Chapter 4
Pathology of Non-cirrhotic Liver Disease

Masayoshi Kage, Reiichirou Kondou, and Jun Akiba

Abstract The pathology of non-cirrhotic liver diseases causing portal hypertension such as extrahepatic portal obstruction, idiopathic portal hypertension, nodular regenerative hyperplasia, veno-occlusive disease, and Budd-Chiari syndrome is mainly explained.
The interrupted region of the portal circulation and hepatic blood flow pattern vary depending on disease, and several factors are combined in the mechanism of portal pressure elevation in many cases. Accordingly, the pathology varies among diseases and cases, showing diversity. Understanding the pathology of the liver and vascular system in patients with non-cirrhotic liver diseases causing portal hypertension is important to accurately clarify the diverse pathology of those diseases and useful in making a diagnosis and prognosis.

Keywords Portal hypertension · Liver pathology · Extrahepatic portal obstruction (EHO) · Idiopathic portal hypertension (IPH) · Budd-Chiari syndrome (BCS)

4.1 Introduction

The liver receives two vascular supplies: the portal vein and hepatic artery. Abnormal blood flow occurs in the liver in various liver diseases, and the blood flows of the two blood vessels interact with each other in the pathology. In this chapter, the

M. Kage (✉)
Kurume University Research Center for Innovative Cancer Therapy, Kurume, Fukuoka, Japan
e-mail: masakage@med.kurume-u.ac.jp

R. Kondou
Department of Pathology, Kurume University, School of Medicine, Kurume, Fukuoka, Japan
e-mail: kondou_reiichirou@kurume-u.ac.jp

J. Akiba
Department of Diagnostic Pathology, Kurume University Hospital, Kurume, Fukuoka, Japan
e-mail: Akiba@med.kurume-u.ac.jp

K. Obara (ed.), *Clinical Investigation of Portal Hypertension*,
https://doi.org/10.1007/978-981-10-7425-7_4

pathologies of non-cirrhotic liver diseases causing portal hypertension considered important in hepatic aberrant hemodynamics are explained. Portal pressure elevation occurs mainly due to increases in vascular resistance and portal blood flow in a region of the portal system between the portal trunk and inferior vena cava. Various diseases cause portal hypertension, and they are roughly divided into prehepatic, intrahepatic, and post-hepatic occlusions based on the obstructed region. In this chapter, representative diseases of each type, extrahepatic portal obstruction (EHO) as a prehepatic occlusion, idiopathic portal hypertension (IPH), nodular regenerative hyperplasia (NRH), and veno-occlusive disease (VOD) as intrahepatic occlusions, and Budd-Chiari syndrome (BCS) as a post-hepatic occlusion, are reviewed. Liver cirrhosis is not included in this chapter because it is explained in another chapter.

4.2 Extrahepatic Portal Obstruction (EHO)

4.2.1 Concept

In this disease, portal pressure rises due to occlusion of the extrahepatic portal vein including the hepatic hilum. The diseases of unknown and known causes of occlusion of the extrahepatic portal vein are classified as primary and secondary, respectively [1, 2]. In addition to the congenital malformation hypothesis, thrombophlebitis is considered likely as a cause of primary extrahepatic portal obstruction (EHO). The causative diseases of secondary EHO include tumors, blood disease, cholecystitis, cholangitis, and pancreatitis, showing diverse causes. In children, the incidence of thrombophlebitis and infection of the portal system is high, such as omphalitis immediately after birth, neonatal sepsis, and catheter operation-induced infection of the umbilical vein. In EHO, occlusion of the portal trunk results in cavernomatous transformation, which is hepatopetal collateral circulation formed in the hepatic hilum, being characteristic of this disease.

On imaging, development of marked hepatopetal collateral circulation consistent with closure of the extrahepatic portal vein including the hepatic hilum and cavernomatous transformation is observed on ultrasonography, CT, and MRI. The intrahepatic branch of the portal vein and hepatic vein is patent.

This hepatopetal collateral circulation is formed 1–2 weeks after portal trunk occlusion [3]. In an animal experiment using rats with EHO obstruction prepared by ligation of the portal trunk, blood flowed into the peribiliary capillary plexus communicating with the portal vein after ligation [4], the plexus gradually dilated, and cavernomatous collateral circulation formed within 1 week. This hepatopetal collateral circulation originates from a small periportal branch around the head of the pancreas, and it is considered that vascularization is involved in cavernomatous transformation.

4.2.2 Pathological Findings

4.2.2.1 Macroscopic View

Hepatopetal collateral circulation develops in the hepatic hilum area with occlusion of the extrahepatic portal vein, showing cavernomatous transformation. No change is observed on the liver surface (Fig. 4.1a, b). The portal trunk can rarely be confirmed. A large protrusion, concavity, and waving-like irregularity on the liver surface, which are observed in IPH, are present only in a few cases. Micro-cavernomatous transformation may be formed in a moderate-size intrahepatic portal vein region (Fig. 4.2a).

4.2.2.2 Histological View

In the extrahepatic portal vein, occlusion with a thrombus or tumor and severe narrowing are observed. Cavernomatous transformation is caused by outgrowth of many thin-walled vessels (Fig. 4.2b).

