An incidental finding of severe hyperferritinaemia: a lesson to be learned

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Abstract

Haemophagocytic lymphohistiocytosis is a rare, under-recognised and often misdiagnosed condition, characterised by a hyperinflammatory response to malignancy or infection. In this case, the cause was a bone marrow isolated anaplastic large cell lymphoma without radiological evidence of systemic disease, a phenomenon rarely described.

We present the case of a previously fit and well 64-year-old female who presented on multiple occasions to primary and secondary care in a stable condition with an undifferentiated illness with the only consistent feature being a marked, unexplained hyperferritinaemia. The history highlights the importance of ferritin as a marker of phagocytic activity and how severely high levels, even in the well patient, should prompt early bone marrow biopsy. The prognosis of haemophagocytic lymphohistiocytosis is invariably poor as the condition is usually secondary to a serious underlying disease such as haematological malignancy as in this case., The diagnostic difficulty often leads to delayed recognition and treatment.

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Case History

A previously fit and well 64-year-old female presented to her GP with a one month history of fatigue, fever and frontal headaches. There was no significant medical or family history, she had no regular medication or known allergies and examination was unremarkable. She was treated with two empirical courses of antibiotics and, as no improvement was seen, a set of routine blood tests was performed. Full blood count, C-reactive protein, liver function tests, fibrinogen and triglycerides were all normal but her ferritin was markedly raised at 18350 ug/L (normal range 20–380); repeat ferritin at 2 weeks had decreased spontaneously to 2208 ug/L.

Over the following month, she was referred twice to hospital with progression of symptoms and new pleuritic chest pain. Laboratory workup was normal except ferritin was again raised to 3207 ug/L, and D-dimer to 4500 ug/L. Computed tomography (CT) pulmonary angiogram excluded a pulmonary embolism and there was no evidence of mediastinal lymphadenopathy. She was discharged with a diagnosis of a viral illness. On the second admission, CT sinus and head demonstrated sinusitis. She was given a further course of oral antibiotics and started on prednisolone.

Eight days later she returned to hospital with high fever, rigors, night sweats and headaches. She appeared systemically unwell with a fever of 40.7°C, tachycardia, hypotension, tachypnoea, and hypoxia; examination revealed no palpable lymphadenopathy or organomegaly.

Her blood tests were haemoglobin 111 g/L, platelets 78, white cell count 3.4, neutrophils 2.3, lymphocytes 0.3, activated partial thromboplastin time 64 s, prothrombin ratio 1.6, fibrinogen 0.4 g/L, lactate dehydrogenase 2483 U/L, beta-2 microglobulin 9.2 mg/L, ferritin > 50,000 ug/L, gamma-glutamyl transpeptidase 250 U/L, alkaline phosphatase 383 U/L, and alanine aminotransferase 710 U/L.

The diagnosis of haemophagocytic lymphohistiocytosis (HLH) was suspected and therefore high dose dexamethasone was started and a bone marrow biopsy obtained.The aspirate demonstrated a pleomorphic population of atypical large lymphoid cells along with haemophagocytosis (Figure 1). Concerns about aggressive lymphoma triggered a request for a full body staging CT. This showed a psoas muscle haematoma, possibly from bone marrow biopsy in the context of coagulopathy, but there were no other abnormalities. Fibrinogen-rich cryoprecipitate

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Figure 1 A hallmark cell, characteristic for ALCL, in bone marrow aspirate with Romanowsky stain. It has an embryo-like nucleus, deeply basophilic cytoplasm with multiple small vacuoles and scanty fine granules

