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Clinicopathologic Analysis of the Liver Explant with Severe Hepatitis A Virus Infection

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The incidence of severe hepatitis A virus (HAV) infection has been increasing. However, clinicopathologic features of severe HAV infection that lead to liver transplantation (LT) have not been reported in Korea. We retrieved 16 LT cases with HAV infection during the last 3 years at Asan Medical Center, Seoul, Korea. Fifteen cases progressed to hepatic encephalopathy. Thirteen cases survived with or without complications, and three patients died of sepsis. The explanted liver showed massive or zonal necrosis with moderate to severe cholestasis. The zonal distribution of necrosis was frequently associated with endothelialitis of portal and/or central veins. Degenerative changes of hepatocytes were various in degree and distribution. Viral inclusions were suspected in two cases. Although HAV infection is usually confirmed by serological tests, significant venulitis of central and/or portal veins and viral inclusions, which are rarely observed, can suggest an HAV infection as a cause of massive hepatic necrosis of unknown mechanism.

Key Words: HAV infection; Liver transplantation; Cholestasis; Venulitis

Hepatitis A virus (HAV) is one of the major etiologies of acute hepatitis, and HAV infection mostly occurs in patients between 5 and 40 years of age, usually as a result of fecal-to-oral transmission.[1] Young children may carry antibodies to HAV without overt clinical features, while the possibility of developing symptomatic hepatitis is greater in adults than children, and the rates of hospitalization and complications appear to be higher in adults.[2,3] HAV hepatitis is usually a self-limiting disease, but rarely results in a serious condition, fulminant hepatic failure (FHF) that may be followed by death.[1] Although FHF develops in less than 1% of cases with HAV infection,[4] it carries a mortality of 30%, in contrast to the fatality rate of 0.01-0.03% in previously reported HAV infection cases.[5]

South Korea has changed from a developing country to a developed country as socioeconomic status, and environmental sanitation has improved.[6] As a result, the seropositivity of anti-HAV IgG has decreased in the young adult population; from 60% in 1980 to less than 10% in 1995. More recently, the number of HAV hepatitis patients has increased remarkably in Korea as the serological prevalence of anti-HAV has been lower at younger ages.[7] For some patients who have progressed to acute fulminant HAV hepatitis, liver transplantation (LT) is the treatment of choice. Although, clinical features and various factors associated with fulminant courses of HAV infection have been described, details of pathological characteristics of the fulminant HAV hepatitis have not been reported. In the present study, we investigated the clinicopathologic characteristics of LT patients with severe HAV hepatitis leading to FHF.

CASE REPORT

We experienced 16 cases of LT with HAV infection during the last 3 years (from September 2006 to September 2009) at Asan Medical Center, Seoul, Korea. Their clinical manifestation and laboratory data are reviewed and summarized in Table 1. Patients' age, sex, period from onset of symptom to LT, aspartate aminotransferase (AST, IU/L), alanine aminotransferase (ALT, IU/L), alkaline phosphatase (ALP, IU/L), γ-glutamyltranspeptidase (IU/L), total bilirubin (mg/dL), prothrombin time, and prognosis were reviewed. Acute or chronic liver diseases other than HAV, including autoimmune hepatitis, toxic hepatitis,

Table 1. Clinical features and outcomes of patients who underwent liver transplantation due to severe HAV hepatitis

	Age (yr)/Sex	Period from onset of symptom to LT (day)	AST/ALT/ALP/γ-GT/TB/PT(INR)	Positive viral marker	Prognosis
1	25/F	30	2,313/795/45/29.5/16.6/2.12	HAV IgM Ab, HBs Ab	Died of graft failure
2	38/M	15	8,686/7,232/181/282/7.1/5.85	HAV IgM Ab	Survived with biliary stricture
3	22/M	78	148/344/123/38/37.1/7.03	HAV IgM Ab, HBs Ab	Survived
4	33/M	9	4,104/4,487/142/12.3/8.2/3.03	HAV IgM Ab, HBs Ab, HBc IgM Ab	Survived
5	47/M	37	8,391/5,449/368/308/8.5/3.56	HAV IgM Ab, HBs Ab	Survived
6	38/M	18	13,623/8,737/328/613/7.0/5.30	HAV IgM Ab, HBs Ab	Died of sepsis
7	45/M	12	207/2,797/238/348/15.8/5.84	HAV IgM Ab, HBs Ab	Survived
8	25/M	17	119/663/121/72/12.8/1.98	HAV IgM Ab, HBs Ab	Survived
9	38/F	68	328/234/65/38/28.0/2/33	HAV IgM Ab, HBs Ab	Survived
10	28/F	10	1,535/1,389/171/102/4.3/1.82	HAV IgM Ab, HBs Ab	Survived
11	42/M	94	310/279/200/83/26.3/1.70	HAV IgM Ab, HBs Ab	Survived
12	40/M	6	5,642/4,958/192/250/10.3/5.88	HAV IgM Ab, HBs Ab	Survived after reLT
13	40/M	6	1,407/1,824/132/153/13.4/5.49	HAV IgM Ab, HBs Ab	Survived
14	26/M	13	823/529/121/265/2.0/1.32	HAV IgM Ab, HBs Ab	Died of necrotizing enterocolitis
15	23/F	7	2,551/2,766/102/136/6.2/3.77	HAV IgM Ab, HBs Ab	Survived
16	37/M	12	13,943/11,191/134/194/5.4/4.2	HAV IgM Ab, HBs Ab	Survived

