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Coexistence of Systemic Lupus Erythematosus and Primary Biliary Cirrhosis

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Abstract

Although autoimmune diseases often coexist, cases of concomitant systemic lupus erythematosus (SLE) and primary biliary cirrhosis (PBC) are rare. In this paper, 20 cases of concomitant SLE and PBC in the English and Japanese literature were reviewed and summarized. In concomitant cases of SLE and PBC, PBC was diagnosed first in 68.4% (13/19) of the cases and SLE occurred first in 31.6% (6/19) of the cases, although one case was suspected to have simultaneous onset. There may be no correlation between SLE activity and PBC development. In 20 reported cases of concomitant SLE and PBC, two elderly patients died because of liver failure as a result of worsening PBC, and hepatocellular carcinoma was detected in only one elderly patient.

Keywords: Systemic lupus erythematosus; Primary biliary cirrhosis; Autoimmune diseases

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that often coexists with other collagen disorders, such as rheumatoid arthritis (RA) and Sjögren's syndrome (SjS) [1,2]; however, cases of concomitant SLE and primary biliary cirrhosis (PBC) are rare [3-19]. SLE is a multisystem autoimmune disease that results from a combination of genetic, environmental, and hormonal factors. On the other hand, PBC is considered an autoimmune disease characterized by chronic progressive cholestasis with destruction of the intrahepatic small bile ducts, particularly the interlobular bile ducts [19,20]. Chronic nonsuppurative destructive cholangitis and granuloma formation are well-known histological findings of PBC. Prognosis of PBC is often dependent on the development of portal hypertension or cirrhosis, indicating liver failure. Although the incidence of concomitant hepatocellular carcinoma (HCC) with PBC is relatively rare, several studies have reported incidence rates of <1.6% [19,21,22]. Harada et al. [20] reported that incidence of HCC in PBC patients has been increasing in recent decades in Japan. Patients with SLE and PBC are suspected to have a common genetic susceptibility toward developing these diseases; however, it is assumed that the coincidence of SLE and PBC is incidental.

In this study, we conducted a literature search of English and Japanese references using the 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, and retrieved cases of concomitant SLE and PBC published since 1981. Moreover, we excluded suspected cases of SLE and those of drug-induced lupus-like syndromes. Cases of SLE diagnosed according to the American Rheumatism Association criteria were included.

Liver Dysfunction in SLE Patients

Although liver dysfunction is not considered to be the main organ pathology in SLE [23], the frequency of liver dysfunction or abnormal liver enzyme values during the course of SLE, reported ranges from 19% to 60% [23-33]. Hence the identification of potential causes of liver dysfunction in SLE (other than lupus hepatitis) from histological findings is often difficult [32,33] because there are several candidates, including autoimmune hepatitis, PBC, hepatic steatosis, nonalcoholic fatty liver disease, and drug-induced liver diseases [27,29,32,34].

Fluctuations in alanine transaminase values corresponding to SLE activity have been reported in some SLE patients [30]; however, no correlation has yet been identified between SLE activity and the incidence of liver disease [23,32]. In addition, other reports have revealed that liver dysfunction is not a major prognostic factor of SLE [27,30,32,35]. One of the reasons for this may be that concomitant end-stage liver dysfunction is rare in patients with SLE [24,30,33,36]. A review by Matsumoto et al. [37] revealed that liver cirrhosis (LC) was evident in only 16 (1.1%) of biopsy findings of 1468 Japanese patients with SLE. The prevalence of LC is estimated to be approximately 0.2%–0.3% per million among the general population in Japan [38]. Therefore, the prevalence (1.1%) of histological LC in patients with SLE who underwent liver biopsy because of liver dysfunction may not be high.

Concomitant Occurrence of PBC in Patients with SLE

The incidence and prevalence of PBC in the general population varies strikingly in different geographic regions, ranging from 0.7 to 49 and 6.7 to 402 per million, respectively [39,40]. The highest incidence and prevalence rates are reported in, Scandinavia, Canada, the UK, and the USA, whereas the lowest rates are found in Australia [39]. The prevalence of PBC in Japan is approximately 400 per million [19].

