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Case study

A case of neonatal cytomegalovirus infection with severe thrombocytopenia that was successfully managed with empiric antiviral therapy

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ABSTRACT

Antiviral therapy against cytomegalovirus (CMV) infection is indicated for symptomatic infection in the fetus and premature neonates. In mature neonates, the benefit of antiviral therapy for severe CMV infection remains controversial. Additionally, when diagnosing symptomatic CMV disease occurring during the early neonatal period, it is difficult to differentiate between congenital and acquired infections. We herein report a neonatal case of CMV infection complicated with severe thrombocytopenia that was successfully managed with antiviral treatment. A 21-day-old male infant presented with low-grade fever and erythema on his extremities. During outpatient follow-up, he developed petechiae and thrombocytopenia (platelet count 17,000/μL). Subsequent serological examination and molecular detection of CMV confirmed the diagnosis of CMV infection. In consideration of the severe thrombocytopenia, antiviral therapy with valganciclovir 32 mg/kg/day was initiated. The platelet counts increased with decreasing CMV loads. After excluding congenital CMV infection, we discontinued antiviral therapy without relapse of the disease. The present case suggests that neonatal cases of severe symptomatic CMV infection may require antiviral therapy while excluding the possibility of congenital infection.

Introduction

Cytomegalovirus (CMV) usually causes asymptomatic or self-limited infections among the majority of immunocompetent children [1]. Thus, antiviral therapy is indicated only for symptomatic congenital CMV infections and infections among premature neonates [2]. However, there is a clinical dilemma in determining the indication of antiviral therapy for those with severe CMV infections because antiviral therapy could be beneficial for them. Additionally, for CMV infections occurring during the neonatal period, it can be difficult to differentiate between congenital and acquired infections [3]. Here, we describe a neonatal case of CMV infection with severe thrombocytopenia that was successfully managed with antiviral treatment.

Case report

The patient was a 21-day-old male infant who presented with low-grade fever and erythema on his hands and legs. He was born at full term with appropriate weight, height, and head circumference for his gestational age. Pregnancy was uncomplicated and he was breastfed after birth. Neonatal sepsis was ruled out by unremarkable blood tests, urinalysis, and negative blood cultures. Lumbar puncture was not performed due to low clinical suspicion of meningitis. Consequently, he was followed up as an outpatient with a possible diagnosis of viral infection. On day of life (DOL) 27 he visited our hospital again because he developed petechiae on the hands and legs. He was admitted for further evaluation. Physical examination showed unremarkable vital signs and normal liver size, but splenomegaly was present. Blood tests revealed thrombocytopenia (platelet count 17,000/μL), non-hemolytic

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anemia (hemoglobin 7.8 g/dL), and leukocytosis (white blood cell [WBC] count 26,760/μL) with an atypical lymphocytosis (10 %). Subsequent blood tests confirmed the presence of CMV infection, as follows: positive CMV-specific immunoglobulin M (IgM), immunoglobulin G (IgG) antibodies on DOL 34, and CMV DNA 1.9×10^4 copies/μg DNA in peripheral blood mononuclear cells on DOL 40. Post-partum maternal CMV serology showed positive CMV-IgG and negative CMV-IgM, indicating past CMV infection. Hence, CMV infection complicated with severe thrombocytopenia was diagnosed. Due to severe thrombocytopenia and high CMV viral loads, empiric antiviral therapy with valganciclovir (VGCV) 32 mg/kg/day was initiated on DOL 41. Antiviral treatment was also administered because congenital CMV infection was still a possibility at that point, considering that his disease onset was within one month of life. On DOL 42, the WBC count was elevated to 45,880/μL (neutrophils 20.5 %, lymphocytes 77.0 %, atypical lymphocytes 1.5 %). Further lymphocyte subsets showed a dominant increase of HLA-DR + CD8+ T cells and the normal proportion of B cells. None of the further workups revealed any sign of congenital CMV infection, as follows: normal head CT scan, ophthalmological examination, auditory brainstem response, electroencephalogram, and negative CMV PCR of the dried umbilical cord. Thus, congenital CMV infection was excluded. Finally, we diagnosed his disease as neonatal, acquired CMV infection.

After the initiation of VGCV, his platelet counts recovered with decreasing CMV loads (Fig. 1). Anemia and the splenomegaly seen on admission gradually improved. His general condition stabilized, he was discharged on DOL 53, and was followed closely as an outpatient. After a 4-week treatment of VGCV, bone marrow toxicity became a concern due to reduced reticulocyte counts without anemia. Hence, VGCV was discontinued to avoid further myelosuppressive adverse effects. An asymptomatic, transient increase of CMV load was observed after cessation of VGCV; however, CMV DNA spontaneously became undetectable four months after onset. Follow-up exams until one year after onset confirmed normal growth and development without any neurological impairment.

