

# Pediatric Kikuchi-Fujimoto Disease Diagnosis by Ultrasound-Guided Needle Biopsy

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## Research

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# Abstract

## Background

Kikuchi-Fujimoto disease (KFD) is a rare form of non-malignant and self-limited disease. It is quite susceptible to be misdiagnosed because of a lack of diagnostic guidelines. Lymph node biopsy has shown promising results to confirm KFD pathology.

## Methods

This is a retrospective study of patients younger than 18 years old diagnosed with KFD between May 2016 and May 2020 in Shandong Provincial Hospital. Electronic medical records and pathological data were thoroughly reviewed. Ultrasound-guided core needle biopsy (US-CNB) method was performed in all 20 patients.

## Results

A total of 20 pediatric patients were recruited to the study. There were 14 boys and 6 girls (boy:girl = 2.3:1) with a median age of  $9.1 \pm 3.5$  years. Fever and lymphadenopathy were the most frequent complaints. The duration of fever ranged from 6 days to 70 days, with a median of 24.2 days. Leukopenia (45.0%) was more predominant than leukocytosis (10.0%) in this cohort. Laboratory findings showed elevated levels of serum amyloid A (SAA), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in 13 (13/20, 65.0%), 5 (5/20, 25.0%) and 17 patients (17/20, 85.0%), respectively. Past episodes of EBV infections in 16 patients (16/18, 88.9%) were confirmed by positive EB-specific viral capsid antigen (EB-VCA) and nuclear antigen (EBNA)-specific IgG antibody tests. Elevated IgE levels were also detected in 9 patients (9/16, 56.3%). The sizes of lymph node swelling ranged from 15–34 mm in long diameter with a median of 23.2 mm. The biopsy sites were mostly selected in the left cervical lymph node (10/20, 50.0%). The histopathological subtype analysis revealed proliferative type (4/20, 20.0%), necrotizing type (13/20, 65.0%), and xanthomatous type (3/20, 15%) of lymphadenopathy. Immunohistochemical staining showed that the infiltrated histiocytes were positive for CD163 (7/20, 35.0%), CD68 (15/20, 75.0%), CD123 (6/15, 40.0%) and myeloperoxidase (14/20, 70.0%). Corticosteroid therapy remained effective. Patients were followed up for 1 to 4.5 years. All patients had a good prognosis. Recurrence occurred in 3 patients (3/20, 15.0%).

## Conclusion

Diagnosis of KFD depends on pathological and immunohistochemical examinations. US-CNB can serve as a primary pathological diagnostic method for children and young adult patients.

# Background

Kikuchi-Fujimoto disease (KFD), also called histiocytic necrotizing lymphadenitis, is typically a non-malignant and self-limited disorder of unknown etiology that mainly occurs in children and young adults, especially women [1]. The most common clinical manifestations of KFD include cervical lymphadenopathy accompanied by hepatosplenomegaly, leukopenia, rash, mild fever, and night sweats. While uncommon symptoms include nausea, weight loss, vomiting, and sore throat. Interestingly, clinical and laboratory findings of KFD are non-specific in most cases. Hence, early diagnosis is crucial not only to treat the KFD in a timely manner but also to reduce extensive examinations related to suspected malignant lymphomas, infection-related diseases, or autoimmune diseases. Diagnosis of KFD depends on pathological examinations and biopsy of enlarged and inflamed lymph nodes. In order to perform lymph biopsy, three standard diagnostic methods, namely ultrasound-guided fine-needle aspiration cytology (US-FNAC), ultrasound-guided core needle biopsy (US-CNB), and excisional biopsy are routinely practiced in clinics [2]. With the development of interventional ultrasound technologies, the US-CNB technique has been more commonly applied for the qualitative diagnosis of lymphadenopathy in adults [3]. However, the diagnostic applications of the US-CNB method have not been optimized for pediatric patients. Here, we demonstrated the precise diagnosis of KFD in 20 pediatric patients using the US-CNB technique. All the clinical manifestations, laboratory results, and the findings from histopathological examinations of these patients were thoroughly reviewed before and after the treatment. Therefore, this case study suggests the suitability of US-CNB application in pediatric KFD patients for a rapid and conclusive diagnosis of the disease.

## Methods

### Case selection

This is a retrospective study of patients younger than 18 years old who were diagnosed with KFD between May 2016 and May 2020. The study protocol was approved by the Ethics Committee of Shandong Provincial Hospital, affiliated with the Shandong First Medical University, Jinan, Shandong, China. The written informed consents were obtained from the legal guardians of the participants. After carefully screening the medical history, laboratory results, and pathological findings, 20 cases were finally enrolled for the study. Patient demographics, including the age, gender, clinical feature, laboratory findings, pathologic characteristics and immunohistochemical analysis, treatment, and follow-up reports, were collected for systematic analyses. All data are presented as the Mean  $\pm$  SD as indicated in the text.

