Cytomegalovirus Retinitis in Three Pediatric Cases with Acute Lymphoblastic Leukemia: Case Series and Review of the Literature

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SUMMARY: Cytomegalovirus (CMV) retinitis is typically diagnosed in patients with AIDS and those who underwent allogeneic hematopoietic cell transplant. However, it may develop in patients with acute lymphoblastic leukemia (ALL) who have not undergone hematopoietic cell transplantation. To increase awareness of CMV retinitis in this group, we describe 3 patients ages 3, 9, and 12, with ALL who developed CMV retinitis. The diagnosis of CMV retinitis was made on the basis of ophthalmological findings suggesting typical retinal lesions. In 2 cases, CMV DNAemia was present, while in 1 patient CMV DNA was detected only in vitreous fluid using the PCR technique. All cases were treated with intravenous ganciclovir for 2 or 3 weeks as induction therapy, followed by oral valganciclovir prophylaxis. Initially, active retinitis lesions resolved in all cases; however, in 1 patient CMV retinitis relapsed 3 times during follow-up. In this case, by using foscarnet therapy, satisfactory responses were achieved and the progression of CMV retinitis lesions stopped and eventually regressed.

Cytomegalovirus (CMV) may cause asymptomatic infection or self-limiting illness in most infected, immunocompetent individuals. In patients with reduced cellular immunity, such as patients infected with human immunodeficiency virus, solid organ transplant recipients, hematopoietic cell transplant (HCT) recipients, and those receiving immune suppression therapy, it may lead to end-organ diseases (1), one of which is CMV retinitis. The majority of CMV retinitis cases are related to the hematogenous spread of the virus to the retina, usually after systemic reactivation of a latent infection, and are usually diagnosed by an experienced ophthalmologist on the basis of typical retinal changes. To the best of our knowledge, CMV retinitis in patients with acute lymphoblastic leukemia (ALL) without autologous or allogeneic HCT, has rarely been reported. This report, in the light of the published literature, describes 3 pediatric patients with ALL who developed CMV retinitis while receiving chemotherapy.

The 1st case is a 12-year-old boy with ALL who was admitted to the hospital with blurred vision in the right eye (RE) (2). The patient was in the maintenance phase of chemotherapy on the ALL-BFM-2003 protocol and was receiving oral methotrexate and mercaptopurine. His white blood cell (WBC) count was 3,200/μL and his neutrophil count was 1,600/μL. The ophthalmological examination revealed a best corrected visual acuity (BCVA) of 20/20 in both the RE and the left eye (LE). The slit lamp examination of the anterior chamber of the LE was normal, whereas a 3+ anterior chamber cellular reaction was observed in the RE. The retinal examination revealed active retinitis lesions (cream-colored lesions associated with hemorrhages) and perivascular cuffing in the retinal periphery in the RE (Fig. 1A). The LE retina was normal. Laboratory studies revealed positive CMV IgM, but negative CMV IgG,
and CMV DNA was quantified as <80 copies/mL in the blood sample and 23,096 copies/mL in the intra-vitreal fluid, as detected by PCR. The patient was diagnosed with CMV retinitis. Treatment with intravenous ganciclovir (10 mg/kg/day) was immediately initiated. On the 3rd day of treatment, identical retinal findings were also seen in the LE, but in a more limited pattern (Fig. 1B). Following intravenous ganciclovir treatment for 2 weeks, oral valganciclovir prophylaxis (1,800 mg/day × 15 days, followed by 900 mg/day × 1 month) was initiated. By the final retinal examination, the active retinal lesions had resolved during the treatment period, and a progressive pigment deposition was found around the lesions, developing into chorioretinal scarring (Fig. 1C and D). The patient was followed for 1 year and no recurrence was detected.

