

Kikuchi-Fujimoto - an enigmatic and rare disease: a report of 3 cases and brief review of the literature

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Abstract

Kikuchi-Fujimoto disease (KFD) is a rare and benign condition mainly characterized by fever and lymphadenopathies. Although many studies have been carried out over time, its aetiology remains unclear, with infectious and autoimmune processes being hypothesized as the main causes. KFD is exceedingly uncommon in pediatric patients, making the diagnosis particularly challenging in this age group.

We report three cases of Kikuchi-Fujimoto disease. All patients were female and presented with fever and cervical lymphadenopathies. Extensive work up was performed, in order to rule out infectious, autoimmune and lymphoproliferative diseases. The diagnosis was established through lymph node excisional biopsy and histopathological examination. All patients were followed-up in a medical appointment, with one developing systemic lupus erythematosus (SLE).

Keywords: Kikuchi-Fujimoto; Lymphadenitis; Persistent fever; Systemic lupus erythematosus; paediatrics.

Key Points

Kikuchi Fujimoto Disease (KFD) is a rare and usually benign condition characterized by fever and lymphadenopathies;

Extensive workup is needed to exclude infectious, lymphoproliferative and autoimmune diseases. Diagnosis is established through lymph node excisional biopsy;

Due to the association with SLE and possibility of recurrence, all patients should maintain long-term evaluation.

Introduction

Kikuchi-Fujimoto disease (KFD), also known as Histiocytic Necrotizing Lymphadenitis is a rare and benign condition, characterized by fever and lymphadenopathies. It is more frequent in females and young adults, with few cases described at paediatric age¹. Although its aetiology remains unclear, infectious and autoimmune processes are hypothesized as the main causes^{1,2}. The only reliable method of establishing diagnosis is through excisional lymph node biopsy (ELNB), since fine needle aspiration material is insufficient^{3,4}. The histological features may vary among individuals and over the course of the disease, and include focal areas of necrosis with fragmented apoptotic cells, prominent histiocytic infiltration surrounding the necrotic areas, and the presence of plasmacytoid monocytes³.

We report three cases of KFD in pediatric patients, underscoring the clinical and diagnostic peculiarities of this rare condition in children. All patients were adolescent, female and presented with fever and cervical lymphadenopathies. After extensive workup, the diagnosis was established through ELNB. One developed systemic lupus erythematosus (SLE) on follow-up.

Case Report

Case 1. Seventeen-year-old female with a 7-day history of fever, diarrhoea, fatigue/malaise, anorexia and weight loss of 4Kg in three weeks. Six months before she initiated pruritic papular lesions of the face, ears and upper limbs. At that time, she had mild pancytopenia and mild elevation of erythrocyte sedimentation rate (ESR). Family history was positive for SLE (father and aunt).

On presentation she had multiple hyperpigmented lesions on the face, ears and left upper limb (Figure 1). The cervical area revealed small, tender, bilateral enlarged lymph nodes (maximum 1,5cm), without inflammatory signs. The remaining systemic examination was normal. Initial laboratory data showed mild leukopenia and thrombocytopenia, raised ESR and transaminases.

There was a resolution of the gastrointestinal symptoms, although persistence of fever and fatigue. Fever worsened in the third week of hospitalization. Multiple painful inguinal lymphadenopathies emerged as well as inflammatory signs in the cervical area. Serial analytical evaluation showed worsening of inflammatory markers (ESR, d-dimers, ferritin, lactate

dehydrogenase), mild pancytopenia, decreased reticulocyte count, raised transaminases and cholestasis markers. Peripheral blood smear demonstrated reactive lymphocytes. Extensive infectious and autoimmune studies were negative, as well as myelogram and bone marrow biopsy (BMB). Abdominal ultrasound showed heterogeneous spleen due to multiple focal lesions. Computed tomography (CT) revealed marked lymphadenopathy in the submental, cervical and supraclavicular areas, and splenic heterogeneity, with small hypodense nodes. ELNB revealed loss of architecture, extensive necrosis and inflammatory infiltrate with numerous histiocytes, compatible with KFD.

After four weeks of hospitalization, there was a progressive resolution of symptomatology. No specific treatment was necessary and she was discharged after one month of hospitalization. She did not develop lymphadenopathy again. Six months after discharge, she was diagnosed with SLE and began treatment with hydroxychloroquine.

