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HOT TOPIC

Oral diseases associated with hepatitis C virus infection. Part 1: sialadenitis and salivary glands lymphoma

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Morbidity associated with hepatitis C virus (HCV) infection is due not only to the sequelae of chronic liver disease, but also to a variety of extraheaptic manifestations (EHM). Some of the most frequently reported EHM of HCV infection involves the oral region predominantly or exclusively and they are the topics of this 2-part review. The current part I discusses the evidences on the association of salivary glands disorders with HCV. HCV-infected patients may frequently have histological signs of Sjögren-like sialadenitis with mild or even absent clinical symptoms. However, the pathogenetic role of HCV in Sjogren Syndrome (SS) development and the characteristics distinguishing classic SS from HCV-related sialadenitis are still an issue. It is unclear if the virus may cause a disease mimicking primary SS or if HCV is directly responsible for the development of SS in a specific subset of patients. Notably, some patients may present a triple association between HCV, SS-like sialadenitis and salivary gland lymphoma and the virus may be involved in the lymphomagenesis. The risk of having a salivary gland lymphoma is particularly high in patients with mixed cryoglobulinemia. Little attention has been paid to the effects of anti-HCV treatment on sialadenitis or lymphoma development.
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Introduction

Hepatitis C virus (HCV) is an enveloped, RNA virus that was isolated in 1989 from a chimpanzee chronically infected by contamination with a human factor VIII concentrate (Choo *et al*, 1989). The virus genome is a linear, single-stranded RNA of ~9600 nucleotides, which contains a single open reading frame (ORF) encoding a polyprotein precursor of about 3000 amino acids (Major and Feinstone, 1997). The ORF is processed into structural (core, E1 and E2) and non-structural proteins (NS2, NS3, NS4a, NS4b, NS5a and NS5b) (Duibuisson, 2007). As HCV genome functions as a messenger RNA for its polyprotein translation, it is also referred to as the positive-strand RNA. The replication of HCV RNA is believed to occur in the cytoplasm, via its transcription into a complementary, genomic-length RNA, alternatively known as negative-strand HCV RNA. Moreover, during the replicative process the double-stranded 'replicative form' form (consisting of the fully base-paired genomic- and negative-strand viral RNA's) and NS proteins are synthesized. Thus, while the mere detection of positive-strand HCV RNA does not definitively prove replication, the most important indicator of HCV genomic replication within a given tissue is the production of negative strand HCV-RNA (Negro *et al*, 1999; Blackard *et al*, 2006). HCV has an extremely variable genome with six distinct genotypes and multiple subtypes that have been identified (Le Guillou-Guillemette *et al*, 2007). Furthermore, sequence variants forming a *quasi*-species may circulate within an individual, possibly as a consequence of ongoing immune surveillance and viral mutations (Toyoda *et al*, 1998). HCV is one of the major causes of chronic liver disease worldwide. The overall estimated prevalence of HCV infection is 2.2%, representing approximately 130 million infected people worldwide (Alter, 2007). The lowest prevalence of anti-HCV antibodies (0.01–0.1%) has been reported in the UK and Scandinavia, whilst the highest HCV prevalence has been reported in Egypt (15–20%) (Alter, 2007). Interestingly, different countries, including the US, Spain, Italy and Japan, belonging to regions of the world with similar overall average prevalences of HCV infection (1.0–1.9%), have different patterns of age-specific prevalence. In the United States, prevalence is highest among persons 30–49 years old whereas in Spain, Italy and Japan persons >50 years old account for most

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infections (Alter, 2007). An estimated 27% of cirrhosis and 25% of hepatocellular carcinoma worldwide occur in HCV-infected patients (Perz *et al*, 2006).

