CASE REPORT

Haemophagocytic Syndrome Presenting as Pyrexia of Unknown Origin

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Summary

Haemophagocytic syndrome (HPS) should be included in the differential diagnosis of pyrexia of unknown origin (PUO). The hallmark of HPS is the accumulation of activated macrophages that engulf haematopoietic cells in the reticuloendothelial system. We describe a patient with unexplained fever in which a final diagnosis of HPS was established in a bone marrow study.

Key Words: Haemophagocytic syndrome, Pyrexia

Introduction

High-grade fever, lymphadenopathy and progressive cytopenia are characteristic presentations of HPS. HPS is a rare, often fatal disorder in which up-regulation of tissue macrophage activity results in uncontrolled haemophagocytosis and release of inflammatory cytokines. Prompt recognition of HPS is essential for the initiation of appropriate therapy. A previously healthy patient was referred for PUO associated with pancytopenia and the bone marrow examination revealed reactive HPS. Thus, a bone marrow study should be considered in all patients with unexplained fever associated with progressive pancytopenia.

Case report

A 19-year-old Malay lady was admitted because of a 2-month history of high grade fever. There was no history of insect bites, residence in a rural area and contact with patients with tuberculosis. She had seen several general practitioners and received various types of antibiotics. There was no history of sexual promiscuity and intravenous drug abuse.

On admission, the patient was febrile (38.2℃) and pale. There were maculo-papular rash over the face, neck and extensor aspect of the upper and lower limbs. There were multiple enlarged tender lymph nodes, measuring 1 to 3 cm over the posterior aspect of the cervical region. The liver and spleen were moderately enlarged. Examination of the other systems was unremarkable.

The haemoglobin was 90 g/l, white cell count 1.0 x $10^9/\ell$ (neutrophils 0.5 x 10^9/l, lymphocytes 0.5 x 10^9/l), and platelet count 68 x 10^9/l. The erythrocyte sedimentation rate and serum lactate dehydrogenase were elevated. Blood cultures, Widal-Weil-Felix test, and serologic tests for EBV, CMV, HIV, Toxoplasma, leptospira, and syphilis were negative. Serologic tests for collagen disease, tuberculin test and chest radiograph were unremarkable. Coagulation profile was normal.

Microscopic examination of the peripheral blood smears (Fig. 1A) showed atypical lymphocytes and no blast. The bone marrow (Fig. 1B) was heavily infiltrated with numerous histiocytes containing

This article was accepted: 15 August 2005

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normoblasts, erythrocytes, granulocytes and platelets consistent with haemophagocytosis. There were no granulomata, lymphoma cells, blast cells and dysplastic changes in the bone marrow (not shown). The lymph node biopsy showed only reactive hyperplasia.

Table I: Conditions associated with haemophagocytic syndrome

Malignant histiocytosis
Reactive haemophagocytic syndromes
• Viral infection: Herpes viruses, adenoviruses, rubella, measles, HIV
• Bacterial infection: Typhoid fever, miliary tuberculosis
• Protozoan: Toxoplasmosis, leishmaniasis
• Rickettsiae: Rocky Mountain spotted fever, Q fever
• Fungi: histoplasmosis, candidiasis
• Leptospirosis
• Lymphomas
• Systemic lupus erythematosus
• Sarcoidosis
• Drug-associated (e.g. phenytoin)
Familial haemophagocytic lymphohistiocytosis

