

## Case Report

# Epstein-Barr virus associated hemophagocytic lymphohistiocytosis presenting with lymphadenopathy diagnosed as Kikuchi-Fujimoto disease: a case report from South India

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## ABSTRACT

We report a rare case of hemophagocytosis and Kikuchi-Fujimoto disease associated with Epstein-barr virus infection, presenting in an eight year old boy hailing from south India. The child presented with fever and cervical lymphadenopathy. Bone marrow aspirate revealed hemophagocytosis. Cervical lymph node biopsy showed Histiocytic necrotizing lymphadenitis typical of Kikuchi's disease. The patient was given non-steroidal anti-inflammatory drug (Naproxen) after which he became afebrile and was discharged.

**Keywords:** HLH, EBV, Kikuchi disease

## INTRODUCTION

Histiocytic necrotizing lymphadenitis was first described independently in 1972 by Kikuchi and Fujimoto et al from Japan.<sup>1,2</sup> Kikuchi Fujimoto disease (KFD) is characterized most commonly by posterior cervical lymphadenopathy, fever and leukopenia, which most commonly resolve spontaneously within about 3 months.<sup>3,4</sup> The disease has been reported in people of all races. A higher incidence in females have been reported, the M:F ratio being 1:4 in some studies and 1.1:1 in other.<sup>5,6</sup> The cause of this disease is unknown although various infections and autoimmune diseases are associated. Infections associated are Epstein-Barr virus, HHV 6 and HHV 8, cytomegalovirus, varicella zoster virus, HIV, parvovirus B19, dengue, yersinia, protozoa.<sup>7,8</sup>

Autoimmune diseases which are associated with KFD include Hashimoto thyroiditis, polymyositis, mixed connective tissue disease, stills disease, autoimmune hepatitis and antiphospholipid syndrome.<sup>9-12</sup> Diagnosis is confirmed by excision lymph node biopsy.

KFD associated with Hemophagocytosis is very rare, to our knowledge this is the first reported case of Kikuchi-Fujimoto disease in India, fulfilling the criteria of HLH with hemophagocytosis in bone marrow, and lymph node biopsy showing histiocytic necrotizing lymphadenitis.

## CASE REPORT

An 8 year old boy, who had been well before, was admitted in September 2013 with complaints of fever for one month. The child was evaluated and treated with multiple antibiotics elsewhere, but the fever was persisting and hence referred to Kanchi Kamakoti child's trust hospital a tertiary care private hospital in Chennai, India. His family history and past medical history was unremarkable, the child was immunized as per universal immunisation schedule.

No history of rash, chills and rigor, jaundice, abdominal pain, loss of weight, bone pain, contact with tuberculosis, or specific drug intake was noted

On examination the patient was febrile, tender lymph nodes were noted in the left posterior cervical triangle (Figure 1), mild hepato-splenomegaly was noted, conjunctival congestion was present, other systems were normal. Hematological investigation showed total WBC count of 2400 cells/cumm, hemoglobin 10.2gm/dl, platelet count-2.3 lakhs/cumm, ESR-67mm, CRP-54.2mg/l, LDH-2440IU/L. Evaluation for infections revealed widal negative, leptospira IgM was negative, malaria-QBC was negative, Mantoux, sputum for AFB and HIV serology were negative, Cerebro-spinal fluid analysis was normal, blood culture was sterile, but reports came positive for EBV Anti-EBV VCA IgM-16.32u/ml (positive), IgG-77.17u/ml (positive).



**Figure 1: Patient, with lymph node biopsy excision site.**

Chest X ray and echocardiogram were normal.

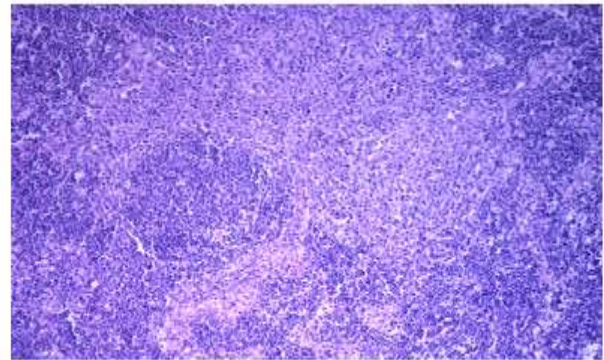
Peripheral smear showed lymphocytic response with few atypical lymphocytes.

Bone marrow aspirate showed moderate cellular marrow, hemophagocytic histiocytosis with foamy cytoplasm. Fasting triglycerides (367mgs/dl) and ferritin (443ng/ml) were elevated. A diagnosis of post viral HLH was made, the child was initially started on antibiotics empirically but they were discontinued once the cultures were negative. After diagnosing HLH the child was treated with IVIG 400mg /kg/day for three days after which the child's fever settled and tenderness in the lymph node came down, the child was discharged after two days.