Morbidity associated with HCV infection is due not only to the sequelae of chronic liver disease, but also to a variety of extraheaptic manifestations (EHM) (Table 1). Up to 74% of the HCV-infected patients might develop at least one EHM during the course of the infection (Cacoub *et al*, 1999, 2000). Because of the paucity of specific symptoms and signs caused by HCV, EHM could represent the first signal of this infection. Moreover, the extraheaptic tissues might act as reservoir for HCV and this may have a profound effect on HCV transmission, morbidity and treatment (Blackard *et al*, 2006). One approach used to study the pathogenesis of HCV-EHM is to follow its replicative pattern in infected tissue and to establish anatomo-clinical correlations. A series of extraheaptic cell types possibly supporting HCV replication has been proposed, including peripheral blood mononuclear cells, pancreas, thyroid, adrenal gland, kidney, lung, spleen, gastric, brain, oral mucosa, and skin cells (De Vita *et al*, 2000; Laskus *et al*, 2000; Nagao *et al*, 2000). Nonetheless, laboratory confirmation of extraheaptic HCV replication is complicated by technical challenges and by the lack of *in vitro* system to investigate non-hepatic replication. 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 (Table 1). Some of the most frequently reported EHM of HCV infection, involve the oral region predominantly or exclusively. Some reviews on non-hepatic diseases associated with HCV infection, focused on its oral manifestations, are available (Lodi and Porter, 1997; Roy and Bagg, 1999; Carrozzo and Gandolfo,2003; Chainani-Wu *et al*, 2004; Nagao and Sata, 2004). This current 2-part review focuses on sialadenitis and salivary gland (SG) lymphomas (Part 1) and on lichen planus and other oral diseases possibly associated with HCV infection (Part 2). Related issues as the possible transmission of HCV by saliva (see Ferreiro *et al*, 2005 for a comprehensive review) and the influence of HIV-coinfection on oral manifestations of HCV are beyond the aims of this review and are not addressed.

Sjögren-like Sialadenitis

Cryoglobulins are abnormal proteins that precipitate as serum is cooled below core body temperature and resolubilize when rewarmed (Dammacco *et al*, 2001). They are detectable in up to 60% of HCV-infected patients (Saadoun *et al*, 2007). Given the strong association between HCV infection and essential mixed cryoglobulinemia (MC) (Ferri *et al*, 1991) and the high prevalence of idiopathic Sjogren syndrome (SS) in essential MC, an association between HCV infection and the SS has been postulated (Gumber and Chopra, 1995). In 1992 a French study found that 57% of HCV-associated chronic liver disease patients exhibited a

Table 1 Classification of extrahepatic manifestations of hepatitis C virus infection (modified from Zignego *et al*, 2007)

A: Association defined on the basis of high prevalence and pathogenesis	*B: Associations defined on the basis of higher prevalences than in controls*	*C: Associations to be confirmed/characterised*	*D: Anedoctal observations*
Mixed cryglubulinemia	B-cell non-Hodgkin lymphoma	Autoimmune thyroiditis	Psoriasis
	Monoclonal gammopathies	Thyroid cancer	Peripheral/central neuropathies
	Porphyria cutanea tarda	Sialadenitis (Sjogren-like)	Chronic polyarthritis
	Lichen planus	Alveolitis-lung fibrosis	Rheumatoid arthritis
		Diabetes mellitus	Polyartheritis nodosa
		Non-cryoglobulinaemic nephropathies	Bechet's syndrome
		Aortic atherosclerosis	Poly/dermatomyositis
			Fibromyalgia
			Chronic urticaria
			Chronic pruritus
			Kaposi's pseudo-sarcoma
			Vitiligo
			Cardiomyopathies
			Mooren corneal ulcer
			Erectile dysfunctions
			Necrolytic acral erythema
			Erythema multiforme
			Eythema nodosum
			Malakoplakia
			Still's disease
			Unilateral nevoid telangectasia
			Disseminated superficial porokeratosis
			Acquired epidermolysis bullosa
			Pulmonary fibrosis
			CRST (calcinosis cutis, Raynaud's phenomenon, sclerodactyly, and telangiectasia) syndrome
			Antiphospholipide syndrome
			Oral carcinoma

