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Case Report



# Kikuchi-Fujimoto Disease Mimicking Mesenteric Lymphadenitis in Children: A Case Report and Systematic Review

**Gyeongseo Jeon**,[1,*] **Si-Hwa Gwag**,[1,*] **Young June Choe**,[1] **Saelin Oh**,[2] **Jun Eun Park**[1]

[1]Department of Pediatrics, Korea University Anam Hospital, Seoul, the Republic of Korea
[2]Department of Radiology, Korea University Anam Hospital, Seoul, the Republic of Korea



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**Correspondence to**
**Young June Choe**
Department of Pediatrics, Korea University Anam Hospital, 73 Goryeodae-ro, Seongbuk-gu, Seoul 02841, the Republic of Korea.
Email: choey@korea.ac.kr

*Gyeongseo Jeon and Si-Hwa Gwag contributed equally to the manuscript.



**ORCID iDs**
Gyeongseo Jeon
https://orcid.org/0000-0002-8549-1114
Si-Hwa Gwag
https://orcid.org/0000-0001-6313-2551
Young June Choe
https://orcid.org/0000-0003-2733-0715
Saelin Oh
https://orcid.org/0000-0002-3815-5599
Jun Eun Park
https://orcid.org/0000-0003-4292-3500

**Conflict of Interest**
No potential conflict of interest relevant to this article was reported.

## ABSTRACT

Kikuchi-Fujimoto disease (KFD) is an acute febrile disease that mainly involves histiocytic necrotizing lymphadenitis in children and young adults. Diagnosis of KFD is even more difficult if image-guided percutaneous biopsy is technically challenging. We present a case of clinically diagnosed KFD in an 11-year-old boy who presented with fever, abdominal pain, and mesenteric lymphadenopathy, resulting in a diagnostic challenge. Additionally, we conducted a systematic review, and our goal was to describe the spectrum of disease, therapy, and outcomes. We identified 15 cases of KFD with symptoms that mimicked mesenteric lymphadenitis. Reports from the Americas, Europe, and Asia were also included. Most patients were male, exhibited leukopenia and elevated inflammatory markers, and recovered without significant sequelae or complications. A high index of suspicion of KFD should be maintained in children presenting with prolonged fever and unusual manifestations, such as mesenteric lymphadenitis.

**Keywords:** Lymphadenitis; Lymphadenopathy; Children; Young adults

## INTRODUCTION

Kikuchi-Fujimoto disease (KFD) is an acute febrile disease. It mainly involves histiocytic necrotizing lymphadenitis in children and young adults.[1] KFD is observed in all ethnic groups and countries, with the highest incidence in the Asian population. Although the diagnosis of KFD is generally not difficult, it is challenging in cases of extra-cervical lymphadenopathy lacking characteristic cervical lymphadenopathy.[2] Diagnosis of KFD is even more difficult if image-guided percutaneous biopsy is technically challenging.

Herein, we report a clinically diagnosed case of KFD in an 11-year-old boy who presented with mesenteric lymphadenopathy in addition to fever and abdominal pain, leading to a diagnostic challenge. We also conducted a systematic review to describe the spectrum of the disease, therapy, and outcomes in patients with KFD and mesenteric lymphadenopathy. This study was approved by the Institutional Review Board (IRB) of Korea University Anam Hospital (IRB No. 2022AN0325).

**Author Contributions**

Conceptualization: Jeon G, Gwag SH, Choe YJ; Data curation: Jeon G, Choe YJ; Investigation: Jeon G, Gwag SH; Methodology: Park JE; Project administration: Park JE; Resources: Gwag SH, Oh S; Supervision: Oh S, Park JE, Choe YJ; Validation: Oh S; Visualization: Oh S; Writing - original draft: Jeon G, Gwag SH, Choe YJ; Writing - review & editing: Choe YJ.