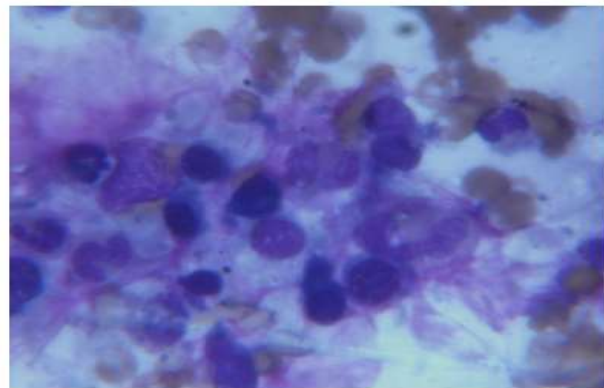
The child was readmitted in our hospital on July 2014 with complaints of fever for ten days and tender lymphadenopathy on the left posterior cervical region.

Investigations repeated again revealed leukopenia, ESR-52 mm, CRP-6.3 mg/l, LDH showed mild elevation (776 IU/L), ANA done this time revealed weak positivity by immunofluorescence method (1:100), dsDNA was negative. Repeat bone marrow aspirate showed reactive marrow and hemophagocytosis. Lymph node biopsy was done this time which revealed histiocytic necrotizing

lymphadenitis Figure 2 and 3. The child was treated with NSAID (naproxen) good response was noted, the child became afebrile by the next day.



**Figure 2: Lymph node biopsy revealing histiocytic necrotizing lymphadenitis (original magnification 10x).**



**Figure 3: Bone marrow aspirate showed hemophagocytosis (original magnification, 100X).**

## DISCUSSION

In the above case we presented a case of Kikuchi's disease with HLH having primary EBV infection. Very few case reports are available in literature about the association of HLH with Kikuchi's disease.

Our case fulfills the criteria of HLH 2004 criteria as given in Table 1.

Our case also had the characteristic necrotizing histiocytic lymphadenitis suggestive of KFD and also other laboratory features like mild elevation of LDH and weakly positive ANA. In previous studies where HLH was associated with KFD, EBV, respiratory syncytial virus and parvovirus B-19 were implicated in the etiology.<sup>13-15</sup> In our case EBV was implicated. There are studies suggesting that both HLH and KFD are two stages of a same disease spectrum.<sup>16</sup>

**Table 1: HLH 2004 criteria.**

The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled.
1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH fulfilled (Five out of the eight criteria below)
<b>A. Initial diagnostic criteria (to be evaluated in all patients with HLH)</b>
Fever
Splenomegaly
Cytopenias ( affecting 2 of 3 lineages in peripheral blood):
<ul style="list-style-type: none"> <li>Haemoglobin &lt;90 g/L (infants &lt;4 weeks: hemoglobin &lt;100 g/L)</li> <li>Platelets &lt;100×10<sup>9</sup>/L</li> <li>Neutrophils &lt;1×10<sup>9</sup>/L</li> </ul>
Hypertriglyceridemia and/or hypofibrinogenemia :
<ul style="list-style-type: none"> <li>Fasting triglycerides ≥3mmol/L (≥265 mg/dl)</li> <li>Fibrinogen &lt;1.5g/L</li> </ul>
Hemophagocytosis in bone marrow or spleen or lymph nodes
No evidence of malignancy
<b>B. New diagnostic criteria</b>
<ul style="list-style-type: none"> <li>Low or absent NK-cell activity (according to local laboratory reference)</li> <li>Ferritin &gt;500 µg/L</li> <li>Soluble CD25 (i.e. soluble IL-2 receptor) ≥2400 U/ml</li> </ul>

The main diagnostic dilemma with Kikuchi's disease is to differentiate it from lymphoma, in Dorfman and Berry's series, 40% patients with Kikuchi's disease were misdiagnosed as having lymphoma and were over treated with chemotherapy, in fact there have also been speculations that KFD may be a manifestation of an early- stage T cell lymphoma in evolution, and recently one case of KFD displaying at (2;16) chromosomal translocation have been published.<sup>17</sup> Conversely Yoshino et al reported two cases of KFD occurring in the course of remission of two diffuse large B cell lymphoma.<sup>18</sup> Histo-pathological features that distinguish KFD from lymphoma includes incomplete architectural effacement with patent sinuses, presence of numerous reactive histiocyte, relatively low mitotic rate, absence of Reed Stenberg cells.<sup>19</sup>

NSAID such as naproxen are commonly used. Systemic steroids are used in more complicated cases such as patients with recurrent episodes or prolonged symptoms. IVIG has been utilized to treat KFD.<sup>20-22</sup>

## CONCLUSION

Although a rare entity Kikuchi Fujimoto disease must be kept in mind as differential diagnosis for unexplained fever with lymphadenopathy, Kikuchi's disease associated with HLH is much more rare entity, but complete resolution is seen in most of the cases. A low

recurrence rate of 3- 4% has been noted and also because of its association with autoimmune diseases, long term follow up is needed.

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