grade 3 or 4 sialadenitis [according to Chisholm and Mason's classification, (Chisholm and Mason, 1968; Haddad *et al*, 1992)]. A subsequent study noted that, in contrast to SS, lymphocytic infiltration in HCV-infected patients was pericapillary rather than periductal, with no destruction of the SG ducts, and that lymphocytic capillaritis resembled an early stage of disease (Pawlotsky *et al*, 1994a). Further data (Almasio *et al*, 1992; Haddad *et al*, 1992; Guisset *et al*, 1993; Pawlotsky *et al*, 1994a; Pirisi *et al*, 1994; Poet *et al*, 1994; Boscagli *et al*, 1996; Taliani *et al*, 1997; Cacoub *et al*, 1999, 2000; Verbaan *et al*, 1999; Coates *et al*, 2000; Ferreiro *et al*, 2001; Henderson *et al*, 2001; Loustaud-Ratti *et al*, 2001) have shown that up to 80% of HCV-infected individuals may have some salivary or lacrimal abnormality, frequently represented by histological signs of mild sialadenitis (Tables 2–3). However, clinical evidence of dry mouth and mainly of dry eyes is often absent (Table 3). Several studies seem indeed to indicate that this sialadenitis may be significantly different from that of SS. There is no female predominance, no specific antinuclear [SS-A (anti-RO) and SS-B (anti-LA)] antibodies, a frequent association with the HLA-DQB1*02 (Smyth *et al*, 2007) rather than with HLA-DR3 allele, milder histopathology (with a CD8+ rather than a CD4+ T-cell predominance), and apparently fewer clinical symptoms (Pawlotsky *et al*, 1994a; Pirisi *et al*, 1994; Scott *et al*, 1997). Moreover, whereas in primary SS there is a predominantly Th1 response, in HCV-associated sialadenitis, the pattern of circulating cytokines indicates a Th2 response (Ramos-Casals *et al*, 2002). HCV may be present in the saliva of 83% of patients with HCV-associated sialadenitis (Jorgensen *et al*, 1996) and is also detectable in tears in concentrations higher than serum (Feucht *et al*, 1994). In contrast, from 0% to 19% of patients with frank SS can be HCV-infected, the frequency varying with the geographical region, the HCV test used, and the inclusion criteria. (Marson *et al*, 1991; Vitali *et al*, 1992; King *et al*, 1994; Marrone *et al*, 1995; Porter *et al*, 1996; Roy and Bagg, 1999; Fox *et al*, 2000; Ramos-Casals *et al*, 2001). Indeed, several authors have reported prevalence of HCV antibodies in SS primary patients ranging from 3% to 75% using second-generation immunoenzymatic (ELISA) tests, from 14% to 19% using third-generation ELISA, and from 5% to 19% using second-generation confirmatory immunoblot assay (RIBA) (Ramos-Casals *et al*, 2001). Moreover, false-positive ELISA HCV tests have been reported when hypergammaglobulinemia (frequently observed in SS) is present (Marson *et al*, 1991; Vitali *et al*, 1992), and thus confirmatory tests are clearly recommended so that bias can be avoided. The problem of the diagnostic criteria used has been highlighted by Loustaud-Ratti *et al* (2001), who reported that the prevalence of SS in a cohort of 45 French HCV-infected patients increased from 8% to 38% according to the Fox and the 1996 European criteria, respectively. In the recently reported American-European classification criteria for SS the presence of HCV is considered an exclusion criterion (von Bultzingslowen *et al*, 2007). However, the pattern of clinical expression of HCV-related sialadenitis is still not well-defined (Carrozzo, 2001) and the term of 'SS-secondary to HCV' has been proposed for those patients with chronic HCV infection who fulfil the 2002 Classification Criteria for SS (Ramos-Casals *et al*, 2005). However, recent epidemiological studies report conflicting results. An extremely large retrospective case-control USA study in 2002 found no significant difference in the prevalence of SS between 32.204 HCV-infected patient and 136.816 randomly chosen controls whereas it found a strong association between HCV infection and lichen planus, porphyria cutanea tarda, cryoglobulimenia and non-Hodgkin lymphoma (El-Serag *et al*, 2002). Similarly, two other studies from dental units found no significant hyposalivation and increased xerostomia in HCV infected patients compared to healthy controls and hepatitis B virus (HBV) infected patients (Ferreiro *et al*, 2001; Ubertalli Ape *et al*, 2006). Contrarily, a Japanese study (Nagao *et al*, 2003) found a significantly higher prevalence of SS in patients with chronic HCV infection compared to patients with chronic HBV infection

Table 2 Prevalence of hepatitis C virus (HCV) infection in patients with Sjögren's syndrome (SS)

