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CASE REPORT

A diagnostic difficulty: two cases of haemophagocytic syndrome in adults

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ABSTRACT

Haemophagocytic syndrome is a rare and life-threatening disease, which often goes unrecognised in adults, with high mortality as a consequence. Here we present two adult patients who were diagnosed with haemophagocytosis of distinct underlying causes which, despite treatment, led to fatal outcomes. Measuring ferritin is an easy and cheap resource in diagnosis.

KEYWORDS

Ferritin, haemophagocytic syndrome, haemophagocytic lymphohistiocytosis

INTRODUCTION

Haemophagocytic syndrome, or haemophagocytic lymphohistiocytosis (HLH), is a rare, potentially life-threatening disease characterised by an inappropriate activation of lymphocytes and histiocytes, which leads to an uncontrolled systemic inflammatory response. Two forms of HLH can be distinguished: primary or familial HLH, which usually occurs at a young age because of underlying genetic immunodeficiencies, and a secondary form, which may occur at all ages and is associated with infection, malignancies (mostly lymphomas) and different types of rheumatological disease.[1,2]

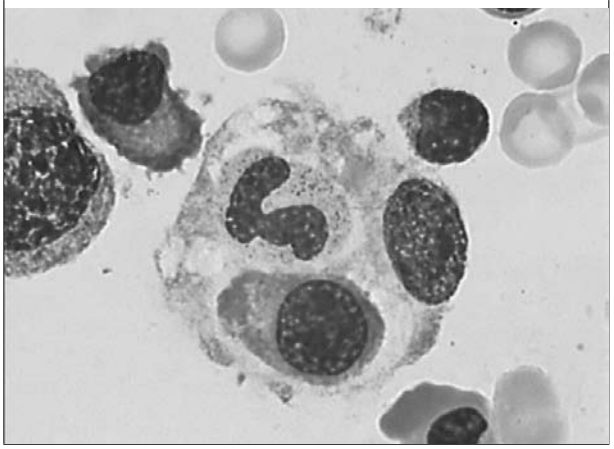
Clinically, the two forms are indistinguishable, characterised by a sepsis-like presentation with splenomegaly, cytopenias, hyperferritinaemia, coagulopathy and haemophagocytosis. Consequently, multi-organ failure often develops, leading to high mortality.[2]

We describe two adult patients with HLH of different underlying aetiologies, illustrating both the severity of the disease, and the need for prompt recognition, diagnostics and adequate treatment. In both patients, among nonspecific clinical and laboratory findings, markedly increased ferritin levels were found, which facilitated the difficult diagnosis.

CASE REPORTS

Case 1, a 35-year-old man was diagnosed with an aggressive cutaneous T-cell lymphoma in 2005, for which he received chemotherapy and finally myeloablative stem-cell transplantation from a related donor. Two months after transplantation, relapse of the cutaneous T-cell lymphoma was diagnosed, for which a donor lymphocyte infusion was scheduled. A few weeks thereafter, the patient developed unremitting high fever without signs of an underlying cause. Laboratory investigation revealed pancytopenia (haemoglobin 6.2 mmol/l, white blood cell count (WBC) 1.4 x 10^9/l, platelets 6 x 10^9/l), abnormal liver enzymatic function (alkaline phosphatase 189 U/l, gamma-glutamyl-transferase (γGT) 172 U/l, asparate aminotransferase (ASAT) 171 U/l, and alanine aminotransferase (ALAT) 67 U/l), elevated triglycerides at 3.36 mmol/l and elevated ferritin at >18,000 µg/l. On polymerase chain reaction (PCR), no active Epstein-Barr virus (EBV), cytomegalovirus (CMV) or herpes simplex infection were found. Bone marrow aspirate and biopsy revealed a strong increase in macrophages and haemophagocytosis, without lymphoma localisation (*figure 1*). HLH was diagnosed and treatment with etoposide 150 mg/m^2 twice weekly, and dexamethasone 10 mg/m^2 daily initiated. After three weeks of treatment, no clinical improvement ensued and haemophagocytosis prevailed, undiminished. Because of elevated liver enzymes, the etoposide dose was reduced by half. Ultimately, clinical improvement followed and the ferritin concentrations diminished to 12,000 µg/l. One week later, the patient was re-admitted because of high fever. The ferritin concentration proved to be >80,000

Figure 1. *Bone marrow showing macrophages with haemophagocytosis*



µg/l. Sepsis caused by a pneumococcal infection followed, and the patient died of respiratory failure.

Case 2, a 63-year-old man with systemic lupus erythematosus (SLE) was admitted because of suspected exacerbation of SLE. His complaints consisted of malaise, weight loss, loss of muscle strength and diminished concentration and memory. Upon physical examination, the patient proved to be a moderately ill man, with slow responses and fever (39.2°C). Laboratory evaluation revealed anaemia and thrombocytopenia (haemoglobin 6.2 mmol/l, platelets 109 x 10^9/l, and WBC 4.5 x 10^9/l), abnormal liver enzymes (ASAT 331 U/l, ALAT 123 U/l, lactate hydrogenase 1619 U/l, alkaline phosphatase 148 U/l, γGT 213 U/l) and a strongly elevated ferritin of 19,000 µg/l, without coagulopathy.

