Original Article:

Kikuchi-Fujimoto disease presenting as pyrexia of unknown origin

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ABSTRACT

Background: Kikuchi-Fujimoto disease, a benign self-limited lymphadenopathy is an uncommon cause of pyrexia of unknown origin (PUO).

Methods: We retrospectively studied the case-records of 13 patients presenting with PUO who were diagnosed to have Kikuchi-Fujimoto disease on peripheral lymph node excision biopsy and report the salient clinical manifestations and histopathological findings in them. All of them received symptomatic treatment.

Results: Their median age was 28 [interquartile range (IQR) 18.5-38.0] years. Women (11/13, 84.6%) were more frequently affected. All of them were human immunodeficiency virus (HIV) seronegative. Prior to presenting to us, two were being treated for lymph node tuberculosis with DOTS. Cervical lymph nodes were predominantly involved, the distribution being: right cervical (n=10, 76.9%); left cervical (n=4); and bilateral cervical (n=2). Axillary and generalized lymphadenopathy were rare being seen in 2 and 1 patient respectively. The median (IQR) erythrocyte sedimentation rate (n=11) was 53 (35-89) mm at the end of first hour. Salient histopathological features were paracortical patchy zones of eosinophilic fibrinoid necrosis with karyorrhectic debris, large numbers of histiocytes, including histiocytes with peripherally placed "crescentic" nuclei. Spontaneous regression of fever and lymphadenopathy was observed over a median (IQR) period of 8 (6.75-10.25) months in all of them.

Conclusions: Kikuchi-Fujimoto disease is a rare but important cause of PUO presenting with peripheral lymphadenopathy. Women are most often affected and cervical lymph nodes are the most frequently involved site. Clinical suspicion and thoughtful collaboration between clinicians and pathologists are essential for accurate diagnosis, and to minimize unnecessary investigations and inappropriate aggressive treatment.

Key words: *Kikuchi-Fujimoto disease, India*

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INTRODUCTION

Kikuchi-Fujimoto disease was first described from Japan in 1972 by Kikuchi;[1] and Fujimoto et al[2] as "lymphadenitis with focal proliferation of reticular cells" accompanied by numerous histiocytes and extensive nuclear debris. Kikuchi-Fujimoto disease is of unknown aetiology. Characteristic clinical manifestations include fever, night sweats, and progressive painful lymphadenopathy, primarily in the cervical region. Most patients are under the age of 30, with a female preponderance.[3] Kikuchi-Fujimoto disease is diagnosed on excision biopsy, histopathological examination of affected lymph nodes; no specific diagnostic laboratory tests are available.[4] Sparse published data are available on this entity from India[5-7] in peer-reviewed indexed journals and this prompted the present study.

MATERIAL AND METHODS

We retrospectively studied the case records of 13 patients who presented to the Medicine out-patient services and to the clinic for staff members of the Sri Venkateswara Institute of

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Medical Sciences (SVIMS) hospital, Tirupati, a tertiary care referral centre and teaching hospital in south India, catering to the population of the Rayalaseema area comprising Chittoor, YSR Kadapa, Kurnool and Anantapur districts and the neighbouring P.S.Nellore district of Andhra Pradesh. All patients had presented during the period 2007-2012 for evaluation of classical pyrexia of unknown origin (PUO) (defined as fever of >101°F on several occasions; of >3 weeks duration; and failure to reach a diagnosis despite three outpatient visits or 3 days in the hospital without elucidation of a cause or 1 week of "intelligent and invasive" ambulatory investigation) by the referring primary physicians[8] and peripheral lymphadenopathy. Our institution is a postgraduate institute teaching hospital and does not have paediatric and otorhinolaryngological services, two areas where a number of such patients could present.

All the patients had undergone serological testing for human immunodeficiency virus (HIV) infection for HIV-l and -2 after obtaining informed consent on a voluntary basis using enzyme-linked immunosorbent assay (ELISA). As a part of the departmental protocol for work-up of PUO, the following investigations were carried out: complete haemogram, serum biochemistry, quantitative buffy coat (QBC) test for malarial parasite, urine routine and microscopy examination, blood culture, anti-nuclear antibody (ANA), anti-double stranded deoxy-ribonucleic acid (anti-dsDNA) antibodies, anti-phospholipid antibodies and rheumatoid factor; chest radiograph and ultrasonography of abdomen, among other investigations. After obtaining informed consent, excision biopsy of the most accessible peripheral lymph node and bone marrow biopsy (where appropriate) was performed as an outpatient procedure in all patients. Conventional haematoxylin and eosin staining was used to analyse the biopsy specimens. Kikuchi-Fujimoto disease was diagnosed based on the classical histopathological findings.[1,2] Basing on the histopathological diagnosis, all patients were reassured and treated with antipyretics, analgesics, non-steroidal anti-inflammatory drugs and were closely followed up for a period of one year.

Details of clinical presentation, salient laboratory abnormalities, histopathological findings were all recorded in a structured proforma.