## CASE

The patient was an 11-year-old boy with no medical history who presented with 2 weeks of fever above 38°C and 1 week of epigastric pain. He had experienced nausea and vomiting 2 days before admission. He had a sore throat, conjunctival injection, and right cervical lymphadenopathy 2 weeks before admission; however, these symptoms subsided within 2 days. His nausea was alleviated by vomiting, and he did not have diarrhea or constipation. He lost his appetite and consequently lost 5 kg within 2 weeks. He visited a local hospital, and oral medication was administered for the symptoms; however, his fever did not subside, and he was admitted for evaluation of the cause for his persistent fever.

On admission, his mental status was alert, blood pressure was 111/62 mmHg, pulse rate was 102 beats/min, and respiratory rate was 22 breaths/min, and body temperature was 39.1°C. His height was 150 cm (50–75th percentile) and body weight was 42 kg (25–50th percentile). He had epigastric pain and tenderness, no palpable abdominal mass, and no palpable cervical or axillary lymph nodes. His abdomen was soft and flat, and bowel sounds were normal. Laboratory investigations (**Table 1**) revealed hemoglobin levels 13.0 g/dL, white blood cell count (WBC) 3,230/μL (neutrophil 59.8%, lymphocyte 35.8%, eosinophil 0.2%), platelet count 256,000/mL, blood urea nitrogen/creatinine 13.0/0.62 mg/dL, aspartate transaminase (AST) 61 IU/L, alanine aminotransferase (ALT) 46 IU/L, erythrocyte sedimentation rate (ESR) 44 mm/hr (normal range: ≤15 mm/hr), C-reactive protein (CRP) 23.11 mg/L (normal range: ≤5.0 mg/L), lactate

**Table 1.** Laboratory findings of the presented case-patient

| Tests | Unit | First admission | Second admission | Reference range |
|---|---|---|---|---|
| Hemoglobin | g/dL | 13 | 13 | 12–15 |
| Hematocrit | % | 38.3 | 37.4 | 34–43 |
| WBC count | ×10³/μL | 3.23 | 4.29 | 4.5–13.5 |
| Platelet count | ×10³/μL | 256 | 346 | 150–400 |
| WBC differential percentage | % | | | |
| Neutrophil | | 59.8 | 59.1 | 35–75 |
| Lymphocyte | | 35.8 | 36.6 | 13–48 |
| Eosinophil | | 0.2 | 0.5 | 0–7 |
| Na | mmol/L | 134 | 134 | 136–146 |
| K | mmol/L | 4 | 4.4 | 3.5–5.1 |
| Cl | mmol/L | 100 | 100 | 98–107 |
| AST | IU/L | 61 | 58 | 3–45 |
| ALT | IU/L | 46 | 46 | 3–45 |
| BUN | mg/dL | 13 | 13.4 | 7–23 |
| Creatinine | mg/dL | 0.62 | 0.59 | 0.7–1.44 |
| ESR | mm/hr | 44 | 34 | 0–15 |
| CRP | mg/L | 23.11 | 14.92 | 0–5 |
| LDH | IU/L | 1,716 | 1,956 | 238–422 |
| CK | IU/L | 55 | 51 | 43–198 |
| NT-proBNP | pg/mL | 75.8 | 9.59 | 0–125 |
| CK-MB | ng/mL | 0.359 | 0.371 | 0–4.87 |
| TSH | uIU/mL | - | 1.36 | 0.17–4.05 |
| Free T4 | ng/dL | - | 1.08 | 0.89–1.79 |
| T3 | ng/dL | - | 72.5 | 78–182 |
| C3 | mg/dL | 139 | - | 90–180 |
| C4 | mg/dL | 69.9 | - | 16–49 |
| CH50 | U/mL | >60 | - | 32–58 |

Abbreviations: WBC, white blood cell; AST, aspartate transaminase; ALT, alanine transaminase; BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate; CRP, C-reactive peptide; LDH, lactate dehydrogenase; CK, creatine kinase; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; CK-MB, creatine kinase-MB; TSH, thyroid-stimulating hormone; T4, thyroxine; T3, triiodothyronine; C3, complement component 3; C4, complement component 4; CH, hemolytic complement.


