

## Original Research Article

# Clinicopathologic study of Kikuchi's disease in children in a tertiary hospital in South India

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### ABSTRACT

**Background:** The aim of this study was to evaluate the clinical and laboratory characteristics, treatment modalities and outcome of children with Kikuchi's disease.

**Methods:** A retrospective cross-sectional study was conducted among all children, histopathologically diagnosed with KFD. Clinical, laboratory data and treatment outcomes were analysed.

**Results:** During the study period, 53 children histopathologically confirmed as KFD were enrolled in the study. There were 36 males and 17 females. The lymph node involvements were mostly cervical with bilateral predisposition (63.5%), firm (88%), matted (30.8%) and tenderness (38.5%). Fever, headache, vomiting, chills, myalgia and rash were other common presentations other than cervical lymphadenopathy. The associated laboratory findings include anemia (71.2%), leukopenia especially lymphopenia (31.4%), monocytosis (21.6%), thrombocytopenia (16.3%), elevated CRP (53.1%), ESR (83.7%), LDH (100%) and elevated liver enzymes. Most of the children were managed conservatively (49.1%). Corticosteroids were administered for (22.6 %) of patients. Recurrence occurred in 4 children (7.5 %) and 13 children (24.5%) had other associated diseases.

**Conclusions:** KFD should be suspected in well children with febrile cervical lymphadenopathy, especially with leukopenia, monocytosis, and elevated CRP, ESR, LDH, Liver enzymes. KFD in children can have rarely atypical presentations and coexist with other diseases.

**Keywords:** C- reactive protein, Erythrocyte sedimentation rate, Kikuchi-Fujimoto disease, Lactate dehydrogenase, Systemic lupus erythematosus

### INTRODUCTION

Kikuchi-Fujimoto disease or histiocytic necrotizing lymphadenitis is a rare self-limiting disorder characterized by prolonged fever and regional lymphadenopathy of unknown origin. It was first described in 1972 by Kikuchi and Fujimoto.<sup>1,2</sup> Multiple studies have attempted to describe its aetiology, clinical features, pathogenesis and treatment modalities, but it

still lacks clarity.<sup>3</sup> As KFD has no pathognomonic clinical symptoms or signs, delay in diagnosis occurs frequently and its rarity in children complicates the scenario.<sup>4</sup>

All though it has worldwide distribution, there is high prevalence in Asian population.<sup>5</sup> Kikuchi-Fujimoto disease varies in its prevalence, clinical profile, severity, outcome among different age groups, ethnicity and gender.<sup>6</sup>

KFD in the children has many difference compared to adult including its clinical presentation, manifestations and prognosis.<sup>7</sup> Fever, cervical lymphadenopathy, leukopenia, thrombocytopenia, elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and lactate dehydrogenase (LDH) along with a self-limiting course are the common features which is described in most of the studies.<sup>7-9</sup> A definitive diagnosis of KFD can be made only by histopathological examination of lymph node. Other studies have shown that KFD could be progressive, recurrent or a comorbid diagnosis with other diseases, especially autoimmune diseases.<sup>10,11</sup>

Kikuchi-Fujimoto disease is a rare diagnosis in children.<sup>12,13</sup> In children, majority of these cases are evaluated as Pyrexia of unknown origin leading on to extensive investigations and procedures before the diagnosis is established. There only a few literatures on pediatric Kikuchi-Fujimoto disease. Authors conducted this retrospective observational study to describe the disease, its characteristics, clinical profile and outcome among Indian pediatric population.

**METHODS**

This is a retrospective, observational cross-sectional study done in a tertiary hospital in South India from January 2005 to November 2017. The study was approved by the Institutional Review Board (Ref IRB11089, dated 20.12.2017).

**Inclusion criteria**

- All children under the age of 16 years, who presented to Department of Pediatrics during this period, with a histopathological diagnosis of KFD, were included in the study.

