Chapter 1
Pathology of Liver Cirrhosis in Japan

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Abstract Liver cirrhosis is defined anatomically by the presence throughout the liver of fibrous septa that subdivide the parenchyma into nodules. Cirrhotic nodules often accompany the loss of parenchyma known as parenchymal extinction. Cirrhosis is considered not as an independent disease entity but as a pathologic feature of the terminal stage of various chronic progressive liver diseases. Portal hypertension is the most important complication of cirrhosis, which is caused by obstruction of portal and hepatic veins and arteriovenous shunts in fibrous septa.

Keywords Fibrous septa · Cirrhotic nodule · Vascular obstruction · Parenchymal extinction · Portal hypertension

1.1 Introduction

Cirrhosis is a serious condition where normal liver tissue is replaced by multiple regenerative nodules that are surrounded by fibrous connective tissue (fibrous septum) throughout the liver. Hepatocytes are persistently injured, followed by excessive deposition of extracellular matrix, and regeneration of hepatocytes progresses in an incomplete fashion, resulting in formation of regenerative nodules (Figs. 1.1 and 1.2). The hepatic vasculature is strikingly transformed by the structural changes that occur in cirrhosis. Cirrhosis is considered not as an independent disease entity but as a pathologic feature of the terminal stage of various chronic progressive liver diseases.

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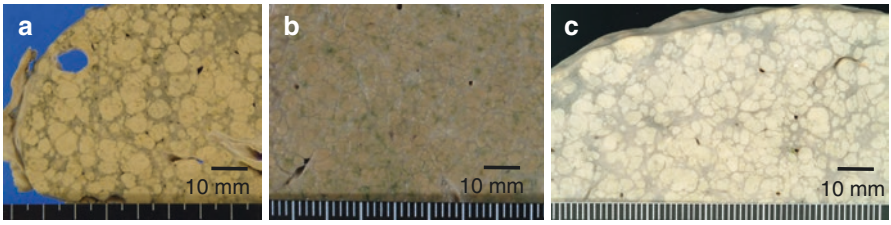

Fig. 1.1 (**a**) HBV-related macronodular cirrhosis. (**b**) Alcoholic micronodular cirrhosis. (**c**) HCV-related mixed nodular cirrhosis

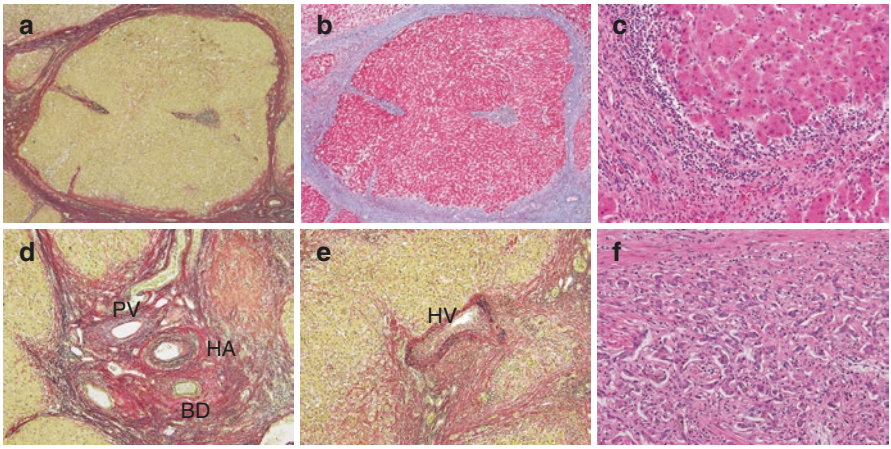

Fig. 1.2 Regenerative nodule separated by fibrous septa in the cirrhosis associated with autoimmune hepatitis. (**a**) Elastica van Gieson stain. (**b**) Azan-Mallory stain. (**c**) Interface hepatitis persists at the periphery of fibrous septum. Obliteration of portal vein (**d**, PV) in the portal tract and hepatic vein (**e**, HV) involved by fibrous septum. (**f**) A nodule is occupied by proliferating bile ductules, which are surrounded by rich collagen fibers. *HA* hepatic artery, *BD* bile duct. (**d**, **e**) Elastica van Gieson stain; (**c**, **f**) hematoxylin-eosin stain

1.2 Definition and Classification

1.2.1 Definition

Cirrhosis is defined anatomically by the presence throughout the liver of fibrous septa that subdivide the parenchyma into nodules [1], as shown in Figs. 1.1 and 1.2. Fibrous septum varies in width. Cirrhotic nodules often accompany the loss of parenchyma known as parenchymal extinction [2].

