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Kikuchi Fujimoto Disease: An Unusual Association with Bicytopenia Mimicking Lymphoma

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Abstract We report a case of Kikuchi-Fujimoto disease (KFD) in an 18-year-old African American female who presents with a high-grade fever, sweating, and painful right-sided cervical lymphadenopathy. Lab analysis showed leukopenia, thrombocytopenia, and an elevated C-reactive protein. The remaining infectious and autoimmune work-up was negative. Given her clinical presentation, an infectious etiology was suspected, and broad-spectrum antibiotics were empirically started. Bicytopenia in the setting of lymphadenopathy raised the suspicion for lymphoma with bone marrow infiltration. An excisional biopsy was performed, and a histological exam of the lymph nodes showed necrotizing histiocytic lymphadenitis consistent with KFD. She was discharged on Naproxen and Tylenol with a referral to Rheumatology. This case highlights the rarity of bicytopenia in KFD and the importance of early and prompt diagnosis in order to avoid unnecessary testing and inappropriate treatment.

Keywords: *Kikuchi-Fujimoto Disease, lymphadenopathy*

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1. Introduction

Kikuchi-Fujimoto Disease (KFD), also known as histiocytic necrotizing lymphadenitis, is a rare and benign form of regional non-granulomatous necrotizing lymphadenitis of unclear etiology. The condition was first described in Japan by a pathologist Dr. Masahiro Kikuchi and separately by Fujimoto Y in 1972. KFD is classically seen in young women of Japanese descent and presents as cervical subacute necrotizing lymphadenitis [1,2].

Kucukardali et al. report 330 cases of KFD worldwide, with approximately 50% of cases in East Asia. The remaining cases have been reported in the United States [3]. KFD has been reported in various ethnicities, races, and across the age spectrum [4,5]. However, it is predominantly linked to HLA subtypes DPA1 and DPAB1, which are commonly present in Asians.

KFD usually presents as localized lymphadenopathy that more commonly affects the posterior cervical group, and is associated with upper respiratory symptoms, fever of unclear origin, and weight loss [6,7]. laboratory results sometimes shows leucopenia (18%) and anemia (9%) but thrombocytopenia (4%) and leukocytosis (2%) are rarely seen in patients with KFD [3].

KFD shares features of serious illnesses including lymphoma, tuberculosis, infectious mononucleosis, and autoimmune diseases, such as sarcoidosis [3]. Many cases can be initially misdiagnosed specially when patients develop bicytopenia, which is why early recognition of the disease is essential.

2. Case Description

An 18-year-old African American female with no significant past medical history presents with a high-grade fever and painful right-sided neck swelling for one week. Associated symptoms included fatigue, myopathy, and hyperhidrosis. There was no prior history of a viral upper respiratory tract infection, sick contacts, recent travel, or intravenous drug use.

On physical examination, she was found to be hemodynamically stable and febrile with a temperature of 103°F. She was also found to have extensive right-sided, posterior cervical lymphadenopathy that was tender and warm to touch. Her cardiovascular and respiratory systems were unremarkable. Her abdomen was

soft and non-tender with no clinically detectable organomegaly.

Laboratory findings showed leucopenia with a WBC count of 2.5×10^6/ml, thrombocytopenia with a platelet count of 96,000 and an elevated C-reactive protein. Erythrocyte sedimentation rate, antinuclear antibody, rheumatoid factor, and angiotensin converting enzyme were negative. HIV, hepatitis panel, rapid plasma reagin test, Cytomegalovirus IgM, Epstein Barr Virus IgM, Toxoplasma, Rubella, and monospot tests were also negative.

A CT scan of the neck showed right cervical, posterior triangle and supraclavicular lymphadenopathy (Figure 1). A CT scan of the chest, abdomen, and pelvis were unremarkable. Given her clinical presentation, an infectious etiology was suspected, and broad-spectrum antibiotics were empirically started. Bicytopenia in the setting of lymphadenopathy and failure to respond to antibiotics raised the suspicion for lymphoma with bone marrow infiltration. Ultrasound-guided lymph node excisional biopsy was performed, which showed necrotizing histiocytic lymphadenitis, consistent with KFD (Figure 2). Grocott-Gomori methenamine silverand acid fast bacillistains were negative for bacterial, fungal, and acid-fast microorganisms. In addition, a lymph node biopsy culture did not grow any organisms. After the diagnosis of KFD was made, antibiotic therapy was discontinued. The patient was managed with Naproxen and Tylenol and was discharged home with a referral to Rheumatology for a full workup.