Several reports indicate that the incidence of co-existing PBC and SLE is <2% [11,23,26,29,30,32], with results ranging from 0% to 2.7%

[11,23,26,27,29,30,32,36,41]. In addition, the frequency of concomitant PBC in patients with SLE who have abnormal liver enzyme values and liver dysfunction is reportedly 0%–7.5% [23,27,29,30,32]. In addition, no obvious correlations between SLE activity and the incidence of PBC have been reported in patients with SLE [9,11,12]. In patients with concomitant SLE and PBC, SLE flare-up is not a usual sequel [11,12]. In fact, no reported cases experienced a flare-up of SLE after developing PBC among five SLE cases followed for the development of PBC [9,11,12,17,18].

Antimitochondrial antibodies (AMA), particularly the M2 antibody, are useful for serological diagnosis of PBC [42,43]. Although the percentage of AMA-positive cases in collagen diseases (other than PBC) is low [9,11,44], 90%–95% of patients with PBC are AMA-positive [11,38]. Moreover, Picceli et al. [45] reported that there was no significant difference in the frequency of AMA positivity between SLE patients and healthy controls. Despite this, AMA antibody titers reportedly decrease and undergo negative conversion over time in approximately 1/3 of patients with concomitant SLE and AMA-positive PBC [8,9,38,46]. Matsumoto et al. [41] reported that 2 (2.7%) of 73 patients with SLE had concomitant PBC. However, both these cases were AMA-negative. Based on this finding, the authors were of the opinion that it may be important to consider AMA-negative PBC in patients with SLE and liver function disorders.

Concomitant Occurrence of SLE in Patients with PBC

At least one autoimmune disorder complicates the course of >60% of PBC cases [9,10]. SjS concomitantly occurs in some PBC cases [4,8,10,47]. Similarly, systemic sclerosis, RA, and chronic thyroiditis (Hashimoto's thyroiditis) are also common [8,10-12,23,31,36,41]. The reported complication rates of connective tissue diseases in patients with PBC are as follows [3,8,10,18,36]: SjS, 4%–36.2%; systemic sclerosis, 1%–6.4%; RA, 0.4%–3.7%; and chronic thyroiditis, 1.9%–6.4%.

The incidence of SLE during follow-up of PBC patients is reportedly ≤ 2% [3,6,11,36,48,49] (range, 0%–3.7% [3,6,11,36,48,49]), although there were differences in the follow-up durations in these reports.

Case	Sex	Age at diagnosis of SLE (years)	Age at diagnosis of PBC (years)	PBC prior to SLE	Remarks	References
1	F	39	33	+		[3]
2	F	58	53	+		[4]
3	M	53	50	+		[4]
4	F	39?	35	+	Sudden death (etiolgy?)	[4]
5	F	25	29	-	Lupus nephritis (renal failure)	[5]
6	F	60	53	+	Liver failure	[6]
7	F	65	64?	+		[7]
8	F	41?	37	+		[8]
9	F	54	72	-	Liver failure	[9]
10	F	57	47	+		[10]
11	F	21	29	-		[11]
12	F	69	70	-		[12]
13	F	63 or 64	62	+	RA, Sjögren's syndrome	[13]
14	F	41	41	Sim	Immune thrombocytopenia	[14]
15	F	34 or 35	31	+	Lupus nephritis	[15]
16	F	48	40	+	Sjögren's syndrome	[16]
17	F	27	44	-	Familial PBC case	[17]
18	F	46?	65	-	Sjögren's syndrome	[18]
19	F	55	52?	+	Sjögren's syndrome	[18]
20	F	81	80	+	Hepatocellular carcinoma	[19]

SLE: Systemic Lupus Erythematosus; PBC: Primary Biliary Cirrhosis; F: Female; M: Male; Sim: Simultaneous

Table 1: Characteristics of 20 Patients with Comorbid Systemic Lupus Erythematosus and Primary Biliary Cirrhosis.

