Liver Cirrhosis

6

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Contents

Abbreviations

ARFI	Acoustic radiation force impulse
DAA	Direct-acting antiviral
EVL	Endoscopic variceal band ligation
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HRS	Hepatorenal syndrome
HSC	Hepatic stellate cell
MELD	The model for end-stage liver disease
MMP	Matrix metalloproteinase
MRE	Magnetic resonance elastography
NA	Nucleos(t)ide analogue
NASH	Nonalcoholic steatohepatitis
SBP	Spontaneous bacterial peritonitis
SWE	Shear wave elastography
TE	Tissue elastography
TGF	Transforming growth factor
TIMP	Tissue inhibitor of matrix metalloproteinase

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Liver cirrhosis is anatomically defined as a diffuse disruption of the normal architecture of the liver with fibrosis and nodule formation. It is the end result of fibrogenesis caused by chronic liver injury. The anatomical architecture is the same with any etiology: continuous inflammation or hepatocyte damage causes fibrogenesis, and fibers extend from central or portal area, and finally fibrous septa is completely formed to

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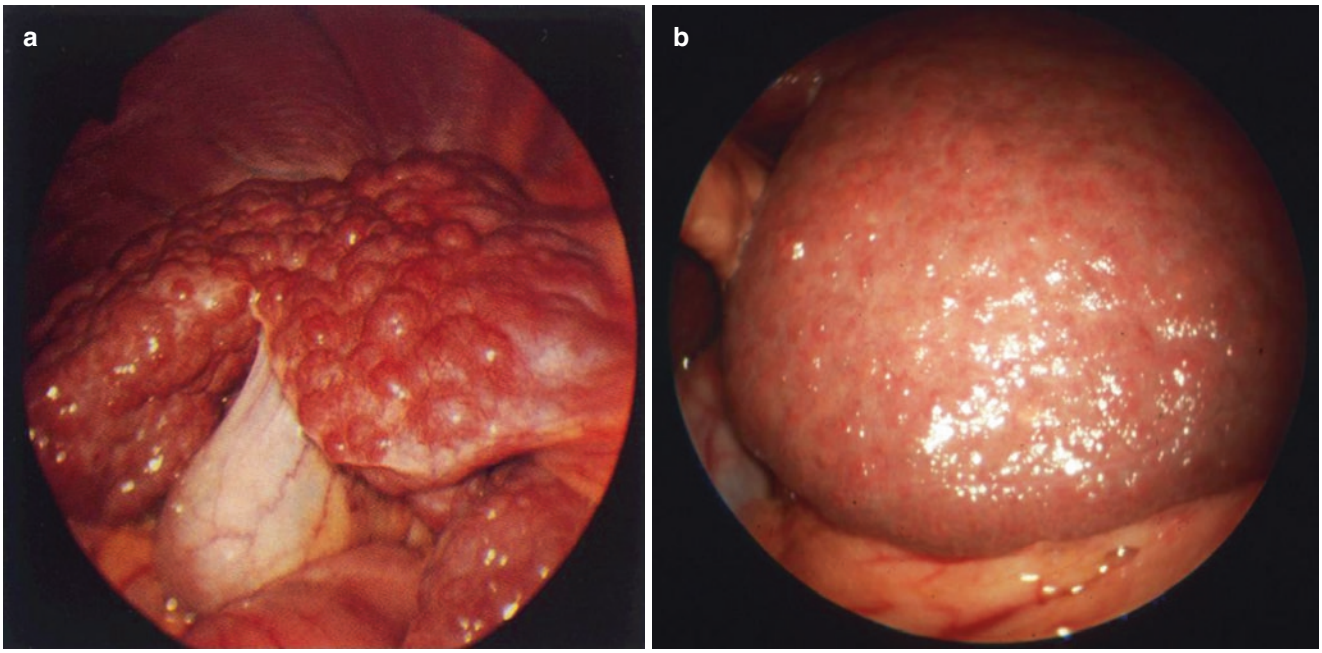

Fig. 6.1 Peritoneoscopic findings in liver cirrhosis. (**a**) Peritoneoscopic examination shows macronodules in the right lobe of liver cirrhosis with HBV infection. (**b**) Peritoneoscopic examination shows micronodules in left lobe of alcoholic liver cirrhosis

Table 6.1 Child-Pugh staging system and MELD score

Child-Pugh staging system			
Parameter	1 point	2 point	3 point
Total bilirubin			
μmol/L	<34	34–50	>50
mg/dL	<2	2–3	>3
Serum albumin			
g/L	>35	28–35	<28
INR	<1.7	1.71–2.3	>2.3
Ascites	None	Mild (controlled by diuretics)	Moderate to severe (refractory to diuretics)
Hepatic encephalopathy	None	Grades I–II (absent with medication)	Grades III–IV (recurrent)

Child A class is 5–6 points; B is 7–9 points; C is 10–15 points
MELD score
MELD = 3.78× [serum bilirubin (mg/dL)] + 11.2× [INR] + 9.57× [serum creatinine (mg/dL)] + 6.43

surround regenerative nodules. Thus liver cirrhosis is characterized with hepatocyte dysfunction and portal hypertension.

6.1 Classification

(a) Morphological classification
WHO classification of macropathology showed three nodular types, namely, macronodular (bigger than 3 mm nodule in diameter), micronodular (smaller than 3 mm nodule in diameter), and mixed. Micronodule is caused by alcohol, cholestasis, or hemochromatosis, and macronodule is caused by viral infection. However the dynamics is not specified, and micronodule can evolve to macronodule (Fig. 6.1) [1].

(b) Functional classification
Clinically cirrhosis is classified as compensated or decompensated stages. No significant symptoms are observed at compensated stage because protein synthesis and detoxification ability are reserved. However decompensation means one or more of the following: jaundice, ascites, bleeding varices, or hepatic encephalopathy.

Child-Pugh classification is used worldwide and is based on jaundice, ascites, encephalopathy, serum albumin concentration, and prothrombin time [2]. The total score classifies patients into grade A, B, or C (Table 6.1).

At the same time, MELD (the model for end-stage liver disease) score is used for prognostication of decompensated stage, which is derived from serum creatinine, prothrombin time (INR), and serum bilirubin. MELD score is applied to liver transplantation and found to predict the mortality in waiting list; thus it is now widely used as a criterion for organ allocation [3].

(c) Etiology
Liver cirrhosis is caused by several etiologies, and the incidence varies between different countries and genetic background. In Western countries the prevalence of alcoholic and nonalcoholic steatohepatitis (NASH) and viral cirrhosis, in particular hepatitis C, are all increasing. In developing countries, the predominant causes are hepatitis virus B and C. In Japan HCV is the cause in about 60%, alcohol 15%, and HBV 13% (Fig. 6.2) [4]. In China and Korea, HBV is the most predominant.

Recently, the incidence of NASH is increasing worldwide, especially in developing country.

6.1.1 Hepatitis C

HCV-mediated infection causes mild and persistent attacks in the liver. When degeneration and regenerative activity are mild, the excavations are small, and regenerative nodules are lower in height [5].

