

# Hemophagocytic Lymphohistiocytosis Secondary to Melioidosis in Paediatric Patients: A Case Series

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**Background:** Melioidosis caused by *Burkholderia pseudomallei* manifests as a variety of infectious symptoms. However, hemophagocytic lymphohistiocytosis (HLH) secondary to bacteraemic melioidosis is rarely documented in the literature. We report a series of fatal cases of melioidosis combined with HLH in one Chinese family.

**Case Presentation:** Three cases of melioidosis with HLH were reported in a family with three children, two boys aged 4 and 6 years and a 12-year-old girl. The most common clinical presentation was fever. A blood culture confirmed *B. pseudomallei*, and bone marrow aspiration revealed hemophagocytosis. Despite the administration of antibiotics, glucocorticoids and other treatments, all the patients died, and their deaths were attributed to HLH.

**Conclusion:** Melioidosis complicating HLH is rare in occurrence, but the mortality rate is high. Clinicians should be aware of the risk of a *B. pseudomallei* bloodstream infection in children.

**Keywords:** melioidosis, *Burkholderia pseudomallei*, hemophagocytic lymphohistiocytosis, family

## Introduction

Melioidosis is an infectious disease caused by *Burkholderia pseudomallei* and is found predominantly in tropical climates, especially in Southeast Asia. It has recently acquired prominence in Hainan Island, China, as an emerging pathogen.<sup>1,2</sup> Melioidosis is typically contracted through direct contact with contaminated soil or water. It can also be transmitted via inhalation or ingestion of contaminated materials. Melioidosis can have a vast array of presentations, ranging from localised infection to disseminated infection and septic shock, which could cause death. The duration of the illness can also vary from acute infection to chronic disease, and it can even remain latent for many years.<sup>3</sup> Melioidosis can be usually identified using blood culture and automated identification systems like VITEK and MALDI-TOF. Molecular tests are used when there is misidentification or if the patient was treated with antibiotics before blood culture.

The broad clinical presentations and diagnostic difficulties related to melioidosis limit its early detection, particularly in children.<sup>4</sup> A confirmed diagnosis requires high levels of clinical suspicion and a number of laboratory tests, including bacterial culture, serological tests, polymerase chain reaction-based tests and, more recently, rapid specific identification technologies such as gene sequencing.<sup>5</sup>

Hemophagocytic lymphohistiocytosis (HLH) is a severe inflammatory syndrome caused by the excessive activation of macrophages and T cells.<sup>6</sup> It is a serious and life-threatening complication that can be familial or sporadic. It can be triggered by a variety of events that disrupt the immune homeostasis and is commonly triggered by viral or bacterial infections.<sup>7</sup> Hemophagocytic syndrome secondary to melioidosis has been reported, but research has concentrated on the adult population.<sup>8–11</sup> Recently, we identified three cases of bacteraemic melioidosis complicated by HLH in one Chinese family.

## Family Report

The Chinese family in this study had three children, two boys aged 4 and 6 years and a 12-year-old girl, and lived in Hainan Island, China.

The 4-year-old boy was admitted to hospital after experiencing fever for 3 days. At admission, the patient had tachypnoea and hypotension, with a respiratory rate of 39 beats/min and a blood pressure of 57/34 mmHg. The results of the blood tests are presented in Table 1. After the collection of blood samples for culture, the patient underwent mechanical ventilation and anti-shock therapy, as well as antibiotic therapy using imipenem and cilastatin sodium (15 mg/kg, every 6 hours). The patient was treated with an injection of 10 mg/kg of methylprednisolone intravenously. Blood cultures were positive for *B. pseudomallei* (Table 2). The patient continued to deteriorate despite effective antibiotic therapy and died on day 1 of admission.