HAV, hepatitis A virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, γ-glutamyltranspeptidase; TB, total bilirubin; PT, prothrombin time; INR, international normalized ratio; F, female; M, male; IgM, immunoglobulin M; Ab, antibody; HBs, hepatitis B surface; HBC, hepatitis B core.

Wilson disease, and other viral infections, were excluded by clinical history and laboratory data.

The formalin-fixed, paraffin-embedded LT tissue samples were stained with hematoxylin and eosin. All specimens were examined to assess the degree and distribution of hepatocyte necrosis, degree of cholestatsis, portal inflammation, venulitis, and degenerative changes of hepatocytes, such as ballooning degeneration, the presence of Mallory bodies or viral inclusions.

Clinical features

Patients' age ranged from 22 to 47 years (mean, 34.2 years). Males predominated over females (male : female = 11 : 5). The mean period from onset of symptoms to LT was 27 days (range, 7 to 92 days). All patients were IgM anti-HAV-positive at the time of LT. Fifteen cases progressed to hepatic encephalopathy and one case (patient 9) showed continuous prothrombin time prolongation and progressed to hemolytic anemia. Nine cases (56.1%) survived without acute or chronic rejection or complications and three cases (18.8%) died of sepsis with graft failure (patient 1), pancreatitis (patient 6) and necrotizing enterocolitis (patient 14). The other three cases (18.8%, patients 2, 5, and 12) showed acute rejection after transplantation but recovered in 5 months. Biochemical abnormalities varied from mild to severe elevation of AST/ALT (peak AST/ALT range, 148/344 to 13,943/11,191 IU/L) and ALP (peak ALP range, 45 to 368 IU/L).

Histologic findings

The characteristic histopathologic features of the explants are summarized in Table 2. The explanted liver showed massive (Fig. 1A) or zonal necrosis (Fig. 1B). The necrosis was observed either in zone 1 (25.5%) or zones 1 and 2 (31.2%). Cholestasis of variable degree was observed in all cases, mostly moderate (37.4%) to severe (56.3%). The zonal distribution of necrosis was frequently associated with endothelialitis of portal veins (12.5%) (Fig. 2A), central veins (18.8%) (Fig. 2B) or both portal and central veins (43.7%). Degenerative changes of hepatocytes were various in degree and distribution (Fig. 2C). Viral inclusions were suspected in two cases (Fig. 2D). Mallory bodies were identified in two cases. The degree of portal inflammation was none in 6.2%, moderate in 50.5%, and severe in 6.3%. Both bile duct damage and fibrosis were negligible.

DISCUSSION

The characteristic histopathologic features of HAV hepatitis have not been fully established because HAV hepatitis is usually confirmed by serological tests and clinical findings,[5] and the incidence of liver failure requiring LT is lower in acute HAV infection than in other forms of viral hepatitis. Furthermore, previous studies have primarily focused on the pathology of HAV hepatitis in liver biopsy specimens before progression to liver failure.[3,5,6,8]

Table 2. Pathologic features of LT cases with severe HAV hepatitis

Factors	n (%)
Age (yr)	22-47 (mean, 34.2)
Sex	
Male	11 (68.8)
Female	5 (31.2)
Period from onset of symptoms to LT (day)	6-94 (mean, 27)
Necrosis	
Minimal (< 1/3)	6 (37.6)
Moderate (1/3 ≤ and < 2/3)	5 (31.2)
Severe (≥ 2/3)	5 (31.2)
Zonal distribution of necrosis	
Zone 1, 2, 3	1 (6.3)
Zone 1, 2	5 (31.2)
Zone 2, 3	2 (12.5)
Zone 1, 3	1 (6.3)
Zone 1	4 (25.0)
Zone 3	3 (18.7)
Cholestasis	
Mild	1 (6.3)
Moderate	6 (37.6)
Severe	9 (56.1)
Portal inflammation	
None	1 (6.3)
Mild	6 (37.6)
Moderate	8 (50.0)
Severe	1 (6.3)
Venulitis	
Portal vein	2 (12.5)
Central vein	3 (18.8)
Portal and central veins	7 (43.7)
None	4 (25.0)
Viral inclusions	
Present	2 (12.5)
Not identified	14 (87.5)
Mallory bodies	
Present	2 (12.5)
Not identified	14 (87.5)
Prognosis	
Died	3 (18.8)
Survived	13 (81.2)

LT, liver transplantation; HAV, hepatitis A virus.

