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Fibrosing Cholestatic Hepatitis
: A Report of Three Cases

Fibrosing cholestatic hepatitis is an aggressive and usually fatal form of viral hepatitis in immunosuppressed patients. We report three cases of fibrosing cholestatic hepatitis in various clinical situations. Case 1 was a 50-year-old man who underwent a liver transplant for hepatitis B virus (HBV)-associated liver cirrhosis. Two and a half years after the transplant, he complained of fever and jaundice, and liver enzymes were slightly elevated. Serum HBsAg was positive. Case 2 was a 30-year-old man in an immunosuppressed state after chemotherapy for acute lymphoblastic leukemia. He was a HBV carrier. Liver enzymes and total bilirubin were markedly elevated. Case 3 was a 50-year-old man who underwent renal transplantation as a known HBV carrier. One year after the transplant, jaundice developed abruptly, but liver enzymes were not significantly elevated. Microscopically lobules were markedly disarrayed, showing ballooning degeneration of hepatocytes, prominent pericellular fibrosis, and marked canalicular or intracytoplasmic cholestasis. Portal inflammation was mild, but interphase activity was definite and cholangiolar proliferation was prominent. Hepatocytes were diffusely positive for HBsAg and HBcAg in various patterns. Patients died of liver failure within 1 to 3 months after liver biopsy in spite of anti-viral treatment.

Key Words: *Hepatitis B; Immunosuppression; Transplant; Cholestasis; Fibrosis; Liver Failure*

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INTRODUCTION

In Korea, the prevalence of hepatitis B virus (HBV) infection is very high in the general population, thus recurrent or reinfection of HBV may cause a serious problem in transplant patients. Pathologic changes within the grafted liver vary widely including normal histological findings, mild self-limiting hepatitis, chronic hepatitis with progression to cirrhosis, and fulminant hepatitis (1, 2). The high recurrence rate of HBV infection after orthotopic liver transplant is well established (1, 3).

Fibrosing cholestatic hepatitis (FCH) is a unique variant of viral hepatitis originally described in HBV-infected recipients of liver allografts (4, 5). The clinical course of FCH, however, is characterized by the rapid degeneration of the liver, leading to death rather than graft dysfunction. FCH have been described mostly in the setting of liver transplantation, while a few cases of FCH occurred in renal or bone marrow transplant recipients (6-11). We experienced three cases of FCH in different settings respectively and present characteristic histopathologic as well as clinical features.

CASE REPORT

Clinical findings

Case 1

A 50-year-old man underwent a liver transplant for HBV-associated liver cirrhosis. He had diabetes mellitus. He had been treated with cyclosporine and prednisolone as immunosuppressive drugs. Two and a half years after the transplant, he complained of fever and jaundice (total/direct bilirubin; 18.4/12.7 mg/dL), and liver enzymes were slightly elevated (AST/ALT, 48/44 IU/L; alkaline phosphatase/γGT, 342/76 IU/L) and prothrombin time was prolongated (29.7%, normal range; 70-140%). Serum HBs antigen and HBe antigen were positive. He experienced azotemia due to cyclosporine toxicity. Liver biopsy was done and α interferon treatment was started. Seven weeks after the biopsy, he died of septic shock with spontaneous bacterial peritonitis and ascites.

Case 2

A 30-year-old man had been markedly immunosup-

pressed because of chemotherapy for acute lymphoblastic leukemia. He was a HBV carrier. A quantitative HBV-DNA level by hybrid-capture assay was over 4,000 pg/mL. During induction chemotherapy, endogenous endophthalmitis and cardiomegaly developed. Four cycles of consolidation chemotherapy (VP; 75 mg/ m^2, Ara-C; 300 mg/m^2) were done during ten months after induction therapy. After the two weeks last consolidation chemotherapy, liver enzymes (AST/ALT, 1,016/294 IU/L; alkaline phosphatase, 247 IU/L) and total bilirubin (25.1 mg/dL) were markedly elevated suddenly. Prothrombin time was also prolongated (10%). Liver biopsy was performed two weeks after the onset of jaundice. He died of hepatic failure and shock after the treatment of lamivudine (150 mg, qd) for 10 days.

Case 3

A 50-year-old man underwent renal transplant with bilateral nephrectomy due to bilateral polycystic kidney disease 2 years ago as a HBV carrier (HBs antigen positive, HBe antibody positive, HBV DNA positive, 680 pg/mL). During post-transplant immunosuppressive treatment (cyclosporine 125 g bid, Celcept 1.0 g bid) for 8 months, jaundice (total/direct bilirubin, 11.3/5.4 mg/dL) developed abruptly, but liver enzymes were not significantly elevated (AST/ALT, 78/12 IU/L; alkaline phosphatase/γGT, 171/276 IU/L). No definite causes of hyperbilirubinemia were identified. Prothrombin time was prologated (25%). He suffered from azotemia and secondary non-insulin dependent diabetes mellitus due to cyclosporine toxicity. Liver biopsy was done 3 weeks after the onset of jaundice. He died of septic shock with spontaneous bacterial peritonitis and ascites, one month after the liver biopsy and the treatment of lamivudine.