Case 6.1
A 65-year-old male suffering from persistent infection of HCV presented with serum HCV RNA 6.0 log copies/mL. Liver function test showed TBIL 1.04 mg/dL, AST 71 IU/L, ALT 48 IU/L, GGT 353 IU/L, PLT 7.8 × 10^4/μL, and hyaluronic acid 400 ng/mL. Peritoneoscopy showed white and wavy surface with dilated peripheral portal veins, and nodules were not apparent; histologically, pseudolobular formation was present, and the internodular space differed in each pseudolobule; and steatosis was seen in hepatocytes, and bile ducts were disorganized (Fig. 6.3).

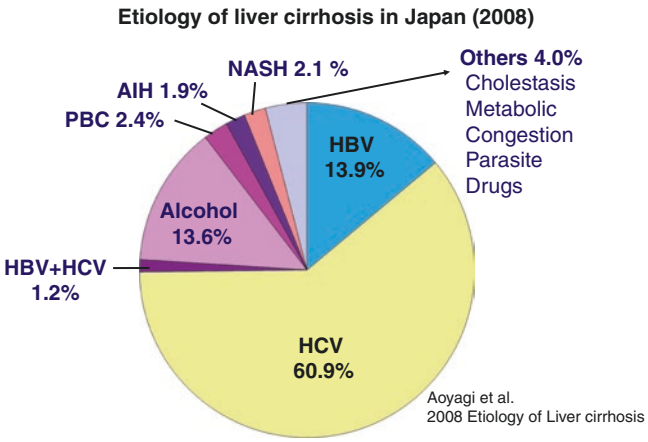

Fig. 6.2 Etiology of liver cirrhosis in Japan. HCV is the most predominant cause

6.1.2 Primary Biliary Cholangitis

In primary biliary cholangitis, interlobular bile ducts or septal bile ducts are initially destroyed, and their destruction is irregularly distributed. Therefore, excavation due to destruction of bile ducts is distributed irregularly, with liver surface becoming wavy or undulating. Nodules may become large and vary in size. Fibrosis spreads from the portal tracts, with destruction or disappearance of bile ducts [6], and proliferated fibrosis may cause the formation of pseudolobules.

Case 6.2
A 53-year-old female was suspected of having ascites and jaundice. Her liver function test showed TBIL 4.6 mg/dL, AST 93 IU/L, ALT 70 IU/L, ALP 1177 IU/L, GGT 331 IU/L, IgG 2350 mg/dL, IgM 645 mg/dL, anti-M2 antibody 2980 U/mL, ANA × 1280, and PLT 7.1 × 10^4/μL. Esophageal varices were detected by esophagogastroduodenoscope. Peritoneoscopy with liver biopsy showed formation of large nodules and presence of lymph follicles on wavy surface, while lobular architecture was microscopically destructed, pseudolobular formation was established, and bile ducts disappeared (Fig. 6.4). Ursodeoxycholic acid was administered, but serum value of TBIL and ALP gradually increased, and she died of hepatic failure after 3.5 years.

6.1.3 Wilson's Disease

In Wilson's disease, there is genetic disturbance of hepatobiliary copper discharge by copper-transporting ATPase [7], and copper is deposited in the liver and brain. Microscopically fatty metamorphosis, chronic active hepatitis, cirrhotic

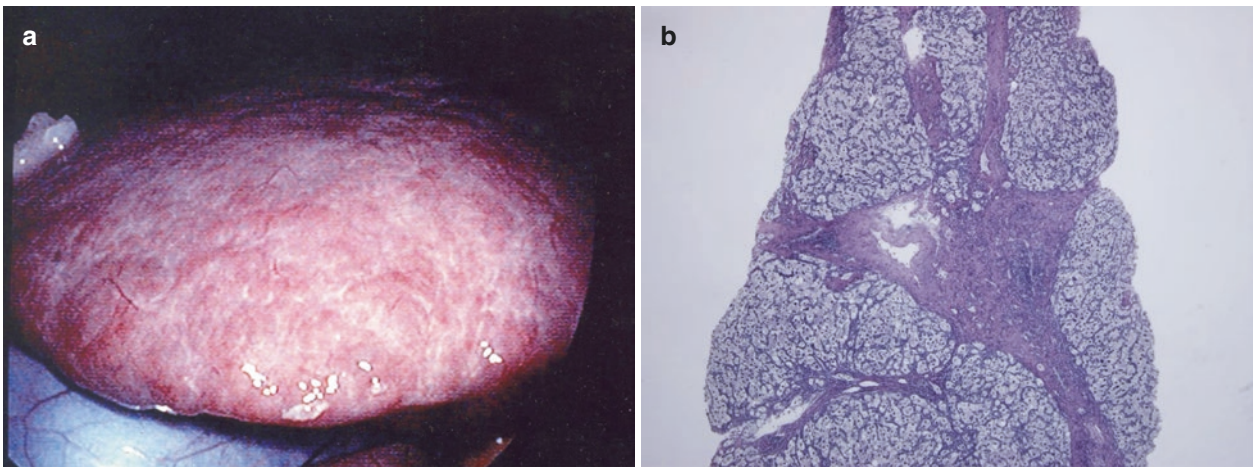

Fig. 6.3 Liver cirrhosis due to hepatitis C virus infection. (**a**) Peritoneoscopy shows nodules are regular in size and are low in height, and internodular space is narrow. (**b**) Pseudolobular formation is seen and nodules vary in size

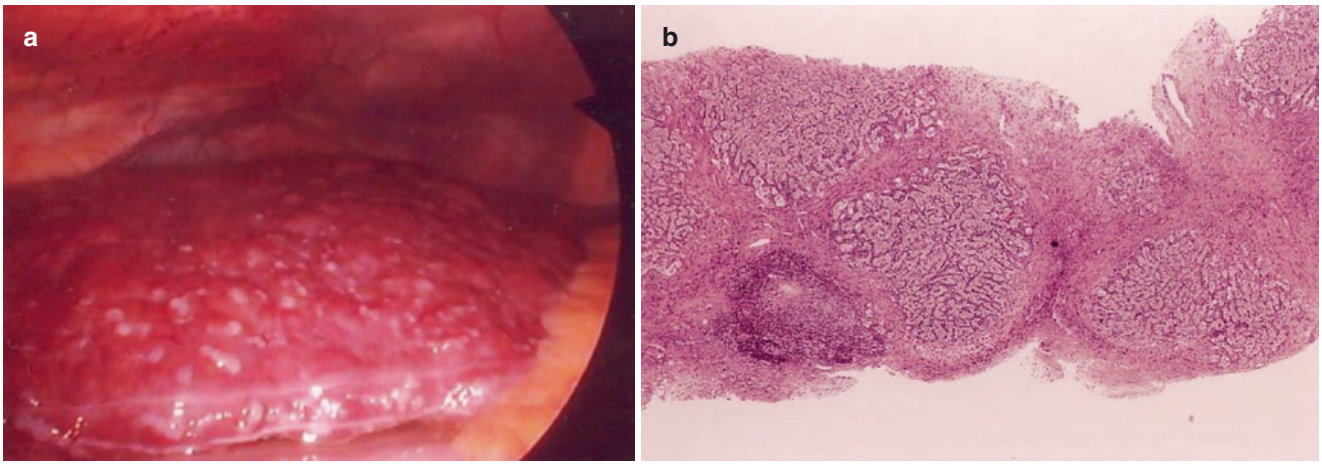

Fig. 6.4 Primary biliary cholangitis. (**a**) Peritoneoscopy shows nodules are irregular in size and are low in height, and lymph vesicles are seen on liver surface. (**b**) Pseudolobular formation with aggregate of lymphocytes is established. Pseudolobules vary in size, and septum fibrosis is wide