The diagnosis of KFD was based on histopathological report of lymph node biopsy, which showed characteristic features of paracortical well-circumscribed necrotic lesions consisting of karyorrhexis, fibrin deposits, plasmacytoid monocytes and infiltration of histiocytes in the absence of plasma cells or neutrophils.<sup>14</sup>

The baseline demographic characteristics, clinical features, laboratory investigations, course of illness, treatment, and data with regard to follow up were obtained from pre-existing medical records.

**Statistical analysis**

Categorical variables were expressed by numbers and percentages; the statistical significance of the comparison was assessed using chi-square test and fisher’s exact test as appropriate. Continuous variables were expressed as mean and standard deviation and were compared between groups using the ANOVA test. P value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS software version 22.0 (IBM

SPSS statistics for windows, version 22.0. armonk, NY: IBM Corp).

**RESULTS**

Fifty-three children with KFD were included in the study and the data was analyzed. The baseline demographic characteristics, clinical features and laboratory data at presentation are shown in Tables 1 and 2.

**Table 1: Characteristics of Kikuchi-Fujimoto disease in children.**

Parameters		N (%)
Age (year), Mean±SD		10.8±3.5
Sex ratio (M/F)	Total	36:17 (2.1:1)
	0-5 year	2:2 (1:1)
	6 -10 year	13:3 (4.3:1)
	11-15year	21:12 (1.8:1)
<b>Lymphadenopathy</b>		
Location	Cervical	
	Unilateral	19/52 (36.5)
	Bilateral	33/52 (63.5)
	Axillary	20/52 (38.5)
	Inguinal	11/52 (21.2)
	Others*	2/52 (3.8)
	Abdominal (Ultrasound)	4/24 (16.6)
	CT thorax and Abdomen	4/4 (100)
Generalized /Multiple		14/52 (26.9)
Character of Lymph node	Firm	44/52 (88)
	Matted	16/52 (30.8)
	Tenderness	20/52 (38.5)
Clinical features	Fever (≥38 <sup>0</sup> C)	46/52 (88.4)
	Headache	8/52 (15.4)
	Vomiting	7/52 (13.5)
	Sore throat	1/52 (1.9)
	Myalgia	5/52 (9.6)
	Chills and rigor	7/52 (13.4)
	Fatigue	4/52 (7.7)
	Arthralgia	8/52 (15.4)
	Weight loss	11/52 (21.2)
	Rash	6/52 (11.5)
	Subcutaneous swelling	2/52 (3.8)
	Hepatomegaly	2/52 (3.8)
	Splenomegaly	2/52 (3.8)
Treatment and outcome	Hospitalization	31/53 (58.4)
	NSAIDS	16/53 (30.2)
	Steroids	12/53 (22.6)
	Recurrence	4/53 (7.5)
	Associated disease	13/53 (24.5)

Others\*-supraclavicular, submandibular. patients whose clinical data were unavailable for analysis were excluded; m=male; f=female; year=years.

Of the cases 36 were males. The overall male-female ratio was 2.1: 1, and it varied among different age groups. The age ranged from 1 to 15 years with a mean of 10.8±3.5 years, with 3 children being below 5 years of age.

**Table 2: Laboratory findings of Kikuchi’s disease in children.**

Parameters	N ( %)
<b>Hemogram</b>	
Anemia, 1-15 year (< 11.0g/dL)	37/52 (71.2)
Leukopenia (<4000/mm <sup>3</sup> )	16/51 (31.4)
Leucocytosis(≥10,000/mm <sup>3</sup> )	6/51 (11.8)
Neutropenia (ANC<1500/ mm <sup>3</sup> )	6/51 (11.8)
Lymphopenia (<1500/ mm <sup>3</sup> )	16/51 (31.4)
Monocytosis (≥10%)	11/51 (21.6)
Thrombocytopenia (<150 x 10 <sup>3</sup> /mm <sup>3</sup> )	8/49 (16.3)
Presence of atypical lymphocytes	2/51 (3.9)
<b>Biochemistry</b>	
Elevated ESR (≥12mm/h)	36/43 (83.7)
Elevated CRP (≥6mg/L)	17/32 (53.1)
Elevated AST (≥40U/L)	15/21 (71.4)
Elevated ALT (≥35U/L)	13/35 (37.1)
Elevated LDH (≥200U/L)	29/29 (100)
Creatinine (≥1mg/dL)	2/40 (5)
<b>Serology and immunology</b>	
ANA (≥1:100)	12/44 (27.3)
DsDNA (<100IU/ml)	2/23 (8.7)
Direct coombs Test positive	4/8 (50)
Decreased C3 (< 90mg/dL)	3/23 (13)
Decreased C4 (< 10mg/dL)	3/23 (13)
<b>Urine analysis</b>	
Urine protein positive	7/33 (21.2)

