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CASE REPORT

A Rare Cause of Prolonged Fever and Cervical Lymphadenopathy: Kikuchi Fujimoto Disease

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ABSTRACT

Kikuchi Fujimato Disease (KFD) is a rare and benign cause of cervical lymphadenopathy associated with fever. It is important to be aware of this disease as it is included in the differential diagnosis of diseases with high morbidity and mortality, such as lymphoma and tuberculosis. This study presents a child diagnosed with KFD to raise awareness of the disease. A 15-year-old female patient was admitted with neck swelling, weight loss, and fever for three weeks without response to antibiotic treatment. On examination, her temperature was 38oC, she had 3-4 fixed, painful, and hard cervical lymph nodes in cervical chains, the spleen was palpable at 1.5 cm, the liver at 1 cm, and other systems examination was normal. Laboratory tests revealed a neutrophil count of 770/L, lymphocyte of 800/L, C-reactive protein of 16.99 mg/L, and erythrocyte sedimentation rate (ESR) of 120 mm/h. Her fever and fatigue persisted during hospitalization, and no tests reveals infectious diseases. Peripheral blood smears, bone marrow aspiration microscopy, and flow cytometry did not reveal any findings in favor of malignancy, and excisional lymph node biopsy was performed for diagnosis. Histopathological examination was consistent with Kikuchi Fujimoto Disease. Antinuclear antibody (ANA) positivity (+++). The patient's fever and partial lymphadenopathy resolved after 14 days of hospitalization, and the ESR decreased to 40 mm/h at 4 months. Systemic lupus erythematous (SLE) and hemophagocytosis can complicated KFD, so the follow-up patient continues. It is difficult to distinguish KFD from serious diseases clinically and in the laboratory. Differential diagnosis through histopathological evaluation is associated with the awareness of the clinician and the experience of the pathologist. With an early diagnosis, unnecessary examinations and treatments can be prevented.

Keywords: Kikuchi, Fujimato, lymphadenopathy, children

INTRODUCTION

Kikuchi Fujimoto disease (KFD), also known as "necrotizing histiocytic lymphadenitis," is a rare disease that was first described in 1972 (1,2). Its frequency is higher among Asians, young women, and whites. The pathogenesis of this disease is not fully understood, and it is generally believed to be due to an autoimmune response to viral infection. The mechanism of cellular destruction was suggested to be apoptosis by cytotoxic CD8-positive T lymphocytes (3,4). Human herpesviruses 6 and 8, Epstein-Barr virüs, parvovirus B19, human immunodeficiency virus (HIV), parainfluenza virus, *Yersinia enterocolitica*, and *Toxoplasma* are some of the associated agents. The most common clinical manifestations are cervical lymphadenopathy and fever (30-50%) in previously healthy young women. Even if it was first described in women, it also occurs in men with a 1/4:1:6 ratio (5). Other symptoms include rash, fatigue, arthritis, and hepatosplenomegaly. KFD is a self-limiting disease. However, some studies have reported that it is associated with systemic lupus erythematosus (SLE), Still's disease, and subsequently, lymphoma, acute leukemia, and hemophagocytosis develop. The diagnosis of KFD is difficult, and misdiagnosis is not uncommon. Patients can be diagnosed as having lymphoma when physicians and pathologists are unfamiliar with this entity. This misdiagnosis leads to extensive investigations and treatment with cytotoxic agents (6). The aim of this study was to increase awareness regarding the diseases among physicians.

CASE

A previously healthy 15-year-old girl was admitted with neck swelling, fever, myalgia, and weight loss lasting approximately 3 weeks. There was no clinical response to the empiric antibiotic administered at the previous admission. On physical examination she had 3-4 fixed, tender, and firm lymph nodes

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that formed clusters in the left cervical chain, the spleen was 1.5 cm palpable, and the liver was 1 cm palpable. Laboratory tests showed a white blood cell count of 1,800/L (4,500-13,000/uL), with 770/L, neutrophils (1,800-8000/uL) and 800/L lymphocytes (1,200-5,200), hemoglobin of 9.7 g/dL (>12), and platelets of 279,000/L. Kidney and liver function tests and coagulation values were within normal ranges. C-reactive protein (CRP) was 16.99 mg/L (<5 mg/L), LDH was 355 U/L (0-248 U/L), and erythrocyte sedimentation rate (ESR) was 120 mm/hour (<20mm/hour). Neck ultrasound showed numerous lymph nodes in all segments of both the right and left cervical areas, initially reactive, with the largest being 17x8 mm in diameter. After blood and urine cultures, empirical antibiotic therapy was initiated.

