

Kikuchi-Fujimoto disease: A diagnostic and therapeutic challenge

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ABSTRACT

Kikuchi-Fujimoto disease (KFD) is a rare, benign, self-limiting disorder that generally presents with cervical lymphadenopathy. Recognition and early diagnosis of this condition is very critical as it can be easily mistaken for tuberculosis, lymphoma or systemic lupus erythematosus. It predominantly affects young adults (mean age 20-30 years), with a slight preponderance in females. There have been very rare reports of KFD in childhood or elderly. We report case of a 9-year-old female child who presented with fever and cervical lymphadenopathy. Examination of other systems and laboratory investigations were normal. Biopsy of the cervical node showed features suggestive of histiocytic necrotizing lymphadenitis (KFD). CD20, CD3 and CD68 stained positive while CD15 and CD30 were negative, thus confirming the diagnosis. The child was treated with steroids and complete remission occurred in few weeks. Although the incidence of KFD is rare, clinicians should be aware of this condition as early recognition and diagnosis of the disease will minimize unnecessary investigations and cytotoxic treatments.

Key words: Female child, histiocytic necrotizing lymphadenitis, Kikuchi-Fujimoto disease, steroids

INTRODUCTION

Kikuchi-Fujimoto disease (KFD) is a rare, benign, self-limiting disorder that typically presents with cervical lymphadenopathy. It was first described by Dr. Masahiro Kikuchi in 1972 in Japan. In a study by Fujimoto *et al.*, KFD was independently described in the same year. The first documented cases outside of Japan were described by Pileri *et al.* depicting cases in Germany, Iran, Italy, Korea and Spain. This was shortly followed by the first cases reported in the United States. Kikuchi 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. Recognition and early diagnosis of this condition is very critical as it can be easily mistaken for tuberculosis, lymphoma or systemic lupus erythematosus (SLE). There have been very rare reports of

KFD in childhood or elderly. We present a case of 9 years female child diagnosed with KFD.

CASE REPORT

The present case report is about a 9-year-old female child who presented to us with the multiple neck swellings and fever of 2 months duration. There was no previous history of tuberculosis or contact with tuberculosis. She did not have a history of any drug intake or atopy.

Clinical examination revealed bilateral, large, mobile and tender cervical lymphadenopathy of levels II and III. Lymph nodes were not palpable in other parts of the body. Ear, nose and throat evaluation was normal. Patient was febrile. Her cardiovascular, respiratory and neurological examinations were normal. Routine hematological parameters such as complete blood count, peripheral smear, erythrocyte sedimentation rate (ESR) and serum lactate dehydrogenase were within the normal limits. Renal and liver function tests were also normal. Blood and urine cultures were negative. Ultrasound computed tomography abdomen and chest radiograph were normal.

Patient was referred to us with biopsy report of cervical lymph nodes as Hodgkin's disease from a peripheral

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hospital. Review of lymph node biopsy [Figure 1] showed geographical patchy irregular area of necrosis containing nuclear debris and surrounded by pale stained foamy histiocytes activated lymphoid series cells and mature small lymphocytes. Neither giant or epithelioid cells characteristic of tubercular pathology nor acid-fast bacteria were seen in pale stained histiocytes. These histological features suggested the diagnosis of histiocytic necrotizing lymphadenitis (KFD).

Immunohistochemistry (IHC) studies were performed to confirm the diagnosis. CD20 was positive in residual follicles and few interstitial B cells [Figure 2a], CD3 positive in interspersed small T cells [Figure 2b], CD68 positive in numerous histiocytes [Figure 2c], Ki-67 positive in 30% nuclei [Figure 3a]. CD15 was negative [Figure 3b] and CD30 negative in the majority of cells, weak positivity in occasional immunoblasts [Figure 3c]. Morphology in correlation with IHC findings was consistent with KFD.

DISCUSSION

KFD is an uncommon, idiopathic, generally self-limited cause of lymphadenitis. The cause of KFD is unknown. Some kind of viral or post-viral etiology has been proposed. There have also been reports of a possible link between KFD and SLE. KFD is an extremely rare disease, more common in females compared with males (4:1). Recent studies quote a figure of 2:1 or even 1:1. People under 30 years of age are more affected by this disease than any other age group.^[1] There has been no strong genetic predisposition established for this disease. Rare familial cases have been reported primarily from Japan and Saudi Arabia.

Kikuchi disease most often presents with cervical lymphadenopathy which may be tender and can be accompanied by fever and upper respiratory tract symptoms. Patient may present with arthralgia, skin rashes, weakness and night sweats. Nausea, vomiting, diarrhea, anorexia, weight loss, chest and abdominal pain have also been reported. The exact etiology of KFD is not known. Viral agents such as Epstein Barr virus, Human Immunodeficiency Virus, Herpes Simplex Virus, Human T Lymphotropic virus 1 (HTLV1) and Parvovirus B19 have been suggested as possible etiological agents, but none have been confirmed so far. Toxoplasma and other bacterial agents like *Yersinia enterocolitica*, *Bartonella*, *Brucella* have also been implemented.^[2] An autoimmune mechanism has also been proposed because KFD is seen in conjunction with SLE. However, no convincing evidence is available to confirm such association. The pathogenesis of KFD is still not fully understood. It is supposed that the primary event may be the activation of T lymphocytes and histiocytes. Proliferating T cells enter the cycle of apoptosis, which

may from the areas of necrosis in lymph nodes and then the cellular debris is removed by histiocytes.^[3]

ESR and C-reactive protein might be elevated in some patients and many patients have a low white blood count. Moreover, 25-31% of patients have atypical peripheral blood

