

Short Communication

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 patient 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/ μ L and his neutrophil count was 1,600/ μ L. 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,

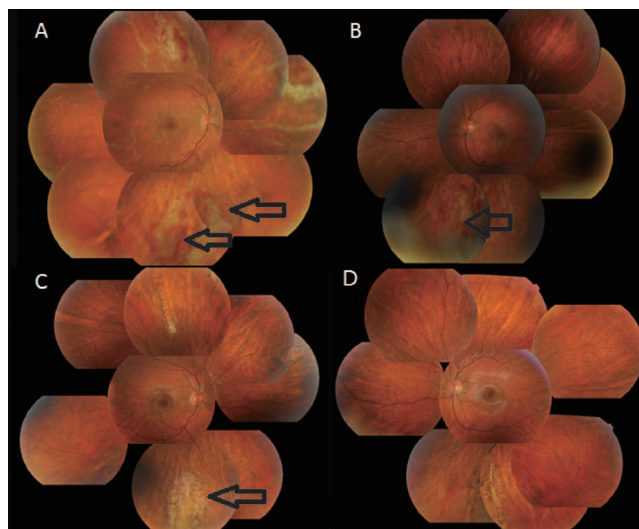


Fig. 1. (Color online) Color photographs of the right (A) and left (B) fundi of Case 1. Right eye fundus photograph showing active cytomegalovirus retinitis (cream-colored lesions associated with hemorrhages). Left eye fundus photograph at the 3rd day of treatment; the same retinal findings were also seen but in a more limited pattern. Two months after treatment, right (C) and left (D) fundus photographs show total resolution of active lesions with the formation of chorioretinal scars and remission of retinitis. These fundus photographs have been already published in ref (2).

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and CMV DNA was quantified as <80 copies/mL in the blood sample and 23,096 copies/mL in the intra-vitreous 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 \times 15 days, followed by 900 mg/day \times 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 $19.0 \times 10^3/\mu\text{L}$, absolute neutrophil count was $1.2 \times 10^3/\mu\text{L}$, and absolute lymphocyte count was $13.5 \times 10^3/\mu\text{L}$. 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 the 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 $300 \times 10^3/\mu\text{L}$, an absolute neutrophil count of $<10^2/\mu\text{L}$, 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

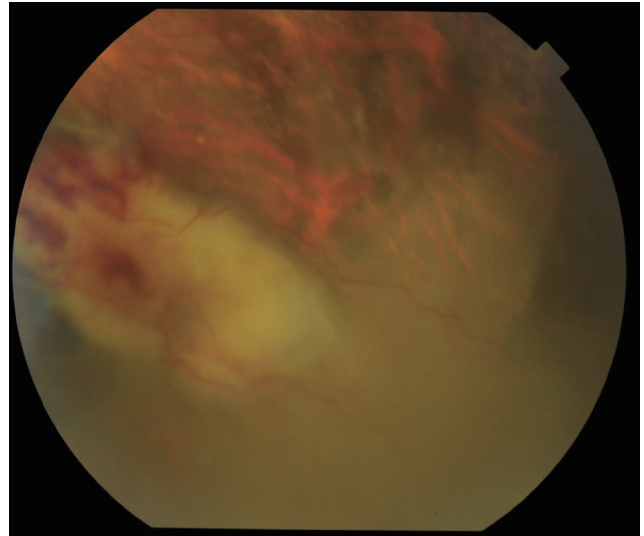


Fig. 2. (Color online) Color photograph of the right fundus of Case 2 showing active retinitis lesions (cream-colored lesions associated with hemorrhages) and subretinal infiltration in the superior temporal area.

