- Med Virol **40**: 35–38, 1993.
- 3) Koike K, Moriya K, Iino S, et al. High-level expression of hepatitis B virus HBx gene and hepatocarcinogenesis in transgenic mice. *Hepatology* **19**: 810–819, 1994.
 - 4) Koike K, Moriya K, Yotsuyanagi H, et al. Compensatory apoptosis in preneoplastic liver of transgenic mouse model for hepatocarcinogenesis. *Cancer Lett* **134**: 181–186, 1998.
 - 5) Yotsuyanagi H, Yasuda K, Iino S, et al. Persistent viremia after recovery from self-limited acute hepatitis B. *Hepatology* **27**: 1377–1382, 1998.
 - 6) Marusawa H, Uemoto S, Hijikata M, et al. Latent hepatitis B virus infection in healthy individuals with antibodies to hepatitis B core antigen. *Hepatology*. **31**: 488–495, 2000.
 - 7) Yotsuyanagi H, Shintani Y, Moriya K, et al. Virological analysis of non-B, non-C hepatocellular carcinoma in Japan: Frequent involvement of hepatitis B virus. *J Infect Dis* **181**: 1920–1928, 2000.
 - 8) Moriya K, Fujie H, Shintani Y, et al. Hepatitis C virus core protein induces hepatocellular carcinoma in transgenic mice. *Nat Med* **4**: 1065–1067, 1998.
 - 9) Koike K. Transgenic mouse models of viral hepatitis: Insight into viral hepatocarcinogenesis. *Viral Hepatitis Rev* **5**: 177–203, 1999.
 - 10) Koike K, Moriya K, Yotsuyanagi H, et al. Sialadenitis resembling Sjögren's syndrome in hepatitis C virus envelope gene transgenic mice. *Proc. Natl. Acad. Sci. U.S.A.* **94**: 233–236, 1997.
 - 11) Nishizawa T, Okamoto H, Konishi K, Yoshizawa H, Miyakawa Y, Mayumi M. A novel DNA virus (TTV) associated with elevated transaminase levels in posttransfusion hepatitis of unknown etiology. *Biochem Biophys Res Commun*. **241**: 92–97, 1997.
 - 12) DiaSorin home page: <http://www.diasorin.com/>, April 10, 2000.

2. Recent Advances in Acute and Fulminant Hepatitis in Japan

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Key words: acute hepatitis, fulminant hepatitis, late onset liver failure, massive liver necrosis, liver transplantation

Introduction

The etiology of acute liver disease in Japan is mostly hepatitis virus infections. Acute liver disease patients without hepatic encephalopathy showing a prothrombin time (PT) of less than 40% of normal values are regarded as acute hepatitis severe type (AH-S). When these patients present encephalopathy within 8 weeks of the disease onset, they are diagnosed as fulminant hepatitis (FH). FH is classified into two subtypes, acute type (FH-A) and subacute type (FH-S) in which the encephalopathy occurs within 10 days and later than 11 days, respectively. The patients in whom the encephalopathy develops 8 to 24 weeks after the disease onset are regarded as late onset hepatic failure (LOHF).

Acute hepatitis in Japan

Acute hepatitis (AH) consists of sporadic and post-transfusion hepatitis. Recently, the latter is extremely rare in Japan, because the surveillance for hepatitis B virus (HBV) and hepatitis C virus (HCV) has been routinely done in blood donors since 1989. In contrast, the number of sporadic hepatitis patients is unchanged during these 20 years except 1983 and between 1989 and 1991, when hepatitis A virus (HAV) infection

prevailed (1).

In Japan, there are several problems in sporadic hepatitis to be solved. Aged patients are subjected to HAV infection, since populations positive for serum anti-HAV are advanced in their ages. Prophylactic procedures are important, as fulminant hepatitis due to HAV infection frequently develops in elderly patients. HBV is transmitted exclusively through sexual intercourse, while HCV infection occurs in some patients during their hospital stay. When persistent HCV infection develops, interferon therapy should be given to eradicate HCV from the circulation. It is noteworthy that the etiology is unknown in half of sporadic hepatitis patients in 1998 (1). A novel single-strand DNA virus, TTV, seems to be responsible for such hepatitis (2). Also, the contribution of silent HBV infection, negative for serological markers, should be considered (3).