Pathologic findings

Microscopic findings of the presented cases were similar each other. Hepatic lobules were markedly disarrayed, showing ballooning degeneration of hepatocytes, marked canalicular or intracytoplasmic cholestasis and prominent pericellular fibrosis. Focal acidophilic degeneration of hepatocytes and fatty change were observed. Portal tracts showed moderate fibrosis with minimal mononuclear cell inflammation. But interphase activity was definite and cholangiolar proliferation was prominent (Fig. 1). By immunohistochemistry, hepatocytes were diffusely positive for HBsAg in intracytoplasmic and cytoplasmic membranous patterns and HBcAg in nuclear and intracytoplasmic patterns (Fig. 2).

DISCUSSION

Three cases of FCH presented in this study showed unique histopathologic features as follows: 1) degenerative changes of hepatocytes including ballooning change, necrosis and steatosis, 2) portal expansion with cholangiolar proliferation, 3) periportal and pericellular fibrosis, 4) severe cholestasis, 5) minimal or no significant in-

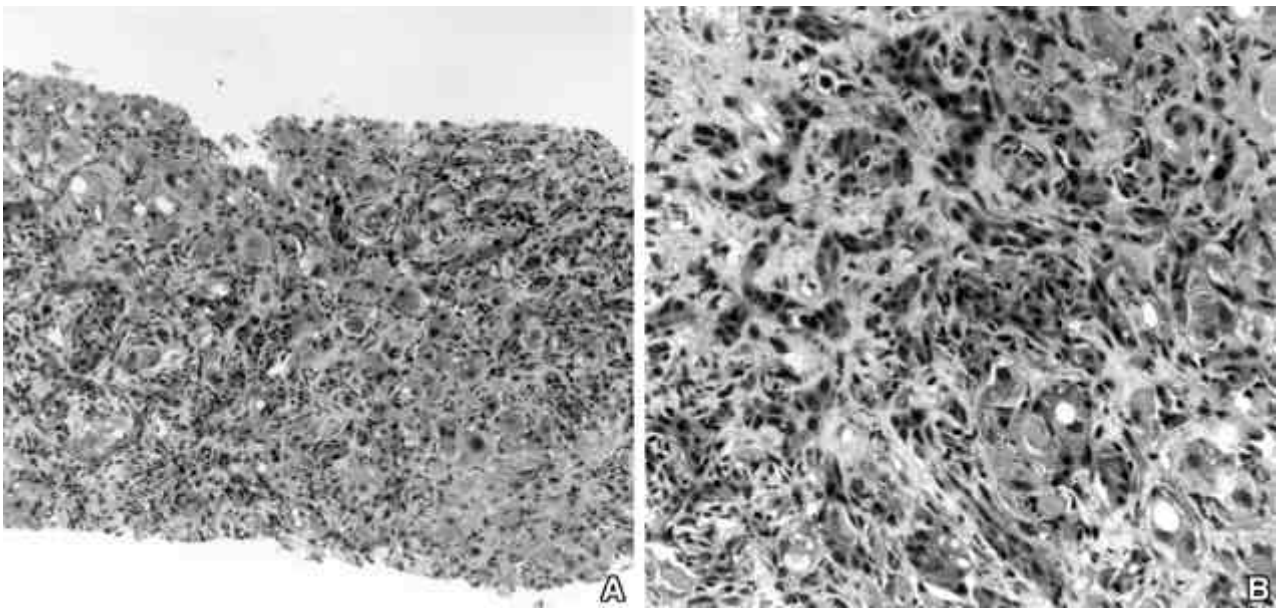

Fig. 1. **A:** Hepatic lobules are markedly disarrayed with diffuse pericellular fibrosis. Inflammatory infiltration is minimal (H&E, ×10). **B:** Portal area is markedly widened by prominent cholangiolar proliferation and fibrosis. Although portal inflammation is minimal, piecemeal necrosis is definite (H&E, ×200).

