Kikuchi–Fujimoto Disease: A Study of 24 Cases

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Abstract Kikuchi–Fujimoto disease (KFD) is a rare benign disorder predominantly affecting young adults and has a site predilection for cervical lymph nodes. The objective of this study is to analyze the clinicopathological features of KFD. A retrospective study of 24 cases of KFD presenting at a tertiary care hospital in southern India over a 4 year period is presented here. Clinical findings, histopathological findings and follow up data were reviewed. Of the 24 cases encountered, 17 were females and 7 were males. Painless cervical lymphadenopathy was the most common presenting feature. All cases showed typical morphology of KFD with necrosis, karyorrhectic debris and presence of the typical cell types namely crescentic histiocytes and plasmacytoid monocytes. Of the 19 cases with follow up, all resolved within 1 month. The pathologist should be aware of the typical presentation and morphology of KFD in order to distinguish it from the more common causes of cervical lymphadenopathy like tuberculosis (especially in countries like India) as well lymphomas.

Keywords Kikuchi–Fujimoto disease · Cervical lymphadenopathy · Necrotizing lymphadenitis · Crescentic histiocytes · SLE

Introduction

Kikuchi–Fujimoto disease (KFD) or histiocytic necrotizing lymphadenitis was first described in Japan in 1972 [1, 2]. A higher prevalence of this disease is seen among the Asian population [3]. Kikuchi disease is a benign self limiting condition of unknown etiology, although infectious and autoimmune causes have been suggested [4–6]. It usually affects young females with a predilection for the cervical group of lymph nodes [2, 3, 5]. The diagnosis is based on histopathology of the excised affected lymph nodes [1–8]. This disease can clinically mimic tuberculous adenitis, malignant lymphoma [9, 10] and systemic lupus erythematosus (SLE) [11, 12]. The association between Kikuchi disease and SLE, which it may resemble closely, has been a matter of intense study and scrutiny [7, 13]. In this study, we describe the clinical profile of patients and the morphological features of lymph nodes with Kikuchi disease.

Patients and Methods

This was a retrospective descriptive study of 24 cases of KFD whose surgical material was received at the Department of Pathology, St. John's Medical College Hospital, Bangalore, India over a 4 year period from September 2007 to November 2011. The demographic data, clinical findings, laboratory data, treatment and follow up information were retrieved from the case files. The morphological features were studied for architecture, presence of necrosis, presence of karyorrhectic debris and the accompanying cell types on hematoxylin–eosin (H&E) stained sections. The diagnosis was based on routinely stained H&E sections in all the cases. The Ziehl–Neelsen staining

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was done on all the biopsies to look for presence of acid fast bacilli and to rule out tuberculous lymphadenitis.

Results

Out of 24 cases, 17 were female and 7 were males. They ranged in age from 9 to 55 years with a median age of 26 years. The most common presenting symptom was painless lymphadenopathy (74 %). Other less common complaints were painful lymphadenopathy, fever, chills, anorexia, joint pain and skin rashes. Table 1 summarizes the clinical features of these patients.

The duration of symptoms ranged from 1 week to 3 months. Cervical lymph nodes were involved in all the 24 cases (100 %) with bilateral involvement in 7 cases (30 %). In addition, axillary lymph nodes were enlarged in 3 cases (13 %) and generalized lymphadenopathy was seen in one case (4.3 %). The lymph nodes ranged in size from 0.5 to 3.5 cm. Other physical findings were mild splenomegaly in 3 cases and mild hepatomegaly in one case.

The most common laboratory findings were leucopenia ($<4 \times 10^9/L$) in 13 of 21 cases tested (65 %), raised erythrocyte sedimentation rates (ESR) in 17 of 19 cases tested (89 %), and raised liver enzymes alanine transaminase (normal values: 15–37 U/L) & aspartate transaminase (normal values: 30–65 U/L) in 7 of 15 cases tested (47 %). The antinuclear antibody test (ANA) was positive in one of the 9 cases tested. This case also fulfilled the other American college of Rheumatology criteria for the diagnosis of SLE.

