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CASE REPORT

Histoplasma capsulatum reactivation with haemophagocytic syndrome in a patient with chronic lymphocytic leukaemia

M.P. van Koeveringe, R.E. Brouwer*

Department of Internal Medicine, Reinier de Graaf Hospital, Delft, the Netherlands,
*corresponding author: tel.: +31 (0)15-260 32 96, e-mail: Brouwer@rdgg.nl

ABSTRACT

We describe a case of haemophagocytic syndrome caused by *Histoplasma capsulatum* reactivation in a patient with chronic lymphocytic leukaemia treated with fludarabine and alemtuzumab. He presented with fever, pancytopenia, increased serum ferritin, lactate dehydrogenase and soluble interleukin-2 receptor. A bone marrow aspirate showed haemophagocytosis and possibly a yeast infection. Treatment with cyclosporine, dexamethasone, etoposide and caspofungin was started. After initial improvement his condition deteriorated. A second bone marrow examination confirmed a *Histoplasma* infection. After treatment with amphotericin B, the fever resolved and blood counts normalised. Haemophagocytic syndrome is a critical condition with high mortality that requires immunosuppressive therapy. The underlying cause should be investigated and treated. In this case a *Histoplasma* reactivation is described in a severely immunocompromised host years after the patient had left the endemic area.

KEYWORDS

Histoplasma, haemophagocytic syndrome, chronic lymphatic leukaemia

INTRODUCTION

Haemophagocytic syndrome or haemophagocytic lymphohistiocytosis (HLH) is a potentially lethal condition caused by inappropriate activation and proliferation of lymphocytes and macrophages with an uncontrolled immune response leading to cellular damage in multiple organ systems causing pancytopenia, hyperferritaemia and hepatosplenomegaly.[1-3] It has been classified into a primary or genetic form and a secondary or reactive form, which is associated with a variety of infections, autoimmune diseases and malignancies (*table 1*). We describe a case of HLH induced by a systemic *Histoplasma* reactivation in a severely immunocompromised patient with chronic lymphatic leukaemia (CLL).

Table 1. *Classification of haemophagocytic syndromes*

Primary haemophagocytic syndrome
Familial haemophagocytic syndrome type 1-4
Hereditary immune deficiencies
Griscelli type 2 syndrome
Chediak-higashi syndrome
X-bound lymphoproliferative syndrome
Hermansky-Pudlak type 2 syndrome
Autoimmune proliferative syndrome
Secondary haemophagocytic syndromes
Infections
• Viral (Herpes, HIV, Hepatitis, etc)
• Bacterial (Mycobacteria, Mycoplasma, Chlamydia)
• Fungal (Aspergillus, Candida, Histoplasma)
• Parasitic (Falcipurum falciforme)
Autoimmune diseases
• Systemic lupus erythematodes
• Reumatoid arthritis
• Still's disease
• Polyarteritis nodosa
• Sjogren's disease
• Mixed connective tissue disease
• Sclerodermia
Malignancies
• Natural-killer, B- and T-cell lymphoma
• Leukaemia
Chemotherapy

