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# A Case of Kikuchi-Fujimoto Disease in a 7-Year-Old African American Patient: A Case Report and Review of Literature

## Authors' Contribution:

Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
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**Conflict of interest:** None declared

**Patient:** Female, 7-year-old  
**Final Diagnosis:** Kikuchi-Fujimoto lymphadenitis  
**Symptoms:** Lymphadenopathy  
**Medication:** —  
**Clinical Procedure:** Biopsy  
**Specialty:** Immunology • Rheumatology

**Objective:** Rare disease

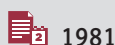
**Background:** Kikuchi-Fujimoto disease (KFD) is a rare self-limited necrotizing lymphadenitis which is likely under-diagnosed in pediatric patients who present with fever of unknown origin and lymphadenopathy. Definitive diagnosis is challenging as it requires an invasive open lymph node biopsy or lymph node needle aspiration cytology that shows pathologic findings of histiocytic necrotizing lymphadenitis.

**Case Report:** We report the case of one of the youngest patients diagnosed with KFD in the United States, at the age of 7 years. KFD has a higher prevalence in patients of Asian descent, but this patient was an African American. This case report shows the often convoluted and complicated course these patients undergo with their presenting complaints of fever of unknown origin and lymphadenopathy and highlights particular clinical findings that suggest KFD.

**Conclusions:** This patient is one of the youngest persons diagnosed with KFD in the United States, with an atypical ethnic background. It is likely that KFD is under-recognized and under-diagnosed in this population. With a broad differential diagnosis for fever of unknown origin and lymphadenopathy, awareness of KFD as a potential diagnosis may reduce other unnecessary investigations. The increased risk of patients with KFD of developing systemic lupus erythematosus (SLE) accentuates the importance of an accurate diagnosis and appropriate referral for heightened surveillance after recovery.

**MeSH Keywords:** Autoimmune Diseases • Histiocytic Necrotizing Lymphadenitis • Lupus Erythematosus, Systemic • Lymphadenitis

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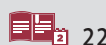
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## Background

Kikuchi-Fujimoto disease (KFD) is a rare, self-limiting disease, first described in 1972 in Japan [1,2]. While the etiology of the disease is unclear, the pathologic findings of histiocytic necrosis without granulocytic infiltration in involved lymph nodes have led to use of the term “histiocytic necrotizing lymphadenitis” for this condition [3]. The disease is most prevalent in the third to fourth decades of life and the mean age of patients is 30 years. It is more common in females than males, and is most common in Asian and East European populations [4,5] malign lymphoma, and many other benign and malignant conditions. To our knowledge, there is no previous study comparing the clinical and laboratory characteristics of patients from different geographical parts of the world. We searched literature records beginning from 1991 and analyzed epidemiological, clinical, and laboratory data of 244 patients (including cases diagnosed in our institution. The clinical manifestation is usually self-limiting lymphadenopathy with prolonged fever [6] this rate appears to be higher in our clinical experience, and rates up to 38.5% have been previously reported. In this retrospective study, we reviewed medical records of children with pathologically confirmed KFD to investigate the factors associated with recurrent KFD. Enrolled children were divided into two groups according to the recurrence of KFD, and clinical and laboratory factors were compared between the two groups. The recurrence of KFD was determined based not on repeated pathologic confirmation but on the presence of clinical febrile lymphadenopathy. A total of 33 children with KFD, 26 boys (78.8%). Fifty percent of patients show leucopenia [5]. Here, we report on a case of Kikuchi-Fujimoto disease in a 7-year-old African American pediatric patient.

## Case Report

A 7-year-old previously healthy African American girl presented to an academic-affiliated community hospital pediatric emergency department (ED) for a rapidly enlarging postauricular lymph node and fever. The patient's mother noticed a mass on the right side of the neck that started 4 weeks prior to the admission while overseas on vacation. This was accompanied by 10 days of fever that ranged from 38.3°C to 38.8°C with a maximum temperature of 39.1°C. In particular, the patient experienced spiking fevers during the night, but during the day, the temperature returned to normal. The patient did not have a fever-free period of more than 24 hours during these 10 days. The postauricular lymphadenopathy remained the same size since the onset of illness. Other than fever and lymphadenopathy, the patient did not experience any other symptoms such as night sweats, chills, or unexplained weight loss.

On examination, the patient was febrile and right postauricular lymphadenopathy was found. The workup revealed neutropenia (WBC 2 K/uL) with ANC 620 cells/ $\mu$ L and mild anemia (Hb 10.2 g/dL). The Epstein-Barr virus (EBV) screen was positive; hence, she was diagnosed with infectious mononucleosis and discharged with appropriate follow-up instructions.

