Autoimmune Liver Disease

9

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Contents

Abbreviations

AIH	Autoimmune hepatitis
ALP	Alkaline phosphatase
AMA	Anti-mitochondrial antibody
ANA	Antinuclear antibody
ASMA	Anti-smooth muscle antibody
CNSDC	Chronic nonsuppurative destructive cholangitis
ERCP	Endoscopic retrograde cholangiopancreatography
GGTP	Gamma-glutamyltranspeptidase
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
GVHD	Graft-versus-host disease
HLA	Human leucocyte antigen
Ig	Immunoglobulin
MRCP	Magnetic resonance cholangiopancreatography
PBC	Primary biliary cholangitis
PSC	Primary sclerosing cholangitis
UDCA	Ursodeoxycholic acid

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9.1 Introduction

Autoimmunity of the human body can be directed toward the hepatocytes or toward the bile ducts. Autoimmune disease affecting the hepatocytes (with elevation of hepatocellular enzymes—AST, ALT) is called autoimmune hepatitis (AIH), whereas the classical example of autoimmune disease affecting small bile ducts is called primary biliary cholangitis (PBC). The latter is associated with elevation of cholestatic liver enzyme (ALP, gamma-GT). The role of autoimmunity in primary sclerosing cholangitis (PSC) affecting the large bile ducts is rather unclear, although in recent years a variant of PSC is certainly caused by IgG4-mediated bile duct injury. Finally, sometimes features of both AIH and PBC or PSC can be present, producing so-called overlap syndrome.

9.2 Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is a chronic self-perpetuating inflammatory disease with a female predominance occurring in all ages and races that may start with an episode of acute hepatitis and may lead to liver cirrhosis, liver cancer, liver transplantation, or death. The etiology of autoimmune hepatitis

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is unknown, though both genetic and environmental factors are likely to be involved. An immune response targeting liver autoantigens is thought to initiate and perpetuate the liver damage. There are particularly strong associations within the HLA-DRB1 locus, with the HLA-DR3 (DRB1/0301) and HLA-DR4 (DRB1/0401) molecules conferring susceptibility to AIH-1 in Europe and North America and DR4 in Japan [1], and susceptibility to AIH type 2 is associated with HLA-DR3 and HLA-DR7 in the United Kingdom and Brazil [2].

The criteria for the diagnosis of autoimmune hepatitis (AIH) are evolving. An initial attempt to define this disease by the International Autoimmune Hepatitis Group [3] was followed by validation studies, a redefinition with still an extensive scoring system [4] and more recently a strong simplification of criteria, [5] and recently EASL published a well-summarized review [6].

AIH is in fact a syndrome, and the diagnosis is based on a combination of clinical features suggesting liver disease, the absence of other causes in conjunction with the presence of autoimmune markers (ANA, SMA, IgG), and typical features on liver biopsy. Autoantibodies are normally detected by indirect immunofluorescence on a rodent substrate that includes the kidney, liver, and stomach.

Severe liver injury and its repeated attack in AIH cause significant parenchymal loss and extinction, resulting in liver failure. Therefore, glucocorticoid with or without other immunosuppressants, such as azathioprine or cyclosporine, should be administered as soon as the diagnosis of AIH is established [7, 8] to achieve normalization of transaminases and immunoglobulin G levels in serum. Liver transplantation may be needed when treatment is delayed or ineffective [9].

Definite diagnosis requires (1) the absence of markers suggesting active viral hepatitis, abstinence from alcohol, no recent blood transfusion, and no recent exposure to hepatotoxic drugs, (2) the presence of autoimmune markers and elevated gammaglobulin, and (3) compatible histological patterns of liver injury [1, 3–5]. The histology in AIH includes interface and panlobular hepatitis, lymphoplasmacytic infiltrate, rosette formation of the periportal hepatocytes, and absence of biliary injury. Interface hepatitis is necroinflammation at the interface between the portal tract stroma and hepatic lobule and is recognized as chronic feature; however, in some patients with acute onset, this finding is less observed, and centrilobular necrosis is the dominant findings [10, 11]. The precise mechanism of autoimmune-related liver damage has not been elucidated in the liver that is known as tolerated organ [12, 13]. Clinically, AIH is classified into acute and chronic types, with or without acute exacerbation. Central necrosis with plasma cell infiltrate is frequently seen in the "acute" phase or acute exacerbation of AIH [14, 15], and syncytial giant cells are sometimes seen in severe AIH [16–19]. Cautiously, "acute" onset AIH frequently shows negative for autoantibodies and elevation of serum immunoglobulin, resulting in a much difficult diagnosis [20]. The histology of AIH varies depending on when the biopsy is taken during the disease. It is important to understand that biopsy cannot lead the definite diagnosis; however, biopsy is essential for ruling out other diseases. There are also various overlap forms of AIH with other autoimmune diseases, including primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and outliers, autoimmune cholangitis [1], and AIH with bile duct injuries [21, 22]. Especially in child the differentiation between AIH and PSC is difficult, suggesting that MRCP should be done in child case. For the diagnosis of such so-called overlap syndrome, initial diagnosis is important and should be diagnosed as AIH with bile duct injury or PBC with liver injury except for overlap syndrome.

Disease severity assessment is important especially at the initial diagnosis [23]. Peritoneoscopy reveals red swollen liver in an acute AIH with fissuring excavation, while chronic AIH demonstrates red mottling on the surface of the enlarged liver and white markings due to dilatation of the peripheral portal vein (Fig. 9.1).

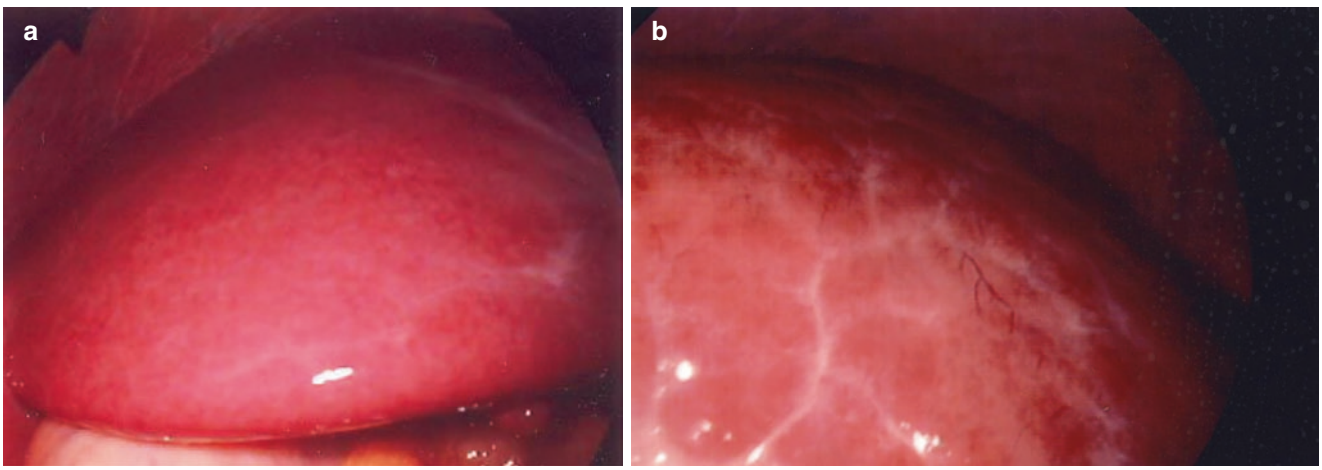

Fig. 9.1 Macroscopic findings of the liver with autoimmune hepatitis. (**a**) Peritoneoscopy shows swollen red liver with red markings in a patient with acute autoimmune hepatitis. (**b**) Peritoneoscopy in a patient with chronic autoimmune hepatitis shows fissure excavation with red markings on the surface of the enlarged liver, and white markings are visible with dilatation of the peripheral portal vein

Case 9.1

A 59-year-old male complained of general malaise, arthralgia, jaundice, and brown urine. His liver function test showed ALT 144 IU/L, AST 121 IU/L, GGT 76 IU/L, IgG 2322 mg/dL, ANA × 160, ASMA × 20, and negative AMA. Liver biopsy showed severe interface hepatitis and dense inflammatory infiltrates in the portal tract, consisting of plasma cells, lymphocytes, and rare eosinophils (Fig. 9.2). Prednisolone 30 mg/day was administered; arthralgia improved, and his liver function test reverted to normal values with maintenance dose. A variety of complications are often associated with AIH. Polyarthralgia, thyroiditis, and ulcerative colitis frequently occur in AIH, and the administration of glucocorticoid generally reduces their symptoms and signs.

Case 9.2

A 74-year-old female complained of general malaise for 6 months, and her liver function test showed ALT 673 IU/L, AST 756 IU/L, ALP 281 IU/L, GGT 420 IU/L, IgG 1361 mg/dL, ANA × 40, and negative AMA. Liver biopsy showed not only severe interface hepatitis but also central necrosis with plasma cell infiltrate (Fig. 9.3a). Prednisolone was administered, and her liver function test improved. Central necrosis with infiltration of plasma cells, such as seen in this case, is often observed in the acute phase of AIH [14, 15, 24].

Case 9.3

A 15-year-old female complained of general malaise and developed jaundice. Liver function test showed TBIL 11.5 mg/dL, AST 1185 IU/L, and ALT 1297 IU/L, and TBIL peaked

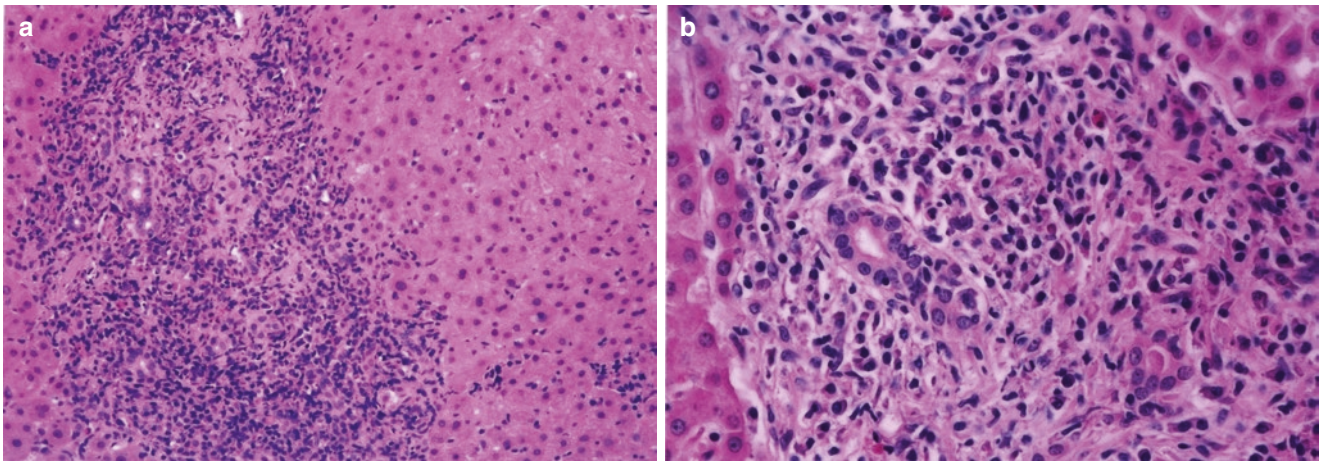

Fig. 9.2 Histological findings in autoimmune hepatitis. (**a**) Interface hepatitis is seen in the periportal area with many inflammatory cells in or around the portal tract. (**b**) The inflammatory cells in the portal tract consist of plasma cells, lymphocytes, and eosinophils. Bile ductules are damaged

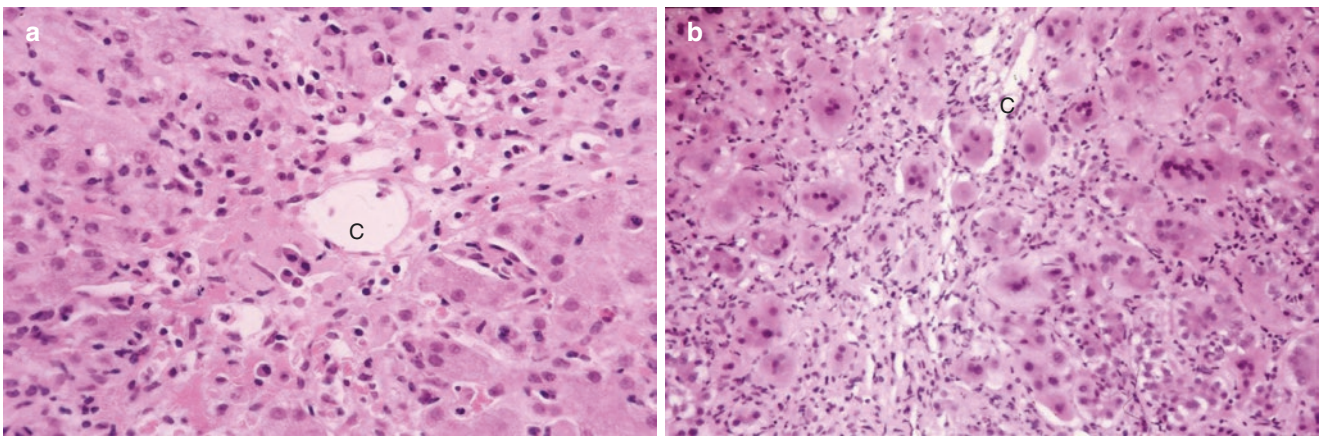

Fig. 9.3 Histological findings in autoimmune hepatitis. (**a**) Central necrosis with infiltration of plasma cells. (**b**) Multinucleated giant cells around the central vein (arrow), surrounded by plasma cells and neutrophils. Small hepatocytes are distributed in a rosette formation in the periportal area. *P* portal tract

36.4 mg/dL in a month, and PT was 55%. Liver biopsy showed syncytial giant cells in the centrilobular area, rosetting of hepatocytes in the periportal area, and neutrophilic and plasma cell infiltrate in the portal tract (Fig. 9.3b). Prednisolone 30 mg/day and azathioprine 50 mg/day were simultaneously administered, and her liver function test reverted to normal values after 3 months. Although giant cell hepatitis is a frequent pattern of liver injury in neonates, multinucleated syncytial giant cells can also be observed in AIH. Their appearance is associated with severe liver injury in AIH [18].