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dehydrogenase (LDH) 1,716 IU/L (normal range: 238–422 IU/L). Other laboratory examinations involving cardiac markers, including N terminal brain natriuretic peptides, and creatine kinase-MB were within normal range. Peripheral blood cell morphology showed mild leukopenia with left-shifted maturation. Urinalysis, stool culture, stool multiplex pathogen panels for acute viral and bacterial gastroenteritis showed no evidence of infection.

Autoimmune laboratory results were negative; C3 (139.0 mg/dL), C4 (69.9 mg/dL), CH50 (>60 U/mL), anti-ds-DNA (<2.5 IU/mL), antineutrophil cytoplasmic antibody, and fluorescent antinuclear antibody were negative. Epstein-Barr virus (EBV) viral capsid antigen (VCA) immunoglobulin (Ig)G and EBV nuclear antigen IgG were positive, whereas EBV VCA IgM was negative. Mycoplasma IgM levels were within the normal range. Radiological studies of the chest and abdominal X-rays were nonspecific. Additional abdominal ultrasonography revealed no remarkable findings. According to these results, it seems probable that the patient had a viral infection, particularly past or apparent EBV infection. Symptomatic treatment was initiated, and antipyretic drugs such as acetaminophen and ibuprofen were administered. The patient's clinical symptoms improved, and fever subsided; he was discharged on the 5th day of admission.

After 6 days, he was readmitted for recurrent fever, abdominal pain, and vomiting. Abdominal pain was aggravated after eating food, and persistent vomiting caused the patient to not drink well. Urination decreased by approximately 50%; however, the patient did not experience diarrhea. His blood pressure was 97/55 mmHg, heart rate was 109 beats/min, respiratory rate was 20 breaths/min, and body temperature was 37.7°C; the peak fever after admission was 39.3°C. He had abdominal tenderness; however, other physical examination findings were unremarkable. On follow-up blood tests, the results were as follows: WBC 4,290/μL (neutrophils 59.1%, lymphocytes 36.6%, eosinophils 0.5%), AST 58 IU/L, ALT 46 IU/L, ESR 34 mm/h, CRP 14.92 mg/L, and LDH 1,956 IU/L. Laboratory tests for other infections, including toxoplasma, cytomegalovirus and hepatitis A, B, and C, were negative. Thyroid function test and fecal calprotectin test results were normal. Abdominal radiography revealed a mild ileus. Abdominal ultrasonography revealed multiple enlarged, homogeneously hypoechoic lymph nodes along the mesentery, measuring up to 1.0 cm on the short axis. Abdominal computed tomography (CT) (**Fig. 1**) showed enlarged lymph nodes along the mesentery, both external iliac areas, and inguinal areas. The enlarged lymph nodes were homogeneously hyperdense, with perinodal infiltration. There were no significant pathological findings on the bone scan, and acetaminophen and ibuprofen were ineffective at the time. Switching medication to naproxen alleviated fever. Based on the patient's CT findings and clinical symptoms, he was treated for Kikuchi Fujimoto disease. He was administered 12 mg of methylprednisolone thrice a day. The mesenteric lymphadenopathy lesion was not accessible for image-guided percutaneous biopsy; therefore, we decided to withhold laparoscopic biopsy and follow the clinical response post steroid treatment. All clinical symptoms improved dramatically on the day of methylprednisolone administration. His abdominal pain improved, and he no longer experienced vomiting. He was followed up at the outpatient clinic with a tuberculin skin test 2 weeks after discontinuation of steroid (negative), and serial complete blood counts were performed at the oncology clinic. No significant complications were noted.

## DISCUSSION

We searched PubMed for eligible clinical reports on KFD and mesenteric lymphadenitis published on June 5, 2022. Titles, abstracts, and full-length texts in English were screened


