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CASE REPORT

An unusual cause of cervical lymphadenopathy: Kikuchi-Fujimoto disease

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ABSTRACT

Kikuchi-Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis, is an uncommon clinical and pathological self-limited feature of benign prognosis that may mimic many other diseases diagnosed chiefly in young adults. The etiology of the disease is unknown although several investigators postulate viral, parasitic and autoimmune etiologies. The most common symptoms are cervical lymphadenopathy and fever. Diagnosis is usually rendered with excisional biopsy of lymph nodes and through histopathological findings. Non-steroidal anti-inflammatory drugs are used for the treatment. In this report, two cases of KFD without any associated infectious and/or non-infectious conditions were presented. *J Microbiol Infect Dis 2012; 2(1): 21-25*

Key words: Kikuchi Fujimoto Disease, histiocytic necrotizing lymphadenitis, lymphadenitis

Nadir görülen bir servikal lenfadenopati nedeni: Kikuchi-Fujimoto Hastalığı

ÖZET

Histiyositik nekrotizan lenfadenit olarak bilinen Kikuchi-Fujimoto Hastalığı (KFH) başlıca genç yetişkinlerde görülen, birçok hastalığı taklit edebilen, prognozu iyi, kendi kendini sınırlayan, sık görülmeyen klinikopatolojik bir tablodur. Hastalığın etiyolojisi tam olarak bilinmemekle birlikte çeşitli viral, parazitik ve otoimmün hastalıklar suçlanmaktadır. En sık servikal lenfadenopati ve ateş şeklinde belirti vermektedir. Tanı eksizyonel lenf nodu biyopsisi ve histopatolojik bulgular ile konmaktadır. Tedavide non-steroidal antiinflamatuar ilaçlar yeterli olmaktadır. Bu raporda, hastalığa eşlik eden herhangi bir infeksiyöz ve/veya infeksiyöz olmayan durumun saptanmadığı iki KFH olgusu sunulmaktadır.

Anahtar kelimeler: Kikuchi Fujimoto hastalığı, histiyositik nekrotizan lenfadenit, lenfadenit

INTRODUCTION

Kikuchi-Fujimoto disease (KFD) is a rare disorder that was first described in Japan in 1972 almost simultaneously by Kikuchi and Fujimoto.[1] This disease has now been recognized in many other countries and has also been referred to as Kikuchi's disease, histiocytic necrotizing lymphadenitis, focal histiocytic lymphadenitis, and subacute necrotizing lymphadenitis.[2] It has a worldwide distribution with a higher prevalence among Japanese and other Asiatic individuals, and only isolated cases are reported in Europe.[1] Affected patients are most often young adults under the age of 30 years; the disease is seldom reported in children. A female preponderance of cases has been underlined in the literature (female to male ratio 4:1). Recent reports seem to indicate that the female preponderance was overemphasized in the past and that the actual ratio is closer to 1:1.[1,3,4]

The two most characteristic features of this disorder are regional tender or not lymphadenopathy (mostly cervical) with or without tenderness and fever. Other findings include night sweats, weight loss, nausea, vomiting and sore throat.[5] Its natural course is usually benign, and the clinical symptoms and signs disappear within a few months without specific treatment.[6] Because the clinical findings and laboratory examinations are nonspecific, the correct diagnosis requires a histopathologic examination by lymph node biopsy.[2] In addition, KFD has been associated with lymphoma, systemic lupus erythematosus (SLE), rheumatic diseases, infectious diseases, neuro-

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logic disorders, interstitial lung disease, and hemophagocytic syndrome.[7]

If the clinician is unaware of the disorder or if the lymphadenopathy is not prominent at presentation, then delayed diagnosis and unnecessary investigations for a "fever of unknown origin" can occur.2 Anti-inflammatory treatment, steroids, and immunosuppressive therapy have all been used to control the disease.[1] However, recurrent and even fatal cases have been reported in the literature.[3]

In this report, we present two cases with KFD who were diagnosed in our hospital. Their clinical course, laboratory data and radiologic evaluation are described. The pathologic findings, differential diagnosis and prognosis of this entity are discussed in the light of the literature.

