

# Kikuchi-Fujimoto Syndrome: An Uncommon Disease With A Familiar Presentation

A Manchanda

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## Abstract

Kikuchi-Fujimoto disease is an enigmatic, benign, and self-limited syndrome characterized by regional lymphadenopathy with tenderness, usually accompanied by mild fever and night sweats. The disease frequently mimics tuberculous lymphadenitis, malignant lymphoma, and some other benign and/or malignant diseases in terms of clinical and laboratory presentation. It is scarcely known in the Western hemisphere. The present case highlights the perplexity in diagnosing KFD which are in close proximity with respect to pathology, behaviour and prognosis with other diseases.

## INTRODUCTION

Kikuchi-Fujimoto disease (KFD; so-called histiocytic necrotizing lymphadenitis) is an enigmatic, benign, and self-limited syndrome characterized by regional lymphadenopathy with tenderness, usually accompanied by mild fever and night sweats. Initially described in Japan, KFD was first reported almost simultaneously by Kikuchi and by Fujimoto and associates in 1972 as a lymphadenitis with focal proliferation of reticular cells accompanied by numerous histiocytes and extensive nuclear debris.<sup>1</sup> KFD usually affects female patients under the age of 30 years. Most of the cases improve within a six-month period. The disease frequently mimics tuberculous lymphadenitis, malignant lymphoma, and some other benign and/or malignant diseases in terms of clinical and laboratory presentation.<sup>2-4</sup>

The aetiology is unknown, although a viral or autoimmune pathogenesis, notably with systemic lupus erythematosus (SLE), has been suggested. It presents most often with cervical lymphadenopathy, which may be painful and can be accompanied by fever and upper respiratory tract symptoms. Unilateral involvement of the posterior cervical group is the commonest picture. Less common manifestations include fever, axillary and mesenteric lymphadenopathy, splenomegaly, parotid gland enlargement, cutaneous rash, arthralgias, myalgias, aseptic meningitis, bone marrow haemophagocytosis, and interstitial lung disease. The cutaneous lesions include erythematous macules, papules, plaques, and nodules. Laboratory investigations are usually

unremarkable except for elevated erythrocyte sedimentation rate (ESR), mild neutropenia, and lymphocytosis in some cases.<sup>3,5</sup> A pathologist, rather than a clinician, usually diagnoses KFD. Morphologically, it is characterized by a necrotizing lymphadenitis associated with karyorrhexis and by paucity, or more commonly, an absence of granulocytes. Open biopsy is the only reliable way to establish the diagnosis, but according to some authors, fine-needle biopsy may also be helpful.<sup>6</sup> KFD is known to have a worldwide distribution with a higher prevalence among Japanese and other Asiatic people.<sup>1</sup> It is scarcely known in the Western hemisphere. In fact, the first description of the disorder outside Asia was made by Pileri and colleagues<sup>7</sup> in 1982 (with Kikuchi as a co-author). The current report highlights a case of Kikuchi-Fujimoto disease in a female.

## CASE REPORT

A 41 year old female with history of asthma and menorrhagia and an associated iron deficiency anemia was hospitalized for syncope. She had been experiencing fatigue, anorexia and excessive thirst for ten days and low grade fevers for one day. History was negative for recent travel, sick contacts, tuberculosis exposure, and smoking, drinking alcohol or illicit drug use. The syncope was attributed to anemia. Examination revealed tender left posterior cervical adenitis, confirmed by CT scan. Extensive work-up including blood cultures, urine cultures, and HIV were all negative. She was empirically started on ampicillin-sulbactam and responded well in terms of decrease in size of neck swelling but fever persisted. She was discharged home

on amoxicillin-clavulanate, but she was non adherent with the same.

Seven days later the patient was readmitted for fever, malaise, nausea, vomiting, anorexia and night sweats. The previously noted adenopathy was unchanged and the remainder of the examination was unremarkable. Pertinent laboratory data included a WBC of 2800mg/dl with 46% neutrophils and 41% lymphocytes, hemoglobin 8 g/dl, platelet count 308,000/ul, CD4 count 503/mm<sup>3</sup>, Iron 19mcg/dl, ESR 19mm/hr, ANA<1:40 and negative anti double stranded DNA. Titres for Bartonella henselae, Lyme's disease, Epstein Bar virus (EBV), Cytomegalovirus (CMV), Coxsackie virus, monospot, TB antigen were all negative. Repeat blood and urine cultures remained negative. CT scan of neck showed persistent lymphadenopathy 1.5 x 2 cm in size on the left jugulodigastric (Figure 1). This was followed by CT scan of the abdomen which showed a well-circumscribed 5.0 cm soft tissue mass left adnexa likely representing an enlarged left ovary as well as bilateral prominent axillary lymph nodes of indeterminate etiology.

