Kikuchi-Fujimoto Disease: Clinical and Laboratory Characteristics and Outcome

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ABSTRACT

Introduction: Kikuchi-Fujimoto disease is an uncommon disorder with worldwide distribution, characterized by fever and benign enlargement of the lymph nodes, primarily affecting young adults. Awareness about this disorder may help prevent misdiagnosis and inappropriate investigations and treatment. The objective of the study was to evaluate the clinical and laboratory characteristics of histopathologically confirmed cases of Kikuchi's disease from a tertiary care center in southern India. **Materials and Methods:** Retrospective analysis of all adult patients with histopathologically confirmed Kikuchi's disease from January 2007 to December 2011 in a 2700-bed teaching hospital in South India was done. The clinical and laboratory characteristics and outcome were analyzed. **Results:** There were 22 histopathologically confirmed cases of Kikuchi's disease over the 5-year period of this study. The mean age of the subjects' was 29.7 years (SD 8.11) and majority were women (Male: female- 1:3.4). Apart from enlarged cervical lymph nodes, prolonged fever was the most common presenting complaint (77.3%). The major laboratory features included anemia (54.5%), increased erythrocyte sedimentation rate (31.8%), elevated alanine aminotransferase (27.2%) and elevated lactate dehydrogenase (LDH) (31.8%). **Conclusion:** Even though rare, Kikuchi's disease should be considered in the differential diagnosis of young individuals, especially women, presenting with lymphadenopathy and prolonged fever. Establishing the diagnosis histopathologically is essential to avoid inappropriate investigations and therapy.

Key words: Histiocytic necrotizing lymphadenitis, Kikuchi, Lymphadenopathy, Prolonged fever

INTRODUCTION

Kikuchi's disease, also known as Kikuchi-Fujimoto disease (KFD) or histiocytic necrotizing lymphadenitis, is a rare disorder with a worldwide distribution, with a higher prevalence among Asians. Although the cause is unknown, infectious and autoimmune etiologies have been proposed for this disease.[1] The disease is characterized by benign enlargement of lymph nodes, frequently cervical, and is often associated with fever.[2] Other symptoms and signs include upper respiratory symptoms, sore throat, night sweats, weight loss, nausea, vomiting, splenomegaly, erythematous papules, plaques, acneiform or morbilliform lesions and facial erythema.[1] Common laboratory findings include anemia, leucopenia and a high erythrocytic sedimentation rate.[3] The disease is frequently mistaken for lymphoma, tuberculous lymphadenitis, systemic lupus erythematosis (SLE), sarcoidosis, infectious mononucleosis, cat-scratch disease, Sweet's syndrome, Still's disease and drug eruptions.[2,4]

The diagnosis may be missed or delayed as it is often not considered in the differential diagnosis due to similarity to other more common conditions, lack of awareness and its rarity. Although the disease is often self limiting, early diagnosis by a biopsy of the lymph nodes is essential to avoid misdiagnosis, unnecessary investigations and inappropriate therapy.[4] The objective of the current study was to describe the clinical and laboratory characteristics of histopathologically confirmed cases of Kikuchi's disease over a period of 5 years from a tertiary care center in southern India.

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MATERIALS AND METHODS

Retrospective analysis of records of all adult patients with histopathologically confirmed Kikuchi's disease

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from January 2007 to December 2011 at a 2700-bed teaching hospital in Southern India was done. A case of Kikuchi's disease was defined as individuals with localized or generalized lymphadenopathy that showed confirmatory findings (necrotizing lymphadenitis with karyorrhexis and a paucity of granulocytes) on histology in the absence of an alternative diagnosis such as tuberculosis, lymphoma, or connective tissue diseases. Relevant data were recorded using a predesigned data collection proforma and analyzed. The data included demographic characteristics, accompanying symptoms, physical findings, co-morbidities, laboratory results, histological findings, treatment offered and therapeutic outcome in terms of relief of symptoms.

RESULTS

There were a total of 22 histopathologically confirmed cases of Kikuchi's diseases over the five year period. Among them, 17 (77.3%) were females. The mean age of the patients was 29.7 years (SD 8.11), ranging from 16 to 45 years old. Lymphadenopathy was present in all the cases, with 21(95.5%) involving the cervical lymph nodes. These cervical lymph nodes were unilaterally involved in 12 (54.5%). Both cervical and axillary lymph nodes were palpable in six (27.2%) patients. The lymph nodes were less than 3 cm in diameter in all the cases.

The majority (77.3%) of patients reported prolonged fever, with a mean duration of 39.7 days (SD 22.7, range 7-90 days) at presentation. The main signs, symptoms and laboratory characteristics of the cases are summarized in Table 1. Anti-nuclear antibody was positive in three cases (13.3%) cases, but additional investigation including anti-dsDNA did not suggest any connective tissue disorder.

All patients were treated with antipyretics and non-steroidal anti-inflammatory drugs. Two individuals initially received an antibiotic which was discontinued once the diagnosis was confirmed. None of them received steroids. The fever settled in all patients without any additional treatment and none had recurrence on 3 month follow-up.

