Chapter 5
Portal Hypertension in Rheumatic Diseases

Tadayuki Takagi and Hiromasa Ohira

Abstract Some rheumatic diseases are complicated by portal hypertension which can cause gastrointestinal varices and ascites requiring adequate treatment. The mechanism leading to portal hypertension often involves idiopathic portal hypertension, pulmonary hypertension, and liver cirrhosis. In systemic lupus erythematosus, mixed connective tissue disease, and systemic sclerosis, in particular, portal hypertension is often reported.

Esophagogastric varices can frequently occur in association with portal hypertension, with high bleeding ratios; special attention is necessary. In addition, in the long-term follow-up process, hepatic atrophy and ascites can be encountered, making treatment of the primary disease quite difficult. Attention should be paid not only to the treatment of the primary disease but also to the possible development of portal hypertension.

Keywords Portal hypertension · Rheumatic disease · Varices · Idiopathic portal hypertension (IPH) · Pulmonary hypertension (pulmonary artery hypertension)

5.1 Introduction

Some rheumatic diseases are accompanied by portal hypertension underlain by idiopathic portal hypertension (IPH) or pulmonary hypertension (pulmonary artery hypertension), resulting in gastrointestinal varices and ascites, which may require treatment. In this paper, we describe the relationship between rheumatic diseases and portal hypertension and discuss their characteristic features.

T. Takagi (✉) · H. Ohira
Department of Gastroenterology, Fukushima Medical University School of Medicine, Fukushima, Japan
e-mail: daccho@fmu.ac.jp; h-ohira@fmu.ac.jp

H. Ohira, K. Migita (eds.), *Gastrointestinal and Hepatic Manifestations of Rheumatic Diseases*, https://doi.org/10.1007/978-981-13-6524-9_5

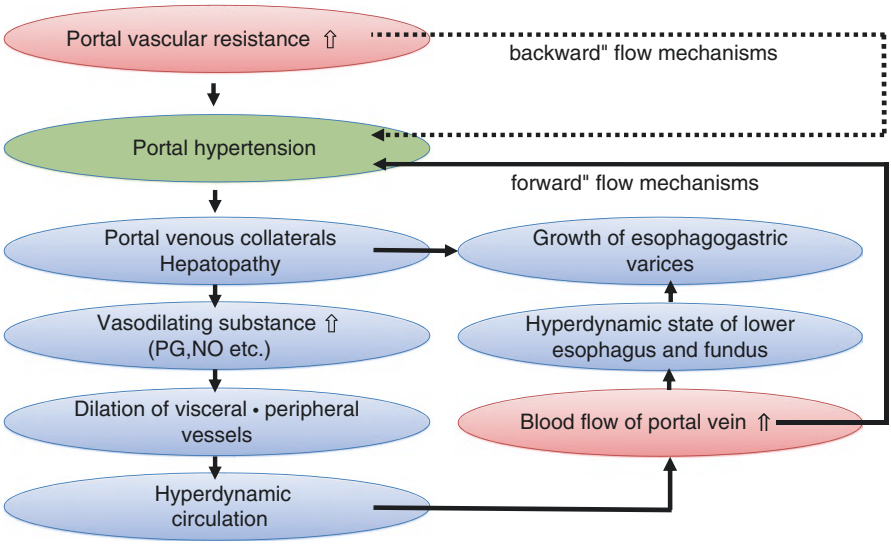

Fig. 5.1 Mechanisms of portal hypertension

5.2 Portal Hypertension

This is a condition in which the portal vein stasis increases portal pressure as a result of increased endovascular resistance in the pathway from the intrahepatic portal vein to sinusoid and hepatic vein, or increased blood inflow from intraperitoneal organs, other than the kidney. The mechanism of onset of portal hypertension involves vasodilating substances such as prostaglandin and nitric oxidases (NOs: inducible nitric oxide synthase [iNOS], endothermic nitric oxide synthase [eNOS]) [1] (Fig. 5.1). Normal portal venous pressure is 100–150 mmH_2O, whereas portal hypertension can involve an increased portal pressure of 200 mmH_2O or higher. There are three types of portal hypertension categorized according to the site of disturbance of blood flow: prehepatic, intrahepatic, and posthepatic. Relevant factors include extrahepatic portal vein obstruction and portal vein defects as prehepatic factors; presinusoidal idiopathic portal hypertension and schistosomiasis japonica and postsinusoidal liver cirrhosis as intrahepatic factors; and Budd-Chiari syndrome and right heart failure as posthepatic factors. Clinical symptoms include gastrointestinal varices (especially in the esophagus and stomach), splenomegaly, and ascites.

5.2.1 Rheumatic Diseases and Portal Hypertension

Although there are only a few reports on rheumatic diseases complicated by portal hypertension, they have been found in various diseases, including systemic lupus erythematosus (SLE) [2–8], mixed connective tissue disease (MCTD) [9–16],

systemic sclerosis (SSC) [17–29], limited cutaneous systemic sclerosis (CREST syndrome) [30, 31], Sjogren's syndrome (SjS) [32], Takayasu arteritis [33], rheumatoid arthritis (RA) [34], dermatomyositis (DM) [35], and Behçet's disease (BD) [36].

In the aforementioned diseases, portal hypertension is caused mainly by the following three factors: IPH, pulmonary hypertension (pulmonary artery hypertension), and liver cirrhosis can occur as complications in the disease. IPH is the most common cause of portal hypertension in all rheumatic diseases. Pulmonary hypertension is one complication of MCTD. As a form of liver cirrhosis due to factors other than infections and alcohol, primary biliary cholangitis (PBC) can complicate CREST syndrome. Proposed causal factors are described in detail below.

