Hepatosplenic γδ T-cell lymphoma associated with hepatitis B virus infection

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Abstract : Hepatitis B virus (HBV) infection has been implicated in the development of hepatocellular and hematopoietic malignancies. We describe a patient with chronic hepatitis B who developed hepatosplenic γδ T-cell lymphoma. A 45-year-old woman presented with marked hepatosplenomegaly and hepatic failure during the course of chronic hepatitis B. Peripheral blood examination revealed 57% abnormal lymphoid cells which expressed the γδ T-cell receptor. The cytogenetic analysis of tumor cells showed an abnormal karyotype ; 47, XX, -13, +2mar in all 20 metaphases examined. A clonal rearrangement of the T-cell receptor genes was demonstrated by Southern blot analysis, showing monoclonal expansion of tumor cells. A liver biopsy specimen showed fibrosis of the portal areas and sinusoidal infiltration of tumor cells. HBV infection was documented by the presence of IgG anti-HBc and anti-HBs antibodies in serum. Although HBV-DNA was not detected in tumor cells by polymerase chain reaction analysis, there is a possibility that proliferation of γδ T cells in response to HBV infection played a role in the pathogenesis of hepatosplenic γδ T-cell lymphoma. J. Med. Invest. 44 : 215-217, 1998

Key Words *: hepatosplenic lymphoma, γδ T-cell, hepatitis B virus, chronic hepatitis, hepatosplenomegaly*

INTRODUCTION

Hepatosplenic γδ T-cell lymphoma is a rare and aggressive T-cell malignancy characterized by the neoplastic proliferation of γδ T cells in the hepatic sinusoids and splenic red pulp (1, 2). An increased number of γδ T cells has also been reported in the hepatic sinusoids of patients with chronic viral hepatitis (3). Human γδ T cells exhibit preferential homing to the sinusoidal areas of lymphoid tissues and can mediate cellular immune functions in response to antigenic stimulation (4). However, the exact mechanism of the proliferation of these cells remains unknown.

Hepatitis B virus (HBV) infection has been implicated in the development of hepatocellular carcinoma (5). Moreover, HBV has been reported to play a pathogenic role in some cases of hematopoietic and lymphoid malignancies (6, 7). Although the role of HBV in the development of malignancies has not been clarified, integration of HBV-DNA into the cellular DNA of neoplasm is frequently found and this has been postulated as essential to HBV-related oncogenesis because of transcriptional activation function (8).

We report a case of hepatosplenic γδ T-cell lymphoma associated with chronic B hepatitis. Although HBV-DNA was absent in lymphoma cells of this patient, proliferation of γδ T cells by an immune response to HBV infection might have played a role in the development of hepatosplenic γδ T-cell lymphoma.

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CASE REPORT

A 45-year-old woman had suffered from liver dysfunction since 1990. Although the opportunity of HBV infection was not known, a diagnosis of chronic hepatitis B was made on the basis of the clinical course and antibody responses against HBV. She was subsequently lost to follow-up for almost 6 years and there was no data on serological examination. In 1996 she presented with jaundice and abdominal fullness. Physical examination revealed ascites and marked hepatosplenomegaly associated with no lymphadenopathy. The hemoglobin level was 10.8 g/dl, platelet count 39 x 10^9/l and white blood cell count 9.3x10^9/l with 57% abnormal lymphoid cells showing irregular nuclei with condensed chromatin. The lymphoid cells from the peripheral blood expressed CD3, CD7 and the γδ T-cell receptor detected by TCRδ 1 (T Cell Sciences, Cambridge, MA), but not the αβ T-cell receptor detected by TCR 1 (Becton Dickinson, San Jose, CA). Other T-cell antigens (CD1, CD2, CD4, CD5, CD8, CD25), NK-cell antigens (CD 16, CD56, CD57), B-cell antigens (CD19, CD20) or HLA-DR were negative. The cytogenetic