Case 9.4

A 51-year-old male underwent a health examination and was found to have TBIL 0.89 mg/dL, AST 95 IU/L, ALT 128 IU/L, ALP 394 IU/L, IgG 3800 mg/dL, ANA × 1280, and PLT 7.4 × 104/μL. Liver biopsy under peritoneoscopy showed nodular formations with lymphoid follicles and red markings on the surface of the liver. Liver histology showed irregularly sized pseudolobules with massive necrosis, broad septa, and a fibrotic area infiltrated with many lymphoplasmacytic cells (Fig. 9.4). The prognosis of AIH is poor if liver cirrhosis has occurred at the time of diagnosis of AIH [25], unless prednisolone is promptly administered. The patient was treated with 30 mg prednisolone, and his liver function test improved [26].

Case 9.5

A 56-year-old male complained of abdominal discomfort with brown urine. Liver function test showed TBIL 8.5 mg/dL, AST 1173 IU/L, ALT 2236 IU/L, PT 65%, thrombocyte 10.4 × 10 [4]/μL, and ANA × 40. Repeat liver function test 1 month later did not show any improvement. Echo-guided liver biopsy showed lobular disarray with abundant inflammatory cells in the portal tracts and central necrosis, and high magnification showed interface hepatitis with mononuclear cell infiltrate comprising CD138-positive plasma cells (Fig. 9.5). Administration of prednisolone and repeat plasma exchange did not improve liver failure after 4 months. Upper abdominal CT showed a reduction in liver size compared to that seen on admission, accompanied by decreasing consciousness. He underwent liver transplantation 5 months after

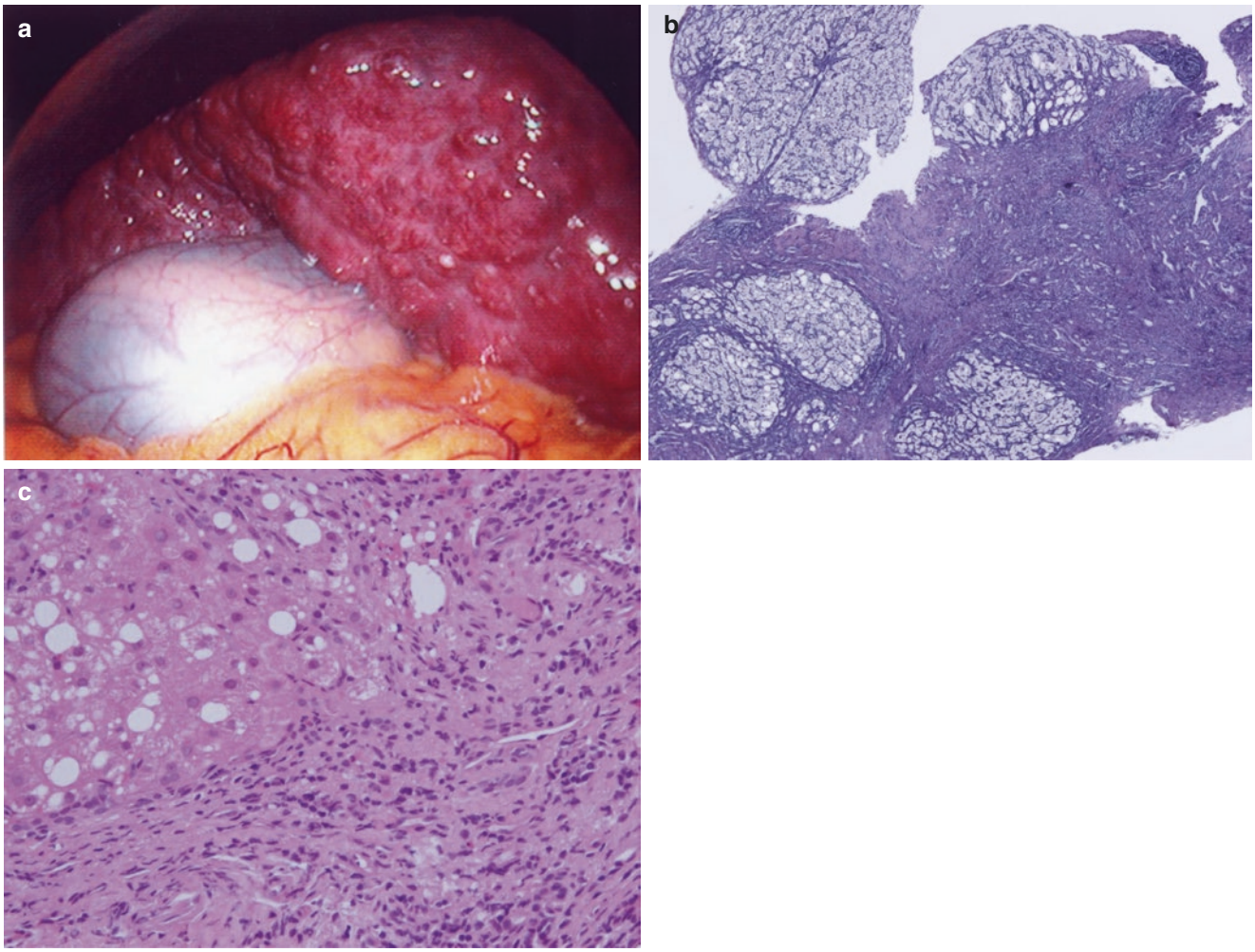

Fig. 9.4 Liver cirrhosis due to autoimmune hepatitis. (**a**) Peritoneoscopy shows irregularly sized nodules on the liver surface with intermittent large excavation. (**b**) Nodules of remaining liver parenchyma (pseudolobules) separated by wide areas of collapse fibrosis. (**c**) Lymphoplasmacellular infiltrate in broad band of fibrosis

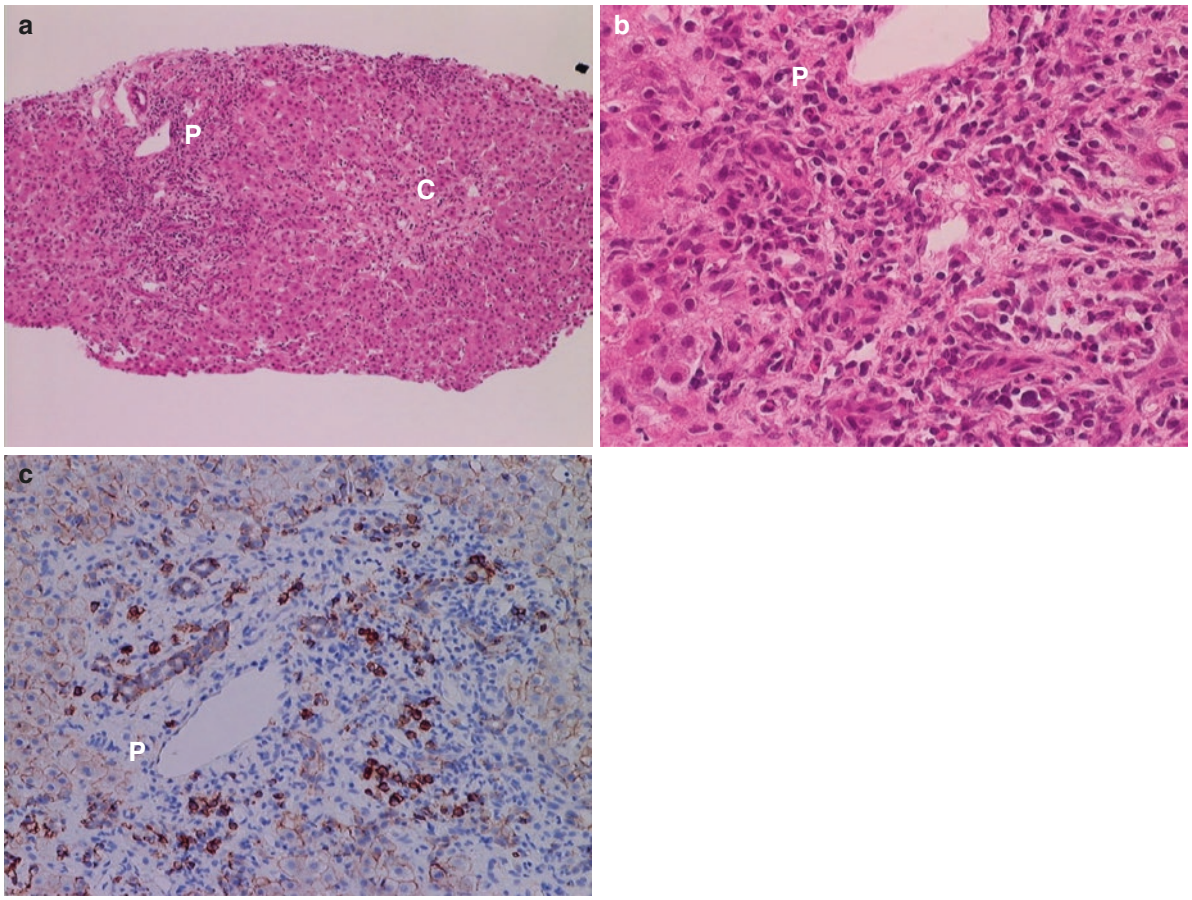

Fig. 9.5 Autoimmune hepatitis. (**a**) Liver histology at admission shows architectural disarray of the lobule, abundant inflammatory cells in the portal tract, and centrilobular necrosis. (**b**) Many inflammatory cells, including plasma cells and lymphocytes, are seen. (**c**) CD138 immunoreactivity is seen in plasma cells. *C* central vein, *P* portal tract

initial treatment. The explanted liver showed submassive hepatic necrosis with abundant ductular reaction and rosetting of hepatocytes in the necrotic area (Fig. 9.6). Liver transplantation is indicated in acute liver failure due to AIH. The patient survived 4.5 years after liver transplantation.

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by disorders of multiple organs, including the liver [27, 28]. The frequency of hepatic involvement in SLE is about 8–23% [28, 29]. Fatty change or congestion of the liver is frequently seen in patients with SLE [30], but concurrent AIH and SLE is quite rare [31, 32]. Furthermore, a differential diagnosis of SLE-associated hepatitis and AIH is clinically difficult [33, 34]. Here, we present a case of SLE with periportal hepatitis and plasma cell infiltrate and discuss the histologic differential diagnosis of SLE-associated hepatitis and AIH.

Case 9.6

A 60-year-old woman complained of fever and fatigue and developed proteinuria and polyarthralgia. Liver function test showed slight elevation of AST and ALT. A diagnosis of SLE was established according to the criteria of the American College of Rheumatology. She was treated with low-dose prednisolone therapy for 6 months and was asymptomatic for 4 years. Subsequently, she developed new onset of polyarthralgia, fatigue, and myalgia and had dark urine and jaundice. There was no history of drug-taking, alcohol abuse, or parenteral exposure to blood products. On admission, her liver function test revealed TBIL 3.28 mg/dL, DBIL 2.11 mg/dL, AST 192 IU/L, ALT 231 IU/L, ALP 1063 IU/L, GGT 332 IU/L, and LDH 253 IU/L. Immunological tests showed ANA × 640, IgG 2130 mg/dL, IgM 148 mg/dL, positive lupus erythematosus cell test, anti-double-stranded DNA, anti-single-stranded DNA, and HLA typing for DR4 and negative anti-ribosomal P antibody. Anti-smooth muscle antibody, anti-mitochondria antibody, and anti-LKM 1 antibody were negative. HBsAg, IgM-HA Ab, and HCV RNA were negative. Serological tests for hepatotropic viruses, including cytomegalovirus and Epstein-Barr virus, were also negative. Peritoneoscopy revealed mild excavations on the liver surface with diffuse white markings, but without any red mottling. Liver biopsy showed fatty metamorphosis in the hepatic lobules, and the portal tracts were fibrotic but without bridging fibrosis; there was mild interface hepatitis with lymphoplasmacytic infiltrate without rosetting of the hepatocytes (Fig. 9.7). After admission,

