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HOT TOPIC

Oral diseases associated with hepatitis C virus infection. Part 2: lichen planus and other diseases

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Some of the most frequent extrahepatic manifestations of hepatitis C virus (HCV) infection involve the oral region predominantly or exclusively. Part 2 of this review discusses the current evidences regarding the association of lichen planus (LP) and other diseases frequently involving the oral cavity with HCV. Epidemiological data suggest that LP may be significantly associated with HCV infections especially in southern Europe and Japan but not in northern Europe. These geographical differences are possibly influenced by immunogenetic factors, the duration of the HCV infection and the design of the published studies. Because of the fact that most of the studies published are retrospective, it is impossible to establish whether the HCV exposure occurred earlier to or after the onset of disease and more prospective studies are clearly warranted. As the virus may replicate in the skin and oral mucosa and HCV-specific T lymphocytes can be found in the oral mucosa of patients with chronic hepatitis C and LP, HCV may be implicated in the pathogenesis of LP. However, little attention has been paid to the variable effect of therapy with interferon-alpha (IFN-α), with or without ribavirin for LP. Conversely, it is unlikely that other oral diseases such as oral carcinoma, pemphigus and Behcet disease are triggered by HCV.

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Hepatitis C virus (HCV) is presently considered as the main etiologic agent of both blood-borne and sporadic non-A and -B hepatitis, and is one of the major causes of chronic liver disease worldwide. However, morbidity associated with HCV infection is on account of not only the sequelae of chronic liver disease, but also a variety of extraheaptic manifestations (EHMs) (Carrozzo, 2007). The association of some of the EHMs with HCV is very close, while for certain others it is strongly suspected and in yet other cases the association is only tenuous and indicated by anecdotal data (Carrozzo, 2007). The recognition of the type and magnitude of EHM in HCV infection is important for several reasons. First, this knowledge may increase the awareness of healthcare providers, leading to early diagnosis and treatment of this disease. Second, some of these disorders may improve in response to antiviral treatment for HCV and third, persons with these EHMs can be targeted for HCV testing. Some of these EHMs may affect the oral cavity exclusively or predominantly. The current two-part review is focused on sialadenitis and salivary glands lymphomas (Part 1) and on lichen planus (LP) and other oral diseases possibly associated with HCV infection (Part 2). All along the text, the term LP has been used generically to indicate both skin and oral LP. When a more specific indication was warranted, the more precise terminology of skin or cutaneous LP and oral LP (OLP) was used.

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Lichen planus

Lichen planus is a chronic inflammatory disease that affects skin and mucous membranes of squamous cell origin. 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 (Lodi *et al*, 2005). 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 (Lodi *et al*, 2005; de Vries *et al*, 2007).

A possible link between hepatitis viruses and LP has been suggested by the fact that LP has been frequently associated with chronic liver disease (CLD) in Mediterranean but not in northern European patients (see Carrozzo and Gandolfo, 2003 for an extensive review). However, the risk of CLD in LP patients appears to be independent of hepatitis B virus (HBV) infection

[GISED (Gruppo Italiano Studi Epidemiologiciin Dermatologia), 1990; del Olmo *et al*, 1990; Carrozzo *et al*, 1996] despite few reports of mainly skin lichenoid eruptions following administration of different HBV vaccines (Rebora *et al*, 1999). Moreover, Epstein–Barr virus (EBV) and the recently discovered viruses, hepatitis G virus and transfusion transmitted virus (TTV), are not significantly associated with LP (Pedersen, 1996; Nagao *et al*, 1997a; Lodi *et al*, 2000; Bez *et al*, 2001; Rodriguez-Inigo *et al*, 2001).

When sensitive HCV diagnostic tests became possible, a great amount of case reports (Mokni *et al*, 1991; Agner *et al*, 1992; Divano *et al*, 1992; Cayla *et al*, 1993; Sassigneux *et al*, 1993; Strumia *et al*, 1993; Amichai *et al*, 1994; Benchikhi *et al*, 1994; Cecchi *et al*, 1994; Gandolfo *et al*, 1994; Jubert *et al*, 1994; Rebora, 1994; Daoud *et al*, 1995; Hyrailles *et al*, 1995; Mouly *et al*, 1995; Bellman *et al*, 1996; Jauregui *et al*, 1996; Tanei *et al*, 1997; Schissel and Elston, 1998; Toure *et al*, 1998; Pellicano *et al*, 2000; del Olmo *et al*, 2000; Calista and Landi, 2001), cohort and controlled studies have been done, which suggested a link between LP and HCV infection (Tables 1–3).

