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Hemophagocytic Syndrome Associated with Occult B-cell Lymphoma: An Autopsy Case

Hemophagocytic syndrome has been observed in various disorders, including malignant histiocytosis, peripheral T-cell lymphoma, and viral or bacterial infections. However, B-cell lymphoma has seldom been associated with hemophagocytic syndrome. We report a case of B-cell lymphoma that was associated with hemophagocytic syndrome. The diagnosis was not made until the time of autopsy.

Key Words : *Hemophagocytic syndrome, Lymphoma, B-cell*

Ji Eun Kim, Chul Woo Kim, Seong Hoe Park, Je G. Chi

Department of Pathology, Seoul National University College of Medicine

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Address for correspondence
Je G. Chi, M.D.
Department of Pathology, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-799. Korea
Tel : (02) 760-3540, Fax : (02) 741-6195

INTRODUCTION

Hemophagocytic syndrome is a clinicopathological entity characterized by fever, hepatosplenomegaly, liver dysfunction, pancytopenia, and proliferation of histiocytes with erythrophagocytosis (1, 2). This syndrome has been observed during the clinical course of a wide variety of disorders, including viral infections and malignancies (1-3). In cases of malignancy-associated hemophagocytic syndrome, the distinction between the malignant cells and reactive histiocytes is often difficult, and an erroneous diagnosis of reactive histiocytosis can be made (1), particularly when the malignancies are not clinically overt. It is now generally known that a great majority of the cases reported as malignant histiocytosis are actually T-cell lymphoma with hemophagocytic reaction. B-cell lymphoma associated with hemophagocytic syndrome are quite rare and the clinical and pathological features are known to be quite different from those of T-cell lymphomas. We report an interesting case of B-cell lymphoma associated with hemophagocytic syndrome which caused diagnostic difficulty until the time of autopsy.

CASE REPORT

A 65-year-old man was admitted to Seoul National University Hospital on October 6, 1995, because of prolonged fever, abdominal pain, and pancytopenia of one month duration. He had undergone cholecystectomy at another hospital on August 17, 1995 with an uneventful postoperative course. Because of thrombocytopenia and splenic infarct detected by CT scan (Fig. 1), a splenectomy was done on September 6, 1995. The spleen weighed 250 g and focal subcapsular infarct was found. Physical examination showed a pale emaciated male with no

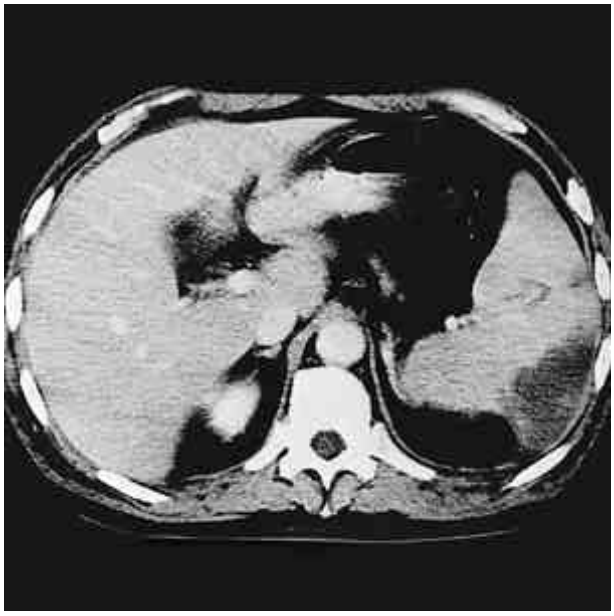

Fig. 1. Abdominal CT reveals a splenic infarct.

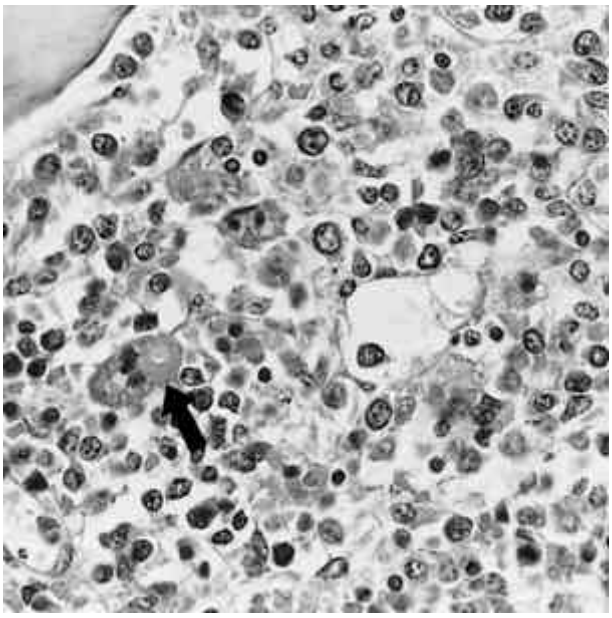

Fig. 2. Cellular bone marrow by infiltration of the tumor cells and hemophagocytic histiocytes (arrow).