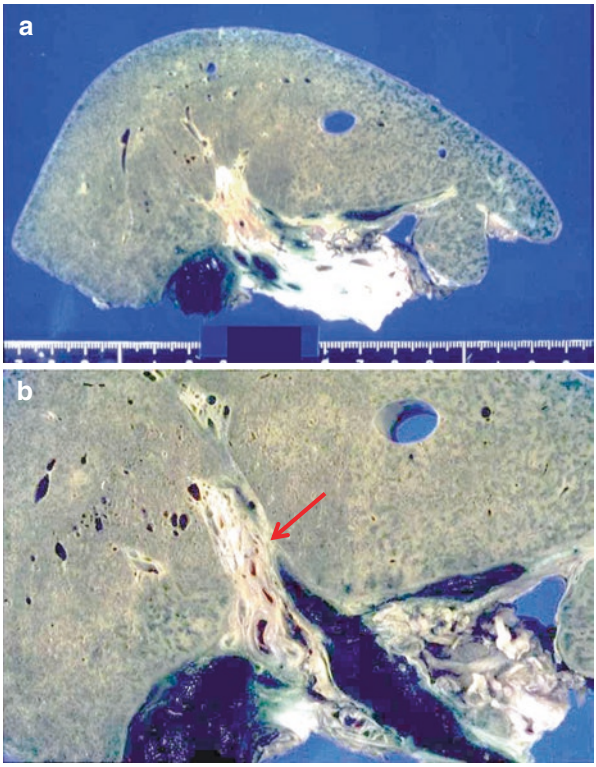

Fig. 4.1 (**a**) A cut surface of the liver of an autopsy case with extrahepatic obstruction (EHO). Cavernomatous transformation is found at the hepatic hilum. Neither cirrhotic nodule nor fibrosis is present. (**b**) Closeup view of the hilum. Many vessels are observed at the cavernomatous transformation (*arrow*)

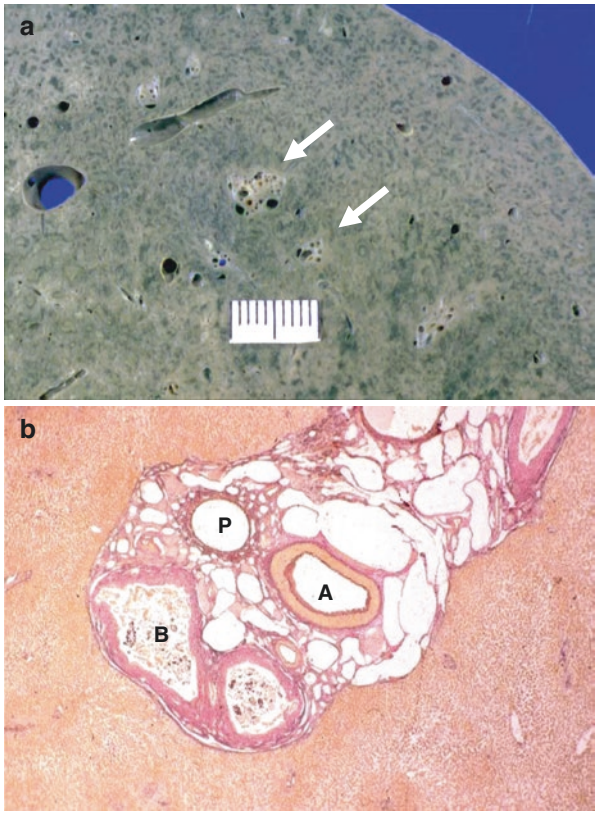

Fig. 4.2 (**a**) A cut surface of the liver of the same EHO case as in Fig. 4.1. Cavernomatous transformation is found in the medium-sized portal tract (*arrow*). (**b**) The histology of the portal tract shows the micro-cavernomatous transformation consists of many thin-walled vessels (EVG stain). *A* hepatic artery, *P* portal vein, *B* bile duct

No finding of liver cirrhosis is observed. Normally, hepatic lobule construction is retained, and the intrahepatic branch of the portal vein is patent, but collapse or narrowing of the portal branch similar to that in IPH may be observed in some cases of EHO.

Some cases show no marked histological change.

4.3 Idiopathic Portal Hypertension (IPH)

4.3.1 Concept

IPH represents diseases in which splenomegaly, anemia, and portal pressure elevation occur but no causative disease, such as liver cirrhosis, occlusion of extrahepatic portal vein/hepatic vein, blood disease, parasitic disease, granulomatous liver disease, or congenital hepatic fibrosis, can be demonstrated [5–7].

Regarding geographical prevalence of IPH, it was previously high in India and developing countries [5], but non-cirrhotic IPH patients have recently decreased worldwide, probably due to improvement of social and environmental conditions.

The main clinical symptoms of this disease are splenomegaly, anemia, portal hypertension, abdominal wall varicosis, and edema. Hematemesis/melena and anemia are observed in about 40% of cases. Esophageal/gastric varix, portal hypertension-associated gastroenteropathy, ectopic varices, and ascites develop in association with portal hypertension, and symptoms of hemorrhagic tendency, liver dysfunction, and hepatic encephalopathy appear [6, 7]. Generally, this disease does not progress to liver cirrhosis; however hepatocellular carcinoma may complicate although it is very rare [5, 7]. Hepatic atrophy may progress to liver failure.

For the cause of this disease, hepatogenic theory, such as intrahepatic peripheral thrombus, splenogeic theory, and abnormal autoimmunity theory have been proposed [5–8].

The hemodynamics of this disease is understood as elevation of portal blood flow resistance by occlusion of the presinusoidal intrahepatic portal vein, and collapse and narrowing of the peripheral branch of the portal vein are considered histopathological findings corresponding to this.

Since this disease frequently develops in middle-aged women, and autoimmune disease is likely to concomitantly develop, abnormal autoimmunity is considered the cause [6]. Regarding the pathological findings of IPH, Nakanuma et al. pointed out that small portal veins and skin findings are similar between patients with scleroderma and those with IPH [9]. They reported that transforming growth factor-β [10] and connective tissue growth factor which are fibrosis-related, and vascular endothelial growth factors, increase in the serum, skin, and the portal vein, attracting attention as a cause of this disease.