5.2.2 Conditions Characterized by Portal Hypertension in Rheumatic Diseases

5.2.2.1 Idiopathic Portal Hypertension (IPH)

IPH is a disease characterized by portal hypertension due to obstruction and stenosis of the peripheral portal vein branch. This disease does not lead to liver cirrhosis and is only rarely accompanied by hepatoma. Although much remains unknown about the mechanism of onset, some hypotheses have been proposed: the intrahepatic peripheral portal vein thrombosis theory, splenic origin theory, and autoimmune abnormality theory [37]. IPH is more prevalent in females than in males, and onset is more often in the 40s–50s age groups than in other age groups. Pathologically, it is characterized by sclerosis in the small portal areas, and it is often accompanied by elastic fiber deposition. The basic pathologic feature of this disease is collapse and obstruction of the peripheral portal vein branch associated with sclerosis in small portal areas; inflammatory cell infiltration can occur, but it is mild. IPH and SSC are histologically similar with increased expression of transforming growth factor-β (TGF-β) and increased collagen fibers in the peripheral portal vein and the skin. In SSC skin, endothelial to mesenchymal transition (EndMT) is observed. It has been hypothesized that endothelial cells acquire a myofibroblastic feature by the action of TGF-β, resulting in fibrosis in the distal portal veins and increased portal pressure [29] (Fig. 5.2). Hepatic parenchyma is reported to include hepatic cord atrophy and sinusoid dilation, with hyperplasic nodules; sometimes no surrounding fibrosis is observed [38]. Hyperplasic nodules are found in 35% (14/35 patients) of IPH necropsies. In recent years, benign hepatocytic nodules, such as IPH, nodular regenerative hyperplasia (NRH), and focal nodular hyperplasia (FNH), have been collectively termed "anomalous portal tract syndrome" (APTS), a group of related diseases underlain by a common causal factor of portal area formation abnormalities [39]. Although FNH rarely complicates portal hypertension, IPH in autoimmune disease has been reported to often complicate NRH. It is relatively common in adults, with rare occurrences in

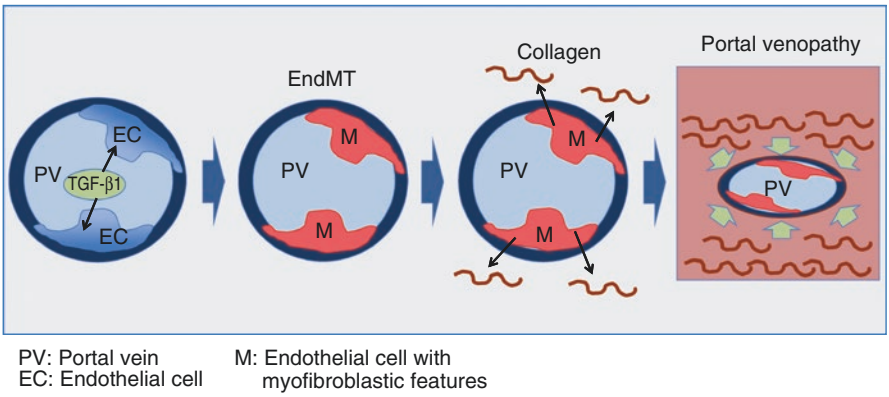

Fig. 5.2 Presentation of portal venopathy and TGF-β1. Transforming growth factor-β (TGF-β1) acts as an inducer of endothelial to mesenchymal transition (EndMT) of endothelial cells (EC) of the peripheral portal vein (PV). ECs acquire myofibroblastic features via the activation of Smad and produce extracellular matrix molecules inducing collagen. Collagen deposits in peripheral portal tracts compress the PVs, resulting in portal venous stenosis and perisinusoidal hypertension

children, the prevalence is higher in females than in males, and it occurs usually as a complication in systemic disease [40]. In Japan, 6–12% of cases of IPH have been reported to occur as a complication in autoimmune disease [41]; in many of the aforementioned rheumatic diseases accompanied by portal hypertension (e.g., SLE, MCTD, SSC), IPH is accompanied by NRH, and this seems a characteristic feature of the disease. Proposed causal factors for NRH include blood flow abnormalities, including portal hypertension, influences of steroids and other drugs, and involvement of autoimmune disease; however, no definite conclusion has been reached.

5.2.2.2 Pulmonary Hypertension

Pulmonary hypertension, a condition defined by a pulmonary arterial pressure of 25 mmHg or higher, is caused by an imbalance in pulmonary vascular dilation and constriction. Increased endothelin levels and decreased NO/PGI2 levels are observed, in addition to vasoconstriction and abnormal proliferation of vascular endothelial cells. Pulmonary vessels show immunoglobulin and complement depositions [42]. The incidence of pulmonary hypertension in rheumatic diseases is relatively high at 19.1% (18/94 patients) in MCTD and 27.7% (193/697 patients) in SSC [43]. However, the pathologic association between rheumatic diseases and portal hypertension or pulmonary hypertension still remains to be elucidated. Pulmonary hypertension in portal hypertension is known as portopulmonary hypertension (POPH). POPH is ranked as the fourth highest cause of pulmonary hypertension, at an incidence of 10.4% (70/674 patients), after idiopathic pulmonary

hypertension 39.2% (674/264 patients), pulmonary hypertension in rheumatic disease at 15.3% (103/674 patients), and pulmonary hypertension due to congenital heart disease at 11.3% (76/674 patients) [44]. In POPH, unlike IPH, the pulmonary vascular resistance is initially normal because of high cardiac outputs due to onset of a shunt and systemic vasodilation. However, increased stress and remodeling in pulmonary vessels and direct inflow of vasoactive factors, which should be inactivated in the liver, into pulmonary vessels can lead to increased pulmonary vascular resistance.

5.2.2.3 Primary Biliary Cholangitis (PBC)-CREST Syndrome

CREST syndrome is a disease characterized by four conditions: calcinosis, Raynaud's phenomenon, sclerodactyly, and multiple telangiectasia of the skin, oral mucosa, and other parts of the body. It differs from SCC by better prognosis and telangiectasia in the normal skin and mucosal membrane and is thus classified as a subtype of SCC. CREST syndrome has been reported to be complicated by PBC [45–48] and can be a cause of portal hypertension. PBC reportedly produces higher portal pressure than common liver cirrhosis (infections, alcohol) and is likely to lead to varices [49].

CREST-complicated PBC is more likely to be complicated by esophageal varices than noncomplicated PBC (28.6% vs. 9.3%); however, good findings of liver function parameters such as AST are found, and the 10-year survival rate is higher (87.5% vs. 45.5%); the prognosis is good [31].

5.2.3 Complications in Portal Hypertension and Their Treatment

Complications in portal hypertension include esophagogastric varices developing as a pressure buffering collateral circulation, splenomegaly, and splenomegaly-associated cytopenia and ascites. Esophagogastric varices, in particular, can cause bleeding and aggravate systemic conditions, often requiring treatment.

5.2.3.1 Esophagogastric Varices

Generally, endoscopic treatments (endoscopic injection sclerotherapy [EIS], endoscopic variceal ligation [EVL]) are performed, with balloon-occluded retrograde transvenous obliteration (B-RTO) sometimes chosen to treat gastric varices. In cases where medical treatment is difficult, a Hassab operation and splenectomy are performed for surgical treatment [37]. Drug therapies include angiotensin II receptor antagonists and nitrites to reduce intrahepatic vascular resistance and propranolol to reduce portal blood flow.

