CASE REPORT

Histiocytic necrotising lymphadenitis (Kikuchi-Fujimoto disease) of axillary lymph nodes

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SUMMARY

Kikuchi-Fujimoto disease (KFD) or histiocytic necrotising lymphadenitis is a rare entity, occurring most commonly in young Asian adults. KFD is characterised by fever with tender lymph node enlargement. The cervical group of lymph nodes is most commonly involved, and the diagnosis is conclusively made by lymph node biopsy and histopathology. KFD is a self-limiting condition, which usually resolves over 1–4 months. Symptomatic treatment with antipyretics and/or non-steroidal anti-inflammatory drugs is recommended. Here we describe an uncommon presentation of KFD in a young woman in which only the axillary lymph nodes were enlarged.

BACKGROUND

Unexplained fever with lymph node enlargement has a wide differential diagnosis. One disorder in this category is Kikuchi-Fujimoto disease (KFD), also known as histiocytic necrotising lymphadenitis. KFD is a benign, self-limiting illness that is characterised by tender enlarged nodes, usually in the cervical region, with fever and night sweats.¹ Less common symptoms include nausea and vomiting, sore throat and weight loss.¹ KFD is characterised by *Orphanet* to be a rare disorder, occurring in 1 of 2000 individuals.¹ This disease has a worldwide distribution with higher prevalence among Asian individuals—most often adults under the age of 30 years.² The differential diagnosis includes lymphoma, tuberculosis, sarcoidosis and metastatic adenocarcinoma. As there is an association between KFD and the later development of systemic lupus erythematosus, long-term follow-up is advisable.

CASE PRESENTATION

A woman in her 20 s, of Indian descent, presented with painful swelling in the left axilla for the past 10 days, accompanied by fever, chills, loss of appetite and generalised weakness for 8 days. The patient had no significant relevant medical or family history. She was initially diagnosed in the emergency department with a viral illness and mild urinary tract infection, and was started on acetaminophen and ciprofloxacin. The patient did not show improvement and was seen in a surgical clinic 1 week later.

On examination, her pulse rate was 108 bpm, blood pressure 107/70 mm Hg, respiratory rate 14 breaths/minute and temperature 102.8°F (39.3°C). Physical examination was unremarkable except for tender left axillary lymphadenopathy, involving medial pectoral and apical nodes, the largest

Table 1 Laboratory test results

Parameter	Value	Normal range
Total WCC count	3.4×10 ⁹ /L	4.0–11.0×10 ⁹ /L
Absolute lymphocyte count	1.0×10 ⁹ /L	1.5–4.0×10 ⁹ /L
Platelet count	106×10 ⁶ /L	140–440×10 ⁹ /L
Lactate dehydrogenase	468 U/L	94–250 U/L
C reactive protein	0.7 mg/dL	<0.6 mg/dL
Erythrocyte sedimentation rate	19 mm/h	0–20 mm/h
Procalcitonin	<0.05 ng/mL	<0.05 ng/mL

WCC, white cell count.

measuring 2×1.5 cm. Examination of ipsilateral breast and upper extremity was normal.

Laboratory tests revealed mild leucopenia, lymphopenia and thrombocytopenia (table 1, above). A blood smear was normal except for mild thrombocytopenia. Serum lactate dehydrogenase (LDH) was elevated. Liver and renal function tests were normal. Erythrocyte sedimentation rate (ESR), C reactive protein (CRP), procalcitonin level (as a marker for infection) and chest radiograph were all normal. Blood cultures were negative for infection.

An ultrasound examination of the left axilla revealed enlarged lymph nodes without evidence of abscess formation (figure 1). Since surgical excisional biopsy is the gold standard for diagnosis of lymphadenopathy, an excisional biopsy of a left axillary lymph node was performed.³ Bacterial staining, and culture and acid-fast bacillus staining were negative. Histopathology of the excised specimen revealed a necrotic lymph node with near complete effacement by inflammation and debris

Figure 1 Ultrasound image of left axilla, demonstrating enlarged hypoechoic lymph nodes.

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Figure 2 H&E staining of left axillary lymph node biopsy (10× magnification), demonstrating effacement of lymph node (black arrows) and necrotic areas with histiocytic infiltration (yellow arrow).

(figure 2). Numerous histiocytes were seen with an absence of neutrophils (figure 3). Flow cytometry of a lymph node specimen did not show any monoclonal B-cell proliferation or aberrant T-cell population. The following 18 antibodies were used: CD10, CD19, CD2, CD20, CD23, CD3, CD38, CD4, CD43, CD45, CD5, CD56, CD57, CD7, CD8, FMC7, κ and λ . The pathologist made a diagnosis of histiocytic necrotising lymphadenitis (Kikuchi-Fujimoto disease).

