

# Characterization and Differentiation of Autoimmune versus Viral Liver Involvement in Patients with Sjögren's Syndrome

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**ABSTRACT. Objective.** To analyze the prevalence and clinical significance of liver involvement in patients with Sjögren's syndrome (SS), focusing on the characterization and differentiation of autoimmune versus chronic viral liver disease.

**Methods.** We investigated liver involvement (clinical signs, analytical data, chronic viral infections, and autoantibodies) in 475 consecutive patients with SS. All patients fulfilled 4 or more of the 1993 European Community Study Group criteria for SS.

**Results.** Liver involvement was detected in 129 (27%) patients. After ruling out chronic illnesses or use of hepatotoxic drugs, the main etiologies were chronic viral liver disease in 64 (13%) cases [chronic hepatitis C virus (HCV) infection in 63 and HBV infection in one] and autoimmune liver diseases in 24 (5%; primary biliary cirrhosis in 16 patients and type-1 autoimmune hepatitis in 8). The analytical liver profile was not useful in differentiating between viral and autoimmune liver disease. In contrast, patients with SS and autoimmune liver disease presented higher mean values of erythrocyte sedimentation rate ( $p = 0.044$ ), circulating gammaglobulins ( $p = 0.007$ ), and a higher prevalence of antinuclear antibodies ( $p < 0.001$ ), antimitochondrial antibodies ( $p < 0.001$ ), anti-smooth muscle antibodies ( $p = 0.026$ ), anti-Ro/SSA ( $p < 0.001$ ), and anti-La/SSB ( $p = 0.01$ ), while patients with chronic viral liver disease had a higher frequency of cryoglobulinemia ( $p < 0.001$ ) and hypocomplementemia ( $p < 0.001$ ).

**Conclusion.** Chronic viral liver disease (associated overwhelmingly with HCV) was the main cause of liver involvement in our patients with SS, with a prevalence of 13%, nearly 3-fold greater than that observed for autoimmune liver involvement. The immunological pattern played a key role in the differentiation of viral (predominance of cryoglobulins and low complement levels) and autoimmune (higher frequency of autoantibodies) liver involvement. (J Rheumatol 2006;33:1593–9)

## Key Indexing Terms:

LIVER DISEASES  
AUTOIMMUNE HEPATITIS

SJÖGREN'S SYNDROME

PRIMARY BILIARY CIRRHOSIS  
HEPATITIS C VIRUS

Sjögren's syndrome (SS) is a systemic autoimmune disease that mainly affects the exocrine glands and usually presents as persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands<sup>1</sup>. The histological hallmark is a focal lymphocytic infiltration of the exocrine glands, and the spectrum of the disease extends from an organ-specific autoimmune disease (autoimmune exocrinopathy)<sup>2</sup> to a systemic process with diverse extraglan-

dular manifestations<sup>3</sup>. A possible association between SS and liver disease began to emerge during the 1960s. In 1965 Bloch, *et al*<sup>4</sup> found a prevalence of liver involvement (hepatomegaly and/or raised alkaline phosphatase) of 27% in the first well-described series of patients with SS. In 1970 Golding, *et al*<sup>5</sup> reported a higher frequency of sicca syndrome in patients with diverse liver diseases including chronic active hepatitis, primary biliary cirrhosis (PBC), or cryptogenic cirrhosis. Further studies confirmed a close association between PBC and SS<sup>6,7</sup>, although reports of other autoimmune liver diseases, such as autoimmune hepatitis or sclerosing cholangitis, are scarce.

Chronic viral liver diseases have recently emerged as an additional cause of liver involvement in patients with SS (especially in some geographical areas), broadening the spectrum of hepatopathies that may affect these patients<sup>8</sup>. Few studies have analyzed the complete spectrum of liver disease in large series of patients with primary SS<sup>9,10</sup>, and none have analyzed the manner of differentiating the 2 main causes of liver disease, namely autoimmune or viral. We analyzed the

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prevalence and clinical significance of liver involvement in patients with SS, focusing on the characterization and differentiation of autoimmune versus chronic viral liver disease.

## MATERIALS AND METHODS

**Patients.** Between 1994 and 2004, we investigated the clinical and immunological characteristics of 475 patients with SS (434 women and 41 men, with a mean age of 59.7 years) seen consecutively in our department. All patients fulfilled 4 or more of the preliminary diagnostic criteria for SS proposed by the European Community Study Group in 1993<sup>11</sup>, including as mandatory criteria either immunological criteria or positive salivary gland biopsy. We retrospectively applied the recent 2002 classification criteria in the 292 patients having all the mandatory tests performed, and found that 260 (89%) fulfilled these more restrictive criteria. Diagnostic tests for SS (Rose-Bengal staining, Schirmer test, parotid scintigraphy, and salivary gland biopsy) were applied according to the recommendations of the European Community Study Group<sup>11</sup>, and clinical and serologic characteristics of all patients were collected in a protocol form. Positive anti-Ro/La antibodies were found in 158 patients and 162/198 patients had a positive salivary gland biopsy. Glandular and extraglandular manifestations of SS were defined according to previous studies<sup>12,13</sup>.