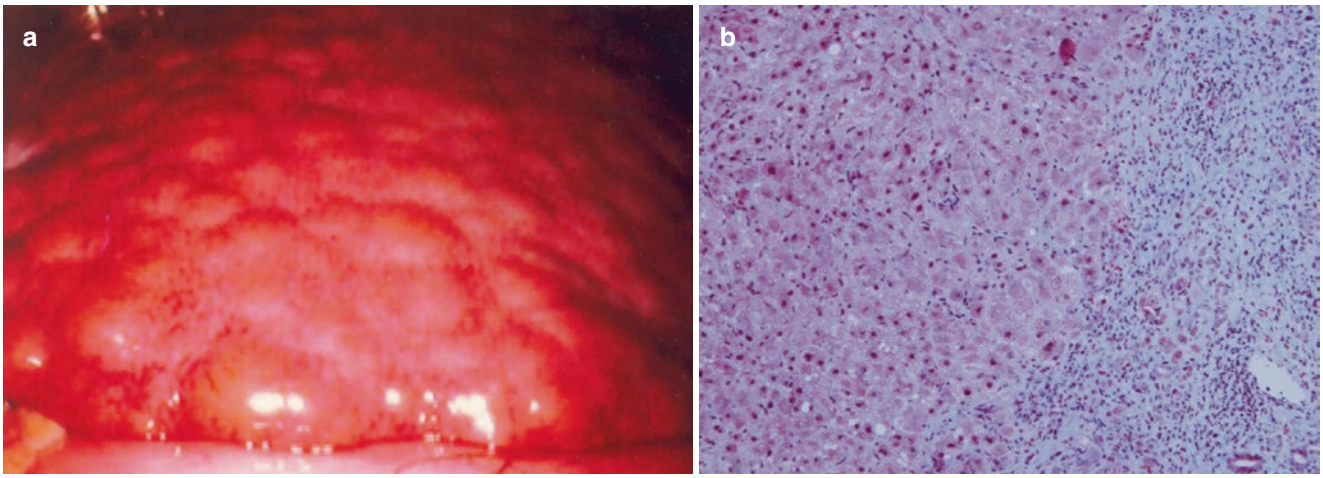

Fig. 6.5 Wilson's disease. (**a**) Peritoneoscopy shows nodular formation on yellow liver surface. Nodules are round and vary in size. (**b**) Masson trichrome stain shows pseudolobular formation, extension of fibrosis from portal tracts, and micro- and macrosteatosis

changes, and submassive necrosis occur in the liver of some patients with Wilson's disease. Cirrhotic change can develop with chronic hepatitis; therefore, the liver surface is typically yellow with red markings [8].

Case 6.3 (See Chap. 12)
Liver test performed on a 12-year-old boy showed abnormal values, including low ceruloplasmin in serum with high urinary copper. Wilson's disease was suspected. Peritoneoscopy showed round nodular formations on yellow liver surface, while pseudolobular formation with microvesicular or macrovesicular fatty change was observed under histology, and active inflammation was seen in portal tracts (Fig. 6.5).

6.1.4 Budd-Chiari Syndrome

Clinical manifestations in Budd-Chiari syndrome (BCS) vary from symptom-free to epigastric pain, hematemesis and hepatic encephalopathy, lower extremity edema, venous dilatation of abdominal wall, and ascites. BCS is classified into two types: with or without membranous obstruction of inferior vena cava (MOVC). Chronic obstruction leads to peliosis and hemorrhage between the parenchyma and portal area or subcapsular space. Hepatic capsule is thick and white in color, and necrosis of hepatocytes is persistent. Liver surface is darkly white, regenerative nodules are low in height, and subcapsular hemorrhage is seen on liver surface [9].

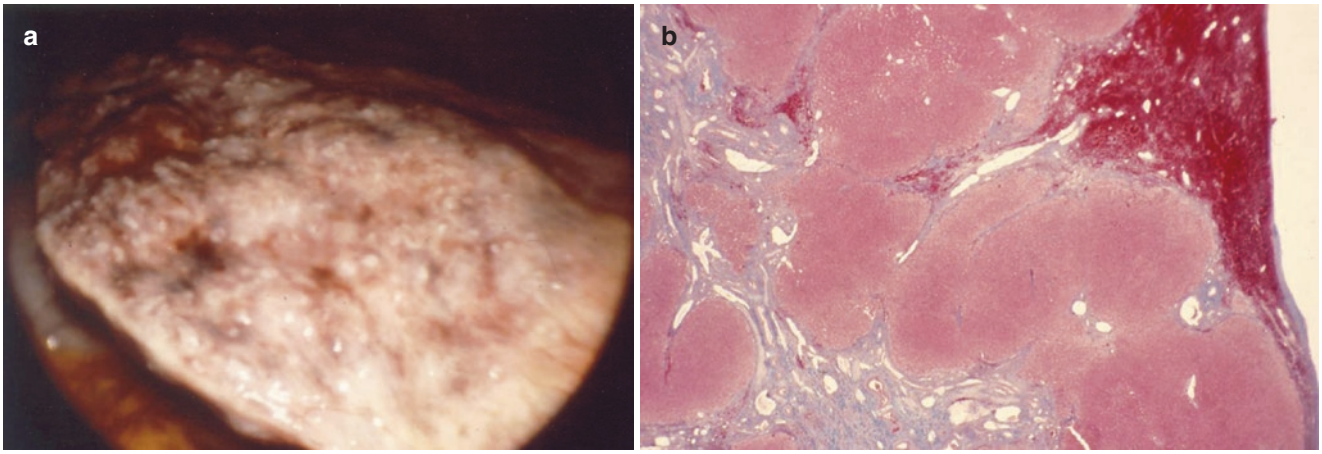

Fig. 6.6 Budd-Chiari syndrome. (**a**) Peritoneoscopy shows wavy and white-colored liver surface, and nodular formations are seen. Internodular space is wide, and subcapsular hemorrhage is observed (Redrawn from Iwai M, et al. Clinical features, image analysis, and laparoscopic and histological liver findings in Budd-Chiari syndrome. Hepato-Gastroenterol 1998; 45: 2359–68). (**b**) Subcapsular or periportal hemorrhage is seen, pseudolobular formation is established, and bridging fibrosis is observed between portal tracts

Case 6.4

A 66-year-old male had an esophagogastroduodenoscopic examination, and early gastric cancer was detected. Upper abdominal CT examination was performed prior to gastrectomy, and thrombus was detected in inferior vena cava (Chap. 11). Peritoneoscopy showed atrophic liver of left lobe with thick capsule, and subcapsular hemorrhage was seen on wavy surface of the liver; pseudolobular formation was established, and hemorrhage was seen in the subcapsular space. On histology, bridging fibrosis between portal tracts was noted, and central veins were not dilated (Fig. 6.6).

6.2 Pathology

Liver cirrhosis is caused by significant fibrosis due to the wound healing steps from continuous liver injuries together with structural changes of lobules and vessels.

