 patients. Four patients were at risk for primary CMV infection, and 3 received ganciclovir prophylaxis for 3 months. One patient was treated for rejection, and 2 patients had induction muromonab-CD3 (Orthoclone; OrthoBiotech). Two of the patients had pulmonary CMV disease, but neither of these patients had hypoxia. Two patients had enterocolitis, one of whom had chronic colitis for a year. These cases may represent a changing epidemiology and clinical presentation of CMV disease in solid-organ transplant recipients in an era of changing immunosuppression and improved CMV disease prevention in the early posttransplantation period.

Cytomegalovirus (CMV) continues to be the most important infectious agent to have an impact on solid-organ transplant recipients [1–4]. Despite the decreased frequency of CMV disease and its complications with improved prophylactic strategies [5], CMV-associated illness remains a cause of considerable morbidity and increased hospital costs for the immunocompromised transplant recipient population [6]. Ten percent to 50% of allograft recipients develop CMV infection [5]. Approximately half of these patients will develop clinical manifestations of disease [3], and up to 30% of successfully treated cases of CMV disease will recur [7]. CMV infection characteristically presents during the first 6 months after organ transplantation [8], and recurrences occur within 3 months of completion of therapy for the initial episode [7]. Late CMV disease is defined as that which presents >6 months after organ transplantation, and it is most often related to the need to increase the level of immunosuppression because of late episodes of rejection [9].

Risk factors associated with the development of CMV disease include receipt of an organ from a CMV-seropositive donor [1], especially if the recipient was CMV-seronegative prior to transplantation, and use of muromonab-CD3 (OKT3; Orthoclone [OrthoBiotech]) or antilymphocyte preparations for induction or for treatment of allograft rejection [10]. In patients who undergo OKT3 or antilymphocyte therapy, CMV disease usually occurs within 1 month of treatment [1].

Fever, which is usually included in the case definition of CMV disease, is the most common symptom and sign [3]; leukopenia, thrombocytopenia, and elevations in hepatic enzyme levels are often noted during laboratory evaluation [11]. Although rare cases of localized CMV disease without viremia do occur, evidence of...
Table 1. Epidemiology of 5 cases of late and atypical cytomegalovirus (CMV) disease after solid-organ transplantation.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>45</td>
<td>45</td>
<td>25</td>
<td>53</td>
<td>50</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Organ transplanted</td>
<td>Liver</td>
<td>Kidney</td>
<td>Heart</td>
<td>Kidney</td>
<td>Kidney</td>
</tr>
<tr>
<td>CMV D/R serostatus</td>
<td>D+R−</td>
<td>D−/R−</td>
<td>D+R−</td>
<td>D−/R−</td>
<td>D−/R+</td>
</tr>
<tr>
<td>CMV disease prophylaxis (duration)</td>
<td>Gan (12 weeks), CMV Ig</td>
<td>None</td>
<td>Gan (10 days), CMV Ig</td>
<td>None</td>
<td>Gan (12 weeks)</td>
</tr>
<tr>
<td>Time of onset of CMV disease after transplantation, months</td>
<td>6</td>
<td>&gt;240</td>
<td>25</td>
<td>38</td>
<td>18</td>
</tr>
<tr>
<td>Use of OKT3</td>
<td>None</td>
<td>None</td>
<td>Induction</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Rejected treatment (date)</td>
<td>None</td>
<td>None</td>
<td>Steroids (October 1995)</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Immunosuppression (dosage)</td>
<td>FK506, Aza, Prd (12.5 mg/day)</td>
<td>Aza</td>
<td>Cysp, MMF, Prd (30 mg/day)</td>
<td>Cysp, MMF, Prd (30 mg/day)</td>
<td>Cysp, Prd (10 mg/day)</td>
</tr>
</tbody>
</table>

**NOTE.** Aza, azathioprine; Cysp, cyclosporin; D, donor; FK506, tacrolimus (Prograf; Fujisawa USA); Gan, ganciclovir; MMF, mycophenalate mofetil; OKTs, muromonab CD-3; Prd, prednisone; R, recipient; “+,” positive; “−,” negative.

Viremia is present almost universally during clinical CMV disease [12]. We describe 5 cases of CMV disease that were diagnosed in early 1999; they occurred late after organ transplantation, and they demonstrated other atypical features. These cases illustrate what may be a changing clinical presentation and epidemiology of CMV-associated illness in the solid-organ transplant recipient population.