Country	*Reference*	*n*	*SS diagnostic criteria*	*HCVve+[a](%)*
France	de Bandt, 1992	20	NA	10
	Loustaud-Ratti *et al*, 1992	26	NA	8
	Mariette *et al*, 1993	20	Fox I[b]	10
	Barrier *et al*, 1993	22	Na	9
	Vidal *et al*, 1994	28	Fox I[b]	14[c]
	Wattiaux *et al*, 1995	109	European	3
	Boscagli *et al*, 1996	23	NA	5[c]
	Jorgensen *et al*, 1996	62	European	19
Greece	Vitali *et al*, 1992	22	Vitali	5
Hungary	Szodoray *et al*, 2001	213	European	6
India	Wanchu *et al*, 2003	23	European	4.4[c]
Italy	Aceti *et al*, 1992	26	Fox I[b]	0
	Vitali *et al*, 1992	44	Vitali	5
	Frisoni *et al*, 1994	26	NA	4
Japan	Masaki and Hayashi, 1995	98	NA	11[c]
Spain	Garcia-Carrasco *et al*, 1999	90	European	14
	Coll *et al*, 1997	31	European	10
	Fernandez-Campillo *et al*, 1997	26	European	19[c]
	Selva-O'Callaghan *et al*, 1999	98	European	7[c]
Sweden	Verbaan *et al*, 1999	53	Copenhagen	2
UK	Porter *et al*, 1996	18	European	0[c]
USA	King *et al*, 1994	44	NA	0
USA	Marrone *et al*, 1995	100	Fox II[d]	1

NA, Not available.
[a]RIBA confirmed.
[b]Fox *et al* (1986). 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.
[c]ELISA only.
[d]Fox and Saito (1994). 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.

Table 3 Lacrimal or salivary abnormality in patients with hepatitis C virus (HCV) infection (modified from Carrozzo and Gandolfo, 2003)

Country	*Reference*	*n*	*Xerostomia (%)*	*Hyposalivation (%)*	*Histological evidence of sialadenitis (%)*	*Lacrimal disturbs (%)*
Australia	Coates *et al*, 2000	87	18.4	50[a]	–	–
France	Haddad *et al*, 1992	28	35.7	–	100	10.3[b]
	Guisset *et al*, 1993	50	–	–	–	50[c]
	Pawlotsky *et al*, 1994a	61	–	–	49	26[b]
	Poet *et al*, 1994	22	0	–	20	–
	Boscagli *et al*, 1996	23	30.7	13.4[d]	60.8	–
	Cacoub *et al*, 1999	1614	11	–	–	11[e]
	Cacoub *et al*, 2000	321	12	–	–	12[e]
	Loustaud-Ratti *et al*, 2001	45	62	–	80	31[e]
Italy	Almasio *et al*, 1992	22	–	–	–	14[b,f]
	Pirisi *et al*, 1994	32	0	–	77	0[b]
	Taliani *et al*, 1997	20	5	–	0	–
	Salaffi *et al*, 1997	36	0	–	47.2%	0[g]
	Ubertalli Ape *et al*, 2006	51	50.9	60.4	–	45.3[e] 30.2 [b]
Japan	Nagao *et al*, 2003	81	27.2	23.4	NA	13.6[e] 24.7[h]
Spain	Ferreiro *et al*, 2001	74	8	16.6[i]	–	–
Sweden	Verbaan *et al*, 1999	21	5	33[d]	11	57[b]
UK	Henderson *et al*, 2001	40	8	NA[l]	–	–

NA, Not available.
[a]Unstimulated and stimulated whole sialometry.
[b]Positive Schirmer test.
[c]Detail of the test used not available.
[d]Unstimulated whole sialometry.
[e]Xerophthalmia.
[f]45% of the patients had not further defined 'lacrimal dysfunctions'.
[g]No evidence of xerophthalmia.
[h]Decreased tear secretion.
[i]Percentage of patients with hyposalivation measured by mean of the Salivette system not available; however, the salivary flow rates in HCV + ve patients were significantly lower than those in healthy controls.
[l]Stimulated whole sialometry; not significantly altered compared with healthy controls.

(25.9% *vs* 3.4%, respectively). However, the HCV group was significantly older of the HBV one and the Authors used the old European criteria, (Vitali *et al*, 1996) probably overestimating the number of patients with SS. There are also scanty and controversial data about the eventual effect of hyposalivation on oral health of HCV-infected patients. Whereas a UK study (Henderson *et al*, 2001), mainly including intravenous drug users, suggested that patients with chronic HCV infection may have significant oral health needs, a more recent Italian study found no significant differences in oral health between patients with chronic HCV and HBV infection (Ubertalli *et al*, 2006).