1.2.2 Classification

1.2.2.1 Classification of Cirrhosis According to Morphology

1. Macronodular Cirrhosis
   Almost all regenerative nodules are composed of large nodules, measuring over 3 mm in diameter (Fig. 1.1a).
2. Micronodular Cirrhosis
   Nodules measure less than 3 mm in diameter (Fig. 1.1b).
3. Mixed Nodular Cirrhosis

Some parts of the liver show micronodular appearance, while other parts show macronodular pattern (Fig. 1.1c). The size of each nodule varies from 1 to 10 mm.

1.2.2.2 Classification of Cirrhosis According to Pathogenesis

It is reported that there are about 400,000–500,000 patients with cirrhosis in Japan, and main etiologic factors are hepatitis C virus in 60% (Fig. 1.1c), hepatitis B virus in 15% (Fig. 1.1a), and alcohol in 15% (Fig. 1.1b) [3]. The annual number of deaths from cirrhosis is about 17,000 [1]. Causes of cirrhosis are shown in Table 1.1.

1. Chronic Viral Hepatitis
   Hepatitis B virus replication often diminishes as cirrhosis advances; therefore, necroinflammatory alteration is attenuated in the fibrous septum, and regenerative nodules get larger, and the fibrous septum becomes narrower in width (Fig. 1.1a). On the other hand, hepatitis C virus replication usually

Table 1.1 Causes of cirrhosis

1. Chronic viral hepatitis, especially chronic hepatitis B and C
2. Autoimmune hepatitis
3. Alcoholic liver disease
4. Nonalcoholic steatohepatitis (NASH)
5. Metabolic disorders
• Hemochromatosis
• Wilson's disease
• Others
6. Biliary cirrhosis
• Biliary atresia
• Primary biliary cirrhosis/cholangitis (PBC)
• Primary sclerosing cirrhosis (PSC)
7. Chronic congestion
• Chronic heart failure
• Budd-Chiari syndrome
8. Cryptogenic cirrhosis

increases as cirrhosis develops; therefore, interface hepatitis gets more severe, and the fibrous septum becomes wider in width (Fig. 1.1c).

2. Autoimmune Hepatitis

   Although autoimmune hepatitis (AIH)-related cirrhosis often lacks pathognomonic findings for AIH, some nodules may show interface hepatitis infiltrated by plasma cells (Fig. 1.2a–f).

3. Alcoholic Cirrhosis

   Pericellular fibrosis precedes the cirrhotic phase in alcoholic liver disease. To keep drinking alcohol suppresses regeneration of hepatocytes, pericellular fibrosis gradually expands, and hepatocytes within fibrous meshwork become atrophic or lost. Thus, central-central or portal-central bridging fibrosis is formed, followed by division of liver parenchyma, nodular formation, and eventually cirrhosis (Fig. 1.1b).

4. Nonalcoholic Steatohepatitis

   Nonalcoholic steatohepatitis (NASH)-related cirrhosis morphologically resembles alcoholic cirrhosis, and it is difficult to distinguish between the two. Fat droplets often disappear or markedly decrease (Fig. 1.3a). There may remain ballooning hepatocytes and pericellular fibrosis in some nodules (Fig. 1.3b).

