73384_Auto_Edited.docx

WORD COUNT 5511
TIME SUBMITTED 26-APR-2022 04:51PM
PAPER ID 85234236

Name of Journal: *World Journal of Gastroenterology*

Manuscript NO: 73384

Manuscript Type: REVIEW

Autoimmune liver diseases in systemic rheumatic diseases

Chrong-Reen Wang, Hung-Wen Tsai

Abstract

Systemic rheumatic diseases (SRDs) are chronic, inflammatory, autoimmune disorders with the presence of autoantibodies that may affect any organ or system. Liver dysfunction in SRDs can be associated with prescribed drugs, viral hepatitis, alternative hepatic comorbidities and coexisting autoimmune liver diseases (AILDs), requiring an exclusion of secondary conditions before considering liver involvement. The patterns of overlap diseases depend predominantly on genetic determinants with common susceptible loci widely distributing in both disorders. In AILDs, it is important to identify the overlapping SRDs at an early stage since such a coexistence may influence the disease course and prognosis. Commonly co-occurring SRDs in AILDs are Sjögren syndrome (SS), rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) in autoimmune hepatitis (AIH), and SS, RA or systemic sclerosis in primary biliary cholangitis. Owing to different disease complications and therapies, it is imperative to differentiate between SLE liver involvement and SLE-AIH overlap disease. Therapeutic options can be personalized to control coexisting conditions of liver autoimmunity and rheumatic manifestations in AILD-SRD overlap diseases. The collaboration between hepatologists and rheumatologists can lead to significant advances in managing such a complex scenario. In this review, we provide a comprehensive overview on coexisting AILDs in different SRDs and the therapeutic approach in managing these overlap diseases.

Key Words: Autoimmune liver disease; Systemic rheumatic disease; Overlap disease; Liver function test; Drug-induced liver injury; Viral hepatitis

Wang CR, Tsai HW. Autoimmune liver diseases in systemic rheumatic diseases. *World J Gastroenterol* 2022; In press

Core Tip: Liver dysfunction in systemic rheumatic diseases (SRDs) can be associated with prescribed drugs, viral hepatitis, alternative hepatic comorbidities and coexisting

autoimmune liver diseases (AILDs), requiring an exclusion of secondary conditions before considering liver involvement. In AILDs, it is imperative to identify the overlapping SRDs at an early stage since such a coexistence may influence the disease course and prognosis. Commonly co-occurring SRDs in AILDs are Sjögren syndrome (SS), rheumatoid arthritis (RA) or systemic lupus erythematosus in autoimmune hepatitis, and SS, RA or systemic sclerosis in primary biliary cholangitis. Therapeutic options can be personalized to control coexisting conditions of liver autoimmunity and rheumatic manifestations in AILD-SRD overlap diseases.

INTRODUCTION

Systemic rheumatic diseases (SRDs) are chronic, inflammatory, autoimmune disorders with the presence of autoantibodies that may affect any organ or system; they include systemic lupus erythematosus (SLE), Sjögren syndrome (SS), systemic sclerosis (SSc), rheumatoid arthritis (RA), idiopathic inflammatory myopathies (IIM), mixed connective tissue disease (MCTD), systemic vasculitis (SV), *etc.*[1]. Although SRDs can have liver involvement, most patients only have abnormal liver enzymes without significant changes in histopathology[2,3]. Hepatic dysfunction can be a secondary phenomenon, associated with prescribed drugs, viral hepatitis (VH), alternative liver comorbidities, and coexisting autoimmune liver diseases (AILDs).

The major cause of abnormal liver function test (LFT) in patients with SRDs is associated with medications, *i.e.* drug-induced liver injury (DILI)[3]. Given that a variety of medications are used in the management of SRDs, it is frequently encountered in clinical practice. High occurrences of DILI in SRDs are due to the chronic or high-dose prescription of medications, the existence of susceptible factors that makes patients prone to hepatotoxicity, and/or the use of herbal or ayurvedic compounds[2,3]. Elevated liver enzymes with predominant cholestatic or hepatocellular damage pattern can be observed in SRDs treated with non-steroidal anti-inflammatory drugs (NSAIDs), synthetic disease modifying anti-rheumatic drugs (SDMARDs), corticosteroids (CS), immunosuppressants, biologic agents or oral small molecules[2]. Most medications only