At present, 63 studies have analyzed the worldwide prevalence of HCV infection among LP patients (Tables 1–2): 46 of them were controlled studies (Table 1) and 26 were included in a recent meta-analysis (Lodi *et al*, 2004). Excluding six studies finding no seropositive patients both in LP patients and controls (Table 1), the proportion of HCV-positive subjects was higher in the LP group compared with controls in 37 out of the 40 other studies and this difference was statistically significant in 27 studies. The mean prevalence of HCV infection calculated from 5516 LP patients in the 63 studies was 16.8%. According to the 2002 meta-analysis (Lodi *et al*, 2004), the summary estimate of odds ratio (OR) showed that LP patients have about a fivefold higher risk than the controls of being HCV seropositive and the OR for exclusive OLP was not substantially different from the global one. However, a marked study reports as per which geographical variability exists for the relationship between HCV and LP. For example, studies from Japan reported a mean prevalence as 38.9% followed by Italy with 24% and Spain with 20.6% whereas the corresponding figure for the United States was 12.4% and for northern Europe was only 6.4%. At the same time, controversial results are reported even in studies performed within the same country (Tables 1 and 2). The meta-analysis has confirmed that the risk of being HCV seropositive among LP patients increased considerably in the Mediterranean studies while halved and became insignificant in northern Europe (Lodi *et al*, 2004). This datum explains the strong regional connotation of the association between LP and CLD that was observed mainly in southern Europe where HCV is highly prevalent. Interestingly, a similar geographic variability has been demonstrated for other EHMs linked to HCV infection, such as porphyria cutanea tarda (PCT), lymphoma and even mixed cryoglobulinemia (MC) (Gisbert *et al*, 2003; Dal Maso and Franceschi, 2006; Cohen Tervaert *et al*, 2007). A recent large-scale study from southern Italy (Campisi *et al*, 2004a) suggests that the previously reported data from southern Italy, favoring a link between OLP and HCV, may be explained by the high prevalence and the age distribution of HCV infection in this area. However, the control data for this study were obtained from previously published papers including patients predominantly from rural areas (Maio *et al*, 2000; Di Stefano *et al*, 2002), whereas the OLP patients were recruited from two major university hospitals (Campisi *et al*, 2004a). This bias could have strongly influenced the results and the conclusions of the study. Indeed, the meta-analysis (Lodi *et al*, 2004) seemed to confute the hypothesis that the high frequency of HCV seropositivity found in LP groups is caused by the increased prevalence of HCV infection in elderly patients. In 16 of the 26 included studies, the control group was sex- and age-matched with the study group and thus the difference in HCV seroprevalence between the two cannot be ascribed to age of the patients with LP. In addition, the subgroup analysis of studies with LP patients ≤50 years also showed an association between HCV infection and LP in these cases (Lodi *et al*, 2004). A more recent study from southern Italy confirms that the association of HCV with OLP patients is not age-related as the HCV seropositivity was more frequent in ≤50 years than in older patients (14.3% *vs* 10.8%) (Giuliani *et al*, 2007).On the other hand, in studies from countries with highest HCV prevalence (e.g. Egypt and Nigeria) there were negative or insignificant associations (Ibrahim *et al*, 1999; Daramola *et al*, 2002), suggesting that any LP–HCV association cannot be explained on the basis of high prevalence in the general population only. In addition, the few studies investigating the frequency of LP among HCV-positive subjects (Table 3) showed prevalences generally higher than expected, independently of the geographical origin. Thus, in countries such as the UK, with a very low prevalence of HCV, LP should be probably identified more closely in HCV-infected patients rather than seeking to find HCV infection in LP patients (Carrozzo, 2001).

Although in some HCV-infected patients the lichenoid lesions could have been secondary to anti-HCV therapy (Giuliani *et al*, 2007), in the majority of the studies the patients were not exposed to antiviral treatments (Table 3). Significantly, in the largest published study on EHMs in HCV-infected patients showing a significant association between LP and HCV infection (El-Serag *et al*, 2002), less than 5% of 32 204 studied patients received antiviral therapies. In another study (Bagan *et al*, 1998), no significant differences in the frequency of OLP were observed between patients who received interferon-alpha (IFN-α) and those who did not.