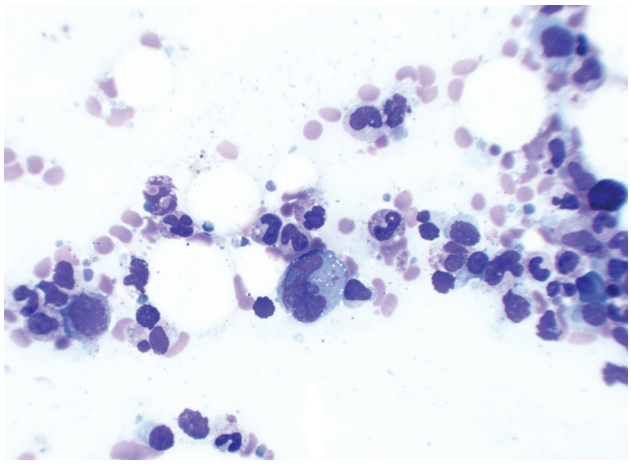
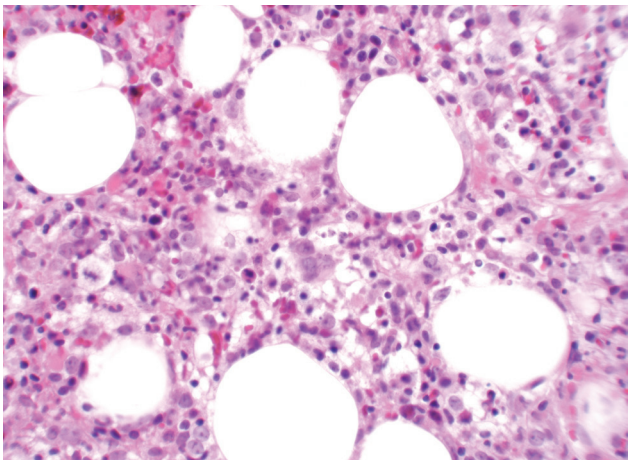


Figure 2 Haemophagocytosis demonstrated on trephine H & E stain. There is also an increased population of pleomorphic large lymphoid cells with irregular nuclei and voluminous cytoplasm including a mitotic form

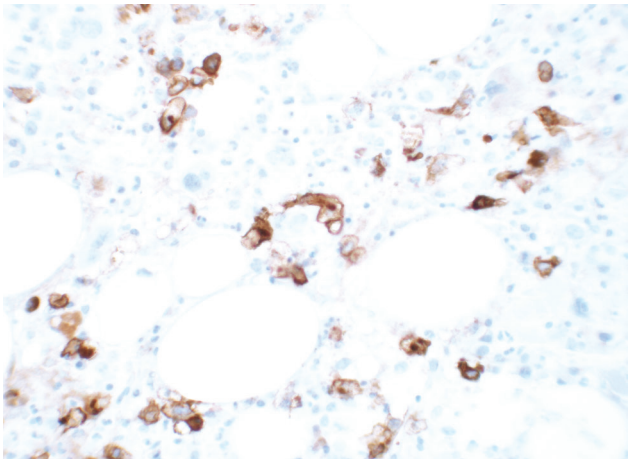


was administered and etoposide commenced as per the HLH-2004 protocol.[1]

Unfortunately, the patient deteriorated with progressive multi-organ failure. Her care was escalated but despite maximum intensive care support she passed away with her family present, just 5 days after admission.

The bone marrow trephine (Figure 2) results subsequently became available; interstitial infiltrates of pleomorphic mononuclear T cells of anaplastic morphology were confirmed on immunohistochemistry (Figure 3). These cells were positive for CD45, CD3, CD30 and EMA, but negative for CD15, granzyme B, TIA-1, EBER and ALK-1. The finding of activated macrophages phagocytosing haematological elements was prominent. Post mortem examination confirmed the clinical diagnosis of multi-organ failure caused by HLH, triggered by ALK negative anaplastic large cell lymphoma. Marrow, adrenal, liver and spleen infiltration was demonstrated histologically but not radiologically.

Figure 3 Immunohistochemistry for CD30 showing many positive cells with membranous and paranuclear Golgi, 'dot-like' reaction



Discussion

HLH is a rare and potentially fatal clinical syndrome characterised by unchecked immunological activation.[1] The diagnosis relies on identifying a genetic mutation associated with primary HLH or, as in this case, satisfying at least five of eight criteria required in secondary HLH (Table 1).[1] The difficulty in meeting the diagnostic criteria in the early stages of disease, its rarity and variable clinical presentation, leads to under-, near-missed and missed diagnosis.

