A Case of Malignant Lymphoma with Hemophagocytic Syndrome Presenting as Hepatic Failure

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Received for publication December 13, 1996

Summary: We report the case of a 50-year-old female with malignant lymphoma presenting hemophagocytic syndrome and liver failure. She developed high fever, marked jaundice, and progressive liver failure, followed by evidence of disseminated intravascular coagulation (DIC). The course was complicated by severe hepatitis and the patient died six days after admission. Pathological diagnosis on autopsy specimens of the lung hilar lymph nodes was non-Hodgkin's T cell lymphoma, of the diffuse small cell type. Histopathologic examination of the liver demonstrated diffuse liver cell destruction with prominent T lymphocyte infiltration in the portal and periportal area. In addition to marked lymphoma cell infiltration, hemophagocytosis by prominent infiltrative macrophages was observed in various organs, such as the liver and bone marrow, indicating the hemophagocytic syndrome. The hemophagocytic syndrome characterized in the present case may have been responsible for the extremely rapid and fulminant course.

Key words hemophagocytic syndrome, malignant lymphoma, VHAS, hepatic failure, immunohistology

Introduction

A few cases of malignant lymphoma with symptoms of liver failure, such as jaundice and impaired liver function, or with a fulminant hepatitis-like course, have been reported. None of the reported cases was diagnosed ante mortem, and those cases showed very poor prognosis (Colby and Labrecque, 1982; Yuki et al. 1988; Nizalik et al. 1989). On the other hand, the hemophagocytic syndrome is characterized by acute onset leading to a fatal course with symptoms such as fever, hepatosplenomegaly, lymph node enlargement, pancytopenia, jaundice, and diffuse histiocytic infiltration in various organs (Arya et al. 1985; Alexander and Jerry, 1988; Blaise, 1992). Virus-associated hemophagocytic syndrome (VAHS) was described as a type of hemophagocytic syndrome associated with systemic...
virus infection (Risdall et al. 1979; McKenna et al. 1981). Recently, especially in the pediatric field, VAHS has been paid attention as a fatal condition with pancytopenia (Ohga et al. 1993).

We report the case of a patient with malignant lymphoma who developed liver failure and DIC and showed tumor cell infiltration in multiple organs, in whom the pathological examination revealed hemophagocytic syndrome. Her clinical course and immunohistologic findings are presented in this report.

**Case Report**

The patient was a 50-year-old female complaining of jaundice and hematemesis. Her elder brother died of hepatocellular carcinoma, and her younger brother had chronic hepatitis. She had no history of drinking or smoking. She delivered a child by Caesarean section in 1974. It is unknown if she ever had a blood transfusion.

She developed malaise in November, 1991, and abnormal liver function was detected by blood chemistry tests undertaken at a local hospital two weeks later. The malaise became aggravated in early February, 1992, and her appetite became poor. In late February, high fever (38-39 °C) and jaundice developed. She was admitted to a local hospital with marked impairment of liver function and was diagnosed as having acute hepatitis. Her serum level of total bilirubin (T. Bil) was elevated and DIC became apparent, diagnosed on the basis of a decreased platelet count, prolonged prothrombin time (PT), increased fibrinogen degradation products (FDP), decline of the erythrocyte sedimentation rate (ESR) and appearance of subcutaneous bleeding. She subsequently developed hematemesis and was admitted to our hospital February 27, 1992 (Fig. 1).

Physical examination on admission showed a blood pressure of 130/78 mmHg, a regular pulse of 70/minute, and a body temperature of 38.2 °C. Her consciousness was clear. She had marked jaundice over the entire body. Subcutaneous hemorrhage was observed in the upper limbs. Neither spider telangiectasis nor palmar erythema was noted. The superficial lymph nodes were not palpable and the cardiac and respiratory sounds were normal. In the abdomen, the liver was palpable 8 cm below the right costal margin on the midclavicular line. The liver had blunt margins and a smooth surface. It was elastic, soft, tender, and sensitive to tapping. The spleen was not palpable.

