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CASE REPORT

Fatal Hemophagocytic Lymphohistiocytosis in a Patient with Miliary Tuberculosis: a Case Report

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome induced by cytotoxic T-cells. Mostly, HLH is secondary to infections, malignancies, or autoimmune disorders. HLH triggered by miliary tuberculosis is rare and mortality rates are high. We report a case of a 58-year-old, Caucasian patient admitted to the ICU with respiratory failure. After extensive tests, the diagnosis of HLH was made. Despite aggressive treatment with antibiotics, etoposide, anakinra, and tocilizumab, our patient succumbed to the illness after 18 days in the ICU. Postmortem, a diagnosis of miliary tuberculosis was made, despite negative PCR and culture of mycobacteria during clinical course. Our case demonstrates the challenges of early diagnosis of HLH and the importance of considering miliary tuberculosis as a possible underlying trigger.

Keywords Hemophagocytic lymphohistiocytosis · Tuberculosis · Intensive care units · Case report

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disorder characterised by an unregulated immune response [1]. HLH can be triggered by multiple causes, for example infections. Tuberculosis accounts for the highest mortality from all infectious diseases worldwide. Europe's tuberculosis burden is one of the lowest, but there is a worrisome rise in the incidence of multidrug resistant tuberculosis [2]. Tuberculosis-associated HLH has been reported in 70 cases in the literature from 1975 to 2014 [3]. We report a rare case of secondary HLH associated with miliary tuberculosis (MTB).

This article is part of the Topical Collection on *Medicine*

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Case Presentation

Our patient was a 58-year-old Caucasian woman, who was referred to the Emergency Department because of dyspnoea. Her past medical history was significant for psoriatic arthritis, treated with adalimumab (tumour necrosis factor blocker) and methotrexate.

She presented with a tachycardia of 124 beats/minute and blood pressure of 126/62 mmHg. Respiratory rate was 30 breaths/min and SpO2 89% at room air. The arterial blood sample at 4L/min supplemental oxygen showed a pH of 7.54 (ref 7.35–7.45), pCO_2 25 mmHg (ref 35–45), pO_2 78 mmHg (ref 75–100), and lactate of 3.44 mmol/L (ref 0.5–2.2). Laboratory tests showed elevated C-reactive protein (CRP) of 150 mg/L (ref 0–5), lactate dehydrogenase of 1327 U/L (ref < 248), and a considerably elevated ferritin of 25,476 mcg/L (ref 22–204). Thrombocytes were 70×10^9/L (ref 150–400 $\times 10^9$/L), whereas haemoglobin and leukocytes were within the normal range. The patient had slightly elevated alanine aminotransferase (ALAT) of 93 U/L (ref 0–34), aspartate transaminase (ASAT) of 410 U/L (ref 0–31), and gamma-glutamyltransferase of 63 U/L (ref 0–35). Chest X-ray showed patchy, bilateral infiltrates. Thoracic computed tomography (CT) scan showed bilateral, coalescent ground-glass opacities and pulmonary embolisms. An abdominal ultrasound showed no signs of cholecystitis, cholelithiasis, or hepatosplenomegaly.

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On admission, the clinical presentation was not clear-cut. The initial working diagnosis was community-acquired pneumonia with concurrent pulmonary embolisms. Antibacterial treatment was started with cefuroxime, ciprofloxacin, metronidazole, and gentamicin to cover for infection of unknown origin. Low molecular weight heparin was started at a therapeutic dose. The thrombocytopenia was devoted to sepsis and disseminated intravascular coagulation. The elevated ferritin was attributed to an underlying infection, though rare causes such as HLH were also examined. On admission, our patient met only two non-specific HLH-2004 diagnostic criteria (Table 1). Nevertheless, soluble IL-2 receptor (sIL-2r) test was initiated.