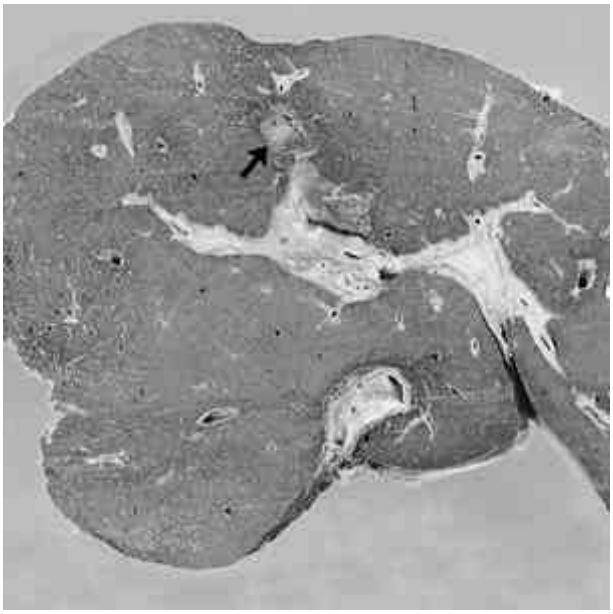

Fig. 3. The liver shows marked cholestasis, focal infarction (arrow) and mottled discoloration.

lymphadenopathy. Conjunctivae were anemic and icteric. No organomegaly was noted. Complete blood counts revealed hemoglobin 11.7 g/dl, hematocrit 27.4% and WBC 16,000/mm^3 (myelocyte 3%, band 1%, segment 71%, lymph 18%, mono 7%, and nucleated RBC 20-30/100 WBCs). Reticulocyte was 2.7%. Serum total bilirubin level was 2.1 mg/dl. Bone marrow examination revealed mild hypercellularity, decreased erythroid and myeloid precursors, and megakaryocytes, many hemophagocytic histiocytes, and few atypical cells of unknown nature (Fig. 2). Involvement of hematologic malignancy or malignant lymphoma was not definite. Extensive study to find a source of infection failed to demonstrate any microorganism. He showed a progressive downhill clinical course, and he died on October 18, 1995.

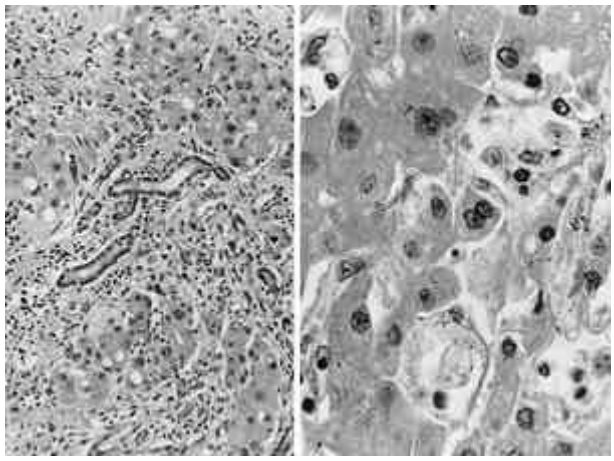

Fig. 4. Microscopic features of the liver showing
Left : multifocal necrosis, parenchymal loss by cellular infiltrates.
Right : hemophagocytic histiocytes in the sinusoids.

Postmortem examination was done 6 hours after the time of expire and limited to thoraco-abdominal incision. The liver revealed multifocal infarcts and extensive cholestasis (Fig. 3). There were no other gross abnormalities except post-splenectomy status. No enlarged lymph nodes or soft tissue mass lesion were detected. However, histological examination showed malignant lymphoid cell infiltration in the liver (Fig. 4), kidneys, adrenals, mesenteric lymph nodes, and skeletal muscle (Fig. 5). The splenic tissue slide was reviewed and focal atypical lymphoid cell infiltration was also found (Fig. 6). The tumor cells were large, round to polygonal, and had round hyperchromatic nuclei and one to two nucleoli. Plasmacytoid differentiation of these tumor cells was often seen and the histologic diagnosis was malignant lymphoma of diffuse large cell type. The tumor cells were dispersed among normal lymphoid cells without forming sheet even in the lymph nodes and spleen. The tumor cells intersected portal tracts of the liver and renal interstitium in the fashion of leukemic infiltration (Fig. 7). Solid proliferation of the tumor cells forming sheet was only observed in the skeletal muscle, sampled from the right iliopsoas. These neoplastic cells were homogeneously positive for B-cell marker (L26) (Fig. 8), but were consistently negative for T-cell marker (CD45RO) and histiocyte marker (CD68). Thrombotic occlusion of blood vessels with surrounding microinfarct was noted in the liver and spleen. In the bone marrow and the liver, proliferation of benign histiocytes showing prominent

