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**Case Report**

# A rare and interesting case report of Kikuchi-Fujimoto disease masquerading as tuberculosis

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## ABSTRACT

Kikuchi-Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis, is a rare benign, self-limited condition, probably genetic, that mainly affects young women which often presents with localised lymphadenopathy and fever. Reporting the case of a 17-year-old girl, with a strong family history of tuberculosis, who presented to the surgery OPD with cervical lymphadenopathy and a history of anti-tubercular treatment for the same complaints two years back. An excision biopsy revealed necrotizing histiocytic lymphadenitis suggestive of KFD. Post-operative period was uneventful and patient had spontaneous resolution of her complaints upon follow up. It is quite difficult to make a pre-operative diagnosis of this disease, until the clinician has got a very high index of suspicion especially because of the more common differential diagnoses including extrapulmonary tuberculosis.

**Keywords**: KFD, Necrotising lymphadenitis, Tuberculosis, Genetic, Cervical lymphadenopathy

## INTRODUCTION

KFD, also known as histiocytic necrotizing lymphadenitis, is a relatively rare condition characterized by subacute necrotizing regional lymphadenopathy. Young adults of Asian ancestry, predominantly females are most commonly affected, but it has been reported worldwide.[1] Patients most commonly present with posterior cervical lymphadenopathy (60%-90% of cases), often painful, frequently with concomitant involvement of axillary and/or supraclavicular lymph nodes. The disease is generally self-limiting with an acute to subacute course, evolving over several weeks.

## CASE REPORT

A 17-year-old female presented to the general surgery OP department with complaints of bilateral neck swelling for 3 months. It was associated with malaise and generalised tiredness without any history of fever, sore throat or significant weight loss. She gave history of extrapulmonary tuberculosis involving cervical lymph nodes 2 years back for which anti-tubercular therapy (ATT) for 6 months was given after biopsy confirmation. There is also a positive history of pulmonary tuberculosis in both parents and maternal grandfather 8 years ago which was reportedly treated and declared negative after treatment.

On examination, there was multiple bilateral cervical lymph node enlargements with the largest lymph node in right posterior triangle about 2cm in greatest dimension. There was no axillary, inguinal or epitrochlear lymphadenopathy. There was no hepatosplenomegaly. Biochemical evaluation revealed leukopenia with elevated Erythrocyte Sedimentation Rate. Mantoux test was inconclusive. Sputum samples were negative for AFB. A fine needle aspiration cytology (FNAC) study of

the lymph nodes was undertaken which was reported as reactive lymphadenitis with focal aggregates of macrophages and suggestion of excision biopsy to rule out granulomatous lesion. Accordingly, the patient was posted for an excision biopsy of the largest cervical lymph node under general anaesthesia.

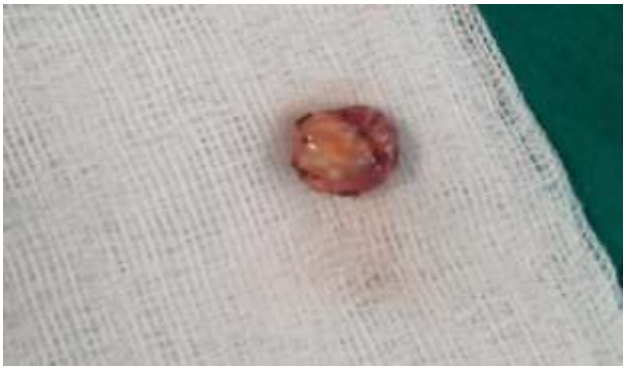

**Figure 1: Gross excision biopsy specimen of cervical lymph node.**

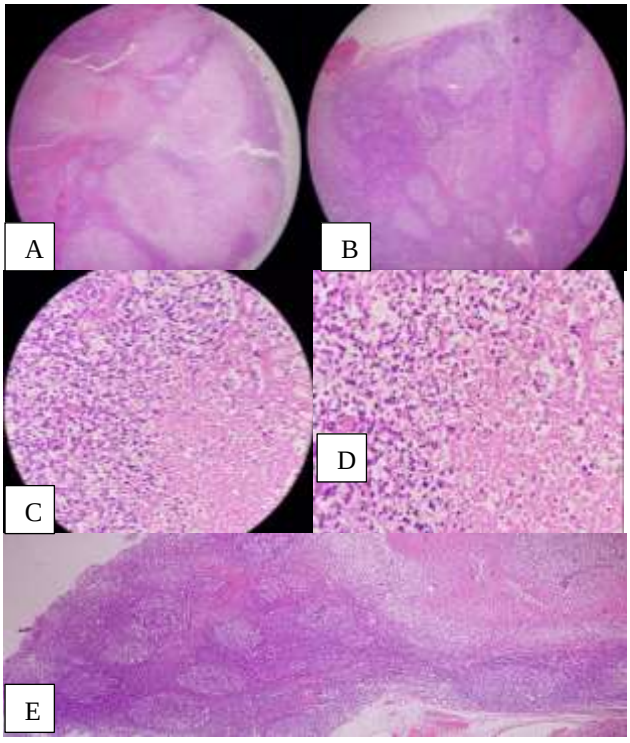


**Figure 2: Histopathological appearance of cut section of lymph node (A-E). (A, B) Lymph node with multiple circumscribed necrotic areas in the paracortex surrounded by aggregates of foamy histiocytes, (C, D) pyknotic nuclear debris present around the necrotic areas, (E) hyperplastic lymphoid follicles with germinal centers, numerous tingible body macrophages, proliferating blood vessels and sheets of plasmacytoid lymphocytes (H and E 10X).**

