4. Immunological Mechanism of Chronic Liver Injury in Viral Hepatitis

Gotaro YAMADA and Takao TSUJI

Key words: viral hepatitis, chronic hepatitis B, chronic hepatitis C

Introduction

Cases of persistent infection and carriers of human hepatitis viruses are known, and types B, C, and D viral hepatitis have been demonstrated in chronic liver diseases. In Japan, chronic hepatitis type B accounts for nearly 40%, type C nearly 60%, and very few cases of type D chronic hepatitis have been confirmed. Therefore, in this study we investigated the immunopathological findings of the liver and compared the mechanisms of liver injuries in type B and type C chronic hepatitis.

Material and Methods

The liver biopsy specimens were obtained from patients with chronic hepatitis B, diagnosed by the presence of hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) in their sera, and from patients with chronic hepatitis C, diagnosed both by detection of anti-C100 (EIA) and hepatitis C virus (HCV)-RNA (PCR) in their sera.

Cellular immune responses in liver tissues were observed by light and electron microscopy based on the indirect enzyme-labeled antibody technique using the following monoclonal antibodies as the first antibodies and horse radish peroxidase (HRPO)-labeled rabbit-Fab' anti-mouse immunoglobins as the second antibody. For the subpopulation of lymphocytes and T cell subsets (1, 2), anti-CD8, anti-CD11b, anti-CD4, anti-CD22, and anti-CD57 were used as the first antibodies. Anti-ABC was used for detection of HLA-class 1 antigen (HLA-1) (3). Anti-DR, anti-DQ and anti-DP were used as the second antibody. Anti-ABC was used for detection of HLA-class 1 antigen (HLA-1) (3). Anti-DR, anti-DQ and anti-DP were used for HLA-class 2 antigens (HLA-2) (2). Anti-intercellular adhesion molecule-1 (ICAM-1), anti-lymphocyte function adhesion molecule-1 (LFA-1) and anti-vascular cellular adhesion molecule-1 (VCAM-1) were used for observation of adhesion molecules (4).

For immunohistochemical detection of hepatitis B virus (HBV) related antigens in liver, anti-HBs, anti-HBc, and anti-HBe were used (5, 6). For intrahepatic HCV (2, 7), an immunohistochemical method using anti-HCV core antigen (HCCAg) and in situ hybridization technique using T-T dimerized oligo cDNA probes were applied.

Results

1) Chronic hepatitis, type B

At the time of onset of hepatitis or when acute exacerbation occurred, numerous CD8(+) and CD11b(–) lymphocytes, that is cytotoxic T lymphocytes (CTL), were seen around the HBc(e)Ag-positive hepatocytes which had HLA-1 on the cell surface (Fig. 1a, c). A point contact or a broad contact of CTL with hepatocytes infected with HBV was often observed by immunoelectron microscopy. ICAM-1 was expressed along the surface of hepatocytes at the site of focal and piecemeal necrosis (Fig. 1b). Most mononuclear cells infiltrating into these areas were positive for LFA-1. Furthermore, immunoelectron microscopic study showed lymphocytes in contact with sinusoidal endothelial cells with surface expression of VCAM-1. HBc(e)Ag-positive hepatocytes decreased or disappeared, and the inflammation regressed in patients whose blood HBeAg decreased rapidly, DNA-polymerase became negative and liver function tests returned to normal after acute exacerbation.

2) Chronic hepatitis, type C

In the liver of patients with chronic hepatitis, type C, a follicular-like aggregation of lymphocytes and injured bile ducts in the portal areas were frequently observed. Numerous T lymphocytes were present immunohistochemically in the liver of patients with chronic active hepatitis, and particularly, numerous OκT(-), OκT-Ilb(–) CTL infiltrated in areas of piecemeal necrosis and focal necrosis (Fig. 2b). In these patients, focal or diffuse distribution of liver cells presenting HLA-1 was observed, whereas liver cells presenting HLA-2 were virtually not found (Fig. 2c, d).

In most patients, HCV-RNA- or HCV-core Ag-positive liver cells were present in small numbers and sporadically (Fig. 2a), but lobular distribution of HCV-positive hepatocytes was observed in some patients. In serial sections of a patient, liver cells presenting HLA-1 on their membrane were diffusely observed in lobules containing HCV-positive liver cells, and numerous CTL were also found to infiltrate the same lobules.
Fig. 1. Immunohistological findings of HLA-class 1 antigen, ICAM-1 and HBcAg in the liver obtained from a patient with chronic hepatitis B in the recovery stage after acute exacerbation. a) Honeycomb-like increased expression of HLA-class 1 antigen on the surface of hepatocytes. b) Similarly diffuse expression of ICAM-1 on the surface of hepatocytes. c) A few hepatocytes containing cytoplasmic HBcAg.

Fig. 2. Immunohistological findings of HCV core antigen, CD8-positive lymphocytes, HLA-class 1 antigen and HLA-class 2 antigen in the liver of a patient with chronic active hepatitis C. a) A few hepatocytes containing granular HCV core antigen in the cytoplasm. b) CD8-positive lymphocytes in areas of focal necrosis and piecemeal necrosis. c) HLA-class 1 antigen expressed on hepatocytes in areas of focal necrosis and piecemeal necrosis. d) HLA-class 2 antigen is not expressed on hepatocytes.
Autoimmune Hepatitis

Gotaro TODA and Mikio ZENIYA

Key words: sulfatide, hepatitis C virus, sinusoidal endothelial cell

Autoimmune liver disease includes autoimmune hepatitis (AIH) and primary biliary cirrhosis (PBC). Here, AIH will be discussed. AIH is a chronic active hepatitis which would progress to liver cirrhosis without appropriate treatment. The etiologic agent is unknown. Hepatitis viruses, alcohol and drugs are basically ruled out as the etiologic agent. However, HCV infection may induce chronic active hepatitis which is hardly differentiated from HCV infection may induce chronic active hepatitis which is the effectiveness of corticosteroid treatment. In the present study, the diagnosis of AIH was made according to the diagnostic criteria proposed by a joint research group for AIH in Japan (1). In the patients with AIH, antinuclear antibody (ANA) was positive and serum IgG concentration was characterized by occurrence of liver-kidney microsomal antibody type 1 and antibody to soluble liver antigen, respectively, are very rare in Japan. Where most cases of AIH belong to type I, which is characterized by the occurrence of antinuclear antibody, anti-smooth muscle antibody and/or antibody to hepatocyte plasma membrane.

In the present study, the diagnosis of AIH was made according to the diagnostic criteria proposed by a joint research group for AIH in Japan (1). In the patients with AIH, antinuclear antibody (ANA) was positive and serum IgG concentration was...