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Case report

KIKUCHI-FUJIMOTO DISEASE (HISTIOCYTIC NECROTIZING LYMPHADENITIS): A CASE REPORT

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ABSTRACT

Kikuchi-Fujimoto disease (KFD) is a self-limited pathological entity that is benign in its course. The main features of this disease are tender regional cervical lymphadenopathy, usually accompanied by low-grade fever and night sweats. Less frequently patients may report weight loss, nausea, vomiting, and sore throat. Often referred to as KFD; Kikuchi-Fujimoto disease has a global prevalence with high report rates from Japan and other Asian regions. That said, it is a very uncommon case to encounter due to its rare occurrence. A viral causation is suggested keeping in view the clinical presentation, the histology and immunohistochemical pattern. The recommended procedure to diagnose this disease is an excisional biopsy of an affected lymph node. This histopathologic analysis is essential for the clinician to differentiate it from similarly presenting conditions like tuberculous lymphadenitis (scrofula), lupus (SLE) or malignant lymphoma to state a few. This is especially pertinent in regions where there is a high index of suspicion for tuberculosis given its high prevalence, like Pakistan and India for example. It is also essential to inculcate an understanding of this clinically and histopathologically challenging disease amongst physicians and pathologists alike to decrease the risk of misdiagnosis. Steps to increase awareness will also help curb the excessive costs and unnecessary interventions that go with wrong diagnoses. In young patients who present with lymph node enlargement in the posterior cervical chain; a biopsied node showing cellular and nuclear fragmentation along with features of necrosis should incite the consideration of KFD amongst other differentials. Once diagnosed; symptomatic treatment with NSAIDs, analgesics, antipyretics and in some cases corticosteroids is sufficient as the self limited disease resolves by itself within a period of 1 month in most cases. It is unlikely to stretch beyond 4 months. Patients with KFD are followed for many years nonetheless, since these patients are at a slightly increased risk of developing systemic lupus erythmatosus later in life than the general population. The case we report is that of an 18 year old female patient who presented with a month history of low grade fever, night sweats and cervical lymphadenopathy, which was minimally tender. She was initially labeled as a case of tuberculous lymphadenitis and put on antituberculous therapy. However, she did not respond and further diagnostic studies revealed the presence of KFD.

Keywords: Cervical lymphadenopathy, Kikuchi-Fujimoto disease, Self-limiting

CASE REPORT

An 18 year old female college student presented to the outpatient department of Medical B unit of Hayatabad Medical Complex, Peshawar, Pakistan, in February of 2012, with a one month history of low grade fever, spiking mostly in the evening and night, and associated with nausea, malaise and sweating. The fever was intermittent in character. There were no aggravating factors, however it was relieved to some extent with Mefenamic acid but not with Paracetamol. She also complained of a few lumps in the cervical and left axillary area for the same duration. There was no history of any chronic medical illness in the past. She had no family history of tuberculosis, no contact history to an active case of TB, no family history of rheumatological disorders like rheumatoid arthritis or systemic lupus erythematosus and no family history of any blood disorders. Her vitals on presentation were, Pulse: 105/min, BP: 130/80, and temperature of 100.5^{o}F. On examination she had pale conjunctivae, and had left cervical and axillary lymphadenopathy. The rest of her general physical and systemic examinations were unremarkable with no pertinent positive findings. Notably she had no visceromegaly on abdominal examination.

Lab Investigations:

CBC: Hb: 9.6mg/dl, TLC: 3600/cmm, Plt: 305000/cmm, ESR: 12mm/1st hr, LDH: 625U/L, RFTs: Urea: 20mg/dl, S.Creat: 0.7 mg/dl, LFTs: Serum total bilirubin: 0.7 mg/dl, ALT: 64U/L, ANA and anti-dsDNA: Negative, Mantoux showed an induration of 6mm, which was reported as borderline positive, HBsAg by ELISA: non-reactive, Anti-HCV antibodies by ELISA: non-reactive, Monospot Test: Negative, Urine R/E: Normal, Chest X-ray: Normal, U/S of the neck showed cervical lymphadenopathy involving the left mid cervical nodes, U/S Abdomen: Normal Study, with no evidence of hepatosplenomegaly.

During a previous admission in another medical unit two weeks back an FNAC from a lymph node is the left cervical region was done with an impression of "chronic granulomatous inflamation most likely due to Tuberculosis". As the FNAC report was inconclusive, a excisional lymph node biopsy was taken and the patient was empirically started on anti-tuberculous therapy while awaiting the biopsy result. She was asked to report back with the same. The biopsy report confirmed findings consistent with "Kikuchi Fujimoto Lympahadenitis."

Treatment: Following the biopsy report the anti-tuberculous medications were stopped. She was started on oral Prednisone (1mg/kg/day), for a period of 06 weeks followed by a rapid taper. She responded dramatically to this treatment and became asymptomatic over the next 4-5 days. She was counseled about the benign nature of this disease and advised a 6 week follow-up in the OPD. On follow up in the OPD six weeks later she was asymptomatic with complete regression of her lymph nodes and abatement of her symptoms. She has remained in remission after one and a half years of follow up.

