Liver cirrhosis and hepatocellular carcinoma in hepatic vena cava disease, a liver disease caused by obstruction of inferior vena cava

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Abstract

Purpose Hepatic vena cava disease (HVD), a form of Budd-Chiari syndrome, is caused by the obstruction of hepatic portion of the inferior vena cava. It is a chronic disease characterized by the development of liver cirrhosis (LC) and hepatocellular carcinoma (HCC). As HVD occurred in areas with high incidence of hepatitis B virus (HBV) infection and some patients tested HBsAg positive, it was thought to be the cause of LC and HCC. To assess the pathogenesis of LC or HCC in HVD, a long-term follow-up study was done.

Method Fifty-six patients with HVD diagnosed by ultrasound (US) and confirmed by cavography in 31 and liver biopsy in 34 were followed up for an average of 14.8 ± 9 years. The occurrence of LC was diagnosed by US and/or liver biopsy and that of HCC by US, elevated level of α -fetoprotein, and liver biopsy or fine-needle aspiration cytology, or computed tomographic scan. Other risk factors for LC/HCC such as alcohol use and HBV and hepatitis C virus (HCV) infections were assayed.

Results Forty-four (78.5%) and 6 (10.7%) patients developed cirrhosis and HCC, respectively. LC/HCC occurred more frequently among those who had severe or frequent acute exacerbations ($P = 0.017$), but it was not related to alcohol use or HBV and HCV infections.

Conclusion HVD is independent risk factors for LC and HCC. Severe and/or recurrent loss of hepatocytes caused by hepatic venous outflow obstruction and/or thrombotic obstruction of small radicals of hepatic and portal veins

that occurred during acute exacerbations was considered important in the pathogenesis of LC and HCC in HVD.

Keywords Budd-Chiari syndrome · Membranous obstruction of IVC · Liver cirrhosis · Hepatocellular carcinoma

Introduction

Budd-Chiari syndrome (BCS) is a disorder in which the hepatic venous outflow obstruction (HVOO) causes intra-hepatic venous congestion and portal hypertension. Obstruction of the hepatic portion of the inferior vena cava (IVCO) is a form of BCS commonly seen in Asia [1–9] and Africa [10–12] but rarely reported from western countries [13, 14]. It is a primary disease of the hepatic portion of the IVC caused by bacterial infection. The initial lesion is a localized thrombophlebitis of the hepatic portion of the IVC at the site where hepatic vein joins it, organization of which results in fibrotic narrowing of the vein resulting in stenosis or complete obstruction [15]. It is a distinct clinical entity with well-defined etiology and epidemiology [16, 17] and is designated “hepatic vena cava disease (HVD)” [15].

Reports from areas with high incidence of the disease such as Japan and South Africa showed that it is frequently complicated by liver cirrhosis (LC) and hepatocellular carcinoma (HCC). The reported incidence (Table 1) of LC in the disease had varied from 71% to 100% [2, 3, 5] and that of HCC from 4.6% to 47% [2, 3, 5, 7, 9, 11, 12, 18, 19]. As HVD occurred in areas endemic for hepatitis B virus (HBV) infection [11, 20], some considered HBV infection as the likely cause of LC/HCC in this disease [21]. Findings of equally high incidence of HCC in IVCO

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Table 1 Prevalence of LC and HCC in patients with IVCO from literature

Authors/country	No. of patients With IVCO	LC (%)	HCC (%)	References
Nakamura et al. 1968, Japan	7	7 (100%)	2 (28.5%)	[2]
Nakamura et al. 1968 from Japanese Lit.	64 ^a	64 (100%)	28 (43.7%)	[2]
Takeuchi et al. 1971, Japan	7	5 (71%)	1 (14%)	[3]
Nakamura and Takezawa 1982, Japan	13 ^b	13 (100%)	6 (46%)	[5]
Simson 1982, South Africa	101		48 (43.7%)	[11]
Rector et al. 1985, USA	10		2 (20%)	[14]
Kew et al. 1989, South Africa	15		6 (47.5%)	[12]
Okuda et al. 1995, Japan	148		10 (6.7%)	[18]
Shrestha et al. 1996, Nepal	150		7 (4.6%)	[9]
Dilawari et al. 1999, India	115		9 (7.8%)	[7]

