J Microbiol Immunol Infect 2010;43(3):253–257

Contents lists available at ScienceDirect

Journal of Microbiology, Immunology and Infection

Journal homepage: http://www.e-jmii.com

Case Report

Primary Epstein-Barr Virus Infection Associated with Kikuchi's Disease and Hemophagocytic Lymphohistiocytosis: A Case Report and Review of the Literature

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An association between hemophagocytic lymphohistiocytosis (HLH) and Kikuchi's disease is rarely seen in children. Here, we present the case of a male adolescent (age 16 years and 3 months) who suffered from spiking fever for more than 1 week, and multiple nodules over the neck and bilateral axilla for 2 months. A skin rash also developed over all four limbs, abdomen and face. Laboratory data and skin biopsy gave results compatible with a diagnosis of Kikuchi's disease. Hemophagocytosis in the bone marrow, hypertriglyceridemia, elevated ferritin, and splenomegaly were also found, fulfilling the criteria for HLH. A recent primary Epstein-Barr virus infection was also diagnosed by serology. The patient ran a relatively benign course. Intravenous immunoglobulins, steroids or etoposide-containing regimens were not used, and his recovery was uneventful. A review of the literature showed that up to February 2009, 11 additional cases of Kikuchi's disease presenting simultaneously with, or mimicking, HLH had been reported. Complete resolution within several weeks, with no recurrence, was seen in all but one patient (a pregnant woman).

KEYWORDS: Epstein-Barr virus, hemophagocytic lymphohistiocytosis, Kikuchi's disease

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Article History:
Received: Feb 25, 2009
Revised: Apr 30, 2009
Accepted: Jun 19, 2009

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a benign proliferation of the hemophagocytic cells of the monocyte-macrophage-histiocyte lineage, resulting in the uncontrolled phagocytosis of normal hematopoietic cells. Clinical severity ranges from complete recovery to rapid deterioration and death. Viruses, bacteria, parasites and fungi are all reported to be associated with this illness.[1,2] Currently, a diagnosis of HLH requires the fulfillment

of five out of eight clinical and laboratory criteria, which include fever, splenomegaly, cytopenia in at least two cell lines, hypertriglyceridemia or hypofibrinogenemia, elevated ferritin levels (≥ 500 ng/mL), raised serum soluble interleukin (IL)-2 receptor levels (sCD25 ≥ 2,400 U/mL), decreased or absent NK-cell activity, and hemophagocytosis in the bone marrow, cerebrospinal fluid or lymph nodes.[3]

Kikuchi's disease, first reported in Japan independently by Kikuchi and Fujimoto et al in 1972,[3,4] is a well-defined clinicopathologic entity often seen in young adults, and usually follows a benign self-limiting clinical course. It is characterized by painful and/or tender cervical lymphadenopathy. It can be accompanied by fever and, less commonly, by other symptoms such as a skin rash, hepatomegaly, and weight loss. Leukopenia is the most consistent laboratory finding. The diagnosis of Kikuchi's disease is based on histological findings. The pathogenesis is unknown, but a viral cause has long been suggested.[2]

The association of HLH with Kikuchi's disease is rarely reported. Here, we report an adolescent case of Kikuchi's disease associated with HLH caused by primary Epstein-Barr virus infection. The literature regarding such associations is also reviewed.

Case Report

A male adolescent (aged 16 years and 3 months) had been well until 2 months prior to admission. During this time he developed multiple nodules over the right side of his neck (2–5 mm in size) without tenderness, local heat, or redness, and developed a fever (up to 39.5°C) 6 weeks later. Several non-itchy erythematous maculopapular rashes developed over all four limbs, abdomen and face. He also complained of fatigue, cough, sore throat, and shoulder pain. There was no nasal obstruction, nausea, vomiting, diarrhea or dysuria, nor a history of animal contact. He was admitted to a medical center. Complete blood cell counts showed leukopenia, chest radiography showed no active lung lesions, and abdominal sonography revealed splenomegaly. Bone marrow aspiration was negative for malignancy and also negative for bacterial cultures. Intravenous ampicillin was given initially, and was changed to cefepime on day 5. However, a spiking fever still persisted. One week later, at his parents' request, the patient was transferred to Chang Gang Children's Hospital for further investigation and management.

