

Kikuchi Disease in a Connective Tissue Disorder

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Summary

A 27-year old woman presented with fever, weight loss, arthralgia, macular skin rash and bilateral axillary lymphadenopathy. The histology of an excised lymph node showed evidence suggestive of Kikuchi disease. Subsequent laboratory tests showed evidence of Systemic Lupus Erythematosus, underscoring the importance of considering other diagnoses in a nodal histological diagnosis of Kikuchi disease, a benign condition of unknown aetiology.

Key Words: Kikuchi disease, Systemic Lupus Erythematosus

Introduction

Kikuchi disease was first described in the Japanese literature in 1972, and presents in young females with fever and lymphadenopathy. It is a benign self-limiting condition of unknown aetiology, and is diagnosed by histological examination of affected lymph nodes. This condition, however, is seldom mentioned in the standard medical textbooks.

Case Report

In January 2001, a 27-year-old woman presented with fever and intermittent rigors of about 6 weeks' duration. She had been feeling generally unwell in the previous three months and had lost appetite and weight. She had on two occasions developed superficial thrombophlebitis affecting

both lower limbs, which settled spontaneously over about two weeks. She also had pain affecting the wrist joints, the small joints of both hands, the shoulder and knee joints. Her major past medical history was a craniotomy for a post-parietal cerebral abscess in 1988 from which she recovered uneventfully. She was not on any medication.

Examination showed that she was pale and had a macular rash on the dorsum of both hands. There was no evidence of lymphadenopathy. There were tenderness and swelling of both wrist joints and the proximal interphalangeal joints. Both the shoulder and knee joints were also tender. BP was 120/80; heart and lungs were normal on examination. Abdominal examination showed no evidence of organ enlargement and neurological examination was normal.

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The results of initial investigations were as follows:

Hb: 9.2 g/dl; WBC: $4.2 \times 10^9/l$; ESR: 118 mm/hr; blood slide for malarial parasites was negative; Platelet count: 258,000 / cu.mm; Reticulocyte count: 2.3 %;

Urea and electrolytes: normal; Serum creatinine: 70.0 micromol/l;

C-reactive protein: negative; IgM anti-dengue antibody: negative;

ANA (repeated twice in one commercial laboratory): negative; RA Factor: negative; Liver Function Tests: normal; Urine microscopy: normal; Blood cultures: negative; Widal test: Salmonella typhi "H": 1:160; Salmonella typhi "O": 1:80; Serum protein electrophoresis showed increased alpha 2 globulins. No paraproteins were detected in the serum. Both the chest x-ray and the ultrasound scan of the abdomen were reported as normal. On different occasions she was given therapeutic trials of antibiotics for presumed bacterial infections, ciprofloxacin for typhoid fever and chloroquine for presumed vivax malaria.

She was lost to follow-up and returned two months later with fever and further weight loss. Examination at this time revealed multiple small lymph nodes in both axillae. An excisional biopsy of one of the axillary lymph nodes showed evidence of histiocytic necrotizing lymphadenitis, suggestive of Kikuchi disease¹. In view of the possible association of this disease with SLE, a repeat ANA test was done in a different laboratory. The result was strongly positive with a titre of 1280, and a speckled and nucleolar pattern of immunofluorescence staining. Tests for SS-A (Ro) and SS-B (La) antibodies were also positive. Antibody to double-stranded DNA was negative and serum complement levels were normal. Serological tests for Epstein-Barr virus, Herpes simplex virus and the protozoan *Toxoplasma gondii* were all negative. Lupus anticoagulant and anticardiolipin antibodies were also negative.

This patient clearly had Systemic Lupus Erythematosus (SLE)² which was one of the diagnoses entertained, but the previous two negative ANA's led to a search for other possible causes, although about 5% of patients with SLE remain persistently ANA-negative. This patient was treated with oral steroids to which she responded dramatically. Within a week, her fever disappeared; the skin rash on the dorsum of the hands and the joint pains cleared and she reported feeling well for the first time.

Discussion

Kikuchi disease is a benign condition of unknown aetiology and usually presents in young women of childbearing age. It presents clinically as fever, weight loss and cervical lymphadenopathy, although in this case the axillary lymph nodes were involved. The disease is self-limiting and usually resolves within 6 months. Specific therapy is not necessary in genuine cases of Kikuchi disease. It is diagnosed histologically by biopsy of affected lymph nodes which shows histiocytic necrotizing lymphadenitis. The distinctive features include patchy areas of central necrosis, karyorrhexis, infiltrates of histiocytes, immunoblasts and plasmacytoid monocytes, and the absence of granulocytes. I know of a case of Kikuchi disease of unknown aetiology (Dr Jagajeet Singh, personal communication).

