CASE REPORT

TB or not to be? Kikuchi-Fujimoto disease: a rare but important differential for TB

C McKenna,¹ T Whitfield,¹ N Patel,¹ A Bonington^{1,2}¹North West Regional Centre for Infectious Diseases, North Manchester General Hospital, Manchester, UK²The University of Manchester, Manchester Academic Health Science Centre, North Manchester General Hospital, Manchester, UK**Correspondence to**Dr C McKenna,
christinemariemckenna@doctors.org.uk

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SUMMARY

A 29-year-old British Pakistani woman presented with a 2-month history of drenching fevers, night sweats, lethargy and tender cervical and axillary lymphadenopathy. Initial investigations, bloods and imaging were unremarkable. Fever persisted during her admission, and treatment for tuberculosis (TB) lymphadenitis was started postbiopsy until histology confirmed a diagnosis of Kikuchi-Fujimoto's disease (KFD). KFD has a non-specific presentation of fever, night sweats and lymphadenopathy and commonly raises a clinical suspicion of a number of other serious conditions such as TB, lymphoma, HIV, systemic lupus erythematosus, toxoplasmosis and infectious mononucleosis. Although rare, KFD should be considered to be a differential diagnosis for fever of unknown origin and tender lymphadenopathy in otherwise well individuals. This case demonstrates the importance of a timely histological biopsy diagnosis to prevent an incorrect diagnosis and administration of unnecessary medications.

BACKGROUND

The triad of symptoms; tender lymphadenopathy, fever and night sweats can point a physician towards a number of different serious diagnoses mimicking TB, lymphoma, HIV, systemic lupus erythematosus, toxoplasmosis and infectious mononucleosis. This case broadens the differential of such a presentation and highlights the importance of a timely histological biopsy diagnosis to prevent the anxiety surrounding a misdiagnosis and the administration of unnecessary medications.

CASE PRESENTATION

A 29-year-old Pakistani woman was admitted to the infectious diseases unit with a 2-month history of drenching sweats, lethargy, malaise and small painful swellings on the right side of her neck and axillae. She initially had intermittent low-grade fevers during the day which progressed to drenching night sweats over the course of the 6 weeks. Prior to this presentation, she had been investigated for a painful left arm axillary swelling and lethargy which was diagnosed initially as an axillary abscess and treated accordingly with a course of antibiotics without symptom resolution. Superficial thrombophlebitis had also been considered and on another presentation to the emergency department she was diagnosed with lymphadenopathy secondary to a viral illness.

She had no significant medical history, and a recent blood borne virus screen was negative. She

had not returned to Pakistan or travelled abroad for 5 years, and there was no history or suggestion of TB in her family or close contacts. She had no history of close contact with animals and employment history was unremarkable.

Clinical examination revealed: bilaterally enlarged, firm lymph nodes measuring 2×2 cm in the cervical region, a palpable 2 cm right axillary lymph node and 1 cm left axillary lymph node.

INVESTIGATIONS

The predominance of systemic symptoms prompted an extensive investigation. Chest X-ray was normal. A thoracic CT scan conducted on a previous admission had reported non-specific findings: right axillary lymphadenopathy and a 1.3 cm left bronchopulmonary lymph node. Blood tests were unremarkable apart from a rise in ALT (92 U/L) (normal range 10–35 U/L). White cell count, differential count and C reactive protein (CRP) were all within normal parameters. Blood cultures were negative, malarial film was also normal and analysis of a Ziehl-Neelsen stain of induced sputum found no acid-fast bacilli. Toxoplasmosis, rubella, cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), HIV and syphilis screens were negative. A cervical biopsy was arranged as an outpatient.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis in patients presenting with fever of unknown origin with lymphadenopathy in this age group include TB, lymphoma, toxoplasmosis and infectious mononucleosis. It is important to rule out HIV and syphilis.

TREATMENT

Following cervical biopsy, this woman was treated for presumed tuberculosis with the standard antituberculosis therapy of rifampicin, isoniazid, pyrazinamide, ethambutol and pyridoxine. After the first day of therapy, a widespread erythematous rash developed which resolved when the rifampicin was omitted.

OUTCOME AND FOLLOW-UP

At 4 days postbiopsy, the histology reported "A tan coloured nodule measuring 10×9×7 mm showing areas of early necrosis, apoptosis and collections of histiocytes many of which have J shaped nuclei. Apoptotic debris was identified and reactive blasts were present (see figures 1–3). The cell proliferation noticed within the para cortex as well as in the subcapsular area is in keeping with Kikuchi

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Figure 1 This low power view (×20) demonstrates the widespread areas of necrosis within the lymph node.

Fujimoto lymphadenitis/histiocytic necrotising lymphadenitis. Immunohistochemistry revealed no CD30-positive Reed-Sternberg type cells. The nodules of histiocytes stained with CD68 in keeping with KFD.”