Regarding IPH-underlain portal hypertension, esophageal varices were observed in 73.8% (31/42) of SLE patients [6], and esophageal varix ruptures were observed in 53.3% (8/15) [4]. Esophageal varices were observed at a very high incidence of 95% (19/20) in SCC [28] and 83.3% (5/6) in MCTD [14] (Table 5.1).

Given pulmonary hypertension as the underlying disease, can esophageal varices be deemed a result of increased shunt blood flow and other changes due to increased portal pressure? On the other hand, although the pathologic mechanism remains to be elucidated considering any right cardiac load due to pulmonary hypertension as the cause of portal hypertension, the two conditions often occur concurrently; attention should be paid to esophagogastric varices as well as to IPH.

5.2.3.2 Splenomegaly and Hypersplenism

Japan's guideline requires that splenectomy and splenic embolization are considered in symptomatic patients and patients with a platelet count of $\leq 5 \times 10^4/mm^3$, WBC count of $\leq 3000/mm^3$, and RBC count of $\leq 300 \times 10^4/mm^3$ [37]. Splenectomy is sometimes followed by thrombosis, necessitating special attention.

5.2.3.3 Ascites Fluid

Although no studies have reported detailed data on the proportion of cases of rheumatic diseases complicated by portal hypertension or ascites, many descriptive case reports have reported ascites. In addition, some patients in the case presentation described below experienced ascites and symptom aggravation over a long-term follow-up. In addition to treatment for the primary disease, protein replenishment, diuretics (spironolactone, tolvaptan), and other therapies are used.

5.3 Case Presentation

5.3.1 Case 1: A Patient with SLE Complicated by IPH and Aplasia Pure Red Cell

This patient was diagnosed with myasthenia gravis at the age of 33 years in 1986 and underwent thymectomy in 1993. In 1996, the patient experienced marked anemia, with aplasia pure red cell diagnosed by bone marrow biopsy, and was treated with cyclosporin A. In 2002, the patient was admitted to hospital with polyarthralgia and renal impairment. Although Raynaud's phenomenon was found, facial erythema was not observed. Swelling was noted in the right heel.

Table 5.1 Literature survey of rheumatic disease and portal hypertension

Cases	Disease	Age Med (range)	Gender (M/F)	Esophageal varices %	Rupture of esophageal varices %	Therapy (EIS/EVL/Ope/Steroid/UK)	Outcome (alive/dead/UK)	Reference
42	SLE	40 (14–64)	4/33 (5:UK)	73.8 (31/42)	41.9 (13/31)	5/2/11/4/20	13/9/20	Yamamoto et al.
15	SLE	37 (14–54)	2/12 (1:UK)	UK	53.3 (8/15)	1/6/2/6	7/5/3	Inagaki et al.
20	SCC	53.5 (33–65)	0/20	95 (19/20)	UK	0/3/7/2/8	10/6/4	Takagi et al.
6	MCTD	45.5 (30–68)	0/6	83.3 (5/6)	UK	UK	4/2/0	Rai et al.

EIS endoscopic injection sclerotherapy, *EVL* esophageal variceal ligation, *Ope* Splenectomy, devascularization, esophageal transection, portosystemic anastomosis, etc., *UK* unknown

Blood testing revealed an increased erythrocyte sedimentation rate of 120 mm/h, decreased levels of WBC 1900/mm^3, Hb 9.9 g/dL, Plt 13.1 × 10^4/mm^3, C3 59 mg/dL, C4 10 mg/dL, and antinuclear antibody 20,480-folds (homogeneous and speckled patterns). Antibody testing was positive with an anti-DNA antibody of 19.8 IU/mL and Sm antibody of 56.7 IU/mL. Based on findings of arthralgia, proteinuria, leukopenia, and increased levels of anti-DNA antibody and antinuclear antibody, SLE was diagnosed. Renal biopsy led to the diagnosis of the WHO class IIIc. Ultrasonography and CT detected portal vein dilation and splenomegaly. Nodular regenerative hyperplasia (NRH) was absent. Liver biopsy did not reveal portal area fibrosis, nor was there any liver cirrhosis finding. Based on the above findings, the condition was diagnosed as IPH. Esophageal varices were observed and treated by EIS, and PSL was administered at a starting dose of 40 mg. From that time, the patient was followed up. In 2007, an esophageal varix recurred (Fig. 5.3a) and was again treated by EIS in 2008 (Fig. 5.3b). At that time, CT showed portal vein dilation and splenomegaly but not HRH; no major change was found (Fig. 5.3c). In 2009, portal vein thrombosis occurred; thrombolytic therapy with warfarin was started. The portal vein thrombosis followed come-and-go cycles; in 2014, ascites developed. Albumin and diuretic treatments were administered. In 2016, CT revealed advanced atrophy of the liver and intensified ascites (Fig. 5.3d). Although tolvaptan was added to the regimen in 2017, ascites has been accumulating.

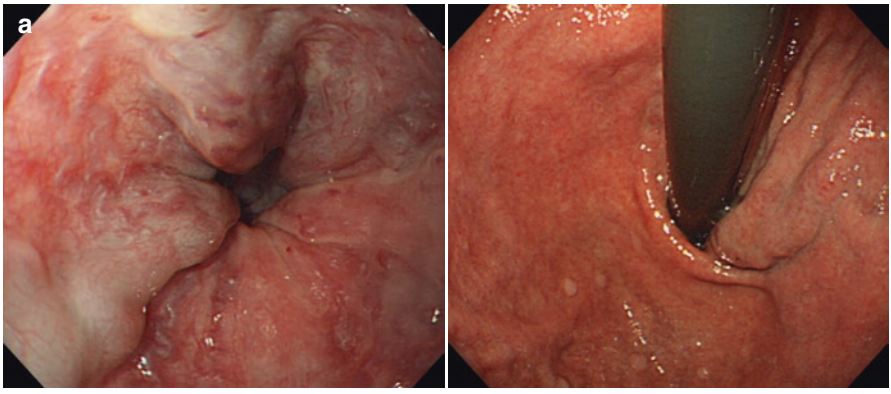

Fig. 5.3 (**a**) Esophagogastroduodenoscopy (EGD) showed recurrence esophageal varices (LmF2CbRC2) and gastric varices (Lg-c F1 RC0). (**b**) EIS was performed using EO (ethanolamine oleate). EVIS (endoscopic varicealography during injection sclerotherapy) revealed palisade vessels and cardiac venous plexus. (**c**) Abdominal-enhanced computed tomography showed portal vain dilation and splenomegaly but not nodular regenerative hyperplasia (NRH) and ascites. (**d**) After 8 years, abdominal-enhanced computed tomography revealed advanced atrophy of the liver and intensified ascites

