Virological, Clinical, and Ophthalmologic Features of Cytomegalovirus Retinitis after Hematopoietic Stem Cell Transplantation

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We identified 10 patients who developed cytomegalovirus (CMV) retinitis after HSCT during a 14-year period. The median day of diagnosis of CMV retinitis after transplantation was day 251 (range, days 106–365). CMV retinitis was associated with CMV serostatus of donor or recipient (P = 0.01), CMV reactivation before day 100 (P = 0.007), delayed lymphocyte engraftment (P < 0.05), and chronic graft versus host disease (GVHD; P < 0.001). In allogeneic recipients of HSCT who were alive at day 100 after transplantation and had chronic clinical extensive GVHD, the incidence of GVHD was 1.4% (8 of 577). Five of 10 patients had other manifestation of CMV disease before retinitis occurred (4 with gastrointestinal disease and 1 with interstitial pneumonia; median time, 70 days before onset of CMV retinitis; range, 58–279 days), and 4 others had CMV excretion. CMV retinitis was bilateral in 4 patients; 9 of 10 patients had ocular symptoms (i.e., decreased vision and floaters). Six of 7 patients responded well to ganciclovir or foscarnet systemic treatment, 1 improved only after switching to cidofovir, and 1 patient who received a transplant in 1983 did not respond to acyclovir treatment. In conclusion, CMV retinitis is an uncommon late complication after HSCT that occurs mainly in seropositive allograft recipients with previous CMV reactivation and chronic GVHD, and with delayed engraftment of lymphocytes.

Cytomegalovirus (CMV) disease is a serious cause of morbidity and mortality in hematopoietic stem cell transplantation (HSCT) recipients [1, 2]. In HSCT recipients, CMV infection typically occurs 30–100 days after transplantation if no ganciclovir prophylaxis or preemptive treatment is given [1]. After engraftment, infection may result from incomplete immune reconstitution or from the immunosuppression associated with graft versus host disease (GVHD) and its treatment [3]. In immunosuppressed patients, hematological dissemination from reactivation of latent CMV as well as exogenously acquired strains of CMV can result in retinitis. Although CMV retinitis is the most common clinical complication of CMV reactivation in people infected with HIV, it has been reported only infrequently in HSCT recipients [4–7]. The reasons for the difference in prevalence in different settings are poorly understood. One possible explanation is the high CMV-related mortality early after transplantation (i.e., during the first 100 days) [8] and the relative paucity of people at risk for CMV reactivation who have prolonged long-term immunosuppression after HSCT. However, with the institution of preemptive ganciclovir therapy early after transplantation [9], most patients survive episodes of CMV infection during the first 3 months after transplantation, and late onset of CMV disease is being recognized more frequently.

We reviewed all cases of CMV retinitis diagnosed in
HSCT patients during a 14-year period at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle. Specifically, we determined the incidence of retinitis, identified associated factors, including viral genotype, and described clinical features, ophthalmologic features, and outcome.

**PATIENTS AND METHODS**

**Patient selection.** All HSCT recipients who received transplants at FHCRC from 1 January 1983 through 31 December 1996 were analyzed retrospectively. Patients diagnosed with CMV retinitis with or without other manifestations of CMV diseases were analyzed in detail. Patients were identified by use of the computerized patient database and virology and pathology records. Clinical characteristics, date of birth, sex, underlying disease, date of bone marrow or stem cell transplantation, risk factors for CMV infection, type and duration of systemic anti-CMV medications, and survival data were obtained from review of patient charts. Screening for CMV retinitis is not part of standard practice at FHCRC. The 1-year follow-up visit data and the yearly questionnaires filled out by patients and by physicians were obtained from the long-term follow-up files. This long-term follow-up information was available for >80% of patients.

**Definitions.** CMV infection was defined as the identification of CMV in cultures of any clinical specimen or detection of CMV antigen in blood. CMV retinitis was defined as the finding of the characteristic ophthalmoscopic picture of necrotizing retinitis with or without hemorrhage, as determined by an ophthalmologist. Other manifestations of CMV disease were defined as demonstration of CMV in bronchoalveolar lavage or visceral biopsy specimens by culture or immunohistology with compatible clinical symptoms [9]. CMV-related death was defined as documentation in autopsy specimens of severe organ damage caused by CMV infection or death within 6 weeks of diagnosis of CMV disease [9]. Lymphopenia was defined as <300 lymphocytes/μL [10]. GVHD was graded according to established criteria [11, 12].