On admission to Chang Gang Children's Hospital, the patient had a high fever (up to 39.6°C). Multiple nodules had developed bilaterally on his neck and axillary area. Several maculopapular rashes were found on his limbs, abdomen and face. Complete blood cell counts showed leukopenia (white blood cell count = 1.24×10^9/L neutrophils, 61%; lymphocytes 30%; monocytes 8%), a hemoglobin level of 12.6 g/dL, a platelet count of 130×10^9/L. Serum biochemistry showed a C-reactive protein level of 17.9 mg/L (normal, < 5 mg/L), aspartate aminotransferase of 71 IU/L, and alanine aminotransferase of 119 IU/L (normal, < 40 IU/L). Because of persistent fever for more than 2 weeks, HLH was suspected and further laboratory tests were performed. Serum ferritin was 892.9 ng/mL, and fasting triglycerides were 275 mg/dL. Rheumatic factors, C3, C4, antinuclear antibody, and anti-double strain DNA were all within normal limits. Bone marrow aspiration (repeated on day 3 post hospitalization), showed reactive lymphohistiocytes, and hemophagocytosis (Figures 1A and 1B). A skin biopsy performed at the same time showed hyperkeratosis, acanthosis, aggregates of histiocytes, crescentic histiocytes, eosinophils, lymphocytes, and nuclear dust without granulocytes in the dermis and around the adnexae of the skin, which was compatible with Kikuchi's disease (Figure 2). Virological studies were positive for anti-Epstein-Barr virus (EBV) capsid IgM, anti-EBV capsid IgG (1:160), anti-EB early antigen antibody (1:20) and anti-EB nuclear antigen, all of which were compatible with a recent primary EBV infection. A cytomegalovirus survey and throat swab taken for virus isolation were both negative, as were blood and bone marrow cultures for bacteria.

The fever disappeared spontaneously on hospital day 12 and the patients' general condition gradually improved. After discussions between the pediatric hematologist/oncologist, the patient, and his parents, a therapeutic regimen for HLH was not initiated. He was discharged on day 18. Transient mild fever for several days was noted within the first week after discharge, but this later subsided. The size of cervical lymph nodes decreased gradually and he remained well during followed-up at the outpatient department for at least 1.5 years.

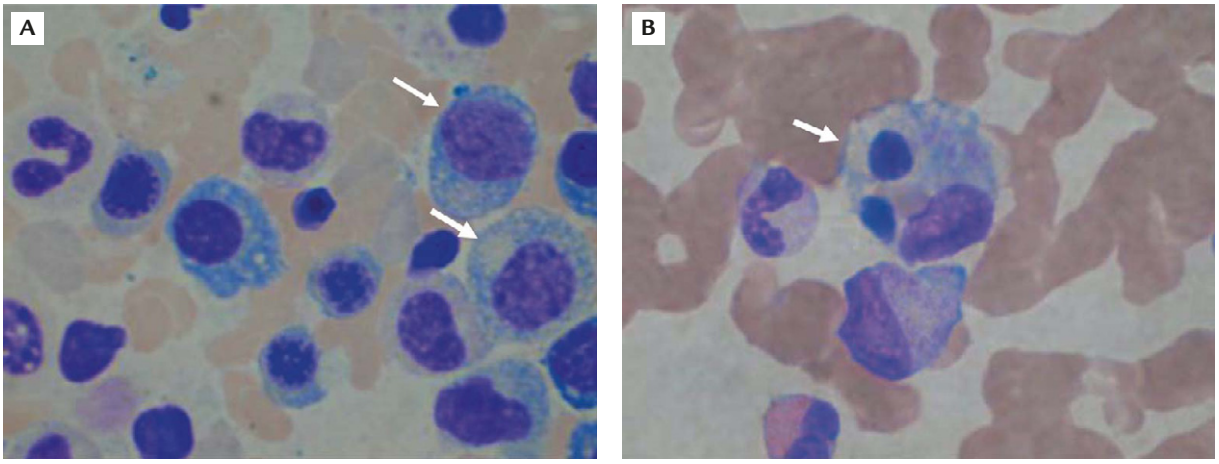

Figure 1. Bone marrow aspirate showed (A) abnormal lymphohistiocytes and (B) hemophagocytosis. (Giemsa stain; original magnification, 1,000×).