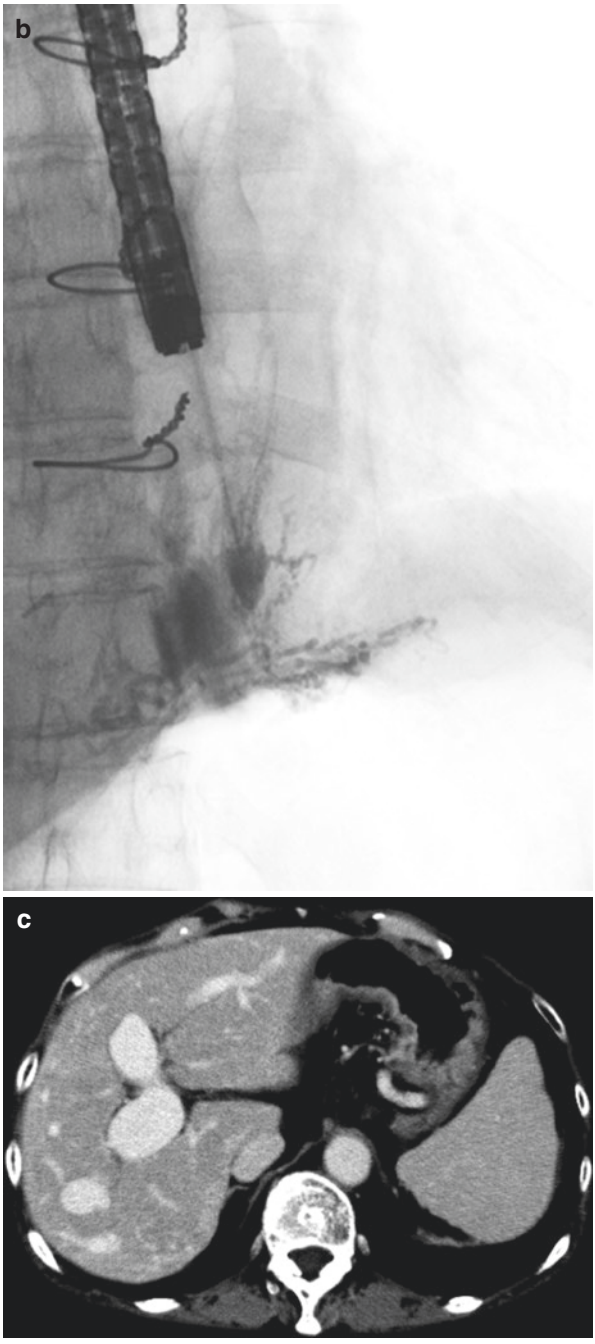

Fig. 5.3 (continued)

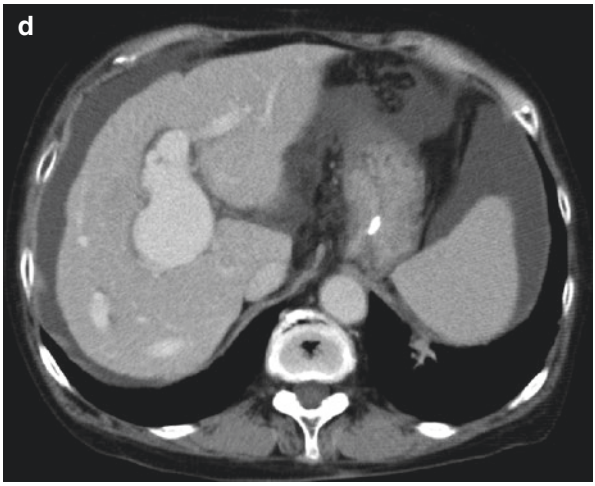

Fig. 5.3 (continued)

5.3.2 Case 2: A Patient with SLE Complicated by Pulmonary Hypertension

This patient experienced edema in the crus and renal impairment at 18 years of age in 2008. In 2010, the patient presented with limb pain, a fever of 37–38.1 °C, facial edema, thirst, dermal erythema, and Raynaud's phenomenon.

With decreased counts of WBC 1600/mm^3, Hb 10.4 g/dL, plt 12.3 × 10^4/mm^3, urinary occult blood (+), and a positive test for antinuclear antibody, the condition was diagnosed as SLE in China. In 2010, the proteinuria and urinary occult blood intensified, and PSL was administered at a starting dose of 30 mg. In August 2016, the patient got married and came to Japan. In September, the patient experienced hematemesis and was admitted to an emergency room. A gastric varix was found, and EIS with Histoacryl was performed. Abdominal CT detected portal vein and splenic vein dilations and megalosplenia, but no intrahepatic nodules or ascites were found. A varix was found in the gastric wall, and pulmonary artery dilation was also observed (Fig. 5.4a). Echocardiography revealed tricuspid regurgitation, with an increased maximum TRPG of 64 mmHg, resulting in the diagnosis of pulmonary hypertension. Secondary to SLE and pulmonary hypertension, portal hypertension was diagnosed, and the patient was transferred to our department. Esophagogastroduodenoscopy revealed a shape of esophagogastric varix, but EIS was not performed (Fig. 5.4b). The patient was treated by steroid pulse therapy. In 2017, endoxan pulse therapy was performed. In 2018, however, abdominal distention and disturbance of consciousness occurred, with CT revealing marked hepatic atrophy and ascites fluid retention (Fig. 5.4c). The patient received an increased dose of diuretic, achieved ascites fluid control, and returned to home country but died soon after at the age of 28 years there.