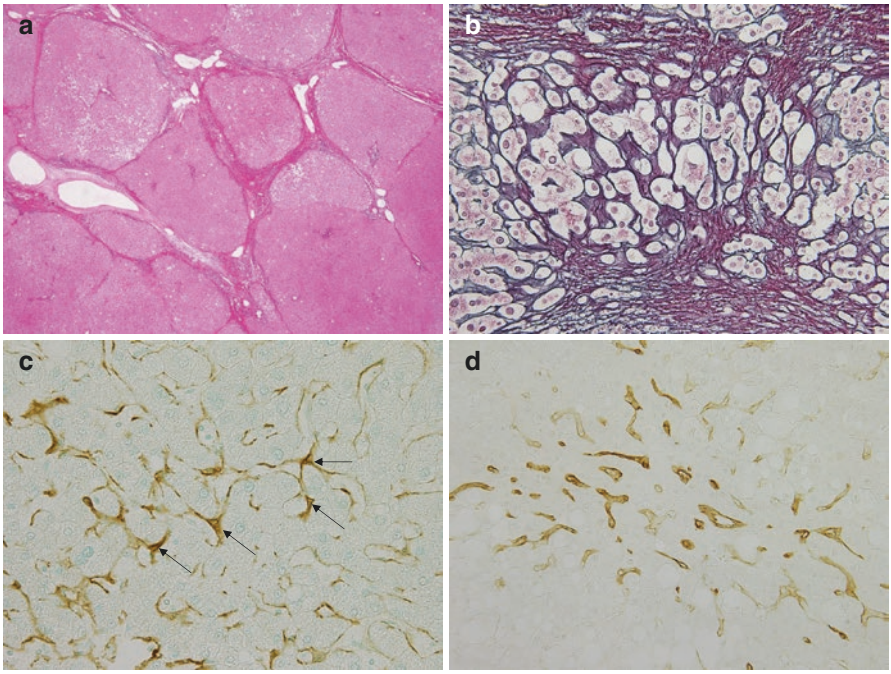

Fig. 1.3 Cirrhosis associated with nonalcoholic steatohepatitis (NASH). (**a**) Nodules vary in size, and fatty change is inconspicuous. (**b**) Ballooning hepatocytes are focally observed with pericellular fibrosis. (**c**) Activated hepatic stellate cells are dispersed in the space of Disse (arrows). (**d**) Capillarization of sinusoids is seen within the nodule. (**a**) Hematoxylin-eosin stain; (**b**) silver impregnation stain; immunostaining for α-smooth muscle actin (**c**) and CD34 (**d**)

Hepatic stellate cells are activated (Fig. 1.3c), and capillarization of sinusoids is shown within a nodule (Fig. 1.3d).

5. Metabolic Disorders

   Cirrhosis caused by Wilson's disease shows characteristic macronodules measuring about 10 mm (Fig. 1.4a). Galactosialidosis is an autosomal recessive lysosomal storage disorder [4] and exhibits micronodular cirrhosis with fat droplet accumulation (Fig. 1.4c, d). Diastase-digested periodic acid (PAS) stain reveals diastase-resistant PAS-positive storage materials in Kupffer cells (Fig. 1.4e).

6. Biliary Cirrhosis

   This type of cirrhosis includes biliary atresia, primary biliary cirrhosis/cholangitis (PBC), and primary sclerosing cholangitis (PSC) [5]. Early phase of PBC is often characterized by "garland" or "jigsaw puzzle"-like regenerative nodules (Fig. 1.5a, b). Nodules become rounded, as the cirrhosis stage advances.

7. Chronic Congestion

   This type of cirrhosis is caused by Budd-Chiari syndrome and right heart failure. Progress in liver fibrosis to cirrhosis is slow, and histology exhibits "reversed lobulation" pattern, in which central-central bridging fibrosis encircles a nodule, and a portal tract locates in the center of the nodule (Fig. 1.5c, d).