DISCUSSION

The study describes the clinical and laboratory characteristics and outcome of 22 pathologically confirmed cases of Kikuchi's disease from a tertiary care center in south India. As reported from other Asian countries, a majority of our subjects with a diagnosis of KFD were young (<30 years) females. A female preponderance has been reported in the literature. However, a few recent studies reported a male to female ratio closer to 1:1.[1,2]

Our finding of cervical lymphadenopathy in majority was consistent with many previous reports. A comprehensive review has reported that the proportion of cases with cervical lymphadenopathy ranged from 56% to 98%, more commonly involving unilateral posterior cervical triangle (88.5%).[1] In our series, a majority of patients (77.3%) had prolonged fever as the presenting complaint. The proportion of cases with fever, as reported by various studies ranges from 35% to 50%.[1] We noticed anemia (54.5%) and high ESR (31.8%) as the common laboratory finding, which is consistent with many previous reports.[3]

Table 1: Signs, symptoms and laboratory characteristics of the cases of Kikuchi's disease (*N* = 22)

Symptoms	Number (%)	Physical examination findings	Number (%)
Fever for more than one week	17 (77.3)	Lymph node enlargement	22 (100)
Joint pain	1 (4.5)		
Sore throat	3 (13.6)	Unilateral cervical	12 (54.5)
Head ache	4 (18.2)	Bilateral cervical	3 (13.6)
Myalgia	1 (4.5)	Both cervical and axillary	6 (27.2)
Vomiting	4 (18.2)	Axillary alone	1 (4.55)
Arthalgia	1 (4.55)		
Fatigue	5 (22.7)	Hepatomegaly	2 (9.1)
Rashes	1 (4.5)	Splenomegaly	1 (4.5)
Weight loss	6 (27.2)		
Night sweats	2 (9.1)		
Laboratory characteristics			
Parameter	**Number (%)**	**Parameter**	**Number (%)**
Anemia (Hb<12 g/dl)	12 (54.5)	High erythrocyte sedimentation rate (>60 mm/h)	7 (31.8)
Leucopenia (<4000 cells/ml)	2 (9.1)	Increased lactate dehydrogenase (>500 IU/l)	7 (31.8)
Leucocytosis (>11,000 cells/ml)	3 (13.6)	Increased alanine aminotransferase (>40 U/l)	6 (27.2)
Thrombocytopenia (<1,00000 cells/ml)	1 (4.5)	ANA positivity	3 (13.3)
Elevated C-reactive protein (>10 mg/L)	5 (22.7)		

An increase in lactate dehydrogenase, C-reactive protein and aminotransferase was also noticed in few subjects, which is a similar finding from many other studies.[1] All these findings were consistent with other case series reported from India.[5-8]

KFD is usually diagnosed on the basis of an excision biopsy of affected lymph nodes. Histology of the lymph nodes in KFD shows paracortical expansion with foci of incipient necrosis laden with karyorrhectic debris both within and outside macrophages. The macrophages with ingested debris are classically described as crescentic because the nucleus is pushed to the periphery[9] [Figure 1]. Neutrophils are absent. Later stages may show sheets of foamy histiocytes replacing the necrotic foci (xanthomatous phase). The necrotic foci can be surrounded by transformed lymphoid cells.[10]

In India, tuberculosis is widely prevalent and is the most commonly considered diagnosis in any one presenting with prolonged fever and lymphadenopathy; and often is started on empiric therapy. Although necrosis is seen in both conditions, epithelioid granulomas are not seen in KFD, a helpful feature in differentiating from tuberculosis.[9]

Collagen vascular diseases will be an important differential diagnosis among young females presenting with fever and lymphadenopathy. The differentiation of Kikuchi's disease from systemic lupus erythematosis may be challenging because both can have same clinical and histological features.[11] Kikuchi's disease has been reported in association with SLE also.[12] Similar histological picture can be seen in both disease conditions, and hence work up for connective tissue disorders are indicated in each case of necrotizing lymphadenitis. The histological features which favor lupus lymphadenitis over Kikuchi's disease are the presence of vasculitis, presence of neutrophils, plasma cells and the presence of hematoxyphil bodies.[9]

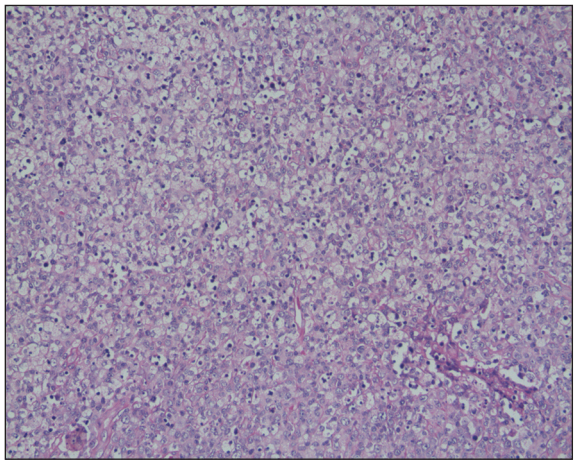

Figure 1: X 200, medium power view of paracortex showing paracortical expansion with foci of incipient necrosis laden with karyorrhectic debris and macrophages with ingested nuclear debris

Several immunohistochemical studies have shown that the predominant proliferating cells in KFD lymph nodes are CD8+ T lymphocyte.[2] Plasmacytoid dendritic cells (plasmacytoid monocytes) which are positive for CD123 have been reported as a striking feature of Kikuchi's disease.[9]

Kikuchi's disease is a self-limiting disorder and the treatment is generally supportive. Spontaneous resolution occurs in most cases within 6 months. Non-steroidal anti-inflammatory drugs (NSAIDs) may be used to alleviate the symptoms and controlling the fever. Treatment with systemic corticosteroids hastens resolution.[13] Immediate resolution has been reported with minocyclin and ciprofloxacin.[14] Excellent response to hydroxychloroquine or immunoglobulins has been reported. The disease has a recurrence rate of 3% to 4%.[1,15]

Even though rare, Kikuchi's disease should be considered in the differential diagnosis of young individuals, especially women, presenting with lymphadenopathy and prolonged fever. Histopathological evaluation should be considered in such cases, as it can mimic common disorders like tuberculous lymphadenitis and lymphoma, which can avoid unnecessary investigations and inappropriate treatment.

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