CASE REPORT

Kikuchi-Fujimoto disease: a rare but important differential diagnosis for lymphadenopathy

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SUMMARY

A 23-year-old man presented with a 6-week history of fevers, cervical lymphadenopathy and fatigue. A CT of the neck, chest, abdomen and pelvis showed left cervical lymphadenopathy, enlarged lymph nodes in the axilla and groin and hepatomegaly. A left cervical excisional lymph node biopsy was undertaken and the histopathological findings were consistent with Kikuchi-Fujimoto disease. He was treated with high-dose prednisolone for 1 week, which was then tapered. Generalised arthralgia and daily episodes of malaise were experienced for a subsequent 2 months following the cessation of corticosteroids. The condition lasted 4 months from the onset of symptoms. This case report highlights the importance of including Kikuchi-Fujimoto disease as a differential diagnosis for lymphadenopathy. Kikuchi-Fujimoto disease has commonly been mistaken for tuberculosis and lymphoma, and unnecessary exposure to agents used to treat these conditions can be avoided by prompt histological diagnosis.

BACKGROUND

Kikuchi-Fujimoto disease (KFD) is a rare self-limiting disease.¹ It is characterised by histiocytic necrotising lymphadenitis, mainly involving the cervical lymph nodes and predominantly affecting females (ratio 4:1).² The clinical presentation and laboratory findings observed in KFD overlap with conditions such as lymphoma, tuberculosis and sarcoidosis. It is important that awareness of this condition is raised, as there have been reports where patients have been misdiagnosed as having lymphoma and tuberculosis with the unnecessary administration of chemotherapeutic and systemic agents.³ This case study reports the occurrence of KFD in a medical student who offers his perspective on the condition.

CASE PRESENTATION

A 23-year-old South Asian man presented to the emergency department with a 6-week history of fevers, cervical lymphadenopathy and extreme fatigue.

Initially, he had noticed a cervical lymph node swelling on the left anterior of the neck that was described as a relatively dull ache, with no other symptoms of note. Two weeks later a second swelling appeared in the left submandibular region, which was excruciatingly painful in the mornings and associated with fevers, but improved through the day with simple analgesia. During this 2-week period, he had occasionally experienced drenching night sweats and noticed some weight loss without

a reduced appetite. Apart from a medical history of mild asthma and previous childhood nephrotic syndrome, he had no other comorbidities. He was a non-smoker and studying at university. There was no recent travel history and there was no significant family history.

He was initially treated in primary care with courses of erythromycin and cephalexin. After 4 weeks of failing to respond, he was reviewed by his general practitioner and treated for a further week with amoxicillin in addition to a tapering dose of prednisolone, which briefly relieved his symptoms. However, his symptoms recurred during the prednisolone taper. After a worsening of the symptoms and fevers that were not effectively responding to paracetamol, he was assessed by the haematology team and admitted via the emergency department.

During his hospital admission, he had fevers with temperatures ranging from 38–40°C. He also developed an erythematous diffusely spread raised rash on his face, which subsequently became hyperpigmented.

INVESTIGATIONS

Laboratory investigations demonstrated a C reactive protein (CRP) that peaked at 100 mg/L (normal range <10 mg/L) and a lactate dehydrogenase of 780 U/L (normal range up to 225 U/L). He had mild anaemia (haemoglobin 112 g/L, normal range 135–180 g/L) and leucopaenia (white cell count $3.7 \times 10^9/L$, normal range $4.0\text{--}11.0 \times 10^9/L$). He had blood cultures on several occasions, all of which showed no growth and a malaria and hepatitis screen were negative. He had evidence of previous Epstein-Barr virus infection, and negative results for *Brucella*, cytomegalovirus, leptospirosis and toxoplasmosis testing. His autoantibody and arthritis screens were normal.

His chest radiograph was normal and a CT scan of the neck, chest, abdomen and pelvis with contrast showed left cervical lymphadenopathy together with enlarged lymph nodes in the axilla and groin (largest nodes up to 20 mm in short axis) in addition to hepatomegaly.

An excision biopsy of one of the enlarged left cervical lymph nodes was undertaken and the histopathological findings were consistent with Kikuchi-Fujimoto disease. These findings were namely distortion rather than effacement of architecture, patchy areas of necrosis comprising brightly eosinophilic fibrinoid deposits, histiocytes with crescentic nuclei and readily identifiable karyorrhectic debris with a conspicuous absence of

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neutrophils and eosinophils (figures 1–3). The histiocytes were immunoreactive for myeloperoxidase and CD68 (figure 4A, B). Admixed were numerous T cells with no evidence of antigen loss and clusters of CD123 positive plasmacytoid dendritic cells. No Reed-Sternberg, Hodgkin-like cells or large activated cells were present to suggest lymphoma, although Ki67 demonstrated a high-proliferative index of 70% (figure 5). B-cell compartments with occasional atrophic follicles were noted in the uninvolved areas. Absence of neutrophils within necrotic areas and absence of vasculitic lesions including deposits of nuclear DNA in vessel walls (Azzopardi effect) militated against the diagnosis of lupus lymphadenitis, which has very similar features.

