

Take a second look: it's Kikuchi's disease! A case report and review of literature

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Abstract

Generalized lymphadenopathy is a common cause of concern for both patients and clinicians. Possible etiologies include infections, malignancies and autoimmune diseases. Kikuchi Fujimoto disease (KFD) is a hyperergic condition that presents with fever, lymphadenopathy and can include systemic involvement, thus being easily mistaken for the above-mentioned entities. We report the case of a previously healthy 18-year old male who presented with a self-limiting generalized lymphadenopathy, high fevers, skin vasculitis and polyserositis. The lymph-node biopsy revealed a histiocytotic necrotizing lymphadenitis, suggestive of Kikuchi's disease. This case emphasizes the importance of KFD in the differential diagnosis of lymphadenopathy, especially in young adults.

Introduction

Kikuchi-Fujimoto disease (KFD), also known as histiocytotic necrotizing lymphadenitis, is a rare, benign, presumably underdiagnosed disease, usually of good prognosis. Although initially considered to affect mostly East-Asian women,^{1,3} it has been meanwhile described in all ethnic groups around the globe.^{4,5} Whilst the pathogenesis is still not clearly understood, the disease probably occurs consequent to immune activation against an infectious agent. It presents with fever accompanied by lymphadenopathy. The laboratory studies mimic other conditions like tuberculosis, lymphoma, sarcoidosis, systemic lupus erythematosus (SLE) and HIV.⁶ The usual management only requires supportive therapy with antipyretics and analgetics and most cases are self-limiting. It is, however, still a poorly recognized entity, posing diagnostic difficulties for both clinicians and pathologists.^{7,8}

This case aims to raise awareness for

the disease and the importance of including KFD in the differential diagnosis of lymphadenopathy to prevent inappropriate treatments.

Case Report

An 18-year-old male was admitted to our infectious disease ward due to recurrent high fever episodes, night sweats and generalized lymphadenopathy. He reported to have noticed a painful swelling in his left axilla two weeks before and to have subsequently developed fevers up to 40°C, fatigue, poor appetite and night sweats. The patient's mother had been diagnosed with SLE. There was no recent travel history or contact to tuberculosis. He had already received an antibiotic regime with an aminopenicillin and a fluoroquinolone, without any clinical improvement. Clinical examination revealed multiple prominent, hard and matted lymph nodes, the largest of them in the left axilla, dense bilateral ankle edema and petechiae on both lower legs, suggestive for skin vasculitis.

The C-reactive protein, procalcitonin and ferritin were moderately elevated. We detected highly increased NT-pro BNP levels and slightly elevated liver enzymes with mild coagulopathy. The differential blood count showed mild anemia of inflammation and lymphopenia.

The serological screening for SLE, HIV, viral hepatitis, leptospirosis, brucellosis, toxoplasmosis and yersiniosis, as well as the TB Interferon gamma release assay and all blood cultures remained negative. The Epstein-Barr- IgG (EBV) antibodies were positive but the IgM antibodies were negative, thus making an acute EBV infection highly improbable. Interestingly, both HHV-6 serology and HHV-6-DNA-PCR were positive, suggestive for an acute infection with human herpes virus 6.

The conventional chest X-ray revealed bilateral pleural effusions. We sonographically detected multiple enlarged lymph nodes, the largest of them (37×25×36 mm) in the left axilla (Figure 1). Due to the ankle edema and the elevated NT pro BNP level, we performed a transthoracic echocardiogram. This revealed a dilated left heart with a mildly reduced ejection fraction and a pericardial effusion.

The immunoserology revealed elevated cryoglobulin levels. The skin biopsy showed minimal leukocytoclasia consistent with incipient vasculitis (Figure 2). An excision biopsy was performed on one of the lymph nodes and the histology studies disclosed extensive necrosis and presence of histiocytes, suggestive for Kikuchi's lymphadenitis (Figure 2).

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phadenitis (Figure 2).

The clinical course was self-limiting. After one week of symptomatic treatment with analgetics and antipyretics the febrile episodes disappeared, the symptoms improved and the petechiae resolved.

We diagnosed a self-limiting, virally induced cryoglobulinaemic vasculitis with polyserositis, hepatitis and histiocytic necrotizing lymphadenitis (Kikuchi disease).

