Case Report

# Kikuchi–Fujimoto disease: A rare cause of cervical lymphadenopathy

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## ABSTRACT

Kikuchi–Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis, is a rare and generally self-limiting disease of uncertain etiology that presents with fever and cervical lymphadenopathy in both the pediatric and adult populations. Here, we present the case of a 5-year-old male who presented with acute onset of fever and cervical lymphadenopathy which was initially diagnosed and managed as staphylococcal lymphadenitis. He underwent an excisional biopsy when symptoms persisted, which confirmed the diagnosis of KFD and was managed conservatively. This case study emphasizes awareness of this entity in the differential diagnosis of fever with persistent lymphadenopathy. Due to its characteristic overlap with other disorders such as tuberculous lymphadenitis, and lymphoma, KFD remains an arduous diagnosis for physicians. Therefore, awareness about its symptoms helps in minimizing potentially harmful unnecessary evaluations and thereby preventing misdiagnosis and inappropriate treatment.

**Key words:** Histiocytic necrotizing lymphadenitis, Kikuchi–Fujimoto disease, Lymphadenopathy, Systemic lupus erythematosus

Kikuchi–Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis, is an uncommon disease characterized mainly by fever and lymphadenopathy. It was first described in Japan in 1972 [1]. Most cases were initially thought to be occurring in Asia, but now there have been cases described worldwide. Being a rare, poorly recognized clinicopathological entity that is often confused with systemic lupus erythematosus (SLE) and lymphoma, only a few case reports are mentioned in the literature that shows female preponderance with a male–female ratio of 1:4 [2]. Although the etiology of KFD is unknown, various viral, bacterial, and autoimmune diseases such as SLE have been associated. The exact pathophysiology is unknown but there are two theories that have been proposed. One is that KFD may result as a reaction to a viral infection [3]. Some of the unidentified agents may include toxoplasmosis, *Brucella*, *Bartonella henselae*, *Yersinia enterocolitica*, human herpes virus, Epstein–Barr virus, parainfluenza, paramyxovirus, parvovirus B19, cytomegalovirus, and human immunodeficiency virus [4]. Support for the viral etiology is provided by the dramatic presence of histiocytes and CD8-positive lymphocytes in KFD-affected lymph nodes. The other proposed theory is that KFD may be associated with an autoimmune disorder, mainly SLE and it can even predate the diagnosis of SLE by many years. There have been many case reports and studies that demonstrate this possible link, but the association is not fully understood [5]. Even though KFD has varied clinical presentation, it usually manifests with fever and lymphadenopathy, with the jugulocarotid and cervical lymph nodes being the most commonly affected [6]. Nodes range in size from 0.5 to 6.0 cm, multiple, painful, or tender in only 50% of cases. The characteristic histologic features include necrosis with karyorrhexis, a histiocytic infiltrate, and plasmacytoid dendritic cells, showing CD123 and T-cell leukemia/lymphoma protein 1 nuclear reactivity, and an absence of neutrophils. It is important to recognize KFD as a clinical identity, as it may mimic other conditions such as infections, inflammatory disorders, and autoimmune diseases, specifically SLE and malignancies such as leukemia and lymphoma.

We report the case of a 5-year-old boy who presented with persistent fever and cervical lymphadenopathy and was diagnosed with KFD.

## CASE REPORT

A 5-year-old boy presented with complaints of fever of 8-day duration and swelling on the left side of the neck of 6-day duration. He also complained of anorexia and weight loss. There was no history of viral upper respiratory infection or any other inciting events. There were no swellings elsewhere in the body and there was no history of contact with the tuberculosis patient. Other than a history of extrahepatic biliary obstruction with cholelithiasis

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4 months back for which, he underwent endoscopic retrograde cholangiopancreatography sphincterotomy and stone removal, there was no other significant past medical history.

The child was active and playful. He had a pulse rate of 94/min, regular rhythm and normal volume, respiratory rate of 22/min, blood pressure of 90/60 mmHg, and temperature of 39°C. The clinical examination revealed multiple enlarged left-sided level 3 cervical lymph nodes, the largest measuring 3×4 cm, firm in consistency, non-tender with no erythema, or matting of lymph nodes.

His total count was normal with mildly elevated erythrocyte sedimentation rate (ESR) (46 mm/h) and a normal C-reactive protein (Table 1). Ultrasound examination of the neck revealed bilateral cervical lymphadenopathy with no abscess. Tuberculosis workup and blood cultures came as negative.

The child was started on anti-staphylococcal antibiotics - cefazolin 100 mg/kg/day in three divided doses intravenously and clindamycin 30 mg/kg/day orally, following which he became afebrile and swelling reduced in size and he was discharged.

