CASE REPORT

Haemophagocytic lymphohistiocytosis associated with coccidiomycosis

Musaab Ramsi, Cristina Alvira, Prashant Purohit, David Cornfield

Department of Pediatric Critical Care, Stanford University, Palo Alto, California, USA

Correspondence to

Dr Musaab Ramsi,
musaab.ali@gmail.com

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SUMMARY

Haemophagocytic lymphohistiocytosis (HLH) is a rapidly fatal disease caused by dysregulated histiocytes leading to an excessive inflammatory reaction. While genetic forms of HLH exist, the most common form is acquired, frequently associated with infection. Here we report the first case of HLH associated with a coccidiomycosis infection. This patient is a 13-year-old previously healthy boy who presented with a flu-like illness, which rapidly progressed to refractory shock, severe ARDS, multiorgan failure and death despite maximal medical therapy, including broad-spectrum antibiotics to treat well-established causes of acquired HLH. Autopsy findings revealed the diagnosis of HLH in the setting of pulmonary coccidiomycosis. Antifungal therapy should be considered in cases of acquired HLH when the underlying aetiology is not clear.

BACKGROUND

Haemophagocytic lymphohistiocytosis (HLH) is a disorder characterised by the dysregulated proliferation of histiocytes with prominent haemophagocytic activity. This entity has been documented in the context of several infectious diseases, including viral, bacterial, fungal and parasitic infections. In addition to immunosuppressive therapy, eradication, or at least, control of the underlying infectious trigger of this life-threatening condition is considered a cornerstone in the management of this life-threatening condition. A high index of suspicion of a potential association between HLH and a specific infection is therefore required in order to promptly initiate treatment directed at the underlying cause. To the best of our knowledge, no case of haemophagocytic syndrome associated with coccidiomycosis has been reported in the literature. Herein, we offer the first description of this unusual association.

CASE PRESENTATION

A previously healthy 13-year-old boy from central California presented to the emergency department at an outside hospital with a 7-day history of influenza-like symptoms, fever, abdominal and back pain that failed empiric outpatient treatment with oral antibiotics. In the emergency department, he was found to be febrile, tachycardic, profoundly hypotensive and in respiratory distress. Aggressive resuscitation was rapidly initiated, but his symptoms progressed to decompensated shock, with cardiovascular collapse and respiratory failure, requiring emergency tracheal intubation, and inotropic support. He was also started on broad-

spectrum antimicrobial medications. Further review of systems was otherwise unremarkable. His family history was significant for a sibling who had coccidiomycosis manifested by fever, cough, an isolated lung nodule and a positive serology test. Given his refractory shock, and severe respiratory failure with persistent hypoxaemia, he was emergently transferred to our institution for possible initiation of extracorporeal membrane oxygenation.

INVESTIGATIONS

The laboratory evaluation of the patient was significant for pancytopenia (white cell count 1.3 k/ μ L, haemoglobin 10.8 g/dL and platelet count 28 k/ μ L), liver dysfunction (total bilirubin 11 mg/dL, direct bilirubin 9.1 mg/dL, aspartate transaminase 3564 units/L and alanine transaminase 1331 units/L), disseminated intravascular coagulation (DIC; D-dimer 14 124 ng/mL, fibrinogen 71 mg/dL and international normalised ratio 2.8) and acute renal failure (blood urea nitrogen 70 mg/dL and serum creatinine 7 mg/dL). Serum C reactive protein was elevated at 15.6 mg/dL. The chest X-ray demonstrated diffuse patchy opacities throughout both lung fields and bilateral pleural effusions. The echocardiogram showed an underfilled, hyperdynamic left ventricle with otherwise well-preserved function and no structural abnormalities. The abdominal CT scan was remarkable only for splenomegaly, and the brain CT scan was negative for acute intracranial pathology. A bone marrow aspirate performed on hospital day 2 demonstrated haemophagocytosis. The infectious workup was unremarkable, and unable to identify an infectious aetiology. Blood, urine, respiratory and bone marrow culture samples were all sterile, and the anti-streptolysin O and anti-DNAse B were negative. The viral serology studies were also negative (including negative analyses for HIV, hantavirus, leptospirosis, Epstein-Barr virus (EBV), parvovirus, cytomegalovirus and herpes simplex virus, and a negative direct fluorescent antibody panel for common causes of viral respiratory disease). Serum coccidiomycosis immunodiffusion assay was also negative. Bronchoalveolar lavage was not performed due to clinical instability and severe coagulopathy.

TREATMENT

In the critical care unit, the patient deteriorated rapidly and developed multiorgan failure requiring extraordinarily high levels of ventilatory support with persistent hypoxaemia, multiple vasoactive medications to treat refractory hypotension and shock, continuous renal replacement therapy to treat fluid overload and acute renal failure and

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aggressive replacement of blood products to treat persistent bleeding and DIC. Owing to his progressive multiorgan failure in the absence of a clear infectious aetiology, HLH was suspected and ferritin level in the blood was measured. The diagnosis of HLH was subsequently established as the patient met six of the eight criteria for HLH, including: fever, splenomegaly, hyperferritinaemia (28 885 ng/mL), hypofibrinogenaemia, cytopaenia (platelet <100 k and ANC <1000) and haemophagocytosis noted on the bone marrow aspirate. In consultation with the paediatric infectious disease team, his antimicrobial regimen was adjusted to target known bacterial causes of acquired HLH. A treatment for HLH was immediately initiated, according to the Hybrid Immunotherapy trial (HIT for the HLH trial) with antithymocyte globulin and dexamethasone. The patient was to begin etoposide on the day of his death, but expired prior to the administration of the first dose.

