



Kikuchi-Fujimoto Disease in a Child: An Uncommon Cause of Fever of Unknown Origin with Cervical Lymphadenopathy

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Kikuchi-Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis is a benign and unusual self-limiting disease, should be included in the differential diagnosis of lymphadenopathy and fever of unknown origin. This disease mostly affects young Asian women, and is rarely reported amongst children. The etiology of KFD remains unclear currently, although the malady may arise secondarily to infection. According to the comments of a number of investigators, the most-common viral pathogens attributed to KFD are of the herpes family, including cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6) and human herpesvirus 8 (HHV-8). Here, we report a 10-year-old child who presented with cervical lymphadenopathy and prolonged fever. Histological examination of involved lymph nodes showed classical KFD.

Key words: Kikuchi's disease, histiocytic necrotizing lymphadenitis, children

INTRODUCTION

Kikuchi-Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis, is a self-limiting disease that was first described in Japan by, independently, both Kikuchi and Fujimoto et al. in 1972^{1,2}. Although the disease is prominent in Asia, it would appear that the malady is being reported increasingly more frequently in other geographical regions³. The disease usually affects women under 30 years of age although it also affects men, however, occasions where children have succumbed to the disease would appear to have rarely been reported³⁻⁵. For a pediatric population, the most-common manifestation of the disease is, reportedly, cervical lymphadenopathy either with or without fever not dissimilarly to an afflicted adult population³. From a number of studies, prolonged fever has been found for 32.8% of pediatric patients suffering from KFD⁶. Other reported malady-associated complaints include malaise, fatigue, diarrhea, body-weight loss, hepatomegaly, headache, pleural effusion, oral ulceration and polyarthritis^{4,6}. At time of writing, the etiology of the disease would appear to remain somewhat unclear al-

though infection and/or autoimmune responses are believed, by some, to be possible causative factors^{5,7}. The most-common disease-associated etiological pathogen is, reportedly, some form of virus, of which the herpesvirus family, including cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6) and human herpesvirus 8 (HHV-8) has been frequently reported⁸⁻¹⁰. We report a case of KFD that occurred in a 10-year-old female child who presented with cervical lymphadenopathy and prolonged fever.

CASE REPORT

A 10-year-old girl was referred to our pediatric emergency department due to persistent fever and a swelling on the left side of her neck that had existed for the preceding ten days prior to her presentation at our clinic. Prior to patient admission at our hospital, this girl had been treated for (presumed) acute upper respiratory tract infection, although the girl was admitted to our department in order to exclude deep neck infection.

Our patient's family history and personal history were unremarkable and we were not able to find any evidence of any previous herpes infection. Upon admission, the patient was febrile with a temperature of 39.2°C. A tender soft, ill-defined mass measuring 4×3cm was found within her left neck. We prescribed an initial trial of Unasyn (ampicillin + Sulbactam) for her. However, subsequent examination revealed no change in her lymphadenopathy one week later. Laboratory studies revealed mild leukopenia (white

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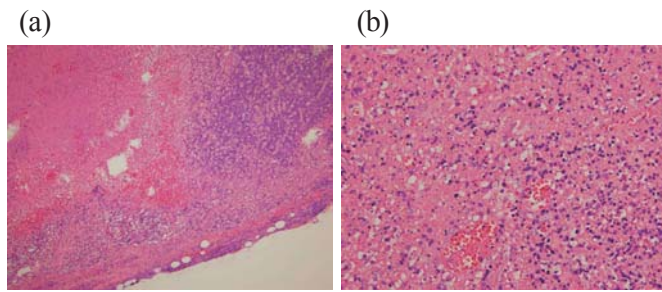


Fig. 1 (a) (Hematoxylin and eosin, original magnification $\times 100$) and (b) (hematoxylin and eosin, original magnification $\times 200$) are histopathological appearance of lymph-node biopsy and reveal cell architecture distorted by diffuse necrosis with histiocyte proliferation, lymphocytes and the presence of nuclear debris.

cell count = $3,500/\text{mm}^3$), anemia (hemoglobin = 10.7g/dL) and a normal platelet count. The girl's C-reactive protein (CRP) serum level was somewhat elevated (2.53mg/dl), as was her lactate dehydrogenase level (304U/L ; normal range = $95\text{--}205\text{U/L}$). Antinuclear antibody (ANA) proved to be negative. Serological tests for Epstein-Barr virus (EBV) and cytomegalovirus (CMV) proved negative, and blood cultures before the administration of antibiotics revealed no bacterial growth.