cause a mild elevation in liver enzymes, which reverses with drug cessation. On rare occasions, severely irreversible hepatic damage may occur and progress into chronic liver disease or fulminant hepatic failure. Despite the relative safety with a low-dose prescription, methotrexate, a SDMARD frequently used in SRD-related arthritis, has been reported to cause acute liver dysfunction with confounding factors like concomitant NSAIDs use, and progressive liver fibrosis and cirrhosis can occur when used chronically[4]. It usually occurs after a prolong use for no less than 2 years and with a total accumulated dose of 1.5 g[5]. Notably, there is a risk of hepatitis B virus (HBV) reactivation depending on the dose and duration of CS use and the status of hepatitis B surface antigen and hepatitis B core antibody in SRDs[6]. Furthermore, acute or progressing liver dysfunction can be related to coexisting VH, requiring screen tests for HBV and hepatitis C virus (HCV) infection to provide early antiviral treatment and avoid reactivating or worsening VH after immunosuppressive therapy[3]. Table 1 summaries the hepatic abnormalities associated with the common medications used in SRDs[2,7,8]. Although immune checkpoint inhibitors have altered the therapeutic paradigm in oncological patients, there is undesirable off-target autoimmune reaction causing adverse effects like musculoskeletal manifestations and immune hepatitis, a pan-lobular active hepatitis resembling AIH[9].

Although the liver is the largest lymphoid organ involved in the immune response against invading pathogens and in the maintenance of tolerance to self-molecules, it can also be a target of autoimmune diseases[10]. AILDs are attributed to a complex interplay of socioeconomic, environmental and genetic factors, all of which may participate in their pathogenesis[11]. Most common AILDs are autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), which may occur individually or in combination[12]. These disorders are characterized by hepatic lymphocyte infiltration, elevated liver enzymes, generation of autoantibodies, and associated HLA loci. Coexisting extra-hepatic autoimmune diseases such as SRDs, have been well described in the literature[13]. AIH often goes into disease remission with first-line therapy, including CS alone or plus AZA[14]. PBC has a normal life expectancy if

treated early with ursodeoxycholic acid (UDCA) in responsive patients, while no effective therapy has been found to alter the natural course of PSC, except liver transplantation (LT)[15,16]. Some patients with AILDs may eventually progress into end-stage liver disease requiring LT, and with an increased risk of recurrent activities and acute or chronic rejection[17,18]. Currently, AILD research has focused on obtaining a better understanding of the pathogenetic process for identification of new therapeutic targets to reduce morbidity and improve survival[15]. Table 2 demonstrates the demographic, clinical, laboratory, pathological, therapeutic and prognostic characteristics of three common AILDs[11-20].

In AILDs, it is imperative to identify the co-occurring SRDs at an early stage by using autoantibody screening, since such a coexistence may influence their natural course and disease prognosis[21]. The patterns of overlap diseases depend predominantly on genetic determinants, with common susceptible loci widely distributing in both disorders[20]. The similar epidemiological links between AILDs and SRDs are further reflected in their shared pathogenesis, best exemplified by the concept of autoimmune epithelitis, *i.e.*, concomitant PBC and SS[22,23]. Furthermore, AILDs and SRDs have common serologic profiles with the presence of particular autoantibodies and hyper-gammaglobulinemia[21,24]. Progressive liver damage can be identified in overlap diseases despite rare complications with liver cirrhosis and hepatic failure[3]. Table 3 shows the reported prevalence of coexisting AILDs in different SRDs.

The therapeutic strategies in AILDs and SRDs are also overlapping, with CS as first-line treatment in most cases, followed by administration of immunosuppressants, and potential application of targeted therapy[21]. Nevertheless, therapeutic options can be personalized to control coexisting conditions of liver autoimmunity and rheumatic manifestations[24]. A collaboration between hepatologists and rheumatologists in clinical practice can lead to significant advances in managing such a complex scenario. Herein, we provide a comprehensive overview on coexisting AILDs in different SRDs and the therapeutic approach in managing these overlap diseases.

SLE

SLE is a less common SRD, occurring mostly in women of childbearing age and having heterogenous clinical manifestations affecting any organ or system as well as presenting antinuclear antibody (ANA) and a variety of autoantibodies[25]. The liver is generally not a target organ in SLE and hepatic involvement is not included in the classification or diagnostic criteria. Abnormal LFT is common in SLE, usually with subtle changes, in up to 60% of cases during the disease course, while elevated liver enzymes occur during disease flares in less than 20% of patients[3,26,27]. Hepatic dysfunction in SLE can be classified into primary form due to disease itself or secondary form including DILI, VH, vascular disorders, alternative liver comorbidities and coexisting AILDs[28]. Before considering the liver involvement in SLE, it is necessary to exclude other secondary conditions.

Lupus hepatitis (LH) is reactive liver damage caused by immune-complex deposition, in contrast to lupoid hepatitis, a term used in the 1950s to define what was later known as AIH[29,30]. This manifestation is usually synchronous with disease activity and affects less than 10% of patients[31-33]. It is characterized by asymptomatic transaminasemia with the presence of anti-ribosomal P antibody (commonly known as ARPA) and non-specific histopathological changes. Although CS may help to improve impaired LFT, there is a risk of flare up upon cessation of its use[34]. Figure 1 shows the liver biopsy finding from a patient with LH demonstrating non-specific histopathological changes.