CASE 1

A 29-year-old woman was admitted to the Emergency Department of our hospital in December 2010, with complaints of pain and tenderness in the left side of her neck with high-grade fever, headache, weakness, nausea, and myalgia for a month. There was no improvement after several cycles of antibiotics, and her temperature rose progressively as high as 40°C, usually increasing at night and peaking in the morning, with night sweats and chills. She had no history of alcohol consumption, or use illicit drugs. There was no recent history of insect bites, residence in a rural area, exposure to cats or other animals, weight loss, cough, abdominal or back pain, and she took no medications.

The patient looked ill and had an axillary temperature of 39.1°C. She had multiple, discrete, and tender lymphadenopathies located in the bilateral cervical and axillary areas; the largest was 1x1 cm diameter. There was no sign of splenomegaly or hepatomegaly.

Complete blood count on admission showed the following values: hemoglobin 11.1 g/dl (range, 12-16 g/dl), platelets 289 000/mm3 (range, 100,000-400,000 /mm3) and leukocytes 6480/mm3 (range, 4000-10000/mm3). Evaluation of the peripheral blood smear revealed 76% of neutrophils, 18% of lymphocytes and 6% of monocytes. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were 45 mm/h (range, 8-15 mm/h) and 65 mg/dl (range, 0-8 mg/dl), respectively. In addition, the routine biochemical test results such as total bilirubin 1.1 mg/dl (range, 0.3-1.2 mg/dl), direct bilirubin 0.2 mg/dl (range, <0.3 mg/dl), alanine aminotransferase 34 U/L (range, 10-35 U/L), aspartate aminotransferase 35 U/L (range, 10-40 U/L), alkaline phosphatase 112 U/L (range, 53-128 U/L), gamma glutamyl transpeptidase 35 U/L, lactate dehydrogenase (LDH) 215 U/L, urea 9 mg/dl and creatinin 0.6 mg/dl were within normal limits. Blood, urine and stool cultures were negative. Sputum cultures grew respiratory tract flora and were negative for acid-fast bacilli. Search for antinuclear and double-stranded DNA antibodies, and rheumatoid factor was negative. Serologic tests for hepatitis A, B, and C, human immunodeficiency virus (HIV), syphilis, toxoplasmosis, brucellosis, Epstein-Barr virus (EBV), parvovirus B19, and cytomegalovirus (CMV) were negative. A chest X-ray examination and a computed tomography of the chest and abdomen were unrevealing. Ultrasonography of the neck confirmed the presence of lymph nodes with normal hili. The patient had recently had a negative tuberculin skin test.

An excision biopsy of a left cervical lymph node was performed. Histological examination, performed in the Department of Pathology at the Osmangazi University Hospital in Eskişehir, Turkey, revealed necrosis, histiocytic accumulation, lymphocyte and immunoblast infiltration, and cellular debris. In the perinodal fat tissue there was evidence of inflammation of the capillaries, with endothelial injury and leukocytoclasis. Special stains for microorganisms were negative. Immunohistochemical staining showed that nearly all the cells in the paracortex, as well as the lymphoid cells mixed with the histiocytes, were T-cells, with a predominance of CD8+ (cytotoxic−suppressor) cells over CD4+ (helper) cells. Using antibodies to B-cell−associated antigens, we found only small numbers of B cells, most of which were just beneath the capsule of the lymph node. The histiocytes were positive for CD68 and CD45. This is the classic immunophenotype of KFD.[1]

The diagnosis of KFD was established on the basis of histological features. No active treatment was instigated, except non-steroid anti-inflammatory drug for symptomatic relief, and she was discharged home after a week in-patient stay. Lymphadenopathy resolved spontaneously after

two months. After a year of follow up she is doing well, with no disease recurrence.

CASE 2

A 22-year-old woman was admitted to the Hematology Department of our hospital, with complaints of pain and tenderness in her neck with arthralgia, night sweats, and fatigue for a month. In addition, she reported 5 kg weight loss over that period. She had a history of upper respiratory tract infections, including acute pharyngitis about one month before the cervical nodes became enlarged. There was no improvement after using antibiotics. Her past medical history was unremarkable. She had no history of tuberculosis (TB), TB contacts, and no recent history of insect bites, residence in a rural area, exposure to cats or other animals. She was not under any medications, smoked 5 cigarettes /day for three years and did not drink alcohol.