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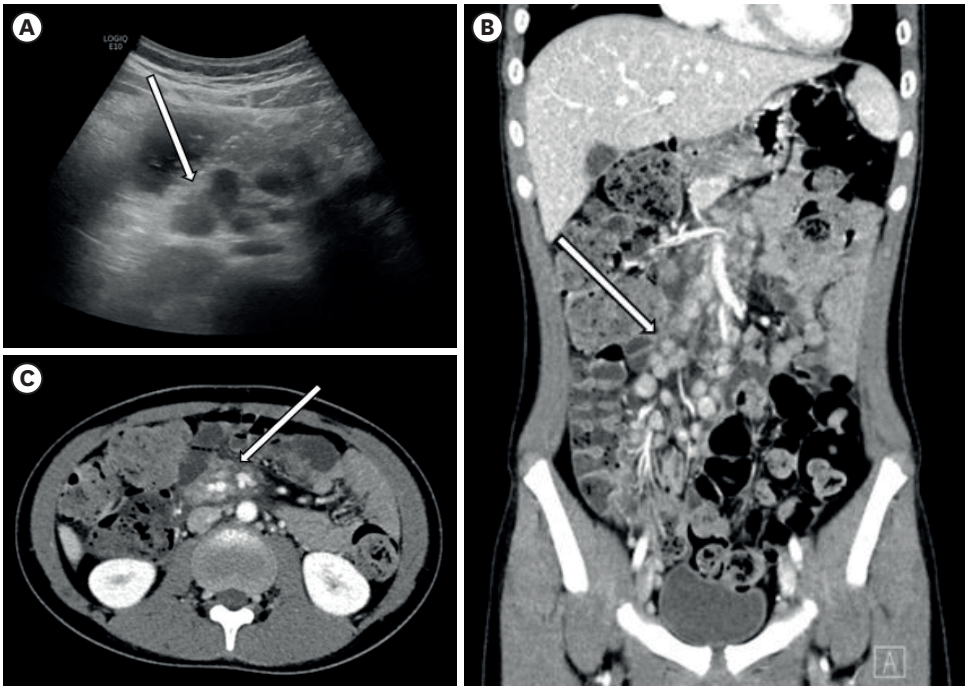


**Fig. 1.** Abdominal ultrasound imaging and computed tomography of the patient.
(A) Multiple enlarged lymph nodes along the mesentery (arrow) are hypoechoic on abdominal ultrasound, (B, C) homogeneously hyperdense with perinodal infiltration on abdominal computed tomography (arrow).

for eligible articles using "Kikuchi" as a Medical Subject Headings search term AND "mesenteric" in all search fields. Duplicate and non-clinical publications were excluded. We extracted and collated relevant data in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Specifically, we recorded the age, sex, year of report, geographic site of study, treatment, and outcome. We investigated 15 case reports that met our inclusion criteria (**Fig. 2**). The publications included five pediatric cases, and the remaining were adult cases. The geographic distribution of the study included four patients in India,[3-6] three in Japan,[7-9] two in the UK,[10,11] two in the USA,[12,13] and one in South Korea,[14]

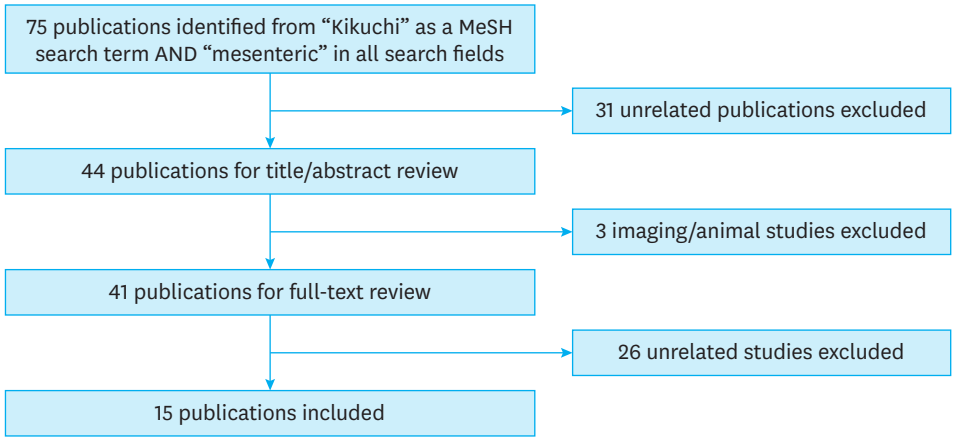


**Fig. 2.** Results of literature search and identification of studies according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses.
Abbreviation: MeSH, Medical Subject Headings.


