



WJG 20th Anniversary Special Issues (2): Hepatitis C virus

Oral manifestations of hepatitis C virus infection

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Author contributions: Carrozzo M collected the underlying material and wrote the initial draft of the manuscript; Scally K finalized and revised the manuscript; all authors have read and approved the final version of the manuscript.

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Received: October 13, 2013 Revised: January 21, 2014

Accepted: March 19, 2014

Published online: June 28, 2014

Abstract

Extrahepatic manifestations (EHMs) of hepatitis C virus (HCV) infection can affect a variety of organ systems with significant morbidity and mortality. Some of the most frequently reported EHM of HCV infection, involve the oral region predominantly or exclusively. Oral lichen planus (OLP) is a chronic inflammatory condition that is potentially malignant and represents cell-mediated reaction to a variety of extrinsic antigens, altered self-antigens, or super antigens. Robust epidemiological evidence support the link between OLP and HCV. As the virus may replicate in the oral mucosa and attract HCV-specific T lymphocytes, HCV may be implicated in OLP pathogenesis. Sjögren syndrome (SjS) is an autoimmune exocrinopathy, characterized by dryness of the mouth and eyes and a multitude of other systemic signs and symptoms. SjS patients have also an increased risk of non-Hodgkin lymphoma. Patients with chronic hepatitis C do frequently have histological signs of Sjögren-like sialadenitis with mild or even absent clinical symptoms. However, it is still unclear if HCV may cause a disease mimicking SjS or it is directly responsible for the development of SjS in a specific subset of patients. Oral squamous cell carcinoma is the

most common oral malignant tumour and at least in some part of the world could be linked to HCV.

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Key words: Hepatitis C virus; Lichen planus; Oral lichen planus; Sjogren's syndrome; Sialadenitis; Oral squamous cell carcinoma

Core tip: Hepatitis C virus can be frequently associated with potentially malignant and malignant oral diseases and could be a triggering factor of some of those disorders or at least influence their outcome. The association is very robust for oral lichen planus, while for Sjogren's syndrome it is strongly suspected and in oral squamous cell carcinoma indicated by recent large epidemiological data.

Carrozzo M, Scally K. Oral manifestations of hepatitis C virus infection. *World J Gastroenterol* 2014; 20(24): 7534-7543 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i24/7534.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i24.7534>

INTRODUCTION

Hepatitis C virus (HCV) is one of the major causes of chronic liver disease worldwide as the global estimated prevalence of HCV infection is 2.2%, representing approximately 170 million infected people worldwide. The lowest prevalence of anti-HCV antibodies (0.01%-0.1%) is in the United Kingdom and Scandinavia, whereas the highest prevalence is reported in Egypt (15%-20%) and intermediate rates (1.5%-3.5%) are found in United States, Japan, Spain and Italy^[1]. An estimated 27% of cirrhosis and 25% of hepatocellular carcinoma worldwide occur in HCV-infected patients^[2].

Extrahepatic manifestations (EHMs) of HCV infection were first reported in the early 1990s^[3] and can affect a variety of organ systems with significant morbidity and

mortality. Forty to 75% of patients with chronic HCV infection exhibit at least one clinical EHM^[3,4].

Because of the paucity of specific symptoms and signs caused by HCV, EHM could represent the first signal of this infection. Moreover, extrahepatic tissues might act as reservoir for HCV and this may have a profound effect on HCV transmission, morbidity and treatment^[5].

The association of some EHM with HCV is very close, while for others it is strongly suspected and in other cases only slightly indicated by anecdotal data^[6]. Some of the most frequently reported EHM of HCV infection, involve the oral region, predominantly or exclusively. The present review aims to report an update on these disorders.

ORAL LICHEN PLANUS

Lichen planus (LP) is an inflammatory mucocutaneous condition which most commonly affects middle-aged adults of both sexes, with a slight predominance in women^[7]. The prevalence of skin lichen planus is unknown, but it is estimated to occur in < 1% of the population. It is thought to be significantly less frequent than exclusive oral LP (OLP) that affects approximately 1%-2% of the population^[8]. Whereas in the majority of instances cutaneous lesions of LP are self-limiting and cause itching, lesions in OLP are chronic, rarely undergo spontaneous remission, are potentially malignant, rarely undergo spontaneous remission and are frequently a source of morbidity^[7,9].

