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Original Article

Autoimmune hepatitis in patients with primary Sjögren's syndrome: a series of two-hundred and two patients

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Abstract: Based on the revised criteria of the American-European Consensus Group, we retrospectively established the diagnosis of primary or secondary Sjögren's syndrome for 202 patients referred to a Sjögren's syndrome clinic. Of these, 58 patients and 8 patients fulfilled criteria for primary and secondary Sjögren's syndrome, respectively. Of the 58 patients with primary Sjögren's syndrome, one (1.7%) had definite autoimmune hepatitis, as defined by the International Autoimmune Hepatitis Group diagnostic criteria. One additional symptomatic patient who did not fulfill criteria for primary Sjögren's syndrome had definite autoimmune hepatitis. None of the patients with secondary Sjögren's syndrome had definite autoimmune hepatitis. Two (1%) of the 194 patients with primary Sjögren's syndrome or clinical symptoms had primary biliary cirrhosis. These values are lower than those reported by prior studies with smaller patient populations and likely represent a more accurate estimate of the true prevalence of these diseases in patients with primary Sjögren's syndrome.

Keywords: Autoimmune hepatitis, Sjögren's syndrome, primary biliary cirrhosis

Introduction

Primary Sjögren's syndrome (pSS) is an inflammatory autoimmune disease of exocrine glands that predominantly affects salivary and lacrimal glands in the absence of other definitively diagnosed rheumatologic conditions. The involvement of non-exocrine organs including the lungs, kidney, thyroid, and central nervous system has been reported in patients with pSS. The association between liver disease and pSS was first suggested by Christiansson in 1954 [1].

The association between liver disease and pSS was considered "surprisingly common," even when compared to the association between liver disease and other autoimmune disorders, such as rheumatoid arthritis [2]. Subsequent case series in the mid 1970s and early 1980s emphasized the biochemical, serologic, and histologic findings consistent with liver disease and their relationship to pSS [3-5]. Additionally, it is known that pSS is common in patients with primary biliary cirrhosis (PBC) [6, 7]. A large study of 300 pSS patients by Skopouli *et al* concluded that although liver involvement in pSS was rare, PBC accounted for nearly all identified liver disease [8]. Others have noted abnormal liver biochemical profiles more frequently in patients pSS who had concomitant kidney, lung, or hematological abnormalities [9-11].

Specifically, the prevalence of autoimmune hepatitis (AIH) in patients with pSS has been reported to be anywhere from 4% to a staggering 47% [10-12]. The exact prevalence of AIH in pSS is therefore unclear. Furthermore, the prevalence of AIH in secondary Sjögren's syndrome (sSS), defined as those with a well defined connective tissue disease and symptoms of Sjögren's syndrome, has not been well documented.

In this retrospective analysis, we evaluate the

anatomic pathology diagnoses and relevant laboratory values of a large cohort of patients referred for evaluation of ocular and/or oral sicca symptoms and rheumatologic disease. This study examines the prevalence of AIH in patients with pSS, sSS, and oral or ocular sicca symptoms.

Materials and methods

We retrospectively reviewed the electronic patient records of 202 patients evaluated for ocular and/or oral sicca symptoms and rheumatologic disease at our institution. For each patient, the diagnosis of pSS or sSS was based on the revised international criteria of the American-European Consensus Group [13]. Associated rheumatologic diseases were noted for those patients with sSS. Patients who did not fulfill criteria for either pSS or sSS were classified as being clinically symptomatic with oral or ocular sicca.

For each patient, all available anatomic pathology diagnoses were identified. All available core liver biopsies were reviewed to confirm the original diagnosis of AIH as defined by the International Autoimmune Hepatitis Group diagnostic criteria [14]. Hepatic activity index (HAI) scores were assigned to those core liver biopsies representing definite AIH [15].

Laboratory values were reviewed for each patient, including antibodies to Ro(SSA) and/or La (SSB) antigens, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, gamma glutamyl transferase (GGT), total bilirubin, anti-mitochondrial antibodies (AMA), anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (SMA), serum immunoglobulins (IgG, IgM, and IgA), and markers of viral hepatitis B and C. Abnormal liver function tests (LFTs) were defined as a recorded elevated ALT (normal ≤ 31 U/L), AST (normal ≤ 31 U/L), or alkaline phosphatase (normal ≤ 120 U/L), at any determination.

Results

Of the 202 patients referred for evaluation, 182, (90%) were women. Patients ranged in age from 21 to 94 years. Fifty-eight patients had confirmed pSS and 8 patients were classified as sSS. One hundred and thirty-six patients fell short of the criteria for pSS and were classified as demonstrating symptomatic oral and/or ocular sicca. In total, 4 of the 202 patients (2%) had liver biopsies available for review. Liver biopsies were performed in two of the fifty-eight (3%) confirmed pSS patients and 2 of the 136 (1%) symptomatic patients. None of the sSS patients had liver biopsies on record.

