Kikuchi-Fujimoto's disease and scrub typhus: A rare association

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ABSTRACT

Kikuchi-Fujimoto's disease (KFD), histologically described as necrotising histiocytic lymphadenitis, is a benign self-limiting disease though a few fatalities have been reported. It is uncommon outside Japan and other Asiatic countries and thus lack of awareness among physicians may have led to its under-diagnosis or misdiagnosis as lymphoma or tuberculosis. It has recently gained importance due to its possible association with autoimmune disorders and viral infections especially Infectious Mononucleosis. Here we report a young South Indian man with fever, upper respiratory tract infection and tender cervical lymphadenopathy confirmed by biopsy to be KFD. He also had coexistent scrub typhus infection evident by positive markers during the course of illness, which became negative six weeks later. Supportive management with non-steroidal anti-inflammatory agents has led to complete remission of symptoms. Association between KFD and scrub typhus has not been previously reported.

Keywords: Histiocytic necrotising lymphadenitis, young male, diagnosis, anti-inflammatory agents, scrub typhus

INTRODUCTION

Necrotising histiocytic lymphadenitis or Kikuchi-Fujimoto's disease (KFD) was identified independently by Kikuchi and Fujimoto in 1972 following analysis of patients with suspected lymphoma who recovered completely with minimal intervention. [1] The precise incidence in the general population is still not defined. The incidence among the biopsy analysed cases of lymphadenopathy has been estimated to be between 0.5 and 5%. [2] Epidemiological data shows preponderance to young Asian females, although cases are reported worldwide in all age groups.

KFD commonly presents with unilateral tender lymphadenopathy (frequently posterior cervical lymph nodes) along with other non-specific symptoms. Blood investigations are usually inconclusive. It should be considered in the differential diagnosis of a patient with lymphadenopathy and in cases of pyrexia of unknown origin. Physician awareness of this disease is thus important in order to arrive at the diagnosis at the earliest. We report the case of a KFD that was associated with

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scrub typhus, an association that has not been previously reported.

CASE REPORT

A 15-year-old male student from Southern India was admitted with low grade fever for five days associated with tender swellings in the neck. He also had cough with minimal non-purulent expectoration and severe myalgia. There was no recent travel or contact with tuberculosis. He had no otorhinolaryngological, dental or scalp symptoms. There was no significant weight loss or other systemic complaints. On examination he was febrile (38.3°C) with multiple bilateral enlarged lymph nodes in the posterior triangle, the largest being in the right posterior triangle. The lymph nodes were firm, tender and mobile, and were not matted. Systemic examination as well as otorhinolaryngological, dental, and scalp examination revealed no evidence of infection.

Haematological investigations revealed normal total white cell counts (4600/mm^3) with a neutrophil count of 3900/mm^3, mild thrombocytopenia of 112,000/mm^3, a haemoglobin of 12.7gm/dl, and an erythrocyte sedimentation rate (ESR) of 24 mm/hour. Urine analysis and renal function tests showed no abnormalities. Hepatic enzymes were mildly elevated with aspartame aminotransferase (AST) at 92 U/L and alanine aminotransferase (ALT) at 48 U/L. Lactate dehydrogenase (LDH) was elevated at 859 U/L and procalcitonin was elevated at 9.68. Ultrasonography of the abdomen revealed mild hepatosplenomegaly and mesenteric lymphadenitis in the right iliac fossa. Fine needle aspiration cytology (FNAC) of cervical lymph node showed reactive changes.

Empirical treatment was initiated with intravenous ceftriaxone considering infection as the most likely cause of the lymphadenopa-