After 1 month, the child got readmitted with complaints of fever of 12-day duration associated with bilateral painful enlarged left cervical lymphadenopathy. He was evaluated by a primary care physician who gave him a course of amoxicillin-clavulanic acid. However, there was no improvement or resolution of the neck mass. Right epitrochlear lymph node was also palpable. Other groups of lymph nodes were not significantly enlarged. Blood examination was unremarkable other than the elevated ESR (51 mm/h). There were no atypical cells in the peripheral smear examination. In addition, an ultrasound of the neck was obtained which demonstrated multiple bilateral neck lymph nodes of level Ib, II, III, and left level IV lymph node stations with maintained fatty hilum and no collection or necrotic material. Fine needle aspiration cytology was done which showed only blood-stained smear. Serology for *Brucella* was negative and so was the workup for SLE, immunodeficiency, and other infectious diseases (Table 1).

The child underwent a cervical lymph node excision biopsy (Fig. 1) because of persistent fever and lymph node enlargement. Histopathological examination showed effacement of normal architecture with extensive paracortical necrosis, abundant karyorrhectic debris, fibrin deposits, and lymphocytic macrophages. The proliferation of histiocytes and dendritic cells was noted and intact neutrophils were absent (Fig. 2). Immunohistochemistry staining was positive for CD3 and 20 and CD68 for histiocytic cells came positive (Fig. 3). Thus, a diagnosis of histiocytic necrotizing lymphadenitis was made. The lymphadenopathy resolved within 2 months and the child on follow-up is asymptomatic.

**Table 1: Laboratory reports of the child**

| Laboratory investigations | May 3, 2021 | June 12, 2021 |
|---|---|---|
| Hemoglobin (g/dL) | 11.4 | 11.7 |
| Total leukocyte count (cells/mm$^3$) | 5100 | 7100 |
| Differential count | P31 L68 M1 | P44 L48 |
| Platelet count (lakhs/mm$^3$) | 2.05 | 2.42 |
| Erythrocyte sedimentation rate (mm/h) | 46 | 51 |
| C-reactive protein (mg/dL) | Non-reactive | Non-reactive |
| AST/ALT (IU/L) | 52/40 | 81/98 |
| Peripheral smear | Relative lymphocytosis. No atypical cells | |
| Tuberculin skin test | No induration | |
| Chest X-ray | Normal | |
| CBNAAT | Tubercle bacilli not detected | |
| Viral markers | Negative | |
| Lactate dehydrogenase (IU/L) | Reference range 60–170 | 310 |
| Anti-nuclear antibody | | Negative |
| C3 (mg/dL) | Reference range 88–201 | 130.4 |
| Infectious mononucleosis IgM | | Negative |
| *Brucella* IgM | | Negative |
| Rapid malarial test | | Negative |

**AST: Aspartate transaminase, ALT: Alanine transaminase, CBNAAT: Cartridge-based nucleic acid amplification test, C3: Complement component 3, IgM: Immunoglobulin M**

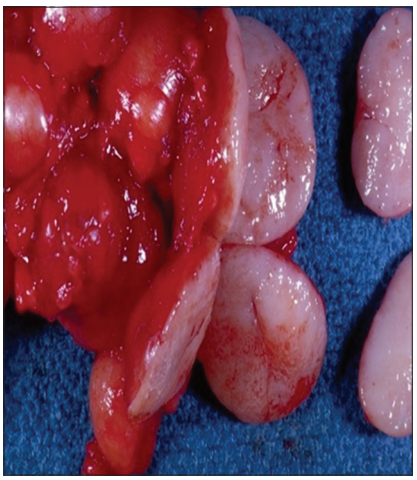

**Figure 1: Excision biopsy specimen of the cervical lymphadenopathy in our child showing enlarged lymph nodes**

## DISCUSSION

KFD is an uncommon cause of lymphadenopathy. Localized lymphadenopathy is the most common symptom associated with KFD [3]. In addition to cervical lymphadenopathy, axillary and supraclavicular lymphadenopathy have also been reported [7]. Usually, the lymphadenopathy associated with KFD is <3 cm, but there have been reports of lymph nodes reaching 5–6 cm [8]. Regarding fever, reports have demonstrated that the duration may range from 1 to 7 weeks with the temperature ranging from 38.6°C to 40.5°C [9]. Tenderness with palpation of the lymph node may or may not be present and in our child, the lymph nodes

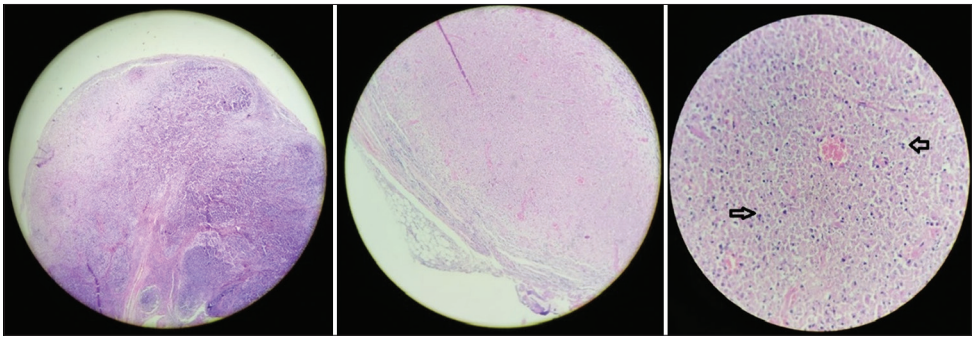

**Figure 2: Histopathological examination of the lymph node showing effacement of normal architecture, extensive paracortical necrosis, and karyorrhectic debris**