In normal liver, low-density basement membrane composed of type IV collagen, glycoprotein (fibronectin and laminin), and proteoglycans is located in the space of Disse, which separates hepatocytes from sinusoidal endothelium. After hepatic injury there is a three- to eightfold increase of extracellular matrix, which is composed predominantly of interstitial fibril-forming collagens (types I and III) as well as other matrices. In addition, there are loss of endothelial cell fenestration and formation of basement membrane which is composed of high-density type IV collagen and laminin. This change is known as capillarization of sinusoid, which impedes the metabolic exchange between blood and hepatocytes.

The activated hepatic stellate cell (HSC) located in Disse's space is the principal cell involved in fibrogenesis. With liver injury, HSC undergoes phenotypic changes referred to as "activation" characterized as myofibroblastic changes. HSC activation can be divided into two phases such as initiation and perpetuation. Initiation is caused by different factors of liver injury depending on the disease etiology. Stimuli include oxidant stress signals, apoptotic bodies, lipopolysaccharide, and paracrine stimuli from neighboring cells such as Kupffer cells, sinusoidal endothelial cells, and hepatocytes which initiate HSC to respond to a host growth factor and cytokines. Perpetuation involves cellular events that amplify the activated phenotype through enhanced cytokine expression and responsiveness. Fibrosis is developing through enhanced HSC proliferation, contractility, chemotaxis, secretion of proinflammatory mediators, direct interaction between HSCs and the immune systems, and altered matrix degradation. Among cytokine, TGF-beta is the most potent fibrogenic cytokine (Fig. 6.7) [10].

Once the initiating injury signal is eliminated, HSCs either revert to the quiescent phenotype or are removed from the liver through programmed cell death or apoptosis.

Liver biopsy is the gold standard for diagnosis [11]. Interpretation may be limited by small size and sampling error. Specialist liver histopathology is essential. Even with small biopsies, the expert histopathologist may be able to make a diagnosis of cirrhosis by recognizing a rim of fibrosis at the periphery of the fragments and the lack of normally related portal tracts and hepatic venules in the parenchyma, often with a widened reticulin pattern or architectural disruption. Liver biopsy contributes to the determination of etiology by identifying features such as micronodule and pericellular fibrosis indicating alcoholic liver cirrhosis (Fig. 6.8), steatosis and balooning indicating NASH, or plasma cell infiltration suggesting autoimmune hepatitis. Liver biopsy is not without risk. If there are contraindications such as ascites or prolonged coagulation time, the transjugular approach is suggested.

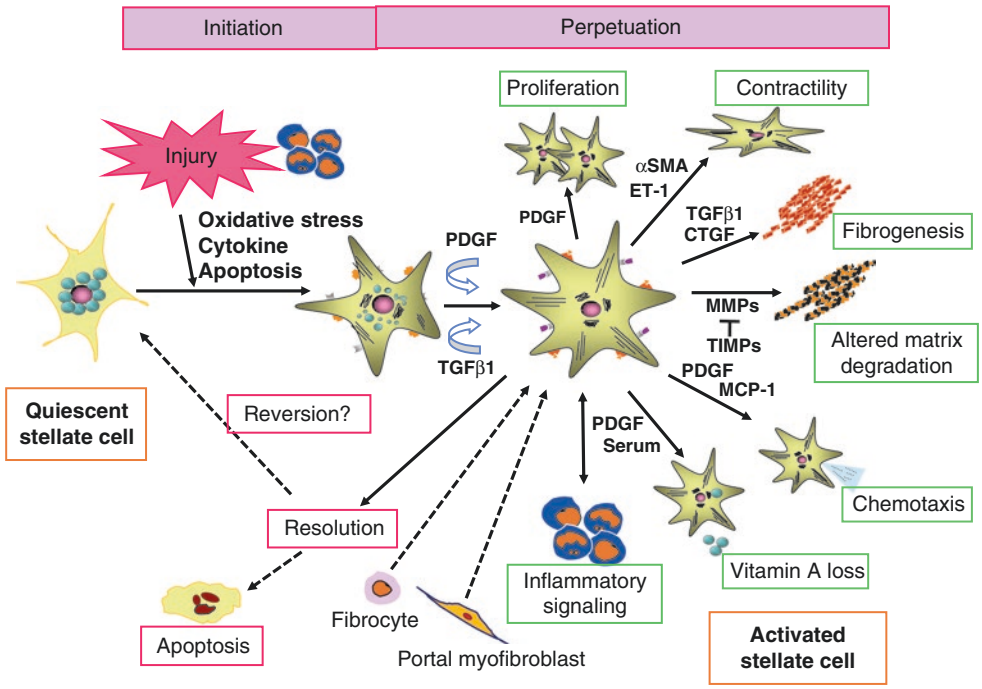

Fig. 6.7 Pathway of hepatic stellate cell (HSC) activation. HSC activation can be divided into two phases: initiation and perpetuation. Initiation is provoked by soluble stimuli including oxidative stress signals, cytokines from neighboring cells such as Kupffer cells, and apoptotic bodies. Perpetuation follows, characterized by a number of specific phenotype changes including proliferation, contractility, fibrogenesis, altered matrix degradation, chemotaxis, and inflammatory signaling

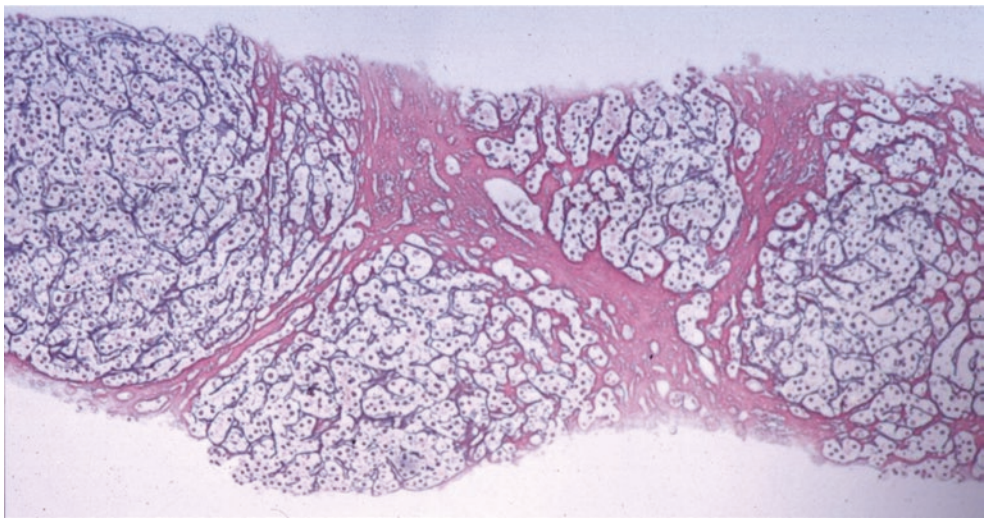

Fig. 6.8 Histology of alcoholic liver cirrhosis. Microscopy shows micronodule formation together with pericellular fibrosis

6.3 Clinical Symptoms

The symptoms are caused by both the loss of hepatocytes function and portal hypertension.

At the compensated stage, no significant symptoms are noted, and it is difficult to distinguish from chronic hepatitis. Non-specific symptom such as general fatigue, easy fatigability, anorexia, muscle cramp, itching, and loss of libido may be noted.

