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Hepatosplenic B-cell Lymphoma Associated with Hemophagocytic Syndrome
: A Case Report

While T-cell non-Hodgkin's lymphoma (NHL) associated with hemophagocytic syndrome (HPS) has been frequently observed, B-cell NHL associated with HPS has been rarely reported. We report a case of hepatosplenic B-cell lymphoma associated with HPS in a 41-year-old woman who presented with fever of unknown origin. An abdominal CT scan revealed splenomegaly with focal splenic infarction. Splenectomy and a liver wedge biopsy showed sinusoidal-pattern infiltration of medium to large tumor cells with positive reaction to a B-lymphocyte marker. Findings on bone marrow examination showed proliferation of histiocytes with avid hemophagocytosis.

Key Words: *Lymphoma, B-cell; Histiocytosis, malignant; Liver neoplasms; Splenic neoplasms; Neoplasms, multiple primary*

Sang-Yong Kwon, Je-Jung Lee, Ik-Joo Chung, Hyeoung-Joon Kim, Moo-Rim Park, Hyung-Seok Kim*, Chang-Soo Park*

Departments of Internal Medicine and Pathology*, Chonnam National University Medical School, Kwangju, Korea

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Address for correspondence
Hyeoung-Joon Kim, M.D.
Department of Internal Medicine, Chonnam National University Medical School, 8 Hak-dong, Dong-gu, Kwangju 501-757, Korea
Tel: +82.62-220-6572, Fax: +82.62-225-8578
E-mail: hjoonk@chonnam.ac.kr

INTRODUCTION

Hemophagocytic syndrome (HPS) is a reactive and systemic proliferation of benign histiocytes (1-4). It is often associated with infections, malignant neoplasms, drugs, autoimmune diseases and various immunodeficiencies (1-4). Most reported cases of non-Hodgkin's lymphoma (NHL) associated with HPS have been T-cell in origin (5, 6). However, HPS has been rarely observed in B-cell lymphomas (7). We report a case of hepatosplenic B-cell lymphoma predominantly confined to the sinusoids of the liver and spleen associated with HPS.

CASE REPORT

A 41-year-old woman was admitted to Chonnam National University Hospital because of fever, chills and general weakness for five weeks. Temperature was 38.8 ℃. On examination, she appeared chronically ill and revealed tender splenomegaly. There was no palpable lymph node.

Blood count showed a white cell count of 6,100/μL, hemoglobin 7.1 g/dL, and platelet count 4,300/μL. Blood chemistry revealed alkaline phosphatase 575 U/L, AST 163 U/L, ALT 42 U/L, LDH 1,948 U/L, and β2-microglobulin 3.5 mg/dL. Coagulation profiles were prothrombin time of 15.3 sec (control, 12.5 sec) and partial thromboplastin time of 31.3 sec (control, from 28 to 40 sec). Cultures of blood, urine and sputum were sterile. Serologic tests for viral infections and connective tissue diseases were negative. CT scan of the abdomen showed splenomegaly with focal wedge-shaped infarction, but no lymphadenopathy (Fig. 1).

She underwent splenectomy and a liver wedge biopsy.

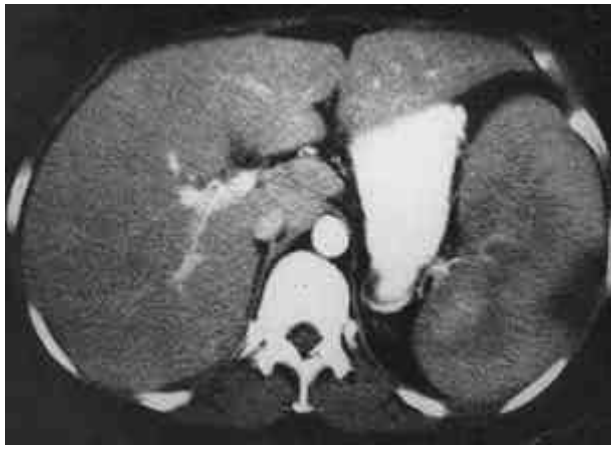

Fig. 1. Abdominal CT scan shows splenomegaly with focal wedge-shaped infarction.

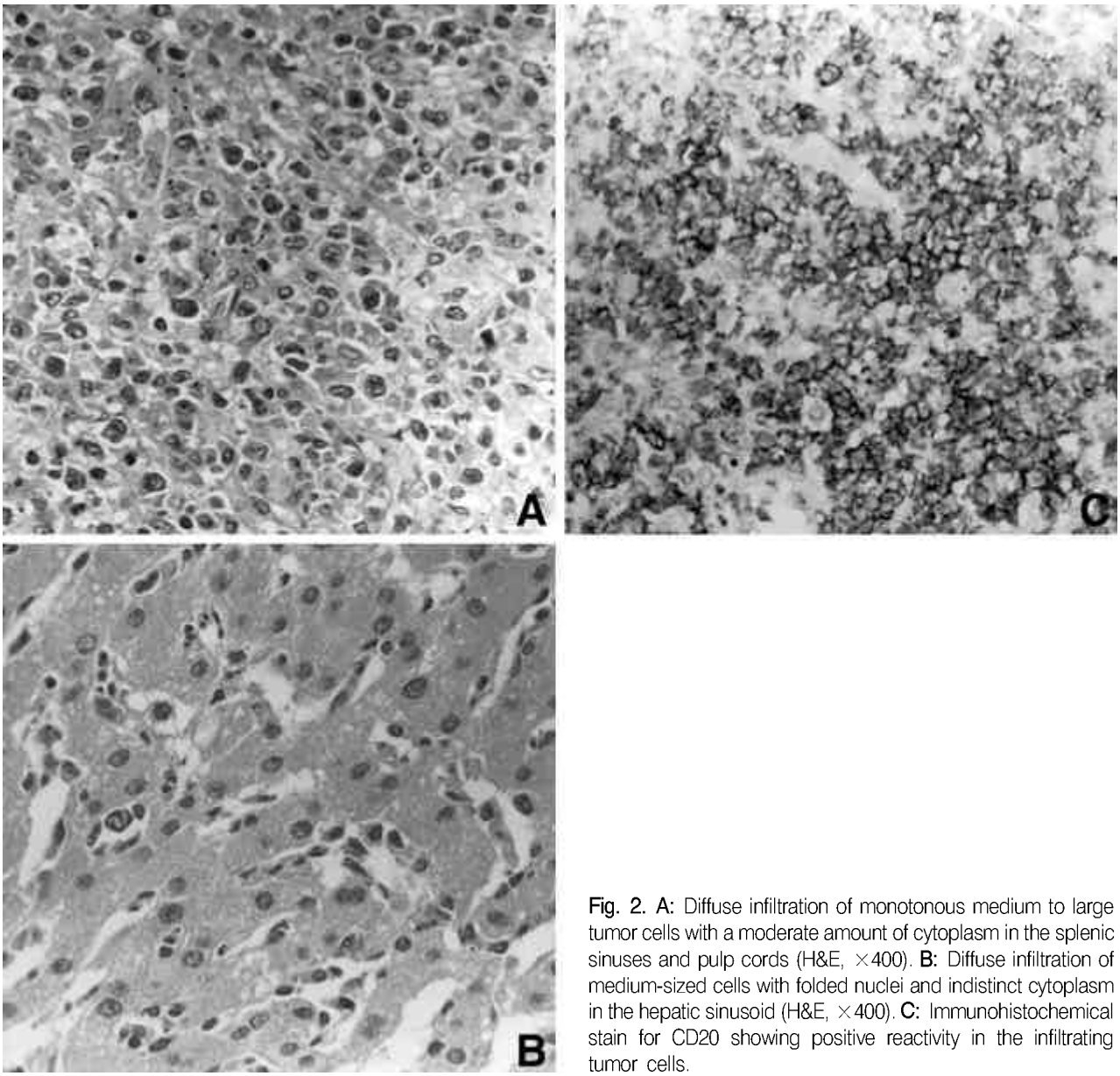

Fig. 2. A: Diffuse infiltration of monotonous medium to large tumor cells with a moderate amount of cytoplasm in the splenic sinuses and pulp cords (H&E, ×400). **B:** Diffuse infiltration of medium-sized cells with folded nuclei and indistinct cytoplasm in the hepatic sinusoid (H&E, ×400). **C:** Immunohistochemical stain for CD20 showing positive reactivity in the infiltrating tumor cells.

Histologic examination of the splenic tissue showed diffuse infiltration of medium to large-sized tumor cells in the splenic sinuses and pulp cords with frequent obliteration of the white pulps (Fig. 2A). This finding was suggestive of malignant histiocytosis. The liver specimen disclosed predominant sinusoidal infiltration of medium-sized neoplastic cells (Fig. 2B). Immunohistochemically, the tumor cells were positive for leukocyte common antigen (LCA, CD45), CD20, and lambda light chain, and were negative for CD45RO (UCHL-1) and kappa light chain (Fig. 2C). They were also negative for acid phosphatase, lysozyme, α_1-antitrypsin, and Ki-1 (CD30). These findings were compatible with B-cell NHL. Bone marrow (BM) aspiration and a biopsy showed proliferation of histiocytes with hemophagocytosis (Fig. 3). In situ hybridization and immunohistochemical stain for EBV were negative in the liver and splenic specimen.

She was diagnosed as hepatosplenic B-cell lymphoma associated with HPS. Clinical stage was IVB and she was allocated in the high-risk group according to international age-adjusted index. Presently, she remains in complete remission, after having received six cycles of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy.

DISCUSSION

The patient presented as fever of unknown origin (FUO) and clinical diagnosis was very difficult initially

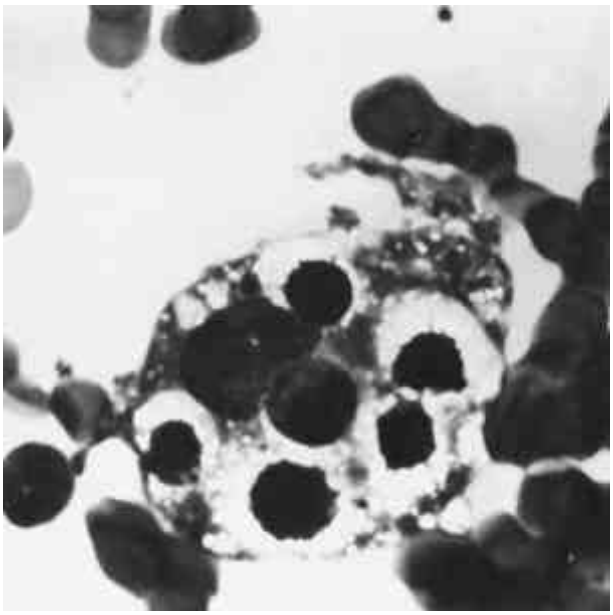

Fig. 3. Bone marrow smear shows histiocytes with avid hemophagocytosis (Wright stain, ×1,000).

despite of extensive evaluation. The patient underwent splenectomy, a liver wedge biopsy and BM examination. Pathologically, the diagnoses of the BM, spleen and liver were very difficult to make, due to the tumor cells were localized to the sinusoids of the biopsed organs and it simulated malignant histiocytosis. However, the diagnosis of B-cell lymphoma was made by immunohistochemical staining in the specimen of the liver and spleen, and hemophagocytosis by benign histiocytes was noted in BM smear specimen. Compared to the classic large B-cell lymphoma, the localization of the tumor cells to the sinusoidal spaces of the liver and spleen without solid mass lesion is unique and this case might be a hepatosplenic B-cell lymphoma, an unusual specific variant of B-cell lymphoma. Clinical symptoms and signs of the patient were improved after CHOP chemotherapy.

HPS has been reported in association with various malignant conditions, such as NHL, Hodgkin's disease, multiple myeloma, acute leukemia, chronic lymphocytic and hairy cell leukemia, gastric carcinoma, and ovarian carcinoma (2). Most NHL in association with HPS has been T-cell type (5-7). B-cell NHL associated with reactive HPS has been rarely reported, including T-cell rich B-cell lymphoma (8), angiotropic B-cell lymphoma (9), immunoblastic B-cell lymphoma (10), splenic large B-cell lymphoma (11), diffuse large B-cell lymphomas (12, 13), and an autopsy case of occult B-cell lymphoma (14).

Patient with HPS usually present with FUO, sweats, weakness, lymphadenopathy, hepatosplenomegaly, pancytopenia, and extranodal involvement of marrow, lungs, central nervous system, heart and other organs (1). The most prominent histopathologic feature is a proliferation and infiltration of benign histiocytes, displaying a striking degree of hemophagocytosis in the bone marrow, lymph node sinuses and medullary cords, hepatic sinusoids and portal areas and splenic red pulps (1, 5).

The pathogenesis of this syndrome is still unclear, although the possible role of cytokines produced by T-cell lymphoma cell has been suggested (15). However, any specific cytokines that may induce hemophagocytosis in B-cell lymphoma have not been identified, and B-cell lymphoma could result in abnormal immune regulation and thus might be associated with HPS (15). Treatment of HPS should be directed to the underlying disease process (1). The prognosis of HPS is not known in B-cell NHL, but frequently fatal in T-cell NHL (6-8), suggesting its correlation with tumor aggressiveness.

In summary, we report a case of hepatosplenic B-cell lymphoma associated with reactive HPS, which may simulate malignant histiocytosis. The patient received six cycles of CHOP chemotherapy and is currently in good condition.

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REFERENCES

1. Lee GR, Bithell TC, Fester J, Athens JW, Lukens JN. *Clinical hematology. Philadelphia, London: Lea & Febiger, 1993: 2189-91.*
2. Wong K, Hui P, Chan J, Chan Y, Ha S. *The acute lupus hemophagocytic syndrome. Ann Intern Med 1991; 114: 387-90.*
3. Risdall RJ, McKenna RW, Nesbit ME, Krivit W, Balfour Jr HH, Simmons RL, Brunning RD. *Virus-associated hemophagocytic syndrome. A benign histiocytic proliferation distinct from malignant histiocytosis. Cancer 1979; 44: 993-1002.*
4. Risdall RJ, Brunning RD, Hernandez JI, Gordon DH. *Bacteria-associated hemophagocytic syndrome. Cancer 1984; 54: 2968-72.*
5. Falini B, Pileri S, de Solas I, Martelli M, Manson DY, Delsol G, Gatter KC, Fagioli M. *Peripheral T-cell lymphoma associated with hemophagocytic syndromes. Blood 1990; 75: 434-44.*
6. Gonzalez CL, Medeiros LJ, Braziel RM, Jaffe ES. *T-cell lymphoma involving subcutaneous tissue. A clinicopathologic entity commonly associated with hemophagocytic syndrome. Am J Surg Pathol 1991; 15: 17-27.*
7. Aung W, Koslosky W, Chin NW, Pincus MR. *Diffuse large*

cell lymphoma of B-cell type associated with reactive hemophagocytosis. Ann Clin Lab Sci 1996; 26: 433-6.

8. Dommann-Scherrer C, Zimmermann D, Hassam S, Odermatt BF, Risti B, Maurer R. *T-cell rich B-cell lymphoma associated with hemophagocytic syndrome. Verh Dtsch Ges Pathol 1992; 76: 122-5.*
9. Okada Y, Nakanishi I, Nomura H, Takeda R, Nonomura A, Takekuma K. *Angiotropic B-cell lymphoma with hemophagocytic syndrome. Path Res Pract 1994; 190: 718-24.*
10. Barberan J, Pastor JM, Menendez MA, Ortiz S, de la Cruz A, Sanchez T. *The reactive hemophagocytic syndrome associated with immunoblastic B-cell lymphoma. Rev Clin Esp 1992; 190: 308-10.*
11. Buchi G, Termine G, Orlassino R, Pagliarino M, Boero R, Zappala C, Grosso E. *Hemophagocytic syndrome in a case of splenic large B-cell lymphoma. Tumori 1996; 82: 621-4.*
12. Yamada K, Katoh K, Okuyama M. *Diffuse B-cell lymphoma associated with hemophagocytic syndrome. Jpn J Clin Hematol 1996; 37: 161-4.*
13. Takahashi T, Kanda Y, Mori M, Saito T, Chiba S, Mitani K, Hirai H, Yazaki Y. *B cell lymphoma-associated hemophagocytic syndrome after PBSCT. Bone Marrow Transplant 1998; 21: 623-5.*
14. Kim JE, Kim CW, Park SH, Chi JG. *Hemophagocytic syndrome associated with occult B-cell lymphoma: an autopsy case. J Korean Med Sci 1998; 13: 77-80.*
15. Simrell CR, Margolick JB, Crabtree GR, Cossman J, Fauci AS, Jaffe ES. *Lymphokine induced phagocytosis in angiocentric immunoproliferative lesions (AIL) and malignant lymphoma arising in AIL. Blood 1985; 65: 1469-76.*