**Evaluation of liver involvement.** Liver involvement was defined as the presence of one or more of the following: (1) Clinical signs of liver disease: hepatomegaly, splenomegaly, jaundice, ascites, encephalopathy, and/or (2) Biochemical data: raised liver enzymes [aspartate/alanine transaminases (ALT/AST)  $\geq 40$  IU/l,  $\gamma$ -glutamyltranspeptidase (GGT)  $\geq 40$  IU/l, alkaline phosphatase  $> 290$  IU/l, and/or elevated bilirubin  $> 1.2$  mg/dl] found in at least 3 analytical determinations over a minimum period of 2 years. (3) Immunological markers: positive antimitochondrial antibodies (AMA) with a specific M2 pattern<sup>14</sup>, or positive antinuclear antibodies (ANA), antismooth muscle antibodies (anti-SMA), or anti-liver-kidney microsome antibodies type-1 (LKM-1)<sup>15</sup> in patients with clinical and/or analytical data of liver involvement. (4) Virological markers for chronic viral infections [anti-hepatitis C and hepatitis B virus surface antigen (HbsAg)]. (5) Histological examination of liver biopsies included hematoxylin and iron stains, stains for connective tissue and copper-associated protein.

### Classification of liver involvement

#### Autoimmune liver disease

**Primary biliary cirrhosis:** The presence of one or more of the following features was considered highly suggestive<sup>16</sup>: (1) positive AMA with a specific M2 pattern; (2) raised alkaline phosphatase levels (at least twice normal upper limit); (3) raised serum IgM levels ( $> 2.6$  g/dl); (4) liver biopsy showing histological features compatible with PBC according to the histological classification stages (1 to 4) proposed by Ludwig, *et al*<sup>17</sup>.

**Autoimmune hepatitis (AIH):** The diagnosis of AIH was based on the scoring system established by the International Autoimmune Hepatitis Group<sup>18</sup>. This group proposed criteria for the definite or probable diagnosis of AIH based on clinical presentation, biochemistry, serology, and biopsy results. A diagnostic score  $> 15$  is considered as definite AIH<sup>17</sup>.

**Autoimmune cholangitis (AMA-negative PBC):** Laboratory evidence of cholestasis in a patient with AMA titer  $< 1:40$  and a liver biopsy compatible with PBC or cholangitis<sup>19</sup>.

**Primary sclerosing cholangitis (PSC):** The diagnosis of PSC required a compatible cholangiogram.

#### Chronic viral liver disease

**HCV infection:** Positive results (at least twice) for HCV antibodies using a second or third-generation ELISA, confirmed by third-generation recombinant immunoblot assay and/or detection of serum HCV-RNA by polymerase chain reaction, as described<sup>8</sup>.

**HBV infection:** positive HBsAg, analyzed by ELISA.

#### Other causes of liver involvement

Drug-related hepatotoxicity [nonsteroidal antiinflammatory drugs (NSAID), antihypertensives, antidiabetic agents, anticonvulsants, lipid-lowering agents, and psychotropic drugs]<sup>20</sup>; nonautoimmune, nonviral liver processes such as steatosis, chronic cardiopulmonary disease, chronic alcoholic consumption, or Gilbert's syndrome.

**Statistical analysis.** We used conventional chi-square and Fisher's exact tests to analyze qualitative differences. For comparison of quantitative measures, the Student t test was used in large samples of similar variance and the non-parametric Mann-Whitney U test for small samples. Results of the analysis of continuous variables are indicated as mean  $\pm$  standard error of the mean (SEM). A value of  $p < 0.05$  indicated statistical significance. Statistical analysis was performed using SPSS (SPSS, Chicago, IL, USA).

## RESULTS

Liver involvement was detected in 129 (27%) out of 475 patients. Chronic viral liver disease was found in 64 (13%) cases, including chronic HCV infection in 63 patients and chronic HBV infection in one. Twenty-four (5%) patients had autoimmune liver diseases, including PBC in 16 patients and type-1 autoimmune hepatitis in 8. The remaining 41 cases had nonautoimmune, nonviral involvement; in 26 patients, liver involvement was related to the chronic use of hepatotoxic drugs, mainly NSAID, statins, and psychotropic drugs. No patient received methotrexate. Analytical evidence of liver involvement was found in 123 patients (26%), with elevated transaminases in 101 (21%) cases, elevated GGT in 92 (19%), raised alkaline phosphatase in 30 (6%), and elevated bilirubin in 24 (5%). Clinical signs of hepatopathy included hepatomegaly in 33 (7%) patients, splenomegaly in 11 (2%), jaundice in 9 (2%), and hepatic decompensation in 9 (2%).

