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The incidence and clinical characteristics by gender differences in patients with Kikuchi–Fujimoto disease

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Abstract

Kikuchi–Fujimoto disease (KFD) is a rare, self-limiting disorder that typically affects the cervical lymph nodes (LNs). Although initially described in young women, KFD also occurs in men. There are no reports on the clinical manifestations and characteristics of male KFD patients. Therefore, this study was conducted to assess the incidence of KFD among males, as well as the most frequent clinical characteristics of these patients. A retrospective, cross-sectional study was performed at a tertiary hospital of patients pathologically confirmed as having KFD from LN biopsy specimens. Clinical and laboratory data, and treatment outcomes of the enrolled patients, were analyzed by gender. A total of 254 patients diagnosed with KFD were enrolled. There were 189 females and 65 males (2.9:1). The mean age was 32.6 ± 11.3 years. Compared to the female patients, the males had more frequent manifestations of fever (48% vs 67%, $P = 0.008$), headache (9% vs 20%, $P = 0.013$), bilateral lymphadenopathy (31% vs 46%, $P = 0.029$), thrombocytopenia (14% vs 29%, $P = 0.014$), elevated C-reactive protein (CRP) (35% vs 78.4%, $P < 0.001$), elevated liver enzymes (15% vs 41%, $P < 0.001$), and elevated lactate dehydrogenase (LDH) (61% vs 80%, $P = 0.021$). Male patients had fewer autoimmune features (9% vs 2%, $P = 0.043$) and fewer positive antinuclear antibodies (32% vs 10%, $P = 0.006$). In this study, 25.6% of the enrolled patients were male, with a 2.9:1 female-to-male sex ratio. Male patients showed a distinctive profile characterized by a higher frequency of fever, headache, bilateral lymphadenopathy, and thrombocytopenia, as well as elevated liver enzymes, CRP, and LDH.

Abbreviations: ANA = antinuclear antibody, AOSD = adult-onset Still disease, CKD = chronic kidney disease, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, KFD = Kikuchi–Fujimoto disease, LDH = lactate dehydrogenase, LFT = liver function test, LN = lymph node, MCD = mixed connective tissue disease, NSAID = nonsteroidal anti-inflammatory drugs, SLE = systemic lupus erythematosus.

Keywords: characteristics, Kikuchi–Fujimoto disease, males

1. Introduction

Kikuchi–Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis, was first reported in Japan in 1972.[1–4] It is a rare cause of lymphadenopathy, characterized by cervical lymphadenopathy, fever, and leukopenia, which is usually clinically benign.[5] The pathogenesis of KFD remains unknown, but an immune response of T cells and histiocytes to an infectious agent is considered to be the most probable cause.[6]

KFD has been most frequently been reported in Asia,[7] but has been identified in many ethnic groups in various countries.[8] KFD mainly occurs at a young age and has been reported to occur more frequently in women.[9–11] The male-to-female sex ratio varies from 1:16 to 1:4.[9–13] The sex distribution is almost equal in adult Asian populations, but among children aged 18 years or younger, male predominance has been reported (8:3).[14]

Prior studies on the clinical manifestations and outcomes of KFD have focused on females, and few studies exist on KFD among young men. Furthermore, to the best of our knowledge, there have been no larger scale reports on differences in clinical manifestations by gender. Therefore, the aim of this study was to identify the male incidence of KFD and investigate the clinical manifestations and laboratory features that are more frequently observed in male KFD patients.

2. Methods

2.1. Study design

A retrospective, observational cohort study was performed at a 2000-bed tertiary hospital in South Korea, from December 1995 to December 2014. Patients aged 18 years or older, with regional or generalized lymphadenopathy, and compatible histologic

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findings (histiocytes and lymphoid cell aggregates or subacute necrotizing lymphadenopathy) in histology analyses from lymph node (LN) biopsy specimens were defined as KFD.[15] Patients diagnosed with a concurrent malignant lymphoma or tuberculosis were excluded from the study. Patients lacking imaging data (computed tomography or ultrasonography of the neck) or sufficient medical records regarding their clinical symptoms were also excluded. This study was approved by the ethics committee of the Yonsei University College of Medicine Severance Hospital. Informed consent was waived from all patients.

