Cytomegalovirus Disease in Children With Acute Lymphoblastic Leukemia in the Nontransplant Setting: Case Series and Review of the Literature

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Summary: Cytomegalovirus (CMV) disease in pediatric acute lymphoblastic leukemia in the nontransplant setting is very rare. We report our experience with 4 such cases, and review the literature (n = 12). The median age at diagnosis was 10 years and 50% of patients were males. Among the 11 cases with available information at the time of diagnosis, CMV disease occurred during maintenance therapy in 10 patients. Fever was present in 9 cases. CMV disease manifested as retinitis in 6, hepatosplenic disease in 3, pneumonitis in 1, and hemophagocytic lymphohistiocytosis in 1 patient. One patient had both CMV retinitis and CMV-related hemophagocytic lymphohistiocytosis. Four of the 7 patients with retinitis complained of visual disturbance at diagnosis. CMV viremia was present in 10 patients. Three patients had at least 1 relapse and developed permanent visual defects, and 1 patient developed recurrent retinal detachment. In conclusion, prolonged immunosuppression is the major etiology and retinitis is the most common manifestation of CMV disease. As a significant number of patients with retinitis are asymptomatic, early diagnosis and treatment is important to prevent permanent visual loss.

Key Words: CMV, ganciclovir, leukemia, lymphoblastic, retinitis, valganciclovir

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In pediatric acute lymphoblastic leukemia (ALL) in the nontransplant setting, cytomegalovirus (CMV) disease is very rare with only a few previous reports in the literature.[1] Here we report our experience with 4 such cases that occurred over a 2-year period in our institution, and review the literature.

MATERIALS AND METHODS

All pediatric patients under 18 years of age who were admitted to our institution (Bahrami Hospital, Tehran University of Medical Sciences, Tehran, Iran) between March 2011 and March 2013 were prospectively followed. Eligible patients had a previous diagnosis of acute myeloid (AML) or lymphoblastic (ALL) leukemia and had been treated with standard chemotherapy using the AML-BFM-83 (daunorubicin, cytarabine, and etoposide) and UK-ALL-X protocols (vincristine, daunorubicin, L-asparaginase, and prednisone), respectively. The maintenance regimen with UK-ALL-X consists of 6-mercaptopurine, methotrexate, vincristine, and dexamethasone. None of the patients received hematopoietic stem cell transplantation.

CMV viremia was defined as 10,000 copies or higher of CMV DNA per mL according to a polymerase chain reaction (PCR; DNA extraction using QIAamp, DNA Mini Kit #51304, TaqMan-MGB probe and QIAGEN Rotor-Gene 6000 cycler). CMV serology (IgG and IgM), using standard ELISA technique (Genesis Diagnostics Ltd., UK), and PCR were performed once before initiation of maintenance therapy in all patients. Screening before induction in the nontransplant setting is not routinely practiced in our institution. Patients with positive results on either test were screened every 3 to 4 months thereafter, whereas those with a negative result on both tests were not screened again unless they developed symptoms or signs suggestive of CMV disease.

Preemptive therapy solely based on rising PCR titers, and in the absence of compatible clinical picture, is not practiced in our institution in the nontransplant setting. The diagnosis of CMV disease was made based on clinical findings supported by laboratory results such as CMV viremia or evidence of organ involvement (eg, transaminitis, hepatosplenomegaly, unexplained cytopenias, or positive tissue biopsy). Patients with CMV disease were treated with oral valganciclovir (10 mg/kg twice daily) for 6 weeks. After discharge from the hospital, the first follow-up was at 2 weeks after completion of the 6-week course of treatment. Four weeks after completion of treatment, patients were reevaluated for clinical improvement and repeat PCR.

Data are presented as mean ± standard deviation or median (range) as appropriate. A χ^2 test (with Fisher exact test when needed) was used to compare proportions between groups. A P value of < 0.05 was considered statistically significant.