CASE REPORT

A 50-year-old man presented with shivering and relapsing fever for two weeks. He had no other physical complaints. Five years before he was diagnosed with CLL with slowly progressing generalised lymphadenopathy. Seven months before admission he developed anaemia and thrombocytopenia with extensive CLL bone marrow infiltration. Treatment with immunochemotherapy was initiated according to the HOVON 68 protocol with alemtuzumab, fludarabine and cyclophosphamide. The fever started two months after the fifth cycle. Born in Suriname, he had been living in the Netherlands since childhood and had not visited his country of birth again. It had been two years since he had been travelling to urban areas in Oman and Qatar, Malaysia and Thailand. Physical examination was unremarkable except for a temperature of 39.8 °C. Laboratory tests revealed pancytopenia with a haemoglobin of 7.6 mmol/l (normal range (N) 8.7 to 10.9 mmol/l), thrombocytes 112 10^9/l (N 150 to 400*10^9/l), leukocytes 1.4 10^9/l (N 4.5 to 11*10^9/l), alanine aminotransferase 58 U/l (N1 to 41 U/l), lactate hydrogenase (LDH) 510 U/l (N <270 U/l) and a C-reactive protein (CRP) of 82 mg/l (N <10 mg/l). Extensive laboratory tests for viral, bacterial or fungal infections were performed with negative results (blood cultures, serology for Varicella Zoster, HIV, Hepatitis A,B,C, Adenovirus, Parvo B19 virus, *Chlamydia, Mycoplasma, Coxiella* and whole blood polymerase chain reaction (PCR) for Epstein Barr virus and cytomegalovirus, and bone marrow PCR for tuberculosis). A computed tomography (CT) scan of the neck, chest and abdomen showed stable enlarged parajugular and para-aortal lymph nodes, no hepatosplenomegaly and no focus of infection. A bone marrow examination showed granulomatous inflammation with suspicion of a yeast infection and signs of haemophagocytosis. The soluble interleukin-2 (IL2) receptor serum concentration was 13,410 pg/ml (N <2500 pg/ml), ferritin was 510 µg/l (N 22 to 270 µg/l) and triglycerides were 2.33 mmol/l (N <2 mmol/l). A diagnosis of HLH was made (*table 2*) possibly secondary to a yeast infection or chemotherapy.[3,4] Treatment was initiated according to the Histiocyte Society 2004 protocol with daily oral dexamethasone and cyclosporine, and etoposide twice a week intravenously.[4] Continuous intravenous caspofungin was added to treat the yeast infection. Initially the fever quickly disappeared with clinical improvement but ten days after starting treatment, the fever relapsed. Serum ferritin levels and LDH increased and pancytopenia worsened after an initial improvement (*figure 1*). Clinical examination, blood and urine cultures, and repeated chest CT scan revealed no focus of infection. A second bone marrow examination showed extensive haemophagocytosis and a yeast morphologically resembling *Histoplasma capsulatum* (*figure 2*). Later this was confirmed by PCR and culture. Caspofungin was switched to amphotericin B intravenously and the fever disappeared. Also ferritin and LDH levels decreased followed by the soluble IL2 (*figure 1*). After five weeks of treatment cyclosporine was stopped and the dexamethasone was tapered. After two weeks of intravenous amphotericin B therapy the patient was placed on oral itraconazole and was discharged. Six months after discharge he was in excellent clinical condition with normal blood counts, LDH and ferritin.

Table 2. *Histiocyte Society 2004 diagnostic criteria for HLH (5 or more criteria should be fulfilled)*

Fever (>38.5 °C for at least 7 days)
Splenomegaly
Cytopenia (at least 2 of 3 cell lines)
Hypertriglyceridaemia and/or hypofibrinaemia
Haemophagocytosis in bone marrow, spleen or lymph nodes, without signs of malignancy
Ferritin ≥500 µg/l
Soluble IL 2 receptor (Soluble CD25) ≥2500 pg/ml
Low or absent NK-cell activity

Figure 1. *The course of patients disease and treatment over time (x-axis days since admission). The y-axis denotes the response to treatment of soluble IL2 receptor and ferritin concentrations*

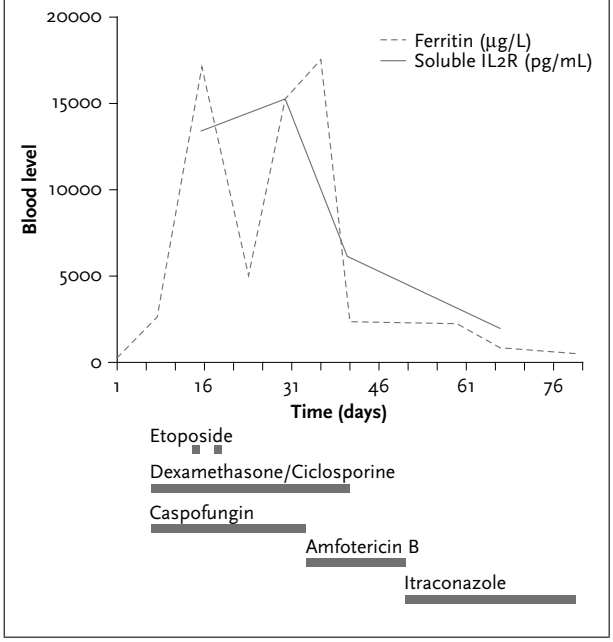
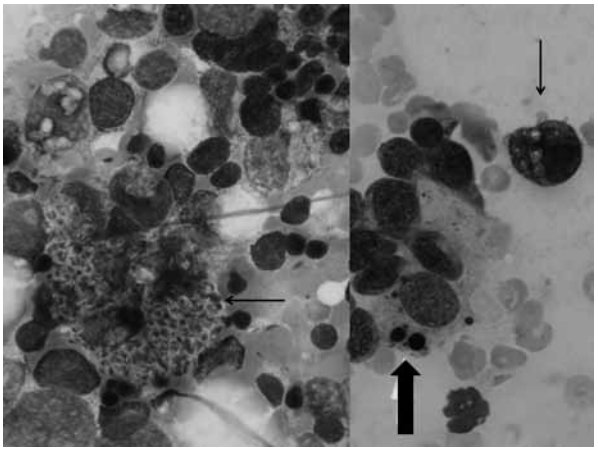