DIFFERENTIAL DIAGNOSIS

A man in his 20 s, who presents with lymphadenopathy, drenching night sweats and weight loss may have lymphoma, tuberculosis, sarcoidosis, systemic lupus erythematosus (SLE), other atypical infections or rare forms of malignancy. HIV should also be included in the differential diagnosis. The clinical presentation and laboratory findings observed in KFD overlap with these differentials, although their treatments vary considerably. It is therefore imperative that KFD is distinguished from these conditions.

Laboratory investigations can sometimes be used to eliminate other aetiologies of lymphadenopathy, such as use of serum ACE levels in sarcoidosis, and autoantibodies including anti-double-stranded DNA antibodies in SLE.³

Radiological investigations such as chest radiography and CT may help identify a potential diagnosis. Although CT findings in KFD and lymphoma are both similar, lymph nodes identified in patients with KFD are generally not as large as those identified in lymphoma.^{3 4}

Lymph node excision biopsy is the critical investigation in providing a definitive diagnosis. Microscopic features including proliferation of large atypical immunoblasts and plasmacytoid dendritic cells with a high-proliferative index and necrosis may be misdiagnosed as non-Hodgkin or Hodgkin lymphoma. However, KFD does have certain characteristic findings that can be used to differentiate it from other aetiologies of lymphadenopathy.⁵ For example, distortion rather than complete effacement of architecture, patent sinuses, the presence of histiocytes and karyorrhexis, absence of neutrophils and eosinophils and inconspicuous mitoses can help differentiate KFD from lymphoma.² Although the histological features are distinct in KFD,

there is known to be some overlap with SLE.³ Clinical correlation is essential to fully exclude lupus lymphadenitis.

It has been reported that 29% of patients with KFD were initially misdiagnosed as having lymphoma.³ There have been reports where patients have been treated with chemotherapy as a result of a misdiagnosis.^{1 5} This reflects the subtle differences in the clinical presentation and histology of these differential diagnoses but also a lack of awareness of this disease among clinicians. This is particularly pertinent to our case as the patient was prescribed allopurinol in anticipation of chemotherapy-associated tumour lysis syndrome associated with lymphoma. Additionally, he was planned to be treated with anti-tuberculous medication by the respiratory physicians while waiting for histology results. Hence an early diagnosis from biopsy findings can prevent patients from being subjected to unnecessary investigations and treatments.

TREATMENT

As a supportive measure, he was treated with prednisolone 40 mg daily for 1 week, which was subsequently tapered. He was also prescribed regular paracetamol, ibuprofen and lansoprazole for symptomatic relief.

OUTCOME AND FOLLOW-UP

He responded well to prednisolone, with fevers subsiding and the lymph nodes reducing in size. However, 3 weeks after completing treatment he experienced generalised arthralgia and daily episodes of malaise for a subsequent 2 months, with symptoms responding well to simple analgesia. Although there was marked improvement of the hyperpigmented facial rash, it did not resolve completely. Overall, 4 months were taken to make a full recovery from the onset of symptoms.

DISCUSSION

Kikuchi-Fujimoto disease is a rare self-limiting disease, first described in 1972.¹ It is characterised by histiocytic necrotising lymphadenitis of an idiopathic nature, mainly involving the cervical lymph nodes and predominantly affecting females (ratio 4:1).² Although the disease has been described in all ethnic groups, it is mostly prevalent in Japanese and Asian populations.² It is typically seen in young female adults in the second and third decades of life.²

Fever is a primary symptom in 30–50% of patients.^{3 4} Cervical lymph nodes are involved in approximately 80% of

Figure 1 Characteristic low-power view with patchy necrosis (pale-staining areas).

Figure 2 High-power view of necrotic area with brightly eosinophilic fibrinoid deposits and karyorrhexis.

Figure 3 Macrophages with crescentic nuclei in necrotic areas.

cases, predominantly affecting the posterior triangle and are often unilateral.^{2 4} Although lymphadenopathy is often localised to cervical or supraclavicular nodes, it can also be generalised with involvement of axillary, inguinal, mediastinal and mesenteric nodes.^{1 5} The nodes are typically 1–2 cm in size and can be firm, smooth, mobile and painful.⁵ Systemic symptoms, although less common, include weight loss, malaise, chills, night sweats and arthralgia.³ Skin lesions that are maculopapular, morbilliform or urticarial in nature have also been reported.⁴

Figure 4 (A) Myeloperoxidase (B) CD68. Macrophages coexpress myeloperoxidase and CD68.