analysis of the tumor cells showed an abnormal karyotype ; 47, XX, -13, +2 mar in all 20 metaphases examined. A clonal rearrangement of the T-cell receptor (TCR)-β, -γ, -δ chain genes was demonstrated but the immunoglobulin heavy chain (IgH) gene was in a germ line state by Southern blot analysis (Fig 1). Serum aspartate aminotransferase was 856 IU/l, alanine aminotransferase 1056 IU/l, alkaline phosphatase 447 IU/l, lactate dehydrogenase 1254 IU/l, total bilirubin 10.1 x 10^{-2}g/l, albumin 32 g/l, ammonia 1.35x10^{3}g/l and soluble interleukin (IL)-2 receptor 4060U/ml (normal range 187.6-637.7). Alpha-fetoprotein and carcinoembryonic antigen were not elevated. Serological tests for human T-cell lymphotropic virus type I and hepatitis C virus (HCV) were negative. Hepatitis B surface antigen was negative. HBV infection was documented by the presence of IgG anti-HBc and anti-HBs antibodies in serum. To explore the possibility that lymphoma cells may become infected with HBV, integration of HBV-DNA was examined by polymerase chain reaction analysis as described previously (9). However, HBV-DNA was not detected in tumor cells. Computed tomography showed an enlarged liver and spleen and peritoneal fluid. No malignant cells were found in ascites. Histological features of the bone marrow showed an infiltration of lymphoma cells. A liver biopsy specimen showed fibrosis of the portal areas and sinusoidal infiltration of tumor cells (Fig 2). These cells were medium-sized lymphocytes with a regular or slightly indented nucleus, and positive for CD3 and CD45RO (UCHL-1) while negative for CD20 (L-26) by immunohistochemistry (data not shown). These findings were compatible with those of hepatosplenic γδ T-cell lymphoma and chronic hepatitis. Chemotherapy was started, but shortly after she developed fungal meningitis and died. Examination at autopsy revealed lymphoid infiltration in the liver, spleen, kidney, lung, bone marrow, anterior mediastinum and esophagus. The spleen weighed 500 g and the red pulp was massively infiltrated by medium-sized neoplastic cells.

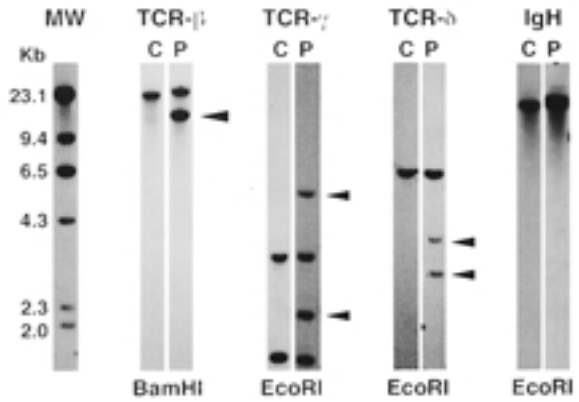

Fig.1. Southern blot analysis of DNA from peripheral blood lymphocytes of the patient (P) and control placenta (C) using TCR-β (cβ2), TCR-γ (Jγ1), TCR-δ (Jδ1) and IgH (JH) as probes. Arrowheads indicate the rearranged bands. Molecular sizes (in kilobases) are given in Lane MW.