Abbreviations: ANC-absolute neutrophil count; ESR-erythrocyte sedimentation rate; CRP-C-reactive protein; AST-aspartate aminotransferase; ALT-alanine aminotransferase; LDH-lactate dehydrogenase; ANA-antinuclear antibody; EB-Epstein-Barr; VCA-viral capsid antigen.

The common symptoms at presentation were fever (88.4%) followed by weight loss (21.2%), headache (15.4%), arthralgia (15.4%), vomiting (13.5%), chills and rigor (13.4%), rash (11.5%), myalgia (9.6%), fatigue (7.7%) and sore throat (1.9%). Most of the children had febrile episodes of around 8 weeks, ranging from 14 days to 150 days. Some rare presentations like alopecia, oral ulcer, epistaxis, profuse sweating of palms and feet’s, neck pain, photophobia, and subcutaneous swelling were also noticed in present study population.

All children had cervical lymphadenopathy of which 63.5% had bilateral involvement and rest had generalized lymphadenopathy. Less common sites of lymph node involvement were inguinal, axillary regions, submandibular, supraclavicular, abdominal nodes and mediastinal nodes (CT Thorax). Lymph nodes were firm in 88%, matted in 30.8% and tender in 38.5% of children. The definitions of laboratory finding are the same as in Table 2.

**Table 3: Univariate analysis of associate disease in children with KFD.**

	Associated disease (13)	Without associated disease (40)	P value
Age, Years, Mean	9.3±4.1	11.2±3.1	0.087
Sex, female	5/13	12/40	0.403
Fever	13/13	33/39	0.317
Arthralgia	2/13	6/39	1.00
Headache	4/13	4/39	0.096
Fatigue	3/13	1/39	0.044
Rash	3/13	3/39	0.157
Weight loss	6/13	5/39	0.019
Generalised LN	5/13	9/39	0.231
Anemia	12/13	25/39	0.078
Lymphopenia	6/13	10/38	0.183
Neutropenia	1/13	5/38	1.00
Monocytosis	0/13	11/38	0.046
Thrombocytopenia	3/13	5/36	0.422
Elevated ESR	8/9	28/34	1.00
Elevated CRP	7/11	10/21	0.472
Elevated AST	7/8	8/13	0.336
Elevated ALT	5/12	8/23	0.726
Elevated creatinine	1/12	1/28	0.515
ANA	7/12	5/32	0.008

P value <0.05 is statistically significant. Patients whose clinical data were unavailable for analysis were excluded.

Anemia (71.2%), leukopenia especially lymphopenia (31.4%), monocytosis (21.6%) and thrombocytopenia (16.3%) were more prominent than leukocytosis (11.8%) in the hemogram. A typical cell in the smear were noticed in 2 children. Most of the children had elevated ESR (83.7%), CRP (53.1%), and LDH (100%). Elevated liver enzymes were also observed but SGOT (71.4%) was raised more often than SGPT (37.1%). Positive ANA (27.3%), direct coombs Test (4 cases), and Ds DNA (3 cases) and along with proteinuria (5 cases) were observed in present study group. Decreased C3 (8.7%) and C4 (13%) values were also noted. Most common finding in abdominal ultrasound was mesenteric lymphadenopathy and hepatomegaly. Among 44 patients tested with antinuclear antibody (ANA), 12 children showed ANA positivity (>1:100) and three had associated decreased C3 and C4 levels. CSF analysis of 9 patients most commonly revealed increased cell count (lymphocytic predominance) and elevated protein levels. One child had unusually high protein on CSF analysis.

