A Case of Primary Biliary Cirrhosis which Developed Eight Years after Diagnosis of Systemic Lupus Erythematosus

Toru Shizuma¹ and Hajime Kuroda²

Abstract

A 29-year-old Japanese female was diagnosed with systemic lupus erythematosus (SLE) at the age of 21 and went into remission after administration of prednisolone. Although no liver dysfunction had been observed upon diagnosis of SLE or during follow-up, an increase of hepatobiliary enzyme levels was seen eight years after the diagnosis of SLE. Antimitochondrial antibodies were positive. Cell infiltration around intrahepatic bile ducts and granuloma formation were observed in the liver. Therefore, she was diagnosed with primary biliary cirrhosis (PBC). Administration of ursodeoxycholic acid resulted in normalization of hepatobiliary enzyme levels. Development of PBC after SLE is extremely rare.

Key words: systemic lupus erythematosus, primary biliary cirrhosis, antimitochondrial antibody

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Introduction

Systemic lupus erythematosus (SLE) and primary biliary cirrhosis (PBC) are autoimmune diseases that develop more commonly in females. PBC is sometimes associated with Sjögren’s syndrome, Hashimoto’s disease, and articular rheumatism, but its co-occurrence with SLE is rare. Moreover, in most reported cases of SLE-PBC co-occurrence, PBC developed before SLE (1, 2). There are only two literature reports (2, 3) and two Japanese case records which describe the development of PBC during the course of SLE, and these all involved middle-aged women (Table 1). Here, we report a young female patient who was diagnosed with PBC eight years after diagnosis of SLE.

Case Report

A 29-year-old Japanese female with no family history of autoimmune disease experienced Raynaud’s phenomenon in 1995 at the age of 17. At the age of 21, she experienced butterfly rash, painless stomatitis, eruption, and fatigue, for which she visited our hospital. Although hepatobiliary enzyme levels were within normal ranges, antinuclear antibody (ANA), anti-double-stranded (ds) DNA antibody, and anti-Sm antibody were all positive, and complement titer was decreased. Since 5 of the 11 diagnostic criteria of the American Rheumatism Association (1982) were met, she was diagnosed with SLE. Prednisolone was initiated at a dosage of 30 mg/day, and gradually tapered to 5 mg/day. No aggravation of SLE was observed, and periodic follow-ups showed no increase of hepatobiliary enzyme levels. However, she developed liver dysfunction in June 2008 and was admitted to our hospital.

At the initial visit, blood pressure and body temperature were 122/62 mmHg and 36.1°C, respectively. Although a trace of butterfly rash was observed on her face, neither redness nor eruption was recognized. Auscultation revealed no abnormality, and there was no hepatosplenomegaly. Hematology results were as follows: albumin 4.0 g/dL (normal range: 3.9-4.9); total bilirubin 0.7 mg/dL (normal range: 0.2-1.2); aspartate aminotransferase (AST) 47 IU/L (normal range: 8-38); alanine aminotransferase (ALT) 49 IU/L (normal range: 4-44); alkaline phosphatase (Alp) 309 IU/L (nor-
Although approximately 10% of PBC cases are AMA-negative, AMA and M2 measurements are generally used as the absence of skin itchiness, she was diagnosed with asymptomatic PBC. The transaminase and γ-GTP levels normalized within one month after the start of ursodeoxycholic acid (UDCA) administration at 600 mg/day. During more than two years since the diagnosis of PBC, the patient has not complained of skin itchiness or liver dysfunction. Values of AMA and M2 have remained unchanged.

Discussion

This is an extremely rare example of a diagnosis of SLE, followed eight years later by liver dysfunction, which was diagnosed as PBC. This is the first such report in a young patient (Table 1). The frequency of occurrence of liver dysfunction during the course of SLE is high, ranging from 25% to 50% (5). However, most involve fatty liver or nonalcoholic fatty liver disease (NAFLD), including prednisolone-induced liver dysfunction (6). In contrast, the frequency of co-occurrence of PBC in SLE patients with liver dysfunction is less than 1% (1, 7). Moreover, liver dysfunction accompanying SLE is generally mild and may be correlated with the activity of SLE. Fatty change without infiltration of inflammatory cells in the liver of SLE patients before administration of prednisolone has been reported (8, 9). Prednisolone itself may induce acute, subacute, and chronic steatohepatitis (10, 11), which are ameliorated when prednisolone is tapered, but may sometimes be induced if the dosage of prednisolone is increased.

In our case, PBC occurred while the patient was receiving a low dosage of 5 mg/day of prednisolone, but histological findings showed no fatty change of the liver. Therefore, we considered that prednisolone-induced liver dysfunction was unlikely. Liver biopsy was inconsistent with CNSDC, but granuloma formation, bile duct degradation and cell infiltration were observed, and were consistent with Scheuer I stage PBC.

There are few reports of SLE/PBC co-occurrence. SLE tends to occur in younger females and PBC most commonly develops in females during and after middle age. In most SLE/PBC co-occurrence cases, PBC develops before SLE. Moreover, in the four reported cases (2, 3) in which SLE developed prior to PBC, the patients were diagnosed with PBC during middle-to-old age, 6-18 years after the diagnosis of SLE. Our patient is the first young patient with SLE occurred while receiving prednisolone 5-15 mg/day. Their symptoms and prognosis were variable. Therefore, it seems likely that neither aggravation of SLE nor prednisolone administration was involved in PBC onset in these patients.

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For serum diagnosis of PBC. However, the AMA-positive rate of healthy people in Japan was 0.64% (11/1714) (12). In addition, enzyme-linked immunosorbent assay (ELISA)/western blot tests indicated that 4.6% (14/302) of the entire spectrum of collagen diseases and 4.2% (3/71) of SLE cases were AMA-positive, while the total AMA-positive rate of collagen diseases (excluding cases diagnosed as PBC) was 3.0% (9/297) (13). It is possible that these patients included early-stage PBC in which AMA became positive before the occurrence of subjective symptoms and liver dysfunction (14). Therefore, it seems reasonable to consider that nonspecific AMA and M2 positive rates are low, even in collagen disease patients, and that measurements of AMA and M2 antibodies are helpful for diagnosis of co-occurrence of PBC in SLE patients.

Although PBC/SLE co-occurrence may involve genetic abnormality, e.g., in early T-lymphocyte activation antigen 1 (Eta-1)/osteopontin (OPN), which is highly expressed in an SLE model mouse (15) and is involved in the formation of liver granulomas in PBC patients (16), the role of genetic factors remains to be established. Cytokines such as Eta-1/OPN may also play a role in SLE/PBC co-occurrence, but at present, so few cases have been reported that a chance relationship cannot be ruled out.

The authors state that they have no Conflict of Interest (COI).

References

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Table 1. Reported Cases of Primary Biliary Cirrhosis Developed after Diagnosis of Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age, sex at diagnosis of PBC</th>
<th>Term from diagnosis of SLE (years)</th>
<th>Dosage of prednisolone (mg/day)</th>
<th>AMA Ab</th>
<th>M2 Ab</th>
<th>Markers of SLE</th>
<th>Symptoms and prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Our case</td>
<td>29 F</td>
<td>8</td>
<td>5</td>
<td>×20</td>
<td>(+)</td>
<td>Anti-ds Ab (−) Anti-Sm Ab (−)</td>
<td>Asymptomatic during 2 years</td>
</tr>
</tbody>
</table>

AMA: antimitochondrial antibody  ds: double-stranded Ab: antibody  ?: uncertain or not reported  
F: female