As mentioned above, LC is rare in patients with concomitant SLE and liver dysfunction [24,30,33,36,37]. Similarly, few patients with concomitant PBC and SLE develop LC. At the time of PBC diagnosis, patient with concomitant PBC and SLE that clinically presented with LC (PBC occurred first and SLE occurred subsequently) has also been reported [7]. No case of LC was detected in 16 patients with concomitant SLE and PBC who underwent liver biopsy at the time of PBC diagnosis [3,4,6,8-11,13-19], which may have been partially because of the relatively high frequency of asymptomatic PBC cases.

Sato et al. [17] reported the case of a Japanese female who developed asymptomatic PBC at 17 years of age after an occurrence of SLE. In addition, her father was diagnosed with PBC, indicating a case of familial PBC. Ishiguro et al. [19] reported the case of an 81-year-old Japanese female who developed SLE and HCC approximately one year after diagnosis of PBC, although the occurrence of HCC is relatively rare in PBC cases [19,21,22]. To the best of knowledge, this is the only case of concomitant PBC and SLE that is concurrent with development of HCC.

Case Reports of Concomitant SLE and PBC

Because PBC is more common in middle-aged women and SLE usually affects women of childbearing age [12,36], it is assumed that SLE is more likely to be first diagnosed in younger patients with concomitant PBC and SLE. However, in 20 patients (male:female ratio, 1:19) with concomitant PBC and SLE (in English [3-12] and Japanese [13-19] references), PBC was first diagnosed in 68.4% (13/19) cases and SLE in 31.6% (6/19), although one case was suspected of simultaneous onset of SLE and PBC [14]. According to the cases retrieved from the English and Japanese references, in 13 patients in whom PBC first occurred, the interval from PBC diagnosis to SLE diagnosis varied from 7 months to 10 years [3,4,6-8,10,13,15,16,19]. Meanwhile, in six patients with preceding SLE, PBC was diagnosed 1–18 years after the diagnosis of SLE [5,9,11,12,17,18]. These findings are summarized in Table 1.

Treatment of Concomitant SLE and PBC

Pharmacotherapies for reported concurrent cases of SLE and PBC are similar to cases with the occurrence of either SLE or PBC. Therapies for SLE in reported cases of concurrent SLE and PBC are as follows: 16 cases of steroid therapy (13 steroid monotherapy, three combination steroid therapy plus other agents), one case of nonsteroidal anti-inflammatory drugs, one case of chloroquine, and two unknown. Steroid therapy often results in remission of SLE in cases of concurrent SLE and PBC, although there are cases in which it was necessary to increase the steroid dosage during the course of SLE. In contrast, therapies for PBC in reported cases of concurrent SLE and PBC are as follows: nine treated with ursodeoxycholic acid, two treated with D-penicillamine, and nine unknown. Suspected drug-induced SLE or PBC cases were excluded in the reported 20 concurrent cases, although a previous study indicated that D-penicillamine may induce SLE [50].

Prognoses for Concomitant SLE and PBC

No fatalities due to SLE were observed after administration of steroid therapy in patients with concomitant SLE and PBC. However, two cases reported worsening of PBC resulting in death (both elderly females) [6,9]. In one of these patients, although liver biopsy at the time of PBC diagnosis showed that the patient had stage I disease, the patient died of liver failure severe enough to cause jaundice two years later [9]. In the other patient, liver biopsy at the time of diagnosis showed no obvious abnormalities but the patient died of liver failure 15 years later [6].

Conclusion

We have summarized 20 cases of concomitant SLE and PBC. PBC was diagnosed first in 68% (13/19) of the concomitant cases and SLE occurred first in 32% (6/19), although PBC was more common in middle-aged women, and SLE usually affected women of childbearing age. The main pharmacotherapy for patients with SLE and PBC was steroids. Moreover, no fatalities due to SLE were observed after administration of steroid therapy in the concomitant SLE and PBC cases. However, two elderly patients developed liver failure because of worsening of PBC resulting in death.

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