**Virological testing.** Pretransplantation CMV serologic testing as well as posttransplantation tube cultures, shell vial centrifugation cultures, and antigenemia testing were all performed weekly during the first 100 days after transplantation, as described elsewhere [13]. For patients who did not have positive results of a surveillance culture for CMV before the onset of CMV retinitis, plasma PCR analysis for CMV DNA was performed retrospectively on stored samples that were collected during the first 3 months after HSCT. Glycoprotein B (gB) typing of CMV isolates was performed by use of PCR analysis with CMV DNA from either frozen viral cultures or from stored plasma samples, as previously described [14, 15].

**RESULTS**

**Patient characteristics.** We identified 10 cases of CMV retinitis in 9 bone marrow transplant recipients and 1 peripheral blood stem cell transplant recipient among the 5721 people who received transplants in the 14-year period we examined. Of the 10 patients, 4 had chronic myeloid leukemia, 2 had acute myelogenous leukemia, 1 had acute lymphocytic leukemia, 1 had non-Hodgkin’s lymphoma, and 1 had ovarian carcinoma. Eight of 10 cases were from transplant recipients who were CMV-seropositive before transplantation. The median day of engraftment was 21 days (range, 13–32 days). Eight of 10 patients who developed retinitis had a prolonged period of postconditioning-related lymphopenia. Eight of 9 patients who received allogeneic HSCTs had chronic clinical extensive GVHD that was being treated with immunosuppressive medications at the time that retinitis was diagnosed (table 1).

**Timing and frequency of CMV retinitis in HSCT recipients.** The clinical and demographic characteristics of the patients with CMV retinitis are shown in table 1. The median day of diagnosis of retinitis was day 251 after transplantation (range, days 106–356). The overall frequencies for different groups of patients who received HSCTs during the study period were as follows: among patients who received allogeneic HSCTs, 0.19% (9 of 4842 patients; 95% CI, 0.09–0.36); among patients who received autologous HSCTs, 0.11% (1 of 879 patients; 95% CI, 0.0–0.63); among CMV-seropositive patients who received allogeneic HSCT, 0.39% (7 of 1808 patients; 95% CI, 0.15–0.8); among CMV-seronegative patients who received allogeneic HSCTs from a seropositive donor, 0.18% (1 of 551 patients; 95% CI, 0.0–0.89); among CMV-seropositive patients who received autologous HSCTs, 0.2% (1 of 479; 95% CI, 0.0–1.15); and among CMV-seropositive patients who received a second allogeneic HSCT, 0.75% (1 of 133; 95% CI, 0.02–4.1). Of the 4842 patients who received allogeneic HSCTs, 3472 were alive after day 100. Five hundred seventy-seven of these patients were CMV-seropositive recipients of HSCT who had chronic clinical extensive GVHD, and the frequency of retinitis in this group was 1.4% (8 of 577; 95% CI, 0.65–2.71).

**CMV gB typing.** Typing for CMV gB type 1 was performed for 7 patients who either had CMV blood isolates available or had stored frozen plasma that tested positive for CMV DNA by use of PCR. We found gB strain type 1 in patients 1, 3, 5, and 9, and gB type 3 in patients 4 and 6; gB types 1, 2, and 4 were found in patient 7.

