Kikuchi Fujimoto disease: sinister presentation, good prognosis

Rahim A. Jiwani a, Daniel N. Jourdan b, Adrian Pona c, Deepak Donthi d, J. Stephen Stalls e and Rita W. Rehana a

Abstract
Kikuchi-Fujimoto disease (KFD) is a rare, benign, self-limiting necrotizing lymphadenitis of unknown etiology. The disease can affect people of all ages and of any sex and ethnicity. Tissue biopsy is needed for accurate diagnosis. The condition commonly masquerades as more sinister conditions such as malignancy and rheumatologic disorders, but has a much better prognosis. Treatment is generally supportive but patients may require corticosteroids with eventual spontaneous resolution. We discuss a case of KFD in a 34-year-old male and highlight the need for prompt and accurate diagnosis.

1. Introduction
Kikuchi-Fujimoto disease (KFD) is an extremely rare self-limiting disease of unknown etiology [1]. Clinical features include fever, anterior cervical lymphadenopathy, and night sweats. The hallmark histopathological finding is necrotizing lymphadenitis with absence of neutrophils [1]. Although KFD traditionally affected young Asian women, recent literature suggests the disease can affect both males and females irrespective of race or ethnicity [2,3]; however, the true incidence is unknown as many cases go undiagnosed [2]. Furthermore, its nonspecific clinical presentation garners a broad differential diagnosis and may be mistaken for systemic lupus erythematosus (SLE), lymphoma, sarcoidosis, disseminated tuberculosis or viral lymphadenitis [2,4,5]. Nonetheless, definitive diagnosis is made by lymph node biopsy demonstrating necrotizing foci in paracortical regions [2]. Since KFD is rare, may occur in any patient irrespective of race or gender, and may present with nonspecific symptoms, it may create a diagnostic challenge. We report a challenging case of Kikuchi-Fujimoto disease in the USA.

2. Case
(Image 1)A 34-year-old African American male with no past medical history presented to the hospital with a 6 week history of generalized malaise, headache, 15 pound weight loss, subjective fevers, in addition to diffuse, non-tender lymphadenopathy. He previously failed two separate courses of doxycycline and levofloxacin in the outpatient setting. On arrival to the emergency department, the patient was febrile (100.4 degrees Fahrenheit) without other vital sign abnormalities. Physical exam findings included diffuse, nontender, nonmobile, cervical, and peri-auricular lymphadenopathy. Initial laboratory studies revealed pancytopenia, elevated erythrocyte sedimentation rate and lactate dehydrogenase (Table 1). Peripheral blood smear showed normal appearing granulocyte and erythrocyte colonies with giant platelets present. The constellation of findings in the setting of B-symptoms were concerning and differential diagnosis included lymphoma, SLE, human immunodeficiency virus, and infection. Both autoimmune and infectious testing were negative (Table 2). Chest computed tomography scan was unremarkable; however, abdominal and pelvic computed tomography reported retroperitoneal and inguinal adenopathy. Since noninvasive diagnostic tests were nonspecific, an excisional lymph node biopsy was performed. Flow cytometry was negative for monotypic B-cells of aberrant CD4:8 ratio that may be indicative of lymphoma. Immunohistochemistry reported histiocytic necrotizing lymphadenitis and lymphoid cells located pericapular with extensive areas of necrosis and apoptotic debris (Image 1 and 2). Since the necrotizing lymphadenitis had absent neutrophils, histopathology was consistent with KFD (Image 3). As the condition is extremely rare in the USA, tissue samples were sent to another institution for pathology review which confirmed the diagnosis. Due to the patient’s ongoing symptoms, he was started on a prednisone taper, 75 milligrams...
viral infection or an autoimmune process are the two most common theories. Disease characteristics suggesting a viral etiology include inadequate antibiotic response and histopathological features representing a viral response; however no association exists between KFD and a specific virus [6]. The theory of autoimmune etiology focuses on a T-cell-mediated immune response to antigens in genetically susceptible individuals [7]. Specific HLA antigens are more frequently found in Kikuchi-Fujimoto patients [8]. Furthermore, some patients with KFD have a history of SLE [9].

(Image 3)Kikuchi-Fujimoto disease typically takes a subacute course, evolving over multiple weeks. Physical exam and laboratory findings in KFD are wide ranging and variable. The two most common findings are tender posterior cervical lymphadenopathy and fevers. However, lymph node involvement can encompass other regions or be generalized. In addition to fevers, patients may also experience weight loss, weakness, arthralgia and night sweats [10]. Laboratory findings can include elevated C-reactive protein, erythrocyte sedimentation rate, LDH as well as anemia, leukopenia and pancytopenia [11]. Our patient had significant constitutional symptoms but interestingly enough, did not have tender lymphadenopathy, Leukopenia and thrombocytopenia were present, however inflammatory markers were only minimally elevated. Overall the findings were not specific for any one diagnosis. Since the differential diagnosis for B-symptoms includes lymphoma, a biopsy is necessary to make the diagnosis of KFD and rule out malignancy [12]. In one retrospective observational study of 75 patients diagnosed with KFD, the most common histopathologic findings included karyorrhectic and eosinophilic granular debris, histiocytes, plasmacytoid monocytes, and variable numbers of immunoblasts [13]. The pathologic findings of lymph node biopsy in our patient reported necrotizing lymphadenitis with focal areas of necrosis and abundant histiocytes, apoptotic debris, occasional eosinophils and marked absence of