During hospitalization despite treatment patient's fever, myalgia and lymphadenopathy were persisted. Further tests were performed; immunoglobulins were in the normal range of IgA, 3.28 g/L; IgM, 0.71 g/L; IgG, 14.58 g/L; viral markers did not show any active infection; anti-CMV IgM, 0.22 U/mL; anti-CMV IgG, 498; EBV EBNA IgM negative; EBV EBNA IgG positive; HBsAg, 0.544; anti-HBs, 36.8; anti-HCV negative; antiHAV IgG, 1.12; antiHAV IgM, 0.31; and anti-HIV, 0.189. Brucella agglutination, *Bartonella henselae* IgG, and *Franciella tularensis* IgG were negative, tuberculin skin test (TST) was anergic, IGRA was negative, RF 6.2 IU/mL, ANA (+++), Anti-dsDNA <10 IU/mL, complement 3 (C3) level 1.18 g/L, C4 0.21 g/L, TSH 1.43 mIU/L, and free T4 was 1.16 ng/dL. Peripheral smear examination did not reveal any atypical cells. Bone marrow aspiration showed normocellular bone marrow with normoactive erythroid and myeloid cells without atypical cells, and flow cytometry did not reveal any evidence of malignancy. Abdominal ultrasonography revealed a normal-sized liver and spleen and not lymphadenopathy. Contrast-enhanced neck magnetic resonance imaging (MRI) revealed reactive lymph nodes on both sides of the neck triangle. Diagnosis could not be obtained with all the tests. Excisional biopsy of the largest cervical lymph node was performed. No microorganisms were detected in the pyogenic and mycobacterium culture, and the polymerase chain reaction was negative for *mycobacterium tuberculosis*. On the other hand, histopathological examination revealed small mature lymphocytes, immunoblastic cells, and numerous histiocytes with vascular proliferation. The histiocytes surruounded wide necrotic areas in various places (Figure 1). Widespread CD68 immunostaining confirmed histiocytic proliferation. was confirmed by (Figure 2). The findings were interpreted as consistent with "necrotizing histiocytic lymphadenitis". The patient was diagnosed with KFD based on histopathological findings and clinical manifestations and laboratory findings. On the 14th day of hospitalization, antibiotic treatment was discontinued because the fever subsided spontaneously regardless of antibiotic treatment. On the 3rd week, the laboratory findings showed a white blood cell count of 4,600 /uL, neutrophil 2,610/uL, lymphocyte 1,400/uL, hemoglobin 12.4 g/dl, and platelet 311,000/uL. On the 4th month of follow-up, the patient's hemogram and biochemical values returned to normal ranges, with an ESR of 40 mm/hour, and a few lymphadenopathies 1 cm in diameter were seen in the posterior cervical triangle on neck ultrasound. She is currently being followed by the pediatric infectious disease, pediatric hematology, and pediatric rheumatology departments.

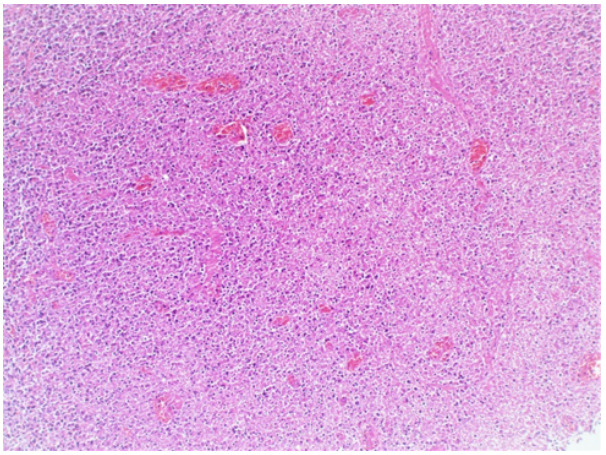

Figure 1: (HEx100) necrotic areas and histiocytes.

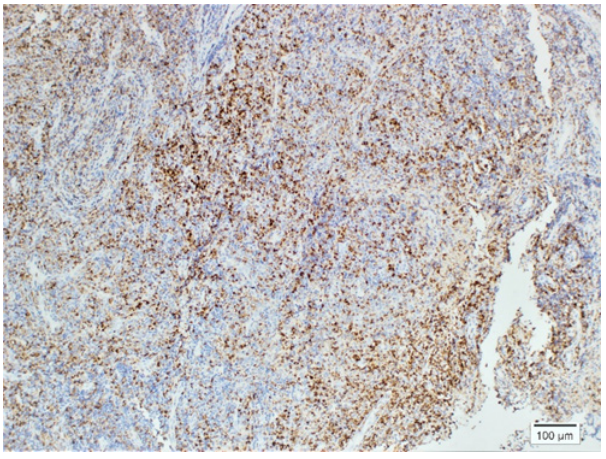

Figure 2: (CD68x100) widespread histiocytic infiltration.

