

A 17 years old girl with Kikuchi-Fujimoto disease (KFD) and severe leukopenia

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ABSTRACT

Background: Kikuchi-Fujimoto disease (KFD) is an enigmatic, benign and self-limited syndrome characterized by regional lymphadenopathy with tenderness, usually accompanied by mild fever and night sweats.

Patient: A 17 years old girl admitted in infectious diseases ward with chief complaint of fever and cervical lymphadenopathy since one week ago. Her problems started with fever and pharyngitis. Three days later, she developed one cervical lymphadenopathy. Blood sample revealed a WBC count of 1700 cells/mm³, platelets count of 137000/mm³. IgG-anti EBV antibody (VCA) level was 98.7 (upper limit of normal 20) and IgM-anti EBV antibody level was 52.7 (upper limit of normal 40). In hospital course her leukopenia became worse and reached 700cells/mm³. After two weeks WBC count recovered, and reached 5100 cells/mm³. Lymph node biopsy was achieved and showed necrotizing lymphadenitis with histiocytic reaction consistent with Kikuchi disease.

Conclusion: Kikuchi-Fujimoto disease must be considered in differential diagnosis of patients with acute severe neutropenia.

Keywords: *Kikuchi-Fujimoto disease, Leukopenia, Cervical lymphadenopathy, Epstein-Barr virus.*
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INTRODUCTION

Kikuchi-Fujimoto disease (KFD; so-called histiocytic necrotizing lymphadenitis) is an enigmatic, benign and self-limited syndrome characterized by regional lymphadenopathy with tenderness, usually accompanied by mild fever and night sweats (1,2). Initially described in Japan, KFD was first reported almost simultaneously by Kikuchi and by Fujimoto and associates in 1972 as a lymphadenitis with focal proliferation of reticular cells accompanied by numerous histiocytes and extensive nuclear debris (3).

KFD is known to have a worldwide distribution with a higher prevalence among Japanese and other Asiatic people. Affected patients most often are adults younger than 40 years (range, 19 months to 75 years). A recent series from Taiwan of 61 patients with KFD revealed a mean age of 21 years (3). In general, a female preponderance has been reported (female/male ratio, 4:1) (1,3,4). In pediatric populations, a male preponderance has been reported (1,3,5). Recent reports from Eastern countries indicate that the female preponderance was overemphasized in the past and that the actual ratio is closer to 1:1 (1).

There is much speculation about the cause of KFD; a viral or autoimmune cause has been suggested (6,7). Some initial reports hinted at

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Yersinia enterocolitica and *Toxoplasma gondii* as possible causative agents of KFD, mainly on the basis of positive serologic test results. But subsequent studies failed to support these hypotheses (1).

The role of Epstein-Barr virus (EBV), as well as other viruses, in the pathogenesis of KFD remains controversial. Serologic tests including antibodies to EBV, cytomegalovirus, and a host of other viruses have consistently proven noncontributory (1). A viral infection is, nevertheless, possible by virtue of clinical manifestations, as described by Unger and colleagues (1) (upper respiratory prodrome, atypical lymphocytosis, and lack of response to antibiotic therapy), and certain histopathologic features (ie, proliferation of immunoblasts, presence of necrotic zones localized to T-cell areas, expansion of the para cortex, and predominance of T cells as revealed by immunologic marker studies). However, no viral particles have been identified ultrastructurally. Histologic, ultrastructural, and immunohistochemical findings might support a hyperimmune reaction, perhaps to several organisms. It is possible that KFD might represent an exuberant T cell-mediated immune response in genetically susceptible people to a variety of nonspecific stimuli (1).

Among others, EBV and herpesviruses 6 and 8 have been suggested as potential causative agents of KFD (8,9). With regard to EBV, there are 2 studies-including 11 cases of KFD-that detected EBV by means of in situ hybridization for EBV-encoded RNA expression (1) and polymerase chain reaction-based methods (Epstein-Barr nuclear antigen-1 DNA) (10). However, there have been several other studies that, by using the same and other molecular pathology procedures (eg, Southern blot analysis) to localize the virus genome, have concluded that neither EBV nor herpesvirus 6 or herpesvirus 8 has a putative role in the pathogenesis of KFD. This conclusion is based on the facts that most cases were negative and that,

if positive results were observed, the percentage of viral detection in control subjects also was augmented (1).