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] = $7 \times$ body surface area \times 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 valganciclovir, 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 to the foscarnet treatment until CMV DNA copy number became undetectable. On his final retinal ex-

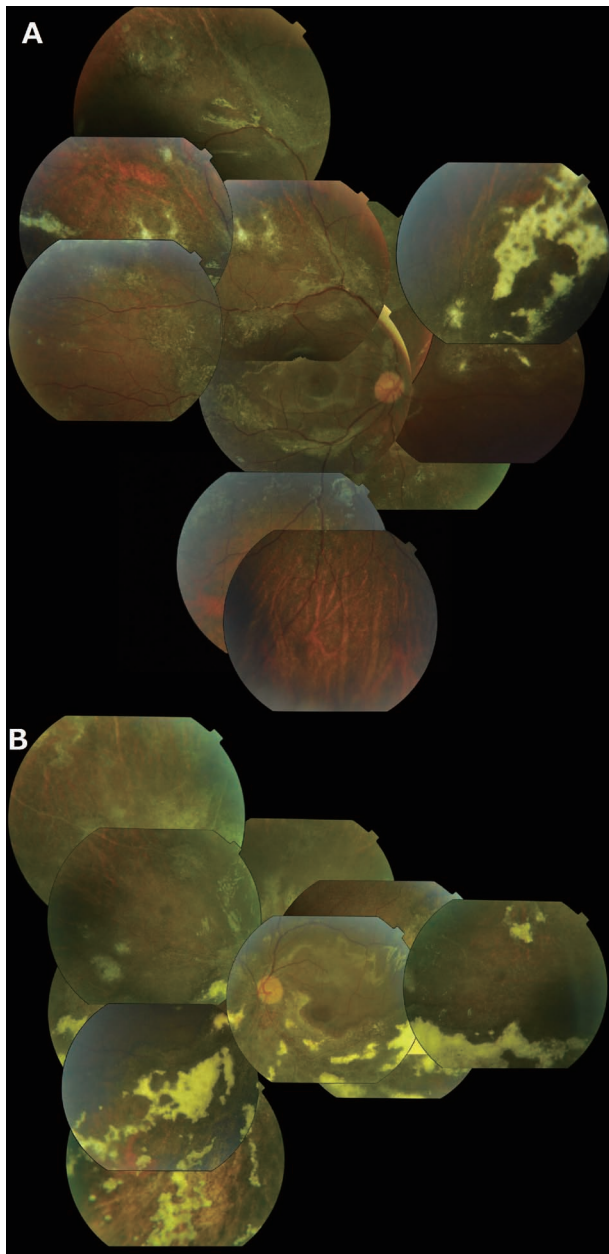


Fig. 3. (Color online) Color photographs of the right (A) and left (B) fundi of Case 3. On the final retinal examination, resolution of the active retinal lesions were observed, and progressive pigment deposition was found around the lesions.

amination, the active retinal lesions had resolved and progressive pigment deposition was localized around these lesions (Fig. 3A and B).

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, Bauml 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