This condition is self-resolving; therefore, all medications were stopped barring antifever treatment. The patient was reassured and advised regarding the possibility of relapse.

DISCUSSION

Kikuchi disease was first reported in the *Japanese Journal of the Haematological Society* by Dr Masahiro Kikuchi in 1972 and again, independently, by Fujimoto and his team in the same year.^{1 2} Dr Masahiro Kikuchi presented a case of lymphadenitis characterised by follicular hyperplasia and paracortical expansion of histiocytes in the initial phase, T-cell and B-cell blasts and lymphocytes in the proliferative phase followed by necrotising phase.¹ Necrosis in the later stages is characterised by a predominance of histiocytes without neutrophilic infiltrate.^{1 2} This helps to differentiate it from other conditions and for this reason Kikuchi-Fujimoto disease (KFD) is also known as histiocytic necrotising lymphadenitis.

The disease is predominantly prevalent in Asian countries, particularly within Japanese populations but it has been reported in all ethnic groups. The disease has a female preponderance in particular, those in the second and third decades of life.^{3 4}

Figure 2 The abundant apoptotic debris admixed with histiocytes (×200).

Figure 3 Higher power (×400) showing histiocytes with J-shaped nuclei. No neutrophils or eosinophils are present.

The most common presentation of KFD is fever, night sweats and lymphadenopathy; less common symptoms include weight loss, rash, joint pain, diarrhoea and fatigue.⁴ These symptoms mimic the presentation of a number of serious conditions such as TB, lymphoma, HIV, systemic lupus erythematosus, toxoplasmosis and infectious mononucleosis.

Diagnosis is confirmed by biopsy of the affected lymph nodes which are usually firm, mobile and smooth in nature. Lymphadenopathy in KFD is normally isolated to a single location in 83% of cases. Cervical nodes are most commonly affected.⁵ Cases of generalised adenopathy involving axillary, inguinal and mesenteric nodes are more unusual.⁵ Biochemical markers are non-specific. A raised CRP and erythrocyte sedimentation rate (ESR) is evident in 70% of patients and leucopenia in 20–32% but otherwise blood tests are often unremarkable.⁶ Anaemia of chronic disease, deranged liver function tests and pancytopenia have also been reported.⁶ The aetiology is unknown, theories postulated include an autoimmune aetiology with a possible infectious trigger with toxoplasmosis, CMV, human herpes virus, varicella zoster virus, para-influenza virus and Epstein-Barr virus all been implicated. Apoptotic cell death mediated by cytotoxic CD8-positive T lymphocytes is the principal mechanism of cellular destruction. Histiocytes may act as enhancers.^{7 8} A possible autoimmune link with systemic lupus erythematosus (SLE) has been considered to be some patients have gone on to be diagnosed with SLE after Kikuchi-Fujimoto diagnosis.⁹

Immunohistochemical stains are helpful in differentiating KFD from lymphomas. The large cells are negative for CD3 and CD20, which excludes the possibility of lymphoma but positive for CD68, which demonstrates their histiocytic feature.¹⁰

Treatment is with supportive therapy, and symptoms normally resolve within 4–6 months. In some cases, however prednisolone, antibiotics, intravenous immune globulins and hydroxychloroquine have also been used to help aid recovery in those with persistent symptoms.^{11–13} Relapse is also possible, and a positive antinuclear antibody test is associated with a higher risk of recurrence.⁸

Although rare, a substantial quantity of research has been conducted on KFD. Only a small number of cases have been reported in the UK.¹⁴ A literature search conducted in the *BMJ Case Notes* reported 14 previous cases, and of those 14, 3 were in the UK and 1 in the Ireland.^{15 16}

It is highly possible that cases are misdiagnosis by clinicians. Reporting such cases would increase awareness and consideration of KFD as a differential diagnosis. KFD should be considered in young patients presenting with fever, night sweats and tender lymphadenopathy. A timely histological diagnosis could prevent misdiagnosis and inappropriate use of antibiotics or immunomodulatory drugs.¹⁰

Learning points

- ▶ Kikuchi-Fujimoto's disease (KFD) should be considered to be a differential diagnosis for fever of unknown origin and tender lymphadenopathy in otherwise, well young individuals.
- ▶ The presentation of KFD mimics a number of serious conditions; tuberculosis (TB), lymphoma, HIV, systemic lupus erythematosus, toxoplasmosis and infectious mononucleosis.
- ▶ Clinicians therefore need to be vigilant in TB endemic areas as this case highlights how KFD can present like TB.
- ▶ A timely histological biopsy diagnosis to prevent a misdiagnosis and administration of unnecessary medications is imperative.
- ▶ KFD is a self-resolving condition with symptoms resolving within 4–6 months. Treatment is supportive therapy.

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regarding the accuracy or integrity of the article are investigated and resolved by all four authors, particularly CM, AB and TW.

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