Serological testing showed a prior infection with Epstein-Barr virus, cytomegalovirus, and herpes simplex virus (HSV), and no signs of human immunodeficiency virus, hepatitis B, and C virus and *Mycoplasma pneumoniae*. SARS-CoV-2 polymerase chain reaction (PCR) on nasopharyngeal specimens was negative twice. Anti-SARS-CoV-2 antibodies turned positive, with no known previous clinical course of COVID-19 or vaccination. A urine legionella antigen test was negative. A broncho alveolar lavage (BAL) was performed: *Influenza virus* A and B, respiratory syncytial virus, *Pneumocystis jirovecii*, *Mycobacterium tuberculosis*, and SARS-CoV-2 PCR were all negative. *Aspergillus fumigatus* and mycobacterial cultures were also negative. No acid-fast bacilli were identified by direct microscopy. A HSV type 2 PCR was positive with a cycle treshold of 37.5 and therefore considered clinically irrelevant.

Four days after admission, the patient was transferred to the intensive care unit (ICU) because of respiratory failure which prompted mechanical ventilation and prone positioning. Dexamethasone 6 mg daily for 10 days was started for treatment of acute respiratory distress syndrome following SARS-CoV-2 pneumonitis. All antibiotics were discontinued after cultures came in negative. Two days later, our patient developed a progressive thrombocytopenia accompanied by gastro-intestinal bleeding and anaemia.

During ICU admission, serum sIL-2r turned out to be elevated. A bone marrow biopsy was performed and the smear showed hypocellular bone marrow with hemophagocytosis (Fig. 1). At that moment, our patient fulfilled six HLH criteria (Table 1). Under the diagnosis of HLH, our patient was started on etoposide 100 mg weekly, dexamethasone 10 mg/m^2 daily for 2 weeks, and intravenous immunoglobulins 1 g/kg daily for 2 days.

At that point, there was no clear underlying aetiology for the HLH. Infectious diseases (post-SARS-CoV-2, HSV type 2) and medication (adalimumab) were considered. No signs of malignancy or lymphadenopathy were seen on imaging.

Bone marrow biopsy did not show signs of lymphoproliferative disease. A cutaneous T cell lymphoma was excluded after biopsies of two erythematosquamous plaques.

The initial HLH treatment did not lead to improvement: respiratory failure persisted and our patient developed a pancytopenia. Three days after HLH treatment initiation, anakinra (interleukin-1 receptor antagonist) 5 mg/kg daily was added. At that moment, we noticed a decrease in ferritin levels down to 7249 mcg/L. However, despite increasing anakinra doses, respiratory failure and cytopenia worsened. Etoposide was discontinued and acyclovir (10 mg three times daily) was added to cover a HSV pneumonitis. Serial chest X-rays and thoracic CT scans showed extensive bilateral consolidations and ground-glass nodules which were repeatedly progressive. One week after start of HLH treatment, our patient developed fever with further respiratory deterioration. Despite lung protective ventilation with high FiO2 levels up to 100%, serial arterial blood gas

Table 1 Fulfilment of HLH-2004 criteria in our patient

Criteria HLH-2004	Upon admission	Upon diagnosis of HLH
Fever (peak temperature of > 38.5 °C for > 7 days)	No	Yes
Splenomegaly (spleen palpable > 3 cm below costal margin)	No	No
Cytopenia involving > 2 cell lines	No	Yes
Hypertriglyceridemia (fasting triglycerides > 177 mg/dL [2.0 mmol/L] or > 3 standard deviations [SD] more than normal value for age) or hypofibrinogenemia (fibrinogen < 150 mg/dL [1.5 g/L] or > 3 SD less than normal value for age)	No	Yes
Hypertriglyceridemia (fasting triglycerides > 177 mg/dL [2.0 mmol/L] or > 3 standard deviations [SD] more than normal value for age) or hypofibrinogenemia (fibrinogen < 150 mg/dL [1.5 g/L] or > 3 SD less than normal value for age)	Unknown	Yes
Hemophagocytosis (in biopsy samples of bone marrow, spleen, or lymph nodes)	Unknown	Yes
Low or absent natural killer cell activity	Unknown	Unknown
Serum ferritin > 500 ng/mL (> 1123.5 pmol/Lng/mL)	Yes	Yes
Elevated soluble interleukin-2-receptor (CD25) levels (> 2400 U/mL or very high for age)	Unknown	Yes

