CASE REPORT

Haemophagocytic lymphohistiocytosis as a consequence of untreated B-cell chronic lymphocytic leukaemia

Chris Bailey,¹ Claire Dearden,² Kirit Ardeshtna³

¹Department of Haematology, Imperial College Healthcare NHS Trust, London, UK

²Department of Haematology, Royal Marsden Hospital, London, UK

³Department of Haematology, UCLH, London, UK

Correspondence to
Dr Chris Bailey,
chrisbailey1@nhs.net

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SUMMARY

Haemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening syndrome characterised by defective cytotoxic function and hypercytokinaemia leading to macrophage expansion and haemophagocytosis. Patients often present with unexplained fevers, hepatosplenomegaly and pancytopenia, with elevation in serum ferritin and triglyceride. Acquired forms are triggered by infection, malignancy or rheumatological disorders. HLH in the setting of chronic lymphocytic leukaemia is rarely reported, however, and is usually associated with infection or as a consequence of chemotherapy. We present a case of HLH in a 64-year-old Caucasian woman with the only identified trigger being her hitherto untreated CLL.

BACKGROUND

Haemophagocytic lymphohistiocytosis (HLH) is a clinical syndrome characterised by fevers, lymphadenopathy, hepatosplenomegaly, pancytopenia and hyperferritinaemia.¹ The aetiology stems from dysregulated activation and proliferation of macrophages and T lymphocytes with hyperproduction of inflammatory cytokines.² Lymphocytic and histiocytic infiltration occurs within haematopoietic organs, from which biopsies may show haemophagocytosis.

HLH is often categorised into primary (inherited) and secondary (acquired) forms. Primary HLH is a heterogeneous autosomal recessive disorder associated with a number of genetic mutations, some of which affecting cytotoxic functions of T lymphocyte and natural killer (NK) cells, such as the *perforin* gene. This condition typically, but not exclusively, presents in childhood.³ Secondary HLH is thought to be precipitated in the context of infection, malignancy or rheumatological disorders. Epstein-Barr (EBV) or herpes viruses are frequently implicated as infectious agents; however, bacterial and fungal infections also occur in this setting.⁴

HLH presenting in chronic lymphocytic leukaemia (CLL) is rarely reported. Of these, cases have been associated with chemotherapy,⁵ or infections such as Histoplasma and EBV.⁶

CASE PRESENTATION

A 64-year-old woman with Rai stage 1 B-CLL, diagnosed 18 years previously and on a watch and wait protocol, presented to hospital with fever,

pancytopenia and splenomegaly to umbilicus on examination. Prior to this, her white blood cell (WBC) count had been gradually increasing over many years, with her WBC count being $86.6 \times 10^9/L$, lymphocytes $80.32 \times 10^9/L$ and platelets $171 \times 10^9/L$ the preceding year.

INVESTIGATIONS

A full blood count on admission revealed haemoglobin 70 g/L, WBC count $18.3 \times 10^9/L$, neutrophil count $0.71 \times 10^9/L$, lymphocytes $16.65 \times 10^9/L$ and platelets $70 \times 10^9/L$. Broad-spectrum antibiotics were started. Blood cultures were negative, with bone marrow aspirate revealing an excess of mature B lymphocytes with cluster of differentiation (CD)38 expression and trephine showing diffuse infiltration by CLL up to 70% with no evidence of haemophagocytosis. Further work up included a ferritin level $31507 \mu g/L$, triglyceride level 4.1 mmol/L and a normal lumbar puncture. A positron emission tomography (PET) CT was reported showing splenomegaly and 2-fluoro-2-deoxy-D-glucose (FDG) uptake (standardised uptake value (SUV) max 8.1) in humeral heads, clavicles, sternum, spine and pelvic bones, with some uptake (SUV 3.3) in the peri-portal nodes and splenomegaly (figure 1).

A diagnosis of HLH made as five of eight diagnostic criteria were fulfilled: fever, splenomegaly, cytopenias, hypertriglyceridaemia and hyperferritinaemia. Investigations to establish an infective aetiology included further blood and urine cultures, EBV, cytomegalovirus (CMV), adenovirus and parvovirus PCR; HIV antigen, CMV, EBV, hepatitis and human T-lymphotropic virus serology, histoplasma antigen, brucella, coxiella, syphilis, mycoplasma, toxoplasma serology, Lyme's C6 peptide, T-SPOT TB test and galactomannan assay. Throat swabs were taken for influenza, RSV, metapneumovirus and parainfluenza PCR. IgG for toxoplasma, CMV and EBV was present, consistent with past infection. All other results were negative.

TREATMENT

The patient was treated according to the HLH-2004 Induction Protocol, with dexamethasone and etoposide, but without ciclosporin. This resulted in a marked improvement in her symptoms with a reduction in the ferritin level and splenomegaly. Her lymphocyte count increased during the initial stages

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Figure 1 PET CT showing moderate FDG uptake (SUV max 8.1) in humeral heads, clavicles and pelvic bones, with some splenic uptake (SUV 3.3). CT, computed tomography; FDG, 2-fluoro-2-deoxy-D-glucose; PET, positron emission tomography; SUV, standardised uptake value.

of treatment, peaking at $79.8 \times 10^9/L$, and then subsequently falling again. This fall is likely due to the direct toxic effect of etoposide. A second, smaller rise in lymphocyte count corresponded to treatment being temporarily withheld during week 4 of the induction protocol. She continued to receive growth colony-stimulating factor and transfusion support. During treatment, there were two admissions to hospital for neutropenic sepsis and diarrhoea. On the second admission, *Escherichia coli* and *Streptococcus mitis* were cultured from blood, for which a course of teicoplanin and piperacillin-tazobactam were completed. Blood tests 1 week post treatment were as follows: haemoglobin 110 g/L, WBC count $3.13 \times 10^9/L$, neutrophil count $1.57 \times 10^9/L$, lymphocytes $1.1 \times 10^9/L$, platelets $59 \times 10^9/L$, ferritin level 2628 $\mu g/L$ and triglyceride level 2.0 mmol/L.

