

Case Reports

Kikuchi-Fujimoto Disease: A Case Report

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Introduction:

Kikuchi-Fujimoto disease also known as Kikuchi disease or histiocytic necrotizing lymphadenitis was reported for the first time in Japan in 1972 by Kikuchi¹ and by Fujimoto et al². Affected patient often presents with cervical lymphadenopathy accompanied by fever, myalgia, neutropenia and rash³. The disease has now been reported throughout the world and in all races with a higher prevalence among Japanese and other Asiatic individuals⁴. The age range of affected individuals is wide but most patients are in their late 20s or early 30s⁵. There is only few case reports of this disease in children⁶. It is also seldom reported in older people⁷. The male-female ratio is as high as 1:3-4 in some studies⁸, although one study of 79 patients found a ratio of 1:1.1⁹. The cause of the disease is unknown although infectious and autoimmune aetiologies have been proposed. The most favoured theory proposes that Kikuchi-Fujimoto disease (KFD) results when one or more unidentified agents trigger a self-limited autoimmune process. Lymphadenitis results from apoptotic cell death induced by cytotoxic T lymphocytes. Various infectious agents like human herpes virus (HHV6 and HHV8), Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, human immunodeficiency virus, adenovirus, parvovirus B19, dengue virus¹⁰, bacteria such as Mycobacterium azulgai, yersinia and protozoa have been linked to the disease¹¹. However no convincing causal relation between these infections and KFD has been shown yet. It has been proposed that Kikuchi disease is a non-specific hyper-immune reaction to a variety of infectious, chemical, physical and neo-plastic agents. For now, the most popular theory is simply that some

type of virus is the culprit. Familial occurrence has been reported and genetic predisposition has been proposed¹². Kikuchi disease has been reported in two non-twin sisters with HLA-identical phenotypes; who presented 10 years apart. KFD causes diagnostic difficulties due to lack of specific symptoms, signs and serological markers¹³. FNA findings are most often non-specific. It had an overall accuracy of 56-70% in diagnosing Kikuchi disease¹⁴. The diagnosis is usually confirmed by excisional lymph node biopsy. The characteristic histopathologic findings of KFD include irregular patchy or confluent areas of paracortical necrosis with abundant karyorrhectic debris, which can distort the nodal architecture and large number of different types of histiocytes at the margin of the necrotic areas. Neutrophils are characteristically absent and plasma cells are either absent or scarce. Importantly, atypia in the reactive immunoblastic component is not uncommon and can be mistaken for lymphoma¹⁵. The diagnosis of the self limiting disease is very crucial because it may be confused with many malignant and serious non-malignant diseases¹⁶ resulting in unnecessary treatment.

Case Report

An 8 year old school girl, had been well until 2 months earlier, when she developed fever which was initially intermittent and low grade in type, subsequently the fever became high grade and continued accompanied by shivering, malaise and loss of appetite. Parents also noticed painful right-sided neck swelling for last two weeks. There was also appearance of rash on the face and chest. The girl was evaluated and treated by different physicians elsewhere; but her condition was worsening with fever and pain. Finally the girl was admitted in Uttara Adhunik Medical College Hospital for further evaluation of fever and neck swelling. Her family and past medical history was unremarkable. She was immunized as per EPI schedule including BCG vaccination. On examination, the patient looked acutely ill and toxic. The temperature was 103^oF, pulse-128/min, respiration 24/min and BP was 90/60 mmHg. Erythematous

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rash was over the anterior chest and on the face. On head and neck examination, a deep cervical lymph node in the posterior triangle measuring 2x1.5 cm was detected. The enlarged node was firm, tender and somewhat mobile. No other cervical masses were detected and findings of the remainder of the head and neck examination were unremarkable. Both of her lungs were clear on auscultation and her cardiac and abdominal findings were normal except hepatomegaly. Haematological investigations revealed leucopenia - $3.4 \times 10^9/L$, Hb-11.4 g/L, platelets count-150,000 and ESR-55 mm in the 1st hour. Laboratory analysis identified an elevation of CRP (24 mg/L) and LDH (4720 u/L) level. Immunological and rheumatological tests were normal. These tests included ANA, anti-ds DNA, rheumatoid factor and serum C3 and C4. The blood and urine cultures were negative. No evidence of tuberculosis was found by examining sputum for AFB, MT and chest radiography. Hepatomegaly was found in ultrasonography of abdomen. Excision biopsy of the enlarged right cervical lymph node was done and the histopathology revealed lymph node with multiple foci of necrosis characterized by the presence of karyorrhectic particles. Also seen is a zone of reactive histiocytes. No granuloma or malignancy is seen (Fig.-1). The findings are consistent with acute histiocytic necrotizing

