OXFORD

Oxford Medical Case Reports, 2025, **1**, 26–29
https://doi.org/10.1093/omcr/omae172
Case Report

Kikuchi-Fujimoto disease: 6 years old boy rare case in Syria

Baseel Tawfik Daoo[1], Shahd Alhayek[2], Dana Alakhrass[3], Mosa Shibani [2,4,*], Mohammad Samih Khallouf[1]

[1]Department of Pediatrics at Al-Baath Hospital, Al-Baath University, Al-Wehda, Homs, Syria
[2]Faculty of Medicine, Syrian Private University, M5, Al Kiswah, Damascus, Syria
[3]Faculty of Medicine, Al-Baath University, Al-Wehda, Homs, Syria
[4]School of Health and Wellbeing, University of Glasgow, 90 Byres Rd, Glasgow, United Kingdom

*Corresponding author: Faculty of Medicine, Syrian Private University, P.O. Box 36822, Damascus, Syria. E-mail: moosa.shibani@gmail.com

Abstract

Kikuchi-Fujimoto disease (KFD) is a rare condition first identified in Japan in 1972. It typically presents with high fever and lymph node swelling, and may be linked to autoimmune conditions or viral infections. A 6-year-old boy presented with cervical enlargement and recurrent high fever. Physical examination revealed enlarged lymph nodes in the neck, axillary, and inguinal regions, along with hepatosplenomegaly. CT scans confirmed widespread lymphadenopathy, and blood tests showed elevated white blood cell count and C-reactive protein levels. Although lymphoma was suspected, biopsies indicated atypical lymphadenitis. Despite a positive Epstein–Barr virus test, no treatment was effective. Further lymph node biopsies ruled out lymphoma, EBV, and TB, ultimately confirming Kikuchi-Fujimoto Disease.

Keywords: paediatrics; immunology

Introduction

First identified in Japan in 1972 by Kikuchi and Fujimoto [1], Kikuchi-Fujimoto disease (KFD) is a rare, benign, and self-limiting form of idiopathic lymphadenopathy, also known as Histiocytic Necrotizing Lymphadenitis (HNL). The typical onset of symptoms is a high fever combined with lymph node swelling and it may present with different other clinical characteristics such as hepatosplenomegaly, weight loss, loss of appetite, and fatigue [2–4]. The cervical lymph nodes are most frequently affected, followed by the axillary nodes. There is a significant risk of misdiagnosis [5] and other differential diagnoses must be excluded to confirm the illness. In histopathological examination of KFD, there are three different morphological types; each has its unique characteristics [3]. Additionally, KFD might be associated with autoimmune conditions such as Systemic Lupus Erythematosus (SLE), or viral infections, including Epstein–Barr Virus (EBV) and Cytomegalovirus (CMV) [3]. To date, only a single case of KFD has been documented in Syria [6]. Whereas, as of 2021, the wider Middle East region has documented approximately 95 cases. In this case report, we discuss the case of a 6-year-old Syrian-boy who presented with recurrent lymphadenopathy of initially undetermined cause, ultimately leading to a diagnosis of KFD.

Case report

A 6-year-old boy presented with cervical enlargement and recurrent bouts of high fever. Physical examination revealed a mobile lymph node enlargement in the left neck region. It was non-adherent to deeper tissues and elicited discomfort upon palpation. A comparable lymph node was also noted on the right side. Axillary lymph nodes were soft and moveable. Lymph nodes in the inguinal appeared smaller. The spleen was palpable. He had a history of recurrent tonsillitis and allergic symptoms.

A CT scan revealed several axillary lymph node enlargements on both sides, with the largest on the left side measuring 12 × 21 mm and the largest on the right measuring 37 × 20 mm. The largest lymph node in the neck is located on the left medial side, directly in front of the sternocleidomastoid muscle, and measures 21 × 23 mm. The pulmonary parenchymal densities exhibited a hypodensified appearance, accompanied by vascular traces linked to bronchial traces and dilatational modifications of the bronchial branches in the impacted regions. Several lesions were found in the posterior apical segment, the anterior segment, the sinus of the upper lobe, and the superior segment of the lower lobe in the left lung. While in the right lung, there were no indications of interstitial lesions or alveolar abnormalities. Many nodular enlargements that appear suspicious are dispersed throughout the pulmonary aortic septum, the mediastinum space in front of the aortic arch, and the area surrounding the pulmonary umbilicus.