A large body of evidence supports a role for immune dysregulation in the pathogenesis of LP, specifically involving the cellular arm of the immune system^[7,10]. Probably, LP is a stereotype cell-mediated reaction to a variety of extrinsic antigens, altered self-antigens, or super antigens. Among the extrinsic factors, several infective agents including some viruses and *Helicobacter pylori* have been linked with LP but apparently on the basis of equivocal data^[7]. An association between LP and HCV was first reported in 1991, whereas the first OLP cases possibly linked to HCV were published in 1994^[11,12]. Case-control studies from around the world produced seemingly contradictory evidence about the validity of the association.

Three recent independent meta-analyses^[13-15] provide robust evidence that LP and HCV are associated (Table 1). The pooled OR and 95%CI of HCV exposure in LP patients *vs* controls ranged from 2.8 (95%CI: 2.4-3.2) to 5.4 (95%CI: 3.5-8.3) mainly because of differences in statistical methods and study inclusion criteria (Table 1). A similar OR of having LP was found in HCV patients *vs* controls^[13,14]. The positive association was noted in studies across all the world but was more evident in East, Southeast Asia and South America and in Mediterranean countries^[16]. Subgroup analyses^[13,14] indicated that OLP was strongly associated with HCV (OR = 5.6, 95%CI: 3.5-8.8 and OR = 4.8, 95%CI: 3.0-7.7, respectively). The association between the isolated cutaneous type of LP and HCV was heavily skewed toward a positive association (OR = 10.2, 95%CI: 0.4-274)^[13].

The putative pathogenetic link between OLP and HCV is still under investigation but molecular mimicry between the virus and host epitopes is unlikely, as well as viral factors such as genotype or viral load^[19]. Clinically and histologically, HCV-related OLP is the same as "idiopathic" OLP^[20], however the Th1 cytokine environment sustaining the oral lesions may be due to the HCV immunologic pressure and not genetically driven, as in idiopathic OLP^[21].

Notably, HCV may replicate in the oral mucosa and may attract specific T cells. Indeed, *in situ* hybridization and extractive polymerase chain reaction (PCR) techniques revealed the presence of replicative intermediate HCV-RNA in skin and oral mucosa from patients with LP (Table 2). When high quality techniques were employed, positive and negative strands were detected by PCR in 75%-100% and 21%-100% of LP tissue specimens respectively and generally were more commonly found in OLP specimens (Table 2).

Pilli *et al*^[25] found HCV specific CD4+ and CD8+ T cells more readily in oral lesional biopsy specimens than peripheral blood in LP patients with HCV infection. CD4+ T cell clones present in the oral mucosa showed a different T-Cell Receptor-Vb chain usage than those circulating in the peripheral blood, suggesting a specific compartmentalization at the site of the OLP lesions. Contrarily, HBV-specific T cells could not be found in the oral mucosa of patients with OLP and chronic HBV infection even if they were detectable in the peripheral blood^[25]. This suggests that HCV-specific T cells among the lichen-infiltrating lymphocytes were not recruited as a result of the liver inflammation and may play a role in the pathogenesis of some OLP cases.

In conclusion, there is quite strong and convincing evidence that HCV is associated with OLP and possibly involved in its pathogenesis whereas similar evidence is not completely available for skin LP.

It would be thus prudent to at least ask OLP patients whether they have risk factors for having HCV and to screen those with significant risk with an ELISA for HCV antibodies^[16]. However, risk factors for HCV acquisition differ substantially among countries and sometimes within the same country (for example in Italy). Indeed, whereas intravenous drug use accounted for 92.5% of infections in United Kingdom, it was the cause of transmission in just 27.8% of the cases in Italy where nosocomial infections were frequent, particularly in the south^[35]. Moreover, some risk factors, for example dental procedures, seem to be peculiar to some countries like Spain, Romania and Turkey^[35].

Because there is some evidence that OLP-HCV-ve+ patients might be at higher risk of malignant transformation^[9] (see also below) and that anti-HCV treatment [particularly interferon alpha (IFN- α)] could worsen or even trigger OLP^[36,37], it could also be worthwhile to screen HCV-ve+ patients for OLP presence. Individual screening strategies may need although to be developed in different countries to identify high risk patients.

