CASE REPORT KERALA MEDICAL JOURNAL

Kikuchi-Fujimoto Disease (KFD)

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ABSTRACT

Published on 30th June 2017

Kikuchi-Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis, is a benign and self-limited disease that mainly affects young women. Patients present with localized lymphadenopathy, fever, and leucopoenia in up to half of the cases. KFD can occur in association with systemic lupus erythematosus. We present here a case of 16 year old patient who presented with cervical lymphadenopathy. Kikuchi disease Kikuchi-Fujimoto disease was diagnosed after cervical lymph node biopsy. Symptomatic treatment was provided and an uneventful full recovery was made.

Keywords: Cervical Lymphadenopathy, Benign, Self Limiting

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BACKGROUND

The presenting complaint of neck masses in association with non-specific systemic signs and symptoms prompt investigation towards the more common diagnoses. However, rarer conditions and atypical presentation of diseases must still be considered especially when a patient's condition fails to abate with the treatment. Kikuchi disease, also called histiocytic necrotizing lymphadenitis or Kikuchi-Fujimoto disease is an uncommon, idiopathic, generally self-limited cause of lymphadenitis.[1,2] Kikuchi first described the disease in 1972 in Japan. Fujimoto and colleagues independently described Kikuchi disease in the same year.

The most common clinical manifestation of Kikuchi disease is cervical lymphadenopathy, with or without systemic signs and symptoms.[3-6] Clinically and histologically, the disease can be mistaken for lymphoma or systemic lupus erythematosus (SLE).[7-9] Kikuchi disease almost always runs a benign course and resolves in several weeks to months. Disease recurrence is unusual, and fatalities are rare, although they have been reported.[1,10] Here we discuss the case of a female patient who presented with a neck mass, fever and associated symptoms.

INTRODUCTION

Kikuchi–Fujimoto disease (KFD) is a rare and benign disease that typically affects the cervical lymph nodes. Its aetiology is unknown and a role of the autoimmune system in the pathogenesis is hypothesized.

Although uncommon, Kikuchi disease has been reported throughout the world and in all races. Most cases have been reported from East Asia, with fewer cases from Europe and North America. Kikuchi disease was first diagnosed and described in Japan. To date, most cases have been reported from East Asia. More recently, the disease has been reported throughout the world and in all races. Outside of Asia, it is possible that Kikuchi disease has been under diagnosed and therefore underreported. Dorfman and Berry reported 108 cases, including 68 in the United States; 63% of the 108 patients were white.[7] This self-limiting disease is often confused with malignancies. No specific management is generally required but long-term follow-up should be planned despite the low risk of recurrence, as recurrences have been described many years after the first episode and there is a high risk of development of an autoimmune disease or even lymphoma. The course of Kikuchi disease is generally benign and self-limited. Lymphadenopathy most often resolves over several weeks to 6 months, although the disease occasionally persists longer. The disease recurs in about 3% of cases. Three deaths have been reported that occurred during the acute phase of generalized Kikuchi disease.

The initial studies of Kikuchi disease reported women

Cite this article as: Jacob JK, Saranraj J. Kikuchi-Fujimoto Disease (KFD). Kerala Medical Journal. 2017 Jun 30;10(2):44–8.

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were affected more often than men, by a ratio of approximately 3:1. However, more recent studies have shown a smaller female preponderance, with a ratio closer to 1.25:1. Kikuchi disease occurs in a wide age range of patients (ie, 2-75 y), but it typically affects young adults (mean age, 20-30 y).

Cervical lymphadenopathy could be a manifestation of a varied group of illnesses ranging from benign infectious causes to malignant lymphomas. It is a rare, benign, and self-limited syndrome of unknown etiology characterized by tender localized lymphadenopathy, constitutional symptoms such as fever and night sweats.[11]

The cause of Kikuchi disease is unknown, although infectious and autoimmune aetiologies have been proposed.[12] The most favoured theory proposes that Kikuchi disease results when one or more unidentified agents trigger a self-limited autoimmune process. Lymphadenitis results from apoptotic cell death induced by cytotoxic T lymphocytes. It is an under diagnosed condition with an excellent prognosis, making it imperative that it is differentiated from a malignant lymphoma. The awareness of this condition amongst clinicians and pathologists alike might help prevent misdiagnosis and inappropriate treatment.[11]

CASE REPORT

A 16 year old girl who is a student residing in Kerala with no medical co-morbidities came to our department with 3 weeks history of fever, 2 week history of pain in the neck, 1 week history of swelling in the neck and 3 days history of vomiting and nausea. Clinical history did not reveal any travel, exposure to animals, insect bites or contact with infection.

