

Second, 2 studies^{1,27} have demonstrated the capability of the HCV to infect and replicate in the salivary gland tissue of HCV patients with sicca syndrome/SS. Third, small clinical studies have shown that the main clinical, histologic, and immunologic features of SS are often observed in HCV patients^{12,20}. This latter point has led to HCV infection being considered an exclusion criterion for the diagnosis of primary SS in the most recent set of criteria, published in 2002 by the American-European Consensus Study Group²⁸.

Due to the scarcity of published clinical data on the association of SS with chronic HCV infection, we conducted a multicenter study with the aim of collecting a large number of patients in order to define the clinical and immunologic pattern of expression of HCV-related SS.

METHODS

In 2002, various reference centers of European and Hispanoamerican countries (see Appendix 1) with substantial experience in the management of autoimmune diseases associated with chronic HCV infection formed the SS-HCV Study Group, with the aim of creating a registry of patients with coexisting SS and chronic HCV infection. Patient selection was based on the following:

- a) Fulfillment of 4 or more of the preliminary classification criteria for SS proposed by the European Community Study Group in 1993²⁹, and
- b) 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.

A protocol form was used to record retrospectively the clinical and serologic characteristics of patients who were seen consecutively by the rheumatology, autoimmune diseases, or hepatology departments of these centers as in- or outpatients between 1994 and 2002. The mean time of follow-up between SS diagnosis and protocol inclusion was 5.6 years, ranging between 1 and 13 years. Some patients have been included in previous studies^{6,14,20,24,25,27}. Salient features included in the protocol form were the following:

- 1) Gender
- 2) Age at diagnosis of SS, defined as the age when the patient fulfilled the current criteria for the classification²⁹
- 3) Age at diagnosis of chronic HCV infection, defined as the first serologic evidence of HCV antibodies
- 4) Age at inclusion in the protocol
- 5) Sicca symptomatology (xerostomia and xerophthalmia)
- 6) Extraglandular SS manifestations, defined according to previous studies^{10,17}
- 7) Diagnostic tests for SS (ocular tests, salivary scintigraphy and/or salivary flow, salivary gland biopsy), according to the recommendations of the European Community Study Group²⁹

- 8) Liver involvement, defined as the presence of elevated liver enzymes (aspartate/alanine transaminases [AST/ALT] ≥ 40 IU/L, γ -glutamyltranspeptidase [GGT] ≥ 40 IU/L, and/or presence of cholestasis). Other data recorded were clinical signs of hepatopathy (hepatomegaly, splenomegaly, and/or jaundice), hepatic decompensation (ascites, encephalopathy, or gastrointestinal bleeding), altered abdominal ultrasound, and results of transcutaneous liver biopsies

- 9) Immunologic findings (antinuclear antibodies [ANA], rheumatoid factor [RF], anti-Ro/SS-A, anti-La/SS-B, cryoglobulins, and complement levels)

- 10) Neoplasia diagnosed after SS diagnosis, including type of neoplasia and age at diagnosis

- 11) Death (age and cause)

To minimize possible interobserver bias, the inclusion criteria and protocol variables were agreed upon by all participating physicians. Information collected by protocol forms was transferred to a computerized database program (SPSS for Windows, Chicago, IL).

Chi-square and the Fisher exact test were applied to analyze qualitative differences. When several independent variables appeared to have statistical significance in the univariate analysis, a logistic regression test was performed for the multivariate analysis to rule out possible confounding variables. For comparison of quantitative parameters, the Student t test was used in large samples of similar variance, and the nonparametric Mann-Whitney U test was used for small samples. Values of quantitative variables are expressed as mean \pm standard error of the mean (SEM). A value of $p < 0.05$ indicated statistical significance. The odds ratio was calculated to assess the risk of appearance of each variable, with a confidence interval of 95%. Statistical analysis was performed by means of the SPSS program, using the information stored in the database program.

