CASE REPORT

Fatal Haemophagocytic Syndrome

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Summary

A fulminant clinical presentation with high fever and hepatosplenomegaly, together with a deteriorating course of worsening pancytopenia, coagulopathy and liver failure, is suggestive of the haemophagocytic syndrome (HPS). Bone marrow examination is diagnostic. We present 3 cases of HPS associated with different aetiologies including acute Ebstein Barr virus infection, T cell lymphoma, and malignant histiocytosis. In all the cases, the diagnosis was made late and the patients succumbed before definitive therapy could be administered.

Key Words: Haemophagocytosis, Malignant histiocytosis, Ebstein Barr virus, Lymphoma, Histiocytes

Introduction

Haemophagocytosis is a phenomenon seen in cytology specimens or tissue sections where histiocytes are seen to engulf a variety of haemopoietic cells. Haemophagocytic syndrome (HPS) presents with fever, pancytopenia, liver dysfunction and increase in haemophagocytic histiocytes in various organs. There are 2 major clinical entities related to the HPS: the aggressive disease known as malignant histiocytosis and the more benign, reactive HPS such as virus-associated HPS[1]. It may be difficult to distinguish malignant HPS from reactive HPS by the clinical course and laboratory data. Early and accurate diagnosis is vital to enhance the chance of success of treatment. This report highlights the need to recognise HPS so that early diagnosis of the associated conditions can be made.

This article was accepted: 15 October 2001

Case Reports

Case 1

A 45-year-old man was referred for evaluation of persistent fever, pancytopenia and liver dysfunction. He presented with a 2-month history of fever, weight loss and anorexia. On examination, he was jaundiced, febrile (T 38.9°C) and toxic looking. There was generalised lymphadenopathy. The liver and spleen were enlarged 6cm below the costal margins. The haemoglobin (Hb) was 8.6g/dl, leucocyte count (WBC) 3.2 x 10^9/l and platelet count (PC) 68 x 10^9/l. The prothrombin time, partial thromboplastin time and thrombin time were markedly prolonged and serum fibrinogen was low. The serum bilirubin (SB), alanine transaminase (ALT) and alkaline phosphatase (ALP) levels were markedly elevated. Blood cultures were repeatedly

negative. There were renal impairment and hypoglycaemia. The serum lactate dehydrogenase (LDH) was raised at 8649 U/l. A CT scan of the abdomen showed multiple nodules in the spleen and enlarged para aortic lymph nodes. Microscopic examination of the peripheral blood showed leucoerythroblastic picture. Bone marrow aspirate showed abnormal lymphoid cells (70% of total nucleated cells) and florid haemophagocytosis. Immunophenotyping of the lymphoid cell showed that they are positive for T cell markers. Trephine biopsy showed similar findings. A diagnosis of T cell lymphoma was made on day 10 of admission. However, the patient was deemed too ill then for initiation of cytotoxic chemotherapy. He had received several broad-spectrum antibiotics but his condition did not improve and he died on day 14 of admission. Histopathologic examination of the liver at autopsy demonstrated massive necrosis, florid haemophagocytosis, and lymphoma cell infiltration in the portal and periportal areas. Similar findings were observed in the splenic and lymph node specimens.

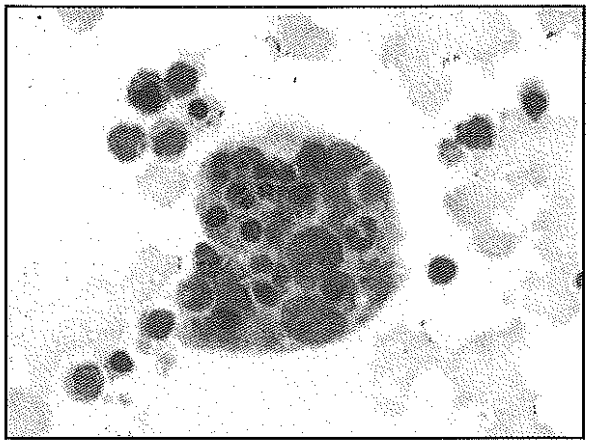

Fig. 1: Smear of the bone marrow aspirate (May-Grunwald-Giemsa, X400) showing haemophagocytosis.