The main hematological and immunological manifestations of patients with SS and liver involvement were compared with the 346 primary SS patients with no evidence of hepatopathy (Table 1). In patients with liver involvement, there was a higher level of erythrocyte sedimentation rate (ESR)  $> 50$  mm/h (44% vs 21%;  $p < 0.001$ ), and a higher mean percentage of circulating gammaglobulins (21.7% vs 18.9%;  $p < 0.001$ ); and a higher frequency of anti-SMA antibodies (66% vs 56%;  $p = 0.030$ ), rheumatoid factor (RF) (54% vs 36%;  $p = 0.001$ ), hypocomplementemia (45% vs 10%;  $p < 0.001$ ), and cryoglobulinemia (45% vs 6%,  $p < 0.001$ ) was found in patients with liver involvement compared to those without, with gammaglobulins and cryoglobulins being significant independent variables in the multivariate analysis.

#### Characterization of chronic viral liver diseases

**HCV infection.** Of the 63 patients with chronic HCV infection, 49 (78%) were women and 14 (22%) men, with a mean age of 61.12 years at SS diagnosis and 64.23 years at diagnosis of HCV infection. HCV-RNA determination was available in 40 patients, and was positive in 36 (90%). Analytical evidence of liver involvement was detected in 60 (95%) patients. Only 8 (13%) patients presented clinical manifestations of hepatic decompensation (ascites, encephalopathy, or gastrointestinal bleeding). Biochemical tests showed raised transaminases in

**Table 1.** Hematological and immunological manifestations of patients with SS and liver involvement compared with the 346 primary SS patients with no evidence of hepatopathy. Data are number (%) or mean  $\pm$  SEM.

	Liver Involvement, n = 129	No Liver Involvement, n = 346	p
ESR > 50 mm/h	57 (44)	59 (21)	0.001
Gammaglobulins (mean $\pm$ SEM)	21.61 $\pm$ 0.84	18.98 $\pm$ 0.38	0.001*
Antinuclear antibodies	103 (81)	273/338 (81)	1.000
Anti-SMA	85 (66)	188/334 (56)	0.030
Anti-Ro/SSA	32 (25)	113/339 (33)	0.094
Anti-La/SSB	27 (21)	74/337 (22)	0.900
Rheumatoid factor	66/123 (54)	116/320 (36)	0.001
Hypocomplementemia	54/119 (45)	32/313 (10)	< 0.001
Cryoglobulinemia	52/116 (45)	16/250 (6)	< 0.001*

\* Statistically significant in multivariate analysis. Anti-SMA: anti-smooth muscle antibodies.

49 (78%) patients, raised GGT in 44 (70%), raised bilirubin in 15 (24%), and raised alkaline phosphatase in 15 (24%). Liver biopsy was performed in 25 patients with informed consent. The main extraglandular features were articular involvement in 20 (32%) patients, cutaneous vasculitis in 14 (22%), peripheral neuropathy in 11 (18%), thyroiditis in 9 (14%), Raynaud's phenomenon (RP) in 8 (13%), pulmonary fibrosis in 4 (6%), and renal involvement in 3 (5%) patients. Salivary gland biopsy was positive in 17/21 patients. In non-biopsied patients, at least one positive immunological marker was found (ANA, RF, anti-Ro/SSA and/or anti-La/SSB). Hematological data included thrombocytopenia (platelet count <  $150 \times 10^9/l$ ) in 35 (56%) patients and leukopenia (leukocyte count <  $4 \times 10^9/l$ ) in 22 (35%). The main immunologic features were cryoglobulinemia in 42 (67%) patients, hypocomplementemia in 42 (67%), ANA in 41 (65%), RF in 36 (57%), anti-Ro/SSA in 7 (11%), and anti-La/SSB in 7 (11%).

**HBV infection.** Only one (0.2%) patient presented positive HBsAg. This was a 53-year-old man with a chronic hepatopathy without decompensation. Biochemical tests showed raised transaminases and GGT.