Table 1 Main summary of the recent 3 meta-analyses on lichen planus and hepatitis C virus

Ref.	Country	Period covered by search	Type of studies included	Studies included in the meta-analysis	Cases/controls	Main results	Quality assessment of the included studies		¹ Quality assessment of the systematic review process
							Tool used		
Shengyuan <i>et al</i> ^[15]	China	NA	Case control or control-existing studies	70	² 4987/65022	The prevalence of HCV exposure among patients with LP was higher than in control participants (OR = 5.4; 95%CI: 3.5-8.3)	Yes	According to Robinson <i>et al</i> ^[17]	High
			Clinical or histological LP diagnosis	58 on HCV prevalence in LP	³ 5570/139120	The risk of LP among patients with HCV was higher than compared controls (OR = 2.5; 95%CI: 2.0-3.1)			
			HCV status diagnosed by serology or PCR	12 on LP prevalence in HCV+					
Lodi <i>et al</i> ^[13]	Italy	Jan 1966-Nov 2007	Controlled studies	39	² 2544/2860	LP patients have significantly higher risk than controls of being HCV seropositive (OR = 4.85; 95%CI: 3.58-6.56)	Yes	Characteristics of the study group, appropriateness of the control group, prospective design	High
			Clinical and histological LP diagnosis	33 on HCV prevalence in LP; 6 on LP prevalence in HCV+	³ 955/1242	HCV patients have an increased risk of having LP (OR = 4.47; 95%CI: 1.84-10.86)			
Petti <i>et al</i> ^[14]	Italy	NA	Cross-sectional or case-control studies	44	NA	The overall risk for OLP among anti-HCV positive subjects was significantly higher than controls (OR = 2.8; 95%CI: 2.4-3.2)	No	NA	Uncertain
			Clinical or histological LP diagnosis. Any HCV testing			The fraction of global OLP cases associated with HCV (population attributable fraction) was 2.1% (95%CI: 1.9%-2.2%)			

Modified from Baccaglini *et al*^[16]. ¹According to PRISMA (Moher *et al*^[18]); ²LP *vs* controls; ³HCV+ *vs* HCV-; NA: Not available; LP: Lichen planus; HCV: Hepatitis C virus.

SJÖGREN-LIKE SIALADENITIS

Sjögren syndrome (SjS) is an autoimmune exocrinopathy, characterized by dryness of the mouth and eyes resulting from a chronic, progressive loss of secretory function of the salivary and lacrimal glands^[38]. SjS can cause consistent oral and dental findings: increased caries rate, mucosal dryness, soreness, increased infections (both fungal and bacterial), altered properties of saliva (thicker, opaque, or viscous secretions), and enlargement of the salivary glands^[38]. But, SjS is also associated with systemic visceral involvement, including pneumonitis, renal tubular acidosis, pancreatitis, myositis, and occasionally lymphocytic proliferation and a variety of neurological complications^[39-41]. Patients with SjS have an excess mortality caused by haematological cancer, particularly non-Hodgkin lymphomas^[42].

The pathogenesis of SjS is not completely clear but is generally considered to be a consequence of autoimmunity because of the presence of characteristic autoantibod-

ies against RNA-binding proteins Ro and La and upon the observation of inflammatory infiltrates in the affected exocrine glands^[38]. However, triggering factors are poorly understood but viral infections are highly regarded^[38].

Diagnosis of SjS can be challenging, particularly in mild cases and still the discrepancy in diagnostic criteria led to substantial confusion in research publications and clinical-trial reports^[38-43].

The first study reporting an association between salivary gland disorders and hepatitis C was published in 1992 and found that 57% of HCV-associated chronic liver disease patients exhibited characteristic SjS histological changes in the salivary glands^[44]. Subsequent studies noted that, in contrast to SjS, lymphocytic infiltration in HCV+ve patients was pericapillary rather than periductal, with no destruction of the SG ducts, and that lymphocytic capillaritis resembled an early stage of disease^[45].