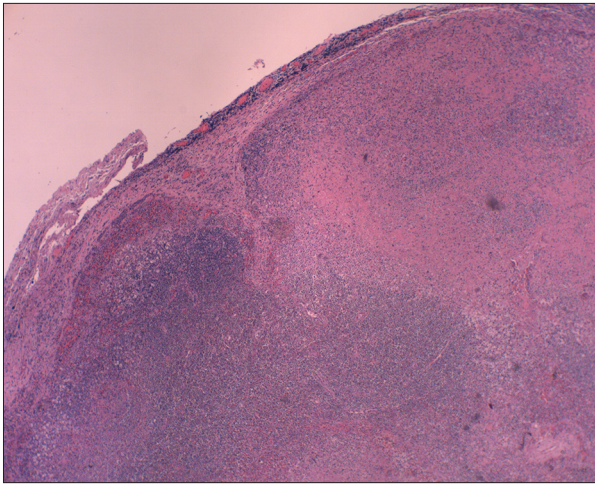
The patient experienced fever for 3 more days, but after 13 days of fever, she defervesced and remained clinically well for 7 days, but her lymphadenopathy persisted. A day prior to her second ED presentation, her mother noticed that the postauricular lymph node had enlarged significantly and she endorsed mild tactile fever, which prompted their return to the ED. There were no other new symptoms. On examination, enlarged lymph nodes were felt on the right side of the neck. The largest mass was located on the right postauricular area, 3 cm diameter in size, and was non-erythematous, non-fluctuant, firm, and tender. Submandibular, anterior, and posterior cervical lymph nodes were palpable and enlarged. No other lymph nodes were palpable. Otherwise, she was afebrile and appeared to be well, and the rest of the physical examination was normal.

Basic labs were repeated in the ED. A complete blood count (CBC) revealed severe neutropenia (2.4 K/uL) with significantly decreased absolute neutrophil count (ANC) 240 cells/ $\mu$ L and mild anemia (Hb 9.2 g/dL). Serum ferritin level was slightly elevated to 258.1 ng/dL, lactate dehydrogenase was elevated to 844 unit/L, and uric acid was 2.1 mg/dL. The patient was admitted for further evaluation due to concern for an infectious or malignant etiology.

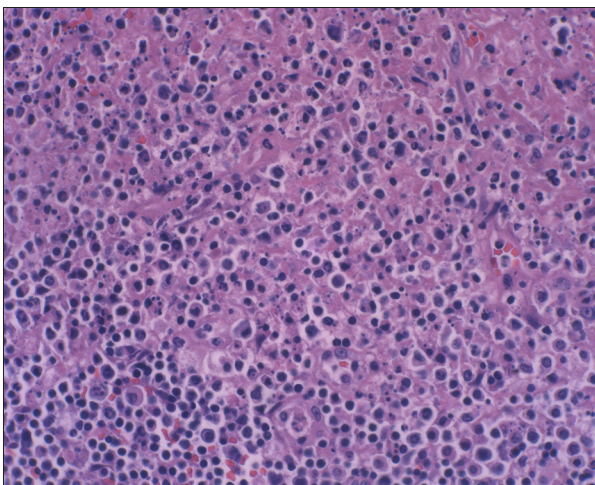
On admission, the patient was started on Ampicillin/Sulbactam. Hematology and infectious disease (ID) services were consulted. Per ID recommendations, testing was performed for EBV, Cytomegalovirus (CMV), Tuberculosis (TB), Bartonella, Brucella, and Parvovirus B19. EBV IgM was equivocal but IgG and EBV nuclear Ab were high. Parvovirus B19 DNA PCR was also positive. CMV DNA, QuantiFERON Gold, Bartonella IgG, IgM and Ab, and Brucella Ab were negative. Anti-nuclear antibody was negative.

On the third day of admission, the CBC showed worsening of neutropenia, with a drop in the ANC to 147 cells/ $\mu$ L, and progressive anemia. A review of the peripheral smear did not reveal atypical lymphocytes or blasts. Assessment of peripheral blood flow cytometry for lymphoid malignancy was negative. The patient continued to be afebrile and clinically stable, and did not show any new symptoms.