Level V right cervical lymph node of size 1.5×1.5 cm was excised which appeared to be necrotic intraoperatively (Figure 1). Specimen was sent for histopathology and gene Xpert studies. Postoperative period was uneventful and she was discharged on the next day. Gene Xpert study with TB DNA quantitative PCR was negative for *Mycobacterium tuberculosis*. Histopathological examination of the lymph node showed multiple circumscribed necrotic areas in the paracortex surrounded by aggregates of foamy macrophages and pyknotic nuclear debris around the necrotic areas, suggestive of Necrotising histiocytic lymphadenitis of KFD (Figure 2: A-E). The patient was kept on regular follow up and she had complete spontaneous remission within 3 months.

## DISCUSSION

KFD was first described in Asia by Kikuchi and Fujimoto et al simultaneously in 1972, and afterwards in the United States and Europe.[2-6] Generalized lymphadenopathy is rarely reported (1-22% of cases).[7] Often there would be mild fever with night sweats. Less frequent symptoms include weight loss, nausea, vomiting and sore throat.[8] Hepatomegaly and splenomegaly can occur rarely. The disease uncommonly occurs in extra nodal locations, most frequently in the skin, and occasionally in bone marrow and liver. Cutaneous involvement mostly affects the face and upper body, manifesting as rashes, nodules, erythematous papules, indurated erythematous lesions, erythema multiforme, and erythematous maculopapular lesions.[9]

The aetiology of KFD is still unknown. Certain causative organisms which have been implicated in the pathogenesis include Epstein-Barr virus, human T-cell leukaemia virus type 1, human herpesvirus type 6, B19 parvovirus, cytomegalovirus, Brucella, Yersinia enterocolitica, and parainfluenza virus. However, no study in the literature has definitively proven a causal relationship between a virus and KFD or identified viral particles ultra-structurally. Other infectious agents studied include *Bartonella henselae*, *Toxoplasma gondii*, *Entamoeba histolytica*, and *Mycobacterium szulgai.*

An autoimmune mechanism has also been proposed because KFD is seen in conjunction with systemic lupus erythematosus (SLE). One theory involves molecular mimicry, in which infectious agents that closely resemble a host peptide affect the ability of T-cells to detect self from nonself.[10] It has been postulated that KFD represents an exuberant T-cell mediated immune response to a variety of antigens in genetically susceptible individuals. Compared with the general population, patients with KFD more frequently have particular human leukocyte antigen (HLA) class II alleles, specifically HLA-DPA1 and HLA-DPB1. These alleles are more prevalent in Asians and are extremely rare or absent in whites, which may account for the more common occurrence of this entity among Asian people.[7]

KFD has also been described in association with a number of systemic diseases and autoimmune conditions, most commonly SLE and others such as Wegener granulomatosis, Sjogren syndrome, Graves' disease and Still's disease. However, in contrast to SLE patients, serologic tests (such as rheumatoid factor, antinuclear antibodies, and anti–double-strand DNA antibodies) have been consistently negative in a majority of KFD patients. Despite negative serology in KFD, there is a degree of clinical and morphologic overlap between KFD and SLE that requires particular merit. In a study by Dumas et al that included 91 KFD patients, 11 patients (12%) had a history of SLE.[11] These cases likely represent lupus lymphadenitis, as both disorders are histologically quite indistinguishable in some cases.

There are few reported instances of familial KFD. In one report, KFD was documented in two human leucocyte antigen (HLA) identical non-twin sisters living in same environment, presenting two years apart at same age with cervical lymphadenopathy, poor dental hygiene and periodontal disease.[12] Another study reported familial occurrence of KFD in two HLA-identical non-twin sisters, not living in same environment, presenting 10 years apart with cervical lymphadenopathy.[13]

Patient gives history of TB in parents and maternal grandfather, which might have been misdiagnosed cases of Kikuchi's disease. However, do not have any evidence to substantiate hypothesis in this regard.