4.3.2 Pathological Findings

4.3.2.1 Macroscopic View of the Liver

The liver surface shows waving-like irregularity and small folds in many cases. Atrophy is not noticeable in early-stage IPH, but when the period with illness becomes prolonged, the liver weight decreases, and the overall liver morphology becomes deformed, or the right or left lobe becomes extremely small at the advanced stage [5, 8, 9] (Fig. 4.3). The main branch of the intrahepatic portal vein is thickened and dilated. The intermediate-sized portal vein regions (regions receiving the fifth to sixth branches of the portal vein) fibrously expand and get close to each other or to the liver capsule, and the branch of the portal vein is narrowed. In the peripheral portal vein regions, narrowing of the branches is noticeable, and the portal venous

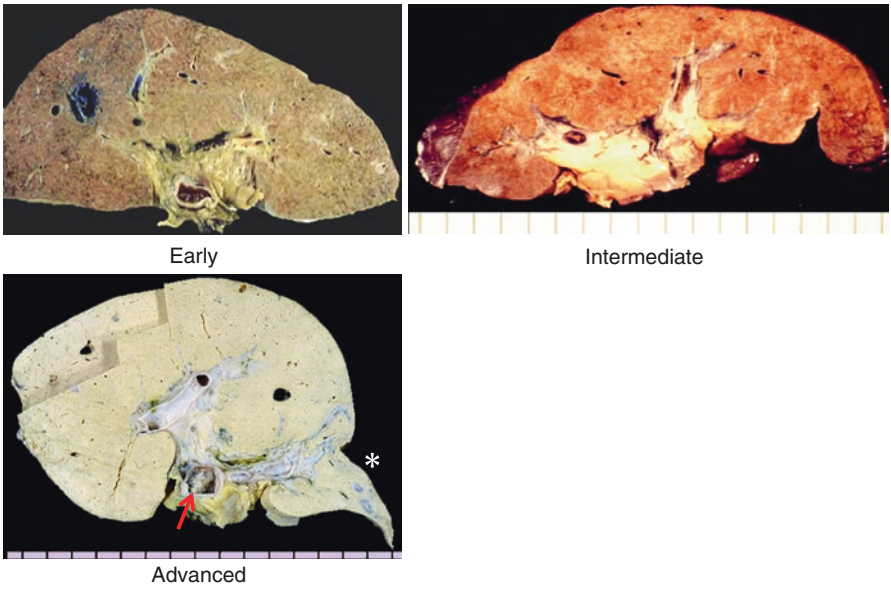

Fig. 4.3 A cut surface of the liver of autopsy cases with idiopathic portal hypertension (IPH) in three stages. Early stage: The liver is mildly atrophic. No cirrhotic nodule is present. Intermediate stage: The atrophy is more pronounced. The shape of the liver is distorted due to irregular extinction of the hepatic parenchyma in the subcapsular region. Advanced stage: The liver is markedly atrophic. A thrombus is observed in the portal vein at the hilum (*arrow*). Note the deformed and shrunken left hepatic lobe (*asterisk*)

regions get close to each other, but depopulation is observed depending on the region. Hyperplastic nodules may be mainly present in the hepatic hilum and around intermediate-size portal vein regions in many cases.

4.3.2.2 Histological View of the Liver

The portal tracts show round fibrous expansion. Extension of irregular fibers into liver parenchyma may occasionally be observed. The wall is markedly thickened, and the lumen is narrowed in the portal branch in many cases. Intermediate-sized portal branches may be accompanied by hyperplasia of smooth muscle layer of the media of the portal vein. In the most peripheral portal tract, narrowing, collapse, and loss of the portal vein branch are observed [5, 8, 9, 11] (Fig. 4.4).

Abnormally dilated vessels with a thin wall (abnormal aberrant vessel) are frequently observed in contact with the portal tract [8, 11] (Fig. 4.5). Generally, inflammatory cell infiltration is not observed.

Hyperplastic nodules are formed by hyperplasia of hepatocytes with no atypia, and lesions of nodular regenerative hyperplasia NRH described in the following Sect. 4.4 and focal nodular hyperplasia (FNH)-like lesions may be present in the histological view.

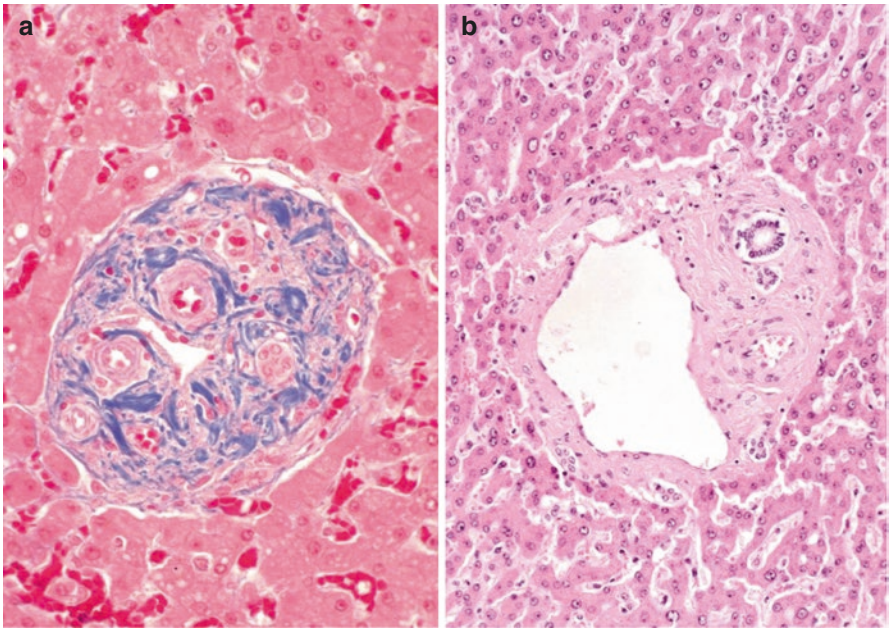

Fig. 4.4 (**a**) A peripheral portal tract shows occlusion of the portal vein (Azan stain). The lumen of the portal vein is not recognized. (**b**) Normal portal tract (H&E stain). The portal vein is patent

