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Liver Complications Associated with Systemic Lupus Erythematosus

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Abstract

Although liver dysfunction is not considered the main organ pathology or prognostic factor in patients with Systemic Lupus Erythematosus (SLE), it is not uncommon during the course of SLE. Liver complications in patients with SLE may be caused by lupus hepatitis (SLE-related hepatitis); autoimmune liver diseases, such as Autoimmune Hepatitis (AIH) and Primary Biliary Cirrhosis (PBC); viral hepatitis; and drug-induced liver injury. Here, liver complications in patients with SLE are reviewed.

Introduction

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease characterized by the presence of pathogenic autoantibodies; inflammatory conditions activated by complementary systems; and effects of a combination of genetic, environmental, and hormonal factors [1]. SLE is usually diagnosed according to at least four of the 11 criteria classified by the American Rheumatism Association [2].

Although liver dysfunction is not considered the main organ pathology in SLE [3,4], the frequency of liver dysfunction or abnormal liver enzyme values during the course of SLE ranges from 19% to 60% [3-15]. The liver-related complications in SLE includes lupus hepatitis (SLE-related hepatitis); autoimmune liver diseases, such as Autoimmune Hepatitis (AIH), Primary Biliary Cirrhosis (PBC), and Primary Sclerosing Cholangitis (PSC); viral hepatitis; steatohepatitis; fatty liver; and drug-induced liver injury.

Moreover, patients with SLE have a high potential of developing thromboembolic disorders or occasionally carrying anti-phospholipid antibodies that can impact hepatic circulation, inducing portal thrombosis and Budd-Chiari syndrome [15,16]. Focal disturbance of the hepatic blood supply associated with lupus may also facilitate the development of benign hepatic lesions, such as Focal Nodular Hyperplasia (FNH) or hemangioma, that are common in patients with SLE [15,17]. Berzigotti et al. [17] have suggested a marked increase of FNH or liver hemangioma, which can be associated with FNH, in patients with SLE versus that in healthy controls.

It is sometimes difficult to distinguish the causes of liver complications in patients with SLE because immunosuppressive therapy may make differential diagnosis more difficult. Liver biopsy sometimes reveals non-specific findings in patients with SLE [15]. However, it is necessary to distinguish the causes of liver dysfunction or abnormal liver enzyme values for effectively treating patients with SLE.

In this report, we reviewed the literature concerning liver complications in patients with SLE.

Methods

We reviewed English and Japanese literature using PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Japana Centra Revuo Medicina (Igaku Chou Zasshi) (http://edb.kulib.kyoto-u.ac.jp/dbe/JA.html) databases, respectively.

Results

Liver dysfunction in patients with SLE

Fluctuations in the levels of alanine transaminase corresponding to SLE activity have been reported in some patients with SLE [11,15]. However, no correlation between SLE activity and the incidence of liver diseases has been identified [3,13]. This discrepancy may be attributed to the different causes of liver dysfunction or abnormal liver enzyme values in patients with SLE. No clear correlation between SLE activity and the development of liver diseases has been generally identified, except in the case of SLE-related hepatitis [3,13].

Some reports have determined that liver dysfunction is not a major prognostic factor for SLE [8,11,13,18]. Large multicenter studies of mortality in patients with SLE have revealed that liver diseases do not influence morbidity or mortality [18]. One of the possible explanations for this may be that end-stage liver diseases with concomitant SLE are uncommon [4,5,11,19]. However, the complications of chronic liver diseases such as viral hepatitis caused by Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV), autoimmune liver diseases, and nonalcoholic steatohepatitis in patients with SLE may exacerbate Liver Cirrhosis (LC) and liver cancer.

Lupus hepatitis

Lupus hepatitis is an SLE-related liver dysfunction, and it has been described as hypertransaminasemia owing to the fluctuations in the levels of alanine transaminase that are consistent with the activity of SLE [11,20]. Lupus hepatitis has generally been reported as a subclinical condition with a lower rate of progression to end-stage liver diseases [15,20]. Zheng et al. [21] reported that the presence of lupus hepatitis in active SLE was higher than that in inactive SLE (11.8% vs. 3.2%).