The 2nd case is a 9-year-old boy with a second relapse of pre-B ALL who was admitted to our pediatric hematology and oncology clinic prior to a scheduled bone marrow transplantation. Therapy using a protocol for relapsing/refractory ALL, consisting of clofarabine, etoposide, and cyclophosphamide, was initiated. One week after his admission, without any fever, a pruritic palpable maculopapular rash appeared on his whole body with 2-3 cm of hepatosplenomegaly; his WBC count was 19.0 × 10^3/μL, absolute neutrophil count was 1.2 × 10^3/μL, and absolute lymphocyte count was 13.5 × 10^3/μL. His serum CMV IgM was negative, serum CMV IgG positive, and the CMV-DNA was quantified as 372 copies/mL in the blood sample. Meanwhile, his vision progressively worsened. The repeated ophthalmological examination revealed a BCVA of 20/400 in the RE and hand movement in the LE. In the slit lamp examination of the RE and LE, we observed a 1 + cellular reaction in both anterior chambers. The retinal examination revealed active retinitis lesions (cream-colored lesions associated with hemorrhages) with subretinal infiltration in the superior temporal area and vitreous inflammation in the inferior area of the RE (Fig. 2). The LE was not illuminated. On the basis of clinical evidence, the patient was diagnosed with CMV retinitis in both eyes. CMV retinitis treatment with intravenous ganciclovir (10 mg/kg/day) for 3 weeks was administered, after which he was switched to oral valganciclovir prophylaxis (1,800 mg/day). However, he died in the intensive care unit due to fungal pneumonia and sepsis while he was on prophylaxis for CMV retinitis.

The 3rd case is a 3-year-old boy with pre-ALL who was being treated on the St. Jude’s Total XV protocol, in the maintenance phase of therapy, receiving mainly methotrexate and mercaptopurine. He was admitted to the hospital for febrile neutropenia. The laboratory findings revealed a WBC count of 300 × 10^3/μL, an absolute neutrophil count of <10^3/μL, a negative CMV IgM, and a positive CMV IgG. CMV-DNA was quantified as 5,264,592 copies/mL in the blood sample. Two days later, tachypnea developed, and the thoracic computed tomography showed widespread ground glass attenuation in both lungs. Although he had no complaints of visual impairment, the ophthalmological examination showed active retinitis lesions (cream-colored lesions associated with hemorrhages) and perivascular cuffing in the posterior pole of the retina in both eyes. Therefore, in addition to CMV pneumonia, the diagnosis of CMV retinitis was made in both eyes. Treatment with intravenous ganciclovir (10 mg/kg/day) was given for 3 weeks. Before discharge, oral valganciclovir prophylaxis (single daily dose [in mg]) = 7 × body surface area × creatinine clearance) was initiated.

Two months after discharge, he was admitted to the hospital with febrile neutropenia. The patient history revealed that valganciclovir prophylaxis was not taken properly. Repeated CMV DNA copy number was 2,890,000 copies/mL in the blood sample. The ophthalmological examination showed that the optic disc and macula were normal; however, active retinitis lesions (cream-colored lesions associated with hemorrhages) around the arcades in the RE were found. In the LE, the macula was normal, and active retinitis lesions were localized around the arcades and retinal periphery. Based on these findings, CMV retinitis relapse was suspected and a 2nd course of intravenous ganciclovir (10 mg/kg/day) treatment was re-initiated for 3 weeks. At the end of the 3rd week of therapy, bone marrow suppression occurred; when we switched to oral valganclovir, bone marrow function returned to normal.

Unfortunately, at the 3rd week of the 2nd course of valganciclovir prophylaxis, the 2nd relapse of retinitis occurred, with 422,198 copies/mL of DNAemia. Intravenous ganciclovir treatment was re-initiated, and he responded well for the first 2 weeks of treatment. DNAemia again raised, becoming constant at around 400,000 copies/mL, which we considered to be the 3rd relapse, and ganciclovir resistance was suspected. At this relapse, intravenous ganciclovir was given for 5 weeks in total, then foscarnet was initiated while the DNAemia was 371,031 copies/mL. After 26 days of foscarnet treatment, the CMV DNA copy number had fallen to 2,400 copies/mL. Because his chemotherapy was still ongoing, our aim was to continue the foscarnet treatment until CMV DNA copy number became undetectable. On his final retinal ex-
Cytomegalovirus retinitis, a major sight-threatening condition for immunocompromised individuals, was first reported as a complication of AIDS in 1982 (3). It also occurs as a problem in immunocompromised conditions other than AIDS, such as solid organ transplant recipients, HCT recipients, and those receiving immune suppression therapy. However, it has been also reported in patients with ALL in the maintenance phase of chemotherapy who have not received HCT, in particular. In this non-transplant setting, the incidence of CMV retinitis (4) has been estimated to be 3.6%. Herein, we present 3 pediatric cases suffering from ALL, showing that even those patients may be immunosuppressed and thereby develop CMV retinitis.