Acute hepatitis severe type and prediction for development of fulminant hepatitis

According to the prospective study by Iwate Medical University to evaluate clinical features and prognosis of AH-S patients in Japan (4), hepatic encephalopathy occurred in 29 of 100 patients, suggesting that FH develops in about 30% of AH-S patients. The extent of liver dysfunction was more severe in AH-S patients developing encephalopathy than in those without the encephalopathy. It appears that FH has already been completed in the mechanisms of development even in the stage of AH-S with no hepatic encephalopathy.

Several criteria have been proposed to predict the develop-

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ment of FH in AH-S patients. However, the usefulness in sensitivity and specificity was found only in the criteria by Muto (5) and Iwate Medical University (4).

Possible mechanisms of development of fulminant hepatitis and therapeutic modalities for the prevention

To inhibit the development of FH, the mechanisms of massive liver necrosis must be understood. There are 3 aspects involved: hepatitis virus, immune response and local factors in the liver.

Viral factors

Super-infection or co-infection of HCV has been proposed to aggravate the extent of liver injury in HAV- or HBV-induced AH patients (6). Also, the mutation of HBV-DNA, especially in pre-core and/or core region, was assumed to be closely associated with FH (7). At present, however, the relation between viral factors and FH is uncertain.

Recently, we treated a FH-S patient, in whom TTV infection might have contributed to the progression of liver injury. In this patient, HCV infection was also observed, and the genotype of co-infected TTV was 1b. Serum ALT levels changed in association with TTV-DNA levels. Nine TTV clones were isolated from the serum of this patient, and amino acid sequences of the hypervariable region were identical in 7 clones (unpublished data). Considering that amino acid sequences of such a region showed quasispecies in patients with persistent TTV infection (8), the major clone that we found might cause FH.

Immunological factors

In general, hepatitis virus itself is not cytotoxic to hepatocytes. Liver injury seems to develop during eradication of virus-infected hepatocytes by cytotoxic T lymphocytes (CTL). CTL can recognize hepatocytes via adhesion molecules and induce their damage through perforin-granzyme B system (9). Hepatocyte injury is further aggravated by CTL through Fas/Fas ligand system and TNF- α (9). Based on these observations, FH is suggested to develop as a consequence of excess immune reaction induced by CTL. Such mechanisms might be involved in the progression of FH-S and LOHF. However, different mechanisms may operate in the development of FH-A, as the amount of CTL infiltrating into the liver is small. Cytotoxic mediators or microcirculatory disturbance can contribute to the provocation of massive liver necrosis.

Local factors in the liver

Massive liver necrosis develops in rats given heat-killed *P. acnes* or undergoing 70% partial hepatectomy after intravenous administration of endotoxin (10, 11). Both models present similar clinical and pathological features to FH-A, and hence local factors responsible for massive liver necrosis was investigated using these models.

When rats received heat-killed *P. acnes*, hepatic macrophages became activated through the cytokine network of IL-18 and IFN- γ (12). Chemokine network through osteopontin, an extracellular matrix which can also promote migration of mac-

rophages, was associated with macrophage infiltration into the liver in this model (13, 14). These macrophages are activated to produce a large amount of TNF- α and superoxide anions (15, 16) and produce destruction of endothelial cells leading to development of fibrin deposition in the hepatic sinusoids (16, 17). In contrast, Kupffer cells became activated through bacterial translocation following 70% liver resection in rats (18, 19). These Kupffer cells are rich in the activity of tissue factor, an initiator of blood coagulation cascade, and fibrin deposition develops after LPS administration in partially hepatectomized rats as a result of deranged blood coagulation equilibrium in the hepatic sinusoids (20). It is noteworthy that hepatocyte damage occurs in both models due to microcirculatory disturbance induced by sinusoidal fibrin deposition (16, 20).

Therapeutic strategy for the prevention of fulminant hepatitis

Peripheral platelets are frequently decreased in number in AH-S patients due to HAV or HBV transient infection. In these patients, hepatocyte injury may be produced through microcirculatory disturbance due to sinusoidal deposition, and anticoagulant therapy using antithrombin (AT) III concentrate is preferable as soon as possible. In contrast, peripheral platelets are unchanged in HBV-carrier patients during the course of hepatitis exacerbation. In such patients, anti-viral therapy such as lamivudine administration may be effective.

Fulminant hepatitis and LOHF in Japan

Ninety-three patients with fulminant hepatitis (46 of acute type and 47 of subacute type) and 11 with LOHF were admitted to 311 hospitals with hepatologists in Japan between January and December 1998. Demographic and clinical features, prognoses and therapies were analyzed in these patients (21). The usefulness of the Guideline for Liver Transplantation (22) (Acute Liver Failure Study Group in Japan, 1996) was also evaluated (21).