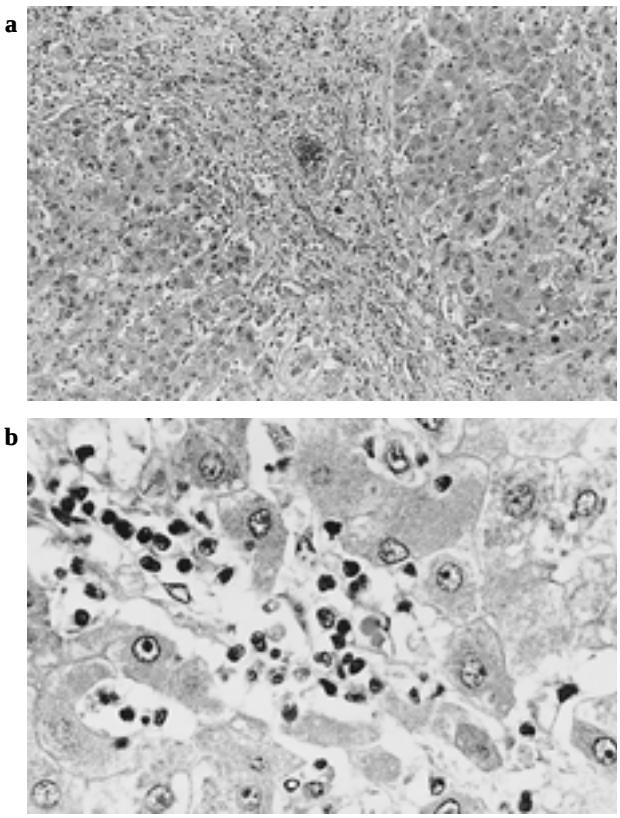

Fig.2. (a) Histological features of the liver showing fibrosis of the portal areas (hematoxylin and eosin stain, x 33). (b) Tumor cells infiltrate the hepatic sinuses (hematoxylin and eosin stain, x 200).

DISCUSSION

We report a case of hepatosplenic γδ T-cell lymphoma in leukemic phase associated with HBV infection. Aggravation of liver functions in this case was considered as a rapid progression of chronic hepatitis B until the proliferation of γδ T cells was found in the peripheral blood and liver. Clonal expansion of neoplastic cells was also demonstrated by cytogenetic and genotypic studies. However, the pathological significance of this chromosome abnormality is unknown and its possible role in the pathogenesis of γδ T-cell lymphoma remains to be elucidated. To our best knowledge, there was no case report of hepatosplenic γδ T-cell lymphoma associated with chronic hepatitis or HBV infection.

Because HBV is both a hepatotropic and lymphotropic virus, the possible pathogenic relationship between hepatitis B and malignant lymphoma has been suggested. Talamo et al. have reported an autopsy case of primary hepatic lymphoma in a patient with hepatocellular carcinoma associated with HBV infection and speculated that HBV could have been the common cause of both neoplasms in the liver (10). In addition, Pontisso et al have reported the detection of HBV-DNA in bone marrow cells of leukemia patients (6). In contrast, HBV gene products have been identified in endothelial cells of the tumor tissues of leukemia and lymphoma patients, suggesting that HBV-infected endothelial cells support and stimulate the tumor growth by producing cytokines (7). However, we were unable to demonstrate HBV-DNA in tumor cells by polymerase chain reaction analysis and there is no evidence to suggest a direct role of HBV in the development of

hepatosplenic γδ T-cell lymphoma in the present patient.

Nevertheless, histological findings showed fibrosis of the portal areas, indicating a chronic inflammatory change of the liver in this case. Primary lymphomas may arise as a monoclonal outgrowth from a pool of proliferating polyclonal lymphocytes involved in a chronic inflammatory process. An increased number of γδ T cells together with $CD3^+$ lymphocyte infiltration has been reported in the hepatic sinusoids of chronic viral hepatitis(3). Thus, HBV infection in the liver may provide a chronic stimulation inciting a γδ T-cell growth. Alternatively, Bukowski et al have reported the expansion of γδ T cells with the cytotoxic activity in response to virus-infected cells (11). This finding suggests that γδ T-cell malignancy may result from monoclonal expansion of γδ T cells with defined antigen specificity directed against virus-infected targets. Taken together, despite the absence of HBV-DNA in neoplastic γδ T cells, there is a possibility that the γδ T-cell expansion in response to HBV caused an evolution of neoplastic γδ T cells. Further investigations are required to elucidate the relationship between HBV infection and γδ T-cell malignancy.

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