OUTCOME AND FOLLOW-UP

Two weeks following completion of the induction protocol, the patient developed fevers $>39^\circ C$, night sweats and general fatigue. Ferritin level was raised to 5222 $\mu g/L$ and triglycerides 3.4 mmol/L. Bone marrow trephine showed extensive infiltration of CLL with no evidence of haemophagocytosis. Etoposide and dexamethasone were recommenced, which resulted in

initial symptomatic improvement. Unfortunately 3 weeks into treatment, the patient was admitted to ICU with septic shock requiring inotropic support and broad-spectrum antibiotics. She died 2 days into admission.

DISCUSSION

HLH is a heterogeneous, hyperinflammatory clinical syndrome of unchecked immune activation that carries a poor prognosis. In a recent case series, the overall median survival among 62 patients was 2.1 months.⁷ It is thought that persistent NK cell antigenic stimulation due to defective cytotoxic removal of this stimulus leads to unregulated cytokine production, lymphocyte and macrophage activation with haemophagocytosis.¹ Production of interleukins (IL) and tumour necrosis factor- α causes fever; activated macrophages secrete ferritin and cytokine-dependent suppression of lipoprotein lipase and haematopoiesis all contribute to the clinical picture. Soluble CD25 has been shown to correlate most reliably with disease severity.⁸ Symptoms are generally non-specific and can be similar to haematologic malignancies or sepsis, which often results in a delay to diagnosis.

The diagnostic criteria were originally described in 1994 by the HLH study Group of the Histiocyte Society.⁹ This requires a molecular diagnosis consistent with HLH, or five of eight criteria to be present: fever, splenomegaly, cytopenias affecting ≥ 2 lineages, hypertriglyceridaemia (fasting, ≥ 3 mmol/L) and/or hypofibrinogenaemia (≤ 1.5 g/L), haemophagocytosis in the bone marrow, spleen or lymph nodes, low/absent NK activity, hyperferritinaemia ($\geq 500 \mu g/L$ g/L) or soluble CD25 (IL-2 receptor) ≥ 2400 U/mL. In this case report, five of eight criteria were present. In 2014, the American College of Rheumatology published the H-Score, based on a retrospective cohort of 312 adult patients.¹⁰ Historically, criteria for diagnosis were based on paediatric research into primary HLH; however, the H-Score uses a set of weighted criteria to aid the diagnosis of secondary forms of HLH. The H-Score in this case report was 224, giving 97% likelihood of HLH diagnosis.

The triggers to acquired HLH can be divided into infectious, malignant and rheumatological causes. Infection with EBV is the most commonly reported trigger, however numerous viral, bacterial, protozoal and fungal associations are reported, highlighting the need for extensive microbiological investigations in these cases.⁴ Common causative malignancies include B-lymphoblastic leukaemia and non-Hodgkin's lymphoma. Secondary HLH in lupus erythematosus, systemic juvenile idiopathic arthritis and macrophage activation syndrome are also reported.¹¹ It should be noted that certain drugs, such as fludarabine and methotrexate, are implicated in the development of HLH. In this case, comprehensive microbiological work-up was performed, including investigations for EBV and histoplasma, where HLH has previously been described in the setting of CLL, and a trigger in this context was ruled out.

There are few reports of CLL-associated HLH in the literature. Many had identified or suspected an infectious trigger, such as histoplasma,⁶ EBV,¹² influenza A¹³ or atypical mycobacterium.¹⁴ Underlying T-cell lymphomas were found in patients with B-CLL and HLH.¹⁵ Other case reports implicate fludarabine or rituximab in the development of HLH in CLL;¹⁶ however, a case report by Meki *et al*¹⁷ concluded that HLH was present in an early stage prior to chemotherapy. It is thought that profound T-cell suppressive effects of fludarabine-based chemotherapy may cause susceptibility to HLH.

This case report describes HLH in the setting of untreated CLL, implicating the progression of the CLL itself as a trigger,

as infective causes were extensively ruled out. Whether initiation of definitive therapy for the CLL would have prevented the recurrence of the HLH remains uncertain. HLH remains a challenging condition to treat due to its rarity, wide range of triggers, poor prognosis and non-specific presentation. A high index of suspicion is required in patients presenting with fever and unexplained pancytopenia where sepsis is not the cause.

Learning points

- ▶ Haemophagocytic lymphohistiocytosis (HLH) can present in the context of untreated chronic lymphocytic leukaemia.
- ▶ A high index of suspicion for HLH is required in patients presenting with fever and unexplained pancytopenia.
- ▶ Useful investigations to establish a diagnosis include fasting triglycerides (≥ 3 mmol/L), fibrinogen (≤ 1.5 g/L), ferritin (≥ 500 μ g/L g/L), soluble CD25 (interleukin-2 receptor) ≥ 2400 U/mL and a bone marrow biopsy.

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