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Case Report

A rare fatal case of a novel bunyavirus-associated hemophagocytic lymphohistiocytosis

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Abstract

Herein we describe a rare fatal case of a novel bunyavirus-associated hemophagocytic lymphohistiocytosis (HLH) in a 62-year-old female patient. The novel bunyavirus infects patients with or without HLH who have similar clinical features such as fever, thrombocytopenia, and leukocytopenia. Therefore, the diagnosis of HLH can be easily missed. When HLH occurs, the disease worsens and the fatality rate rises. Our finding highlights the importance of bone marrow biopsy performed as soon as possible for patients suspected of having a novel bunyavirus infection and showing marked cytopenia in three cell lines.

Key words: novel bunyavirus; severe fever; thrombocytopenia syndrome; hemophagocytic lymphohistiocytosis; HLH.

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Introduction

A novel bunyavirus that causes severe fever with thrombocytopenia syndrome (SFTS) is a member of *Phlebovirus* genus of the *Bunyaviridae* family [1]. It was termed SFTS virus (SFTSV), and has been reported mostly in China [1]. Patients with SFTS have severe clinical symptoms. The disease progresses rapidly to multiple organ dysfunction syndrome (MODS), with a high fatality rate of 12%–30% [1]. Infection with the virus can cause hemophagocytic lymphohistiocytosis (HLH), in which case the disease progresses and the fatality rate is increased. Patients infected with SFTSV who further developed HLH have been rarely reported in the literature.

Here, we present a case of a novel bunyavirus-associated HLH and describe a close correlation of the clinical manifestations and laboratory findings with disease severity and prognosis.

Case Presentation

The patient was a 62-year-old female farmer who lived in the hilly areas of Zhejiang province, China, and had no contact with individuals with similar clinical manifestations. She had no underlying conditions or infectious diseases, no history of drug or food allergies or blood transfusion, and no history of tick bites. Ten days before the onset of the disease, the patient had been picking tea leaves at Huangtan Village, Baishuiyang Town, Linhai City, Zhejiang Province for five days. She suffered from an insect bite on her left foot at that time. Her colleagues experienced the similar fever symptoms.

The patient had a sudden onset of fever and her body temperature reached a peak of 39.5°C, which was accompanied by muscle pain, lower abdominal pain, fatigue, drowsiness, dizziness, and loss of appetite, on 14 April 2014. On 17 April, the patient obtained medical treatment at a local hospital; she was admitted and given intravenous antibiotics, but no clinical improvement was observed. Her body temperature remained over 38.0°C and her lower abdominal pain got worse.

On 19 April, the patient was transferred to our hospital with fever, body aches, lower abdominal pain, fatigue, and drowsiness. Physical examination findings included enlarged right inguinal lymph nodes with obvious tenderness and an insect bite with a scab on her left lower limb, around 6 mm in diameter. The laboratory findings included a significantly decreased number of white blood cells and blood platelets (Table 1). The patient was clinically suspected of having SFTS. She was treated with injected imipenem and

cilastatin sodium and oral fluconazole capsules after admission.

On 20 April, the patient's body temperature remained at 38.2°C, her drowsiness got worse, and her abdominal pain extended to the whole abdomen. The laboratory findings included further decline in white blood cell counts and blood platelet counts and a prolonged activated partial thromboplastin time (APTT) (Table 1).

On 21 April, the patient's body temperature remained at 39.3°C. She had diarrhea three times and suffered from abdominal pain. Hypotension occurred, with her blood pressure measuring 81/50mmHg. The laboratory findings revealed thyroid function with TT3 0.39 ng/mL, FT3 1.7 pg/mL, TSH 0.18 uIU/mL. Antinuclear antibody and anti-neutrophil cytoplasmic antibody were normal. Results of the tests for bacteria, fungi, tuberculosis, and other viruses including human immunodeficiency virus (HIV), cytomegalovirus, *Toxoplasma gondii*, herpes simplex virus I and II were all negative. A computed tomography (CT) scan showed pulmonary exudation as well as pleural effusion on both sides (Figure 1A and 1B) and splenomegaly (data not shown). Cytological examination of bone marrow showed engulfed mature erythrocytes and erythroblasts in phagocytic histiocytes (Figure 1C).

Figure 1. A and B: CT scan of chest performed on D8 (22 April 2014) indicating exudate along bronchi on both sides of the lung (white arrow) and mild bilateral pleural effusion. C: Cytological examination of bone marrow showing phagocytic histiocytes (black arrow), which are large in size and have dense chromatin and pink cytoplasm, where phagocytosed mature erythrocytes and erythroblasts can be observed (Giemsa stain, oil lens ×1,000). D: Chest X-ray examination performed on D9 (23 April 2014) showing worsening of pulmonary exudation on both sides (black arrow), especially the areas along the heart border and in the upper parts of the lung; left side pleural effusion; heart shadow is enlarged.