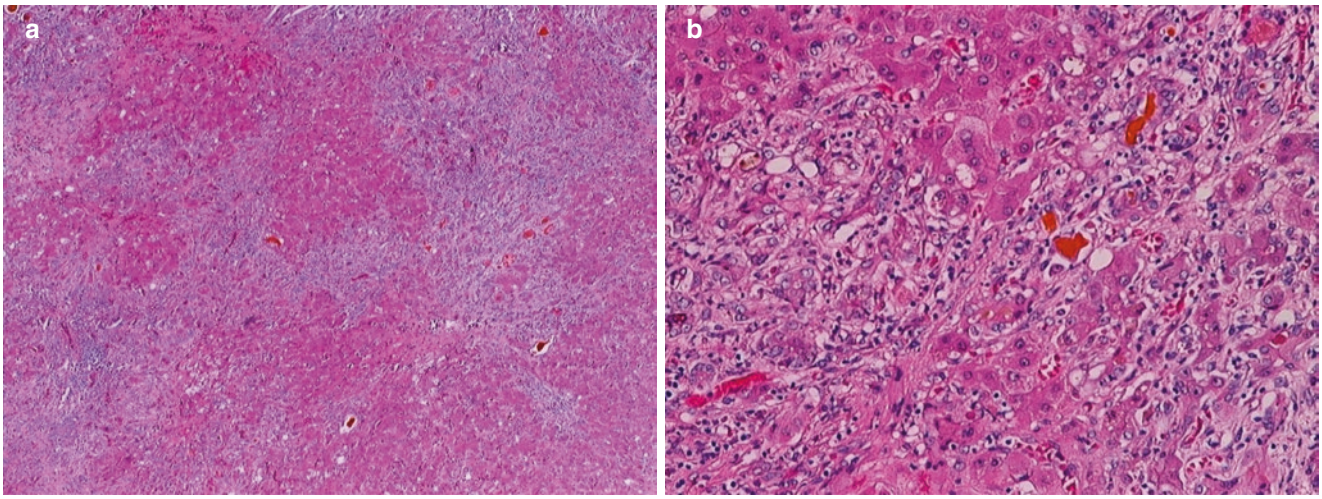

Fig. 9.6 Autoimmune hepatitis. (**a**) Submassive hepatic necrosis in the recipient liver. (**b**) Oval cells or small hepatocytes are seen around the portal tract

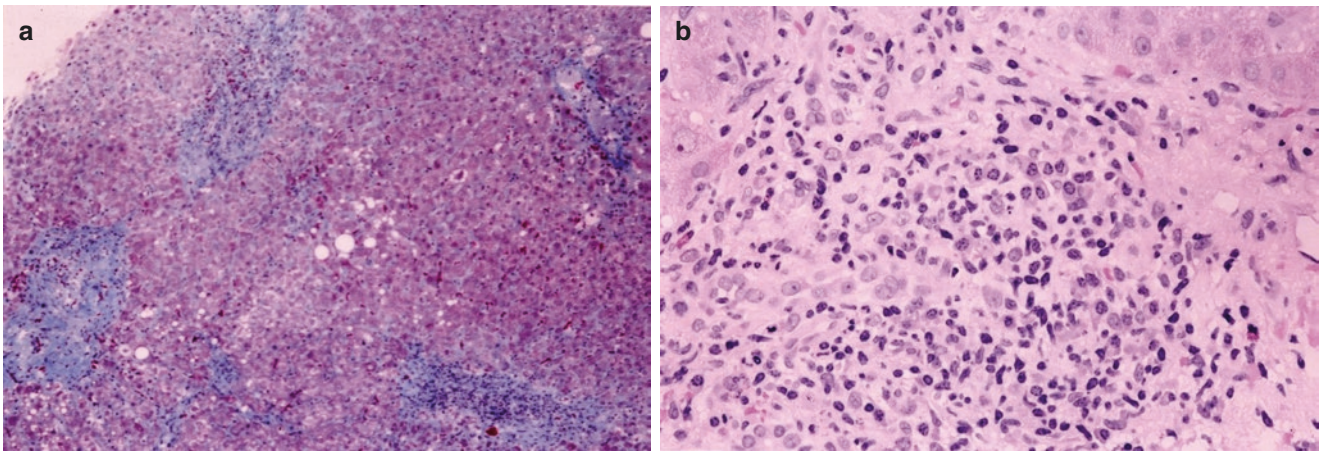

Fig. 9.7 Autoimmune hepatitis in systemic lupus erythematosus. (**a**) Mallory-Azan stain shows the portal tract is enlarged, with portal tract fibrosis. Neither bridging fibrosis nor pseudolobular formation is seen. Fatty metamorphosis is seen in hepatocytes. (**b**) Hematoxylin and eosin stain shows the portal tract is infiltrated with many plasma cells and lymphocytes, and configuration of the biliary epithelium is irregular. *C* central vein, *P* portal tract. (Reuse of Iwai M, et al. Autoimmune hepatitis in a patient with systemic lupus erythematous. Clin Rheumatol 2003; 22: 234–6., with permission from Springer)

her ALT and AST were elevated to 422 IU/L and 347 IU/L, respectively. Massive proteinuria (11 g/day), fever, massive pleural effusion, and pericardial effusion developed. Prednisolone was administered orally at an initial dose of 40 mg/day and tapered to a maintenance dose of 10 mg over a period of 3 months. Subsequently, pericarditis, pleuritis, and proteinuria disappeared, and her liver function tests reverted to normal levels. A seropositive lupus erythematosus test became negative, and serum complements returned to normal levels. Serum IgG and the ANA titers were decreased. Her AIH score was 19 before treatment and 21 after treatment. Pericarditis and pleuritis resolved after administration of prednisolone, and her liver function tests reverted to normal values for 4 years. SLE is sometimes complicated by liver injury, and it is difficult to distinguish chronic hepatitis in SLE from AIH [34, 35]. The histologic findings of interface hepatitis with lymphoplasmacytic infiltrate are those of AIH in SLE [36].

9.3 Primary Biliary Cholangitis

Primary biliary cirrhosis is recently renamed as primary biliary cholangitis (PBC) and generally regarded as an autoimmune disease. PBC is histologically characterized as chronic nonsuppurative destructive cholangitis [37]. The disease affects the small bile ducts (interlobular or septal bile ducts) in contrast to sclerosing cholangitis that affects mostly the large bile ducts.

Serum anti-mitochondrial antibody is the major marker of PBC and is positive in 90% of patients with PBC [38]. The disease usually affects middle-aged to elderly women, with a peak incidence between 40 and 60 years old. PBC is clinically classified into asymptomatic PBC (a-PBC), PBC with esophageal varices (v-PBC) [39], and symptomatic PBC (s-PBC). With the increasing number of medical checkups including laboratory testing, PBC is now frequently diagnosed at an early and completely asymptomatic stage. Most patients with

a-PBC remain stable for long periods of time, but some may gradually progress to s-PBC. The presenting features in s-PBC are intense pruritis, lethargy, skin pigmentation, and cholestatic jaundice, occasionally followed by liver failure, and some patients are associated with the Sjogren disease with or without CREST (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) syndrome [40].

Histological staging [37] can be summarized as follows:

- Stage 1 = inflammation and nonsuppurative destructive cholangitis (florid bile duct lesion).
- Stage 2 = destruction of parenchymal limiting plates with variable degrees of ductular proliferation and early short radiating septa.
- Stage 3 = extension of the portal-septal fibrosis to include portal to portal bridging septa (biliary fibrosis).
- Stage 4 = fully developed biliary cirrhosis.

Recently more clinical scoring system for both staging and grading has been shown, and this scoring is much practical and useful for assessing the disease [41].

Ursodeoxycholic acid (UDCA) is the treatment of choice for early-stage PBC [42]. Monotherapy of UDCA improves serum biochemical markers of bilirubin, alkaline phosphatase, γ-GTP, cholesterol, and IgM levels [43, 44] and slows down histological progression to liver cirrhosis, [45] and obeticholic acid and bezafibrate, probably by activating nuclear receptor, have shown promising results for non-responders of UDCA [46, 47]. Combination therapy of UDCA with bezafibrate is reported to improve biochemical tests in patients with PBC, with partial response to UDCA [48].

Case 9.7

A 73-year-old female underwent a health examination and was found to have AST 25 IU/L, ALT 14 IU/L, ALP 358 IU/L, and GGT 73I U/L. Further examination showed IgG 1113 mg/dL, IgM 205 mg/dL, AMA ×40, and ANA ×1280. Liver biopsy under peritoneoscopy showed small scattered excavations on the liver surface with white capsular thickening, infiltration of the portal tracts by inflammatory cells, and bile duct proliferation accompanied by many inflammatory cells including lymphocytes and plasma cells (Fig. 9.8).

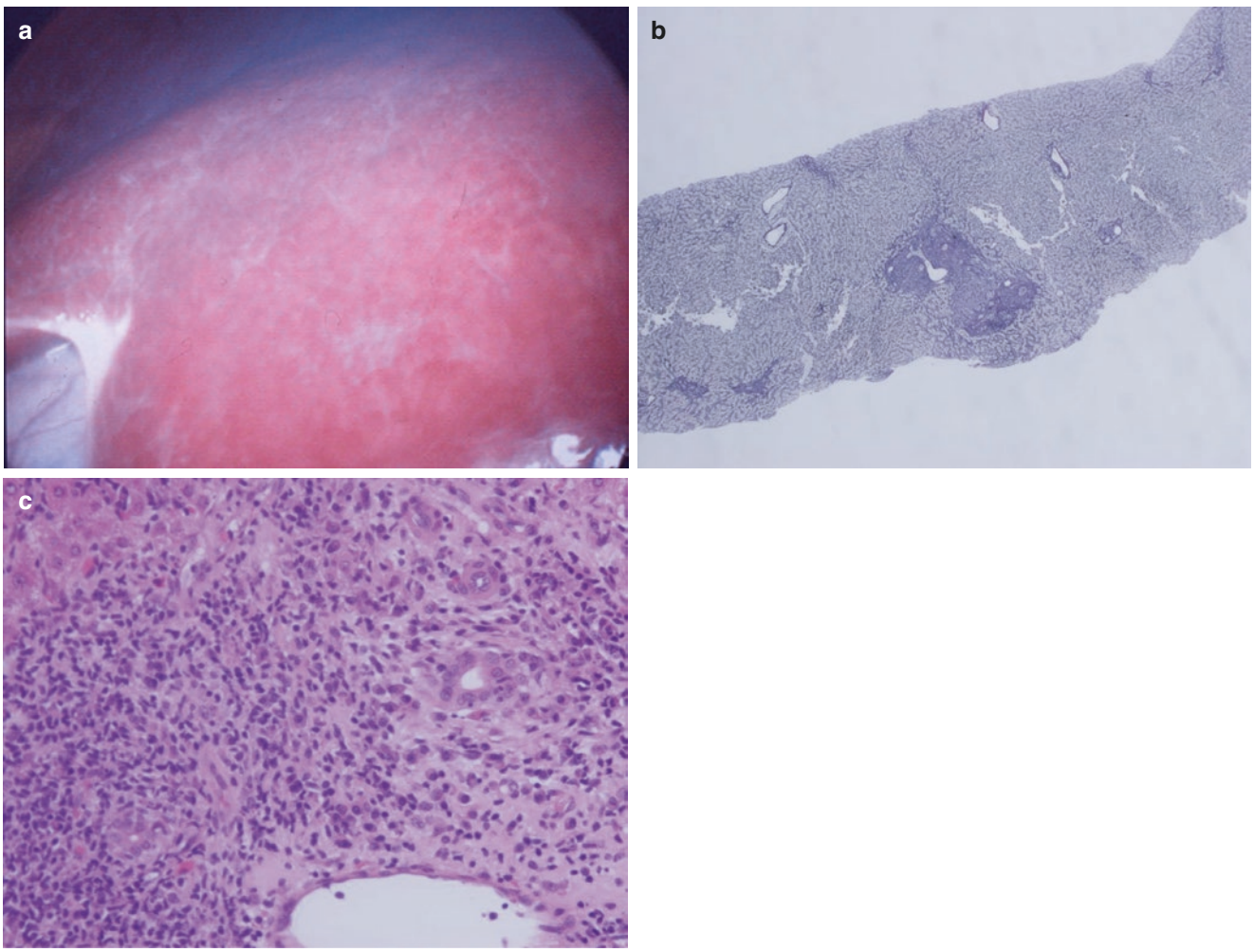

Fig. 9.8 Primary biliary cholangitis. (**a**) Peritoneoscopy shows small excavations of the liver surface, with white capsules. (**b**) Silver-stained liver tissue shows the presence of an enlarged portal tract. (**c**) Proliferating bile ductules and many lymphocytes and plasma cells in the enlarged portal tract are seen

UDCA 600 mg/day was administered, and ALP and GGT reverted to normal values after 2 months. Her liver function test remained within normal limits for a long time, which proved the efficacy of UDCA in treating a-PBC.

Patients with PBC have a complication of Sjogren syndrome, and PBC should be also considered the main cause of liver disease in primary Sjogren syndrome [49].

Case 9.8

A 45-year-old female usually complained of dry eye or mouth and Raynaud' phenomenon in cold season. Physical examination showed AST 55 IU/L, ALT 62 IU/L, ALP 525 IU/L, and GGT 198 IU/L, and detailed examinations showed AMA ×1280, ANA ×1280, thyroid test ×6400, microsomal test ×100, SS-A Ab negative, SS-B Ab negative, and HLA-DR2 positive. Peritoneoscopy with liver biopsy showed mosaic pattern of leopard with acinus markings on the surface, and there are histologically, enlarged portal tracts with infiltration of inflammatory cells and neither infiltration nor necrosis was seen in central area. In portal tract bile ducts were destructed with degeneration of epithelial cells, and lymphoplasmacytic infiltration was observed (Fig. 9.9). UDCA of 300 or 600 mg/day was administered, and serum value of ALP/GGT was reverted to normal value as well as that of AST/ALT for 3 years.