The most consistently observed features in explanted livers were minimal to severe hepatocyte necrosis with predominant distribution in zone 1 and 2, and unremarkable portal inflammation. The previous studies of liver biopsies reported less conspicuous parenchymal changes, prominent portal inflammation with predominantly plasma cell infiltration, moderate to severe cholestasis and periportal hepatocyte necrosis.[3,5,9] The histopathologic differences might be attributable to multiple factors leading to diverse clinical severity.

However, the zonal distribution of necrosis was similar between the explanted livers in our cases and the biopsy specimens in the previous studies. The hepatic necrosis seems to be associated with venulitis of portal and/or central veins. Vasculitis can be observed in cytomegalovirus or hepatitis C virus (HCV) hepatitis. However in case of hepatitis B virus- or HCV-associated fulminant hepatitis, severe interface hepatitis results in necrosis of periportal hepatocytes.

Severe HAV infection that leads to LT occurs predominantly in young patients (mean age, 34.2 years). This is consistent with the increased seronegativity of anti-HAV IgG in young adults as environmental sanitation improves. According to previous studies on fulminant hepatitis A in our hospital, the mean age of acute hepatitis A patients was 31.4±8.7 years, the mean age of fulminant hepatitis A patients was 31.3±8.3 years, and for transplanted patients, it was 30.3±8.9 years, supporting the idea of predominance in young adults.[7]

The mean period from the onset of symptoms to LT was 27 days, which supports the acute process in severe HAV infection. Therefore, prompt identification of HAV infection is critical in patients with an unusual clinical course to determine better treatment modalities. HAV hepatitis is usually confirmed by

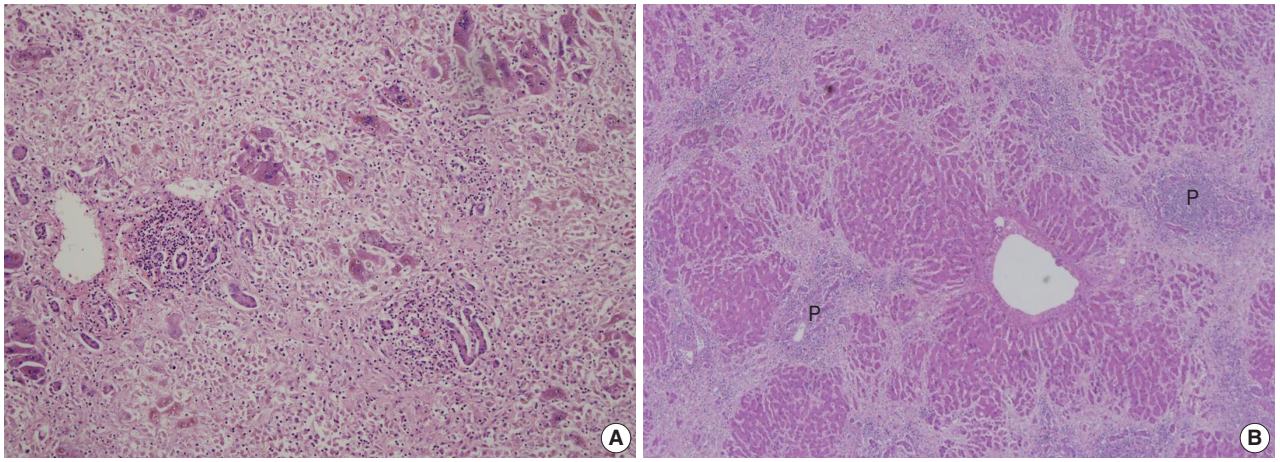

Fig. 1. The explanted livers show massive (A) or zonal (B) necrosis with moderate to severe cholestasis. Zonal necrosis occurs predominantly in periportal area (B). P, portal space.