Discussion

Kikuchi-Fujimoto disease is an uncommon, self-limiting lymphadenopathy, usually affecting young individuals in their 2nd and 3rd decade,^{9,10} with a higher prevalence in South-East Asia.³ It commonly presents with fever accompanied by lymphadenopathy, either cervical or generalized. Other possible symptoms include night sweats, myalgia, arthralgia, nausea, weight loss, hepatosplenomegaly.^{2,6} The lymphadenopathy most often involves the cervical region,

but generalised involvement has been described. Lymph nodes are moderately enlarged, firm, mobile and sometimes painful.^{6,11}

Our patient presented with a sepsis-like clinical syndrome unresponsive to antibiotic treatment. Having diagnosed a rare case of acute HHV-6 infection in an adult, we consider the poly-serositis, the Kikuchi's lymphadenopathy and the incipient vasculitis to be a hyperimmune state of viral etiology. At initial presentation SLE could be excluded due to lack of typical serological markers. We do consider our patient at risk to develop such hyperergic reactions because of the positive family history for SLE.

By the time we had established a diagnosis, the clinical features had resolved almost completely only on symptomatic therapy, proving that Kikuchi's disease is usually a benign, self-limiting inflammatory condition. On follow-up, three months after discharge, he reported that all symptoms had completely disappeared.

No laboratory study is pathognomonic for this pathology. Patients frequently present with increased inflammatory markers (C-reactive protein, erythrocyte sedimentation rate), leukopenia or atypical leukocytes, anemia of chronic disease and, in case of hepatic involvement, slightly elevated liver enzymes.¹²

Clinical course and histology point toward a hyperergic state potentially induced by infectious agents, leading to T cell- and histiocyte- activation and apoptosis.¹³ Toxoplasma, Yersinia enterocolitica, human herpesvirus 6 and 8, Epstein-Barr virus have been supposed to trigger KFD.⁶ Human herpes virus 6 causes febrile diseases in infants, mostly responsible for exanthema subitum. Acute infections in adults are uncommon but have been associated with acute lymphadenitis. Moreover, the virus was associated with a risk of developing perimyocarditis and vasculitis.¹⁴ Lysis of infected cells leads to increased numbers of autoantigens, enhancing the risk of autoimmunity in predisposed individuals.¹⁵

The diagnosis of KFD is based on excisional lymph node biopsy, which is also essential for the exclusion of other clinically similar entities: lymphoma, metastasis, tuberculous adenitis. The histological landmarks are: follicular hyperplasia, paracortical histiocytic and lymphocytic infiltrates, necrotising foci with a high degree of karyorrhexis and the absence of neutrophils and eosinophils. Immunohistochemical studies reveal an abundance of CD68+ histiocytes, CD123+ plasmacytoid dendritic cells and CD8+ T cells.^{6,8,11}