^a Idiopathic IVCO, autopsy report

^b Long term follow-up

in Japan and South Africa, the two countries with four times difference in HBsAg carrier rates, led others to believe that IVCO was etiologically related to HCC [5, 11, 19]. Here, we report a longitudinal study of HVD patients in Nepal, a country endemic for HVD [9] and low HBsAg carrier rate of 0.9% [22], and discuss the pathogenesis of LC/HCC in HVD.

Materials and methods

Fifty-six patients of HVD (29 women and 27 men, mean age = 29 ± 9 years), were followed for an average of 14.8 ± 9.5 years (5–41 years, and a total of 776 patient years). Two patients intended for long-term follow-up who died within 2 years of the onset of the disease were also included. The diagnosis of HVD was based on clinical features and ultrasound (US) examination [23, 24]. It was confirmed by inferior vena cavography [10] in 31, hepatography or transhepatic venography [25] in 5, and liver biopsy in 34 patients. Patients were assessed for other risk factors for cirrhosis and HCC such as alcohol (alcohol consumption of ≥ 40 g of ethanol per day for ≥ 5 years was considered significant), hepatitis B (HBsAg, anti-HBc, and HBV DNA) and hepatitis C virus (HCV) infections (anti-HCV, HCV RNA) by methods described earlier [20].

Liver tests and US examination were done during follow-up. Patients with fever also had white blood cells (WBC) count and blood culture for aerobic organism. Those with ascites had ascitic fluid examination for total and differential WBC count, determination of serum ascitic albumin gradient, and bedside inoculation in blood culture bottle for aerobic microorganisms.

The diagnosis of LC was based either on (i) liver biopsy or (ii) US examination that showed coarse echo-texture of liver parenchyma, with rounded edge and irregular surface with or without the evidence of portal hypertension. HCC was diagnosed in those who developed hypoechoic space-

occupying lesion in the liver parenchyma at follow-up US examination and elevated α -fetoprotein level (>500 ng/ml) or histological or fine-needle aspiration cytological confirmation or computed tomographic (CT) scan.

Results

Liver cirrhosis

Forty-four patients (78.5%), of whom 22 (50%) were women, developed cirrhosis. Cirrhosis was diagnosed by liver biopsy in 22 patients and by US in the remainder. In those in which LC was detected by both US and biopsy, US evidence of LC developed a few years after histological diagnosis. Among those in whom the diagnosis was based on US, 14 had at least one liver biopsy in the past that showed features of HVD. Nine had centrilobular congestion and fibrosis and 5 had fibrosis around central vein and in portal tracts and mild-to-moderate sinusoidal dilatation and sinusoidal fibrosis. LC developed in patients with congestive fibrosis in 2–15 years (average = 8.7 years) and patients with perivenular and portal tract fibrosis in 3–18 years (average = 9 years). In HVD, cirrhosis not only developed at comparatively younger age (among 48%) but also in some developed at early stage of the disease, especially in those with prolonged or severe acute exacerbations (see Tables 2 and 3).