RESULTS

General Characteristics

The clinical and laboratory features of patients are summarized in Table 1. Of the 137 patients, 104 (76%) were women and 33 (24%) were men. At entry to the study, the mean age was 65 years (range, 31–89 yr). One hundred thirty-three (97%) patients showed xerostomia, 126 (92%) xerophthalmia, and 22 (16%) parotidomegaly. Moreover, 115 of 127 (91%) patients were positive (according to European criteria) for ocular diagnostic tests (Schirmer test and/or rose Bengal staining). Parotid scintigraphy was positive in 54 of 64 (84%) patients, and salivary gland biopsy showed lymphocytic infiltrates (grade 3 or 4) in 61 of 84 (73%) patients. The main extraglandular features were articular involvement in 60 (44%) patients, cutaneous vasculitis in 27 (20%), peripheral neuropathy in 22 (16%),

TABLE 1. Clinical Features of 137 Patients With Sjögren Syndrome Associated With HCV Infection

	SS-HCV Patients (n = 137)	(%)
Xerostomia	133	97
Xerophthalmia	126	92
Ocular tests (+)	115/127	91
Parotid scintigraphy (+)	54/64	84
Salivary gland biopsy (+)	61/84	73
Raised transaminases	93	68
ANA (+)	89	65
Hypocomplementemia	68/133	51
Cryoglobulinemia	69	50
RF (+)	69	50
Articular involvement	60	44
Raised GGT	60	44
Hepatomegaly	46	34
Anti-Ro/SS-A (+)	29	21
Cutaneous vasculitis	27	20
Peripheral neuropathy	22	16
Parotidomegaly	22	16
Anti-La/SS-B (+)	22	16
Cholestasis	19	14
Thyroiditis	18	13
Raynaud phenomenon	14	10
Splenomegaly	13	10
Liver decompensation	12	9
Pulmonary fibrosis	10	7
Jaundice	6	4
Renal involvement	5	3

thyroiditis in 18 (13%), Raynaud phenomenon in 14 (10%), pulmonary fibrosis in 10 (7%), and renal involvement in 5 (3%) patients. The main immunologic features were ANA in 89 (65%) patients, hypocomplementemia in 68 of 133 (51%), cryoglobulinemia in 69 (50%), RF in 69 (50%), anti-Ro/SS-A in 29 (21%), and anti-La/SS-B in 22 (16%) patients.

Liver involvement was detected in 107 (78%) patients. The most common clinical manifestations of liver disease were hepatomegaly in 46 (34%) patients, splenomegaly in 13 (10%), and jaundice in 6 (4%) patients. Only 12 (9%) patients presented clinical manifestations of hepatic decompensation (ascites, encephalopathy, or gastrointestinal bleeding). Biochemical tests showed raised transaminases (ALT >40 IU/L and/or AST >40 IU/L) in 93 (68%) patients, raised GGT (>40 IU/L) in 60 (44%), and raised bilirubin (>1 mg/dL) or raised alkaline phosphatase (>300 IU/L) in 19 (14%). Transcutaneous liver biopsy was performed in 64 patients after informed consent. Specimens obtained showed chronic

active hepatitis with varying degrees of portal inflammation in 41 patients, parenchymal nodules with loss of normal liver structure (cirrhosis) in 18, and other findings in the remaining 5 cases.

Clinical Subsets of HCV-Related SS

Extraglandular Manifestations

Clinically, 58 (42%) patients presented only sicca symptomatology (without extraglandular features), while the remaining 79 (58%) presented a systemic process with diverse extraglandular manifestations. When we compared patients with and without extraglandular involvement, those with a sicca-limited disease presented a lower prevalence of parotidomegaly (5% vs 24%, $p = 0.004$), RF (37% vs 61%, $p = 0.009$), anti-Ro/SS-A (7% vs 32%, $p = 0.001$), anti-La/SS-B (4% vs 25%, $p = 0.001$), hypocomplementemia (34% vs 64%, $p = 0.001$), and cryoglobulinemia (35% vs 62%, $p = 0.003$) in the univariate analysis, although only parotidomegaly and hypocomplementemia were statistically significant in the multivariate analysis (Table 2).

Liver Involvement

Thirty (22%) patients had normal liver enzymes with no clinical evidence of liver involvement. Compared with patients with liver involvement, these 30 patients were predominantly female (90% vs 72%, $p = 0.034$) and had a higher prevalence of articular involvement (70% vs 36%, $p = 0.002$), anti-Ro/SS-A (47% vs 14%, $p = 0.001$), and anti-La/SS-A antibodies (40% vs 9%, $p < 0.001$), together with a lower prevalence of hypocomplementemia (28% vs 58%, $p = 0.006$) in the univariate analysis, although only articular involvement and hypocomplementemia were significant independent variables in the multivariate analysis (see Table 2).

