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DIAGNOSIS OF KIKUCHI-FUJIMOTO DISEASE BASED ON ULTRASOUND AND CLINICAL FINDINGS

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ABSTRACT

Kikuchi-Fujimoto disease (KFD) shares similar clinical manifestations and ultrasonic features with non-specific reactive lymphadenopathy (NSRL). This study aims to elucidate the independent predictors distinguishing these two diseases. A total of 136 lymph nodes (136 patients) with pathologically proven KFD from January 2015 to December 2019 were included. The control group comprised 117 NSRL lymph nodes (117 patients). Clinical information and imaging features were collected and analyzed. The main complaints of KFD were fever (84.6%). The patients with KFD and immune system diseases were older and had longer duration of symptoms. No significant differences ($p< 0.05$) were observed in sex, white blood cell count, short and long axis, shape, and margin. A binary logistic regression analysis revealed that the independent diagnostic factors were patient age (odds ratio [OR]=3.120, p=0.008), fever or pain (OR=0.100, p=0.038), failure of empirical antibiotic or antiviral therapy (OR= 305.88, $p<0.001$), vascular pattern (OR=0.049, p=0.042), CRP (OR=2.679, p=0.035), laterality (OR=0.352, p=0.020), and loose conglomeration (OR=3.605, p=0.019). The combined diagnosis effectiveness was 88.9%. Fever/pain, age range of 20-32 years, increased CRP, ineffective empirical treatment, loose conglomeration, unilateral, and non-abnormal vascular pattern were independent predictors differentiating KFD from NSRL.

Keywords: Kikuchi-Fujimoto disease, ultrasound, non-specific reactive lymphadenopathy

INTRODUCTION

The pathological classification of lymph node (LN) diseases mainly includes reactive and neoplastic lymphoproliferation (lymphoma, metastatic cancer, etc.), of which the reactive changes comprise specific reactive lymphadenopathy and non-specific reactive lymphadenopathy (NSRL) (1,2). We classified reactive lymphadenopathy without special definition (sinus histiocytosis, follicular hyperplasia, and paracortical hyperplasia) according to Jaffe (1) as NSRL. Both specific and non-specific lymphadenopathies share similar clinical manifestations, such as fever, local swelling, and pain; however, their clinical treatments are different. Kikuchi-Fujimoto disease (KFD) is a type of specific reactive lymphadenopathy that is not alleviated by treatment using antiviral or antibacterial drugs as in the case of NSRL. Since it could easily be mistaken, significant diagnostic challenges are posed in clinical practice. Some studies have explored the differences between KFD and malignant diseases (3); however, few studies have focused on the differences between KFD and NSRL. In this study, we aimed to analyze the features of KFD and compare them with those of NSRL in order to achieve a more accurate imaging-based diagnosis and guide clinical treatment.

METHODS

This study was conducted at our hospital from January 2015 to December 2019. In total, 136 LNs (136 patients) with pathologically proven KFD were included in the experimental group. The control group comprised 117 LNs (117 patients) with features of NSRL from January 1, 2019, to December 30, 2019. All the patients signed informed consent for participation in this study. This study was approved by the Ethics Committee and Institutional Review Board of Beijing Friendship Hospital (approval number: 2019-P2-093-02) Inclusion criteria was: 1) clear pathological results obtained on ultrasound-guided core needle biopsy (CNB) (4), 2) complete imaging data, including those of the pathological LN and the surrounding LN, and 3) an interval of one week or less between ultrasonic examination and pathological results. Exclusion criteria was: 1) history of a malignant tumor (includeing lymphoma) in the drainage area of the LN, 2) a final diagnosis of specific reactive lymphadenopathy or neoplastic lymphoproliferation, even when the pathological examination of the biopsy specimen had confirmed NSRL, and 3) absence of any definite pathology.