#### Characterization of autoimmune liver diseases

**PBC.** Sixteen (4%) patients presented features highly suggestive of PBC. All were women, with a mean age of 49 years at SS onset and 51 years at diagnosis of PBC. All patients presented AMA-M2: 5 had AMA titers of 1/80, 7 of 1/160, 2 of 1/320, and 2 of 1/640. Anti-PDH complex antibodies were confirmed by ELISA in 6 patients. Thirteen (81%) patients had analytical evidence of liver involvement, with elevated GGT in 12 (75%), elevated transaminases in 8 (50%), raised alkaline phosphatase in 5 (31%), and elevated bilirubin in 2 (13%). Liver biopsy was performed in 4 patients with informed consent, with specimens showing a histological pattern compatible with PBC in 3 cases (one had stage 1 and two stage 2) and normal liver structure in one. The main extraglandular SS manifestations consisted of articular involvement in

9 (56%) patients, RP in 7 (44%), and pulmonary involvement in 3 (19%). Anemia (defined as a hemoglobin value < 10 g/dl) was detected in 6 patients, leukopenia in 4 (25%), and thrombocytopenia in 6 (38%). Hypergammaglobulinemia (gamma-globulin percentage > 25%) was detected in 9 (56%) patients, with raised IgM levels (> 2.6 g/dl) in 6 (38%). Other immunologic features were positive ANA in all patients, anti-SMA in 13 (81%), anti-Ro/SSA in 11 (69%), RF in 10 (63%), and anti-La/SSB in 8 (50%).

**AIH.** Eight (2%) patients presented type-1 AIH. All were women, with a mean age of 53 years at SS onset and of 58 years at diagnosis of AIH. All patients had analytical evidence of liver involvement, with elevated transaminases in all, elevated GGT in 6 (75%), raised alkaline phosphatase in 4 (50%), and elevated bilirubin in one (13%). Liver biopsy was performed in 5 patients with informed consent, with specimens showing a histological pattern compatible with AIH in 4 cases and normal liver structure in one. The main extraglandular SS manifestations consisted of articular involvement in 3 (38%) patients and cutaneous vasculitis in 2 (25%). Anemia was detected in one patient and thrombocytopenia in 3 (38%). Hypergammaglobulinemia was detected in 3 (38%) patients. The main immunologic features were positive ANA in all patients, anti-SMA in 7 (88%), anti-Ro/SSA in 3 (38%), and RF in 3 (38%).

**Differentiation between viral and autoimmune liver disease**  
Demographically, viral liver disease was characterized by a higher frequency of men (23% vs 0%;  $p = 0.009$ ) and an older age at SS diagnosis ( $67.46 \pm 1.18$  vs  $57.67 \pm 2.70$  yrs;  $p < 0.001$ ) compared with autoimmune liver disease (Table 2). Although a similar prevalence of the main extraglandular features was found, there was a higher frequency of RP in patients with autoimmune liver disease (33% vs 13%;  $p = 0.033$ ). Liver involvement was expressed similarly, with no differences in the prevalence of altered analytical liver profile, including transaminases, GGT, bilirubin, and alkaline phosphatase (Table 2). In contrast, a clearly differentiated hemato-

Table 2. Epidemiological and clinical features of SS patients with autoimmune liver disease in comparison with patients with chronic viral infections. Data are number (%) or mean  $\pm$  SEM.

	Autoimmune Liver Disease, n = 24	Chronic Viral Disease, n = 64	Bilateral p (< 0.05)
Epidemiological features			
Sex (female)	24 (100)	49 (77)	0.009
Mean age, yrs	57.67 $\pm$ 2.70	67.46 $\pm$ 1.18	< 0.001
Extraglandular SS features			
Articular involvement	6 (25)	21 (33)	—
Pulmonary involvement	4 (17)	4 (6)	—
Thyroiditis	4 (17)	9 (14)	—
Cutaneous vasculitis	2 (8)	14 (22)	—
Peripheral neuropathy	1 (4)	11 (17)	—
Raynaud phenomenon	8 (33)	8 (13)	0.033
Renal involvement	1 (4)	3 (5)	—
Liver involvement			
Altered liver profile	21 (87)	61 (95)	—
Raised transaminases	16 (67)	50 (78)	—
Raised gammaglutamyl transferase	18 (75)	44 (69)	—
Raised bilirubin	3 (12)	15 (23)	—
Raised alkaline phosphatase	9 (37)	15 (23)	—
Liver decompensation	1 (4)	8 (13)	—
Hepatocarcinoma	0 (0)	4 (6)	—

logic and immunologic profile was observed (Table 3). SS patients with autoimmune liver disease presented higher mean values of ESR (53.7 vs 39.0;  $p = 0.044$ ), circulating gammaglobulins (26.1% vs 20.2%;  $p = 0.007$ ), and a higher prevalence of ANA (100% vs 66%;  $p < 0.001$ ), AMA (67% vs 6%;  $p < 0.001$ ), anti-SMA (83% vs 55%;  $p = 0.026$ ), anti-Ro/SSA (58% vs 11%;  $p < 0.001$ ), and anti-La/SSB (38% vs 11%;  $p = 0.01$ ), while patients with chronic viral hepatopathy had a higher frequency of cryoglobulinemia (66% vs 9%;  $p < 0.001$ ) and hypocomplementemia (66% vs 17%;  $p < 0.001$ ).