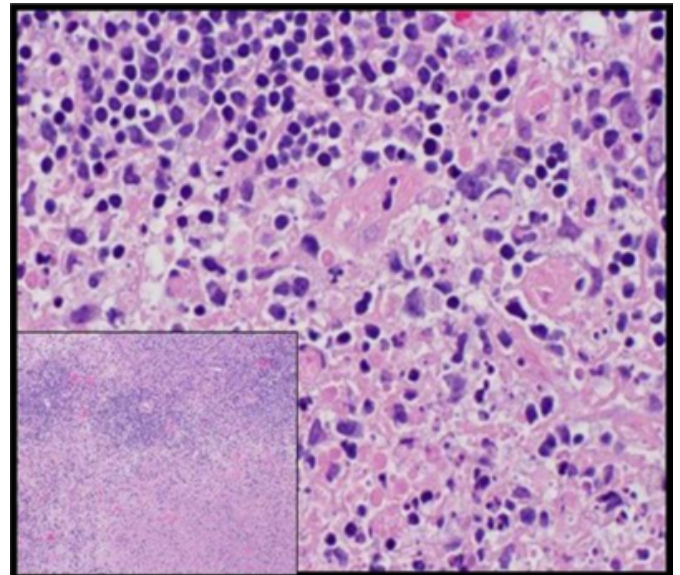
**Figure 1**

Figure 1: CT scan showing lymphadenopathy on the left jugulodigastric



**Figure 2**

Figure 2: Photomicrograph showing lymph node containing small lymphocytes and histiocytes. Histiocytes had phagocytosed debris and a crescentic nuclei (H&E, 40X). Inset showing an effaced lymph node. (H&E, 10X)



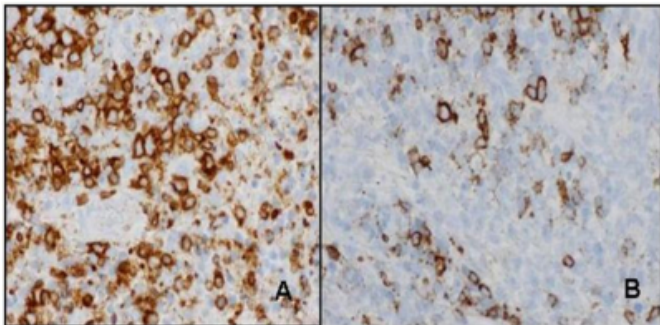
Lymph node microscopic examination showed an effaced nodal architecture with extensive apoptosis and confluent necrosis (Figure 2, Inset). Viable cells were seen mainly consist predominantly of small lymphocytes and histiocytes. Many histiocytes had phagocytosed cellular debris and peripheral crescentic nuclei (Figure 2). Neutrophils and eosinophils were inconspicuous. The tissue was negative for Reed-Sternberg cells or any metastatic tumor. AFB (acid fast bacilli), GMS (Grocott methenamine silver), and Warthin-Starry stains were negative for microorganisms. Immunohistochemical stains for CMV, EBV, and Herpes simplex virus (HSV) were also negative. Evaluation of a Wright-stained touch imprint and cytopsin preparation shows degenerated cellularity.

A portion of the sample was allocated for flow cytometric evaluation. A cell suspension of the allocated material was prepared and incubated with a panel of antibodies that identified lymphocyte maturation and differentiation antigens and its lineage. Lymphocytes consisted of a mixture of CD3-positive T-cells (Figure 3 A) and CD20-positive B-cells (Figure 3 B). B-cells were positive for BCL2 and largely negative for BCL6. B-cells were negative for CD43. Histiocytes were positive for CD68 (Figure 4). Rare cells were positive for CD30 and appeared negative for CD15. The proliferation index by Ki-67 was 5-10% in the viable regions. Pankeratin was negative. These features were

consistent with diagnoses of histiocytic necrotizing lymphadenopathy (Kikuchi-Fujimoto disease). The patient was started on hydroxychloroquine with a good response.

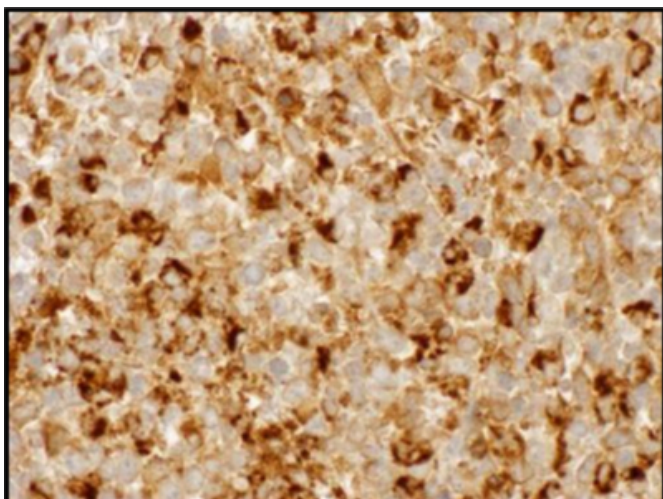
**Figure 3**

Figure 3A: Photomicrograph showing lymphocytic positivity for CD 3. (40 X), Figure 3B: Photomicrograph showing CD 20 positive B cell population. (40 X)