Lupus hepatitis has been reported in 3%-9% of patients affected by SLE [11,15,20,21]. Serum anti-ribosomal P antibody occurrence in lupus hepatitis is relatively high [15], and the appearance of the high levels of serum anti-ribosomal P antibody may contribute to the progression of liver dysfunction in patients with SLE [15,22].

Pertaining to the histopathological aspects of lupus hepatitis, inflammation is usually lobular and occasionally periportal with a paucity of lymphoid infiltrates [23]. These findings may be useful for distinguishing lupus hepatitis and other concomitant liver diseases.

In general, the levels of liver enzymes seen in lupus hepatitis return to normal following glucocorticosteroid therapy [15].

AIH in patients with SLE

AIH is a progressive autoimmune liver disease of unknown etiology that predominantly affects women [24]. The autoimmune attack is possibly perpetuated via molecular mimicry and is influenced by the impaired control of T-regulatory cells [24]. AIH is characterized by the elevated levels of liver enzymes, hypergammaglobulinemia, the presence of autoantibodies and typical histological changes [25], and association with the Human Leukocyte Antigens (HLA) DR3 or DR4 [24]. Furthermore, AIH can be divided two subtypes (types 1 and 2). Type 1 AIH is characterized by positive Antinuclear Antibody (ANA) and anti-smooth muscle antibody, and type 2 AIH is characterized by anti-liver-kidney microsome type 1 antibody and/or anti-liver cytosol antibodies [25]. The prominent histopathological aspects of AIH include periportal piecemeal necrosis associated with lobular activity, the rosetting of liver cells, or dense lymphoid infiltrates [23].

Concomitant SLE and AIH is uncommon; in previous studies, the frequency of AIH during the course of SLE ranged from 2.1% to 3.7% [3,4,7,10,11,13,26]. The status of patients with AIH sometimes progresses to fulminant hepatic failure and may progress to LC. Therefore, differential diagnosis between AIH/SLE overlap and lupus hepatitis is important in patients with SLE [13]. However, it is sometimes difficult to distinguish AIH from lupus hepatitis because immunosuppressive therapy makes differential diagnosis more challenging. Moreover, anti-ribosomal P antibody is not a true marker of lupus hepatitis [4] because patients with overlapping AIH/SLE or AIH alone also test positive [13]. Although anti-double-stranded DNA antibody has been reported to be SLE-specific, it is also common in ANA-positive type 1 AIH [27]. Diagnostic criteria for SLE are not considered to be useful for distinguishing AIH from lupus hepatitis [28]. Therefore, the histological examination of the liver is required [23,28,29].

Standard pharmacotherapies for AIH include immunosuppressive therapy such as glucocorticosteroids as well as other pharmacotherapies for SLE. In general, these treatments have also been administered for the concomitant cases of SLE and AIH.

PBC in patients with SLE

PBC is considered as an autoimmune disease of unknown etiology. It is described as an organ-specific disturbance characterized by chronic progressive cholestasis that destroys the intrahepatic small bile ducts, particularly the interlobular bile ducts [30-34]. Pertaining to histopathological aspects of PBC, the findings in florid bile duct lesions such as chronic, nonsuppurative destructive cholangitis and epithelioid granuloma formation are established and useful for diagnosing PBC [34].

The clinical features and natural history of PBC vary markedly from asymptomatic to progressive among different patients [34]. Jaundice, pruritus derived from cholestasis, and general fatigue are typical symptoms in patients with PBC; however, up to 60% of the patients may be asymptomatic. Standard pharmacotherapy for PBC is the administration of Ursodeoxycholic Acid (UDCA). Prognosis is often dependent on the development of portal hypertension or LC. Furthermore, patients with end-stage liver failure require an organ transplant [35]. In such cases, prognostic models such as the Mayo risk score and bilirubin levels are useful for determining the optimal timings for the liver transplantation [36].

