An Unusual Presentation of Kikuchi-Fujimoto Disease with Recurrent Fever and Syncope

QUYNH-LAN DAO, MD; BRIDGET HOTTENSTEIN, MD; VIJAIRAM SELVARAJ, MD, MPH

ABSTRACT

Kikuchi-Fujimoto (KF) disease, also known as necrotizing histiocytic lymphadenopathy, is a rare, benign disorder of the lymph nodes of young adults, predominantly young females. The exact cause of KF disease is unknown. Here, we report a young female with recurrent fever and syncopal episodes diagnosed with KF disease on lymph node biopsy.

KEYWORDS: Kikuchi-Fujimoto disease, Kikuchi's disease, syncope, fever of unknown origin

INTRODUCTION

Kikuchi-Fujimoto (KF) disease, also known as Kikuchi's disease, or necrotizing histiocytic lymphadenopathy, is a rare cause of fever of unknown origin (FUO). Most common causes of FUO are infections, malignancy, or autoimmune disease. We present a unique case of KF disease in a young female with Hodgkin's lymphoma who presented with recurrent fevers and syncope.

CASE PRESENTATION

A 34-year-old female with a history of Hodgkin's lymphoma status post-six cycles of Brentuximab Vedotin- doxorubicin/vinblastine/dacarbazine (July 2018–Dec 2018) in complete remission presented to the hospital with recurrent syncopal episodes for one month. She reported sitting on the toilet to urinate and then lost consciousness upon standing up. She denied hitting her head and did not have any prodromal symptoms. She has had approximately 9 to 10 episodes previously. She also endorsed having intermittent nonproductive cough, persistent high-grade fevers of up to 106F, nausea, vomiting, and unintentional weight loss. She had a similar presentation one week ago when an extensive workup was done that only showed new cervical and axillary lymphadenopathy, for which she underwent fine-needle aspiration of one of the lymph nodes. This showed a polymorphous lymphocytic population, favoring reactive lymphadenopathy. She improved with intravenous fluids and anti-emetics and was advised to follow up with her outpatient providers.

She denied having any chills or rigors during the febrile episodes, which occurred randomly throughout the day and without clear association with day/night cycles. She reported mild dysphagia due to thrush for which she was started on fluconazole as outpatient. Her medical history was significant for gestational diabetes mellitus. She is originally from Cape Verde and came to the United States approximately 14 years ago. She denied any traveling since then and has remained in the state of Rhode Island. She has no pets at home, nor does she have any animal exposures. She denied any tobacco use, alcohol use, or drug use. She denied any significant outdoor activities recently. She is fully vaccinated for COVID-19. She only takes fluconazole at home. Physical exam revealed two palpable nodes in the posterior neck/retrotruncal area (biggest was 2 cm, the other 1 cm). Orthostatic vital signs were negative.

A complete blood count showed leucopenia with borderline lymphopenia. A CT scan of the neck/chest/abdomen/pelvis with contrast found interval enlargement of the cervical and thoracic lymph nodes. Infectious diseases were consulted who recommended extensive workup. Liver function panel showed mild transaminitis with AST 318 IU/L (10–42 IU/L) and ALT 187 IU/L (6–45 IU/L). CRP was 16.56 mg/L (0-10mg/L) and ESR was 25mm/h (0-20mm/h). Parasite smear, hepatitis panel, treponemal antibody, anaplasma PCR, human herpesvirus-6 (HHV-6) PCR, QuantiFERON gold, Human Immunodeficiency Virus (HIV), toxoplasma, and antinuclear antibody (ANA) were negative. Cytomegalovirus (CMV) IgG was elevated, but CMV IgM was negative. Respiratory pathogen panel including SARS-CoV2 was negative. Blood cultures had no growth after five days. Epstein Barr Virus (EBV) IgG and Nuclear Ag Ab was elevated. Alpha 1 antitrypsin was mildly elevated. Echocardiogram was normal.

Surgery was consulted, who performed a left axillary lymph node biopsy. Flow cytometry revealed 64% T-cells; CD4:CD8 ratio = 2.2. The T-cell subsets showed polytypic TRBC1 expression. 32% B-cells; sIg kappa: sIg lambda light chain ratio = 1.6. Histiocytes were positive for CD4 and CD68. The cytotoxic marker Granzyme B was positive in numerous lymphocytes. The final biopsy diagnosis was KF lymphadenitis. She was discharged from the hospital with outpatient hematology follow-up. One week following discharge, she reported mild fatigue although her fevers had resolved, and lymphadenopathies improved.