The patient's medical history and improvement in symptoms following treatment was observed (age, sex, symptoms, duration of symptoms, white blood cell [WBC] count, C - reactive protein [CRP], medication history, concomitant diagnosis, and prognosis). Patients with KFD were divided into Group 1 (G1, with immune system diseases), Group 2 (G2, with viral inflammation), Group 3 (G3, with bacterial inflammation), Group 4 (G4, without accompanying diseases) according to different concomitant diagnoses. Comparisons were made between each group and to Group 0 (G0, group of all the patients with KFD). Diagnosis of viral, bacterial, or mycoplasma-induced inflammation was based on the clear detection of the pathogen by laboratory examination. Diagnosis of immune system diseases, including hemophagocytic syndrome, systemic lupus erythematosus (SLE), and adult Still's disease, were based on the clinical diagnostic guidelines and the latest research reports (5-7). Details on past history, follow-up data for half a year following treatment (up to June 2020 at the latest), and recurrence were recorded for all patients.

All the patients underwent a thorough neck or armpit or groin examination using grayscale ultrasonography (US) and power Doppler US. Sonographic examinations were performed by senior sonologists using Hi Vision Ascendus (Hitachi, Kashiwa, Chiba, Japan) US units and a high-frequency (7.5-12 MHz) linear-array transducer. All US images were carefully reviewed by two physicians with more than 10 years of experience. They recorded laterality of the involved LNs (unilateral or bilateral), short diameters, long diameters, shape (ratio of the short diameter to the long diameter, S/L), margins (fused, circumscribed), borders (sharp, ill-defined), echogenic hilum, echogenicity of the cortex (homogeneous hypoechoic cortex, inhomogeneous cortical echo, including local enhancement or reduction and necrosis and calcification), peripheral hyperechoic rims, conglomeration, and vascular pattern. The long diameter was measured at the longest axis, and the short diameter was measured at the greatest diameter among the lines perpendicular to the long diameter. Conglomeration was defined as the clustering of more than three LNs. If a gap was present between the LNs, it was considered a loose conglomeration, otherwise it was considered a tight conglomeration. Peripheral hyperechoic rims indicated increased echogenicity surrounding the LN compared to adjacent fat tissues. The vascular patterns were divided into abnormal vascular (peripheral vascular and mixed vascular) and normal vascular (hilar vascular and avascular) (8).

US-guided CNB was performed by an experienced physician using an 18 gauge, double-action, spring-activated needle (1.1 cm excursion; TSK Ace-cut; Create Medic, Yokohama, Japan) following local anesthesia with 2% lidocaine (Beijing Yimin Pharmaceutical Company, Beijing, China). The biopsy needle tip was manually advanced to the nodule using a free-hand technique under US guidance, and the stylet and cutting cannula were

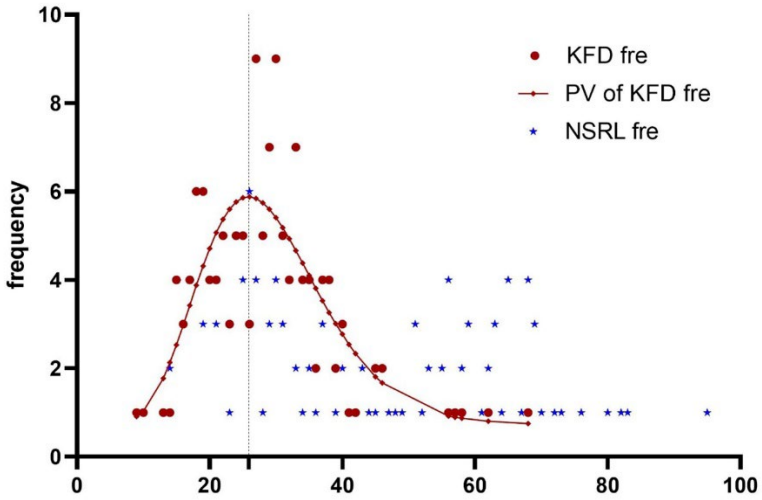

Fig. 1. *Age distribution by maximum curve fit in patients with Kikuchi-Fujimoto disease (KFD). Age distribution of patients with KFD (red dots) and maximum curve fit for KFD patients (red line) with distribution of NSRL patients (blues stars). X-axis: Age (years), Y-axis: Frequency (number).*

fired in sequence. Two biopsy samplings were performed. All biopsy specimens were stored immediately in 10% neutral-buffered formalin solution and were fixed and stained according to the standard protocol for histologic examination. The patients were monitored for an additional 30 minutes for potential complications.