Several reports indicate that the incidence of coexisting PBC in patients with SLE ranges from 0% to 2.7% [3,7,8,10,11,13,19,26,37]. The frequency of PBC in patients with concomitant SLE who have abnormal levels of liver enzymes or liver dysfunction reportedly is 0%-7.5% [3,8,10,11,13].

We reviewed 34 patients with concomitant SLE and PBC [38], which included 33 women. PBC was first diagnosed in 58.8% (20/34) of the patients, whereas SLE was diagnosed in 26.5% (9/34) of the patients; moreover, 14.7% (5/34) patients were diagnosed with both the conditions. The most common disease that concurrently presented with SLE and PBC was Sjögren's syndrome (23.5%, 8/34), a common complication involving both SLE and PBC. Immune thrombocytopenia was diagnosed in three patients (8.8%), and rheumatoid arthritis, Hashimoto's thyroiditis, and pulmonary hypertension were diagnosed in two patients (5.9%). Only 1/20 patients with SLE and concomitant PBC who underwent liver biopsy at the time of PBC diagnosis was rated with stage IV liver disease according to the Scheuer classification, indicating LC. Among the five reported deaths, two patients (both elderly women) presented liver failure secondary to the worsening of PBC [39,40].

Although the incidences of Hepatocellular Carcinoma (HCC) with concomitant PBC are relatively rare[30,41], Ishiguro et al. [30] have reported the case of an 81-year-old Japanese woman who developed SLE and HCC approximately one year after the diagnosis of PBC. To the best of our knowledge, this is the only case report of PBC with concomitant SLE that was concurrent with the development of HCC.

In the concomitant cases of SLE and PBC, the administration of UDCA is a standard pharmacotherapy for PBC; however, progressive cases required liver transplantation. Because some patients with PBC progress to portal hypertension, which is not consistent with the histological findings of PBC, the evaluations of portal hypertension such as esophageal varices may be required in patients with concomitant SLE and PBC.

PSC in patients with SLE

PSC is a chronic cholestasis liver disease of unknown etiology, characterized by progressive inflammation, fibrosis, and the stricturing of the intra- and extrahepatic bile ducts [42]. The clinical presentation of PSC can vary; some patients are asymptomatic, whereas others show fatigue, jaundice, or pruritus [42,43]. The histopathological findings of PSC include bile duct proliferation, periductal fibrosis with typical onion-skinning appearance, and periductal inflammation [42]. Although PBC and PSC are associated with chronic cholestatic liver diseases, there are many clinical or epidemiological differences [36]. PSC is more common in men, and it is best known for its hepatobiliary manifestations with ulcerative colitis [42,43]; however, the coexistence of PBC and inflammatory bowel disease remains uncommon [44].

SLE with concomitant PSC appears to be extremely rare. To the best of our knowledge, four case reports pertaining to SLE exist with concomitant PSC [45-48]. One of the reasons for the scarcity of reported cases is the low prevalence of PSC itself, which ranges from 4 to 16/million [44]. In contrast, the reported prevalence of PBC is 19-402/million [34,35,49]. It remains unclear whether SLE with concomitant PSC occurs by chance or these entities have a common immunological basis.

Although standard pharmacotherapy for PSC may be the administration of UDCA or immunosuppression including glucocorticosteroids, recent studies reported that these pharmacotherapies did not show any significant benefit pertaining to the survival of patients with PSC [42,43]. At present, therapies for patients with concomitant PSC and SLE do not seem to be clearly established, because concomitant cases are rare and their case reports are limited. In general, immunosuppressive agents were used in patients with SLE and PSC [48].

HCV infection in patients with SLE

HCV is the major cause of non-A and non-B hepatitis [50], and some patients with HCV infection develop cirrhosis and liver cancer.

