

Hemophagocytic lymphohistiocytosis due to *Streptococcus suis* in a 12-year-old girl

A case report

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Abstract

Rationale: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome that can be caused by bacterial infection. *Streptococcus suis* (*S. suis*) is a zoonotic pathogen that can cause severe disease in both pigs and humans. We report the first-ever documented case of HLH secondary to *S. suis* infection.

Patient concerns: A 12-year-old girl presented with fever, rash, hepatosplenomegaly, pancytopenia, and elevated levels of ferritin and soluble CD25. Bone marrow examination revealed hemophagocytosis. Blood culture was positive for *S. suis*.

Diagnosis: A diagnosis of hemophagocytic syndrome due to *S. suis* was established.

Interventions: We treated the patient with intravenous immunoglobulin, intravenous imipenem, and supportive care.

Outcomes: The patient eventually showed complete recovery.

Lessons: Inflammatory response plays an important role in *S. suis* infection. Aberrant inflammatory response to *S. suis* infection may induce HLH. This case report illustrates that early definitive diagnosis and prompt treatment is a key imperative in patients with suspected *S. suis* infection.

Abbreviations: CRP = C-reactive protein, EBV = Epstein-Barr virus, HLH = Hemophagocytic lymphohistiocytosis, NK = natural killer.

Keywords: children, hemophagocytic lymphohistiocytosis, infection, pancytopenia, *Streptococcus suis*

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome that results from a highly stimulated but ineffective immune response to antigens. HLH is of 2 different forms: primary and secondary HLH. The condition is associated with various infections. The infectious triggers include viruses, bacteria, parasites, and fungi.^[1–3] Among these, Epstein-Barr virus (EBV) is the most frequent trigger. *Streptococcus suis* (*S. suis*) is a zoonotic pathogen that can cause severe disease in both pigs and humans. Till date, there are no case reports on *S. suis* infection associated with HLH in the

published literature. Herein, we describe the first case of HLH secondary to *S. suis* infection in a previously healthy girl.

2. Case presentation

A 12-year-old previously healthy girl had a 6-day history of fever (T_{\max} 39.5°C) with chills and did not respond to treatment administered at a local clinic. Skin rash was present 1 day before admission to our hospital. During her illness, a pig reared by her family died from infection, with ecchymosis in its ear. Physical examination of the patient revealed dense, rice grain-sized rash over her face and trunk; however, there was no superficial lymph node enlargement. Slightly hyperemic pharynx and mild swollen tonsils were observed. Abdominal examination revealed hepatosplenomegaly. Patient has provided informed consent for publication of the case.

Laboratory tests showed leukopenia (white blood cell [WBC] count $1.05 \times 10^9/L$), neutropenia (neutrophils [N] count $0.68 \times 10^9/L$), thrombocytopenia (platelet count $71 \times 10^9/L$), and anemia (hemoglobin 96g/L). Additionally, elevated levels of lactate dehydrogenase, α -hydroxybutyric dehydrogenase, cholinesterase, liver enzymes, ferritin, and C-reactive protein were observed. Blood glucose, triglycerides, prothrombin time, activated partial prothrombin time, erythrocyte sedimentation rate, and reticulocyte counts were normal (Table 1). Serum antibodies for hepatitis B and C, HIV, EBV, and T-SPOT TB test were negative. Serology tests for Widal reaction, Brucella sp., toxoplasmosis and hemorrhagic fever viruses were negative. Autoantibodies (anti-nuclear, anti-endothelial cell, anti-smooth muscle cell antibodies) and Coombs' tests were also negative. Serum level of soluble CD25 (interleukin [IL]-2 receptor, normal

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Table 1**Results of laboratory investigations.**

Laboratory parameter	Results	Reference range
Lactate dehydrogenase (U/L)	1384	120–250
α -hydroxybutyric Dehydrogenase (U/L)	288	78–182
Serum aspartate Aminotransferase (U/L)	48.9	15–35
Serum alanine Aminotransferase (U/L)	57	7–40
Serum cholinesterase (U/L)	3262	4300–12000
Triglycerides (mmol/L)	1.02	0.28–1.80
Fibrinogen (g/L)	2.35	2–4
Reticulocyte (%)	1.49	0.59–2.07
Ferritin (μ g/L)	605.0	20–200
C-reactive protein (mg/L)	11.70	0–3

range: 223–710 U/mL) was 3817 U/mL, and low natural killer (NK) cell activity was observed. Chest and abdominal computed tomography revealed mild inflammation in right middle lung, splenomegaly, and scattered lymph nodes in the abdominal cavity and retroperitoneum. Bone marrow examination showed evidence of hemophagocytosis (Fig. 1). Increased proportion of peripheral lymphocytes was observed; the proportion of peripheral blood atypical lymphocytes was 6%, and toxic granules in neutrophils were increased.

