Short Communication

A Case Report of Scrub Typhus-Associated Hemophagocytic Syndrome and a Review of Literature

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SUMMARY: A 34-year-old woman presented with septic shock, disseminated intravascular coagulation (DIC), and multiorgan dysfunction with a 1-week history of fever, abdominal pain in the right upper quadrant, and dull pain in the right flank. Physical and laboratory data showed cytopenia (thrombocytopenia and anemia), splenomegaly, hyperferritinemia, hypofibrinogenemia, and an elevated level of interleukin-2 receptor (soluble CD25). Bone marrow examinations disclosed hypercellular marrow with increased infiltration of histiocytes with hemophagocytosis. This diagnosis was confirmed by positive Weil-Felix test results (*Proteus mirabilis* OX-K titer, 1:80), the presence of IgG and IgM antibodies, and positive PCR results for *Orientia tsutsugamushi*. The patient developed a severe intracranial hemorrhage 3 days after admission and expired due to systemic inflammatory response syndrome with DIC and multiorgan failure on the 13th day of hospitalization. Scrub typhus with hemophagocytic syndrome can be complicated by DIC and multiorgan failure. Patients with scrub typhus usually have an excellent response to treatment; therefore, early diagnosis and prompt administration of antimicrobial therapy may prevent the development of serious complications.

Scrub typhus is a rickettsial disease, which is caused by *Orientia tsutsugamushi*. This disease is endemic in many Asian countries, including China, Japan, Korea, Taiwan, and others in southeast Asia (1). A diagnosis of scrub typhus can be confirmed by positive labeling with immunofluorescent antibodies and polymerase chain reaction (PCR) analysis (1). Tetracycline is the drug of choice. Mortality rates of untreated patients range from 0 to 30% (1). Causes of death include shock, acute renal failure, acute respiratory failure, multiorgan failure, and disseminated intravascular coagulation (DIC) (1,2).

Hemophagocytic syndrome (HPS), also called hemophagocytic lymphohistiocytosis (HLH), is caused by dysregulation of natural killer T-cell function, thereby resulting in activation and proliferation of lymphocytes or histiocytes with uncontrolled hemophagocytosis and cytokine overproduction (3). HLH is a rare but severe complication of scrub typhus (4–9). Here, we report a case of scrub typhus associated with HLH and review 6 reports of 7 patients from literature (4–9). The present study was approved by the Institutional Review Board of Taichung Veterans General Hospital (CE13024).

A 34-year-old woman presented with septic shock, DIC, and multiorgan dysfunction with a 1-week history of fever, abdominal pain in the right upper quadrant, and dull pain in the right flank area. Her medical histo-

ry included drug abuse and hepatitis C infection. On physical examination, she appeared irritable and had a temperature of 39.7°C, a heart rate of 120 beats/min, a respiration rate of 24 breaths/min, and a blood pressure of 92/58 mmHg. She exhibited no abnormal signs of lymphadenopathy and eschar, except for a positive Murphy sign. Splenomegaly was not palpable due to obesity and abdominal distension. Laboratory test results showed that both prothrombin and partial thromboplastin times were prolonged. Blood biochemical test results were as follows: aspartate aminotransferase, 152 U/L; alanine aminotransferase, 87 U/L; total bilirubin, 2.2 mg/dL; direct bilirubin, 1.1 mg/dL; lactic dehydrogenase, 535 mg/dL; triglyceride, 113 mg/dL; fibrinogen, 76.1 mg/dL; D-dimer, 9.52 µg/mL; fibrin degradation products, 27.4 µg/mL; ferritin, 3,212 µg/L; and interleukin-2 receptor (soluble CD25) level, >5,000 pg/mL. Three days after admission, laboratory data showed a leukocyte count of 3,500 cells/µL, a hemoglobin level of 8.4 g/dL, and 16×10^3 platelets/µL. Because of abnormal liver function tests, abdominal computerized tomography was performed, which showed splenomegaly (13.7 cm) and gall bladder distension. Percutaneous drainage of the gall bladder was performed and the drained bile was clear. Bile and blood cultures did not yield bacterial growth; therefore, acute cholecystitis or cholangitis was unlikely.

Antibody test results for *Leptospira* were negative, whereas those of the Weil-Felix agglutination test for the diagnosis of rickettsial infections were positive (*Proteus mirabilis* OX-K titer, 1:80). Serological results were positive for IgM (>1:160) and IgG (>1:640) antibodies against *O. tsutsugamushi*, and PCR analysis results for *O. tsutsugamushi* were also positive. A bone

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Fig. 1. (Color online) Bone marrow examinations disclosed hypercellular marrow with increased infiltration of histiocytes with hemophagocytosis ([A] The arrows indicate phagocytosis of erythrocytes by histiocytes in histology; [B] The arrow indicates phagocytosis of platelets by histiocytes in cytology).

marrow examination revealed hypercellular marrow with increased infiltration of histiocytes with hemophagocytosis (Fig. 1). Results for both Epstein-Barr virus (EBV)-VCA IgM and cytomegalovirus (CMV) IgM were positive. On the 1st day of hospitalization, mechanical ventilation and hemodialysis were initiated for treatment of multiorgan failure. Ceftriaxone (2,000 mg once a day) and minocycline (100 mg every 12 h) were started as empiric therapy. However, she developed a severe intracranial hemorrhage (ICH) due to progressive DIC 3 days after admission and expired because of systemic inflammatory response syndrome with DIC and multiorgan failure on the 13th day of hospitalization.

