Kikuchi-Fujimoto Disease Mimicking Tuberculous Lymphadenitis

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Abstract

A 28-year-old woman was referred to our hospital for treatment of tuberculous lymphadenitis, after presenting with fever, left cervical lymphadenopathy, and a positive interferon-gamma release assay (QuantiFERON®-TB Gold In-Tube; QFT) result. Surprisingly, biopsy specimens of the cervical lymph nodes showed necrotic lesions with prominent nuclear debris and a proliferation of histiocytes, consistent with Kikuchi-Fujimoto disease (KFD). A diagnosis was made of KFD complicated by latent tuberculosis infection (LTBI), and all symptoms had resolved completely two months post-diagnosis. KFD may be misdiagnosed as tuberculous lymphadenitis, and antibiotics unnecessarily prescribed. Careful attention should therefore be paid when diagnosing cervical lymphadenopathy.

Key words: Kikuchi-Fujimoto disease, tuberculous lymphadenitis, interferon-gamma release assay, QuantiFERON®-TB Gold In-Tube


Introduction

Histiocytic necrotizing lymphadenitis, or Kikuchi-Fujimoto disease (KFD), was first described in 1972 (1, 2); it is a benign disease mainly affecting young women (3-6). The presenting symptoms of fever and cervical lymphadenopathy mimic those of tuberculous lymphadenitis (5, 6), and care should be taken to distinguish between the two; comprehensive history-taking and physical examination are important for establishing a correct diagnosis of lymphadenopathy (7). Although definitive diagnosis requires surgical biopsy, patients may be hesitant to consent to the procedure because of cosmetic concerns (4). For this reason, non-invasive approaches (including blood examination, interferon-gamma release assay [QuantiFERON®-TB Gold In-Tube; QFT], fluorodeoxyglucose positron emission tomography [FDG-PET], and gallium scintigraphy) are helpful in differentiating KFD from similarly presenting diseases like malignant lymphoma, metastasis, tuberculous lymphadenitis and sarcoidosis (7). We report a case of KFD in a 28-year-old woman, which affected the left cervical lymph nodes, and was initially thought to be tuberculous lymphadenitis.

Case Report

A 28-year-old woman, a nurse, was referred to Kinki-Chuo Chest Medical Center for treatment of suspected tuberculous lymphadenitis. She had been in good health until one month previously, when she developed a low-grade fever and neck pain on the left side. Her family physician diagnosed a suspected case of tuberculous lymphadenitis based on a positive QFT result, with an interferon-gamma concentration of more than 15 IU/mL. As only 1.9% of healthy young women in their twenties are reported to have a positive QFT result (8), a QFT positivity of the present patient was the strong reason suggestive of active tuberculosis disease. Her sputum and gastric contents were negative for acid-fast bacilli, and her tuberculin skin test was posi-

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She did not have an unusual medical history. Physical examination revealed movable smooth hard lymph nodes swollen to walnut size in the left anterior cervical region at multiple sites. Her laboratory data showed an elevated erythrocyte sedimentation rate (ESR) (52 mm/hr; normal value: 3-15 mm/hr), but a normal white blood cell count (WBC) (5,000/μL; normal value: 3,000-8,000/μL) and normal C-reactive protein (CRP) level (0.23 mg/dL; normal value: less than 0.30 mg/dL). Anti-nuclear antibody (ANA) was negative and serum levels of C3 and C4 were also normal, making systemic lupus erythematosus (SLE) unlikely. Full laboratory data, including an infectious disease screen, are given in Table 1. Chest radiographic examinations were performed, including computed tomography, FDG-PET and gallium scintigraphy, and revealed no suggestion of infection, sarcoidosis or malignancy (including lymphoma).

Although the patient at first refused the recommended cervical lymph node biopsy because of cosmetic concerns, she made agreed to receive biopsy 4 days after referral. Biopsy specimens showed multiple necrotic lesions, prominent nuclear debris (Fig. 1a, b) and a proliferation of CD68-positive histiocytes (Fig. 1c). There were no epithelioid cell granulomas. The necrotic lesions contained comparatively few CD20-positive B-cells (Fig. 1d) and numerous CD3-positive T-lymphocytes (Fig. 1e), with a predominance of CD8-positive cells over CD4-positive cells. There were no keratin-positive cells on the AE1/AE3 and CAM5.2 stains (data not shown), and no evidence of microorganisms on Grocott, PAS, Ziehl-Neelsen, Gram or Warthin stains. Based on these findings, we made a histopathologic diagnosis of histiocytic necrotizing lymphadenitis (5, 6). The patient’s clinical course and histopathologic findings were consistent with the distinctive self-limiting nature of KFD. Repeated testing with QFT continued to yield positive results, and overt tuberculosis was excluded after further medical evaluations. We therefore diagnosed her as having latent tuberculosis infection (LTBI) and recommended treatment for it, especially in light of the patient’s status as a health care worker. However, the patient refused treatment because she had resigned from her job a week before referral, and had had no recent close contact with known cases of infectious tuberculosis. She also had concerns about the potential side effects of LTBI medication. We therefore followed her closely without the use of therapy, and all symptoms had completely resolved two months after the biopsy had been taken.

