Gastrointestinal and Hepatic Manifestations of Rheumatic Diseases

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ISBN 978-981-13-6523-2 ISBN 978-981-13-6524-9 (eBook)
https://doi.org/10.1007/978-981-13-6524-9

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Preface

The first edition of *Gastrointestinal and Hepatic Manifestations of Rheumatic Diseases* includes state-of-the-art knowledge of the field of digestive and hepatobiliary complications of the most common rheumatic disorders. Rheumatic diseases are disorders of systemic connective tissue and are thought to be caused by autoimmunity. They present with a diverse array of gastrointestinal and hepatobiliary manifestations, so it is important for rheumatologists to be aware of the diagnostic procedures and management of such complications.

The gastrointestinal disorders accompanying rheumatic diseases can be divided into two major categories: intestinal disorders and disorders of the liver, biliary tracts, and pancreas.

Gastrointestinal symptoms are common in patients with rheumatic diseases and can be classified as gastrointestinal damage from the rheumatic disease itself, adverse events caused by pharmacotherapies, and gastrointestinal tract infections following immunosuppressive treatments. No specific autoantibodies have been identified for the diagnosis of gastroenteropathy in rheumatic diseases, but imaging studies, particularly abdominal computed tomography and tissue pathology through biopsy, are helpful.

Abnormalities of liver function tests frequently occur in patients with rheumatic diseases, and many diagnostic possibilities exist. Rheumatic diseases can be accompanied by liver abnormalities secondary to the presence of a coexisting autoimmune liver disease (such as primary biliary cholangitis, autoimmune hepatitis, and primary sclerosing cholangitis), or portal hypertension and the toxicity of medical treatments (particularly methotrexate). The rheumatologist should also be aware of the impact of immunosuppressive agents on the reactivation of viral infections, particularly hepatitis B virus (HBV). Additionally, a number of extrahepatic manifestations of pancreatic disorders have been reported, including autoimmune pancreatitis. For example, immunoglobulin G4-related disease (IgG4-RD) is a systemic fibroinflammatory condition affecting the pancreas as a pathological form of autoimmune pancreatitis. It is also important to perform a systematic diagnostic workup for malignancy, including digestive and hepatobiliary organs in patients with

polymyositis/dermatomyositis (PM/DM), because there is a high incidence of cancer in PM/DM.

Gastro-hepatic manifestations in rheumatic diseases are not rare, so clinicians should be aware of their existence and the fact that they may occur concomitantly or serially. It is also necessary for both rheumatologists and gastroenterologists to cooperate with each other and proceed with precise management of these disorders.

We and our colleagues have reviewed the clinical findings and management of gastrointestinal and hepatobiliary manifestations accompanying rheumatic disorders. This book aims to be a practical guide for the identification, typical case presentation, diagnosis, and management of these digestive and hepatobiliary complications of rheumatic diseases that will be useful for both rheumatologists and gastroenterologists. We also highlight recent developments in relevant diagnostic procedures and therapeutic strategies. We hope that readers will enjoy these advances in their classification, diagnosis, and management and an understanding of the mechanisms responsible for immune-mediated digestive and hepatobiliary disorders. We thank our collaborators at the Department of Gastroenterology and Rheumatology, Fukushima Medical University, for their contributions in producing this valuable book.

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Contents

Chapter 1
Liver Involvement in Rheumatic Diseases

Atsushi Takahashi and Hiromasa Ohira

Abstract Liver dysfunction may be caused by various factors such as viruses, disease treatments, alcohol use, and metabolic or autoimmune diseases. The associations between rheumatic diseases and the liver are complex, because rheumatic diseases target multiple systemic organs, including the liver. In addition, both treatment with immunosuppressants and secondary viral infections can cause liver dysfunction. Although liver dysfunction in rheumatic diseases is usually mild, liver failure has been reported in some cases. Therefore, understanding the characteristics of liver failure that may occur with different rheumatic diseases is essential for the treatment of these diseases. Clinicians must consider and treat liver dysfunction in patients with a rheumatic disease with both disorders in mind.

Keywords Liver dysfunction · Rheumatic diseases · Image findings · Histological findings · Autoimmune hepatitis · Primary biliary cholangitis · Viral infection · Fatty liver · Macrophage activation syndrome

1.1 Introduction

Rheumatic diseases affect multiple organs, including the liver. Moreover, the treatment and clinical course of rheumatic diseases may lead to adverse effects or complications that also cause liver dysfunction. Therefore, liver dysfunction in patients with a rheumatic disease can be caused by multiple factors. In addition to various causes of liver dysfunction, understanding the differences in the association between each rheumatic disease and the liver is essential for treatment of patients with rheumatic disease. In this chapter, we differentiate liver dysfunction that occurs with rheumatic diseases from other causes of liver dysfunction.

