Kikuchi-Fujimoto disease as a rare cause of benign lymphadenopathy and ^{18}F-FDG PET/CT findings

Abstract

Kikuchi-Fujimoto disease (KFD) is an uncommon benign and self-limited disease, characterized by cervical lymphadenopathy. This disease is generally diagnosed on the basis of an excisional biopsy of affected lymph nodes. However, clinical presentation and histopathological findings of KFD could lead to a wrong initial diagnosis, of tuberculosis, systemic lupus erythymatosus or malignant lymphoma. Laboratory tests are not specific. Imaging modalitites give confusing results. Affected lymph nodes of patients with KFD can exibit ^{18}F-FDG uptake on PET/CT imaging similar to malignant lymphoma. Therefore, the differential diagnosis of KFD should be considered in patients with cervical and/or generalized lymphadenopathy. Accurate diagnosis of KFD by histology is essential in avoiding unnecessary emotional and mental distress associated with the diagnosis of lymphoma.

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Seval Erhamamci[1] MD, Mehmet Reyhan[1] MD, Nazım Emrah Kocer[2] MD

1. Department of Nuclear Medicine and
2. Department of Pathology, Faculty of Medicine, Baskent University, Ankara, Turkey

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Correspondence address:
Seval Erhamamci, MD
Baskent University, Faculty of Medicine
Saray Street No. 1, 42080: Selcuklu, Konya, TURKEY
Tel: +090 332 2570606
Fax: +090 332 2570637
E-mail: sevaler@yahoo.com

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Introduction

Kikuchi-Fujimoto disease (KFD), also known as necrotizing histiocytic lymphadenitis, is a benign and self-limited disease, usually characterized by tender cervical lymphadenopathy accompanied by fever. This disease is extremely rare although it has worldwide distribution with higher prevalence among Japanese and other Asiatics [1, 2]. Our knowledge about KFD is mostly based on case reports. Therefore, the true prevalence of KFD is unknown [1-3]. Affected patients are most often young female adults under 30 years of age [1]. The onset of KFD is acute or subacute, developing during a period of 2 to 3 weeks [1]. Usually, KFD is limited in the cervical area, but it may also involve the whole body lymph nodes [4]. Generalized lymphadenopathy has rarely been reported [4]. The involvement of mediastinal, peritoneal, and retroperitoneal lymph nodes is uncommon [1]. Fever is present in 30% to 50% of cases, associated with upper respiratory symptoms [1, 5, 6]. The clinical course is typically benign, with symptoms lasting 6-8 weeks. A low recurrence rate of 3% to 4% has been reported [7]. The cause of KFD is unknown, although a viral infection, such as cytomegalovirus, Epstein-Barr virus, human herpes virus, or autoimmune diseases, especially systemic lupus erythematosus, have been mentioned as related to/or causing KFD [1, 8-10].

Kikuchi-Fujimoto Disease is generally diagnosed on the basis of an excisional biopsy of a lymph node and histopathology. Laboratory findings show no specific findings except mild leukopenia. Clinical presentation and histopathological findings of KFD could lead to a wrong initial diagnosis of tuberculosis, SLE or malignant lymphoma [3-6, 11-15]. Imaging modalitites can give confusing results. This disorder does not have a characteristic appearance on ultrasonographic (USG) or computed tomographic (CT) examinations. The findings of CT and magnetic resonance imaging (MRI) of KFD can be variable and mimic not only lymphoma but also various nodal diseases with necrosis, including metastases and tuberculosis [14-16]. A distinctive lymphadenopathy pattern in patients with KFD consisting of many small clustered lymph nodes has been reported by using CT and MRI [17]. A definitive imaging modality for distinguishing between KFD and malignancy has not yet been identified.

Fluorine-18-2′-deoxy-2fluoro-D-glucose positron emision tomography/CT (^{18}F-FDG PET/CT) scan is an essential diagnostic and follow-up method for various malignant diseases. However, ^{18}F-FDG is not cancer specified; ^{18}F-FDG avidity due to increased glycolysis and glucose transporter activity can often cause false-positive ^{18}F-FDG uptake in PET/CT scans of benign lesions [18]. Tuberculosis, sarcoidosis, fungal infections and also KFD can show localized ^{18}F-FDG uptake and limit the specificity of ^{18}F-FDG PET scan.

Positron emission tomography imaging findings in KFD were first reported by Liao el in 2003 [19]. Few case reports and few recent studies using ^{18}F-FDG PET/CT have suggested that the lymph nodes of patients with KFD exhibit high ^{18}F-FDG uptake [4, 19-26], which makes it difficult to distinguish them from malignant lymph nodes using only PET/CT imaging [18-26].