Han et al. (5) reported a 17-year-old boy diagnosed with CMV retinitis 3 months after maintenance chemotherapy for ALL, and his retinitis was assumed to be caused by a delayed immune reconstitution after chemotherapy.

Since early diagnosis is one of the main prognostic factors for CMV retinitis, clinicians should be aware of this rare occurrence in this patient population. The factors that complicate early diagnosis include the absence of external ocular signs of disease and the child’s inability to express visual symptoms. On the other hand, the nature of CMV retinitis is more aggressive in children, usually involving both eyes and located in the posterior pole of the eyes, where the risk of irreversible blindness is high. In a review of 9 children with CMV retinitis, Baumal et al. (6) found predominantly bilateral (89%) and posterior pole involvement. Wren et al. (7) also supported this pattern of presentation. In our 3 cases, the lesions were bilateral, and in one case, the posterior poles of the retina in both eyes were involved. In light of these data, early diagnosis and immediate management are of the utmost importance to preserve vision and prevent future visual loss. Therefore, regular ocular examination as a part of the routine follow-up of ALL patients should be considered.

In addition to the current study, 9 pediatric patient with ALL and CMV retinitis have been reported in the literature to date (4–12). Table 1 shows all reported cases. The median age of these patients at the time of diagnosis was 10.4 years (range: 3 to 17 years). Nine of 12 (75%) patients were men. Eight suffered from visual disturbance at the time of diagnosis. Positive CMV DNAemia, which was defined as >1,000 copies of CMV DNA/mL; was present in 8 patients, absent in 3, and unknown in 1. CMV retinitis occurred during the maintenance phase of chemotherapy in 11 of 12 cases, which was considered to be unlikely. This finding could be explained as the chemotherapeutic agents used in this phase. A recent study from Dutch Childhood Oncology Group-ALL 9 trial, using intensive vincristine and dexamethasone pulses, has shown a higher frequency of infectious deaths during the maintenance phase (13). In 9 patients, treatment mainly consisted of methotrexate, 6-mercaptopurine, vincristine, and steroids, while only methotrexate and 6-mercaptopurine were used in 2 cases. Moreover, Moritake et al. (8) assumed that, in maintenance therapy, the addition of vincristine and dexamethasone to 6-mercaptopurine and methotrexate remarkably increased the risk of CMV retinitis.

We analyzed the response of these reported cases to antiviral therapy; intravitreal ganciclovir used in 2 cases yielded a complete response, 1 case was successfully treated with oral valganciclovir; 9 cases received intravenous ganciclovir, with treatment resistance observed in 2 of them, leading to a treatment change to foscarnet. In our 1st case (2), we used intravenous ganciclovir successfully, and it protected the previously non-involved eye from CMV infection. Based on the current experience, and as the other 2 cases had systemic involvement, we re-administered ganciclovir intravenously as induction therapy. The duration of induction
### Table 1. Review of reported cases of CMV retinitis in children with ALL