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H. Ohira, K. Migita (eds.), *Gastrointestinal and Hepatic Manifestations of Rheumatic Diseases*, https://doi.org/10.1007/978-981-13-6524-9_1

1.2 Prevalence of Liver Dysfunction in Patients with Rheumatic Diseases

Many studies have reported treating liver dysfunction in patients with a rheumatic disease using different definitions of liver dysfunction [1–31]. Therefore, determining the prevalence of liver dysfunction specific to a rheumatic disease is difficult. Table 1.1 summarizes the prevalence and major causes of liver dysfunction in patients with different rheumatic diseases. Rheumatic disease activity and drug treatments are major causes of liver dysfunction in rheumatic diseases. However, primary biliary cholangitis (PBC) is a major cause of liver dysfunction in patients with systemic sclerosis (SSc) or Sjögren's syndrome (SjS). Moreover, fatty liver can also cause liver dysfunction in patients with systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA).

Table 1.1 Prevalence and major causes of liver dysfunction in patients with different rheumatic diseases

Rheumatic disease	Prevalence of liver dysfunction	Major causes of liver dysfunction	References
Systemic erythematosus (SLE)	43% (46/106)	Disease related (22/46), drug (8/46)	Kojima et al. [1]
	9.3% (47/504)	Disease related (47/47)	Zheng et al. [2]
	20.9% (43/206)	Fatty liver (19/43)	Runyon et al. [3]
	32.3% (84/260)	Drug (28/67), alcohol (8/67)	Miller et al. [4]
	35.6% (80/225)		Luangjaru and Kullavanijaya [5]
	20.8% (40/192)	Viral hepatitis (8/40), fatty liver (8/40)	Chowdhary et al. [6]
	18.6%(45/242)	Drug (18/45), disease related (14/45)	Piga et al. [7]
	32.6% (46/141)	Drug (11/46)	Her et al. [8]
	8.6% (134/1553)	Drug (35/134), fatty liver (31/134)	Huang et al. [9]
	59.7% (123/206)	Drug (38/123), disease related (35/123)	Takahashi et al. [10]
Rheumatoid arthritis (RA)	41% (24/59)	Drug (8/24), disease related (7/24)	Kojima et al. [1]
	35.9% (79/220)	Drug (32/79), fatty liver (5/79)	Takahashi et al. [11]
	45.0% (45/100)	Not reported	Fernandes et al. [12]
	45.9% (45/98)	Not reported	Spooner et al. [13]
	77.4% (48/62)		Lowe et al. [14]
	47.0% (86/183)		Akesson et al. [15]

Table 1.1 (continued)

Rheumatic disease	Prevalence of liver dysfunction	Major causes of liver dysfunction	References
Sjögren's syndromes (SjS)	52.1% (37/71)	Disease related (11/37), PBC (10/37)	Kojima et al. [1]
	45.5% (20/44)	PBC (14/20), AIH (2/20)	Takahashi et al. [11]
	7.0% (21/300)		Skopouli et al. [16]
	26.7% (12/45)		Lindgren et al. [17]
	44.2% (42/95)		Montaño-Loza et al. [18]
Systemic sclerosis (SSc)	37% (10/27)	Drug (3/10), disease related (2/10), fatty liver (2/10)	Kojima et al. [1]
	44.7% (21/47)	PBC (16/21)	Takahashi et al. [11]
	1.1% (8/727)		Chen [19]
Vasculitis syndrome	54.0% (7/13)	Disease related (5/7), drug (2/7)	Kojima et al. [1]
	48.0% (12/25)	Disease related (7/12)	Takahashi et al. [11]
	16–56%		Ebert et al. [20]
Adult-onset Still's disease (AOSD)	81.3% (13/16)	Disease related (13/13)	Takahashi et al. [11]
	75.8%(47/62)		Pouchot et al. [21]
	73.6% (53/72)		Fautrel et al. [22]
	62.1% (59/95)		Pay et al. [23]
	35.7% (30/84)		Cagatay et al. [24]
	62.3% (48/77)		Zhu et al. [25]
	62.5% (65/104)		Kong et al. [26]
	75.0% (57/76)		Colina et al. [27]
	70.5% (43/61)		Chen et al. [28]
	54.0% (27/50)		Gerfaud-Valentin et al. [29]
	89.3% (25/28)		Mehrpoor et al. [30]

1.3 Laboratory Findings

Liver dysfunction is generally classified into two patterns: predominantly hepatocellular (with elevated alanine aminotransferase [ALT] and aspartate aminotransferase [AST] levels) or predominantly cholestatic (with elevated alkaline phosphatase [ALP] and gamma-glutamyl transferase [γ-GTP] levels). Liver dysfunction with rheumatic diseases has been generally defined as the elevation of liver and biliary enzyme levels. However, AST and ALT are also muscle-derived enzymes; thus, rather than liver dysfunction, elevations in these parameters may reflect disease activity in patients with polymyositis and dermatomyositis. Other muscle-derived enzymes such as creatine phosphokinase, aldolase, lactate dehydrogenase (LDH), and isozymes of LDH may be useful to diagnose liver dysfunction in these patients.

