Case Report

Disseminated Cytomegalovirus Infection in a Child with Langerhans Cell Histiocytosis

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Abstract

Cytomegalovirus (CMV) reactivation is well known in post-transplant immunocompromised children. However, the incidence in non-transplant patients is significantly less, and only scarce case reports are available in the literature regarding CMV disease in children with solid tumors. We present a 3-year-old male child with multisystem refractory Langerhans cell histiocytosis, who had very high CMV viremia and disseminated CMV infection with secondary hemophagocytic lymphohistiocytosis and was successfully treated without organ damage and sequelae. Although routine screening is not recommended, CMV viremia/disease needs to be considered in non-transplant immunocompromised children with multisystem involvement with unexplained cytopenia.

Keywords: Cytomegalovirus viremia, disseminated cytomegalovirus, immunocompromised, interstitial pneumonia, secondary hemophagocytic lymphohistiocytosis, solid tumors

Introduction

Cytomegalovirus (CMV) infection is a significant cause of morbidity and mortality in post-allogeneic hematopoietic stem cell transplant (HSCT) and primary immunodeficiency (PID) children; however, CMV is not routinely considered in the infectious workup of children with hematological malignancies or solid tumors in the non-transplant setting. Literature on CMV infections in non-transplant children undergoing chemotherapy is very limited. In this case report, we describe a case of a child with refractory Langerhans cell histiocytosis (LCH) treated with intensive chemotherapy who developed disseminated CMV infection and recovered completely with appropriate treatment.

Case Report

We describe a 3-year-old male child with Group-I multisystem LCH with skin involvement, right eye proptosis, lymphadenopathy, and hepatosplenomegaly, refractory to three lines of chemotherapy (vinblastine and steroids, low-dose cytarabine, lenalidomide, and dexamethasone) and six cycles of fourth salvage chemotherapy (cladribine and cytarabine). After complete recovery from the last cycle of cladribine and cytarabine chemotherapy-induced pancytopenia, he presented with fever and cough for 7 days and breathing difficulty for 2 days. At admission, he had respiratory distress requiring oxygen. COVID reverse transcription-polymerase chain reaction (PCR) was negative.

Complete blood count on day 2 of fever revealed hemoglobin of 9.5 g%; total leukocyte count (TLC) of 6700/cumm with neutrophils 65% and lymphocytes 25%; and platelet count of 1.8 lakhs/cumm. There was a serial drop in counts leading to pancytopenia by day 10 of illness (hemoglobin – 7.2 g%; TLC of 1300/cumm with neutrophils 23% and lymphocytes 71%; and platelet count of 35,000/cumm).

Biochemical investigations revealed transaminitis (serum glutamic-oxaloacetic transaminase - 86 U/L; serum glutamic

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pyruvic transaminase - 225 U/L), hypoalbuminemia (2.3 g/dl), and elevated serum ferritin level (4547 ng/ml). Blood culture was sterile.

Chest X-ray showed bilateral interstitial opacities [Figure 1a]. Child was treated initially with broad-spectrum antibiotics, azithromycin, and empirical oseltamivir; subsequently, added on liposomal amphotericin-B and therapeutic dose of cotrimoxazole in view of persistent high-grade fever and serial drop in counts. Computed tomography (CT) of thorax showed bilateral diffuse ground-glass opacities [Figure 1b]. Nasopharyngeal swab for H1N1 PCR was negative; serum galactomannan was negative; and sputum for *Pneumocystis carinii* was also negative. By day 11 of illness, he developed loose stools, had persistent fever spikes and distress, worsening pancytopenia, increase in serum ferritin to 32,000 ng/ml, and worsening transaminitis. Serum fibrinogen and triglycerides were normal.

In view of persistent fever with multisystem involvement, quantitative PCR for CMV was done, and it was sky-high positive at 703,407,730 copies/mL. Hence, diagnosis of disseminated CMV infection with secondary hemophagocytic lymphohistiocytosis was made. The child was treated with 2 g/kg of intravenous immunoglobulin and intravenous ganciclovir. Significant clinical improvement was noted (afebrile after 4 days and weaned off oxygen in the next 2 weeks). His serial CMV PCR and serum ferritin showed declining trend [Figure 2]. He was treated with ganciclovir for 6 weeks and oral valganciclovir till complete clearance of CMV viremia for a total duration of 7 months.

Discussion

LCH is characterized by proliferation of Langerhans type dendritic cells, mainly affecting young children. Although the possible link of viruses including CMV in the pathogenesis of LCH was described in studies, it remains debated. Apart from the pathogenesis link between CMV and LCH, even the increased risk of CMV infection in LCH has not been documented clearly in the literature.