Two patients who rapidly developed LC documented by serial biopsy are described. The first biopsy performed in a 20-year-old man with fever, acute jaundice, hepatomegaly, massive right-side pleural effusion, coliform bacteremia, and localized thrombus in IVC in the cavogram but no ascites showed extensive collapse of the parenchyma and diffuse fibrosis (Fig. 1a). Terminal hepatic venules were not identified and two sublobular hepatic veins were occluded by organized thrombus. Extensive parenchymal necrosis was probably related to the thrombosis of the

Table 2 Age of the HVD patient at the time of development of LC

Age group (years)	Number (%)
0–9	0
10–19	0
20–29	10 (22.7)
30–39	11 (25.0)
40–49	8 (18.1)
50–59	5 (11.3)
60–69	5 (11.3)
70–79	3 (6.8)
80–89	2 (4.5)

Table 3 Duration of hepatic vena cava disease at the time development of LC

Duration of IVCO at the onset of LC (years)	Number of patient (%)
1–9	19 (43.1)
10–19	15 (34.0)
20–29	7 (15.9)
30–39	1 (2.2)
40–49	2 (4.5)

sublobular hepatic veins, which appeared to be related to bacteremia. The second biopsy taken 8 months later showed congestive cirrhosis (Fig. 1b). A repeat cavogram at this stage showed mild IVC stenosis. Cavograms of this patient was reported earlier [26]. The second patient was a young woman who following a bout of severe persistent bacterial diarrhea for several weeks developed acute ascites with moderate elevation of serum bilirubin and alanine aminotransferase (ALT) that persisted for several months. She was nonalcoholic and was negative for seromarkers of HBV and HCV infections. US examination showed localized “thrombophlebitis” of IVC near cavoatrial junction, and liver biopsy showed centrilobular congestion. Despite the features of HVOO, she was treated with tubercular chemotherapy for 9 months by her physician. Nine months later, she went to a hospital in Bangkok for second opinion where a repeat liver biopsy was reported as unremarkable, but because of mildly elevated ALT she was advised further evaluation at 6 months. Cavography performed a year after the onset of the illness at our clinic showed IVC stenosis. During her second visit to the hospital in Bangkok, 6 months after her first visit, CT scan showed features of cirrhosis and a third liver biopsy was done under peritoneoscopy, which confirmed the presence of cirrhosis. The development of cirrhosis within 6 years after the acute disease was documented in another patient who had two serial biopsies. This nonalcoholic patient had persistent intermittent upper abdomen discomfort after meals that

Fig. 1 **a** Congestive fibrosis of the liver with extensive necrosis of parenchyma in zone 2 and 3 with hemorrhage. The hepatic venous radical shows thrombotic occlusion. **b** Repeat liver biopsy of the same patient 1 year later showing congestive liver cirrhosis

followed an acute jaundice 6 months earlier. Examination revealed mild hepatomegaly with mild ALT elevation and complete obstruction of the IVC, which was confirmed by cavography. Liver biopsy specimen showed perivenular and portal tract fibrosis and sinusoidal dilation. Six years later at follow-up, US showed features of cirrhosis and this was confirmed by a second liver biopsy.

Assessment of other risk factors for cirrhosis

Five patients had evidence of HBV infection (1 HBV DNA positive and 4 HBsAg and HBV DNA positive). One HBV-infected patient also had HCV coinfection (anti-HCV and HCV RNA positive). Of these, only one patient was HBsAg and HBV DNA positive before the onset of LC. But this patient had evidence of chronic HVD as indicated by dilated superficial veins in abdomen noted since childhood (Fig. 2). Others developed viral infection later after LC was established and was probably related to multiple

Fig. 2 Dilated superficial veins in body trunk in HVD

blood transfusions they had received in the past for variceal bleeding. The patient positive for HBV DNA and HCV RNA who ultimately developed HCC also had longstanding HVD as suggested by early observation of dilated superficial veins in the body trunk, a long segment of IVC obstruction (Fig. 3a), and a collateral formation around the liver (Fig. 3b), markedly dilated deep collaterals that included azygos vein and a bullet-shaped calcification of the IVC lesion (Fig. 3c).

Thirteen patients had history of alcohol use, but none consumed it in significant amount or duration. Twelve had mild diabetes, but none were obese or hyperlipidemic. Thus, the development of cirrhosis among our patients with HVD was not related to HBV or HCV infection or alcohol use.