Patient was apparently normal before 3 weeks following which she developed pain in the right side of the neck which was dull, aching, deep seated and non radiating. Pain increases with movements and was not relieved even after taking pain killers. Swelling was initially small in size which gradually increased later. The fever was insidious in onset, intermittent, low grade associated with chills; no rigors; not associated myalgia but evening rise of temperature was present. She had 2-3 episodes of vomiting per day, for last three days before presentation, which contained food particles and she gives history of taking tablets from outside pharmacy.

There was no history of cough, productive sputum, cold, headache, chest pain, palpitation, pedal edema, dyspnea. No history of night sweats, joint pain, malaise, myalgia. No history of any other swelling over the body, skin rashes, neck rigidity, ear ache or discharge. No history of abdominal pain, loose stools, dysuria, haematuria, bleeding gums, epistaxis, melaena. She denied any history of smoking tobacco, drinking alcohol or using illicit drugs. No family history suggestive of similar disease or other relevant diseases.

Physical Examination: Patient was comfortable, moderately built and nourished young woman with pallor (+), fever(101F), posterior cervical lymphadenopathy. Lymph nodes were fluctuant, firm and non tender. Skin overlying the lymphadenopathy was not erythematous. And there was no rash on the trunk and limbs. There was no hepatosplenomegaly, scleral icterus or clinically appreciable lymphadenopathy elsewhere. The remainder of the examination was normal. Patient was worked up as fever under evaluation.

Laboratory Studies: showed mild leucopenia, thrombocytopenia and anaemia (Hb- 10.1g %) with raised liver enzymes (SGOT/SGPT 257/234) and hypoproteinemia. Renal functions were normal. Blood and urine cultures did not reveal any organism or infection. Serology titres for HBsAg, HCV, HIV, ASO, RA, CRP were negative. Card test for malarial parasite was negative. Dengue and leptospirosis tested negative.

Mantoux test was 13mm. Sputum stain and culture for acid fast bacilli was negative.

ANA (Antinuclear antibody) and Anti-ds DNA tests were also negative for SLE

Ultrasound of neck revealed multiple enlarged lymph nodes in the right side inferior to lower pole of parotid gland. Both lobes and isthmus of thyroid showed normal size, shape and echo texture.

Fine needle aspiration cytology (FNAC) of the lymph node swelling in the right sub mandibular region was done, which revealed showing ill formed granuloma, excision was advised for definitive diagnosis. Following consultation with the surgery department of our hospital, an excision biopsy was done. Pulmonologists consultation obtained and was suggested to start the patient on anti tubercular drugs (ATT), suspecting tubercular lymphadenitis; hence the patient was started on AKT-4. Patient didn't get any better with ATT; rather it worsened her condition with severe gastritis and vomiting.

The diagnosis of Kikuchi-Fujimoto disease was finally suggested based on the histopathology report of the lymph node biopsy.

1. Lymph nodes with partly affected architecture
2. The paracortex is expanded by an infiltrate of lymphocytes, macrophages and few plasma cells. Collections of histiocytes with large immunoblasts like cells, few lymphocytes and nuclear debris seen.
3. The infiltrate is seen extending into the capsule which is thickened and involving the attached adipose tissue.
4. The paracortex in addition shows many proliferating vascular channels.

Patient was started on Piperacillin + Tazobactum and doxycycline 100mg after the/ was managed conservatively with symptomatic measures and she was completely relieved of symptoms without the necessity of steroids. There was no further swelling or any systemic symptoms at the time of discharge.

Patient was followed up and reviewed after 3 months, she was doing well without any swelling or systemic symptoms .But after 6 months of discharge, when she travelling to her hometown (Salem, Tamilnadu) she had fever with swelling in the neck, which was treated with antibiotics and was relieved with conservative management in a week. There was no any further recurrence of the disease.

DISCUSSION

The main diagnostic problems encountered by clinicians and histopathologists are distinguishing Kikuchi disease from malignant lymphoma and systemic lupus erythematosus (SLE). In Dorfman and Berry's series, 40% of patients with Kikuchi disease were initially misdiagnosed as having lymphoma and were consequently over treated with chemotherapy. Kikuchi can present with lymphadenopathy and fever, and the cutaneous findings seen in 30% of Kikuchi disease patients can resemble those seen in SLE. Results from autoimmune antibody studies may help distinguish Kikuchi disease from SLE. In Kikuchi disease, antinuclear antibodies (ANA), rheumatoid factor (RF), and lupus erythematosus (LE) preparations are usually, although not always, negative.