Case 2. Fourteen-year-old female presented with persistent unremitting fever and cervical lymphadenopathy for a 4-week period associated with anorexia, abdominal pain and weight loss of 5Kg. Three months prior admission she had travelled to Angola and maintained a regular contact with cats and dogs.

At initial examination, she was ill looking, poor nourished, with multiple, tender, painful and mobile adenopathies in the cervical, supraclavicular, axillary and inguinal areas. The remaining systemic examination was normal. Laboratory investigations revealed mild anemia, leukopenia and raised ESR.

Infectious aetiology was excluded, including tuberculosis, malaria, toxoplasmosis, toxocariasis, bartonellosis and ehrlichiosis (Table I). Anti-nuclear antibody (ANA) (1/160) and anti-Sm antibody were detected. Cervical/abdominal ultrasound and CT scan revealed multiple cervical and hepatic hilus lymphadenopathies with no evidence of necrosis. Myelogram and BMB were innocent.

Empiric antibiotic therapy was initiated, without improvement. ELNB showed loss of architecture, with necrosis, extensive karyorrhectic debris and numerous histiocytes at the edge of the necrotic foci (Figure 2).

Four days after biopsy, she became afebrile and there was a progressive recovery. No specific treatment was required and she was discharged 18 days after admission. She maintained follow-up, without evidence of relapse but with persistent positive autoantibodies.

Case 3. Twelve-year-old female with a 3-week history of progressive cervical and submandibular lymphadenopathies. She was previously treated with antibiotic without improvement.

She had multiple painful adenopathies of the cervical and submandibular area bilaterally (maximum 4cm), with inflammatory signs. She also presented smaller, painless, adenopathies in the axillar, epitrochlear and inguinal areas. The remaining systemic examination was normal. Initial laboratory data showed leukopenia, raised ESR and transaminases.

She initiated fever and was treated with antibiotic due to suspicion of bacterial adenitis, without improvement. Infectious workup and BMB were negative (Table I). Autoimmune study revealed positive ANA (1/320). Cervical CT scan showed adenopathies with suggestive areas of necrosis. Submandibular ELNB revealed extensive infiltrate of B-lymphocytes, with necrotic foci and karyorrhexis.

The patient recovered uneventfully, with total resolution on the sixth week of disease. She did not recur.

Discussion

Despite rare, KFD has been described worldwide, with few pediatric cases (Table II)¹⁻¹¹. Typical cases occur in females, as seen in this report.

Its aetiology remains unclear. Infections, namely viruses, have been proposed due to its similar presentation and benign course. Numerous viruses have been hypothesized, however none has proven a causative link and the incidence of these viruses in patients with KFD is similar to controls^{2,12}. In our patients, no infectious cases were identified. A second hypothesis is that KFD may represent a self-limiting T-cell-mediated immune response, triggered by one or more agents in genetically susceptible patients. In fact, KFD shares common features with autoimmune disorders, namely SLE, such as clinical presentation and higher prevalence in females. Although most KFD patients have negative autoimmune study, it is described an association with SLE, that may present before, simultaneously or after KFD^{13,14}. Our first patient subsequently developed SLE, which demonstrates the importance of maintaining follow-up. Additionally, the second patient had positive ANA and anti-Sm antibodies, despite not meeting the criteria for the diagnosis of SLE. Since anti-Sm are very specific for SLE, in this particular case, it is essential to continue close follow-up¹⁵.

The onset of the disease might be acute or subacute. Fever and lymphadenopathies are the commonest manifestations^{3,12}. Fever can range from 1 to 7 weeks duration. Almost all patients present cervical lymphadenopathies and less frequently in other locations, with generalized lymphadenopathies being rare. The lymph nodes are usually painful, tender and small (<3cm). Other less frequent symptoms include weight loss, night sweats, fatigue/malaise, splenomegaly/hepatomegaly (<5%) and rash (30%). Cutaneous lesions usually present on the

face or upper body, as in our first patient, and include erythematous papules, plaques, nodules, indurated lesions and ulcers^{3,16}.