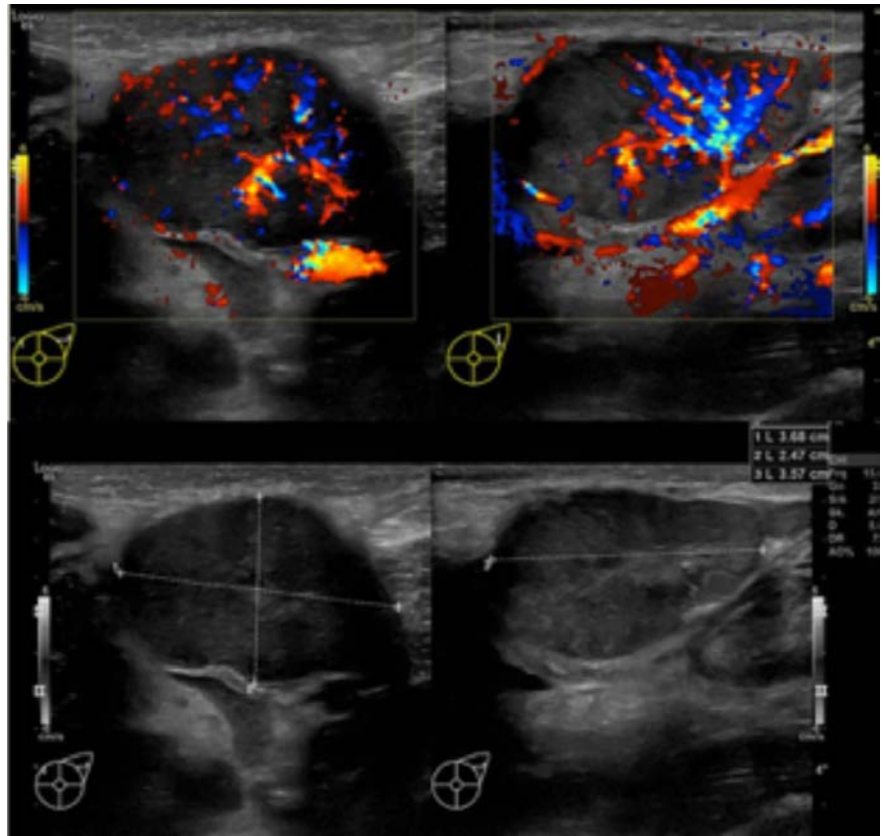


Figure 1. Sonographical findings: hypervascularisation in enlarged axillar lymph nodes.

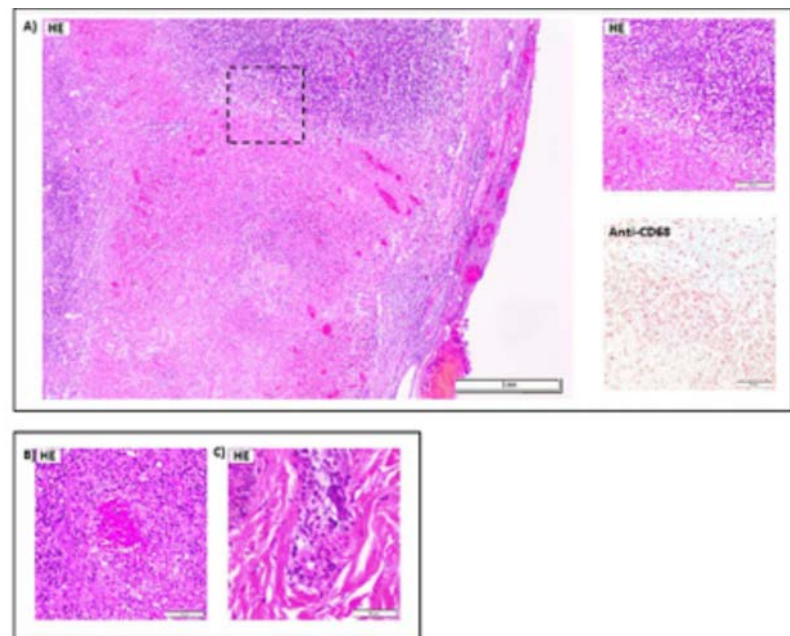


Figure 2. A) Lymphnode (Hematoxylin-eosin, HE) with extensive necrosis, surrounded by a histiocytic (CD 68+) infiltrate (insets); B) Early thrombus of a small vessel in a lymphnode involved in Kikuchi-lymphadenitis (HE); C) Initial and subtle leucozytotoxic vasculitis of a small cutaneous vessel.

In rare cases, patients that had been diagnosed with KFD developed systemic lupus erythematosus within months or years after initial presentation.^{2,16} It has been hypothesized that KFD is an excessive apoptotic answer to an infectious agent.⁶ SLE was related to insufficient processing of cell debris upon apoptosis, leading to generation of autoantibodies.¹⁷ It is conceivable that a hyperimmune response marked by increased apoptosis could precipitate the production of autoantigens and, in prone individuals, of autoantibodies. Moreover, the abundant plasmacytoid dendritic cells in KFD lymph nodes, responsible for the type 1- IFN-signature, might be another link between Kikuchi's disease and SLE. A rheumatological follow-up is hence strongly recommended. The natural course of the disease is commonly self-limiting, and the patients require only supportive treatment. In rare cases of persisting or recurrent symptoms corticoids, immunoglobulins or hydroxychloroquine have been effective. Since the disease's description in 1972, only few fatal cases have been described.¹⁸

Infaust pathologies characterized by lymphadenopathy and fever should be excluded: tuberculosis, leprosy, lues, toxoplasmosis, sarcoidosis, lymphoma, HIV, systemic lupus erythematosus. KFD has been misdiagnosed as non-Hodgkin's lymphoma, tuberculosis or relapsing infections and patients have occasionally received aggressive, inappropriate courses of treatments based on false diagnoses.^{8,19,20}

Conclusions

With its chameleonic clinical and laboratory features, Kikuchi-Fujimoto disease can mimic a manifold of pathologies, posing difficulties to experienced clinicians and pathologists. This case underlines the importance of considering KFD in the differential diagnosis of lymphadenopathy to prevent inadvertent therapeutic interven-

tions.

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