Caval lesion in LC

The caval lesion in cirrhotic patients was complete obstruction in 22 (50%), stenosis in 16 (36%), and localized thrombophlebitis in 4 (9%) patients that converted to complete obstruction or stenosis later. The obliterative lesion was more than a few centimeters thick in 20 (45%) and was calcified in four patients. Ostia of middle and left hepatic veins were obstructed in 83% of the patient with complete obstruction and 29% of those with stenosis. An additional observation in US examination was echogenicity of the walls of intrahepatic blood vessels (Fig. 4). This

Fig. 3 a US showing long segment obliteration of IVC and HCC. b US showing dilated collaterals on the surface of the liver. c X-ray showing bullet shaped calcification in IVC and dilated Azygos vein

appeared to be the sonographic counterpart of the histological changes of intimal thickening or thrombotic obliteration of the vessels seen in the liver biopsy of these patients.

Histological features of cirrhosis in HVD

LC in HVD was commonly associated with dense fibrosis (Fig. 5). The lesions noted in liver biopsy before the development of cirrhosis included centrilobular congestion and fibrosis, sinusoidal fibrosis, or massive necrosis with

Fig. 5 Liver cirrhosis in HVD is associated with dense fibrosis

Fig. 4 Thrombosed intrahepatic blood vessels in a patient with IVCO

thrombosis or intimal thickening of sublobular hepatic veins. Necroinflammation of hepatocyte was not observed in any biopsy specimens.

Clinical features of cirrhosis in HVD

Cirrhosis in HVD was associated with mild-to-moderate hepatomegaly in 38 (86%) and splenomegaly in 15 (34%), dilated superficial veins in the body trunk in 15 (34%), varicose veins in the legs in 8 (18%), and chronic changes of venous congestion in the legs in 5 (9%) patients. Extensive deep collaterals were seen in all those for whom cavograms were obtained. Patients had long compensated phase with occasional recurrent acute exacerbations characterized by fever, ascites, or edema of the legs that responded to treatment with antibiotic and diuretic, or variceal bleeding that was commonly well tolerated. The frequency of acute exacerbation had decreased on regular follow-up even in patients with cirrhosis (Table 4). Gynecomastia, spider nevi, testicular atrophy, palmer erythema, cyanosis, clubbing, hyperkinetic circulation, azotemia, encephalopathy, or coagulopathy was uncommon.

Hepatocellular carcinoma

Six (10.7%) patients (3 men), whose age varied from 40 to 70 (mean = 55.5) years, developed HCC during the follow-up period (Table 5). Three patients had mild diabetes and none were alcoholic. Three patients, including one with hepatitis B and hepatitis C viremia, had calcification of the IVC lesion, extensive internal and external collaterals, and changes of chronic venous congestion in the legs suggestive of longstanding IVCO. HCC developed 1–12 years after the development of LC and 2–23 years after the development of IVCO. HCC was first detected by US as a space-occupying lesion. The diagnosis was supported by elevated α -fetoprotein level, CT scan in two, histology in one, and cytology in two patients. Chronological events before the development of HCC are briefly described in Table 6. HCC in HVD showed dense fibrosis around the malignant lesion (Fig. 6a, b).

Table 4 Comparison of HVD patients with and without LC

Liver cirrhosis	Number	Male	Age of onset of the disease	Duration of disease in years	Acute exacerbation		Follow-up period
					Before LC	After LC	
Developed	44	22 (50%)	30.4 $\pm$ 6.1	9.2 $\pm$ 9.7	6.5 $\pm$ 4.5	2.2 $\pm$ 1.7	14.5 $\pm$ 8.8
Undeveloped	12	5 (42%)	29.0 $\pm$ 12.6	10 $\pm$ 12	3.5 $\pm$ 3.2	1.5 $\pm$ 1.7 ^a	15.2 $\pm$ 9.2
<i>P</i> value		NS	NS	NS	0.017	NS	NS