The main cause of liver dysfunction in SLE was salicylate toxicity in the 1950s[35]. Later on, owing to a rare prescription, another common finding of liver biopsy was steatohepatitis, an alternative liver comorbidity. Nowadays, the known risk factors for development of non-alcoholic fatty liver disease (NAFLD) include obesity, physical inactivity and sedentary lifestyle[36], which are also shared by SLE. Furthermore, patients with SLE have been shown to have higher incidences of metabolic syndrome and insulin resistance[37], especially with the use of CS[38]. Increased frequencies of NAFLD have been found in liver biopsy specimens from patients with SLE[39].

The presence of antiphospholipid antibody (aPL) in SLE underlies an increased probability of thrombophilia, leading to antiphospholipid syndrome (APS) with vascular thrombosis[40]. APS can affect the hepatic circulation, causing hepatic arterial thrombosis, portal vein thrombosis and Budd-Chiari syndrome (BCS) as well as the rarely-observed liver infarction and hepatic veno-occlusive disease[40-42]. Notably, BCS resulting from the obstruction of hepatic venous outflow[43] can be an initial manifestation of patients with SLE-associated APS[44]. In particular, aPL has been reported to be involved in the pathogenesis of hepatic nodular regenerative hyperplasia (referred to herein as NRH), small-nodule transformation of hyperplastic hepatocytes with a later development of non-cirrhotic portal hypertension[3,45]. Although higher frequencies of aPL could be detected in AILDs, there was no definite clinical or histological correlation with their presence in such patients[3,46].

Autoimmune gastrointestinal diseases have been linked to SLE with shared pathogenic mechanisms responsible for the development of both disorders[47]. Although AIH and PBC are rare AILDs, the coexistence with either of these diseases is not uncommon among SLE patients with liver enzyme abnormalities, suggesting a causal relationship between their overlap[28,48,49]. Since SLE-PSC overlap disease rarely occurs (but has been described in case reports[28,48]), it remains to be ascertained whether they are casual associations. A review on individual AILD coexisting with SLE is depicted as follows.

AIH is a rare AILD characterized by interface hepatitis as the most specific histological change, and the presence of autoantibodies including anti-liver kidney microsomal-1 (LKM-1)/liver cytosol-1 (LC-1) in type II, a rare subgroup affecting female pediatric patients, and ANA/anti-smooth muscle antibody (ASMA) in type I[50]. Clinical manifestations vary from asymptomatic to nonspecific symptoms of varying severity, including fatigue, malaise, nausea, anorexia and abdominal pain. The criteria established by the International Autoimmune Hepatitis Group (commonly known as the IAHG) are usually used for the diagnosis of AIH[51]. Due to different disease complications and therapeutic regimens between AIH and LH, it is imperative to

differentiate between two disease entities[28,34]. AIH may lead to end stage liver disease, and its immunosuppressive therapy needs to be continued for at least 2 years of hepatic biochemical remission before attempting withdrawal[50]. Liver biopsy is highly recommended for their distinguishment[28,34]. LH usually demonstrates lobular infiltrates or occasionally mild periportal infiltrates, whereas AIH is characterized by portal mononuclear infiltrates invading nearby lobules to induce interface hepatitis and form hepatocyte rosettes, followed by confluent lytic necrosis and finally cirrhosis[30].

SLE-AIH overlap disease is defined by fulfilling American College of Rheumatology (commonly known as the ACR) criteria for the classification of SLE in patients who also meet IAIHG criteria for the diagnosis of AIH[34,51,52]. The prevalence of AIH in SLE ranges from 1.6% to 15%, lower in general cohorts and higher in patients with abnormal LFT[39,53-58]. Immunosuppressive treatment for AIH is also effective for SLE, and has been demonstrated to successfully apply to their overlap cases[28]. Most cases with coexisting SLE and AIH responded well to CS or plus immunosuppressants[48]. The long-term outcome for SLE-AIH overlap disease has been observed to be better than AIH alone[34]. Nevertheless, there are sporadic cases of acute liver failure or end-stage liver disease requiring LT[59,60].

PBC is the most common AILD affecting women predominantly. It is characterized by destructive lymphocytic cholangitis involving small bile ducts, and leading to progressive ductopenia, hepatic cholestasis and biliary fibrosis[61]. Clinical manifestations vary from asymptomatic to non-specific symptoms with jaundice and pruritus. According to the guidance from American Association for the Study of Liver Diseases (commonly known as the AASLD), the diagnosis of PBC is established when two of three items are met, including biochemical cholestasis based on alkaline phosphatase (ALP) elevation, presence of antimitochondrial autoantibody (AMA), and histological evidences of nonsuppurative destructive cholangitis and interlobular bile ducts destruction[62]. The nomenclature of PBC has already shifted from cirrhosis to cholangitis, reflecting the dramatically improved prognosis upon first-line UDCA therapy without the development of cirrhosis[63,64].