KFD may be associated with multiple non-specific laboratory changes such as cytopenias, namely mild anaemia and leukopenia (20-58%), elevated inflammatory markers, lactate dehydrogenase and aminotransferases^{12,13}. Rarely, leucocytosis may be present (2-5%). As seen in first case, pancytopenia can also be present.

A correct diagnosis is of utmost importance since differential diagnosis encompasses multiple pathologies, including infectious, autoimmune and lymphoproliferative disorders^{16,17}. According to one study, approximately 30% of KFD cases were misdiagnosed as lymphoma¹⁶. Given the rarity, and sometimes exuberant presentation of KFD, it is important to raise awareness for this disease.

KFD is usually benign and self-limited. Treatment mainly involves supportive measures, although in severe cases or relapsing disease it can be considered the use of corticosteroids. Symptoms usually resolve spontaneously within 4 months, although recurrence has been reported in rare cases (3-4%)^{17,18}. Given the favorable evolution, none of our patients required specific treatment.

In conclusion, KFD presents challenges related to its unclear etiology, extensive differential diagnosis and the need for long-term follow-up. More research is required to understand the underlying causes, improve diagnostic accuracy and clarify a potential association with SLE.

Tables and Figures

Table I – Summarized laboratory data, infectious work-up and immunological studies of all three cases.

Variable	Case 1	Case 2	Case 3
Laboratory data			
Haemoglobin (g/dL)	10-11,9	10,5	13
WBC (/μL)	2900-3600	2400	2600
Platelets (/μL)	113.000-130.000	173.000	160.000
AST (UI/L)	162-306	51	250
ALT (UI/L)	121-282	35	521
Ferritin (ng/mL)	266-51638	-	-
ESR (mm/h)	27-112	130	82
CPR (mg/dL)	1,17-3	2,61	0,2
Infectious work-up			
RSV / Influenza A/B	Negative	Negative	Negative
SARS-CoV-2	Negative	-	-
Epstein-Barr	Immune (IgM-IgG+)	Immune (IgM-IgG+)	Immune (IgM-IgG+)
Cytomegalovirus	Immune (IgM-IgG+)	Immune (IgM-IgG+)	Negative
B19 Parvovirus	Negative	Negative	Negative
Toxoplasma gondii	Negative	Negative	Negative
HIV 1/2	Negative	Negative	Negative
Hepatitis A antibody	Negative	Negative	Negative
Hepatitis B panel	Negative	Negative	Negative
Hepatitis C antibody	Negative	Negative	Negative
Brucella	Negative	Negative	Negative
Bartonella	Negative	Negative	Negative
Coxiella	Negative	-	-
Leishmania	Negative	Negative	-
Leptospira	Negative	-	-
QuantiFERON®	Negative	Negative	Negative
Mantoux test	Anergy	2mm	3mm
Plasmodium	-	Negative	-
Toxocara	Negative	-	-
Echinococcus	Negative	-	-

Fasciola	Negative	-	-
Coprocultures	Negative	Negative	Negative
Virology faeces	Negative	Negative	Negative
Blood cultures	Negative	Negative	Negative
Immunology			
Anti-nuclear antibody (ANA)	Negative	1/160 (fine granular pattern)	1/320 (mosque pattern)
Anti-dsDNA antibody	Negative	Negative	Negative
Anti-Sm antibody	Negative	POSITIVE	Negative
Anti-SSA/SSB	Negative	Negative	Negative
Anti-RNP antibody	Negative	Negative	Negative
Rheumatoid factor	Negative	Negative	Negative
Lupus anticoagulant	POSITIVE	-	-
Anti-neutrophil cytoplasmic antibody (ANCA)	Negative	Negative	-
Complement C3	Normal range	Normal range	Normal range
Complement C4	Normal range	Normal range	Normal range
Complement CH50	Normal range	Normal range	Normal range
Immunoglobulins	Normal range	Normal range	Normal range

Table II – Summary of pediatric cases of KFD reported in the literature. The table includes key clinical details, such as age, sex, presentation, duration of fever, treatment approaches, recurrence, association with autoimmune diseases and authorship of each case. AB – antibiotics; C – corticosteroids; CH – chloroquine; HLH – hemophagocytic lymphohistiocytosis; F – female; M – male