Reference No. Case No.	Underlying leukemia	Age/ Sex ¹⁾	Protocol of chemotherapy	Time of CMV disease	Type of CMV disease	Treatment	Outcome
(4)	T-cell ALL	15 yr/M	St. Jude's Total XV	24th mo of maintenance	retinitis	ganciclovir (19 days)	complete response, relapse, permanent visual defect
(4)	T-cell ALL	12 yr/W	St. Jude's Total XV	20th mo of maintenance	retinitis	ganciclovir (19 days) + valganciclovir (6 mo)	complete response, relapse × 3, permanent visual defect
(5)	B-cell ALL	17 yr/M	CMCP-ALL-2005	3 mo after completion of maintenance of chemotherapy	retinitis	intravitreal + intravenous ganciclovir (6 wk)	complete response
(6)	NA ²⁾	16 yr/M	NA	NA	retinitis	ganciclovir (3 wk)	complete response, relapse, permanent visual defect
(8)	B-cell ALL	3 yr/W	ALL-BFM-95	10th mo of maintenance	retinitis	valganciclovir (transient), ganciclovir (36 days)	complete response
(2)	B-cell ALL	12 yr/M	ALL-BFM-2003	20th mo of maintenance	retinitis	intravenous ganciclovir (2 wk) + valganciclovir (3 wk)	complete response
(9)	B-cell ALL	6 yr/M	ALL02	16th mo of maintenance	retinitis	ganciclovir (resistance), foscarnet	recurrent retinal detachment
(10)	T-cell ALL	7 yr/M	HEX/BFM-95	7th mo of maintenance	HLH + retinitis	ganciclovir (7 days), valganciclovir (21 days)	complete response
(11)	NA	11 yr/M	UK-ALL-2003	33rd mo of maintenance	retinitis	intravitreal ganciclovir	complete response
(12)	T-cell ALL	14 yr/W	UK-ALL-X	6th mo of maintenance	retinitis	valganciclovir (6 wk)	complete response
Case 2	B-cell ALL	9 yr/M	Relapse/refractor	treatment of 2 relapse of ALL	viral syndrome retinitis	ganciclovir (3 wk) + valganciclovir (3 wk)	complete response
Case 3	B-cell ALL	3 yr/M	St. Jude's Total XV	19th mo of maintenance	pneumonia + retinitis	× 3 (ganciclovir [3 wk] + valganciclovir [3 wk]) (resistance), foscarnet (3 wk)	complete response, relapse × 3, response

HLH, hemophagocytic lymphohistiocytosis. ¹⁾ M, man. W, woman. ²⁾ NA, not available.

therapy for the 1st case was 2 weeks, and for the other two was 3 weeks. We then used oral valganciclovir prophylaxis for maintenance therapy. Initially, in our all cases, the lesions resolved. During the 1 year of follow-up, the 1st case had no reoccurrence. The 2nd case also produced a good response to the treatment; however, he died due to fungal sepsis. In addition, the 3rd case completed intravenous ganciclovir treatment for 3 weeks. Initially, all lesions resolved; however, 3 relapses were observed, with re-activated retinal lesions following prophylactic treatment. This patient was still on intravenous foscarnet on Day 26.

Although early treatment of CMV retinitis is critical, no consensus on the optimal therapy has been reached. The Center for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association guideline recommendations are consistent; as such, oral valganciclovir, intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet or intravenous cidofovir are recommended (14). The ganciclovir implant, a surgically-implanted reservoir of ganciclovir, which lasts about 6 months, also is very effective but is no longer being manufactured, and such is not a treatment option. However, in its absence, some experts use intravitreal ganciclovir or foscarnet injections with oral valganciclovir to provide high levels of drugs, for faster control of retinitis (14). On the other hand, the choice of initial therapy for CMV retinitis should be individualized based on the location and severity of the lesions and other factors, such as concomitant medications and ability to adhere to treatment. In addition, CMV retinitis ideally should be treated with active participation of an ophthalmologist who has experience with the diagnosis and management of retinal disease. Indirect opthalmoscopy through a dilated pupil should be performed at the time of diagnosis of CMV retinitis, 2 weeks after initiating therapy, and monthly thereafter while the patient is on anti-CMV treatment, in order to evaluate the efficacy of treatment and to detect complications, such as retinal detachment. Furthermore, adverse effects of ganciclovir/valganciclovir, including anemia, neutropenia, thrombocytopenia, nausea, diarrhea, and renal impairment, should be kept in mind, and complete blood counts, serum electrolytes, and renal function should be monitored twice weekly during induction and at least once weekly during maintenance therapy (14).

In conclusion, in children with ALL, particularly in the maintenance phase of chemotherapy, prolonged immune suppression appeared to be the factor that allows CMV retinitis to develop. Hence, early diagnosis and prompt antiviral treatment is critical to prevent visual loss. Clinicians should be aware of this rare occurrence of CMV retinitis in patients with ALL in the maintenance phase of chemotherapy who have not received HCT.

Conflict of interest None to declare.

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