SLE-PBC overlap is defined by fulfilling the diagnostic criteria for both diseases[34,52,62]. SLE usually affects younger females of childbearing age, whereas PBC is more common in middle-aged women. By genome-wide studies, both diseases have been reported to share the IRF5-TNPO3 gene-spanning haplotype loci[65]. The prevalence of PBC in SLE patients with liver dysfunction ranges from 2.2% to 7.5%, usually lower than that of AIH[39,53-55,57]. In a review of SLE overlapping with PBC, 69% were diagnosed first by PBC, 24% had coexisting SS, and 2 deaths were due to PBC-related hepatic failure[66]. For patients with concomitant SLE and PBC, regardless of the SLE treatment, UDCA is effective first-line therapy for PBC[49].

The diagnosis of PBC-AIH overlap is established with coexisting features of both diseases[67]. Two commonly used criteria for the diagnosis of PBC-AIH overlap syndrome are the IAIHG and Paris criteria[51,68]. Patients with overlapping PBC and AIH have been described to exhibit significantly higher rates of LC, portal hypertension and mortality as compared with those with AIH or PBC alone[69]. PBC with features of AIH should be considered for immunosuppressive therapy[49], while PBC-AIH overlap disease can benefit from combination treatment with UDCA and CS or plus AZA[69]. There is a rare association between SLE and PBC-AIH overlap disease[70]. In a large case series with 71 overlap patients, EHAIDs were identified in 31 (44%), while only 2 (3%) had concurrent SLE[71].

In contrast to western countries, AIH had been considered a rare etiology in the Asia-Pacific region, where VH is a major diagnosis in patients with chronic liver diseases[72]. A very low prevalence of AIH was found in Taiwan in earlier years, raising concerns about under-recognition in an area with a high prevalence of HBV infection and associated liver cirrhosis and hepatocellular carcinoma complications[73], where clinicians would have been more familiar with VH and might have tended to overlook AIH[74]. Recent findings, however, have shown increasing annual incidences of AIH, indicating improved recognition of AIH in this region[72].

The clinical, laboratory, therapeutic and outcome profiles in 3 patients with SLE-AIH overlap disease diagnosed by ourselves are shown in Table 4. All met IAIHG diagnostic

criteria for AIH[51], and case 2 also fulfilled AASLD diagnostic criteria for PBC[62]. Despite CS plus AZA therapy, case 1 progressed into advanced LC, and received LDLT with stabilized LFTs and low SLE activity. Case 2 had the initial diagnosis of AIH with transaminasemia, followed by the development of hepatic cholestasis and sicca symptoms, and finally full-blown manifestations of SLE. Under the diagnosis of coexistent AIH, PBC, SLE and SS, in addition to CS/AZA and UDCA, the patient received B-cell depleting therapy with anti-CD20 monoclonal antibody, with low-dose CS for maintenance, resulting in normalized LFT and low SLE activity. Figure 2 demonstrates histopathological findings in liver biopsy specimens from cases 1 and 2.

PSC is a rare cholestatic AILD characterized by persistent, progressive inflammation, fibrosis and stricture of the intrahepatic and extrahepatic bile ducts, leading to cirrhosis[75]. About half of the patients are asymptomatic. The diagnosis is made by cholestasis with ALP elevation and imaging of bile duct strictures, excluding secondary causes. Liver biopsy is indicated only when suspecting overlapping with other AILDs or small-duct PSC, a variant with normal cholangiogram. UDCA is the subject of debate with conflicting data to support its use in PSC[49], and end-stage liver disease requiring LT may develop in affected patients.

Although the association of SLE with PSC is considered to be extremely unusual[34,48], there are several published cases with SLE-PSC overlap disease[76-80]. Furthermore, a 1.7% occurrence of SLE was observed in a Swedish PSC cohort[81]. Whether such a coexistence indicates that both diseases might share common pathogenic pathways remains to be elucidated.

SS

SS is a common SRD affecting the exocrine glands with typical symptoms of dryness of eyes and mouth, histological evidence of focal lymphocytic sialadenitis and the presence of anti-Ro and -La antibodies[82]. The treatment of SS-related dry eyes and mouth is symptomatic with the use of artificial tear and saliva preparation. LFT abnormalities can be identified in nearly half of patients, either persistent or

intermittent, and usually mild with cholestatic or hepatocellular pattern[3]. Liver involvement is considered as the most common extra-glandular feature, correlating with the disease activities of SS involving other organs[83]. In a large-scale investigation of 475 cases, after excluding DILI and alternative hepatic comorbidities, the main causes of liver dysfunction were VH in 50% and AILDs in around 20% of patients[84]. Several studies have confirmed a higher prevalence of AILDs among SS, mainly PBC (3.4% to 8.9%), followed by AIH (0.4% to 4.4%)[84-87].

