Comorbid Liver Diseases in Patients with Systemic Lupus Erythematosus

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Abstract

The incidence of liver dysfunction in systemic lupus erythematosus (SLE) is relatively high. Liver dysfunction in patients with SLE includes liver injury caused by SLE itself (lupus hepatitis [LH]) and other comorbid liver diseases. This article aimed to conduct a literature review of cases regarding the SLE and comorbid liver diseases. The prevalence of liver dysfunction in SLE is up to 60%. According to most studies, patients with SLE have a high prevalence of hepatitis C virus infection and a low prevalence of hepatitis B virus infection compared with those without SLE. The patients with SLE, particularly complicated with antiphospholipid syndrome, are highly at risk of developing portal thrombosis and Budd–Chiari syndrome. Cases of comorbid autoimmune hepatitis (AIH) and SLE are relatively uncommon, and distinguishing LH from comorbid SLE and AIH is necessary. Comorbidities of primary biliary cholangitis and SLE were relatively well documented. Prognosis may be favorable except for those with liver failure. Meanwhile, this review found a few case reports of comorbidity of primary sclerosing cholangitis in patients with SLE.

Keywords

Systemic lupus erythematosus, Lupus hepatitis, Hepatitis virus infections, Autoimmune hepatitis, Primary biliary cholangitis

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease caused by a combination of genetic, environmental, and hormonal factors, frequently affecting females of childbearing age (Hoi et al, 2024). In SLE, pathogenic autoantibodies such as anti–double–stranded (ds) DNA and immune complexes are present in the serum and target tissues, activating the complement system and subsequently inducing serious inflammatory conditions (Hoi et al, 2024). Clinical manifestations in SLE can be very heterogeneous because different organs may be involved (González-Regueiro et al, 2020). The liver is not considered as the main organ pathologically affected by SLE (Efe et al, 2011). However, the incidence of liver dysfunction or abnormal liver enzyme values during the SLE course was relatively high in previous studies, reaching 19%–60% (Shizuma, 2024). Liver dysfunction in patients with SLE includes liver injury caused by SLE itself (lupus hepatitis [LH]) and other comorbid liver diseases. In this article, a literature search and review of case reports and studies regarding the SLE and liver disease comorbidities were conducted.

Methods

This article reviewed and summarized the literature on SLE. Scientific articles in the English and Japanese languages were searched in the PubMed and Japana Centra Revuo Medicina (Igaku Chuo Zasshi) databases, respectively, to retrieve cases of comorbid SLE and liver diseases.

Liver Dysfunction in Patients with SLE

The following points may explain the high incidence of liver dysfunction in patients with SLE: 1) liver parenchymal damage caused by SLE autoimmunity, commonly referred to as LH, 2) specific liver injury by autoimmune liver diseases (AILDs), and 3) combination with other nonautoimmune liver diseases such as steatotic liver disease (SLD), viral hepatitis, and vascular diseases (González-Regueiro et al, 2020; Bessone et al, 2014). Given these numerous points, identifying the potential causes of liver dysfunction in SLE is sometimes difficult (De Santis et al, 2013; Takahashi et al, 2013). On physical examination, the most common findings are hepatomegaly (12%–55%) and jaundice (1%–4%) in patients with SLE with liver dysfunction (González-Regueiro et al, 2020).

Liver dysfunction is also reported to be not a major prognostic factor for SLE (Takahashi et

al, 2013; Piga et al, 2010; Chowdhary et al, 2008), partly because end-stage liver dysfunction with comorbid SLE is generally rare (De Santis et al, 2013; Piga et al, 2010). A review article revealed that liver cirrhosis (LC) occurred in only 1.1% of biopsy findings among 1,468 patients with SLE (Matsumoto et al, 1992). A retrospective single-center study in China indicated that LC was prevalent by only 0.34% among patients with SLE (24/6994) (You et al, 2020). Liver failure is also rare in patients with SLE (Zhang et al, 2023; González-Regueiro et al, 2020). A clinical study involving 21 SLE cases with liver failure indicated that the degree of liver dysfunction was less in patients with SLE with autoimmune hepatitis (AIH) than in those with other liver diseases (Zhang et al, 2023). Currently, the efficacy of glucocorticoids in patients with SLE suffering from liver failure remains controversial; thus, further discussion is required (Zhang et al, 2023). Large multicenter studies revealed that a comorbid liver disease does not influence morbidity or mortality in patients with SLE (Ippolito et al, 2008).