Statistical analysis

Descriptive statistics of the salient clinical manifestations and histopathological findings in these 13 patients diagnosed to have Kikuchi-Fujimoto disease are described as percentages.

RESULTS

The median age of presentation was 28 [interquartile range (IQR) 18.5-38] years. Females outnumbered males (male: female = 2:11). Physical examination revealed peripheral lymphadenopathy. The distribution of peripheral lymphadenopathy in these patients is shown in Figure 1.

Prior to presenting to us, 2 out of 13 patients were already receiving DOTS therapy for peripheral lymph node tuberculosis that was diagnosed on fine needle aspiration cytology (FNAC). All of them were HIV-seronegative. The median erythrocyte sedimentation rate (ESR) (n=11) was 53 (IQR 35-89) mm at the end of first hour. Connective tissue disease work up was negative. Nine of the 11 patients had an elevated ESR (> 20 mm at the end of the first hour, Westergren method); the ESR was more than 50 in 6 patients and was more than 100 in two patients. On the chest radiograph (postero-anterior view) and ultrasonography of the abdomen, there was no evidence of intrathoracic or intraabdominal lymphadeno-pathy in any of the patients. Bone marrow

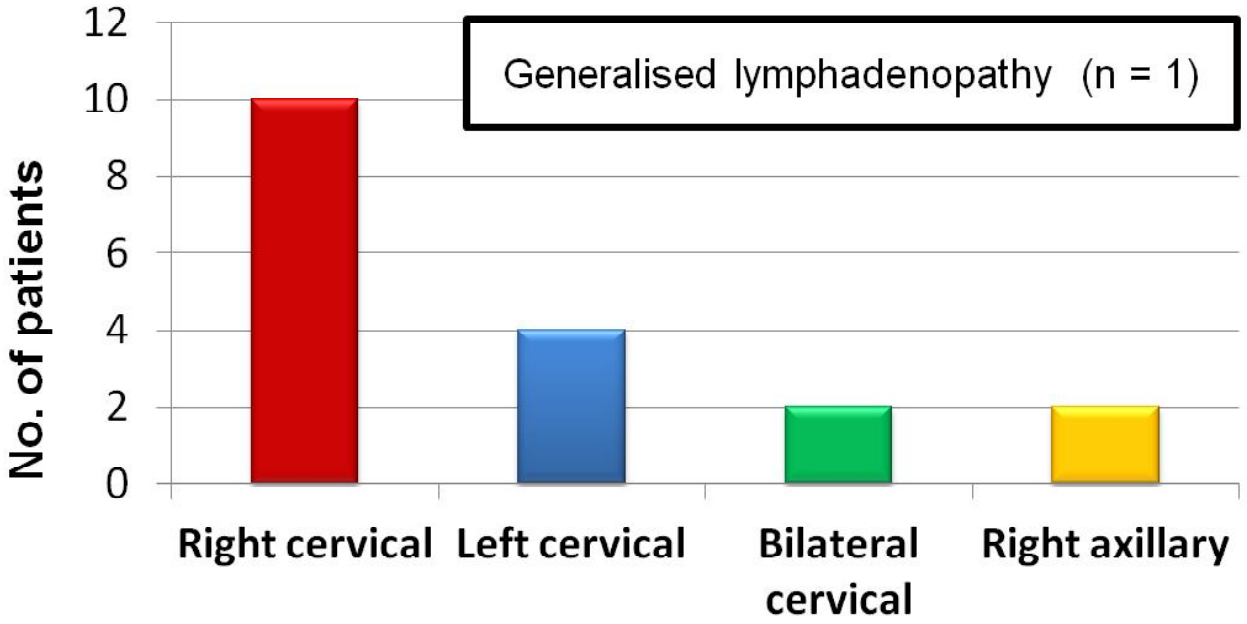

Figure 1: Distribution of peripheral lymphadenopathy in 13 patients with Kikuchi-Fujimoto disease

biopsy done in 3 patients revealed cellular reactive bone marrow with no evidence of granulomas or malignancy.

Salient histopathological features observed included paracortical patchy zones of eosinophilic fibrinoid necrosis with karyorrhectic debris, distortion of the nodal architecture, and large numbers of histiocytes at the margins of necrotic areas, including histiocytes with peripherally placed "crescentic" nuclei and some lymphoid cells (Figures 2 and 3).

Outcome of treatment

Spontaneous regression of fever and lymphadenopathy was observed with symptomatic treatment over a median (IQR) period of 8 (6.75-10.25) months in all of them.