**METHODS**

New England Medical Center Hospital (NEMCH), Boston, is a 300-bed tertiary care referral center with a solid-organ (liver, heart, and kidney) transplantation program. In early 1999, 5 cases of atypical and late CMV disease were diagnosed in a heart transplant recipient, a liver transplant recipient, and 3 kidney transplant recipients. Chart review and review of histopathological findings and laboratory records were performed for each patient.

Diagnosis of CMV-associated disease was based upon laboratory and/or pathologic confirmation of the presence of CMV in the affected patient, observation of clinical resolution of disease after initiation of ganciclovir therapy, and lack of evidence of other pathogenic processes, including infection, to explain the disease manifestations.

Blood buffy coat was evaluated for the presence of CMV, by means of conventional culture techniques, on the basis of demonstration of cytopathic effect [13], and/or the rapid shell-vial technique [14], and/or the Hybrid Capture CMV DNA Assay, version 2.0 (Digene; Mierex) [15]. Biopsy material was examined histologically for the presence of characteristic CMV-induced changes, and/or was cultured by a conventional technique, and/or rapid shell-vial technique.

**CASE REPORTS**

Pertinent epidemiological and clinical information for all 5 cases is presented in tables 1 and 2. The case reports are summarized as follows.

**Case 1**

Patient. A 45-year-old man underwent orthotopic liver transplantation in August 1998; he received CMV infection prophylaxis that consisted of oral ganciclovir for 3 months and CMV Ig (CytoGam; MedImmune) for 4 months, because he was a CMV-seronegative recipient of a CMV-seropositive transplant. He underwent maintenance therapy with FK506 (tacrolimus; Prograf, Fujisawa USA), azathioprine, and prednisone for immunosuppression, and had not had a rejection episode. In February 1999, he was admitted to NEMCH after 4 weeks of dyspnea on exertion that had worsened during the 2 weeks prior to presentation, as well as dysphagia with solid food.

At the time of admission, he was afebrile and appeared comfortable, and his examination findings were unrewarding except for oral thrush. His admission laboratory values were remarkable for an elevated creatinine value (2.6 mg/dL; baseline, 1.5–1.9 mg/dL), mild leukocytosis (WBC count, 13,200 cells/mm³), and an elevated FK506 level. Hepatic enzyme levels were normal. A chest radiograph revealed “left–lower-lobe infiltrate or atelectasis,” and therapy with trovafloxacin was started empirically for pneumonia, but a chest radiograph obtained the...
Table 2. Clinical features of 5 cases of late and atypical CMV disease after solid-organ transplantation.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of onset of CMV disease after transplantation, months</td>
<td>6</td>
<td>&gt;240</td>
<td>25&lt;sup&gt;a&lt;/sup&gt;</td>
<td>38&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18</td>
</tr>
<tr>
<td>Symptoms at initial presentation (duration)</td>
<td>Dyspnea on exertion (4 weeks)</td>
<td>Fever, fatigue, diarrhea (3 days)</td>
<td>Fever, weight loss, cough (4 weeks)</td>
<td>Watery diarrhea (3 months)</td>
<td>Fever, nausea, decreased urine output (4 days)</td>
</tr>
<tr>
<td>Type of CMV disease</td>
<td>Pulmonary</td>
<td>Enteritis, hepatitis</td>
<td>Pulmonary</td>
<td>Colitis</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Finding at admission</td>
<td>Fever</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>WBC count</td>
<td>Elevated</td>
<td>Decreased</td>
<td>Elevated</td>
<td>Normal</td>
<td>Elevated</td>
</tr>
<tr>
<td>Platelets</td>
<td>Normal</td>
<td>Thrombocytopenia</td>
<td>Normal</td>
<td>Elevated</td>
<td>Normal</td>
</tr>
<tr>
<td>Liver function values</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV DNA assay value, pg/mL</td>
<td>228.4</td>
<td>45.84</td>
<td>&lt;2.1</td>
<td>&lt;2.1</td>
<td>429.9</td>
</tr>
<tr>
<td>CMV shell vial assay</td>
<td>Late; resolution with Gan in parallel with decrease in CMV DNA</td>
<td>Late; resolution with Gan CV in parallel with decrease in CMV DNA</td>
<td>Late; resolution with Gan after failure of treatment for bacterial pneumonia</td>
<td>Late; complete resolution of illness with Gan after 1 year of diarrhea</td>
<td>Late; resolution with Gan in parallel with decrease in CMV DNA</td>
</tr>
<tr>
<td>Comment</td>
<td>Positive (BAL fluid)</td>
<td></td>
<td>Positive (colon biopsy specimen)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Findings in boldface are atypical for CMV disease after solid-organ transplantation. BAL, bronchoalveolar lavage; Gan, ganciclovir.