The following variables were assessed: demographic and baseline clinical characteristics (age, gender, presence of hypertension, diabetes, malignant disease, chronic kidney disease [CKD], and autoimmune diseases), clinical signs and symptoms at diagnosis (pain, fever, night sweats, sore throat, weight loss, rash, myalgia, arthralgia, nausea, and headache), lymphadenopathy features (duration of onset, lesions [cervical, extracervical, single, or multiple], size of the largest LN, laterality, and sites of cervical involvement) and laboratory results (complete blood cell counts, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], liver function tests [LFTs], lactate dehydrogenase [LDH], and antinuclear antibodies [ANAs]), and outcomes (treatment options, cure or relapse, and all-cause mortality).

2.2. Definitions

Patients with malignancy included those with a history of solid organ cancer or hematologic malignancy at the time of KFD diagnosis. Diabetes was defined based on the American Diabetes Association diagnostic criteria.[16] Hypertension was defined in patients with a systolic blood pressure of 140 mm Hg or more, or a diastolic blood pressure of 90 mm Hg or more, or taking antihypertensive medication.[17] CKD was defined as either kidney damage or a decreased glomerular filtration rate of less than 60 mL/min/1.73 m^2 for at least 3 months.[18] Autoimmune disease was defined in patients diagnosed with systemic lupus erythematosus (SLE), adult-onset Still disease (AOSD), Sjögren syndrome, or *Behçet disease*.

Fever was defined as a temperature over 38.0 °C as an initial symptom. A headache was defined as symptoms lasting for more than a week. Extracervical LN involvement was defined as involvement of the axillary, mesenteric, or inguinal LNs. Multiple LN involvement was defined as having multiple levels of cervical lymphadenopathy. Relapse was defined as pathologically proven KFD on rebiopsy due to recurring symptoms of fever or lymphadenopathy during a 3-month follow-up.

Leukopenia was defined as a white blood cell count lower than 4000 cells/μL. Neutropenia was defined as an absolute neutrophil count of lower than 1500 cells/μL. Anemia was defined as having a hemoglobin level lower than 12 g/dL.[11] Thrombocytopenia was defined as a platelet count below 150,000 cells/μL.[19] Elevated ESR was defined as a level exceeding 60 mm/h.[11] Elevated CRP was defined as a level exceeding 8 mg/L.[11] An abnormal LFT was defined as an alanine aminotransferase level exceeding 40 IU/L.[11] Elevated LDH was defined as a level exceeding 500 IU/L.[11]

2.3. Data analysis

Normally distributed continuous variables are expressed as means ± standard deviation, and categorical variables are presented as numbers and percentages. The statistical significance of the comparisons was assessed using a paired *t* test and the χ^2 test. A *P* value <0.05 was considered statistically significant. Analyses were performed using SPSS software (ver. 23.0; SPSS Inc., Chicago, IL).

3. Results

A total of 284 patients were diagnosed with KFD during the study period. After excluding 30 patients (20 patients had no imaging data, 7 had incomplete medical records, and 3 were diagnosed with concurrent tuberculosis), 254 patients were finally enrolled in this study (Fig. 1).

Of these patients, 25.6% (n = 65) were male, and the female-to-male sex ratio was 2.91:1. The mean age at diagnosis was 30.5 ± 11.0 years in males and 30.0 ± 9.3 years in females. There were no significant differences in age or underlying disease, except for autoimmune diseases, between males and females. Seventeen female subjects had been diagnosed with an autoimmune disease, which showed a female predominance, as only 1 male patient had a history of autoimmune disease (n = 17 [9%] vs n = 1 [2%], *P* = 0.043). There were no patients in this study who were diagnosed with rheumatoid arthritis, systemic sclerosis, polymyositis/dermatomyositis, or vasculitis. There was 1 patient who was diagnosed with mixed connective tissue disease (MCD) (Table 1).