3. Discussion

(Image 2)Although the pathogenesis of Kikuchi-Fujimoto disease is not well known, a preceding

Table 1. Comprehensive Metabolic Panel, Complete Blood Count, Lactate Dehydrogenase.

| Labs                        | Value   | Reference range |
|-----------------------------|---------|-----------------|
| White blood cells           | 1.5 k/ul| 4.5–11.0 k/ul   |
| Neutrophils                 | 810 (55%)| 2200–8900/ul    |
| Lymphocytes                 | 580 (39.5%)| 1200–3400/ul    |
| Monocytes                   | 70 (4.8%)| 100–600/ul      |
| Eosinophils                 | 0 (0%)  | 0–500/ul        |
| Basophils                   | 10 (0.7%)| 0–200/ul        |
| Red blood cells             | 4.1 M/ul| 3.8–5.2 M/ul    |
| Hemoglobin                  | 11.9 g/dL| 12–16 g/dL      |
| Platelets                   | 117 k/ul| 150–440 k/ul    |
| Lactate Dehydrogenase       | 1,016 U/L| 50–160 U/L      |
| Aspartate aminotransferase  | 117 U/L | 5–34 U/L        |
| Alanine aminotransferase    | 91 U/L  | 0–55 U/L        |
| Bilirubin, total            | 0.5 mg/dL| 0.1–1.2 mg/dL   |

Table 2. Hepatitis panel, inflammatory markers, autoimmune and infectious work up.

| Labs                        | Value   | Reference range |
|-----------------------------|---------|-----------------|
| Hepatitis C antibody        | Negative| N/A             |
| Hepatitis A antibody, IgM   | Negative| N/A             |
| Hepatitis B core antibody   | Negative| N/A             |
| ANA titer                   | <1:40   | <1:40           |
| Anti-dsDNA antibody         | Negative| N/A             |
| Complement C3               | 99 mg/dL| 82–185 mg/dL    |
| Complement C4               | 30 mg/dL| 15–53 mg/dL     |
| Monospot test               | Negative| N/A             |
| Streptococcus A antigen     | Negative| N/A             |
| RSV/Influenza A/B           | Negative| N/A             |
| HIV antigen/antibody        | Negative| N/A             |
| HIV RNA                     | Negative| N/A             |
| C-Reactive protein, High sensitivity | 6.0 mg/L | <5.0 mg/L |
| Erythrocyte sed rate        | 23 mm/h | 0–12 mm/h       |

ANA: antinuclear antibody; Anti-dsDNA: anti-double stranded DNA; RSV: respiratory syncytial virus; HIV: human immunodeficiency virus; RNA: Ribonucleic acid

(mg) for 2 weeks; 50 mg for 1 week, 20 mg for 1 week and finally 5 mg for 1 week. At 3-week follow-up, his B symptoms, lymphadenopathy, and pancytopenia resolved; however, patient was referred to a rheumatologist due to increased risk of SLE.

Image 1 20x (H&E) – Section shows predominantly lymphoid population in sheets (black arrows) with areas of necrosis, without neutrophilic infiltrate.
neutrophils. Since the presence of eosinophils in areas of necrosis is uncommon, our biopsy was confirmed at another tertiary care institution to be most indicative of Kikuchi lymphadenopathy.

The most common associated autoimmune disease in KFD is SLE [14]. KFD can precede SLE or present simultaneously [15]. Some studies suggest screening for SLE with an antinuclear antibody test during the initial diagnostic workup, especially in patients with cutaneous involvement [15]. Some studies believe KFD may represent a self-limiting lupus-like spectrum induced by lymphocytes [6,16]. Such findings favor an autoimmune process causing Kikuchi-Fujimoto disease, however, further research is necessary to confirm the aforementioned theory. Since a long-standing correlation between SLE and KFD exists, general consensus recommends a rheumatologic follow-up for all patients with KFD.

Kikuchi-Fujimoto disease is generally self-limiting and resolves within 6 months [17]. Patients with more severe or relapsing disease may benefit from systemic corticosteroids or hydroxychloroquine as some studies reported successfully treating relapsing KFD [17,18]. However, no therapeutic guidelines exist as evidence for treating KFD are limited to observational studies. Kikuchi-Fujimoto patients should be followed with periodic blood work as 5% of patients develop symptom recurrence [17]. Some cases may suffer fatal complications such as myocardial involvement, cerebral hemorrhage, or hemophagocytic lymphohistiocytosis, however, such complications are rare [11].

