

Short reports

Prominent dyserythropoiesis in four cases of haemophagocytic lymphohistiocytosis

M Macheta, A M Will, J B Houghton, R F Wynn

Abstract

Haemophagocytic lymphohistiocytosis (HLH) is a disease characterised by peripheral blood pancytopenia secondary to haemophagocytosis of formed blood cells by activated histiocytes. The demonstration of haemophagocytosis may be difficult and the diagnosis may require repeated tissue sampling (including bone marrow, cerebrospinal fluid, lymph nodes, spleen, and liver) and the demonstration of associated clinical or laboratory features. This report describes pronounced dyserythropoiesis in the bone marrow aspirates in four patients with HLH, including familial and secondary cases. In three patients, bone marrow haemophagocytosis was inconspicuous or absent, and the prominent dyserythropoiesis may have suggested an alternative diagnosis. The dyserythropoiesis observed should be added to the constellation of clinical and laboratory features associated with HLH.

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Haemophagocytic lymphohistiocytosis (HLH) is a generalised, non-malignant histiocytic proliferation with prominent phagocytosis of formed blood cells resulting in pancytopenia. It presents with fever and symptoms of anaemia, thrombocytopenia, and neutropenia. On clinical examination there is typically splenomegaly and there may be a macular rash, lymphadenopathy, and evidence of central nervous system (CNS) involvement. Pathologically, there is accumulation of haemophagocytic histiocytes in the bone marrow, spleen, lymph nodes, and CNS.

HLH can be acquired or inherited in an autosomal recessive fashion (familial haemophagocytic lymphohistiocytosis (FHL)). FHL is a rare and rapidly fatal disorder presenting in infancy and early childhood with the typical features of HLH. The diagnosis is justified by a family history of HLH or parental consanguinity. Epstein-Barr virus infection is an important trigger of both FHL and acquired HLH. Cytomegalovirus, herpes simplex, human

immunodeficiency virus, bacteria, and parasitic agents have also been implicated.^{1–4} Non-Hodgkin's lymphoma and connective tissue diseases may also be associated with HLH.⁵

The diagnosis of HLH requires the demonstration of haemophagocytic histiocytes in tissue biopsies in association with pancytopenia, fever, and hepatosplenomegaly, and may be supported by the demonstration of hypofibrinogenemia or hypertriglyceridemia.⁶ Raised cerebrospinal fluid (CSF) protein concentrations and CSF pleocytosis are found in 50% of patients. However, haemophagocytosis in the marrow aspirate and other tissues may be inconspicuous and repeated biopsies may be necessary.

We describe four cases of HLH in which pronounced dyserythropoiesis was seen in the bone marrow aspirate. In three cases, this was the only abnormality in the presentation sample.

Case reports

CASE 1

A 14 week old boy presented with seven days of fever, abdominal swelling, and upper respiratory tract symptoms. Findings on examination were a fever of 39.9°C, jaundice, and pronounced hepatosplenomegaly. The haemoglobin concentration was 50 g/litre, white blood cell count (WCC) was 2.5×10^9 /litre, neutrophils were 0.8×10^9 /litre, platelets were 54×10^9 /litre, and fibrinogen was < 0.5 g/litre (normal, 2.0–4.0 g/litre). The bilirubin concentration was 85 μ mol/litre (normal < 17), ALT was 229 iu/litre (normal, 0–45), and alkaline phosphatase was 260 iu/litre (normal,

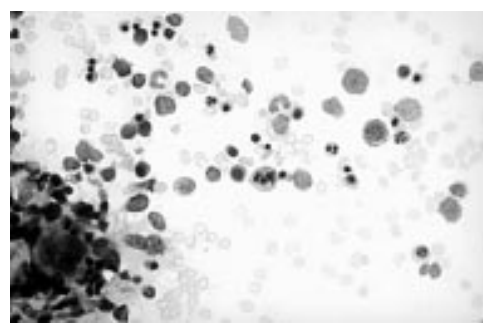


Figure 1 Photomicrograph of the bone marrow aspirate in case 1 showing erythroblasts with trilobed and "clover leaf" nuclei, chromatin fragmentation, and early megaloblastic changes (Wright's stain).