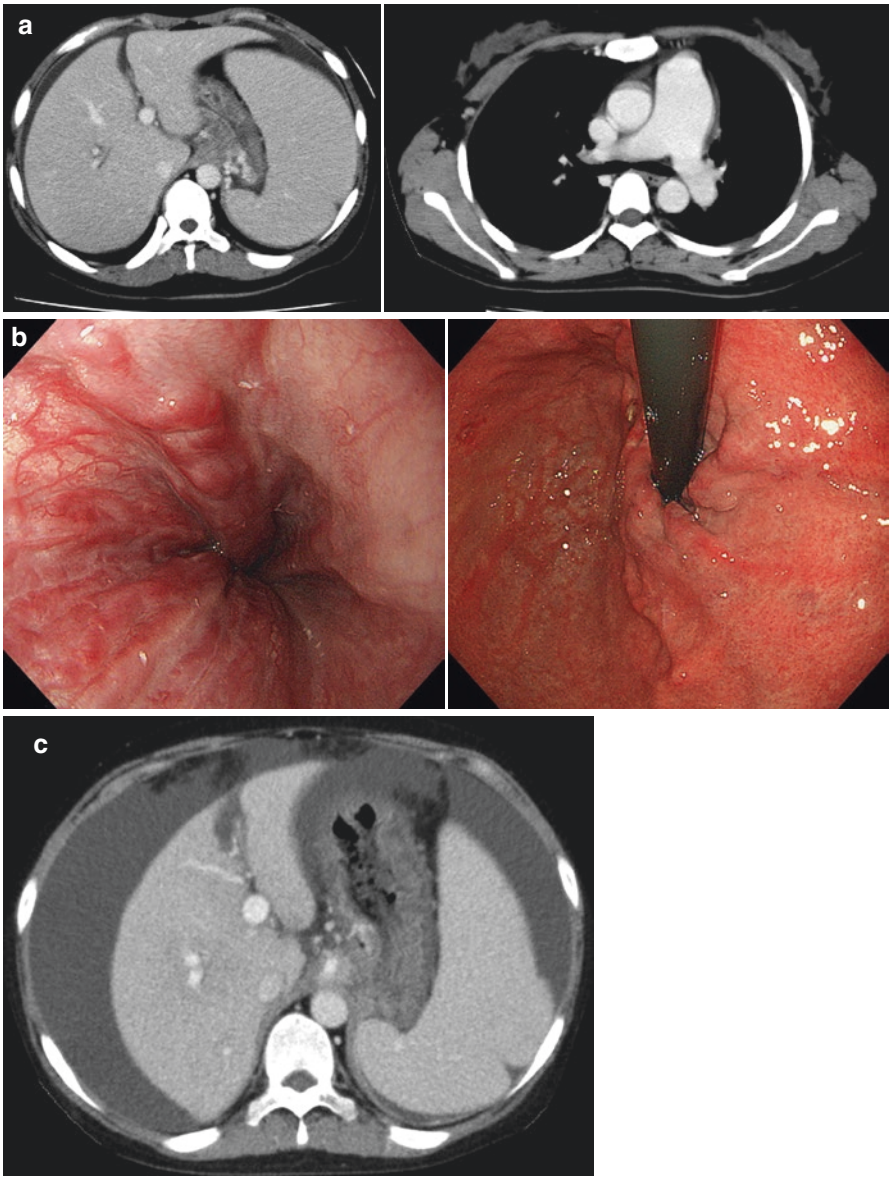

Fig. 5.4 (**a**) Abdominal CT detected portal vein and splenic vein dilations and megalosplenia, but no NHR or ascites were found. A varix was found in the gastric wall, and pulmonary artery dilation was also observed. (**b**) EGD showed esophageal varices (LmF1CbRC1) and gastric varices (Lg-c F1 RC0). (**c**) After 2 years, abdominal-enhanced computed tomography revealed advanced atrophy of the liver and intensified ascites

5.3.3 *Case 3: A Patient with Sjogren's Syndrome Complicated by Pulmonary Hypertension*

This patient began to complain of general malaise around 16 years of age in 2014. In 2015, the patient became unable to attend school and visited a nearby psychiatric clinic, where hematological examination detected hepatopathy and cytopenia. Chest radiography detected cardiomegaly and pulmonary congestion (Fig. 5.5a), and abdominal echography suggested ascites fluid and splenomegaly. Echocardiography suggested a tricuspid regurgitation pressure gradient of −66.0 mmHg and pulmonary hypertension. Esophagogastroduodenoscopy detected a solitary gastric varix (F2-3, RC sign negative) in the gastric fundus (Fig. 5.5b). Thoracoabdominal contrast-enhanced CT suggested ascites, splenomegaly, and portal collateral circulation hyperplasia. 3D-CT revealed a gastric varix hemodynamic profile in which blood is supplied from short gastric vein (SGV) and post gastric vein (PGV) and discharged via a renal venous shunt and inferior phrenic venous shunt (Fig. 5.5c). The patient was referred and admitted to our hospital for extensive examination and treatment. Blood pressure was 154/87 mmHg, and tachycardia was noted at a heart

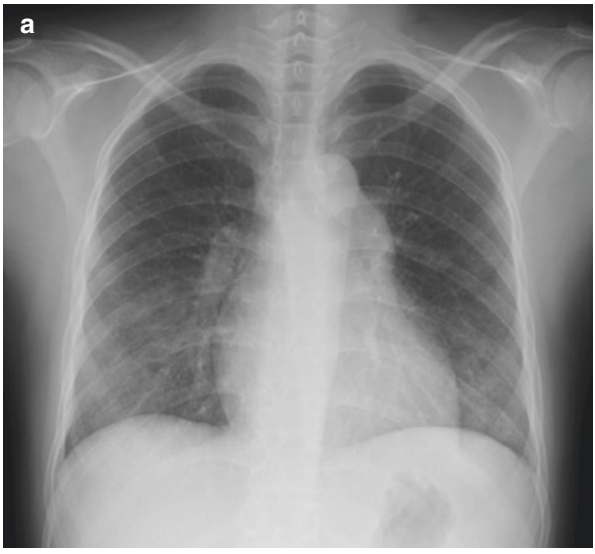

Fig. 5.5 (**a**) Chest radiography revealed cardiomegaly and pulmonary congestion. (**b**) EGD showed gastric varices (Lg-c F3 RC0). (**c**) Abdominal-enhanced computed tomography revealed splenomegaly with massive ascites and gastric varices in the gastric wall. 3D-CT revealed a gastric varix hemodynamic profile in which blood is supplied from short gastric vein (SGV) and post gastric vein (PGV) and discharged via a renal venous shunt and inferior phrenic venous shunt. (**d**) Photomicrograph of the liver biopsy specimen was revealed neither fibrosis nor bridging but a dilated sinusoid continuous to the central vein dilation in the form of cysts. (**e**) A gastric varix was treated by EIS using Histoacryl. EVIS revealed short gastric vein, post gastric vein, and a part of inferior phrenic venous shunt