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China,[15] Australia,[16] and Switzerland[17] each. Only 2 patients were female (**Table 2**).[7,10] None of the reported patients had underlying comorbidities, except for one patient who had a history of laparotomy in childhood for unknown reasons,[10] and the other had a history of a month-long episode of fever of unknown origin.[9] All patients, except one who complained of back pain and diarrhea,[13] had fever and abdominal pain in common. The duration of the fever before presentation ranged from 1 to 2 months. Common clinical manifestations were gastrointestinal symptoms such as nausea, vomiting, and diarrhea. The patients also complained of loss of appetite and weight. A classical presentation of KFD is cervical lymphadenopathy, which is rarely localized to the mesentery. Four patients had peripheral lymph node involvement in the cervical,[3,7,15] inguinal,[12,15] and axillary areas.[15] Leukocytopenia was observed in patients from four cases,[7,13,16,17] and the level of inflammatory markers was elevated in most cases. Although most patients underwent mesenteric lymph node biopsy either intraoperatively or laparoscopically, patients with accessible peripheral lymph nodes underwent biopsies performed at other sites. One patient had a cervical lymph node biopsy,[3] another had a submandibular lymph node biopsy,[7] and the other had an inguinal lymph node biopsy,[12] which resulted in KFD from the pathology review. Ten patients underwent laparotomy, and steroid therapy was performed in 5 cases. One patient developed a stitch

**Table 2.** Systematic review of reported cases of Kikuchi-Fujimoto disease in children presenting mesenteric lymphanopathy

| Author | Year of report | Country | Case-patient | | Clinical findings | Investigations | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Age | Sex | Accompanying symptoms and signs | WBC | Inflammatory marker | Treatment | Outcome |
| McLoughlin et al.[10] | 1988 | UK | 29 | Female | Malaise, fever, and vomiting | Normal | None | Laparotomy | Improved |
| Kita et al.[9] | 1997 | Japan | 27 | Male | Malaise and fatigue | Normal | Elevated | Laparotomy, Antibiotics | Fever continued for 1 month after operation, Improved after 9 months after operation |
| Min et al.[14] | 2007 | South Korea | 11 | Male | Nausea and vomiting | Elevated | Elevated | Appendectomy and lymphadenectomy | Improved, discharged 3 days after surgery |
| Teranishi et al.[8] | 2008 | Japan | 9 | Male | Lethargy | Elevated | Elevated | Antibiotics, lymphadenectomy and steroid | Improved after steroid therapy, discharged on 29th hospital day |
| Vijayaraghavan et al.[6] | 2011 | India | Teenager | Male | None | Elevated | Elevated | Appendectomy, lymphadenectomy, Wedge biopsy of the liver and Steroid | Improved after steroid therapy, discharged |
| Shrestha et al.[11] | 2013 | UK | 26 | Male | None | Elevated | Elevated | Lymphadenectomy and radical right hemicolectomy | Discharged on 10th postoperative day |
| Aneja et al.[3] | 2014 | India | 19 | Male | Polyarthralgia | Normal | Elevated | Antibiotics and anti-tuberculosis drugs | Improved |
| Noda et al.[7] | 2014 | Japan | 29 | Female | Loss of appetite and sore throat | Decreased | Elevated | Antibiotics | Improved |
| Patel et al.[12] | 2014 | USA | 29 | Male | Nausea, vomiting, diarrhea, night sweats, myalgia and weight loss | Normal | Elevated | Antibiotics | Improved |
| Anikhindi et al.[5] | 2017 | India | 32 | Male | Weight loss and decreased appetite | Normal | Elevated | Laparotomy and steroid | Improved |
| Pandey et al.[4] | 2017 | India | 30 | Male | Vomiting | Elevated | Elevated | Appendectomy and lymphadenectomy | Improved |
| Hua et al.[15] | 2021 | China | 14 | Male | Vomiting and diarrhea | Normal | Elevated | Antibiotics, appendectomy, lymphadenectomy and steroid | Improved after steroid therapy |
| Miller et al.[16] | 2021 | Australia | 7 | Male | None | Decreased | Elevated | Laparotomy | Improved |
| Fiori et al.[17] | 2022 | Switzerland | 34 | Male | Loss of appetite and fatigue | Decreased | Elevated | Laparoscopic lymph node excision | Improved |
| Rana et al.[13] | 2022 | USA | 24 | Male | Diarrhea, insomnia, anorexia, and weight loss | Decreased | None | Steroid and rituximab | Improved |

Abbreviations: WBC, white blood cell count.