Neoplasia

After SS diagnosis, 19 (14%) patients developed neoplasia: 8 hematologic neoplasia (non-Hodgkin lymphoma in 6 and myelocytic leukemia in 2), 6 hepatocellular carcinoma, 2 gastric adenocarcinoma, 2 epithelial oral neoplasia, 1 pulmonary oat-cell carcinoma, 1 vesical neoplasia, and 1 cervical carcinoma. Two patients developed more than 1 neoplasia. The main extraglandular manifestations were arthritis in 7 (37%) patients and vasculitis in 6 (32%). The most frequent immunologic markers were hypocomplementemia in 15 (79%) patients, RF in 13 (68%), and cryoglobulins in 11 (59%). Compared with patients without neoplasia, patients with neoplasia showed a higher frequency of hypocomplementemia (79% vs 46%, $p = 0.012$), elevated GGT (68% vs 40%, $p = 0.025$), and elevated bilirubin (32% vs 11%, $p = 0.027$), although only hypocomplementemia was a significant independent variable in the

TABLE 2. Clinical Subsets of SS Associated With HCV: Main Features According to the Presence or Absence of Extraglandular Features, Liver Involvement, and Neoplasia

Extraglandular Manifestations				
	SS-HCV With Sicca-Limited Disease (n = 58) No. (%)	SS-HCV With Extraglandular Features (n = 79) No. (%)	p Value	OR (95% CI)
Parotidomegaly	3 (5)	19 (24)	0.004*	5.81 (1.56–31.95)
RF (+)	21 (37)	48 (61)	0.009	2.73 (1.28–5.85)
Ro/SS-A (+)	4 (7)	25 (32)	0.001	6.25 (1.95–26.07)
La/SS-B (+)	2 (3)	20 (25)	0.001	9.49 (2.12–86.38)
Hypocomplementemia	14/56 (34)	49/77 (64)	0.001*	5.25 (2.31–12.19)
Cryoglobulinemia	20 (35)	49 (62)	0.003	3.10 (1.45–6.70)
Liver Involvement				
	SS-HCV Without Liver Involvement (n = 30) No. (%)	SS-HCV With Liver Involvement (n = 107) No. (%)	p Value	OR (95% CI)
Female	27 (90)	77 (72)	0.034	0.29 (0.05–1.04)
Articular involvement	21 (70)	39 (36)	0.002*	0.25 (0.09–0.63)
Anti-Ro/SS-A (+)	14 (47)	15 (14)	0.001	0.19 (0.07–0.51)
Anti-La/SS-B (+)	12 (40)	10 (9)	<0.001	0.15 (0.05–0.46)
Hypocomplementemia	8/29 (28)	60/104 (58)	0.006*	3.58 (1.36–10.16)
Neoplasia				
	SS-HCV Without Neoplasia (n = 118) No. (%)	SS-HCV With Neoplasia (n = 19) No. (%)	p Value	OR (95% CI)
Hypocomplementemia	53/114 (46)	15 (79)	0.012*	4.60 (1.34–19.97)
Elevated GGT	47 (40)	13 (68)	0.025	3.27 (1.06–11.17)
Elevated bilirubin	13 (11)	6 (32)	0.027	3.73 (0.98–12.80)

Abbreviations: OR = odds ratio; CI = confidence interval.

*Independent variables in the multivariate analysis.

multivariate analysis (see Table 2). Elevated GGT and bilirubin were predominantly observed in patients with hepatocellular carcinoma.

Fulfillment of the 2002 American-European Criteria

In 92 HCV patients all diagnostic tests included in the American-European criteria were performed. Of these patients, 78 (85%) fulfilled the more restrictive 2002 criteria²⁸, while the remaining 14 patients fulfilled only the previous 1993 criteria²⁹. No significant differences in the clinical and immunologic profiles were observed when SS-HCV patients were compared according to the criteria fulfilled.

Immunologic Subsets of HCV-Related SS

We found negative immunologic markers (ANA, RF, Ro/SS-A, and La/SS-B) in 20 (15%) patients. This immunonegative subset of SS-HCV showed no significant differences in clinical manifestations (glandular, extraglandular, or hepatic) compared with immunopositive SS-HCV patients.