In this study, male patients experienced fever (n = 90 [48%] vs n = 43 [67%], *P* = 0.008) and headache (n = 16 [9%] vs n = 13 [20%], *P* = 0.013) more frequently than females. The duration of fever was shorter in male patients, with a mean duration of 8 days, compared to 13 days in females (*P* = 0.014). Fever (67%), tenderness on the affected LN (32%), and headache (20%) were the most frequent symptoms experienced by male patients. Male patients also had more frequent bilateral LN involvement compared to females (n = 59 [31%] vs n = 30 [46%], *P* = 0.029). Cervical lymphadenopathy was seen in 95.7% of the total subjects, with no difference observed between genders. The duration of onset, or size, or site of cervical involvement also showed no difference between the genders (Table 1).

Thrombocytopenia was more frequently observed in male versus female patients (22 [14%] vs 17 [29%], *P* = 0.014). Male patients also had more frequent abnormal LFTs (21 [15%] vs 24 [41%], *P* < 0.001), elevated serum LDH (62 [61%] vs 39 [80%],

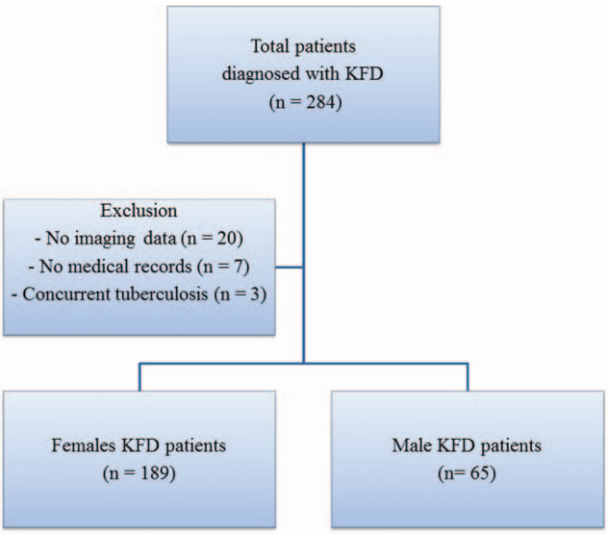

Figure 1. Patient inclusion algorithm.

Table 1

The baseline characteristics and clinical features of the patients.

	Female (n = 189)	Male (n = 65)	P
Age, y	30.0 ± 9.3	30.5 ± 11.0	0.870
Underlying diseases (n, %)			
Malignancy	11 (5.8)	5 (7.7)	0.592
Diabetes	1 (0.5)	0 (0)	1.000
Hypertension	2 (1.1)	0 (0)	1.000
CKD	0 (0)	1 (1.5)	0.256
Autoimmune disease	17 (9.0)	1 (1.5)	0.043
SLE	9 (4.8)	1 (1.5)	0.249
AOSD	3 (1.6)	0 (0)	0.572
Sjögren	3 (1.6)	0 (0)	0.572
Behçet	2 (1.1)	0 (0)	1.000
MCD	1 (0.5)	0 (0)	1.000
Clinical manifestation (n, %)			
Pain	75 (40.1)	20 (31.7)	0.237
Fever (≥38.0 °C)	90 (48.1)	43 (67.2)	0.008
Fever duration, d	13 ± 20.9	8 ± 13.4	0.014
Night sweat	6 (3.2)	6 (9.2)	0.083
Sore throat	19 (10.2)	9 (13.8)	0.415
Weight loss (≥10%)	18 (9.6)	6 (9.2)	0.926
Rash	12 (6.4)	3 (4.6)	0.597
Myalgia	25 (13.4)	10 (15.4)	0.686
Arthralgia	12 (6.4)	2 (3.1)	0.311
Nausea	10 (5.3)	4 (6.2)	0.807
Headache	16 (8.6)	13 (20.0)	0.013
Lymphadenopathy (n, %)			
Involved LN			
One level cervical LN	179 (94.7)	64 (98.5)	0.200
Multiple levels of cervical LNs	176 (93.1)	62 (95.4)	0.517
Extracervical LNs*	29 (15.3)	17 (26.2)	0.051
Size, cm			
<1	18 (9.5)	3 (4.6)	0.215
1–2	116 (61.4)	37 (56.9)	0.527
>2	50 (26.5)	24 (36.9)	0.109
Laterality			
Left	64 (33.9)	18 (22.7)	0.359
Right	65 (34.4)	17 (26.2)	0.220
Both	59 (31.2)	30 (46.2)	0.029
Onset, mo			
Less than 1	131 (69.3)	50 (76.9)	0.242
1–2	47 (24.9)	11 (16.9)	0.188
More than 2	10 (5.3)	4 (6.2)	0.793
Cervical site			
Anterior triangle	17 (9.0)	4 (6.2)	0.473
Posterior triangle	155 (82.0)	54 (83.1)	0.846
Both triangles	17 (9.0)	7 (10.8)	0.673

