

Kikuchi's disease with systemic manifestations: a link to the Epstein-Barr virus

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ABSTRACT

Kikuchi's disease is a rare benign disease that presents with fever and cervical lymphadenopathy. The importance of this disorder, lies in distinguishing it from more sinister disorders, such as lymphoma, in order to avoid unnecessary investigation and treatment. Systemic manifestations are rare in Kikuchi's disease but are not unknown. We present two cases of varying degrees of systemic involvement due to Kikuchi's disease. Both these patients, a 22-year-old woman and a 44-year-old woman, were also found to have evidence of recent Epstein-Barr virus (EBV) infection. The evidence of a causative role for EBV in Kikuchi's is also reviewed.

Keywords: cervical lymphadenopathy, Epstein-Barr virus, Kikuchi's disease, necrotising histiocytic lymphadenitis

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INTRODUCTION

Kikuchi's disease (KD), also known as Kikuchi-Fujimoto disease and histiocytic necrotising lymphadenitis, is a rare, benign, self-limiting condition of unknown aetiology. It is usually characterised by cervical lymphadenopathy and fever.⁽¹⁾ The histopathology of the involved lymph nodes differentiates KD from several more serious conditions, which it may mimic. Occasionally, KD may present with skin manifestations. Splenomegaly is present in a minority of patients. Laboratory tests may reveal an elevated erythrocyte sedimentation rate, neutropenia and atypical lymphocytosis. Systemic involvement and even a fatal outcome have been reported, but are rare.^(2,3) It usually resolves spontaneously within a period of two months. However, recurrences have been reported in some instances. It has a well-recognised association with lupus erythematosus.⁽⁴⁾ However, the aetiology of this disorder remains unknown. Various viral pathogens have been proposed, but none have been conclusively proven to be causative of this condition.

CASE REPORTS

Case 1

The first patient was a 22-year-old woman who presented

with a history of fever for 20 days. Fever was intermittent and high grade, and accompanied by abdominal pain for ten days. She had developed icterus for the last five days, and breathlessness for the past three days. There was no history of rash, arthralgia or contact with tuberculosis. On examination she was conscious, febrile and in some distress. She had two tender, enlarged left cervical lymph nodes of 1 cm × 1 cm size and an enlarged axillary node on the same side. She also had pallor and icterus. The examination of other systems revealed hepatosplenomegaly and bilateral pleural effusions. Investigations revealed a haemoglobin level of 5.5 g/dL, total leucocyte count (TLC) of 8,000 cells/mm³ with a left shift, and a platelet count of 26,000/mm³. Liver function test (LFT) showed an elevated alkaline phosphatase of 417 U/L, and lactate dehydrogenase (LDH) was 4,390 U/L. Urine analysis revealed 10–12 white blood cell/high power field, with no casts, proteinuria or haematuria. Blood and urine cultures were sterile. Mantoux, Widal, Weil-Felix, Leptospirosis-IgM, Scrub typhus-IgM, HbsAg and HIV by ELISA were negative.

Chest radiograph showed bilateral pleural effusions which were transudative on thoracentesis. Ultrasonography of the abdomen showed mild hepatosplenomegaly, mild ascites and mild bilateral pleural effusions. She was empirically started on antibiotics initially, till investigations showed no evidence of infection. Paul Bunnell test, rheumatoid factor and antinuclear antibody test (ANA) were negative. Her direct Coombs test (DCT) was negative. Bone marrow study showed that reactive marrow and culture was sterile. Echocardiography was normal. Viral capsid antigen (VCA) IgM for Epstein-Barr virus (EBV) were positive. An excision biopsy of the enlarged left cervical node was done, and the histopathology revealed a lymph node with essentially preserved architecture and multiple areas of histiocytic aggregates showing necrosis and karyorrhexis with few C-shaped monocytoïd cells. No granuloma was seen. There were no neutrophils in the area of karyorrhexis. The findings were consistent with necrotising histiocytic lymphadenitis, i.e. KD.

Case 2

The second patient was a 44-year-old woman who presented with a history of fever for three weeks. The fever was intermittent, high grade and not accompanied by

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chills or rigors. There was no history of rash, arthralgia, icterus or contact with tuberculosis. On examination, she was conscious, febrile and was not in distress. She had multiple tender, enlarged left cervical lymph nodes of 2 cm × 2 cm size. The examination of other systems was essentially unremarkable. Investigations revealed haemoglobin 12.1 g/dL, TLC 8,100 cells/mm³ with a left shift, and platelet count 310,000/mm³. LFT revealed serum glutamic oxaloacetic transaminase of 250 U/L and serum glutamic pyruvic transaminase of 329 U/L. LDH was 960 U/L. Urine analysis was normal. Blood and urine cultures were sterile. Mantoux, Widal, Weil-Felix, Leptospiriosis-IgM, Scrub typhus-IgM, HbsAg, IgM hepatitis E virus, hepatitis A virus, and HIV by ELISA were negative.

Chest radiograph and ultrasonography of the abdomen were normal. Paul Bunnell test, rheumatoid factor and ANA were negative. Her DCT was negative. Bone marrow study was normal and culture was sterile. Echocardiography was normal. VCA and IgM for EBV were positive. An excision biopsy of the enlarged left cervical node was done, and the histopathology revealed a lymph node with essentially preserved architecture and multiple areas of histiocytic aggregates showing necrosis and karyorrhexis with few C-shaped monocytoïd cells. No granuloma was seen. There were no neutrophils in the area of karyorrhexis. The findings were consistent with necrotising histiocytic lymphadenitis, i.e. KD.

DISCUSSION

We have presented two cases of KD, one of whom had systemic involvement with multiorgan dysfunction and the other who had hepatic involvement. Systemic involvement has been rarely described in KD.^(2,3) Both cases had spontaneous resolution with supportive treatment. It was notable that both patients tested positive for EBV

IgM by ELISA. EBV has been proposed as one of the viral infections that may be causative for KD. Studies involving the isolation of viral RNA/DNA from lymph nodes in patients with KD have not shown a link to EBV.⁽¹⁾ However, there have been case reports of patients with KD having evidence of recent EBV infection, including EBV IgM by ELISA, detection of EBV DNA by PCR and EBV encoded RNA by hybridisation.^(5,6) EBV IgM ELISA is a specific test for a recent infection with EBV. It may thus be possible that KD occurs as a paraimmune phenomenon in acute EBV infection. In our setting, it was not possible to isolate EBV RNA from the affected lymph nodes. If this was possible, it would lend further credence to the association between EBV and KD. These cases are also meant to highlight that KD should be considered as a differential in a case of pyrexia of unknown origin, even in cases with multiorgan involvement, as demonstrated in our first case. The importance of KD also lies in accurate histological diagnosis, to differentiate it from lymphoma, so as to prevent unnecessary costs due to further testing or treatment with toxic drugs.

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