Department of Paediatric Haematology, Royal Manchester Children's Hospital, Hospital Road, Pendlebury, Manchester M27 4HA, UK

M Macheta
A M Will
R F Wynn

Department of Haematology, Hope Hospital, Stott Lane, Manchester M6 8HD, UK

J B Houghton

Correspondence to: Dr Wynn
rwynn@mch.srht.nwest.nhs.uk

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150–1100). A bone marrow aspirate on the second day was normocellular and erythropoiesis was dysplastic. In many erythroblasts the nuclei were bilobed or trilobed and some had “clover leaf nuclei” (fig 1). Other cytological abnormalities in the erythroid precursors were fragmentation and delayed maturation of nuclear chromatin, Howell-Jolly bodies, and basophilic stippling. Occasional histiocytes and haemophagocytosis were seen. The patient did not respond to initial treatment with broad spectrum antibiotics or amphotericin and he became increasingly hypoxic with interstitial shadowing on chest x ray. Fasting plasma triglycerides were normal. Liver function tests and the blood counts deteriorated further. Respiratory syncytial virus was isolated from nasopharyngeal secretions and nebulised ribavirin was given. Many large haemophagocytic histiocytes were present in a repeat marrow aspirate taken on the fifth day. Treatment for HLH was commenced with etoposide 150mg/m² twice weekly and dexamethasone 10 mg/m² daily but there was no clinical or haematological response, and he later died from multiorgan failure.

CASE 2

An 18 month old boy presented with seven days of coryza, cough, fever, and diarrhoea. The findings on examination were a fever of 38°C, a macular rash, and signs of basal consolidation in the right lung. The haemoglobin concentration was 79 g/litre, WCC was 2.1×10^9 /litre, platelets were 125×10^9 /litre, neutrophils were 0.15×10^9 /litre, and fibrinogen was 0.9 g/litre. Bilirubin was 11 µmol/litre, ALT was 5 iu/litre, and alkaline phosphatase was 1880 iu/litre. The patient was treated with broad spectrum antibiotics and amphotericin but he remained febrile. Bacteriological and viral studies were negative. Fasting plasma triglycerides were normal. A bone marrow aspirate on the second day was normocellular and erythropoiesis was dysplastic. Many erythroblasts were binucleated or trinucleated, and there was fragmentation and delayed maturation of nuclear chromatin, nuclear lobulation, and basophilic stippling. Occasional histiocytes and haemophagocytosis were noted in the marrow aspirate. Later examination of the marrow trephine biopsy showed a diffuse infiltrate of haemophagocytic histiocytes. On examination of the CSF, the WCC was 160/mm³ (monocytes 70%, lymphocytes 30%), red blood cell count was 12/mm³, and the total protein concentration was 0.75 g/litre (normal, < 0.45 g/litre). Treatment for HLH was begun with dexamethasone 10 mg/m² daily, etoposide 150 mg/m² twice weekly, and intrathecal methotrexate, following which there was a gradual clinical improvement and normalisation of haematological abnormalities. There was no evidence of haemophagocytosis or dyserythropoiesis when a repeat bone marrow aspirate was examined 10 weeks later.

CASE 3

A 7 month old girl of consanguineous parents presented with a three week history of fever,

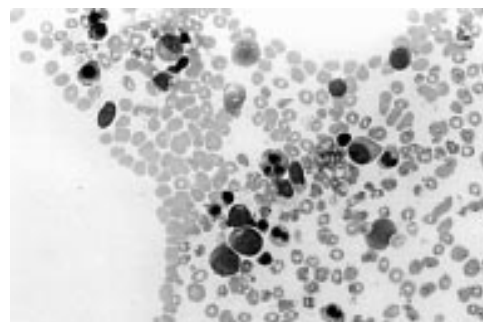


Figure 2 Photomicrograph of the bone marrow aspirate in case 3 showing abnormal erythroblasts with three nuclei or bilobed nuclei (Wright's stain).