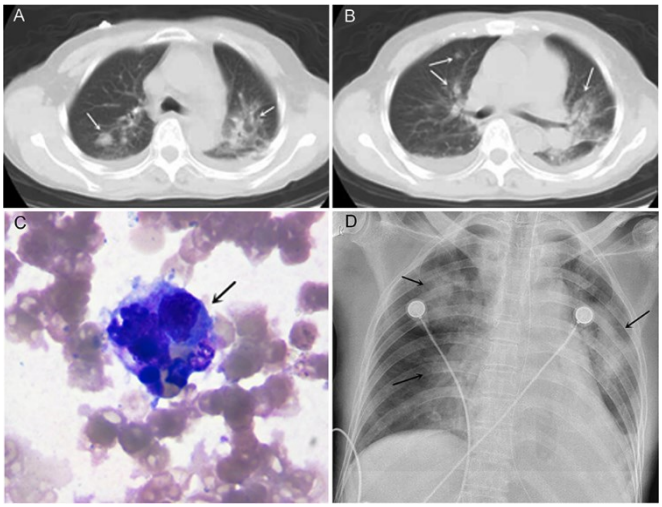


Table 1. Laboratory findings of the case of a novel bunyavirus-associated hemophagocytic lymphohistiocytosis.

Laboratory parameters	Reference value	D5 (4.19)	D6 (4.20)	D7 (4.21)	D8 (4.22)	D9 (4.23) Death
WBC ($\times10^9$/L)	3.5–9.5	1.0	0.5	0.4	1.0	2.8
NEUT ($\times10^9$/L)	1.8–6.3	0.71	0.70	0.2	0.3	1.1
LYMPH ($\times10^9$/L)	1.1–3.2	0.22	0.23	0.2	0.6	1.3
PLT ($\times10^9$/L)	125–350	33	33	25	18	26
Red cell count ($\times10^{12}$/L)	3.8–5.1	4.06	3.7	3.8	3.52	3.12
HGB (g/L)	115–150	115	108	109	111	98
ALT (U/L)	7–40	30	42	179	/	/
AST (U/L)	13–35	/	120	533	/	/
LDH (U/L)	103–227	/	355	595	/	170
CK (U/L)	< 167	/	174	385	/	/
CR (μmol/L)	40–88	53	35	52	/	/
BUN (mmol/L)	1.78–7.14	5.6	4.52	3.36	/	/
TT (Second)	14.0–21.0	/	20.6	28.3	/	45.5
PT (Second)	11.0–14.5	/	14.5	13.6	/	16.7
APTT (Second)	28.0–42.0	/	63.3	72.5	/	111.4
D2 (mg/L)	0.00–0.50	/	/	6.40	/	2.03
Fibrinogen (g/L)	2.0-4.0	/	2.4	2.2	/	1.5
Positive urine protein	(-)	/	1+	/	/	2+
Occult blood in urine	(-)	/	(-)	/	/	(-)
Occult blood in stool	(-)	/	/	(-)	/	(-)

D: day of illness; WBC: white blood cell; LYMPH: lymphocyte; NEUT: neutrophil; PLT: platelet; HGB: hemoglobin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; CK: creatine kinase; CR: creatinine; BUN: blood urea nitrogen; TT: thrombin time; PT: prothrombin time; APTT: activated partial thromboplastin time; D2: d-dimer.

At 8:20 p.m. on 21 April, the patient suffered from dyspnea and respiratory failure. Her arterial partial pressure of oxygen (PaO_2) declined to 58 mmHg and saturation of oxygen (SaO_2) to 89%. A certain degree of improvement was achieved after the patient received oxygen treatment through a face mask and medications for raising blood pressure, as well as recombinant human granulocyte-macrophage colony stimulating factor.

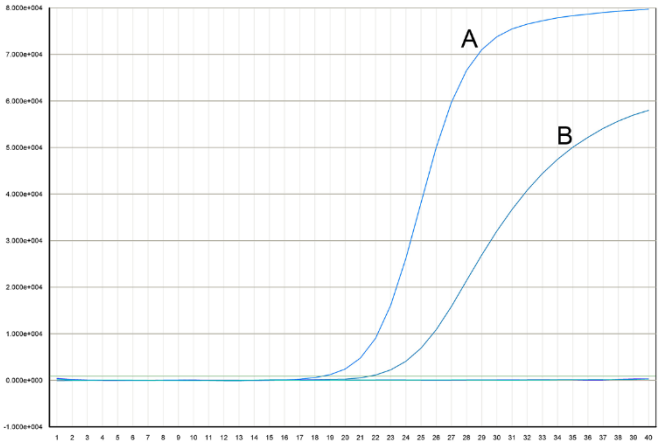
On 22 April, the patient experienced worsening of dyspnea and abdominal pain, especially right lower abdominal pain. Her body temperature remained at 38.7°C. She also experienced gum bleeding and lack of alertness. Her blood pressure declined to 87/57 mmHg. The patient was transferred to the respiratory intensive care unit, where injections of imipenem, cilastatin sodium, vancomycin, and ribavirin were administered, along with and doxycycline tablets. The patient also received fresh frozen plasma therapy and other supporting and symptomatic treatments but did not show any improvement.