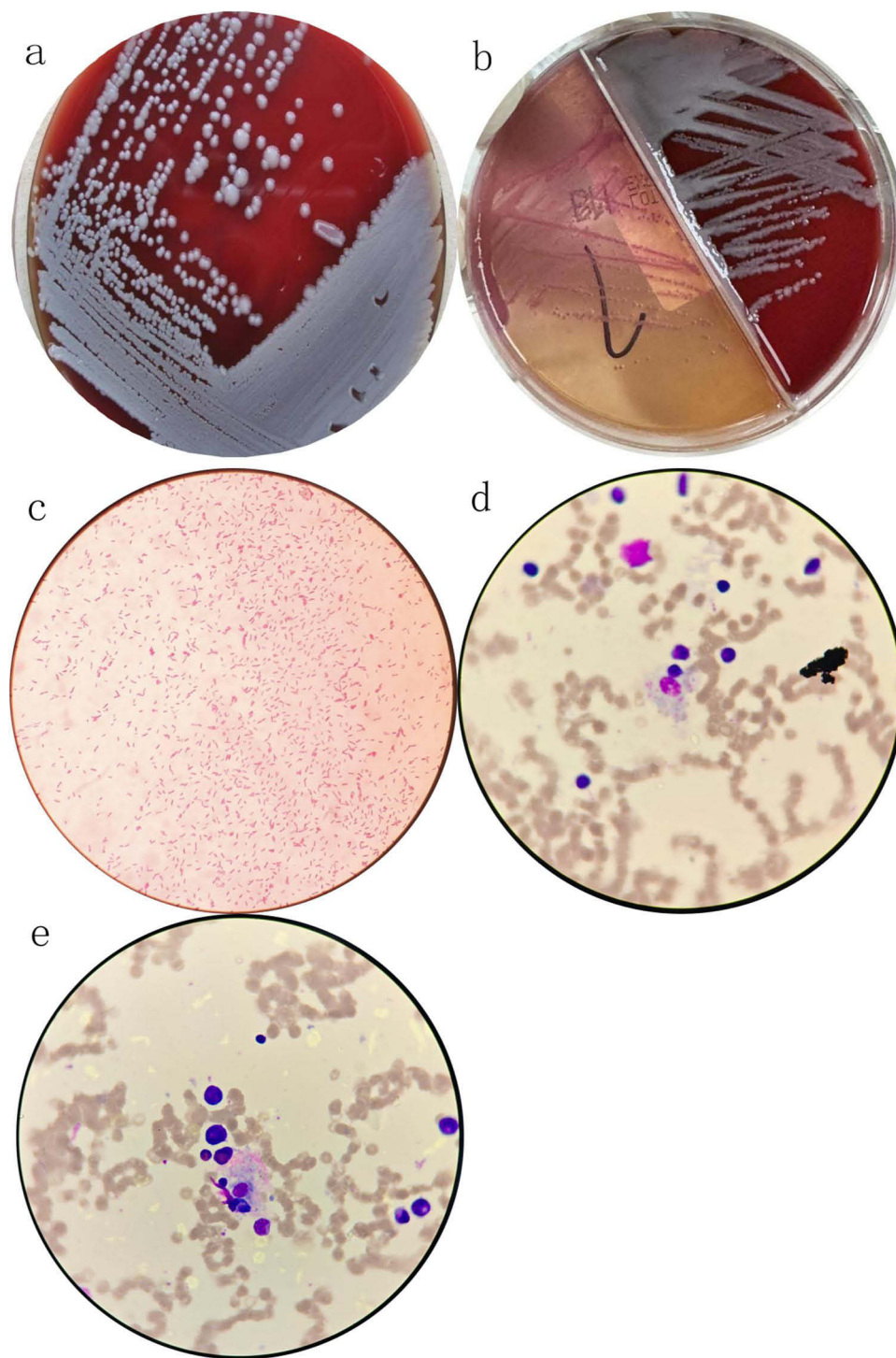
The daughter, a previously healthy 12-year-old, exhibited symptoms of fever for 4 days and cough for 2 days. Chest X-ray revealed extensive bilateral alveolar infiltrates in both lungs. The blood test results are presented in Table 1. Blood cultures collected on admission subsequently grew *B. pseudomallei* (Figure 1a and Table 2), confirming a diagnosis of melioidosis.

**Table 1** Blood Investigations

Test	Value			Normal Range
	Case One	Case Two	Case Three	
White blood cell(WBC)	0.6	0.83	0.8	5–12×10 <sup>9</sup> /L
Hemoglobin	104	83	79	105–145 g/L
Platelets	184	23	161	120–440×10 <sup>9</sup> /L
Aspartate transaminase(AST)	104	329.9	330.4	5–80 U/L
Alanine transaminase(ALT)	43	101.4	67.6	5–40 U/L
Total bilirubin	27.2	89.07	59.86	0–21 mmol/L
Direct bilirubin	20.1	51.46	37.4	0–8 mmol/L
Creatinine	89	157	58	62–115 umol/L
LDH	669	1226.7	749.7	109–245 U/L
Prothrombin time(PT)	21.1	53.6	22	11.8–15.1 s
APTT	34.2	>180	57.8	26–35 s
CRP	>200	239.04	235.93	0–10 mg/L
ESR	33	–	69	0–15mm/h
PCT	98.67	73.54	1.21	0–0.1 ng/mL
Ferritin	815.1	14,586	508.43	4.63–204 ng/mL
IL-2	–	1.87	1.35	0–5.71 pg/mL
IL-4	–	1.68	0.34	0–3 pg/mL
IL-6	–	1452.9	2030.82	0–5.30 pg/mL
IL-10	–	5754.38	28.78	0–4.91 pg/mL
IL-17A	–	1.36	0.95	0–20.6 pg/mL
INF-γ	–	3143.99	50.79	0–7.42 pg/mL
TNF-α	–	42.28	11.16	0–4.60 pg/mL