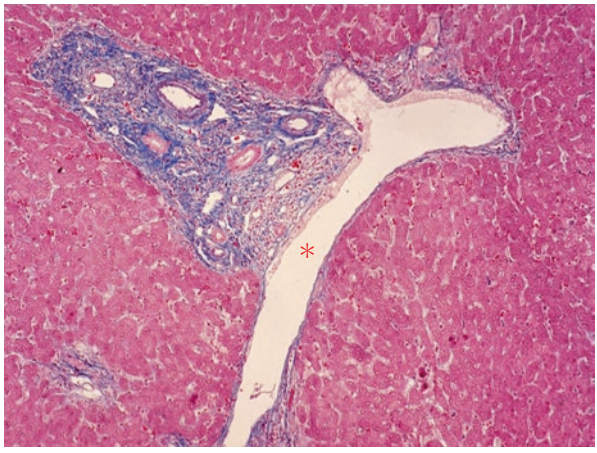

Fig. 4.5 There is a thin-walled vessel, an aberrant pathway (*asterisk*), adjacent to a peripheral portal tract (Azan stain)

4.4 Nodular Regenerative Hyperplasia (NRH)

4.4.1 Concept

NRH is a pathological concept proposed by Steiner in 1959 [12]. Its characteristic is small nodule formation comprised of diffuse hyperplastic hepatocytes, and many

nodules are smaller than hepatic lobules. The difference of NRH from liver cirrhosis is the absence of fibrous septum surrounding nodules observed in liver cirrhosis. These lesions have been expressed as various terms, such as miliary hepatocellular adenomatosis, nodular transformation of the liver, nodular noncirrhotic liver, and non-cirrhotic nodulation [13, 14].

NRH is mainly observed in adults, and it is rare in children. Regarding sex difference, the incidence is slightly higher in females. Normally, NRH develops concomitantly with system disease [12–16]. Steiner [12] found NRH in a congestive liver associated with non-compensatory heart failure, but it is also observed in various diseases. The frequency is high in autoimmune diseases, such as Felty syndrome, rheumatoid arthritis, systemic lupus erythematosus, CREST syndrome, and polyarteritis nodosa, but it also develops with diverse underlying diseases, such as polycythemia vera [16], lymphoproliferative disease, blood disease, congestive heart failure, diabetes, and primary biliarycholangitis. Clinically, it is asymptomatic. In cases in which NRH was incidentally discovered at autopsy, rupture of esophageal varices with portal pressure elevation or hypersplenism was observed in some cases. No or mild abnormality is observed in the liver function on biochemistry.

4.4.2 Pathological Findings of the Liver

The disease concept of NRH is based on the pathological morphology of the liver, and it is simple and clear. However, the pathological morphology of the liver previously reported as NRH has been found diverse, and nodule formation is not necessarily diffuse, or the nodule size is heterogeneous in some cases, i.e., cases not meeting Steiner's criteria [12] are also regarded as NRH.

4.4.2.1 Macroscopic Findings

The typical macroscopic features of NRH are a microgranular liver surface and the presence of diffuse-white or yellowish-white nodules with a homogenous size of 3 mm in the cross-section surface throughout the liver with an appearance similar to that of liver cirrhosis (Fig. 4.6a). When it is carefully observed, a peripheral portal vein region appearing as a dot is present in the center of the nodules. Nodules have a lobule-unit size in typical cases but may reach several centimeters in some cases (Fig. 4.6b).

4.4.2.2 Histological Findings

The hepatic lobular architecture is recognizable. Nodules are mainly formed in peripheral portal tracts, and the nodule size is relatively homogeneous and small, being smaller than the original hepatic lobule size, i.e., recognized as sublobular nodules (Fig. 4.6c). Hepatic cords of hepatocytes forming nodules are two to three