## DISCUSSION

Liver involvement was one of the first reported extraglandular manifestations of the systemic expression of SS, although new developments in the field of hepatic diseases have changed the diagnostic approach significantly. In the first studies in SS patients in the 1960s, liver involvement was evaluated by the presence of hepatomegaly, with a prevalence of 20%<sup>4</sup>. AMA were included as a marker of liver disease in SS patients in the 1970s, with later studies finding a closer association between SS and PBC than with other types of

Table 3. Analytical features of SS patients with autoimmune liver disease in comparison with patients with chronic viral infections. Data are number (%) or mean  $\pm$  SEM.

	Autoimmune Liver Disease, n = 24	Chronic Viral Disease, n = 64	Bilateral p (< 0.05)
Hematological data			
ESR (mean $\pm$ SEM)	53.71 $\pm$ 6.13	39.05 $\pm$ 3.87	0.044
Leukopenia	4 (17)	22 (34)	—
Thrombocytopenia	9 (37)	35 (55)	—
Gammaglobulins (mean $\pm$ SEM)	26.18 $\pm$ 1.78	20.25 $\pm$ 1.25	0.007
Immunological markers			
ANA	24 (100)	42 (66)	< 0.001
AMA	16 (67)	4 (6)	< 0.001
Anti-SMA	20 (83)	35 (55)	0.026
Anti-Ro/SSA	14 (58)	7 (11)	< 0.001
Anti-La/SSB	9 (38)	7 (11)	0.01
Rheumatoid factor	13 (54)	37 (58)	—
Hypocomplementemia	4 (17)	42 (66)	< 0.001
Cryoglobulinemia	2 (8)	42 (66)	< 0.001

ANA: antinuclear antibodies. AMA: antimitochondrial antibodies. Anti-SMA: antismooth muscle antibodies.



autoimmune liver disease<sup>6,7</sup>. It was not until the 1990s that the spectrum of liver disease in patients with primary SS, including the evaluation of clinical signs of liver disease, liver function, and a complete panel of autoantibodies<sup>9,10</sup>, was characterized in 2 studies, both of which identified PBC as the main liver disease. However, patients were not evaluated systematically for chronic viral liver diseases and other causes of hepatopathy.

Chronic HCV infection was the main cause of liver involvement in our patients with SS, with a prevalence of 13%, nearly 3-fold greater than that observed for autoimmune liver involvement. This underlines the importance of chronic HCV infection as a cause of liver disease in SS patients from regions, such as the Mediterranean area, with higher prevalences of HCV infection in the general population. Recent experimental<sup>21,22</sup>, virological<sup>23,24</sup>, and clinical evidence<sup>25-27</sup> has revealed a close association between HCV and SS and, in a recent large multicenter study<sup>8</sup>, SS-HCV was indistinguishable in most cases from the primary form using the most recent sets of classification criteria.

How then should this SS be classified? Current evidence suggests that chronic HCV infection should be considered an exclusion criterion for the classification of primary SS, not because it mimics primary SS, but because it seems to be directly responsible for the development of SS in a specific subset of HCV patients<sup>8</sup>. SS-HCV patients should be considered a separate subset from the primary form, and it would be more appropriate to classify these patients as having “SS associated with HCV.” The term “SS secondary to HCV” might be used in those cases in which infection of salivary gland epithelium by HCV is directly observed.

The existence of SS-HCV patients with repeated positive anti-HCV ELISA and negative HCV-RNA was an interesting finding. Four (10%) of 40 SS-HCV patients had negative HCV-RNA viremia, although their characteristics did not differ from those of patients with positive viremia. We think that this finding is probably due to the existence of patients with an undetectable amount of serum HCV-RNA and not to repeated false results of a highly-specific fourth generation anti-HCV ELISA.

Two-thirds of our patients with SS-HCV had cryoglobulinemia, which may be considered the key immunological marker of SS associated with HCV and the main cause of vasculitis in these patients. Cryoglobulins also played a predominant role in the immunological pattern of these patients, having a close association with hypocomplementemia and RF. The RF activity due to HCV-related cryoglobulinemia has additional clinical significance, as it is a criterion for the fulfillment of the 1993 European criteria for SS diagnosis. In spite of the high frequency of cryoglobulins, only 13% of our patients with SS-HCV had RP. The prevalence of RP in large series of patients with cryoglobulinemia varies widely. We found RP in only 5% of our cohort of 443 patients with cryoglobulinemia<sup>28</sup>, while Ferri, *et al*<sup>29</sup> found a prevalence of

36%, a finding that may be related to the definition of RP used in each study. However, it is interesting that we have found a higher frequency of RP in our SS-HCV patients than in our series of cryoglobulinemic patients (13% vs 5%).