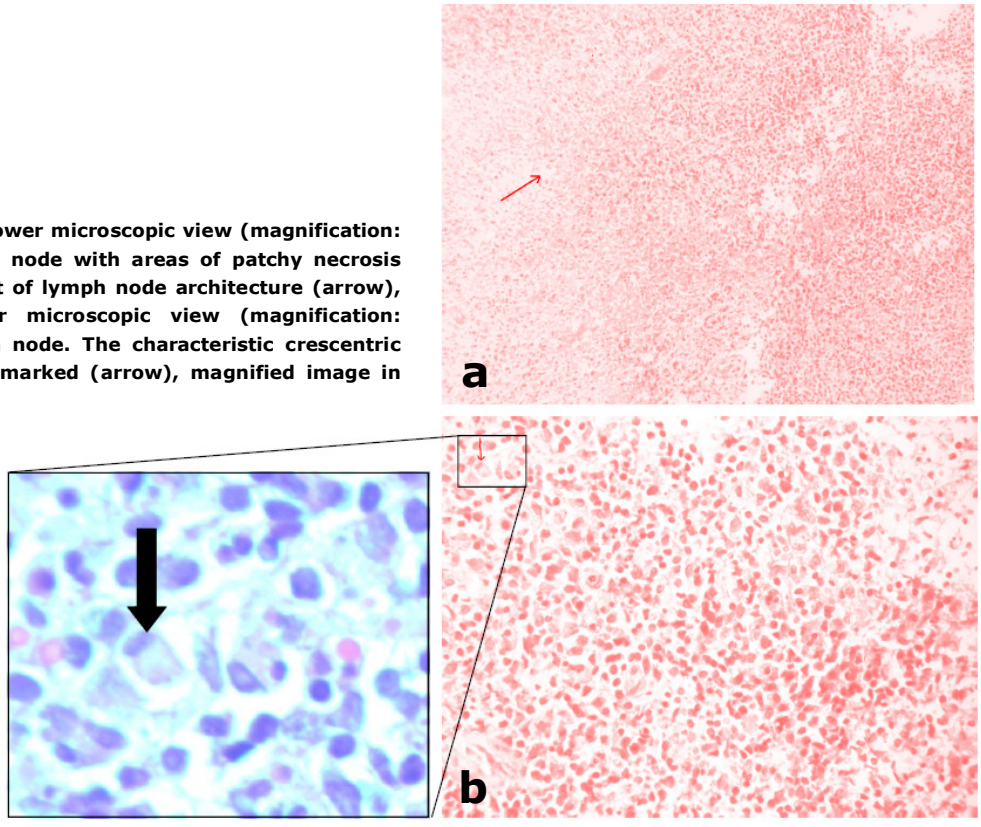

Fig 1: a) Low power microscopic view (magnification: x100) of lymph node with areas of patchy necrosis with effacement of lymph node architecture (arrow), b) High power microscopic view (magnification: x400) of lymph node. The characteristic crescentric histiocytes are marked (arrow), magnified image in the insert.

thy. The absence of clinical improvement prompted a change of therapy to broad-spectrum antibiotics (Piperacillin-Tazobactam). During the course of admission, the platelet levels showed a progressive decrease and fever spikes persisted.

Serological analysis was negative for Cytomegalovirus IgM, HIV-1 and -2 (ELISA), HBsAg, and Dengue IgM and IgG. Paul Bunnel test was also negative. Blood, urine, and stool cultures were sterile. Autoimmune investigations using ELISA revealed positive antinuclear antibody (ANA) and double-stranded DNA (dsDNA). Rheumatoid factor was weakly positive with a titre of 15U/L. Weil-Felix test for scrub typhus was positive with a dilution of 1:320 for OX K titre and treatment was thus begun with Doxycycline 100mg twice daily.

Histopathologic examination of the right cervical lymph node biopsy specimen showed partial effacement of lymph node architecture (Figure 1a) with irregular areas of eosinophilic necrosis with fibrinoid deposits. Karyorrhectic debris was present. Histiocytes with eosinophilic cytoplasm and eccentrically placed cresentric nuclei were observed (Figure 1b). Neutrophils and Eosinophils were absent, as were granulomas and haematoxylin bodies. Staining to detect acid-fast bacilli (AFB) was negative. All these features are consistent with KFD.

Treatment with Piroxicam was then begun at 20 mg once daily. His febrile spikes settled and lymph node swellings regressed within 48 to 72hrs of commencement of treatment. Haematological investigations showed improvement in the platelet count and procalcitonin level. The patient was discharged, and was doing well when reviewed two weeks later.

DISCUSSION

Several hypotheses have been proposed regarding the possible aetiology of KFD. As seen in our patient, KFD is usually preceded by a viral-like prodromal illness. This suggests a post-viral hyper-immune reaction to various organisms, [4] among which the association with Epstein-Barr virus (EBV) has been studied extensively. Peripheral smear obtained from patients with KFD showed the presence of atypical lymphocytes which prompted the workup for EBV. Studies have been conducted which isolated EBV nucleic acids in a significant proportion of patients. [5, 6] In our case Paul-Bunnel test was negative and we did not carry out specific tests for EBV antibody titres or EBV genetic studies owing to financial constraints faced by the patient.

Our patient also had concurrent scrub typhus infection which has not been reported earlier, the significance of this is currently not established.

There have been quite a few cases reported in association with rheumatological diseases like systemic lupus erythematosus (SLE) and some studies have analysed this association. [7, 8] KFD can precede, follow, or coincide with the diagnosis of SLE [7] thus stressing the importance of its early detection. Dorfman *et al.* believed that KFD may even be an attenuated manifestation of SLE considering the clinical and histological overlap between the two diseases. Yilmaz *et al.* hypothesised that SLE and KFD might share a common hyperimmune reaction directed

against different antigens which then diverge into the two distinct manifestations. [9] During the course of illness, our patient had positive autoimmune markers including dsDNA which is specific to SLE.

Genetic susceptibility to this disease is under research. An elevated LDH as in our patient has been associated with hepatic dysfunction [10], suggesting the need for serial evaluation of liver function in such patients.

It is remarkable to note that the symptoms in our patient settled within 48 to 72hrs of treatment, though it has been estimated that the disease usually resolves spontaneously in about four to six months. [11] The recurrence rate of KFD is estimated to be between 3% and 4% of all cases. [10]

In conclusion, the non-specific and non-persistent presentation of this disease poses a diagnostic challenge. Clinically and histologically, KFD can be mistaken for tuberculosis, lymphoma, or SLE. Physicians' and pathologists' awareness of this disease is necessary to avoid under diagnosis or misdiagnosis especially considering the simplicity of treatment and the rapid, complete response thus achieved. Appropriate evaluation for KFD in cases of PUO will thus avoid the unnecessary, invasive, and expensive investigations and treatment. In view of the possible association of KFD and SLE we recommend that all cases diagnosed with KFD be screened for underlying autoimmune pathology and followed up for the same.

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