A rare disease presenting as pyrexia, hepatosplenomegaly and pancytopenia

Introduction

This article examines the case of a 48-year-old North African man presenting with fevers, night sweats, a dry cough and weight loss. He was initially treated with antibiotics for sepsis of unknown origin and was investigated extensively to identify a cause. Liver biopsy revealed an increase in histiocytes and blood results were consistent with a diagnosis of haemophagocytic lymphohistiocytosis. He was treated with etoposide, dexamethasone and prophylactic co-trimoxazole and itraconazole. Although initial response was promising, he unfortunately died of neutropenic sepsis, despite intensive care support.

Discussion

Haemophagocytic lymphohistiocytosis is an exceedingly rare but life-threatening condition with an estimated prevalence of 1 in 100 000 persons less than 18 years of age (Niece et al, 2010). The pathogenesis is complex and poorly understood but is characterized by an exaggerated inflammatory response, involving uncontrolled activation of lymphocytes and macrophages with resulting cytokine storm. Evidence of haemophagocytosis within the bone marrow is an important but not essential diagnostic finding. The HLH Study Group of the Histiocyte Society has formulated criteria to assist in the challenge of diagnosing the disorder (*Table 1*).

Occurring at any age, two distinct forms (primary/genetic *vs* secondary/acquired) have been described. At least four distinct genetic mutations have been found in primary haemophagocytic lymphohistiocytosis, and it has been postulated that derangement of Toll-like receptor signalling pathways may be a common feature (Janka and Lehmberg, 2013). Secondary haemophagocytic lymphohistiocytosis is often associated with concomitant infection; Epstein–Barr virus infection in particular, may be a common trigger. Haemophagocytic lymphohistiocytosis may also be precipitated by malignancy, rheumatological disease and immunodeficiency syndromes (Janka and Lehmberg, 2013).

Treatment of the condition is difficult, but involves immunosuppresive regimens (including etoposide and dexamethasone) with a goal of suppressing the hyperinflammatory response. Consolidation with stem cell transplantation can be considered as the disease can relapse without warning (Henter et al, 2007). The trigger should be sought with extensive testing and specific treatment commenced once identified. For those unresponsive to conventional therapy, plasmapheresis remains an option (Matsumoto et al, 1998). BJHM

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Case Report

A 48-year-old North African man presented with a 4-week history of fevers, night sweats, weight loss, and a dry cough. Past medical history included tuberculosis (fully treated in 1985), which had presented with similar symptoms at the time. He took no regular medications. Aside from an uncle with leukaemia, there was no significant family history. He denied use of alcohol, tobacco, recreational drugs or risk-taking behaviours. He had been to North Africa 3 months previously.

On admission, his temperature was 39.1°C. Respiratory rate was 16 breaths per minute, oxygen saturations 98%, pulse 95 beats per minute and blood pressure 101/66 mmHg. Examination of his respiratory, cardiovascular and neurological systems was unremarkable. Abdominal examination revealed tender hepatosplenomegaly, with no palpable lymphadenopathy.

The full blood count showed pancytopenia, with white cell count 2.1×10^9/litre, neutrophils 0.7×10^9/litre, haemoglobin 122 g/litre and platelets 62×10^9/litre. Liver function tests were deranged, with alanine transaminase 111 IU/litre, alkaline phosphatase 226 IU/litre, gamma glutyl-transferase 126 IU/litre and bilirubin 20 μmol/litre. Blood film showed reactive lymphocytes and no blasts. Chest X-ray and urine dipstick were unremarkable.

He was treated for sepsis of unknown origin with broad-spectrum antibiotics. A computed tomography scan of the chest, abdomen and pelvis showed an enlarged liver (20 cm) and spleen (20 cm) but no other significant abnormalities.

Serial blood cultures and serology for human immunodeficiency virus, viral hepatitis, leishmaniasis, bilharzia, cytomegalovirus, Epstein–Barr virus, malaria, tuberculosis and brucellosis were all negative. Bone marrow aspirate and trephine revealed hypercellular trilineage haematopoiesis, increased macrophage activity, with some erythrophagocytosis, but no evidence of abnormal infiltrate or leukaemia. Liver biopsy revealed an increase in histiocytes, which in conjunction with the bone marrow findings were suggestive of a haemophagocytic syndrome. Soluble CD25 levels were >20 000 U/ml, ferritin 20 109 ng/ml and triglycerides 3.12 mmol/litre, which were consistent with a diagnosis of haemophagocytic lymphohistiocytosis.