NS not significant

^a Similar period of follow-up

Table 5 HCC in hepatic vena cava disease

Sr. No	Name of patients	Age	Sex	Duration of HVD (years)	Duration of LC (years)	HBsAg	HBVDNA	Anti-HCV	HCV RNA
1	PBT	48	M	30	12	+	+	+	+
2	GBR	70	M	28	2	–	–	–	–
3	TS	61	M	2	1	–	–	–	–
4	TMK	46	F	23	5	–	–	–	–
5	GLB	68	F	6	11	–	–	–	–
6	CMS	40	F	22	4	–	–	–	–

HVD patients who did not develop LC

Twelve patients did not develop LC. HVD was diagnosed in this group by US and confirmed by cavography in 10 and liver biopsy in eight patients. They were followed for 15.2 ± 9.2 years. Six (50%) had complete obstruction, three (25%) had stenosis, and three initially had localized thrombophlebitis that converted to stenosis in one and complete obstruction in two patients. The obstructive lesion in seven (58%) patients was more than a few centimeters thick.

Difference between the patients who developed LC and who did not develop LC

As regards the duration of the disease and the nature of the caval lesion, the two groups with or without cirrhosis were not significantly different. Similarly, the incidence of ascites in these two groups was not significantly different. But those who developed LC had more severe and more frequent episodes of acute exacerbation than the group that did not develop LC (Table 4). The difference becomes more significant ($P = 0.002$) when patients with 10 years or more follow-up were compared.

Discussion

HVD was associated with high incidence of LC and moderate incidence of HCC. Although six patients had hepatitis B viremia, one of which also had hepatitis C viremia, the viral infections had developed later after the development of LC except in one patient. All had clinical evidence of longstanding HVD. Thus, the development of LC was not related to HBV or HCV infection. In addition, because none had history of significant alcohol intake and because the incidence of aflatoxin exposure in Nepal was very low [27], it was assumed that HVD was directly related to the development of LC and HCC in these patients.

Cirrhosis occurred not only in younger age groups (Table 2) but it developed early in the course of the disease (Table 3). Among the eight cases of IVCO also reported by Nakamura et al. [2], the age of five patients at the time of development of cirrhosis was between 24 and 31 years; and of the seven cases reported by Takeuchi et al. [3], it developed within 5 years of the onset of the disease in three. The average age of HCC patients in HVD was also comparatively younger. Fifty percent of our patients with HCC were in their fourth decade, as was 48 patients with HCC with IVCO reported by Simson [11] from South Africa. Gender incidence of patients with LC and HCC in HVD was equal. This was in contrast to other major causes of cirrhosis and HCC such as alcohol use, hepatitis B infection, and hepatitis C infection in which these complications occurred more frequently in male and at later period of life. In HCV infection, the reported interval from blood transfusion to diagnosis of cirrhosis was 20–25 years and the interval between blood transfusion and diagnosis of HCC was about 30 years [28]; the average age of clinical presentation of patients with alcoholic cirrhosis was fifth decade [29].

Pathogenesis of LC/HCC in HVD

Pathogenesis of LC or HCC in HVD was not clear. Unlike in chronic viral infection, there was absence of necroinflammation in HVD, indicating absence of continued liver cell damage. Prolonged congestion that resulted in loss of hepatocytes with failure to regenerate due to continuing high sinusoidal pressure and its replacement by fibrous tissue was assumed to be the mechanism of development of cirrhosis [17, 30–32]. Regenerative nodules formed in such patients with longstanding disease led to the development of venocentric or reversed lobulation cirrhosis [17, 30].