Clinical manifestations and histological features in PBC with or without Sjogren syndrome were not different, and stage 1 PBC is considered to be one of the first extraglandular manifestations in patients with primary Sjogren syndrome [49], and then relation between PBC and Sjogren syndrome should be studied more in detail.

Case 9.9

A 34-year-old female complained of general malaise and itching for 2 years, which was exacerbated after the delivery of her second child [50]. After delivery, her liver function tests reverted to normal values, but were elevated later. Liver

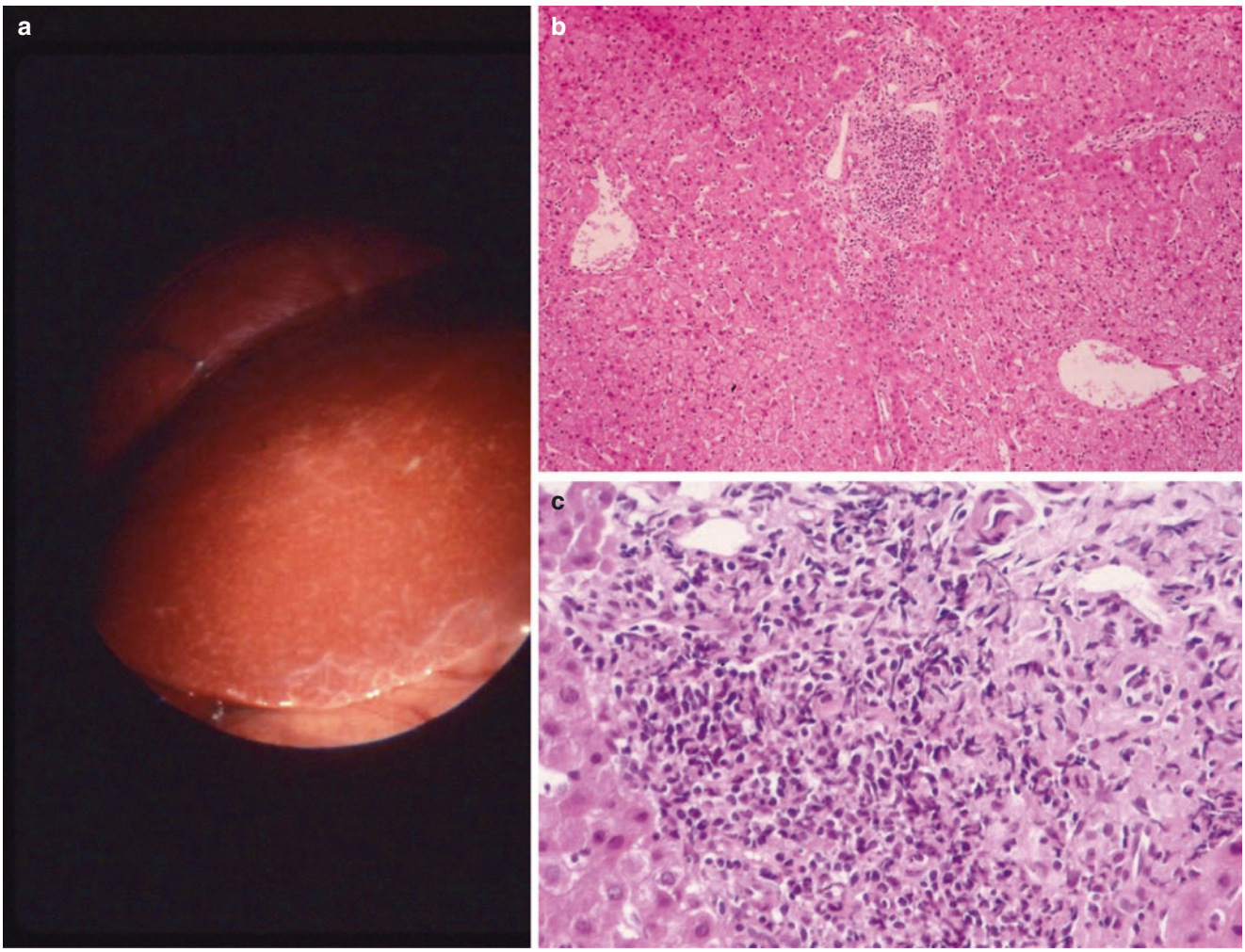

Fig. 9.9 Primary biliary cholangitis in a patient with Sjogren syndrome. (**a**) Peritoneoscopy shows appearance of leopard crest with white markings on the liver surface. (**b**) Microscopic view shows an enlarged porta tract with infiltration of inflammatory cells, and there are few necrotic areas. (**c**) There are lymphoplasmacytic cells in portal tract, and bile ducts are destructed with degenerated epithelial cells

function tests showed TBIL 0.74 mg/dL, AST 89 IU/L, ALT 131 IU/L, ALP 416 IU/L, GGT 177 IU/L, IgM 689 mg/dL, and AMA × 320. Peritoneoscopy showed a patchy liver surface, and liver biopsy showed an enlarged portal tract and fibrosis; the bile duct was damaged, with ductular proliferation accompanied by many lymphocytes and plasma cells (Fig. 9.10). UDCA 600 mg/day was effective, and the ALP, ALT, AST, and GGT levels were decreased to some extent.

Case 9.10

A 62-year-old female suffering from arthralgia with abnormal liver function tests for 10 years had TBIL 0.96 mg/dL, AST 164 IU/L, ALT 196 IU/L, ALP 483 IU/L, GGT 422 IU/L, IgM 345 mg/dL, and AMA ×320. Peritoneoscopy with liver biopsy showed early nodular formation on the liver, liver biopsy showed bridging fibrosis, and bile duct loss, interface, and intralobular hepatitis were noted (Fig. 9.11). The findings in liver biopsy were consistent with PBC stage 3. The administration of UDCA with and without bezafibrate did not improve liver chemistry. Ascites and leg edema followed by liver failure occurred 6 years later. The levels of ALP, ALT, AST, and GGT in serum were high, and UDCA did not improve liver chemistry in this a-PBC patient.

Clinical manifestations and liver histology with peritoneoscopic findings in a patient of s-PBC is demonstrated in Chap. 6 (Case 6.2), and the patient died of hepatic failure with encephalopathy 3.5 years after initial presentation.

The PBC-AIH overlap syndrome is defined by the association of PBC and AIH in a patient, either simultaneously or consecutively [51]. The overlap syndrome has been applied to some cases with aggregate scores of definite or probable AIH using the modified scoring system of the International Autoimmune Hepatitis Group and cholestatic state of biochemical study combined with seropositivite-AMA [51]. Other study suggests requirement for two out of three diagnostic criteria of AIH and PBC among patients suspecting of overlap syndrome (Table 9.2) [52], and about 10% of AIH and PBC belongs in the overlap category [53]. The histological features include a variable combination of inflammatory

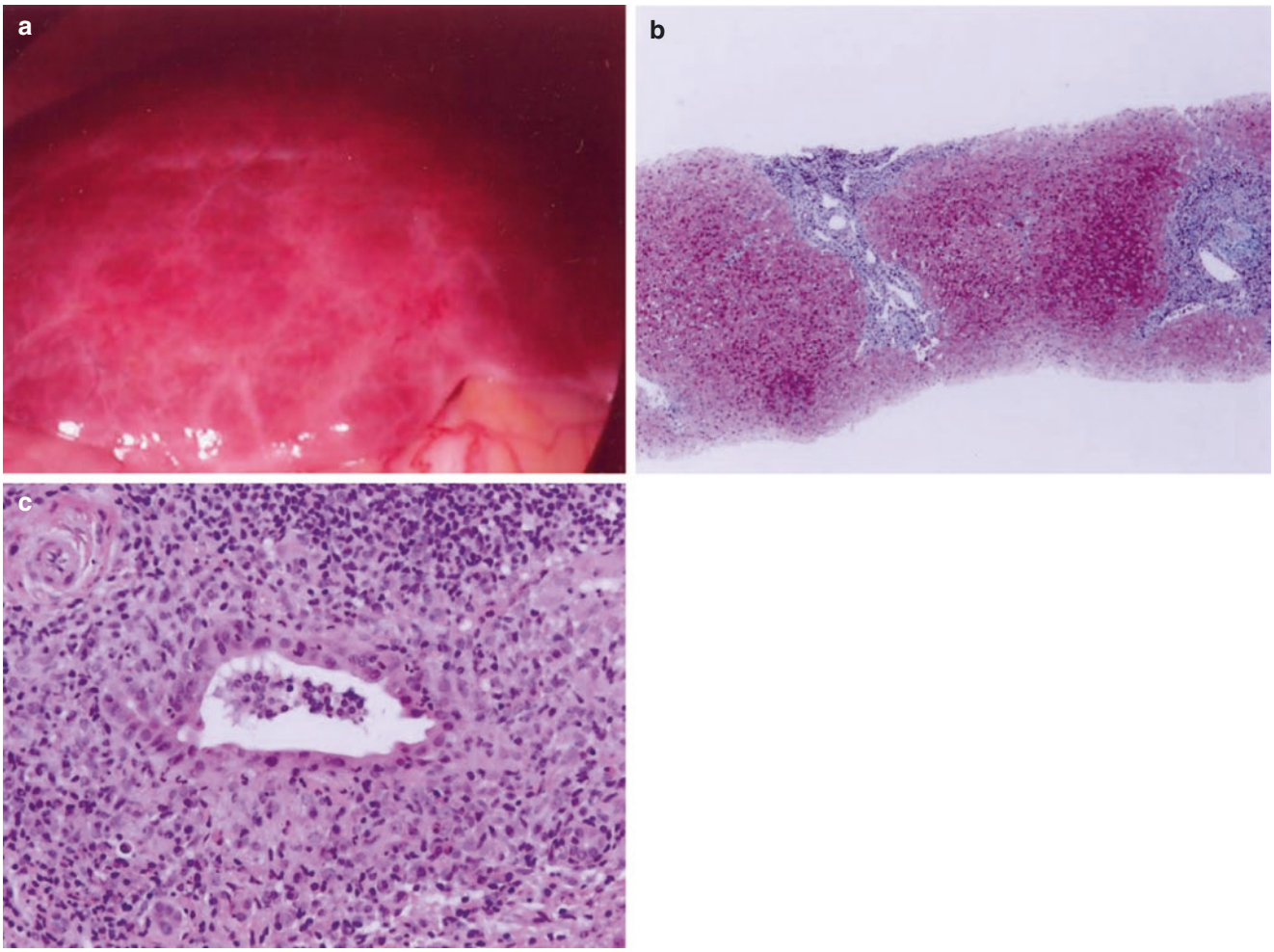

Fig. 9.10 Primary biliary cholangitis. (**a**) Peritoneoscopy shows patchy markings on the liver surface. (**b**) The portal tract is enlarged, and fibrosis extends into the lobules. (**c**) The interlobular bile duct is damaged, with an aggregate of lymphocytes, neutrophils, and eosinophils surrounding the damaged bile duct. Their inflammatory cells infiltrate beyond the basement membrane of the bile duct

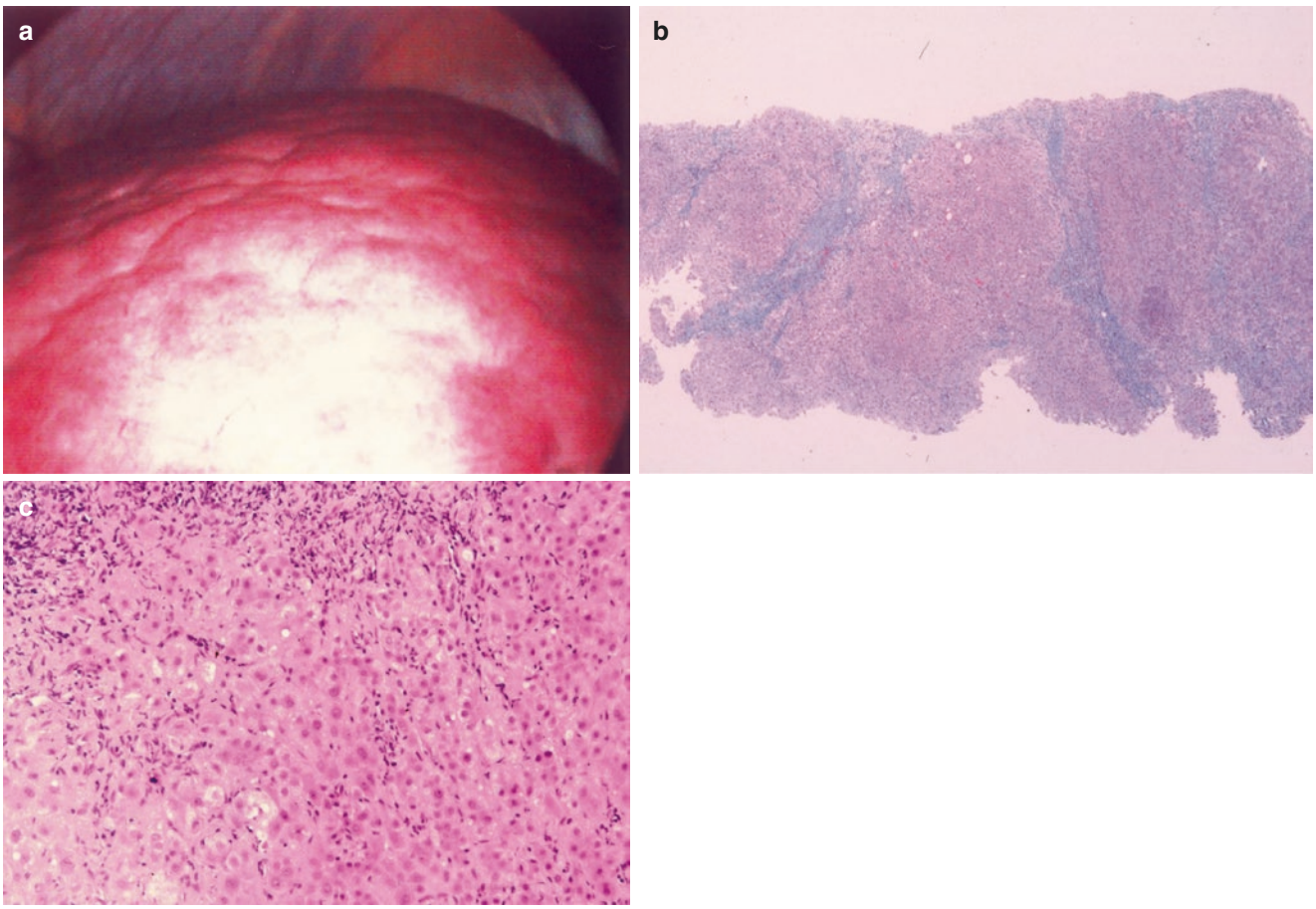

Fig. 9.11 Primary biliary cholangitis. (**a**) Peritoneoscopy shows early nodular formation and deep fissuring excavation on the liver surface. (**b**) Masson's trichrome stained liver biopsy shows bridging fibrosis, and the portal tract is expanded. (**c**) Interface or intralobular hepatitis is seen