### Biopsy Procedures

All 20 patients agreed to undertake the US-CNB-mediated lymph node diagnosis with their signed informed consents. Patients were routinely examined for blood coagulation function and platelet counts. Ultrasonography was used to monitor the size and texture of lymph nodes and their delineation against

the adjacent tissues. Routine monitoring of the lymphatic system was performed to avoid damage to major blood vessels and nerves. Local anesthesia with 2% lidocaine was applied prior to the biopsy procedure. A 16 or 18-gauge automated core biopsy needle with the free-hand technique was used to collect two or three specimens from the affected nodes. The specimens were then stored in the fixative solution overnight for pathological examinations. The patient was observed for 30 minutes after the surgery. In case the patient did not present any notable complications, such as hematoma, bleeding, infection, severe pain, and nerve injury signs, the patient was allowed to leave. Designated pathological and immunohistochemical examinations were performed for each case for the diagnosis of KFD.

## Results

### Clinical characteristics of KFD patients

A total of 20 pediatric patients were enrolled for this study. There were 14 boys and 6 girls (boy: girl = 2.3:1) with a median age of  $9.1 \pm 3.5$  years, and age ranged from 2 to 14 years. Fever and lymphadenopathy were the most common complaints of all patients. Ten patients (50.0%) complained of fever only of three different patterns, including remittent, continued, and intermittent fever. The other ten patients (50.0%) reportedly suffered from both fever and lymphadenopathy. The duration of fever ranged from 6 days to 70 days with a median of  $24.2 \pm 14.4$  days. In these patients, the most frequently involved site was the bilateral cervical lymph node (45.0% of the patients). Notably, all the patients were initially diagnosed with multiple types of diseases, including fever of unknown origin (50%), lymphadenitis (35.0%), sepsis (5.0%), and Epstein-Barr virus (EBV) infection (5.0%) at admission. Interestingly, only one patient (5.0%) was suspected of KFD. Taken together, these findings suggest that the rates of misdiagnoses were relatively high for KFD.

### Laboratory findings

Leukopenia (45.0%) was more prominent than leukocytosis (10.0%) in this cohort of 20 cases. Serum inflammatory tests, such as the levels of serum amyloid A (SAA), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) revealed elevated levels in 13 (13/20, 65.0%), 5 (5/20, 25.0%) and 17 patients (17/20, 85.0%), respectively. Moreover, serum levels of lactate dehydrogenase (LDH), antistreptolysin O (ASO), and ferritin were also elevated in 16 (16/17, 94.1%), 1 (1/17, 5.9%), and 5 patients (5/15, 33.3%), respectively. Furthermore, the liver function tests exhibited abnormally high aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in 38.5% (8/18) and 33.3% (6/18) of cases, respectively. In addition, past EBV infections in 16 patients (16/18, 88.9%) were detected by positive EBV-specific viral capsid antigen (EB-VCA) and nuclear antigen (EB-NA) IgG antibody tests. Interestingly, *Pseudomonas aeruginosa* appeared in the sputum culture of one patient, and elevated IgE levels were confirmed in 9 patients (9/16, 56.3%). Also, blood culture, cerebrospinal fluid (CSF) routine, bone marrow (BM) morphology examination was subsequently performed and tested negative in some patients. All detailed pathological data are presented in **Table 1**.

**Table 1 Laboratory findings of Kikuchi Fujimoto disease in 20 children.**

Positive Findings	N (%)	Negative Findings	N (%)
Leukopenia(<4x10 <sup>9</sup> )	9/20 (45.0%)	Blood Culture	0/17
Neutropenia(<1.5x10 <sup>9</sup> )	7/20 (35.0%)	Cerebrospinal Fluid Routine	0/2
Leukocytosis(>10x10 <sup>9</sup> )	2/20 (10.0%)	Bone Marrow Morphology	0/17
SAA >10mg/L	13/20(65.0%)	TB-PPD	0/14
CRP >8mg/L	5/20(25.0%)	Mycoplasma RNA	0/19
PCT>0.05mg/L	0/16(0.0%)	TB-IGRA	0/19
FER >336ng/L	5/15(33.3%)	G+GM	0/12
ASO >200KU/L	1/17(5.9%)	ANA	0/15
ESR >15mm/h	17/20(85.0%)		
Sputum Culture	1/6(16.7%)		
EBV-CA IgG $\geq$ 20	16/18(88.9%)		
EBV-NA IgG $\geq$ 5	16/18(88.9%)		
EB-DNA $\geq$ 5000copies	1/20(5.0%)		
Mycoplasma IgM	4/19(21.1%)		
LDH>250U/L	16/17(94.1%)		
AST>40U/L	8/18(38.5%)		
ALT>50U/L	6/18(33.3%)		
Elevated IgE	9/16(56.3%)		

SAA: serum amyloid A; CRP: C-reactive protein; PCT: procalcitonin; ESR: erythrocyte sedimentation rate;; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; TB-PPD: purified protein derivative of tuberculin; ANA: anti-nuclear antibody.

