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CASE REPORT

An unusual case of Kikuchi–Fujimoto disease presenting as haemophagocytic lymphohistiocytosis

Kavina Shah[1]

Raj Amarnani[1]

Leah Owen[2]

Jessica Manson[1]

Alexis Jones[1]

Author details can be found at the end of this article

Correspondence to:
Alexis Jones;
alexis.jones@nhs.net

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Introduction

This article reports a case of haemophagocytic lymphohistiocytosis secondary to Kikuchi–Fujimoto disease in a patient presenting with fevers, lymphadenopathy, cytopenias and hyperferritinaemia. Early treatment with anakinra, an interleukin-1 receptor antagonist, was

Case report

An otherwise well 37-year-old North African man presented with a 10-day history of fevers and right axillary pain. He had no other symptoms of infection, no recent foreign travel, unwell contacts or animal exposures.

On admission, he had a fever of 39.6°C, a heart rate of 120 beats/minute, and normal blood pressure and respiratory rate. Examination revealed palpable cervical and axillary lymph nodes. Cardiorespiratory, abdominal, neurological, musculoskeletal and skin examinations were unremarkable.

Blood tests revealed a leukopenia ($2.25x10^9$/litre), lymphopenia ($0.73x10^9$/litre), neutropenia ($1.0x10^9$/litre) and a down trending platelet count ($148x10^9$/litre). His C-reactive protein level was 59.8 mg/litre and erythrocyte sedimentation rate was 9 mm/hour. The ferritin level rose from 305 ug/litre (normal range 30–400 ug/litre) to 18 139 ug/litre during his admission. Renal and liver function tests were normal.

Screening for infection revealed negative urine and blood cultures. Viral serology was compatible with previous exposure to cytomegalovirus, Epstein–Barr virus, parvovirus B19 and hepatitis C infection, but no active viral infection was found. A transthoracic echocardiogram was normal. The patient had positive anti-Ro antibodies, but all other autoantibodies were negative. Immunoglobulin levels, protein electrophoresis and lactate dehydrogenase were normal.

A positron emission tomography–computed tomography scan revealed multiple enlarged lymph nodes above and below the diaphragm, raising the suspicion of a lymphoproliferative disorder (Figure 1). A core biopsy of the largest node in the right axilla was taken for histopathology and microbiology.

The patient was diagnosed with probable haemophagocytic lymphohistiocytosis and subcutaneous anakinra was commenced while a bone marrow aspiration and trephine biopsy were obtained. Following the collection of biopsies, intravenous methylprednisolone was administered, followed by intravenous immunoglobulin as the HScore (Fardet et al, 2014) escalated to 217 points (based on fever, 2 line cytopenia, hyperferritinaemia, elevated triglyceride levels of 4.0 mmol/litre (normal range 0.4–2.3 mmol/litre), and low fibrinogen levels of 1.26 g/litre (normal range 1.5–4.0 g/litre)).

The patient's cytopenias, fevers and lymphadenopathy subsequently resolved and his serum ferritin level returned to normal (Figure 2). Anakinra was stopped after 8 days and the patient completed a course of oral steroids.

Mycobacterial culture was negative on both bone marrow and lymph node biopsies. Leishmania culture and polymerase chain reaction test were also negative on the bone marrow sample. Histology of the lymph node biopsy showed relatively well-defined foci of necrosis which comprised abundant apoptotic debris, histiocytes with occasional crescentic forms, and variably sized lymphocytes (Figure 3). Occasional macrophages showed haemophagocytic activity. The overall morphological features and immunophenotype of the lymph node histology were those of Kikuchi lymphadenitis.

Histology of the bone marrow aspirate and trephine reported evidence of haemophagocytic lymphohistiocytosis but no evidence of malignancy. This patient was diagnosed with Kikuchi–Fujimoto disease, presenting acutely as haemophagocytic lymphohistiocytosis.

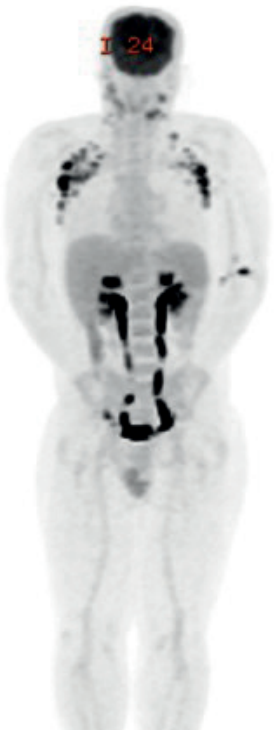

Figure 1. Coronal section of positron emission tomography-computed tomography scan demonstrating cervical and axillary uptake (black) of fluorodeoxyglucose. Intense physiological fluorodeoxyglucose tracer uptake is seen in the brain as glucose is the predominant substrate for brain metabolism. Fluorodeoxyglucose is renally excreted, hence the apparent avidity in the renal collecting system.

