Disseminated Cytomegalovirus Disease in Hosts without Acquired Immunodeficiency Syndrome and without an Organ Transplant

Mettassebia Kanno,1 Pranatharthi H. Chandrasekar,1 Gail Bentley,2 Richard S. Vander Heide,3 and George J. Alangaden1

1Division of Infectious Diseases and 2Department of Pathology, Wayne State University School of Medicine, Detroit

We describe 7 histologically proven cases of cytomegalovirus disease in patients without human immunodeficiency virus and without organ transplants, all of whom had associated comorbid conditions. Therapy with ganciclovir generally resulted in a favorable outcome.

The occurrence of cytomegalovirus (CMV) disease in transplant recipients and patients with AIDS is well described [1]. In an immunocompetent host, primary infection with CMV can manifest as a mononucleosis-like syndrome. Reactivation of CMV, which is commonly seen in transplant recipients and in patients with AIDS [1], is rare in immunocompetent people [2]. Three patients with CMV disease who were HIV seronegative and who had not received any transplants were identified at our institution during a period of 6 months. These cases of CMV disease prompted us to identify and review the clinical features of other such cases at our institution during the past 5 years.

From September 1997 through February 1998, the Division of Infectious Diseases at the Detroit Medical Center (DMC; a large tertiary-care university hospital) was consulted about 3 patients (patients 1–3) who had CMV disease, who were HIV negative, and who had not received any transplants. We proceeded to undertake a review of the DMC Pathology Database for the period of 1994–1998 to identify all cases of histologically proven CMV disease. This included a review of all autopsies that were done as well as a review of tissue biopsies obtained from patients with clinically suspected CMV disease. Only patients who were HIV seronegative and who had not received any transplants were included. Medical records of the patients identified were reviewed with regard to demographics, clinical, laboratory data, and outcome.

CMV disease was defined as histological evidence of inflammation and the presence of CMV inclusion bodies confirmed by means of immunohistochemical staining, and the exclusion of any other pathogen, in a patient with clinical features compatible with CMV disease. Histological identification of CMV disease was made on the basis of the identification of CMV inclusion bodies in hematoxylin and eosin–stained and CMV–specific immunohistochemical stained sections of formalin–fixed, paraffin–embedded samples [3]. In patient 1, CMV cultures of vitreous fluid were performed by use of the shell vial procedure [4], and CMV PCR assay was performed with primer sets specific for a 368–bp amino acid signature sequence of the CMV early genome (Sharp Signal System; Digene Diagnostics) [5]. In the same patient, CMV pp65 antigen testing was performed by use of CMV Brite (Biotest Diagnostics).

Patients 1–3 were identified through infectious disease consultations. A review of the DMC Pathology Database from 1994 through 1998 indicated that 575 autopsies had been performed. CMV disease was identified in 11 (1.9%) of the autopsied patients. Of these 11 patients, 7 were HIV positive, 1 was a bone marrow transplant recipient, and 1 was a renal transplant recipient; the remaining 2 patients (patients 6 and 7) had none of the conventional risk factors. During the same time period, 284 biopsies were performed for clinically suspected CMV disease, and 60 patients (21%) had histological evidence of CMV disease. Of these 60 patients, 49 (82%) were HIV positive, 9 (15%) were transplant recipients, and only 2 (3%; patients 4 and 5) were neither. Thus, our results include 7 histologically proven cases of CMV disease (5 diagnosed antemortem and 2 diagnosed at autopsy). The clinical characteristics of the 7 patients identified are summarized in Table 1.