Ascites is a clinical marker of increased sinusoidal pressure in HVOO. Not only the incidence of ascites in the two groups who developed cirrhosis and who did not develop cirrhosis in this study was not significantly

Table 6 Chronology of important clinical events in six HVD patients who developed HCC**I. PBT. Non-alcoholic (Figs. 2 and 3)**

- 1980: at 27 years age: admission to a hospital with prolonged fever and jaundice
- 1981–1988: recurrent episodes of jaundice and fever
- 1988: at 35 years age: admission to a hospital with esophageal variceal bleeding. Dilated superficial veins in body trunk and hepatomegaly. HBsAg: negative
- 1989: at 36 years age: liver biopsy showed LC. HBsAg: negative
- 1989: two episodes of fever, jaundice, ascites, edema legs, and variceal bleeding
- 1990: *admission to our unit*. High fever, deep jaundice, variceal bleed, gross ascites, and edema legs—responded to treatment with blood transfusion, antibiotic, and diuretic. Cavogram confirmed IVCO with extensive internal collaterals. HBsAg and anti-HCV negative
- 2001: at 48 years age: HCC detected. HBsAg: negative, HBV DNA (+). Refused treatment for HCC
- 2003: at 50 years age: fever, hemorrhagic ascites, and *E. coli* peritonitis. HBsAg, HBV DNA, anti-HCV, and HCV RNA (all +). Died

II. GBR. Non-alcoholic, mild diabetic

- 1954: at 26 years age: prolonged fever and jaundice
- 1960: at 32 years age: mild hepato-splenomegaly with normal LFT
- 1990: at 62 years age: *attended Liver Clinic*. US showed IVC stenosis, mild ALT elevation, HBsAg and anti-HCV negative, detected mild diabetes
- 1996: at 68 years age: right hip operation followed by non-healing ulcer at the site of operation. Recurrent episodes of fever
- 1997: at 69 years age: ascites, fever. *E. coli* peritonitis. LC (US)
- 1998: at 70 years age: recurrence of ascites, culture negative neutrocytic ascites
- 1999: at 71 years age: recurrence of ascites, frank hemorrhagic, HCC detected. AFP elevated
- 2000: at 72 years age: death

III. TS. Mild diabetic. Alcohol 120 ml daily for 15 years

- 2000: at 55 years age: intermittent prolonged fever. US: cholelithiasis, normal liver
- 2004: fever, jaundice, mod elevation of serum bilirubin and ALT, US: dilated GB, liver normal
- 2005: *attended Liver Clinic* with h/o prolonged and recurrent jaundice with fever for almost a year
- 2005 December: US & color doppler study: LC, cholelithiasis, IVC stenosis. HBsAg, HBV DNA, anti-HCV, HCV RNA all negative
- 2006: ascites. Klebsiella peritonitis
- 2006: at 61 years age: recurrence of ascites after 5 months, ascites was frank hemorrhagic, HCC detected, confirmed by CT scan, and elevated AFP. Died

IV. TMK. Non-alcoholic

- 1982: at 22 years age: prolonged illness with jaundice following infection after induced abortion
- 1983: recurrence of fever and jaundice for 3 months
- 1984: ascites, leg swelling, hepatomegaly, and dilated superficial veins in body trunk
- 1987: at 27 years: *attended Liver Clinic* with fever, jaundice, ascites, and edema legs. Abortion at 5 months of pregnancy. US: IVCO, obstruction of middle and left hepatic veins. HBsAg negative, anti-HCV: negative
- 1988: abortion at 5 months. Liver biopsy—congestive fibrosis
- 1989–1994: Recurrent episodes of fever with jaundice. Cavogram 1994—complete IVCO with extensive internal collaterals
- 2001: at 41 years age: LC (US). HBsAg, HBV DNA, and anti-HCV: all negative
- 2006: at 46 years age: HCC (US, CT scan, and elevated AFP)
- 2008: marked weight loss, recurrence of ascites. Died

