A case of primary biliary cirrhosis in a patient with rheumatoid arthritis

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The true prevalence of PBC in RA is not well known. Herein, we report an unusual case of a patient with PBC and RA, and discuss the association between these two diseases. PBC should be ruled out in the differential diagnosis of patients with RA having abnormal liver function tests.

Keywords
Genome-wide association studies, primary biliary cirrhosis, rheumatoid arthritis, ursodeoxycholic acid.

Introduction
Primary biliary cirrhosis (PBC) is an autoimmune disease in which the intrahepatic bile ducts are targeted by an immune-mediated injury. This disease tends to progress to liver cirrhosis and hepatic failure [1]. PBC is associated with a range of conditions, including Sjögren’s syndrome in 70% of patients [2], autoimmune thyroid disease in approximately 10%, and systemic sclerosis in 15% [3]. However, PBC is suggested to only rarely be associated with rheumatoid arthritis (RA), and the true prevalence of PBC in RA is not well known [4]. In this article, we report an unusual case of a patient with PBC and RA, and discuss the association between these two diseases.

Case report
In 2013, a 71-year-old man with rheumatoid arthritis (RA) was admitted to our hospital with elevated transaminase levels. He had been taking prednisone (6 mg/day) and salazosulfapyridine (1000 mg/day) for RA since 2012 (Fig. 1). He reported no consumption of alcohol, recent travel, or sexual contact. He had not recently been treated with any new medications. On examination, he was icteric with mild pruritus. An abdominal ultrasound scan, computed tomography (CT), and magnetic resonance cholangiopancreatography (MRCP) revealed neither biliary obstruction nor space-occupied lesions. Blood test results (Table 1) revealed the following: total bilirubin (T-Bil), 3.76 mg/dL; direct bilirubin (D-Bil), 3.12 mg/dL; aspartate aminotransferase (AST), 167 IU/L; alanine aminotransferase (ALT), 435 IU/L; \( \gamma \)-glutamyltranspeptidase (\( \gamma \)GT), 590 IU/L; immunoglobulin G (IgG), 1322 mg/dL; immunoglobulin M (IgM), 705 mg/dL; antinuclear antibodies (ANA), \( \times \)40; antimitochondrial antibodies (AMA), \( \times \)20; AMA-M2 antibodies, 34.1 (normal; <6); Anti-gp210 antibodies, 0.2 U/mL (normal; <6); Anti-cen-
tromere antibodies, 55.6 U/mL (normal; <9.9). A liver biopsy at day 4 showed marked inflammatory cell infiltration surrounding and destroying the interlobular bile ducts in the portal area (Fig. 2A). There was no evidence of chronic nonsuppurative destructive cholangitis (CNSDC) or granuloma. On the basis of these results, a diagnosis of PBC corresponding to Sheuer’s stage I was confirmed. Treatment with ursodeoxycholic acid (UDCA) (600 mg/day) was started 3 days after admission. The patient’s clinical findings and biological data showed improvement and the patient was discharged 19 days after admission. He has been followed up in our outpatient clinic. A second biopsy after 445 days of UDCA treatment showed marked improvement of inflammation in the portal area (Fig. 2B).

Discussion

Hepatic involvement is common in rheumatic diseases and is usually related with nonspecific findings such as...
drug-related liver dysfunction. However, more serious hepatic involvement, including nodular regenerative hyperplasia, vasculitis, and PBC, have been observed in specific rheumatic diseases, such as RA [3, 5]. RA is present in about 1% of the population and PBC is even rarer, with an estimated prevalence of 0.02% in females and 0.002% in males. The association of both diseases by chance is very unusual [6]. However, there are some reports that describe their association with individuals or families [4, 7].

PBC patients often have concomitant autoimmune diseases, such as Sjögren’s syndrome (70%), systemic sclerosis (15%), and thyroiditis (10%). The association of PBC and RA is unclear, although previous studies on large series of PBC patients have suggested that the prevalence of RA in PBC is 1.8–5.6% [4, 8, 9]. Meanwhile, several previous studies have indicated the presence of PBC-related features in RA patients. One autopsy series of RA patients found that 65% of 182 RA cases had evident liver pathology, including chronic inflammatory infiltration of the portal tracts and small foci of necrosis, as well as steatosis [10]. However, it is unclear whether any of these patients were diagnosed with PBC. A Japanese study by Takahashi et al. [11] noted that 3.8% of a cohort of 220 RA patients had concomitant PBC. Furthermore, another study indicated AMA positivity in RA patients to be 18% [12]. In our case, AMA testing was not performed at the diagnosis of RA because liver dysfunction was not observed. Although the etiologic and pathologic mechanisms of these diseases are not yet understood, several factors have been suggested, such as genetic factors, epigenetic factors, and infectious agents.

Genome-wide association studies (GWAS) have shed light on the genetic background of PBC and RA recently. Genetic studies have indicated that several genes implicated in PBC lay within non- HLA and HLA regions [13, 14]. Several common genes have been identified in PBC and RA, although the majority of implicated genes in both diseases do not overlap. Overlapping genes include HLA-DQB1, CTLA4, MMEL1, IRF5, STAT4, and possibly CXCR5. Among these genes, STAT4 is essential for IL-12 signal transduction via the IL-12 receptor (IL12R) for IFN-γ production and Th1 polarization. In a GWAS for PBC in the Japanese population, Nakamura et al. [15] reported that, in addition to possessing two significant susceptibility loci (TNFSF15 and POU2AF1), STAT4 showed a suggestive association with PBC in Japanese and European patients. In our case, we did not perform a genetic analysis; however, individuals with a common genetic profile may be more susceptible to developing concomitant RA and PBC.

Assuming that several common genes exist in RA and PBC patients, it has been suggested that common
Infectious triggers may be involved in the induction of both diseases. Most studied infection trigger of PBC is Escherichia coli (E. coli) [16]; due to the high incidence of recurrent urinary tract infections (rUTIs) in PBC patients [17]. Several infectious agents (including E. coli) have also been linked to RA [18, 19]. Of note, in RF-positive patients, anti-E. coli IgM has been found to be elevated [20]. In our case, no symptoms of bacterial infection, including rUTIs, were observed during the clinical course. However, a possible role of E. coli has been suggested in the early pathogenesis of RA.

In our case, the patients showed rapid elevation in ALT as well as ALP and γGTP. Sodha et al. [21] previously reported a rare case of rapid-onset PBC. In their case, drug-induced liver injury (DILI) and overlap syndrome between PBC and autoimmune hepatitis (AIH) were suspected at first. However, the patient was finally diagnosed as PBC by laboratory data, histology findings, and clinical course. In our case, DILI and viral hepatitis were denied from past medical history and laboratory data. Overlap syndrome between PBC and AIH was also suspected, however, serum level of ALT was normalized after 2 months of UDCA treatment. Since then, the liver function has remained normal for 19 months. For these findings, we thought that the diagnosis in our case was also closer to PBC than overlap syndrome.

In conclusion, concomitant PBC in patients with RA is rare; however, PBC should be ruled out in the differential diagnosis of any patients with RA having abnormal liver function tests. To determine the relationship between these two diseases, further studies are needed, in particular cohort studies related to PBC occurrence in a large cohort of RA patients.

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Conflict of interest

None declared.

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