Antibiotics were stopped despite ongoing fevers and he was commenced on a regimen of etoposide, dexamethasone and prophylactic co-trimoxazole and itraconazole (Henter et al, 1997). Initial response to chemotherapy was promising, with resolution of fever, along with reduction in organomegaly and ferritin levels. He was discharged with a plan for weekly etoposide and steroids. Unfortunately he was readmitted with neutropenic sepsis, from which he died 4 days later despite intensive care support.

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Janka GE, Lehmberg K (2013) Hemophagocytic lymphohistiocytosis: Pathogenesis and treatment. *Hematology Am Soc Hematol Educ Program* 2013: 605–11 (doi: 10.1182/asheducation-2013.1.605)
Matsumoto Y, Naniwa D, Banno S, Sugiura Y (1998) The efficacy of therapeutic plasmapheresis for the treatment of fatal hemophagocytic syndrome: Two case reports. *Ther Apher* **2**(4): 300–4 (doi: http://dx.doi.org/10.1111/j.1744-9987.1998.tb00127.x)
Niece JA, Rogers ZR, Ahmad N, Langevin AM, McClain KL (2010) Hemophagocytic lymphohistiocytosis in texas: Observations on ethnicity and race. *Pediatr Blood Cancer* **54**(3): 424–8 (doi: 10.1002/pbc.22359)

Table 1. Diagnostic criteria of haemophagocytic lymphohistiocytosis (Histiocyte Society)

Diagnosis is based on fulfilling one or both criteria:	
1. Molecular diagnosis consistent with haemophagocytic lymphohistiocytosis	
2. Five of the following features:	Fever
	Splenomegaly
	Cytopenias (affecting two or more of three lineages in the peripheral blood)
	Hypertriglyceridaemia
	Hypofibrinogenaemia
	Elevated ferritin level
	Elevated soluble CD25 level
	Low or absent natural killer-cell activity
	Haemophagocytosis in bone marrow, spleen or lymph nodes

From Henter et al (2007)

LEARNING POINTS

- Although rare, the diagnosis of haemophagocytic lymphohistiocytosis should be considered in any patient presenting with the triad of persistent pyrexia, hepatosplenomegaly and cytopenias.
- Early haematology involvement in suspected cases is essential.
- Management is challenging and involves immunosuppressive regimens and treatment of any specific trigger.

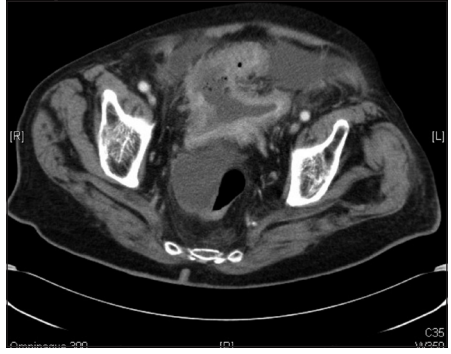
Spontaneous rupture of the urinary bladder

Rupture of the urinary bladder is usually traumatic following penetrating injury, perurethral manipulation or blunt trauma to the abdomen. The normal anatomical position and elasticity of the urinary bladder is protective, but any pathological changes in the bladder wall (inflammation, malignancy) or the urinary bladder predispose it to rupture or perforation.

An 80-year-old man presented with acute non-traumatic spontaneous urinary bladder perforation with generalized peritonitis. The patient was septic and in hypotensive shock, with four quadrant peritonitis and ongoing pyuria. He suffered from severe parkinsonism and dementia and was bed bound with poor mobility in a care home.

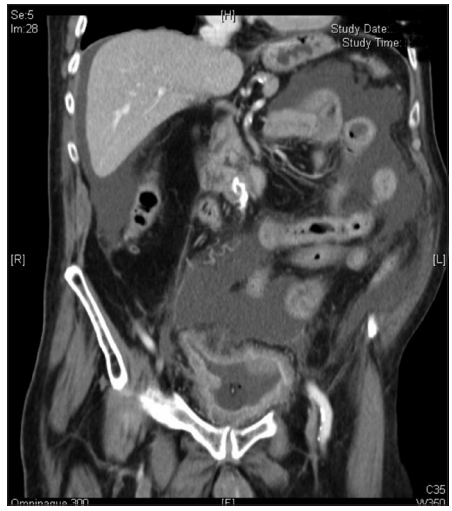
The diagnosis was clinched from preoperative imaging (*Figures 1* and *2*) and confirmed at laparotomy. Primary repair of the chronically infected, thickened urinary bladder wall perforation was performed.

Figure 1. Computed tomography image showing thick-walled urinary bladder with rupture and intra-peritoneal free fluid.



Spontaneous urinary bladder rupture is rare and a high index of suspicion and prompt diagnosis is essential for appropriate treatment. BJHM

Figure 2. Computed tomography image showing intra-peritoneal bladder rupture.



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