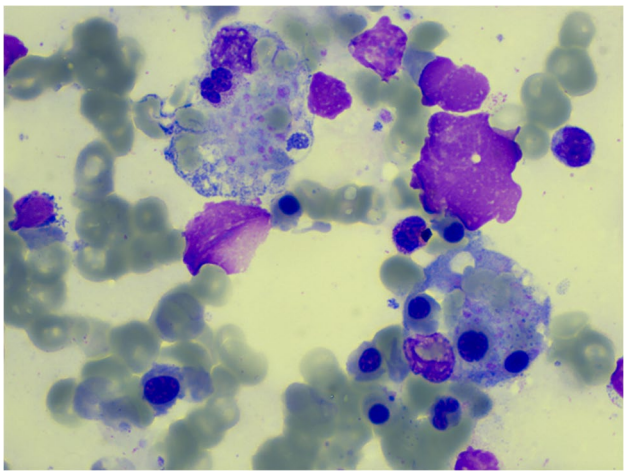

Fig. 1 Histopathological features of the bone marrow showing hemophagocytosis

analyses showed a progressive hypoxia (pO2 57–88 mmHg). After the initial drop in ferritin levels, there was an evident increase up to 9899 mcg/L. Anakinra was replaced by the anti-IL-6 receptor monoclonal antibody tocilizumab (8 mg/kg) and piperacillin/tazobactam (4 g/500 mg four times daily) and hydrocortisone (50 mg four times daily) were started. Despite aggressive supportive care, our patient showed no improvement and succumbed to the illness after 18 days in our ICU.

Autopsy was performed and confirmed striking hemophagocytosis in bone marrow. More surprisingly, it revealed a miliary pneumonia involving all pulmonary lobes (Fig. 2) with Ziehl–Neelsen staining showing acid-fast bacilli. In fact, epithelioid cell granulomatosis of all organs was found. *Mycobacterium tuberculosis* PCR was positive in paraffin-embedded lung tissue. In conclusion, our patient died as a result of HLH with underlying miliary tuberculosis.

Discussion and Conclusion

This case illustrates the challenges of diagnosing HLH and the difficulties of determining the underlying aetiology. HLH has a yearly estimated incidence of 1.2 cases per 1,000,000 individuals [4]. Patients mostly suffer from the triad of fever, bicytopenia, and splenomegaly. The diagnosis is often indistinct due to nonspecific symptoms and a presentation similar to sepsis. Mortality rates are high, ranging from 50 to 70%. HLH can be familial (primary) or acquired (secondary), the latter accounting for the majority of adult cases. Primary HLH is caused by several genetic abnormalities and secondary HLH might be triggered by infections, autoimmune disorders, malignancies, and medication [5]. HLH was thought to occur in children predominantly, though it became more recognised in adults over the last years. Nevertheless, clinical guidelines and diagnostic criteria are mainly based on paediatric trials and are not validated for use in adults.

The diagnosis is based on the presence of five out of eight diagnostic criteria or a molecular diagnosis consistent with HLH [6]. Several of these criteria are however not easily accessible, such as a bone marrow biopsy, NK cell activity, and sIL-2r concentration. Moreover, the majority of criteria such as fever, cytopenia, increased serum ferritin, and even hemophagocytosis lose their specificity in the ICU where sepsis, transfusions, and multi-organ failure are a daily occurrence [7].

Timely diagnosis of HLH is highly important for a favourable outcome [1]. In our patient, the diagnosis of HLH was considered on admission, but at that moment, only two criteria (increased ferritin and fever) were met. We know that elevated ferritin, being an acute phase reactant, is not specific for HLH [8]. Nevertheless, HLH was diagnosed in 14.2% of patients with ferritin > 10,000 ug/L and ferritin reduction is shown to be a prognostic marker in HLH [9].