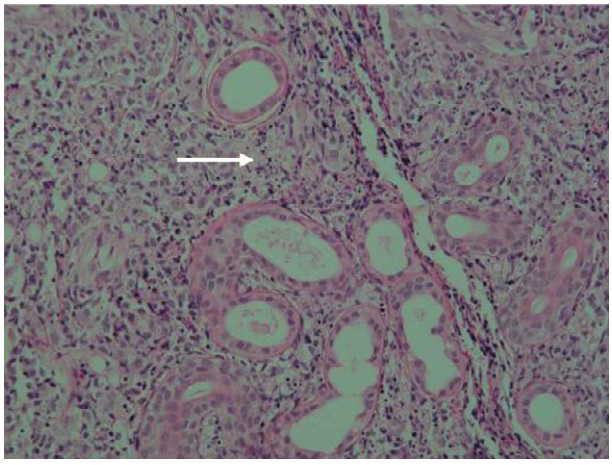

Figure 2. Skin biopsy showed periadnexal infiltration of histiocytes admixed with nuclear dust (arrow) (Original magnification, 200×).

Discussion

In this report, we documented a case of primary EBV-associated Kikuchi's disease mimicking HLH. A recent primary EBV infection in this patient was confirmed by EBV specific serological tests.[6] Kikuchi's disease was confirmed by skin biopsy.[7,8] HLH was diagnosed by established clinical criteria, in which at least five of the eight criteria were met: fever for more than 1 week, hypertriglyceridemia, elevated ferritin levels, hemophagocytosis in the bone marrow, and splenomegaly. In addition, leukopenia, mild anemia and thrombocytopenia were also found. Serum soluble IL-2 receptor levels and NK-cell activity were not measured.

Up to February 2009, a total of 12 cases mimicking HLH presenting simultaneously with Kikuchi's disease had been reported in the literature.[9–18] However, only four of these cases fulfilled the criteria for HLH (our case and other reports[8,13,15]). Other cases did not fulfill the criteria for HLH, but assumed a diagnosis of HLH because hemophagocytosis was found in the bone marrow. Interestingly, lymph node hemophagocytosis, which can be seen in HLH, was absent in these cases. Of the 12 reported cases, nine were children or adolescents (Table 1).[7–16] The pathogen associated with HLH and Kikuchi's disease was identified in only three cases: respiratory syncytial virus, parvovirus B19 and EBV. The case presented here was also an adolescent, and primary EBV infection was identified at the time of admission.

There were many overlaps in the etiology, clinical symptoms and signs between Kikuchi's disease and HLH (Table 2). Findings from our previous reports[2,19] and those of others[20] indicate that lymphadenopathy was the most important finding in Kikuchi's disease, but was also found in 68.4% of the childhood cases of HLH. Fever, splenomegaly and cytopenia were the diagnostic criteria for HLH, but were also found in patients with Kikuchi's disease, especially in those with prolonged fever.[2,19,20] Hence, Kelly et al thought that HLH and Kikuchi's disease may be two stages of a disease continuum, rather than different entities.[14]

Childhood HLH, if associated with EBV infection, runs a relatively severe and potentially fatal course.[19–21]

Table 1. Cases of concomitant Kikuchi's disease and those mimicking hemophagocytic lymphohistiocytosis reported in the literature