Additionally, numerous homogenous nodular enlargements were observed in the liver's navel as well as along the course of the abdominal aortic branches behind the peritoneum and lateral to the left kidney. The liver measured 12 cm in apical-caudal diameter on the anterior axillary line. The spleen also

Received: June 30, 2024. **Revised:** September 25, 2024. **Accepted:** October 30, 2024

Table 1. Laboratory data.

Parameter	Test 1	Test 2	Reference range
WBC	10 770/mm^3	10 300/mm^3	4500–10 200/mm^3
neutrophils	48.6%	55.8%	Adult: 40–65 Child: 30–50
lymphocytes	43.4%	35.5%	Adult: 25–40 Child: 30–60
Monocytes	4.0%	6.7%	2–8
Eosinophils	3.7%	1%	0–4
Basophils	0.3%	0%	0–1
Erythrocytes	4.19 x10^6/mm^3	4.33 x10^6/mm^3	4.5–6.2
HGB	10.0 g/dl	10.90 g/dl	13–16
Hematocrit	31.2%	34%	40–54
MCHC	32.1 g/dl	32.1%	31–35
MCV	74.5 fl	78.5 fl	78–96
MCH	23.9 pg	25.2 pg	27–32
RDW	7.9 fl	17.3%	11–16
Platelets	310 10^3/mm^3	309 10^3/mm^3	150–450 x10^3/mm^3
CRP	23 mg/L	4.3 mg/L	0–5.0
calcium		8.4 mg/dl	8.5–10.5
Izoniazed calcium		0.98 mmol/l	1.10–1.30
Iron		42 ug/dl	50–145
TIBC		443 ug/dl	110–370
ALP, Alkaline phosphate		259 U/L	Up to 673
Ferritin		29.8 ng/ml	7.0–140
zinc		57 ug/dl	60–110
Immunoglobulin G		759 mg/dl	420–1200
Immunoglobulin A		118 mg/dl	18–160
Immunoglobulin M		402	1–8 years: 45–200
CMV Ab IgG		466 U/ml	Neg: less than 4 Pos: more than 7
CMV Ab IgM		0.315 index	Neg: less than 0.4 Pos: more than 0.5
EBV IgM		8.04 index	negative: up to 0.5, positive: more than 1.0
EBV IgG		128.75 index	negative: up to0.8, positive: more than 1.2

measured 12 cm. Lymphoma was suspected, and it needed further investigations.

An initial blood test revealed a slightly elevated white blood cell count (WBC), and high C-reactive protein (CRP) levels. A low hemoglobin level with a slight decrease in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) were also noted, (Table 1).

In the peripheral blood smear study, the erythrocytes appeared slightly small, but their shape was within normal limits, and there was a slight pigment deficiency. Furthermore, a biopsy from an axillary lymph node showed reactive lymphoid follicles with germinal centers and an increase in the Para cortex with histiocytes and immunoblasts that were focally affected in the architecture. There were no malignant alterations, necrosis, or epithelioid granulomas seen. An immunohistochemistry (IHC) study showed CD30 and CD20 positive scattered immunoblasts. The Antimitochondrial Antibody (AMA) marker was negative. This indicated signs consistent with atypical lymphadenitis, but autoimmune etiology could not be excluded. A 5-day prednisolone course at a dosage of 1–2 mg/kg was prescribed, resulting in a reduction of the lymph node size. However, two weeks later, they were enlarged once more, necessitating further investigation. A Second blood test was ordered, and it revealed a high WBC count with neutrophil predominance, and low HGB with iron deficiency. It also tested positive for EBV IgM and IgG as shown in (Table 1).

Based on these blood results, acyclovir intravenously was prescribed, in addition to iron supplements. Unfortunately, no improvement was observed two weeks later.

After the first treatments were discontinued, an uncommon form of tuberculosis (TB) was suspected. The patient underwent TB medication therapy for six weeks; however, there were no signs of recovery, leading to the cessation of the drugs.

Therefore, for further investigation samples from different lymph nodes were collected. Examination revealed enlargement with mixed lymphoid cells, histiocytes, and partial effacement of the architecture. Areas of necrosis, suggesting a reactive inflammatory response, were also observed. These findings led to the consideration of Kikuchi lymphadenitis as a potential diagnosis.

Immunostaining results revealed Positive markers for CD3 and CD4, with some clusters positive for CD20. Markers for CD15, CD10, CD34, TdT, and CD117 were negative, as were markers for EBV, and strong Ki67 proliferation marker.

These results indicated an absence of malignancy. Although certain cells were labeled with the CD30 marker, they were identified as immunoblasts rather than normal or Hodgkin cells. There was also benign salivary gland tissue.