**Table 2** Antibiotic Susceptibility Pattern for *B. pseudomallei*

Antibiotic	Susceptibility		
	Case One	Case Two	Case Three
Doxycycline	–	–	Susceptible
Tetracycline	–	–	Susceptible
Cotrimoxazole (SXT)	Susceptible	–	Susceptible
Imipenem	Susceptible	–	Susceptible
Ceftazidime	Susceptible	–	Susceptible



**Figure 1** (a) Colonies of *Burkholderia pseudomallei* on blood agar; (b) Colonies of *Burkholderia pseudomallei* on MacConkey agar; (c) Gram stain of peripheral blood showing Gram-negative bacilli; (d) Bone marrow biopsy showing erythroid phagocytosis; (e) Bone marrow biopsy showing erythroid phagocytosis.

Bone marrow aspiration revealed hemophagocytosis (Figure 1d). Therefore, the diagnosis was confirmed as septicaemic melioidosis with secondary HLH. No pathogenic variant genes were identified in a whole exome genetic test. The patient received empirical intravenous meropenem (20 mg/kg, every 6 hours) and methylprednisolone (10 mg/kg). She rapidly deteriorated and required intubation for respiratory failure. She continued to deteriorate despite ongoing antibiotic therapy and died on day 2 of admission. The cause of death was respiratory and circulatory failure caused by HLH.

The 6-year-old boy presented with fever for 3 days. He was admitted to hospital on 11 September 2024. The laboratory results are presented in Table 1. Chest computed tomography revealed multiple lung infiltrates with patchy areas of consolidation. The results of the bronchoalveolar lavage fluid and blood mNGS tests revealed the presence of *B. pseudomallei*, and blood cultures were also positive for *B. pseudomallei* (Figure 1b and c, Table 2), further confirming the diagnosis of melioidosis. Bone marrow aspiration revealed hemophagocytosis (Figure 1e). Therefore, the diagnosis was confirmed as septicaemic melioidosis with secondary HLH. Hemophagocytic syndrome causes respiratory failure, low blood pressure and oliguria. Despite a series of aggressive treatments, including the antibiotic meropenem (20 mg/kg, every 6 hours), mechanical ventilation, intravenous glucocorticoids (methylprednisolone, 10 mg/kg) and continuous renal replacement therapy, the patient's condition continued to deteriorate, and he died after 1 day of treatment.

## Discussion

A review of the medical literature was performed, with few culture-confirmed cases of melioidosis complicated with HLH in adults identified.<sup>12–16</sup> Our case series adds valuable data to the literature by documenting such cases in paediatric patients.

*Burkholderia pseudomallei*, a Gram-negative bacterium, is the infective pathogen of melioidosis. Melioidosis is generally thought to be epidemic in the tropical and sub-tropical zone of Southern China, with Hainan Island one of the endemic areas.<sup>17</sup> In the present study, the patients were the children of farmers living in the endemic area, but the infection route is unknown.

Melioidosis is an infectious disease involving almost every system of the body and has complicated clinical characteristics. Melioidosis complicating HLH is rare.<sup>18</sup> A review of the medical literature was performed, with only four culture-confirmed cases of melioidosis complicated with HLH in adults identified.