Pathogenesis of HCV-related sialadenitis

Viral factors such as genotype or viral load are not apparently related to the onset of sialadenitis (Pawlotsky *et al*, 1994b; Loustaud-Ratti *et al*, 2001) even if it has been reported that patients with HCV-RNA in the saliva are more likely to complain of xerostomia (Roy *et al*, 1998). However, the whole salivary flow is not associated with the presence of the virus in the saliva (Ferreiro *et al*, 2001). HCV is uncommon in SS patients without MC (King *et al*, 1994; Verbaan *et al*, 1999). Nevertheless, not all the HCV-positive patients with evidence of SG abnormalities have detectable serum cryoglobulinemia (Pawlotsky *et al*, 1994a; Loustaud-Ratti *et al*, 2001). HCV is distantly related to flaviviruses (Houghton *et al*, 1991), which are able to infect the SGs of their arthropod vector. Unfortunately, the available data on direct HCV replication of SGs are still scanty and controversial. HCV antigens have been immunohistochemically detected in SG epithelial cells (De Vita *et al*, 1995) but not invariably (Verbaan *et al*, 1999). Whereas SGs of patients with chronic HCV infection but without clinical and histological signs of sialadenitis were not infected (Taliani *et al*, 1997), positive- and negative-strand HCV-RNA has been detected in minor SGs of patients with sialadenitis and chronic hepatitis C by PCR and *in situ* hybridization (Takamatsu *et al*, 1992; Biasi *et al*, 1995; Arrieta *et al*, 2001). In particular, HCV seems to infect and replicate in epithelial cells of the SG acini. However, there is no correlation between the percentage of infected SG epithelial cells and the serum HCV-RNA titre, and the infected cells did not show any differences with respect to unaffected ones (Arrieta *et al*, 2001). A more recent study using *in situ* hybridization, western blot and immunohistochemistry reports negative results (Ohoka *et al*, 2003). An animal model of transgenic mice carrying the HCV envelope genes E1 and E2 has been constructed (Koike *et al*, 1997). 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 resembling the Chisholm and Mason grade 3 or 4 sialadenitis noted in humans (Haddad *et al*, 1992). 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 model clearly suggests a direct role of the viral proteins in the pathogenesis of HCV-related sialadenitis. Moreover, because lymphocytic capillaritis preceded sialadenitis, this may reflect the pathological sequence in Sjögren-like sialadenitis occurring in human patients. The model also predicts that xerophthalmia, would be a late development. The pathogenesis of this sialadenitis in transgenic mice is unclear, but it seems 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. Alternative explanations include the induction of interferon-γ or interleukin 2 by HCV proteins or the induction of an immunological disturbance by the transgene. Human La antigen (also called SS-B) is an RNA-binding protein of 50/52-kDa, which is predominantly localized within the nucleus. Anti-La autoantibodies are characteristically detected in SS patients although the implication of these autoantibodies in disease pathogenesis is still unclear. Nearly 70% of SS–HCV patients had positive antinuclear antibodies (ANA) but two-thirds of these ANA+ patients had negative Ro/La antibodies (Cacoub *et al*, 2000). Of note, a higher rate of anti-Ro/La positivity has been recently reported when HCV+ patients with subjective and objective sicca manifestations were more strictly selected and anti-Ro/La+ were investigated by means of both ELISA and immunoblot assays (De Vita *et al*, 2002). Interestingly, it has been shown that La protein specifically interacts with both the 5′- and 3′-UTR of HCV RNA (Spangberg *et al*, 2001). La protein plays a functional role in internal initiation of translation of the polyproteins of the HCV RNA stimulating HCV internal ribosome entry site-mediated translation (Ali and Siddiqui, 1997; Ali *et al*, 2000). La protein is a potent regulator and enhancer of HCV replication (Honda *et al*, 2005) and the expression of this autoantigen is significantly reduced after the administration of interferon-α (IFN-α) in a dose-dependent manner. However, there are no studies on the role of La in HCV-related sialadenitis. The possible presence of a common epitope between the HCV-E2 protein and an antigenic protein in the SGs has been suggested (Ohoka *et al*, 2003) but not substantiated further. On the other hand, Cacoub *et al* (2002) did not observed frank improvement in patients with sicca syndrome under anti-HCV antiviral course, even after sustained virological response and in an other small study more than 50% of the patients with sicca-syndrome and HCV develop severe immune-complication under IFN-α treatment (Doffoel-Hantz *et al*, 2005). Sicca syndrome was improved only in patients treated with IFN-α and ribavirin but it is unclear if this improvement was due to HCV eradication or ribavirin treatment (Doffoel-Hantz *et al*, 2005).