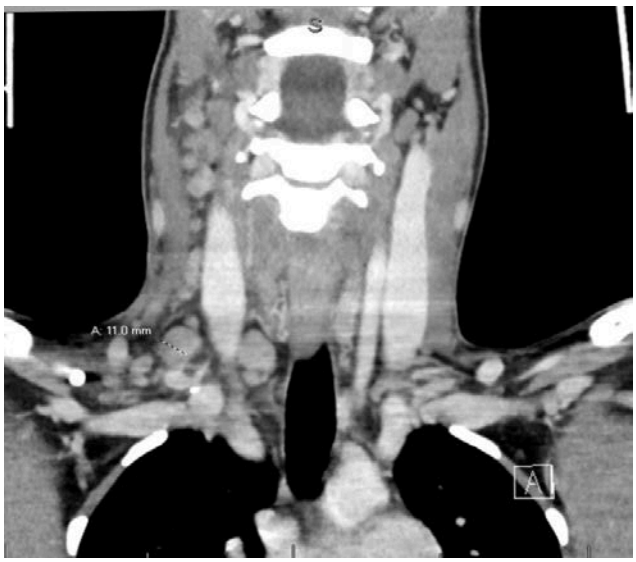

Figure 1. CT Scan of the Neck showing regional lymphadenopathy (white arrow)