Given these findings, KFD was ultimately diagnosed.

Discussion

Our patient is a 6-year-old boy who presented with cervical enlargement and recurrent bouts of high fever. Physical examination revealed lymph node enlargements in the neck, axillary, and inguinal regions, as well as an enlarged spleen and liver. A CT scan showed several lymph node enlargements in various parts of the body, and a blood test revealed slightly

elevated white blood cell count and C-reactive protein levels. Lymphoma was suspected, but a biopsy showed signs consistent with atypical lymphadenitis. Later, the patient tested positive for Epstein–Barr virus but no treatment was efficient. Samples from different lymph nodes were collected, the result denied any sign of lymphoma, EBV, or Tb and ultimately it confirmed Kikuchi-Fujimoto Disease.

Kikuchi-Fujimoto disease (KFD) is a rare condition characterized by lymphadenopathy. While it was initially thought to predominantly affect women, more recent studies have shown that KFD can occur in men as well. In pediatric populations, four separate studies conducted at different hospitals between 1992 and 2021 reported male-to-female ratios of 1.4:1, 1.2:1, 1:1, and 1.9:1, respectively [7–10]. These studies collectively involved approximately 252 affected children, suggesting a potentially higher incidence among boys in pediatric cases, a finding supported by earlier research [11].

Kikuchi-Fujimoto disease (KFD) is more commonly observed in individuals from East Asia or those of East Asian descent. The most frequent symptoms include fever and lymphadenopathy, typically affecting the superficial cervical nodes, followed by the axillary and inguinal nodes. Hepatosplenomegaly is also frequently noted in patients with KFD [2, 3]. Other reported symptoms include weight loss, loss of appetite, gastrointestinal complaints, fatigue, headaches, arthralgias, myalgias, rash, and night sweats [4]. Since these symptoms are not specific to KFD, misdiagnosis is common [5]. KFD is often mistaken for lymphoma due to its concerning overlap in symptoms [4]. Similarly, in our case, the patient was initially suspected of having lymphoma, but subsequent blood tests and biopsy results ruled out this diagnosis.

There are numerous differential diagnoses for neck masses and cervical lymphadenopathy, including infectious, inflammatory, neoplastic, vascular, and congenital causes. Viral lymphadenopathy is particularly common, and a variety of viruses should be considered, including Epstein–Barr virus (EBV), cytomegalovirus (CMV), adenovirus, rubella, rhinovirus, and HIV. Bartonella henselae, the causative agent of cat-scratch disease, must also be considered, along with other infectious causes of lymphadenitis, such as toxoplasmosis and fungal infections [12]. Medical imaging offers a quick and non-invasive method for diagnosing certain conditions, though pathological tests are often necessary for confirmation. While no specific radiographic findings can definitively diagnose KFD, imaging can still provide valuable information. A chest X-ray is often part of the routine evaluation for patients presenting with fever and lymphadenopathy of unknown origin [13]. In many cases, magnetic resonance imaging (MRI), positron emission tomography (PET), and neck ultrasonography have been used [11]. In our case, computed tomography (CT) was performed to confirm lymph node enlargement, which is typically useful prior to biopsy. However, CT findings in KFD are usually nonspecific and can resemble those of malignant lymphoma or other forms of lymphadenitis, necessitating further investigation [11].

Excisional lymph node biopsy is the primary method for excluding other diseases and confirming a diagnosis of KFD. Histopathological examination of KFD reveals three distinct morphological types, each with unique characteristics. The most common is the proliferative type, characterized by the proliferation of various lymphoid cells, dendritic cells, and histiocytes, accompanied by active phagocytosis and apoptosis. The necrotic type is identified by areas of necrosis surrounded by cellular components. The xanthomatous type, although less frequently observed, is distinguished by foamy histiocytes surrounding a necrotic area [3]. Recognizing these pathological variations is essential for an accurate diagnosis and to differentiate KFD from other lymphadenopathies [3]. In our case, histopathological examination of the lymph nodes showed partial effacement of the architecture, along with vascular proliferation, histiocytes, mixed lymphoid cells, and areas of necrosis.

The exact etiology of KFD remains unknown, though two predominant theories exist: viral and autoimmune. The viral theory suggests that KFD results from a hyperimmune response in previously exposed individuals, while the autoimmune theory is supported by the observed correlation between KFD and autoimmune disorders [6]. In our case, elevated levels of EBV IgG and IgM indicate that a viral etiology is more likely. KFD typically has a course lasting between 1 to 3 months, though in some cases, it may persist for up to a year [2]. Generally, KFD is a self-limiting disease, and most patients require only a short hospital stay with symptomatic treatment [11].