LH

LH reportedly occurs in 3%–9% of patients with SLE (Imran et al, 2021; Shizuma, 2015; Piga et al, 2010), and its presence was higher in active SLE than in inactive SLE (11.8% vs. 3.2%) (Zheng et al, 2013). Most LH cases have only mildly or moderately elevated liver enzymes (Piga et al, 2010). Additionally, serum antiribosomal P antibody occurrence is relatively high in LH (Piga et al, 2010); its high level may contribute to liver dysfunction progression in patients with SLE (Shizuma, 2015). In a retrospective monocentric study, LH was nearly half presenting with symptoms such as jaundice, hepatomegaly, abdominal pain, portal hypertension, and hepatic insufficiency during diagnosis (Khalifa et al, 2011). Nonetheless, high-dose glucocorticoid administration is associated with LH resolution (Piga et al, 2010).

Hepatitis Virus Infections in Patients with SLE

Hepatitis viruses are the major cause of acute and chronic liver diseases. Globally, hepatitis C virus (HCV) and hepatitis B virus (HBV) infections are the main causes of chronic liver disease and hepatocellular carcinoma. Possibly, HCV acts as a triggering factor in some patients with autoimmune diseases (Ramos-Casals et al, 2009), although its pathogenic role in systemic autoimmune diseases is still unclear. The association between SLE and HCV infection may be based on several observations as follows: 1) viral infection may be one of the factors triggering SLE development, 2) some of the most common extrahepatic

manifestations in HCV infection may mimic rheumatic diseases, and 3) SLE and HCV infection share many common immunological features, such as the presence of autoantibodies or hypocomplementemia (Jadali et al, 2010).

According to most of the studies, chronic HCV infection is more prevalent in patients with systemic autoimmune diseases than in the general population (Jadali et al, 2010; Ramos-Casals et al, 2009). In some epidemiological studies, the prevalence of anti-HCV antibody in patients with SLE was similar to that in the general population (Chowdhary et al, 2008; Mercado et al, 2005). However, using polymerase chain reaction, other studies reported that HCV was more prevalent in patients with SLE than in blood donors (Chowdhary et al, 2008; Ahmed et al, 2006; Ramos-Casals et al, 2000). Moreover, a meta-analysis study (according to the articles published before June 2017) identified that patients with SLE had a higher prevalence of HCV infection than those without SLE (Wang et al, 2017). The prevalence of cryoglobulin without mixed cryoglobulinemia syndrome was significantly higher in patients with SLE with positive anti-HCV antibody than in those without HCV infection (Perlemuter et al, 2003).

HBV infection is prevalent worldwide, especially in South East Asia. It reportedly serves a triggering factor for the development of systemic autoimmune diseases (Wang et al, 2017). Conversely, HBV infection reportedly offers protection against the development of autoimmune disorders (Wang et al, 2017). A recent prospective study in China demonstrated that patients with SLE after HBV infection have an increased degree of inflammatory response in their organism, an altered state of immunoglobulin and T-lymphocyte subsets, and a loss of organism immune function, leading to an increase in disease activity (Duan et al, 2023). Furthermore, the prevalence of HBV infection in patients with SLE is similar to that in the general population (Chowdhary et al, 2008; Mercado et al, 2005). In China, a prospective study reported that the hepatitis B surface (HBs) antigen-positive rate was lower in patients with SLE than in controls (Zhao et al, 2010). In Italy, a recent study indicated that none of all 92 patients with SLE were positive for HBs antigen (Lo et al, 2022). A cross-sectional study in Thailand reported that the prevalence of HBV infection in patients with SLE was 1.5% (2/134), which is lower than that of the general population (Sumethkul et al, 2017). A meta-analysis study (according to the articles published before June 2017) identified a low prevalence of HBV infection in patients with SLE compared with those without SLE (Wang et al, 2017). A recent Mendelian randomization analysis using summary statistics from genome-wide association studies (GWAS) involving individuals of East Asian ancestry supported a causal relationship between SLE and a low risk for HBV infection (Li et al, 2023). Although the precise mechanism remains obscure, the possible mechanisms of the low

prevalence of HBV infection were as follows: 1) enhanced production of interleukin-6 in patients with SLE may have an inhibitory effect on HBV infection, and 2) androgen deficiency observed in patients with SLE may prevent the establishment of chronic HBV infection (Wang et al, 2017). However, a cross-sectional population-based study in Israel indicated that the prevalence of hepatitis B carrier was significantly higher in patients with SLE (0.9% [45/5018]) than in those without SLE (0.4% [111/25,090]) (Gendelman et al, 2017).

