CASE REPORT

# SUSPECTING HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) IN PATIENTS WITH A HIGH FERRITIN

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Heamophagocytic Lymphohistiocytosis (HLH) is problematic to diagnose. The conditions that predispose to HLH present in a similar fashion, such as sepsis and haematological cancers. We look at the case of a 66-year-old man with a diagnosis of CLL, who presented with pyrexia and non-specific symptoms which included abdominal discomfort and weight loss. Sepsis, the principal suspicion was thoroughly investigated and excluded. Routine autoimmune pathologies were exhausted with comprehensive panels. The patient was trialled on steroids, presumptively, with a limited response. What was most peculiar in his blood tests was an unusually high Ferritin of > 50000. The parent clinical team was at a loss to explain the unusually high ferritin when a locum consultant suggested the diagnosis of Haemophagocytic Lymphohistiocytosis based on a similar presentation she had observed many years ago. The patient was started on pulsed Etoposide and Dexamethasone, however, unfortunately, he could not make a recovery.

**Keywords:** Hyperferritinemia; Haematology; Haemophagocytic Lymphistiocytosis; Rare diseases

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## INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is defined as an inflammatory condition of uncontrolled immune activation.[1] Since its discovery in 1939, at which point it was known as histiocytic medullary reticulosis, HLH has proven to be a perplexing condition. It is uncommon, but life-threatening and usually occurs either as a result of inherited genetic mutations in the cytotoxic functions of T and Natural Killer (NK) cells (primary HLH) or due to infectious, autoimmune, or malignant instigators (secondary HLH).[2] Conventionally, HLH is grouped into two distinct categories: primary and secondary. Primary occurs more often in children, in the setting of a genetic predisposition, which disrupts cytotoxic T cell and inflammasome functions. Secondary occurs more often in adults, in the absence of a genetic predisposition, but in the context of an immunological trigger.[3] The guideline to diagnose HLH was set out by the Histiocyte Society but are not widely read. Ferritin levels are well studied in the adult HLH population group and high levels are extremely sensitive to HLH, however it is a nonspecific marker and is elevated in many other disease processes. The literature varies on how sensitive ferritin is at higher limits to HLH.[4] This case is presented to highlight the importance of suspecting HLH in cases of unexplained profound hyperferritanemia as promptly instigated specialist treatment reduces mortality and morbidity.

## CASE REPORT

A 66-year-old Caucasian man, under surveillance for Chronic Lymphocytic Leukaemia (CLL), was admitted to the ward after presenting with a swinging fever, epigastric discomfort and weight loss. He was found to have sudden onset of pancytopenia, which was anomalous in comparison to the general trend of his CLL progression. In addition to this, tear drop cells were noted on blood film as well as an elevated ferritin of 2,164 µg/L on admission with a transferrin saturation of 31%. A full septic screen, including viral and fungal screening, was negative and no source of infection was identified. Bone marrow biopsies were performed which showed extensive CLL and hyper plasticity in the intervening marrow, however despite this there was insufficient evidence for the working diagnosis of Myelodysplastic Syndromes. A CT abdomen showed lymphadenopathy and splenomegaly. His Oesophago Gastro Duodenoscoy (OGD) was unremarkable. The case was discussed at the multidisciplinary team meeting, where it was highlighted that the pancytopenia and clinical picture were incongruent with CLL and thus a hypothesis of an autoimmune aetiology was made and subsequently, treatment with IV steroids was started, however the subsequent

autoimmune panel was negative. Repeat bloods now showed a profoundly elevated Ferritin of >50000 µg/L. A diagnosis of HLH was suggested by a locum doctor who had seen a patient many years ago with a similar presentation. Hyperferritinaemia, coupled with this patient's history of haematological malignancy, presence of high-grade pyrexia and splenomegaly, a diagnosis of HLH was made and the HLH-94 treatment protocol of Dexamethasone and pulsed Etoposide was initiated.

## DISCUSSION

Hemophagocytic lymphohistiocytosis has seen a rise in documented cases, from less than ten studies per year in the eighties to over a hundred per year in the twenty first century.[5] The devastating nature of the disease, greater understanding of the disease process and technological advancement has meant a greater focus for researchers and therefore higher recognition within the field. This however does not translate to a definite epidemiological understanding of HLH in adults as the incidence is still not truly understood.[6] This syndrome is defined by excessive inflammation due to defective NK and cytotoxic T cell function causing unrestrained macrophage action. This results in 'cytokinetic storm' picture. HLH is categorised as primary (predominantly due to genetic cause in children) or secondary (triggered by underlying malignant, autoimmune, or infectious disease) and if untreated ultimately leads to tissue damage, organ damage and death.[1] Extensive research of paediatric HLH in comparison with adults has led to the use of paediatric guidelines in adult care, despite a lack of evidence indicating a similarity in treatment response.[5] Therefore, current best evidence is represented by the using the HLH-2004 criteria.[3]As well as an underlying lymphoproliferative disorder, the patient in this case fulfilled 6/8 of these criteria: 1) Fibrinogen 0.7 g/l and Fasting Triglycerides 3.6 mmol/l 2) Splenomegaly 3) Cytopenias 4) Fevers >38.5 5) High Ferritin (>50,000) 6) BMB reviewed – probable haemophagocytosis. Resemblance of the typical HLH immune pathway activation with that of the common macrophagic response, increases the difficulty of HLH diagnosis.[7] Mortality is almost guaranteed in patients with HLH without treatment. The patient in our case fell under a subset of secondary HLH – malignant HLH (MHLH). One study by Li *et al*.[8] demonstrated a mortality rate of 79.6% in the cohort of patients with MHLH, more than double that of the viral-related HLH cohort. This may be related to the concealing of HLH features by the overlying malignant pathology, therefore delaying treatment. In this case the patient was investigated for progression of his malignancy and empirically treated for other causes of systemic illness such as sepsis, illustrating the disguised nature of HLH. It is clear that prompt recognition and initiation of treatment is key in HLH. Incorporation of the HLH-2004 guidelines significantly reduces mortality rates.[6] Diagnosis of this patient was prompted by significantly raised serum ferritin levels. The relationship of ferritin and HLH has been examined. Intrinsically it is part of HLH-2004 diagnostic criteria (>500 µg/L). Allen *et al*.[4] showed in the paediatric population100% sensitivity, with all patients fulfilling this condition. The sensitivity at the minimum level of 10,000 µg/L was 90% sensitive and 96% specific for HLH. Unfortunately, this level of specificity has not been replicated in adult studies.[9] One study showed 19 out of 113 patients that had ferritin over >50 000 µg/L were diagnosed with HLH. The specificity of ferritin has been shown to be more specific when coupled with fever for HLH, and the rate at which ferritin rises (1,174 µg/L/day) was distinctive in HLH.[4] Similar to our case, MHLH combined with ferritin over 50,0000 µg/L indicated high mortality within thirty days. Ferritin is a simple and readily available laboratory test, in comparison with other markers for HLH diagnosis, with results returning on the same day. Other tests, such as IL-2Rα levels and NK cells, are not as accessible and time is required to receive the results. This is problematic when a rapid diagnosis and treatment plan is required, thus, hyperferritinemia may be valuable as a screening mechanism with pyrexia, to investigate HLH.

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**Consent:** Patient deceased. All patient identifiable information has been purposefully removed.

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