Findings from recent studies

Other authors have studied 7 patients with KFD and found that the maximum standardized uptake values (SUVmax) of ^{18}F-FDG uptake in the affected lymph nodes was 2.05-13.94 (mean±SD: 6.25±3.32) [25]. Although the SUVmax values are usually useful for diferentiating between benign and malignant tumors, this study showed that SUVmax values in the affected lymph nodes of patients with KFD were as high as in malignancies. However, ^{18}F-FDG PET/CT helped to exclude metastases and the involvement of extranodal sites in malignant lymphoma. In addition, ^{18}F-FDG PET/CT showed the general distribution of the enlarged lymph nodes and aided decisions regarding appropriate biopsy sites, as biopsy is necessary to define diagnosis.

In another study, authors, enrolled 22 patients (8 with KFD and 14 with non-Hodgkin's lymphoma (NHL)), in order to distinguish KFD from NHL by PET/CT [26]. They performed analyses by SUV and by partial volume corrected SUV (SUVcor) and showed that SUV could not differentiate between KFD and NHL. However, KFD showed a higher SUVcor as compared with indolent NHL, which did not differ from the SUVcor in aggressive NHL. For the differential diagnosis by PET/CT between KFD and NHL and for better assessment of treatment and of the outcome of these patients, more cases should be studied.

As symptoms of KFD are nonspecific and some of its histological features are similar to other diseases, it is never easy to distinguish KFD from SLE or lymphoma [12, 13]. Up to 30% of patients with KFD have been reported to be initially misdiagnosed with malignant lymphoma and some of them had unnecessarily received chemotherapy [11]. While the loss in the immunohistochemical expression of bcl-2 is one of the common findings in KFD, this is also commonly seen in peripheral T cell lymphomas. Furthermore, a recent study showed that the loss of pan T antigens, one of the diagnostic criteria commonly encountered in peripheral T cell lymphomas, also existed in KFD [12]. Oligoclonality, which may be an indicator of a T cell lymphoma in evolution, is also detected in T cell receptor rearrangement studies, in a subset of KFD patients, and its presence in KFD implies a benign immune reaction rather than a malignant transformation [13]. T cell proliferations in young female patients should be evaluated with caution before a definite diagnosis of a peripheral T cell lymphoma is established.

A typical personal case is as follows: A 32 years old female with no previous medical history was admitted to our hospital, because of painful swelling on the right side of her neck for nearly 2 weeks, without fever. This case indicated how difficult sometimes may be to set the correct diagnosis. There was no recent history of travelling and of being exposed to tuberculosis, autoimmune disease or of any contact with animals. On admission, physical examination showed no abnormalities except for right cervical lymphadenopathy, tender in palpation. Laboratory tests revealed mild leukopenia with white blood cell count of $3.55x10^9/mm^3$, (reference range $4.5\text{-}11.0x10^9/mm^3$), and no abnormalities in other peripheral blood cells or in blood chemistry data including hepatic, renal, pancreatic function, electrolytes, and glucose. Serum levels of immunoglobulins, complements, carcinoembryonic antigen, α-fetoprotein, CA19-9 were within normal limits. A Mantoux test and cytomegalovirus, Epstein-Barr virus, cyclooxygenase tests and tests for dsDNA, extractable nuclear antigen, and antinuclear antibody were all negative. Blood and urine cultures were negative. Neck USG revealed a 3x3cm in diameter lymphadenopathy in the right cervical region. The patient was treated with oral antibiotics for 2 weeks, but there was no improvement in neck swelling. The patient underwent excision biopsy of the enlarged lymph node. Histopathological examination revealed a lymph node with a thickened capsule and fibrous septates. There was a patchy infiltration of medium-to-large lymphoid cells with rough chromatin adjacent to the normal or reactive germinal centres (Fig. 1). There were small foci of nuclear debris, neutrophil polymorphs and histiocytes intermixed with this cell population (Fig. 2). In the immunohistochemical examination, cells forming the patchy infiltration were positive with CD3, CD7, CD8 while there was a loss of bcl-2 expression. There was also a loss of expression in CD4, CD2, and to a degree in CD5. Along with the CD20 and CD79a, TDT and bcl-6 were also negative. Based on the loss of CD2, CD4, bcl-2 and partial loss of CD5 expression, the initial pathological diagnosis was consistent with peripheral T-cell lymphoma.