No abnormalities were seen on the chest X-ray, ultrasound, CT abdomen, and MRI of the cerebrum. Lumbar puncture showed no signs of infection. Under suspicion of neuro-SLE, treatment with methylprednisolone was initiated. A few days later, spontaneous bleeding from the jaw occurred, caused by diffuse intravasal coagulation. The patient was transferred to intensive care, and because of respiratory failure he was intubated and artificial ventilation was started. Bone marrow biopsy revealed increased iron-containing macrophages and haemophagocytosis. HLH was diagnosed and treatment with prednisolone and cyclophosphamide was started. After a brief improvement and detubation, the patient developed respiratory failure and haemodynamic insufficiency due to peritonitis based on perforated diverticulitis. A laparotomy was performed but, postoperatively, fulminant sepsis lead to his death.

DISCUSSION

Haemophagocytic syndrome is a rare disease. The primary or familial form has an autosomal recessive inheritance with an incidence of approximately 1 in 50,000 live-born children.[3] The disease usually occurs in the first two years of life, although cases in adulthood have been described.[4,5] The incidence of secondary HLH is unknown; it probably exceeds the incidence in children. Because of clinically overlapping presentations, it is probable that HLH is overlooked in patients considered to have severe inflammatory response syndrome (SIRS) on the ICU.[1]

Secondary HLH is associated with several diseases in a more or less convincing way (*table 1*).[1] Most case reports describing HLH in adults concern patients with haematological malignancies or EBV infections as the underlying disease.[1,6-8]

HLH is characterised by lymphohistiocytosis with marked proliferation of histiocytes, T lymphocytes and natural killer (NK) cells. Analysis of families with primary HLH has revealed markedly low NK and T-cell mediated cytotoxicity, with distinctive genetic abnormalities in genes encoding proteins involved in NK and T-cell induced cytotoxicity. Perforin deficiency is often found. Deficient cytotoxicity could lead to continuous immune activation and a cytokine storm, with concomitant phagocytosis of erythropoietic cells due tot proliferation and activation of macrophages.[2,7,9] Consequently, a severe inflammatory reaction is seen with fever, pancytopenia, coagulopathy and hyperferritinaemia due to release of ferritin by the reticulo-endothelial system.[10] The pathogenetic background

Table 1. *Diseases associated with secondary HLH*

Infections
Viral (mostly Epstein-Barr virus)
Bacterial
Parasitic (mostly visceral leishmaniasis)
Fungal
Rheumatological disease
Rheumatoid arthritis (mostly Still's disease)
Systemic lupus erythematosus
Sarcoidosis
Systemic sclerosis
Dermatomyositis
Autoimmune diseases
Glomerulonefritis
Inflammatory bowel disease
Vasculitis
Hashimoto thyreoiditis
Malignancy
Haematological malignancy (mostly lymphoma of T and NK cell type)
Solid tumours
Secondary immunodeficiency
HIV/AIDS
Transplantation
Chemotherapy
Immunosuppressive therapy
Dermatological disease
Pyoderma gangrenosum

of secondary HLH remains unclear. As in primary HLH, the dysregulation of the immune system probably leads to an ongoing immune activation and cytokine storm. HLH associated with malignant lymphoma could possibly be triggered by tumour-induced cytokine secretion.[1,11]

Diagnostic criteria for HLH, developed by the Histiocyte Society, are described in *table 2*.[12] Haemophagocytosis can be established not only in bone marrow, but also in other lymphoid tissue such as liver, spleen and lymph nodes. While histologically proven haemophagocytosis is regarded as the gold standard for HLH, it cannot be found on the first bone marrow biopsy in 20% of patients.[13] As localisation of haemophagocytosis may differ during the course of the disease, repetitive biopsies are sometimes required for diagnosis.[11] Therefore, an important diagnostic parameter is ferritin; mildly elevated ferritin is seen in many inflammatory illnesses, and therefore nonspecific. Nonetheless, ferritin concentrations greater than 10,000 µg/l are only seen in HLH, Still's disease, malignant histiocytosis, and after multiple blood transfusions. For HLH, research in children has shown a specificity of 96% for ferritin concentrations greater than 10,000 µg/l, increasing to 98% when fever is present.[14] Therefore, in combination with clinical and laboratory findings, extremely high ferritin levels are highly specific for HLH.[1,15] As in our cases, finding markedly elevated ferritin concentrations could lead to prompt recognition of the disease.

Table 2. *Diagnostic criteria (≥5) for HLH according to the Histiocyte Society*

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 CD25 ≥2400 U/ml*
Low or absent NK-cell activity*

*No routine measurement.

Treatment of primary HLH is, because of its low incidence, done in multicentre trials coordinated by the Histiocyte Society, (HLH 94 and HLH 2004 studies). The aim of treatment is the induction of remission with etoposide 150 mg/m² twice weekly, dexamethasone 10 mg/m² daily, and cyclosporine-A 6 mg/kg/day in combination with maximum supportive care with antibiotics, antiviral therapy and intravenous immune globulins. Ultimately stem cell transplantation should follow.[12] In secondary HLH, treating the underlying cause is essential. In infection-induced mild HLH, this is possibly sufficient. However, without intensive treatment, severe HLH is fatal without exception. Early intensive treatment in adults could possibly increase the chances of survival.[7] Therefore, treatment according to HLH protocols is recommended.[12]

CONCLUSION

The patient histories described above illustrate the severity of the secondary form of HLH in adults. Diagnosis is difficult, as many symptoms are nonspecific and often present in severely ill patients. Although rare, HLH should be considered in patients with unexplained fever and signs of SIRS. For prompt diagnosis and treatment, ferritin can be used as an easy and cheap diagnostic clue.

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