* Twenty-two months after initial CMV disease episode.

<sup>b</sup> Thirty months after rejection therapy.

next day for comparison showed no evidence of pulmonary disease.

Esophagogastroduodenoscopy was performed, and it revealed changes consistent with candidal esophagitis. Administration of fluconazole was started and the dysphagia resolved, but the patient continued to report dyspnea. Other studies, including trans-thoracic echocardiography and lower-extremity duplex Doppler examination, did not reveal the etiology of the dyspnea. Pulmonary function studies, including an arterial blood gas determination while the patient was breathing room air, revealed only a moderate decrease in diffusing capacity. CMV-DNA analysis of blood buffy coat revealed a level of 228.4 pg/mL (undetectable, <2.1 pg/mL), and ganciclovir therapy was initiated. The dyspnea resolved with this therapy, and the CMV DNA level decreased as the patient’s clinical condition improved.

Comment. Despite the presentation 6 months after high-risk (seropositive donor/seronegative recipient) liver transplantation, this case of CMV disease is remarkable for the lack of typical features of CMV-associated disease. The patient did not have fever, and his laboratory values, including hematologic and hepatic enzyme values, were normal or at baseline levels. Chest radiography did not reveal abnormalities, and multiple other diagnostic modalities revealed no cause of the patient’s dyspnea.

On pulmonary function testing, the patient demonstrated only a moderate reduction in diffusing capacity; he was neither hypoxemic nor hypocapnic. This case did not meet strictly defined criteria for CMV pneumonia [2]; however, CMV-related pulmonary disease was most likely responsible for his symptoms, because they resolved completely with ganciclovir therapy and their resolution paralleled a decrease in CMV DNA level.

Case 2

**Patient.** A 45-year-old woman had received a fully human leukocyte antigen (HLA)—matched kidney transplant from a living, related donor in May 1977; she was CMV seronegative at the time of transplantation, as was her donor. She had been receiving maintenance therapy with azathioprine (50 mg b.i.d.) for immunosuppression, and her baseline creatinine level was <1.0 mg/dL. In December 1998, she was admitted to NEMCH because of a 3-day history of fatigue, watery diarrhea, abdominal cramping, and fever.

At the time of admission, the patient was afebrile and the findings of her physical examination were unremarkable. Her admission laboratory values were remarkable for leukopenia (WBCs, 26,000 cells/mm<sup>3</sup>), a mildly elevated creatinine level (1.2 mg/dL), and mildly elevated transaminase concentrations (alanine aminotransferase [ALT] level, 40 U/L; aspartate aminotransferase [AST] level, 63 U/L) but no elevation in alkaline phosphatase or bilirubin levels. Administration of piperacillin-
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Case 3

Patient. A 25-year-old man received a heart transplant in January 1997; he received oral ganciclovir for 3 months and CMV Ig for 4 months because he was a CMV-seronegative recipient of a seropositive transplant. His immunosuppressive regimen consisted of cyclosporine, mycophenolate mofetil, and prednisone. He had undergone a 14-day course of OKT3 induction immediately after transplantation and had not had any rejection episodes.

In April 1997, he had an episode of CMV enteritis, which presented with nausea, vomiting, abdominal pain, pancytopenia, and elevated hepatic enzyme levels. The results of blood buffy coat culture were positive for CMV, and his symptoms resolved with ganciclovir treatment.

In February 1999, he was admitted to NEMCH because of a 4-week history of fever, malaise, anorexia, weight loss (9 kg), and nonproductive cough that had become productive of green sputum within the week of admission. At the time of admission, he was afebrile, and the examination findings were remarkable for diffuse wheezes, rales, rhonchi, and mild abdominal tenderness. His admission laboratory values revealed acute renal failure (creatinine level, 10.4 mg/dL; baseline, 2.0–3.0 mg/dL), leukocytosis (WBC count, 17,400 cells/mm³), and anemia (hematocrit, 25%); his hepatic enzyme levels were normal. A chest radiograph revealed bilateral interstitial infiltrates and a retrocardiac nodule. Empirical treatment with azithromycin and pentamidine were started. The patient had right–upper-quadrant pain and an elevated bilirubin concentration (4.1 U/L), and the azithromycin was withdrawn (with resolution of abdominal pain and hyperbilirubinemia).