V. GLB. Non-alcoholic and mild diabetic

- 1986–1991: recurrent persistent diarrhea treated with antibiotic
- 1992: US detected cholelithiasis. Detected LC at cholecystectomy, Bx LC. HBsAg, anti-HCV negative
- 1996: bleeding from duodenal ulcer
- 1996: recurrence of persistent diarrhea followed by ascites with bacterial peritonitis. Responded to treatment with antibiotic
- 2002: recurrence of fever, diarrhea, ascites, bacterial peritonitis. *Seen at Liver Clinic*. IVC Stenosis. HBsAg, HBV DNA, anti-HCV, and HCV RNA all negative
- 1992–2003: persistent mild fluctuating elevation of ALT
- 2003: recurrence of fever, hemorrhagic ascites, left-side pleural effusion. HCC detected (US, CT scan, elevated AFP). Died

VI. CMS: non-alcoholic (Fig. 7)

- 1981: at 18 year's age: post-partum pelvic infection—prolonged illness

Table 6 continued

1982–1992: recurrent illness with fever and jaundice
1992: attended hospital with bleeding from leg varices
1994: <i>attended Liver Clinic</i> with fever and jaundice. Had mild hepatomegaly, dilated superficial veins in body trunk. US: IVCO, obstruction of middle- and left-hepatic veins
1997: liver biopsy—congestive fibrosis
1999: at 36 years age: LC (US), Cavogram: Complete IVCO
2003: at 40 years age: US & Biopsy: HCC. Treated with percutaneous ethanol injection
2005: fever <i>E. coli</i> bacteremia, ascites and bacterial peritonitis
2006: at 43 years age: died

Fig. 6 a and b HCC in HVD showing dense fibrosis

different, but 22 of 44 (50%) patients who developed cirrhosis never had clinically evident ascites. Furthermore, three patients who had undergone serial liver biopsy before the development of cirrhosis showed no evidence of prolonged congestion. In addition, the duration it took to develop cirrhosis in nine patients whose earlier liver biopsy showed congestive fibrosis (average = 8.7 years) was not significantly different from those five patients whose earlier liver biopsy showed mild centrilobular and portal tract fibrosis (average = 9 years). These and the observation of rapid development of cirrhosis in a patient mentioned earlier with sublobular hepatic vein obstruction but no clinical evidence of HVOO indicated to the possibility of other additional mechanism(s) in the pathogenesis of LC and HCC in HVD.

Among our patients, cirrhosis developed in patients with more frequent episodes of acute exacerbations ($P = 0.017$). Recurrent acute exacerbation was an important clinical feature of this disease. Acute exacerbation was precipitated by bacterial infection, and it resulted in the deposition of fresh thrombus in the obstructed IVC [33] and thrombotic occlusion of small hepatic and portal veins, which could be demonstrated in the US examination of the IVC and the liver. Many earlier workers had also reported autopsy findings of layers of organized thrombus of different ages in the IVC [3, 34–38] and hepatic vein ostia [35] and had correlated the deposition of fresh thrombus to

Fig. 7 Layers of organized thrombus in IVC and its conversion of IVC into a thick cord like structure and development of HCC

clinical exacerbations [3, 35, 36]. The occurrence of intimal thickening or thrombotic obstruction of small hepatic and portal veins in this disease has been described by Man and Hall [34], Parkar [32], and Kage et al. [38]. The incidence of thrombosis of small branches of portal veins was 20% in the large series reported by Parkar [32]. Thus, acute disease or acute exacerbation was not only associated with HVOO but also caused thrombotic obstruction of small portal and hepatic veins. Ischemic loss of hepatocytes due to portal and hepatic vein obstruction may lead to venoportals cirrhosis [30].

Development of cirrhosis even in chronic heart failure was thought to be due to intrahepatic venous thrombosis rather than to generalized venous congestion [39]. The authors postulated that the thrombus began in sinusoids and propagated to hepatic veins and caused secondary local portal vein thrombosis resulting in ischemia and parenchymal extinction and fibrosis [39]. Thrombosis of small hepatic and portal veins in HVD, however, appeared to be related to bacterial infection and occurred during acute stage or acute exacerbations. When hepatic vein is obstructed, the patency of local portal veins may protect the parenchyma from stasis and congestive damage by allowing arterial flow and pressure to be dissipated by retrograde portal vein flow. Periportal fibrosis commonly noted in the histology of patients with HVD indicated the possible loss of this protective mechanism. Thrombotic obstruction of portal vein radical in this situation was thus likely to cause more damage to hepatocytes. Further occurrence of thrombotic obstruction of the small hepatic and portal veins of the same area was likely to be associated with massive necrosis of the hepatocytes [30].

