

Kikuchi's Disease Associated with Hemophagocytosis

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We report the case of a 40 year-old Nepali man admitted to the hospital with a one month history of fever associated with swelling, pain, and redness on the right side of the neck. On examination, tender lymph nodes were palpated in the right posterior cervical triangle. Bone marrow aspiration and biopsy showed hemophagocytosis. Cervical lymph node biopsy showed the typical necrotizing lymphadenitis of Kikuchi's disease. The patient was given non-steroidal anti-inflammatory drugs (Naproxen 500 mg twice daily orally). After ten days, the fever and lymphadenopathy subsided and he was consequently discharged. (*Chang Gung Med J* 2007;30:370-3)

Key words: Histiocytic necrotizing lymphadenitis, hemophagocytosis, Kikuchi's disease, naproxen

Histiocytic necrotizing lymphadenitis was first described independently in 1972 by Kikuchi⁽¹⁾ and Fujimoto et al,⁽²⁾ both from Japan. Consequently, the entity is also known as Kikuchi-Fujimoto's disease or simply Kikuchi's disease (KD). Although first described in people of Asian origin, the disease has now been reported in individuals of all races. KD associated with hemophagocytosis is especially rare. A search through PubMed revealed only four cases of KD associated with hemophagocytosis reported in the literature. To our knowledge, this is the first reported case of Kikuchi's disease in the state of Qatar, characterized by histiocytic necrotizing lymphadenitis and hemophagocytosis.

CASE REPORT

A 40 year-old Nepali man was admitted to the hospital with a one month history of fever associated with swelling, pain, and redness on the right side of the neck. During this period he received several antibiotics without any benefit. On direct questioning, he mentioned weight loss and arthralgia. The

medical history was otherwise unremarkable. On examination, the patient appeared ill. His temperature was 39.5°C, his pulse 126/minute, and his respiration was 22 per minute. Blood pressure was 120/70 mm Hg. Tender lymph nodes were palpated in the right posterior cervical triangle. Examination of the abdomen revealed splenomegaly, while examination of other systems was unremarkable.

Initial investigations showed a hemoglobin level of 13.2 g/dL, a total leucocyte count of 2700/μL and a platelet count of 82000/μL; the erythrocyte sedimentation rate (ESR) was 34 mm/hour. Blood chemistry, liver profile, and coagulation tests were within normal limits. His fasting lipid profile showed a total cholesterol level of 5.2 mmol/L and a triglyceride level of 4 mmol/L. A tuberculin skin test was negative. Blood culture, urine analysis, urine culture, and Brucella serology were negative. Hepatitis C antibodies, hepatitis B markers and antibodies to human immunodeficiency virus were likewise negative. Antinuclear antibodies (ANA), anti double strand DNA (anti-dsDNA) antibodies and syphilis serology were also negative, whereas the levels of serum C3

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and C4 were normal. Abdominal sonography showed splenomegaly while chest X-rays were normal.

On the third day of hospitalization, the patient developed diarrhea and a maculopapular rash over the anterior chest and abdomen wall. Ciprofloxacin, was initiated orally and the diarrhea stopped, but the fever continued. Fine needle aspiration of a cervical lymph node was carried out, but the cytological diagnosis was not informative. Bone marrow aspiration and biopsy showed hemophagocytosis (Fig. 1). On the seventh day, the patient developed left axillary lymphadenopathy. A cervical lymph node biopsy was carried out, showing the typical necrotizing lymphadenitis of Kikuchi's disease (Figures 2A and 2B). Microscopy and cultures on the lymph node biopsy for mycobacteria and fungi were negative. The patient was given non-steroidal anti-inflammatory drugs (Naproxen 500 mg twice daily orally) for arthralgia and fever. After ten days the fever and lymphadenopathy subsided, and the patient was consequently discharged. After six months the patient was seen again in the clinic and was well.