In 20 of the lymph node biopsies, fragmentation was evident on scanning magnification. On low power examination, the architecture was preserved in 2 (9 %) cases, partially effaced in 18 (75 %) cases and completely effaced in 4 (17 %) cases (Fig. 1). Paracortical expansion was seen in 17 (71 %) cases. Minimal necrosis was seen in 2 (9 %)

cases, moderate necrosis in 15 (63 %) cases and massive necrosis in 7 (30 %) cases. Blood vessel proliferation was seen in 19 (79 %) cases. On high power examination, the necrotic areas were surrounded by proliferating histiocytes and karyorrhectic debris. Many of the histiocytes appeared crescentic with a peripherally pushed nucleus (Fig. 2). Additional cell types seen were plasma cells and plasmacytoid monocytes. The plasmacytoid monocytes are intermediate sized cells with a slightly peripheral nucleus, dispersed chromatin and absent nucleoli (Figs. 3, 4). Neutrophils and eosinophils were hardly noted in any of the cases. Ziehl–Neelsen staining for acid fast bacilli was done in all the cases and was negative.

Initial evaluation with fine needle aspiration was done in 14 cases. Nine of these cases were reported as reactive hyperplasia and 3 as necrotizing inflammation. KFD was diagnosed in one case whereas a lymphoproliferative disorder was suggested in another.

Treatment data was available in 19 patients; all were treated with a course of antibiotics. In addition, 3 patients received steroids. Follow up data was available for 19 patients with a duration ranging from 1 week to 6 months. Symptoms resolved within one month in all of them.

One patient had a recurrence of lymphadenopathy after 2 months for which he was treated with steroids and it resolved within 1 month.

Discussion

This series of cases of KFD is one of the largest reported from the Indian subcontinent and highlights the morphological features and clinical course of patients with KFD [3, 5, 6, 8]. KFD is a rare disorder of unknown etiology with characteristic clinical and morphological findings.

KFD or histiocytic necrotizing lymphadenitis is a well known self limiting disease. It primarily affects young females and the reported female to male ratio varies from 1:1 to 4:1 [2–4]. In our series, female to male ratio was 2.4:1. Our youngest patient was a 9 year old girl and the oldest, a 55 year old man.

All our cases were conclusively diagnosed as KFD only after histopathological examination of the involved nodes. In 14 cases (58 %), tuberculosis was suspected clinically whereas in one case, a lymphoma was considered clinically. One of the cases also fulfilled the criteria for a diagnosis of SLE. In 5 cases (21 %) the patients were initially investigated for ‘pyrexia of unknown origin’.

The cervical lymph node is affected in most cases, however other groups such as preauricular, mesenteric, axillary, inguinal and supraclavicular may be involved [2–5]. In our series, all the cases showed cervical lymph node enlargement with bilateral cervical lymph nodes being affected in 30 %.

Table 1 Clinical features of the patients

No. of cases	24
Age (years): range	9–55
Median	26
Female: male ratio	17:7 (2.4:1)
Presenting symptoms	
Painless lymphadenopathy	18 (75 %)
Painful lymphadenopathy	6 (25 %)
Fever	13 (54 %)
Chills	3 (13 %)
Anorexia	3 (13 %)
Joint pain	2 (8.3 %)
Skin rashes	2 (8.3 %)

Fig. 1 Lymph node under scanner view to show loss of architecture and geographic areas of necrosis (hematoxylin–eosin, original magnification $\times 40$)

Fig. 2 Karyorrhectic debris and necrosis surrounded by crescentic histiocytes with paucity of neutrophils (hematoxylin–eosin, original magnification $\times 100$)

One of our cases presented with generalized lymphadenopathy which has been rarely reported in the literature [2]. Painful lymphadenopathy was also a feature in some of our cases (26 %) whereas some also had fever, chills, anorexia, joint pain and skin rashes.

The most common laboratory finding in our cases was the presence of leucopenia in 62 % of the patients and raised ESR in 89 %. This is in concordance with the laboratory findings as observed in the other studies [12, 13].