A bronchoscopy revealed mucoid secretions from both lower-lobe bronchi and punctate erythematous lesions in the distal left mainstem bronchus. Bronchoalveolar lavage (BAL) specimens yielded sparse normal oropharyngeal flora, rare Staphylococcus aureus, and sparse Haemophilus influenzae, and viral cultures of the BAL fluid did not yield influenza virus, parainfluenza virus, adenovirus, respiratory syncytial virus, or herpes simplex virus.

Although the blood buffy coat CMV DNA level was <2.1 pg/mL, the results of a CMV shell vial assay of the BAL specimen were positive. Pentamidine was withdrawn and ganciclovir therapy was initiated. The patient’s illness, which had not improved significantly with the azithromycin and pentamidine, resolved with the ganciclovir.

Comment. This patient had late and atypical CMV disease: he presented 20 months after completing therapy for his initial episode of CMV disease, but he had not received antirejection treatment in the interim. He had bilateral pneumonia but was not hypoxemic, and he lacked fever and the typical laboratory abnormalities associated with CMV disease. As with case 1, despite the lack of stringent diagnostic criteria for CMV pneumonia, it is likely that this patient’s pulmonary disease was due to CMV, because his illness resolved completely with ganciclovir.
therapy after failing to respond to treatment for community-acquired pneumonia.

Case 4

Patient. A 53-year-old woman had received a fully HLA-matched cadaveric renal transplant in February 1995; she was previously CMV seropositive, and her donor was CMV seronegative. She was treated with 14-day course of OKT3 for primary nonfunction of the allograft and had an episode of acute rejection in October 1995, which resolved with high-dose steroids. Her subsequent posttransplantation course was uneventful, and her baseline creatinine level was 2.5–3.0 mg/dL. She received maintenance therapy with cyclosporine, mycophenolate mofetil, and prednisone immunosuppression.

In January 1998, the patient began to experience watery diarrhea after each meal. After an extensive evaluation at another hospital, “microscopic colitis” was diagnosed and administration of olsalazine was started. The symptoms diminished, but in April 1998, the diarrhea became severe and she was admitted to NEMCH, where she underwent another extensive gastrointestinal workup. Stool studies were unrevealing, a colonoscopy demonstrated diverticula and hemorrhoids, and a colon biopsy revealed mild nonspecific inflammation, but no inclusion bodies were visualized. The mycophenolate dosage was reduced, the diarrhea abated somewhat, and she was discharged.

In January 1999, the patient was admitted because of anorexia, mild nausea, and multiple episodes of watery diarrhea per day. She was afebrile, and the physical examination findings were unremarkable. Laboratory tests at the time of admission revealed slight leukocytosis (WBC count, 11,600 cells/mm³), an elevated creatinine level (5.0 mg/dL), and acidosis. Stool studies were again unrevealing. The mycophenolate dose, which had been increased in December 1998, was reduced again, and administration of loperamide was started. The patient’s symptoms diminished and she was discharged.

In April 1999, the patient developed nausea, vomiting, and increased diarrhea and was admitted to NEMCH. She was afebrile, and the examination findings were unremarkable. Laboratory values were significant for acidosis and an elevated creatinine level; the findings of a complete blood cell count and liver function tests were normal. The findings of stool studies were again normal. Abdominal radiography revealed a dilated colon with air-fluid levels. An upper gastrointestinal study with visualization of the small bowel demonstrated a 5-mm polypoid filling defect in the area of the cecum. The mycophenolate mofetil was withdrawn. The patient’s symptoms diminished and renal function improved, and she was discharged.

The patient underwent colonoscopy 1 week after discharge for evaluation of the abnormalities discovered on her radiograph. This again revealed hemorrhoids and diverticula, but now colitis was noted in the area of the cecum, and biopsies of this area revealed nonspecific inflammation; no inclusion bodies were visualized. The CMV DNA level was undetectable, but the results of a CMV shell vial assay of the cecal biopsy sample were positive.

The patient was admitted for initiation of iv ganciclovir therapy. The diarrhea finally resolved completely with this treatment. She was finally able to gain weight, and her gastrointestinal function returned to normal after more than 1 year of acute and chronic diarrhea.