All statistical analyses were performed using SPSS, version 20.0 (SPSS, Inc., IL, USA). The chi-square test was used for the comparison of count data. One-way ANOVA was used for comparisons of multi-group data, and the independent-sample t-test was used for the comparisons of two-group data. P ≤0.05 was considered statistically significant. The age of the patients with KFD were measured with the maximum value function, and the age classification interval was estimated according to the maximum value. We conducted a binary logistic regression analysis to determine the independent predictors among the factors with a p-value of ≤0.05 in the univariate analysis.

RESULTS

Comparisons among Patients with KFD

In total, 136 patients (136 LNs) with KFD were enrolled. There were 50 males and 86 females, and the ratio of males to females was 1:1.72, with an average age of 28.6 ± 10.1 years (range, 9-68 years). The data showed a maximum curve distribution (Fig. 1), with a peak age of 25.8 years.

The main patient complaints were fever (84.6%), local or systemic pain (63.2%), local mass (45.6%), arthralgia (13.2%), and rash (10.3%). Most of the patients showed normal or decreased white blood cell counts (65.4%) and increased levels of CRP (67.6%). Nearly half of the patients (52.9%) had immune system diseases or viral, bacterial, or mycoplasma-induced inflammation. During follow-up, KFD recurred in 8.9% of patients, and one of the patients experienced four relapses in 38 years. One patient died during the treatment. The patient had KFD accompanied with hemophilic syndrome and sepsis and died owing to multiple organ failure resulting from sepsis. Thirty-one patients (22.8%) had two types of inflammation, and two patients (1.5%) had all the types of inflammation including immune, bacterial, and viral inflammation. In total, 20 patients (14.7%) had immune system diseases, including SLE (n=4), adult Still's disease (n=4), and hemophilic

TABLE 1
Demographic, Diagnostic, and Outcome Data among Patients with Kikuchi-Fujimoto Disease (KFD)

	G0（n=136）	G1（n=20）	G2（n=48）	G3（n=25）	G4（n=64）	p value (A&B)
Sex (male/female) (M%/F%)	50/86 (36.8%/63.2%)	2/18 (10%/90%)	21/27 (43.8%/56.2%)	14/11 (56.0%/44.0%)	21/43 (32.8%/67.2%)	0.021（G1&G3）
Age (year)	28.6±10.1	35.0±12.2	25.4±7.1	28±6.4	29.6±10.5	0.006（G1&G2）
symptoms						
fever	115（84.6%）	20（100%）	48（100%）	25（100%）	43（67.2%）	＜0.01* (G4&G0123,G0&G2)
pain	86（63.2%）	16（80%）	32（66.7%）	16（64.0）	24（37.5%）	0.015 (G4&G012)
mass	62（45.6%）	8（40%）	23（47.9%）	12（48.0%）	30（46.9%）	0.98
rash	14（10.3%）	13（65%）	6（12.5%）	7（28.0%）	0	＜0.016* (G4&G123,G1&G024)
arthralgia	18（13.2%）	16（80%）	7（14.6%）	7（28.0%）	2（3.1%）	＜0.017* (G1&G0234,G4&G13)
other	8（5.9%）	7（35.0%）	5（10.4%）	2（8.0%）	1（1.6%）	＜0.018* (G1&G04)
duration of symptoms (days)	41.4±99.3	163.5±218.0	29.0±36.1	61.2±143.8	20.5±32.5	＜0.01（G4&G03,G1&G0234）
normal or decreased WBC	89（65.4%）	16（80%）	39（81.3%）	10（40.0%）	45（70.3%）	0.05 (G2&G3)
increased CRP	92（67.6%）	20（100%）	40（83.3%）	9（36.0%）	55（85.9%）	＜0.01 (G1&G0,G3&G0124)
empirical antibiotic or antiviral therapy	128（94.1%）	18（90%）	47（97.9%）	25（100%）	58（90.6%）	0.287
outcomes						
recovery	123（90.4%）	16（80%）	42（87.5%）	19（96.0%）	58（90.6%）	0.198*
recrudescence	12（8.9%）	3（15%）	6（12.5%）	5（20.0%）	6（9.4%）	0.440*
died	1（0.7%）	1（5%）	0	1（4.0%）	0	0.126*