DISCUSSION

A disease that most often presents with cervical lymphadenopathy in young women; histiocytic Necrotizing Lymphadenitis or more frequently known as KFD, has now been established as a pathologic entity with global prevalence. It was an entity unheard of until the first case was reported and recorded in 1972 from Japan.[1,2] In as much as half the patients, the clinical picture includes fever and low leucocyte counts.[3]

When a clinician has the job to draw differentials for a patient presenting with cervical lymphadenopathy and fever; he has a lot on his plate all the way from the most obvious entities like infectious mononucleosis and bacterial pharyngitis to the more ominous ones like

tuberculosis and lymphoma. Other considerations might be cytomegalovirus infection, toxoplasmosis, syphilis and even HIV. With so much to work out, it is often a taxing diagnostic workup that ensues. If the culture and stains for the various organisms are negative and the presence of unifocal or multifocal necrosis and histiocytic infiltrate in the backdrop of capsular invasion and inflammation around the nodes[4] is detected under a microscope; it is strongly suggestive of KFD.

Some authors have described an association between systemic lupus erythmatosus and histiocytic necrotizing lymphadenitis (KFD).[5] Others have even gone on to propose the notion that KFD is merely an unusual presentation of SLE itself. In 2003 a Medline/LILACS (Latin American and Caribbean Health Sciences) search was performed by Santana et al.; that discovered 35 instances where KFD and SLE were reported in the same patients. As per their findings; most of the cases of SLE were either found after the diagnosis of KFD or at the time of labeling.[6] Our patient was tested serologically for SLE but all her results returned negative.

Since KFD is a disease that has a self-limited course and is deemed benign to add to its rarity in presentation; not much has been achieved in the way of creating a targeted treatment for it. It is recommended that symptomatic measures to relieve localized and systemic distress associated with the disease be employed. To counter tenderness in the enlarged lymph nodes and the fever that accompanies it; most clinicians rely on NSAIDs, analgesics and antipyretics. Although the efficacy of their use is not established epidemiologically, corticosteroids have been prescribed in cases with systemic involvement outside the nodal region or a more severe presentation of KFD. Neurological involvement that often presents with aseptic meningitis or cerebellar ataxia and/or a fulminant lupus like presentation with positive serologic titers for ANA have been cited by some authors as indications for steroid use in KFD patients. Another similar indication for steroid use is involvement of the liver with high LDH levels. This latter finding was positive in our patient. Although the evidence for these widely accepted indications for steroid use is insufficient itself; some have gone on to suggest inclusion of a less severe presentation amongst the indication for steroid usage. Jang and colleagues suggested Prednisolone prescription in patients with recurrent disease, refractory patients who remain symptomatic despite two weeks or more of treatment with NSAIDs and for those who desire a quicker recovery. The monitoring must not be ignored though since there is always a risk of developing SLE and/or, much rarely, a recurrence of KFD later in life.[7]

Kikuchi's disease is an entity with an unclear etiology. However, several hypotheses have been put forth with regards to its etiology and pathogenesis. A number of organisms like human herpes virus 6, Epstein-Barr virus, HTLV-1 (human T-cell leukemia virus type 1), cytomegalovirus, parvovirus B19, Yersinia enterocolitica and parainfluenza virus have been suggested as organisms that might be implicated in the etiology of KFD.[8]

Since it has been observed and reported in association with SLE; autoimmune processes contributing to the etiological picture of KFD have also been suggested. One of the theories in regards to its causation cites the concept of molecular mimicry. It proposes that an antigen of an infectious agent that is similar to a self-antigen leads to an attack against self by the activated T-cells.[9] This concept can be exemplified by quoting Lyme disease where such cross-reaction between LFA-1 (human leucocyte function associated antigen type 1) and Borrelia burgdorferi antigen results in chronically inflamed joints.[10] Yet another proposal puts forth a theory based on apoptotic cells that express nuclear antigens on their surface, a process very strongly implicated in the pathogenesis of SLE. If such apoptotic cells are not adequately and promptly cleared (i.e. due to complement deficiency), these can act as a nidus for an

autoimmune process culminating in severe damage to self tissues.[11]

CONCLUSION

In view of the lingering fever and fatigue that often accompany Kilkuchi's disease, it can become quite distressing and frustrating for both the patient and caring physician whilst running its course. Stating that observation, we are of the opinion that clinicians should be reminded to always consider it on the list of differentials for young patients who present with cervical lymphadenopathy. We also suggest an effort to inculcate awareness amongst the pathologists to look for the characteristic histopathologic findings of KFD when deciding on specimen from patients with the aforementioned features. These steps are bound to culminate in a decrease in the number of opinions sought, unrequired interventions performed and valuable resources expended. It deserves mention here that in our review of literature of the disease, we concluded that whilst associations of KFD with systemic lupus erythmatosus and other autoimmune diseases are cited[12,13]; these claims are yet to be adequately verified.

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