Comment. This patient had late and atypical CMV disease. She had chronic CMV colitis, with acute exacerbations, that lasted for 1 year. Her symptoms had begun 3 years after kidney transplantation and 2 years after treatment for an episode of rejection. The diagnosis of her diarrheal illness was extremely difficult because of the lack of characteristic manifestations of CMV disease, such as fever, leukopenia, and serum hepatic enzyme abnormalities. Repeated colonoscopies demonstrated nonspecific lesions, and repeated colon biopsies revealed none of the histologic findings associated with CMV. After initiation of treatment with ganciclovir, the patient’s symptoms completely resolved.

Case 5

Patient. A 50-year-old man received a fully HLA-matched cadaveric renal transplant in September 1997; he received oral ganciclovir for 3 months because he was a CMV-seronegative recipient of a CMV-seropositive transplant. His immunosuppressive regimen consisted of cyclosporine and prednisone, and his baseline creatinine level was 0.9–1.3 mg/dL. He had not had an episode of rejection of the transplanted kidney. He was admitted to NEMCH in March 1999 because of 4 days of anorexia, mild nausea, and decreased urine output, as well as 1 episode of fever.

At the time of hospitalization, the patient was afebrile. He appeared dehydrated, but his physical examination findings were unchanged from baseline. The admission laboratory tests revealed an elevated creatinine level (3.1 mg/dL) and elevated serum hepatic enzyme levels (ALT level, 534 U/L; AST level, 555 U/L; alkaline phosphatase level, 471 U/L; bilirubin level, 1.5 mg/dL); the complete blood cell count revealed baseline levels. Findings of right–upper-quadrant ultrasonography were normal. The results of admission blood and urine cultures were negative. Administration of iv ganciclovir was initiated empirically. Serological findings were nonreactive for hepatitis A (IgG and IgM), hepatitis B (surface antigen and surface antibody), and hepatitis C (antibody). The CMV DNA level was 429.9 pg/mL (undetectable level, <2.1 pg/mL). The patient’s illness and laboratory abnormalities resolved after initiation of treatment with ganciclovir, and the CMV DNA level became undetectable.

Comment. The patient had symptomatic CMV hepatitis.
18 months after renal transplantation. He had completed CMV prophylaxis 1 year before this illness, he had not received any antirejection therapy, and his allograft had functioned well until this illness. Although the diagnosis of CMV hepatitis usually depends upon biopsy evidence of CMV-induced liver disease, this patient had several characteristic symptoms and laboratory findings indicative of CMV hepatitis without evidence of any other etiology. The CMV DNA level was markedly elevated, and symptoms and laboratory abnormalities resolved after ganciclovir therapy. The CMV DNA level decreased as the patient’s clinical condition improved.

**DISCUSSION**

We have presented 5 cases of CMV disease that occurred after solid-organ transplantation that were atypical because of the timing (table 1) and because of the lack of characteristic signs and symptoms (table 2). All of the cases occurred >6 months after the patient had undergone transplantation, and none were temporally related to treatment for an episode of rejection. Despite reports of fever by 3 of the 5 patients, all were afebrile at the time of (initial) hospital admission. Four patients had leukocytosis rather than leukopenia, and 3 had normal hepatic enzyme levels. Two of the patients had CMV disease syndromes, with shell vial assays of clinical specimens that demonstrated CMV, but viremia was not detectable.

Case reports about late and atypical CMV disease are rare in the medical literature [17–24], but newer studies allude to delayed onset after prolonged (≥3 months) ganciclovir prophylaxis [25–27]. In addition, the immunosuppressive agent mycophenolate mofetil reportedly increases the incidence of CMV disease without changing the overall CMV infection rate in renal transplant recipients [28]. The appearance of 5 cases of late and atypical CMV disease within a few months raises questions concerning a possible shift in the epidemiology of CMV disease in the solid-organ transplant recipient population.

On preliminary review, since 1997, the rate of CMV disease among our organ transplant recipients has decreased from 20% to 8%, whereas the proportion of late cases that have occurred ≥6 months after transplantation has increased by 35%. Until more information becomes available regarding this apparent trend, we suggest that suspicion of CMV disease be maintained beyond the “traditional” 6 months after organ transplantation and that the definition of CMV disease needs to evolve with the changes in immunosuppressive medications and prophylactic regimens.

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