A neck ultrasound was performed, showing enlarged right-sided neck lymph nodes involving level II, III, and IV, of which the



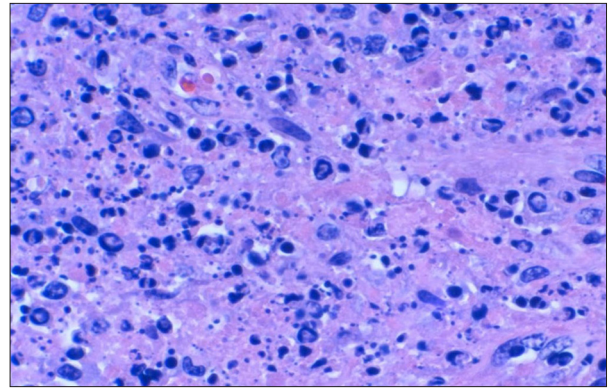
**Figure 1.** H&E stains of the patient's cervical lymph nodes obtained from open excision biopsy showing large coalescent areas of ischemic necrosis involving the cortex and paracortex.



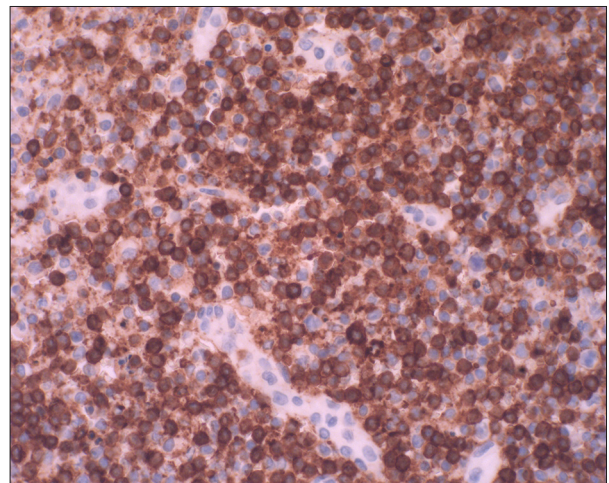
**Figure 2.** Close-up magnification of the H&E stains of the patient's cervical lymph nodes showing the characteristic features of histiocytic necrotizing lymphadenitis. The well-defined necrotic area includes histiocytic infiltrate with karyorrhectic debris and the notable lack of neutrophils.

largest was 2.5×1.0×1.7 cm, with no abscess formation. A CT of the neck and soft tissue agreed with the ultrasound result.

On the fifth day of admission, due to the lack of clinical improvement with antibiotics, a postauricular lymph node biopsy was performed. Cultures were sent from the specimen including acid-fast bacilli (AFB) and TB. On gross pathology of the lymph node, serial cross-sections revealed pink-brown smooth cut surfaces at the periphery and a focal opaque dull yellow area in the center, with focal hyperemic areas. On hematoxylin & eosin (H&E) staining, large coalescent areas of



**Figure 3.** Higher magnification of the H&E stains showing crescentic histiocytes.



**Figure 4.** Immunohistochemistry of the patient's cervical lymph nodes obtained from excision biopsy. CD68-positive histiocytes surround the necrotic areas.

ischemic necrosis involving the cortex and the paracortex were seen (Figure 1), with some areas surrounded by prominent foamy histiocytes. The necrotic areas contained karyorrhectic nuclear debris and some lymphocytes and monocytes, with a notable lack of neutrophils (Figure 2). Numerous crescentic histiocytes were also seen (Figure 3). Immunohistochemistry (IHC) showed CD68-positive monocytes and histiocytes surrounding necrotic areas (Figure 4). In the biopsied samples, there were many more CD3-positive T lymphocytes than CD20-positive B lymphocytes within and surrounding necrotic areas. There were also more CD8-positive lymphocytes than CD4-positive lymphocytes within and surrounding necrotic areas.

There was no evidence of malignancy. Given the patient's recent history of EBV infection and positive Parvovirus B19 PCR, along with the histological findings, a diagnosis of histiocytic necrotizing lymphadenitis or KFD was made.



During the hospital stay, the patient remained afebrile and was stable. The postauricular node remained unchanged in size until discharge. On the seventh day of admission, the patient was discharged with recommendations for follow-up with hematology and ID.

## Discussion

KFD is an uncommon, self-limited, necrotizing lymphadenitis which is likely under-diagnosed in pediatric patients who present with fever of unknown origin and lymphadenopathy. This case report of a 7-year-old African American girl is the first in this age group and ethnicity, and underscores the importance of considering KFD in the differential diagnosis of pediatric patients with prolonged fever and lymphadenopathy.

Classically, KFD has a higher prevalence in females than males (4: 1) [5] and has a higher prevalence in Japan and other Asian countries, although cases have been reported all over the world. There are few cases reported in North America regardless of age. Most patients are of Asian descent with some cases reported in the white population [5]. Only 7 cases have been reported in African Americans in the United States [7].