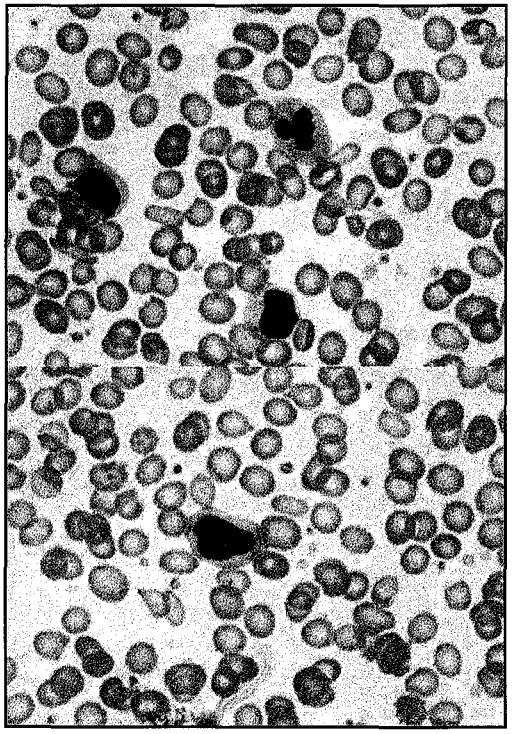

Fig. 1a:Full blood picture showed atypical lymphocytes

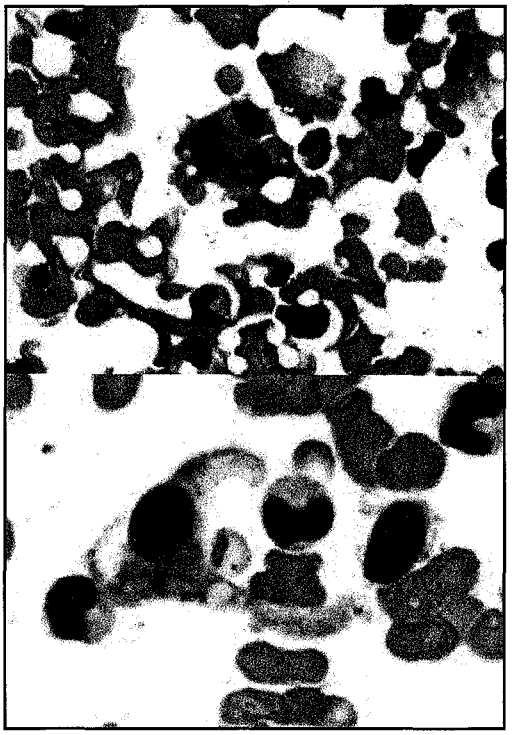

Fig. 1b:The bone marrow was infiltrated with numerous histiocytes demonstrating haemophagocytosis

Discussion

Haemophagocytosis is a phenomenon seen in cytology or tissue sections where histiocytes are seen to engulf a variety of haematopoietic cells. HPS results from increased proliferation of macrophage or histiocyte precursors associated with haemophagocytosis in the bone marrow and elsewhere in the reticuloendothelial system, which, when marked, leads to various cytopenias[2]. The proliferating histiocytes may be part of a malignant clone or may be reactive. Since the incidence of malignant histiocytosis is currently believed to be very rare, a rigorous search is required for underlying lymphoid malignancy or infection once the diagnosis of HPS is made. Reactive HPS are commonly caused by bacterial or viral infections, and lymphoma, particularly T cell and NK cell lymphoma (Table I)[1]. Occasionally, reactive HPS occurred in the absence of obvious underlying disease as observed in the present case.

BM examination can differentiate malignancy-associated HPS from reactive HPS with a high level of accuracy. In reactive HPS, the most prominent histologic feature is the proliferation of benign histiocytes displaying a high degree of haemophagocytosis. The macrophages are mainly mature and lack atypical features and the bone marrow aspirate may also show other abnormalities due to the primary disease e.g. lymphoma cells or granuloma. In malignant histiocytosis, the bone marrow is infiltrated with mainly immature and atypical histiocytes and phagocytosis is minor in comparison with that seen in reactive conditions.

Common clinical features of HPS are fever, hepatosplenomegaly and lymphadenopathy and in severe cases, coagulopathy and organ failure[1]. The clinical features in patients with HPS can be explained by hypercytokinemia that results from T cell and/or macrophage activation. Various cytokines such as IFN-γ, TNF-α, IL-6 and IL-2 play a major role in the pathogenesis of HPS[2]. Serum cytokine levels may thus be monitored to predict the severity and prognosis of HPS patients.

Most cases of reactive HPS have a fulminant course with a mortality rate of 20 – 42% for infection-associated HPS (IAHS) and almost 100% for non-IAHS[3]. Standard treatment has not yet been well established. However, successful therapy aiming at cytokine regulation has been reported in viral-associated HPS[6]. Outcome of bacterial- and malignancy-associated HPS mainly depends on the effectiveness of treatment directed to the associated disorders[1].

The combination of prolonged fever, skin rash, lymphadenopathy, hepatosplenomegaly and pancytopenia associated with haemophagocytosis in the present cases is supportive of a diagnosis of HPS. While in the ward, the patient developed oral thrush, new cervical lymphadenopathy and worsening pancytopenia. Apart from fluconazole, the patient did not receive specific therapy. The outcome of HPS in the absence of overt infection or malignancy as observed in the present case is not known. Three weeks after admission, the symptoms disappeared and the blood counts normalised.

The prognosis of patients with HPS depends significantly on the severity of the magnitude of cytokine storm, the underlying disease and the immune status of the patient. Accordingly, as demonstrated in the present case, reactive HPS with no vital organ involvement and no associated infection or lymphoid malignancy in an immunocompetent host has a favourable outcome and may resolve without specific treatment.

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