On admission, the patient was in a good general condition and had an axillary temperature of 37.3°C. She had multiple, discrete, and tender lymphadenopathies located in the bilateral cervical areas; the largest was 1x1 cm diameter. The lymph nodes were tenderness, moveable, had slightly increased consistency and a smooth surface. No other lymph nodes were palpable. Other physical findings were normal.

Laboratory investigations showed the following values at admission: hemoglobin level of 14.7 g/dl, platelet count 239 K/UL and total leukocyte count 5960/mm3. Evaluation of the peripheral blood smear revealed 56% of lymphocytes, 37% of neutrophils, and 7% of monocytes. The ESR and CRP were 36 mm/h and 40 mg/dl, respectively. In addition, the routine biochemical test results were within normal limits. Blood, urine and stool cultures were negative. Sputum cultures grew respiratory tract flora and were negative for acid-fast bacilli. Search for antinuclear and double-stranded DNA antibodies, and rheumatoid factor was negative. Serologic tests for hepatitis A, B, and C, HIV, syphilis, toxoplasmosis, brucellosis, EBV, and CMV were negative. The serum complement component 3 (1.47 g/l; range, 0.9-1.8 g/l) and component 4 (0.32 g/l; range, 0.1-0.4 g/l) levels were within normal limits. A chest X-ray and abdominal ultrasonography did not show any abnormalities. An ultrasound of the cervical region revealed multiple lymphadenopathy in the bilateral posterior cervical triangle. She had recently had a negative tuberculin skin test.

An excisional nodal biopsy from the right cervical region was performed, and the pathological diagnosis was non-Hodgkin's lymphoma. We re-examine the pathological specimens of her in another pathology laboratory. After the second opinion, the diagnosis was changed to KFD. The lymph node showed foci of necrosis with abundant apoptotic bodies surrounded by histiocytic cells and transformed lymphocytes, but without neutrophils.

The diagnosis of KFD was established on the basis of histological features. No active treatment was instigated. The patient has been followed since the diagnosis. Lymphadenopathy resolved spontaneously after a month, and no other symptoms developed after six months follow up.

DISCUSSION

KFD is recognized as a distinctive clinicopathologic entity, and it has been well described in the pathology literature.[2] It is more prevalent in Asians, although the disease can sporadically occur worldwide, including Turkey.[5-7] Tanaka et al reported that two HLA class II genes, the DPA*01 allele and the DPB1*0202 allele, which is common in Asians but not in whites, might be related to KFD.[8] It commonly affects young population with a peak age of incidence occurring in the third decade, but rarely affects patients under 16 years of age.[9] Early reports suggest affected female cases are more common; however more recently this view has changed to one of equal prevalence in both genders, but both of our cases were female and they were 29 and 22 years old, respectively.[10]

The cause of the KFD is unknown. Several possible etiologies have been postulated and investigated because clinicians have suspected that an infectious process was at work on the basis of the transient and self-limited nature of KFD and the associated constitutional and upper respiratory tract infection-like symptoms. Several infectious agents such as Yersinia enterocolitica, CMV, human herpesvirus-6, varicella-zoster virus, parainfluenza virus, parvovirus B19 and EBV have been suggested, but none have been confirmed.[11] The histologic and immunologic findings together with the typical clinical presentation suggest a hyperimmune reaction of immune cells to

unidentified agents.[2] Autoimmune mechanisms have also been suggested because of case reports associated with SLE, Hashimoto disease, and adult Still's disease.[12] Nevertheless, serologies of our patients were negative and their past medical history was unremarkable.