Data are expressed as the mean ± standard deviation or n (%). AOSD = adult onset Still disease, CKD = chronic kidney disease, LN = lymph node, MCD = mixed connective tissue disease, SLE = systemic lupus erythematosus.

* Extracervical LN: para-aortic, mesenteric lymph nodes.

$P = 0.021$), and elevated CRP (41 [35%] vs 40 [78.4%], $P < 0.001$). However, ANA positivity was significantly more frequent in female patients (32 [32%] vs 4 [10%], $P = 0.006$) (Table 2).

Regarding the final outcomes, 35.8% of patients showed spontaneous clinical improvement, that is, improvement without treatment. Monotherapy, of steroids or nonsteroidal anti-inflammatory drugs (NSAIDs), was administered to 18% and 33.8% of the patients, respectively; 12% of the patients received both types of treatment. Pathologically proven relapse and disease-related mortality occurred more frequently in female patients, but there was no statistically significant difference between males and females (4 [2%] vs 0 [0%], $P = 0.237$) (Table 3).

Table 2

The laboratory findings of the patients.

	Female (n = 189)	Male (n = 65)	P
Laboratory findings (n, %)			
Leukopenia	86 (55.8)	33 (55.9)	0.991
Neutropenia	86 (55.8)	33 (55.9)	0.991
Anemia	44 (28.6)	13 (22.0)	0.335
Thrombopenia	22 (14.3)	17 (28.8)	0.014
Elevated ESR	107 (56.6)	41 (63.1)	0.362
ESR, mm/h, mean ± SD	43.0 ± 26.0	38.8 ± 22.7	0.312
Elevated CRP	41 (35.0)	40 (78.4)	<0.001
CRP, g/dL, mean ± SD	17.2 ± 35.2	41.6 ± 1.6	0.003
Abnormal LFTs	21 (14.7)	24 (41.4)	<0.001
Elevated LDH	62 (60.8)	39 (79.6)	0.021
ANA positivity	32 (31.7)	4 (9.8)	0.006

ANA = antinuclear antibody, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, LDH = lactate dehydrogenase, LFT = liver function test.

4. Discussion

In this study, the ratio of KFD-affected females to males was 2.9:1. A study by Seo et al,[14] of Korean individuals younger than 18 years of age, showed no difference in KFD incidence by gender. However, Kang et al[20] reported a female-to-male sex ratio of KFD of 1.32:1 among Korean children. This difference may be explained by the age differences of the patients between these studies, where the median ages were 13.2 and 12.45 years, respectively. In 3 studies on adults, the ratios of affected females to males were 4:1, 1.6:1, and 1.26:1, respectively.[9,10,12]

Among our male patients, fever (67%), tenderness on the affected LN (32%), and headache (20%) were the most frequent symptoms. Although tenderness of the affected site showed no difference between genders, headache (20%) was more frequent in male patients. Fever was also more frequent in males, with 67% of male patients presenting with fever as an initial symptom. However, the total duration of fever was longer in female patients, with a mean duration of 13 ± 20.9 days. In a retrospective review by Kucukardali et al[13] of 244 KFD patients (in which 77% of the patients were female), fever (35%), fatigue (7%), and joint pain (7%) were the most frequent symptoms. The most common symptoms of the female patients in this study were fever (48%), tenderness of the affected LN (40%), and myalgia (13%). Arthralgia was present in 6% of the female patients, similar to the results of the Kucukardali study.