The primary management strategy for KFD focuses on symptomatic relief and patient support. Antibiotics are generally ineffective, though they may be administered to prevent secondary bacterial infections. Systemic corticosteroids are effective in treating patients with prolonged fever, symptoms lasting more than two weeks, or recurrent disease. In milder cases, nonsteroidal anti-inflammatory drugs (NSAIDs) are usually sufficient to manage fever and lymph node tenderness. Additionally, hydroxychloroquine, either as monotherapy or combined with systemic corticosteroids, has shown effectiveness in treating severe or steroid-resistant KFD [11].

Conflict of interest

The authors declare that they have no competing interests.

Funding

This project did not receive any funding from any agencies in the public, commercial, or non-profit sectors.

Data Availability

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

Ethics approval and consent to participate

The study protocol was approved by the Research Ethics Committee in Al-Baath Hospital. Informed consent was obtained from patient parents prior to participation.

All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Written informed consent was obtained from the patient's guardians for the publication of this case report.

References

1. Kikuchi M. Lymphadenitis showing reticulum cell hyperplasia with nuclear debris and phagocytes. *Acta Hematol Jpn* 1972;**53**: 379–80.

2. Xu S, Sun W, Liu J. Kikuchi-Fujimoto disease: a case report and the evaluation of diagnostic procedures. *BMC Oral Health* 2019;**19**:223. https://doi.org/10.1186/s12903-019-0920-4.
3. AlShieban S, Masuadi E, Alghamdi R. *et al.* Pathological features and clinical characteristics of Kikuchi-Fujimoto disease: a tertiary hospital experience in Riyadh, Saudi Arabia. *Cureus* 2023;**15**:e33683. https://doi.org/10.7759/cureus.33683.
4. Chisholm KM, Bohling SD, Tsuchiya KD. *et al.* A malignant mimicker: features of Kikuchi-Fujimoto disease in the Pediatric population. *Pediatr Dev Pathol* 2022;**25**:538–47. https://doi.org/10.1177/10935266221103882.
5. Menasce LP, Banerjee SS, Edmondson D. *et al.* Histiocytic necrotizing lymphadenitis (Kikuchi–Fujimoto disease): continuing diagnostic difficulties. *Histopathology* 1998;**33**:248–54. https://doi.org/10.1046/j.1365-2559.1998.00469.x.
6. Youssef A, Ali R, Ali K. *et al.* Kikuchi–Fujimoto disease: a case report of a multi-drug resistant, grueling disease. *Oxf Med Case Rep* 2017;**2017**. https://doi.org/10.1093/omcr/omx024.
7. Shen Z, Ling J, Zhu X. *et al.* Macrophage activation syndrome in children with Kikuchi-Fujimoto disease. *Pediatr Rheumatol* 2023;**21**:10. https://doi.org/10.1186/s12969-023-00788-w.
8. Lin Y-C, Huang HH, Nong BR. *et al.* Pediatric Kikuchi-Fujimoto disease: a clinicopathologic study and the therapeutic effects of hydroxychloroquine. *J Microbiol Immunol Infect* 2019;**52**:395–401. https://doi.org/10.1016/j.jmii.2017.08.023.
9. Choi S, Choi HS, Ryu YJ. *et al.* Characterization of Kikuchi-Fujimoto disease in children and risk factors associated with its course. *J Pediatr* 2023;**260**:113515. https://doi.org/10.1016/j.jpeds.2023.113515.
10. Kim TY, Ha K-S, Kim Y. *et al.* Characteristics of Kikuchi–Fujimoto disease in children compared with adults. *Eur J Pediatr* 2014;**173**:111–6. https://doi.org/10.1007/s00431-013-2131-3.
11. Mahajan VK, Sharma V, Sharma N. *et al.* Kikuchi-Fujimoto disease: a comprehensive review. *World J Clin Cases* 2023;**11**:3664–79. https://doi.org/10.12998/wjcc.v11.i16.3664.
12. Singh JM, Shermetaro CB. Kikuchi-Fujimoto disease in Michigan: a rare case report and review of the literature. *Clin Med Insights Ear Nose Throat* 2019;**12**:117955061982868. https://doi.org/10.1177/1179550619828680.
13. Mohseni S, Shojaiefard A, Khorgami Z. *et al.* Peripheral lymphadenopathy: approach and diagnostic tools. *Iran J Med Sci* 2014;**39**:158–70.

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https://doi.org/10.1093/omcr/omae172
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