lymphadenitis, i.e., Kikuchi disease. Considering the patient's initial condition on hospital admission the treatment was started with ceftriaxone, antipyretics, intravenous fluids and other supportive measures. No improvement occurred by five days of treatment. After getting biopsy report ceftriaxone was omitted and prednisolone was added with antipyretics. The girl improved and discharged on the 5th day of prednisolone therapy. Prednisolone was gradually tapered off. The patient was followed up on several occasions in last one year having no complaints.



Fig.-1: Photograph of the patient with dressing in the excised lymph node

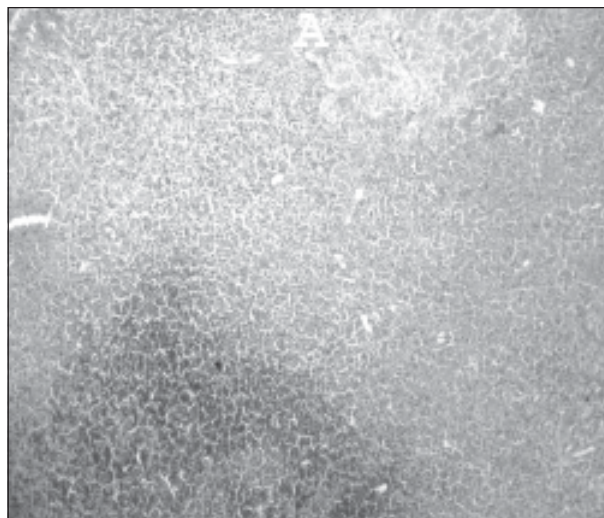


Fig.-2a: Histopathological appearance of the excised lymph node. Multiple foci of necrosis, presence of karyorrhectic particles and zone of reactive histiocytes with preservation of normal lymph node architecture.

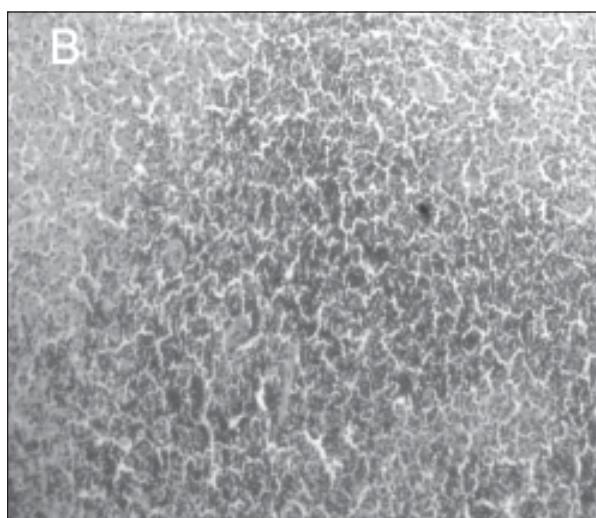


Fig.-2b: Histopathological appearance of the excised lymph node: an area of reactive histiocytes (higher magnification).

