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Hemophagocytic Syndrome Associated with Kikuchi's Disease

A 13-yr-old female was admitted to our hospital with fever, seizure, and cervical lymphadenopathy. Laboratory data showed pancytopenia, elevation of serum transaminase, lactate dehydrogenase, triglyceride, and ferritin levels. Lymph node biopsy revealed features of Kikuchi's disease and there were signs of histiocytosis and hemophagocytic phenomenon in bone marrow. She recovered after treatment with intravenous immunoglobulin and corticosteroids therapy. Hemophagocytic syndrome can be associated with Kikuchi's disease especially in childhood and seems to have a less aggressive clinical course and better prognosis.

Key Words : *Histiocytic Necrotizing Lymphadenitis; Kikuchi's Disease; Histiocytosis*

Young Mi Kim, Yoon Jin Lee, Sang Ook Nam, Su Eun Park, Ji Yoen Kim*, Eun Yup Lee†

Department of Pediatrics, Surgical Pathology*, and Clinical Pathology†, College of Medicine, Pusan National University, Busan, Korea

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Address for correspondence
Su Eun Park, M.D.
Department of Pediatrics, College of Medicine, Pusan National University, 10, 1-Ga, Ami-dong, Suh-gu, Busan 602-739, Korea
Tel : +82.51-240-7298 Fax : +82.51-248-6205
E-mail : pse0731@hanmail.net

INTRODUCTION

Kikuchi's disease is a benign, self-limited disease with well-defined clinical entity that typically involves the cervical lymph nodes of adolescents and young adults and occurs commonly in Asian (1). Hemophagocytic syndrome is a histiocytic reactive process of strong immunologic activation, such as severe infection, malignancy, autoimmune diseases, and metabolic diseases (2). It is characterized by histiocytic proliferation, hemophagocytosis, fever, hepatosplenomegaly, generalized lymphadenopathy, hypertriglyceridemia, and hypofibrinogenemia.

There are eight cases of hemophagocytic syndrome simultaneously associated with Kikuchi's disease in the literature (3-9). The prognosis and treatment for hemophagocytic syndrome in Kikuchi's disease is still unknown. We report a case of a 13-yr old girl with simultaneous Kikuchi's disease and hemophagocytic syndrome.

CASE REPORT

A 13-yr-old girl was admitted to our hospital because of a 4-week history of fever, generalized maculopapular rash, progressive cervical lymph node swelling, and an attack of generalized tonic-clonic seizure 2 days before admission. On examination, she had a temperature of 38°C and submandibular lymphadenopathy (3 to 4 cm in diameter). The liver and spleen were not palpable. She developed progressive pancytopenia (white blood cell count, 1,500/μL; hemoglobin 10.3 g/dL; platelets 39,000/μL). Hepatic dysfunction (AST 1156 IU/L and ALT 657 IU/L), cholestasis (total bilirubin 2.47 mg/dL and direct bilirubin 1.88 mg/dL) and acute renal failure (blood urea nitrogen 18.15 mg/dL, creatinine 1.96 mg/dL) were present. Prothrombin time and international normalized ratio were normal and activated partial thromboplastin time was mildly prolonged (64.1 sec). Her triglycerides and ferritin levels were increased to 144 mg/dL (normal range, 37-134 mg/dL) and 14,955.2 ng/mL (normal range, 6-282 ng/dL), respectively. Antinuclear antibody, anti-double stranded DNA antibody, cytomegalovirus immunoglobulin (Ig) M, herpes simplex virus IgM, and viral serology for hepatitis A, B, and C were negative. Epstein-Barr virus IgM was under 1:10 (normal range under 1:10) and Epstein-Barr virus IgG was 1:160 (normal range under 1:10). Bacterial and viral cultures of blood, urine, and stool were negative. On the following day, she developed an acute respiratory distress syndrome that required mechanical ventilation. A bone marrow aspiration and biopsy showed many histiocytes and obvious hemophagocytic histiocytes (20% of total histiocytes) (Fig. 1). Fine-needle aspiration biopsy of lymph nodes revealed paracortical necrotizing lesions with typical features of Kikuchi's disease (Fig. 2, 3).

Intravenous immunoglobulin (0.4 g/kg/day for 5 days) and methylprednisolone (1 g/d for 3 days) were administered. There were no further seizure attack any more and we did not prescribed any antiepileptic drug. The clinical symptoms and signs improved gradually. On day 3, she was administered

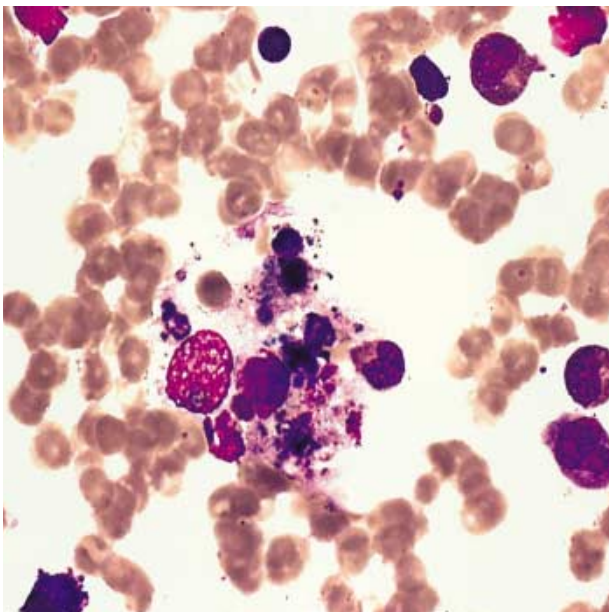

Fig. 1. Bone marrow aspirate shows histiocytes engulfing erythrocytes (Wright stain, ×1,000).