Figure 5 Ki67 showing high-proliferative index.

Although the aetiology is unknown, viral, postviral and bacterial causes have been implicated. It has been hypothesised that there is an immune response of T cells and histiocytes to a provoking agent.⁵ Epstein-Barr virus, toxoplasma, parvovirus, *Yersinia enterocolitica*, parainfluenza and paramyxoviruses have been described as potential pathogens.⁵ An association with SLE, mixed connective tissue disease and Still's disease has also been postulated.²

Laboratory findings may show anaemia, leucopaenia, raised CRP, elevated immunoglobulin levels and elevated lactate dehydrogenase (although these features can also be found in other disorders and are not specific for KFD).^{1 5} The definitive diagnosis is based on excision lymph node biopsy and histological examination as the clinical presentation is often indistinguishable from lymphoma, tuberculosis and sarcoidosis.

There is a characteristic histopathological diagnosis with lesions affecting the cortical and paracortical areas of the node.⁶ The lymph nodes that are affected have patchy areas of coagulative necrosis, largely in the paracortical areas.³ Microscopic examination can also demonstrate paracortical foci with histiocytic infiltrate.⁵ Well-circumscribed regions of eosinophilic fibrinoid material with a significant degree of karyorrhexis are often noted.³ The absence of neutrophils and eosinophils with few or no plasma cells is also characteristic of KFD.^{1 5} Immunophenotyping can also be helpful in differentiating KFD from other disorders that may give a similar morphological histology appearance such as SLE and high-grade lymphoma. In the patient described here, the high-proliferative index (demonstrated by Ki67 staining) may have raised suspicion of lymphoma as an isolated finding; however, the other histological features present confirm the diagnosis of KFD.

Although the histological features are characteristic and distinct, it is important that histology reports are checked and acted on by those with experience in treating the condition. This will avoid misinterpretation of pathology findings and resultant unnecessary treatment.

KFD is associated with a benign course and typically resolves over a period of 1–6 months.^{2 3} Treatment is supportive with paracetamol or non-steroidal anti-inflammatory drugs to alleviate painful lymphadenopathy and fevers. Corticosteroids are used in cases that are severe or unresponsive to simple analgesia.^{2 3} The use of hydroxychloroquine, immunoglobulins and minocycline has also demonstrated favourable results in some cases.⁴ Patients are generally followed up for a few years even after resolution of symptoms, as recurrences (3–4%) have been

reported and there has been an association with KFD and the development of SLE.^{5 7}

This case report highlights the importance of including Kikuchi-Fujimoto disease as a differential for lymphadenopathy. The diagnosis in this case was originally postulated to be tuberculosis or lymphoma and, hence, without the histological result our patient could have been subjected to unnecessary and unhelpful potentially toxic treatment.

Patient's perspective

- ▶ As a fourth-year medical student, being on the other side of the stethoscope was a real eye-opening experience. Not only was I able to empathise with patients who are in a similar situation, I was able to see first hand the impact that the differential diagnosis can have on the patient and their management.
- ▶ From what I hoped was a relatively minor viral infection, to what the haematologists differentiated could be lymphoma and the respiratory physicians hypothesised was tuberculosis, the diagnosis of Kikuchi-Fujimoto disease was not only an educational experience but also a relief. In fact, if it were not for the timely diagnosis from histology, there would have been unnecessary administration of antituberculous medication. It was indeed a shock to discover that there have been instances where patients with Kikuchi-Fujimoto disease had wrongly been administered chemotherapy as a result of an incorrect diagnosis.
- ▶ I hope by writing this case report, others will be able to appreciate that the presenting symptoms of lymphadenopathy, weight loss and night sweats do not immediately indicate a grave diagnosis and that a reactive differential such as Kikuchi-Fujimoto disease could be a possibility.

Learning points

- ▶ Kikuchi-Fujimoto disease (KFD) is a rare self-limiting disease but an important differential for painful lymphadenopathy and fever.
- ▶ Lymph node excision biopsy is important in providing a definitive diagnosis for KFD. It should be considered for patients with cervical lymphadenopathy, fever and systemic symptoms, especially when there is diagnostic uncertainty.
- ▶ The treatment for KFD is generally supportive, with corticosteroids reserved for severe cases, which differs dramatically to conditions with similar presentations such as lymphoma and tuberculosis.
- ▶ Owing to recurrence of the disease and the subsequent development of systemic lupus erythematosus in some patients, follow-up is required for several years.

Contributors MS wrote this case report. PM edited and reviewed the manuscript. BV provided the histology images and reviewed the manuscript. GCL edited and supervised this case report.

Competing interests None.

Patient consent Obtained.

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