### Discussion

We report here a case of KFD that was originally thought to be cervical tuberculous lymphadenitis. Cervical lymphadenopathy can be indicative of such conditions as malignant lymphoma, metastasis, tuberculous lymphadenitis, sarcoidosis and KFD (5, 6), all of which can be associated with enlarged lymph nodes and fever. KFD is generally diagnosed on the strength of histopathologic findings in the affected lymph nodes (6), although patients are sometimes unwilling to undergo biopsies due to cosmetic concerns. However, because the clinical features of KFD are remarkably similar to those of tuberculous lymphadenitis, the two are commonly...
eral months. In the present case, all symptoms resolved totally benign and followed by complete recovery within several months. In the present case, the histologic findings associated with KFD are difficult to distinguish from those of SLE-associated lymphadenitis (3-6, 11-13). However, there was no evidence of any autoimmune disorders or active infection (including tuberculosis) in the present case. The clinical course of KFD is usually benign and followed by complete recovery within several months. In the present case, all symptoms resolved completely with no recurrence; the benign course of the disease in the absence of any therapy further supports the diagnosis of KFD in this patient.

QFT is a whole-blood diagnostic test that uses a mixture of synthetic peptides to simulate the TB proteins ESAT-6, CFP-10, and TB7.7 (14). The test results have high sensitivity and specificity (15), and are not affected by Bacillus Calmette-Guérin (BCG) vaccination or sensitization by most environmental mycobacteria. The United States Centers for Disease Control and Prevention (CDC) 2010 guidelines discuss interferon-gamma release assays in the diagnosis of LTBI (16). They note that the objective of testing for LTBI is to identify individuals who are at increased risk of developing tuberculosis, and who would therefore benefit from the treatment of LTBI. As noted, the present patient refused LTBI medication for reasons given earlier. The present patient’s lymphadenopathy and fever were manifestations of KFD, while QFT positivity was related to LTBI. However, the concurrent development of KFD and LTBI in the present case, as well as of KFD and active tuberculosis in another case report (17), lead us to wonder if the two conditions

misdiagnosed (9, 10). In the present case, for example, a positive QFT result seemed sufficient to diagnose tuberculosis. For this reason, a surgical lymph node biopsy should always be considered in order to accurately diagnose febrile cervical lymphadenopathy.

Also known as subacute necrotizing lymphadenitis, KFD often presents as a painful cervical lymphadenopathy in young women (3, 4, 6). It was first described in 1972 by both Kikuchi (1), and Fujimoto and colleagues (2). The most common clinical symptom is cervical lymphadenopathy, with or without fever. Laboratory findings are nonspecific (4, 11). There is much speculation as to the etiology of KFD. One possibility is that it is a lupus-like autoimmune condition triggered by certain infections, and in some cases the histologic findings associated with KFD are difficult to distinguish from those of SLE-associated lymphadenitis (3-6, 11-13). However, there was no evidence of any autoimmune disorders or active infection (including tuberculosis) in the present case. The clinical course of KFD is usually benign and followed by complete recovery within several months. In the present case, all symptoms resolved completely with no recurrence; the benign course of the disease in the absence of any therapy further supports the diagnosis of KFD in this patient.

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may be related. Further studies are needed in order to better elucidate the etiology of KFD.

In conclusion, recognition of KFD is crucial because its clinical course and treatment differ dramatically from those of malignant lymphoma, metastasis, tuberculous lymphadenitis, sarcoidosis and SLE (6, 7, 18). It is highly likely that cases of KFD have been missed, or misdiagnosed as tuberculous lymphadenitis, resulting in the unnecessary prescription of antibiotics (9). Physicians should therefore pay careful attention when diagnosing febrile cervical lymphadenopathy.

The authors state that they have no Conflict of Interest (COI).

References