*WBC: white blood cell, CRP: c-reactive protein, G0: the group of all patients with KFD, G1: the group of patients with KFD with immune system diseases, G2: the group of patients with KFD with viral inflammation, G3: the group of patients with KFD with bacterial inflammation, G4: the group of patients with KFD without accompanying diseases, *: Fisher's exact test, A & B: Groups with statistical significance*

TABLE 2
Comparison of Demographic, Symptomatic, and Ultrasound Features of Patients with Kikuchi-Fujimoto disease (KFD) Or Non-Specific Reactive Lymphadenopathy (NSRL)

	KFD (n=136)	NSRL (n=117)	p value
Sex (male/female) (M%/F%)	50/86 (36.8%/63.2%)	48/69 (41.0%/59.0%)	0.286
Age (years)	28.6±10.1	43.2±18.7	<0.01
Symptom			
fever or pain	115 (84.6%)	71 (60.7%)	<0.01
normal or decreased WBC	89 (65.4%)	63 (53.8%)	0.06
increased CPR	92 (67.6%)	24 (20.5%)	<0.01
empirical therapy failure	128 (94.1%)	23 (19.7%)	<0.01
US features			
Neck	111 (81.6%)	82 (70.1%)	0.032
Unilateral	73 (53.7%)	41 (35.0%)	0.003
Short axis length (cm)	0.96±0.42	0.88±0.50	0.487
Long axis length (cm)	2.29±0.78	2.26±1.10	0.531
S/L ratio	0.43±0.14	0.41±0.15	0.272
Sharp border	117 (86.0%)	98 (83.8%)	0.615
Loss of echogenic hilum	80 (58.8%)	53 (45.3%)	0.009
homogeneous hypoechoic cortex	129 (94.9%)	91 (77.8%)	<0.01
peripheral hyperechoic rims	86 (63.2%)	56 (47.9%)	0.014
conglomeration	93 (68.4%)	50 (42.7%)	<0.01
Pattern (loose/tight)	52/41	17/33	0.012
-fused	9 (6.6%)	6 (5.1%)	0.617
Vascular (normal/abnormal)	136/0	99/18	<0.01*

*: Fisher's exact test

syndrome (n=12). Patients with immune system diseases were older, and the duration of symptoms was longer (Table 1). Patients diagnosed with KFD without accompanying diseases had lesser and shorter duration of symptoms (Table I).

Comparisons between KFD and NSRL

Data of the comparison between KFD and NSRL are summarized in Table 2. No significant differences ($p<0.05$) were observed regarding sex. The mean age of patients with KFD was significantly less ($p<0.01$) than that of the patients with NSRL. Considering the clinical symptoms, both categories of the patients had fever or pain; however, a higher proportion of patients with KFD had fever or pain ($p<0.01$), and a higher proportion had failure of empirical antibiotic or antiviral therapy ($p<0.01$). Considering the US imaging features, there were no significant differences ($p<0.05$) in the size, shape, margin, and border; both categories of patients showed smaller size, oval shape, circumscribed margin, and sharp border. The LNs of patients with KFD and the LNs of patients with NSRL showed features of the homogeneous hypoechoic