DISCUSSION

Kikuchi's disease is a self-limiting condition, which usually presents with lymphadenopathy or fever of unknown etiology, or both. Its classical presentation is as a painful cervical lymphadenopathy in young adults, usually females. Unilateral involve-

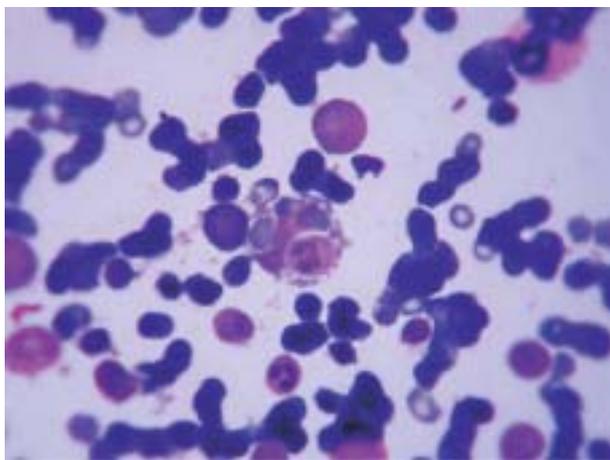


Fig. 1 Bone marrow aspirate shows hemophagocytic macrophage engulfing a neutrophil (MG Giemsa stain x 1000).

ment of the posterior cervical group is the most common picture associated with fever, however the lymphadenopathy may be generalized.⁽³⁾

Its true incidence is unknown. A higher incidence in females has been reported, with a female to male ratio between 1.1:1 and 2.75:1.⁽⁴⁾ The etiology of the disease remains unknown. It has been reported in association with toxoplasmosis, *Yersinia*, Epstein-Barr virus and parainfluenza viruses.^(5,6) Cases associated with systemic lupus erythematosus (SLE) and Hashimoto's disease also have been reported.^(7,8)

Less common manifestations include axillary

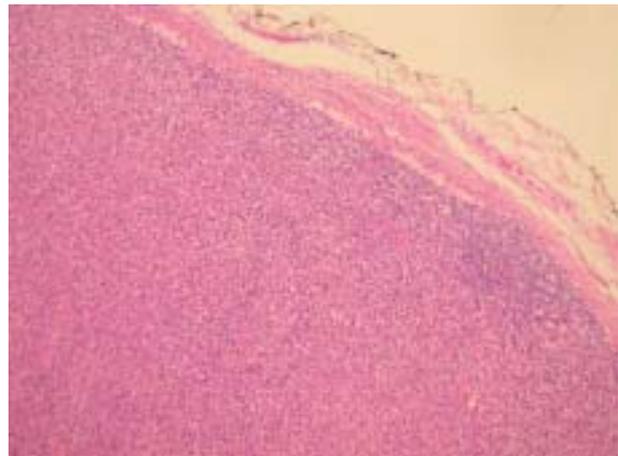


Fig. 2A A low power view of a hematoxylin and eosin stained section of the lymph node showing a subcapsular cortical pale histiocytic infiltrate replacing most of the original lymph node tissue (original magnification x 64).

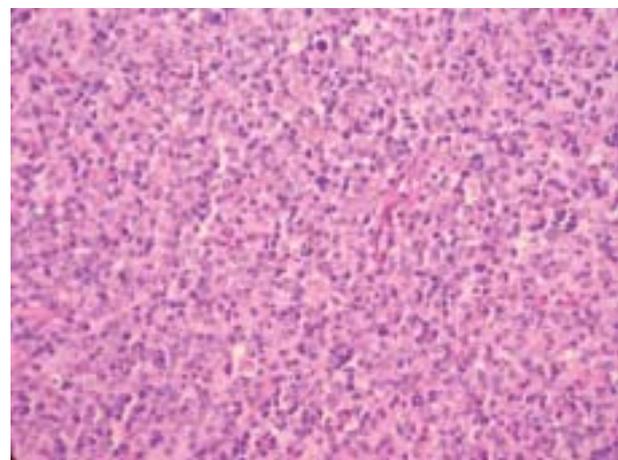


Fig. 2B Higher power view of the cortical infiltrate showing mostly pale histiocytic cells speckled with darker staining minute fragmented nuclei (original magnification x 180).

and mesenteric lymphadenopathy, splenomegaly, parotid gland enlargement, cutaneous rash, arthralgias, myalgias, aseptic meningitis,⁽⁹⁾ bone marrow hemophagocytosis⁽¹⁰⁻¹³⁾ and interstitial lung disease.⁽¹⁴⁾

The cutaneous lesions include erythematous macules, papules, plaques and nodules.⁽¹⁵⁾

The ESR in the first hour has been reported as ranging between 30 and 60 mm.