This patient presented with fever, cytopenia for 2 lineages (thrombocytopenia and anemia), splenomegaly, hyperferritinemia, hypofibrinogenemia, and an elevated interleukin-2 receptor (soluble CD25) level. A bone marrow biopsy revealed hemophagocytosis. A diagnosis of HLH was made according to the HLH-2004 diagnostic and therapeutic guidelines (10). The diagnostic criteria of HLH include fever, cytopenia, splenomegaly, hypertriglycemia or hypofibrinogenemia, tissue biopsy-confirmed hemophagocytosis, hyperferritine-

mia, low or absent natural killer cell cytotoxicity, and elevated CD25 levels. A diagnosis of hemophagocytosis requires the presence of 5 of the above 8 criteria (10). HPS is associated with cytokine overproduction, which subsequently may lead to DIC and multiorgan failure. Therefore, it is important to differentiate HPS from other causes of DIC. In addition to these 8 criteria, other abnormal clinical and laboratory findings are also consistent with a diagnosis of HLH, including cerebromeningeal symptoms, lymph node enlargement, jaundice, skin rash, hepatic enzyme abnormalities, increased very low-density lipoprotein, and decreased high density lipoprotein (10). The key indicator of an accurate diagnosis is the presence of hemophagocytosis in bone marrow biopsy.

HLH comprises 2 different clinical spectrums that may be difficult to distinguish from one another: a primary (familial) and a secondary form (10). Secondary HLH consists of various conditions associated with infection (3,11), autoimmune disorders (12), and malignancy (13). The most common pathogens reported to cause HLH include EBV, CMV, human immunodeficiency virus (HIV), and mycobacterium (3,14). A diagnosis of virus-associated HPS depends on serology, virus culture, and quantitative PCR analyses. The serological results of this patient were positive for EBV-VCA IgM and CMV IgM but negative for HIV. PCR was not performed to confirm the presence of CMV and EBV. The seroprevalence rates of CMV and EBV are relatively high in Taiwan (15,16). An earlier study reported that the seropositive rates of CMV IgG and IgM among 483 mothers were 91.1% and 3.5%, respectively, in Taiwan (15). Therefore, a limitation to the present study was that diagnosis of HLH could not be confirmed by a single positive serology test in an area with a high prevalence of EBV and CMV infections.

Our patient expired due to systemic inflammatory response syndrome with DIC and multiorgan failure. The clinical signs and symptoms, diagnosis, and response to treatment as well as the laboratory data of our patient and 7 previously reported cases were summarized as follows: fever, 100%; palpable lymph nodes, 50%; eschar, 50%; skin rash, 37.5%; seizure, 12.5%; pulmonary hemorrhage, 12.5%; hepatosplenomegaly, 37.5%; splenic infarction, 12.5%; respiratory failure, 25%; thrombocytopenia, 100%; leukocytopenia, 37.5%; anemia, 25%; DIC, 37.5%; abnormal liver function tests, 62.5%; and elevated ferritin level, 37.5%. All patients were diagnosed by positive immunofluorescence test for *O. tsutsugamushi* (IgM) and hemophagocytosis by bone marrow biopsies (4-9).

A potentially fatal cytokine storm is characteristic of HLH. The HLH-2004 guidelines propose a treatment protocol with or without evidence of familial or genetic disease, regardless of documented or suspected viral infections (10). The initial recommended therapy includes dexamethasone, etoposide, and cyclosporin A administration for the first 8 weeks (10). This treatment protocol is mainly based on the clinical data of familial HLH. Secondary HLH is a very complicated syndrome that has various causes and is characterized by critical clinical presentation and varied treatment responses (13,17). However, therapeutic strategies for secondary HLH are not well established. Among the previous 7

scrub typhus cases complicated with HPS, 5 were treated doxycycline (or minocycline) alone; 1 with clarithromycin, dexamethasone, and etoposide; and 1 with doxycycline and dexamethasone. All of these 7 patients survived. Our patient died despite receiving treatment with minocycline and dexamethasone. Etoposide was not used for this patient because we were concerned about etoposide-induced neutropenia, which could have been fatal because of the development of ICH. According to the previous case reports, some patients responded well to treatment with tetracycline alone or combined with dexamethasone (4–9). Early use of dexamethasone could be helpful for the control of systemic inflammatory response syndrome; however, there were too few patients to draw any conclusions. Thus, further studies are required to confirm a therapeutic strategy for scrub typhus with HPS (10).

The mortality rate of HPS for all cases ranged from 22% to 60% (17–19). Early diagnosis and treatment could improve the clinical outcomes and reduce complications of HLH in children (20). This patient arrived at our hospital too late and presented with late-stage HPS (DIC, ICH, and multiorgan failure). Therefore, she failed to respond to minocycline and steroid treatment because HPS progresses rapidly and has a high mortality rate despite appropriate management (21,22).

Serious complications of scrub typhus, such as meningoencephalitis, pneumonia, myocarditis, acute renal failure, and gastrointestinal bleeding, are not uncommon and may be fatal (2,23). Scrub typhus with HPS can be further complicated by DIC and multiorgan failure (17). However, early diagnosis of scrub typhus and antimicrobial therapy may prevent the development of serious complications because patients usually demonstrate an excellent response to treatment.

Conflict of interest None to declare.

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