### Pathological characteristics and immunohistochemical (IHC) analysis

The amounts of acquired specimens were sufficient enough for histopathological diagnosis, and the satisfaction rate of sampling was 100.0% (20/20) All patients had no obvious discomfort and complications. The sizes of lymph node swelling ranged from 15 mm to 34 mm in long diameter with a median of 23.2 mm, and 6-15mm in short diameter with a median of 9.6 mm. The most predominant biopsy sites were the left cervical lymph node (10/20, 50.0%), while other examined sites included the right submaxillary lymph node (1/20, 5.0%), the right inguinal lymph node (1/20, 5.0%), and the right cervical lymph node (8/20, 40.0%). Histopathological features showed extensive apoptosis and

degeneration of lymphoid cells with coagulative necrosis and karyorrhetic debris and highly infiltrated macrophages, lymphocytes, crescent histiocytes, and monocytes in the affected lymph nodes. Based on Kuo's histopathological definition of KFD [4], the histopathological subtype analysis exhibited proliferative type (4/20, 20.0%), necrotizing type (13/20 65.0%), and xanthomatous type (3/20, 15.0%) of lymph nodes in these patients. IHC staining showed that the infiltrated histiocytes were positive for the immune-modulatory markers like CD163 (7/20,35.0%), CD68 (15/20, 75.0%), CD123 (6/15, 40.0%), myeloperoxidase (14/20,70.0%). All the detailed data are presented in **Table 2**.

**Table 2 Pathological immunohistochemical characteristics in 20 children.**

Parameters	N (%)
Sites of US-CNB	
Right submaxillary lymph node	1/20 (5.0%)
Right Inguinal lymph node	1/20 (5.0%)
Right cervical lymph node	8/20 (40.0%)
Left cervical lymph node	10/20 (50.0%)
Diameter of the lymph node	
Long Diameter (mm)	23.2±5.8
Short Diameter (mm)	9.6±2.6
Pathological type	
Proliferative type	4/20(20.0%)
Necrotizing type	13/20(65.0%)
Xanthomatous type	3/20(15%)
Immunohistochemical staining	
CD163	7/20 (35.0%)
CD68	15/20 (75.0%)
CD123	6/15(40.0%)
MPO	14/20 (70.0%)

### Treatment and follow-up

Seven patients (46.7%) were misdiagnosed with an infectious disease and subsequently received combination antibiotic treatments, including cephalosporin and penicillin, before pathological diagnosis.

Additionally, all patients were treated with nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen and acetaminophen. Seven patients recovered without any specific therapy, as the fever spontaneously disappeared. While other thirteen patients recovered after receiving the low-dose dexamethasone or methylprednisolone for 1-4 weeks. Patients were followed up for 1 to 4.5 years. All patients had a good prognosis. None of the patients developed systemic lupus erythematosus (SLE) or malignant lymphoma during the follow-up period. Unfortunately, recurrence occurred in 3 patients (3/20, 15.0%) after six months to one year from the first episode. Histopathological diagnosis to prove recurrence was performed in one patient by excisional biopsy while the remaining two patients had a clinical recurrence, and corticosteroids therapy remained effective for them.

## Discussion

The prevalence of KFD has been found to be associated with ethnicity, age, and gender. KFD onset has a genetic susceptibility, as genetic factors like certain human leukocyte antigen (HLA) class II genes are more commonly found in Asian populations compared to Caucasians [5]. Although young adults, especially females (3–4:1 ratio), of Asian ancestry, are predominantly affected by KFD, however, studies suggest that this trend exists worldwide [6, 7]. Notably, in the case of pediatric patients, the male to female ratio has been found to be reversed with the male predominance. In this study, the youngest KFD patient was just 20 months old. The male to female ratio was 2.3:1 in this cohort of KFD patients, which was consistent with previous reports [8, 9].

