Kikuchi-Fujimoto Disease: Two Case Reports from North East India

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Abstract
Kikuchi-Fujimoto disease (KFD) is also known as histiocytic necrotizing lymphadenitis. Kikuchi-Fujimoto disease (KFD) or histiocytic necrotizing lymphadenitis is a rare benign, self-limiting cervical lymphadenitis of unknown etiology. The disease mainly affects young women and can closely mimic infective and immunological disorders. KFD should be included in the differential diagnosis of suspected cases of tuberculosis, lymphoma and systemic lupus erythematosus. The disease is benign and self-limiting and an excisional biopsy of an affected lymph node is necessary for diagnosis. This study reports on two cases of female patients with KFD who were presented with fever and cervical lymphadenopathy. Although the incidence of Kikuchi-Fujimoto disease is rare, clinicians should be aware of this condition as early recognition of the disease will minimize potentially harmful and unnecessary evaluations and treatments.

Keywords: kikuchi-fujimoto disease, histiocytic necrotizing lymphadenitis, cervical lymphadenopathy.

Introduction
Kikuchi-Fujimoto disease (KFD) or histiocytic necrotizing lymphadenitis is an uncommon, idiopathic, generally self-limited cause of lymphadenitis.¹² KFD is a form of histiocytic necrotizing lymphadenitis first described in Japan in 1972 almost simultaneously by Kikuchi¹ and Fujimoto et al.² They studied patients treated for lymphoma who evolved surprisingly well, showing much faster recovery than expected. In fact, these patients did not have lymphoma but a condition that has been called Kikuchi-Fujimoto disease since its initial description.³ KFD represents a condition most frequently found in East Asian and Japanese populations. Male and female ratio is 1:4 with female preponderance and largely affects young adults (<30 years old).⁴ Clinically, KFD manifests as cervical (usually unilateral) lymphadenopathy with fever and is frequently associated with other nonspecific symptoms.⁵⁶ Laboratory test results are almost always unchanged, except for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level.⁶⁷ An excisional biopsy from an affected lymph node is necessary for diagnosis.⁵ The etiology of Kikuchi-Fujimoto disease is
uncertain and speculations exist regarding relationship with previous viral infections or autoimmune processes.

**Case Reports**

**Case 1**

A 29 year old woman of north East Indian origin came to us with complaints of cervical masses on her right side of neck and fever for 3 weeks of duration. The cervical masses were mildly painful. The patient did not report any other complaints. Clinical examination revealed multiple mobile mildly tender lymph nodes in the right posterior triangle, right post auricular and right submandibular region of neck. The largest lymph node being the posterior triangle was about (2x3.5) cm in size. There was no palpable lymph node in left side of neck and any other parts of the body. Ear, nose and throat examinations were normal. Other systemic examinations were within normal limits. Blood tests were normal except mild neutropenia and raised ESR (65mm in first hour). Abdominal ultrasound and chest X-ray were within normal limits. Montoux test showed induration of 03 mm. Antinuclear antibody (ANA) and anti-ds DNA antibody were negative. Fine needle aspiration cytology of cervical lymph node revealed the features of reactive lymphadenitis. The patient was started an oral antibiotic for 7 days. Since the patient continued to have fever and persistent lymphadenopathy despite a course of antibiotic, lymph node biopsy was done and histopathological examination suggested the diagnosis of Kikuchi-Fujimoto disease. Histopathological analysis revealed partial effacement of lymph node architecture with confluent paracortical necrosis and apoptotic cells with nuclear debris (figure 1&2). Patient was treated symptomatically and after 4 weeks of follow up, lymphadenopathy was regressed spontaneously.

**Case 2**

A 17 year old women patient from north east region of India presented with 15 days history of fever, anorexia and upper respiratory tract symptoms. There were no other complaints. She had been previously fit and well and there was no history of
medication. On examination, she was lethargic and febrile but hemodynamically stable. Significant findings were multiple palpable lymph nodes in the cervical region. There was no evidence of hepatosplenomegaly. Blood tests revealed raised C-reactive protein and ESR. Electrocardiogram, abdominal ultrasonography and chest radiograph were normal. Her initial management consisted of antibiotic and regular paracetamol, whilst results of further tests were awaited. These included blood, urine and sputum cultures, autoimmune and viral screens.

Subsequently there was a reduction in size and tenderness of the cervical lymph nodes. But there were persistent intermittent temperature spikes. Blood and urine cultures were negative. Sputum culture revealed normal respiratory tract flora and sputum was negative for acid-fast bacilli. The autoimmune screen was negative and viral screen including toxoplasma, herpes simplex virus and cytomegalovirus was negative.

Excisional biopsy of a cervical lymph node was done and confirmed the diagnosis of Kikuchi-Fujimoto disease (KFD). Histological analysis showed histiocytic proliferation with extensive paracortical necrosis of the lymph node, extensive karyorrhectic debrid, histiocytes with crescent shaped nuclei and sheets of foam cells (figure 3&4). Special stain for acid fast bacilli (Ziehl-Neelsen) did not reveal any micro-organisms.