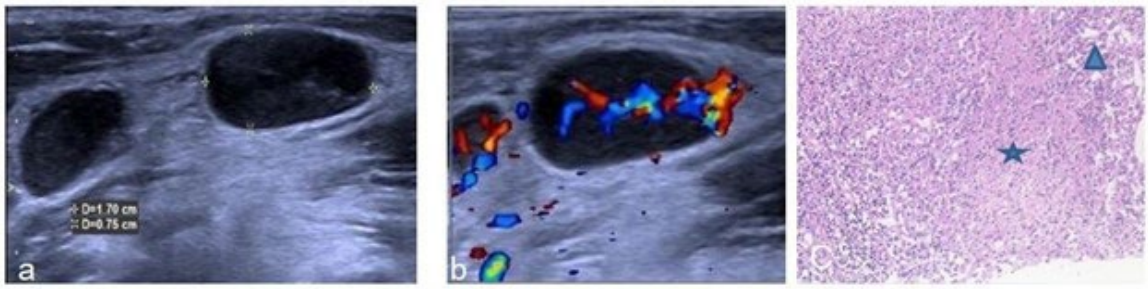

Fig. 2. *Ultrasound images of lymph nodes (LNs) of a patient with Kikuchi-Fujimoto disease. (a) The maximum size of the LN is 1.7 × 0.8 cm, with a short diameter-to-long diameter ratio (S/L) of < 0.5. Loss of echogenic hilum, a homogeneous hypoechoic cortex, and peripheral hyperechoic rims are seen. (b) Color Doppler flow image of the LN reveals a hilar vascular pattern. (c) Pathological specimen obtained by ultrasound-guided core needle biopsy. Abundant karyorrhectic nuclear debris (star) and histiocytes (triangle) are observed.*

cortex and non-abnormal vascular pattern (Fig. 2); however, the LNs of patients with KFD showed significantly higher proportions ($p<0.05$) of these features. There were 26 (22.2%) LNs of patients with NSRL that showed non-homogeneous cortical echo (15 with local enhancement, 13 with local reduction, four with necrosis, and three with calcification), and 19 (16.2%) LNs of patients with NSRL had abnormal vascular patterns (nine with peripheral vascular pattern and 10 with mixed vascular pattern). Only five (3.7%) LNs of patients with KFD showed local echo enhancement or reduction, while none of the LNs of patients with KFD showed necrosis, calcification, and abnormal vascular pattern. In comparison with the LNs of patients with NSRL, the LNs of patients with KFD also showed significant differences ($p<0.01$) in the loss of echogenic hilum, peripheral hyperechoic rims, conglomeration, and loose conglomeration.

Binary logistic regression analysis including factors with a p-value of ≤0.05 in the univariate analysis revealed that the independent factors for diagnosis were: patient age (odds ratio [OR]=3.120, 95% confidence interval [CI]=1.339-7.268, p=0.008), fever or pain (OR=0.100, 95% CI=0.011-0.880, p= 0.038), failure of empirical antibiotic or antiviral therapy (OR=305.88, 95% CI=38.376-2438.071, p<0.001), vascular pattern (OR= 0.049, 95% CI=0.003-0.903, p=0.042), CRP (OR=2.679, 95% CI=1.071-6.699, p=0.035), laterality (OR=0.352, 95% CI=0.147-0.846, p=0.020), and loose conglomeration (OR= 3.605, 95% CI=1.235-10.529, p=0.019) (Table 3) (Fig. 3). The effectiveness of the combined diagnosis was 88.9%.

DISCUSSION

KFD, also known as histiocytic necrotizing lymphadenitis, is a benign, self-limiting condition of unknown etiology. There are two types of KFD: infectious and autoimmune. The most commonly observed is the nonspecific high immune response (9). Some studies suggest that KFD and SLE are different stages of the same disease (1). A study conducted in 2016 detected three patterns among patients with both KFD and SLE: 30% of the patients had KFD before they developed SLE, 47% had simultaneous onset and diagnosis of both conditions, and 23% had SLE and subsequently developed KFD (10). In the present study, less than half of the patients (47.1%) had simple KFD, and most of them had KFD associated with immune system diseases or viral or bacterial inflammation; this suggests that KFD can be related to both infection and autoimmunity. Hence, its clinical manifestations are complex, which increases the difficulty in diagnosis. Most patients with KFD, especially those with concomitant diagnoses, easily undergo misdiagnosis for common inflammation and lymphadenopathy since fever and pain are the first symptoms and laboratory tests are