Further studies^[3,4,44-56] have shown controversial results but up to 80% of HCV-infected individuals may have some salivary or lacrimal abnormality, frequently

Table 2 Hepatitis C virus detection in lichen planus lesional tissue *n* (%)

Country	Ref.	<i>n</i>	Patients HCV positive	Patients with oral lesions	Detection of HCV in specimens of lichen planus	Tissue sample	Technique	Ratio of +/- strands	Oral mucosa/skin HCV RNA	
									Genomic strand	Negative strand
Italy	Sansonno <i>et al</i> ^[22]	7	0	NA	0 (0)	Fresh	IHC	-	-	-
	Mangia <i>et al</i> ^[23]	19	19	0	0 (0)	Fresh	rTth RT-PCR	-	-	-
	Carrozzo <i>et al</i> ^[24]	12	12	12	10 (83)	Fresh	rTth RT-PCR, SA, PhA	1-64 Various	10 (83)	4 (33)
Japan	Pilli <i>et al</i> ^[25]	4	4	4	3 (75)	Fresh	rTth RT-PCR	-	3 (75)	0 (0)
	Femiano <i>et al</i> ^[26]	25	25	25	0 (0)	Unclear	RT-PCR	-	0 (0)	NA
	Nagao <i>et al</i> ^[27]	14	14	14	13 (93)	Fresh	PCR, SA	-	13 (93)	3 (21)
Spain	Kurokawa <i>et al</i> ^[28]	3	3	2	3 (100)	Fresh	rTth RT-PCR	-	3 (100)	3 (100)
	Arrieta <i>et al</i> ^[29]	23	23	23	23 (100)	paraffin-embedded	ISH	-	23 (100)	23 (100)
Turkey	Lazaro <i>et al</i> ^[30]	5	5	0	5 (100)	paraffin-embedded	ISH, IHC	-	5 (100)	5 (100)
	Erkek <i>et al</i> ^[31]	5	5	4	5 (100)	paraffin-embedded	RT-PCR	-	5 (100)	NA
United Kingdom	Roy <i>et al</i> ^[32]	27	0	27	0 (0)	NA	RT-PCR	-	0 (0)	NA
	Boyd <i>et al</i> ^[33]	27	2	NA	0 (0)	paraffin-embedded	IHC	-	-	-
United States	Harden <i>et al</i> ^[34]	4	4	1	0/0	paraffin-embedded	RT-PCR	-	0 (0)	NA
Total	OLP (%)		85		56 (66)				56	32 (58)
	LP (%)		21		7 (33)				7	6 (85)

Modified from Baccaglioni *et al*^[16]. NA: Not available; IHC: Immunohistochemistry; ISH: *In situ* hybridization; PCR: Polymerase chain reactions; rTth: Recombinant *Thermus thermophilus*; SA: Sequence analysis; PhA: Phylogenetic analysis; LP: Lichen planus; HCV: Hepatitis C virus; RT-PCR: Real-time reverse transcription-polymerase chain reaction.

represented by histological signs of mild sialadenitis. However, clinical evidence of dry mouth and mainly of dry eyes is often absent^[57,58].

Several studies seem indeed to indicate that this sialadenitis may be significantly different from that of SjS. There is no female predominance, no specific antinuclear anti-Ro and anti-La antibodies, a frequent association with the HLA-DQB1*02^[59] rather than with HLA-DR3 allele, milder histopathology (with a CD8+ rather than a CD4+ T-cell predominance), and apparently fewer clinical symptoms^[45,48,58] (Table 3). On the other hand, from 0% to 19% of patients with frank SjS can be HCV-infected, the frequency varying with the geographical region, the HCV test and the SjS diagnostic criteria used (Table 4)^[6]. The confusion about epidemiological data is enhanced by the fact that whereas the most recent American-European classification criteria for SjS the presence of HCV is considered an exclusion criterion^[83,85], the term of "SjS-secondary to HCV" has been proposed for those patients with chronic HCV infection who fulfil the same criteria^[86].

Available data on direct HCV replication of SGs are also scanty and controversial^[51,52,87-90] and two recent studies suggest that sialadenitis in patients with chronic hepatitis C is not directly related to HCV^[91,92].

An animal model of transgenic mice carrying the HCV envelope genes E1 and E2 has been constructed^[93]. The mice developed an exocrinopathy involving the SGs and lachrymal glands (LGs) in 84% of cases. Initially, pericapillary lymphocytes were found, but soon focal infiltrates of small lymphocytes appeared, closely resem-

bling sialadenitis noted in humans^[44,93]. Nests of lymphatic infiltrates were also noted in the LGs, but they occurred later and were less extensive than those found in the SGs. This mode clearly suggests a possible direct role of the viral proteins in the pathogenesis of HCV-related sialadenitis. The pathogenesis of this sialadenitis in transgenic mice is however unclear: it seems indeed unlikely to be induced by an immune reaction against ductal cells expressing viral antigens, as only one out of 20 transgenic mice showed a weak antibody reaction to E1 protein^[93].

