CASE REPORT

Kikuchi-Fujimoto Disease Triggered by *Mycoplasma pneumoniae* Infection: A Case Report.

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Abstract
Kikuchi-Fujimoto disease (KFD) is a rare inflammatory disorder which typically presents with cervical lymphadenopathy and pyrexia. It is frequently misdiagnosed as other more common medical conditions which share similar clinical manifestations. The diagnosis of KFD is often established only after a lymph node biopsy and histopathology evaluation that demonstrates the characteristic features of histiocytic necrotizing lymphadenitis. While the aetiology of KFD remains poorly-understood, certain microbial agents have been implicated as triggering factors. Here, we highlight a case of a young Asian woman who developed prolonged fever and cervical lymphadenopathy. She was initially being investigated for possible lymphoma, but was subsequently found to have KFD, alongside a *Mycoplasma pneumoniae* infection. She recovered well following the treatment with azithromycin.

Keywords: *Azithromycin, Kikuchi-Fujimoto disease*, *Mycoplasma pneumoniae.*

Introduction

Kikuchi-Fujimoto disease (KFD) is a rare form of benign lymphadenitis which was first recognized in Japan in year 1972 and since then, has been reported worldwide [1-4]. It mostly affects young adults with varying gender distribution and ethnic background [5,6]. KFD typically presents with localized lymphadenopathy with a predilection to cervical lymph nodes, along with systemic symptoms, notably fever, weight loss, and fatigue [5,6]. Hence, it is difficult to distinguish KFD clinically from other more serious illnesses such as malignant lymphoma, tuberculous lymphadenitis, systemic lupus erythematosus, and certain viral infections like infectious mononucleosis, until a lymph node biopsy is done, which reveals the distinctive features of histiocytic necrotizing lymphadenitis.

Case report

A 19-year-old female boutique assistant, previously healthy and fit, presented with intermittent fever, reduced appetite, and progressive fatigue for three weeks. At the same time, she also noticed small swellings on both sides of her neck. Otherwise, there were no specific respiratory symptoms, night sweats, skin rashes, joint pain, any bleeding tendency, or lumps elsewhere in the body. She had no history of high-risk behaviour, contact with sick people, recent travel abroad, or jungle trekking. She initially took paracetamol to relieve the fever and received a five-day course of antibiotics from a private clinic one week after the onset of her illness. However, the effect of the treatment was short-lived. The fever persisted, and she lost 6 kg of weight before seeking medical attention in the hospital.

Upon review, she appeared pale and had a temperature of 38 °C but otherwise not in distress. Her pulse rate was 102 beats/minute, blood pressure was 112/73 mmHg, and respiratory rate was 18 breaths/minute. Bilateral cervical lymphadenopathy was noted at levels II to IV. The nodes were mobile, firm, with sizes ranging from 1 to 3 cm, and some were mildly tender. Other peripheral lymph nodes were not palpable. No lesions were found in the ears, nose, or oral cavity. Abdominal examination revealed hepatomegaly (liver span 13 cm). The spleen was not enlarged. Examination of other organ systems was unremarkable.

Her initial haematological indices showed leukopenia (total white cell count, TWBC 1.9 x 10^9/L) with absolute neutropenia (0.86 x 10^9/L) and lymphopenia (0.9 x 10^9/L), hypochromic microcytic anaemia (haemoglobin 8.8 g/dL, mean corpuscular volume 60.2 fl, mean corpuscular haemoglobin 18.3 pg), a low reticulocyte count 0.34%, and normal platelet count. No blast cells were seen on the peripheral blood smear but some atypical lymphocytes were present. Considering possible lymphoproliferative disorder with neutropenic sepsis, she was initiated on broad-spectrum antibiotics upon admission, including intravenous piperacillin/tazobactam, tablet doxycycline, and tablet azithromycin. Subsequent laboratory studies revealed a positive direct coombs test, low serum iron 4.6 µmol/L, total iron binding capacity 39.5 µmol/L, and elevated levels of serum ferritin 1626.8 µg/L, C-reactive protein 39.9 mg/L, lactate dehydrogenase 954 U/L, alanine transaminase 173.8 U/L, and aspartate transaminase 249 U/L. Her erythrocyte sedimentation rate, renal profile, serum bilirubin, and alkaline phosphatase were normal.

Extensive microbiological testing was carried out to exclude various infections being considered as the differential diagnoses. A significant titre (1:320) of anti-Mycoplasma immunoglobulin (Ig) M was noted. Both the anti-Epstein-Barr virus and anti-cytomegalovirus IgG were reactive but the IgM were non-reactive, indicating previous exposure. Her chest radiograph was normal. The blood culture, leptospira and parvovirus B19 serology, human immunodeficiency virus test, malaria parasites, viral hepatitis screen, and tuberculosis work-up were negative. Abdominal ultrasound confirmed the enlarged liver with no focal lesions and excluded intraabdominal lymphadenopathy or abscesses. In addition, the

autoantibody screen for systemic lupus erythematosus was negative.

