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Case report

# Hemophagocytic lymphohistiocytosis in a neonate with enterovirus infection: Case report and literature review

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ABSTRACT

Viruses are the most common organisms causing hemophagocytic lymphohistiocytosis (HLH), and enterovirus infection is the most frequently diagnosed virus infection in the newborn period. However, in recent years, there have been relatively few reports of enterovirus infection in Chinese neonates complicated by HLH. Here, we describe a female preterm infant who contracted echovirus 11 at day 4 and rapidly developed sepsis during the following three days, along with fever, lethargy, disseminated intravascular coagulation (DIC), and sepsis. She was ultimately identified as having echovirus 11 complicated by HLH. This report will contribute to increasing public awareness of the link between HLH and echo 11 infection, which can aid in early identification and treatment.

**What's New:** We reported female preterm infant who contracted echovirus 11 at day 4 and rapidly developed sepsis during the following three days, it was the first report from central China that we are aware of.

## Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a clinical syndrome characterized by the uncontrollable activation of macrophages and T lymphocytes [1,2]. It may have hereditary causes due to abnormalities in the genes that control how naturally occurring killer (NK) cells and cytotoxic T lymphocytes function (CTLs). Infections, cancers, autoimmune and autoinflammatory illnesses, as well as acquired immune deficiency states are other situations in which HLH may develop [3,4].

Numerous examples of acquired HLH caused by virus infection have been recorded in earlier investigations; among these viruses are the herpes simplex virus (HSV). [5], adenovirus [6], cytomegalovirus [7], enterovirus [8,9] and Epstein-Barr virus (EBV) [10]. The majority of cases, nevertheless, involved adults and older children. The most common virus infection in the newborn period is enterovirus infection, and several cases of neonatal enterovirus infection complicated by HLH have been documented in recent years [11–16], while few of them involved Chinese infants. We provide a case of a Chinese infant with confirmed enterovirus-associated HLH in order to draw attention to the link and promote early treatment and diagnosis.

## Case report

The patient was a female newborn infant who was 35 weeks and 3 days gestational age and weighed 2700 g at birth. Her mother had a history of Gravida 2, Para 2, a scarred uterus, and had a fever of 39°C with an increased C-reaction protein (CRP). The patient was born after a cesarean delivery with Apgar scores of 9 at 1 min and 10 at 5 min. Due to her groaning and shortness of breath after birth, she was placed on a noninvasive ventilator and cefoperazone sulbactam (CPZ-SBT) simultaneously. She began to exhibit lethargy and a 39°C fever at 4 days-old along with a decreased appetite. With a positive fecal occult blood test and a low fibrinogen level, she was suspected of having coagulopathy (Table 1).

On the fifth day after birth, she was transferred to our hospital for additional care, and developed to disseminated intravascular coagulation (DIC) upon admission: hypotension, apnea, large ecchymosis of skin, hematuria with elevated blood urea nitrogen (BUN, 7.36 mmol/L), and bleeding from the site of blood collection, Further examination revealed that her PLT count and fibrinogen continued to decline, the D-dimer climbed to 26.71 g/mL as shown Supplemental Table 1. Additionally, she had a poor hepatic function with elevated transaminases, bilirubin and lactate dehydrogenase (LDH) as shown in Table 1.

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**Table 1**
Evidences for Diagnostic criteria for HLH and ecovirus 11 infection.

| HLH | | Patient |
|---|---|---|
| Diagnostic criteria for HLH fulfilled five of the eight criteria below: | | |
| **1. Fever** | | Max 39 ℃ |
| 2. Splenomegaly | | - |
| **3. Cytopenia (affecting ≥2/3 lineages in peripheral blood)** | | |
| | Platelets $< 100 \times 10^9$/L | Min $15 \times 10^9$/L |
| | Hemoglobin < 100 g/L | Min 85 g/L |
| | Neutrophils $< 1.0 \times 10^9$/L | |
| **4. Hypofibrinogenemia and/or hypertriglyceridemia** | | |
| | Hypofibrinogenemia ≤ 1.5 g/L | Min 0.7 g/L |
| | Fasting triglycerides≥ 265 mg/dL | |
| 5. Hemophagocytosis in bone marrow or spleen or lymph nodes, no evidence of malignancy | | - |
| 6. Low or absent NK-cell activity | | - |
| **7. Ferritin> 500 μg/L** | | Max 1185.50 μg/L |
| **8. sIL−2r ≥ 2400 U/mL** | | Max 2415 U/mL |
| Supportive evidence is cerebal symptoms with moderate pleocytosis and/or elevated protein, elevated transaminases, bilirubin, LDH | | 1. Elevated transaminases: ALT (2891.4 U/L) , AST (431.7 U/L), LDH (5339 U/L), bilirubin (direct bilirubin (DBIL), 13.6 mol/L)<br>2. the WBC of CSF, $124 \times 10^6$/L |
| **Ecovirus 11 infection** | | |
| In blood | | + |
| In CSF | | + |