TABLE 3
Multiple Logistic Regression Analysis

Features	Definition	p	OR	95% CI
fever or pain	absent=0, present=1	0.038	0.1	0.011-0.880
empirical therapy failure	absent=0, present=1	<0.001	305.88	38.376-2438.071
CDFI	non-abnormal=0,abnormal=1	0.042	0.049	0.003-0.903
conglomeration	absent=0, present=1	0.159	2.128	0.745-6.080
conglomeration(1)	present=0,loose conglomeration=1,tight	0.019	3.605	1.235-10.529
conglomeration(2)	conglomeration=2	0.149	2.498	0.721-8.651
age	">20 and <32"=0," <20 or >32"=1	0.008	3.12	1.339-7.268
peripheral hyperechoic rims	absent=0, present=1	0.458	1.391	0.582-3.322
CPR	normal or reduce=0, increase=1	0.035	2.679	1.071-6.699
location	neck=0,armpit or groin=1	0.644	0.765	0.245-2.382
laterality	unilateral=0, bilateral=1	0.02	0.352	0.147-0.846
echogenic hilum	present=0, absent=1	0.409	1.475	0.587-3.708
hypoechoic cortex	homogeneous=0,inhomogeneous=1	0.066	0.274	0.069-1.089

OR: adjusted odds ratio CI: confidence interval; CDFI: Color Doppler Flow Imaging

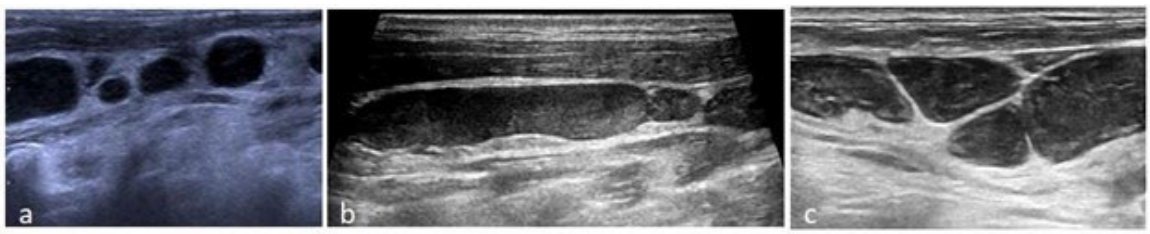

Fig. 3. *Ultrasound images demonstrating conglomeration of lymph nodes. (a) Loose conglomeration in a patient with Kikuchi-Fujimoto disease). (b) Tight conglomeration in a patient with non-specific reactive lymphadenopathy). (c) Tight conglomeration in a patient with lymphoma highlighting sharp edges.*

not specific. Kucukardali et al demonstrated that the most frequent symptoms were lymphadenopathy (100%) and fever (35%) (11). In the present study, the incidence of fever was 84.6%, which was much higher than that reported. A possible reason could be that our samples were collected from patients who underwent LN biopsy, while patients with mild symptoms might not seek timely medical treatment or have a self-limiting disease and no clinical data. Fever or pain was more common in patients with KFD than in those with NSRL and was an independent predictor in the present study. In addition, 128/136 cases received empirical anti-inflammatory treatment owing to early misdiagnosis, which proved to be unsuccessful. Experimental and failed treatment was another independent predictor. Therefore, in clinical practice, we should consider the possibility of KFD if antibacterial or antiviral treatment is unsuccessful in a patient with fever, and the possibility of

association with other immune system diseases if hormone therapy is unsuccessful in a patient with KFD.

Based on the on the US characteristics, the LNs of patients with KFD and NSRL had many similarities since they both are inflammatory diseases. The sizes of the LNs in both cases were small when compared with the LNs affected by malignant diseases (12), and rarely exceeded 3 cm. The S/L ratio of the LNs of patients with KFD and NSRL was less than 0.5. The LNs were oval unlike those affected by malignant diseases, which tend to be round, possibly because benign nodes do not extend or spread, and are limited by the fascial plane (3).