DISCUSSION

Kikuchi-Fujimoto (KF) disease, also known as Kikuchi's disease, or necrotizing histiocytic lymphadenopathy, was first described in Japan by Masahiro Kikuchi and Y. Fujimoto et al. in 1972.[1] It has a worldwide distribution and affects predominantly young adults, especially young women of Asian descent. Patients most often present with cervical lymphadenopathy (most commonly in the posterior cervical triangle and the jugular carotid chain), and sometimes associated with fever and leucopenia. Affected individuals may also develop mild fever, myalgia, night sweats, and a rash. Less common symptoms include headaches, fatigue, joint pain (arthralgia), and nausea and vomiting. There is no definitive lab test for KF disease, although 25.5% to 58.3% of patients present with leucopenia[2].

Various infections such as toxoplasma, brucellosis, Yersinia enterocolitica, Bartonella henselae, and viruses such as herpes viruses, HIV, EBV, rubella are thought to play a role[3]. Some authors also hypothesize that KF disease may represent the body's autoimmune response to various stimuli, including the bacterial and viral agents listed above and dietary sources such as raw fish. There is also a possible role for interferon-gamma, interleukin-6 and apoptotic cell death in some cases[4]. KF disease has been known to have an association with the development of SLE in patients[5]. The diagnosis of SLE has been noted to occur before, during, or after the diagnosis of KF disease[6]. Electron micron studies have identified tubular reticular structures within the cytoplasm of histiocytes and lymphocytes in KF disease, that are also seen in patients with SLE and other autoimmune conditions[7]. Some investigators also believe KF disease could be an incomplete or self-limited form of an autoimmune condition due to an exuberant T cell response to a variety of non-specific stimuli.[8] Even though the two conditions share many clinical features, they are distinct in their histopathologic criteria.[9]

Confirmatory diagnosis is through lymph node biopsy. The minimum criteria for the diagnosis of KF disease are the presence of aggregated histiocytes with occasional crescent-shaped nuclei, plasmacytoid histiocytes, and scattered karyorrhexis.[10] Immunohistochemical stains typically demonstrate CD68+/CD123 plasmacytoid dendritic cells, CD68+/myeloperoxidase+ histiocytes, immunoblasts, abundance of CD8+ lymphocytes, and paucity of neutrophils.[8] Differential diagnoses of KF disease should include malignant lymphoma, metastatic carcinoma, Systemic Lupus Erythematosus (SLE), Hemophagocytic lymphohistiocytosis (HLH), toxoplasmosis and cat-scratch disease, and HIV/AIDS. Serologic testing for SLE is advisable whenever a diagnosis of KF disease is made. Diagnosis of SLE typically requires at least 4 of the 11 criteria to be met, and lymphadenitis is not one of the criteria. Lymph node biopsies typically reveal follicular hyperplasia, plasma cells, Azzopardi phenomenon and presence of hematoxylin bodies.[5] In our case, ANA and anti-ds DNA were negative. HLH was considered unlikely as the patient's triglyceride and fibrinogen levels were normal. Lymphoma was considered unlikely as fine-needle aspiration of the lymph nodes did not show findings consistent with malignancy.

The prognosis is good, and in most cases, the disease resolves spontaneously within several months. Therapy is rarely indicated in KF disease, and when required, it is geared towards symptomatic management. In some cases, glucocorticoids or hydroxychloroquine have been used with some success.[11,12] The recurrence rate can be anywhere from 4% to 15%.[13] To our knowledge, this is the first case of KF disease presenting with recurrent fever and syncopal episodes. There was one prior case report of a patient with FUO that had KF disease associated with EBV.[14] There is no known correlation between KF disease and Hodgkin's Lymphoma. In conclusion, although KF disease is benign, physicians must be aware of KF disease as early biopsy can be instrumental in reducing unnecessary investigations and in shortening the length of hospital stay. Patients with KF disease should also have continued long-term follow-up care due to their increased risk of developing SLE.