Electron microscopic studies have identified tubular reticular structures in the cytoplasm of stimulated lymphocytes and histiocytes in patients with KFD (1). Because these structures also have been noted within endothelial cells and lymphocytes of patients with systemic lupus erythematosus (SLE) and other autoimmune disorders, Imamura and coworkers hypothesized that KFD might reflect a self-limited SLE-like autoimmune condition induced by virus-infected transformed lymphocytes (6,11). Yet the results of serologic studies testing antinuclear antibodies, rheumatoid factor, and other immunologic parameters consistently have been negative in these patients (1), providing no support for an autoimmune nature of the disease. Nevertheless, as we will comment, the association between KFD and SLE has been reported with a frequency probably greater than that expected by chance alone. Recent data support that patients with Kikuchi-Fujimoto disease should be followed-up for several years to survey the possibility of the development of systemic lupus erythematosus (6,11).

The results of a wide range of laboratory studies usually are normal in KFD (1,4,8). Some patients have anemia and a slight elevation of the erythrocyte sedimentation rate (1). Mild leukopenia has been observed in 25% to 58% of patients, whereas leukocytosis is found in 2% to 5% of cases (1). Moreover, 25% to 31% of patients have atypical peripheral blood lymphocytes (1,4,12) which might support the aforementioned speculated viral cause. The mechanism of granulocytopenia in a patient with KFD has been studied using an in vitro culture system (1).

The number of granulocyte precursor cells (colony forming units in culture [CFU-C]) in the bone marrow was found to be decreased. While T lymphocytes from the patient had no significant

suppressor effect on the CFU-C, the patient's serum blocked CFU-C in vitro (1). The authors proposed that one or more inhibitory factors might cause granulocytopenia in patients with KFD. Finally, serum levels of lactate dehydrogenase and aminotransferases are increased in some patients with KFD (1).

CASE PRESENTATION

A 17 years old girl admitted in infectious diseases ward with chief complaint of fever and cervical lymphadenopathy since one week ago. Her problems started with fever and pharyngitis. Three days later, she developed one cervical lymphadenopathy.

She was febrile on admission; her cervical LAP was single, tender, motile and firm. She had no organomegaly. Other physical exams were within normal limits. Blood sample revealed a WBC count of 1700 cells/mm³, platelets count of 137000/mm³, a C-reactive protein level of 48mg/L (upper limit of normal, 6 mg/L), ESR of 55 and lactate dehydrogenase of 941. IgG anti EBV antibody (VCA) level was 98.7 (upper limit of normal 20) and IgM anti EBV antibody level was 52.7 (upper limit of normal 40).

Anti nuclear antibody, anti DSDNA and ANCA were negative. Abdominal sonography and CXR were within normal limits.

In hospital course, her leukopenia became worse and reached 700cells/mm³. Two weeks later during which only one dose of G-CSF was injected, her WBC count recovered, and reached 5100 cells/mm³. She did not receive any other medication. Lymph node biopsy was achieved and showed necrotizing lymphadenitis with histiocytic reaction consistent with Kikuchi disease. The patient discharged in a good condition.

During the past year she was on close follow up and enjoyed her life and all her lab data are within normal limits.

DISCUSSION

KFD is an extremely uncommon, self-limited, and perhaps under diagnosed process of unknown cause with an excellent prognosis that seems to be more prevalent among Asiatic people. The clinical, histopathologic and immunohistochemical features seem to point to a viral cause, an extreme that has not been proven. But with our knowledge EBV fingerprint was observed. Recognition of this condition is crucial, especially because it can be mistaken for malignant lymphoma leukemia or, rarely, adenocarcinoma. Awareness of this disorder not only by clinicians but also by pathologists might help prevent misdiagnosis and inappropriate treatment. The diagnosis of KFD merits active consideration in any nodal biopsy showing fragmentation, necrosis, and karyorrhexis, especially in young people with posterior cervical lymphadenopathy.

We reported this case with cervical lymphadenopathy, severe leukopenia, pathological documented of KFD and serological diagnosis of acute EBV infection.

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