Kikuchi disease and SLE can also have similar histopathologic appearances. Kikuchi disease is suggested by the absence or paucity of the Hematoxylin bodies, plasma cells, and neutrophils usually seen in SLE. Additionally, T lymphocytes predominate in Kikuchi disease, whereas B lymphocytes predominate in SLE

LAB DIAGNOSIS

In patients with Kikuchi disease, diagnostic laboratory and radiologic test findings are nonspecific. Although results of fine-needle aspiration (FNA) may be suggestive,[13,14] the diagnosis of Kikuchi disease is confirmed only by excisional lymph node biopsy.

Complete blood cell (CBC) count findings includes, mild granulocytopenia is observed in 20-50% of patients. Leukocytosis is present in 2-5% of patients. Additional blood study findings include, atypical lymphocytes are observed in 25% of patients; Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels may be elevated.

Diagnostic imaging studies confirm the presence of enlarged lymph nodes in the affected areas, but they cannot specifically confirm a diagnosis of Kikuchi disease.

On computed tomography (CT) scanning and magnetic resonance imaging (MRI), uniform enlargement of lymph nodes in affected areas is noted. Post contrast enhancement may be observed.

In a study of 96 patients with Kikuchi disease, Kwon et al reported the following CT findings.[15] Homogeneous lymph node enlargement (83.3% of patients), Perinodal infiltration (81.3%) and prominent areas of low attenuation suggestive of focal necrosis (16.7%). Chest radiography findings are generally unremarkable in Kikuchi disease. However, a chest radiograph is recommended in the evaluation of cervical adenopathy to look for evidence of tuberculosis or malignancy. [8]

A definitive diagnosis of Kikuchi disease can be made only by tissue evaluation. Cytologic examination by fine needle aspiration (FNA) can suggest the diagnosis of Kikuchi disease, but excision biopsy of an involved lymph node is needed to confirm the diagnosis in doubtful cases.

Excisional lymph node biopsy can reveal histologic findings consistent with Kikuchi disease: Paracortical necrosis may be patchy or confluent, and the degree of necrosis varies considerably from patient to patient. Histiocytes - crescent-shaped nuclei (crescentic nuclei). Other cells Lymphocytes, plasmacytoid monocytes, macrophages, and immunoblasts (predominantly T cells). Karyorrhexis- Histiocytes and macrophages containing phagocytized debris from degenerated lymphocytes. Absent or rare features in Kikuchi disease include neutrophils, granulomas, and plasma cells

The three histologic phases of Kikuchi disease are as follows:[6]

1. Proliferative phase: Initial phase with typical findings as noted in Procedures
2. Necrotizing phase : Extensive necrosis that may destroy the normal architecture of the lymph node .Xanthomatous ("foamy cell") phase:
3. The recovery phase with resolution of necrosis.

The Immunophenotyping of Kikuchi disease is primarily composed of mature CD8-positive and CD4-positive T lymphocytes; lymphocytes and histiocytes also exhibit a high rate of apoptosis. Relatively few B cells and natural killer (NK) cells are present. Positive immunostaining results by monoclonal antibody Ki-M1P are seen in Kikuchi disease but not in malignant lymphoma.

Features of Kikuchi disease that may help prevent its misdiagnosis as malignant lymphoma include the following:

1. Incomplete architectural effacement with patent sinuses.
2. Presence of numerous reactive histiocytes.
3. Relatively low mitotic rates.
4. Absence of Reed-Sternberg cells.

Kikuchi disease and SLE have similar histopathologic appearances. Distinguishing the two entities can be difficult. Kikuchi disease is suggested by the absence or paucity of the following: Hematoxylin bodies, Plasma cells and Neutrophils.

Treatment of Kikuchi disease is generally supportive. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be used to alleviate lymph node tenderness and fever. The use of corticosteroids, such as prednisone, has been recommended in severe extranodal or generalized Kikuchi disease.[2]

Indications for corticosteroid use include the following:

- Neurologic involvement - Aseptic meningitis, cerebellar ataxia
- Hepatic involvement - Elevated lactate dehydrogenase (LDH) level
- Severe lupus like syndrome - Positive antinuclear antibody (ANA) titres

Jang and colleagues recommended expanding the indications for corticosteroid use to less-severe disease.[16] They administered prednisone when patients had prolonged fever and annoying symptoms lasting more than 2 weeks despite NSAID therapy, as well as for recurrent disease and for patients who desired a faster return to work. Immunosuppressants have been recommended as an adjunct to corticosteroids in severe, life-threatening disease.

END NOTE

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Conflict of Interest: None declared

Editorial Comments: The case report highlights the clinical course of a case of cervical lymphadenopathy in a 16 year old student. This unusual cause needs to be recognised and the patient had an uneventful recovery.

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