Our patient presented with unexplained fever and right cervical lymphadenopathy. He later developed erythematous skin lesions, arthralgia and weight loss. Hematologic investigations revealed leucopenia; 2700 /uL, thrombocytopenia and an elevated ESR of 34 mm/hour. Biopsy of skin lesions in KD would show leucocytoclastic vasculitis, but a skin biopsy was not performed in this case. Bone marrow aspiration and biopsy showed hemophagocytosis, which is extremely rare. A search through PubMed revealed only four cases of KD associated with hemophagocytosis reported in the literature.⁽¹⁰⁻¹³⁾

Hemophagocytic lymphohistiocytosis (HLH) syndrome is a clinicopathological entity describing the engulfment of hematopoietic cells by histiocytes, also called macrophages, in the bone marrow. It is characterized by fever, hepatosplenomegaly, pancytopenia, infiltration of various organs by histiocytes, and high serum ferritin. This condition has been described in association with an autosomal recessive familial syndrome,⁽¹⁶⁾ viral and other infections, and in various malignant diseases, mainly of lymphoid origin,⁽¹⁷⁾ autoimmune and metabolic disorders. Viral and other infections include, cytomegalovirus, Epstein-Barr virus, *Mycobacterium tuberculosis*,⁽¹⁸⁾ human immunodeficiency virus, parvovirus B19 and, more rarely, hepatotropic viruses.

The most important differential diagnoses to consider in patients presenting with features typical of KD are malignant lymphoma, tuberculous lymphadenitis and SLE.

Yoshino et al reported two cases of KD occurring in the course of remission of diffuse large B-cell lymphoma.⁽¹⁹⁾ Immunohistochemistry can be used to differentiate KD from malignant lymphoma. This patient had many clinical manifestations of systemic lupus erythematosus: lymphadenopathy, erythematous skin lesions, unexplained fever, arthralgia and weight loss. But the absence of autoantibodies, ANA, anti-dsDNA antibodies and hypocomplementemia, which are relatively sensitive and specific

for diagnosis of systemic lupus erythematosus, left SLE unconfirmed. On the other hand tuberculous adenitis was effectively excluded in this patient by negative microscopy and culture for mycobacteria on the lymph node biopsy, along with spontaneous recovery.

The diagnosis of KD depends entirely on examination of the excised lymph nodes, which are characterized by necrosis and preservation of the nodal architecture. The extent of the necrosis is variable, ranging from 5% to 95% of the node, and is characteristically associated with marked karyorrhexis, histiocytic infiltrate and absence of granulocytes.^(1,2)

The treatment and prognosis of Kikuchi's disease associated with hemophagocytic syndrome is unclear. Review of the literature revealed that Kikuchi's disease associated with hemophagocytic syndrome in children seems to have a less aggressive course and better prognosis than its adult counterpart.⁽¹³⁾

Although our patient recovered after oral administration of naproxen for ten days, it is not clear whether this remission was due to naproxen or was spontaneous.

In conclusion, Kikuchi's disease associated with hemophagocytic syndrome seems to follow a benign course, the exact anti-HLH therapy required varies from high dose steroids alone +/- the addition of IV gamma globulin, to the more significant immunosuppression prescribed by the HLH-94 and 2004 protocols of the histiocyte society.