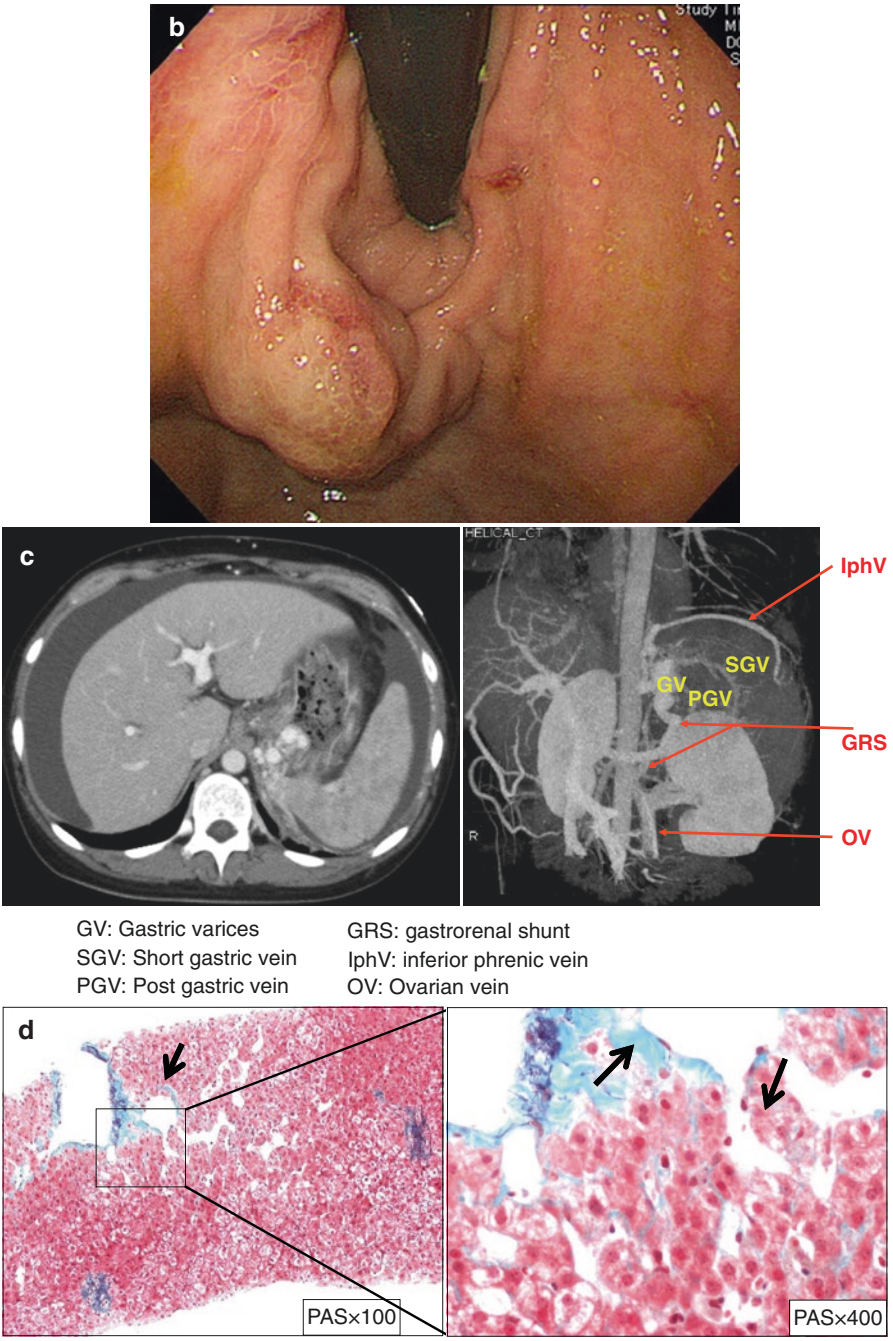

Fig. 5.5 (continued)

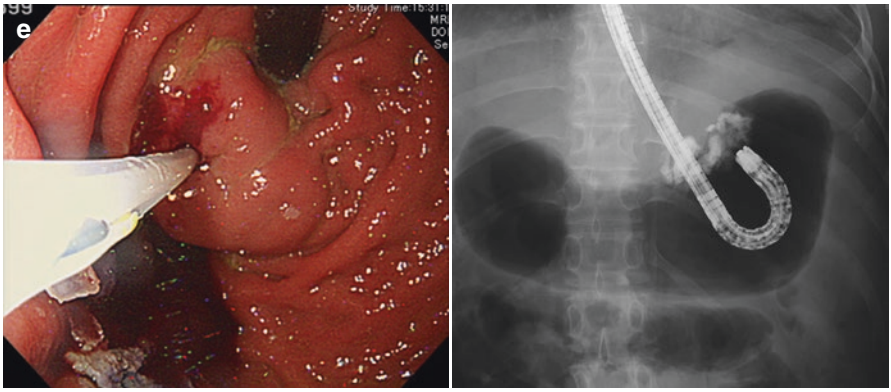

Fig. 5.5 (continued)

rate of 120 beats/min, with edema found in the lower extremities. WBC 2100/mm^3, Hb 7.6 g/dL, plt 4.3 × 10^4/mm^3, Alb 2.6 g/dL, AST 61 U/L, AST 30 U/L, C3 40 mg/dL, C4 9 mg/dL, ANA 160-folds, anti-DNA antibody 7.8 IU/mL, anti-Sm antibody 1.3 IU/mL, anti-SS-A antibody 185 IU/mL, and anti-SS-B antibody 1.3 IU/mL. The patient tested positive in Schirmer's test and had a Saxon test value of 2.31 g; SjS and pulmonary hypertension were diagnosed. Liver biopsy did not detect portal area fibrosis or cross-linking. A dilated sinusoid continuous to the central vein dilation in the form of cysts was observed, suggesting influence on the inferior vena cava and hepatic vein sides (Fig. 5.5d). Steroid pulse therapy was initiated, and endoscopic injection sclerotherapy (EIS) with Histoacryl was performed for the gastric varix (Fig. 5.5e). The patient received tolvaptan and spironolactone to control ascites fluid and was discharged from hospital.

5.3.4 Case 4: A Patient with MCTD Complicated by IPH and Pulmonary Hypertension

At 29 years of age in 1998, the patient was diagnosed with MCTD because of the presence of Raynaud's phenomenon, SLE-like symptoms (pyrexia, pleurisy, pericarditis), SCC-like symptoms (finger ulceration), increased ANA, and a positive test for U1-RNP antibody. At the age of 40 years, the patient was diagnosed with hepatosplenomegaly, with esophagogastric varix detected by esophagogastroduodenoscopy. Extensive examination of the liver led to the diagnosis of IPH, and EIS was performed (Fig. 5.6a). At 45 years of age, the patient underwent a Hassab operation for IPH and had postoperative portal vein thrombosis (Fig. 5.6b). Thrombolytic therapy was performed, and since then, the patient has been followed up periodically. At 59 years of age, echocardiography revealed an increased TRPG of 60 mHg, and intensified pulmonary arterial dilation was detected by CT, and thus a diagnosis of pulmonary hypertension was made (Fig. 5.6c).