Positive anti-Ro/SS-A and/or anti-La/SS-B autoantibodies were detected in 32 (23%) patients. These patients were more frequently women (91% vs 72%, $p = 0.033$) and showed a higher prevalence of parotidomegaly (28% vs 12%, $p = 0.038$), articular involvement (62% vs 38%, $p = 0.024$), and Raynaud phenomenon (22% vs 7%, $p = 0.021$), together with a lower frequency of liver involvement (50% vs 86%,

p < 0.001) in the univariate analysis, although only liver involvement was a significant independent variable in the multivariate analysis (Table 3).

We found positive RF in 69 (50%) patients. These patients showed a higher prevalence of cutaneous vasculitis (27% vs 12%, p = 0.031), hypocomplementemia (64% vs 39%, p = 0.005), and cryoglobulinemia (68% vs 32%, p < 0.001) in the univariate analysis, although only cryoglobulinemia was a significant independent variable in the multivariate analysis (see Table 3).

Cryoglobulins were detected in 69 (50%) of the SS-HCV patients. These patients showed a higher prevalence of cutaneous vasculitis (36% vs 3%, p < 0.001), hypocomplementemia (74% vs 28%, p < 0.001), elevated GGT (54% vs 33%, p = 0.016), and RF (68% vs 33%, p < 0.001) in the univariate analysis, although only cutaneous vasculitis, RF, and hypocomplementemia were significant independent variables in the multivariate analysis (see Table 3).

DISCUSSION

The association of SS with HCV has originated an intense debate in the last decade. In 1992, Haddad et al¹¹ found histologic evidence of SS (Chisholm-Mason classification grade 3 or 4) in 16 of 28 patients with chronic HCV infection. Since then more than 250 cases of SS-HCV have been reported, making SS one of the systemic autoimmune diseases most closely associated with HCV²¹. In addition, SS is the systemic autoimmune disease with the highest prevalence of chronic HCV infection, which was detected in 156 (12%) of 1309 SS patients tested by ELISA⁹.

Clinical studies have shown sicca symptomatology, positive ocular tests, lymphocytic infiltration of salivary glands, and autoantibodies in patients with HCV infection¹⁹. These findings have led to HCV infection being considered as an exclusion criterion for the diagnosis of primary SS in the 2002 American-European Criteria²⁸. In addition,

TABLE 3. Immunologic Subsets of SS Associated With HCV: Main Features According to the Presence or Absence of Anti-Ro/La Antibodies, Rheumatoid Factor, and Cryoglobulinemia

Presence of Anti-Ro/La Antibodies (ENA+)				
	SS-HCV ENA (+) (n = 32) No. (%)	SS-HCV ENA (-) (n = 105) No. (%)	p Value	OR (95% CI)
Female	29 (91)	75 (72)	0.033	3.87 (1.06–21.15)
Parotidomegaly	9 (28)	13 (12)	0.038	2.77 (0.92–7.98)
Articular involvement	20 (62)	40 (38)	0.024	2.71 (1.11–6.74)
Raynaud phenomenon	7 (22)	7 (7)	0.021	3.92 (1.05–14.29)
Liver involvement	16 (50)	90 (86)	<0.001*	0.17 (0.06–0.44)
Presence of Rheumatoid Factor				
	SS-HCV RF (+) (n = 69) No. (%)	SS-HCV RF (-) (n = 68) No. (%)	p Value	OR (95% CI)
Cutaneous vasculitis	19 (27)	8 (12)	0.031	2.85 (1.07–8.14)
Hypocomplementemia	42/66 (64)	26/67 (39)	0.005	2.76 (1.29–5.92)
Cryoglobulinemia	47 (68)	22 (32)	<0.001*	6.41 (3.02–13.72)
Presence of Cryoglobulinemia				
	SS-HCV Cryoglobulins (+) (n = 69) No. (%)	SS-HCV Cryoglobulins (-) (n = 68) No. (%)	p Value	OR (95% CI)
Cutaneous vasculitis	25 (36)	2 (3)	<0.001*	18.75 (4.24–168.23)
Hypocomplementemia	49/66 (74)	19/67 (28)	<0.001*	7.28 (3.18–16.87)
Elevated GGT	37 (54)	22 (33)	0.016	2.42 (1.14–5.14)
RF	47 (68)	22 (33)	<0.001*	4.47 (2.06–9.76)

Abbreviations: See Table 2.