RESULTS

A total of 172 patients (males: 48%) with a median (range) age of 8 years (2 to 17 y) were included. The majority of patients (n = 158; 92%) had a previous diagnosis of ALL and the remainder had been treated for AML. Median (range) values for hemoglobin, white blood cells, platelets, alanine aminotransferase, and aspartate aminotransferase

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TABLE 1. Summary of Reported Cases of ALL in Nontransplant Setting Complicated by CMV Disease

Country/Age/Sex	Type	Protocol	Chemotherapy at Dx of CMV Disease	Time of CMV Disease	Disease
Lebanon/15 y/M[2]	T	St Jude's TOTAL-XV	6MP/MTX/VCR/Dex/Cytoxan/Ara-C	24th month of maintenance	Retinitis
Lebanon/12 y/F[2]	T	St Jude's TOTAL-XV	6MP/MTX/VCR/Dex/Cytoxan/Ara-C	20th month of maintenance	HS
Japan/3 y/F[3]	B	ALL-BFM 95	6MP/MTX/VCR/Dex	10th month of maintenance	Retinitis
Japan/6 y/M[4]	B	ALL02	6MP/MTX/VCR/P	16th month of maintenance	Retinitis
Japan/7 y/M[5]	T	HEX/BFM95	6MP/MTX	7th month of maintenance	HLH, retinitis
Turkey/1.5 y/F[6]	B	NA	NA	During consolidation	HLH
India/11 y/M[7]	NA	UK-ALL-2003	6MP/MTX/VCR/Dex	33rd month of maintenance	Retinitis
Canada/16 y/M[8]	NA	NA	6MP/MTX/VCR/Dex	NA	Retinitis
Iran/14 y/F/This study	T	UK-ALL-X	6MP/MTX/VCR/Dex	6th month of maintenance	Retinitis
Iran/15 y/F/This study	B	UK-ALL-X	6MP/MTX/VCR/Dex	18th month of maintenance	HS
Iran/3 y/M/This study	B	UK-ALL-X	6MP/MTX/VCR/Dex	14th month of maintenance	HS
Iran/9 y/F/This study	B	UK-ALL-X	6MP/MTX/VCR/Dex	12th month of maintenance	Pneumonitis

6MP indicates 6-mercaptopurine; ALL, acute lymphoblastic leukemia; Ara-C, cytarabine arabinoside; CMV, cytomegalovirus; Dex, dexamethasone; HLH, hemophagocytic lymphohistiocytosis; HS, hepatosplenic; MTX, methotrexate; NA, not available; P, prednisone; VCR, vincristine.

were 9.8 g/dL (7.9 to 13.6 g/dL), 4.7×10^9/L (1.5 to 11.2×10^9/L), 235×10^9/L (36.8 to 470×10^9/L), 32 U/L (10 to 133 U/L), and 33 U/L (15 to 83 U/L), respectively. Two (1%) patients had hepatosplenomegaly. A total of 11 (6%) patients with previous ALL, and none of those with previous AML, had CMV viremia ($P = 1.00$). Males and females comprised 3 and 8 of the 11 viremic patients, respectively ($P = 0.09$). Four patients developed CMV disease; the characteristics of these patients are described below (Tables 1 and 2).

Case 1

A 14-year-old girl with T-cell ALL presented, 9 months after achieving a complete remission (CR) and while on maintenance treatment, with left-sided blurred vision. The absolute lymphocyte count (ALC) was 0.73×10^9/L. Ophthalmologic examination revealed left-sided optic nerve edema and central retinal vein occlusion, and a serum PCR for CMV was positive at a titer of 696,250 copies/mL. A diagnosis of CMV retinitis was established. Treatment with oral valganciclovir (10 mg/kg twice daily) for 6 weeks resulted in complete recovery of vision and a negative CMV PCR.