Perhaps, the greatest difficulty with a case of Kikuchi's disease would be its diagnosis itself. Clinically, several other common conditions can easily replace KFD on presentation. The notable differential diagnoses for KFD are infectious lymphadenitis of different etiologies, autoimmune lymphadenopathy (primarily SLE lymphadenopathy), and non-Hodgkin lymphoma. Some of the infectious causes of lymphadenopathy may be even difficult to differentiate histologically. These include tuberculosis, leprosy, cat-scratch disease, infectious mononucleosis, histoplasmosis, syphilis, herpes simplex infections and yersinia. Lymphomas are another common differential diagnosis come across. Both Hodgkin's and Non-Hodgkin's lymphomas are implicated as well as myeloid sarcomas.

Systemic lupus erythematosus lymphadenopathy is the most difficult differential diagnosis to resolve, and in some cases, it is histologically and immunohisto-chemically indistinguishable from KFD. KFD is known to occur in conjunction with SLE. Some experts even suggest that KFD is one unusual presentation of SLE. Santana et al did a medline/LILACS (Latin American and Caribbean Health Sciences) search in 2003 and found 35 reported cases in which KFD and SLE occurred together.[14]

The diagnostic laboratory and radiologic test findings in KFD are nonspecific. Complete blood counts reveal leukopenia in about 50% of cases with atypical lymphocytes in about 25%. Elevated ESR and CRP values are also usual accompaniments. Imaging studies, particularly CT and MRI may be suggestive at times, although with less specificity and are not generally indicated. In a study of 96 patients with Kikuchi disease, Kwon et al reported CT findings of homogeneous lymph node enlargement (83.3%) Perinodal infiltration (81.3%) and prominent areas of low attenuation suggestive of focal necrosis (16.7%).[15] Shim et al reported that CT imaging pattern analysis of cervical lymph nodes can be of help to differentiate Kikuchi disease from tuberculous lymphadenopathy and reactive hyperplasia. In their study, high cortical attenuation combined with an indistinct nodal architecture supported the diagnosis of Kikuchi disease.[16] In a study by Kato et al of MRI findings in nine patients with Kikuchi disease, cervical lymphadenopathy showed predominantly a unilateral distribution at levels II-V. On T2-weighted images, areas of hypo intensity were visible at the peripheries of enlarged cervical nodes; these corresponded to histopathological findings of coagulative necrosis.[17]

A definitive diagnosis of Kikuchi disease can be made only by tissue evaluation. Cytologic examination by fine needle aspiration (FNAC) can be suggestive of Kikuchi disease, especially when supported by typical clinical findings, but excisional biopsy of an involved lymph node is needed to confirm the diagnosis in majority of cases. The characteristic cytologic findings in FNAC include crescentic histiocytes, plasmacytoid monocytes, and extracellular debris. Excision biopsy can reveal patchy or confluent paracortical necrosis, histiocytes and pyknotic nuclear debris. Immunohistochemical stains are helpful in challenging cases. Tabata et al reported that CD30 immunostaining may help in the differentiation of Kikuchi disease from SLE.[18]

In patient, FNAC was inconclusive and had proceeded with an excision biopsy which clinched the diagnosis of KFD. Clinically, tuberculosis of the lymph nodes was the working diagnosis and she was considered to be having a relapse. The positive family history of TB in parents and maternal grandfather further strengthened the likelihood of the same. However, a negative TB DNA quantitative PCR first raised the suspicion of an alternative diagnosis which was later confirmed with the biopsy report. This raised the possibility of a probable genetic component as well though reported literature with respect to familial KFD was very limited. A retrospective analysis showed histopathological examination of biopsy sample two years back as caseating granulomatous lymphadenitis only which was in favour of Koch's disease.

KFD is a benign, self-limited disease that usually resolves in 1 to 6 months. Patients should be monitored, however, since they may subsequently develop SLE or, in unusual circumstances, develop a recurrence of KFD. About 3% of patients experience recurrence. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be

used to alleviate local tenderness and fever. The use of corticosteroids, such as prednisolone, has been recommended in severe extra nodal or generalized Kikuchi disease.[19] These are however restricted to those cases with neurological or hepatic involvement and also when KFD occurs in conjunction with SLE. In steroid-resistant and recurrent Kikuchi disease, case reports have described successful use of hydroxychloroquine and intravenous immunoglobulin.[20]

Patient was kept under follow up and she had spontaneous remission of all the nodal swellings over a period of 3 months following surgery and has been asymptomatic since then.

## CONCLUSION

KFD is a Masquerader and hence poses significant diagnostic challenges to clinicians and pathologists alike. Unless there is a very high index of suspicion, it is quite difficult for the surgeon to make a pre-operative diagnosis of KFD. The diagnosis of KFD should be considered in the differential diagnosis in all young females particularly of Asian origin presenting with fever and cervical lymphadenopathy. Histopathological examination following excision biopsy of lymph nodes help in confirming the diagnosis with fair accuracy and to differentiate from other common causes of cervical lymphadenopathy such as tuberculosis. Though Kikuchi's disease is self-limiting without any specific treatment, these patients have to be kept on long-term follow up due to chances of progression to SLE and also to rule out recurrences.

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