A computed tomography (CT) scan of the patient's neck demonstrated diffuse soft-tissue swelling with multiple enhancing, and the presence of necrotic nodes within the left neck, and also a few small nodes featuring apparent central necrosis or enhancement within the right neck. A cervical lymph node was excised and revealed no growth of acid-fast bacilli. The pathological findings included architecture distorted by diffuse necrosis and histiocyte proliferation and an unclear picture of resident debris (Fig. 1).

Following these investigations, the patient was treated symptomatically. One week later, she made a spontaneous and complete recovery. The patient has remained asymptomatic and well during 6 months of follow-up.

DISCUSSION

KFD may actually be more prevalent amongst a pediatric population than had been previously thought¹¹. Fortunately, patients typically feature a rather good prognosis and recover spontaneously within a few weeks to months of developing initial symptoms without any (apparent) serious sequelae⁸. KFD can affect patient of any age, gender, and ethnic background. The female-to-male ratio generally varies from 3:1 up to 4:1; however, rela-

tively low female-to-male ratio in Asian series were reported^{3,12}. The gender incidence of KFD in one pediatric series has a complete different predominance compared with the adult population and shows male-to-female ratio of 1.9:1¹³. Various infections have been postulated to feature some sort of a causative role, notable pathogens reported to have been associated with KFD include parasites (eg, those responsible for toxoplasmosis), bacteria (eg, *Yersinia enterocolitica*), and viruses (eg, EBV, parvovirus B19, HHV-6 and HHV-8, human T-lymphotropic virus type 1 [HTLV-1], rubella, parainfluenza, and varicella zoster virus), although as we are aware currently, none of the viruses have been definitively confirmed as causative agents for KFD⁹.

The most common presentation of KFD is localized lymphadenopathy with or without fever. Cervical lymph nodes are the principal site of disease. The next most common sites of lymph node involvement are the axillary and then the supraclavicular lymph node⁵. The diameter of the affected lymph nodes are smaller than 2 cm in most reported cases¹². Additional signs and symptoms include hepatosplenomegaly, headache, skin lesions, oral ulcer, night sweats, general malaise and body weight loss^{6,12}.

No definite laboratory test is available for the diagnosis of KFD. Leukopenia was one of the characteristic findings of KFD with the reported incidence ranging from 23% to 44%. Other findings including atypical peripheral blood lymphocytes (3–30%), elevated CRP level (12–26%), elevated ESR level (14–41%), impaired liver function (14–25%), elevated LDH level, anemia and thrombocytopenia are also presented^{3–6,12,13}.

The diagnosis of KFD is confirmed only by histologic examination. The classic morphologic findings of KFD involving lymph nodes have the following features: (1) Lymph node involvement is patchy in the paracortex and/or cortex, (2) fibrinoid necrosis is present in all early lesions, (3) a mixture of benign histiocytes, immunoblasts, plasmacytoid monocytes, and small lymphocytes surrounds the necrotic areas, (4) granulocytes are absent and plasma cell are absent or rare, (5) abundant predominantly extracellular apoptotic debris is present^{14,15}. Kuo particularly classified the histopathologic changes into three histologic types: proliferative, necrotizing, and xanthomatous type³. Recent studies have found that apoptotic cell death might be the mechanism of cellular destruction, relevant investigators suggesting that apoptosis is mediated by certain specific cytotoxic lymphocytes⁵. These findings support that KFD arises secondarily to either a viral or autoimmune pathogenesis.

As mentioned before, KFD is a self-limiting disease,

and the treatment is usually symptomatic and supportive. Most of the patients with spontaneous improvement with complete resolution within a period of 1 to 4 months. However, some patients with severe systemic manifestations might benefit from systemic glucocorticoids or intravenous immunoglobulin^{16,17}. Recurrence rate of KFD ranged from 3% to 4%^{3,6}. The recurrent episodes may develop in any parts of the body from the time of initial diagnosis of KFD of about 4 months to 8 to 9 years^{3,18}. A small number of patients initially diagnosed as KFD developed the SLE subsequently with an average time of several months to 5 years^{3,4}. Yet, KFD has not been reported to subsequently develop into malignant lymphoma to date.

KFD typically affects the cervical lymph nodes and its etiology remains quite unclear at time of writing. KFD may arise secondarily to apoptosis which is mediated by cytotoxic lymphocytes, a condition caused either by infection or by autoimmune pathogenesis⁵. Various viruses have been attributed to the occurrence of KFD. KFD is a self-limiting disease and most patients with KFD have spontaneous complete resolution without treatment. Thus, each pediatrician should consider the possibility of KFD when patients have prolong fever and cervical lymphadenopathy in order to avoid unnecessary inspections or examinations. Furthermore, it is important to follow up the patients of KFD for the possible development of autoimmune disease.

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