SLD in Patients with SLE

SLE is associated with a high risk for cardiovascular disease and metabolic syndrome (Baeza-Zapata et al, 2024). In particular, SLD is associated with an increased risk not only for end-stage liver disease but also for cardiovascular disease, chronic kidney disease, and cancer (Miao et al, 2024). A recent cross-sectional study indicated that SLD prevalence was lower in patients with SLE (22%) than in the general population; SLE also showed no association with SLD (Baeza-Zapata et al, 2024). This result is similar to the study reported by other authors (23%) (Yetginoglu et al, 2022). The prevalence of asymptomatic fatty liver in SLE varies widely, ranging from 4.6% to 41% in previous studies (Imran et al, 2021). In addition, fatty liver reportedly reverses after treatment with glucocorticoids; therefore, fatty liver may be a direct manifestation of SLE in some cases (Imran et al, 2021).

Vascular Disease in Patients with SLE

Patients with SLE have a high potential of developing thromboembolic disorders or occasionally carrying antiphospholipid antibodies (antiphospholipid syndrome [APS]). Comorbid APS in patients with SLE can impact hepatic circulation, inducing portal thrombosis, Budd–Chiari syndrome (Solela et al, 2023; Berzigotti et al, 2011), and rarely, hepatic infarction (Li et al, 2019). SLE is the most common cause of secondary APS, and most patients present with Budd–Chiari syndrome as an APS manifestation after SLE diagnosis (Solela et al, 2023). The loss of intrahepatic vessels is caused either by the presence of APS-provoked coagulopathy or the deposits of immune complexes, both causing their obliteration (González-Regueiro et al, 2020). These thrombotic events can result in noncirrhotic portal hypertension (NCPH), which is a rare complication in patients with SLE (Suárez-Díaz et al, 2023).

Nodular regenerative hyperplasia (NRH), which follows hepatic vein thrombosis and

hepatic circulation disorders, is also reportedly associated with SLE (Leung et al, 2009). The pathogenesis of NRH complicating SLE may be related to the vasculitis of intrahepatic arteries, leading to secondary portal venous obliteration and thrombosis of the adjacent portal veins (González-Regueiro et al, 2020; Bessone et al, 2014). According to the Japanese autopsy registry data of 1,468 patients with SLE, the frequency of SLE complicated with NRH is only 0.3% (Matsumoto et al, 1992). NCPH is one of the background diseases causing NRH (Yang et al, 2018). In a literature review of 22 cases of SLE with NCPH, the interval of NCPH diagnosis was 0–18 years, 55% (12/22) had liver dysfunction, and NRH was the most popular histologic finding of the liver (Yang et al, 2018). Focal disturbance of the hepatic blood supply associated with SLE might also facilitate the hyperplastic development of benign lesions in the liver, such as focal nodular hyperplasia (FNH) and hemangiomas (Berzigotti et al, 2011). Authors have suggested a marked increase of FNH or liver hemangioma in patients with SLE compared with that in healthy controls (Berzigotti et al, 2011).

Comorbidity of SLE and AILDs

AILDs that are induced by several autoimmune mechanisms encompass AIH, primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). AILDs account for approximately 5% of all liver diseases (Tanaka et al, 2020). According to recent epidemiological studies, AILD prevalence is increasing worldwide (Tanaka et al, 2020). Approximately one-third of patients with AILD are accompanied with extrahepatic autoimmune diseases, including SLE (Gao et al, 2024). Possibly, similar mechanisms are responsible for the development of both AILDs and autoimmune diseases such as SLE, thereby likely causing confusion in the diagnoses (González-Regueiro et al, 2020). The scores of comorbid AILDs have been revealed in patients with SLE in several case reports, but only a few cases of comorbid PSC were found in patients with SLE. In addition, systematic review articles regarding the comorbidity of SLE and AILDs remain limited. Although the causal relationship between SLE and various AILDs remains obscure, a recent Mendelian randomization analysis using a GWAS indicated that SLE is positively related to PBC and PSC, but no such link was discerned between SLE and AIH (Huang et al, 2024).