Interestingly, human La antigen (also called SS-B) which is an RNA-binding protein of 50/52-kDa, and is a typical target of SjS-autoantibodies, plays a functional role in internal initiation of translation of the polyproteins of the HCV RNA stimulating HCV internal ribosome entry site-mediated translation^[94,95]. La protein is a potent regulator and enhancer of HCV replication^[96] and the expression of this autoantigen is significantly reduced after the administration of IFN- α in a dose-dependent manner. However, there are no studies on the role of La in HCV-related sialadenitis. Data about the effects of anti-HCV treatment on sicca symptoms are also patchy and controversial^[97,98].

In conclusion, the epidemiologic and pathogenetic role of HCV in SjS development and the characteristics distinguishing classic SjS from HCV-related sialadenitis are still controversial and further studies are clearly warranted. The virus could cause a disease mimicking primary SjS or alternatively HCV might be directly responsible for the development of SjS in a specific subset of patients. Some patients may present a triple association

Table 3 Main clinical, serological, histological, genetic differences between sialadenitis in Sjogren's syndrome and hepatitis C virus +ve patients

Variable	Sjogren's syndrome	Hepatitis C virus
Sicca symptoms	Commonly present	Usually absent or modest
Parotid swelling	Moderate to severe	Mild to moderate
Extra-glandular manifestations	Mainly pulmonary, gastrointestinal, renal, and neurologic involvement	Mainly gastrointestinal and musculo-skeletal involvement
Histology	Periductal lymphocytic infiltration	Pericapillary lymphocytic infiltration
Infiltrating lymphocytic phenotype	Predominantly CD4 ⁺ T cells	Mixed CD4 ⁺ /CD8 ⁺ T cells
Autoantibodies	High-frequency RF, ANA, anti-Ro/SSA and anti-La/SSB, alpha-fodrin antibodies	High frequency of RF, ANA, alpha-fodrin, low prevalence of anti-Ro/SSA and anti-La/SSB antibodies, high frequency of cryoglobulins
HLA association	B8, DR2 and DR3	DQB1*02
Lymphomagenesis	Preferentially affecting salivary glands	Affecting both liver and salivary glands

Modified from Vitali^[60]. Sicca symptoms: Dry eyes/dry mouth. ANA: Antinuclear antibodies; RF: Rheumatoid factor; HLA: Human leukocyte antigen.

between HCV, SjS-like sialadenitis and salivary glands lymphoma and the virus may be involved in the lymphomagenesis^[99].

ORAL SQUAMOUS CELL CARCINOMA

Oral cavity cancer comprises of 2% to 3% of all malignancies and oral squamous cell carcinoma (OSCC) is the most common type of oral malignant tumours^[100]. The identified risk factors of OSCC include tobacco use, alcohol consumption, chewing of betel leaves and areca nuts, low socioeconomic status^[100]. Also viruses are supposed to potentially be involved in oral carcinogenesis^[100,101].

Six human viruses have been considered by the International Agency for Research on Cancer as being carcinogenic based on sufficient evidence supporting their etiologic association with human cancers: they are Epstein-Barr virus, HBV, several types of human papilloma virus (HPV), human T-cell lymphotropic virus type 1, HCV, and Kaposi's sarcoma-associated herpesvirus^[102].

Oral verrucous and squamous cell carcinomas have been reported in HCV-infected patients with or without OLP^[9,103-109], although the epidemiological relevance of this observation is unclear and HCV is a common cause of liver cirrhosis, which may itself represent an independent risk factor for the development of oral cancer^[110].

Apart from OLP, HCV prevalence is generally not increased in patients with other potentially malignant oral lesions such as leukoplakia or dysplasia^[111-113].

A study conducted at a veterans administration medical centre in New Orleans reported that 21.2% of 99 patients with squamous cell carcinoma of the head and neck were co-infected with HCV, which was significantly higher than previously published data (9.9%) ($P = 0.004$)^[114]. Contrarily, in another study from Japan assessing the prevalence of HCV in 4402 patients requiring oral surgery, HCV antibody was more prevalent in patients with oral cavity cancer than in those with impacted teeth (OR = 2.433; $P = 0.05$), but this difference was reversed after age adjustment (OR = 0.443; $P = 0.05$)^[115].