Laboratory examination on admission showed a serum T. Bil of 14.4 mg/dl, sGOT of 1028 KU and sGPT of 647 KU. The serum lactate dehydrogenase (LDH) level was markedly increased, the serum total protein concentration was 3.8 g/dl, the serum total cholesterol was 69 mg/dl and PT was 17 sec (normal level; 10-13 sec). These results indicated markedly impaired liver synthetic and reserve functions. The white blood cells (WBC) count was 7,400/mm³, with 4% abnormal lymphocytes, there was hypochromic microcytic anemia and the platelet count was 148,000/mm³. The hepatitis B virus surface (HBs) antigen, HBs antibody, hepatitis B virus core (HBc) antibody, IgM-anti hepatitis A virus (HAV) antibody, and the hepatitis C virus (HCV)
antibody were negative, and all other virus markers except the IgG anticytomegalovirus (CMV) antibody were negative. The carcinoembryonic antigen (CEA), alpha fetoprotein (AFP) and carbohydrate antigen 19-9 (CA19-9) tumor markers were normal.

Emergency endoscopy revealed multiple gastric ulcers with active bleeding. Bleeding was stopped by local injection of ethanol. The diagnosis of severe hepatitis and DIC was made, and a continuous venous infusion of glucagon-insulin, prostaglandin E1 and gabexate mesilate was initiated. On the next day, flapping tremor appeared and plasma exchange was immediately initiated with a diagnosis of fulminant hepatitis with grade 2 coma. However, no improvement was observed. Dyspnea developed three days after admission and she died six days after admission.

At autopsy the liver was not atrophic, weighing 1,110 g. Yellowish
parts were mixed with dark purple parts, and diffuse liver cell necrosis and exfoliation were observed. The spleen was markedly swollen, weighing 400 g. Bilateral pulmonary edema and bleeding from multiple gastric ulcers were seen. Additional bleeding was detected in the small and large intestines and kidneys. The lung hilar lymph nodes were slightly enlarged, but the superficial, celiac, and periaortic lymph nodes were not enlarged.

Light microscopy after hematoxylin-eosin staining of the liver showed marked infiltration of the portal and periportal area by small abnormal lymphocytes. Diffuse liver cell necrosis was present (Figs 2a, b). Most of the liver cells were exfoliated, and round cell infiltration mainly in the portal and periportal area was observed. There was marked hemorrhage in some areas of the hepatic lobe. In the periportal area, abnormal lymphocyte infiltration into the sinusoids, marked phagocyte infiltration and phagocytosis was noted (Fig. 3). The lung hilar lymph nodes were infiltrated with small lymphocytes similar to those seen in the liver. The bone marrow also showed diffuse infiltration by abnormal lymphocytes and many phagocytes with ingested erythrocytes and other bone marrow cells (Fig. 4). Similar lymphocyte infiltration was observed in the spleen, lungs, and adrenal glands. Thrombosis and bleeding were seen in the small vessels of all organs.

Immunohistochemical analysis showed that the abnormal lymphocytes were positive for UCHL-1 (Fig. 5a), CD8 and CD4. The phagocytes observed around lymphocytes were positive for HAM56.
Fig. 4. Sections from the bone marrow show diffuse infiltration of tumor cells and hemophagocytic macrophages can be seen. (H.E. ×100)

Fig. 5. Immunohistochemical staining for UCHL-1 and HAM56.

a) Infiltrated tumor cells in the portal and periportal area are positive for UCHL-1. (×100)
b) Phagocytes surrounding the area of infiltrating tumor cells are positive in the stain with HAM56, an antimacrophage antibody. (×50)

Fig. 6. Cytomegalovirus inclusion bodies are seen in the epithelial cells of the intrahepatic bile duct. (H.E. ×100)

(Fig. 5b) and slightly positive for lysozyme and CD68 but negative for α1-antichymotrypsin or S100 protein. These findings suggested multi-organ infiltration by diffuse intermediate-small cell type, non-Hodgkin’s T cell lymphoma complicated by the hemophagocytic syndrome. In the bile duct epithelium, intranuclear inclusions were present (Fig. 6). Similar intranuclear inclusions were observed in the stomach, lungs, adrenal glands, and lymph nodes. Examination for cytomegalovirus (CMV) nucleic acid by the polymerase chain (PCR) reaction using paraffin embedded sections was positive.

Discussion

A few patients with malignant lymphoma have shown a course similar to that of acute hepatitis or fulminant hepatitis. The major symptoms in these patients are jaundice, fever, and hepatosplenomegaly. The superficial lymph nodes are not always enlarged, and the course is acute. Therefore, ante mortem diagnosis is not made, or an
erroneous diagnosis is made (Colby and LaBrecque, 1982; Nanno et al. 1988; Yuki et al. 1988; Nizalik et al. 1989). Yuki et al. (1988) have reported that severe hepatopathy due to malignant lymphoma can be distinguished from fulminant viral hepatitis or liver failure by virtue of tender hepatosplenomegaly, a marked elevation of LDH, hyperuricemia, a strongly positive C reactive protein (CRP) test, a markedly decreased WBC, and hepatic hilar lymph node enlargement. In our patient, the uric acid level was normal, the decrease in WBC was slight, and no hepatic hilar lymph node enlargement was observed. Therefore, histologic diagnosis such as by liver biopsy is important. However, in the present case, the liver biopsy has not been done due to hemorrhagic tendency and an extremely rapid fulminant course.

