Rheumatic Manifestations in Autoimmune Liver Disease

Carlo Selmi, MD, PhD[a,b,*], Elena Generali, MD[a], Merrill Eric Gershwin, MD[c]

KEYWORDS

• Immune tolerance • Personalized medicine • Autoimmune comorbidity • Cholangitis • Hepatitis • Osteoporosis • Methotrexate • Autoantibody

KEY POINTS

- Autoimmune hepatitis (AIH) is a rare disease that is the result of an autoimmune destruction of the hepatocytes, manifesting with high liver aminotransferase and serum autoantibody levels that may be specific for the disease.
- Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are chronic autoimmune cholestatic diseases that affect the biliary tree. PBC is characterized by antimitochondrial antibody positivity in almost all cases, whereas, conversely, PSC has no association with autoantibodies, suggesting a different pathogenesis.
- Rheumatic diseases are found in nearly 20% of patients with autoimmune liver diseases and may be associated with different prognoses for the patients. For this reason, the identification of the co-occurring disease at an early stage or even preclinically (using autoantibodies) is of pivotal importance.
- Bone density is reduced in patients with AIH because of prolonged steroid use and in PBC/PSC because of chronic cholestasis; therefore, osteoporosis management is an important issue in the care of these patients.
- Treatment options should be personalized to address coexisting conditions, especially if overlapping with specific rheumatic or autoimmune diseases.

INTRODUCTION

The link between autoimmune liver diseases and rheumatologic disease traces back to the first report in the mid-1950s, when findings of active chronic hepatic disease were described in the setting of systemic lupus erythematosus (SLE). These findings

Conflicts of Interest: The authors have no conflicts of interest.

[a] Division of Rheumatology and Clinical Immunology, Humanitas Research Hospital, Via A. Manzoni 56, Rozzano, Milan 20089, Italy; [b] BIOMETRA Department, University of Milan, Via Luigi Vanvitelli, 32, 20129 Milano, MI, Italy; [c] Division of Rheumatology, Allergy, and Clinical Immunology, University of California, Davis, 4860 Y Street, Suite 2500, Sacramento, CA 95817, USA
* Corresponding author. Division of Rheumatology and Clinical Immunology, Humanitas Research Hospital, via A. Manzoni 56, Rozzano, Milan 20089, Italy.
E-mail address: carlo.selmi@unimi.it

Rheum Dis Clin N Am 44 (2018) 65–87
https://doi.org/10.1016/j.rdc.2017.09.008
rheumatic.theclinics.com

led to the concept of lupoid hepatitis with positive LE cell tests and mild signs of rheumatic disease.[1,2] When discussing autoimmune liver disease, it is possible to distinguish autoimmune hepatitis (AIH; affecting hepatocytes) from primary biliary cholangitis (PBC, until recently known as primary biliary cirrhosis), and primary sclerosing cholangitis (PSC) based on the target tissue.[3,4] Cirrhosis and liver failure are potential complications shared by inflammatory hepatobiliary diseases, regardless of the target tissue, whereas the pathogenesis and therapeutics may vary within the clinical spectrum.[5] The epidemiology of autoimmune liver diseases is similar to that of other rare autoimmune or inflammatory disorders.[6–8] Similarly, serum autoantibodies represent the hallmark for AIH and PBC, but not PSC, and are usually positive years before the diagnosis (**Table 1**).[9–11]

Since the earliest reports, several others have shown the associations between PBC and systemic sclerosis (SSc),[12,13] as well as Sjögren syndrome (SjS).[14] Moreover, the epidemiologic links between these liver diseases and systemic rheumatic manifestations are also reflected in shared pathogenic mechanisms. These links are elegantly represented by the concept of autoimmune epithelitis, coined as a descriptor for PBC and SjS.[15] Serologic profiles are also similar with regard to antinuclear antibody (ANA) positivity[16] and common laboratory abnormalities are present, as is the case for hypergammaglobulinemia.[17] Most importantly, therapeutic strategies may also overlap, because steroids represent the first-line therapy in most cases,[18] whereas new targeted approaches are emerging.[19,20] Nonclassic associations have been also reported between spondyloarthritis and PSC with regard to inflammatory bowel diseases (IBD).[21] In addition, because corticosteroids and chronic liver diseases are associated with bone density loss, osteoporosis and bone fractures demand the attention of rheumatologists managing such patients.[22–24]

This article (1) provides an overview of the characteristics of the 3 major autoimmune liver diseases, namely AIH, PBS, and PSC; and (2) elucidates the existing associations between these conditions and rheumatic diseases. Particular attention is paid to both the shared and unique epidemiology, serum autoantibodies, and treatments, as well as the approach to bone density loss. The term lupoid hepatitis was introduced by our unit in 195CiL to describe cases of active chronic hepatitis associated with a positive LE cell test and occasionally minor manifestations of SLE.

AUTOIMMUNE HEPATITIS

AIH is a chronic inflammatory disease of unknown cause resulting from the immune-mediated destruction of hepatocytes with autoimmune features.[25,26] AIH is characterized by the presence of typical but nonspecific findings on liver biopsy, serum autoantibodies, and increased serum aminotransferase and gamma-globulin levels.[27] The incidence, although not precise, is estimated at approximately 1 per 100,000 person-years, with higher possible incidence in Scandinavia.[28] AIH most commonly affects women, with a male/female ratio of 1:4,[28] and manifests a 2-peak incidence during adolescence and at 30 to 45 years of age.[25,29] The onset of AIH is most frequently insidious, with 20% to 30% of patients presenting with an acute icteric hepatitis, consistently associated with hypergammaglobulinemia. Clinical manifestations are nonspecific and include hepatosplenomegaly, jaundice, anorexia, and fatigue.[27,30] The most common extrahepatic manifestations are arthralgia and rash.

Clinical Features

Two types of AIH are distinguished, primarily based on autoantibody patterns: AIH type 1 with ANA and/or anti–smooth muscle antibodies (anti-SMA), and AIH type 2