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Kikuchi-Fujimoto disease in a Patient with Systemic Lupus Erythematosus presented with Fever and Lymphadenopathy

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ABSTRACT

Kikuchi-Fujimoto disease is a rare benign cervical lymphadenopathy, which often affects young adult women. Its etiology and pathogenesis are unknown. Kikuchi is an uncommon cause of pyrexia of unknown origin (PUO).Here; we report the association between necrotizing lymphadenitis suggestive of Kikuchi in a young lady newly diagnosed with Systemic Lupus Erythematosus (SLE). Our patient presented with PUO, cervical and axillary lymphadenopathy as well as autoimmune hemolytic anemia (AIHA) and was managed successfully with prednisolone and azathioprine.

Keywords: SLE, Kikuchi-Fujimoto, Histiocytic necrotizing lymphadenitis.

1. INTRODUCTION

Kikuchi-Fujimoto disease is a benign self-limiting cervical lymphadenopathy of unknown etiology first described in Japan in 1972. It often affects young adult women (Bosch et al. 2006) and reported during pregnancy as well (Alijotas-Reig et al. 2008). Although, the etiology of the lesion is still unclear, the possible association with EBV, HHV6, HHV8, parvovirus B19, Toxoplasma gondii, and Yersinia enterocolitica suggests an infectious cause. KD has also been recorded in HIVand HTLV-1-positive patients (Pileri et al. 2005). Clinically, cervical lymphadenopathy in Kikuchi-Fujimoto disease is observed (Bosch et al. 2006) but enlargement of lymph nodes in other regions also reported mainly axillary (Kim et al. 2011), (Yilmaz et al. 2006), (Rao et al. 2006), (Dalkiliç et al. 2001), (Vilá et al. 2001) , but mediastinal, supraclavicular, submandibular, inguinal, para-aortic (Kim et al. 2011), mesenteric (Alijotas-Reig et al. 2008) also reported, sometimes in the form of generalized lymphadenopathy (Kim et al. 2011). The affected lymph

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nodes vary in size from 0.5 to 7 cm of diameter with median size of 1.5 cm, and may be tender or painful (Hrycek et al. 2005). In addition to lymphadenopathy, 30 to 50% of patients with KFD may have fever, usually of low-grade, associated with upper respiratory symptoms. Less frequent symptoms include weight loss, nausea, vomiting, sore throat and night sweats (Bosch et al. 2006) Sometimes splenomegaly and hepatomegaly are encountered (Hrycek et al. 2005). Laboratory findings are not specific including approximately 50% of patients with Kikuchi-Fujimoto disease show leukopenia, 5% have leukocytosis, and 25% have atypical lymphocytosis (Kim et al. 2011). Kikuchi-Fujimoto disease is typically self-limited within one to four months. A low but possible recurrence rate of 3 to 4% has been reported. In some few patients, SLE may occur some year's later (Bosch et al. 2006). However, fatal outcome was reported in KFD associated with SLE (Hrycek et al. 2005), (Quintás-Cardama et al. 2003).

2. CASE REPORT

A 27 year old Saudi lady admitted as a case of PUO and lymphadenopathy for further workup. She is known case of thrombocytopenia which didn't respond to glucocorticoids for which she underwent splenectomy few years ago. She has been well untill 2 weeks prior to admission when she developed fever, high grade with no obvious history suggestive of infection. No weight loss, night sweat, cough or hemoptysis but there was a positive history of contact with open pulmonary tuberculosis (TB) in her sister. There is no history of raw milk ingestion, mosquito bite or animal contact. No pruritus, epistaxisis, recurrent infections or jaundice. No skin rashes or chest symptoms. No history suggestive of connective tissue diseases. No history of drug or herbal medicine intake. The patient did not receive vaccinations prior to splenectomy. Socially she is married with 3 kids, no abortions or adverse pregnancy outcomes. Family history of TB and discoid lupus are in her sister. Her examination revealed well looking lady, fever 39 and tachycardia. Palpable firm non tender lymph nodes are in cervical and axillary area bilaterally. No skin rashes. No mouth or nasal ulcers. Eyes exam is normal. Muskeloskeletal exam is normal. Cardiovascular exam normal, chest is clear, abdomen hepatomegaly. Her laboratory workup on presentation showed total white blood cellcount (WBC) 1.2, neutrophil count 0.5, lymphocyte 0.6, platelets count: 280 normal and hemoglobin (Hb) 8.6 normocytic normochromic, which then Normalized 1 month after treatment. Direct Coomb's test (DAT) positive, LDH 1127 which then normalized 2 weeks after treatment. Her liver function tests (LFT) total protein, albumin, alkaline phosphatase and bilirubin Normal but ALT was high223 which then normalized 2 weeks after treatment. Renal function Normal, Tyroid function test is normal. ESR 43 & CRP 73 or both which then normalized 2 weeks after treatment. All cultures blood, urine and sputum are negative and acid fast bacilli culture is negative. Hepatitis A,B,C, Cytomegalovirus and Epestien Barr Virus serologies are negative. Anti-nuclear antibodies (ANA) are positive 1:160, speckeled, Complements C3 and C4 normal, Urine analysis +1 protein, no blood and no casts. Lupus anticoagulant is positive in single time only and negative when it was repeated. Anticardiolipin and Beta-2 glycoprotein antibodies negative. Anti-SSA and anti-SSB are positive. Anti- DNA and Anti-smith are negative. Echocardiogram is Normal. CT scan chest and abdomen showed multiple axillary lymphadenopathy largest 2x3 cm, no mediastinal or retroperitoneal lymph nodes, liver enlarged 16cm. Histopathology shows necrotizing lymphadenitis with a reactive lymph node showing patchy areas of necrosis. No granuloma or metastatic carcinoma seen. Acid Fast Bacilli and fungi are negative.