Background, etiology and prognosis of the patients

Regarding the patients, 20.9% of FH-A and 23.9% of FH-S were HBV carriers. Complications other than hepatitis, such as diabetes, cancer and psychological diseases, were underlying in 41.3% of the patients with FH-S and 63.6% with LOHF. Most of these patients received daily medication. According to the previous publication (23), the present data revealed that there is an increasing tendency in the frequency of HBV carriers and/or complications other than hepatitis in patients with FH and LOHF.

Survival rate in patients who did not undergo liver transplantation was 51.1%, 25.6% and 0% in FH-A, FH-S and LOHF, respectively: the rate was significantly higher in the FH-A group than in the other 2 groups. The prognosis of the patients seemed to improve especially in those with FH-S.

There were 4 patients with HAV infection. All of these patients had FH-A and survived without liver transplantation. It is noteworthy that HBV infection was found in 48 patients (44.4%); transient infection in 23, persistent infection in 23, and undetermined infection in 2. The majority of the patients

with transient HBV infection had FH-A, while HBV carriers were more frequent in FH-S than in FH-A. There were 42 patients (40.7%) with no evidence of HAV or HBV infections; 9, 25 and 8 with FH-A, FH-S and LOHF, respectively. Suspicious causes of these patients were autoimmune liver diseases such as autoimmune hepatitis in 7. The precise analysis of these patients will be necessary, because the prognosis was extremely poor even though corticosteroid therapy was performed.

Treatments of fulminant hepatitis and LOHF

Most FH and LOHF patients received artificial liver support such as plasma exchange and blood dialysis and filtration. Anticoagulant therapy was done in about 60%. AT III concentrate was effective for DIC in FH patients, but its efficacy was limited. Clinical usage of a novel anticoagulant, recombinant TFPI, which can act targeting the hepatic sinusoids would be more useful (24, 25). Lamivudine for HBV infection has become the prevailing agent. Ten patients received lamivudine, and therapeutic efficacy was found in 5.

Liver transplantation was considered in 11 patients with FH-A (23.9%), 18 with FH-S (38.3%) and 7 with LOHF (63.6%), but was performed in only 6 patients, 1, 4 and 1 patients with FH-A, FH-S and LOHF, respectively. Predictive accuracy of the guideline, assessed from the prognosis of patients undergoing no liver transplantation, was higher in FH-S (90.0%) than in FH-A (78.0%). There were several patients with FH-A and LOHF, in whom the indication for liver transplantation could not be assessed, because they died immediately after the onset of hepatic encephalopathy. It is necessary to establish a guideline for liver transplantation for the patients of FH-A and LOHF.

Conclusion

The following problems must be clarified to improve the prognosis of acute liver disease patients in Japan; 1) the criteria for prediction of the development of FH in AH-S patients should be made, 2) Anticoagulant and anti-viral therapies for the prevention of the development of FH in AH-S patients should be established, and 3) the guidelines for liver transplantation for FH-A and LOHF should be improved. To answer these problems, it will be necessary to elucidate the mechanisms of massive liver necrosis in FH patients.

References

- 1) Yano M. Sporadic acute hepatitis. *KAN · TAN · SUI* **39**: 173–178, 1999.
- 2) Okamoto H, Nishizawa T, Kato N, et al. Molecular cloning and characterization of a novel DNA virus (TTV) associated with posttransfusion hepatitis of unknown etiology. *Hepatology Res* **10**: 1–16, 1998.
- 3) Uchida T, Saitoh T, Shinzawa H. Mutations of the X region of hepatitis B virus and their clinical implications. *Pathol Int* **47**: 183–193, 1997.
- 4) Sato S, Suzuki S, Takikawa Y. Prospective study to clarify the prognosis of patients with acute hepatitis severe type and fulminant hepatitis in Japan. Intractable Liver Diseases Study Group of Japan, The Ministry of Health and Welfare. Annual Report at 1998, pp 67–69, 1999 (in Japanese).
- 5) Muto Y. Fulminant hepatitis in Japan (1992). Intractable Liver Diseases Study Group of Japan, The Ministry of Health and Welfare. Annual Re-