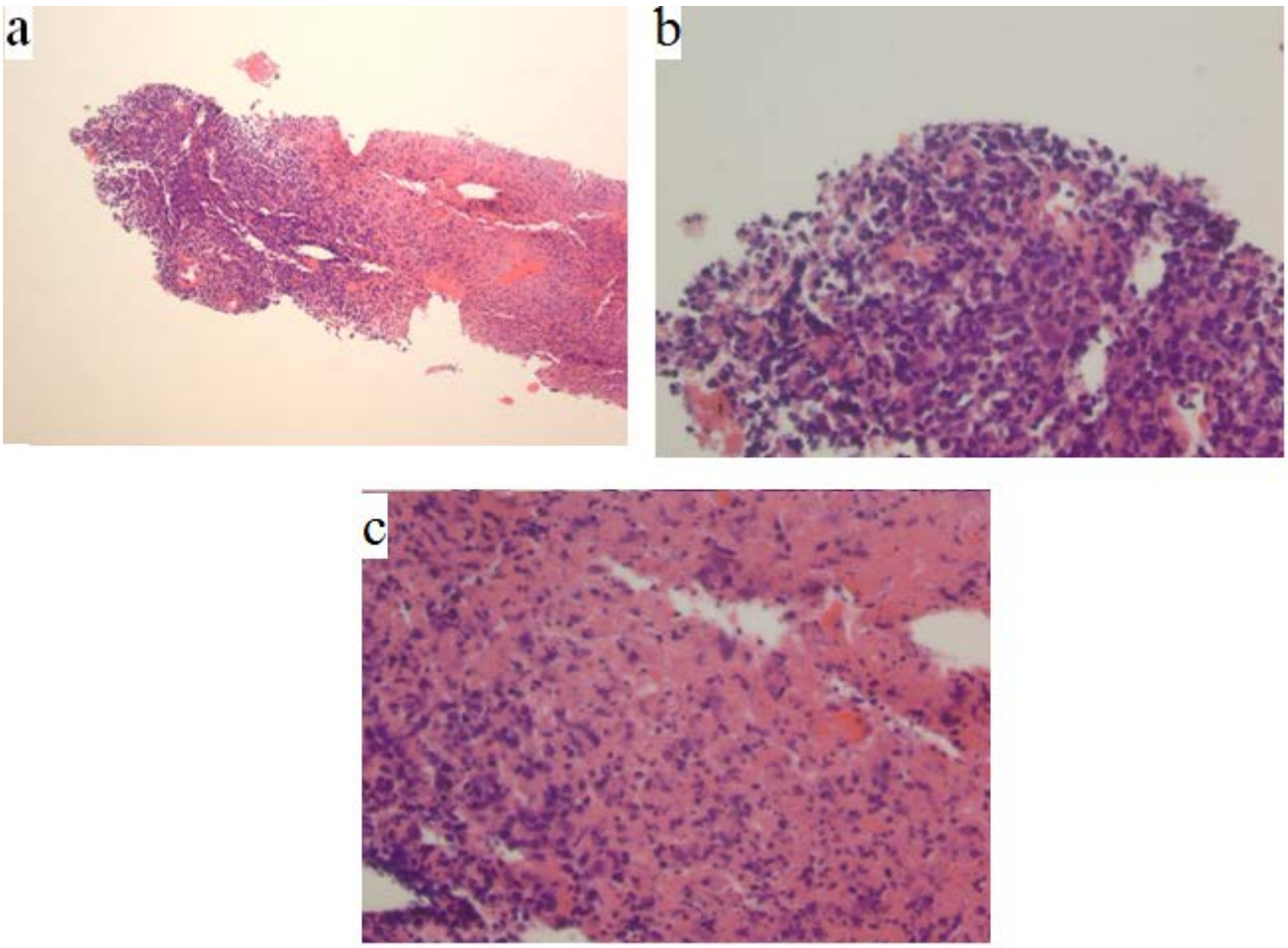

Figure 2. a. Low power view showing residual lymph node tissue (on the left part of the slide) transitioning to necrotizing area. b. Higher power view of the residual lymphoid tissue showing a mixture of small and large lymphocytes (these are reactive changes). c. Higher power view of the necrotizing area showing necrosis, apoptosis and focal histiocytes.

3. Discussion

KFD is a rare condition especially in the United States [3] such that many theories had been proposed for the pathogenesis of KFD based on the observation of positive serology of various viral infections. One theory is the link of KFD to Systemic Lupus Erythematosus (SLE) [8,9]; Kucukardali et al. reported that 32 cases of KFD were associated with SLE. Of these cases, 18 had both KFD and SLE simultaneously, 6 developed SLE later, and 4 had a past medical history significant for SLE. Baenas et al. identified three patterns of association: a diagnosis of KFD before the onset of SLE (30%), occurrence of both diseases simultaneously (47%), and KFD after SLE (23%). Therefore, Long-term follow up of KFD patients is important to look for manifestations of SLE. Despite a multitude of studies that demonstrate a link between KFD and SLE, the exact pathogenesis of this association is not well understood [3,10,11]. Another is that KFD could be secondary to a viral infection based on the fact that there is significant histiocytes and CD8-positive lymphocytes in KFD-affected lymph nodes. Moreover; some studies have demonstrated an association between HHV6 and KFD. Dominguez et al. reports 42 KFD patients who were tested for HHV6 serology and 32 of them were found to have highly positive titration. The polymerase chain reaction and in situ hybridization detected HHV6 in the lymphoid tissue in ten and four of the cases, respectively. However, other studies failed to demonstrate an association [3,10].

Others theorize that KFD could be a manifestation of a broader autoimmune disease [10]. KFD is self-limiting in the majority of patients and treatment is generally supportive [12,13]. Nevertheless, many patients report persistent symptoms that require further treatment. Of those patients many have responded to the combination of a high-dose glucocorticoid and intravenous immune globulin [14]. Alternatively, Hydroxychloroquine monotherapy or in combination with a glucocorticoid has shown some benefit [15,16,17].

Differentiation between KFD and lymphoma is crucial as both have similar clinical picture and typical F-FDG PET/CT findings. However, patients with lymphoma tend to have extranodal involvement in comparison with KFD patients [18]. Therefore, histopathology is the gold-standard to make the diagnosis, FNAC diagnostic accuracy has been estimated at 56.3%. It has been considered the earliest recognizable foci and minimum diagnostic criterion of KFD are paracortical clusters of plasmacytoid monocytes with interspersed karyorrhexis and crescentic histocytes. Irregular paracortical areas of coagulative necrosis is recognized finding, which together with the cytological composition of karyorrhectic debris distort the nodal architecture. Kuo had proposed 3 evolving histologic stages according to the predominant cells: Proliferative stage with various plasmacytoid monocytes, Necrotizing when coagulative necrosis is the predominant finding and Xanthomatous when foamy histocytes predominates. Kuo also pointed out that these 3 histologic types might represent different stages of the disease or might reflect differences in etiologies or host reaction. However, sequential biopsy specimens were not available in the study by Kuo to verify this postulated concept [6].

4. Conclusion

KFD can mimic lymphoma, tuberculosis, and infectious lymphadenitis but favorable prognosis. Henceforth, and in the interest of high quality and cost-effective medical care, KFD should be kept in the differentials, especially in young patients, presenting with cervical lymphadenopathy. Also, rare findings like thrombocytopenia can be seen in KFD.

Abbreviations

KFD: Kikuchi-Fujimoto Disease
HLA: Human Leukocyte Antigen
SLE: Systemic Lupus Erythematosus
WBC: White Blood Cells
HHV-6: Human herpesvirus 6
GMS: Gram, Grocott-Gomori'smethenamine silver
AFB: acid fast bacilli
CT scan: Computed tomography Scan
HIV: Human Immunodeficiency Virus
IgM: Immunoglobulin M
CD8: Cluster of Differentiation 8

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