The patient underwent a whole body ^{18}F-FDG PET/CT scan using Discovery-STE 8 camera (General Electric Medical System, Milwaukee, Wisconsin, USA) 60min after intravenous injection of 307.1MBq of ^{18}F-FDG. The images revealed increased ^{18}F-FDG uptake of lymph nodes in the left cervical and left auxillar regions (Fig. 3). Due to the clinical symptoms

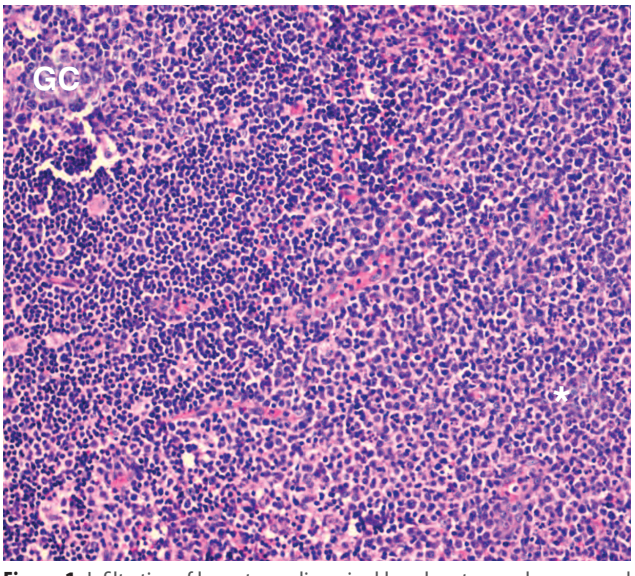

Figure 1. Infiltration of large-to-medium sized lymphocytes nearby a reserved germinal center (hematoxylin and eosin stain, original magnification, x200, GC: germinal center, *: infiltration).

of the patient as well as the results of the laboratory tests that did not correspond to the initial histopathologic diagnosis of NHL, additional consulting examination of the histopathology films, finally set the diagnosis of KFD.

After the diagnosis of KFD, regular follow-up by USG was planned. After 8 weeks, the patient recovered spontaneously and completely, without treatment and her lymphadenopathy was improved. She remained asymptomatic during the next 12 months.

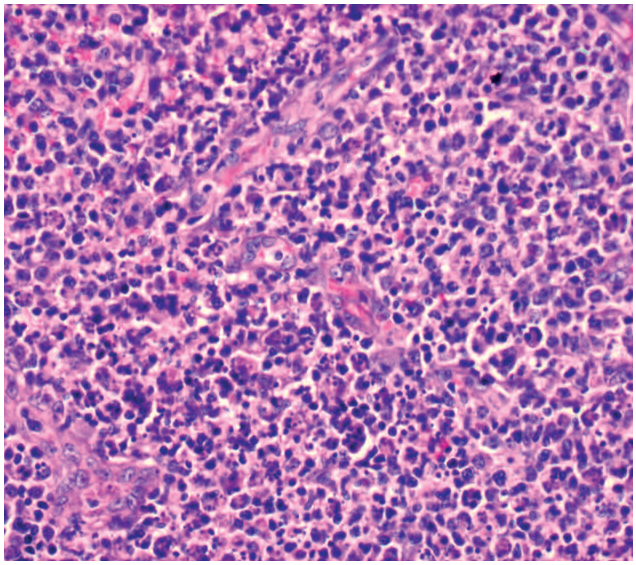

Figure 2. Neutrophil polymorphs, nuclear debris and histiocytes intermixed with atypically appearing cells (hematoxylin and eosin stain, original magnification, x400).

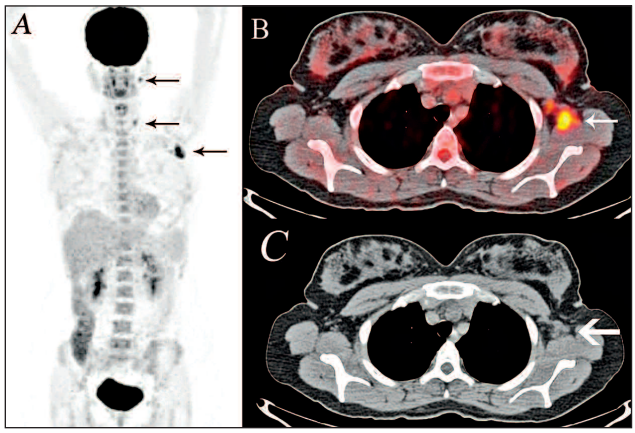

Figure 3. Maximum intensity projection (A), fusion (B) and CT (C) images of ^{18}F-FDG PET/CT showed increased ^{18}F-FDG uptake in the left cervical (in levels IIB and IV-V, maximum standardized uptake value (SUVmax), 4.6) and left axillary lymph nodes (SUVmax, 8) (arrows). Mild ^{18}F-FDG uptake in the right cervical region was considered as due to surgery involvement.

