

# Haemophagocytic syndrome and histiocytic necrotising lymphadenitis (Kikuchi's disease)

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## Abstract

**A young boy presented with a rash, fever, and cervical lymphadenopathy, originally thought to be caused by tuberculosis. A lymph node biopsy showed the features of Kikuchi's disease, with necrosis and histiocytic infiltration without neutrophils. No evidence of tuberculosis was found on staining, culture, or the polymerase chain reaction. Bone marrow biopsy revealed prominent haemophagocytosis, and a diagnosis of haemophagocytic syndrome was reached. The aetiology of haemophagocytic syndrome, and its association with Kikuchi's lymphadenitis, is discussed.**

(J Clin Pathol 2000;53:636-638)

Keywords: Kikuchi's disease; histiocytic necrotising lymphadenitis; histiocytic haemophagocytosis; haemophagocytic syndrome

Haemophagocytic syndrome, or histiocytic haemophagocytosis,<sup>1</sup> describes the engulfment by histiocytes of haematopoietic cells together with erythrocytes, leucocytes, and platelets; it is seen most prominently in bone marrow aspirates. This condition has been described in the context of an autosomal recessive familial syndrome (FHS),<sup>2</sup> in association with viral (VAHS)<sup>3</sup> and other infections,<sup>4</sup> and in various malignant diseases, mainly of lymphoid origin.<sup>5</sup> The organisms linked to haemophagocytic syndrome thus far include parvovirus B19, herpes simplex virus (HSV), varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), influenza virus, coxsackie viruses, adenoviruses, fungi, parasites, rickettsia, *Mycobacterium tuberculosis*, and other bacteria, including *Streptococcus pneumoniae*.<sup>1</sup> It is well documented that VAHS shows a predilection for children and immunocompromised adults; in Risdall's original series, 14 of the 19 patients were on azathioprine and prednisolone, 13 following renal transplantation and one for systemic lupus erythematosus (SLE).<sup>3</sup> Children displaying FHS often show defects of cellular and humoral immunity.<sup>1,6</sup>

Kikuchi's disease (Kikuchi-Fujimoto disease)<sup>7</sup> is an entity characterised by fever, normal peripheral white blood cell count, and self limiting tender cervical lymphadenopathy, with a histological picture of histiocytic necrotising lymphadenitis. The relapse or recurrence rate is low, at approximately 3%.<sup>7</sup> The aetiology is unknown, but a viral infection has been hypothesised; this is supported by the finding of tubuloreticular inclusions on electron microscopy.<sup>8</sup>

We present the case of a young boy who, after extensive investigation, showed the features of

both histiocytic haemophagocytosis and Kikuchi's disease. To our knowledge, this is only the second published report in the English language suggesting an association between the two conditions. Possible pathogenetic links are discussed.

## Case history

A boy of south Asian origin initially presented at the age of 4 years with fever and a hot, tender axillary lymph node. He was started on anti-tuberculous treatment (ciprofloxacin, ethambutol, and prothionamide, after two months of amikacin) but developed a generalised rash, followed by recurrent prolonged seizures and multiorgan failure. He was ventilated for five days and gradually improved with dexamethasone and broad spectrum antibacterial/anti-mycobacterial antibiotics. He subsequently had difficulty adhering to the antituberculous regimen, which was modified and then stopped after he developed weak legs (with no signs of peripheral neuropathy). A lymph node biopsy showed partial effacement of the architecture by large, geographic areas of karyorrhexis, heavily infiltrated by T lymphoblasts (CD45RO and CD3 positive; CD79a and CD20 negative). At the interface between these areas and the residual normal follicles there was an accumulation of CD68 positive histiocytes. The histiocytes did not show haemophagocytosis, and granulomas, multinucleate giant cells, neutrophils, and haematoxylin bodies were not seen. Slides were originally reported as showing a single cluster of beaded acid fast bacilli, but upon retrospective review of the sections two years later the bacteria could not be identified and the features were felt to be consistent with histiocytic necrotising lymphadenitis (Kikuchi's disease). Bone marrow biopsy was not performed. A history of a similar illness, treated empirically as tuberculosis without microbiological confirmation, in the patient's 13 year old brother was elicited.

The patient then remained well until the age of 6 years, when he presented with a few months' history of malaise with fever, a dental abscess, and submandibular lymphadenopathy. Despite surgical treatment of the abscess the cervical lymphadenopathy worsened and he developed sweats, rigours, prostration, and an erythematous rash, which was most pronounced, with induration, over the face and neck (in a Ludwig's angina-type distribution).

A lymph node biopsy (fig 1) showed features similar to two years previously, as described above. Culture of the node yielded a haemolytic and non-haemolytic streptococci but not *M tuberculosis*. Tonsillar biopsy showed acute inflammation and focal ulceration without specific features.

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Accepted for publication  
7 January 2000



Figure 1 Lymph node biopsy showed sharply demarcated areas of necrosis, with infiltration by histiocytes and lymphoblasts (Haematoxylin and eosin stain).