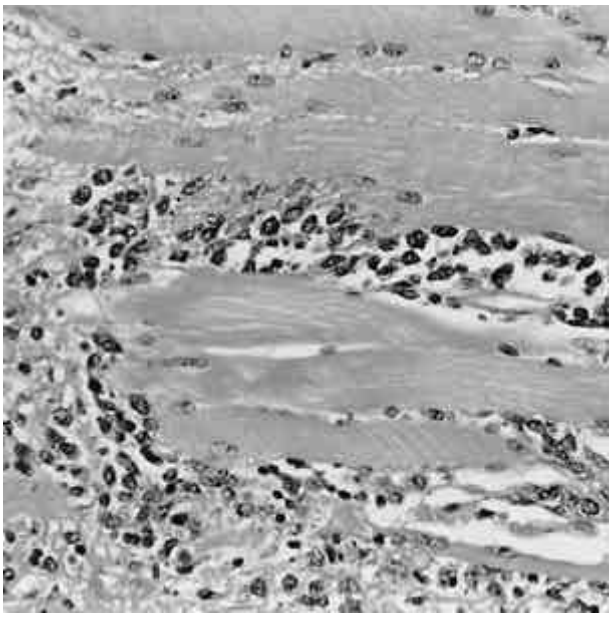

Fig. 5. Atypical lymphoid cells infiltration in the psoas muscle splittig muscle fibers.

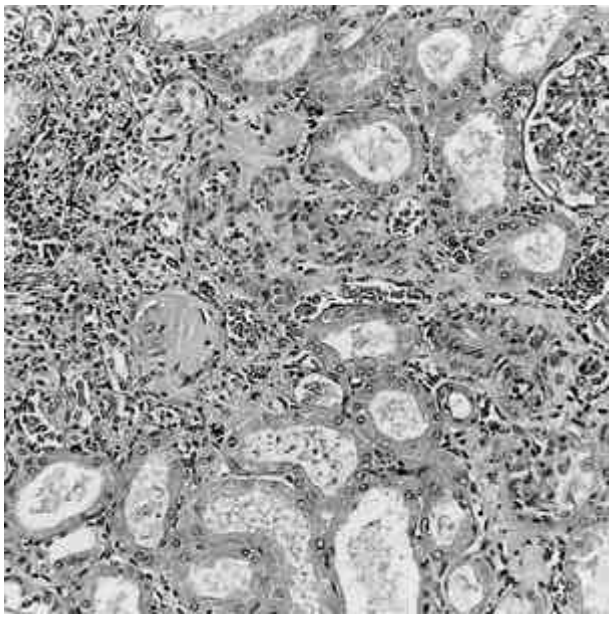

Fig. 7. Atypical lymphoid cell infiltration in the kidney mainly confined to the interstitial tissue.

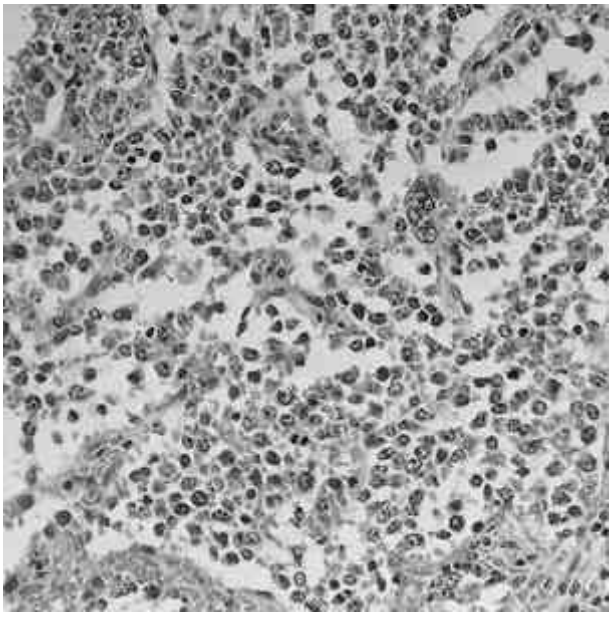

Fig. 6. Large atypical lymphoid cell collection in the subcapsular area of spleen.

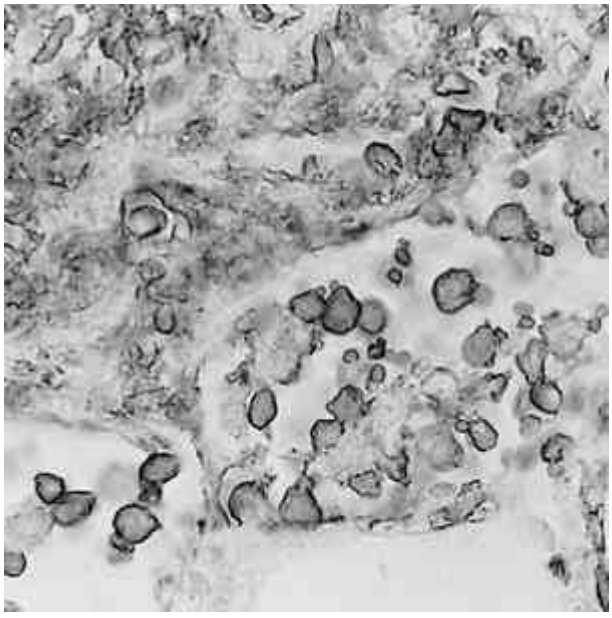

Fig. 8. Psoas muscle. Tumor cells show positive immunoreactivity to L26.

hemophagocytosis was found. Polymerase chain reaction for EBV, EBNA-1 gene using paraffin embedded tissue revealed no viral genome.

DISCUSSION

Clinically our patient showed the characteristic features of a hemophagocytic syndrome. On initial bone marrow biopsy, the infiltrating atypical cells were interpreted as histiocytic cells. These cells, however, turned out to be B-lymphoid cells. Malignant histiocytosis (MH) is a clinicopathological term, used in the past, but most cases of MH turned out to be benign hemophagocytic syndrome or Ki-1 positive anaplastic large cell lymphoma (1). Although hemophagocytic syndrome is caused by reactive proliferation of histiocytes, it can cause a fatal outcome through multiorgan failure (1, 4). Most cases of hemo-

phagocytic syndrome caused by hematologic malignancy are associated with T-cell lymphoma and only rarely can B-cell neoplasm be associated with them (1). In the cases of previously reported B-cell lymphoma with hemophagocytic syndrome, the characteristic findings are involvement of splenic white pulp, sinusoidal infiltration in lymph node, hepatosplenomegaly and absence of gross tumor formation or lymphadenopathy (4-6). In peripheral T-cell lymphoma, hemophagocytic syndrome was assumed to be caused by the cytokines secreted by neoplastic T-cells (1). However, in the case of B-cell lymphomas, no explanation has yet been available. A possibility of cytokines secretion from macrophage or even from the neoplastic B-cells might be considered. Hypercoagulability is also a phenomenon of hematologic derangement, and it would explain the splenic infarct in our case.

Viruses are common cause of hemophagocytic syndrome and one likely mechanism may be the viral-stimulated production of soluble macrophage/histiocyte-activating factors with secondary histiocytic activation (3). Several viruses can provoke immunologic dysregulation, the most famous one being Epstein-Barr virus (EBV) (3). On this case, virus could be an underlying mechanism of hemophagocytic syndrome, but extensive serologic studies and postmortem sample failed to show any evidence of viral infection. Therefore, we presume the hemophagocytosis in our case was probably attributable to B-cell lymphoma.

Most reported cases of B-cell lymphoma with hemophagocytic syndrome are characterized by early extranodal involvement, no mass formation, sinusoidal or interstitial infiltration pattern of lymph node and liver, hepatosplenomegaly, rapid and aggressive behaviour, and poor clinical outcome (4, 5). Involvement of bone marrow can be initial presentation, but often be subtle, and be missed on causual examination (7, 11). But these findings are not specific for B-cell lineage, and quite a many cases of T-cell lymphoma with hemophagocytic syndrome can be presented as above features (7, 8).

There are several cases of angiotropic B-cell lymphoma associated with hemophagocytic syndrome (9). Angiotropic B-cell lymphoma is a rare systemic condition in which small blood vessels throughout the body are occluded by malignant lymphoid cells, usually in the absence of significant extravascular tumor (10). Our case does not exhibit angiotropism, so is different from angiotropic B-cell lymphoma.

The histological findings in our case suggested the possibility of lymphoid leukemia because of its pattern of involvement. However, the cytologic features of tumor cells and histologic features of bone marrow biopsy are not compatible with lymphoid leukemia. This case therefore represents an infrequent variant of B cell lymphoma that is associated with hemophagocytic syndrome.

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