

## Case Report

### Kikuchi-Fujimoto Disease: A Case Report and Review of the Literature

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#### Abstract:

Kikuchi-Fujimoto disease is a rare benign, condition of necrotizing histiocytic lymphadenitis. Presenting complaints of neck masses in association with non-specific systemic signs and symptoms prompt investigation towards the more common diagnoses. However, rarer conditions must still be considered especially when a patient's condition fails to abate. Herein I discuss a case of female patient who presented with a neck mass that was not attributable to the more common causes. A 28 year old lady presented with feverish feeling, weight loss and tender cervical lymph nodes. Initially tuberculous lymphadenitis was suspected but Kikuchi-Fujimoto disease was diagnosed after cervical lymph node biopsy. Symptomatic treatment was provided and an eventful full recovery was made.

**Key words:** Kikuchi-Fujimoto, Necrotizing lymphadenitis.

#### Case History:

A 28 year old lady presented with a four weeks history of fever, anorexia and weight loss. She had no other complaints. She was previously fit and well. On examination she was a bit lethargic, but otherwise looked well. She was afebrile and haemodynamically stable. Significant finding was lymphadenopathy of left posterior cervical region. Lymph node was firm, tender and discrete. There was no overlying erythema, ulceration or sinus formation. There was no organomegaly. Blood tests revealed neutropenia, ESR was 48mm in 1<sup>st</sup> hour. Liver and renal function were normal. Montoux test was 06 mm on 3<sup>rd</sup> day. Chest radiograph and abdominal USG were normal. FNAC was done but showed nonspecific lymphadenitis. Excisional biopsy of cervical lymph node was done and showed loss of nodal architecture with large area of necrosis with devoid of polymorphs and confirmed a diagnosis of Kikuchi-Fujimoto disease (KFD). Treatment was given with Ibuprofen 400mg 12 hourly for one month in combination with prednisolone 1mg/kg/day for one month then tapering was done over next two months. On first follow up visit at one month she feels better, fever subsided, appetite improved and she also gained weight by two kg. On Second follow up at third month of therapy she fully recovered and there was no residual lymphadenopathy.

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#### Discussion:

Kikuchi-Fujimoto Disease (KFD) is a benign histiocytic necrotising lymphadenitis. It is rare, but most common in Asia. In the early 1970s both Kikuchi and Fujimoto first described cases of KFD in Japan<sup>1,2</sup>. KFD frequently found in East Asian countries, is rare in the UK. Its aetiology has not yet been fully determined, however it is believed that it may be of viral origin, EBV, HHV6 and 8 have been suggested. Raw fish was postulated as a cause, but the recent literature doesn't support this<sup>3</sup>. An autoimmune aetiology is also likely as it has been reported in association with SLE. 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>4</sup>. Early reports suggest affected female cases are more common; however more recently this view has been changed to one of equal prevalence in both genders. In my case, she is also a 28 years young female of Asian origin.

The most common signs and symptoms are lymphadenopathy, fever, sweats, malaise, anorexia, weight loss, hepatomegaly and leucopenia<sup>3</sup>. Viral aetiology of KFD is supported by its non-specific self-resolving symptoms, which are of slow, insidious onset. My case also has same presentation but there was no hepatomegaly.

A definite diagnosis is made by tissue biopsy, indeed whole lymph node biopsy. Histopathological assessment of affected lymph nodes reveals

characteristic findings. There are three main patterns identified, proliferative, necrotizing and xanthomatous. The proliferative picture is seen in approximately a third of cases and has a dominant inflammatory infiltrate. Half of cases show necrotizing pattern and the xanthomatous type is rare and has abundant foam cells<sup>5</sup>. Immunoblast cell changes seen in lymph nodes mimic those of malignancy and are a source of diagnostic confusion. Cellular protein structures have been noted in the cytoplasm of lymphocytes and histiocytes that have also been found in those cells of patients with SLE. This adds strength to the hypothesis that KFD is a self-limiting SLE-like disorder.

As the symptoms are non-specific and some of the histological features are similar to other diseases it is easy to misdiagnose KFD with SLE or lymphoma. This is important as the treatment of KFD is symptomatic and supportive, spontaneous recovery is usual, while the latter two conditions require prompt specific treatments.

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<sup>6-8</sup>. In a review of KFD cases by Kucukardali et al the reported overall mortality rate associated with KFD is 2.1%<sup>9</sup>.

## Literature Review

### 1. History of KFD

In 1972, Dr. Masahiro Kikuchi presented a case of lymphadenitis characterized by focal proliferation of reticular cells accompanied by numerous histiocytes and extensive nuclear debris in the Japanese Journal of the Haematological Society. In the same month, Dr. Fujimoto presented a similar case in a separate Japanese journal<sup>10</sup>.

### 2. Epidemiology

KFD represents a condition most frequently found in East Asian and Japanese populations. The incidence is unknown but is rare in the UK and continental Europe. Extrapolating from the larger case series reports, the male to female ratio is roughly equal with slight female preponderance<sup>11</sup> and largely affects young adults (<30 years old).