The most frequently associated SRDs in PBC is SS with a prevalence ranging from 3.5% to 38%[88-94]. PBC can be considered a SS of the liver, whereas SS has been equally regarded as a PBC of the exocrine glands[21]. In addition to frequent clinical coexistence and comparable epidemiological features, SS and PBC have similar pathogenic mechanisms and genetic susceptibility backgrounds[95]. Pyruvate dehydrogenase complex E2 subunit, a PBC autoantigen, is also present on the surface of salivary epithelial cells in SS, while HLA-DR2 and -DR3 have been reported as the common susceptibility genes in both disorders[20].

Despite a higher frequency of ASMA than AMA in SS[96], the prevalence of coexisting AIH is lower than PBC[84,85,97]. Owing to a much higher prevalence of SS than SLE in the general population, the occurrence of concomitant SLE and SS in patients with AIH are 0.7% to 2.8% and 0.8% to 7.2%, respectively, lower in SLE than in SS[98-102].

There are published cases and case series describing SS-PSC overlap disease as well as a higher prevalence in small-scale PSC studies[84,103,104], implicating a causative association rather than sporadic occurrence. Notably, almost all reported patients with overlapping SS and PSC have chronic pancreatitis, demonstrating a triad syndrome complex[103]. A possibility of co-occurring IgG4-related disease (IgG4-RD) should be considered in SS-PSC overlap disease with the presentation of autoimmune pancreatitis (AIP)[104].

SSC

SSc is an uncommon SRD characterized by vasculopathy and fibrosis of the skin and internal organs, with the presence of anti-topoisomerase I and anti-centromere antibodies (ACA) in diffuse and limited cutaneous subsets, respectively[105]. It has a higher mortality rate than other SRDs. The gastrointestinal tract is affected in up to 90% of patients[106], and hepatic fibrosis has been identified at autopsy[107]. Since liver involvement is rarely observed in SSc[3], abnormal LFT should exclude other possibilities first before considering disease *per se*. There are diverse autoimmune diseases like AILDs co-occurring within SSc patients and their family members[108], suggesting common pathophysiological mechanisms between these disorders.

Increased prevalence of PBC has been observed in SSc, varying from 0.8% to 3.3%[108-112], and there is a 2.3% to 12.4% occurrence of SSc in PBC[90-94,111]. SSc-PBC overlap disease has the presence of both ACA and AMA[113], and tends to occur in older females with the limited cutaneous subset[114]. This overlap disorder has a slower disease progression in comparison with PBC alone; however, survival is similar due to an increase in SSc-related non-liver death. The use of UDCA has been observed to reduce skin lesions in addition to improved hepatic cholestasis in overlap patients[115].

A 0.8% prevalence of SSc has been reported from a AIH cohort[98], and patients with SSc-AIH overlap disease can be found in the literature[116,117]. In a review with 11 cases[117], all had positive ACA and a later presentation of AIH, 9 with limited cutaneous subtype and 3 with AIH-PBC overlap. Despite a risk of scleroderma renal crisis under the higher dosages of CS use, there were normalized or improved LFT without the occurrence of scleroderma renal crisis in overlap patients receiving such a treatment[116].

Overlap condition with large- or small-duct PSC has been observed in patients with SSc[118,119], suggesting that the extensive disturbance of connective tissues in SSc can lead to abnormal collagen deposition in the bile duct epithelium of PSC[120].

RA

RA is a common SRD primarily affecting the joints and causing cartilage and bone damage, with extra-articular presentations and the presence of rheumatoid factor (commonly referred to as RF) and anti-cyclic citrullinated peptide (commonly referred to as CCP) autoantibodies[121]. Among patients with chronic inflammatory joint diseases, liver involvement has been recognized in RA, despite not showing a significant extra-articular manifestation[122]. Elevated liver enzymes have been identified in up to 50% of patients with RA[2]. DILI is not uncommonly observed in RA, especially under the treatment of NSAIDs and SDMARDs including leflunomide, methotrexate, penicillamine and sulfasalazine, all with potential hepatotoxicity[2,7,123]. Patients are at the hazard of developing NAFLD with the risk factors of chronic inflammation and CS use[2]. Prior to the widespread use of methotrexate in RA, the hepatic histopathological findings at autopsy were most commonly mild portal tract inflammation, rarely diffuse fibrosis of advanced grades[124]. Two rare extra-articular manifestations, rheumatoid vasculitis and Felty syndrome, have been reported to cause necrotizing hepatic arteritis with liver rupture and NRH with portal hypertension, respectively[125,126].