REFERENCES

1. Kikuchi M. Lymphadenitis showing focal reticulum cell hyperplasia with nuclear debris and phagocytes. *Acta Hematol Jpn* 1972;35:379-80.
2. Fujimoto Y, Kozima Y, Yamaguchi K. Cervical subacute necrotizing lymphadenitis. A new clinicopathological entity. *Naika* 1972;30:920-7.
3. Pilevi S, Kikuchi M, Helborn D, Lennert K. Histiocytic necrotizing lymphadenitis without granulocytic infiltration. *Virchows Archives A (pathology, anatomy, histology)* 1982;395:257.
4. Kuo T. Kikuchi's disease (histiocytic necrotising lymphadenitis): a clinicopathologic study of 79 cases with an analysis of histologic subtypes, immunohistology and DNA ploidy. *Am J Surg Pathol* 1995;19:798-809.
5. Imamura M, Ueno H, Matsuura A, Kamiya H, Suzuki T, Kikuchi K, Onoe T. An ultrastructural study of subacute necrotizing lymphadenitis. *Am J Pathol* 1982;107:292.

6. Ali M, Horton LWL. Necrotizing lymphadenitis without granulocytic infiltration (Kikuchi disease). *J Clin Pathol* 1985;38:1252.
7. Rao GS, Vohra D, Kuruvilla M. Is Kikuchi-Fujimoto disease a manifestation of systemic lupus erythematosus? *Int J Dermatol* 2006;45:454-6
8. Santana A, Lessa B, Galrao L, Lima I, Santiago M. Kikuchi-Fujimoto's disease associated with systemic lupus erythematosus: case report and review of the literature. *Clin Rheumatol* 2005;24:60-3.
9. Sato Y, Kuno H, Oizumi K. Histiocytic necrotizing lymphadenitis (Kikuchi's disease) with aseptic meningitis. *J Neurol Sci* 1999;163:187-91.
10. Wano Y, Ebata K, Masaki Y, Takeshita S, Ogawa N, Kim CG, Okada J, Saito H, Hirose Y, Tohyama T, Sugai S. Histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto's disease) accompanied by hemophagocytosis and salivary gland swelling in a patient with systemic lupus erythematosus. *Rinsho Ketsueki* 2000;41:54-60.
11. Mahadeva U, Allport T, Bain B, Chan WK. Haemophagocytic syndrome and histiocytic necrotising lymphadenitis (Kikuchi's disease). *J Clin Pathol* 2000;53:636-8.
12. Kelly J, Kelleher K, Khan MK, Rassam SM. A case of haemophagocytic syndrome and Kikuchi-Fujimoto disease occurring concurrently in a 17-year-old female. *Int J Clin Prac* 2000;54:547-9.
13. Kim YM, Lee YJ, Nam SO, Park SE, Kim JY, Lee EY. Hemophagocytic syndrome associated with Kikuchi's disease. *J Korean Med Sci* 2003;18:592-4.
14. Sharma OP. Unusual systemic disorders associated with interstitial lung disease. *Curr Opin Pulm Med* 2001;7:291-4.
15. Yasukawa K, Matsumura T, Sato-Matsumura KC, Takahashi T, Fujioka Y, Kobayashi H, Shimizu H. Kikuchi's disease and the skin: case report and review of the literature. *Br J Dermatol* 2001;144:885-9.
16. Perry MC, Harrison EG Jr., Burgert EO Jr., Gilchrist GS. Familial erythrophagocytic lymphohistocytosis: Report of two cases and clinicopathologic review. *Cancer* 1976;38:209-18.
17. Linn YC, Tien SL, Lim LC, Lee LH, Teoh G, Goh YT, Tan P. Haemophagocytosis in bone marrow aspirate-a review of the clinical course of 10 cases. *Acta Haematol* 1995;94:182-91.
18. Claessens YE, Pene F, Tulliez M, Cariou A, Chiche JD. Life-threatening hemophagocytic syndrome related to mycobacterium tuberculosis. *Eur J Emerg Med* 2006;13:172-4.
19. Yoshino T, Mannami T, Ichimura K, Takenaka K, Nose S, Yamadori I, Akagi T. Two cases of histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto's disease) following diffuse large B-cell lymphoma. *Hum Pathol* 2000;31:1328-31.