Clinical Characteristics of Severe Histiocytic Necrotizing Lymphadenitis (Kikuchi-Fujimoto Disease) in Children

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Objectives To analyze the clinical characteristics of children with Kikuchi-Fujimoto disease focusing on cases with prolonged fever.

Study design This was a retrospective study of children diagnosed with Kikuchi-Fujimoto disease from March 2003 to February 2015 in South Korea. Electronic medical records were searched for clinical and laboratory manifestations.

Results Among 86 histopathologically confirmed cases, the mean age was 13.2 (SD ± 3.1) years, and male to female ratio was 1:1.32. Cervical lymph node enlargement, found in 85 of the patients (99%), was predominantly unilateral in 64 (75%), and involved the cervical lymph node level V in 67 (81%). Fever was present in 76% of the cases, with a median duration of 9 days (IQR 0.25-17.0). Multivariate analysis revealed that a high fever peak ≥39.0°C (P = .010) and presentation with ≥2 systemic symptoms other than fever (P = .027) were factors that were significantly associated with longer fever duration. As the size of the largest lymph node's short diameter increased, the fever duration increased (P = .015). Leukopenia (P = .022) also had a significant association with a longer fever duration. Patients with sonographic findings of conglomerated enlarged lymph nodes had a longer median duration of fever compared with those with separate enlarged lymph nodes (11 vs 4.5 days, P = .019).

Conclusions Patients with high fever, more systemic symptoms, leukopenia, and larger lymph nodes with a conglomerated distribution may benefit from early recognition and selective consideration of corticosteroid therapy. *(J Pediatr 2016;171:208-12)*.

Histiocytic necrotizing lymphadenitis, also known as Kikuchi-Fujimoto disease (KFD), is characterized by regional lymphadenopathy and fever. It is a self-limiting disease of unknown etiology, endemic in Asia, and usually has a benign course and low recurrence rate. KFD has a wide clinical spectrum ranging from absence of systemic symptoms to prolonged fever and significant symptoms such as night sweats, myalgia, arthralgia, weight loss, and hemophagocytic lymphohistiocytosis.[1-7] KFD is a rare form of lymphadenitis described in both adults and children.[8-11]

KFD is confirmed by histopathologic findings of lymph node biopsy.[12] Early diagnosis is important in order to avoid unnecessary evaluations for various other causes of cervical lymphadenopathy.[5] However, biopsy often is delayed because of the risks involved with the procedure, the need for admission or sedation in children, or simply because of waiting for the lymphadenitis to resolve. The delay in diagnosis along with prolonged systemic symptoms leads to frequent hospital visits, long admission periods, or missed schooling. Immune modulating drugs such as corticosteroids have been used in these patients, which may shorten the clinical course.[13-15] However, there are no guidelines for corticosteroid use, and because KFD generally has a self-limiting course, drug misuse and overuse are concerns.

The primary aim of this study was to investigate the clinical characteristics of children with KFD to assess factors associated with a more severe clinical course, focusing on patients with prolonged fever.

Methods

This was a retrospective study of patients <19 years old who were diagnosed with KFD between March 2003 and February 2015 at Seoul National University Bundang Hospital, a tertiary care referral hospital located in the outskirts of Seoul.

KFD was diagnosed when all of the following criteria were fulfilled: (1) systemic symptoms or physical findings compatible with KFD (systemic symptom such as fever, headache, dizziness, loss of appetite, fatigue, myalgia, gastrointestinal disturbance, and arthralgia and physical findings such as lymph node enlargement, hepatomegaly, splenomegaly, and rash); (2) exclusion of any other causes of lymphadenopathy; and (3) histology for lymph node biopsy showing

CT	Computed tomography
KFD	Kikuchi-Fujimoto disease

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nodal paracortical and cortical lesions composed of karyorrhexis, nuclear debris, and infiltration of histiocytes, lymphoid cells, and plasmacytoid monocytes.[16-19]

The electronic medical records of the patients were reviewed. Data collected included age, presenting symptoms, laboratory test results, biopsy methods, histologic findings, treatment, and outcome including duration of symptoms. The ultrasound or computed tomography (CT) images were reviewed by a single pediatric radiologist for uniform measurements of the short and long diameter of the largest lymph nodes, distribution of the enlarged lymph nodes, and other imaging characteristics of the enlarged nodes specific to KFD. The duration of fever was defined as the number of days for which the patient had a body temperature of ≥38.0°C with an interval of <24 hours between each episode of fever. All cases with splenomegaly and hepatomegaly were confirmed via abdomen ultrasonography or CT.