While there is no single disease specific marker for HLH, severe hyperferritinaemia as defined by ferritin > 10,000 can be a useful marker of phagocytosis.[2] A large study in a Texas children's hospital demonstrated that this level is 90% sensitive and 96% specific for HLH.[2] The specificity in adults is not known; a study of 113 hospitalised patients from a large academic centre showed levels > 50,000 were also observed in renal failure, hepatocellular injury and haematological malignancy.[3] In our case the patient was well with no significant medical history. We therefore support the argument that ferritin specificity for HLH is maintained in the well adult presenting with undifferentiated illness.

Bone marrow biopsy is an important investigative tool in HLH as haemophagocytosis is one of the diagnostic criteria and assists in identifying the underlying cause. It is important to note that early in the HLH presentation, a bone marrow biopsy may not show haemophagocytosis and therefore it is important to repeat if clinical suspicion remains high.[4]

HLH can be inherited; however, acquired forms secondary to autoimmune and metabolic conditions, infections (mostly viral) or haematological malignancies, as in this case, are more common.[4] Malignancies are characterised by T cell immunosuppression, as in T cell lymphomas, NK cell leukaemia and EBV driven T cell and B cell lymphomas.[4] If secondary HLH is suspected, a rapid search for the underlying

Table 1 Acquired HLH Diagnostic Criteria from Henter et al.[1]

Five of eight criteria required for acquired HLH diagnosis
1. Fever
2. Splenomegaly
3. Cytopenias affecting at least two cell lineages in peripheral blood
4. Fasting hypertriglyceridaemia or hypofibrinogenaemia
5. Hyperferritinaemia (> 500 ug/L)
6. Raised soluble CD25 (soluble interleukin-2 receptor)
7. Haemophagocytosis in bone marrow, spleen or lymph node biopsy
8. Low or absent natural killer cell activity

cause is vital, as treating this simultaneously is required to achieve remission.[5]

In this case HLH was the sole manifestation of malignant T cell lymphoma. The lymphoma was occult clinically and radiologically as there was no nodal enlargement or hepatosplenomegaly detected on repeated imaging. Had a bone marrow biopsy been performed earlier, the rare entity of primary anaplastic large cell lymphoma of the marrow may have been found.[6,7] Commencing etoposide treatment at that early stage may have improved the outcome.[8]

This case demonstrates the difficulty in diagnosing HLH and the usefulness in performing ferritin assay in the febrile patient with an undifferentiated presentation. It underscores the importance of early collection of a bone marrow biopsy in the setting of unexplained hyperferritinaemia > 10,000 and finally highlights the high mortality risk if diagnosis is delayed until multi-organ involvement occurs and ferritin reaches exceptionally high levels (> 50,000).[9]

References

1 Henter JI, Horne A, Aricó M et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007; 48: 124–31.

2 Allen CE, Yu X, Kozinetz CA et al. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocystosis. *Pediatr Blood Cancer* 2008; 50: 1227–35.

3 Schram AM, Campigotto F, Mullally A et al. Marked hyperferritinemia does not predict for HLH in the adult population. *Blood* 2015; 125: 1548–52.

4 Rosado FG, Kim AS. Hemophagocytic lymphohistiocytosis: an update on diagnosis and pathogenesis. *Am J Clin Path* 2013; 139: 713–27.

5 Schram AM, Berliner M. How I treat hemophagocytic lymphohistiocytosis in the adult patient. *Blood* 2015; 125: 2908–14.

6 Gudgin E, Rashbass J, Pulford KJ et al. Primary and isolated anaplastic large cell lymphoma of the bone marrow. *Leuk Lymphoma* 2005; 46: 461–3.

7 Szomor A, Al Saati T, Delsol G et al. Primary bone marrow T-cell anaplastic large cell lymphoma with triple M gradient. *Pathol Oncol Res* 2007; 13: 260–2.

8 Arca M, Fardet L, Galicier L et al. Prognostic factors of early death in a cohort of 162 adult haemophagocytic syndrome: impact of triggering disease and early treatment with etoposide. *Br J Haematol* 2015; 168: 63–8.

9 Otrock ZK, Eby CS. Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophagocytic lymphohistiocytosis. *Am J Hematol* 2015; 90: 220–4.