References

1. Kikuchi, M. Lymphadenitis showing focal reticulum cell hyperplasia with nuclear debris and phagocytosis. Nippon Ketsueki Gakkai Zasshi. 1972; 35: 379–380.
2. Kikuchi's disease (histiocytic necrotizing lymphadenitis). A clinicopathologic study of 79 cases with an analysis of histologic sub-types, immunohistology, and DNA ploidy. Kuo TT. https://insights.ovid.com/crossref?an=00000478-199507000-00008. Am J Surg Pathol. 1995;19:798–809.
3. Lerosey Y, Lecler-Scarcella V, Francois A, Guitrancourt JA. A pseudo-tumoral form of Kikuchi's disease in children: a case report and review of the literature. Int J Pediatric Otorhinolaryngol. 1998;45:1–6.
4. Kubota N, Tsukamoto R, Kurakawa K, Imai T, Furusho K. Elevated serum interferon gamma and interleukin-6 in patients with necrotizing lymphadenitis (Kikuchi's disease). Br J Haematol. 1996;95:613–615.
5. Deaver D, Horna P, Cualing H, Sokol L. Pathogenesis, diagnosis, and management of Kikuchi-Fujimoto disease. Cancer Control. 2014 Oct;21(4):313-21. doi: 10.1177/107327481402100407. PMID: 25310212.
6. Martínez-Vázquez C, Hughes G, Bordon J, Alonso-Alonso J, Anibarro-Garcia A, Redondo-Martínez E, Touza-Rey F. Histiocytic necrotizing lymphadenitis, Kikuchi-Fujimoto's disease, associated with systemic lupus erythemotosus. QJM. 1997 Aug;90(8):531-3. doi: 10.1093/qjmed/90.8.531. PMID: 9327032.
7. Dorfman RF. Histiocytic necrotizing lymphadenitis of Kikuchi and Fujimoto. Arch Pathol Lab Med. 1987 Nov;111(11):1026-9. PMID: 3662766.
8. Bosch X, Guilabert A, Miquel R, Campo E. Enigmatic Kikuchi-Fujimoto disease: a comprehensive review. Am J Clin Pathol. 2004 Jul;122(1):141-52. doi: 10.1309/YF08-1L4T-KYWV-YVPQ. PMID: 15272543.
9. Hu S, Kuo TT, Hong HS. Lupus lymphadenitis simulating Kikuchi's lymphadenitis in patients with systemic lupus erythematosus: a clinicopathological analysis of six cases and review of the literature. Pathol Int. 2003 Apr;53(4):221-6. doi: 10.1046/j.1320-5463.2003.01458.x. PMID: 12675765.

10. Tsang WY, Chan JK, Ng CS. Kichuchi's lymphadenitis. A morphologic analysis of 75 cases with special reference to unusual features. Am J Surg Pathol. 1994;18(3):219-231.
11. Yoshioka K, Miyashita T, Nakamura T, Inoue T, Yamagami K. Treatment of histiocytic necrotizing lymphadenisis (Kikuchi's disease) with prolonged fever by a single course of methylprednisolone pulse therapy without maintenance therapy: experience with 13 cases. Intern Med. 2010;49:2267–2270.
12. Rezai K, Kuchipudi S, Chundi V, Ariga R, Loew J, Sha BE. Kikuchi-Fujimoto disease: hydroxychloroquine as a treatment. Clin Infect Dis. 2004; 39:124–126.
13. Cheng CY, Sheng WH, Lo YC, et al. Clinical presentations, laboratory results and outcomes of patients with Kikuchi's disease: emphasis on the association between recurrent Kikuchi's disease and autoimmune diseases. J Microbiol Immunol Infect. 2010;43(5):366-371.
14. Moyer A, Hanafi MZ, Scordino T, Bronze M. Kikuchi-Fujimoto Disease: An Atypical Presentation of a Rare Disease. Cureus. 2019 Feb 1;11(2):e3999. doi: 10.7759/cureus.3999. PMID: 30989008; PMCID: PMC6445562.

Authors

Quynh-Lan Dao, MD, Division of Hospital Medicine, The Miriam Hospital, Providence, RI.

Bridget Hottenstein, MD, Division of Hospital Medicine, The Miriam Hospital; Warren Alpert Medical School of Brown University, Providence, RI.

Vijairam Selvaraj, MD, MPH, Division of Hospital Medicine, The Miriam Hospital; Warren Alpert Medical School of Brown University, Providence, RI.

Correspondence

Vijairam Selvaraj, MD, MPH
The Miriam Hospital
164 Summit Ave, Providence, RI, 02906
vijairam.selvaraj@lifespan.org