Note: CSF, cerebrospinal fluid; HLH, hemophagocytic lymphohistiocytosis; NK, natural killer; sIL-2r, soluble IL-2 receptor. AST, aspartate aminotransferase; ALT, alanine aminotransferase LDH, lactate dehydrogenase; WBC, white blood count.

We took an examination of cerebrospinal fluid (CSF) because she exhibited a sliding twitch at 6 days old, results showed elevated white blood count (WBC) and positive enterovirus, so does that of peripheral blood. The polymerase chain reaction (PCR) and further genetic sequencing showed the enterovirus was echovirus type 11 (echo 11). At day 7, the patient developed to moderate anemia with hematocrit (HCT), 0.26 L/L; and hemoglobin (HGB), 90 g/L. What's more, the PLT count and fibrinogen were $15 \times 10^9$/L and 0.88 g/L, respectively (Supplemental Table 1).

The following tests were performed because HLH was suspected (fever, cytopenia, fibrinogen 1.5 g/L, LDH > 500 U/L, and impaired hepatic function): [1] ferritin (1185.5 ng/mL), soluble interleukine-2 receptor (sIL-2r) (2415 U/mL), and 2-microglubin (5939 ng/mL). Increased megakaryocytes in the bone marrow smear cytology, while hemophagocytic macrophages were not seen. The patient's liver gradually became larger, with its edge 2.5 cm below the subcostal boundary according to the result of abdominal ultrasounds. Above all, the patient most importantly met 5 of the 8 clinical and laboratory diagnostic criteria for HLH-2004, details were shown in Table 1. [1].

The patient is receiving the following primary treatments: (i) Ampicillin and Meropenem for the treatment of an infection; (ii) mechanical breathing; (iii) intravenous immunoglobulins (IVIG) at days 6, 8, 9, and 10; (vi) Methylprednisolone for the treatment of an inflammation, given every 12 h; and (v) transfusion and coagulation factor supplementation. After the treatment at 14 days of life, hemogram gradually normalized. The patient was treated and released from the hospital after spending 21 days there, her condition was stable, and the ecchymosis had lessened. HGB, PLT, and fibrinogen tests in the lab revealed that they were all normal. (Fig. 1). In the phone interviews one month and three months after discharge, the patient's family members indicated that no significant abnormal conditions had occurred in the child.

## Discussion

We presented a premature infant who had enterovirus infection and displayed HLH symptoms. The neonate met 5 of the 8 HLH-2004 diagnostic criteria. It was the first report from central China that we are aware of.

Table 2 displays previously known neonatal cases of enterovirus-related HLH, and there were no significant gender differences among these cases. The majority of cases manifest within a period of 5 days following birth. Out of all the recorded cases, it has been observed that only two of them involve premature babies. Coxsackievirus was the most common infection in cases where enterovirus has been accurately identified, while echovirus 11 was never reported or identified. Enteroviruses are detectable in the blood in most neonatal cases. Three examples that show symptoms of HLH-like sickness but cannot be identified with HLH under the HLH-2004 diagnostic criteria, and no fever was present in these three cases. Except for the unknown case reported by Suzuki et al., all confirmed cases had bleeding or severe coagulopathy symptoms. Half of cases had hepatomegaly and/or splenomegaly. For the outcomes of these cases, only one of the eight instances perished, and the onset times for seven of the eight cases were five days after life.

In contrast to cases of familial hemophagocytic lymphohistiocytosis (FHL) and HSV linked HLH, which were reported in a statewide study of Japan, the prognosis of EV-HLH individuals looked to be significantly better [14]. However, since all of those cases were reported from outside China, it was impossible to determine the true morbidity and mortality rates for any HLH subtypes there. Therefore, additional research into HLH is required to enable early diagnosis and treatment.