Salivary gland lymphoma

B-cell non-Hodgkin's lymphoma (NHL) is a complication of both SS and chronic HCV infection (Ferri *et al*, 1994; Luppi *et al*, 1996; Zuckerman *et al*, 1997; Ascoli *et al*, 1998). In a recent meta-analysis, the pooled relative risk (RR) of all NHL among HCV-positive individuals was 2.5 (95% CI, 2.1–3.0), but substantial heterogeneity was found between studies and by study design. The strongest source of heterogeneity seemed to be the prevalence of HCV among NHL-free study subjects. RRs were consistently increased for all major B cells-NHL subtypes, T cells-NHL, and primary sites of NHL presentation (Dal Maso and Franceschi, 2006). Cases of primary SG lymphoma in patients with HCV infection have been reported (De Vita *et al*, 1995; Luppi *et al*, 1996; Ascoli *et al*, 1998; Ambrosetti *et al*, 2004; Ramos-Casals *et al*, 2007), mainly associated with type II cryoglobulinemia or SS. Most of the cases involved a single SG, usually the parotid, but very rarely also the submandibular and even minor SGs were affected (Ambrosetti *et al*, 2004). Clinically, these patients may present with frequent parotid enlargement and cryoglublins-related vasculitis (Ramos-Casals *et al*, 2007). Lymphomas occurring in SS and HCV infection share several characteristics, such as predominance of low-grade, marginal zone histological type, frequency of mucosal localization (mucosa-associated lymphoid tissue [MALT] lymphomas), possible transformation into a large B-cell lymphoma, association with asymptomatic low-level cryoglobulinemia (De Vita *et al*, 1997; Mariette, 2001). In a recent Italian multicentre study, the estimated risk for lymphoproliferative disorders was found to be 35 times higher in patients with MC than in the general population (Monti *et al*, 2005). It has been proposed that, in both diseases, the first event of lymphomagenesis may be chronic stimulation of polyclonal B-cells capable of secreting rheumatoid factor (RF) at the site of the disease (De Vita *et al*, 1997; Mariette, 2001). In primary SS, lymphoma seems to be triggered by RF-secreting B cells closely associated with the 17109 and G-6 idiotypes (Tzioufas, 1996), while in HCV-infected patients, a possible association with an antibody response to the protein E2 of HCV has been suggested (Starkebaum and Sasso, 2004). A predictive value of RF for lymphoma developing in patients with chronic HCV has been postulated but not demonstrated (Ramos-Casals *et al*, 2007). The effectiveness of IFN-α in inducing clinical remission of a MALT lymphoma of both parotid and submandibolar SGs in a SS-HCV patient has been reported (Caramaschi *et al*, 1999). However, there are scanty available data on the effect of anti-viral treatment in patients with HCV-related SS who developed a SG-lymphoma.

Conclusions

The pathogenetic role of HCV in SS development and the characteristics distinguishing classic SS from HCV-related sialadenitis are still an issue. It is unclear if the virus may cause a disease mimicking primary SS or if HCV is directly responsible for the development of SS

in a specific subset of patients. Notably, some patients may present a triple association between HCV, SS-like sialadenitis and SG lymphoma and the virus may be involved in the lymphomagenesis. The risk of having a NHL is particularly high in patients with MC. Little attention has been paid to the effects of anti-HCV treatment on sialadenitis or lymphoma development and specific trials are clearly warranted. The recent development of new experimental animal models and effective cell culture system (Duverlie and Wychowski, 2007) for HCV should enable to achieve a broad number of applied studies on HCV pathogenesis including further insight on the possible sialotropism of this virus.

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