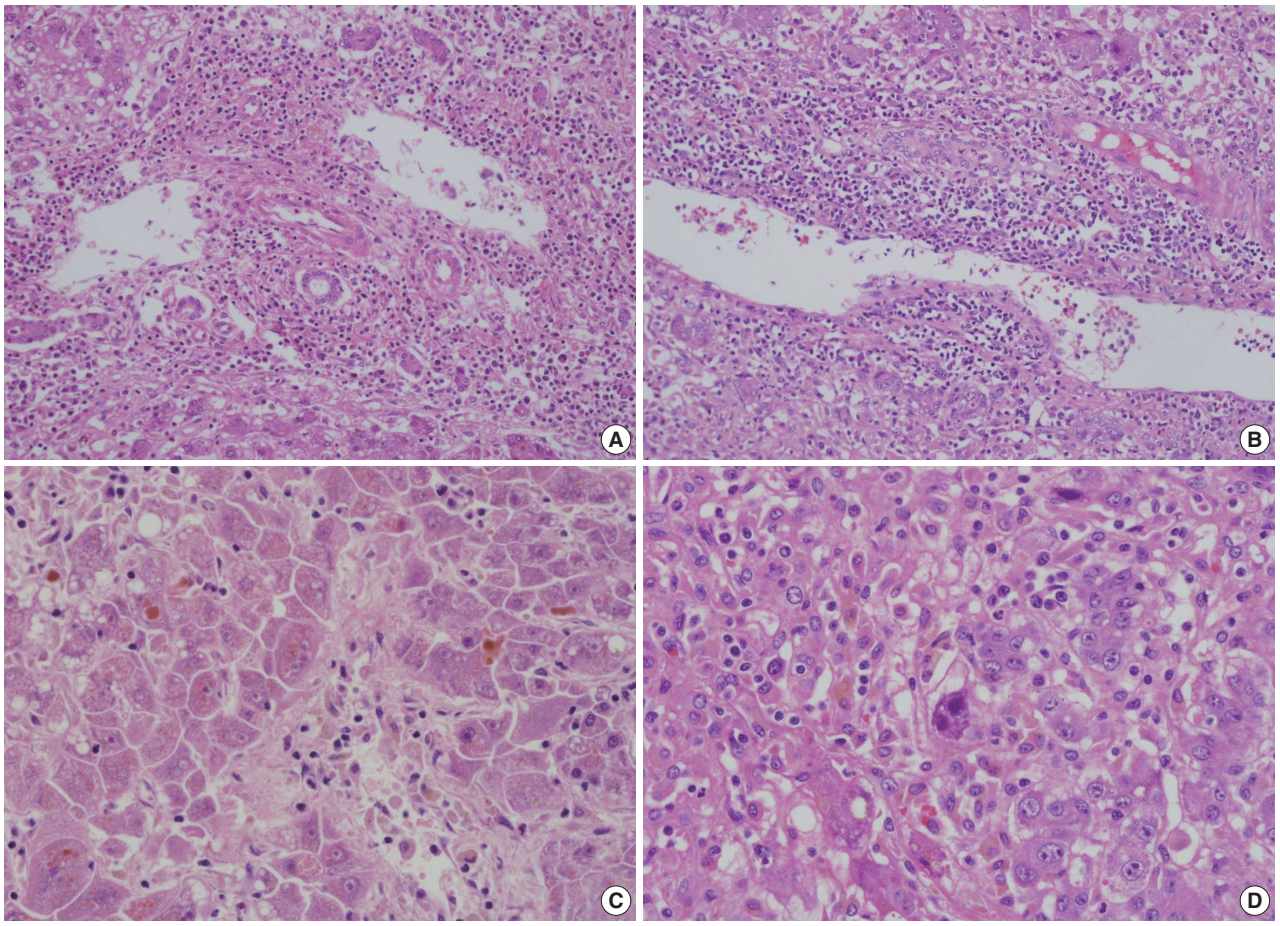

Fig. 2. The zonal distribution of necrosis is associated with endothelialitis of portal veins (A) and central veins (B). Moderate to severe cholestasis, ballooning degeneration of hepatocytes (C) and viral inclusions (D) are identified in the lobule.

serological tests. However, when histologic examination of liver biopsies was done before the result of serologic tests were obtained, the histopathologic features, such as coagulative necrosis of periportal hepatocytes with either portal or central venulitis and smudged large hepatocytes with suspicious viral inclusions may be helpful to in suggesting fulminant HAV hepatitis as a cause of massive hepatic necrosis.

The prognosis of severe HAV hepatitis is poor (survival rate, 81.2%), even after the LT was performed. In contrast, the mortality rate of HAV infection in general is 0.01-0.03%.[10] The much poorer prognosis is due to the fact that we had to assess patients who have undergone LT because of fulminant hepatitis. In addition to the occurrence of HAV infection itself, the incidence of severe HAV infection progressing to FHF has significantly increased during the last five years, reaching 1.7% to 3.5% of all causes of fulminant hepatic failure in Korea.[11,12] Therefore, a multi-center, large scale study on clinicopathologic features of HAV hepatitis is required to establish better treatment and follow-up protocols for severe hepatitis A patients who may finally undergo LT.

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