As lymphoma remained the major concern, an excisional lymph node biopsy was performed on day 3 of admission, and the histopathology examination (HPE) findings revealed histiocytic necrotizing lymphadenitis, consistent with Kikuchi-Fujimoto disease (Figure 1 and 2).

Her condition was stable throughout her stay in the hospital. The fever subsided two days after administration of the antimicrobial therapy. The HPE result was obtained one week after her admission, and by that time, she had completed three days of azithromycin, seven days of doxycycline, and five days of piperacillin/tazobactam followed by two days of amoxicillin/clavulanate. Haematinics were prescribed for the iron-deficiency anaemia. She regained her appetite and reported marked improvement in her general well-being. The TWBC and reticulocyte count improved and normalized after one week. The LDH declined steadily following treatment. The transaminases fluctuated but eventually demonstrated a downward trend. She was discharged well and was scheduled for follow-up in the specialist clinic to monitor her haemoglobin level, liver enzymes, and her future outcome.

Discussion

Kikuchi-Fujimoto disease (KFD) is a rare cause of lymphadenopathy, and it frequently poses challenges in the diagnosis. While localized cervical lymphadenitis remains the most classical presentation of KFD, generalized lymphadenopathy and enlargement of the lymph nodes in other regions such as the axilla, groin, and within the abdominal cavity have been described [3,7-9]. The involved nodes are typically mobile, firm, usually small with sizes less than 3 cm, and at times tender [7]. Besides the common associated systemic features which mimic the B symptoms in lymphoma, other unusual extranodal manifestations recognized in KFD include skin rashes, hepatosplenomegaly, arthritis, and neurological dysfunction [10-12]. Laboratory abnormalities commonly observed in KFD, although non-specific, are leukopenia, presence of atypical lymphocytes in the peripheral blood, increased erythrocyte sedimentation rate, elevated lactate dehydrogenase, and elevated transaminases [5,6,13]. In view of the wide range of differential diagnoses, serology tests for viral infections, tuberculosis work-up, and autoantibody panels are frequently carried out as part of the diagnostic evaluation. A definitive diagnosis of KFD requires a histopathological examination of the involved nodes. Excisional biopsy is helpful to exclude lymphoma. A recent study by Park et al indicated that ultrasound-guided core needle biopsy had a 95.6% accuracy in the diagnosis of KFD, making it a suggested diagnostic modality when KFD is a a clinical consideration [14]. In KFD, histologically, patchy areas of necrosis with abundant karyorrhectic nuclear debris are seen at the paracortical region, surrounded by extensive infiltrates of histiocytes, small lymphocytes, immunoblasts, and plasmacytoid dendritic cells [13]. The neutrophils are notably absent [13]. In addition, immunohistochemistry can further contribute to the diagnosis as the histiocytes in KFD are positive for myeloperoxidase, CD163, and CD68; the lymphocytes are predominantly T cells expressing CD3; and CD123 highlights the plasmacytoid dendritic cells [13,15].

The etiopathogenesis of KFD has not been fully elucidated. Li et al had demonstrated that KFD is associated with an aberrant type 1 interferon response, which is likely mediated by the T-lymphocytes and the plasmacytoid dendritic cells [16]. However, the initiating signals of this dysregulated immune response remain undetermined. Various factors have been implicated as the drivers for KFD, particularly the microbial agents and the autoimmune mechanisms [17]. In our patient, the KFD was associated with an acute *Mycoplasma pneumoniae* infection as evidenced by the high anti-mycoplasma IgM titre along with a positive Coombs test. KFD triggered by *Mycoplasma*

pneumoniae infection is uncommon and our literature search identified only four reported cases [18-20]. Interestingly, our patient also had previous contact with cytomegalovirus and Epstein-Barr virus. Although numerous infectious triggers particularly the viruses have been linked to KFD, microbial analysis by RNA sequencing of the biopsied materials in KFD had not identified any specific pathogens and hence, failed to prove a causal relationship between the microorganisms and KFD [21]. The intricate interplay between the microbial agents and the immune system leading to increased susceptibility to, and the onset of, the inflammatory cascade in KFD, would require further research. The development of KFD has been linked to an autoimmune origin, as multiple cases of KFD associated with systemic lupus erythematosus (SLE) and Sjögren's syndrome have been reported [22,23]. KFD could occur simultaneously with, before, or after the onset of the autoimmune disorders. Furthermore, pathological analysis of the lymph nodes in certain patients with active SLE did reveal the presence of necrosis and histiocytic infiltration which were indistinguishable from KFD [24]. This similarity in the histopathological findings further supports the autoimmune process as a trigger of KFD.