Case 2

A 15-year-old girl with pre-B-cell ALL presented, 18 months after achieving a CR and while on maintenance treatment, with fever and fatigue. Hepatosplenomegaly was detected on physical examination and ultrasonography. The ALC was 0.70×10^9/L. Relapse was ruled out by a bone marrow examination. A serum PCR for CMV was positive at a titer of 328,000 copies/mL. With a diagnosis of hepatosplenic CMV disease, treatment with oral valganciclovir (10 mg/kg twice daily) was initiated. After 6 weeks of treatment, the patient had full resolution of symptoms, hepatosplenomegaly resolved, and PCR became negative.

Case 3

A 3-year-old boy with pre-B-cell ALL presented, 14 months after achieving a CR and while on maintenance

TABLE 2. Further Details on Reported Cases of ALL in Nontransplant Setting Complicated by CMV Disease

References	Symptoms	Viremia/CD4/IgG	Treatment	Outcome
2	Visual disturbance	−/normal/low	Ganciclovir (19 d)	Complete response, relapse, permanent visual defect
2	Fever, visual disturbance, emesis	+ /low/low	Ganciclovir (19 d), valganciclovir (6 m)	Complete response, relapse x3. Permanent visual defect
3	Fever	+ /NA/normal	Valganciclovir (transient), ganciclovir (36 d)	Complete response
4	Fever, visual disturbance	+ /low/low	Ganciclovir (resistant), foscarnet	Recurrent retinal detachment
5	Fever	+ /low/NA	Ganciclovir (7 d), valganciclovir (21 d)	Complete response
6	Fever	+ /NA/NA	Ganciclovir (4 wk)	NA
7	Visual disturbance	+ /NA/NA	Intravitreal ganciclovir	Complete response
8	None	NA/NA/NA	Ganciclovir (3 wk)	Complete response, relapse, permanent visual defect
This study	Fever, fatigue, visual disturbance	+ /NA/NA	Valganciclovir (6 wk)	Complete response
This study	Fever, fatigue	+ /NA/NA	Valganciclovir (6 wk)	Complete response
This study	Fever, fatigue	+ /NA/NA	Valganciclovir (6 wk)	Complete response
This study	Fever, respiratory distress	+ /NA/NA	Valganciclovir (6 wk)	Complete response

NA indicates not available.

treatment, with fever and fatigue. Hepatosplenomegaly was detected on physical examination and ultrasonography. The ALC was 1.10×10^9/L. ALL relapse was ruled out by a bone marrow examination. A serum PCR for CMV was positive at a titer of 1,324,000 copies/mL. With a diagnosis of hepatosplenic CMV disease, treatment with oral valganciclovir (10 mg/kg twice daily) was initiated. Four weeks after completion of a 6-week course of treatment, the patient had full resolution of symptoms, hepatosplenomegaly resolved, and PCR became negative.

Case 4

A 9-year-old girl with pre-B-cell ALL presented, 12 months after achieving a CR and while on maintenance treatment, with fever, respiratory distress, and an interstitial infiltrate on the chest x-ray. The ALC was 0.61×10^9/L. A serum PCR for CMV was positive at a titer of 1,600,000 copies/mL. With a diagnosis of CMV pneumonitis, treatment with oral valganciclovir (10 mg/kg twice daily) was initiated. Two weeks after completion of a 6-week course of treatment, the patient had full resolution of symptoms and the chest x-ray cleared.