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Reference of chemotherapy</th>
<th>Protocol of chemotherapy</th>
<th>Underlying disease</th>
<th>Sex</th>
<th>Age</th>
<th>Time of CMV disease</th>
<th>Type of CMV disease</th>
<th>Time of treatment</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T-cell ALL 15 yr/M</td>
<td>St. Jude’s Total</td>
<td>T-cell ALL</td>
<td>M</td>
<td>15</td>
<td>24th mo of maintenance</td>
<td>Retinitis</td>
<td>19 days</td>
<td>Ganciclovir</td>
<td>Complete response, relapse, permanent visual defect</td>
</tr>
<tr>
<td>2</td>
<td>B-cell ALL 17 yr/M</td>
<td>CMCP-ALL-2005</td>
<td>B-cell ALL</td>
<td>M</td>
<td>17</td>
<td>20th mo of maintenance</td>
<td>Retinitis</td>
<td>2 wk</td>
<td>Intravenous ganciclovir</td>
<td>Complete response</td>
</tr>
<tr>
<td>3</td>
<td>B-cell ALL 13 yr/M</td>
<td>ALL-BFM-95</td>
<td>B-cell ALL</td>
<td>F</td>
<td>13</td>
<td>20th mo of maintenance</td>
<td>Retinitis</td>
<td>4 wk</td>
<td>Valganciclovir</td>
<td>Complete response</td>
</tr>
<tr>
<td>4</td>
<td>T-cell ALL 12 yr/M</td>
<td>St. Jude’s Total</td>
<td>T-cell ALL</td>
<td>M</td>
<td>12</td>
<td>30th mo of maintenance</td>
<td>Retinitis</td>
<td>19 days</td>
<td>Ganciclovir</td>
<td>Complete response, relapse, permanent visual defect</td>
</tr>
<tr>
<td>5</td>
<td>B-cell ALL 17 yr/M</td>
<td>ALL-BFM-2005</td>
<td>B-cell ALL</td>
<td>F</td>
<td>17</td>
<td>20th mo of maintenance</td>
<td>Retinitis</td>
<td>6 wk</td>
<td>Intravenous + intravenous ganciclovir</td>
<td>Complete response</td>
</tr>
<tr>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>10th mo of maintenance</td>
<td>Retinitis</td>
<td>19 days</td>
<td>Intravitreal ganciclovir</td>
<td>Complete response</td>
</tr>
<tr>
<td>7</td>
<td>Case 1</td>
<td>15 yr/M</td>
<td>B-cell ALL</td>
<td>M</td>
<td>15</td>
<td>20th mo of maintenance</td>
<td>Retinitis</td>
<td>19 days</td>
<td>Intravenous ganciclovir</td>
<td>Complete response</td>
</tr>
<tr>
<td>8</td>
<td>Case 2</td>
<td>3 yr/W</td>
<td>ALL-BFM-95</td>
<td>W</td>
<td>3</td>
<td>10th mo of maintenance</td>
<td>Retinitis</td>
<td>3 wk</td>
<td>Val + ganciclovir</td>
<td>Complete response, relapse, permanent visual defect</td>
</tr>
<tr>
<td>9</td>
<td>Case 3</td>
<td>6 yr/M</td>
<td>ALL-BFM-95</td>
<td>M</td>
<td>6</td>
<td>10th mo of maintenance</td>
<td>Retinitis</td>
<td>7 d</td>
<td>Intravitreal ganciclovir</td>
<td>Complete response</td>
</tr>
<tr>
<td>10</td>
<td>B-cell ALL 7 yr/M</td>
<td>UK-ALL-X</td>
<td>B-cell ALL</td>
<td>M</td>
<td>7</td>
<td>20th mo of maintenance</td>
<td>Retinitis</td>
<td>6 wk</td>
<td>Intravenous + intravenous ganciclovir</td>
<td>Complete response</td>
</tr>
<tr>
<td>11</td>
<td>Case 4</td>
<td>11 yr/M</td>
<td>T-cell ALL</td>
<td>M</td>
<td>11</td>
<td>20th mo of maintenance</td>
<td>Retinitis</td>
<td>6 wk</td>
<td>Intravenous + intravenous ganciclovir</td>
<td>Complete response</td>
</tr>
<tr>
<td>12</td>
<td>Case 5</td>
<td>14 yr/M</td>
<td>T-cell ALL</td>
<td>M</td>
<td>14</td>
<td>31st mo of maintenance</td>
<td>Retinitis</td>
<td>6 wk</td>
<td>Intravenous + intravenous ganciclovir</td>
<td>Complete response</td>
</tr>
</tbody>
</table>

**Treatment Outcome**
- Complete response: The retinitis resolved without recurrence.
- Relapse: The retinitis recurred after initial clearing.
- Permanent visual defect: Vision was lost permanently due to retinitis.

**Type of CMV disease**
- Retinitis: Inflammation of the retina.
- Pneumonia: Inflammation of the lungs.

**References**