Table 9.2 Diagnostic criteria of overlap syndrome (Paris criteria)

AIH	1.	ALT>5 times upper limit of normal
	2.	IgG > 2 times upper limit of normal, or anti-SMA positive
	3.	Chronic hepatitis pattern of injury on liver biopsy
PBC	1.	Alkaline phosphatase>2 times upper limit of normal
	2.	AMA positive
	3.	Florid duct lesion on liver biopsy

cell infiltrates directed at the bile ducts and hepatocytes, and development of superimposed AIH can result in rapid progression toward cirrhosis and liver failure [54].

Case 9.11

A 67-year-old male was found to have AST 447 IU/L, ALT 712 IU/L, ALP 266 IU/L, GGT 247 IU/L, ANA × 1280, and AMA × 40. Peritoneoscopy showed an irregular surface with red markings, formation of large nodules, and lymphangiectasia; liver biopsy showed nodule formation separated by broad septa and lymphoplasmacytic infiltration from the portal tracts, while the bile ducts decreased in number (Fig. 9.12). Administration of UDCA reduced the ALP, ALT, AST, and GGT levels for a while, but transaminase was then elevated again. Prednisolone and UDCA administration reverted both ALT/AST and ALP/GGT to near-normal values and reduced ANA titer. UDCA and a small dosage of prednisolone maintained normal liver function in the long term.

9.4 Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease caused by chronic inflammatory destruction of intrahepatic or extrahepatic bile ducts (large duct), and is frequently accompanied by inflammatory bowel disease, usually chronic ulcerative colitis [55]. Many patients are <50 years old at the time of diagnosis, with a male preponderance of 3 to 1. There is a variant form of small duct PSC in which findings from cholangiographic study are normal [56] and of PSC overlapped with autoimmune hepatitis [57].

Genetic and environmental factors contribute to the pathogenesis of PSC, and genome-wide association studies identified genomic region of HLA antigen-B locus most important for its development, and several other genomic regions are said to associate with disturbance of immune self-recognition and adaptive immunity in PSC [58]. Microbial component

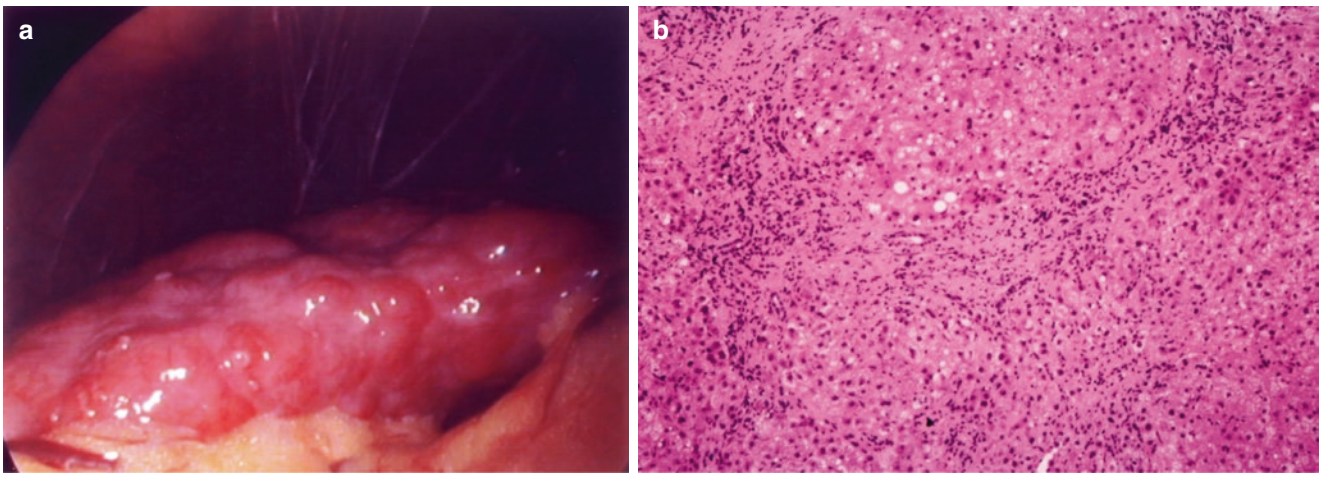

Fig. 9.12 Macroscopic and microscopic liver findings in overlap syndrome of primary biliary cholangitis and autoimmune hepatitis. (**a**) Peritoneoscopy shows adhesion of liver surface to the peritoneum. The liver surface is wavy. Large and irregularly sized nodules are visible, with red markings. (**b**) Liver histology reveals broad septum fibrosis, and inflammatory cells are seen in the portal tract

entering into the portal circulation from the gut could contribute to biliary inflammation [59]. Moreover gut-derived activated T lymphocytes may home to the liver during the development of PSC [60], and cholangiocytes undergo the phenomenon of cellular senescence influenced by various cytokines [61] and participate in pathogenesis of PSC [62].

In the early stage, PSC is asymptomatic in some patients, and 5–25% of them are discovered because of elevated serum alkaline phosphatase. In some cases, the disease progresses, and biliary cirrhosis develops; this is followed by liver failure [63].

Follow-up studies have shown considerable variations in the clinical course. The diagnosis of PSC is based on clinical, laboratory, and morphological findings as well as by endoscopic retrograde cholangiopancreatography (ERCP). Serum biliary enzyme is elevated, and protoplasmic-staining antineutrophil cytoplasmic antibodies are positive. ERCP or magnetic resonance cholangiopancreatography (MRCP) [64] shows irregular wall contour and stenosis of intrahepatic or extrahepatic bile ducts with prestenotic dilatation.

Liver biopsy is rarely done in these patients unless issues remain. Histological features are classified into four stages. In stage 1, changes are confined within the portal boundaries, with infiltration of lymphocytes, plasma cells, and neutrophils. Lymphoid follicles or aggregates are occasionally present. Small bile ducts are degenerated, and the portal stroma is edematous. In stage 2, the portal tracts are swollen, with disruption of the parenchymal limiting plates and cholangitis. Biliary interface activity is accompanied by focal ductular proliferation. In stage 3, portal fibrosis develops with formation of portal-to-portal fibrous septa and, in stage 4, biliary cirrhosis. The natural course of PSC shows different survival rates—depending on the histological stage—and its association with autoimmune diseases is far less than in PBC. It is complicated by cholecystolithiasis or choledocholithiasis and cholangiocarcinoma. However, the disease may reappear in about 25% of patients after transplantation [65].

Treatment varies from conservative therapy with UDCA [66] to invasive therapy using balloon and stent insertion to reduce isolated stenosis of intrahepatic or extrahepatic stenosis of bile ducts [67]. Liver transplantation is the therapy of choice in late-stage PSC [68] and may have a role in treatment of cholangiocarcinoma.

Case 9.12

A 20-year-old male came to our clinic complaining of epigastric pain, fever, and bloody stools. Laboratory data showed TBIL 0.32 mg/dL, ALT 32 IU/L, AST 23 IU/L, ALP 587 IU/L, GGT 130 IU/L, IgG 2270 mg/dL, ANA ×40, and negative AMA. ERCP showed irregularly narrowed and dilated intrahepatic bile ducts (Fig. 9.13). Laparoscopy showed white markings with dilated peripheral portal veins on the liver surface, and liver biopsy revealed onion-skin fibrosis surrounding small bile ducts (Fig. 9.14). UDCA was administered orally. Ulcerative colitis was diagnosed by colonoscopy.

Case 9.13

An asymptomatic 66-year-old female has TBIL 0.93 mg/dL, ALT 55 IU/L, AST 40 IU/L, ALP 674 IU/L, and GGT 390 IU/L. ERCP showed stenosis or stricture of the intrahepatic or extrahepatic bile ducts (Fig. 9.15). Peritoneoscopic findings revealed a wide excavation at the edge of the left lobe and a thick hepatic capsule with white markings (Fig. 9.16a). UDCA was administered. Excavation developed extensively on the liver surface, with increased white markings after 7 years (Fig. 9.16b). Liver biopsy from the first peritoneoscopy showed proliferating bile ducts with lymphocytic and eosinophilic infiltrate in the portal tract (Fig. 9.17).

To investigate liver fibrogenesis in PSC, we examined the expression of stem cell factor (SCF), a ligand of c-kit, in the injured bile ducts of four patients with overt PSC and histologically classified as stage 2 or 3. Mast cells were identified by immunohistochemistry using anti-human mast cell tryptase

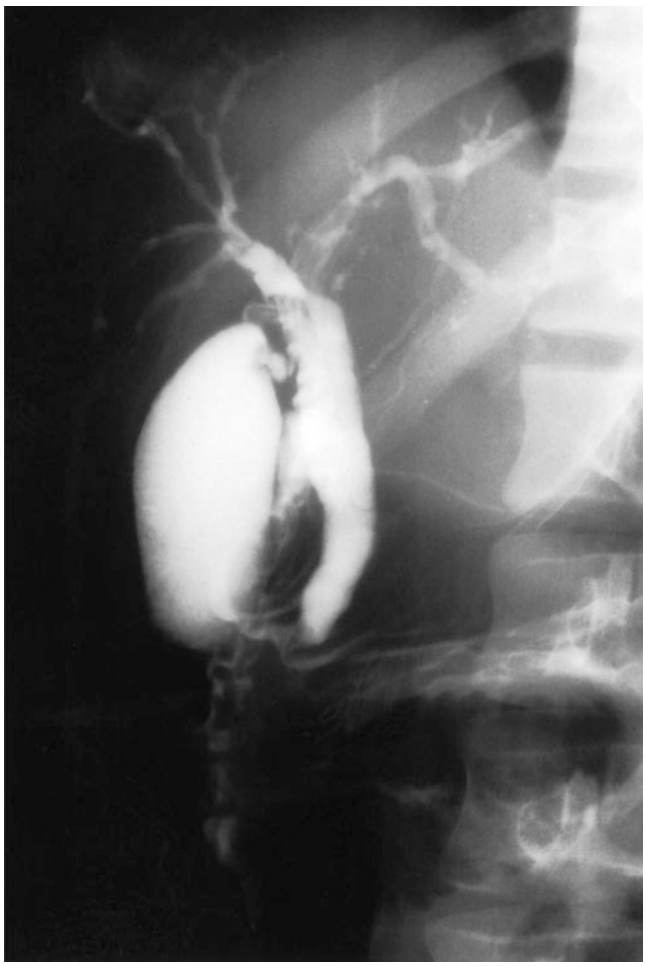

Fig. 9.13 Early-stage primary sclerosing cholangitis. Endoscopic retrograde cholangiopancreatography shows narrowing and dilatation of intrahepatic bile ducts

