CASE REPORT

Kikuchi's Disease: A Rare Cause of Fever of Unknown Origin

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ABSTRACT

Kikuchi Fujimoto Disease (KFD) or histiocytic necrotizing lymphadenitis can present with unexplained fever and lymphadenopathy. It is often mistaken for more serious conditions like malignant lymphoma or tuberculosis. First case was described by Kikuchi in Japan, very few cases have been reported in Pakistan. A middle aged female presented with fever and body aches for one month. She was investigated extensively for pyrexia of unknown origin, all of which came out to be normal except a raised ESR. Anti-tuberculous drugs were started on clinical suspicion, with no improvement after a month. Later, a detailed physical examination revealed cervical lymphadenopathy. One of the lymph nodes was excised and biopsied. The histopathology suggested Kikuchi's disease. Oral Prednisolone was started showing improvement. Her fever subsided and lymph nodes disappeared at the follow-up visit. No relapse was encountered in the subsequent visits.

Key Words: *Kikuchi's disease. Fever of unknown origin. Histiocytic necrotizing lymphadenitis. Cervical lymphadenopathy.*

INTRODUCTION

Kikuchi's disease, also called Kikuchi-Fujimoto disease or Kikuchi's histiocytic necrotizing lymphadenitis is a rare, benign condition of unknown etiology.[1] It is usually characterized by cervical lymphadenopathy and fever, and often mistaken for more serious conditions like malignant lymphoma or tuberculosis. It was originally described in young Asian women but has been observed in patients of any age, gender, and race.[2] It was first described by Kikuchi and Fujimoto in 1972 in Japan.[3] Very few cases have been reported in Pakistan and there appears to be a general lack of awareness about the condition among the physicians, leading to misdiagnosis and unnecessary treatment.

This report describes a case of Kikuchi's disease in a 51-year-old woman who presented with fever of unknown origin and right cervical lymphadenopathy.

CASE REPORT

A 51-year female from Abbottabad presented with low grade fever and body aches for one month. She had undergone extensive investigations and multiple courses of antibiotics in the preceding month for fever but without success. Physical examination revealed an obese lady with a temperature of 100°F. Systemic examination was otherwise unremarkable. She was admitted and a temperature record was maintained while she was investigated.

Investigations (Table I), including a complete blood count, anti-nuclear antibody, rheumatoid factor, serology for typhoid and brucellosis (typhidot test and brucella antibodies) were all normal except an ESR of 95 mm in first hour. Montoux test was negative after 72 hours. Chest X-ray, ultrasound abdomen and urinalysis were also normal. Blood and urine cultures were sent to lab after stopping antibiotics for 2 days. No growth was obtained after 7 days of incubation. She was finally started on anti-tuberculous therapy and advised a follow-up visit after 2 weeks.

Table I: Investigation profile of the patient.

Haemoglobin	12.2 g/dl
Total leukocyte count	6500/mm^3
Platelet count	357000/mm^3
Malarial parasite	Negative
ESR	95/1st hour
Bilirubin	0.5 mg/dL
ALT	33 IU/L
ALP	219 IU/L
Urea	43 mg/dL
Creatinine	0.8 mg/dL
Blood sugar random	130 mg/dl
Montoux test	Negative
Antinuclear antibody	Negative
Anti-ds-DNA	Negative
Rheumatoid factor	Negative
Blood culture	No growth after 7 days incubation
Brucella antibodies	Negative
Typhidot test	Negative

At the follow-up visit, there was no improvement in terms of her fever and body aches. She was again admitted and a careful physical examination was done again, which revealed a right sided cervical lymphadenopathy. Excision biopsy of a lymph node was done which showed activated lymphocytes, immunoblasts and plasma cells at the periphery of necrotic zones. Immunohistochemical studies showed that CD20 was positive in reactive B-cells. A diagnosis of Kikuchi's disease was suggested by the histopathologist based on

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these findings. Anti-tuberculous drugs were stopped and prednisolone was started in a dose of 45 mg/day. Her fever subsided in a week of starting the treatment. She was sent home and advised a follow-up visit after one month. At the follow-up visit, she was asymptomatic and lymph nodes had also disappeared. She was advised a prednisolone taper over the next month.

DISCUSSION

Kikuchi's disease, also called histiocytic necrotizing lymphadenitis or Kikuchi-Fujimoto disease, is an uncommon, idiopathic, and generally self-limiting cause of lymphadenitis.[4] In 1972, Kikuchi first described the disease in Japan. Fujimoto *et al*. separately described the disease in the same year.