Comorbidity of AIH in Patients with SLE

AIH is a progressive, idiopathic AILD predominantly affecting women (Mack et al, 2020). In

AIH, liver enzyme elevation, hypergammaglobulinemia, autoantibody presence, and typical histological changes may occur (Deen et al, 2009). Furthermore, AIH can be divided into two subtypes: types 1 and 2 AIH (Deen et al, 2009). Generally, AIH diagnosis is based on the diagnostic scoring systems of the International Autoimmune Hepatitis Group (IAIHG) (Mack et al, 2020).

The comorbid case of SLE and AIH is confirmed if both the criteria for SLE classification and the IAIHG criteria are met (Wang et al, 2022). Although genetic loci such as HLA-DR4 are widely distributed in both diseases (Huang et al, 2024), SLE and AIH comorbidity remains relatively uncommon (Wang et al, 2022). Immunosuppressive treatment for AIH is also effective for SLE (Wang et al, 2022); administering immunosuppressive agents such as glucocorticoids in patients with SLE may suppress or delay the onset of AIH. AIH reportedly occurs in 0.2%–2.9% of patients with SLE (Heijke et al, 2021). A multicenter cohort study indicated that AIH was prevalent in patients with childhood-onset SLE by 0.8% (7/847), and all of these cases were diagnosed during adolescence (Balbi et al, 2018). In other studies, the prevalence was 9.8% (9/92) (Irving et al, 2007) or 11.4% (8/69) (Sönmez et al, 2017). The insight into whether such existing cases indicate shared common pathogenesis between them remains unclear (Wang et al, 2024). A retrospective cross-sectional study in the USA using The National Inpatient Sample database showed that the mortality rate was significantly lower (1.35%, 15/1115) in inpatients with comorbid AIH and SLE than in those with AIH alone (3.01%, 480/15,935) (Ahmed et al, 2022).

The differential diagnosis between comorbid AIH and LH may be necessary for patients with SLE (Takahashi et al, 2013). Distinguishing AIH from LH is sometimes difficult, partly because immunosuppressive therapy makes the differential diagnosis more challenging. Moreover, antiribosomal P antibody is not a true marker of LH (De Santis et al, 2013) because patients with comorbid AIH and SLE or AIH alone also test positive (Takahashi et al, 2013). Anti–dsDNA antibody, although reportedly specific for SLE, is also common in type 1 AIH (Czaja et al, 1997). Hence, the diagnostic criteria for SLE are not useful for distinguishing AIH from LH. Therefore, histological examination of the liver is generally required (Shizuma, 2015), though it does not necessarily distinguish AIH from LH.

Comorbidity of PBC in Patients with SLE

PBC is an autoimmune disease characterized by chronic progressive cholestasis accompanied with intrahepatic bile duct destruction, affecting mostly middle-aged women (Tanaka, 2021). Its typical symptoms include jaundice, cholestasis-induced pruritus, and general fatigue, but

more than half of PBC cases can be asymptomatic (Wang et al, 2022; Tanaka, 2021). Histopathologically, PBC is characterized as chronic nonsuppurative destructive cholangitis with granuloma formation in the liver and biliary epithelial cell degeneration; consequently, small or middle-sized intrahepatic bile ducts could disappear (Lleo et al, 2017). According to the guidance from the American Association for the Study of Liver Diseases, the diagnosis of PBC is established when two of three items are met; such items include biochemical cholestasis based on alkaline phosphatase elevation, presence of antimitochondrial autoantibody, and histological evidence of nonsuppurative destructive cholangitis and interlobular bile duct destruction (Boberg et al, 2011).

The insight into whether the SLE incidence during PBC follow-up is significantly higher than that in the general population without autoimmune diseases remains unclear. However, a large-scale study (Gershwin et al, 2005) reported that among 1,032 patients with PBC, 27 had SLE and that the SLE incidence was significantly higher in patients with PBC (2.61%, 27/1032) than in the control group (0.48%, 5/1041). In a recent two-sample bidirectional Mendelian randomization analysis, SLE and PBC were both high risk factors for the occurrence and development of the other party (Wu et al, 2024). SLE and PBC comorbidity is confirmed if the diagnostic criteria for both diseases are met (Wang et al, 2022). The incidence of PBC in patients with SLE is 0%–2.7% (Heijke et al, 2021). The SLE activity does not significantly correlate with PBC incidence in patients with SLE (Wang et al, 2024). Furthermore, the incidence of SLE during follow-up is within 0%–3.7% in patients with PBC (Liang et al, 2024). According to a recent systematic review and meta-analyses study, the insight into whether the complication rate of SLE in patients with PBC was significantly higher than that in those without PBC still remains unclear (Liang et al, 2024). A recent review and meta-analyses study involving 3,944 PBC cases and 9,414 SLE cases indicated that 1.1% of patients with SLE had concomitant PBC (0.02%–7.5%), while approximately 2.7% of those with PBC concurrently had SLE (1.3%–7.5%) (Polpichai et al, 2024). Additionally, PBC was prevalent by 2%–7.5% in patients with SLE presenting with hepatic dysfunction or abnormal liver enzymes (Polpichai et al, 2024). Moreover, the prevalence of AIH/PBC overlap syndrome was 2% in patients with SLE who obtained abnormal liver function tests (González-Regueiro et al, 2020).