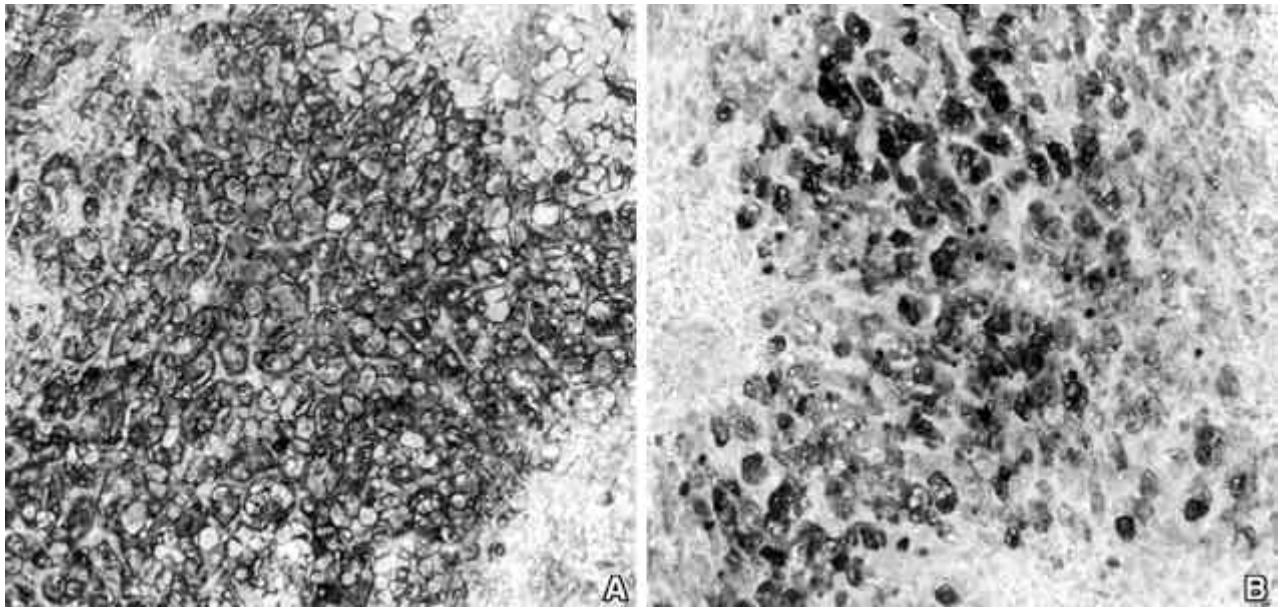

Fig. 2. Hepatocytes are diffusely positive for HBsAg (A) in intracytoplasmic and membranous patterns and HBcAg (B) in nuclear and intracytoplasmic patterns by immunohistochemical staining (×10).

flammatory component. Overexpression of HBV antigens in the hepatocytes is another typical feature of this condition. These histopathologic features of FCH are not commonly encountered in the general population. This is probably related to effects of immunosuppression and MHC non-identity between the liver and recipient. It has been proposed that immunosuppression may result in a striking increase in viral replication, markedly enhanced viral transcription and overexpression of HBsAg and HBcAg in virtually all hepatocytes. The cytopathic changes of hepatocytes in FCH are associated with the extensive expression of hepatitis B core antigen on the surface of hepatocytes, which become targeted for destruction by MHC-restricted cytotoxic T lymphocytes (12, 13), while HBV is not thought to be cytopathic under normal circumstances. In a liver allograft recipient, potent immunosuppression needed to prevent rejection interferes with normal mechanims of viral clearing, and contributes to the chronic progression of the disease in most recipients. In addition, since there is no attempt to prospectively match the donor and recipient for MHC antigens in liver transplantation, normal pathways of cytotoxic T lymphocytic lysis of virally infected hepatocytes may also be disrupted.

Minimal or no significant inflammatory reaction in FCH may result from immunosuppression and may lead to erroneous diagnosis without clinical information. Although MHC mismatching has the potential to significantly disrupt the manifestations of HBV-related disease in a liver allograft, massive viral replication in class II MHC mismatched deteriorating liver allografts with little or no hepatic inflammation led to the suggestion that under special circumstances, the virus may be directly cytopathic (14-16).

Although FCH was first documented in liver allograft, and most FCH were described in liver transplant patients, FCH occurred in severely immunosuppressed patients such as renal and bone marrow allograft recipients and those with AIDS (7-11, 17). The two cases presented here add to the list of FCH in settings of non-liver transplant and supported that immunosuppression provided a favorable environment for FCH to develop.

The natural course of the presented cases was similar to that which has occurred in previously described cases. FCH, as described in liver transplant recipients, is a rapidly progressive disease, resulting in graft loss, cirrhosis, or death within weeks or months (4, 5, 15, 16). Cases described in non-liver transplant patients have also been rapidly fatal (9, 10). The highly infectious nature of HBV and presence of extrahepatic reservoirs of virus probably account for the difficulty in eradicating the virus before transplant and its high recurrence rate after transplant. Various treatment modalitites have been used in an attempt to break the cycle of reinfection and recurrent disease which often leads to allograft failure and/or death. These include hepatitis B immune globulin, various antiviral drugs, active vaccination with HBsAg, and α-interferon (18-23). The presented patients had rapidly progressive clinical course, and were eventually fatal in spite of the treatment of either lamivudine or α interferon. Although FCH is a rare variant of viral hepatitis, it should be emphasized that prompt diagnosis of FCH on

the basis of characteristic clinicopathologic features is important for the management of patients who are in a severely immunosuppressed state such as after an organ transplant.

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