There were no differences in the prevalence of HBV and HCV infection in RA as compared with the general population[127]. Nevertheless, immunosuppressive therapy for RA may significantly worsen underlying VH, and further affect the clinical course and disease prognosis, requiring the survey of viral markers and their antibodies before its initiation[123]. Since the use of tumor necrosis factor (TNF) blockades in RA can cause inactive HBV reactivation[7,128], HBsAg-positive individuals should receive anti-viral prophylactic treatment[129]. Although the TNF pathway is involved in perpetuation of hepatic inflammation and fibrosis progression in HCV infection[130], further studies are needed to verify the safety of anti-TNF therapy in HCV-infected patients[131]. Notably, the use of TNF antagonists has been reported to be associated with the development of AIH in RA[7,132].

The most common coexisting AILDs in RA is PBC with a prevalence of 3.8% to 6.3%[53,97,123], while the occurrence of RA in PBC has been reported to be 1.8% to 13%[90-94]. Around 50% of patients with PBC were shown to be positive for RF[133]. Since RA is

usually diagnosed before PBC in patients with the overlap disease, AMA should be screened in RA with elevated cholestatic liver enzymes[134]. Genetic studies have shown that RA has HLA-DQB1, STAT4, IRF5, MMEL1 and CTLA4 genes in common with PBC, predisposing to develop PBC in RA with the overlapping genetic trait[135]. Potentially hepatotoxic drugs used in RA can be avoided in patients with RA-PBC overlap disease[123].

AIH is rarely observed in RA with a 1.3% prevalence reported from patients with liver dysfunction[97]. Furthermore, in patients with AIH, there is a 1.6% to 5.4% prevalence of RA[98,100-102]. AIH can be diagnosed during the RA progression as acute or chronic hepatitis, but rarely fulminant hepatic failure[123]. In addition, in patients with AIH-PBC overlap disease, RA is accounting for an occurrence of 4.2%[71].

High circulating levels of TNF were found in AIH, while a TNF antagonist etanercept has been demonstrated to improve the AIH histological lesions in RA[136]. Nevertheless, anti-TNF therapy can induce the production of autoantibodies, including ANA and ASMA, leading to the development of distinct autoimmune diseases[137]. Notably, anti-TNF-inhibitor-associated AIH (also known as ATIAIH), a serious idiosyncratic DILI, has been well documented in a large-scale analysis of 389 cases[138]. ATIAIH has a female predominance, a period of 3-14 mo between starting therapy and AIH occurrence, and improvement upon medication stoppage and CS use. Infliximab is the most frequently administrated medication, and RA is the most commonly reported indication.

There was a 1.2% and a 3.4% prevalence of RA in two large-scale PSC cohorts[81,139]. In patients with RA-PSC overlap disease, the presence of HLA-DR4 has been reported to have unusual progression to cirrhosis, 14-48 mo after the diagnosis of PSC[140], implicating a clinical marker at a high risk of cirrhosis development.

Psoriatic arthritis (PsA) is a less common SRD with psoriasis (PsO) and inflammatory arthritis, associating with extra-articular manifestations which have an impact on their therapeutic regimens[141]. Similar to RA, liver enzyme abnormalities in PsA and PsO can be caused by comorbid NAFLD and used medications including NSAIDs and

conventional or biologic/targeted SDMARDs. Despite an increased association of AIH in PsA and PsO[142], these patients might be under anti-TNF therapy, and both diseases are commonly observed complications in ATIAIH[138].

IIM

IIM including polymyositis (PM) and dermatomyositis (DM), an uncommon group of SRDs with the presence of myositis-specific/associated antibodies, have weakness due to skeletal muscle inflammation and extra-muscular involvement[143]. Since transaminases are also muscle-derived enzymes with increased levels during IIM disease activity, an increase of aspartate aminotransferase and alanine aminotransferase more than creatine kinase or an alteration of cholestatic enzymes should consider a possibility of hepatic dysfunction[3]. During the first 3 years to 5 years after the onset of DM, the risk of cancer is increased, rarely hepatocellular carcinoma. Since DM can be associated with malignancy as a paraneoplastic syndrome[144], sporadic cases had HBV-associated hepatocellular carcinoma with a concurrent or later diagnosis of DM[145,146].

Although IIM usually occur alone, these SRDs may associate with other extra-muscular autoimmune diseases including AILDs, more frequently in patients with PM than DM[147]. Positive AMA could be identified in 2.5% of patients with IIM[148], and there were sibling cases of familial clustering with PBC-PM overlap disease[149]. PBC can be identified in IIM with a prevalence of 0.7%[148], while the occurrence of PM in PBC ranges from 0.6% to 3.1%[90,92,93]. There are sporadic cases with PM coexisting with AIH, AIH-PBC overlap disease or PSC[150-152].