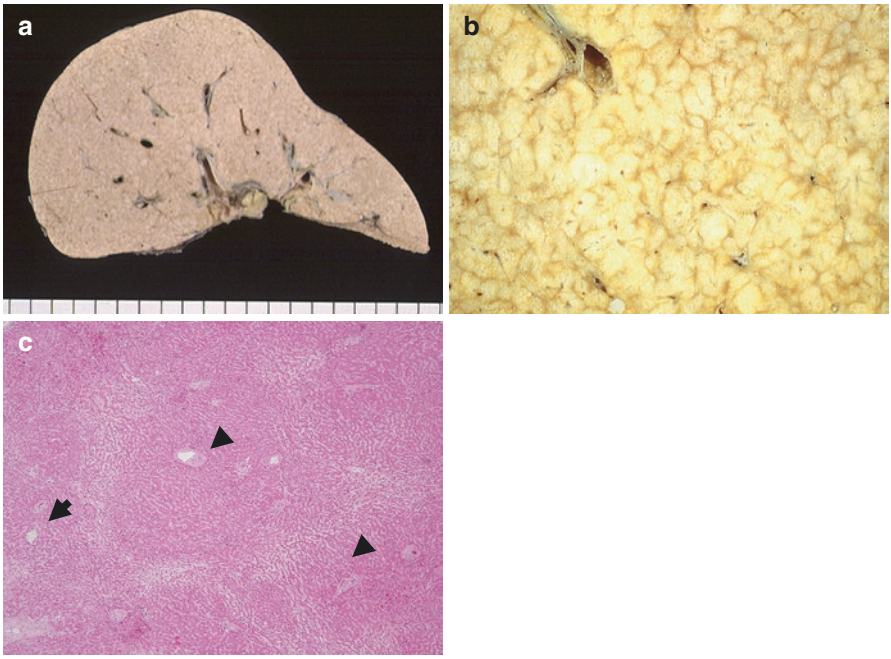

Fig. 4.6 Liver pathology of nodular regenerative hyperplasia (NRH). (**a**) The cut surface of the liver of an autopsy case with NRH, showing diffuse nodular formation. (**b**) Closeup view of (**a**), showing uniform micro-nodules. (**c**) The histology of the nodules. The nodules are composed of hyperplastic hepatocytes and have peripheral portal tracts (*arrow head*) in the center of nodules (H&E stain)

layers thick. No fibrous septum is present between nodules, being different from that in liver cirrhosis. Fibrosis is absent or mild in the portal tracts.

4.5 Veno-Occlusive Disease (VOD)

4.5.1 Concept

In VOD, severe congestion of the liver is caused by non-thrombotic occlusion or stenosis of the hepatic central vein or sublobular vein [17]. However, it was recently considered that the main pathology of VOD is impairment of sinusoidal endothelial cells, subsequent sinusoidal fibrosis and microcirculatory disorder, and resulting impairment of hepatocytes in zones 2–3, and a name, sinusoidal obstructive syndrome (SOS), has been proposed [18].

The causes of VOD are diverse, such as allogeneic bone marrow transplantation, plant alkaloid poisoning, and administration of immunosuppressors and anticancer agents, and the incidence varies depending on the cause [17–19].

Clinically, hepatomegaly, ascites, jaundice, and weight gain are observed, and some cases develop liver failure. The disease course is chronic, and some cases progress to congestive liver cirrhosis. Serologically, endothelial cell markers, such as hyaluronic acid and inflammatory cell markers, such as tumor necrosis factor-alpha (TNF-α), increase in conjunction with increases in ALT, AST, and bilirubin [17–19].

4.5.2 Pathological Morphology of the Liver

4.5.2.1 Macroscopic Findings

The cut surface of the liver with VOD is characteristic where expansion of congestion is irregular and distributed in a geographic pattern. This liver congestion is also observed in right-sided heart failure and BCS, but congestion regularly appears in the centrilobular zone (zone 3) in these diseases, being different from the macroscopic view of VOD.

4.5.2.2 Histological Findings

The lumen of the sublobular or central vein occlusion [17, 18] is associated with congestion and hepatic necrosis (Fig. 4.7a, b). The sinusoid is congested, extravascular leakage of red blood cells into Disse's space occurs, and hepatocytes necrotize. Sinusoidal occlusion results in ischemia, internal sinusoidal pressure elevation, and fragmentation of hepatic cords. Fragmented hepatocytes further promote circulatory disorder, causing reflux into the portal vein and embolism of the damaged central vein. Occlusion of the central vein is not observed in some cases of VOD (Fig. 4.7a). It has been reported that the occlusion was observed in 55% of

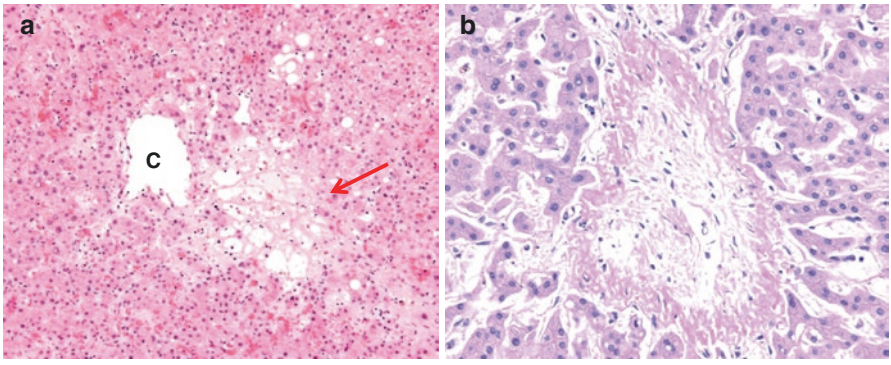

Fig. 4.7 Liver histology of veno-occlusive disease. (**a**) An indistinct area of focal hepatocyte necrosis (*arrow*) near the patent central vein (**c**). (**b**) A completely occluded sublobular hepatic vein

mild-moderate VOD cases and 75% of severe VOD cases among autopsied cases clinically diagnosed as VOD [17]. As described above, occlusion of the central vein is not a universal feature of VOD.

4.6 Budd-Chiari Syndrome (BCS)

4.6.1 Concept

BCS is defined as a disease developing symptoms of occlusion or stenosis of the three main trunks of the hepatic vein or hepatic inferior vena cava [20].

BCS is divided into cases with a clear cause such as blood coagulation disorder including polycythemia vera and protein S deficiency, thrombus formation in the hepatic vein or inferior vena cava induced by oral contraceptive ingestion, and tumor embolism with hepatocellular carcinoma and kidney cancer, and idiopathic cases of unknown cause. In Western countries, the cause of BCS is clear as occlusion of a thick hepatic vein in most cases [21], whereas most cases are idiopathic in Japan [22] and developing countries such as South Africa [23] and Nepal [24], where the hepatic inferior vena cava is occluded in many cases.