Group B coxsackieviruses, and echovirus 11 are the most common causes of severe neonatal enterovirus infections [13]. The most common route of transmission for echovirus 11 in the temperate region is the fecal-oral route, with respiratory droplets serving as a minor secondary mode [8]. Following virus exposure, the respiratory and gastrointestinal epithelium undergoes initial viral replication, which is followed by viremia and coagulopathy [17]. Hepatic dysfunction may proceed to acute hepatic failure in the severe multisystemic form of newborn enteroviral infection known as coagulopathy. Clinical indicators of inflammation brought on by viralemia include elevated triglycerides and anemia. One of the most frequent symptoms of EV infection is fever, although hepatosplenomegaly may be a particular sign in cases of EV infection in newborns.

Hepatosplenomegaly, cytopenia, and protracted fever are the hallmark signs of acquired HLH. High triglycerides, transaminases, bilirubin (mainly conjugated), sIL-2r, and reduced fibrinogen are typical laboratory findings in HLH [3], and the elevated level of sIL-2r and serum ferritin were above 90 % sensitivity and specificity for HLH [18]. While diminished NK cell activity is primarily a hallmark of family cases [19] and hemophagocytosis is present in 50 % of infected HLH cases [20], decreased or absent NK cell activity and hemophagocytosis in bone marrow, CSF, or lymph nodes also support the diagnosis of HLH. The literature on newborn enteroviral infection and HLH has been examined, indicating the continuum between the inflammation caused by enteroviral infection and the formation of HLH. As documented, neonatal EV infection and HLH exhibit overlapping clinical and laboratory characteristics [12]. It's crucial to distinguish between enteroviral infection and neonatal HLH for the purposes of prognosis and treatment. As soon as HLH is suspected, tests should be run to look for hemophagocytosis in the bone marrow, as well as levels of sIL-2R, serum ferritin, and NK-cell activity.