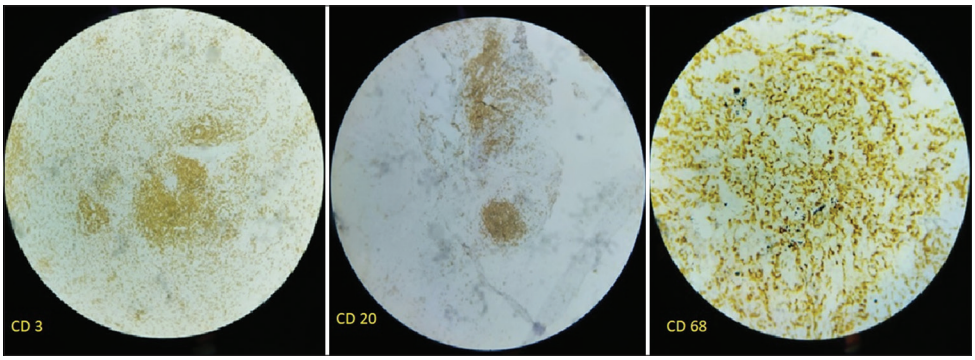


**Figure 3: Immunohistochemistry staining positivity with CD3, CD20, and CD68**

were non-tender. There may be several other associated signs and symptoms, which include chills, weight loss, headache, fatigue/malaise, vomiting, night sweats, arthralgia, splenomegaly, and rash of which fatigue and weight loss (1 kg in 2 months) after rash were present in our case. It has been reported that up to 30% of patients with KFD will have some sort of skin manifestation of the disease, which may include acneiform eruptions, facial erythema, papules, plaques, purpura, or nodules but none were noticed in our child. When skin manifestations are present, it is indicative of a more severe clinical presentation [3].

There are no specific laboratory investigations for the diagnosis of KFD. Laboratory studies have been reported to show a wide variety of results, including leukopenia or leukocytosis, anemia, increased ESR, increased C-reactive protein, elevated transaminases, and increased lactate dehydrogenase, but other than elevated ESR, elevated lactate dehydrogenase and mild transaminitis none were seen in our child [3,9]. The literature has reported that leukopenia is present in anywhere from 25% to 58%, and leukocytosis is present in approximately 2–5% of patients with KFD [3]. As the presentation of KFD is variable, and there is no specific set of symptoms or laboratory features that reliably establish the diagnosis, histopathology is crucial for its definitive diagnosis as we proceeded with it in our child [10].

Histologically, KFD is characterized by partially preserved nodal architecture with intermittent areas of fibrinoid necrosis and apoptosis and surrounded by histiocytes (with crescentic nuclei), activated T-lymphocytes, and plasmacytoid monocytes. The crescentic histiocytes are normally found in the necrotic foci with karyorrhectic debris. Characteristically, there is a paucity of neutrophils and eosinophils [3,11]. All these findings were consistent in our case as well (Fig. 2).

As mentioned earlier, KFD is classically believed to be a self-limited, benign condition that typically resolves within 6 months. An estimated 3–4% of patients may experience relapse [3]. Treatment is aimed at symptomatic control, and non-steroidal anti-inflammatories have been recommended for lymph node tenderness or febrile illness. If severe, glucocorticoids have been recommended, but there is no consensus on dosing or duration [12].

There are case reports in the literature depicting the association of KFD with SLE. The diagnosis of KFD can precede, postdate, or coincide with the diagnosis of SLE. Our child is on follow-up for 4 years and is so far healthy. There are also rare case reports in the literature that demonstrate an association between KFD and more aggressive and life-threatening outcomes such as disseminated intravascular coagulation, hemophagocytic syndrome and severe infection, pulmonary hemorrhage, and acute heart failure [13,14]. The pathophysiologic mechanisms are not understood, and further, research is needed before any conclusions can be discerned.

## CONCLUSION

KFD is a rare disease that typically follows a benign and self-limiting course. It manifests classically with lymphadenopathy and fever but may be associated with a number of other symptoms. It should be considered in the differential diagnosis of patients presenting with persistent lymphadenopathy. Treatment is symptomatic, but if severe, corticosteroids may be considered. Although symptoms usually resolve within 6 months, there are

reports of KFD being associated with poor outcomes. The purpose of this article is to highlight and bring to attention the possibility of KFD in the differential of cervical lymphadenopathy in a pediatric patient.

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