In present study 13 children (24.5%) with KFD coexisted with other systemic diseases. One child who was diagnosed with systemic lupus erythematosus (SLE), simultaneously had a lymph node biopsy showing features of Kikuchi disease. Four children with KFD developed SLE during the follow up period (2 children

after 6 months, one after 1 year and one child after 3 year). Three children had aseptic meningitis; two had hemophagocytic lymphohistiocytosis (HLH) and one child each with psoriasis, pulmonary alveolar proteinosis, and immunodeficiency along with KFD. Among six cases that were tested for CMV, Parvo and EBV specific antibodies, positive CMV and EBV, IgM antibody was detected in one each. Skin biopsy was done for two children in view of cutaneous involvement, in which one was suggestive of Kikuchi disease and in the other biopsy of subcutaneous nodule showed parts of cysticercus.

Univariate analysis was done to analyses significance of parameters associated with gender, age group and coexisting disease. On comparison between age groups weight loss, leukopenia and lymphopenia had significant associations with the disease in children above 10 years ( $P < 0.05$ ) on comparison with children below 10 years of age. With regards to gender, there was no parameter which showed statistical significance between the two groups. On comparing weight loss, fatigue, Monocytosis and ANA positivity had shown statistical significance in children with coexisting disease.

More than half of the patients (58.4%) were hospitalized during the courses of KFD. Almost half of children with KFD (49.1%) had self-limiting courses and received conservative management. Remaining children (50.9%) was managed with medications; mostly HCQ, aceclofenac (1-2 weeks), brufen (1-2 weeks), naproxen (2-12 weeks) and oral corticosteroids (3-12 months) while a few got a combination of NSAID and steroids. The mean duration between initial diagnosis and the last follow-up was around 6 months to 2 year. Four children (7.5%) had recurrence at a later date.

## DISCUSSION

This study is one of the largest cohorts from Asian population on pediatric Kikuchi's disease, and is in fact one of the first of its kind from Indian population. Most of the large-scale studies were among adults with Kikuchi's disease. It is mostly diagnosed in women of Asian descent between the age of 20 to 35 years.<sup>15</sup> Kikuchi-Fujimoto disease is a distinctive clinic-pathological entity in children. The male predominance in younger age groups as shown in present study group were similar to other studies on childhood Kikuchi disease.<sup>6,7</sup> Authors are reporting two cases that presented at very young age (1 year and 3 years of age), both of which are very rare age of presentation in pediatric Kikuchi disease. The first child had associated primary immunodeficiency (agammaglobulinemia) and the 2<sup>nd</sup> child presented with HLH. In present study, majority of cases were around 11 to 15 years of age (62.3%). The etiopathogenesis of KFD is still unknown. Most reports have suggested a possible association with a variety of microorganisms from virus to bacteria like Epstein -Barr virus, Herpes virus 6 and 8, cytomegalovirus, Parvovirus B19, hepatitis B, HIV etc.<sup>16</sup> However no study has identified the causative agent so

far.<sup>17,18</sup> Other possible aetiologies include autoimmune causes and genetic susceptibility.<sup>19</sup> Out of 6 children tested for viral Antibody titers in present study population, one was positive for EBV IgM and other for CMV IgM respectively. In a meta-analysis, Chong Y et al, looked into causative agents of Kikuchi-Fujimoto disease concluded that HHV8 rather than EBV was most likely associated to KFD and none of the other viruses was associated with the disease.<sup>18</sup>

In KFD, the most common clinical manifestation is cervical lymphadenopathy, which is almost always present, and it consist of unilateral, tender lymph nodes, mostly located in the posterior cervical triangle.<sup>20</sup> Lymph node size has been found to range from 0.5 to 4 cm.<sup>21</sup> In present study all cases presented with cervical lymphadenopathy, mostly bilateral (63.5%), then unilateral lymphadenopathy. Generalized lymphadenopathy was observed in (26.9%) of cases, which was similar to the observation in other studies.<sup>6,7</sup> Majority of cases were firm (88%), tender (38.5 %), and matted (30.8 %). These features were also similar to other studies on pediatric Kikuchi disease.<sup>22-24</sup> In present study group, cervical lymphadenopathy was associated with fever in 88% of cases, while weight loss, nausea, vomiting, upper respiratory symptoms, sore throat, fatigue, headache, arthralgia, and night sweats were less frequent symptoms which was comparable to other studies on pediatric KFD.<sup>25-27</sup> The laboratory value characteristics of present study population were comparable with previous studies reported from India.<sup>28-31</sup>