8. Cryptogenic Cirrhosis

   There is firm epidemiological data to suggest that NASH should be a dominant cause of cryptogenic cirrhosis in Japan as well as in many areas of the

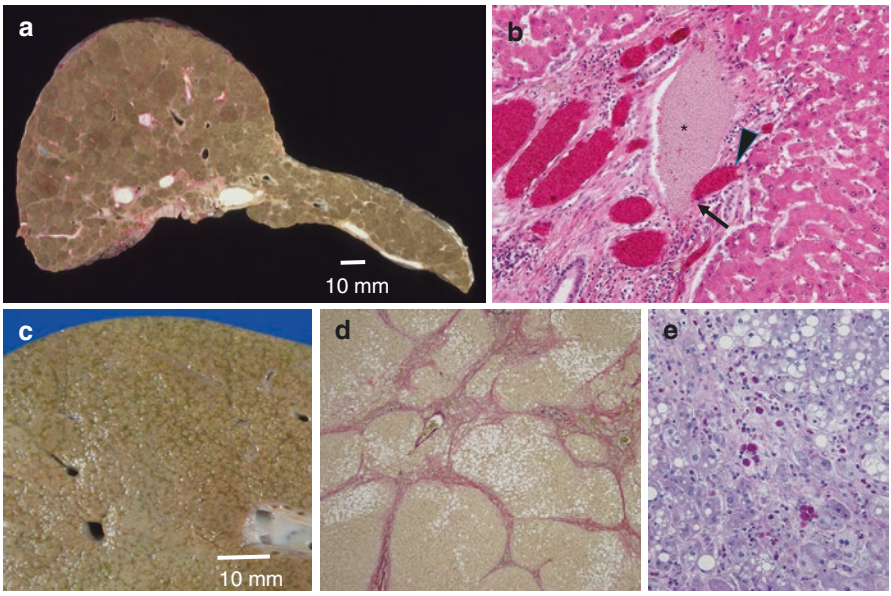

Fig. 1.4 Cirrhosis associated with metabolic disorders. (**a**, **b**) Wilson's disease. Large nodules measuring about 10 mm are shown. White- and red-colored materials are contrast medium injected into portal vein and hepatic artery at autopsy. (**b**) Direct interconnection (arrow) is found between portal vein (asterisk) and arteriolar branch (arrow head). (**c**, **d**, **e**) Micronodular cirrhosis with fat droplet accumulation caused by galactosialidosis. (**d**) Elastica van Gieson stain; (**e**) diastase-digested PAS stain reveals diastase-resistant PAS-positive storage materials in Kupffer cells

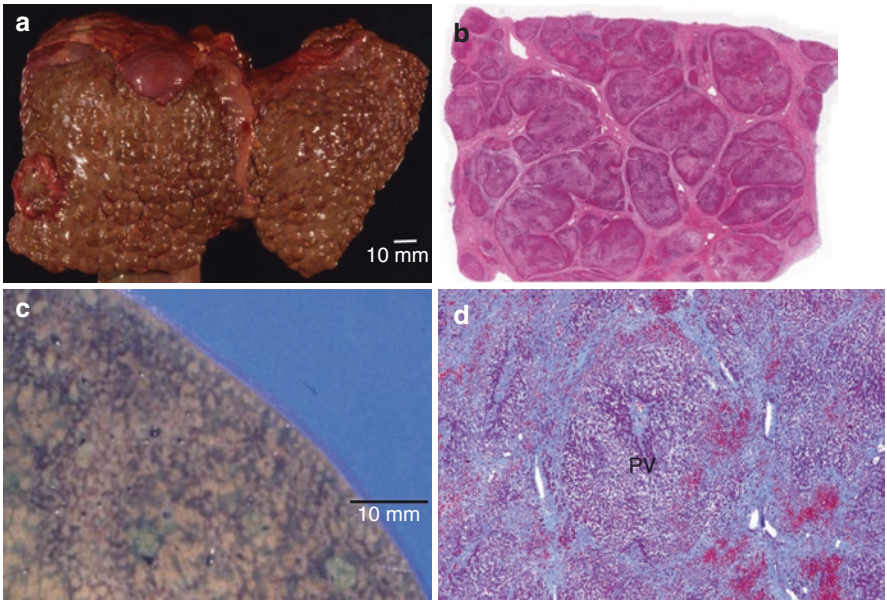

Fig. 1.5 (**a**, **b**) Primary biliary cirrhosis/cholangitis. Regenerative nodules show pathognomonic "garland" or "jigsaw puzzle" pattern. (**b**) Luxol fast blue stain. (**c**, **d**) Congestive cirrhosis. Macroscopic view shows micronodules and surrounding congestion. Histology shows portal tract (PT) locates in the center of the nodule (so-called reversed lobulation), which is encircled by central-central bridging fibrous septa with surrounding congestion