Regarding clinical symptoms, some cases rapidly develop symptoms such as fever, abdominal pain, and ascites, while others become chronic with unclear onset time of symptoms [24]. When the course becomes chronic, congestive liver progresses to congestive liver fibrosis and then liver cirrhosis. Important concomitant diseases are hepatocellular carcinoma and portal hypertension. In portal hypertension, esophageal varices, splenomegaly, and ascites develop.

4.6.2 Cause and Pathological Morphology of Obstruction of the Inferior Vena Cava and Hepatic Vein

In idiopathic BCS described above, the inferior vena cava in the hepatic region is occluded in many cases. This inferior vena cava occlusion was conventionally called membranous obstruction of the inferior vena cava (MOVC) based on its shape, but the occluded region and its morphology are diverse, the shape of obstruction is far different from thin "membrane" in some cases, and occlusion extends to a 2–3 cm in length or is funnel-shaped in other cases [22, 25]. Thus, the morphology of MOVC is diverse, and the body of the "membrane" was organized thrombus in our autopsy cases on pathological examination [25] (Fig. 4.8). Not all organized thrombi were old, but various old and new thrombi were coexisting, and recanalization of thrombus, calcification, and hemosiderin deposition were observed. It is likely that MOVC is derived from acquired thrombus formation in addition to congenital malformation, and Shrestha et al. reported a study supporting this from Nepal [24].

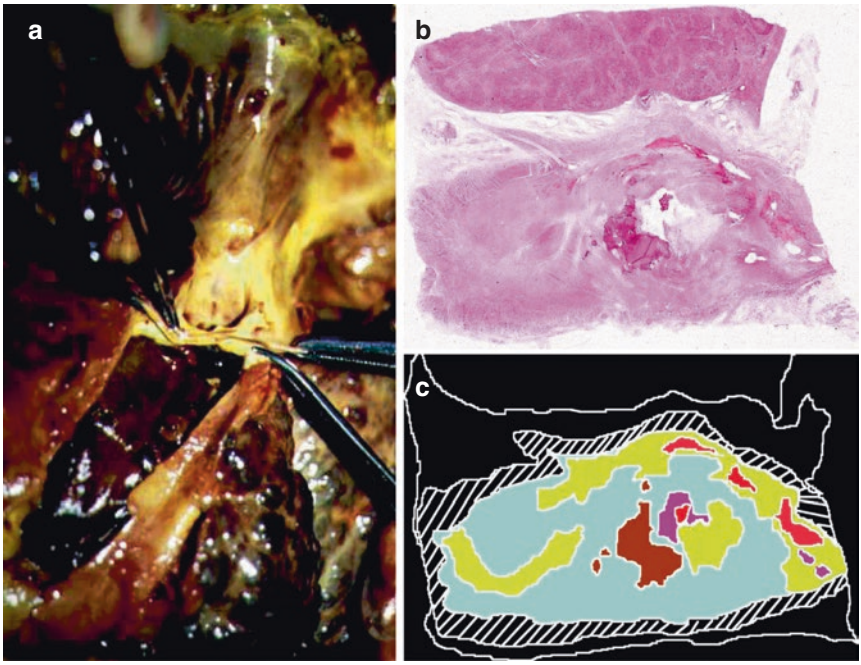

Fig. 4.8 (**a**) Gross appearance of membranous obstruction of the inferior vena cava (IVC) at the hepatic portion in an autopsy case with Budd-Chiari syndrome. The membrane, 2 mm in thickness, is picked by the forceps. Asterisk: fresh thrombus in the IVC. (**b**) The histology of the membrane at the IVC. (**c**) Schema of the histology of the membrane in (**b**). The membrane of the IVC is composed of thrombus in the diverse process of the organization including calcification and recanalization

The characteristics of the epidemiology and clinical view of MOVC in Nepal are background factors, such as malnutrition and alcoholism, being of low socioeconomic status in regions with poor hygiene conditions, and MOVC frequently develops with bacterial infection. Causative bacteria, such as *Escherichia coli* and *Staphylococcus*, were confirmed by blood culture in about 1/3 of cases. It is assumed that infection causes thrombophlebitis of the hepatic inferior vena cava and forms MOVC as the outcome of organized thrombus.

4.6.3 Pathological Morphology of the Liver

4.6.3.1 Macroscopic View

Acute or chronic congestive hepatic lesions develop. The grade and expansion of congestion or progression of fibrosis vary among patients. In acute cases, congestive hepatomegaly develops. Long-term cases progress to congestive hepatic fibrosis and then congestive liver cirrhosis.

4.6.3.2 Histological View

In acute cases, sinusoidal congestive dilation and necrosis of hepatocytes are observed in the central zone of hepatic lobules, and thrombotic obstruction of branches of the hepatic vein is often observed in a wide range of acute fetal cases. In chronic cases, fibrosis advances from the central zone of hepatic lobules and results in reversed lobulation due to bridging fibrosis between the central veins (Fig. 4.9). Reversal of the hepatic lobular structure represents a state in which the portal vein region is present in the center of the hepatocyte population surrounded by the fibrous band. Obstruction of the hepatic vein branch with thrombus is often observed, but the grade and expansion vary among cases.