The 58 patients with pSS included 53 (91%) women. The average age was 61 years with ages ranging from 22 to 84 years old. Of these 58 patients, 18 (31%) had normal LFTs and 14 (24%) had abnormal LFTs. No LFTs were on record for the remaining 26 (45%) patients.

Of the 14 patients with abnormal LFTs, one (1.7%) patient had the clinical, biochemical and histologic findings to support a diagnosis of AIH. This patient, a woman, was 28 years-old at the time of diagnosis. Review of two core needle hepatic biopsies demonstrated chronic portal lymphoplasmacytic inflammation with interface activity (**Figure**s **1** and **2**). The hepatic activity index was determined to be 8/18 [15]. A minor salivary gland biopsy revealed chronic sialoadenitis, grade 2 of 4. Antibodies to Ro (SSA) antigens were identified.

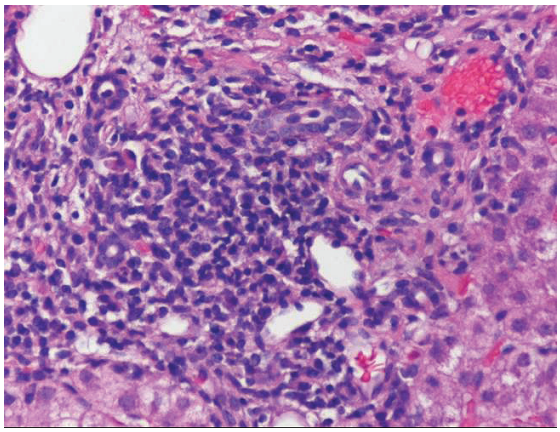

Figure 1. Lymphocyte and plasma cell rich portal inflammation with a focus of mild interface activity (40x magnification)

All 8 patients with sSS were women. These patients had an average age of 58 years with ages ranging from 45 to 75 years. Two patients had been previously diagnosed with Systemic Lupus Erythematosus (SLE), 5 with rheumatoid arthritis (RA), and 1 with mixed connective tissue dis-

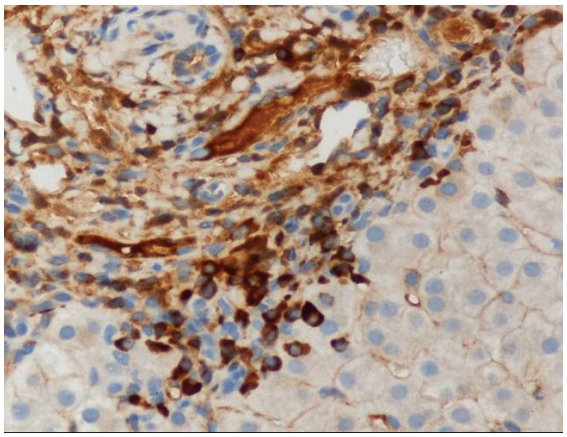

Figure 2. Immunohistochemical staining demonstrates many plasma cells expressing surface IgG.

ease (MCTD). Of these patients, 3 had normal LFTs and 4 had abnormal LFTs. No LFTs were on record for one patient. No patient with confirmed sSS was diagnosed with AIH.

Of the 136 patients with clinical oral and/or ocular sicca symptoms, 121 (89%) were women. The average age was 57 years with ages ranging from 21 to 94 years. Of these 136 patients, 59 had normal LFTs and 32 had abnormal LFTs. No LFTs were on record for the remaining 45 patients. Of the 32 patients with abnormal LFTs, one patient was diagnosed with AIH.

This patient, a woman, was, reported to have abnormal LFTs at 33 years-old. She was diagnosed with AIH twenty years later. Six years following diagnosis with AIH, she required orthotopic liver transplantation. Pre-transplantation core needle hepatic biopsies were not available for review. The patient demonstrated both ocular and oral symptoms, but antibodies to Ro(SSA) and La(SSB) antigens were not identified. A Schirmer's I test was not performed.

Additionally, two (1%) of the 194 patients with confirmed pSS or clinical oral and/or ocular sicca symptoms were diagnosed with PBC. Both patients were women, one 70 years-old and one 52 years-old. The elder patient demonstrated a positive AMA with elevated LFTs. The younger patient had a positive AMA and symptoms of cholestasis reported at an outside institution. However, a liver biopsy was not recorded for either patient.

