Case report

A neonatal case of coxsackievirus B3 vertical infection with symptoms of hemophagocytic lymphohistiocytosis

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A B S T R A C T

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome of excessive immune activation that most commonly affects infants. We report the case of a term female neonate with HLH associated with coxsackievirus B3 Infection. Her mother was hospitalized due to high fever 4 days before the delivery. The patient was delivered by vaginal delivery after the induction of labor. She was admitted to the neonatal care unit due to continuous high fever and poor sucking on her 4th day of life. She developed apnea on her 5th day of life. Laboratory findings on the patient’s 7th day of life indicated severe thrombocytopenia, liver dysfunction, coagulation abnormality and hyperferritinemia. Coxsackievirus B3 was isolated from all cultured specimens by the PCR method. She received intravenous transfusion of platelets and immunoglobulin. Her platelet count gradually increased to the normal range by her 14th day of life and she was discharged without any sequelae on her 25th day of life. To the best of our knowledge, this is the first case report of neonatal HLH associated with a vertical transmission of coxsackievirus B3. Coxsackievirus is an important virus that can cause HLH in neonates. An early diagnosis and timely treatment are crucial.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome of excessive immune activation that most commonly affects infants, with the highest incidence at <3 months of age [1]. A national survey in Japan showed that overall survival rate in neonates was 40 % [2]. HLH can occur as a familial or sporadic disorder, and can be triggered by various events that disrupt immune homeostasis. Infection is a common trigger. Prompt treatment is crucial. However the diagnosis of neonatal HLH is usually difficult due to the rarity of this syndrome, variable clinical presentation, and lack of specificity of the clinical and laboratory findings.

Enteroviral infection is the most frequently diagnosed viral infection in the neonatal period [3]. Group B coxsackievirus serotypes 2–5 and echovirus 11 have most frequently been associated with overwhelming systemic neonatal infections [4]. They can trigger the occurrence of HLH.

We herein report a neonatal case of coxsackievirus B3 vertical infection accompanied by probable hemophagocytic lymphohistiocytosis.

Case presentation

The patient was a Japanese girl born at 38 weeks and 0 day of gestation body weight at birth, 2860 g. Her 35-year-old mother Gravida 3, Para 3 took prophylatic tablets due to Basedow disease; her anti-TSH receptor antibody titer remained negative during pregnancy. Her HIV test result in pregnancy was negative. At 37 weeks and 3 days of pregnancy, the mother was hospitalized due to high fever.

The patient was delivered by vaginal delivery after the induction of labor with Apgar scores of 8 at 1 min and 9 at 5 min. From her 3rd day of life, she had high fever. On her 4th day of life, she was admitted to the neonatal care unit for observation due to continuous high fever and poor sucking. At that time, she was slightly pale and hypoactive. Her body temperature was 39.6°C. Her heart rate, and blood pressure remained stable. The patient was slightly icteric, and the liver and spleen were not palpable. Muscular tonus was appropriate, and neurological findings were normal. There were no signs of respiratory distress or bowel disease. Laboratory investigations of

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the patient revealed an inflammatory reaction (CRP 20 mg/L) with normal leukocyte (10.7 × 10⁹/L) and platelet (215 × 10⁹/L) counts. Treatment with intravenous ampicillin, gentamicin and acyclovir was initiated due to the possibility of perinatally acquired bacterial or herpes infection. On her 5th day of life, a laboratory analysis revealed profound thrombocytopenia (17 × 10⁹/L) with elevated deviation enzyme levels: aspartate aminotransferase (AST), 327 U/L; alanine aminotransferase (ALT), 42 U/L; lactate dehydrogenase (LDH), 1872 U/L. These results suggested hemolysis. She developed apnea on the same day. On her 6th day of life, petechiae were detected on her abdomen. Intracranial hemorrhage was ruled out by ultrasonography. Laboratory findings on the patient’s 7th day of life indicated liver dysfunction, coagulation abnormality and hyperferritinemina without pancytopenia: leukocyte count, 9.2 × 10⁹/L; hemoglobin, 144 g/L; platelet count, 17 × 10⁹/L; AST, 636 U/L; ALT, 221 U/L; LDH, 2001 U/L; CRP, 31 mg/L; triglyceride, 43 mg/dL; fibrinogen, 1.42 g/L; fibrinogen/fibrin degradation product, 67.0 μg/mL; D-dimer, 39.8 mg/L; ferritin, 3300 μg/L; soluble interleukin-2 receptor, 2439 U/mL; natural killer-cell activity, 23 % (reference range, 18–40 %). Flow cytometry of the peripheral blood revealed the normal expression of perforin protein and no increase in activated T cells (HLA-DR+/CD3+CD8 + 1.05 %) which are usually found in familial HLH. The patient received concentrated platelet suspension on her 5th day of life for 3 days and intravenous transfusion of high-dose immunoglobulin on her 9th day of life. Bacterial cultures of nasopharyngeal, stool, blood and urine specimens were negative for pathogenic microorganisms. Coxackievirus B3 was isolated from all cultured specimens by the VP1 reverse transcription-semi-nested PCR method. In a neutralization test, the mother’s antibody titer was found to be increased 512-fold on her 9th day of life, indicating a recent Cox B3 infection. The mother’s test results of herpes simplex virus and cytomegalovirus antibodies showed no recent infection of those viruses. Thus, the vertical transmission of Cox B3 was suspected. The patient was diagnosed with neonatal coxackievirus B3 infection accompanied by probable hemophagocytic lymphohistiocytosis. Without additional treatment, the patient’s platelet count gradually increased to 166 × 10⁹/L by her 14th day of life. She was discharged from our hospital without any sequelae on her 25th day of life (Fig. 1).