In BCS, benign hepatic hyperplastic nodules and hepatocellular carcinoma may be observed [21–23, 25]. The association of the frequency and cause of hyperplastic nodules with carcinogenesis in the liver has not been sufficiently clarified. Nodular lesions similar to FNH and NRH are also observed even in early congestive liver. Regarding the cause of hyperplastic nodules, FNH-like nodules or NRH are assumed to be formed due to abnormal intrahepatic circulation based on its histological findings [21].

In idiopathic BCS, concomitant hepatocellular carcinoma frequently develops. According to Kew et al. [23] from South Africa, the frequency of MOVC in all liver

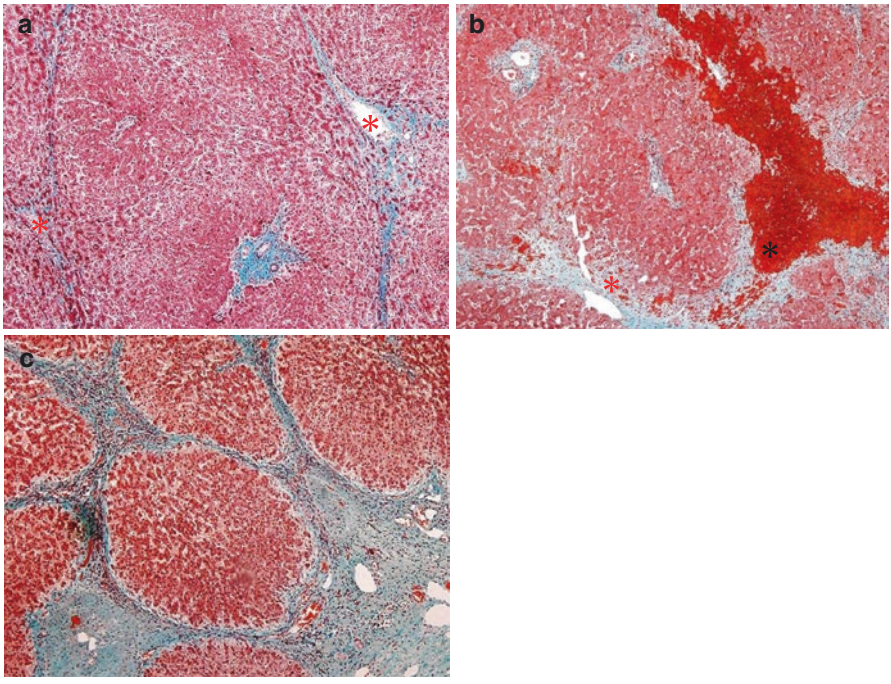

Fig. 4.9 Liver histology of chronic passive congestion in Budd-Chiari syndrome (Azan stain). (**a**) Mild fibrosis starts from the central zone (*asterisk*). (**b**) Reversed lobulation: Bridging fibrosis between the central zones (asterisk) to form a nodular change. (**c**) Congestive liver cirrhosis

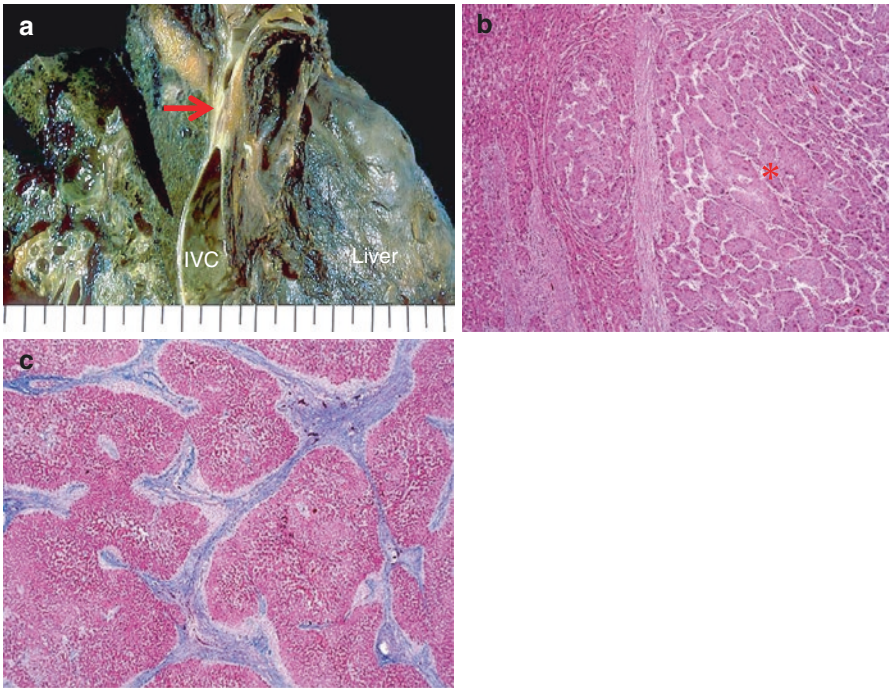

Fig. 4.10 (**a**) Gross appearance of an autopsy case with Budd-Chiari syndrome with obstruction of the IVC (*arrow*). (**b**) The liver histology shows complication of hepatocellular carcinoma (*asterisk*). (**c**) Non-cancerous liver shows chronic congestive fibrosis (Azan stain)

cancer cases was 3.7% (6/166) in black liver cancer patients. They organized references concerning MOVC in South Africa and observed that the frequency of liver cancer was high (43.5%; 57 of 131 MOVC cases including their patients). In Japan, Nakamura et al. [26] reported that the frequency of concomitant liver cancer was high (42%). Thus, BCS is as high a risk factor for liver cancer as viral hepatitis.

The non-cancer region appears like liver cirrhosis in most BCS patients with concomitant liver cancer, but there is also a risk of developing liver cancer from the state of hepatic fibrosis (Fig. 4.10).