KFD is self-limiting and the majority of patients will have a favourable outcome with spontaneous recovery within a few months, although recurrence has been observed in 3 to 4% of cases [6]. The treatment for KFD is primarily supportive. Paracetamol and non-steroidal anti-inflammatory drugs are frequently prescribed as antipyretics and analgesics. In severe cases with a more prolonged course of illness and extensive nodal or extranodal involvement, systemic corticosteroids, immunomodulators, and intravenous immunoglobulin have been utilized [25-27]. Our patient had a dramatic improvement with resolution of fever, which was apparent soon after the administration of the antimicrobial therapy. Although multiple antibiotics were initiated as the diagnosis of her clinical problem was unclear upon admission, we believed that the patient responded to the azithromycin as it was the appropriate treatment for the *Mycoplasma pneumoniae* infection. The outcome of our patient was similar to the reported cases by Yu et al, indicating that macrolide may play a role in the resolution of KFD if it is associated with *Mycoplasma pneumoniae* infection [18].

Conclusion

This case underscores the fact that Kikuchi-Fujimoto disease is easily misdiagnosed. It is crucial that the clinicians should be aware of this rare clinical entity to streamline the diagnostic evaluations and avoid unnecessary interventions. Further research remains highly anticipated to determine the aetiology and the molecular pathways in the pathogenesis. Despite being self-limiting, the specific targeted therapy to the recognized trigger might contribute to early resolution of the disease and improved outcome.

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Conflicts of interest
None to declare.

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Authors contribution
LHS: Ideas, data collection, manuscript writing, and formatting
OPS: Intellectual input to the manuscript
CKY: Analysis of the lymph node biopsy

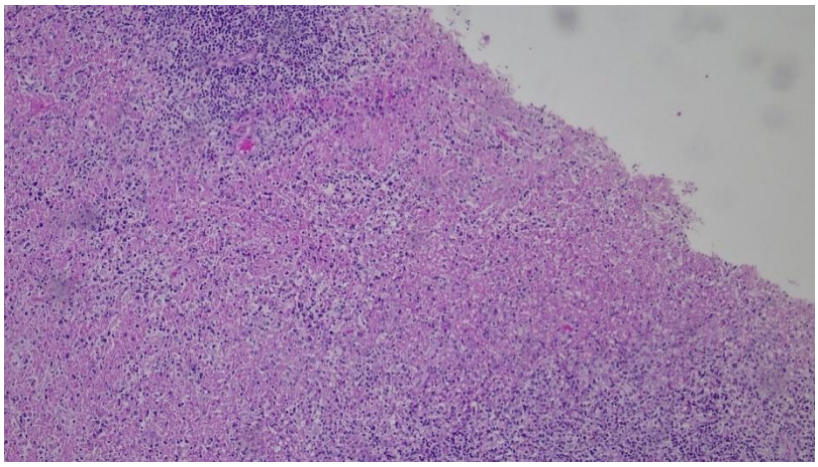

Figure 1. Histopathology of the lymph node showing areas of necrosis consisting of brightly eosinophilic fibrinoid deposits.

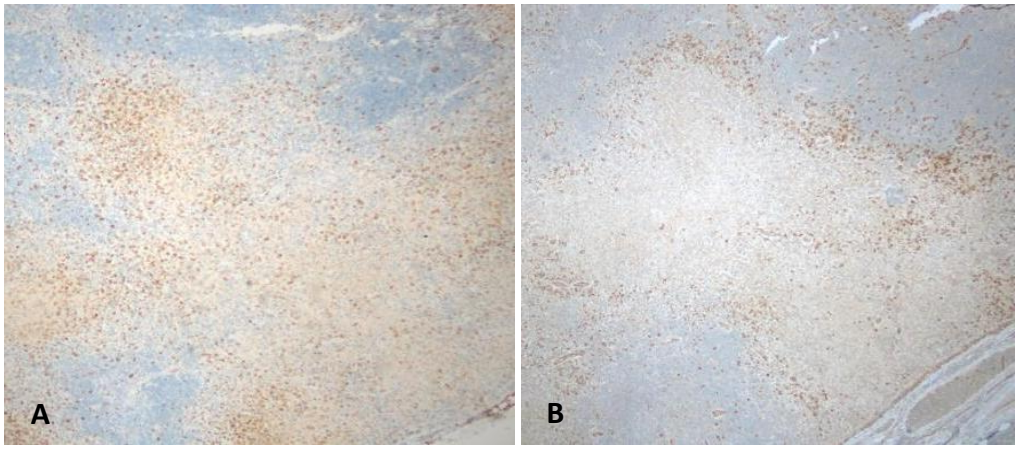

Figure 2. Immunohistochemical staining of the lymph node. **A.** CD163 highlighted the aggregates of histiocytes surrounding the areas of necrosis. **B.** CD123 labeled the plasmacytoid dendritic cells which formed clusters at the edges of the necrotic foci.

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