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A case of Kikuchi-Fujimoto disease misdiagnosed as Hodgkin's lymphoma: the importance of second opinion

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Summary

Kikuchi-Fujimoto disease (KFD), a rare clinicopathological entity, is a benign and self-limiting disease. It was first described in 1972 by Kikuchi and Fujimoto in Japan independently. KFD is prevalent in Asia, although it may be seen in wide geographical areas, including Turkey. It mainly affects young women. Cervical lymphadenopathy is the most prominent sign and should be differentiated from lymphoproliferative, autoimmune, and infectious diseases. We report on a 30-year-old female patient who was referred to our medical oncology unit for chemotherapy and/or radiotherapy with diagnosis of Hodgkin's lymphoma. Ultimately her diagnosis was corrected as KFD after second opinion of the pathology specimens. We herein provide a brief review about KFD and the importance of second opinion of the pathology specimens.

Key words: Hodgkin's lymphoma, Kikuchi Fujimoto disease, misdiagnosis, lymphadenopathy, lymphoma, second opinion

Introduction

KFD is a subacute necrotizing lymphadenopathy of unknown etiology and is more common among young Asian women. It usually affects the cervical lymph nodes and is histologically characterized by histiocytic proliferation and necrosis of the involved lymph nodes [1]. It is thought to be a benign disorder with a typically self-limiting course. Malignant lymphomas represent a heterogeneous group of tumors with a wide range of clinical behavior. Accurate diagnosis and prognosis is critical in order to guide appropriate therapeutic decisions and, thus provide systemic or locoregional treatment. The value of consultative second opinions has been proven for general surgical pathology. In a study done by Westra et al. [2], the investigators reported that among 814 cases reviewed, the second opinion of surgical diagnosis resulted in 7% changed diagnoses. Of the changed diagnosis 24% involved a change from a benign to a malignant diagnosis; 15% involved a change from malignant to a benign diagnosis.

Herein we describe a woman who was misdiagnosed as Hodgkin's lymphoma experiencing an episode of KFD and referred to the medical oncology clinic for chemotherapy and/or radiotherapy.

Case presentation

A 30-year-old woman visited her primary care physician complaining of lymph nodes' swelling and tenderness on the left side of the neck with fever, night sweats, fatigue and weight loss for one month. Her past medical history was unremarkable. She was not under any medications, smoked 5 cigarettes/day for 20 years and did not drink alcohol.

He gave her a short course of antibiotics for a presumed upper respiratory tract infection which improved some of her symptoms, but the nodal enlargement per-

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sisted. There was 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.

Lab investigations showed normal complete blood count, erythrocyte sedimentation rate (ESR) 35 mm/h, C-reactive protein (CRP) 19 mg/dL (normal 0-5), lactate dehydrogenase (LDH) 510 IU/L (normal 0-450) and antistreptolysin (ASO) 470 units/ml (normal <200). The rest of the biochemical tests were within normal limits. Serologic examinations for hepatitis B surface antigen, syphilis, toxoplasma, Epstein-Barr virus (EBV) and cytomegalovirus (CMV) were negative.

A chest X- ray and computed tomography of the chest and abdomen were negative. An ultrasound of the cervical region revealed multiple lymphadenopathy (LAP) (maximum diameter 14 mm) in the posterior cervical triangle and supraclavicular region.

An excisional nodal biopsy from the left cervical region was performed, and the pathological diagnosis was Hodgkin's lymphoma. The patient was referred to our oncology unit for chemotherapy and/or radiotherapy.

As a rule, we re-examine the pathological specimens of our patients with lymphoma diagnosis, especially in cases where immunohistochemical staining has not been done. After the second opinion, the diagnosis was changed to Kikuchi-Fujimoto disease. The lymph node showed foci of necrosis with abundant apoptotic bodies surrounded by histiocytic cells and transformed lymphocytes, but without neutrophils (Figure 1).

The patient was given only meloxicam for symptomatic relief. Her symptoms and signs disappeared within 3 months. Her tests for autoimmune diseases, especially systemic lupus erythematosus (SLE) (such as ANA and anti-dsDNA), were negative. After 4 years of follow-up she is doing well, with no disease recurrence or no known autoimmune disease occurrence.

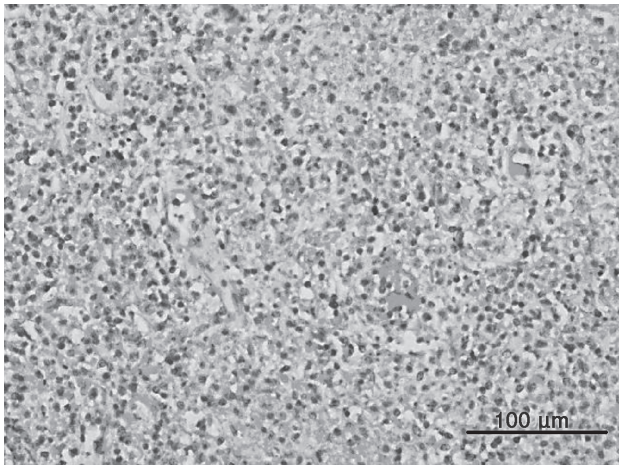

Figure 1. Necrosis, apoptosis, histiocytes, and lymphoid cells (H&E ×40).