The etiology and pathogenesis of KFD remained unclear. Autoimmune and infectious diseases have been related to trigger KFD onset. Some of the most common and fatal viral infections, such as EBV, herpes viruses, cytomegalovirus (CMV), and human immunodeficiency virus (HIV) infections, have been implicated in the etiology of KFD. Although, none of these viral diseases have been found to be consistently associated with the KFD [5]. In this study, most patients had a history of EBV infection. But there was no effective treatment against EBV infection. Additionally, IgE levels were significantly higher in 9 patients, indicating hyperimmune reaction that might have been initiated during the process of infection.

Accurate diagnosis of KFD is imperative to prevent the adverse effects of unwarranted diagnostic procedures and inappropriate treatments [10]. Fever and lymph node enlargement are the typical clinical signs of KFD. Laboratory findings are usually non-specific and cannot be used as the conclusive diagnostic basis but can help distinguish KFD from other diseases. In the case of children with long-term fever of unknown origin with no clear infection foci and obvious superficial lymphadenectasis, if the antibiotic treatment remains ineffective, lymph node biopsy should be immediately performed to examine the possibility of KFD.

US-CNB can be applied to superficial lymph nodes in all parts of the body, and pathological diagnosis can be obtained in most cases with enough amounts of specimens. The enlarged lymph nodes, surrounding tissues, and puncture needles can be clearly monitored by ultrasound imaging, and the biopsy material

can be collected repeatedly without damaging nearby large vessels and nerves. Therefore, the US-CNB method is safe, inexpensive, highly sensitive, and specific for lymph node biopsy tests. Compared to surgical procedures, the US-CNB undertaking patients suffer from less injury pain, recover faster and experience less cost burden of the diagnosis. However, in many instances, diagnosis of KFD cannot be made with certainty based on a small amount of specimen. In such instances, a larger amount of biopsy samples should be requested. A generous incisional or excisional biopsy can offer an optimal amount of specimen for KFD diagnosis.

To the best of our knowledge, this was the first study to apply US-CNB in the diagnosis of pediatric KFD in a cohort of 20 patients. However, the study suffers from certain limitations, which should be considered during any future application of this method. First, the small sample size might induce bias in the interpretation of diagnostic accuracy. We will compare the effects of US-FNAC, US-CNB, and the excisional biopsy in future studies with statistically larger cohorts. Second, US-CNB under local anesthesia was found to be safe and effective. This procedure was easy to perform in this study since most participants were either school-goers or young adults who could clearly follow the instructions and cooperate with doctors. However, the US-CNB method may not be suitable for pre-school children or infants.

So far, there are still no specific guidelines for KFD diagnosis. The treatment strategies are mainly symptomatic to relieve the discomforts of the patient, usually with the administration of oral antipyretic drugs and enough rest. Temporary courses of NSAIDs and steroids are also frequently applied [11]. The application of hydroxychloroquine may be considered as an alternative agent to corticosteroids, considering the toxicities of steroids [9]. Notably, the time and dosage of corticosteroids are still not clearly defined. In this study, corticosteroids were administered for 1–4 weeks at lower dosages (dexamethasone, 0.1-0.2mg/Kg; methylprednisolone, 1-2mg/Kg). Fever was significantly relieved within a short period of time, and gradual shrinkage of lymph nodes was readily observed. Most patients showed a good prognosis and lower recurrence rate. However, previous reports suggest that the recurrence rates may range from 3–15% in some cases [12–13].

## Conclusions

The clinical manifestations and laboratory examinations of KFD might be non-specific, leading to unnecessary and aggressive therapy. For patients suspected of KFD, lymph node biopsy should be seriously considered at the initial diagnosis. Furthermore, we demonstrated for the first time that US-CNB could be used as a primary pathological diagnostic method for children but might not be suitable for infants.

## Abbreviations

KFD

Kikuchi-Fujimoto disease; US-CNB:ultrasound-guided core needle biopsy; US-FNAC:ultrasound-guided fine-needle aspiration cytology; SAA:serum amyloid A; CRP:C-reactive protein; ESR:erythrocyte sedimentation rate; AST:aspartate aminotransferase; ALT:alanine aminotransferase; EB-VCA:EB-specific viral capsid antigen; EBNA:EB-specific nuclear antigen; LDH:lactate dehydrogenase; ANA:anti-nuclear antibody; TB-PPD:purified protein derivative of tuberculin; NSAIDs:nonsteroidal anti-inflammatory drugs; SLE:systemic lupus erythematosus

## Declarations

### Ethics approval and consent to participate

The current study was approved by the Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University.

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on request.

### Competing interests

The authors declare that they have no competing interests.

### Funding

NO

### Authors' contributions

LY designed the study and wrote the original draft. PM, GCY and LFQ collected the data, YJ and DN analyzed the patient data. CX designed the study and made critical revisions of the article. All authors read and approved the final manuscript.

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