Althought clinical presentation and laboratory tests were not suggestive of malignancy, initial histopathologic examination of the patient was mistakenly that of a malignant lymphoma.

In conclusion, an affected lymph node in patients with KFD can exibit ^{18}F-FDG uptake on PET/CT imaging similar to malignant lymphoma. Therefore, KFD although a rare disease, can be considered in the differential diagnosis of patients with cervical lymphadenopathy and/or without, other lymph nodes involvement. Accurate diagnosis of this condition by histopathology is essential in preventing unnecessary emotional and mental distress associated with the diagnosis of lymphoma.

The authors declare that they have no conflicts of interest.

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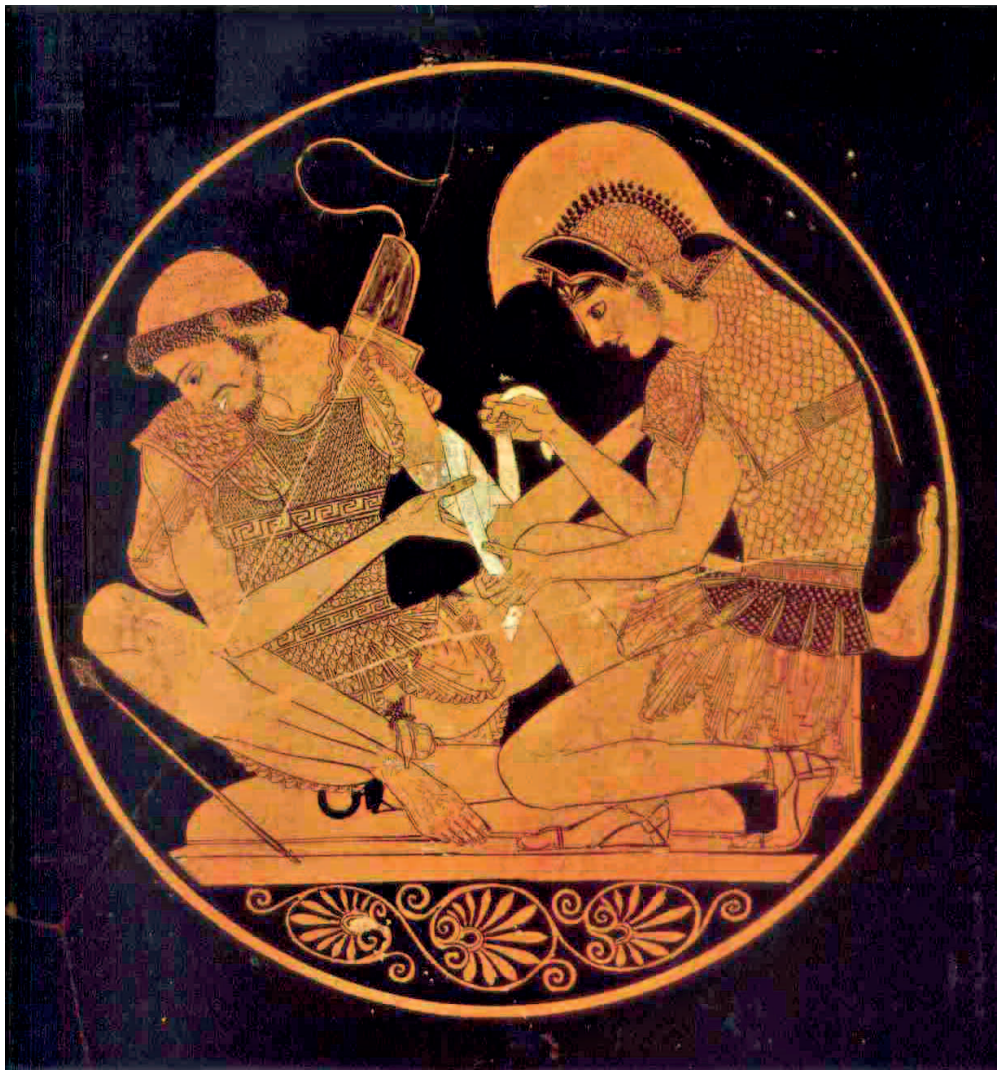

Achilles banding Patroclus wound (10X32cm). From the vase of potter Sosias (500 B.C.), one of the oldest images of medical practice. State Museum of Berlin (notice the sight and the eye of Achilles and of Patroclus)