Discussion

Kikuchi disease is described as a rare, benign, enigmatic, self-limited clinico-pathological condition; the aetiology of which has not yet been identified. The most common clinical manifestation of KFD is cervical lymphadenopathy with or without systemic signs or symptoms^{9,17}. Cervical nodes are affected in 80% cases. Posterior cervical lymph nodes are affected in 65 to 70% of cases^{18,19}, other affected sites include the axillary (14%) and supraclavicular (12%) nodal chains²⁰. Lymphadenopathy is isolated to a single location in 83% cases. In our patient only posterior cervical chain was involved. Generalized lymphadenopathy occurs in a minority (5%) of cases. Although extranodal involvement is rare, it has been described in kidneys, liver, gastrointestinal tract, nervous system, eye, bone marrow, thyroid, parathyroid and adrenal glands. Fever usually of low grade; present in 33-50% patients²¹. High fever has also been reported¹³. In our patient fever was initially low grade; later became high grade. A cutaneous involvement has been observed in 30% of patients with KFD. The skin lesion may be maculopapular, rubellaform, drug eruption, urticaria or disseminated erythema. But none of the lesions reported is however pathognomonic²². Additional signs and symptoms include anorexia, nausea, vomiting, headache, hepatosplenomegaly and other constitutional disturbances (e.g., night sweats, weight loss and malaise). Our patient has some clinical manifestations similar to SLE: unexplained fever, erythematous skin rash, lymphadenopathy. But the diagnosis of SLE was ruled out by the absence of ANF, anti-ds DNA and normal levels of serum C3 and relationship between Kikuchi disease and SLE is not yet completely understood and remains complex. There are also reports on Kikuchi disease progressing to SLE²³, justifying the surveillance of KFD patients using immunological studies such as ANF testing. It was mentioned in literature that a patient of KFD with ANCA positivity subsequently developed SLE. Moreira²⁴ also reported a case of Kikuchi disease revealed by malar rash, fever, arthritis and lymphadenopathy suggesting systemic lupus erythematosus.

The main diagnostic problem encountered by the histopathologist is to distinguish Kikuchi disease from non Hodgkin's Lymphoma⁵. In Dorfman and Berry's series, 40% of patients with Kikuchi disease were misdiagnosed as having lymphoma and were consequently over-treated with chemotherapy. Some

authors described the patient with KFD and concomitant pulmonary tuberculosis. KFD is also misdiagnosed as tuberculosis by FNAC of cervical lymph node and anti-TB chemotherapy was started²⁵. However in a country like Bangladesh with a high prevalence of TB; the concomitant diagnosis of tuberculosis should be well investigated²⁶. Due to multi-system involvement and spontaneous resolution of lymphadenopathy, sarcoidosis can also be included in the differential diagnosis²⁷. Other differential diagnosis includes Toxoplasmosis, Tularemia, Infectious mononucleosis, HIV disease, vasculitis, Kawasaki disease, Cat-scratch disease, Still's disease, metastatic carcinoma, etc.

There is no effective treatment; it is generally supportive. The signs and symptoms usually resolve within 4 months²⁸. Excisional biopsy hastens recovery²⁹. NSAIDs may be used to alleviate lymphnode tenderness and fever. The use of corticosteroids, such as prednisolone has been recommended in severe extranodal or generalized Kikuchi disease³⁰. Jang and colleagues recommended the expansion of the indications for corticosteroid use to less severe disease³⁰. They administered prednisolone 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. The recommended dose in paediatric patients is 0.5-1 mg/kg ; taper as symptoms resolve. A low but possible recurrence of 3-4% has been reported³¹. Follow up evaluation should be performed due to disease recurrence and the possibility of SLE development. A lag time of 10 months to 3 years has been reported between the diagnosis of Kikuchi disease and the subsequent onset of SLE^{9,32}. Therefore it is recommended that patient with Kikuchi disease be monitored long term for the development of SLE^{5, 33}. The specific frequency and duration of follow up is not known, but perhaps as more data are collected and awareness of the association between the two diseases increases, patients will be monitored more often and the ideal frequency and length of a prudent follow up can be defined. Mortality is extremely rare and usually due to hepatic, respiratory or cardiac failure. The review of literature revealed 10 reported fatalities involving 9 adults and 1 paediatric patient. The 19 months old child died during the acute phase of the disease^{29,34,35}.

Conclusion

The prevalence of Kikuchi-Fujimoto disease in Bangladesh is not known. This could be that this disease is underrecognized and underreported in our country. The disease can be very distressing to the patient when the fever and other symptoms are prolonged. Hence, early recognition of Kikuchi disease will minimize unnecessary evaluations and potentially harmful treatments. It is strongly recommended to consider Kikuchi disease as a differential diagnosis in a patient with cervical lymphadenopathy and fever of unknown origin. Moreover, the clinicians' and pathologists' awareness of this rare disorder may prevent misdiagnosis and inappropriate treatment.

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