Case	Age (yr)/ sex	Virus	Therapy	Outcome	Year [Reference]
1	15/F	Parvovirus B19	Prednisolone (60 mg/d)	Clinical symptoms resolved within 3 wk; cytopenia normalized within 2 mo	1997 [7]
2	37/F	–	Methylprednisolone pulse therapy (1 g for 3 d)	Clinical symptoms resolved within 2 wk	2000 [8]
3	4/M	RSV	Prednisolone, etoposide, cyclosporine A	Rapid resolution of symptoms and remains well.	2000 [9]
4	10/F	–	IVIG (1 g/kg/day for 2 d), prednisolone (2 mg/kg/day)	Dramatic response, no recurrence	2000 [10]
5	14/M	–	IVIG (1 g/kg/day for 2 d), prednisolone (2 mg/kg/day)	Improved gradually after administration of prednisolone, no recurrence	2000 [10]
6	24/F	EBV	IVIG 60 g for 3 d, acyclovir 750 mg IV every 12 hr	Postpartum death	2000 [11]
7	17/F	–	IVIG	Complete continuous response to therapy	2000 [11]
8	1/F	–	IVIG 2 g/kg, methylprednisolone (20 mg/kg) followed by oral prednisolone 1 mg/kg/day, methotrexate, cyclosporine (3 mg/kg/day)	Made a good recovery on cyclosporin and is currently in remission with no systemic features or joint problems	2003 [12]
9	13/F	–	IVIG (0.4 g/kg/day for 5 d) and methylprednisolone (1 g/d for 3 d), etoposide (150 mg/m^2), oral dexamethasone and trimethoprim/sulfamethoxazole	Complete resolution within 1.5 mo and no evidence of disease recurrence during the following 8 mo	2003 [2]
10	2/M	–	Prednisolone (2 mg/kg)	Good response on treatment of autoimmune-phenomena with prednisolone, but death due to transplant failure for juvenile myelomonocytic leukemia	2006 [15]
11	40/M	–	Naproxen 500 mg twice daily po	Fever and lymphadenopathy subsided after 10 d	2007 [16]
12	16/M	EBV	No IVIG or steroid	Improved gradually, no recurrence	Present study

RSV=Respiratory syncytial virus; EBV=Epstein-Barr virus; IVIG=intravenous immunoglobulin; IV=intravenous; po=orally.

Kikuchi's disease is usually self-limiting,[2] and supportive treatment alone may be sufficient. Combination therapy with intravenous immunoglobulins and steroids is the treatment of choice for HLH, and etoposide-containing regimens are reserved for those who fail to respond to the combination therapy.[19,22] However, intravenous immunoglobulin, steroids or etoposide-containing regimens were not used in this patient, and the patient recovered uneventfully. All 12 patients with concomitant Kikuchi's disease and mimicking hemophagocytic lymphohistiocytosis shown in Table 1 had complete resolution of disease within several weeks with no recurrence, except for one patient who is a pregnant woman. Our case indicates that primary EBV infection with Kikuchi's disease may progress to HLH, and the prognosis is not always poor.

Table 2. Comparison of Kikuchi's disease and hemophagocytic lymphohistiocytosis[a]

	Kikuchi's disease (n=64) [2]	HLH (n=18/19) [19,22]
Prolonged fever	32.8	100
Splenomegaly	7.8/23.8[b]	61.1–94.7
Lymphadenopathy	98.4	44.4–68.4
Skin rash	6.3	55.6–57.9
Leukopenia (WBC < 4.0×10^9/L)	44.1/61.9[b]	50.0
Anemia (Hb < 10 mg/dL)	3.4/10.0[b]	84.2
Thrombocytopenia	9.3[c]	55.6–78.9[d]
Elevated liver enzyme (AST or ALT > 45 IU/L)	25.0/37.5[b]	83.3–89.5

[a]Data presented as %; [b]in patients with prolonged fever; [c]platelet < 150×10^9/L; [d]platelet < 100×10^9/L. WBC=white blood cell; Hb=hemoglobin; AST=aspartate aminotransferase; ALT=alanine aminotranferease; HLH=hemophagocytic lymphohistiocytosis.