Figure 2: Photomicrograph showing paracortical patchy zones of eosinophilic fibrinoid necrosis (Haematoxylin and eosin, × 40)

DISCUSSION

Kikuchi-Fujimoto disease is an uncommon disease originally described from Japan and is common in people of Asiatic origin. It is an uncommon cause of peripheral lymphadenopathy. In an earlier publication from our institute, Kikuchi-Fujimoto disease was found in 36 of the 1724 lymph node (2.1%) specimens submitted for histopathological examination.[9]

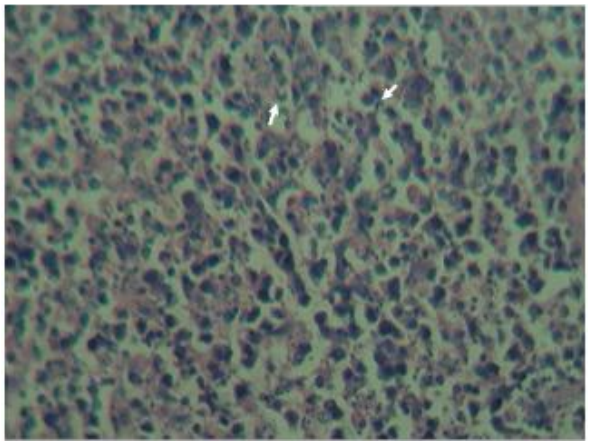

Figure 3: Photomicrograph showing foci of karyorrhectic debris, fibrinoid necrosis, large numbers of histiocytes, including histiocytes with peripherally placed "crescentic" nuclei (arrows) and some lymphoid cells (Haematoxylin and eosin, × 400)

Kikuchi-Fujimoto disease is most often seen in young adults under the age of 30 years with female preponderance.[1,2] In our study out of 13 patients 7 were under the age of 30 years and 11 were under the age of 40 years. In another study[6] from Chennai, India (n=30), the mean age at presentation was 18 years. The onset of Kikuchi-Fujimoto disease is acute or subacute, evolving during a period of 2 to 3 weeks. Cervical lymphadenopathy, often unilateral involving the posterior cervical triangle is usually evident; and the enlarged lymph nodes are tender.[3] Similar findings were observed in the present study and the study from Chennai.[7] Other manifestations of this disease include fever, axillary and mesenteric lymphadenopathy, splenomegaly, parotid gland enlargement, cutaneous rash, arthralgias, myalgias and aseptic meningitis.[1-3]

Kikuchi-Fujimoto disease is an uncommon cause of PUO[10] and was confirmed as the aetiological cause on histopathological examination in all our patients. Nine of the 11 (82%) patients in the present study had elevated ESR at the time of initial presentation. In the study from Chennai, elevated ESR[7] was observed in 56.7% of the patients. Presence of fever, tender lymphadenopathy and elevated ESR, thus appear to provide valuable clinical clues raising the suspicion of Kikuchi-Fujimoto disease especially in young women.

The differential diagnosis for Kikuchi-Fujimoto disease include tuberculosis, lymphoma (esp., non-Hodgkin's lymphoma), systemic lupus erythematosus, plasmacytoid T-cell lymphoma, Kawasaki's disease, and myeloid tumour. In the present study, care was taken to rule out rheumatoid arthritis and systemic lupus erythematosus by conducting appropriate diagnostic work-up. Prior to consulting us, 3 of the 13 patients in the present study were diagnosed to have peripheral lymph node TB on FNAC examination and were started on DOTS. However, as there was no clinical improvement, they were referred to our institute for further evaluation. Fever is not a common manifestation of isolated peripheral lymph node tuberculosis.[11] In a study from Bangladesh,[11] fever was present only in 18 (5%) of 300 patients with lymph node tuberculosis. Some workers[12] have suggested that FNAC features of Kikuchi-Fujimoto disease, such as, karyorrhectic and granular debris mixed with two distinctive cell types are characteristic and facilitate the diagnosis of the disease. These include, phagocytic histiocytes with peripherally placed "crescentic" nuclei and abundant cytoplasm containing phagocytosed karyorrhectic or eosinophilic granular debris and medium-sized cells possessing eccentrically placed round nuclei, fairly condensed chromatin, and a moderate amount of amphophilic cytoplasm, consistent with plasmacytoid monocytes. The other findings include presence of nonphagocytic histiocytes and immunoblasts that sometimes show atypical features such as irregular foldings of the nuclei with sparce or absent neutrophils. However, other workers[13] have found that FNAC had low accuracy (56.3%) in the diagnosis of Kikuchi-Fujimoto disease and advocate the use of lymph node biopsy instead. Furthermore, immunohistochemistry has been found to be useful in differentiating Kikuchi-Fujimoto disease from other causes of lymphadenopathy.[14] In order to procure adequate tissue for diagnostic testing and to rule out other differential diagnosis, we preferred to perform excision biopsy rather than repeat FNAC for diagnostic confirmation in these patients. A high index of clinical suspicion, meticulous diagnostic work-up for other causes that constitute differential diagnosis and careful histopathological examination help in ascertaining the diagnosis of Kikuchi-Fujimoto's disease.

Our observations suggest that Kikuchi-Fujimoto disease is an important but uncommon cause of PUO in young women. Careful

physical examination, detection of peripheral lymphadenopathy and biopsy can help in confirmation of diagnosis. Kikuchi-Fujimoto disease must be suspected in young women presenting with fever and peripheral lymphadenopathy. Clinical suspicion and thoughtful collaboration between clinicians and pathologists are essential for accurate diagnosis, and to minimize unnecessary investigations and inappropriate aggressive treatment.

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