**Ophthalmologic characteristics.** The initial symptoms that prompted ophthalmologic examination were decreased vision in 5 patients (unilateral in 3 patients and bilateral in 2), blurred vision in 1 patient, blurred vision and floaters in 1 patient, and visual field deficit in 1 patient. Uveitis and peripheral visual field deficit was observed in 1 patient. Only 1 patient was asymptomatic; this patient had retinitis diagnosed through an
Table 1. Clinical and demographic characteristics of patients with cytomegalovirus (CMV) retinitis.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age in y, sex</th>
<th>Type of TR; HLA match</th>
<th>Results of serologic testing of recipient/donor</th>
<th>First manifestation of CMV infection/disease (day of diagnosis)</th>
<th>Duration of lymphopeniaa before onset, d</th>
<th>Time of onset, d after:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33, M</td>
<td>BM, related; m</td>
<td>R+/D–</td>
<td>Viremia (43), pneumonia (48)</td>
<td>40 d (days −4 to 36)</td>
<td>226</td>
</tr>
<tr>
<td>2</td>
<td>22, M</td>
<td>BM, unrelated; m</td>
<td>R+/D–</td>
<td>Retinitis (293)</td>
<td>73 d (days −1 to 72)</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>32, F</td>
<td>BM, related; m</td>
<td>R+/D+</td>
<td>Viruria, pharyngeal shedding (48); retinitis (106)</td>
<td>2 episodes: 15 d (days −1 to 14) and 18 d (day 70 to 88)</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>25, F</td>
<td>BM, unrelated; m</td>
<td>R+/D–</td>
<td>Viruria, pharyngeal shedding (41); retinitis (186)</td>
<td>100 d (days −3 to 97)</td>
<td>125</td>
</tr>
<tr>
<td>5</td>
<td>36, M</td>
<td>BM, related; m</td>
<td>R+/D–</td>
<td>Viremia (58), esophagitis, duodenitis (124)</td>
<td>Not documented</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>48, M</td>
<td>BM, unrelated; mis</td>
<td>R+/D–</td>
<td>Pharyngeal shedding, viruria (53); esophagitis (69)</td>
<td>101 d (days −4 to 97)</td>
<td>206</td>
</tr>
<tr>
<td>7</td>
<td>28, M</td>
<td>BM, unrelated; m</td>
<td>R+/D+</td>
<td>Viruria, pharyngeal shedding (27); gastric ulceration (27)</td>
<td>73 d (days −1 to 71)</td>
<td>216</td>
</tr>
<tr>
<td>8</td>
<td>57, F</td>
<td>PBSC, autologous</td>
<td>R+</td>
<td>Viremia (47), retinitis (130)</td>
<td>12 d (days −3 to 9)</td>
<td>83</td>
</tr>
<tr>
<td>9</td>
<td>27, F</td>
<td>BM, unrelated; m</td>
<td>R+/D–</td>
<td>Viremia (33), enteritis, retinitis (287)</td>
<td>5 episodes before day 100, then 164 d (days 127 to 287)</td>
<td>254</td>
</tr>
<tr>
<td>10</td>
<td>21, M</td>
<td>BM, related; m</td>
<td>R−/D+</td>
<td>Esophagitis, duodenitis (76)</td>
<td>55 d (days −7 to 48)</td>
<td>279</td>
</tr>
</tbody>
</table>

**NOTE.** Acy, acyclovir; ALL, acute lymphatic leukemia; BM, bone marrow; CCE, chronic clinical extensive; Cd, cidofovir; D–, donor’s serostatus was CMV-negative before transplantation; F, female; Fos, foscarnet; Gan, ganciclovir; GVHD, graft versus host disease; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplant; m, HLA-matched; M, male; mis, HLA-mismatched; NHL, non-Hodgkin’s lymphoma; OD, right eye; OS, left eye; PBSC, peripheral blood stream; R–, recipient’s serostatus was CMV-negative before transplantation; R+, recipient’s serostatus was CMV-positive before transplantation; RSV, respiratory syncytial virus; TR, transplant or transplantation.

*a De®ned as <300 cells/mm³.

*b No further details available.

ophthalmologic check performed during a follow-up exam for manifestation of GVHD. The retinal disease was unilateral in 6 patients and bilateral in 4. The retinal involvement was macular in 1 patient, macular and peripheral in 1 patient, para-macular in 2 patients, and peripheral in 5 patients. In 1 patient, the clinical and ophthalmologic feature of CMV was papillitis (table 1).

**CMV infection and disease before the diagnosis of retinitis.** CMV reactivation was documented in 9 of 10 patients before the onset of retinitis. In 6 of these patients, CMV infection was detected first in blood by use of CMV pp65 antigenemia testing (3 patients) or viral blood cultures (3 patients). In the remaining 3 patients, CMV infection was first detected in cultures from urine, throat, and esophagus-duodenum tissue. The median time from first detection of CMV infection to retinitis was 206 days (range, 58–279 days). Five of 10 patients had evidence of CMV disease before the onset of retinitis, 4 of whom with gastrointestinal disease and 1 with pneumonia. In 1 patient (patient 2), retinitis was the first manifestation of CMV infection, without previous positive findings for CMV in any surveillance or diagnostic tests performed before the onset of retinitis itself. Also negative were the results of retrospective PCR analysis for CMV DNA of frozen plasma samples that had been obtained weekly during the first 100 days after transplantation. In this patient (patient 2), CMV retinitis was diagnosed on day 298 after marrow transplantation, after oph-
**Retinitis data**