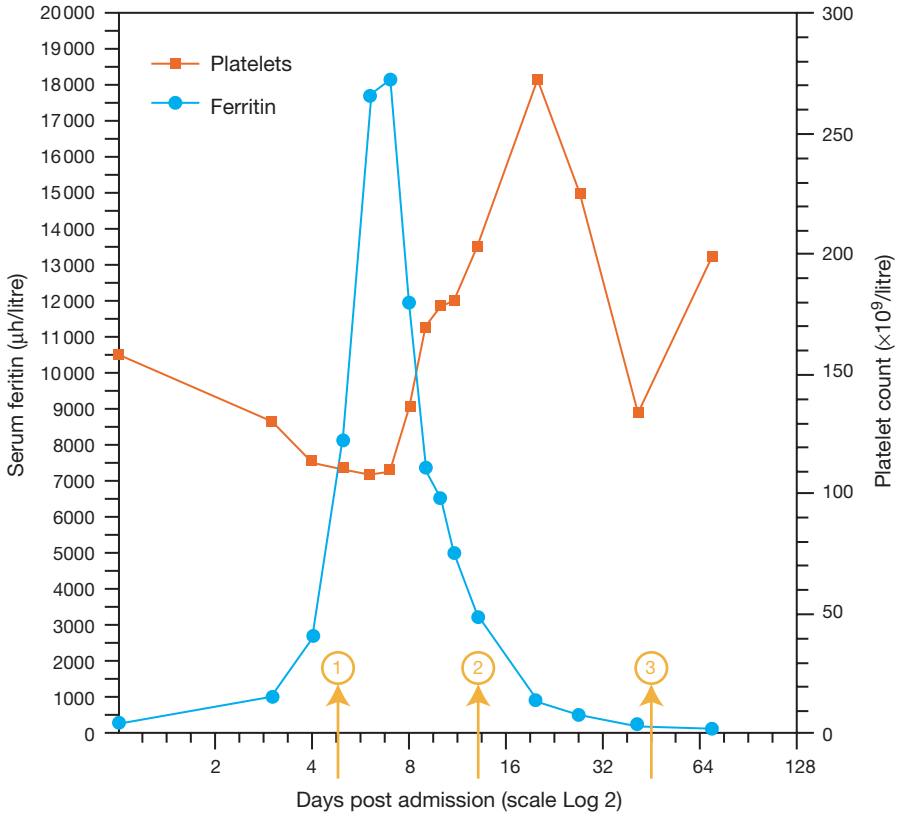

Figure 2. Trend in haemophagocytic lymphohistiocytosis markers: serum ferritin and platelet count. Timepoints: 1 – initiation of anakinra; 2 – discharge home from hospital; 3 – cessation of corticosteroids (following weaning period).