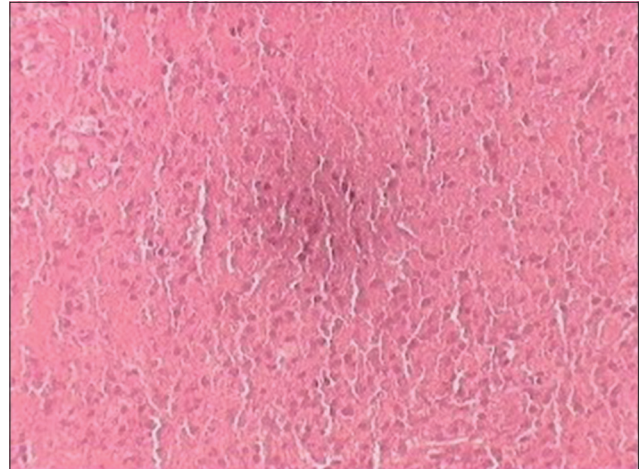


Figure 1: Photomicrograph showing areas of necrosis and foamy histiocytes (H and E, x40)

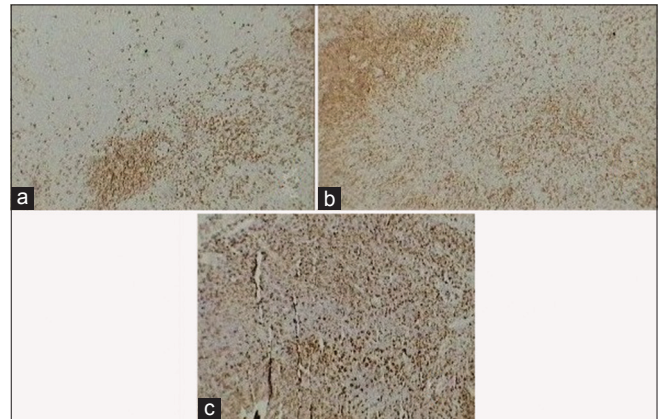


Figure 2: (a) CD20 +ve, (b) CD3 +ve, (c) CD68 +ve

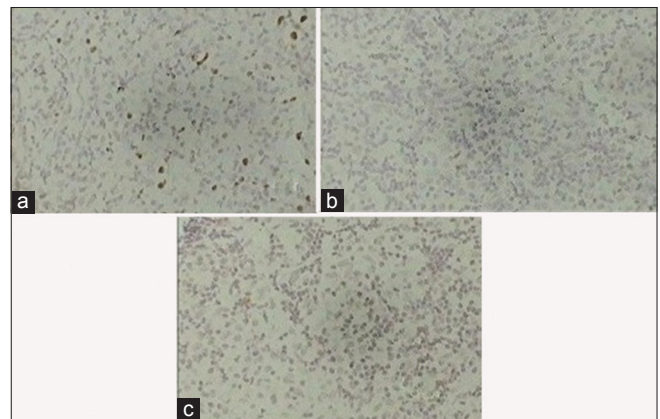


Figure 3: Photomicrograph showing immunostaining patterns (a) Ki67 positive in approximately 15% cells, (b) CD15 negative, (c) CD30 negative

lymphocytes. However, these investigations were normal in the case under discussion. Fine-needle aspiration cytology alone has a limited role in establishing the diagnosis of KFD with the overall diagnostic accuracy estimated 56%.^[2] Diagnosis is based on histopathological findings of a lymph node biopsy. Morphologically, it is characterized by irregular paracortical areas of coagulative necrosis with abundant karyorrhectic debris, which can distort the nodal architecture and a large number of different types of histiocytes at the margin of the necrotic areas. The karyorrhectic foci are formed by different cellular types, predominantly histiocytes and plasmacytoid monocytes but also immunoblasts and small and large lymphocytes. Neutrophils are characteristically absent and plasma cells are scarce if present. The immunophenotype of KFD is primarily composed of mature CD8 positive and CD4 positive T lymphocytes. High rate of apoptosis is also seen among lymphocytes and histiocytes. The histiocytes express histiocyte associated antigens such as lysozyme, myeloperoxidase (MPO) and CD68 which can be detected by IHC. Plasmacytoid monocytes are also positive for CD68 but not for MPO.^[4]

Clinically KFD may mimic SLE or lymphoma (especially T-cell non-Hodgkin's lymphoma) as both these diseases can present with lymphadenopathy and fever and the skin lesions of KFD patients can resemble those seen SLE.^[5-8] Careful histopathologic examination can help to distinguish KFD from other diseases. Histological feature that helps in the differentiation of KFD from the lymphadenopathy of SLE is almost total absence of plasma cells in the involved nodal tissue. Moreover, appropriate serologic tests should be done to exclude SLE. Features that distinguish KFD from malignant lymphoma include incomplete architectural effacement with patent sinuses, presence of numerous reactive histiocytes, relatively low mitotic rates and absence of Reed-Sternberg cells.^[4]

No specific treatment is available for KFD. Treatment is generally supportive. Non-steroidal anti-inflammatory drugs may be used to alleviate lymph node tenderness and fever. The use of corticosteroids has been recommended in severe form of the disease.^[9] Intravenous immunoglobulin has also been tried with some success.^[10] The disease usually runs a benign course and self-limiting, resolving usually in several weeks to months. Recurrence rates of 3% to 4% have been reported.^[2,11]

The authors would like to conclude with the message that though KFD is a rare disease, this disorder must be considered among the differential diagnosis when a young child presents with fever and cervical lymphadenopathy. Clinically KFD may mimic tuberculosis, lymphoma or SLE. Therefore, a careful histopathological examination is necessary for the diagnosis. Early recognition of the disease is of crucial importance in minimizing unnecessary investigations and cytotoxic treatments.

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