In addition, elevation of AST levels may simply reflect damage to systemic organs, except the liver, which is caused by macrophage activation syndrome (MAS) [32], a severe comorbidity with some rheumatic diseases. Therefore, elevations in AST levels without elevations in ALT levels require attention, whether or not they represent true liver dysfunction.

These elevations of liver and biliary enzyme levels are, on the whole, mild in patients with a rheumatic disease with liver dysfunction. However, liver dysfunction shows different tendencies by disease. ALT levels are higher in adult-onset Still's disease (AOSD) than in other collagen diseases [11]. This finding may explain the high frequency of MAS in AOSD. Conversely, ALP or γ-GTP levels are higher in vasculitis syndrome than in other collagen diseases [1, 11]. Aminotransferase and bilirubin levels are generally normal in patients with RA, though ALP levels are increased in 18–46% of these patients [11, 12, 33]. Moreover, γ-GTP levels are elevated in 23–77% of patients with RA and correlate with disease activity [12, 14, 33]. The degree of liver and biliary enzyme elevation is generally associated with disease activity and is generally the basis for liver dysfunction that occurs with a rheumatic disease.

1.4 Histologic Findings

Histologic liver findings have been reported to vary widely not only among different rheumatic diseases but among cases with the same rheumatic disease. Vascular changes such as arteritis, abnormal vessels in portal tracts, hemangioma, peliosis hepatis, and infarcts due to arthritis have been well described in rheumatic diseases with liver dysfunction [1, 34, 35]. Portal changes such as interface hepatitis, chronic active hepatitis, non-specific reactive hepatitis (Fig. 1.1), cholestasis, and

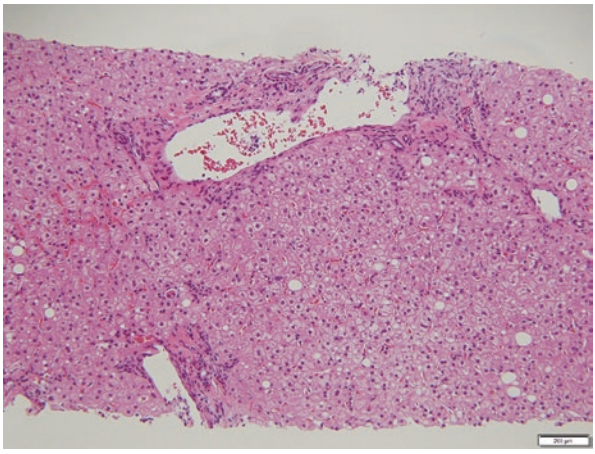

Fig. 1.1 Non-specific reactive hepatitis in a patient with SLE

cholangiolitis have also been reported [1, 34, 35]. Although lobular changes are not as frequent as portal changes, lobular inflammation, steatosis, and focal necrosis have been reported [1, 2, 36]. In addition to variations in rheumatic disease itself, viral infection, therapeutic drugs, hepatic congestion, and autoimmune disease mimic histologic liver findings. Therefore, interpretation of liver histology should consider the clinical course of the specific rheumatic disease.

1.5 Image Findings

Hepatomegaly is a relatively common finding in patients with a rheumatic disease. It is seen in about 40% of patients with SLE [3] and 76.5% of patients with AOSD with hemophagocytic lymphohistiocytosis [37]. Congestion of the liver is observed in patients with a rheumatic disease with heart failure.