Recently, a nationwide, population-based, cohort

study from Taiwan reported that the incidence of oral cavity cancers was 2.28-fold higher among patients with HCV alone than non-viral hepatitis group (6.15 *vs* 2.69 per 10000 person-years). After adjusting for socio-demographic factors, HCV alone was significantly associated with an increased risk for oral cavity cancer (HR = 1.90, 95%CI: 1.20-3.02). This positive association was highest among individuals in the 40-49-year age group (HR = 2.57, 95%CI: 1.21-5.46)^[116].

Despite some potentials limitations, this study strongly suggests that, at least amongst Chinese ethnicity, HCV could represent a etiologic agent of OSCC and further perspective cohort studies are certainly warranted.

Notably, both positive and negative HCV-RNA strands were detected in oral cancer tissues^[103], but further data are required for these preliminary observations to be confirmed.

In conclusion, HCV might be involved in oral carcinogenesis and more studies are needed to clarify this association.

OTHER DISEASES

Other disorders commonly causing oral lesions such as paraneoplastic pemphigus and pemphigus vulgaris and Behcet's disease have been only anecdotally linked to HCV^[117-125].

CONCLUSION

At least three of the most studied EHM of HCV infection, involve the oral region predominantly or exclusively. Convincing epidemiological evidence support the association between OLP and HCV. As HCV may replicate in the oral mucosa and attract virus-specific T lymphocytes, it may be implicated in OLP pathogenesis. Conversely, the epidemiologic and pathogenetic role of HCV in SjS development and the characteristics distinguishing classic SjS from HCV-related sialadenitis are still controversial. Emerging recent data highlight a possible link between OSCC and HCV and further studies are clearly warranted.

Table 4 Prevalence of hepatitis C virus infection in patients with Sjögren's syndrome

Country	Ref.	n	SjS Diagnostic Criteria	HCVve+ (%)
France	de Bandt ^[61]	20	NA	10
	Loustaud-Ratti <i>et al</i> ^[56]	26	NA	8
	Mariette <i>et al</i> ^[62]	20	¹ Fox I	10
	Barrier <i>et al</i> ^[63]	22	NA	9
	Vidal <i>et al</i> ^[64]	28	¹ Fox I	14
	Wattiaux <i>et al</i> ^[65]	109	European	3
	Boscagli <i>et al</i> ^[50]	23	NA	5
	Jorgensen <i>et al</i> ^[66]	62	European	19
	Potthoff <i>et al</i> ^[67]	73	² AECG	18
	Greece	Vitali <i>et al</i> ^[68]	22	Vitali
Hungary	Szodoray <i>et al</i> ^[69]	213	European	6
India	Wanchu <i>et al</i> ^[70]	23	European	4.4
Italy	Aceti <i>et al</i> ^[71]	26	¹ Fox I	0
	Vitali <i>et al</i> ^[68]	44	Vitali	5
	Frisoni <i>et al</i> ^[72]	26	NA	4
	Ceribelli <i>et al</i> ^[73]	305	² AECG	3
	Japan	Masaki <i>et al</i> ^[74]	98	NA
Spain	García-Carrasco <i>et al</i> ^[75]	90	European	14
	Coll <i>et al</i> ^[76]	31	European	10
	Fernandez-Campillo <i>et al</i> ^[77]	26	European	19
	Selva-O'Callaghan <i>et al</i> ^[78]	98	European	7
	Sweden	Verbaan <i>et al</i> ^[52]	53	Copenhagen
United Kingdom	Porter <i>et al</i> ^[79]	18	European	0
United States	King <i>et al</i> ^[80]	44	NA	0
United States	Marrone <i>et al</i> ^[81]	100	³ Fox II	1

Modified from Carrozzo^[61], ¹Fox *et al*^[82]. In contrast to the Fox (San Diego) classification system, the European-proposed (including Vitali and Copenhagen) criteria can be fulfilled without a requirement for histologic or serologic abnormality; ²American-European Consensus Guidelines (AECG) (Vitali *et al*^[83]): in this classification the presence of HCV is considered an exclusion criterion for SjS; ³Fox and Saito^[84]. The last Fox classification excludes patients with a history of pre-existing diseases such as hepatitis C, lymphoma, sarcoidosis, or other causes of lymphocytic infiltrative disease. SjS: Sjögren's syndrome; HCV: Hepatitis C virus; NA: Not available.

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