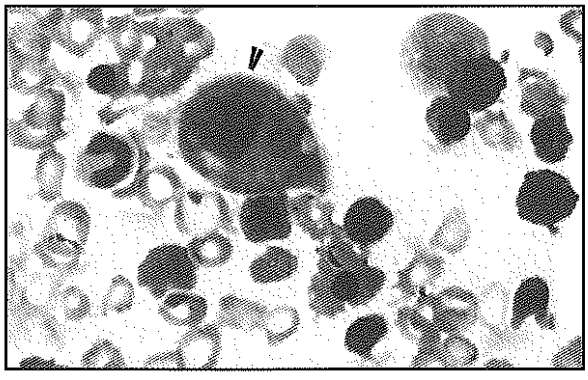

Fig. 2: Smear of the bone marrow aspirate (May-Grunwald-Giemsa, X400) showing a malignant histiocyte.

Case 2

A 24-year-old man presented with a 3-week history of fever and myalgia. Examination revealed an ill patient who was febrile (T 38.6°C) and tachypnoeic. The blood pressure was 90/58 mmHg and pulse rate 124 per minute. The cervical lymph nodes were enlarged. The liver was enlarged 5cm below the right costal margin and it was tender. The spleen was palpable 3 cm below the left costal margin. The Hb was 8.7g/dl, WBC 2.8 x 10^9/l, PC 45 x 10^9/l. The liver function test was grossly abnormal. Serum LDH was raised and coagulation study was consistent with the presence of disseminated intravascular coagulopathy (DIC). The chest radiograph showed nodular opacities in the middle and lower zones of the lung. Peripheral blood smears showed 35% atypical lymphocytes and no blast cell. Prominent haemophagocytosis was evident in the bone marrow specimens (Figure 1). The EBV IgM was positive and HIV serology was negative. A diagnosis of EBV-associated haemophagocytic syndrome was made on day 14 of admission. The patient was ventilated and despite aggressive supportive measures, he died 3 days after the diagnosis was made.

Table I
Summary of Clinical Features of Patients with Fatal Haemophagocytic syndrome

Parameters	Case No.		
	1	2	3
Age/Sex	45 yrs, Male	24 yrs, Male	37 yrs, Male
Presenting Complaint	Fever, weight loss Anorexia 2 month	Fever, myalgia 3 weeks	Fever, malaise 4 weeks
Presenting findings	Jaundice, generalised LN hepatosplenomegaly	Jaundice. cervical LN hepatosplenomegaly	Jaundice hepatosplenomegaly
FBC	Hb 8. g/dl, WBC 3.2x10^9/l PC 68 x 10^9/	Hb 8.7g/dl, WBC 2.8 x 10^9/l PC 45 x 10^9/l	Hb6.9 g/dl, WBC 2.1 x 10/l PC 38 x 10^9/l
LFT	TP 52, Alb 20, SB 265 ALT 448, ALP 734	TP 55,Alb 28, SB 250 ALT 248, ALP 534	TP 53, Alb 24, SB 218 ALT 360, ALP 454
Se LDH	8649	1068	2035
BM findings	Lymphoma cells Haemophagocytosis	Reactive haemophagoctosis	Malignant histiocytes Haemophagocytosis
Final diagnosis	T-cell Non-Hodgkin's lymphoma	EBV-associated HPS	Malignant histiocytosis
Outcome	Died on day14 of admision	Died on day 17 of admision	Died on day 27 of admision

TP = total protein (62 - 80g/l); Alb = albumin (30 - 51g/l), SB = serum bilirubin (3 - 24 umol/l);
ALT = alanine transminase (7 - 40U/l); ALP = alkaline phosphatase (32 - 110U/l);
LDH = lactate dehydrogenase (230 - 460U/l); LN = lymph nodes; BM = bone marrow