Liver tumors are sometimes observed in patients with a rheumatic disease. Hepatocellular carcinoma (HCC) develops in patients with other risk factors, such as hepatitis B or C infection, alcohol intake, fatty liver disease, and use of immunosuppressants. On the other hand, HCC can develop in patients with a rheumatic disease without any other risk factors. We previously experienced a rare case of HCC with mixed connective tissue disease [38]. Liver hemangioma is seen in 0.4–20% of the general adult population [39], whereas it occurs in 54.2% of patients with SLE [40]. The high frequency of liver hemangioma can be explained by increases in circulating estrogen or angiogenetic factors, such as vascular endothelial growth factor and IL-18, which occur with rheumatic diseases [41–43]. Rheumatic diseases such as SLE, RA, and SjS have been associated with malignant lymphoma [44–46]. However, the liver is rarely the primary organ associated with malignant lymphoma, accounting for less than 1% of all extranodal lymphomas [47]. Immunosuppressive treatment for rheumatic disease tends to cause primary hepatic lymphoma [48, 49]. In particular, methotrexate (MTX) can cause lymphoid proliferation or lymphomas and is referred to as MTX-associated lymphoproliferative disorders (MTX-LPD) [45]. Some studies reported that patients with RA treated with MTX showed hepatic involvement [50–53]. Our case report is presented here [53].

Case. A 54-year-old woman was diagnosed with RA and treated with prednisolone, nonsteroidal anti-inflammatory drugs (NSAIDs), MTX, and biologic agents. Twelve years later, at the age of 66, she presented with retroperitoneal lymph node swelling and hepatosplenomegaly, but these symptoms disappeared after MTX withdrawal. Two years later, she was admitted to our hospital for anorexia and general fatigue with swelling in several lymph nodes and multiple liver tumors (Fig. 1.2). She was diagnosed with Hodgkin lymphoma based on the results of aspiration biopsy of a liver tumor. She died from liver failure and disseminated intravascular coagulation before chemotherapy could be initiated.

Enhanced computed tomography images are useful for diagnosis of liver tumors such as hepatocellular carcinoma and liver hemangioma. However, hypodense

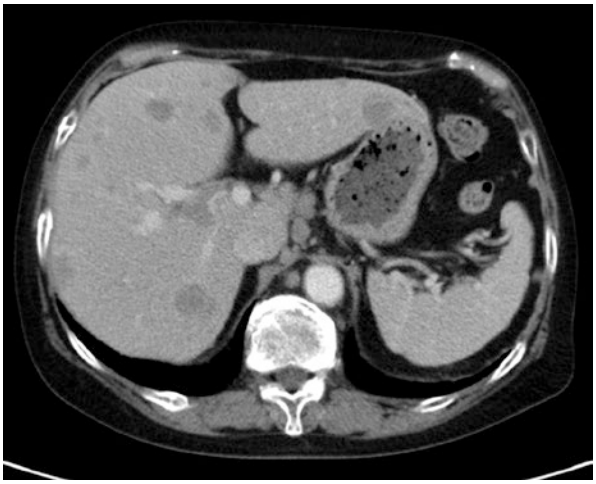

Fig. 1.2 Enhanced CT image in a RA patient with methotrexate-associated lymphoproliferative disorder

tumors are often difficult to diagnose accurately. Therefore, tumor biopsy is often performed to provide a definitive diagnosis. Hypodense lesions other than tumors can also appear in patients with rheumatic disease. Various causes such as abscess, piecemeal necrosis, necrotizing granuloma, infarction, and rupture show hypodense spots in the liver of patients with a rheumatic disease [20, 54]. With the exception of liver abscess, recognition of these lesions is especially important in determining the treatment strategy.

Vasculitis shows various image findings in the liver [20]. *Hepatic arteriograms* show caliber changes with corkscrew and distal microaneurysms. Vasculitis can also show *atrophy of a liver lobe*, liver infarction, and nodular regenerative hyperplasia involving the portal vein and hepatic arteries. *Intrahepatic sclerosing cholangitis* is also induced by vasculitis of small arteries that supply the small bile ducts.

1.6 Liver Dysfunction Associated with Rheumatic Diseases Alone

1.6.1 Systemic Lupus Erythematosus

The liver dysfunction caused by SLE itself has traditionally been referred to as "lupus hepatitis" [6, 55]. However, older reports may have used this term without ruling out other causes such as drug-induced liver injury, viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), and autoimmune liver diseases. The prevalence of liver dysfunction caused by SLE itself varies. Our

previous report based on lenient discrimination criteria reported a prevalence of 59.7% among 206 patients with SLE [10], whereas Zheng et al., using much stricter discrimination criteria, reported a prevalence of 9.3% among 504 patients with SLE [2].

The mechanism of liver damage in patients with SLE remains unknown. Apoptosis has been proposed as a potential cause based on histologic liver findings [56]. A recent longitudinal study showed a significant association between the prevalence of liver disease and the production of antiphospholipid antibodies [57]. This finding is consistent with results of a meta-analysis of patients with antiphospholipid syndrome (APS) [58]. The mechanistic target of rapamycin complex 1 (mTORC1)-dependent mitochondrial dysfunction contributed to the generation of antiphospholipid antibodies in lupus-prone mice [59]. On the other hand, hepatic-deposited immunoglobulin G (IgG) has been proposed as an important factor in the development of liver injury in SLE in experiments in mice [60]. However, hepatic deposition of IgG is also observed in liver histology of patients with autoimmune hepatitis [61]; thus, other mechanisms may be associated with liver dysfunction in patients with SLE.