**Discussion**

To the best of our knowledge, this is the first case report of neonatal hemophagocytic lymphohistiocytosis associated with a vertical transmission of coxackievirus B3. The diagnosis of HLH is challenging. The diagnosis of HLH is fulfilled when at least 5 of the following 8 designated criteria are present: fever, splenomegaly, cytopenia affecting ≥2 of 3 lineages, hemophagocytosis, elevated ferritin, elevated triglycerides or hypofibrinogenemia, an impaired natural killer cell function, and elevated soluble interleukin-2 receptor levels [5]. The diagnostic criteria were originally established to diagnose familial HLH (FHL). The patient fulfilled 4 of the diagnostic criteria for HLH. We did not perform bone marrow aspiration because it was an invasive procedure and because the platelet counts were low. Bone marrow aspiration is infrequently performed for neonates in clinical practice. Thus, we could not directly evaluate bone marrow findings. However, given the clinical course, hemophagocytosis was likely to manifest as a result of bone marrow examination. Some clinical findings are observed less frequently in neonates than in older children, for example, neutropenia, hypertriglyceridemia and splenomegaly are uncommon in neonates in Japan [2,6]. Ethnic differences might have also affected those findings. Furthermore, the normal range of natural killer cell activity in neonates is not defined. These factors make the diagnosis of HLH difficult in neonates. In addition to fulfilling 4 of the 8 criteria, the detection of viral infection, a high LDH and D-dimer level, and high AST/ALT ratio supported the diagnosis of HLH in our case. She had significant signs/symptoms of viral sepsis which can very much overlap with HLH. Intravenous transfusion of high-dose immunoglobulin can be used for the treatment of the both. However highly elevated ferritin and LDH level can distinguish between the two [7,8]. In light of the above-mentioned facts, it is important to initiate treatment as HLH if there are other supporting factors even though at least 5 designated criteria are not present.

There are many causes of HLH. In our case, primary (familial) HLH was precluded because there was no family history suggesting it and because the patient's natural killer cell activity was normal and flow cytometry showed the normal expression of perforin and no increase in activated T cells in the peripheral blood. Perforin deficiency is detected in FHL type 2, which is prevalent in Kyushu region, Japan including the site of this case. Herpes simplex virus (HSV) is the most common virus causing secondary (sporadic) HLH in neonates [2]. Thus, acyclovir was administered in our case until all viral tests were negative for HSV.

There are no proper guidelines for the treatment of HLH in neonates. The patient received intravenous transfusion of high-dose immunoglobulin for 1 day and no additional treatment for HLH was needed. High-dose intravenous immunoglobulin therapy has mainly been successful for treating virus-associated HLH [9]. The literature also suggested that the prognosis of HLH due to

Fig. 1. The clinical course of the patient. The patient showed fever and apnea with the laboratory findings of rapidly progressive thrombocytopenia and elevation of LDH. The clinical condition gradually improved after therapy. She had VPC at the late phase of the clinical course. This improved without additional treatment. ABPC, ampicillin; GM, gentamicin; PC, platelet concentrate; IVIG, intravenous immunoglobulin; Plt, platelet; LDH, lactate dehydrogenase.
enterovirus was better in comparison to familial HLH or HLH due to Herpes simplex virus [2,3,9,10]. Thus etoposide should not be routinely administered due to the adverse effects of the drug.

In summary, the index case of Cox B3 infection with hemophagocytic lymphohistiocytosis highlights the importance of an early diagnosis and treatment according to the severity of the disease.

CRediT authorship contribution statement

Yasuhiro Miyoshi: Writing - original draft. Sachika Yoshioka: Visualization, Investigation. Hirokazu Gosho: Visualization, Investigation. Shoichi Miyazoe: Visualization, Investigation. Hideyo Suenaga: Supervision. Mikihiro Aoki: Supervision. Kunio Hashimoto: Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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