Vascular spider at the neck to forechest, palmar erythema, gynecomastia, asterixis, white nails, dark skin, malnutrition, and sarcopenia are also noticed. Right lobe of the liver becomes atrophic, and left lobe is hypertrophic; thus hard liver is palpable at epigastrium. Splenomegaly is also noted. Venous collaterals of abdominal wall from umbilical area, known as "caput medusa," are caused by portal hypertension (Fig. 6.9).

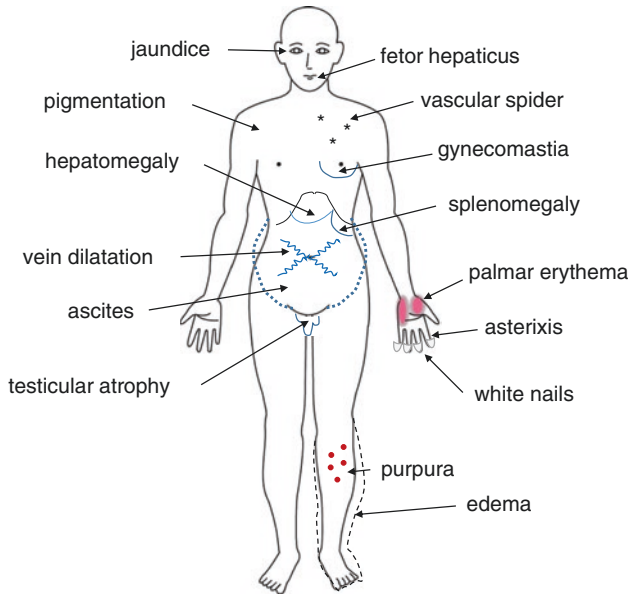

Fig. 6.9 Clinical symptoms of cirrhotic patient

At decompensated stage, leg edema and ascites, jaundice, consciousness disturbance due to hepatic coma, and hematemesis occur.

6.4 Laboratory Examination

(a) Biochemistry and blood cell count: Disturbance of hepatocyte function causes low level of synthesis, such as albumin, cholesterol, and cholinesterase, and elevated level of bilirubin and prothrombin time (INR) (Table 6.2). AST and ALT are rather low compared with that of chronic hepatitis, and AST is higher than ALT. Gamma globulin is elevated, and albumin/globulin ratio (A/G) is decreased. Hepatic fibrosis markers such as hyaluronic acid, type IV collagen, and Mac-2 binding protein glycan isomer (M2BPGi) are elevated together with fibrosis progression [12]. High level of ammonium suggests hepatic coma. Low level of Fisher ratio (BCAA/AAA) suggests the disturbance of protein metabolism. Indocyanine green tolerance test at 15 min (ICG R15) is more than 20% at cirrhotic stage. Alpha-fetoprotein is sometimes increased due to hepatocyte regeneration. Portal hypertension causes splenomegaly and pancytopenia, especially decrease in white blood cells and platelets.

(b) Image analyses: Many kinds of images are used because liver cirrhosis is highly associated with liver cancer. Ultrasonography is not reliable for the diagnosis of cirrhosis but useful for screening for hepatocellular carcinoma. US shows the coarse echo pattern in the liver, irregular surface, dull edge, left lobe enlargement, splenomegaly, and sometimes ascites. CT scan can assess liver size and shape and identify liver nodules (Fig. 6.10). It provides an objective record for evaluating changes over time. Fatty change, focal liver lesions, ascites, collateral vessels, and splenomegaly can be identified. MRI is also useful for evaluating liver nodules.

Table 6.2 Laboratory investigations

Investigations		
Hematology	Red blood cell	↓
	White blood cell	↓
	Platelet	↓
	Prothrombin time (INR)	↑
Biochemistry	Albumin	↓
	Cholinesterase	↓
	Total cholesterol	↓
	Bilirubin	↑
	Transaminase	↑
	AST/ALT>1	
	Ammonia	↑
	ICG (R15)	↑
	Fischer ratio	↓
Protein fraction	g-globulin	↑
	IgG	↑
Fibrosis marker	P-III-P	↑
	Type IV collagen	↑
	Hyaluronic acid	↑
	M2BPGi	↑

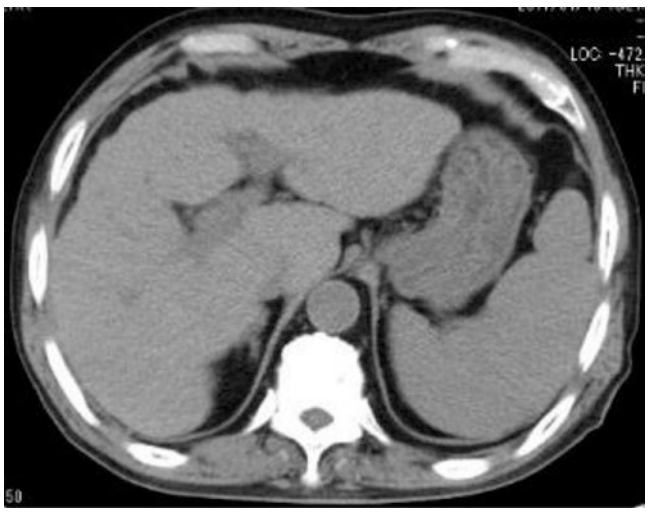

Fig. 6.10 CT scan in liver cirrhosis. CT shows the liver with irregular surface, enlargement of left lobe, and splenomegaly

(c) Noninvasive assessment of cirrhosis: Serum markers of fibrosis can be subclassified as direct and indirect markers. Direct markers such as serum hyaluronic acid, type IV collagen, procollagen type III amino-terminal peptide (PIIINP), matrix metalloproteinase-2 (MMP-2), tissue inhibitor of metalloproteinase-1 (TIMP-1), and TIMP-2 have been implicated in hepatic fibrosis. Indirect markers of fibrosis involve combinations of standard laboratory tests including AST/ALT, GGT, bilirubin, coagulation parameters, platelet count, and so on. APRI (AST to platelet ratio index) is a simple indirect marker that can be calculated from routine laboratory data. It has proven effective in predicting the presence of cirrhosis in HCV patients [13]. FIB-4 is another simple indirect marker that found to be a predictor of cirrhosis [14].

Liver stiffness measurement appears to have a better diagnostic accuracy compared with serum markers. Liver stiffness measurement has the advantage of being liver-specific and unaffected by extrahepatic inflammation and scarring. However, stiffness measurement has some disadvantages such as requiring a dedicated device and subjection to inter- and intraobserver variability unlike serum markers. Also it may not be measurable in certain patients, such as those with obesity or ascites [15]. Tissue elastography (TE) using FibroScan measures the velocity of a low-frequency (50 Hz) elastic shear wave propagating through the liver. The velocity is directly related to tissue stiffness, called the elastic modulus (expressed as $E = 3\,pv^2$, where v is the shear velocity and p is the density of tissue, assumed to be constant). The stiffer the tissue, the faster the shear wave propagates. The standard M probe is estimated to examine a liver volume 100 times larger than a standard biopsy. The results are expressed in kilopascals (kPa) and range from 1.5 to 75 kPa with normal values around 5 kPa. Result more than 17.0 kPa suggests liver cirrhosis (Fig. 6.11). TE takes only 5–10 min for the procedure and is simple, inexpensive, and reproducible. Acoustic radiation force impulse (ARFI) imaging, also called point shear wave elastography (pSWE), is an ultrasound-based elastography technique. Short acoustic pulse (~262 μs) generates shear waves causing microdisplacement of the hepatic parenchyma. The shear wave velocity is measured in m/sec. Liver stiffness measured by 2D shear wave elastography (2D-SWE) is another modality. The technique involves the real-time capture of transient shear waves induced in the hepatic parenchyma by focused ultrasonic beams. 2D-SWE has a lower failure rate than TE, and there has been a suggestion that 2D-SWE has better performance than both TE and ARFI/pSWE (Fig. 6.12). Magnetic resonance elastography (MRE) has not yet been adopted in routine clinical use due to its expense and time commitment. However, MRE provides excellent quantification of shear wave propagation using modified phase-contrast imaging.