3. DISCUSSION

KFD, also known as histocytic necrotizing lymphadenitis, is a benign, self-limited disease of lymph nodes predominantly affecting young women. It is characterized clinically by the acute onset of fever and lympadenopathy which primarily is cervical. Less frequently, patients show generalized lympadenopathy, weight loss, nausea, vomiting, night sweats and hepatosplenomegaly (Yilmaz et al. 2006). accompanying reported diseases are SLE, Other non-infectious inflammatory diseases such as: Arthritis, mixed connective tissue disease, anti-phospholipid syndrome, thyroiditis, polymyositis, scleroderma, autoimmune hepatitis, Still's disease, Viral diseases, Fever of unknown origin, Neurological involvement: Aseptic meningitis, mononeuritis multiplex, hemiparesis, brachial neuritis, photophobia, Hemaphagocytic syndrome, Tuberculosis and Lymphoma (Kucukardali et al. 2007).

Initially we suspected disseminated infection in splenectomized lady but culture and Echocardiography was normal. And given the contact with TB it was suspected, initially AFB stain was negative but we need to rule out extrapulmonary TB. Given the ongoing hemolysis and the evidence of AIHA, we started the patient on prednisolone 1mg/kg after appropriate antimicrobial coverage and axillary lymph node biopsy was obtained which showed evidence of KFD. Here, we report the association between SLE and KFD. Our patient admitted for work up of fever and lymphadenopathy. She had AIHA, lymphopenia, positive ANA. In addition, to her past history of thrombocytopenia, we believe that our patient is case of SLE although she doesn't fulfill the American College of Rheumatology (ACR) criteria for SLE (Tan et al. 1982). Revewing the literature showed more than 50 patients with KFD develop SLE either concomitantly diagnosed before or after the onset of SLE (Kim et al. 2011). KFD may in fact be a

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histopathologic characteristic of SLE supporting the hypothesis that KFD is a rare manifestation of SLE (Cramer et al. 2010).

Patients with KFD should receive periodical follow-up for several years to detect possible evolution of SLE (Goldblatt et al. 2008). Lymphadenopathy in patients with SLE is not uncommon and is seen in 12% to 59% of patients with SLE in different series (Khanna et al. 2010). Lymphadenopathy is a frequent and usually nonspecific feature SLE, but besides the disease itself, other causes such as infections, immunological or malignant diseases must be considered in the differential diagnosis. On the other hand, the increased risk of lymphoproliferative diseases in SLE was reported in several studies. Since there is a considerable overlap between the features of SLE and lymphoma, there can be a difficulty in diagnosing lymphoma in lupus patients (Melikoglu et al. 2008).

Some authors believe that there is a connection between KD and lupus based on: (Bosch et al. 2006) KD can precede, coincide, or evolve with the diagnosis of lupus; (Alijotas-Reig et al. 2008) patients with KD may present rash and leukopenia; (Pileri et al. 2005) lymphadenopathy is a common clinical manifestation of both conditions; (Kim et al. 2011) Kikuchi's histiocytic necrotizing lymphadenitis is pathologically indistinguishable from lupus lymphadenitis; and (Yilmaz et al. 2006) immunohistologic findings also are similar in both diseases Thus, it seems that histiocytic necrotizing lymphadenitis may be an initial feature of lupus (Mercado, 2010).

The differential diagnosis between SLE-associated lymph node necrosis and Kikuchi's disease is occasionally difficult. Features that can be seen in SLE include presence of H-bodies, polymorphous neutrophils and plasma cells. Absence of cytotoxic T-cells with T-cell intercellular antigen 1 (TIA-1) and/or granzyme B in lymph node necrosis associated with SLE (Kojima et al. 2007). Kikuchi lymphadenitis and malignant lymphoma however could be differentiated histologically. Morphological features that exclude malignancy included: polymorphous nature of cellular infiltrate, absence of abnormal mitosis, preservation of sinusoidal pattern on intervening areas and presence of extracellular and intracellular karyorrhectic debris (Helal et al. 2001).

Regarding the high transaminases in our patient we believe that transaminitis was autoimmune (Lupoid hepatitis) in nature after we ruled out possible viral etiologies, the enzymes normalized with corticosteroid treatment. A similar case with KFD associated with SLE had high transaminases and negative smooth muscle antibody had the same conclusion that KFD is associated with SLE, and SLE in turn can be associated with abnormal liver function tests, which in a minority of cases may be due to autoimmune hepatitis (Shusang et al. 2008).

As the management of KFD is basically supportive (Bosch et al. 2006). We started our patient for AIHA on prednisolone 1mg/kg, Hydroxychloroquine 400mg daily and Azathioprine. Follow up 2 weeks showed absence of fever and normalization of hemoglobin, total WBC count with persistence of lymphopenia and liver enzymes. Follow up in 3 months showed disappearance of lymph nodes as well as maintainance of the previously improved laboratory.

4. CONCLUSION

In conclusion, KFD is an unusual, self-limited and perhaps under-diagnosed, benign cause of fever and lympadenopathy. Clinical suspicion and thoughtful collaboration between clinicians and pathologists are essential for accurate diagnosis, and to minimize unnecessary investigations and inappropriately aggressive treatment. KFD also should be considered in the differential diagnosis of pancytopenia and lympadenopathy. At least until we understand this clinical entity further, long-term follow-up of KFD patients for subsequent development of SLE and other autoimmune diseases is probably warranted.

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