A diagnosis of septicemia, pneumonia, hepatic lesion, and HLH was considered and she was managed with azithromycin, cefoperazone/sulbactam, compound glycyrrhizin, and intravenous immunoglobulins for 3 days. However, she failed to respond to treatment. Therefore, cefoperazone/sulbactam was substituted by imipenem. After 2 days, she no longer suffered from fever and the rash was gradually fading. Blood tests indicated WBC count $1.50 \times 10^9/L$, N count $0.71 \times 10^9/L$, hemoglobin 94 g/L, and platelet count $134 \times 10^9/L$. Blood culture was positive for *S. suis*; antibiotic susceptibility testing showed sensitivity to imipenem. Hence, she continued to receive intravenous imipenem for 10 days. At the time of discharge, she had completely recovered with no fever or rash. The laboratory tests indicated WBC count $2.28 \times 10^9/L$, N count $1.15 \times 10^9/L$, hemoglobin 108 g/L, platelet count $248 \times 10^9/L$, and ferritin 228.8 μ g/L. Blood culture was negative. Her blood counts, blood biochemistry, coagulation profile, and soluble

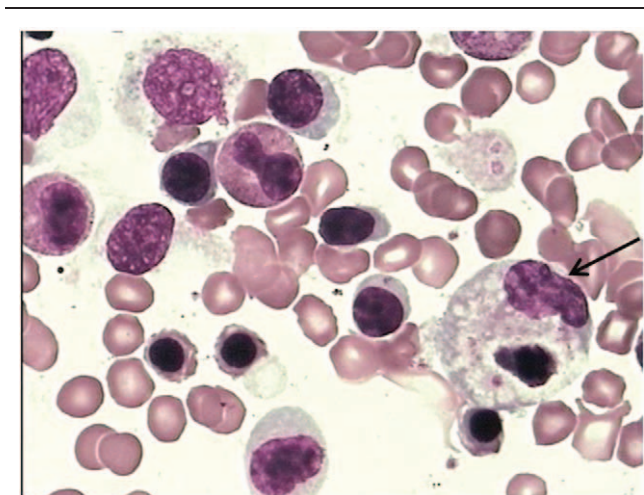


Figure 1. Bone marrow smear of the patient showing hemophagocytosis. Arrow shows a macrophage engulfing blood cell.

CD25 levels were normal on follow-up examination at 1 month and 3 months after discharge.

3. Discussion

A previously healthy girl presented with fever, hepatosplenomegaly, pancytopenia (anemia, leucopenia, and thrombocytopenia), elevated ferritin, low NK cell activity, elevated soluble CD25, and hemophagocytosis in bone marrow. The diagnosis of hemophagocytic syndrome was established as the patient qualified 7 of the 8 criteria proposed by the Histiocyte Society.^[4]

HLH usually occurs in association with various underlying genetic and/or acquired conditions. HLH frequently develops in patients with underlying genetic disease. However, in this case, there were no strong indications for a genetic predisposition, such as familial disease or recurrent episodes of HLH. Therefore, the patient was classified as a case of “secondary” HLH. There was no evidence of malignancy (such as leukemias or lymphomas), metabolic or autoimmune disease as the potential trigger for “secondary” HLH. The most common form of “secondary” HLH, that is, infection-associated HLH, was the likely cause of “secondary” HLH. This is supported by the recent history of death of a pig reared by the family, ostensibly due to infection, positive blood culture for *S. suis*, and complete recovery with intravenous imipenem therapy. Based on the above, a diagnosis of hemophagocytic syndromes secondary to *S. suis* was established. Other infectious triggers for “secondary” HLH have been described such as EBV, HIV, human herpes virus, cytomegalovirus, varicella zoster, herpes simplex, influenza, and parainfluenza and measles virus; besides these, there have been several bacterial etiologies, such as *Mycobacteria*, *Brucella*, *Rickettsia*, *Haemophilus influenzae*, and *Serratia* sp.^[5–13]

S. suis is an ovoid-shaped gram-positive coccus that forms short chains. To date, 35 serotypes of *S. suis* have been described, of which, serotype 2 is a major and virulent human and pig pathogen.^[14] Schwerk et al^[15] reported that *S. suis* infection is associated with release of pro-inflammatory cytokines and chemokines (e.g., IL6 and IL8). de Greeff et al^[16] reported significantly altered expression of macrophage-specific genes (IL-1- β , MIP-2- α , and TNF- α) in the setting of *S. suis* infection, which suggests that MAP-kinase signaling pathway and NF- κ B signaling are associated with the response of porcine alveolar macrophages to *S. suis* infection. Apparently, the inflammatory response plays an important role in *S. suis* infection. Hence, *S. suis* infection may induce HLH owing to aberrant inflammatory response.

Additionally, immunosuppressive conditions can predispose persons to *S. suis* infection^[17]; the 12-year-old girl with a normal immune system may have been susceptible, owing to the generally low immunity during childhood like other children. The most common clinical manifestations of *S. suis* infection in humans are bacteremia and/or septicemia, meningitis, endocarditis, arthritis, endophthalmitis, and spondylodiscitis;^[18] a case of pneumonia has also been reported earlier.^[19] Septicemia and pneumonia were observed in our patient. Because of the successful treatment, complications that are associated with high mortality were not found in the girl.

4. Conclusion

This case report describes a previously healthy girl who developed HLH secondary to *S. suis* infection. She fully recovered with intravenous immunoglobulins, intravenous imipenem, and supportive care, without HLH protocol. Our experience with this

patient suggests the need for a high index of suspicion for diagnosis of HLH due to *S. suis* in HLH patients who have a history of porcine exposure before the onset of symptoms. It also reminds us not to delay treatment while waiting for a definitive diagnosis of HLH, owing to the risk of potentially serious complications such as secondary sepsis with multi organ dysfunction and failure with high mortality. In other words, once *S. suis* infection is suspected, immediate steps should be taken to make a clear diagnosis and institute prompt treatment.

Author contributions

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