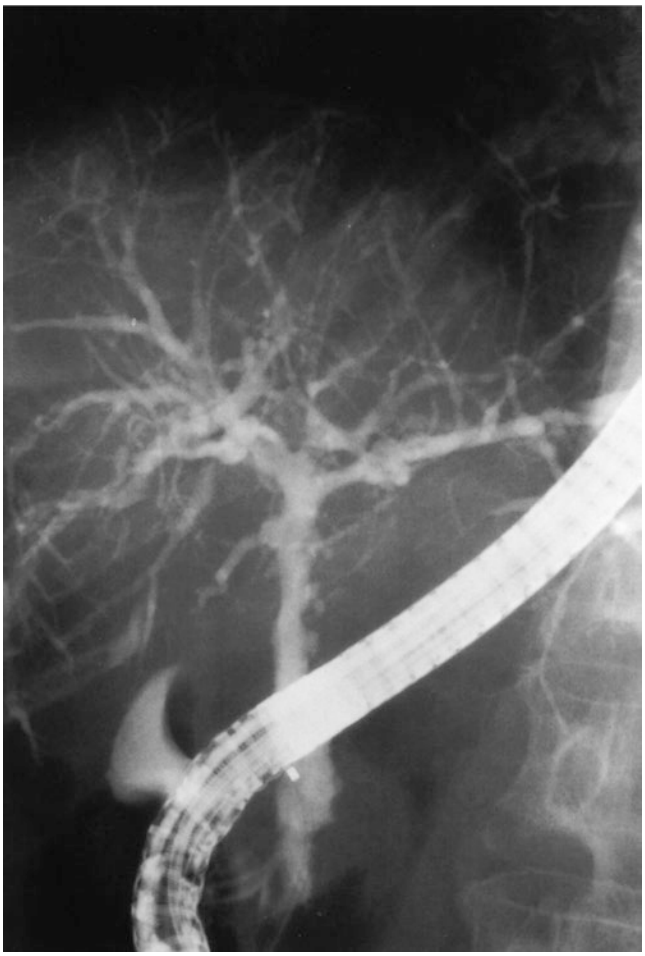

Fig. 9.15 Late-stage primary sclerosing cholangitis Endoscopic retrograde cholangiopancreatography shows irregular and narrowing wall of the intrahepatic or extrahepatic bile duct

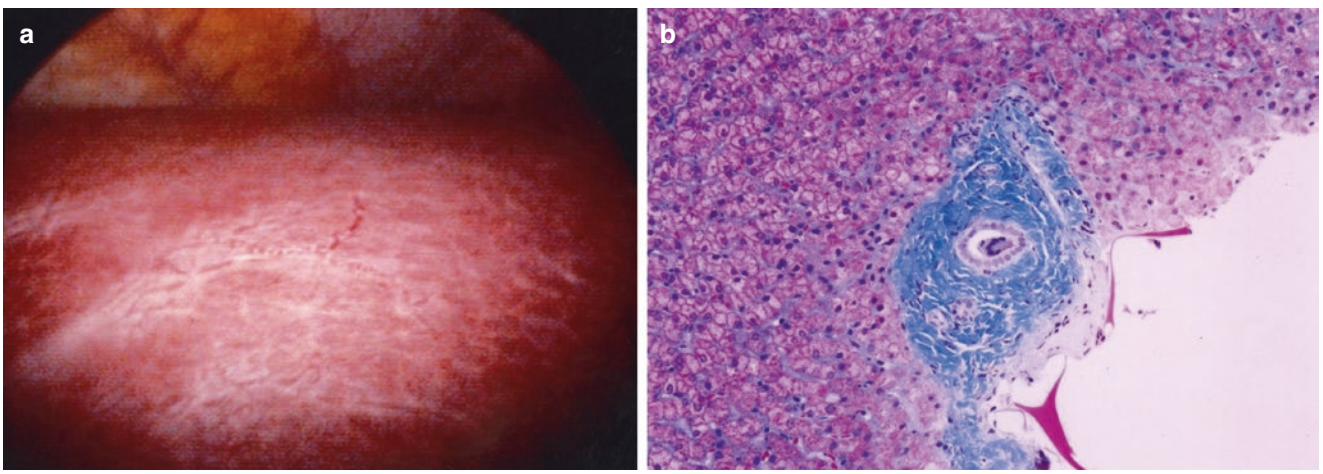

Fig. 9.14 Early-stage primary sclerosing cholangitis (**a**) Peritoneoscopy shows white markings on the smooth surface of enlarged liver. (**b**) Masson's trichrome stain shows onion-skin fibrosis in the portal tract

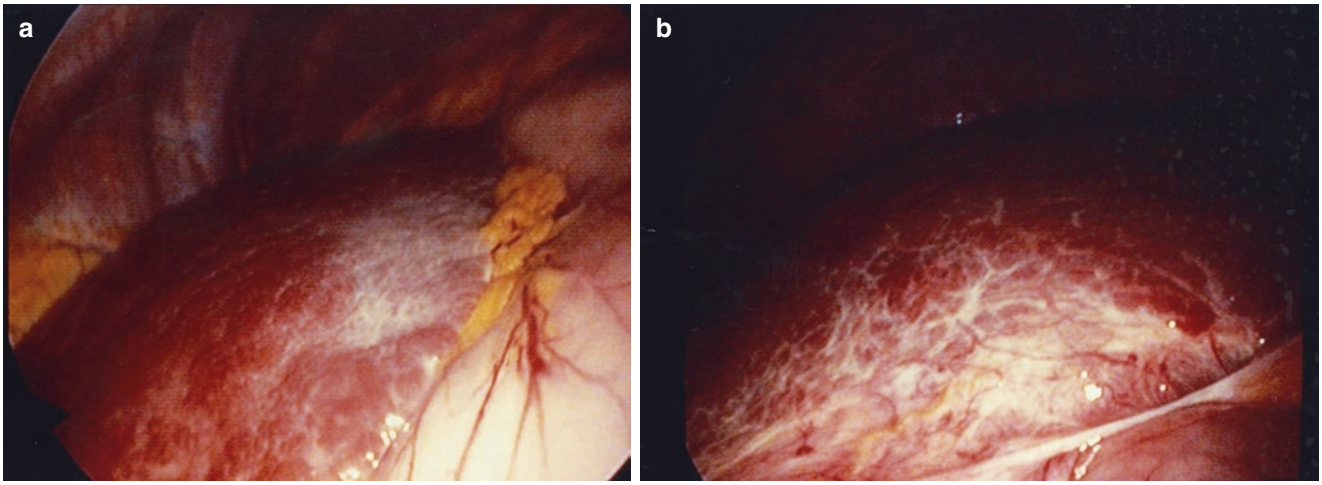

Fig. 9.16 Peritoneoscopic findings in advanced primary sclerosing cholangitis (**a**) Peritoneoscopy shows large excavation on the edge of the left lobe, and white markings are clearly demarcated on the surface. (**b**) Repeat peritoneoscopy shows wide development of excavation on the left lobe, and the liver surface is more irregular. The liver capsule has become thick

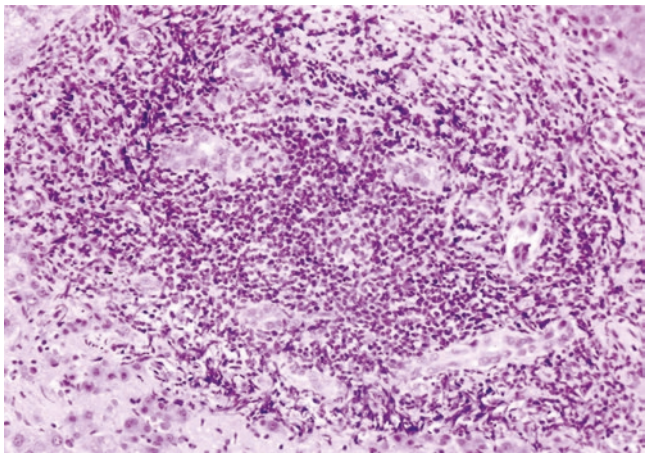

Fig. 9.17 Liver histology from the first peritoneoscopy. The portal tract is infiltrated with many lymphocytes and lymphoid follicles. Proliferating bile ductules and damaged bile duct are visible

(HMCT) and anti-c-kit antibodies to clarify their relationship with portal fibrosis and damaged bile ducts. SCF was detected in the epitheliums of most bile ducts in PSC, and many HMCT- and c-kit-positive mast cells were found in the portal tracts (Fig. 9.18). Image analysis showed more significant numbers of c-kit-positive mast cells per area of portal tract in PSC than in chronic hepatitis C, which may be increased from stage 2 to 3. The infiltration of c-kit-positive cells in SCF-positive portal tracts destroyed bile ducts, and c-kit mast cells were suggested to associate closely with hepatic fibrosis in PSC [69–73].

The overlap syndrome of primary sclerosing cholangitis and AIH is defined as meeting criteria of probable or definite AIH with cholangiographic evidence of PSC and characterized by ANA- or SMA-seropositive, interface hepatitis and hypergammaglobulinemia in mixture with cholestatic change of serum alkaline phosphatase, occurrence of inflammatory bowel disease, and fibrous obliterative cholangitis. The overlap syndrome of PSC and AIH is in general resistant to corticosteroid.

9.5 IgG4-Related Sclerosing Cholangitis

IgG4-related sclerosing cholangitis is referred to the biliary manifestation of IgG4-related systemic disease [74] and is an autoimmune inflammatory condition associated with autoimmune pancreatitis [75]. This type of sclerosing cholangitis involves the extrahepatic ducts, is characterized by IgG4-positive lymphoplasmacytic infiltrate, and is steroid-responsive [76]. It should be distinguished from PSC (Table 9.1) [77].

The clinical presentation of IgG4-related sclerosing cholangitis is different from PSC. Diabetes mellitus, pseudotumor in the lung or pancreas [78, 79], and multifocal fibrosclerosis often precede or follow IgG4-related sclerosing cholangitis, and autoimmune hepatitis is rarely seen [80, 81]. The typical imaging findings of intrahepatic or extrahepatic bile ducts and pancreas in IgG4-related sclerosing cholangitis and autoimmune pancreatitis [82], and the histological findings of autoimmune pancreatitis, are fairly well recognized. However, the pathogenesis remains unclear.

Glucocorticoid therapy reduces IgG4-positive plasma cell infiltrate [80], and a consensus on the treatment of IgG4-related sclerosing cholangitis has been reached: an initial dose of prednisolone 30–40 mg/day and long-term administration are recommended [83]. Azathioprine appears useful in patients with partial response to prednisolone [84]. There are cases of IgG4-associated autoimmune hepatitis, [85] which should be distinguished from classical one. Further study is needed on this new disease entity.

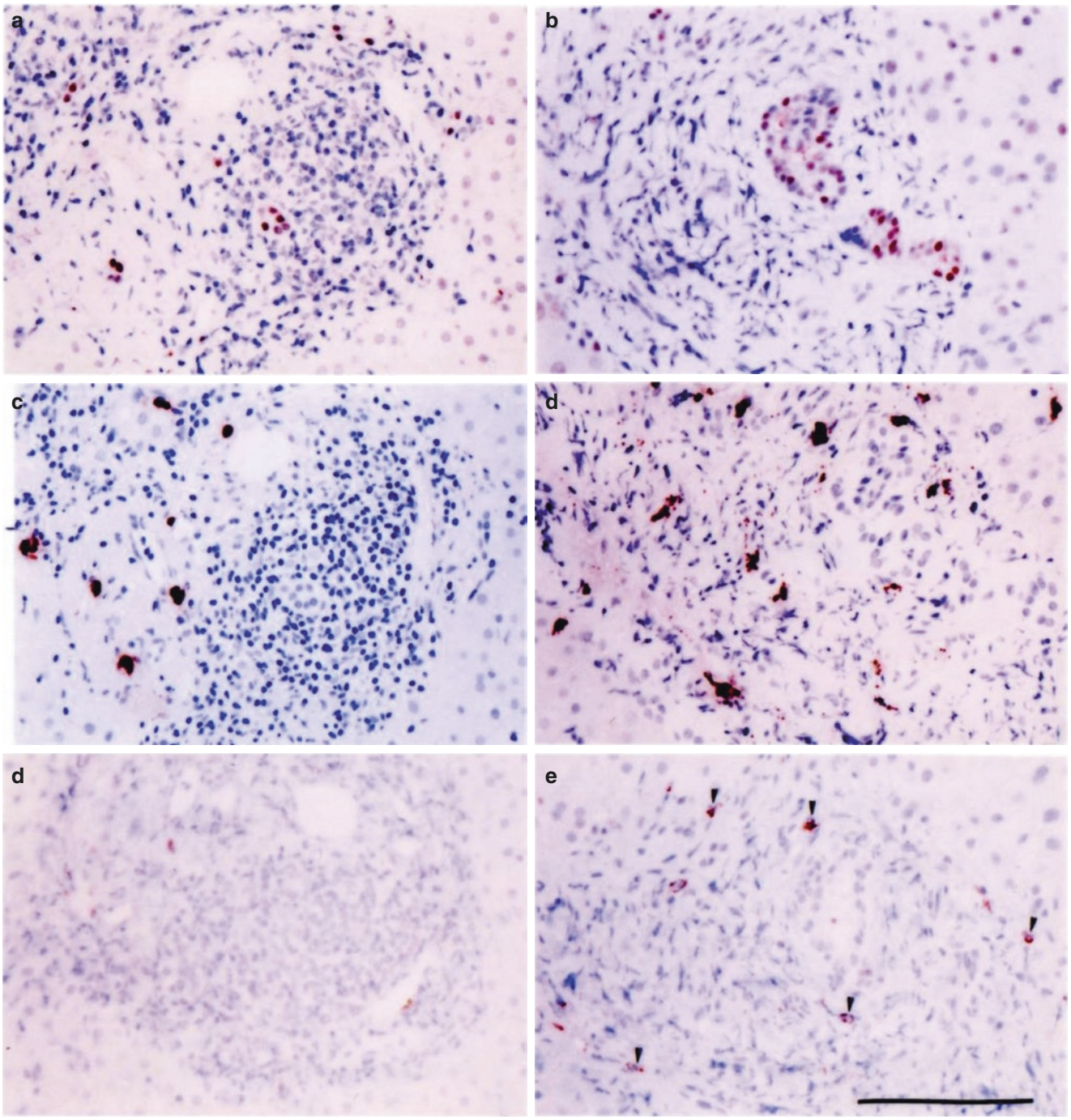

Fig. 9.18 Expression of stem cell factor, human mast cell tryptase, and c-kit in patients with chronic hepatitis C and primary sclerosing cholangitis. (**a**) Biliary epithelial cells in a portal tract show weak staining of stem cell factor in chronic hepatitis C. (**b**) Immunoreactivity of stem cell factor in most epithelial cells of bile ducts in primary sclerosing cholangitis. (**c**) Several positive human mast cells are shown in the portal tract in chronic hepatitis C. (**d**) Many positive human mast cells are visible in the portal tract in primary sclerosing cholangitis. (**e**) Few c-kit-positive cells are seen in the portal tract in chronic hepatitis C. (**f**) Several c-kit-positive cells (arrowheads) are visible in the portal tract in primary sclerosing cholangitis. Bar = 100 μm. Reuse of Ishii M, et al. A role of mast cells for hepatic fibrosis in primary sclerosing cholangitis. Hepatol Res 2005; 31: 127–31., with permission from Wiley

Case 9.14

A 77-year-old male suffered from chronic pancreatitis and complained of anorexia.