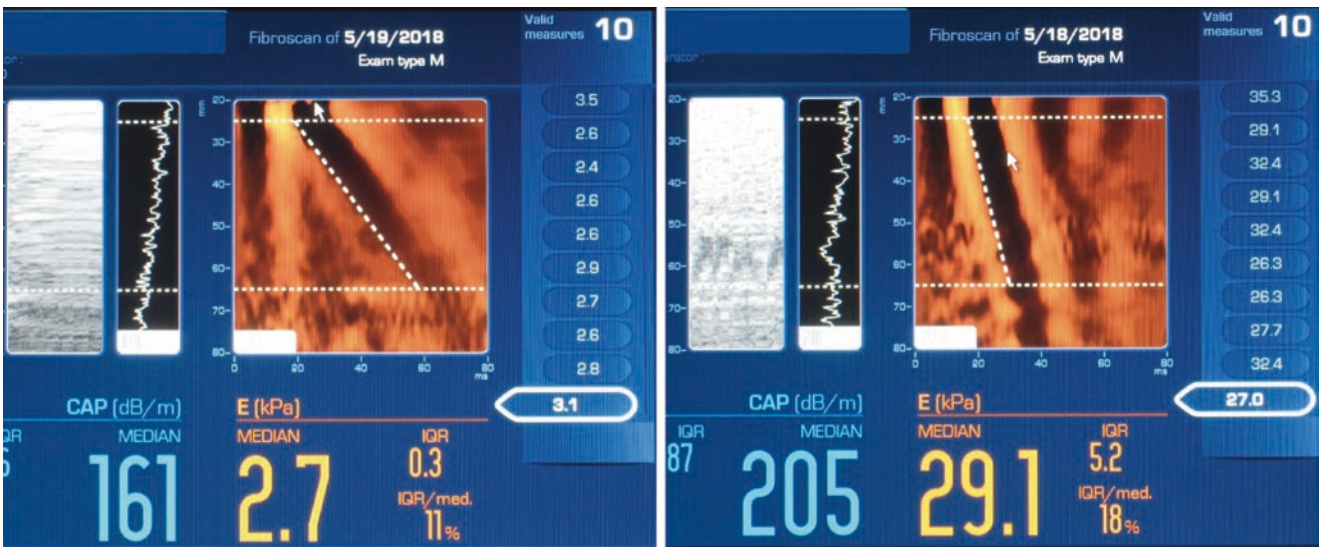

Fig. 6.11 Tissue elastography using FibroScan. Left: normal liver. The inclination is mild. Elasticity is 2.7 kPa. Right: liver cirrhosis. The inclination is steep. Elasticity is 29.1 kPa

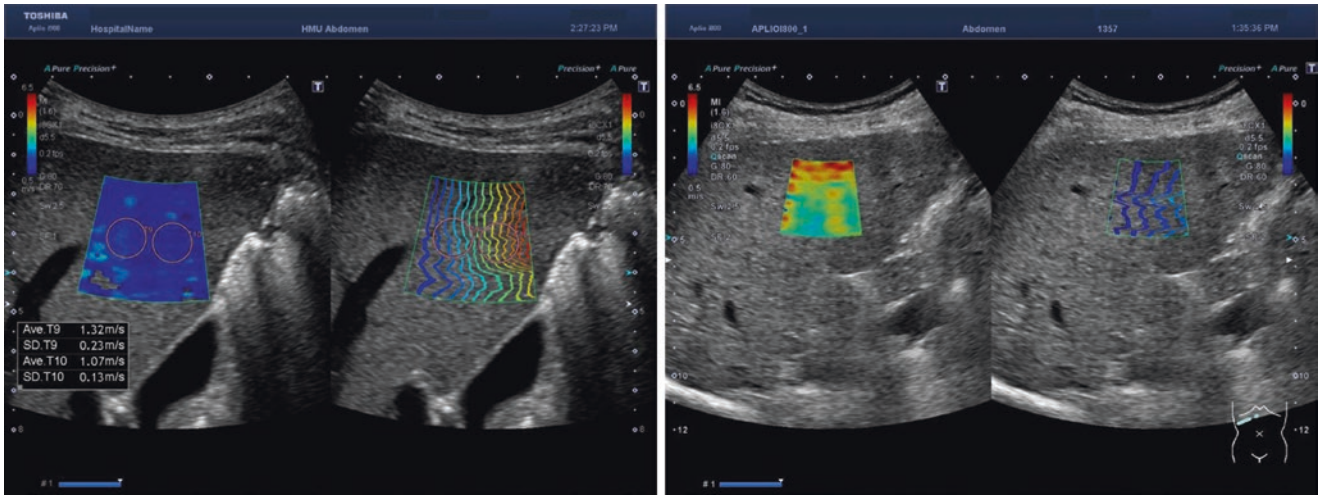

Fig. 6.12 2D-share wave elastography. Left: normal liver. Shear wave speed is slow (blue). The propagation is parallel and narrow. Right: liver cirrhosis. Shear wave speed is fast (red to yellow), and the propagation is wide

6.5 Complications

(a) Hepatocellular carcinoma (HCC): The most dreadful complication is HCC. The risk of HCC differs with the etiology of liver cirrhosis. The occurrence rate of HCC is reported at 7–8% per year in hepatitis C [16]. The guideline recommends regular imaging examination and tumor markers such as alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) in liver cirrhosis patients.

(b) Portal hypertension: Portal hypertension is noticed as gastroesophageal varices, portal hypertensive gastropathy, splenomegaly, and hepatic coma. Esophagogastroduodenoscopy is required to show gastroesophageal varices. Red color sign (RC sign), which is reddish area on the varices, is particularly important to evaluate the possibility of bleeding and to decide the preventive treatment (Fig. 6.13).

(c) Ascites: The ascites of liver cirrhosis is transudative with clear and yellowish fluid. The mechanisms of ascites formation are complicated, but portal (sinusoidal) hypertension and renal retention of sodium are universal. The natural history of cirrhotic ascites progresses from diuretic-responsive (uncomplicated) ascites to the development of dilutional hyponatremia, refractory ascites, and finally hepatorenal syndrome.

(d) Spontaneous bacterial peritonitis (SBP): One of the most common bacterial infections in cirrhosis is SBP. It is called spontaneous because it occurs in the absence of a contiguous source of infections and in the absence of an intra-abdominal inflammatory focus. The diagnostic puncture of ascites shows the increase of white blood cell more than 750/mm^3 or polymorphonuclear cells more than 250/mm^3 as an indication of SBP. Culture of bacteria is negative in approximately 50% of patients with clinical manifestations suggestive of SBP.