### 3. Aetiology

The authors were unable to find any definitive evidence of an aetiological factor in the literature. Most articles on this subject concentrate on either an infective cause or an autoimmune disorder.

### 3.1. Infection

*Yersinia enterocolitica*, Brucellosis, *Bartonella henselae*, *Entamoeba histolytica*, *Mycobacterium szulgai*, and *Toxoplasma gondii* have been isolated in case reports. However, subsequent studies have failed to support these findings. The fact that most patients with KFD are unresponsive to antibiotics suggests that these microbiological organisms were incidental findings. Epstein-barr virus, herpes viruses, cytomegalo virus, parvovirus, paramyxo virus, parainfluenza virus, rubella, hepatitis B virus, Human Immunodeficiency Virus (HIV), human T-cell lymphotropic virus type 1, and the Dengue virus<sup>12-17</sup> have all been implicated in the aetiology of KFD.

### 3.2. Autoimmune

Immunological screening of patients with KFD rarely reveals any autoimmune component in these patients. Imamura et al<sup>18</sup> in 1982 performed an ultra-structural analysis of pathological tissue from patients with KFD, which drew some similarities with the histological findings in patients with systemic lupus erythematosus (SLE). However, association of Kikuchi with SLE remains unclear.

There is also evidence of a genetic susceptibility for KFD. Tanaka et al<sup>19</sup> found certain human leukocyte antigen (HLA) class II genes were more common found in those with KFD. These genes were found to be more common in Asian populations compared to Caucasian groups. The implication of this evidence is that KFD represents a self-limiting autoimmune response to an upper respiratory tract viral infection in genetically-susceptible individuals. Some evidence suggests that KFD can initiate the onset of SLE, or is a short-lived version of SLE.

### 4. Clinical Features

The typical pattern of presentation is one of general flu-like symptoms with posterior cervical, tender lymphadenopathy. Other less common nonspecific symptoms are headache, nausea, fatigue, and arthralgia. The disease process continues for approximately two to three months before resolving spontaneously<sup>20</sup>.

### 5. Diagnosis

The diagnosis of KFD is rather problematic due to its relative obscurity, nonspecific symptoms, and imprecise histological diagnosis. Currently, the only reliable method of diagnosis is histological examination of a lymph node excision biopsy. Unfortunately, samples from a fine-needle aspiration are generally not sensitive enough to provide a reliable diagnosis with an overall accuracy of 56.3%. Blood tests classically show a mild neutropenia with mildly raised C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Imaging techniques such as CT, MRI, PET/CT scanning also rarely provides conclusive diagnostic results<sup>20,21</sup>. An incorrect provisional diagnosis of lymphoma or tuberculosis is made in many instances. In a study of 96 retrospective scans of confirmed KFD, Kwon et al<sup>22</sup> found that on CT scanning, cases of KFD had the following typical appearances: (i) multiple homogeneous lymphadenopathy involving levels II to V, (ii) 94% were smaller than 2.5 cm, this allows some differentiation from lymphoma which typically produces few but larger nodes, (iii) perinodal infiltration and necrosis is commonly found.

Ultrasonography scans frequently show lymph nodes with a hypoechoic center and a hyperechoic rim. Again, these features have a low specificity for KFD. These findings certainly do not allow the diagnosis of KFD with imaging techniques. However, linked to the clinical history, one may at least be suspicious of KFD rather than a neoplastic lesion.

A 2010 study by Kim et al. noted the following in cutaneous Kikuchi disease patients: (i) slight predominance of CD8+ lymphocytes, (ii) lymphohistiocytic infiltration and non-neutrophilic karyorrhexis (usually). The immunophenotype 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. There are relatively few B cells and natural killer (NK) cells are present. Positive immune-staining results by monoclonal antibody Ki-M1P are seen in Kikuchi disease but not in malignant lymphoma.

## 6. Differential Diagnoses

These are among (i) lymphoma, (ii) systemic lupus erythematosus (SLE), (iii) infectious mononucleosis, (iv) kawasaki disease, (v) sarcoidosis, (vi) tuberculosis, (vii) syphilis.

## 7. Management

KFD is a self-limiting condition that rarely requires specific treatment in most cases. Management is, therefore, based on supportive therapy, such as analgesia and anti-inflammatory medication. In patients with neurological symptoms or in those cases where KFD is found with another medical condition, immunosuppression with corticosteroids appears to improve the patient's condition rapidly. A high initial oral dose of prednisolone with a subsequent reducing dose is the advocated regime. There are reports of excellent responses to hydroxychloroquine, immunoglobulins, and minocycline<sup>23-27</sup>. Recurrence of KFD is approximately 3%.

## Conclusion:

KFD is uncommon, but should include 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. Recurrence has been reported. KFD has been reported within a family, but not between parent and child. It may suggest a genetic predisposition or a common environmental factor. Long term follow up will give us more data.

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