MCTD

In addition to the presence of anti-U1 small nuclear ribonucleoprotein (known as snRNP) antibody in high titers, MCTD has distinct features including Raynaud's phenomenon and puffy hands as well as mixed findings from PM, SLE and SSc[153]. It is a rare SRD with a strong HLA linkage, distinctly differing from ethnically matched healthy controls and other SRDs. Hepatic dysfunction occurs in MCTD usually caused

by DILI and pulmonary hypertension-related liver congestion[97,153]. Coexistent AILDs are rarely observed in patients with MCTD[153]. In addition to published case reports, a 1.6% prevalence of AIH was found in MCTD[154], while a 0.6% prevalence of MCTD could be identified in PBC[90]. There was no observed association with MCTD in two PSC case series[81,141].

SV

SV is a rare SRD characterized by inflammation of vascular walls, resulting in a broad spectrum of clinical manifestations dependent on the site, type, and size of involved vessels[155]. Although the diagnosis relies on clinical presentations confirmed by histopathological findings, large/medium and small vessel involvement can be supported by angiographical examinations and laboratory tests (*e.g.*, ANCA), respectively[155,156]. Owing to hepatic vascular involvement[2,53], polyarteritis nodosa (referred to herein as PAN), a medium-vessel SV associated with HBV infection[157], may have elevated liver enzymes. A 2.2% prevalence of SV has been reported from a large-scale PBC series with 361 cases[94], while a 1.6% occurrence of SV was identified in a 122-patient AIH series[98]. There were sporadic cases of AIH coexisting with PAN[158].

Testing for ANCA can support the diagnosis of ANCA-associated vasculitis including eosinophilic granulomatosis with polyangiitis (also referred to as EGPA), granulomatosis with polyangiitis and microscopic polyangiitis (also referred to as MPA) in spite of seropositivity in only one-third of EGPA cases[159]. Notably, ANCA has a diagnostic relevance beyond SV, justifying its occurrence in suspected type I AIH which is lacking conventional autoantibodies[160]. AILDs usually develop atypical perinuclear-ANCA not targeting the classical myeloperoxidase with the positive frequencies highest in patients with PSC[21,156]. There is no clinical nor prognostic value of ANCA testing in patients with AILDs. This atypical autoantibody, referred to as peripheral anti-nuclear neutrophil antibody, can react with beta-tubulin isotype 5 and shares structural homology with the intestinal bacterial protein FtsZ[161]. Nevertheless, it is not specific for AILDs, and it is also present in VH and alcoholic liver disease[162].

Interestingly, ANCA was detected in the bile of PSC patients and correlated with the severity of bile duct stricture[163]. Sixteen cases of ANCA-associated vasculitis-AILD overlap disease have been reported, with twelve involving women, PBC in eleven, and MPA in eight[164-166].

OTHER SRDS

Adult-onset Still's disease (AOSD) is a rare SRD usually affecting young adults, with spiking fever, polyarthritis, evanescent rash and marked hyperferritinemia as well as uncommon life-threatening macrophage activation syndrome[167]. In medical practice, hyperferritinemia is a non-specific finding related to iron overload in only 10% of cases such as hereditary hemochromatosis, while underlying causes attributing to a reactive increase in the rest 90% patients such as AOSD[168]. Hepatic dysfunction is commonly observed in AOSD, mostly due to the disease itself and without any specific histological finding[97,167]. Coexisting AILDs have rarely been observed, and there are sporadic cases of AIH-AOSD overlap disease[169].

Behçet's disease (BD) is a SRD with a variable worldwide prevalence, characterized by vasculitis affecting the small/Large venous and arterial vessels, and presenting with orogenital ulcers, ocular lesions and systemic involvement[170]. The liver is rarely involved, and the commonest hepatic complication is BCS with thrombosis of the inferior vena cava and hepatic vein[171]. Elevated ALP levels of liver origin has been reported in 10% of patients, with a correlation to disease activity[172]. Case reports of Behçet's disease concomitant with AIH or PBC can be found in the literature[173,174].

IgG4-RD is a rare SRD, characterized by elevated serum IgG4 concentrations and fibroinflammation in the affected tissues, with dense lymphoplasmacytic infiltrates rich in IgG4-positive plasma cells and storiform fibrosis[175]. Cases of type I AIP and IgG4-related sclerosing cholangitis (commonly referred to as IgG4-SC), two common forms of IgG4-RD usually occurring in combination, have painless jaundice and cholestatic LFT abnormalities due to liver involvement[176,177]. Although CS has favorable therapeutic efficacy[49], AIP and IgG4-SC are associated with significant morbidity and mortality

due to extra-pancreatic organ failure and malignancy[176]. AIP has been reported to be associated with PBC and PSC[178,179]. Infiltrating IgG4-positive plasma cells can be observed in the AIH liver, suggesting involvement of IgG4 in its pathogenesis[180]. Nevertheless, the disease concept of IgG4- AIH remains to be established[181].