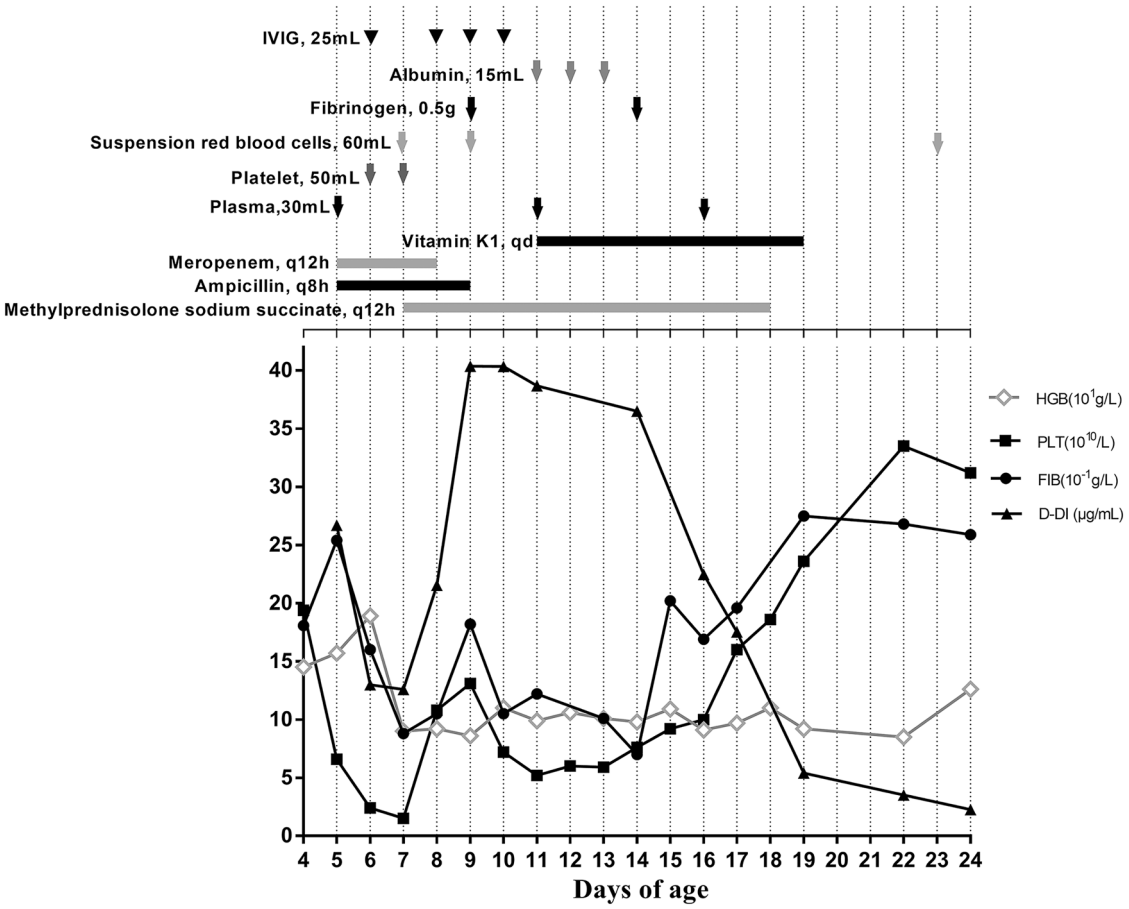


**Fig. 1.** Treatments and changes of hemogram at the time of hospitalization. On admission, the patient's changes of hemogram were watched. Fig. 1 had shown the abnormal indicators including platelet count (PLT, range: 125–350 $\times 10^9$/L), hemoglobin (HGB, range: 115–150 g/L), fibrinogen (FIB: range: 2.38–4.98 g/L), D-dimer (D-DI, range: μg/mL), monocyte count (MONO, range: 0.1–0.6 $\times 10^9$/L).

**Table 2**
Previous reported neonatal cases of *Enterovirus* complicated with hemophagocytic lymphohistiocytosis.

| Authers | Year | Sex | GA (weeks) | Onset time (days after birth ) | Matched numbers of HLH-2004 diagnostic criteria | Enterovirus | Virus isolation | Outcome | Initial symptoms | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Fever | Bleeding or severe coagulopathy | Hepatomegaly and/or splenomegaly |
| Barre et al. | 1998 | M | 39 | 3 | 5/8 | Enterovirus | Blood, CSF | Alive | + | + | + |
| Suzuki et al. | 2009 | F | 33 | 11 | 5/8 | Coxsackievirus | Unknown | Alive | + | Unknown | + |
| Lindamood et al. | 2010 | F | 41 | 0 | 4/8 | Enterovirus | Blood, CSF | Alive | - | - | + |
| Lindamood et al. | 2010 | M | 37 | 3 | 6/8 | Enterovirus | Blood | Alive | + | + | + |
| Lindamood et al. | 2010 | M | 38 | 5 | 4/8 | Enterovirus | Blood | Dead | - | - | - |
| Fukazawa et al. | 2013 | M | 35 | 4 | 4/8 | Coxsackievirus B1 | Pharynx, stool, CSF | Alive | - | - | - |
| Watanabe et al. | 2019 | M | 37 | 4 | 5/8 | echovirus 7 | CSF, Pharynx, urine, and stool | Alive | + | + | - |
| Miyoshi et al. | 2020 | F | 38 | 3 | 5/8 | coxsackievirus B3 | Nasopharyngeal, stool, blood and urine | Alive | + | + | - |

Note: GA, gestational age; CSF, cerebrospinal fluid.

While high-dose IVIG therapy has been successfully employed mostly in virus-related HLH, there is no clear consensus on any single treatment strategy for the treatment of EV linked HLH. It can inhibit immunoglobulin synthesis, inhibit immune activation, cause phagocyte Fc receptor blockage, lessen the immune response, and stop excessive cytokine release [13]. Additionally, early IVIG injection may serve as a less harmful initial substitute for chemotherapy and systemic immunosuppression for the treatment of HLH in newborns [12]. Corticoid therapy should begin as soon as feasible for newborns who have central nervous system symptoms (CNS), such as lethargy and aberrant CSF indications, at the time of diagnosis [1]. Furthermore, given the inherent cytotoxicity associated with chemotherapy, the administration of

etoposide for treating hemophagocytic syndrome in bone marrow should be carefully evaluated based on the extent of hemophagocytosis [12].

This study still has several limitations: firstly, given the need to reduce medical costs and avoid potential risks to the child patient from unnecessary tests, we have decided not to conduct further virus tests after the patient's clinical symptoms had subsided. Secondly, we did not conduct relevant genetic testing to rule out the possibility of this case being primary HLH.

## Ethical approval

This study has been approved by the Biomedical Ethics Committee of Wuhan Polytechnic University. The protocol number of Ethical approval is: BME-2023–3–105.

## Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

## Author statement

During the preparation of this work the author used "QuillBot" in order to refine the paper to make it more idiomatic. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

## Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used "QuillBot"in order to refine the paper to make it more idiomatic. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

## Conflict of Interest

None.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.idcr.2025.e02177.

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