Recently, the H-score was introduced as an alternative algorithm for diagnosing HLH. A cut-off value of 169 was determined, corresponding with a sensitivity of 93% and specificity of 86% [10]. Our patient had an H-score of 150 upon admission, corresponding to 25% probability of HLH, though two criteria (triglycerides and bone marrow biopsy) were missing. Once the results of the sIL-2r test and bone marrow biopsy came in, our patient fulfilled six of the HLH-2004 criteria and she had an H-score of 209, corresponding to 93% probability of HLH. sIL-2r has shown to be an excellent diagnostic test for HLH. The challenge remains the technical delay in assessment, due to determination in limited number of laboratories [11].

HLH treatment follows two strategies: suppression of the cytokine storm and treating the underlying factor. In our patient, corticosteroids, etoposide, and immunoglobulins were initiated at time of diagnosis, according to the proposed protocols [12]. Anakinra and tocilizumab were used because of insufficient response.

In our patient, a SARS-CoV-2 pneumonitis was initially identified as underlying trigger. SARS-CoV-2-associated HLH has been described especially in critically ill patients [13]. However, the fact that SARS-CoV-2 PCR was negative raised suspicion for other triggers. Despite a low viral load, reactivation of HSV type 2 has been considered and eventually treated, though not until an advanced stage of disease. Other cases of HSV type 2-associated HLH showed that early treatment is vital [14]. Cases have also been reported of adalimumab-induced HLH [15], though our patient had been treated with adalimumab for 13 years already, making this less likely. Autopsy finally revealed an unexpected MTB. MTB is a form of widely disseminated haematogenous tuberculosis with a variable presentation.