<table>
<thead>
<tr>
<th>Clinical manifestation at onset; involved zone</th>
<th>Treatment</th>
<th>Outcome</th>
<th>GVHD: type, day of onset, grade</th>
<th>Time from retinitis to death, d</th>
<th>Outcome and cause of death (day of death or day of last contact after HSCT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased vision OS, IOS macular; OD peripheral; bilateral</td>
<td>Not treated</td>
<td>Not known</td>
<td>Acute, 9, III; CCE, 91</td>
<td>Died of CMV pneumonia (340)</td>
<td>71</td>
</tr>
<tr>
<td>Uveitis symptoms OS; OS peripheral, unilateral</td>
<td>Gan, days 298–369&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Not known</td>
<td>Acute, 7, I; CCE, 99</td>
<td>Died of disseminated candidiasis (369)</td>
<td>71</td>
</tr>
<tr>
<td>Lateral field visual deficit, OD; OD paramacular, OD peripheral</td>
<td>Gan, 5 g/kg bid, days 112–132; then 5 mg/kg qd, days 138–182</td>
<td>Improved</td>
<td>Acute, 2, II; CCE, 109</td>
<td>Died, relapse of ALL (182)</td>
<td>76</td>
</tr>
<tr>
<td>Asymptomatic retinitis; peripheral, bilateral</td>
<td>Acy, days 167–172; then Gan, 5 mg/kg bid for 1 w, then 5 mg/kg qd, days 180–300</td>
<td>Improved; no relapse</td>
<td>Acute, 25, II; CCE, 244</td>
<td>Alive (3330)</td>
<td>—</td>
</tr>
<tr>
<td>Blurriness OS; OS peripheral, unilateral</td>
<td>Gan, 5 mg/kg bid, days 147–158, then 5 mg/kg qd, days 199–248</td>
<td>Improved; no relapse</td>
<td>CCE, 88</td>
<td>Alive (2950)</td>
<td>—</td>
</tr>
<tr>
<td>Decreased vision OD; OD peripheral, unilateral</td>
<td>Gan for ~6 w&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Improved; no relapse</td>
<td>Acute, 10, III; CCE, 91</td>
<td>Died, relapse of NHL (2001)</td>
<td>1742</td>
</tr>
<tr>
<td>Decreased vision OD; OD paramacular, unilateral</td>
<td>Fos, 90 mg/kg qd, days 243–267</td>
<td>Improved; no relapse</td>
<td>Acute, 15, II; CCE, 147</td>
<td>Died of pneumonia due to RSV and CMV (267)</td>
<td>24</td>
</tr>
<tr>
<td>Blurred vision and floaters OS; OS peripheral, unilateral</td>
<td>None</td>
<td>Improved; no relapse</td>
<td>Not applicable</td>
<td>Alive (1118)</td>
<td>—</td>
</tr>
<tr>
<td>Decreased vision OD; OD macular, then spread OS peripheral, bilateral</td>
<td>Gan, Fos, Cd</td>
<td>Worsened with Gan therapy, improved with Cd</td>
<td>Acute, 33, I; CCE, 112</td>
<td>Died of fungal pneumonia (515)</td>
<td>385</td>
</tr>
<tr>
<td>Decreased vision OD; CMV papillitis OD, unilateral</td>
<td>Acy</td>
<td>Worsened</td>
<td>Acute, 36, II</td>
<td>Died of CMV pneumonia (443)</td>
<td>87</td>
</tr>
</tbody>
</table>

**Thalmologic evaluation of uveitis symptoms, and CMV was isolated from a sample of the vitreous body. He was a seronegative recipient with a seronegative donor and received his transplant in 1988. Analysis of these serological data suggests that the patient probably acquired CMV from unscreened blood products. In 1 patient (patient 9), the diagnosis of retinitis was made concomitantly with the diagnosis of gastrointestinal disease on day 287 after HSCT. In 3 patients (patients 3, 4, and 8), the diagnosis of retinitis was the first manifestation of CMV disease and occurred after CMV infection was detected by use of surveillance cultures (urine and throat in 1 patient, blood and throat in 1, and blood in 1). Retinitis was diagnosed in these patients 58, 166, and 83 days after the first positive culture results, respectively.**

**Analysis of factors associated with development of CMV retinitis.** The following factors were analyzed for a possible association with the development of CMV retinitis: allogeneic transplant status, CMV serostatus, CMV reactivation before day 100, GVHD, and delayed lymphocyte engraftment. Results are shown in table 2 and indicate an association with CMV serostatus before transplantation, CMV reactivation before day 100, and delayed lymphocyte engraftment. Because of the small number of events, a formal multivariable analysis could not be performed.

**Treatment and outcome.** Quiescence of retinitis was observed in 6 patients treated either with ganciclovir (<i>n</i> = 5) or foscarnet (<i>n</i> = 1) after 6–18 weeks of treatment. No relapse of retinitis was observed in these patients. Most patients received an induction course for 1–3 weeks and after that a maintenance regimen (table 1). Worsening of the visual function and a unilateral to bilateral spread was reported in 1 patient (patient 9) during treatment with ganciclovir. Infection caused by a gan-
months after the diagnosis; and 2 (20%) died of CMV retinitis (patient 7); 4 patients (40%) died within 3 months after the diagnosis of CMV retinitis. Three patients (30%) are still alive. The cause of death was related to CMV in 3 patients; patients 1 and 10 died of CMV pneumonia, and patient 7 died of CMV and respiratory syncytial virus pneumonia. The cause of death was not related to CMV in the other 4 patients (see table 1 for further details). It is of note that 2 of the patients who died of CMV complications did not receive appropriate treatment for retinitis (patients 1 and 10).

