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Fatal hemophagocytic lymphohistiocytosis-induced multiorgan dysfunction may secondary to Burkholderia pseudomallei sepsis: A case report

Burkholderia pseudomallei sepsis associated with hemophagocytic lymphohistiocytosis:A case report and literature review

Abstract

BACKGROUND

Burkholderia pseudomallei (BP) is a short, straight, medium-sized gram-negative coccobacterium that mostly exists alone, without a capsule or spores, has more than three flagella at one end, and actively moves. BP confers high morbidity and mortality, with frequent granulocytopenia in BP sepsis-related deaths. However, mortality may be related to hemophagocytic lymphohistiocytosis (sHLH) secondary to BP infection.

CASE SUMMARY

A 12-year-old girl was referred from a local hospital to the pediatric intensive care unit (PICU) with suspected septic shock and fever, cough, dyspnea, and malaise. After admission, supportive symptomatic treatments including fluid resuscitation, anti-infective therapy, mechanical ventilation, and a vasoactive drug maintenance cycle were carefully initiated. The patient became unconscious, blood pressure could not be maintained even uder the exposure of vasoactive drugs, and had a cardiorespiratory arrest. The patient died due to ineffective high-quality in-hospital cardiopulmonary resuscitation was ineffective. A subsequent bone marrow smear examination revealed extensive phagocytosis, and the blood culture was positive for BP. Family history revealed a sibling death from BP sepsis 5 years earlier.

CONCLUSION

The higher mortality rate in patients with BP sepsis may be related to secondary HLH after infection, wherein multiorgan dysfunction syndrome may be directly related to infection or immune damage caused by sHLH. Patients with BP can be asymptomatic, and can become an infective source.

Key Words: Burkholderia pseudomallei; sepsis; septic shock; Hemophagocytic lymphohistiocytosis; Asymptomatic carrier; Case Report

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Core Tip: Given the high mortality rate associated with BP, it is particularly important to fully understand the pathogenesis. This report presents the clinical characteristics of a case of BP infection and some clinical data of the patient's brother, who also died from BP infection. The chronic carrier status of BP and secondary HLH warrants attention in the pathogenesis and treatment of BP sepsis.

INTRODUCTION

Burkholderia pseudomallei (BP) is a non-fermentative gram-negative bacterium that is positive for oxidases and enzymes, does not form spores, and does not contain metachromatic particles. Approximately 165,000 cases of BP infection and 89000 deaths are reported annually worldwide. The incidence rates in South and East Asia and the Pacific are 44% and 40%, respectively, and the mortality rates are 47% and 35%, respectively[1]. Sequential dysfunction of two or more organs usually referred as Multiorgan dysfunction syndrome (MODS). MODS caused by sepsis likely contributes

to the high mortality rates associated with BP infections. However, granulocytopenia, which is common in areas where such cases have been reported, has been largely neglected. Combined with the clinical data on elevated ferritin levels, there is a need to examine the status of hemophagocytosis in deaths due to BP[2].

Herein, we describe the clinical characteristics of a patient infected with BP and the clinical data of her brother, who died from the same illness.

CASE PRESENTATION

Chief complaints

A 12-year-old girl was transferred from a local hospital to our PICU with 4 days of fever, cough for 2 days, and dyspnea and malaise since 1 day.

History of present illness

Before the patient was transferred to the PICU ward of our hospital 4 days later, the patient had a very high fever (>40.0 °C) and was administered oral antibiotic treatment after a routine blood examination in the local clinic; however, the patient's parents were unaware of the type of antibiotics administered. After treatment, the patient developed a high fever, cough, and other new symptoms. Routine blood examination at a local hospital indicated that the patient had agranulocytosis, and blood cell and platelet levels were significantly lower than those in the last test. After receiving ceftazidime at the hospital, the body temperature remained high, and dyspnea and fatigue persisted. Arterial blood gas analysis suggested lactic acidosis, indicating that the patient was experiencing consolidated septic shock.

History of past illness

The patient denied a history of hepatitis, tuberculosis, measles, mumps, or other common infectious diseases. The patient had no history of surgery, trauma, or blood transfusions.