Jaundice was indicated, and serum examination showed TBil 1.92 mg/dl, DBil 1.58 mg/dl, AST 137 IU/l, ALT 186 IU/l, ALP 2227 IU/l, GGT 871 IU/l, P-amy 54 IU/l, CA19–9185 U/ml, IgG 2124.8 mg/dl, and IgG4 471 mg/dl. US and CT with contrast medium revealed enlarged pancreas, dilation of choledochus and intrahepatic bile ducts, and enlarged gall bladder (Fig. 9.19a–d). MRCP and

Table 9.1 Clinicopathological difference between IgG4-related sclerosing cholangitis and primary sclerosing cholangitis

Variable	IgG4-related sclerosing cholangitis	Primary sclerosing cholangitis
Age	Old	Young and old
Sex	Male > female	Male = female
Liver chemistry	Jaundice	Liver functional disturbance
IgG4 in serum	High	Normal
Complication	Diabetes mellitus, pancreatitis, multifocal fibrosclerosis, interstitial pneumonia	Irritable bowel syndrome
Therapy	Glucocorticoid	Transplantation
Prognosis	Good	Worse
IgG4-positive cells	Positive	
Obliterative phlebitis	Positive	Negative
Onion-skin lesion	Rare	Positive
Stage (Ludwig criteria)	I–II	I–IV

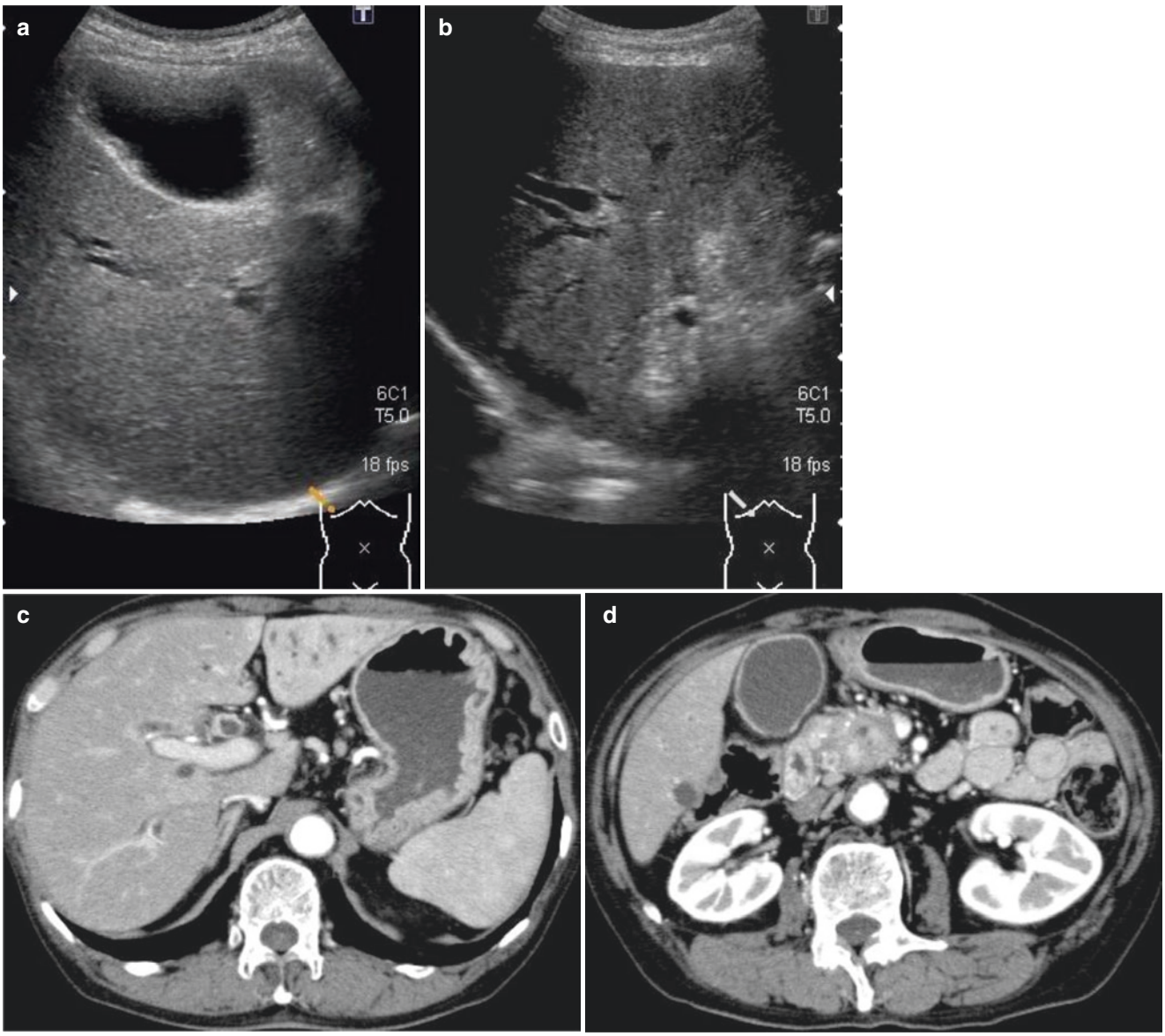

Fig. 9.19 (**a**, **b**) US shows enlarged gall bladder with stone shadow and dilated bile ducts. (**c**, **d**) CT present thickened wall of gall bladder, and dilated common and intrahepatic bile ducts are found. Head of pancreas is swollen. (b, c & d. Reuse of Douhara A, et al. Gastroenterol Endosc 2011; 53: 1617–25., with permission from Jpn Soc Gastroenterol Endosc)

ERCP presented dilated middle portion and stenotic lower portion of choledochus, and main duct of pancreas was irregularly dilated. Enlarged papilla Vater was detected by ERCP (Fig. 9.20a–d). Biopsied tissue from papilla Vater showed normal arrangement of columnar epitheliums and edematous submucosa area with infiltration of inflammatory cells. Magnified view revealed abundant plasma cells and eosinophilic leukocytes in submucosal area, and many of plasma cells contain IgG4-positive immunoreaction (Fig. 9.21a–d).

Case 9.15

A 65-year-old male had obstructive jaundice, and cholangiocarcinoma was suspected by abdominal ultrasound. Percutaneous transhepatic cholangiodrainage and endoscopic retrograde biliary drainage reduced jaundice, and his general status was stable for 1.5 years. MRCP showed reduced tail size of pancreas, and liver chemistry showed TBIL 1.39 mg/dL, AST 99 IU/L, ALT 77 IU/L, ALP 1135 IU/L, GGT 737 IU/L, IgG 2307 mg/dL, and IgG4 165 mg/dL. ERCP revealed stricture and dilatation of intrahepatic bile ducts.

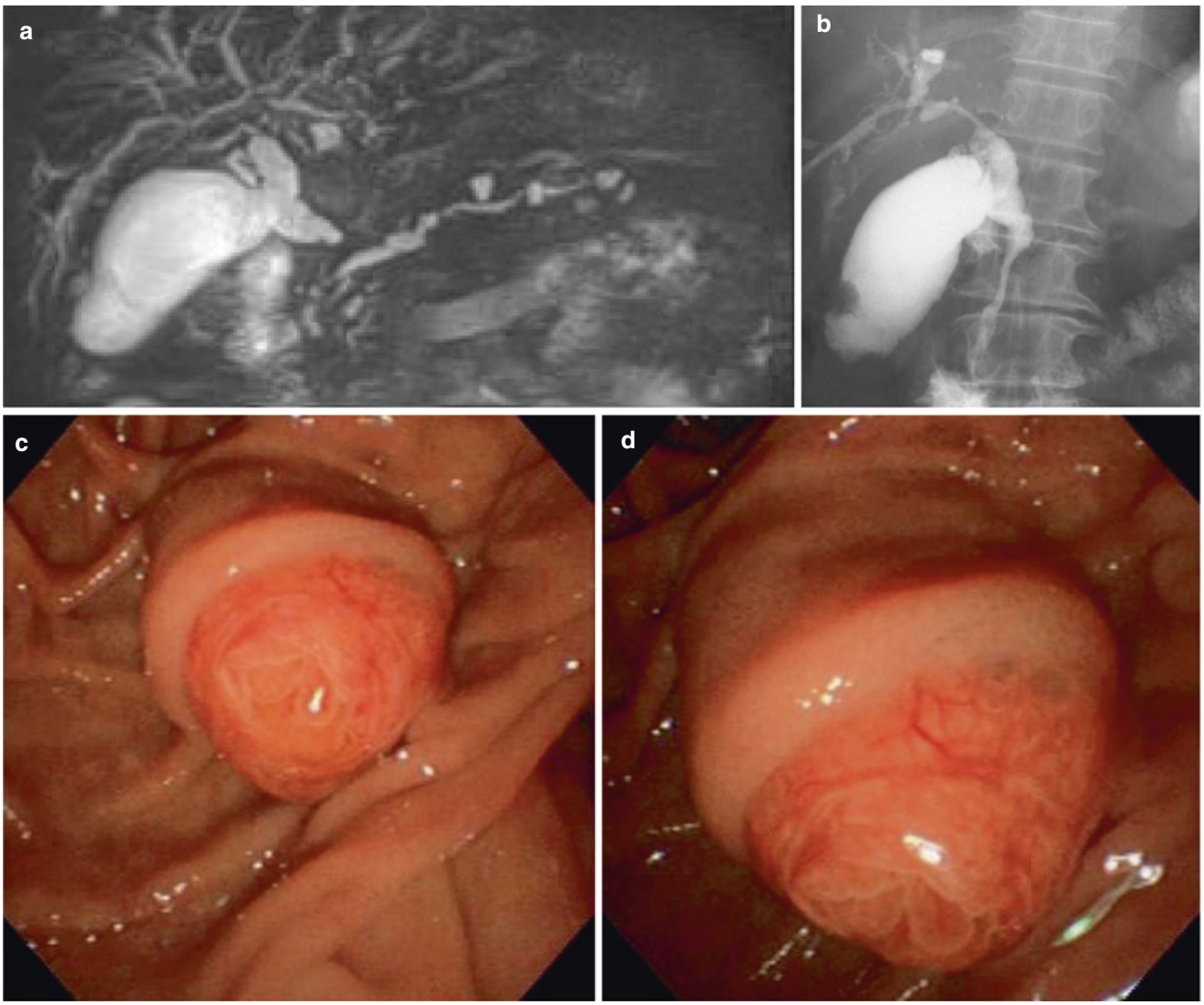

Fig. 9.20 (**a**, **b**) MRCP and ERCP shows dilated common in upper portion and intrahepatic bile ducts, and irregularly dilated pancreatic duct is seen. c.d. ERCP shows hyperemic and enlarged papilla Vater (a, b & d. Reuse of Douhara A, et al. Gastroenterol Endosc 2011; 53: 1617–25., with permission from Jpn Soc Gastroenterol Endosc)