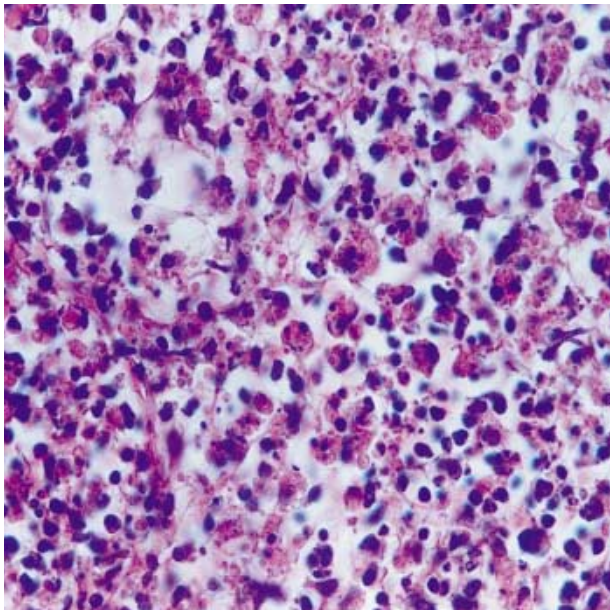

Fig. 3. High power view of necrotizing lymphadenitis shows numerous apoptotic bodies (H&E stain, ×400).

with etoposide (150 mg/m^2), which was discontinued due to subsequent pancytopenia (white blood cell count 410/μL; hemoglobin 9.2 g/dL; platelets 19,000/μL on day 12). We continued supportive care and prescribed oral dexamethasone (10 mg/m^2/day every 8 hr for 2 weeks, followed by 7.5 mg/m^2/day every 8 hr for 2 weeks, 5 mg/m^2/day every 8 hr for 2 weeks, and 2.5 mg/m^2/day every 8 hr for 1 weeks) and bactrim (5 mg/kg in 2 divided doses, three times per week) with dramatic response. She required mechanical ventilation for 7 days. There was complete resolution of the hemophagocytic syndrome within 1.5 months and no evidence of disease recurrence during the following 8 months.

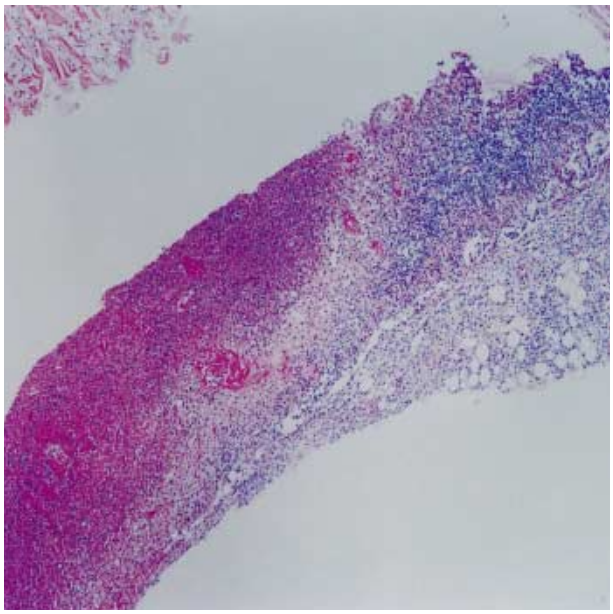

Fig. 2. Low power view of necrotizing lymphadenitis shows necrosis with infiltration of numerous lymphocytes and histiocytes (H&E stain, ×40).

DISCUSSION

Diagnosis of hemophagocytic syndrome can be made with fever of unknown etiology for 7 or more days, unexplained cytopenia affecting at least 2 cell lines, abnormal liver function tests, disseminated intravascular coagulopathy, and bone marrow that contains greater than 3% histiocytes undergoing hemophagocytosis. Clinical severity ranges from complete recovery to rapid deterioration. The mortality rate is 20-42% (10).

Our patient had necrotizing lymphadenitis followed by fulminant hemophagocytic syndrome. Eight cases of hemophagocytic syndrome combined with necrotizing lymphadenitis have been reported in the literature thus far (3-9). Four patients aged from 14 to 17 yr and three were Asians. Two patients had underlying systemic lupus erythematosus and one patients was pregnant. Six patients recovered after treatment with corticosteroids with or without intravenous immunoglobulin.

Kikuchi's disease is usually self-limited and supportive treatment alone is sufficient for the disease. The treatment and prognosis of childhood Kikuchi's disease associated with hemophgocytic syndrome remain unclear. According to our review of the literature, childhood Kikuchi's disease is more frequently associated with hemophagocytic syndrome and seems to have a less aggressive course and better prognosis than the adult

counterpart.

Our case shows that childhood hemophagocytic syndrome can be associated with Kikuchi's disease and assume a relatively benign course. Administration of intravenous immunoglobulin and corticosteroids may be the treatment of choice of hemophagocytic syndrome associated with Kikuchi's disease and may provide satisfactory results. Chemotherapy, such as etoposide-containing regimen, can be reserved for those who fail to respond to intravenous immunoglobulin and corticosteroids.

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