Case 3

A 37-year-old man presented with a 4-week history of fever and malaise. On examination, he was jaundiced, febrile (T 40.2°C) and pale. The peripheral lymph nodes were not palpable. The liver and spleen were enlarged 6cm below the right and left costal margins respectively. There was pancytopenia. Serum LDH was raised and the DIC test was positive. The liver function test was impaired. Serum ferritin was markedly elevated at 68000ng/ml. Septic work up including blood, urine, and marrow cultures were negative. Serological tests for EBV, CMV, HSV, VZV, HIV, dengue virus, Hepatitis A and B virus were negative. Bone marrow study revealed histiocytic hyperplasia with relatively few haemophagocytosis. The histiocytes constituted either 50 or 60% of the total nucleated cells in the marrow and appeared immature (Figure 2). Immunohistochemical studies of the trephine biopsy were positive for macrophage markers and negative for CD30 (Ki-1), T or B cell markers. There was no histological evidence of fungal or mycobacterium infection. A diagnosis of malignant histiocytosis was made after 3 weeks of admission. There was worsening of the cytopenia and liver function. The patient developed acute renal failure, upper gastrointestinal bleeding and bronchopneumonia while he was ventilated in the intensive care unit and succumbed 6 days after confirmation of the diagnosis.

Discussion

In 1985 the Histiocytic Society[2] set guidelines for the diagnosis of haemophagocytic lymphohistiocytosis, which included (1) fever ≥38.5°C for 7 days or more; (2) splenomegaly 3cm below costal margin; (3) bicytopenia or pancytopenia with Hb < 9g/dl, neutrophlis < 1 X10⁹/l and PC < 100 x 10⁹/l; (4) hypertrigliceridaemia or hypofibrinogenaemia (fasting triglyceride >2.0mmo/l, fibrinogen <1.5g/l), and (5) haemophagocytosis in marrow, spleen or lymph nodes. The 3 cases described above presented with classical features of HPS including high fever, hepatosplenomegaly, and a deteriorating course with worsening pancytopenia, coagulopathy and liver failure and increase haemophagocytic histiocytes in various organs. Among many kinds of viruses that could cause HPS, Epstein Barr virus (EBV), cytomegalovirus, herpes simplex virus and varicella zoster virus are the common causes of viral-associated HPS (VAHS). Recent report[1] suggests that VAHS due to EBV may be a preneoplastic condition; cytotoxic chemotherapy is indicated for fulminant VAHS induced by EBV. The absence of a positive EBV serology may exclude an acute EBV infection but does not exclude an EBV-associated disease. There are reports of cases of peripheral T cell lymphoma with detectable EBV genome without elevated EBV lgM but with other serological markers of past infection[3]. Among the lymphomas, T cells and NK cells are the predominant cell types associated with HPS. Reactive HPS often follows a rapidly progressive, fulminant and fatal course, so it may be difficult to distinguish malignant histiocytosis from HPS due to viruses or lymphomas[1]. Reactive HPS (as noted in Case 1 and Case 2) should be suspected when the invading histiocytes show maturity and display a high degree of haemophagocytosis, while the presence of immature and atypical histiocytes with minimal phagocytic activity (as observed in Case 3) strongly suggests a malignant nature of the histiocytic proliferation.

The 3 cases described here had a fulminant course where deterioration developed within a few weeks of onset of the illness. In addition, the lack of recognition of the presence of HPS among these cases had contributed to the delay in making the diagnosis of its related conditions. All of our patients were too ill to receive cytotoxic chemotherapy when the diagnosis was confirmed and died within 2 to 4 weeks of presentation to the hospital. The overall survival malignancy-associated HPS was reported to be less than 6 weeks in untreated cases[3]. Prognosis seems to be better in those cases where cytotoxic treatment was given early. A 68% complete response and 2 years median survival had been obtained with CHOP chemotherapy[3]. This strongly supports the early institution of chemotherapy, even in critically ill patients as it offers the only chance of survival.

In conclusion, HPS must be considered in the differential diagnosis of persistent fever associated with hepatosplenomegaly, progressive pancytopenia, liver dysfunction and coagulopathy. Early diagnosis and treatment of malignancy associated HPS may lead to improved survival in an otherwise aggressive and rapidly fatal condition.

References

1. Kaito K, Kobayashi M, Katayama T *et al.* Prognostic factors of hemophagocytic syndromes in adults: analysis of 34 cases. Eur J Haematol 1997; 59: 247-53.
2. Henter JH, Elinder G, Ost A, the FHL Study Group of the Histiocytic Society. Diagnostic guidelines for hemophagocytic lymphohistiocytosis. Semin Oncol 1991; 18: 29-33.
3. Linn YC, Tien SL, Lim LC *et al.* Haemophagocytosis in bone marrow aspirate - A review of the clinical course of 10 cases. Acta Haematol 1995; 94: 182-91.