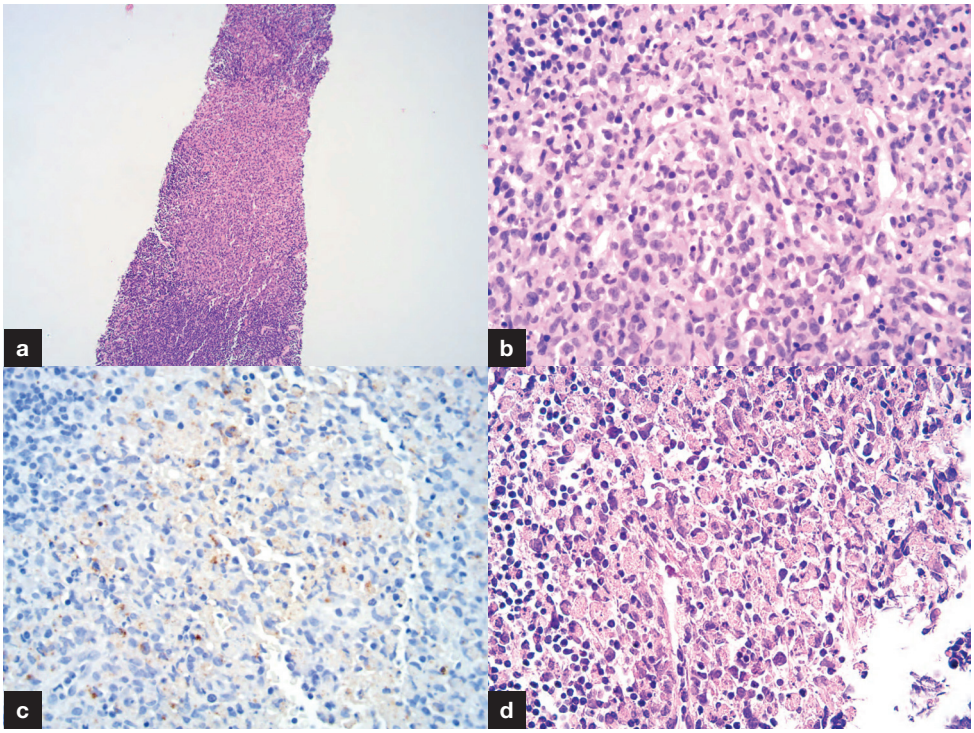

Figure 3. Histopathology slides from lymph node core biopsy. a. Low power view (x10) of lymph node core with pale areas = histiocytic collections. b. Higher power view (x40) of histiocytic collections with histiocytes with crescentic nuclei and apoptotic debris. c. Myeloperoxidase stain (x60) showing myeloperoxidase-positive granules in histiocytes. d. Different area of histiocytes with intracellular fragmented red blood cells (erythrophagocytosis x60).

used to obviate any steroid-induced changes in the assessment of bone marrow and lymph node tissue. Histology of the lymph node demonstrated well-defined foci of necrosis in keeping with Kikuchi–Fujimoto disease. Haemophagocytic activity was seen in both lymph node and bone marrow biopsy. The case highlights the importance of a tissue diagnosis in haemophagocytic lymphohistiocytosis and the use of anakinra to treat hyperinflammation.

Discussion

Kikuchi–Fujimoto disease is typically a benign, self-limiting condition of subacute onset (2–3 weeks), with features of tender cervical lymphadenopathy and associated mild fever and night sweats (Bosch and Guilabert, 2006). It is a rare disease with a predilection for young women. It has a higher prevalence in Japan, where it was initially described by Kikuchi (1972) and Fujimoto et al (1972) as a histiocytic necrotising lymphadenitis. The underlying cause is not entirely clear, but viral and autoimmune aetiologies are recognised.

Haemophagocytic lymphohistiocytosis is a disorder of hyperinflammation associated with multi-organ failure and high mortality (Hutchinson et al, 2019). It is broadly divided into primary (genetic) and secondary (acquired) haemophagocytic lymphohistiocytosis. Causes of secondary haemophagocytic lymphohistiocytosis include malignancy (commonly haematological), inflammatory diseases and infection.

Anakinra, an interleukin-1 receptor antagonist, has been used successfully to treat haemophagocytic lymphohistiocytosis (Wohlfarth et al, 2019), and its use in Kikuchi–Fujimoto disease overlapping with adult onset Still's disease has been described (Toribio et al, 2015).

Five previous cases of Kikuchi–Fujimoto disease with haemophagocytic lymphohistiocytosis have been reported in patients under the age of 18 years and one case in a 30-year-old man. All cases were in Asia (Japan, South Korea) and were managed with steroids and intravenous immunoglobulin. Etoposide and ciclosporin were used in severe cases (Mahadeva et al, 2000; Lim et al, 2008; Nishiwaki et al, 2016). One case of Kikuchi–Fujimoto disease complicated by haemophagocytic lymphohistiocytosis in a

17-year-old man in Sri Lanka, with an initial negative autoimmune screen (including anti-nuclear antibody, double-stranded deoxyribonucleic acid and complement), later developed features of systemic lupus erythematosus (Vithoosan et al, 2019).

To the authors' knowledge, this is the first case of Kikuchi–Fujimoto disease complicated by haemophagocytic lymphohistiocytosis, treated successfully with interleukin-1 blockade. The patient's condition is now stable, and he remains well off all medication.

Author details

[1]Department of Rheumatology, University College London Hospital, London, UK

[2]Hospital for Tropical Diseases, University College London Hospital, London, UK

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Learning points

- Prompt recognition of haemophagocytic lymphohistiocytosis enables early treatment and prevention of life-threatening complications.
- Tissue analysis in patients with haemophagocytic lymphohistiocytosis is essential: haematological malignancies are the most common cause.
- There is often a mismatch in an elevated C-reactive protein level compared to a relatively normal erythrocyte sedimentation rate.
- A ferritin level of greater than 10 000 ug/litre is typical for haemophagocytic lymphohistiocytosis.
- Anakinra, an interleukin-1 receptor antagonist, can be used to treat hyperinflammation in haemophagocytic lymphohistiocytosis and prevent the need for steroids while tissue biopsies are obtained.
- While Kikuchi–Fujimoto disease is typically a benign condition, complications such as haemophagocytic lymphohistiocytosis can occur.

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