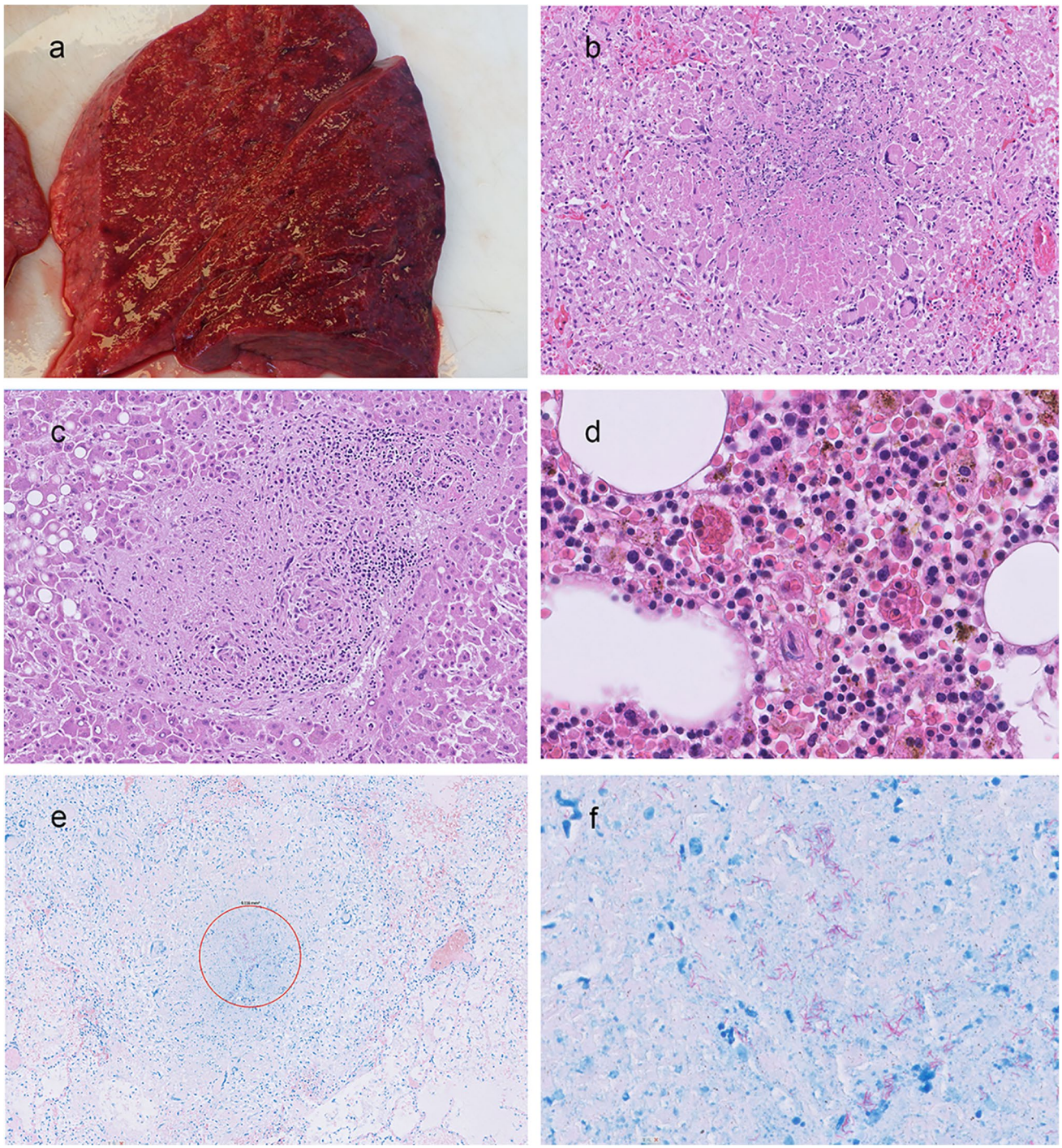

Fig. 2 Overview of histopathological findings during autopsy. **a** Imaging of the lung showing millet-like grains. **b**, **c** Microscopic photograph of granuloma in the lung and liver. **d** Hemophagocytosis in bone marrow. **e**, **f** Positive Ziehl–Neelsen staining in the lung

MTB is diagnosed by a clinical presentation consistent with MTB responding to chemotherapeutics, the presence of a diffuse miliary infiltrate on imaging, or miliary tubercles in multiple organs during surgery or autopsy. Furthermore, the diagnosis needs to be confirmed by diagnostic tests for *M. tuberculosis* [16].

There are several potential scenarios in our patient. First, MTB might be a progressive primary infection or might have progressed by reactivation of a latent focus, being a possible trigger for HLH. Secondly, the HLH treatment might have resulted in exacerbation from latent to miliary tuberculosis, indicating a different trigger. A

negative Mantoux test was obtained before start of adalimumab. Besides the immunosuppressant, our patient did not have other risk factors for TB. BAL during admission did not show signs of acid-fast bacilli using auramine staining, mycobacterial PCR, and culture examination. CT scan did not show typical micronodules either. All these findings point towards a previously latent TB. When TB is suspected, additionally TB bone marrow and blood cultures might be used. They yield comparable sensitivity of around 54–67% [17, 18].

Tuberculosis-associated HLH is rare but has been reported. A search from 1975 to 2014 showed 70 cases of TB-HLH [3]. In 12.7% of the cases, the diagnosis of TB was made at autopsy. TB-HLH has a mortality rate ranging from 44 up to 100% if not treated with anti-tuberculosis treatment [3, 19].

In conclusion, this case illustrates the challenges of early diagnosis of both HLH and MTB. It provides an in-depth understanding of the possible triggers of HLH, with an emphasis on MTB-associated HLH. However, we could not prove that MTB was the direct trigger of HLH in this case, since there were several other possibilities. We recommend, with an unclear trigger of HLH, to consider the diagnosis of tuberculosis, even despite negative diagnostic tests for *M. tuberculosis* in sputum and BAL like in our case. Clinicians should consider additional bone marrow aspiration and blood culture assessment, not only because TB can be a trigger for HLH, but also because of the risk of fulminant TB when HLH treatment is initiated in patients with latent TB.

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Author Contribution All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability All data used to support the findings of this study are available from the corresponding author upon request.

Code availability Not applicable.

Declarations

Ethics Approval This case report is compliant with ethical standards.

Consent to Participate Not applicable.

Consent for Publication Informed consent for submission of the case report was obtained from the patient's family.

Competing Interests The authors declare no competing interests.

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