The lymphadenopathy in SLE and in malignant lymphoma may present with similar histological features, thus underscoring the importance of excluding these two diseases in a patient with a nodal histological diagnosis of Kikuchi disease. Thus when faced with a diagnosis of Kikuchi disease, the clinician must exclude these diagnoses in addition to other differential diagnoses, such as tuberculous lymphadenitis, infections associated with Cytomegalovirus, Epstein-Barr virus, Herpes Simplex virus, toxoplasmosis and yersiniosis. About 10-15% of

histologically diagnosed Kikuchi disease may be due to tuberculous lymphadenitis (Dr R. Pathmanathan, unpublished data). In ANA-negative SLE, antibodies to extractable nuclear antigen (ENA), anti-SSA (anti-Ro) and anti-SSB (anti-La)² need to be tested. Anti-Ro and Anti-La antibodies are linked to subacute cutaneous lupus, skin photosensitivity, Sjogren syndrome and the neonatal lupus syndrome, the latter rarely associated with congenital heart block. The presence of anti-ds-DNA antibodies and hypocomplementaemia is predictive of the development of lupus nephritis. The past history of thrombophlebitis in this patient suggests the possible association of SLE with the antiphospholipid syndrome³ (sometimes called the Hughes syndrome after Graham Hughes, St. Thomas' Hospital, London), characterised by the presence of widespread arterial and venous thrombosis, recurrent miscarriages in pregnant women and thrombocytopenia. It is associated with the presence of lupus anticoagulant and anticardiolipin antibodies. These are antibodies to negatively charged phospholipids, and the

binding of these antibodies to phospholipids is absolutely dependent on the presence of beta-2 glycoprotein 1 in the serum.

This case also illustrates the importance of ensuring regular follow up in a patient without a definitive diagnosis and to relate laboratory tests to the clinical features, never in isolation. The disparity in the results of the laboratory test for ANA clearly indicates the need for stringent quality control by diagnostic laboratories to ensure the validity and accuracy of laboratory results. This incidentally highlights the much-debated role of practising physicians to be generalists first and then as specialists, in a developing country.

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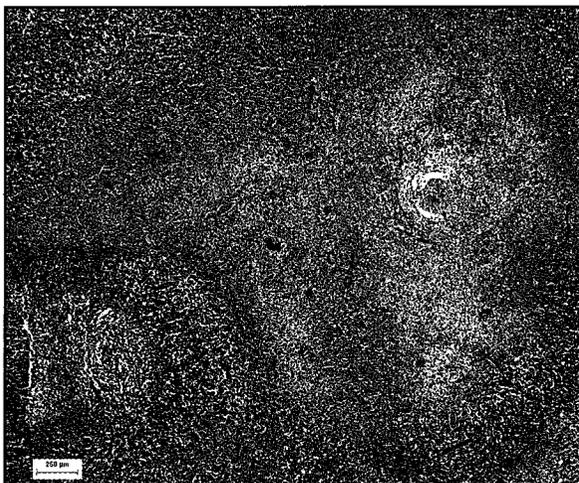


Fig. 1: Low power view showing non-expansile irregular mottled patches, typical of necrotizing lymphadenitis

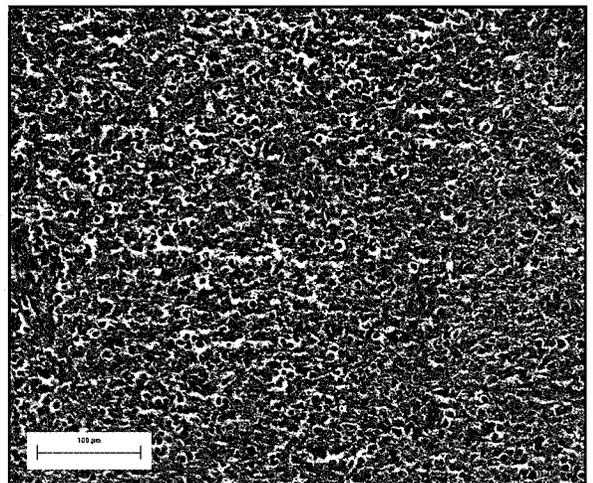


Fig. 2: The necrotic foci contain abundant karyorrhectic debris and crescentic histiocytes, as well as occasional larger immunoblasts

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References

1. Kikuchi M. Lymphadenitis showing focal reticulum cell hyperplasia with nuclear debris and phagocytes: a clinicopathological study. *Nippon Ketsueki Gakkai Zassho*; 1972; 35: 379-80.
2. Ruiz-Iratorza G, Khamashta MA, Castelino G and Hughes GRV. Seminar Systemic lupus erythematosus; *Lancet* 2001; 357: 1027-32.
3. Greaves M. Seminar Antiphospholipid antibodies and thrombosis; *Lancet* 1999; 353: 1348.