Liver dysfunction in patients with SLE mostly presents as mild-to-moderate elevations of serum aminotransaminase levels, whereas ALP and γ-GTP elevations are less frequent [1, 2]. The diagnosis of liver dysfunction caused by SLE itself is achieved by ruling out other causes in addition to the activity of SLE itself [2]. The incidence of nervous system involvement is higher in patients with liver dysfunction caused by SLE itself [10]; thus, extrahepatic symptoms may help diagnose liver dysfunction caused by SLE itself.

Histologic findings of the liver in patients with SLE-induced liver dysfunction show a broad morphologic spectrum. Common histopathologic findings in SLE include fatty liver, portal inflammation, arthritis, congestion, nodular regenerative hyperplasia (NRH), abnormal vessels in portal tracts, and vascular changes such as hemangioma [34, 36].

Survival rates do not differ between patients with SLE with and without liver dysfunction [10]. Liver dysfunction caused by SLE itself is generally subclinical with a fluctuating course and responds well to moderate-to-high doses of prednisone without progression to end-stage liver disease [7]. Acute liver failure is rarely reported in patients with SLE. However, underlying MAS should be taken into account if acute liver failure does occur.

1.6.2 Rheumatoid Arthritis

The prevalence of liver dysfunction caused by RA itself is 2.5–29.2% [1, 11]. In general, the degree of liver dysfunction correlates with factors associated with RA activity, such as C-reactive protein levels and the erythrocyte sedimentation rate [33]. Elevation of biliary enzymes, but not aminotransferase, suggests liver involvement in patients with RA. Both levels of ALP and γ-GTP are usually

elevated, but one third of patients show elevation of ALP levels alone [62]. The ALP elevations in RA require attention, because increased ALP levels reflect not only liver damage but also bone lesions. Examination of ALP isozymes is therefore needed to evaluate the liver dysfunction caused by RA in patients showing ALP elevations alone. The histology of the liver with dysfunction caused by RA itself does not show any consistent structural abnormalities. A previous paper reported non-specific findings, such as non-specific reactive hepatitis, hepatic arthritis, and fatty liver [34]. Moreover, NRH is also associated with RA and has been seen in Felty's syndrome, a subtype of RA characterized by leucopenia and splenomegaly [63].

1.7 Autoimmune Liver Disease

1.7.1 Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is an immune-mediated hepatic disease characterized by the presence of antinuclear antibody (ANA). Histopathologic liver findings such as interface hepatitis, hepatocyte rosette formation, and emperipolesis help diagnose AIH and are included in its diagnostic criteria. Some patients with AIH develop rheumatic disease (Table 1.2), and some patients with rheumatic disease develop AIH.

Table 1.2 Prevalence of rheumatic diseases in patients with autoimmune liver disease

Overlap	Prevalence	References
Autoimmune hepatitis (AIH)		
AIH + SLE	3.1% (51/1659)	Takahashi et al. [66]
	2.6% (27/1056)	Abe et al. [67]
	3.1% (5/162)	Oka [68]
	0.7% (2/278)	Teufel et al. [69]
AIH + RA	3.4% (56/1659)	Takahashi et al. [66]
	2.8% (30/1056)	Abe et al. [67]
	1.8% (5/278)	Teufel et al. [69]
AIH + SjS	5.7% (95/1659)	Takahashi et al. [66]
	7.2% (76/1056)	Abe et al. [67]
	1.4% (4/278)	Teufel et al. [69]
Primary biliary cirrhosis (PBC)		
PBC + SLE	0.4% (33/9233)	Hirohara [81]
	3.7% (12/322)	Wang et al. [83]
	1.3% (2/160)	Watt et al. [84]
	2.6% (27/1032)	Gershwin et al. [85]
	1.8% (3/170)	Marasini et al. [86]

Table 1.1 (continued)