Sarcoidosis is an uncommon SRD, characterized by the formation of noncaseating granulomas in various organs, predominantly the lungs, lymphatic system, skin, and eyes, or a different combination of these sites[182]. Abnormal LFT has been observed in one-fourth of patients with chronic sarcoidosis; among which, 15% are suspected of having liver involvement with cholestatic pattern of injury[183]. Although hepatic sarcoidosis is mainly asymptomatic, it can progress to LC, while such cases are rare[184]. AILDs coexisting with sarcoidosis have been reported, having a prevalence of 0.6% in AIH and 0.8% in PSC[81,99]. Several case reports have described the association of sarcoidosis with PBC[88]. A 2.7% prevalence of sarcoidosis was found in a PBC cohort from Greece[185], whereas an epidemiological study with 1510 patients from the United Kingdom failed to show an association between the two disorders[186].

Relapsing polychondritis is a rare SRD, characterized by cartilaginous inflammation throughout the body, especially involving the hyaline cartilage of the ears, nose and joints, and the respiratory tract[187]. Liver involvement with cholestatic hepatic dysfunction has been observed scarcely in such patients[188]. The association of relapsing polychondritis with AILDs has been reported with PBC or PSC overlap diseases[189,190].

CONCLUSION

SRDs are chronic, inflammatory, autoimmune disorders with the presence of autoantibodies that may affect any organ or system. Liver dysfunction in SRDs can be associated with prescribed drugs, VH, alternative hepatic comorbidities and coexisting AILDs, requiring an exclusion of secondary conditions before considering liver involvement. The patterns of overlap diseases depend predominantly on genetic determinants with common susceptible loci widely distributed in both disorders. In AILDs, it is important to identify the overlapping SRDs at an early stage, since such a

coexistence may influence the disease course and prognosis. Commonly co-occurring SRDs in AILDs are SS, RA or SLE in AIH, and SS, RA or SSc in PBC. Owing to different disease complications and therapies, it is imperative to differentiate between SLE liver involvement and SLE-AIH overlap disease. Therapeutic options can be personalized to control coexisting conditions of liver autoimmunity and rheumatic manifestations in AILD-SRD overlap diseases. The collaboration between hepatologists and rheumatologists in clinical practice can lead to significant advances in managing such a complex scenario.

73384_Auto_Edited.docx

ORIGINALITY REPORT

4%
SIMILARITY INDEX

PRIMARY SOURCES

1	Hao Li, Yanling Guan, Chenchen Han, Yu Zhang, Qian Liu, Wei Wei, Yang Ma. "The pathogenesis, models and therapeutic advances of primary biliary cholangitis", Biomedicine & Pharmacotherapy, 2021 Crossref	33 words — 1%
2	Maria De Santis, Chiara Crotti, Carlo Selmi. "Liver abnormalities in connective tissue diseases", Best Practice & Research Clinical Gastroenterology, 2013 Crossref	30 words — < 1%
3	test.dovepress.com Internet	19 words — < 1%
4	Atsushi Tanaka, Xiong Ma, Osamu Yokosuka, Martin Weltman et al. "Autoimmune liver diseases in the Asia–Pacific region: Proceedings of APASL symposium on AIH and PBC 2016", Hepatology International, 2016 Crossref	15 words — < 1%
5	Mohammad Mawardi, Abduljaleel Alalwan, Hind Fallatah, Faisal Abaalkhail et al. "Cholestatic liver disease: Practice guidelines from the Saudi Association for the Study of Liver diseases and Transplantation", Saudi Journal of Gastroenterology : Official Journal of the Saudi Gastroenterology Association Internet	15 words — < 1%

6	ebin.pub Internet	15 words — < 1%
7	docksci.com Internet	14 words — < 1%
8	ueg.sagepub.com Internet	14 words — < 1%
9	"Autoimmune Liver Diseases", Springer Nature, 2014 Crossref	13 words — < 1%
10	www.tandfonline.com Internet	13 words — < 1%
11	www.touchrespiratory.com Internet	13 words — < 1%
12	"Oral and Poster abstracts", Journal of Scleroderma and Related Disorders, 2020 Crossref	12 words — < 1%
13	"Scleroderma", Springer Science and Business Media LLC, 2017 Crossref	12 words — < 1%
14	www.edmcasereports.com Internet	12 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS