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EBV-Elicited Familial Hemophagocytic Lymphohistiocytosis

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Familial hemophagocytic lymphohistiocytosis (FHL) is a rapidly fatal illness, usually encountered in infancy, characterized by fever, hepatosplenomegaly, pancytopenia, and central nervous system involvement. Microscopic examination of tissue shows a non-malignant lymphohistiocytic infiltrate, with prominent erythrophagocytosis. FHL is an autosomal recessive hereditary disorder but may develop secondarily to other conditions such as immunosuppression, malignancies, fat overload and certain infections. We recently experienced a case of siblings developing FHL, which may be associated with EBV infection.

Key Words: Familial hemophagocytic lymphohistiocytosis, EBV infection

Familial hemophagocytic lymphohistiocytosis (FHL) is very likely a genetically-transmitted disease affecting infants and very young children (Gencik *et al.* 1984). In 1952, Farquhar and Claireaux described a rapidly fatal disease in two siblings which they termed familial hemophagocytic reticulosis (Farquhar and Claireaux, 1952). FHL is characterized clinically by intermittent fever, hepatosplenomegaly, cytopenia, hypertriglyceridemia, and hypofibrinogenemia and histologically by a non-malignant lymphohistiocytic accumulation with hemophagocytosis in reticuloendothelial organs and a family history of hemophagocytic lymphohistiocytosis (Henter *et al.* 1991a). FHL may develop secondarily to other conditions such as immunosuppression, malignancies, fat overload and certain infections (Henter *et al.* 1993). We recently experienced a case of siblings developing FHL, which may be in association with Epstein-Barr virus (EBV) infection.

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CASE REPORT

Case 1

A 19-month-old male, first child to unrelated parents, developed an abdominal distension and fever which persisted even after treatment with antibiotics. He had an enlarged liver and spleen and multiple lymphadenopathy. The blood picture showed normochromic anemia and thrombocytopenia, but no leukopenia. The AST was 145 IU/L, ALT 100 IU/L, total protein 4.2 g/dl, albumin 2.5 g/dl and total cholesterol 116 mg/dl. Serologic tests were made for hepatitis B virus, herpes simplex virus, rubella virus, cytomegalovirus, and rota virus. Serologic tests for EBV viral capsid antigen (VCA) IgM antibody and VCA IgG antibody were negative. A bone marrow aspirate showed many histiocytes with erythropha-

gocytosis. The biopsy specimen from the neck node demonstrated diffuse sinusoidal infiltration of histiocytes showing active erythrophagocytic activity and reactive paracortical hyperplasia (Fig. 1). In situ hybridization using a fluorescin-conjugated oligonucleotide probe complementary to a portion of the EBER1 gene (Dako, Carpinteria, CA, USA) was performed on the formalin-fixed, paraffin-embedded sections. It revealed a negative reaction. The patient was diagnosed as hemophagocytic lymphohistiocytosis and was given steroids, after which his fever declined and the hepatosplenomegaly decreased. But he had ongoing disease and was admitted frequently due to fever and splenomegaly and was transiently-improved by steroids. Five years and eight months after the onset of disease, he was readmitted due to fever and hepatosplenomegaly. The blood picture showed a normochromic anemia, reduced platelets and leukopenia. The serum triglyceride was 250 mg/dl, fibrinogen 180 mg/dl and serologic tests for EBV early antigen (EA)-IgM antibody and EBV nuclear antigen (EBNA) antibody were positive. He was diagnosed as FHL because his younger sister (see Case 2) was simultaneously admitted due to same disease. The boy was given etoposide intravenously and steroids, after which his fever declined and the hepatosplenomegaly decreased. He was discharged 3 weeks later. He continued to survive 12 months after diagnosis as FHL with positive serologic tests for EBV EA-IgM antibody and EBNA antibody.

Case 2

The four-year and eight-month-old sister of case 1 also developed fever, hepatosplenomegaly and lymphadenopathy and pancytopenia, five years and eight months after the onset of disease in her brother. The triglycerides were 369 mg/dl, ferritin 4241 mg/dl, fibrinogen 165 mg/dl. She was positive for EA-IgM antibody and anti EBNA antibody. Her parents and brother were also positive for EA-IgM antibody and anti EBNA antibody at that time. Serologic tests for EA-IgM antibody and anti EBNA antibody were continuously positive until she died. A bone marrow smear and biopsy showed many histiocytes with erythrophagocytosis. She was diagnosed as FHL and given etoposide and steroids, after which her fever declined and the hepatosplenomegaly decreased, she died 5 months after diagnosis. Autopsy of the liver revealed hypertrophy of Kupffer cells which showed erythrophagocytosis. There was portal and periportal lymphocytic infiltrates and they showed an activated and atypical appearance (Fig.

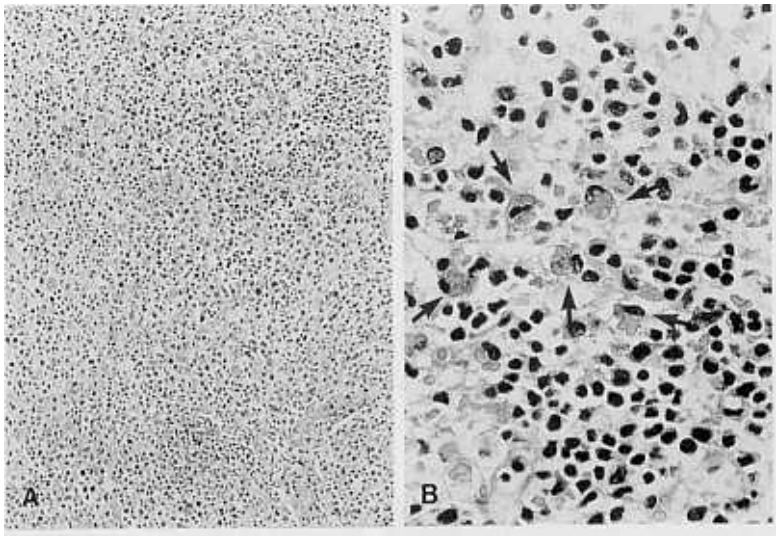

Fig. 1. *Lymph node showing diffuse infiltration of sinusoidal histiocytes with active erythrophagocytosis (arrows) (A, H&E, ×40; B, H&E, ×400).*

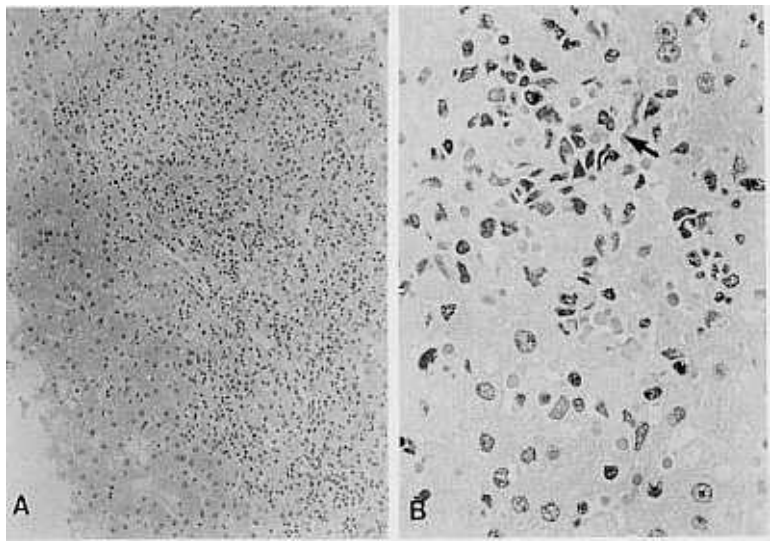

Fig. 2. The core of liver showing A) portal and periportal lymphocytic infiltration and B)hypertrophy of Kupffer cells with erythrophagocytosis (arrow) and sinusoidal lymphocytosis (A, H&E, ×40; B, H&E, ×400).

2). Immunohistochemical stain was performed on the formalin-fixed, paraffin-embedded sections by labelled streptabidin-biotin method. Primary antibodies applied were CD3 and CD45RO for the T cell phenotype and CD20 for the B cell phenotype (Dako, Carpinteria, CA, USA). The majority of atypical cells in the portal tracts revealed T cell phenotype.

DISCUSSION

The etiology and pathogenesis of FHL are unknown at present. Immunological studies present evidence for a disturbed function of T lymphocytes, but a secondary immune defect seems to be more likely than primary immune deficiency (Ladisch *et al.* 1982). B cell function as judged by normal or elevated immunoglobulin levels were intact in the majority of the patients with few exceptions (Ladisch *et al.* 1978). A genetic deficiency in immunomodulation is a plausible cause of the immunological hyperactivation involved (Henter *et al.* 1991b). The association between FHL and infections may be only a concomitant finding without pathophysiological significance. On the other hand, immunological stress, such as that caused by a viral infection, may result in inappropriate T lymphocyte activation of the mononuclear phagocyte system, including hypercytokinemia with an elevation of interferon-gamma, tumor necrosis factor-alpha and interleukin-6 and possibly, also interleukin-1, which may well explain the symptoms of FHL (Henter *et al.* 1993).

In our cases, with the onset of disease in case 2, serologic tests for EBV-related antibodies were positive in all family members and it is suggested that EBV infection may elicit a bout of FHL. Our report indicates that a viral infection may elicit this activation and consequently, the syndrome itself in certain genetically-predisposed individuals.

Viral infection results in stimulation of the immune systems; T cells are transiently reactivated and secrete cytokines, probably with a feedback regulation. Thereafter, the infection usually subsides and cytokine production subsequently ceases within a few weeks. But in EBV infection, a specific C3d/EBV receptor is expressed in about 30% of human peripheral blood T cells (Fischer *et al.* 1991; Kawaguchi *et al.* 1993). EBV-infected T cell proliferation may follow a progression analogous to EBV-infected B cell proliferation. And a systemic hypercytokinemia

caused by the clonal proliferation of EBV-infected T cells may secondarily play a critical role in the development of EBV associated hemophagocytic syndrome (Kikuta, 1995).

Gaffey *et al.* reported that there were no significant histologic differences noted between the infection-associated hemophagocytic syndrome and FHL cases, either in terms of the pattern or the severity and distribution of hemophagocytosis (Gaffey *et al.* 1993).

Many reported cases of hemophagocytic syndrome have shown lymphocyte depletion and histiocytosis in lymph nodes and spleen (Janka, 1983). In our case, polymorphous lymphoid proliferation was observed in case 2. Similar lymphoid proliferations have been previously reported in patients with EBV-related hemophagocytic syndrome (Sullivan *et al.* 1985; Daum *et al.* 1987; Mroczek *et al.* 1987). These findings indicate that EBV infection may be associated with a proportion of cases of infection-related and familial hemophagocytic syndrome. The association may result from an uncontrolled activation of the cellular immune system stimulated by virus.

At first, Henter *et al.* reported that an association with an infection was found in 13 of the 16 familial cases, among these 4 siblings following EBV infections (Henter *et al.* 1993). In Korea, this is, to our knowledge, the first report of siblings developing FHL in association with on EBV infection.

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