References

1. Kikuchi M. Lymphadenitis showing focal reticulum cell hyperplasia with nuclear debris and phagocytes. *Acta Haematol Jpn* 1972;35:379–80.
2. Fujimoto Y, Kojima Y, Yamaguchi K. Cervical subacute necrotizing lymphadenitis. *Naika* 1972;30:920–7.
3. Kikuchi M. Lymphadenitis showing focal reticulum cell hyperplasia with nuclear debris and phagocytes. *Acta Haematol Jpn* 1972;35:379–80.
4. Fujimoto Y, Kojima Y, Yamaguchi K. Cervical subacute necrotizing lymphadenitis. *Naika* 1972;30:920–7.
5. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. *Eur J Pediatr* 2007;166:95–109.
6. Jenson HB. Epstein-Barr virus. In: *Nelson Textbook of Pediatrics*, 18th edition. Philadelphia, Pa: Saunders, Elsevier 2007;1372–7.
7. Kuo TT. Cutaneous manifestation of Kikuchi's histiocytic necrotizing lymphadenitis. *Am J Surg Pathol* 1990;14:872–6.
8. Yen HR, Lin PY, Chuang WY. Skin manifestations of Kikuchi-Fujimoto disease: case report and review. *Eur J Pediatr* 2004;163:210–3.
9. Yufu Y, Matsumoto M, Miyamura T. Parvovirus B19-associated haemophagocytic syndrome with lymphadenopathy resembling histiocytic necrotizing lymphadenitis (Kikuchi's disease). *Br J Haematol* 1997;96:868–71.
10. Wano Y, Ebata K, Masaki Y. Histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto's disease) accompanied by hemophagocytosis and salivary gland swelling in a patient with systemic lupus erythematosus. *Japan J Clin Hematol* 2000;41:54–60.
11. Mahadeva U, Allport T, Bain B. Haemophagocytic syndrome and histiocytic necrotising lymphadenitis (Kikuchi's disease). *J Clin Pathol* 2000;53:636–8.
12. Chen JS, Chang KC, Cheng CN. Childhood hemophagocytic syndrome associated with Kikuchi's disease. *Haematologica* 2000;85:998–1000.
13. Chmait RH, Meimin DL, Koo CH. Hemophagocytic syndrome in pregnancy. *Obstet Gynecol* 2000;95:1022–4.
14. Kelly J, Kelleher K, Khan MK. A case of haemophagocytic syndrome and Kikuchi-Fujimoto disease occurring concurrently in a 17-year-old female. *Int J Clin Pract* 2000;54:547–9.
15. Ramanan AV, Wynn RF, Kelsey A. Systemic juvenile idiopathic arthritis, Kikuchi's disease and haemophagocytic lymphohistiocytosis—is there a link? Case report and literature review. *Rheumatology* 2003;42:596–8.
16. Kim YM, Lee YJ, Nam SO. Hemophagocytic syndrome associated with Kikuchi's disease. *J Korean Med Sci* 2003;18:592–4.
17. Gerritsen A, Lam K, Marion Schneider E. An exclusive case of juvenile myelomonocytic leukemia in association with Kikuchi's disease and hemophagocytic lymphohistiocytosis and a review of the literature. *Leukemia Res* 2006;30:1299–303.
18. Fahmi YK, Morad NA, Fawzy Z. Kikuchi's disease associated with hemophagocytosis. *Chang Gung Med J* 2007;30:370–3.
19. Chen CJ, Huang YC, Jaing TH. Hemophagocytic syndrome: a review of 18 pediatric cases. *J Microbiol Immunol Infect* 2004;37:157–63.
20. Palazzi DL, McClain KL, Kaplan SL. Hemophagocytic syndrome in children: an important diagnostic consideration in fever of unknown origin. *Clin Infect Dis* 2003;36:306–12.
21. Pohl M, Niemeyer CM, Hentschel R. Haemophagocytosis in early congenital syphilis. *Eur J Pediatr* 1999;158:553–5.
22. Janka GE, Schneider EM. Modern management of children with haemophagocytic lymphohistiocytosis. *Br J Haematol* 2004;124:4–14.