KFD usually affects young adults in their 30s, and pediatric cases have rarely been reported [3]. Most of the pediatric cases are adolescents. Patients younger than 10 years of age have been rarely reported in the literature worldwide. There were only 8 cases reported in the pediatric population in the United States, with the youngest patient officially reported being an 11-year-old girl [7].

In previous reports in children, the main clinical manifestation was unilateral lymphadenopathy (from 86% to 99%), with the majority of cases involving posterior cervical lymph nodes (from 91% to 96%). Most of the patients had fever at diagnosis, which lasts on average 7–9 days [8,9]. In a study from Korea of 86 patients under 19 years of age, 42% showed 2 constitutional symptoms (from among fatigue, weight loss, night sweats, and myalgia), and 28% had 3 or more symptoms other than fever at the time of diagnosis [8].

The most common hematologic changes in the disease are leukocytopenia (from 43% to 74%) with neutropenia and relative lymphocytosis. In some cases, atypical lymphocytes were detected in peripheral blood smears [8,10]. Less commonly, patients show anemia (from 23% to 46%) or an elevated erythrocyte sedimentation rate (ESR) [8,10].

The imaging modality most commonly performed in pediatric patients concerning for KFD is ultrasonography, which usually reveals nonspecific enlarged lymph nodes with little

differentiation from other causes such as lymphoma, tuberculosis lymphadenitis, or systemic lupus erythematosus (SLE) lymphadenitis. As the clinical picture and laboratory findings of these conditions are very similar, patients with KFD have occasionally been clinically misdiagnosed as having lymphoma, tuberculosis, or SLE lymphadenitis [10–12].

Some articles published in the United States reported 30% to 40% of cases were initially misdiagnosed as lymphoma or malignancy and these patients underwent unnecessary, extensive, and invasive work-ups, including bone marrow biopsy or liver biopsy [13]. Hence, it is important to keep KFD in mind in the differential diagnosis of cervical lymphadenopathy with constitutional symptoms.

The diagnosis of Kikuchi-Fujimoto disease is made predominantly on the basis of morphologic evaluation from pathology samples. The definitive diagnostic test for KFD is an open excisional lymph node biopsy. Fine-needle aspiration cytology (FNAC) has also been used for accurate diagnosis, with increasing success [14,15]. However, the quality of the specimen from FNAC is sensitive to operator skills and may require a dedicated cytopathologist [15]. The specimen also requires careful preparation to preserve the architecture of the lymph node. This is particularly important because the histological differential diagnosis includes lymphoma, SLE, and tubercular lymphadenitis.

KFD does not have a pathognomonic finding on pathology. Rather, it is a constellation of findings that is diagnostic. In our patient's pathology sample, these findings included yellow necrotic foci in the center of the lymph node on gross cross-sections. On H&E stains, well-circumscribed areas of necrosis with karyorrhectic nuclear debris, large accumulation of histiocytes in the periphery, and the notable absence of neutrophils are characteristics of KFD in the "necrotizing phase" [16]. The histiocytes have crescent-shaped nuclei and phagocytosed debris, which differentiate it from other lymphadenopathies such as tubercular lymphadenitis or lymphoma [7,9,11]. Some previous research proposed that cytotoxic T cells are important in the pathogenesis of, and on IHC, CD8-positive T cells were predominant in the lymphoid follicles [17]. Our IHC also confirmed a dominance of CD8-positive T lymphocytes. While the cause of KFD is unclear, there is some suggestion that the disease is triggered by EBV or Parvovirus B19 infections, but the current literature is inconclusive [5,18,19].

There is stronger evidence showing some overlap in the clinical presentations of KFD and SLE, as well as histological findings of focal necrosis with histiocytes in lupus lymphadenitis [20,21]. Some researchers have attempted to explain a potential association between these 2 diseases [9,20,21]. There have also been reports that patients with KFD eventually developed SLE later [9,22].

## Conclusions

This patient is one of the youngest persons diagnosed with KFD in the United States with an atypical ethnicity and clinical manifestation, which made the initial diagnosis challenging. Because fever of unknown origin with lymphadenopathy is a common presentation for pediatric patients in primary care and emergency department settings, it is likely that KFD is under-recognized and under-diagnosed in this population. With a broad differential diagnosis including infection,

malignancy, SLE, and tuberculosis, awareness of the potential for KFD as a diagnosis may reduce unnecessary and invasive investigations such as bone marrow biopsies. Further, due to its potential association with SLE, even though KFD is a self-limiting disease, patients may need surveillance for SLE after recovery from KFD.

## Conflicts of interest

None.

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