*Independent variables in the multivariate analysis.

experimental studies have found evidence supporting the sialotropism of HCV. Koike et al¹³ reported the development of an SS-like exocrinopathy in transgenic mice carrying the HCV envelope genes, and Arrieta et al¹ have shown that HCV infects and replicates in epithelial cells from salivary glands of patients with SS or chronic sialadenitis, a fact also confirmed by Toussirof et al²⁷ in 3 SS-HCV patients. The reasons for this specific predilection of HCV for exocrine gland tissue are unknown.

Thus, there is epidemiologic, experimental, clinical, histologic, and virologic evidence for the existence of a SS secondary to HCV (Table 4). However, the pattern of clinical expression of SS-HCV is not well defined, as only small series have been published. It is not established whether this is a virus-induced disease mimicking primary SS or whether it is a true etiopathogenic subset of SS⁶, which falls within the multifaceted etiopathogenic spectrum of primary SS.

TABLE 4. Evidence for the Existence of a SS Secondary to HCV Infection*

EPIDEMIOLOGIC EVIDENCE

More than 250 cases of SS-HCV reported (21)
HCV infection in 156 (12%) of 1306 SS patients tested by ELISA (9)

EXPERIMENTAL EVIDENCE

Development of SS-like exocrinopathy in transgenic mice carrying the HCV envelope genes (13)

CLINICAL EVIDENCE

Xerostomia in 18% of HCV patients (19)
Xerophthalmia in 17% of HCV patients (19)
Positive ocular tests in 38% of HCV patients (19)
Positive anti-Ro/anti-La antibodies in 23% of SS-HCV patients (present report, 6)
Triple association between SS, HCV, and lymphoma (7,22,24)
Shared clinical, histologic, and molecular characteristics in SS and HCV-related lymphomagenesis (5,15)

HISTOLOGIC EVIDENCE

Positive salivary gland biopsy in 25% of HCV patients (19)
Sialadenitis histologically indistinguishable (Chisholm-Mason classification grade 3 or 4) (11,12,20)
Similar immunohistochemical characteristics of the HCV-related sialadenitis (3,16,23)

VIROLOGIC EVIDENCE

Detection of HCV-RNA of both positive and negative polarity in epithelial cells of SS-HCV patients (1)
Detection of HCV core antigen in epithelial cells of SS-HCV patients (1)
HCV infection of epithelial cells from salivary glands of SS-HCV patients (1)
Detection of HCV-RNA in salivary glands from SS-HCV patients with high HCV viremia (27)

*References in parentheses.

By analyzing the 137 SS-HCV patients in the current multicenter study, we have been able to characterize clinical aspects of this specific group of SS patients and identify different clinical and immunologic patterns of disease expression. However, the observational design of the study does not allow us to draw definite conclusions on the development of liver and neoplastic involvement, due to the recruitment of patients with different degrees of disease progression.

To evaluate the differences between SS-HCV and primary SS, we compared the current multicenter study with a large series of HCV-negative patients with primary SS¹⁰, bearing in mind the different recruitment and design of these 2 studies (Table 5). Demographically, SS-HCV is characterized by a reduced female:male ratio (3:1) and an older age at SS diagnosis. Although a similar prevalence of glandular features was found, specific extraglandular manifestations such as articular, vasculitic, and neuropathic involvement (the classic triad of the cryoglobulinemic syndrome), were more frequently observed in SS-HCV patients. This suggests that cryoglobulinemia may play a more important role in the extraglandular features observed in SS associated with HCV than it does in primary SS, although these manifestations also might be related to the underlying SS or the HCV infection itself.

In addition, a clearly differentiated immunologic profile was observed, closely associated with the existence of the virus. SS-HCV was characterized by a higher prevalence of cryoglobulinemia, RF, and hypocomplementemia. Nearly 70% of our SS-HCV patients had positive ANA, but two-thirds of these ANA-positive patients had negative Ro/La antibodies, an immunologic pattern (ANA+/ENA-) typically observed in chronic HCV infection². In fact, positive anti-Ro/SS-A antibodies have been described in only 30 (4%), and anti-La/SS-B in 27 (3%), of 765 HCV patients⁹. Although negative Ro/La has been considered a typical immunologic feature of SS associated with HCV^{12,20}, it is instructive to note the existence of a subset of 32 SS-HCV patients with positive ENA, representing 23% of our patients. The patients in this subset of SS-HCV-ENA-positive patients were predominantly female and had a higher prevalence of specific SS features and a lower frequency of liver involvement. It therefore appears that Ro/La positivity may form part of the immunologic expression of some SS-HCV patients (although at a lower level than that observed in primary SS). Of note, a higher rate of anti-Ro/La positivity has been reported when HCV-positive patients with subjective and objective sicca manifestations were more strictly selected, and anti-Ro/La positivity was investigated by means of both ELISA and immunoblot assays⁶. On the other hand, the alternative hypothesis of a casual association between a true primary SS and HCV infection should also be considered.