DISCUSSION

CMV viremia occurs in 13.6% of patients with lymphoid malignancies who did not receive stem cell transplantation.[1] In the nontransplant setting, an estimate of 3.6% has been made for the incidence of CMV retinitis affecting children with ALL.[2] A total of 12 cases (including ours) of CMV disease in pediatric ALL have been reported. A summary is shown in Tables 1 and 2. The median age at diagnosis was 10 years (range, 1.5 to 16 y) and 6 (50%) patients were males. The exact time of CMV disease was not reported in 1 case. In the remaining 11 cases, CMV disease occurred during maintenance therapy (after at least 6 mo) except in 1 case affected during consolidation therapy. In support of these results are those of a large previous report of 111 pediatric ALL patients treated with the St Jude's TOTAL-XV protocol. All 4 cases of CMV retinitis occurred during maintenance.[2] The chemotherapy regimen for maintenance for 10 of the 11 cases in our collected cases included 6-mecaptopurine, methotrexate, vincristine, and steroids. In the remaining case, only 6-mercaptopurine and methotrexate were used for maintenance. Fever was present in 9 cases, and 1 patient was completely asymptomatic. CMV disease manifested as retinitis in 6, hepatosplenic disease in 3, pneumonitis in 1, and hemophagocytic lymphohistiocytosis in 1 patient. One patient suffered from both CMV retinitis and CMV-related hemophagocytic lymphohistiocytosis. Four of the 7 patients with retinitis complained of visual disturbance at diagnosis and the disease was asymptomatic in the remainder. CMV viremia was present in 10 patients, absent in 1 patient, and unknown in 1 patient. Initial therapy was with intravenous ganciclovir in 6 patients, oral valganciclovir in 5 patients, and intravitreal ganciclovir injections in 1 patient. Outcomes were available in 11 cases. From these, 7 patients had complete response and never relapsed during the follow-up period, whereas 3 patients had at least 1 relapse and developed permanent visual defects. One patient continued to suffer from recurrent retinal detachment.

It has been suggested that maintenance therapy for ALL can cause profound immunosuppression.[3] This hypothesis is supported by low ALC, $CD4^+$ T-cell count, and immunoglobulin levels in the maintenance period.[4] All of our 4 patients had low ALC values at the time of diagnosis of CMV disease. It has been shown that although reconstitution of B cells and natural killer cells occurs early, recovery of both T-helper and T-suppressor cells is delayed in pediatric patients with ALL.[9] Moritake et al[3] believed that the addition of vincristine and dexamethasone to 6-mercaptopurine and methotrexate significantly increases the risk of CMV retinitis. They diagnosed a pediatric ALL patient with CMV retinitis during maintenance therapy using 6-mercaptopurine, methotrexate, vincristine, and dexamethasone. Although viremia initially responded to valganciclovir, retinitis worsened following a dose reduction in valganciclovir. Once a complete response was achieved using ganciclovir, vincristine and dexamethasone were discontinued. CMV did not recur in this case, no further immunoglobulin supplementation was required, and the $CD4^+$ T-cell count remained >250 cells/μL.[3]

CONCLUSIONS

We reported 4 new cases of CMV disease in pediatric ALL in the nontransplant setting. Our observations and a review of the literature suggest this is indeed a rare entity, and with potentially high morbidity. Although not completely clear, prolonged immunosuppression (and the resulting lymphopenia) seems to be the main etiologic mechanism and retinitis is the most common manifestation of CMV disease in this population. A significant number of patients with retinitis are asymptomatic, and hence, early diagnosis and treatment is critical to prevent permanent visual loss.[3]

Preemptive anti-CMV therapy (ie, routine active screening and treating patients with progressively increasing viral titers) is the most popular strategy in the transplant setting. When compared with a watch-and-wait strategy (ie, treat only patients with CMV disease), the preemptive strategy results in significantly lower frequency of CMV disease and prolonged overall survival.[10] PCR assays are more sensitive than pp65 antigenemia assays and blood culture for detection of CMV in blood specimens.[11] Considering the extreme rarity of CMV disease in pediatric ALL in the nontransplant setting, a randomized clinical trial to find the effectiveness of screening and preemptive therapy is not feasible, and any firm recommendation would be premature. Nonetheless, certain patients are likely at higher risk for developing CMV reactivation and disease. These include patients with a positive serology before induction and prolonged $CD4^+$ T-cell lymphocytopenia (common during maintenance therapy). A risk-adapted strategy to screen and offer preemptive therapy to high-risk patients may be beneficial and help avoid unnecessary costs and potential side effects of universal screening and prophylaxis in the nontransplant setting.

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