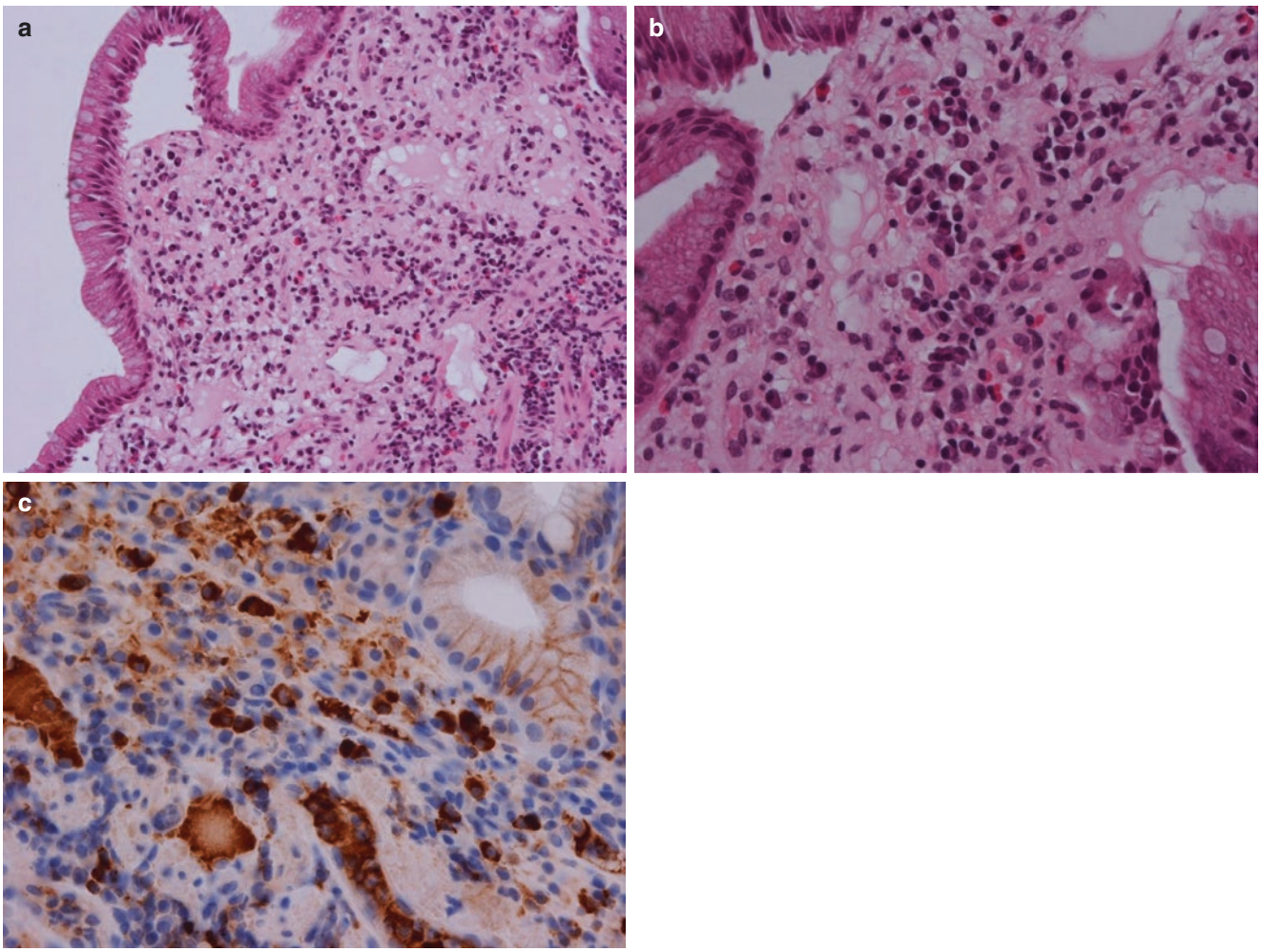

Fig. 9.21 (**a**) HE staining of papillae Vater shows edematous submucosa with many inflammatory cells. (**b**) Magnified view shows many plasma cells and eosinophilic leukocytes. (**c**) Immunohistochemistry shows IgG4 immunoreactivity in plasma cells. (a, b & c. Reuse of Douhara A, et al. Gastroenterol Endosc 2011; 53: 1617–25., with permission from Jpn Soc Gastroenterol Endosc)

The lower portion of the common bile duct was narrowed, and liver biopsy showed an enlarged portal tract with bile ductular proliferation and cluster of plasma cells and lymphocytes (Fig. 9.22). Prednisolone 20 mg/day was administered. Gradually, the dosage was tapered and ceased after 34 months, and liver function tests reverted to normal values.

Case 9.16

An 81-year-old male complained of appetite loss, weight loss, and general malaise. His liver tests showed AST 63 IU/L, ALT 54 IU/L, ALP 583 IU/L, GGT 373 IU/L, IgG 2437 mg/dL, and IgG4 487 mg/dL. ERCP showed stricture or dilatation of intrahepatic biliary ducts and strictured lower portion of the common bile duct with an irregularly sized pancreatic duct, and liver tissue showed an enlarged and inflamed portal tract with fibrous bands, neutrophils, eosinophils, and lymphoplasmacytic cells (Fig. 9.23). Prednisolone 25 mg/day was administered. The dosage was gradually tapered and ceased after 5 months, and his liver function returned to normal.

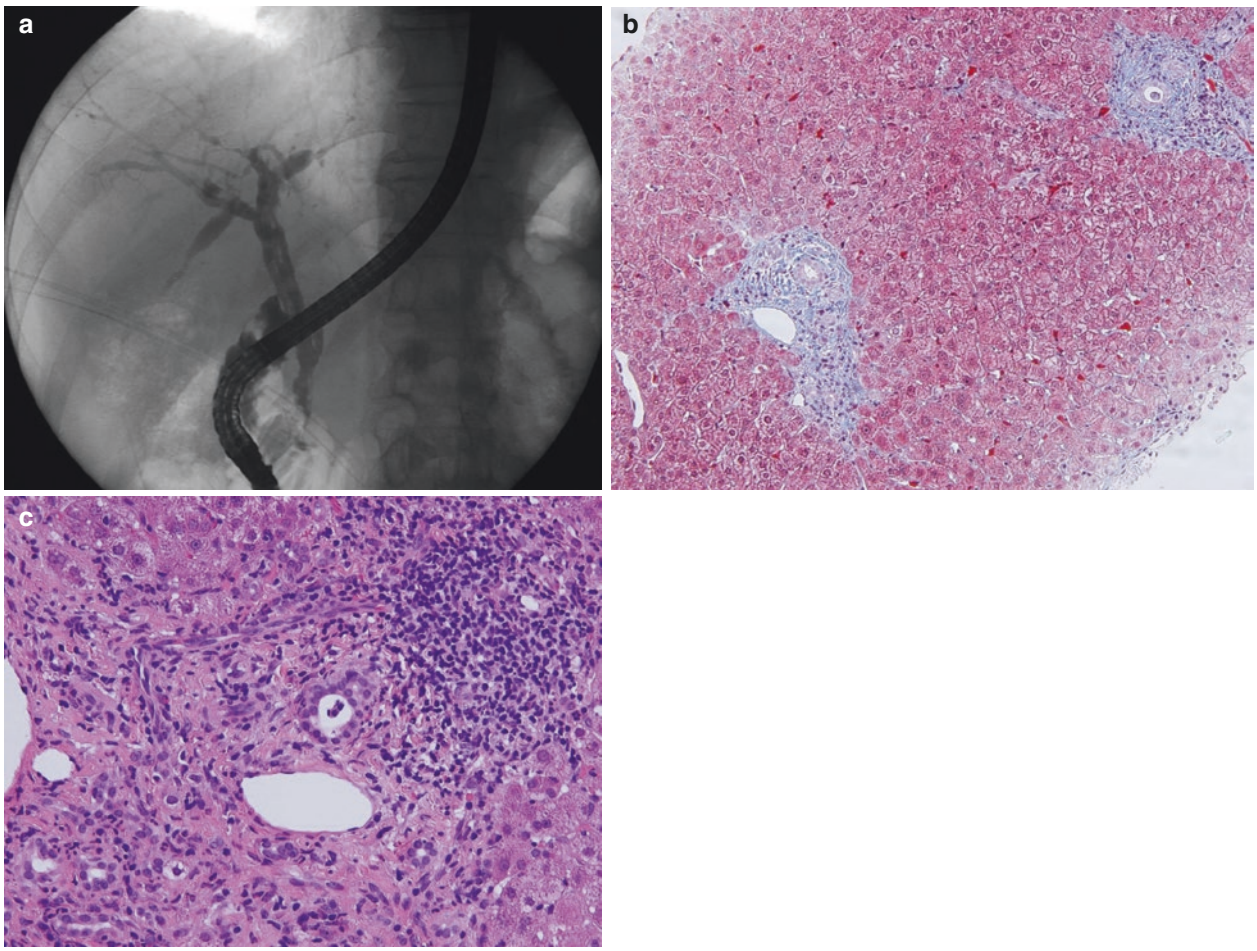

Fig. 9.22 IgG4-related sclerosing cholangitis. (**a**) Endoscopic retrograde cholangiopancreatography shows irregular stenosis of intrahepatic bile ducts, and stenotic area is seen in the lower portion of the choledochus. (**b**) Liver tissue stained by Masson's trichrome stain shows a portal tract enlarged by fibrosis. (**c**) The portal tract is enlarged by fibrosis, and proliferating bile ductules are seen. Clusters of lymphocytes are present with scattered plasma cells

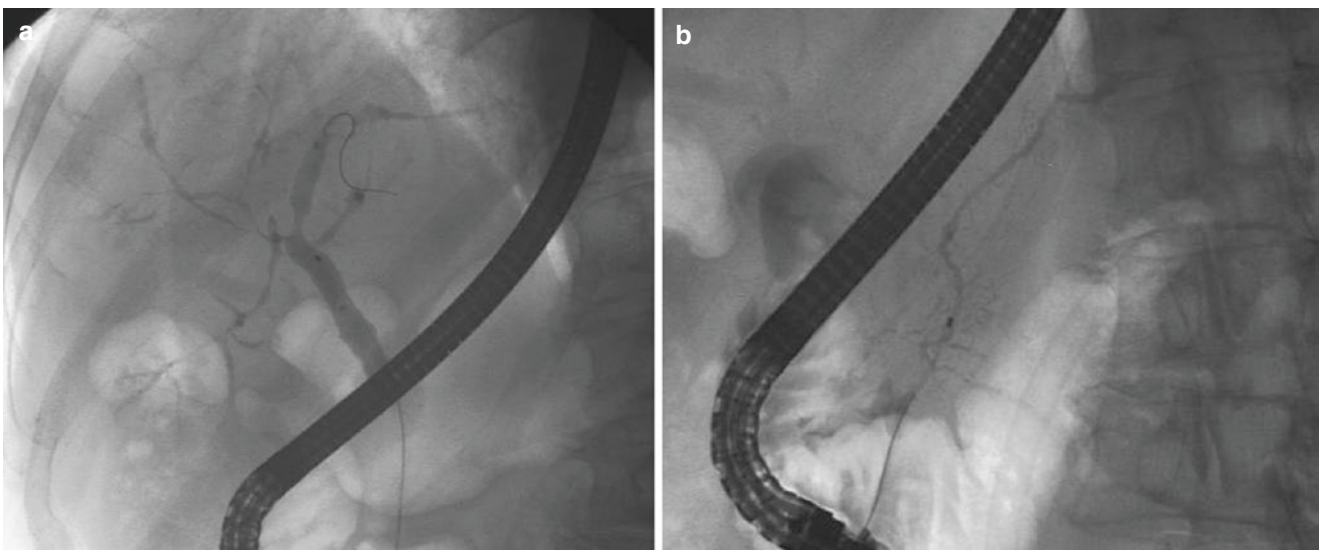

Fig. 9.23 IgG4-related sclerosing cholangitis. (**a**) Endoscopic retrograde cholangiopancreatography shows irregular stenosis of the intrahepatic bile ducts. (**b**) Endoscopic retrograde cholangiopancreatography shows irregular stenosis of the pancreatic duct. (**c**) Masson's trichrome stained liver tissue shows proliferating fibrosis from an enlarged portal tract, and inflammatory cells are present along the fibrotic area. (**d**) Interface hepatitis is seen, and the epitheliums of the bile ductule are damaged, with lymphoplasmacytic and eosinophilic infiltrate

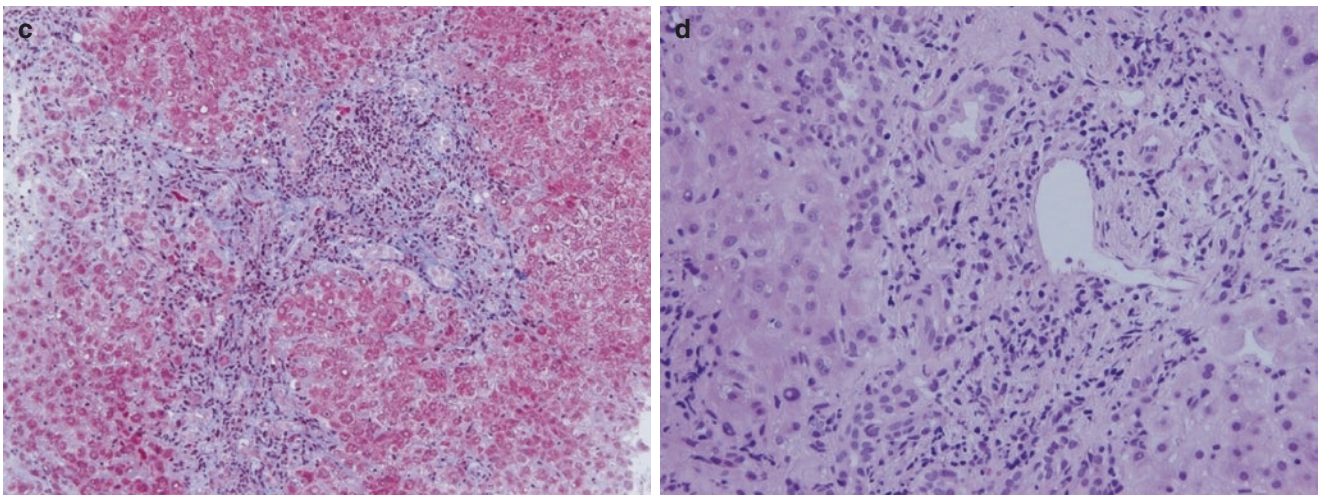

Fig. 9.23 (continued)

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