Histological features were typical in all our cases as observed by other authors [1–8]. The presence of well defined necrosis surrounded by proliferating histiocytes, karyorrhectic debris and paucity of granulocytes are features documented in almost all the reported cases [1–12]. Other cell types observed in our cases were crescentic histiocytes, macrophages, plasma cells and plasmacytoid

Fig. 3 Cellular area with plasmacytoid monocytes and immunoblasts. Prominent blood vessel proliferation is also noted (hematoxylin–eosin, original magnification $\times 100$)

Fig. 4 Plasmacytoid monocytes, characteristic cells of KFD (hematoxylin–eosin, original magnification $\times 400$)

monocytes. Kuo [2] proposed a classification for KFD into 3 subtypes—proliferative, necrotizing and xanthomatous types. We were not able to strictly categorize our cases into these subtypes as we found a substantial overlap in the morphological features. Prominent blood vessel proliferation, a feature not described hitherto was observed in most of our cases.

The association of KFD with SLE is a well documented phenomenon [7, 13, 14]. KFD may precede, occur concurrently or follow the diagnosis of SLE [2]. The histology of the lymph node may be similar in these two diseases. Lupus adenitis is characterized by prominent necrosis, presence of hemotoxyphilic bodies, presence of neutrophils and numerous plasma cells and the presence of a true vasculitis [13, 14]. One of our cases fulfilled the American College of Rheumatology criteria for SLE and was

diagnosed as a case of SLE. A biopsy of the lymph node histology showed necrosis with karyorrhectic debris and lacked hematoxyphilic bodies, neutrophils and plasma cells and was therefore diagnosed as KFD rather than lupus lymphadenitis. This case was therefore considered as a case of SLE with concurrent KFD of the lymph nodes.

In all lymph nodes that show necrosis, tuberculous lymphadenitis must be entertained as a differential diagnosis, especially in our region where tuberculosis is a very common affliction. Presence of granulomas with epithelioid cells and Langerhan cells, and the presence of caseous necrosis rather than karyorrhectic debris favor a diagnosis of tuberculosis over KFD. In all cases, special stains for acid fast bacilli must be performed.

Plasmacytoid monocytes and immunoblasts may appear 'atypical' in some cases and accompanied by loss of lymph node architecture may erroneously suggest the diagnosis of a malignant lymphoma in some cases of KFD [9, 10]. The presence of pale foci of necrosis and mottling by histiocytes along with the clinical setting should suggest the diagnosis of KFD. Immunohistochemistry (IHC) may be necessary to make the distinction. In two of our cases where atypical features were seen, IHC was performed to rule out a lymphoproliferative disorder. However, in a low resource settings such as ours, when typical morphology in association with clinical features are noted, a diagnosis of KFD may be offered.

The immunophenotype of KFD typically consists of a predominance of T cells, with very few B cells. There is a predominance of CD8+ cells over CD4+ cells owing to the intense CD8+ T cell apoptosis in the necrotic foci [2, 4, 11, 15]. The histiocytes express histiocyte-associated antigens such as lysozyme, myeloperoxidase (MPO), and CD68. The plasmacytoid monocytes are thought to be immature myeloid and lymphoid early-committed dendritic cells [11]. They express CD68 and either myeloid antigens CD13 and CD33 (so called myeloid dendritic cells) or CD303 and CD123 (so called plasmacytoid dendritic cells).

There is no specific treatment for KFD [11, 15]. Analgesics, antipyretics and non-steroidal anti-inflammatory drugs may be used to alleviate the painful lymphadenopathy and fever. The use of corticosteroids has been recommended in severe extranodal and generalized Kikuchi disease but is of uncertain efficacy [6]. Most of our patients received antibiotics and three of them also received steroids. Most of our cases resolved without any sequelae. However recurrences of lymphadenopathy and even fatal cases have been reported in the literature [2, 4, 16]. In our series, one case had recurrence of lymphadenopathy after 2 months, and was treated with antibiotics and steroids which resolved after a month.

Summary

We conclude that KFD although typically described in young females, may also affect males and older individuals. Cervical lymphadenopathy is the commonest manifestation although additional nodes may be affected. The commonest laboratory findings are leucopenia and raised ESR. Although the morphological features are well defined, the pathologist should be aware that the accompanying cells may appear 'atypical' and an erroneous diagnosis of lymphoma should not be made. Immunohistochemistry must be performed to rule out a lymphoma in doubtful cases. KFD is a self limiting disorder although it may persist for a few months in some individuals before it resolves fully. Finally, in a country such as ours where tuberculosis is very common, KFD must be distinguished from tuberculosis which it can mimic closely.

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