Discussion

KFD, an histiocytic necrotizing lymphadenitis, is a rare clinicopathological entity which is a benign and self-limiting cause of LAP, and is usually seen in young (<30 years) females. It was first described in Japan in 1972 by Kikuchi and Fujimoto almost simultaneously [3,4].

The disease has a higher prevalence among Asiatic populations. Most cases were reported from the Far-East countries, especially Taiwan and Japan.

The etiology of the disease still remains unclear but viral or autoimmune causes have been suggested [5].

The onset of KFD is acute or subacute, evolving over a period of 2-3 weeks. About one third of the patients experience fever and other constitutional symptoms such as fatigue, joint pain, weight loss, anorexia, night sweats and rashes. LAP (unilateral tender LAP mostly in the posterior cervical region) is the *sine qua non* of the disease, while other frequent findings are erythematous rash and arthritis. Lab exams are usually nonspecific and suggest a viral disease. Mild leucopenia, increased ESR and anemia are the most frequent findings. Elevated transaminases and LDH may also be seen. One third of the patients have atypical peripheral blood lymphocytes [6].

The usefulnes of the fine needle aspiration biopsy (FNAB) to establish a diagnosis of KFD has been limited, thus diagnosis is usually based on excisional biopsy. Histological findings include paracortical areas of coagulative necrosis with abundant karyorrhectic debris. Karyorrhectic foci consist of various types of histiocytes, plasmacytoid monocytes, immunoblasts and small and large lymphocytes. There is abundance of T cells with predominance of $CD8^+$ over $CD4^+$ T cells [7].

In general KFD has a benign course. According to a recent review, 64% of KFD cases self-improved without any treatment, and 34% of the patients needed various anti-inflammatory drugs. Only 2.1% of patients had died of KFD [6].

One of the most important aspects of KFD is the differential diagnosis from other more important diseases by means of the clinical picture and pathologic examination. Any disease that causes enlargement of the cervical lymph nodes should be in the list of differential diagnosis. Since its course and treatment differ dramatically from those of lymphoma, TBC, SLE, other viral diseases, and metastatic adenocarcinoma, histological differential diagnosis is crucial. Histologically, the most important differential diagnosis is malignant lymphoma. Incomplete effacement of architecture by plasmacytoid monocytes and bland cytologic features are helpful for differentiating KFD from lymphomas [8]. Although immunoblasts are seen around the necro-

sis, classical Reed-Sternberg cells are not observed in these cases. In general, the experienced pathologist can differentiate KFD from Hodgkin's lymphoma.

The final diagnosis of the presented case was done by a second opinion of the pathology specimen. A report published by the Institute of Medicine on medical errors and public safety in the United States declared about 40-100,000 deaths per year resulting from different sort of medical errors. Indeed, pathologic misdiagnoses accounted for some (but unknown) percentage of those deaths [9]. Some studies argued about the routine or mandatory review by a second pathologist. In general, intradepartmental slide reviews would be easier in institutions that have more than one specialist but extradepartmental consultations do not seem to be a practical way for routine practice, at least in Turkey. The consensus conference of the American Society of Clinical Pathologists states that a pathologist should seek for second opinion in cases that are "problem-prone", as defined by the individual, the group or the literature. KFD has a well-defined perplexing histology that should be differentiated from malignant lymphomas. Thus, not for all lymphoma cases but for early-stage ones and if the clinical status and the pathological diagnosis are discordant, it would be safer to get a second opinion from an experienced hematopathologist.

Large series of second opinions about suspected cancer cases are to be found in the literature. Varying degrees of disagreement (0.26-10.5%) between referring physician and the consultant pathologist were seen and this depends on study design, institutional degree of care and specific organ of care [9]. Currently in Turkey, we do not have any report published concerning either intradepartmental interpathologist or extradepartmental interpathologist variability of the diagnosis, especially in oncopathology.

We accept that routine or mandatory second opinion is a debatable practice in terms of cost-effectiveness. But one should admit that changes in the pathological diagnosis and staging of some cancers may lead to changes in treatment modalities or a change in survival expectancy. Moreover, a shift in diagnosis from a malignant to a benign condition will prevent application of useless and toxic treatments. With this concern, we currently prefer to get a second opinion from our experienced pathologists for those patients with a "malignant" diagnosis anywhere except a tertiary medical center. Compared with western countries, the relatively low costs of pathologic examination in Turkey make us to think that routine second opinion is currently a feasible and cost-effective practice.

Histiocytic necrotizing lymphadenitis or KFD is a rare clinicopathological entity which should be kept in mind by both clinicians and pathologists in the differential diagnosis of cervical LAP. There are cases in the literature diagnosed as KFD after a few months of treatment for another disease. Thus, any patient in whom clinical suspicion arises, an excisional lymph node biopsy should be taken.

The true diagnosis of our case which was reported as Hodgkin's lymphoma was achieved with the second opinion of our hematopathologist. As an oncology unit in a tertiary center in Istanbul, Turkey, we always recommend getting a second opinion for the pathological diagnosis done in another center. This safe approach is feasible for the physician and the patient. In this paper, we first would like to mention that second opinion by a an experienced pathologist is an easy, cost-effective way of confirming the diagnosis of rarely encountered diseases and preventing patients from getting toxic and useless treatments. Also, as a second message, some rarely seen diseases, like KFD, should be taken into consideration in the differential diagnosis of cervical lymphadenopathy, otherwise it would be possible to administer primary chemoradiotherapy to a benign disease and follow the patient as if she/he has been cured with the therapy administered.

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