The association between SS and other types of chronic viral hepatitis is very infrequent. We found only one case of chronic HBV infection in 475 patients with SS, compared with 63 patients with chronic HCV infection. Only 3 additional cases<sup>30-32</sup> of HBV-related SS have been reported (one associated with HBV vaccination), compared with more than 300 cases of HCV-related SS<sup>33</sup>. Similarly, chronic hepatitis G virus infection also plays an insignificant role in liver disease in patients with SS. This predominant etiopathogenic role of HCV is probably due to its specific lymphotropism and sialotropism<sup>21,34</sup>, which means it can infect and replicate in both circulating lymphocytes and epithelial cells from the salivary glands<sup>35</sup>.

After discarding HCV infection, PBC was the main cause of liver disease in our patients with primary SS, similar to the studies of Lindgren, *et al*<sup>9</sup> and Skopouli, *et al*<sup>10</sup>. Although historically these patients have been considered to have “secondary” SS, it seems more rational to use the term “SS associated with PBC,” because of the clinical-based evidence that SS is associated with (and not secondary to) other autoimmune diseases. SS patients with AMA-M2 showed a broad spectrum of abnormalities in the analytical liver profile, including 3 patients with no clinical or analytical data suggestive of liver disease, as has been reported in 5 previous cases<sup>9,10,36</sup>. Previous studies in non-SS patients have shown that AMA-M2 patients with any clinical or analytical sign of liver involvement have a high risk of developing symptomatic PBC<sup>37</sup>, underlining the key role of AMA-M2 as an early immunological marker of PBC<sup>38</sup>. Although there are no therapeutic guidelines for these asymptomatic patients, early use of ursodeoxycholic acid may be considered, since some studies in non-SS patients with mild analytical abnormalities have suggested that treatment with ursodeoxycholic acid might prevent a possible progression to liver cirrhosis<sup>39</sup>. For these reasons, we recommend the inclusion of AMA in the routine immunologic followup of SS patients, independently of whether the analytical liver profile is altered or not, due to the strong association between AMA and the development of PBC.

AIH was the other autoimmune liver disease found in our patients with SS, although less frequently than PBC. There are 51 reported cases of AIH in patients with primary SS (including our 8 cases) and all are type-1 AIH<sup>40</sup>. An additional characteristic of the AIH associated with primary SS is that most of the reported cases (33 out of 51, 65%) are from Japan, Korea, and China. Other autoimmune liver diseases have infrequently been described in patients with primary SS (Table 4), including 13 cases of sclerosing cholangitis, 6 cases of autoimmune cholangitis, and one case of nodular regenerative hyperplasia of the liver<sup>41</sup>.

Table 4. Main causes of liver disease in patients with SS: total number of cases reported<sup>33,40</sup>.

	No. of Cases Reported
Chronic HCV infection	325
Primary biliary cirrhosis	170
Type-1 autoimmune hepatitis	43
Primary sclerosing cholangitis	13
Autoimmune cholangitis	6
Chronic HBV infection	3
Nodular regenerative hyperplasia	1
Type-2 autoimmune chronic hepatitis	0

Detection of an altered liver profile in a patient with SS requires a sequential diagnosis. The first step is to discard processes not associated with SS, mainly the chronic use of potentially hepatotoxic drugs, steatosis, and congestive heart failure, all of which are frequently found in the elderly. The second step is to differentiate between autoimmune and viral liver disease. Evaluation of epidemiological factors may be helpful. For example, HCV infection is more frequently found in SS patients from the Mediterranean area than in those from northern Europe<sup>42</sup>. Similarly, HCV diagnosis is more frequent in older and male SS patients, while younger and female SS patients are more likely to have an associated autoimmune liver disease. The third step is the analytical liver profile, although in our study, this was not useful in differentiating between HCV- and autoimmune-related liver diseases. The fourth step is the immunological profile, which plays a key role in differentiating between the main etiologies: patients with chronic HCV infection have a higher frequency of cryoglobulins and hypocomplementemia, while those with autoimmune liver disease present hypergammaglobulinemia and autoantibodies (ANA, SMA, Ro, and La) more frequently. Of SS patients with autoimmune liver disease, the existence of AMA with a specific M2 pattern indicates PBC, while high titers of ANA and anti-SMA suggest type-1 AIH.