Patients (no)	Age (years) / Sex	Presentation	Duration of fever (days)	Treatment	Recurrence	Autoimmune disease	Authors
1	12 / M	Fever, cervical lymphadenopathies, skin rash, GI symptoms	21	AB; CH	Yes	No	Al Mosawi et al
2	13 / F	Fever, cervical lymphadenopathies, GI symptoms	60	CH	Yes	No	Al Mosawi et al
3	10 / M	Fever, cervical lymphadenopathies	60	C, CH	No	No	Al Mosawi et al
4	4 / F	Fever, cervical lymphadenopathies	90	AB, CH	No	No	Al Mosawi et al

5	9 / F	Fever, cervical lymphadenopathies, skin rash, GI symptoms	30	AB	No	No	Al Mosawi et al
6	9 / M	Fever, cervical lymphadenopathies, skin rash, GI symptoms	14	CH	No	No	Al Mosawi et al
7	10 / M	Fever, cervical lymphadenopathies	2	None	No	No	Al Mosawi et al
8	9 / M	Fever, cervical lymphadenopathies, GI symptoms	10	CH	No	No	Al Mosawi et al
9	11 / F	Fever, cervical lymphadenopathies, skin rash	14	CH	No	No	Al Mosawi et al
10	9 / M	Fever, cervical lymphadenopathies, GI symptoms	14	AB	No	No	Al Mosawi et al
11	12 / F	Fever, cervical lymphadenopathies	10	AB	No	No	Al Mosawi et al
12	12 / M	Fever, cervical lymphadenopathies, GI symptoms, skin rash	15	None	Yes	No	Lelii et al
13	16 / F	Fever, cervical, inguinal and axillary lymphadenopathies, fatigue, syncope, HLH	28	AB, C	No	No	Lelii et al
14	Teenage / M	Fever, abdominal lymphadenopathies, GI symptoms, hepatosplenomegaly	21	AB, C	No	No	Vijayaraghavan et al
15	13 / M	Fever, cervical lymphadenopathies, GI symptoms, weight loss	28	AB	No	No	Al Ghadeer et al
16	11 / M	Cervical lymphadenopathies	-	None	No	No	Singh et al
17	10 / F	Fever, cervical lymphadenopathies, skin rash, oral ulcers	7	AB, C, CH	No	SEL	Danai et al
18	7 / M	Fever, cervical lymphadenopathies, skin rash, polyarthritis	15	C	No	No	Bernardo et al
19	7 / M	GI symptoms and abdominal lymphadenopathies	-	C	No	No	Miller et al

20	17 / F	Fever, cervical and supraclavicular lymphadenopathies, skin rash	5	AB, C	No	Autoimmune thyroiditis	Go et al
21	7 / F	Fever, cervical lymphadenopathies, skin rash	15	AB	No	No	Saito et al
22	1 / M	Fever, axillary lymphadenopathies, skin rash	30	AB	No	No	Inamo Y



Figure 1 – Hyperpigmented lesions of the left upper limb

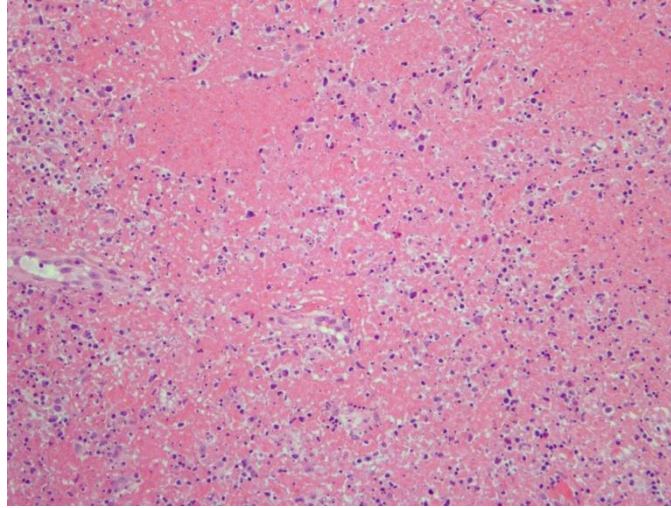


Figure 2 – Histology of resected cervical lymph node (hematoxylin-eosin), with loss of architecture, with necrosis, extensive karyorrhectic debris and numerous histiocytes at the edge of the necrotic foci.

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