Most patients were men (5 [71%] of 7) and the age range was 44–80 years. All patients had underlying comorbidities. The underlying illnesses most commonly identified were malignancy (4 [57%] of 7) and chronic renal failure (3 [43%] of 7). The most frequently affected organ was the colon (4 [57%] of 7). Clinical presentation was subacute, and symptoms were related to the specific organs affected. Constitutional symptoms, such as fever, were uncommon. Histopathological findings of CMV disease in tissue confirmed the diagnosis in all patients. Moreover, patient 1 had a positive result of PCR analysis of
Table 1. Characteristics of patients with histopathologically proven CMV disease.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age in y, sex</th>
<th>Underlying disease</th>
<th>Immunosuppressive therapy</th>
<th>Site of CMV disease</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72, F</td>
<td>Chronic lymphocytic leukemia</td>
<td>Prednisone, 5 mg/d</td>
<td>Retina</td>
<td>Visual floaters in right eye for 2 weeks treated with intracocular steroid injection, which was followed by sudden loss of vision. Retinal examination revealed severe retinitis and retinal detachment.</td>
</tr>
<tr>
<td>2</td>
<td>44, M</td>
<td>CRF, DM, HTN admitted with myocardial infarction and cardiogenic shock</td>
<td>None</td>
<td>GI tract</td>
<td>Bloody diarrhea after 5 weeks of hospitalization. Colonoscopy revealed recto-sigmoid colitis.</td>
</tr>
<tr>
<td>3</td>
<td>54, M</td>
<td>DM, Whipple’s procedure for pancreatic cancer 6 years previously</td>
<td>None</td>
<td>GI tract</td>
<td>Abdominal pain, watery diarrhea for 2 weeks, and 18-kg weight loss for 2 months. Tenderness and guarding; lower left abdominal quadrant colonoscopy showed diffuse colitis.</td>
</tr>
<tr>
<td>4</td>
<td>68, M</td>
<td>CRF, colon cancer with prior partial colectomy in remission</td>
<td>None</td>
<td>GI tract</td>
<td>Abdominal pain, watery diarrhea. Colonoscopy revealed diffuse colitis.</td>
</tr>
<tr>
<td>5</td>
<td>72, M</td>
<td>HTN, CRF, COPD</td>
<td>None</td>
<td>GI tract</td>
<td>Fever, diarrhea, and bleeding in the lower GI tract. Colonoscopy revealed colonic mass, which was biopsied.</td>
</tr>
<tr>
<td>6</td>
<td>80, F</td>
<td>CAD with recent CABG and cardiac valve replacement</td>
<td>None</td>
<td>Lung, liver</td>
<td>Developed postoperative fevers and adult respiratory distress syndrome, followed by progressive multi-organ failure.</td>
</tr>
<tr>
<td>7</td>
<td>61, M</td>
<td>Recurrent squamous cell lung cancer</td>
<td>Chemotherapy 3 months ago</td>
<td>Lung</td>
<td>Fever, progressive dyspnea, and hemoptysis. Chest radiograph showed new parenchymal infiltrates in right lung.</td>
</tr>
</tbody>
</table>

NOTE. ARDS, adult respiratory distress syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; DM, diabetes mellitus; GCV, ganciclovir; GI, gastrointestinal; HTN, hypertension; NA, not available.

the vitreous fluid and concurrent CMV antigenemia. Five (71%) of 7 patients were diagnosed antemortem, and 4 of the 5 were treated with ganciclovir. Treatment with ganciclovir resulted in clinical improvement in all 4 treated patients. Patient 1 had improvement of retinitis but remained blind because of retinal detachment. Patients 2–4 all had colitis that resolved with therapy. Patient 5 entered a hospice program and was not treated.

As our report indicates, CMV disease is rare in the patient population without HIV infection and without organ transplants. This is comparable to the experience reported in the literature. Autopsy studies of patients with cancer noted 3.3 cases of CMV disease per 1000 autopsies performed [6] and 2.2 cases of CMV pneumonia per 1000 autopsies performed [7]. A review of CMV disease of the gastrointestinal tract [8] in the patient population without HIV infection and without organ transplants identified only 38 cases in 1976–1992. As in our series, all of these reported cases occurred in patients with cancer or some other serious comorbidity.

CMV disease rarely occurs in people with no clinically apparent underlying illness [2, 9]. A retrospective review of all gastrointestinal biopsies performed in 1978–1992 identified CMV disease in 15 apparently immunocompetent patients [9]. More recently, Eddleston [2] described 1 case and identified an additional 33 that were described in the literature during a period of 29 years. However, underlying immunosuppressive conditions were not entirely excluded in these series [9], and only 10 of 34 cases reported [2] were proven histologically. Therefore, the actual prevalence of well-documented CMV disease in immunocompetent hosts remains unclear. Since then, only a few additional case reports of histologically proven CMV colitis and retinitis in patients not usually at risk for CMV have been published [10–15].