Chronic HCV infection was the main cause of liver involvement in our patients with SS, with a prevalence of 13%, nearly 3-fold greater than that observed for autoimmune liver involvement (PBC and type-1 AIH). No differences in the analytical liver profile or the main extraglandular SS manifestations were found when comparing the 2 types of liver involvement, with the immunological pattern being the main identifying factor in the differentiation of viral (predominance of cryoglobulins and low complement levels) and autoimmune (higher frequency of autoantibodies) liver involvement. The differential diagnosis of liver disease in patients with primary SS (viral versus autoimmune) is clinically important, since the 2 processes have a different therapeutic approach and prognosis.

## REFERENCES

1. Fox RI. Sjogren's syndrome. *Lancet* 2005;366:321-31.
2. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjogren syndrome. *Arch Intern Med* 2004;164:1275-84.
3. Ramos-Casals M, Tzioufas AG, Font J. Primary Sjogren's syndrome: new clinical and therapeutic concepts. *Ann Rheum Dis* 2005;64:347-54.
4. Bloch KJ, Buchanan WW, Wohl MJ, Bunim JJ. Sjogren's syndrome. A clinical, pathological, and serological study of sixty-two cases. *Medicine Baltimore* 1965;44:187-231.
5. Golding PL, Bown R, Mason AM, Taylor E. "Sicca complex" in liver disease. *BMJ* 1970;4:340-2.
6. Alarcon-Segovia D, Diaz-Jouanen E, Fishbein E. Features of Sjogren's syndrome in primary biliary cirrhosis. *Ann Intern Med* 1973;79:31-6.
7. Tsianos EV, Hoofnagle JH, Fox PC, et al. Sjogren's syndrome in patients with primary biliary cirrhosis. *Hepatology* 1990;11:730-4.
8. Ramos-Casals M, Loustaud-Ratti V, De Vita S, et al; SS-HCV Study Group. Sjogren syndrome associated with hepatitis C virus: a multicenter analysis of 137 cases. *Medicine Baltimore* 2005;84:81-9.
9. Lindgren S, Manthorpe R, Eriksson S. Autoimmune liver disease in patients with primary Sjogren's syndrome. *J Hepatol* 1994;20:354-8.
10. Skopouli FN, Barbatis C, Moutsopoulos HM. Liver involvement in primary Sjogren's syndrome. *Br J Rheumatol* 1994;33:745-8.
11. Vitali C, Bombardieri S, Moutsopoulos HM, et al. Preliminary criteria for the classification of Sjogren's syndrome. *Arthritis Rheum* 1993;36:340-7.
12. Ramos-Casals M, Font J, Garcia-Carrasco M, et al. Primary Sjogren syndrome: hematologic patterns of disease expression. *Medicine Baltimore* 2002;81:281-92.
13. Garcia-Carrasco M, Ramos-Casals M, Rosas J, et al. Primary Sjogren syndrome: clinical and immunologic disease patterns in a cohort of 400 patients. *Medicine Baltimore* 2002;81:270-80.
14. Ramos-Casals M, Parés A, Jara LJ, et al. Antimitochondrial antibodies in patients with chronic hepatitis C virus infection: description of 18 cases and review of the literature. *J Viral Hepat* 2005;12:648-54.
15. Doniach D. Laboratory correlations in liver diseases. In: Vyas GN, Stites DP, Brecher G, editors. *Laboratory diagnosis of immunologic disorders*. New York: Grune & Stratton; 1975:163-82.
16. Talwalkar JA, Lindor KD. Primary biliary cirrhosis. *Lancet* 2003;362:53-61.
17. Ludwig J, Dickson ER, McDonald GS. Staging of chronic non-suppurative destructive cholangitis (syndrome of primary biliary cirrhosis). *Virchows Arch* 1978;379:103-12.
18. Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol* 1999;31:929-38.
19. Czaja AJ. Frequency and nature of the variant syndromes of autoimmune liver disease. *Hepatology* 1998;28:360-5.
20. Chitturi S, George J. Hepatotoxicity of commonly used drugs: nonsteroidal antiinflammatory drugs, antihypertensives, antidiabetic agents, anticonvulsants, lipid-lowering agents, psychotropic drugs. *Semin Liver Dis* 2002;22:169-83.
21. De Vita S, Sansonno D, Dolcetti R, et al. Hepatitis C virus infection within a malignant lymphoma lesion in the course of type II mixed cryoglobulinemia. *Blood* 1995;86:1887-92.
22. Koike K, Moriya K, Ishibashi K, et al. Sialadenitis histologically resembling Sjogren syndrome in mice transgenic for hepatitis C virus envelope genes. *Proc Natl Acad Sci USA* 1997;94:233-6.
23. Arrieta JJ, Rodriguez-Inigo E, Ortiz-Movilla N, et al. In situ detection of hepatitis C virus RNA in salivary glands. *Am J Pathol* 2001;158:259-64.
24. Toussiot E, Le Huede G, Mougin C, Balblanc JC, Bettinger D,