Cervical lymphadenopathy (70-80%) and fever (30-50%) are the most common presentations of the disorder.[2,12] However, the clinical presentation may vary from patient to patient. Some patients with lymphadenopathy complain of malaise, fatigue, night sweats, weight loss, rash, sore throat, joint pain and gastroenteric symptoms without any fever. Although lymphadenopathy usually affects the cervical lymph nodes, the axillary lymph nodes and lymph nodes in other regions can be affected.[1-4] The sizes of the affected lymph nodes usually are 2 to 3 cm, but sometimes these nodes can be ≥5 cm, and affected lymph node is solid, movable, and painful but not suppurative.[2] The involvement of extranodal sites such as liver, spleen and skin rarely occur in KFD.[13] Although multiple lymph nodes were observed in our patients on the affected side or on both sides of the neck by palpation or sonography, the main affected lymph node was usually solitary. Lymphadenopathy with or without fever, as in our patients, is commonly observed in children and is frequently overlooked.[2] This finding, along with the self-limited nature of the KFD, suggests that the disease may be more common than originally thought.

Laboratory investigation is usually unremarkable and less suggestive for establishing a diagnosis of KFD, but negative results might help to exclude other conditions.[4,5] It revealed leukopenia (30-70%), neutropenia and anemia. The ESR and LDH levels were increased, but the transaminase level was unaffected. Low C4 levels can be detected. In addition, atypical peripheral blood lymphocytes (15-30%) with a relatively low CRP value and elevated immunoglobulin G and immunoglobulin E values were noted.[1,3,5,9,12] In our patients, laboratory work-up revealed only high ESR and CRP levels, and lymphocytosis in Case 2.

There is no radiographic finding specific for KFD. Computed tomography and magnetic resonance imaging do not yield features that distinguish KFD from other diseases which commonly involve lymph nodes such as lymphoma, tumor metastases, or tuberculosis.[14]

A definitive diagnosis of KFD is determined by a lymph node biopsy. Characteristic histopathologic findings of KFD include irregular paracortical areas of coagulative necrosis with abundant karyorrhectic debris, which can distort the nodal architecture, and large number of different types of histiocytes at the margin of the necrotic areas. The karyorrhectic foci are formed by different cellular types, predominantly histiocytes and plasmacytoid monocytes but also immunoblasts and small and large lymphocytes. Neutrophils are characteristically absent and plasma cells are either absent or scarce. Importantly, atypia in the reactive immunoblastic component is not uncommon and can be mistaken for lymphoma.[1,3] The immunophenotype of KFD typically consists of a predominance of T-cells, with very few B cells. There is an abundance of CD8+ T-cells over CD4+.15 The histiocytes express histiocyte-associated antigens such as lysozyme, myeloperoxidase (MPO) and CD68. Finally, striking plasmacytoid monocytes are also positive for CD68 but not for MPO.[1] In our cases, the diagnosis of the disease was also done by excisional biopsy of affected lymph nodes.

Although KFD is considered very uncommon, this disorder must be included in the differential diagnosis of "lymph node enlargement" since its course and treatments differ dramatically from those of lymphoma, TB and SLE. The histological differential diagnosis of KFD mainly includes reactive lesions as lymphadenitis associated with SLE or herpes simplex, non-Hodgkin's lymphoma, plasmacytoid T-cell leukemia, Kawasaki's disease, myeloid tumor and even metastasic adenocarcinoma.[1,4] The differentiation of KFD from SLE can sometimes be problematic because both can show similar clinical and histological features. Furthermore, KFD has been reported in association with SLE. In this case, before making the diagnosis of KFD, laboratory tests including C3, C4, anti-Sm, and LE cells are needed to rule out SLE. The diagnosis of KFD is generally not difficult, although early lesions lacking overt necrosis can be misdiagnosed as malignant lymphoma, due to the presence of abundant immunoblasts.[1] Features of KFD that may help prevent its misdiagnosis as malignant lymphoma include incomplete architectural effacement with patent sinuses, presence of numerous reactive histiocytes, relatively low mitotic rates, absence of Reed-Sternberg cells. The recognition of KFD

is necessary because one can avoid laborious investigation for infectious and lymphoproliferative diseases.

There is no specific therapy for KFD. It is a rare, benign, self-limiting disease that resolves spontaneously in one to four months.[11,13] Only severe cases require treatment with anti-inflammatory drugs. Fever and tender lymph nodes are the most frequent reasons why treatment is started. Pharmacological treatment includes non-steroidal anti-inflammatory drugs, minocycline, hydrochloroquine, and corticosteroids.[1-4,7] Antibiotics are recommended if a bacterial infection is confirmed. Successful combined treatment of KFD within days of starting intravenous immunoglobulin has been reported.[16] In our cases, we gave non-steroidal anti-inflammatory drug to Case 1 and no active treatment was instigated to Case 2. Recurrence rate is reported as 3-4%.[3,13] Our patients were followed regularly at one month intervals. Case 1 and 2 are free of the disease after a year and six months of follow-up, respectively.