OUTCOME AND FOLLOW-UP

Despite maximal medical therapy, on hospital day 3 the patient developed irreversible shock, progressive and unrelenting lactic acidosis, with massive pulmonary haemorrhage and consequent severe hypoxia refractory to increases in respiratory support as the proximate cause of death. The autopsy findings were significant for active pulmonary coccidiomycosis based on Grocott's methenamine stain (figures 1 and 2), extensive pulmonary haemophagocytosis (figure 3) and marked bone marrow histiocytosis (figure 4). The postmortem liver biopsy was negative for perforin (*PRF 1*) gene mutations, the most common genetic cause of familial HLH. Given the age of presentation, the absence of known genetic mutations or family history suggesting a genetic form of HLH, the patient most likely had an acquired form of HLH secondary to an underlying infection. Based on these findings, the patient was diagnosed with secondary HLH associated with a coccidiomycosis infection.

DISCUSSION

Coccidiomycosis, also known as valley fever, is caused by two species of fungi, *Coccidioides immitis* and *C. posadasii*. The former is a soil fungus found in southwestern USA, and the latter is predominantly found in South America. While there are some immunological differences between the fungi, the manifestations of the diseases caused by the two species are identical.^{1 2}

Coccidiomycosis is transmitted predominantly through inhalation of airborne spores, with a predilection for the lungs. The

Figure 2 Lung lymph node (Grocott's methenamine stain) showing endospores (arrow).

presentation includes influenza-like symptoms and pneumonia in approximately 60% of exposed patients.² Disseminated coccidiomycosis is described in immunosuppressed and immunocompetent patients and can be rapidly fatal, underscoring the importance of expeditiously determining the underlying cause.^{3 4}

HLH is a rare and potentially fatal condition caused by over-activation and dysregulation of the immune system. It is commonly classified as either primary (familial) or secondary.⁵ The secondary, or acquired, form of HLH can be associated with infections, autoimmune disorders or malignancies. Viral, bacterial, fungal and parasitic infections have been implicated, with EBV being the most common cause.⁶

The fundamental characteristics of both types are histiocyte proliferation and haemophagocytosis. The pathophysiology is related to dysregulation of the immune system, resulting in hypercytokinaemia and abnormal T-cell function.⁷ The T-cell abnormalities range from production of a lymphokine by the CD4 lymphocytes to excessive stimulation of cytotoxic T cells, resulting in the increased production of interferon γ , stimulation of macrophages and release of tumour necrosis factor.^{7 8} This immune dysregulation ultimately leads to excessive cellular damage, tissue destruction and multiorgan failure.⁷

The diagnosis of HPS syndrome is based on the clinical, laboratory and histopathological findings. The Histiocytic Society proposed diagnostic guidelines in 1994, which were

Figure 1 Lung lymph node (Grocott's methenamine stain) showing spherule (arrow).

Figure 3 Lung lymph node, haemophagocytosis: macrophage (circle) stuffed with blood cells.

Figure 4 Bone marrow biopsy: marked histiocytosis (CD163+).

updated in 2004.^{9 10} The diagnosis of HLH is established by a molecular diagnosis or based on the presence of five of the following eight criteria: (1) fever $\geq 38.5^{\circ}\text{C}$, (2) splenomegaly, (3) peripheral blood cytopenia, with at least two of the following: haemoglobin $< 9 \text{ g/dL}$; platelets $< 100\,000/\mu\text{L}$; absolute neutrophil count $< 1000/\mu\text{L}$, (4) hypertriglyceridaemia (fasting triglycerides $> 265 \text{ mg/dL}$) and/or hypofibrinogenaemia (fibrinogen $< 150 \text{ mg/dL}$), (5) haemophagocytosis in bone marrow, spleen, lymph node or liver (6) low or absent natural killer cell activity, (7) ferritin $> 500 \text{ ng/mL}$, (8) elevated soluble CD25 (soluble interleukin-2 receptor α). Our patient had six of the eight diagnostic criteria. Although small amount ($< 10\%$) of haemophagocytosis can be observed in patients with severe sepsis, the extent of haemophagocytosis and histiocytosis seen in our patient was very high and can only be attributed to HLH.¹¹

The treatment of secondary HLH includes three main components: (1) eradication of the underlying aetiology; (2) stopping T-cell proliferation and activation and (3) blocking excessive cytokine production.⁵ Even if treatment is initiated to control the hyperinflammatory state, secondary HLH in response to infection is often rapidly progressive without prompt elimination of the infectious trigger.¹² Coccidiomycosis is sensitive to both amphotericin and azole antifungals.² Empiric fluconazole was initiated in this patient to address fungal causes of septic shock and respiratory failure. Unfortunately, fluconazole was discontinued once the diagnosis of HLH was established as the association between the two conditions had not been previously known or reported. Given the profound severity of the patient's multiple organ failure on presentation to our institution, it is not clear whether appropriate antifungal therapy would have changed the ultimate outcome in this case. However, it is clear that recovery from acquired HLH is less likely in the absence of effective treatment targeting the underlying cause. Moreover, the standard immunosuppressive therapy used to treat primary

HLH may not be beneficial in cases like ours where the inciting event is a systemic infection, and in fact could be detrimental.

Learning points

- ▶ Early diagnosis and immediate introduction of targeted therapy is crucial for the effective treatment of acquired forms of haemophagocytic lymphohistiocytosis (HLH).
- ▶ Coccidiomycosis is an unusual cause of acquired HLH, and clinicians should consider it in the differential diagnosis of acquired HLH so that antifungal therapy can be promptly initiated.
- ▶ Antifungal therapy should be considered in patients at high risk for coccidiomycosis who are presenting with multiorgan failure and shock, and may have an acquired form of HLH.

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Competing interests None.

Patient consent Obtained.

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