INVESTIGATIONS

Beyond the history and physical which should inform the imaging and laboratory phase of data gathering. Basic testing—including complete blood count, ESR, chest X-ray and purified protein derivative—would be the initial line of inquiry, as well as any findings on the history or physical that should be pursued via testing (such as a breast mass). Ultimately, however, the answer lies within the lymph node. Fine-needle aspiration for culture and cytology can be helpful, but the histology of the node is necessary for definitive diagnosis—which can only be observed via an excisional lymph node specimen. Excisional biopsy is considered to be the gold standard for the diagnosis of lymphadenopathy.³

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of KFD involves lymphoma, tuberculosis, systemic lupus erythematosus (SLE), blastic plasmacytoid dendritic cell neoplasm, Kawasaki's disease, sarcoidosis, herpes

Figure 3 H&E staining of left axillary lymph node biopsy (400× magnification), demonstrating necrotic areas with absence of neutrophilic infiltration.

simplex virus (HSV) and Epstein-Barr virus (EBV) and metastatic adenocarcinoma.⁴

TREATMENT

Systemic treatment with antipyretics and non-steroidal anti-inflammatory drugs is recommended for KFD, although rarely corticosteroids may be needed.⁴ Treatments with hydroxychloroquine, immunoglobulins and minocycline have also been reported.^{5–7}

OUTCOME AND FOLLOW-UP

A diagnosis of histiocytic necrotising lymphadenitis (Kikuchi-Fujimoto disease) was made. The patient received antibiotics for a presumed urinary tract infections and ibuprofen for discomfort following the procedure. Twenty-four hours following the biopsy procedure, the patient was feeling much better and continues to feel well at 5 months postdiagnosis of KFD.

DISCUSSION

KFD was first described in Japan, in 1972, by Kikuchi and Fujimoto as separate case reports.^{8–9} KFD is a rare disease, more commonly seen in Asian populations.^{8–10} Its occurrence in males and females is similar and usually afflicts young adults (<30 years).¹⁰ The exact aetiology of KFD is not known, but it has been suggested to be a self-limiting autoimmune response to a viral infection (eg, Epstein-Barr, herpes, parvo B₁₉, cytomegalovirus or HIV) in genetically-susceptible individuals.^{11–18} An association of previous KFD with the development of SLE also points to a possible autoimmune role.¹⁹ In our case, we did not test for HSV 1, 2, zoster or EBV as cause for the lymph node involvement as the patient exhibited no clinical signs of HSV infection, such as rash or shingles.

The clinical presentation of KFD is typically fever and tender lymphadenopathy usually involving the cervical nodes (56–98%); rarely inguinal and retroperitoneal nodes are also involved.^{4 20–21} The involvement of axillary lymph nodes and even internal mammary nodes has been reported.^{22–24} Our patient's presentation was unusual in that the axillary lymph nodes were predominantly involved. Constitutional symptoms of night sweats, weight loss and loss of appetite are also reported.⁴ Extranodal involvement may include hepatomegaly, splenomegaly, rash and rarely, arthritis and meningitis.^{4 25–26}

Leucopenia is seen in about 50% of cases of KFD, with some atypical lymphocytes seen in the peripheral blood smear examination.²⁷ Other laboratory findings reported an elevated LDH, ESR and CRP.²⁷ The present patient demonstrated leucopenia with lymphopenia and thrombocytopenia, as well as an elevated LDH.

Lymph node excision biopsy with microscopic examination is the best modality for obtaining a KFD diagnosis.^{3–4} The ultrasonographic features of axillary lymphadenopathy are varied and thus, identification of a malignant lymph node in the axilla by ultrasonography is difficult.²⁸ A series of ultrasound examinations, of 29 axillary lymph node enlargements due to KFD in seven patients, showed at least one radiological feature of malignancy in every lymph node and 66% of nodes showing three or more features of malignancy.²⁹ It is important to correctly identify a benign cause of lymph node enlargement, as opposed to a malignant cause, before an assessment of the treatment plan.

The approach to evaluation of axillary lymph node enlargement should include the likelihood of malignancy. While painful enlargement associated with fever, chills and sweating point towards an inflammatory process, similar findings can be seen in other lymphoid malignancies. In the present case, initial evaluation for an infective aetiology, such as blood culture, CRP, ESR

and procalcitonin, was negative. In the absence of a clinically palpable breast mass, due to her young age and no contributory family history of breast masses, an epithelial tumour of the breast was considered unlikely. Evaluation for a lymphoid-origin tumour by cytological or biopsied tissue specimen analyses should be considered as a necessary step in its management.

Fine-needle aspiration cytology and cutting needle biopsy combined with immunohistochemical study of myeloperoxidase may be useful in minimally-invasive diagnostic procedures; a non-invasive diagnosis by means of gene expression profile analysis of peripheral blood mononuclear cells has also been reported.^{30–32} Although different approaches are being tried to enable easier diagnosis, excisional biopsy remains the gold standard for the diagnosis of KFD. Microscopic examination of the lymph nodes usually shows necrotic areas with effacement of the nodal architecture in paracortical regions with abundant histiocytes, and scant or absent neutrophils. This was consistent with the microscopic examination of lymph tissue from our patient (figures 2 and 3). Three stages of the disease have been described: proliferative, necrotising and xanthomatous.³³

Accurate and early diagnosis of KFD can prevent improper management with antitubercular or anticancer drug therapy. Recurrent Kikuchi's disease in the axilla 12 years after the original episode has also been reported.³⁴ Long-term follow-up is warranted to check for development of SLE.⁴

Learning points

- Unexplained fever and tender lymphadenopathy, especially in young women, should raise the suspicion of Kikuchi-Fujimoto disease.
- Nodal sites other than cervical lymph nodes can be affected.
- Long-term follow-up is important to monitor the development of systemic lupus erythematosus.

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Competing interests None.

Patient consent Obtained.

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