Conclusion

KFD is an unusual, self-limited and perhaps under-diagnosed, benign cause of fever and lymphadenopathy especially in young patients. Because of its self-limiting character, prevalence of KFD may be much more than mentioned in the clinical experience. Clinical suspicion and thoughtful collaboration between clinicians and pathologists are essential for accurate diagnosis, and to minimize unnecessary investigations and inappropriately aggressive treatment.

REFERENCES

1. Bosch X, Guilabert A. Kikuchi-Fujimoto Disease. Orphanet J Rare Dis 2006; 1: 18.
2. Lee KY, Yeon YH, Lee BC. Kikuchi-Fujimoto disease with prolonged fever in children. Pediatrics 2004; 114: e752-e756.
3. Küçükardalı Y, Solmazgül E, Kunter E, Öncül O, Yıldırım Ş, Kaplan M. Kikuchi-Fujimoto Disease: analysis of 244 cases. Clin Rheumatol 2007; 26: 50-54.
4. Duskin-Bitan H, Kivity S, Olchovsky D, Schiby G, Ezra D, Mouallem M. Kikuchi-Fujimoto disease. Isr Med Assoc J. 2010; 12: 617-621.
5. Yılmaz M, Camcı C, Sarı I, et al. Histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto's Disease) mimicking Systemic Lupus Erythematosus: a review of two cases. Lupus 2006; 15:384-387.
6. Köybasi S, Saydam L, Güngen Y. Histiocytic necrotizing lymphadenitis of the neck. Am J Otolaryngol 2003; 24: 344-347.
7. Altuntaş F, Sarı İ, Canöz Ö, et al. Kikuchi-Fujimoto Disease: A rare but important cause of fever and lymphadenopathy in pregnant women. Am J Hematol 2006; 81: 118-120.
8. Tanaka T, Ohmori M, Yasunaga S, Ohshima K, Kikuchi M, Sasazuki T. DNA typing of HLA class II genes (HLA-DR, -DQ and -DP) in Japanese patients with histiocytic necrotizing lymphadenitis (Kikuchi's disease). Tissue Antigens 1999; 54: 246-253.
9. Primrose WJ, Napier SS, Primrose AJ. Kikuchi-Fujimoto disease (cervical subacute necrotizing lymphadenitis): An important benign disease often masquerading as lymphoma. Ulster Med J 2009; 78: 134-136.
10. Ifeacho S, Aung T, Akinsola M. Kikuchi-Fujimoto's Disease: A case report and review of the literature. Cases J 2008; 1: 187.
11. Parappil A, Rifaath AA, Doi SAR, Pathan E, Surrun SK. Pyrexia of unknown origin: Kikuchi-Fujimoto's Disease. Clin Infect Dis 2004; 39: 138-143.
12. Micozkadioglu SD, Erkan AN, Kocer NE. Necrotizing lymphadenitis of the neck. B-ENT 2009; 5: 51-53.
13. Kolodziej-Klek A, Orlowska-Florek R, Galazka K, Gryzwa M. Kikuchi-Fujimoto's Disease. Pol Arch Med Wewn 2009; 119: 826-829.
14. Sagit M, Akın I, Elverici BO, Yurdakul C. An unusual cause of cervical lymphadenopathies. Neth J Med 2008; 66: 262-263.
15. Dane F, Öztürk MA, Tecimer T, et al. A case of Kikuchi-Fujimoto Disease misdiagnosed as hodgkin's lymphoma: the importance of second opinion. J BUON 2009; 14: 1-3.
16. Mahmood A, Mir R, Salama SR, Miarrostami RM, Lapidus C, Pujol F. Kikuchi's disease: an unusual presentation and a therapeutic challenge. Yale J Biol Med 2006; 79: 27-33.