According to the cases retrieved from the English and Japanese literature and since 1980, 28 cases of comorbid SLE and PBC were found (Carvoeiro et al, 2024; Shizuma, 2024; Urata et al, 2022; Sato et al, 2003; Michel et al, 1998; Clark et al, 1991). Among the 28 patients, 27 (96.4%) were women. Given that PBC more commonly occurs in middle-aged women and rarer in teenagers and that SLE generally affects women of childbearing age, SLE may be

more likely diagnosed first in patients with comorbid SLE and PBC. However, in the 28 patients with comorbid SLE and PBC, PBC was first diagnosed in 53.6% (15/28) of patients and SLE in 35.7% (10/28), while 10.7% (3/28) were diagnosed with SLE and PBC simultaneously. Moreover, two (7.1%) patients were diagnosed with immune thrombocytopenia, and two had familial PBC (Urata et al, 2022; Sato et al, 2003). Furthermore, among the three patients who died, two presented with liver failure secondary to PBC worsening (both elderly women) (Michel et al, 1998; Clark et al, 1991).

Comorbidity of PSC in Patients with SLE

PSC is a chronic, idiopathic cholestasis liver disease characterized by progressive inflammation, fibrosis, and stricturing of the intra- and extrahepatic bile ducts (Yimam et al, 2014). Its clinical presentation varies; some patients are asymptomatic, while others exhibit fatigue, jaundice, or pruritus (Yimam et al, 2014). Its histopathological findings include bile duct proliferation, periductal fibrosis with typical onion-skinning appearance, and periductal inflammation (Yimam et al, 2014). However, these findings are often undetectable. Liver biopsy is indicated only when suspecting overlapping with other AILDs or small-duct PSC, a variant with normal cholangiogram (Wang et al, 2022). Eventually, PSC diagnosis relies considerably on elevated alkaline phosphatase and imaging studies of biliary tracts through endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography (Tanaka et al, 2020).

In a previous study, approximately a quarter of PSC cases had at least one autoimmune disease outside the gastrointestinal tract (Saarinen et al, 2000). In a cohort study, SLE occurred in 1.7% (2/119) of patients with PSC (Wang et al, 2022; Saarinen et al, 2000). Cases of comorbid SLE and PSC are rarely reported, possibly because of the low prevalence of PSC itself compared with PBC. The insights into whether SLE with comorbid PSC occurs incidentally or whether these entities have a common immunological basis remain unclear. Only five cases of SLE with comorbid PSC were reported. These cases are as follows: 1) a female with SLE was diagnosed with PSC accompanied with vitamin K deficiency (Okubo et al, 2021); 2) a female with SLE and type 1 diabetes was diagnosed with PSC accompanied with weight loss, icterus, and pruritus (Alberti-Flor et al, 1984); 3) a young male was diagnosed with SLE, protein-losing enteropathy, and PSC almost simultaneously (Oh et al, 2006); 4) a middle-aged female with lupus nephritis and PSC attenuated by the administration of glucocorticoids and ursodeoxycholic acid (Kadokawa et al, 2003); and 5) a young male with SLE, PSC, and UC comorbidity (Stevens et al, 1994).

Conclusion

This review discusses the comorbidity of liver dysfunction in patients with SLE. Although the prognosis of SLE with liver dysfunction may generally not be apparently worse than that of those with SLE without liver dysfunction, some patients develop LC or liver failure. Therefore, the causes of liver dysfunction in patients with SLE should be distinguished, although differentiating AIH from LH may be sometimes difficult. Moreover, the incidental occurrence of SLE and comorbid AILDs and the existence of a common immunological basis between these conditions remain unclear. Accumulation of studies or case reports or series is necessary to investigate the pathophysiology of comorbid SLE and AILDs.

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