In our patient, a proliferation and infiltration of small abnormal T-lymphocytes was observed in the liver, bone marrow, lymph nodes, lungs, and spleen. Based on cellular morphology, a diagnosis of intermediate-small cell type, non-Hodgkin's T cell lymphoma was made. A variety of mechanism have been involved to explain liver failure in patients with malignant lymphoma. Direct damage of liver cells by tumor cells (Roos et al. 1977) or by cytokine-like substances produced by tumor cells (Jaffe et al. 1983; Biemer, 1984; Falni et al. 1990), ischemic changes caused by infiltration of tumor cells in vessels and liver sinusoids (Zafrani et al. 1983), and damage mediated by endotoxemia or DIC have been hypothesized as the cause of liver failure in patients with malignant lymphoma. None of these factors has been clearly demonstrated in the present case and a multifactorial etiology may be responsible for liver failure in many cases.

An interesting finding in our case was a marked phagocyte infiltration in multiple organs such as the liver and bone marrow. The absence of neoplastic proliferation together with immunohistologic findings have suggested that these cells were macrophages (Hibi et al. 1988). The hemophagocytic syndrome (HPS) is characterized by acute onset leading to a fatal course with symptoms such as fever, hepatosplenomegaly, lymph node enlargement, pancytopenia, jaundice, and diffuse histiocytic infiltration (Arya et al. 1985; Alexander and Jerry, 1988; Blaise, 1992). Virus-associated hemophagocytic syndrome (VAHS) was described by Risdall et al. as a type of hemophagocytic syndrome associated with systemic virus infection and histocyte proliferation (Risdall et al. 1979; McKenna et al. 1981). Previous studies indicated that hypercytokinemia, induced by proliferating and activated T lymphocytes and macrophages, produced various symptoms in HPS (Chan et al. 1987; Pileri et al. 1992). Lymphoma cells are considered to produce great amounts of cytokines in T cell lymphoma; VAHS with an impaired immune reaction against bacterial and virus infection can be associated with hypercytokinemia (Imashuku et al. 1991; Shinmyozu et al. 1991). Ohga et al. (1993) reported that, in VAHS, serum levels of IFN-γ and TNF-α correlated with the clinical course and disease activity, and that serum levels of IFN-γ could be the most sensitive indicator of the disease activity. Fujiwara et al. (1993) suggested that
levels of IFN-γ, IL-2R and IL-6 are closely related to pathogenesis and prognosis of HPS. Although the etiology and pathogenesis of HPS have not been determined, the destruction of the immune system to regulate activation of the macrophage, playing an important role in host defense, may induce the HPS (Rosenthal, 1980; Unanue and Allen, 1987; Alexander and Jerry, 1988). In the present case, marked tumor T-cell infiltration may have directly caused hepatic tissue damage or indirectly caused it through the production of IFN-γ by tumor T cells that induced proliferation and activation of macrophages. Responsive phagocyte infiltration of the damaged area may have induced HPS, followed by aggravation of liver damage by coagulofibrinolytic abnormality in the sinusoidal microcirculation, which may have resulted in liver failure (Shinmyozu et al. 1991). Recently the Epstein-Barr (EB) virus infection, although not demonstrated in the present case, has been shown to play an important role in the pathogenesis of HPS and T-cell lymphoma (Kawaguchi et al. 1993; Su et al. 1993). In addition, CMV infection was demonstrated by PCR of the liver tissue specimen. These findings raise the possibility that the immunosuppression, hypercytokinemia and liver failure caused by malignant T-cell lymphoma aggravated a latent virus infection and induced a VAHS-like syndrome.

Conclusion

We report a patient with malignant lymphoma complicated by liver failure and DIC. Marked infiltration of phagocytes as well as tumor cells was observed in multiple organs. The potential role of the hemophagocytic syndrome and VAHS in this patient's clinical course was discussed.

Acknowledgments: We express deep gratitude to Prof. Masahiro Kikuchi, the First Department of Pathology, Fukuoka University, for valuable advice.

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