TABLE 5. Epidemiologic Data, Clinical and Immunologic Features, and Diagnostic SS Tests in SS-HCV Patients Compared With Patients With Primary SS

	SS-HCV* (n = 137) No. (%)	Primary SS† (n = 400) No. (%)	p Value
Female	104 (76)	373 (93)	<0.001
Mean age at SS diagnosis (yr)	58.3 + 1.17	52.7 + 0.85	<0.001
Xerostomia	133 (97)	390 (98)	–
Xerophthalmia	126 (92)	371 (93)	–
Parotidomegaly	22 (16)	73 (18)	–
Articular involvement	60 (44)	147 (37)	–
Raynaud phenomenon	14 (10)	62 (16)	–
Thyroiditis	18 (13)	61 (15)	–
Vasculitis	27 (20)	47 (12)	0.019
Lung involvement	10 (7)	37 (9)	–
Peripheral neuropathy	22 (16)	29 (7)	0.002
Renal involvement	5 (4)	25 (6)	–
Ocular tests (+)	115/127 (91)	351/371 (95)	–
Parotid scintigraphy (+)	54/64 (84)	253/328 (77)	–
Salivary gland biopsy (+)	61/84 (73)	169/228 (74)	–
ANA	89 (65)	288/392 (74)	–
RF	69 (50)	146/388 (38)	0.009
Ro/SS-A	29 (21)	153/385 (40)	<0.001
La/SS-B	22 (16)	102/385 (26)	0.014
Cryoglobulins	69 (50)	27/293 (9)	<0.001
Hypocomplementemia	68/133 (51)	35/302 (12)	<0.001

*Present report.
†Reference 10.

Immunogenetic analysis of SS-HCV-ENA-positive patients might determine whether they have a genetic substrate similar to or different from that of the Ro/La-positive patients with primary SS.

Half of our SS-HCV patients presented cryoglobulinemia, which may be considered the key immunologic marker of SS associated with HCV. Above, we noted the important contribution of cryoglobulinemia to the extraglandular features of patients with SS-HCV. Cryoglobulins also play a predominant role in the immunologic pattern of these patients, having a close association with hypocomplementemia (present in 71% of the SS-HCV-cryo patients) and RF (present in 68% of these patients). The RF activity due to HCV-related cryoglobulinemia has an additional clinical significance, being a criterion for the fulfillment of the 1993 European criteria for SS diagnosis. Another key immunologic marker of SS-HCV was hypocomplementemia, which was closely associated with the presence of not only circulating cryoglobulins, but also liver involvement and neoplasia.

Although some SS-HCV patients fulfilled all 6 European classification criteria for SS, most fulfilled only the minimum 4 criteria required. However, when the criteria proposed in 2002²⁸ were applied in the 92 patients in whom all diagnostic tests were performed, only 15% did not fulfill these more restrictive criteria, a percentage similar to that observed in the large series of primary SS patients¹⁰. The reason is the substantial number of SS-HCV patients who had 1 of the 2 mandatory 2002 criteria (positive salivary gland biopsy or anti-Ro/La antibodies). Taken together, the evidence suggests that HCV infection may account for the pathogenesis of a subgroup of patients with “primary” SS, above all patients with liver involvement or cryoglobulinemia.