The pathogenesis of Kikuchi's disease is unknown, the clinical presentation, course, and histologic changes suggest an immune response of T-cells and histiocytes to an infectious agent. Numerous inciting agents have been proposed, including Epstein Barr Virus (EBV), Human Herpes Virus 6, Human Herpes Virus 8, Human Immunodeficiency Virus (HIV), Parvovirus B19, Paramyxoviruses, Parainfluenza virus, Yersinia enterocolitica and Toxoplasma.[5] Apoptotic cell death mediated by cytotoxic CD8 positive T-lymphocytes is the principal mechanism of cellular destruction. Histiocytes are thought to act as enhancers.

Kikuchi-Fujimoto syndrome is a rare disease known to have a worldwide distribution with a higher prevalence among Japanese and other Asiatic individuals.[6] Kikuchi's syndrome shares gender and age predisposition, as well as histologic features, with Systemic Lupus Erythematosus (SLE). Tubulo-reticular structures in the endothelial cells and lymphocytes in patients with SLE have been observed to be similar to those seen in Kikuchi's syndrome. One ultra-structural study suggested that Kikuchi's syndrome is a self-limited, SLE-like autoimmune condition precipitated by virus-infected transformed lymphocytes.[7]

Most patients with Kikuchi's disease are less than 40 years of age. Mean age of presentation is 30 years, but the disease has been reported in patients from 6 to 80 years. Kikuchi's disease presents most commonly as low-grade fever and cervical lymphadenopathy.[8] The most prominent symptom is fever which can persist for a week. Patients can also present with systemic signs and symptoms such as night sweats, rash, diarrhoea, weight loss, and arthritis. Lymphadenopathy is present universally in all the patients.

Patients usually present with cervical lymphadenitis (80%), although any lymph node region can be involved.[8] Neck involvement is usually unilateral. Cervical lymphadenopathy is common in the jugular, carotid chain and posterior cervical triangle. Other affected areas include the axillary (14%) and supraclavicular (12%) nodal chains.[8] The lymphadenopathy may be firm and sometimes painful as well. It is usually isolated, but 1% to 20% of patients have generalized lymphadenopathy.[8] In a small subset of patients, cutaneous symptoms have also been noted. Skin lesions have been described as maculopapular, morbilliform or rubella-like, and urticarial. Disseminated erythema has also been reported.[9]

Neurological symptoms such as ataxia, tremors and aseptic meningitis have also been described in some patients. Anemia, leukopenia (granulocytopenia), lymphocytosis with atypical lymphocytes, elevated immunoglobulin levels, and elevated erythrocyte sedimentation rate can be seen in the laboratory studies.[1] Bone marrow examination can reveal an increase in macrophages without atypical cells. Antinuclear antibodies and rheumatoid factor are generally negative. However, some patients diagnosed with Kikuchi's disease can develop auto-immune disorders.[4]

Differential diagnoses for Kikuchi's disease include lymphoma, tuberculous adenitis, SLE, lymphogranuloma venereum, Kawasaki disease, metastatic carcinoma, infectious mononucleosis, toxoplasmosis, Yersinia, cat-scratch disease, AIDS, and Still's disease in children. CT scan of the neck and chest will show diffuse enhancing lymphadenopathy. Lymph node biopsy is the definitive way to make the diagnosis of Kikuchi's disease. Biopsy should be done to exclude serious disorders like lymphoma. Patients have been misdiagnosed as having lymphoma and have been treated with chemotherapy. The histology of the lymph node in Kikuchi's disease is distinctive and can be differentiated from infectious causes of lymphadenopathy; the exception being systemic lupus erythematosus.[4] Necrotic foci can be seen on gross examination. Paracortical foci with histiocytic infiltrate are seen on microscopic examination. The histological appearance of the lymph node can vary according to progression of the disease. The proliferative phase in Kikuchi's disease shows the presence of follicular hyperplasia with T and B blast cells which can be confused with lymphoma. The necrotizing phase can show necrosis with histiocytes. Immunohistochemical stains will be positive for CD68 plasmacytoid monocytes and histiocytes with predominantly CD8 T-lymphocytes.

There is no effective treatment for Kikuchi's disease. Kikuchi's 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.

Patients with severe and persisting symptoms have been treated with glucocorticoids or high dose glucocorticoids with intravenous immunoglobulin with apparent benefit.[10]

Kikuchi's disease is self-limiting but the patients should be followed for a few years since some of the patients can go on to develop SLE.

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