KFD has been reported in association with different systemic disease mainly autoimmune conditions.<sup>19</sup> Lymphadenopathy diagnosed as KFD could represent an autoimmune necrotizing lymphadenitis. KFD was also been reported with rare atypical manifestation like cutaneous meningitis, myocarditis, acute renal failure, and hemophagocytic syndromes.<sup>32-38</sup> In present study out of 53 children, 13 children (24.5%) presented with co-existing diagnosis. Among 13 children, 5 were diagnosed with SLE (1 was diagnosed concomitantly with KFD while 4 had SLE during follow up), 2 with HLH, 3 with aseptic meningitis, one each with PID, Psoriasis and Alveolar proteinosis. One child was treated as TB meningitis in view of high protein in CSF, but all TB work up was negative. There are no other reports in literature, showing coexisting alveolar proteinosis, Primary immunodeficiency and Psoriasis in children with KFD. Duma et al, reported out of 91 adult cases with KFD, 11 patients had SLE.<sup>25</sup> Although KFD can seldom precede SLE, the association between these two diseases remains unclear. In a systemic literature review, Sopena et al, described about the clinical association between Kikuchi's disease and systemic lupus erythematosus.<sup>19</sup> Hu et al, suggested that if Kikuchi's lymphadenitis coexists with SLE, it should be regarded as lupus lymphadenitis. KFD in SLE patients should be likely considered as lupus lymphadenitis and treated.<sup>39</sup>

Cutaneous manifestation were extremely rare and are reported mostly in adults.<sup>32</sup> In present study one child presented with skin involvement which on biopsy was suggestive of Kikuchi disease. There are many case reports of Kikuchi disease association with HLH.<sup>37,38</sup> Sykes et al, reported a 16-year-old child presented acquired and self-limited simultaneous Hemophagocytic lymphohistiocytosis and Kikuchi-Fujimoto disease.<sup>40</sup> Two children had coexisting HLH in our cohort, and in one child it resolved spontaneously but the other child died secondary to HLH sequelae. Recurrence of KFD were also reported in adults but rarely reported in children.<sup>8</sup> Comparison of children with and without recurrence of KFD, the analysis did not reveal a reliable predictor for recurrence. The small number of cases with recurrence may have prevented us from finding a suitable marker of recurrence in present study. Conservative management or short course of non-steroidal anti-inflammatory drugs (NSAID) are sufficient for most occurrences, but short courses of corticosteroids, intravenous immunoglobulin (IVIG) or hydroxychloroquine (HCQ) might be required in more complicated cases.<sup>15,25</sup> Most of our KFD children had self-limiting courses and received conservative management (49.1%). Corticosteroids and NSAIDs were used in the other groups. Some children got both NSAID and steroids, but only one child got HCQ. Oral steroids were administered in 12 cases (22.6%) and were mostly determined by its clinical severity and associated diseases. The mean duration between initial diagnosis and the last follow-up was around 6 months to 2 year. Four children (7.5%) had recurrence. In those children NSAIDs was the mainstay of treatment and none of them received steroids. Although authors report a relatively large number of patients in our retrospective study, there are several limitations. First, laboratory data for some patients was missing and bias in the analysis of these results is to be expected. Also due to the limited number of patients, present study was not sufficiently powered to detect differences in the clinical characteristics that may predict recurrence, co-existing disease or evolution into another autoimmune disease. However, present study highlights the importance of early diagnosis, management and long-term follow-up for all children presenting with KD.

## CONCLUSION

KD is usually a benign disease with symptoms of fever and cervical lymphadenopathy but may occasionally be associated with SLE and other diseases. High index of suspicion and early detection of the disease may ensure a better prognosis. Long-term follow-up of patients with KD is necessary.

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