Among our patients, the likely factors in the development of cirrhosis appeared to be (i) acute massive ischemic loss of hepatocytes due to acute thrombotic obstruction of small hepatic and/or portal veins and (ii) recurrent ischemic loss of hepatocytes related to recurrent acute exacerbation caused by recurrent HVOO and/or recurrent thrombotic obstruction of small radicals of hepatic and/or portal veins. The first mechanism would result in rapid development of cirrhosis within a few months and the second would result in cirrhosis over several years.

Disorganization and rearrangement of hepatocellular DNA play an important role in the molecular pathogenesis of HCC [40]. Any exogenous factor or factors that contribute to chronic, low-grade liver cell damage and mitosis potentially increase the risk of HCC because hepatocytic DNA becomes more susceptible to genetic alteration [41]. Kew et al. [12] postulated that HCC in IVCO was probably caused by some as yet unidentified carcinogen because centrilobular congestion, cell necrosis, regeneration, and fibrosis render hepatocytes susceptible to one or more

environmental carcinogens. According to Okuda [19], the high incidence of HCC in this disease, “higher than in any other liver disease,” was probably due to long duration of chronic liver damage. HVD patients who developed HCC in this series had not only cirrhosis but also clinical history of recurrent acute exacerbations associated with bacterial infection, and US evidence of recurrent deposition of thrombus in IVC suggesting recurrent ischemic loss of hepatocytes. Regenerative activities that followed the recurrent loss of hepatocytes caused by recurrent acute exacerbations appeared to be a possible cause of hepatocarcinogenesis in our HVD patients.

The incidence of congestive cirrhosis and IVCO among 110 cases of HCC for which autopsy was performed in Japan in 1927 was 8% [42], which dropped to 0.09% during 1984–1985 (18-quoted). With improvement in hygiene not only the incidence of HCC due to this disease has dropped but also the disease itself had now almost disappeared from the West and Japan. In addition, the observations of a prolonged survival of HVD patients on conservative treatment alone [2, 43, 44] and improved survival without LC/HCC in the group on regular follow-up with less frequent acute exacerbations than the group with frequent acute exacerbations suggested that it may be possible to prevent LC and HCC in HVD by improving hygiene and nutrition and early and adequate treatment of bacterial infection.

In developing countries, the cause of 25–55% of LC and 42–46% of cases of HCC is unknown [45–50]. High incidence of HVD in Nepal and reports of 2,677 cases of IVCO from four hospitals in China during the period 1981–2003 [51] suggested that HVD is still an important cause of HVOO in developing countries. In addition, it is likely that at least some cases of LC and HCC of unknown etiology in developing countries may be due to HVD. However, the disease is not mentioned in medical text books. As such, it still remains an underdiagnosed entity [52] in developing countries.

In conclusion, HVD was a definite risk factor for LC and HCC. The development of these complications was related to the frequency or severity of acute exacerbations. LC in HVD might occur because of three mechanisms—due to massive ischemic loss of hepatocytes caused by (i) prolonged centrilobular congestion due to prolonged HVOO or (ii) acute thrombotic obstruction of small hepatic and/or portal veins, and more frequently due to recurrent ischemic loss of hepatocytes caused by (iii) recurrent HVOO and/or recurrent thrombotic obstruction of small hepatic and/or portal veins associated with recurrent acute exacerbations. Increased regenerative activities of hepatocytes related to the recurrent ischemic loss of hepatocytes probably led to the development of HCC in HVD.

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