Discussion

Based on our data, the prevalence of AIH in patients with pSS is approximately 1%. Of the 58 patients with pSS, one (1.7%) was identified as having AIH. If the symptomatic sicca patients are included in the population, a total of 2 (1%) of 194 patients were diagnosed with AIH. Articles by Lindgren *et. al*. and Montaño-Lozo *et. al*. have reported the prevalence of AIH in patients with pSS to be 4% and 2%, respectively [1,3]. These prevalence rates are similar to the rate identified in the current study. Thus, our results likely represent an accurate estimate of the true prevalence of AIH in patients with pSS.

When considering the prevalence of AIH in patients with pSS and abnormal LFTs, the similarities between studies are fewer (**Table 1**). Lindgren *et al* and Montaño-Lozo *et al* reported the prevalence of AIH in patients with pSS and abnormal LFTs to be 16.6% (2/12) and 8.7% (2/23), respectively [10,11]. An article by Matsumoto *et al* reported the prevalence of AIH in patients with pSS and abnormal LFTs to be 47% (8/17) [12]. In our study, only 2 (4.3%) of the 46 patients with pSS or sicca symptoms and abnormal LFTs were diagnosed with AIH.

Table 1. Prevalence of AIH in patients with pSS, by publication

Authors	Total # patients	Patients with pSS	Patients with AIH (%)
Lindgren, *et al.* (1994)	55	45	2 (4)
Matsumoto *et al.* (2005)	17	17	8 (47)
Montaño-Loza, *et al.* (2007)	156	95	2 (2)
Present study	202	58	1 (1.7)

The significant variation in the prevalence of AIH in patients with abnormal LFTs may be at least partially explained by differences in study design. First, the definition of abnormal LFTs is not universal and, thus, allows for significant variation among studies. Second, the prior studies by Lindgren *et al*, Matsumoto *et al*, and Montaño-Loza *et al* were conducted in Sweden, Japan, and Mexico, respectively [10-12]. These

very distinct populations may result in prevalence rates that are equally disparate.

Although the two patients diagnosed with AIH also had abnormal LFTs, it should be noted that 94% (47/50) of patients with abnormal LFTs were not diagnosed with either AIH or PBC. This finding should reassure physicians that the majority of patients with abnormal LFTs and any form of Sjögren's syndrome have neither AIH nor PBC. Thus, while abnormal LFTs in this patient population are of clinical importance, the likelihood of diagnosing AIH is small.

None of the 8 patients diagnosed with confirmed sSS were diagnosed with AIH. The prevalence of AIH in patients with confirmed sSS has not been described in previous reports. Future studies may helpful in addressing the prevalence of AIH in a larger cohort of patients with sSS.

Most surprisingly, we examined the association between pSS and PBC. The prior studies by Lindgren *et al*, Matsumoto *et al*, and Montaño-Loza *et al* have reported the prevalence of PBC in patients with pSS to be 9% (4/45), 35% (6/17), and 5.3% (5/95), respectively [10-12]. In the current study, only two (1%) of the 194 patients with pSS or symptomatic sicca was identified as having PBC.

One might note that as the sample population in the above studies grows larger, the prevalence of PBC grows smaller. This would suggest that our study, with the largest patient population, is likely a more accurate estimate of the prevalence of PBC in patients with pSS. That being said, the patients with symptomatic sicca may be artificially lowering our reported prevalence.

Several characteristics distinguish our study from prior investigations. First, our study reflects an American patient population. Again, the prior studies by Lindgren *et al*, Matsumoto *et al*, and Montaño-Loza *et al* were conducted in Sweden, Japan, and Mexico, respectively. Their findings may be representative of a more homogeneous patient population and may not be readily applicable to the heterogeneous populations seen by American clinicians. Furthermore, our study included a larger cohort size than those of the previous studies. While Lindgren *et al*, Matsumoto *et al*, and Montaño-Loza *et al* studied 55, 17, and 156 patients, respectively, our study included 202 patients [10-12].

Our study demonstrates that the prevalence of autoimmune hepatitis in a heterogeneous group of patients with primary Sjögren's syndrome is approximately 1%. This likely represents a more accurate estimate of the true prevalence of autoimmune hepatitis in patients with primary Sjögren's syndrome.

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Abbreviations: Alanine transaminase (ALT), antimitochondrial antibodies (AMA), anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (SMA), aspartate transaminase (AST), autoimmune hepatitis (AIH), gamma glutamyl transferase (GGT), Hepatic activity index (HAI), liver function tests (LFTs), mixed connective tissue disease (MCTD), primary Sjögren's syndrome (pSS), rheumatoid arthritis (RA), secondary Sjögren's syndrome (sSS), Systemic Lupus Erythematosus (SLE)

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