**Figure 4**

Figure 4: Photomicrograph showing CD 68 positivity for Histiocytes. (40 X)



**DISCUSSION**

Kikuchi-Fujimoto disease was regarded to be very rare in non-Asian countries but it was reported in patients from Germany, Italy, Spain, Iran, and the United States of America.<sup>8</sup> The patients of non-Asian origin with Kikuchi-Fujimoto disease have recently been described in Greece, Portugal, and Czech Republic, indicating a world wide geographical distribution of this disease.<sup>8,9</sup>

Its aetiology has not yet been fully determined, however it is believed it may be of viral origin, EBV, HHV6 and HHV8 have been suggested. Raw fish was postulated as a cause, but the recent literature doesn't support this.<sup>10</sup> An autoimmune aetiology is also likely as it has been reported in association

with SLE. Electron microscopic studies have identified tubular reticular structures in the cytoplasm of stimulated lymphocytes and histiocytes in patients with KFD.<sup>1</sup> Because these structures also have been noted within endothelial cells and lymphocytes of patients with SLE and other autoimmune disorders, Imamura and coworkers<sup>11</sup> hypothesized that KFD might reflect a self-limited SLE-like autoimmune condition induced by virus infected transformed lymphocytes. Yet the results of serologic studies testing antinuclear antibodies, rheumatoid factor, and other immunologic parameters consistently have been negative in these patients<sup>1</sup>, providing no support for an autoimmune nature of the disease. The viral aetiology of KFD is supported by its non-specific self-resolving symptoms, which are of slow, insidious onset.

It tends to affect a young population under 30 years of age, including children, although the latter are less commonly affected. There are reported cases in an older age group and pregnant women too.<sup>12</sup> Early reports suggest affected female cases are more common; however more recently this view has changed to one of equal prevalence in both genders. The most common signs and symptoms are lymphadenopathy, fever, sweats, malaise, anorexia, weight loss, hepatomegaly and leukopenia.<sup>10</sup>

The microscopic picture of KFD is characterized by presence of coagulative necrosis with the proliferation of histiocytes without granulocytic infiltration. Such histological picture is typical enough to resign from carrying out any additional immuno cytochemical tests. The presence of necrosis, karyorrhexis, and cellular debris are characteristic of the necrotizing type of Kikuchi-Fujimoto disease.<sup>8,13</sup> The remaining histopathological types of the disease include: proliferative type with the presence of lymphocyte, immunoblasts and histiocytes infiltration with the coexisting lack of coagulative necrosis as well as the xanthomatous type characterized by the presence of foamy histiocytes. Presumably they may form the following stages of the disease progression ranging from the proliferative type, through the necrotizing to the xanthomatous one.<sup>14</sup> In our case, the diagnosis of Kikuchi-Fujimoto disease was based on histopathological examination of the lymph node and the diagnosis was typical of the necrotizing type of KFD.

A special attention should be paid to the differentiation between the Kikuchi-Fujimoto disease and lymphadenitis accompanying SLE.<sup>8,14</sup> The diagnosis of SLE can be

supported by the relatively great number of plasma cells, as well as hematoxyphilic bodies, DNA deposits in the vascular walls, neutrophilic infiltrations and the presence of a diffuse cellular coagulative necrosis.<sup>14,15</sup> It is worth noticing that the immunophenotype of the cells found in the SLE-related lymphadenopathy affected nodes can be similar to the one found in patients with the third histopathological type of Kikuchi-Fujimoto disease.<sup>14</sup>

Long term follow-up of these patients is necessary as recurrent cases of KFD have been reported and there is some belief that KFD may be a precursor for SLE, as both diseases have had concurrent and co-existing disease patterns in the same patients. In a review of KFD cases by Kucukardali et al.<sup>16</sup> the reported overall mortality rate associated with KFD is 2.1%.

## CONCLUSION

KFD is uncommon, but should feature in a list of differential diagnoses of tender lymphadenopathy, especially affecting the cervical region. Its treatment differs significantly from the other conditions that would be on that list such as SLE, lymphoma and TB. Lymph node biopsy will aid accurate diagnosis, but if confusion with SLE occurs differentiation can be made with the aid of blood tests for complement levels amongst others. The present case highlights the perplexity in diagnosing KFD which are in close proximity with respect to pathology, behaviour and prognosis with other diseases.

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**Author Information**

**Adesh Manchanda**

Final year MDS Post Graduate student, Department of Oral and Maxillofacial Pathology and Microbiology, I.T.S. Center for Dental Studies and Research