DISCUSSION

In this study, we have shown that CMV retinitis is a late complication after HSCT. The median time of diagnosis of CMV retinitis was 251 days (range, 106–356 days). CMV retinitis was mainly seen in those patients with antecedent CMV reactivation or disease during the first 3 months after transplantation. Also, 88% of allogeneic patients developed retinitis in a setting of chronic clinical-extensive GVHD. The overall prevalence of CMV retinitis in CMV-seropositive patients with chronic clinical-extensive GVHD was 1.4%, which defines this group of patients as the group at the highest risk to develop CMV retinitis. CMV retinitis accounts for ~5% of late CMV disease in the HSCT population we studied [9]. This risk may be somewhat underestimated because of the slowly progressive nature of CMV retinitis, which may start in the periphery of the retina and have minimal visual symptoms. Ophthalmologic screening for this complication is not part of standard practice for patients who undergo HSCT. Therefore, some cases of spontaneous resolution that may have occurred concomitantly with immune reconstitution may have easily been missed. Moreover, additional cases were probably missed among patients who died and among patients with an atypical presentation of retinitis. Today, for such cases, one could take advantage of newer diagnostic procedures such as the study by use of PCR analysis of aqueous humor [16] or of a sample from the vitreous body [17]. However, because 9 of 10 patients had clinical symptoms and the ophthalmologic presentation of CMV retinitis was characteristic, we believe that our figures are reasonably accurate for clinically relevant disease.

We found that CMV retinitis after HSCT responds well to systemic anti-CMV treatment with ganciclovir, foscarnet, or cidofovir, as documented by the quiescence observed in all the patients who were treated and for whom we had complete clinical records (table 1). The duration of treatment ranged from 6 to 18 weeks, and no relapse occurred.

Interestingly, lymphopenia appeared to be an important factor in the pathogenesis of CMV retinitis. We found that lymphocyte engraftment was delayed in patients with CMV retinitis (table 2). This is consistent with earlier reports, which showed that lymphopenia is an important risk factor for CMV disease [10] and for poor outcome of CMV infection [18]. However, in most patients of this series, retinitis developed long after they recovered from lymphopenia, which was present for prolonged periods during the first 100 days (table 1). Also, 4 of 5 patients with CMV disease early after transplantation did not have a recurrence of their disease at the original site when...
retinitis was diagnosed. In allogeneic HSCT recipients, the recovery of major histocompatibility complex I-restricted CD8+ CMV-specific cytotoxic T lymphocytes represents the effectors of the anti-CMV activity [19], and it confers protection against CMV pneumonia [20]. It is conceivable that the repertoire of CMV-specific CD8+ cytotoxic T cell and CD4+ T helper cell clones reconstituted during early CMV infection in the presence of lymphopenia is limited and that retinal tissue is a site of CMV latent infection not easily detected by the immune surveillance mechanisms. The difficult migration of the CD8+ CMV-specific clones through the vascular endothelium of the internal compartment of the eye has also been reported as a possible immunological escape mechanism that could prevent immune effector cells from reaching the eye [21]. Alternatively, the onset of retinitis after recovery of lymphopenia could also be related to the recovery of the CD8+ and CD4+ CMV-specific clones reacting to a subclinical CMV ocular infection [22]. Evaluation of the underlying mechanisms of CMV retinitis in this setting is warranted.

In conclusion, we report that CMV retinitis is a rare complication after HSCT, is mainly seen in HSCT recipients with chronic clinical extensive GVHD, especially in those patients with CMV-positive results of serologic testing before transplantation. Preexisting CMV infection or disease and delayed lymphocyte engraftment are other important factors associated with the development of this potentially sight-threatening complication. Patients with these characteristics should be counseled not to ignore visual symptoms, such as blurred vision and floaters. Patients with these symptoms should be immediately reported to an ophthalmologist. This particular ocular localization of CMV disease is a late complication after HSCT; it may be unilateral as well as bilateral and usually responds well to systemic treatment. Finally, a more prolonged survival rate after HSCT, as well as a more aggressive treatment of GVHD, jointly with the emergence of ganciclovir-resistant strains of CMV, could lead to a higher frequency of CMV retinitis in HSCT recipients in the future.

Acknowledgments

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References