Hemophagocytic lymphohistiocytosis occurs in both primary and secondary forms. Primary, or genetic, HLH presents as familial HLH syndrome. The HLH-2004 diagnostic criteria<sup>19</sup> include the following eight criteria: (1) fever  $\geq 38.5^{\circ}\text{C}$ ; (2) splenomegaly; (3) peripheral blood cytopenia affecting at least two cell lines (hemoglobin  $< 90\text{ g/L}$ , platelets  $< 100 \times 10^9/\text{L}$ , neutrophils  $< 1.0 \times 10^9/\text{L}$ ); (4) hypertriglyceridemia (fasting triglycerides  $\geq 3.0\text{ mmol/L}$ ) and/or hypofibrinogenemia (fibrinogen  $\leq 1.5\text{ g/L}$ ); (5) hemophagocytosis in bone marrow, spleen, lymph nodes, or liver; (6) low or absent NK cell activity; (7) ferritin  $\geq 500\text{ }\mu\text{g/L}$ ; and (8) elevated soluble CD25 (soluble IL-2 receptor  $\geq 2,400\text{ U/mL}$ ). A diagnosis of HLH can be established if five out of these eight criteria are met. In our cases, all three patients presented with persistent fever  $> 38.5^{\circ}\text{C}$  for 3–4 days. Laboratory findings revealed significant cytopenias, with all patients showing decreased white blood cell counts ( $< 1.0 \times 10^9/\text{L}$ ) and thrombocytopenia ( $< 100 \times 10^9/\text{L}$ ). Ferritin levels were markedly elevated ( $> 10,000\text{ }\mu\text{g/L}$  in all cases), far exceeding the diagnostic threshold. Hepatosplenomegaly was consistently observed in all three cases through physical examination and imaging studies. Bone marrow examination confirmed the presence of hemophagocytosis in all patients. While NK cell activity and soluble CD25 levels were not assessed due to the rapid progression of disease, the presence of five diagnostic criteria was sufficient to confirm the diagnosis of HLH in all three cases. In the present study, genetic tests on the daughter and her parents did not reveal any genes associated with primary hemophagocytic syndrome.

Hemophagocytic lymphohistiocytosis can be triggered by conditions that disrupt immune homeostasis, such as infections, autoimmune diseases and malignancy. Viral infections are the most common triggers for HLH, such as Epstein–Barr virus, cytomegalovirus, parvovirus and herpes simplex virus.<sup>20</sup> Herein, we report a rare bacterial infection triggering this serious complication. The three cases in this study are the first reported cases of paediatric patients that developed HLH secondary to melioidosis.

Hemophagocytic lymphohistiocytosis is a life-threatening complication that is associated with excessive immune activation and is common in children. In this study, interleukin (IL)-6, IL-10, and INF- $\gamma$  in peripheral blood were significantly elevated, suggesting a cytokine storm that may have contributed to the development of hepatitis, coagulopathy, liver failure, central nervous system involvement, multi-organ failure, and other manifestations. The syndrome has a high mortality rate.<sup>21</sup> To inhibit cytokine expression and suppress the excessive immune response, methylprednisolone at a dose of 10 mg/kg was used as an immunosuppressive agent. Unfortunately, even after vigorous rescue, our patients eventually died. The cause of death was multiple organ failure caused by HLH. HLH triggered by bacterial infections,

such as melioidosis, involves dysregulation of cytokine pathways, leading to uncontrolled immune activation. This process is characterized by the overproduction of pro-inflammatory cytokines, including IL-6, IL-10, and INF- $\gamma$ , which drive the pathogenesis of HLH.<sup>22</sup> Early recognition and intervention are critical in managing these cases.

In addition to the cases documented in this study, HLH has been reported in various contexts, including as a complication of gene therapy. For instance, Galletta et al reported a case of HLH following gene replacement therapy in a child with type 1 spinal muscular atrophy.<sup>22</sup> This highlights the diverse triggers and presentations of HLH, emphasizing the need for a comprehensive approach to diagnosis and treatment.

These cases illustrate the varied presentation of secondary HLH and highlight the importance of early diagnosis and treatment of the underlying aetiology. In summary, to the best of our knowledge, this is the first report of HLH secondary to *B. pseudomallei* infection in children. Hemophagocytic lymphohistiocytosis is a serious complication of melioidosis and can lead to high mortality rates. Paediatricians in endemic areas should be vigilant for signs of melioidosis and HLH, especially in children presenting with fever, hepatosplenomegaly, and cytopenia. Early diagnostic measures, such as blood cultures and bone marrow aspiration, are essential. Treatment protocols should include aggressive antimicrobial therapy, immunosuppressive agents, and supportive care to manage multi-organ failure. We recommend heightened vigilance and specific diagnostic protocols for clinicians in endemic regions to improve outcomes in these patients.

## Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

## Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Hainan General Hospital (Hainan Affiliated Hospital of Hainan Medical University) (Approval No. YLY [2024] 568).

Written informed consent was obtained from the legal guardians.

## Consent for Publication

Written informed consent for publication was obtained from the legal guardians.

## Funding

There is no funding to report.

## Disclosure

The authors report no conflicts of interest in this work.

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