The pathogenic role of HCV in systemic autoimmune diseases is unclear. It is possible that HCV acts as a triggering factor in some patients with autoimmune diseases [50]. Although there have been few investigations, the association between SLE and HCV infection may be based on several observations: 1) viral infection may be one factor triggering the development of SLE; 2) some of the most common extrahepatic manifestations in HCV infection may mimic rheumatic diseases; and 3) SLE and HCV infections share many common immunological features such as the presence of autoantibodies or hypocomplementemia [51].

Majority of the studies analyzing the prevalence of chronic HCV infection found a higher prevalence in patients with systemic autoimmune diseases than in the general population [50,51]. In some epidemiological studies, the prevalence of HCV in patients with SLE was similar to those of anti-HCV antibodies found in the general population [8,52,53]. However, using polymerase chain reaction, other studies reported that the prevalence of HCV in patients with SLE was found to be higher than that in blood donors [8,51,54,55].

Standard pharmacotherapy for chronic hepatitis due to HCV is the anti-viral therapy, including a combination therapy with interferon and ribavirin. Treatment with interferon for infection caused by HCV or HBV may also induce the development of SLE [8,56]. Therefore, it may be necessary to monitor the exacerbation of the lupus activity during or after the anti-viral therapy.

HBV infection in patients with SLE

HBV infection is a global health problem; approximately two billion people are infected, particularly in Asia and Pacific regions and 350 million individuals have chronic HBV infection [57]. Although most of the chronically infected patients remain asymptomatic and without life-threatening liver diseases, HBV is the major cause of acute and chronic liver diseases; some patients with HBV infection develop LC and liver cancer [58].

Although several studies suggest that HBV and HCV are involved in the pathogenesis of some forms of glomerulonephritis, including lupus nephritis [51,58,59], some studies using Hepatitis B Surface Antigen (HBsAg) reported that the prevalence of HBV found in patients with SLE is similar to that in the general population [8,52,53,57]. Moreover, some studies in China reported that the HBsAg-positive rate was lower in patients with SLE than that in the general population [60]. Further studies are required for clarifying the progression of HBV-related chronic liver diseases in patients with SLE.

Rituximab, one of the therapeutic drugs used in the treatment of SLE, is described as being able to reactivate HBV even in HBsAg-negative and -positive patients [15]. Therefore, monitoring of HBV biomarkers may be necessary in patients with SLE and current or past HBV infections during the administration of therapeutic drugs for SLE.

At present, because the existing reports are limited [61], further studies are needed to evaluate the effects of the nucleoside analogue prophylactic treatment on patients with SLE and HBV infection or on patients with SLE and HBV activation undergoing immunosuppressive therapy.

Drug-induced liver injury in patients with SLE

Drug-induced liver injury has been reported as one of the common causes of SLE with liver dysfunction [15]. Takahashi et al. [10,13] have suggested that drug-induced liver injury may be the cause of approximately 30% of the incidences liver dysfunction in patients with SLE.

Liver dysfunction induced by glucocorticosteroids is a common cause of drug-induced injury in patients with SLE [8,10,13,15,29]. Statistical analysis indicates that exposure to large dosages of glucocorticosteroids is a significant factor in the etiology of severe fatty liver [62]. Some authors have reported a case of steroid induced non-alcoholic steatohepatitis in patients with SLE [63,64].

The causes of several cases of drug-induced liver injury include therapeutic drugs for SLE such as Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), methotrexate, azathioprine, and antimalarial drugs other than glucocorticosteroids.

Conclusion

In this report, a review of liver complications in patients with SLE was conducted. The liver diseases in patients with SLE in some cases may progress to end-stage liver failure and liver cancer. Therefore, it is important to distinguish the causes of liver dysfunction in patients with SLE. Among the cases of the involvement of liver in the patients with SLE, some patients with autoimmune liver diseases or viral hepatitis due to HCV or HBV may progress to end-stage liver failure or liver cancer. Therefore, long-term management or follow-up of liver diseases in patients with SLE may be necessary. Moreover, optimal therapies for concomitant liver diseases in patients with SLE may be required. Further clinical studies in this area are recommended.

Acknowledgment

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