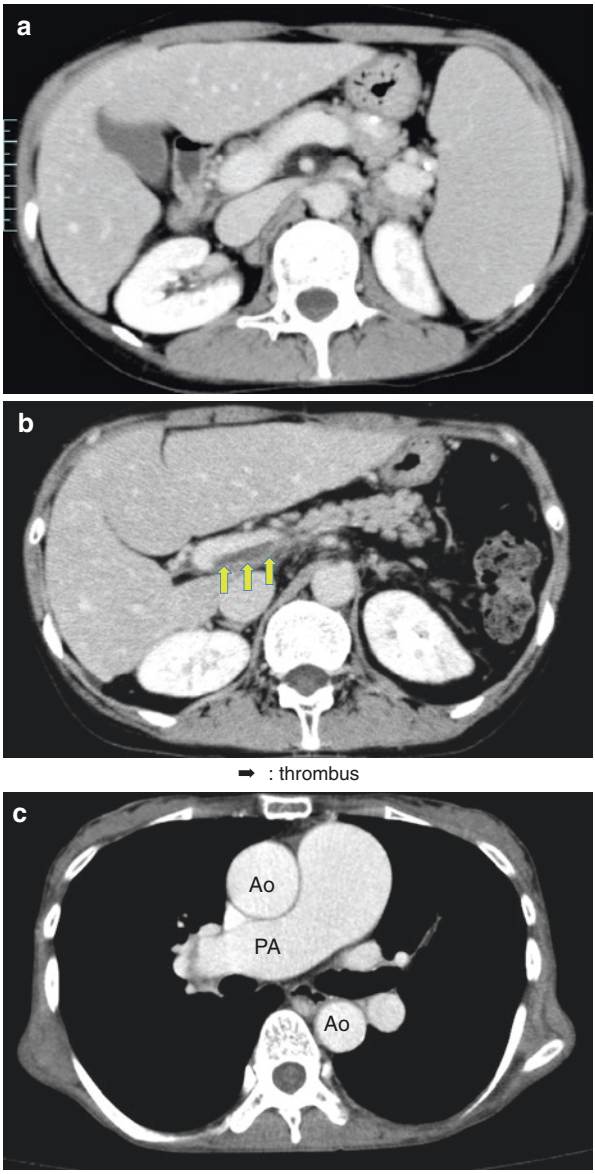

Fig. 5.6 (**a**) Abdominal-enhanced computed tomography showed portal vain dilation and splenomegaly but not NRH and ascites. (**b**) After Hassab operation, CT revealed thrombus in the portal veins (arrow). (**c**) After 14 years, abdominal-enhanced computed tomography revealed dilated pulmonary artery in thoracic cavity

5.4 Conclusion

Rheumatic diseases, portal hypertension, and the accompanying symptoms have been described briefly, including discussion of some case reports. In rheumatic diseases accompanied by portal hypertension, attention should be paid to the onset of gastrointestinal varices and gastrointestinal bleeding in the early stages and to hepatic atrophy, increased ascites fluid volume, onset of pulmonary hypertension, and other changes in the medium- to long-term perspectives.

References

1. Benoit JN, Womack WA, Hernandez L, et al. “Forward” and “backward” flow mechanisms of portal hypertension. Relative contributions in the rat model of portal vein stenosis. Gastroenterology. 1985;89:1092–6.
2. Kato M, Noma K, Takeuchi Y, et al. A case of idiopathic portal hypertension supervening on SLE (systemic lupus erythematosus)—a study on the possible role of SLE in the pathogenesis of IPH. Nippon Naika Gakkai Zasshi. 1986;75(12):1836–40.
3. Takahashi M, Okada J, Irisawa A, et al. A case of SLE associated with antiphospholipid syndrome and mitral stenosis. Nihon Rinsho Meneki Gakkai Kaishi. 1995;18(1):90–7.
4. Inagaki H, Nonami T, Kawagoe T, et al. Idiopathic portal hypertension associated with systemic lupus erythematosus. J Gastroenterol. 2000;35(3):235–9.
5. Horita T, Tsutsumi A, Takeda T, et al. Significance of magnetic resonance imaging in the diagnosis of nodular regenerative hyperplasia of the liver complicated with systemic lupus erythematosus: a case report and review of the literature. Lupus. 2002;11(3): 93–196.
6. Yamamoto M, Taniguchi H, Ohara M, et al. Beneficial effect of glucocorticosteroids for esophageal varices due to idiopathic portal hypertension following systemic lupus erythematosus. Jpn J Clin Immunol. 2004;27(1):40–7.
7. Iwadate H, Kobayashi H, Shio K, et al. A case of systemic lupus erythematosus comolicated by pure red cell aplasia and idiopathic portal hypertension after thymectomy. Mod Rheumatol. 2006;16:109–12.
8. Park YW, Woo H, Jeong YY, et al. Association of nodular regenerative hyperplasia of the liver with porto-pulmonary hypertension in a patient with systemic lupus erythematosus. Lupus. 2006;15(10):686–8.
9. Sawai T, Tukikawa K, Watanabe T, et al. A case of mixed connective tissue disease (MCTD) complicating pulmonary hypertension and portal hypertension. Ryumachi. 1988;28:164–9.
10. Muryoi T, Harata N, Tamata E, et al. A case of mixed connective tissue disease with idiopathic portal hypertension. Noppon Naika Gakkai Zasshi. 1989;78:984–5.
11. Ozawa T, Nakagawa O, Hasegawa S, et al. A case of mixed connective tissue disease accompanied with idiopathic portal hypertension and pulmonary hypertension. Noppon Naika Gakkai Zasshi. 1989;78:1799–800.
12. Hirasaki S, Koide N, Ogawa H, et al. Mixed connective tissue disease associated with idiopathic portal hypertension and chronic thyroiditis. J Gastroenterol. 1997;32:808–11.
13. Sekiguchi Y, Amano K, Takano Y, et al. Portal and pulmonary hypertension in patient with MCTD. Ryumachi. 1999;39:657–63.
14. Rai T, Ohira H, Fukaya E, et al. A case of merged idiopathic portal hypertension in course of mixed connective tissue disease. Hepatol Res. 2004;30:51–5.
15. Horai Y, Miyamura T, Hirata A, et al. Idiopathic portal hypertension in a patient with mixed connective tissue disease and protein C deficiency. Intern Med. 2010;49:2013–6.