Statistical Analyses

Multivariate logistic regression analysis was performed to identify factors associated with the duration of fever using the selection method (backward selection) for variables that were statistically significant in the univariate analysis. Statistical analyses were performed using the R v 3.2.1. (R Foundation for statistical computing, Vienna, Austria). Fisher exact test was used to compare categorical variables for analyzing the clinical characteristics of patients according to the distribution of the enlarged lymph nodes. Continuous variables for treatment response were compared by the Mann-Whitney U test. SPSS v 21.0 (SPSS Inc, Chicago, Illinois) was used to perform statistical analyses. All the statistical tests performed were 2-tailed and a P value of ≤.05 was considered significant.

Results

During this 12-year period, a total of 86 patients <19 years of age fulfilled the case definition of KFD. The mean age was 13.2 years old (SD ± 3.1), and the age range was 5-18.8 years (**Table I** and **Figure 1**; **Figure 1** available at www.jpeds.com). The male to female ratio was 1:1.32, and seasonal distribution showed that the onset of KFD was more common during the winter (34%, n = 29) than other seasons of the year (**Figure 2**; available at www.jpeds.com). Lymph node biopsies were performed on median day 10 (IQR 5-19.5 days) of illness.

Table I shows general characteristics of patients with KFD. Of 86 cases, 85 (99%) had cervical lymph node enlargement. One patient did not come to attention with cervical lymphadenitis but had multiple axillary, inguinal, and retroperitoneal nodes enlarged. The majority of the patients (64, 75%) had unilateral cervical node involvement. Lymph node tenderness was present in 53 (62%).

Fever was present in 65 of the patients (76%), of whom 40 (47%) had a fever of ≥39.0°C. The median duration of fever was 9 days (IQR 0.25-17.0). Furthermore, 32 of the patients (37%) had prolonged fever of ≥2 weeks, and 7 of the patients (8%) had a fever of ≥4 weeks.

Table I. General characteristics of children with KFD

	No. of cases (%), N = 86
Age, y, mean (±SD)	13.2 (±3.1)
Female	49 (57)
Lymphadenopathy	
Cervical	85 (99)
Axillary	6 (7)
Inguinal	5 (6)
Mesenteric	2 (2)
Retroperitoneal	1 (1)
Systemic symptoms	
Fever	65 (76)
Loss of appetite	25 (29)
Fatigue	21 (24)
Headache	21 (24)
Night sweats	16 (19)
Arthralgia	11 (13)
Myalgia	8 (9)
Physical findings	
Rash	16 (19)
Splenomegaly	9 (10)
Oral mucosal ulceration	5 (6)
Uveitis	4 (5)
Parotitis	4 (5)
Thyroiditis	2 (2)
Pericardial effusion	1 (1)
Laboratory findings*	(mean ± SD, range)
Hemoglobin (mg/dL)	12.1 ± 1.3 (9.1-15.7)
WBC ($4 \times 10^3/mm^3$)	3.4 ± 1.7 (1.1-9.4)
ANC ($\times 10^3/mm^3$)	1.5 ± 1.0 (0.3-6.9)
Platelet ($\times 10^3/mm^3$)	193 ± 57 (69-337)
ESR (mm/h)	31 ± 20 (4-116)
CRP (mg/dL)	2.7 ± 3.4 (0.01-16.9)
AST (mg/dL)	60 ± 77 (16-479)
ALT (mg/dL)	67 ± 108 (8-728)
Ferritin (mg/dL)	480 ± 565 (54-2000)
LDH (mg/dL)	479 ± 300 (168-1970)

ALT, alanine aminotransferase; *ANC*, absolute neutrophil count; *AST*, aspartate aminotransferase; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *LDH*, lactate dehydrogenase; *WBC*, white blood cell count.
*Patients whose laboratory findings were unavailable of analysis were excluded: total (N = 73).

Overall, 42% (n = 36) of the patients had >2 systemic symptoms other than fever, and 28% (n = 24) had >3 systemic symptoms. Of these, loss of appetite, fatigue, and headache were predominant. The most common extranodal manifestations included rash, splenomegaly, and oral mucosal ulceration, but none occurred in <20% of patients.

Of the 76 patients who had laboratory findings available for analysis, 35 (46%) had anemia (Hb <11 mg/dL), 57 (74%) had leukopenia (white blood cell count $<4 \times 10^3/mm^3$), 26 (34%) had neutropenia (absolute neutrophil count $<1 \times 10^3/mm^3$), and 19 (25%) had thrombocytopenia (platelet $<150 \times 10^3/mm^3$).

Image Findings

Ultrasound or CT images were unavailable for re-evaluation in 3 patients. Of the 83 patients with images of enlarged lymph nodes, 78 (94%) were ultrasound images and 5 (6%) were CT images. All patients had multiple enlarged lymph nodes, and the most common area of involvement was the posterior triangle at cervical lymph node level V (n = 67, 81%). The mean short and long diameters of the largest lymph node were 9.4 mm (range 3-22 mm) and 19.0 mm (range 10-35 mm), respectively. Also, 39%