Kikuchi-Fujimoto diseases’ rarity and nonspecific clinical presentation provides a diagnostic challenge that can only be solved with definitive testing in the form of tissue biopsy [19]. Nonetheless, prognosis is good. Although there are no therapeutic guidelines, the reported use of systemic corticosteroids from observational studies is beneficial [1,17]. Increased awareness of Kikuchi-Fujimoto disease may lead to heightened recognition by providers and avoidance of unnecessary diagnostics or therapeutics.

Acknowledgments
We thank East Carolina University departments of Internal Medicine and Pathology for support.

Author contributions
R. Jiwani wrote and edited the manuscript and is the article guarantor. D. Jourdan, R. Rehana both wrote and edited the manuscript. A. Pona edited and revised the manuscript. D. Donti and S. Stalls provided images and descriptions for the manuscript.

Disclosure statement
The author declares that there is no conflict of interest regarding the publication of this article.
ORCID
Rahim A. Jiwani http://orcid.org/0000-0002-1324-865X
Adrian Pona http://orcid.org/0000-0002-0087-7326

References
[1] Rammohan A, Cherukuri SD, Manimaran AB, et al. Kikuchi-Fujimoto disease: a sheep in wolf’s clothing. J Otolaryngol Head Neck Surg. 2012;41(3):222–226.
[2] Archibald DJ, Carlson ML, Gustafson RO. Kikuchi-Fujimoto disease in a 30-year-old caucasian female. Int J Otolaryngol. 2009;2009:901537.
[3] Bosch X, Guilabert A. Kikuchi-Fujimoto disease. Orphanet J Rare Dis. 2006;1:1.
[4] Magnani G, Cocca G, Mezzadri S, et al. Kikuchi’s disease: an uncommon cause of fever of unknown origin. Ann Ital Med Int. 1999;14(3):205–208.
[5] Dorfman RF, Berry GJ. Kikuchi’s histiocytic necrotizing lymphadenitis: an analysis of 108 cases with emphasis on differential diagnosis. Semin Diagn Pathol. 1988;5(4):329–345.
[6] Bosch X, Guilabert A, Miquel R, et al. Enigmatic Kikuchi-Fujimoto disease: a comprehensive review. Am J Clin Pathol. 2004;122(1):141–152.
[7] Jamal A. 2012. Kikuchi Fujimoto disease. Clinical medicine insights: arthritis and Musculoskeletal Disorders. 5. p.CMAMD.S9895.
[8] Tanaka T, Ohmori M, Yasunaga S, et al. 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(3):246–253.
[9] Dumas G, Prendki V, Haroche J, et al. Kikuchi-Fujimoto disease: retrospective study of 91 cases and review of the literature. Medicine (Baltimore). 2014;93 (24):372–382.
[10] Kucukardali Y, Solmazgul E, Kunter E, et al. Kikuchi-Fujimoto Disease: analysis of 244 cases. Clin Rheumatol. 2007;26(1):50–54.
[11] Dever D, Horna P, Cualing H, et al. Pathogenesis, diagnosis, and management of Kikuchi-Fujimoto disease. Cancer Control. 2014;21(4):313–321.
[12] Storck K, Brandstetter M, Keller U, et al. Clinical presentation and characteristics of lymphoma in the head and neck region. Head Face Med. 2019;15(1):1.
[13] Tsang WY, Chan JK, Ng CS. Kikuchi’s lymphadenitis. A morphologic analysis of 75 cases with special reference to unusual features. Am J Surg Pathol. 1994;18 (3):219–231.
[14] Goldblatt F, Andrews J, Russell A, et al. Association of Kikuchi–Fujimoto’s disease with SLE. Rheumatology. 2008 April;47(4):553–554. .
[15] Vithoosan S, Karunarathna T, Shanjeeban P, et al. Kikuchi-Fujimoto disease associated with systemic lupus erythematosus complicated with hemophagocytic lymphohistiocytosis: a case report. J Med Case Rep. 2019;13(173).
[16] Correa H. Kikuchi-Fujimoto disease: an exuberant localized T cell activation arrested by histiocytes? Medscape Womens Health. 1996;4(3):5.
[17] Jang YJ, Park KH, Seok HJ. Management of Kikuchi’s disease using glucocorticoid. J Laryngol Otol. 2000;114 (9):709–711.
[18] Honda F, Tsubo H, Toko H, et al. Recurrent Kikuchi-Fujimoto disease successfully treated by the concomitant use of hydroxychloroquine and corticosteroids. Int Med. 2017;56(24):pp.3373–3377.
[19] Bakir R, Lecapitaine AL, Chevalier J, et al. [Kikuchi-Fujimoto’s disease or histiocytic necrotizing lymphadenitis: A report of two familial cases]. Rev Med Interne. 2016;37(11):771–774.