No active treatment was initiated and the patient was discharged after a one week hospital stay. At follow up he reported no symptoms, remained well and there were no abnormalities on clinical examination.

Figure 3: Lymph node biopsy section shows extensive karyorrhectic debrid and histiocytes with crescent shaped nuclei(H&E, High power view).
Figure 4: Lymph node biopsy section shows sheets of foam cells with extensive necrosis (H&E, High power view).

Discussion
KFD is rare in India, with few reports in the literature. This disorder is therefore frequently underdiagnosed. Many cases are given a presumptive diagnosis of viral infections, especially among young patients with cervical lymphadenopathy and fever. KFD has no pathognomonic clinical signs or symptoms and a definitive diagnosis can only be made by histopathological examination of lymph node biopsy.

Kikuchi-Fujimoto disease most often presents with cervical lymphadenopathy which may be tender and can be accompanied by fever, upper respiratory tract symptoms. Less common symptoms include arthralgia, skin rashes, weakness and night sweats. Weight loss, diarrhea, anorexia, chills, nausea, vomiting, chest and abdominal pain have also been reported. The exact etiology of Kikuchi-Fujimoto disease is not known. Viral agents such as Epstein barr virus (EBV), Human immunodeficiency virus (HIV), Herpes simplex virus, dengue virus, Human T lymphotrophic virus 1 (HTLV1) and Parvovirus B19 have been suggested as possible etiological agents, but none have been confirmed so far. Toxoplasma and other bacterial agents like Yersinia enterocolitica, Bartonella, Brucella have also been implemented. An autoimmune mechanism has also been proposed because KFD is seen in conjunction with systemic lupus erythematosus (SLE). There are several reports suggesting an association between Kikuchi’s disease and systemic lupus erythematosus (SLE). However no convincing evidence is available to confirm such association. The pathogenesis of the disease remains unclear since its initial description by Kikuchi and Fujimoto et al, despite many case reports and case studies. Based on clinical presentation, histopathologic features, and laboratory findings, it has been hypothesized that KFD might represent an exuberant T-cell–mediated hyper response to certain antigen stimuli in genetically susceptible individuals. Some studies have shown that the primary proliferative cells are the CD8+ T lymphocytes, which induce target cell apoptosis and also undergo apoptosis themselves, accounting for the characteristic necrosis and nuclear debris seen in KFD.

Routine laboratory investigations usually does not help in the diagnosis of KFD except for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be elevated in some cases and many patients have neutropenia. Moreover 25% to 31% of patients have atypical lymphocytes in peripheral blood smear. Fine-needle aspiration cytology (FNAC) only has a limited role in establishing the diagnosis of Kikuchi-Fujimoto disease with the overall diagnostic accuracy estimated at 56%. Diagnosis is based on histopathological findings of a lymph node biopsy. There are three main patterns identified proliferative, necrotizing and xanthomatous. The proliferative picture is seen in approximately a third of cases and has a dominant inflammatory infiltrates in absence of neutrophil. Half of cases show necrotizing pattern and the xanthomatous type is rare and has abundant foam cells.
Clinically Kikuchi-Fujimoto disease may mimic systemic lupus erythematosus (SLE) or lymphoma (especially T-cell non-Hodgkin’s lymphoma) as both these diseases can present with lymphadenopathy and fever and the skin lesions of KFD patients can resemble those seen in SLE. Careful histopathological examination will help us to distinguish KFD from other diseases. Histological feature which helps in the differentiation of KFD from the lymphadenopathy of systemic lupus erythematosus is almost total absence of plasma cells in the involved nodal tissue. Moreover appropriate serologic tests should be done to exclude systemic lupus erythematosus. Antinuclear antibodies (ANA) and anti-DNA antibodies were done in our patients and were negative. Features of KFD that may help prevent its misdiagnosis as malignant lymphoma include incomplete architectural effacement with patent sinuses, presence of numerous reactive histiocytes, relatively low mitotic rates, absence of Reed-Sternberg cells.

No specific treatment is available for kikuchi-fujimoto disease. Treatment is largely supportive. The disease usually runs a benign course and the condition is self-limiting, usually resolves in one to six months. A low but possible recurrence rate of 3 to 4% has been reported.

Conclusion

Although the incidence of Kikuchi-Fujimoto disease is rare, this disorder must be considered among the differential diagnosis when a young female patient presents with fever and cervical lymphadenopathy. Clinically Kikuchi-Fujimoto disease may mimic lymphoma or systemic lupus erythematosus (SLE). Therefore a careful histopathological examination is necessary in arriving at the diagnosis. Early recognition of the disease is very necessary for harmful and unnecessary evaluations and treatments.

References