Microscopy and culture for mycobacteria and fungi were negative on lymph node biopsy, bronchoalveolar lavage, bone marrow aspirates, early morning urine, and stool specimens. Polymerase chain reaction (PCR) for mycobacteria, HSV, CMV, EBV, and parvovirus B19 were negative, as was serology for a wide range of other microorganisms (human immunodeficiency virus (HIV), human herpesvirus 8 (HHV-8), enterovirus, measles, brucella, histoplasma, coxiella, cat scratch bacteria, yersinia, and toxoplasma). The only positive microbiological/virological results were positive serology for mycoplasma, CMV, rubella, parvovirus B19, mumps, and respiratory syncytial virus (RSV); IgM was detected for the latter but in all the others only IgG antibodies were present.

Cerebrospinal fluid showed normal cell, protein, and glucose content without oligoclonal bands. Auramine and India ink stains were negative; cryptococcus was not isolated; CMV and HHV-6 PCR were negative and viral culture was negative.

The haemoglobin was 124 g/litre and the white blood cell and platelet counts were also normal ( $3.2$  and  $238 \times 10^9$ /litre, respectively). Notable abnormal haematological indices were an erythrocyte sedimentation rate (ESR) of 110 mm/hour and a positive sickle cell test. Haemoglobin electrophoresis showed the child to have sickle cell trait. A blood film showed microcytic, hypochromic red blood cells, neutropenia, and lymphopenia. Abnormal chemical pathology results included alanine transaminase 570 (normal,  $< 50$  U/litre),  $\gamma$  glutamyl transferase 270 (normal,  $< 40$  U/litre), lactate dehydrogenase 8340 (normal, 150–450 U/litre), ferritin 35 500 (normal, 20–230 ng/ml), and amylase 531 (normal,  $< 90$  U/litre). A full autoantibody screen was negative. Serum immunoglobulins (IgG, IgA, and IgM) were normal.

Despite the administration of prednisolone the fever did not settle so bone marrow aspiration and trephine biopsy were performed. Both showed haemophagocytosis (fig 2). Etoposide and dexamethasone were started, with rapid resolution of symptoms, and the patient remains well on cyclosporin A.<sup>1</sup>

### Discussion

The most important differential diagnoses of a lymph node biopsy showing infiltration by

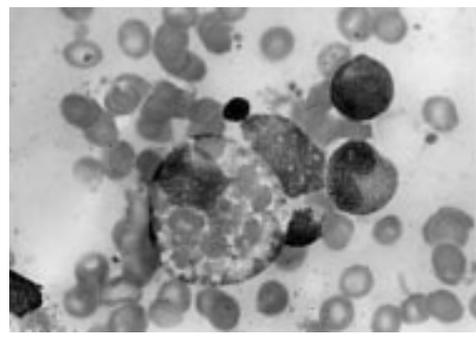


Figure 2 Bone marrow aspirate showed haemophagocytic histiocytes (May Grünwald Giemsa stain).

blasts and histiocytes with extensive necrosis or karyorrhexis are malignant lymphoma, tuberculosis, SLE, and Kikuchi's disease. The first three of these were effectively excluded in our patient by clinical features and appropriate investigations, as outlined above. The features of the lymph node biopsy were histologically indistinguishable from those seen in Kikuchi's disease. However, because Kikuchi's disease is not reported to be familial and recurrences are uncommon, we suggest that our patient has an inherited immunological abnormality predisposing him to produce this pattern of inflammatory response in the lymphoreticular system to an infective trigger, without having classic FHS, (which, in 80% of cases presents in the 1st year of life<sup>1</sup>).

The only other published report of a patient with Kikuchi's disease and haemophagocytic syndrome in the English language literature describes an association with parvovirus B19 infection.<sup>9</sup> There was no evidence of recent parvovirus B19 infection in our patient. Extensive microbiological investigations showed evidence of recent infection only with RSV and non-haemolytic and  $\alpha$  haemolytic streptococci. To our knowledge, there has been only one report, in the French literature, claiming an association between RSV and haemophagocytosis.<sup>10</sup> However, RSV infection is so common and histiocytic haemophagocytosis so uncommon, with an incidence of about two for every million children each year,<sup>1</sup> that a meaningful aetiological link appears unlikely. We hypothesise that the streptococcal dental abscess (and some other, unknown, infection at first presentation) triggered both the histiocytic haemophagocytosis and the Kikuchi like lymph node response in our patient. Hence, histopathologists should be aware that a histiocytic necrotising lymphadenitis picture on lymph node biopsy might result not only from Kikuchi's disease, tuberculosis, SLE, and malignant lymphoma, but also from haemophagocytic syndrome.

### Conclusion

This is the second published case in the English language literature associating haemophagocytic syndrome and histiocytic necrotising lymphadenitis. We suggest that the latter histological picture is not specific for Kikuchi's disease, and discuss the possible pathogenetic links with the haemophagocytic syndrome.

We thank Dr Alan Ramsay, Consultant Histopathologist, Great Ormond Street Hospital for Sick Children, London and Professor Michael Levine, Department of Paediatrics, St Mary's Hospital Medical School, London.

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