Overlap	Prevalence	References
PBC + RA	3.5% (327/9233)	Hirohara [81]
	2.8% (9/322)	Wang et al. [83]
	16.9% (27/160)	Watt et al. [84]
	10.0%(103/1032)	Gershwin et al. [85]
	1.8% (3/170)	Marasini et al. [86]
PBC + SjS	11.2% (1031/9233)	Hirohara [81]
	37.6% (121/322)	Wang et al. [83]
	25.0% (40/160)	Watt et al. [84]
	9.9% (102/1032)	Gershwin et al. [85]
	3.5% (6/170)	Marasini et al. [86]
PBC + SSc (CREST)	2.9% (272/9233)	Hirohara [81]
	2.8% (9/322)	Wang et al. [83]
	7.5% (12/160)	Watt et al. [84]
	2.3% (24/1032)	Gershwin et al. [85]
	12.4% (21/170)	Marasini et al. [86]

SLE systemic erythematosus, *RA* rheumatoid arthritis, *SjS* Sjögren's syndromes, *SSc* systemic sclerosis; *CREST* calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia

Liver damage, whether by AIH or SLE itself, is often difficult to treat in patients with overlap of AIH and SLE [64, 65]. The prevalence of SLE-AIH is 0.7–3.1% among patients with AIH [66–69]. Serum markers for SLE such as anti-double-stranded DNA (anti-dsDNA) and anti-ribosomal P protein are also found in patients with AIH [10]. Although specific markers such as anti-smooth muscle antibody (ASMA) and liver-kidney microsomal (LKM) antibody for AIH may help differentiate AIH from SLE serologically, their positive rate is relatively low in Japan. Histologic assessment of the liver is the gold standard for differentially diagnosing AIH and SLE-associated hepatitis [70].

The prevalence of RA among patients with AIH is similar to that of SLE. We diagnosed AIH in 1.3% of 79 patients with RA [11]. On the other hand, the prevalence of RA is 1.8–3.4% in patients with AIH [66, 67, 69]. A study of patients with RA on long-term, low-dose MTX therapy reported that 13 (52.5%) of 25 patients with elevated liver enzymes showed AIH-like lesions on liver biopsy specimens [71]. Interestingly, these AIH-like lesions improved by treatment with etanercept for 6 months [72]. On the other hand, use of biologic agents may lead to the development of autoimmune diseases, including AIH [73]. Among the biologic agents, antitumor necrosis factor (TNF)-α has frequently been shown to trigger AIH [74]. Discontinuation anti-TNFα and corticosteroid therapy are effective for AIH induced by anti-TNFα. Unfortunately, it is impossible to completely distinguish AIH from drug-induced liver injury in patients with rheumatic disease because characteristics may be similar in both diseases.

SjS is present in 1.4–7.2% of patients with AIH [66, 67, 69]. On the other hand, AIH is found in 1–4% of patients with SjS [17, 18, 75, 76]. Two thirds of cases of

AIH with SjS have been reported to be from Asia, and nearly 10% of them had positive antimitochondrial antibodies (AMA) [77]. SjS is the most frequent extrahepatic autoimmune disease in AIH-PBC overlap syndrome (6 [8.4%] of 71 patients) [78]. Histologic findings of patients with SjS patients and AIH include a predominance of CD3-positive T-cell infiltrates in both the salivary glands and liver [79].

1.7.2 Primary Biliary Cholangitis

Primary biliary cholangitis (PBC) is an autoimmune cholestatic disease of unknown etiology characterized by progressive destruction of intrahepatic bile ducts [80]. Overlapping conditions of PBC and rheumatic diseases are well recognized, indicating the involvement of autoimmune mechanisms in the pathogenesis of PBC. An epidemiologic study from Japan showed that 2559 (27.7%) of 9233 patients with PBC were affected by another autoimmune disease at the time of PBC diagnosis [81]. The autoimmune diseases co-occurring with PBC include SjS (11.2%), Hashimoto disease (6.3%), RA (3.5%), Raynaud's phenomenon (3.1%), and SSc (2.9%) [81].

PBC is a main cause (27–70%) of liver dysfunction in patients with SjS [1, 11]. In previous studies, 47–73% of patients with PBC had sicca symptoms [82]. Furthermore, 26–93% of patients with PBC showed histologic changes in the salivary gland that were compatible with SjS [82]. The prevalence of SjS is 4–38% in patients with PBC [81, 83–86]. On the other hand, the prevalence of PBC is 4–9% in patients with SjS [17, 18, 75, 87]. Antimitochondrial antibodies (AMA) are detected in 1.6–13% (using indirect immunofluorescence) or 22–27% (using indirect immunofluorescence) of patients with SjS [88]. Among AMA-positive patients with SjS, 60% have elevated ALP levels, and 82% have histologic findings of PBC [16]. Bile duct and salivary gland epithelia are common major findings in both SjS and PBC. In addition, SjS and PBC have a common histologic characteristic—a predominance of CD4-positive T-cell infiltrates—around the bile duct in PBC and around the salivary duct in SjS. Both biliary and salivary epithelial cells are associated with autoimmune mechanisms induced by cytokines, human leukocyte antigen (HLA) class II molecules, and adhesion molecules [88]. Although the prevalence of liver dysfunction caused by SjS itself has been reported to be 30% [1], some patients may be affected by PBC, including subclinical PBC.