(e) Hepatorenal syndrome (HRS): HRS is a severe complication of cirrhosis that occurs in patients with ascites and hyponatremia and consists of the development of renal failure in the absence of any identifiable renal pathology. It is a functional disturbance, and the histology of the kidney is mostly normal. The syndrome involves intense splanchnic and peripheral vasodilation with consequent renal vasoconstriction.

(f) Hepatic encephalopathy: Hepatic encephalopathy in liver cirrhosis is characterized by neuropsychiatric abnormalities, ranging from indiscernible changes in cognition to obvious changes in intellect, behavior, motor function, and consciousness. This complication has detrimental effects on health-related quality of life, safety, and survival. Both hepatocellular failure and portal-systemic shunting are key to this development. Ammonia plays a key role in the pathogenesis of the syndrome via the induction of astrocyte swelling, and the development of low-grade cerebral edema, oxidative stress, disrupted glial-neuronal communication, and neuronal dysfunction follow. Asterixis (flapping tremor) is the best-known motor abnormality. Fetor hepaticus, a sour, musty, feculent smell, can be detected on the breath of some patients.

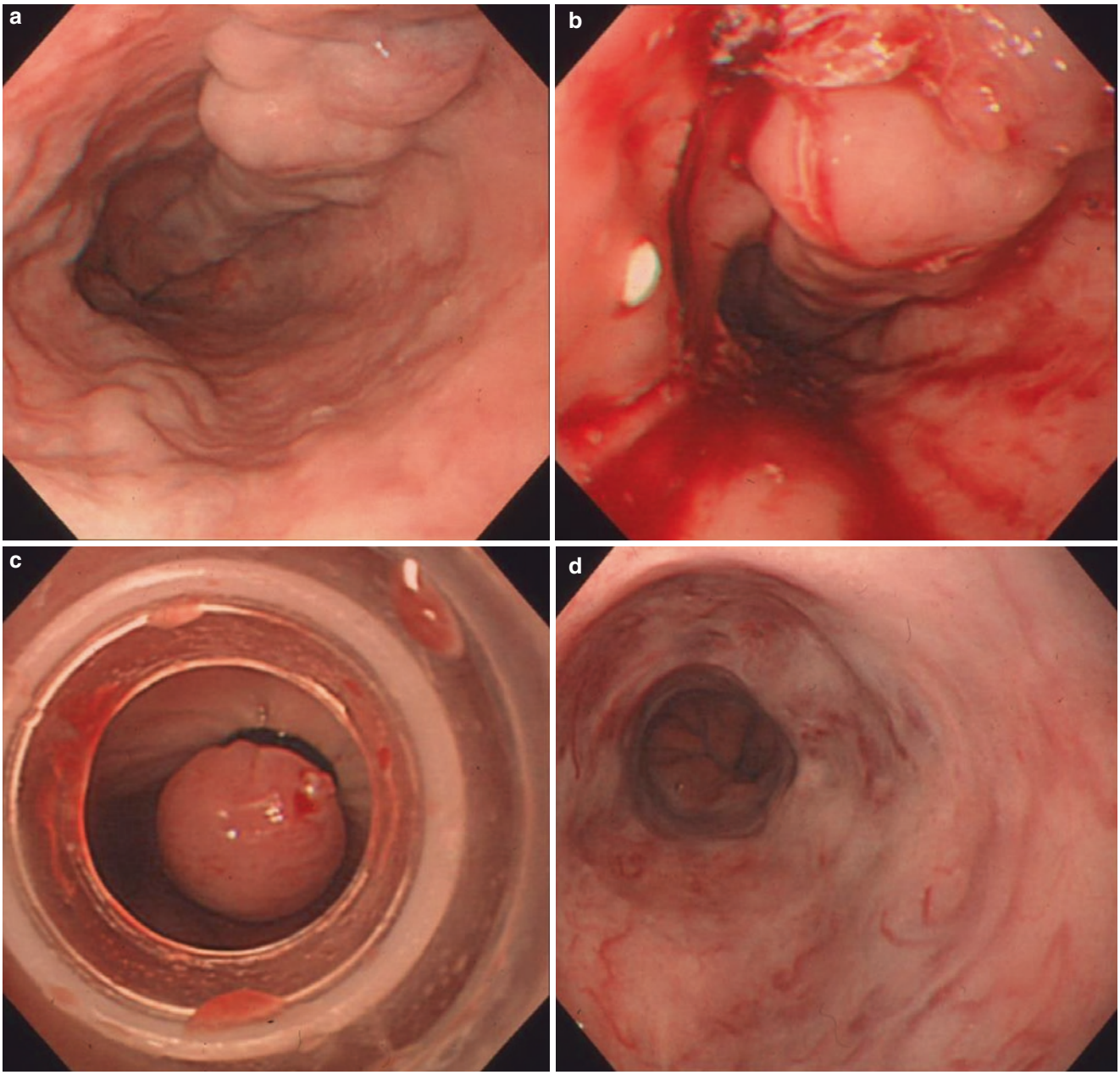

Fig. 6.13 Esophagogastroduodenoscopic findings. (**a**) Esophagogastroduodenoscopy shows meandered blue esophageal varices. (**b**) Bleeding from esophageal varices. (**c**) Endoscopic variceal band ligation is done to the ruptured varices. (**d**) Esophageal scaring is seen after EVL

6.6 Prognosis

Poor prognosis is associated with a prolonged prothrombin time, marked ascites, gastrointestinal bleeding, high serum bilirubin, low albumin values, and poor nutrition. If liver transplantation is done, the prognosis is getting better. The appearance of ascites is the most common first decompensating event, followed by variceal bleeding, encephalopathy, and jaundice.

6.7 Therapy

Treatment consists of two factors. One is the treatment for the cause of cirrhosis. The other is for treatment of its complications.

6.7.1 Etiology-Based Therapy

(a) Hepatitis B virus
Liver cirrhosis with hepatitis B infection is treated with antiviral drug. Nucleos(t)ide analogue (NA) rather than interferon is used for the treatment of liver cirrhosis because interferon has many adverse events compared with NA. Tenofovir and entecavir are used as first-line drugs. Regression of fibrosis and reversal of cirrhosis can be observed in patients with maintained viral suppression after 3–5 years of continuous NA administration [17].

(b) Hepatitis C virus
Treatment of hepatitis C has dramatically changed within recent several years. The efficacy of direct-acting antiviral (DAA) on hepatitis C is more than 95%. The sustained viral response will lead to resolution of the extended fibrosis, together with decreased incidence of HCC [18].

(c) Autoimmune hepatitis
Autoimmune hepatitis can be treated with immunosuppressant reagents. Two general treatment strategies have developed: (1) prednisolone monotherapy and (2) combination therapy, either from the onset or with addition of azathioprine a few weeks later. Some may choose budesonide as first-line treatment instead of prednisolone.

(d) Primary biliary cholangitis
The first-line licensed treatment is ursodeoxycholic acid (UDCA). Obeticholic acid (OCA) is now approved for use in both Europe and the USA in patients showing an inadequate response to or intolerant of UDCA. Liver transplantation remains the only effective treatment for patients with end-stage disease. Bilirubin level of >100 μmol/L (6 mg/dL) is a useful threshold at which transplant is actively considered.

(e) Alcoholic liver cirrhosis
The most important measure is to ensure total and immediate abstinence from alcohol. Psychological and pharmacological treatments are available to help abstinence and prevent relapse.