Figure 2. *The second bone marrow aspirate with intracellular Histoplasma capsulatum micro-organisms (fine arrowheads) and haemophagocytosis: two erythrocyte precursor cells phagocytised by a macrophage (thick arrowhead)*



DISCUSSION

Haemophagocytic lymphohistiocytosis presents diagnostic and therapeutic challenges. As symptoms may be non-specific together with the rarity of the disease, HLH is often diagnosed in a late phase.[5] In our patient who presented primarily with fever and pancytopenia the haemophagocytic syndrome was recognised relatively early in the first bone marrow examination. Furthermore, a yeast infection was suggested in this bone marrow specimen. Extensive microbiological investigation for other possible underlying infections delivered negative results. Immunochemotherapy and antifungal therapy with *Candida* and *Aspergillus* species coverage was started. After a short period of clinical improvement, the HLH relapsed. A second bone marrow biopsy showed HLH and *Histoplasma capsulatum* infection. This yeast proved to be resistant to caspofungin and after switching to amphotericin B the HLH was controlled.

When left untreated, primary HLH patients rarely survive; however, since implementation of immunochemotherapeutic interventions survival has increased to more than 50%.[5] Infection-associated HLH mortality has been estimated at 52 to 73%.[1,2] Treatment is aimed at suppression of the uncontrolled, inappropriate inflammatory response and elimination of the underlying cause (*table 1*). Our patient was treated according to the Histiocyte Society 2004 protocol with a combination of dexamethasone, cyclosporine for lymphocyte specific toxicity and etoposide for its antimacrophage action.[4] Although treatment of the underlying infection alone has been associated with recovery in 60 to 70% of patients, immunosuppressive therapy is recommended rather than antimicrobial monotherapy in infection-related HLH.[1,2] Our patient did not complete the Histiocyte Society protocol because of worsening pancytopenia after two gifts of etoposide. This was stopped and dexamethasone and cyclosporine were continued for a total of five weeks (*figure 1*). As no randomised studies concerning secondary HLH treatment have been performed, there is no golden standard for therapy. As the clinical course of our patient showed, treatment of the underlying cause of HLH is of utmost importance.

Histoplasma capsulatum associated HLH has been described before[6-15] in association with HIV infection[6-8] renal and heart transplant recipients,[9,10] patients on prolonged corticosteroid therapy for sarcoidosis or hepatitis C,[11,12] CLL[13] and a few non-immunocompromised patients.[14,15] However, histoplasmosis is rarely diagnosed in northern Europe.[16] *Histoplasma* is endemic in the Mississippi River valley, Central and South America and has been found frequently in southern Europe, South-East Asia and Africa. *Histoplasma* is a dimorphic fungus that behaves like a yeast at 37 °C and can survive in soil like a mould at room temperature. Infection occurs through inhalation of microconidia formed in the mould phase. In the lung the organism is phagocytised by macrophages, converts to a yeast form inside the macrophage and is transported through the reticulo-endothelial system. After weeks cellular immunity mediated by T-helper cells is acquired and macrophages are activated to kill the microorganism.[16] Less than 1% of primarily infected subjects will develop clinical illness: a self-limiting pneumonia with fever, malaise, headache and a dry cough. Older patients are at risk for chronic cavitary pulmonary histoplasmosis. Disseminated histoplasmosis including sepsis and HLH occurs almost exclusively in immunocompromised patients.[17] As with other intracellular microorganisms *Histoplasma* can remain latent in macrophages. When cell-mediated immunity is suppressed, reactivation can cause disease even decades after leaving the endemic area.[16]

CONCLUSION

Histoplasma capsulatum associated HLH is a rare but potentially dangerous cause of fever in immunocompromised patients. Bone marrow examination, ferritin and soluble IL2 receptor are the diagnostic tests of choice. Extensive microbiological testing for underlying infectious causes should be performed. Treatment consists of immunomodulation and elimination of the underlying infection. In this case determination of the infective agent was critical. In addition *Histoplasma* reactivation can occur in immune-suppressed residents of northern European countries years after leaving histoplasma capsulatum endemic areas such as South America.

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