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abscess as a postoperative complication.[6] Three patients spontaneously resolved without surgery or steroids. Only 1 patient experienced recurrence of mesenteric KFD and cervical lymphadenopathy at the first diagnosis.[13]

The diagnosis of KFD in unusual anatomical lesions is challenging, particularly in children who do not fulfil the criteria for cervical lymphadenopathy. We found that most cases of KFD in children who presented with mesenteric lymphadenopathy underwent challenging diagnostic procedures, including laparotomy and antibiotic treatments. In the case described here, we did not suspect KFD readily after the initial presentation, and the diagnosis was further delayed owing to an atypical presentation, thus leading to a delay in treatment. Although KFD is usually a self-limiting disease that does not require disease-specific treatment, continued fever and other constitutional symptoms should be addressed clinically.

Pediatricians occasionally encounter children with prolonged fever and lymphadenopathy in various anatomic lesions. In such cases, suspicion of KFD is often delayed, which can lead to delays in diagnosis and management. Pathological diagnosis is the gold standard for KFD diagnosis; however, it can sometimes be challenging, as in the present case. In Asian countries, with a high prevalence of KFD in children, biopsies are often spared when the diagnosis is made through clinical and radiological assessments. A study from South Korea showed that >60% of KFD diagnoses were made without pathological assessment.[18] However, it is prudent to perform invasive procedures such as laparoscopic or open biopsy in cases that do not respond well to KFD treatment.[19]

A significant proportion of KFD mimicking mesenteric lymphadenopathy occurs in men compared to women, which seems different from the epidemiology of KFD, in general. Leukopenia and elevated inflammation may be the only laboratory manifestations of KFD in these patients; however, radiologic findings can guide the diagnosis of KFD with atypical presentation.[20] Despite these limitations, our case report and systematic review show the clinical magnitude of challenging cases of KFD mimicking mesenteric lymphadenopathy reported globally. The presence of fever and abdominal pain in children and young adults can be mistakenly attributed to other etiologies such as infections or appendicitis. Owing to the elusive nature of presentation, it is prudent to understand why the diagnosis and subsequent treatment of KFD are delayed in such presentations.

A high index of suspicion of KFD should be maintained in children presenting with fever and unusual manifestations, such as mesenteric lymphadenitis. In cases of inaccessible lymphadenopathy lesions, a trial of steroid therapy with cautious monitoring of relapse or complications may be considered for the clinical management of such cases.

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## 요약

기쿠치-후지모토병(Kikuchi-Fujimoto disease, KFD)은 주로 소아 및 젊은 성인에서 발생하는 급성 발열성 질환이며, 주로 조직구증성 괴사성 림프선염을 특징으로 한다. KFD는 조직검사를 통한 병리학적 검증이 어려울 경우 진단이 제한적일 수 있다. 본 논문에서는 복통과 복강내 림프선염 등으로 진단이 늦어졌던 11세 남아의 사례를 보고한다. 추가로 체계적인 문헌고찰을 수행하였으며, KFD 질병의 범위, 치료 및 예후를 기술하고자 하였다. 본 체계적 문헌고찰에서는 미국, 유럽 및 아시아에서 출간된 장관막 림프선염과 유사한 증상을 보이는 KFD 증례 15건을 분석하였다. 대부분의 환자는 남성이었으며, 백혈구 감소증(leukopenia)과 염증 표지자 상승이 나타났으며, 대부분 중대한 후유증이나 합병증 없이 회복되었다. 복강내 림프선염을 동반한 발열을 주소로 내원하는 소아에 대해서 KFD 가능성을 검토하는 것이 필요할 수 있다.



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