Discussion

We described a neonatal case of acquired CMV infection complicated with severe thrombocytopenia that was successfully managed with antiviral therapy. Usually, immunocompetent individuals with primary CMV infection do not require antiviral therapy [1]. This applies to neonates—except for congenital CMV infection and CMV infection among preterm neonates [2]. However, controversy remains about antiviral therapy for severe symptomatic CMV infection. Nishio et al. reported a case of a 20-month-old boy with CMV infection and severe thrombocytopenia. This CMV infection resolved spontaneously with a decrease in CMV DNA load along with the recovery of platelet counts [4]. On the other hand, DiMaggio et al. reported an immunocompetent three-year-old girl and an immunocompetent nine-year-old boy who presented with thrombocytopenia due to CMV infection [5]. Their thrombocytopenia was severe and persisted for one month. However, after the initiation of antiviral therapy, the viral loads decreased followed by the recovery of platelet count. A case series from Korea revealed that among immunocompetent children between one month and 15 years of age with CMV-related thrombocytopenia, 34.8 % required antiviral therapy due to refractory thrombocytopenia [6]. These reports suggest the benefit of antiviral treatment when infants and young children receive a diagnosis of CMV infection complicated with refractory or severe thrombocytopenia. Similarly, our neonatal case showed recovery of platelet counts and a decrease in viral load after the initiation of antiviral therapy.

Additionally, when CMV disease is found in the neonatal period, it is necessary to consider the possibility of congenital CMV infection because some of those require prolonged antiviral therapy. Kimberlin et al. reported that treating congenital CMV infection with VGCV for six months improved long-term hearing and neurodevelopmental outcomes [7]. However, in some cases, it is difficult to discriminate congenital CMV infection from acquired infection [3]. Given the neonatal onset of our case and the fact that congenital CMV infection may cause thrombocytopenia [8], congenital infection was also included in the differential diagnosis. Therefore, we began the treatment before the diagnosis and subsequently excluded congenital CMV infection with several findings and laboratory tests. Finally, we confirmed the case diagnosis as neonatal acquired CMV infection. Making this diagnosis was crucial for our patient to avoid prolonged antiviral therapy, especially when the patient had adverse effects from VGCV treatment [9].

In conclusion, neonatal CMV infection with severe thrombocytopenia may be an indication for a short course of antiviral therapy. As the benefit of antiviral therapy against CMV infection with severe symptoms is obscure, it is valuable to report those cases to determine which young children require treatment for symptomatic CMV infection and when it should be administered. Additionally, exclusion of congenital CMV infection is important to avoid unnecessary prolonged antiviral therapy.

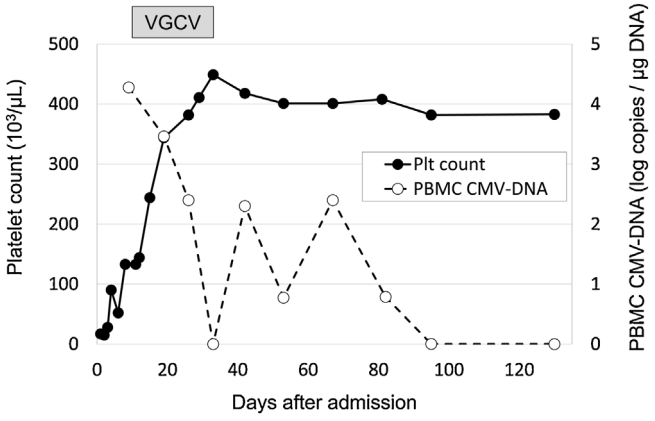

Fig. 1. Patient's clinical course after admission. Platelet count recovered and CMV load decreased after initiating valganciclovir (VGCV). Cytomegalovirus (CMV) load rose again after stopping VGCV, but platelet (Plt) count remained normal. Later, CMV load decreased again. Closed circles show platelet counts, and open circles represent CMV load in peripheral blood mononuclear cells (PBMC).

Informed consent

Informed consent was obtained from the living patient's parent for publication of this case report.

Authorship statement

All authors meet the ICMJE authorship criteria.

Authorship contribution statement

K. Fujimori: Writing – Original Draft, Data curation; M. Yamada: Writing – Original Draft, Writing – Review & Editing; T. Maekawa: Writing – Original Draft, Writing – Review & Editing; N. Yotani: Writing – Review & Editing; E. Tamura: Review & Editing; K. Imadome: Review & Editing, Data curation; M. Kubota: Review & Editing; A. Ishiguro: Review & Editing, Supervision.

Declaration of Competing Interest

None declared.

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