On the morning of 23 April, the patient became unconscious and experienced shortness of breath. Her heart rate declined, her SaO_2 was 80%, and anuria occurred. Large areas of ecchymosis could be seen in groin areas where blood had been drawn previously. Mucosal active bleeding occurred in her oral and nasal cavity, and pneumorrhagia was observed. The patient suffered from a severe coagulation disorder. The laboratory test results revealed APTT 111.4 s, hemoglobin 98g/L, fibrinogen 1.5g/L, brain natriuretic peptide 801 pg/mL, and troponin I (TnI) 0.553 ng/mL. An ultrasound scan of the groin showed significant swelling of the subcutaneous soft tissues. Chest X-ray indicated increase in pulmonary exudate on both sides (Figure 1D).

Thereafter, the patient was treated with prednisone, blood red cells and plasma transfusion, as well as mechanical ventilation through a tracheal cannula, but she died at 12:00 p.m. on 23 April.

Blood samples collected on the day of death were sent to the Center for Disease Control and Prevention of Taizhou, and the pathogen was confirmed as SFTSV by real-time quantitative polymerase chain reaction (Figure 2). It was concluded that the patient was infected by a novel bunyavirus, which caused fever and thrombocytopenia. She suffered from HLH and died of multiple organ failure, including renal and respiratory failure, as well as disseminated intravascular coagulation.

Figure 2. The amplification curve of real-time quantitative polymerase chain reaction. A: Positive control of SFTSV with Ct value 18.44. B: Patient's serum sample with Ct value 21.56.



Discussion

Novel bunyavirus-associated HLH is rare and has been reported mostly in China [2-4]. Our case documents the diagnosis of HLH due to infection with a novel bunyavirus. Novel bunyavirus-associated HLH often progresses rapidly with significantly decreased blood platelet counts, and those infected tend to suffer from multi-organ failure.

HLH demonstrates a clinical inflammatory syndrome, which results from uncontrolled activation and excessive proliferation of lymphocytes and mononuclear macrophages, leading to a phagocytosis and cytokine storm. It is characterized by fever, hepatomegaly, splenomegaly, and low complete blood cells. Virus or bacterial infection and lymphoma are relatively common causes of HLH, and Epstein-Barr virus is found to be the predominant viral pathogen [5]. In addition, a recently reported case of HLH outside of China resulted from a brown recluse spider bite [6]. The case we reported was diagnosed with HLH resulting from a novel bunyavirus infection. The patient worked in wooded and hilly areas. There was an insect bite on her left lower limb, which was considered to be a tick bite, suggesting that HLH in this patient resulted from infection with a novel bunyavirus, which was consistent with the previously reported cases in China [2-4]. We performed a series of screening tests and excluded hepatitis B virus, hepatitis C virus, HIV, cytomegalovirus, and Epstein-Barr virus infection. In addition, the results from blood, sputum, and bone marrow cultures were all negative.

The diagnosis of HLH in this patient was made according to the diagnostic criteria established by the Histiocyte Society in 2004 [7]. Since the cause of HLH in this patient was confirmed to be a novel bunyavirus

infection, the final diagnosis was novel bunyavirus-associated HLH. The clinical findings in line with the diagnostic criteria for HLH in this patient included fever, hemorrhage, central nervous system disorder, cytopenia of two cell lines, coagulation disorder, decreased fibrinogen, increased ferritin, increased aminopherases, increased bilirubin, decreased albumin, and hemophagocytosis in the bone marrow. Novel bunyavirus-associated HLH often progresses rapidly, with remarkable cytopenia of three cell lines and a high fatality rate. The hemophagocytic macrophages will further decrease the cell number in the three cell lines. Patients with SFTS will have significantly decreased blood platelet counts and tend to suffer from multi-organ failure, which eventually leads to death [8].

Novel bunyavirus-infected patients with or without HLH will have similar clinical features such as fever, decreased white blood cells, and decreased blood platelets; therefore, the diagnosis of HLH can be easily missed and patients cannot receive appropriate treatment. The treatment effect is difficult to evaluate because of the small number of cases. Ribavirin is an effective treatment for bunyavirus infection *in vitro* [9], but not in clinical trials. In some cases, short-term chemotherapy was utilized and the patients recovered [3]. However, this kind of therapy is controversial and needs further clarification. The therapy for the disease is mainly the combination of underlying condition treatment and supporting treatment. In cases of secondary or concurrent infection with Rickett's organism, bacteria or fungi occurs and specific antibiotics must be used. HLH is a life-threatening disease and progresses rapidly.

For secondary HLH, the top priority is to determine the cause of the disease. Any underlying conditions should be treated when supporting treatment is given. The remission of the underlying conditions will play a positive role in the treatment of HLH.

Conclusions

Novel bunyavirus infection can cause damage to various organs and systems, leading to dysfunction of these organs and systems, and even to death. For patients with SFTS, if there is a history of tick bite or epidemic, the test for novel bunyavirus should be performed immediately. For patients suspected of having a novel bunyavirus infection and showing marked cytopenia in three cell lines, bone marrow biopsy should be performed as soon as possible.

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