PBC is also the main cause of liver dysfunction in patients with SSc [1, 11]. About 2–12% of patients with PBC have been reported to have scleroderma [81, 83–86]. In a large-scale, nationwide study in Japan, 272 (2.9%) of 9233 patients with PBC were reported to show an overlap with SSc [81]. CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome represents limited cutaneous SSc. PBC was detected in 16 (2%) of 817 patients with SSc, of whom 13 (81%) displayed CREST syndrome [89]. Anticentromere antibody (ACA), a hallmark antibody of SSc, has also been

detected in 9–30% of patients with PBC [90]. In a study of patients with PBC with ACA, 10 (63%) of 16 patients showed features of CREST syndrome [91]. The prevalence of ACA is higher in patients with PBC-SSc or PBC-CREST overlap than in patients with PBC alone [92]. In addition to a higher prevalence of ACA, characteristics of patients with PBC-CREST overlap compared with PBC alone are as follows: female gender, older age, milder clinical features of both PBC and CREST syndrome, more frequent occurrence of esophageal varices, better prognosis, lower serum levels of AST and IgM, lower median titers of AMA, and a higher prevalence of HLA-DR9 [93]. PBC-CREST overlap syndrome patients are generally incomplete types of CREST syndrome, such as CRST (calcinosis, Raynaud's phenomenon, sclerodactyly, and telangiectasia) and RST (Raynaud's phenomenon, sclerodactyly, and telangiectasia) [93]. Compared to patients with PBC alone, the rates of progressive jaundice and liver transplantation are significantly lower in patients with PBC-SSc [92].

SLE-PBC overlap is relatively rare. The prevalence of SLE in patients with PBC has been reported to be 0.4–3.7% [81, 83–86], whereas the prevalence of PBC in patients with SLE was shown to be 1.4–7.5% [6–8, 11]. In 15 SLE-PBC overlap cases, PBC developed before SLE (73.3%) [94]. Although the incidence of SLE in patients with PBC was significantly higher than that in the healthy controls [85], the frequency of AMA positivity in patients with SLE is similar to that of healthy controls [95]. This may be explained by the fact that AMA titers change negatively or decrease in one third of patients with SLE and AMA-positive PBC. SLE-PBC overlap patients had lower white blood cell counts and higher frequencies of renal involvement than patients with PBC alone [83]. SLE-PBC patients appeared to have much less extensive liver damage, suggesting that SLE may protect against progression of PBC [96]. There is no association between SLE activity and the incidence of PBC; moreover, SLE flare-ups are unusual in patients with SLE-PBC overlap [97, 98]. Although SLE-PBC overlap may involve a genetic abnormality (e.g., IRF5-TNPO3) [99], the detailed role of genetic factors remains to be established.

PBC is the most common autoimmune liver disease in patients with RA. PBC occurs in 1–10% of patients with RA [100], whereas RA occurs in 1.8–16.9% of patients with PBC (Table 1.2). Among 25 patients with PBC-RA overlap, 17 patients were diagnosed with RA before PBC [101]. About half of patients with PBC become rheumatoid factor-positive during the clinical course of PBC, whereas 10–18% of patients with RA are AMA-positive [102–104]. An AMA-positive status in patients with RA represents PBC overlap or future development of PBC [105]. Genome-wide association studies have indicated several common genes, such as HLA-DQB1, CTLA4, MMEL1, STAT4, IRF5, and CXCR5 in RA and PBC [106]. These common serum and genetic profiles support the possibility of PBC-RA overlap. Laboratory findings from patients with PBC-RA overlap have shown lower hemoglobin levels and higher ALP levels, IgG levels, erythrocyte sedimentation rate, and positive rheumatoid factor findings than in patients with PBC without RA [83].

1.8 Viral Infection

1.8.1 Hepatitis C Virus

Extrahepatic manifestations of hepatitis C virus (HCV) infection have been reported in rheumatic diseases such as SjS, inflammatory arthritis, and cryoglobulinemia vasculitis. A recent meta-analysis showed the prevalence of SjS in patients with HCV was 11.9% compared with 0.7% in non-HCV controls [107]. The risk ratio for SjS patients with HCV is 2.29 compared with non-HCV-infected individuals. A large cohort study of 783 patients with SjS reported patients who were HCV-IgG-positive were older, more frequently male, and more frequently presented with vasculitis, peripheral neuropathy, or neoplasia compared with patients without HCV [108]. HCV RNA is present in the salivary glands of patients with SjS with HCV infection [109]. Moreover, transgenic mice of the HCV envelope genes develop SjS-like exocrinopathy. These findings introduce the possibility of a direct impact of HCV on the development of SjS [110].