A direct comparison of the patients in our study and those described in other case series is difficult because of the lack of documentation regarding histologically proven CMV disease. Moreover, clinical features, treatment, and outcomes were not provided in many of the earlier reports. However, certain similarities and contrasts can be distinguished. Most cases of CMV disease occurred in men [2, 6–15]. CMV disease was diagnosed in older patients (median age, 72 years) in our series and in most other reports [6–9]. Malignancy was the most common comorbidity identified in the patients in our study and among other patients reported [6–8]. Although the exact mechanism
Tissue positive for CMV on histopathology | CMV serology | CMV culture | Therapy for CMV | Outcome | Comments
--- | --- | --- | --- | --- | ---
NA | IgG positive | Vitreous fluid positive | GCV, 21 days | Improvement of retinitis but no improvement of vision. | Result of CMV PCR of vitreous fluid was positive; also had concurrent CMV antigenemia. Steroids discontinued.
Colon | IgG positive | NA | GCV, 28 days | Resolution of diarrhea. | Results of bacterial stool cultures for enteric pathogens and Clostridium difficile toxin assays were negative.
Colon | IgG positive | NA | GCV, 21 days | Symptoms resolved after 2 weeks of GCV. Repeated colonoscopy revealed no colitis but identified adenocarcinoma of the appendix, which was resected. | Results of bacterial stool cultures for enteric pathogens and C. difficile toxin assays were negative.
Colon | IgM/IgG positive | NA | GCV, 7 days | Resolution of diarrhea and abdominal pain. | Results of stool cultures for enteric pathogens and C. difficile toxin assays were negative.
Colonic mass | NA | NA | None | Continued to have fevers and diarrhea and died of respiratory failure. | No autopsy
Liver, lung (postmortem case) | NA | NA | None | Died of progressive multiorgan failure. | Autopsy revealed disseminated CMV.
Lung (postmortem case) | NA | Lung tissue positive | None | Treated with empiric broad-spectrum antibiotics and steroids for possible ARDS but died. | Died of respiratory failure. CMV disease of lung diagnosed at autopsy.

or mechanisms that predispose people to CMV disease is not clearly known, most of the comorbid conditions identified can affect cell-mediated immunity [16].

Clinical presentation of CMV disease reported elsewhere [8, 10–15] was similar to that noted in the patients in our study, with symptoms generally subacute in nature and related to the organs affected; constitutional symptoms, including fever, were uncommon. The colon was the most affected organ in the patients in our study and in those described earlier [2, 6, 8–11]. Disseminated CMV disease at the time of diagnosis was uncommon in patients with gastrointestinal CMV disease [8–11], a finding also noted in the patients in our study. This is in contrast to multiorgan involvement, which was reported in ~50% of immunocompetent patients [2] and in autopsies of patients with cancer [6, 7]. Multiorgan involvement was associated with CMV pneumonia in almost all cases [2, 6–7] and was noted in 1 (patient 6) of 2 patients in our study.

Histological evidence is generally required to establish the definitive diagnosis of CMV disease, with the exception of CMV retinitis. CMV cultures may support the diagnosis, but cultures were not performed for most patients, suggesting that the diagnosis of CMV disease often was not suspected before the histopathological report. Serological assays generally are not useful in the diagnosis of reactivation of CMV disease [1]. Newer tests, such as PCR and CMV antigen detection, appear to correlate with invasive CMV disease in high-risk, HIV-seropositive patients and transplant recipients [1]. Patient 1 had CMV detected in the vitreous humor by means of PCR, and also had concurrent CMV antigenemia. Therefore, these new noninvasive tests may have a potential but as-yet-undefined role in screening for CMV disease in appropriate low-risk patients.

Four of 5 patients in our series were promptly treated with ganciclovir, and all appeared to have a good clinical response, with resolution of symptoms and a favorable outcome. Similarly, 9 (75%) of 12 immunocompetent patients with CMV disease who received some antiviral therapy survived, in contrast to 10 (45%) of 22 who received no therapy [2].

This case series had the intrinsic limitations of a retrospective study and included relatively few patients. However, the observations noted are useful, because the rare occurrence of invasive CMV disease in HIV-seronegative patients and in patients who did not receive transplants would likely preclude any large prospective study. In conclusion, CMV disease is rare but should be considered in patients with cancer or other serious illnesses who present with colitis or a compatible clinical
syndrome, because early diagnosis and appropriate therapy with
ganciclovir may improve outcome.

References