A study conducted in the United States showed that 83% of patients had localized lymphadenopathy, particularly of the posterior cervical area.[12] In another study of 79 Chinese patients, 97% presented with cervical lymphadenopathy, and there was bilateral involvement in 18 (22%) patients.[21] In this

Table 3

The treatment outcomes of the patients.

	Female (n = 189)	Male (n = 65)	P
Treatment (n, %)			
No treatment	67 (35.4)	24 (36.9)	0.831
Steroid	36 (19.0)	10 (15.4)	0.508
NSAIDs	67 (35.4)	19 (29.2)	0.361
Both	19 (10.1)	12 (18.5)	0.074
Relapse (n, %)	2 (1.1)	0 (0)	0.405
Death (n, %)	4 (2.1)	0 (0)	0.237

NSAID = nonsteroidal anti-inflammatory drug.

study, 95.7% of patients presented with cervical lymphadenopathy, most frequently in the posterior cervical triangle. In total, 46% of male patients had bilateral lymphadenopathy, while this was seen in only 31% of the female patients. The results in this study are similar to those of previous studies, in which KFD commonly presented as posterior cervical lymphadenopathy, and they show that male patients present with bilateral lymphadenopathy more frequently than females.

In this study, elevated LDH (80%), leukopenia (56%), elevated CRP (78.4%), and elevated liver enzymes (41%) were the most frequent laboratory findings in male patients. Furthermore, thrombocytopenia, elevated liver enzymes, and LDH are all markers of severe inflammation and were seen more frequently in male patients. Keogh et al[22] reported a case of a young man diagnosed with KFD who developed respiratory failure, parotidomegaly, and thyroiditis, requiring intensive care unit management. These findings suggest that KFD in males may be more commonly associated with severe systemic inflammation and presents as a more severe form of illness compared to that seen in females. These findings are consistent with the results of previous studies.[13]

An autoimmune mechanism is often proposed in KFD, since many studies have described an association between KFD and SLE.[23,24] In this study, SLE was present in 9 (5%) female patients and 1 (2%) male patient. This shows that autoimmune diseases are more frequent in females, which agrees with the results of previous studies.[10] Since KFD and SLE share similar sex and age profiles, that is, occur more often in young females,[25] several studies recommend ANA testing in patients initially diagnosed with KFD to exclude concomitant SLE.[10,12] In this study, the ANA-positive rate was also higher among females.

In the majority of patients, KFD is a benign, self-limiting disease.[15] Our study results did not differ from those of previous studies, with more than 35% of the patients showing a spontaneous resolution without any specific treatment. Death occurred in 4 female patients, and there was no KFD-related mortality in the male patients. No male, and only 2 female, patients experienced a single episode of relapse. Smith et al[26] reported a female patient with 4 episodes of recurrent KFD over a period of 18 years. However, as our study only enrolled patients with histologically proven KFD, the recurrence rate may have been underestimated.

There were several limitations to this study. First, it was conducted retrospectively, and cases without sufficient clinical data on the symptoms were excluded. This may have resulted in a reduced number of patients with KFD being enrolled. Second, only cases that were histopathologically confirmed at initial diagnosis and recurrence were included. Those patients who were very likely to have KFD based solely on their clinical data were not included. Third, a total of 15 patients (12 patients on steroids; 6 for SLE, 2 for Sjogren disease, 1 for Behçet disease, 2 for AOSD, 1 for MCD, and 3 patients on NSAIDs due to SLE) already receiving NSAIDs or steroids for treating autoimmune diseases were included in the study, and this may have interfered with the evaluation.

In conclusion, 25.6% of enrolled patients were males, with a 2.9:1 female-to-male sex ratio. Male patients showed a distinct profile characterized by a higher frequency of fever, headache, bilateral lymphadenopathy, and thrombocytopenia, as well as elevated liver enzymes, CRP, and LDH. Female patients presented with autoimmune disorders and ANA positivity more frequently.

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