The prevalence of rheumatoid-like arthritis among patients with HCV is 1%, whereas the prevalence in non-HCV controls is 0.09% [107]. The risk for HCV-related inflammatory arthritis is two times higher than in non-HCV patients. Patients with RA with concomitant HCV have higher disease activity scores [111]. Patients who are HCV-positive were more likely to be treated with prednisone and anti-TNFα therapies and less likely to receive MTX compared with HCV-negative patients [111].

Cryoglobulinemia is defined as the presence of circulating immunoglobulins that precipitate at cold temperatures and dissolve with rewarming. This phenomenon was reported in patients with liver disease before the discovery of HCV [112]. Mixed cryoglobulinemia vasculitis is related to HCV infection in 70–80% of cases and is associated with a type II immunoglobulin M kappa mixed cryoglobulin [113]. Arthralgia is reported in 35–58% of patients with HCV with positive findings for mixed cryoglobulin [114, 115]. Although rheumatoid factor is found in 70–80% of patients with cryoglobulinemia vasculitis, anti-cyclic citrullinated peptide antibodies are usually negative, and there is no evidence of joint destruction [113].

Interferon is contraindicated in patients with HCV with rheumatic disease because it can induce a flare of rheumatic disease. Over the last few years, the development of direct-acting antivirals (DAAs) for HCV had enabled high cure rates and reduced the HCV-related disease progression to cirrhosis and hepatocellular carcinoma. One report showed a decrease of cryoglobulin levels in patients with HCV cryoglobulinemia vasculitis after DAAs [116]. Another study also reported improvement of symptoms in patients with HCV with cryoglobulinemia vasculitis after DAAs [113]. Future studies can elucidate the efficacy of DAAs on other rheumatic diseases such as SjS and inflammatory arthritis.

1.8.2 Other Viruses

Many viral infections other than HCV have been documented in SLE at presentation and during the course of the disease. The prevalence of *hepatitis B* is lower than that of hepatitis C in patients with SLE [3, 5, 7]. Among 1031 patients in Japan with SLE, the rate of hepatitis B surface antigen (HBsAg) is 0.3%, whereas that of hepatitis B core antibody (HBcAb) is 13.7% [117]. On the other hand, among patients in Japan, 50 (0.7%) of 7650 patients with RA are current HBV carriers, and 214 (25.6%) of 837 are positive for HBcAb, indicating that the prevalence of HBV infection in patients with RA was higher than that in patients with SLE [117]. Screening and careful monitoring of HBV is essential during immunosuppressive therapy in all rheumatic diseases to avoid HBV reactivation.

Immunosuppressive therapy increases the risk for bacterial and viral infections. *Cytomegalovirus* (CMV) infection is associated with the occurrence and development of SLE and also correlates with disease activity and mortality in SLE [118]. Liver dysfunction is the most common clinical manifestation in patients with SLE with active CMV infection [119]. Although biologic agents are recognized as having a low risk for CMV reactivation, the potential for CMV reactivation remains, as shown in a case report of a patient with RA [120]. Moreover, *hepatitis E virus* (HEV) infection should be suspected in patients with immunosuppressive therapy and elevated liver enzymes [121]. Discontinuation of immunosuppressive therapy and antiviral therapy usually lead to recovery in these patients; however, one death due to fulminant hepatitis has been reported [122]. Therefore, prevention or early diagnosis of HEV infection is essential for patients with rheumatic disease.

1.9 Drug-Induced Liver Injury

Drugs are a major cause of liver dysfunction in patients with rheumatic disease, and all drugs can cause drug-induced liver injury (DILI) in all individuals regardless of whether they are healthy or not. The causative drugs vary. About 80% of patients with SLE are treated with NSAIDs and analgesics for major symptoms such as arthralgia, serositis, and headache [123]. Patients with SLE usually present with a higher rate of NSAID-related complications than patients without SLE. Common complications include increased aminotransaminase levels, skin rashes, retention of body fluids, gastric ulcers, and aseptic meningitis [124]. Aspirin is the most common drug associated with DILI in patients with SLE; the liver toxicity of aspirin is considered dose-dependent. Aspirin can injure the mitochondria, leading to free fatty acid accumulation in the liver and hepatic steatosis [124]. Azathioprine (AZA) is an immunosuppressive drug used