The present study also found a high frequency of neoplasia in SS-HCV patients, including both lymphoproliferative malignancies (mainly related to SS, but also to HCV) and hepatocarcinoma (overwhelmingly related to HCV). HCV is a virus with a multiple tissue tropism (hepatotropism, lymphotropism, and sialotropism)¹⁸, which could explain the development of chronic active hepatitis, cryoglobulinemia, and sicca syndrome in some patients who evolve to hepatocarcinoma and lymphoproliferative diseases. We found 6 patients with SS, HCV infection, and non-Hodgkin lymphoma. The main clinical characteristics of these patients were hypocomplementemia and cryoglobulinemia, negative anti-Ro/SS-A and anti-La/SS-B antibodies, and extranodal involvement in specific sites such as the liver, ocular annexa, prostate, or ovary. We identified 21 additional cases in the literature review, most incompletely described²². Extranodal involvement was detailed in only 5 cases (parotid gland in 2, liver in 2, and stomach in 1). Taking these cases together with our cases, the most frequent sites of lymphoma involvement in SS-HCV patients were the liver and exocrine glands^{7,8}, in contrast to general series of

TABLE 6. Clinical and Immunologic Subsets of SS Associated With HCV: Comparison With Patients With Primary SS

	SS-HCV* (n = 137) No. (%)	Primary SS† (n = 400) No. (%)	p Value
Sicca-limited disease	58 (42)	139 (35)	–
Liver involvement	107 (78)	37 (9)	<0.001
Neoplasia	19 (14)	29 (7)	0.019
Fulfill 2002 criteria	78/92 (85)	253/298 (85)	–
Immunonegative patients	20 (15)	84 (23)	–
ANA+/ENA- patients	61/89 (69)	141/288 (49)	0.001
RF associated with cryoglobulins	47/69 (68)	21/103 (20)	<0.001

*Present report.
†Reference 10.

TABLE 7. Ten Characteristics Suggesting the Need for HCV Antibody Testing in Patients Diagnosed With "Primary" Sjögren Syndrome

Epidemiologic characteristics	
1.	Male gender
2.	Older age at SS diagnosis
Clinical features	
3.	Cutaneous vasculitis
4.	Peripheral neuropathy
5.	Liver involvement (clinical and/or analytical)
6.	Neoplasia (lymphoma or hepatocarcinoma)
Immunologic parameters	
7.	Cryoglobulins
8.	Rheumatoid factor
9.	Hypocomplementemia
10.	Negative Ro/La

patients with B-cell non-Hodgkin lymphoma, in whom the primary lymphoma location is rarely in these organs²⁶. Lymphomas in both SS and HCV patients share several characteristics, such as a predominance of low grade, marginal zone histologic type, the frequency of mucosal localization, a possible transformation into a large B-cell lymphoma, a close association with cryoglobulinemia, and the localization of lymphomas in organs where HCV or SS are active¹⁵. In addition, De Re et al⁵ described remarkable homologies between the antigen combinatory regions of the IgR expressed by both SS and HCV-associated lymphoproliferative diseases, which suggest an immunologic cross-reactivity or molecular mimicry among the agents that underlie these disorders.

In the current study we describe the broad clinical expression of SS associated with HCV, which includes both hepatic and extrahepatic features, specific immunologic abnormalities, and neoplastic processes. As in primary SS¹⁰, various clinical and immunologic subsets have been identified, defining more homogeneous patterns of clinical expression (Table 6). The clinical expression of SS-HCV is similar to that of primary SS with respect to the prevalence of extraglandular features and the percentage of fulfillment of the 2002 Criteria²⁸, but shows a higher percentage of patients with liver involvement and neoplastic processes. The immunologic expression of SS-HCV includes a higher presence of ANA+/ENA- patients (due to the lower presence of anti-Ro/La antibodies) and cryoglobulinemia (which also explains the higher prevalence of RF and low complement levels). In Table 7 we present the 10 epidemiologic, clinical, and immunologic criteria that should alert clinicians to the possible existence of an underlying chronic HCV infection in a patient with "primary" SS. In patients with SS associated with HCV, we propose using the term "SS secondary to HCV" in patients who fulfill the 2002 classification criteria

and the term "sicca syndrome secondary to HCV" in those who fulfill only 3 criteria or who fulfill only the 1993 European criteria.

In conclusion, chronic HCV infection should be considered an exclusion criterion for the classification of primary SS, not because it mimics primary SS, but because the virus may be implicated in the development of SS in a specific subset of patients. We propose using the term "SS secondary to HCV" in those patients with chronic HCV infection who fulfill the 2002 classification criteria for SS. Future research in primary SS should consider the identification of additional exogenous agents involved in the multifaceted etiopathogenesis of the disease.

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APPENDIX 1. THE SS-HCV STUDY GROUP

The members of the SS-HCV Study Group are listed below.

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