- Wendling D. Presence of hepatitis C virus RNA in the salivary glands of patients with Sjogren's syndrome and hepatitis C virus infection. *J Rheumatol* 2002;29:2382-5.
25. Jorgensen C, Legouffe MC, Perney P, et al. Sicca syndrome associated with hepatitis C virus infection. *Arthritis Rheum* 1996;39:1166-71.
  26. Ramos-Casals M, Garcia-Carrasco M, Cervera R, et al. Hepatitis C virus infection mimicking primary Sjogren syndrome. A clinical and immunologic description of 35 cases. *Medicine Baltimore* 2001;80:1-8.
  27. De Vita S, Damato R, De Marchi G, Sacco S, Ferraccioli G. True primary Sjogren's syndrome in a subset of patients with hepatitis C infection: a model linking chronic infection to chronic sialadenitis. *Isr Med Assoc J* 2002;4:1101-5.
  28. Trejo O, Ramos-Casals M, Garcia-Carrasco M, et al. Cryoglobulinemia: study of etiologic factors and clinical and immunologic features in 443 patients from a single center. *Medicine Baltimore* 2001;80:252-62.
  29. Ferri C, Sebastiani M, Giuggioli D, et al. Mixed cryoglobulinemia: demographic, clinical, and serologic features and survival in 231 patients. *Semin Arthritis Rheum* 2004;33:355-74.
  30. Toussiot E, Lohse A, Wendling D, Mougin C. Sjogren's syndrome occurring after hepatitis B vaccination. *Arthritis Rheum* 2000;43:2139-40.
  31. Iakimtchouk K, Myrnel H, Jonsson R. Serological screening for hepatitis B and C and human herpesvirus 6 in Norwegian patients with primary Sjogren's syndrome. *J Rheumatol* 1999;26:2065-6.
  32. Aprosin ZG, Serov VV, Lopatkina TN. [The hepatitis B virus as a probable etiological factor in Sjogren's disease]. *Ter Arkh* 1993;65:73-8.
  33. Ramos-Casals M, Loustaud-Ratti V, Zeher M. [Hepatitis C virus and autoimmune diseases]. In: Ramos-Casals M, García-Carrasco M, Rosas J, Calvo J, Font J, editors. *Enfermedades autoinmunes sistémicas y reumatológicas*. Barcelona: Masson; 2005:742-58.
  34. Ramos-Casals M, Garcia-Carrasco M, Cervera R, Font J. Is hepatitis C virus a sialotropic virus? *Am J Pathol* 2001;159:1593-4.
  35. Ramos-Casals M, Font J. Extrahepatic manifestations in patients with chronic hepatitis C virus infection. *Curr Opin Rheumatol* 2005;17:447-55.
  36. Csepregi A, Szodoray P, Zeher M. Do autoantibodies predict autoimmune liver disease in primary Sjogren's syndrome? Data of 180 patients upon a 5 year follow-up. *Scand J Immunol* 2002;56:623-9.
  37. Prince MI, Chetwynd A, Craig WL, Metcalf JV, James OF. Asymptomatic primary biliary cirrhosis: clinical features, prognosis, and symptom progression in a large population based cohort. *Gut* 2004;53:865-70.
  38. Abraham S, Begum S, Isenberg D. Hepatic manifestations of autoimmune rheumatic diseases. *Ann Rheum Dis* 2004;63:123-9.
  39. Beswick DR, Klatskin G, Boyer JL. Asymptomatic primary biliary cirrhosis. A progress report on long-term follow-up and natural history. *Gastroenterology* 1985;89:267-71.
  40. Coll J, Pelusa F, Corominas JM. [Liver involvement in Sjögren's syndrome]. In: Ramos-Casals M, Garcia-Carrasco M, Anaya JM, et al, editors. *Síndrome de Sjögren*. Barcelona: Masson; 2003:225-32.
  41. Gonzalez-Alvaro I, Carmona-Ortell L, Amigo-Etxenagusia A, Castaneda Sanz S. Nodular regenerative hyperplasia of the liver and primary Sjogren's syndrome. *J Rheumatol* 1994;21:168-9.
  42. Ramos-Casals M, Jara LJ, Medina F, et al; HISPAMEC Study Group. Systemic autoimmune diseases co-existing with chronic hepatitis C virus infection (the HISPAMEC Registry): patterns of clinical and immunological expression in 180 cases. *J Intern Med* 2005;257:549-57.