While CMV infection in immunocompromised patients could be fulminant, in non-HSCT setting, it is usually mild and self-limiting. CMV reactivation and disease are very common, with 48%–57% in post-allogenic HSCT population and 40%–60% in children with PID. Periodic CMV monitoring and empirical therapies are standard practices in post-HSCT setting.

However, in non-HSCT, especially in hematological malignancies, it is less prevalent with CMV viremia noted in 16%–30% and CMV disease noted even less at 4%–9% of cases.[1] Phasuk *et al*. evaluated 141 samples from 50 acute lymphoblastic leukemia (ALL) patients and found CMV viremia (≥1000 copies/mL) in 16%. Except for one patient who had CMV retinitis, none of the others had any end-organ involvement.[2]

Agrawal *et al*. revealed that 41% of adults with solid malignancies were tested positive for CMV but did not have clinical disease.[3] Schlick *et al*. showed in adults that 50% of patients with solid tumor on chemotherapy developed CMV disease.[4] Reported CMV disease in children on chemotherapy for solid tumors is scarce.

Conflicting reports regarding monitoring of CMV viremia in non-HSCT settings arise, especially in developing countries, because of frequent reactivations in seropositive cases. Sen *et al*. have pointed out the importance of monitoring for CMV in ALL patients and highlighted that even low CMV-DNA levels may also lead to organ involvement.[5]

A retrospective study of 2331 patients with hematological malignancies showed that 36 (1.5%) patients had CMV reactivation and 56% of patients improved without anti-CMV medication.[6] Al Talhi *et al*. found that though one-third of prolonged febrile neutropenic episodes in pediatric oncology non-HSCT setting had CMV viremia, it had no significant impact on fever duration or mortality, and hence, in concordance with the IDSA guidelines, routine screening for CMV or treatment for only viremia is not recommended.[7]

Hearing loss after acquired CMV infection in a child with LCH has been reported who was presumed to have acquired CMV infection due to a blood transfusion.[8] Hesseling *et al*. have postulated that hemophagocytic syndrome and LCH were

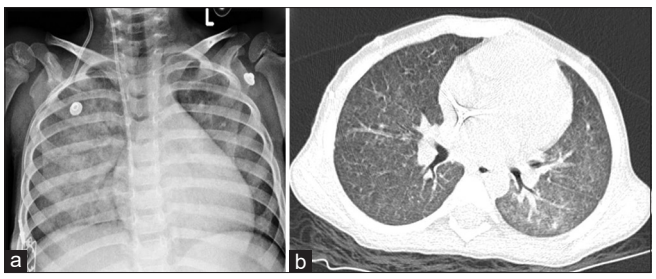

Figure 1: Chest X-ray showing bilateral fluffy opacities (a) and computed tomography (b) thorax showing bilateral diffuse ground-glass opacities in interstitial pattern favoring cytomegalovirus pneumonia

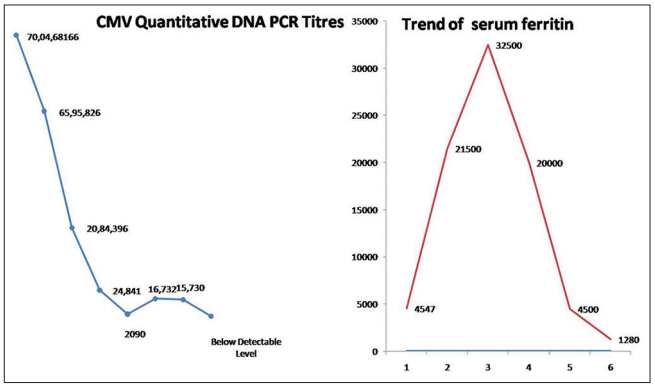

Figure 2: Graphs showing the declining trends of cytomegalovirus quantitative polymerase chain reaction and serum ferritin after initiation of ganciclovir

triggered by CMV infection by reporting a 10-month-old female child with the histologic proof of both hemophagocytosis in the liver and bone marrow and LCH in the skin.[9] Chen *et al*. reported CMV infection occurred in one (20%) of the five patients of LCH treated with the combination of chemotherapy and pediatric liver transplantation.[10]

Conclusion

We report this case to raise awareness among pediatric hemato-oncologists and infectious diseases specialists to consider CMV infection in nontransplant setting also when appropriate, as timely treatment is the key to successful outcome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's parent has given his consent for his images and other clinical information to be reported in the journal. The patient's parent understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Research quality and ethics statement

The authors followed applicable EQUATOR Network guidelines (http://www.equator-network.org/), notably the CARE guideline, during the conduct of this report.

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Conflicts of interest

There are no conflicts of interest.

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