world. Kojima et al. demonstrated that the prevalence rates of body mass index ≥25 kg/m^2, visceral fat area ≥100 cm^2, and type 2 diabetes mellitus were 54.2%, 40.0%, and 54.2%, respectively, in 24 Japanese patients with cryptogenic cirrhosis [6]. Large fatty droplets and other pathognomonic findings for NASH have disappeared in the advanced cirrhotic stage of NASH, and thus this condition is called "burnt-out NASH" (Fig. 1.3). Other potential causes of cryptogenic cirrhosis include burnt-out autoimmune hepatitis and occult viral hepatitis (hepatitis X) [7].

1.3 Secondary Liver Damage Accompanying Progress in Cirrhosis

1.3.1 Alteration of Vascular Channels

1.3.1.1 Capillarization of Sinusoids

In combination with the loss of fenestrations in the sinusoidal endothelial cells and the deposition of aberrant extracellular matrix (ECM) in the space of Disse by stellate cells, the sinusoidal space comes to resemble a capillary [1].

1.3.1.2 Remodeling of Vascular Structures

1. Vascular Obstruction
   Many of the portal veins and hepatic veins are fastened by fibrous connective tissue in septa and obstructed (Fig. 1.2d, e). Such findings are excellently shown by a detailed study of the angioarchitecture of the human liver with graphic reconstructions from thousands of serial sections, which was performed by Matsumoto and colleagues [8, 9]. Mural thrombosis of portal veins and hepatic veins are also found. Regenerative nodules compress hepatic veins.
2. Arterio-portal Shunt and Bypass

Arterio-portal shunt is formed through peribiliary vascular plexus (Fig. 1.4b). In addition, porto-venous or arteriovenous shunt is also formed in fibrous septa. Since blood flows through such shunts, bypasses, and hepatic parenchyma, blood supply to hepatocytes is impaired.

1.3.2 Alterations of Hepatic Parenchyma: Secondary Collapse of Hepatic Parenchyma (Parenchymal Extinction)

Obstruction and thrombosis of portal veins and hepatic veins and blood flow bypassing the liver parenchyma cause acute or chronic circulatory disturbance irrespective of etiology of cirrhosis. A collapsed regenerative nodule is sometimes replaced by bile ductules with indistinct lumen (Fig. 1.2f).

1.4 Pathophysiology of Portal Hypertension Caused by Cirrhosis

1.4.1 Presinusoidal Block

Presinusoidal blood flow resistance rises due to portal vein obstruction in fibrous septa.

1.4.2 Sinusoidal Block

Sinusoidal blood flow resistance increases because of sinusoidal constriction and ECM deposition in sinusoidal wall [1]. Such features are caused by activation of hepatic stellate cells, which produce contractile peptide, endothelin-1 (ET-1), and ECM. ET-1 contracts stellate cells in an autocline loop, resulting in a vasoconstriction.

1.4.3 Post-sinusoidal Block

Hepatic venules compressed by regenerative nodules and fastened in the fibrous septa raise portal pressure.

1.4.4 Arterio-Portal Shunt

Arterio-portal shunt is formed in fibrous septa, and arterial blood flow increases in cirrhosis. Inflow of arterial blood to portal vein through the arterio-portal shunt raises portal flow pressure.

1.5 Regression of Cirrhosis

Cirrhosis has been considered as an irreversible disease until recently. However, it is reported that in a case with elimination of etiology, early phase cirrhosis without advanced vascular remodeling often regresses to the non-cirrhotic phase according to progress in modern therapy. For example, in a viral cirrhosis case from whom hepatitis virus was eliminated, intrahepatic necroinflammatory lesion disappeared, and fibrosis regressed. The main mechanisms for absorption and extinction of collagen fibers are considered as activation of matrix metalloproteinase and inactivation of tissue inhibitor of matrix proteinase-1 [10].

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