coughing, and vomiting. There was a history of unexplained death of a sibling at the age of 1 year. The findings on examination were fever of 38.4°C and hepatosplenomegaly. The haemoglobin concentration was 79 g/litre, WCC was 2.8×10^9 /litre, neutrophils were 0.6×10^9 /litre, platelets were 22×10^9 /litre, and fibrinogen was 1.36 g/litre. A bone marrow aspirate on the first day was normocellular and erythropoiesis was dysplastic. Many erythroblasts were binucleated or trinucleated (fig 2). Fragmentation and delayed maturation of nuclear chromatin in the erythroblasts was also seen. A slight increase in histiocytes but only occasional haemophagocytosis was present. The patient was initially treated with broad spectrum antibiotics but the fever continued and she later developed a macular rash, axillary lymphadenopathy, and abnormal posturing. Liver function tests were normal and the fasting plasma triglycerides were 3.62 mmol/litre (normal, 0.9–1.4). Viral and bacteriological studies were negative. On CSF examination the total protein concentration was 1.16 g/litre, WCC was 3/mm³ (92% lymphocytes, 8% histiocytes), and red blood cells were < 1/mm³. Histological examination of an axillary lymph node showed pronounced loss of follicles with large numbers of haemophagocytic histiocytes in the paracortex and sinuses. A repeat bone marrow aspirate on the sixth day showed a diffuse increase in haemophagocytic histiocytes. Treatment for FHL was begun with dexamethasone 10 mg/m² daily and etoposide 150 mg/m² twice weekly. Her symptoms and signs gradually resolved and the blood count and coagulopathy normalised. Three months later she received a bone marrow transplant from her older HLA identical sister and she remains well in remission 12 months later.

CASE 4

A 26 year old woman presented with three weeks of malaise, fevers, and myalgia. The findings on examination were a fever of 39°C and widespread bruising. The haemoglobin concentration was 104 g/litre, WCC was 2.2×10^9 /litre, neutrophils were 1.1×10^9 /litre, platelets were 70×10^9 /litre, and fibrinogen was 0.5 g/litre. Bilirubin was 52 µmol/litre, ALT was 64 iu/litre, and alkaline phosphatase was 788 iu/litre (normal, 30–130). A bone marrow aspirate showed a pronounced increase in haemophagocytic histiocytes. Many erythroblasts

were abnormal with irregular or lobulated nuclei, and fragmentation and delayed maturation of nuclear chromatin. The only abnormality on a computed tomography scan of the chest, abdomen, and pelvis was slight splenomegaly. She was initially treated with broad spectrum antibiotics and 5 mg/kg cyclosporin A. She remained febrile, and the pancytopenia and liver function tests progressively deteriorated. Bacteriological and viral studies were negative. A bone marrow trephine biopsy showed no evidence of infiltration with lymphoma. She later died from hepatic failure.

Discussion

Dyserythropoiesis was a prominent feature of the bone marrow cytology in these cases. In each case, the morphology of the myeloid and megakaryocytic series was normal, the bone marrow karyotype was normal, haematinic assays were within the normal range, iron was demonstrated in the bone marrow by Perls' stain, and siderotic granulation was not seen in the erythroid precursors. In none of these patients was there a history of exposure to toxins, cytotoxic drugs, or radiation. Therefore, there was no other explanation for the dyserythropoiesis seen in the bone marrow in these cases. In two cases, dyserythropoiesis had resolved on repeat bone marrow examination after treatment.

Although haemophagocytic histiocytes are central to the pathology of HLH, they may be difficult to demonstrate in the early stages. They are most commonly seen in spleen or lymph node biopsies. Lymph node histology may initially show only an immunoblastic proliferation and in the later stages infiltration with haemophagocytic histiocytes. The initial bone marrow aspirate is non-diagnostic in two thirds of cases and often shows hyperplasia with inconspicuous or absent histiocytes.⁷ The first bone marrow aspirate was non-diagnostic in three of the cases reported here. Infiltration by haemophagocytic histiocytes was seen in repeat samples or was present in a trephine biopsy sample that became available later. The finding of occasional haemophagocytic histiocytes in these cases is non-specific and may also occur in cases of severe infection, aplastic anaemia, or

bone marrow allograft rejection, and following blood transfusion or parenteral nutrition.

In the absence of histological evidence of haemophagocytosis the diagnosis may rest on the presence of associated clinical and laboratory features.⁶ Confirmation may require repeated tissue sampling. However, untreated or unrecognised HLH may be rapidly progressive and fatal, particularly in immunosuppressed patients. Therefore, early recognition is important because treatment with steroids and etoposide, or cyclosporin A, may be effective.^{8,9} In life threatening cases, treatment must be started before the complete clinical picture, including haemophagocytosis, can be documented.

Abnormal dysplastic erythropoiesis as seen in these four cases has not previously been described. The presence of pronounced dyserythropoiesis in the absence of increased haemophagocytic histiocytes may suggest an incorrect diagnosis, such as myelodysplasia, haematinic deficiency, toxic or drug effects, congenital dyserythropoietic anaemia, haemolytic anaemia, or aplastic anaemia, and so delay the diagnosis of HLH and the start of potentially life saving treatment. We believe that dyserythropoiesis may be added to the constellation of clinical and laboratory features accompanying HLH.

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