(f) Wilson's disease
Patients will require continuous treatment throughout their lifetime. The frontline agents are copper chelators such as D-penicillamine and trientine. After successful initial treatment, options for maintenance treatment include a reduction in the dose of chelator or its substitution by zinc.

(g) Hemochromatosis
Venesections of 500 mL are carried out weekly and are continued until the serum ferritin level falls into low normal range. Other endpoints have been the development of anemia and a reduction in the mean cellular volume (MCV).

(h) NASH
NASH has no approved pharmacotherapy yet. The mainstay of treatment remains diet and lifestyle change to promote weight loss. But this is either unattainable or not maintainable in some patients; thus pharmacotherapy is warranted. Exercise, calorie reduction, and weight loss are first recommended. Only vitamin E and thiazolidines have the beneficial evidence in treatment of NASH.

6.7.2 Complication Treatment

(a) Hepatocellular carcinoma (HCC): The strategy of HCC treatment is based on liver function and tumor status. Treatments can be divided into "curative" including liver resection, liver transplantation, and local ablation (mainly radiofrequency ablation) or "palliative" including hepatic artery embolization, chemoembolization, radiotherapy, various chemotherapy regimens, and recently targeted agents sorafenib, regorafenib, and lenvatinib.

(b) Portal hypertension: Pharmacological therapy aims at decreasing portal pressure. Traditional nonselective beta-blockers include propranolol and nadolol decrease portal pressure by reducing portal vein inflow. Carvedilol and terlipressin are also used. As an endoscopic treatment, endoscopic variceal band ligation (EVL) is more effective and safer than endoscopic variceal sclerotherapy (Fig. 6.13). As intervention procedure, transjugular intrahepatic portosystemic shunt (TIPS) and balloon-occluded retrograde transvenous obliteration (BRTO) are considered for constructing a shunt connecting the high-pressure portal vein with a low-pressure systemic vein.

(c) Ascites: Therapy of ascites reduces clinical symptoms and improves quality of life. The spectrum of therapeutic intervention ranges from sodium restriction alone to diuretic use, therapeutic paracentesis, and, for the most severe groups, TIPS and eventually liver transplantation. For diuretics, spironolactone is administered alone or in combination with furosemide in refractory case. Tolvaptan, a new vasopressin V2 receptor antagonist, may be considered to add if available. Recently long-term albumin administration was proved to prolong overall survival in uncomplicated ascites patients by decreasing the rate of spontaneous bacterial peritonitis and hepatorenal syndrome [19].

(d) Spontaneous bacterial peritonitis (SBP): When complicated with SBP, 10–33% of patients will die during the hospital admission. Main predictors of mortality are the development of renal dysfunction and lack of response to initial empirical antibiotic therapy. The most common infecting organisms are Escherichia coli and Klebsiella. Antibiotics should be started empirically, and first-line drugs are third-generation cephalosporins, usually cefotaxime, administered intravenously. Amoxicillin-clavulanic acid is as effective as cefotaxime. Lack of response can be due to resistant bacteria or secondary bacterial peritonitis. Then extended spectrum antibiotics (carbapenems, piperacillin/tazobactam) should be used as initial empirical therapy. In a randomized study, the administration of intravenous albumin to patients with SBP treated with cefotaxime significantly reduced the incidence of renal impairment [20].

(e) Hepatorenal syndrome: Liver transplantation is the only definitive therapy for HRS, resulting in improved survival, though the opportunity is limited. As pharmacological treatment, vasoconstrictors plus intravenous albumin constitute the current mainstay therapy. Administration of vasoconstrictors (ornipressin, terlipressin, noradrenaline) for periods greater than 3 days is associated with significant increases of mean arterial pressure and decreased serum creatinine. The best evidence supports the use of terlipressin, a synthetic analogue of vasopressin. Alternative vasoconstrictive therapy is the use of intravenous noradrenaline infusion, which has been shown to be as effective as terlipressin.

(f) Hepatic encephalopathy: Patients with cirrhosis are unable to effectively store glycogen. Patients should avoid fasting for longer than 3–6 h during the day time. Branched-chain amino acids have a beneficial effect on hepatic encephalopathy by promoting ammonia detoxification, correcting the plasma amino acid imbalance, and reducing the brain influx of aromatic amino acids. There are additional benefits associated with consumption of a late evening snack. The nonabsorbable disaccharide lactulose or lactitol is used widely as first-line treatment for hepatic encephalopathy. This disaccharide has several beneficial effects: a laxative effect, bacterial uptake of ammonia, reduction of intestinal ammonia production, and improving gut microbiome. Antibiotics can be also used selectively to eliminate urease-producing organisms from the intestinal tract, thereby reducing the production of ammonia. Neomycin and rifaximin are poorly absorbed antibiotics and are used to treat hepatic encephalopathy. L-ornithine L-aspartate promotes hepatic removal of ammonia by stimulating residual hepatic urea cycle activity and by promoting glutamine synthesis, particularly in skeletal muscle.

6.8 Reversibility

It is widely believed that cirrhosis is an irreversible process that leads ultimately to liver failure. However, it has recently been reported that upon cessation of the injurious process, cirrhosis may reverse or at least improve histologically [17, 18]. Dense micronodular cirrhosis can undergo remodeling to a more attenuated, macronodular pattern, and fibrous septa is shown to become attenuated and then discontinued. Incomplete septal cirrhosis, a previously obscure entity, is now recognized as an indication of regression in fibrosis and a reversal of cirrhosis [21]. Histological clues of regression include delicate perforated septa, isolated thick collagen fibers, delicate periportal fibrosis spikes, portal tracts remnants, hepatic vein remnants, minute regenerative nodules, and aberrant parenchymal veins—so-called hepatic repair complex (Fig. 6.14). Despite the lack of significant fibrosis, patients with regressed cirrhosis may have portal hypertension. It has been advocated that the use of the word

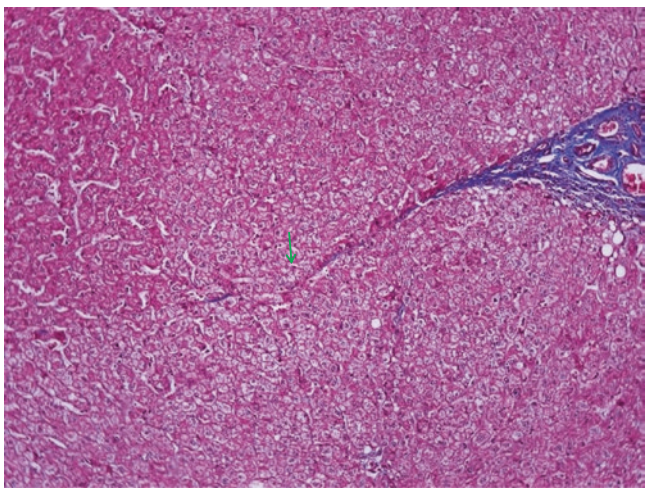

Fig. 6.14 Incomplete septal cirrhosis (cirrhosis with regressing fibrosis). Trichrome stain highlights a slender fibrous septum with perforation (arrow)

"cirrhosis" should be discontinued because of its connotation and that these patients labeled as having "chronic liver disease of advanced stage" should be provided treatment on the basis of clinicopathologic correlation of all available findings with the hope of disease regression [22].

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