- port at 1993, pp 44–50, 1994.
- 6) Ohnishi H, Sugihara J, Moriawaki H, et al. Detection of anti-hepatitis C virus antibody in fulminant hepatic failure. *Gastroenterol Jpn* **26** Suppl 3: 212–215, 1991.
- 7) Omata M, Ehata T, Yokosuka O, et al. Mutations in the precore region of hepatitis B virus DNA in patients with fulminant and severe hepatitis. *N Engl J Med* **324**: 1699–1704, 1991.
- 8) Nishizawa T, Okamoto H, Tsuda F, et al. Quasispecies of TT virus (TTV) with sequence divergence in hypervariable regions of the capsid protein in chronic TTV infection. *J Virology* **73**: 9604–9608, 1999.
- 9) Ando K, Hiroishi K, Kaneko T, et al. Perforin, Fas/Fas ligand, and TNF- α pathway as specific and bystander killing mechanisms of hepatitis C virus-specific human CTL. *J Immunol* **158**: 5283–5291, 1997.
- 10) Yamada S, Ogata I, Hirata K, et al. Intravascular coagulation in the development of massive hepatic necrosis induced by *Corynebacterium parvum* and endotoxin in rats. *Scand J Gastroenterol* **24**: 293–298, 1989.
- 11) Mochida S, Ogata I, Hirata K, et al. Provocation of massive hepatic necrosis by endotoxin after partial hepatectomy in rats. *Gastroenterology* **99**: 771–777, 1990.
- 12) Toshima K, Mochida S, Ishikawa K, et al. Contribution of CD14 to endotoxin-induced liver injury may depend on types of macrophage activation in rats. *Biochem Biophys Res Commun* **246**: 731–735, 1998.
- 13) Kawashima R, Mochida S, Matsui A, et al. Expression of osteopontin in Kupffer cells and hepatic macrophages and stellate cells in rat liver after carbon tetrachloride intoxication: A possible factor for macrophage migration into hepatic necrotic areas. *Biochem Biophys Res Commun* **256**: 527–531, 1999.
- 14) Wang YH, Mochida S, Kawashima R, et al. Increased expression of osteopontin in activated Kupffer cells and hepatic macrophages during macrophage migration in *Propionibacterium acnes*-treated rat liver. *J Gastroenterol* 2000 (in press).
- 15) Mochida S, Ogata I, Ohta Y, et al. *In situ* evaluation of the stimulatory state of hepatic macrophages based on their ability to produce superoxide anions in rats. *J Pathol* **158**: 67–71, 1989.
- 16) Arai M, Mochida S, Ohno A, et al. Sinusoidal endothelial cell damage by activated hepatic macrophages in rat liver necrosis. *Gastroenterology* **104**: 1466–1471, 1993.
- 17) Mochida S, Ohno A, Arai M, et al. Role of adhesion molecules in the development of massive hepatic necrosis in rats. *Hepatology* **23**: 320–328, 1996.
- 18) Mochida S, Ohta Y, Ogata I, et al. Gut-derived substances in activation of hepatic macrophages after partial hepatectomy in rats. *J Hepatol* **16**: 266–272, 1992.
- 19) Arai M, Mochida S, Ohno A, et al. Selective bowel decontamination of recipients for prevention against liver injury following orthotopic liver transplantation: Evaluation with rat models. *Hepatology* **27**: 123–127, 1998.
- 20) Mochida S, Arai M, Ohno A, et al. Deranged blood coagulation equilibrium as a factor of massive liver necrosis following endotoxin administration in partially hepatectomized rats. *Hepatology* **29**: 1532–1540, 1999.
- 21) Fujiwara K, Mochida S, Matsui A. Fulminant hepatitis and late onset hepatic failure in Japan (1998). Intractable Liver Diseases Study Group of Japan, The Ministry of Health and Welfare. Annual Report at 1999, 2000.
- 22) Ishiki Y, Sugihara J, Naito T, et al. Guideline of liver transplantation for fulminant hepatitis. *Acta Hepatologica Jpn* **73**: 760–761, 1996.
- 23) Sato S, Suzuki K, Takigawa Y. Fulminant hepatitis and late onset hepatic failure in Japan (1998). Intractable Liver Diseases Study Group of Japan, The Ministry of Health and Welfare. Annual Report at 1998, pp 62–66, 1999.
- 24) Arai M, Mochida S, Ohno A, et al. Blood coagulation equilibrium in rat liver microcirculation as evaluated by endothelial cell thrombomodulin and macrophage tissue factor. *Thromb Res* **80**: 113–123, 1995.
- 25) Yamanobe F, Mochida S, Ohno A, et al. Recombinant human tissue factor pathway inhibitor as a possible anticoagulant targeting hepatic sinusoidal walls. *Thromb Res* **85**: 493–501, 1997.