Personal and family history

The patient did not have a history of preterm delivery, birth asphyxia, intrauterine hypoxia, intrauterine conditions, or infection. The patient's brother died 5 years earlier due to BP sepsis and septic shock (results of laboratory tests are shown in Table 1).

Physical examination

Body temperature, respiratory rate, and heart rate were 37.5 °C, 34 times/min, and 146 times/min, respectively. Furthermore, the body weight was 40 kg and skin oxygen saturation was 87% on room air. The patient's mentality was depressed. Both pupils were equal in size, and responsive to light. The nasal wings were flapped, the lips were cyanotic, breathing was rapid, the three concave signs were positive; auscultation revealed dense moist rales. Heartbeat sounds were low. The liver and spleen were palpable under the costal margin (1.5 cm below the right midclavicular costal margin and 1.5 cm below the left midclavicular coastal margin, respectively). The extremities were cold, and CRT was performed for 6 s; however, no obvious abnormality was observed in the neurological examination.

Laboratory examinations

Routine blood tests revealed agranulocytosis, thrombocytopenia, and anemia. Arterial blood gas analysis revealed sustained hypoxia and acidosis. Monitoring of coagulative parameters indicated hypofibrinogenemia. The levels of CRP, PCT, ESR, and other inflammatory indicators significantly increased. A complete biochemical examination revealed varying degrees of multiorgan dysfunction. The levels of interleukin and inflammatory factors, such as ferritin, were higher than normal, and no biomarkers related to hemophagocytic syndrome were found in the whole-exon test (described in Table 2).

Imaging examinations

Chest radiography revealed exudative lesions in both lungs (Figure 1).

Bone marrow smear

Bone marrow smear shows hemophagocytosis (Figure 2)

FINAL DIAGNOSIS

The patient was finally diagnosed with BP sepsis, septic shock, MODS, acute respiratory distress syndrome (ARDS), respiratory failure, severe pneumonia, metabolic acidosis, disseminated intravascular coagulation (DIC), electrolyte metabolism disorder, agranulocytosis, and thrombocytopenia, with a high suspicion of sHLH.

TREATMENT

Meropenem was initiated and the patients was immediately administered a 2:1 isotonic solution to expand the volume twice along with nasal catheter oxygen inhalation (oxygen flow ≤5 L/min). We established a femoral vein infusion path to simultaneously implement subsequent fluid support simultaneously. As the blood pressure of the patient cannot be maintained after volume expansion, and the analysis of arterial blood gas indicates continuous hypoxia due to irregular spontaneous respiration, we gave norepinephrine 0.5 μg/kg/min continuous pumping to maintain blood pressure and invasive mechanical ventilation with endotracheal intubation (PC-SIMV mode: FiO_2 60%, VT 300 mL, PEEP 5 cmH_2O, RR25 times/min). Supportive treatments, such as granulocyte-stimulating factor, plasma, coagulation factor cryoprecipitate, and suspended red blood cells, were also administered. Nevertheless, the patient experienced respiratory and cardiac arrest 4 h after admission, and a pink foam-like liquid gushed from the endotracheal tube. After cardiopulmonary resuscitation and intravenous morphine administration, the patient recovered heart rate, but the results of arterial blood gas analysis worsened (Table 2). In addition to hypoxia, the patient had serious carbon dioxide retention; we changed the invasive mechanical ventilation mode

to high-frequency mode (FiO_2 60%, average airway pressure 35 cmH_2O, amplitude 75 cmH_2O, sighing time 0.3s, frequency 7 Hz). After the above rescue, the patient's condition continued to deteriorate, and norepinephrine (1 μg/kg/min) combined with dopamine (6 μg/kg/min) still failed to maintain normal blood pressure. The patient's consciousness gradually turned into coma, and diffuse bleeding spots appeared on the whole-body skin. We urgently punctured the bone marrow, injected vitamin K1, ethylphenesulfonate, and snake venom hemocoagulase to stop bleeding, and added m-hydroxylamine to raise the blood pressure. At the same time, we also actively administered bedside blood purification treatment and adjusted norepinephrine to 1.4 μg/kg/min, dopamine to 12 μg/kg/min, and m-hydroxylamine to 2 μg/kg/min during continuous renal replacement therapy (CRRT) The patient's blood pressure remained unstable, and the maintenance of transcutaneous oxygen saturation was unsatisfactory. After 12 h of hospitalization, the patient died.