The involvement of hepatitis virus in carcinogenesis in the liver with MOVC has not been emphasized in any previous report.

References

1. Sarin SK, Sollano JD, Chawla YK, Amarapurkar D, Hamid S, Hashizume M, Jafri W, Kumar A, Kudo M, Lesmana LA, Sharma BC, Shiba SG, de Silva HJ, Members of the APASL Working Party on Portal Hypertension. Consensus on extra-hepatic portal vein obstruction. Liver Int. 2006;26:512–9.
2. Kunio O, Aoki H. Extrahepatic portal vein obstruction. In: Okuda K, Benhamou JP, editors. Portal hypertension. Tokyo: Springer; 1991. p. 365–79.

3. Ohnishi K, Okuda K, Ohtsuki T, et al. Formation of hilar collaterals or cavernous transformation after portal vein obstruction by hepatocellular carcinoma. Observations in ten patients. Gastroenterology. 1984;87:1150–3.
4. Cho KJ, Lunderquist A. The peribiliary vascular plexus: the microvascular architecture of the bile duct in the rabbit and in clinical cases. Radiology. 1983;147:357–69.
5. Okuda K, Nakashima T, Okudaira K, et al. Liver pathology of idiopathic portal hypertension. Comparison with non-cirrhotic portal fibrosis of India. Liver. 1982;2:176–92.
6. Dhiman RK, Chawla Y, Vasishta RK, et al. Non-cirrhotic portal fibrosis (idiopathic portal hypertension): experience with 151 patients and a review of the literature. J Gastroenterol Hepatol. 2002;17:6–16.
7. Siramolpiwat S, et al. Idiopathic portal hypertension: natural history and long-term outcome. Hepatology. 2014;59:2276–85.
8. Okudaira M, Ohbu M, Okuda K. Idiopathic portal hypertension and its pathology. Semin Liver Dis. 2002;22:59–71.
9. Nakanuma Y, Sato Y, Kiktao A. Pathology and pathogenesis of portal venopathy in idiopathic portal hypertension: hints from systemic sclerosis. Hepatol Res. 2009;39(10):1023–31. https://doi.org/10.1111/j.1872-034X.2009.00555.x.
10. Kitao A, Sato Y, Sawada-Kitamura S, et al. Endothelial to mesenchymal transition via transforming growth factor-beta1/Smad activation is associated with portal venous stenosis in idiopathic portal hypertension. Am J Pathol. 2009;175(2):616–26. https://doi.org/10.2353/ajpath.2009.081061.
11. Ohbu M, Okudaira M, Watanabe K, et al. Histopathological study of intrahepatic aberrant vessels in cases of noncirrhotic portal hypertension. Acta Hepatol. 1994;20:302–8.
12. Steiner PE. Nodular regenerative hyperplasia of the liver. Am J Pathol. 1959;35:943–53.
13. Wanless IR. Micronodular transformation (nodular regenerative hyperplasia) of the liver: a report of 64 cases among 2500 autopsies and a new classification of benign hepatocellular nodules. Hepatology. 1990;11:787–97.
14. Stromeyer FW, Ishak KG. Nodular transformation (nodular regenerative hyperplasia) of the liver-a clinico-pathologic study of 30 cases. Hum Pathol. 1981;12:60–71.
15. Nakanuma Y. Nodular regenerative hyperplasia of the liver: retrospective survey in autopsy series. J Clin Gastroenterol. 1990;12:460–5.
16. Wanless IR, Goldwin TA, Allen F, et al. Nodular regenerative hyperplasia of hematologic disorders: a possible response to obliterative portal venopathy-a morphometric study of nine cases with hypothesis on the pathogenesis. Medicine. 1980;59:367–79.
17. Shulman HM, Fisher LB, Schoch HG, et al. Veno-occlusive disease of the liver after marrow transplantation: histological correlates of clinical signs and symptoms. Hepatology. 1994;19:1171–81.
18. DeLeve LD, Shulman HM, McDonald GB. Characterization of a reproducible rat model of hepatic veno-occlusive disease. Hepatology. 1999;29:1779–91.
19. McDonald GB, Sharma P, Matthews D, et al. Venoocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. Hepatology. 1984;4:116–22.
20. Valla DC. The diagnosis and management of the Budd-Chiari syndrome: consensus and controversies. Hepatology. 2003;38:793–803.
21. Tanaka M, Wanless I. Pathology of the liver in Budd-Chiarisyndrome: portal vein thrombosis and the histogenesis of veno-centric cirrhosis, veno-portal cirrhosis, and large regenerative nodule. Hepatology. 1998;27:488–96.
22. Okuda K. Membranous obstruction of the hepatic portion of the inferior vena cava. Etiology and relation to hepatocellular carcinoma. Gastroenterology. 1982;82:376–9.
23. Kew MC, McKnight A, Hodkinson J, et al. The role of membranous obstruction of the inferior vena cava in the etiology of hepatocellular carcinoma in Southern African blacks. Hepatology. 1989;9:121–5.

24. Shrestha SM, Okuda K, Uchida T, et al. Endemicity and clinical picture of liver disease due to obstruction of the hepatic portion of the inferior vena cava in Nepal. J Gastroenterol Hepatol. 1996;11:170–9.
25. Kage M, Arakawa M, Kojiro M, et al. Histopathology of membranous obstruction of the inferior vena cava in the Budd-Chiari syndrome. Gastroenterology. 1992;102:2081–90.
26. Nakamura T, Nakamura S, Aikawa T, et al. Obstruction of the inferior vena cava in the hepatic portion and the hepatic veins. Angiology. 1968;19:479–98.