Homogeneous hypoechoic cortex, peripheral hyperechoic rims, and echogenic hilum were different in the univariate analysis, but not significantly different in the logistic regression analysis. Although these features were not independent discriminators, they could be useful in the differential diagnosis of the two conditions. Pathologically, the reason for peripheral hyperechoic rims was the inflammatory cells infiltration into the surrounding tissues (3); some studies have reported this feature (3,13). The LNs of both the groups had homogeneous hypoechoic cortices. None of the LNs of patients with KFD and a few (3/117) LNs of patients with NSRL had internal calcification, unlike tuberculous LNs for which a higher frequency of internal calcification was observed (13). Although KFD is known as histiocytic necrotizing lymphadenitis, the LNs in patients with KFD rarely showed necrosis on US. KFD revealed pathological characteristics of an expanded paracortex and patchy, well-circumscribed areas of necrosis. Necrotic foci showed abundant karyorrhectic nuclear debris and large accumulation of histiocytes at the margin of the necrotic area (14,15). However, no corresponding necrosis was observed on the US images. This could be due to the insufficient resolution. Some studies showed a higher rate of necrosis observed on computed tomography images (16). The heterogeneous rate of cortical echo of the NSRL group was higher than that of the KFD group, which could be due to the destruction of the LN structure during severe inflammation. The loss of echogenic hilum was observed in 58.8% of patients with KFD and 45.3% of patients with NSRL. The echogenic hilum observed on US comprised sinuses, small intranodal arteries and veins, and fatty tissue, which provided sufficient interfaces to reflect the ultrasound waves (12) and was considered one of the indicators distinguishing benign from malignant conditions (17). Previous studies have reported that 71.4% of benign LNs demonstrate an echogenic hilum (18). However, the proportions of loss of echogenic hilum for both groups in this study were higher, which could be due to the different definitions by the observers for "loss" and the aforementioned selection bias. It was also of no significance in the multivariate analysis, similar to the homogeneous hypoechoic cortex.

Loose conglomeration, unilateral and normal vascular pattern revealed an independent association with KFD in the multivariate analysis. The proportion of unilateral lymphadenitis in patients with KFD was higher than that in patients with NSRL. Reactive hyperplasia of the LNs caused by the inflammation of the drainage area was mainly involved in the pathology of NSRL; bilateral involvement was more common. Conglomeration can be observed in many diseases, such as KFD, NSRL, and lymphoma (Fig. 3); however, their characteristics vary. The LNs of patients with KFD showed loose conglomeration, which could be related to the swelling of the surrounding tissue caused by inflammatory cell infiltration and was consistent with the peripheral hyperechoic rims observed previously. In patients with NSRL, the LNs were arranged along the blood vessels and gathered like beads, and there was no space among the LNs. Conglomeration has also been observed in the LNs affected by lymphoma, with sharp edges and no space among the LNs (but no fusion) owing to crowding of the enlarged LNs (3). The normal vascular pattern was another independent predictor. The LNs of patients with KFD and NSRL showed hilar vascular patterns in the majority of cases, which was considerably different from the LNs affected by malignant diseases. However, the LNs of patients with NSRL rarely showed abnormal

vascular patterns, although a small proportion (16.2%) of LNs of patients with NSRL showed abnormal vascular patterns owing to structural destruction caused by severe inflammation.

The present study had several limitations. First, the aforementioned selection bias was present owing to the pathological inclusion criteria. Furthermore, this was a single-center, retrospective study; hence, all the inherent biases of retrospective analysis were inevitable.

In conclusion, in the differential diagnosis of diseases affecting the LNs, fever or pain, age range of 20-32 years, ineffective empirical treatment, increased CRP, loose conglomeration, unilateral, and non-abnormal vascular patterns could be considered independent predictors for differentiating KFD from NSRL. KFD identification enables preventing misdiagnosis of cases. Careful attention should be paid to the patient's medical history during ultrasonic examination.

CONFLICT OF INTEREST DISCLOSURE STATEMENT

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