OUTCOME AND FOLLOW-UP

The patient eventually died, and blood culture was positive for BP. The patient's brother also had fever at the same time, and the parents were asked for hospitalization. Based on the blood culture and drug sensitivity results, imipenem was administered to the patient's brother. Finally, the patient's brother was discharged with normal body temperature, and no pathogenic bacterial growth was observed in subsequent blood cultures.

DISCUSSION

HLH is a macrophage proliferative disease mostly causde by Epstein-Barr virus (EBV) infection, whereas HLH caused by bacterial infections is relatively rare. According to the HLH-2004 guidelines, the diagnosis of HLH needs to meet five of the eight diagnostic criteria:1) fever; 2) spleen enlargement; 3) decrease of peripheral blood cells, involving 2–3 Lines, that is hemoglobin <90 g/L, platelet count <100 × 10^9/L, neutrophils <1.0 × 10^9/L; 4) hypertriglyceridemia and/or low fibrinogen: fasting

triglyceride ≥3.0 mmol/L (≥2.65 g/L), fibrinogen≤1.5 g/L, 5) blood phagocytic cells were found in the bone marrow, spleen, or lymph nodes, and there was no evidence of malignant tumor; 6) activity of natural killer cells (NK) is reduced or completely absent; 7) serum ferritin ≥500 μg/L, and 8) soluble CD25 (interleukin-2 receptor)≥2400 U/mL[3]. According to the guidelines for fever, a temperature ≥38.5°C for more than 7 days is required. The patient reported in this article was declared clinically dead on the fifth day of the heat course; therefore, the patient's clinical data only met criteria 2, 3, 5, and 7. Unfortunately, the whole-exon test failed to identify the molecular biological markers supporting HLH. Many indicators cannot be reviewed or improved over time because of the rapid worsening of a patient's condition. Although the clinical diagnosis of HLH was not confirmed, the results of the patient's bone marrow examination and MODS caused by HLH cannot be ignored among the many factors that lead to patient death. In addition, case reports of focal infections have shown that most patients have a good prognosis, and the examination indicators for these patients are quite different from the clinical manifestations of HHL[4-6]. Systemic infections are not complicated by MODS[2]. Therefore, the final progression of secondary HLH to BP sepsis contributes to patient mortality, and BP infection is mainly observed during the rainy season in tropical and subtropical regions. The seasonal incidence may be related to the survival of bacteria in the soil. A history of contact between pestilence-related soil and water sources is particularly important for early treatment by doctors. Several preclinical studies have shown that the lungs, liver, and spleen are the most common target organs for chronic BP infection [7]. Studies have shown that BP regulates phagocytic death and aids in the progression of acute or chronic infections [8]. After BP invade the body, they recruit host complement regulatory proteins via pathogens for immune evasion [9]. Furthermore, bacteria can survive in small abscesses formed in target organs. Over time, the chronic infection site forms granulomas with neutrophils, macrophages, and lymphocytes as the main components[10]. During this process, the patient's symptoms gradually improve, which is often considered a clinical cure. However, the patient was a chronic disease carrier. The patient reported in this article does not include any history of living

in an endemic area. Based on the patient's brother's history, we suspected that the source of infection was an asymptomatic carrier who came into contact with the patient. Most BP strains were sensitive to imipenem. The most important step is to identify the causative pathogen as soon as possible and provide effective interventions before severe clinical events occur. Early diagnosis based on bioinformatic analysis may help solve these problems[11]. Future vaccine development and bacteriophage therapy will help to reduce the incidence and mortality of BP[12, 13].

CONCLUSION

A person infected with BP may be an asymptomatic carrier owing to the unique mechanism of chronic BP infection. The high fatality rate of BP may be related to MODS caused by sHLH, as observed in this case.

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