Written informed consent was obtained from the patient and her parents for the presentation.

DISCUSSION

KFD is often observed in women and individuals aged 40 years old (7,8). Regarding ethnic distribution, 75% of cases occur in white individuals, and it is most commonly observed in Asians. Accordingly, this case involved a 15-year-old female from Turkiye.

The strongest hypothesis regarding the pathogenesis of the disease is an inflammatory response by T cells and histiocytes to an infectious agent. Epstein-Barr virus (EBV), human herpes virus 6 (HHV6), human herpes virus 8 (HHV8), HIV, parvovirus B19, paramyxoviruses, and parainfluenza virus have been shown as triggering agents (9,10). Serological tests performed to find clues about the infectious agents that might be trigger for disease were nonspecific in this patient, and no etiologic triggering agent was shown.

In this case, the clinical manifestations were fever and myalgia accompanied by cervical lymphadenopathy, as observed in most patients with KFD. Lymphadenopathy is observed in all, fever in approximately 30-50% of patients and generally resolves in 7-10 days, sometimes it lasts about 3 weeks. The other expected clinical findings are rash (10%), fatigue (7%), arthritis, and hepatosplenomegaly (3%) (5). Lymph node involvement is usually characterized by unilateral involvement of the cervical lymph nodes and is painful. Bilateral cervical, axillary, mediastinal, and inguinal lymphadenopathy can also be observed. A typical lymphadenopathy picture is multiple, distinct lymph nodes with regular borders and a diameter of 1-2 cm. This case had 3-4 fixed, painful, and hard cervical lymph nodes in bilateral cervical chains. Although the patient had no extracervical lymph node involvement, involvement of abdominal, pelvic, and inguinal axillary lymph nodes has been reported in some cases of bilateral cervical disease and leukopenia.

There are no typical laboratory findings for the disease, and thus, differential diagnosis is challenging. In most patients, complete blood count parameters are normal, and leukopenia can be observed (43%), whereas thrombocytopenia and pancytopenia can also be seen in some cases (11,12). ESR is high in about 70% of cases. In this case, leukopenia, neutropenia, lymphopenia, and a high sedimentation rate were observed. The presence of fever, lymphadenopathy, cytopenia, and high sedimentation rate raised suspicion for malignancy; especially leukemia and lymphoma. In fact, the differential diagnosis of KFD includes infectious mononucleosis, tuberculosis lymphadenitis, systemic lupus erythematous, cat scratch disease, and malignancy. Ultrasonographic findings can also raise suspicion of lymphoma. Tuberculosis is another type of disease present in the differential diagnosis of KFD. However, compared with tuberculous lymphadenitis, lymph nodes in KFD are smaller, less round, have more echogenic hilus, appear less necrotic, and have less calcification (13). In the ultrasound images of this case, the lymph nodes appeared homogeneous and reactive. Histopathologic examination of lymph node biopsy is a diagnostic method and will show necrosis and histiocytic infiltration together in paracortical foci. In KFD, CD 8 (+) cytotoxic T cells are abundant around necrotic areas, which helps distinguish KFD from SLE and reactive lymph node hyperplasia. Furthermore, the absence of intact polymorphonuclear leukocytes in necrotic areas can help exclude infectious and malignancy-related conditions (such as HSV, Hodgkin's lymphoma). Histopathological findings on microscopic examination of the patient's lymph node material were consistent with necrotizing histiocytic lymphadenopathy, also known as KFD.

There is no proven treatment for KFD. Spontaneous recovery occurs within one to four months. Glucocorticoids or intravenous immunoglobulin therapies have been tried in cases with severe or prolonged manifestation, and significant benefits have been observed. Some patients have shown good response to hydroxychloroquine and interleukin-1 inhibitors (14-17). In our patient, the disease resolved spontaneously during observation. Recurrence of the disease is observed in approximately 10% of patients, and in 2.7% of patients, autoimmune disease has been reported to develop; therefore, monitoring for relapse or development of autoimmune disease, hemophagocytosis in the long term is logical. This case did not show any signs of autoimmune disease, but ANA became positive during follow-up, and she is currently being followed up by pediatric infectious disease, pediatric hematology, and oncology outpatient clinics.

CONCLUSION

It is difficult to distinguish KFD from serious diseases clinically and in the laboratory. Differential diagnosis through histopathological evaluation is associated with the awareness of the clinician and the experience of the pathologist. With an early diagnosis, unnecessary examinations and treatments can be prevented.

Informed Consent: Written informed consent was obtained from the patient and her parents for the presentation.

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