16. Hayano S, Naganuma A, Okano Y, et al. A case of idiopathic portal hypertension associated with nodular regenerative hyperplasia-like nodule of liver and mixed connective tissue disease. Nippon Naika Gakkai Zasshi. 2016;113(5):828–36.
17. Morris JS, Htut T, Read AE, et al. Scleroderma and portal hypertension. Ann Rheum Dis. 1972;31:316–8.
18. Yui S, Fukamizu A, Nishino K, et al. A case of idiopathic portal hypertension complicated by progressive systemic sclerosis. Hepatology. 1982;23:325–31.
19. Umeyama K, Yui S, Fukamizu A, et al. Idiopathic portal hypertension associated with progressive systemic sclerosis. Am J Gastroenterol. 1982;77:645–8.
20. Tajima H, Inoue O, Furukawa R, et al. A case of progressive systemic sclerosis complicated by esophageal varices. Nippon Naika Gakkai Zasshi. 1985;74:1108–11.
21. Nakamura Y, Harada K. An autopsy report of a patient with scleroderma who developed idiopathic portal hypertension. In: 2004 reports of the research group on abnormal portal circulation. Ministry of Health, Labour and Welfare; 1995. p. 34–37.
22. Kaburaki J, Kuramochi S, Fujii T, et al. Nodular regenerative hyperplasia of the liver in a patient with systemic sclerosis. Clin Rheumatol. 1996;15:613–6.
23. Asai T, Gunji T, Inamori H, et al. A case of idiopathic portal hypertension complicating chronic non-suppurative destructive cholangitis and systemic sclerosis. Kanzo. 1998;39:834–8.
24. Querfeld C, Eckes B, Huerkamp C, et al. Expression of TGF-beta 1, -beta 2, and -beta 3 in localized and systemic scleroderma. J Dermatol Sci. 1999;21:13–22.
25. Watanabe Y, Mizukami T, Egawa T, et al. A case of progressive systemic sclerosis complicated by idiopathic portal hypertension with severe anemia. Ryumachi. 1999;39:586–90.
26. Tsuneyama K, Harada K, Katayanagi K, et al. Overlap of idiopathic portal hypertension and scleroderma: report of two autopsy cases and a review of literature. J Gastroenterol Hepatol. 2002;17:217–23.
27. Ishii M, Katada Y. Idiopathic portal hypertension in a systemic sclerosis patient heterozygous for factor V Leiden mutation. Rheumatol Int. 2003;23:44–6.
28. Takagi K, Nishio S, Akimoto K, et al. A case of systemic sclerosis complicated by idiopathic portal hypertension: case report and literature review. Mod Rheumatol. 2006;16:183–7.
29. Nakanuma Y, Sato Y, Kiktao A. Pathology and pathogenesis of portal venopathy in idiopathic portal hypertension: hints from systemic sclerosis. Hepatol Res. 2009;39:1023–31.
30. Sanchez MJ, Seco GJL, Saez-Royuela F, et al. Idiopathic portal hypertension, multiple focal nodular hepatic hyperplasia, the CREST syndrome and protein C deficiency. Rev Enferm Dig. 1997;89:55–9.
31. Tojo J, Ohira H, Suzuki T, et al. Clinicolaboratory characteristic of patients with primary biliary cirrhosis associated with CREST symptoms. Hepatol Res. 2002;22:187–95.
32. Kitamura Y, Tsukada N, Atsukawa K, et al. A case of non-cirrhotic portal hypertension complicated with Sjögren syndrome and thrombocytosis. Nihon Shokakibyo Gakkai Zasshi. 1995;92(1):95–100.
33. Herrera CN, Tomale-Haz JE. Portal hypertension: an uncommon clinical manifestation of Takayasu arteritis in a 9-year-old child. Open Access Rheumatol. 2016;8:115–8.
34. Sasajima T, Suzuki T, Mori K, et al. A case of idiopathic portal hypertension associated with rheumatoid arthritis. Mod Rheumatol. 2006;16:92–6.
35. Nishikawa K, Igarashi Y, Takayasu N, et al. Dermatomyositis accompanied with liver cirrhosis and esophageal varices: report of a case. Gastroenterol Endosc. 1984;26(12):2426–31.
36. Philips C, Paramaguru R, Kumar L, et al. A rare cause of portal hypertension: Behcet's disease and nodular regenerative hyperplasia of the liver. Cureus. 2017;9(3):e1125. https://doi.org/10.7759/cureus.1125.
37. Working Subgroup for Clinical Practice Guideline for Aberrant Portal Hemodynamics. Diagnosis and treatment guidelines for aberrant portal hemodynamics: the aberrant portal Hemodynamics Study Group supported by the Ministry of Health, Labor and Welfare of Japan. Hepatol Res. 2017;47(5):373–86.
38. Nakanuma Y, Tsuneyama K, Ohbu M, et al. Pathology and pathogenesis of idiopathic portal hypertension with an emphasis on the liver. Pathol Res Pract. 2001;197:65–76.

39. Fukuo K. Benign nodular hepatocellular lesions caused by abnormal hepatic circulation: etiological analysis and introductal of a new concept. J Gastroenterol Hepatol. 2001;16:1319–28.
40. Nakanuma Y. Nodular regenerative hyperplasia of the liver: retrospective survey in autopsy series. J Clin Gastroenterol. 1990;12:460–5.
41. Ohta G, Saito K, Nakamura Y. A survey of idiopathic portal hypertension (IPH) associated with autoimmune phenomena. In: Okuda K, editor. 1983 report of the Ministry of Health and Welfare Research Committee on IPH. Tokyo: Japan Ministry of Health and Welfare; 1984. p. 176–9.
42. Quismorio FP Jr, Sharma O, Koss M, et al. Immunopathologic and clinical studies in pulmonary hypertension associated with systemic lupus erythematosus. Semin Arthritis Rheum. 1984;13(4):349–59.
43. Wigley FM, Lima JA, Mayes M, et al. The prevalence of undiagnosed pulmonary arterial hypertension in subjects with connective tissue disease at the secondary health care level of community-based rheumatologists (the UNCOVER study). Arthritis Rheum. 2005;52:2125–32.
44. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med. 2006;173:1023–30.
45. Murray-Lyon IM, Thompson RPH, Williams R, et al. Scleroderma and primary biliary cirrhosis. Br Med J. 1970;3:258–9.
46. Reynold TB, Denison EK, Peters RL, et al. Primary biliary cirrhosis with scleroderma, Raynaud's phenomenon and telangiectasia. Am J Med. 1971;50:302–12.
47. Clarke AK, Galbraith RM, Williams R, et al. Rheumatic disorders in primary biliary cirrrhosis. Ann Rheum Dis. 1978;37:42–7.
48. Bernstein RM, Galbraith ME, Williams R, et al. Anticentromere antibody in primary biliary cirrhosis. Ann Rheum Dis. 1982;41:612–4.
49. Takahashi A, Monoe K, Sakamoto N, et al. Esophagogastric varices in patients with primary biliary cirrhosis. JJPH. 2011;17:1–5.