However, given the retrospective design of most of the case–control and cohort studies published, it is impossible to establish whether the HCV exposure occurred earlier to or after the onset of LP. As a result, HCV-infected patients might have an increased risk of developing LP or conversely, patients with LP could have an enhanced risk of HCV infection. Notably, a very recent epidemiologic study from Japan suggests that OLP prevalence in

Table 1 Controlled studies analyzing the prevalence of hepatitis C virus infections in patients affected by lichen planus (LP)

			LP			*Controls*	
			HCV			*HCV*	
Country	*Reference*	*N*	*Serology (%)*	*HCV-RNA (%)*	*N*	*Serology (%)*	*HCV-RNA (%)*
Arabia	Asaad and Samdani (2005)	114	26.3	NA	65	4.6[a]	NA
	Ali and Suresh (2007)	40[b]	0	NA	40	0[c]	NA
Brasil	Issa *et al* (1999)	34	5.9	NA	60	1.7[c]	NA
	Figueiredo *et al* (2002)	68[b]	8.8	NA	1055[d]	1.4[a]	NA
	Guerriero *et al* (2005)	66	7.5	NA	44 947	0.7[a]	NA
	de Mattos Camargo Grossmann *et al* (2007)	50[b]	2	2	1.173.406[e]	1.2[c]	1.2
Egypt	Ibrahim *et al* (1999)	43	20.9	NA	30	10[c]	NA
	Amer *et al* (2007)	30	NA	70	30	NA	3.3[a]
France	Cribier *et al* (1994)	52	3.8	NA[b]	112	2.6[c]	NA
	Dupin *et al* (1997)	102[b]	4.9	NA	306	4.5[c]	NA
Germany	Imhof *et al* (1997)	83	16	14	87	1.1[a]	1.1[a]
Iran	Rahnama *et al* (2005)	66	1.5	NA	140	2.1[c]	NA
	Ghader and Makhmalbaf (2007)	73	4.1	NA	150	0.7[a]	NA
India	Arup *et al* (2006)	104	1.9	NA	150	0[c]	NA
Israel	Yarom *et al* (2007)	62	4.8	NA	65	1.5[a]	
Italy	Rebora, 1994	56	23	NA	100	8[a]	NA
	Carrozzo *et al* (1996)	70[b]	27.1	21.4[f]	70	4.3[a]	NA
	Serpico *et al* (1997)	100[b]	32	NA	100	3[a]	NA
	Mignogna *et al* (1998)	263[b]	28.8	NA	100	3[a]	NA
	Lodi *et al* (2004)	303[b]	19.1	NA	278	3.2[a]	NA
	Campisi *et al* (2004a,b)	895[b]	27.7	NA	822[g]	18.7[c]	NA
	Giuliani *et al* (2007)	82[b]	11.4	11.4	466	5.4[a]	NA
Japan	Tanei *et al* (1995)	45	37.8	NA	45	6.7[a]	NA
Nepal	Garg *et al* (2002)	86	0	NA	43	0	NA
The Netherlands	Laeijendecker *et al* (2005)	100[b]	0	NA	100	0	NA
Nigeria	Daramola *et al* (2002)	57	15.8	NA	24	6[c]	NA
Serbia	Bokor-Bratic (2004)	48[b]	0	NA	60	0	NA
Spain	Santander *et al* (1994)	50	38	NA	27	3.7 [a]	NA
	Gimenez-Arnau *et al* (1995)	25	44	NA	18	5[a]	NA
	Sanchez-Perez *et al* (1996)	78	20	16	82	2.4[a]	2.4[a]
	Bagan *et al* (1998)	100[b]	23	NA	100	5[a]	NA
	Gimenez-Garcia and Perez-Castrillon (2002)	101	8.9	NA	99	2[a]	NA
	Luis-Montoya *et al* (2005)	36	2.8	NA	60	0[c]	NA
Taiwan	Chung *et al* (2004)	32	43.8	NA	1043	27.5[a]	NA
Thailand	Klanrit *et al* (2003)	60	8.3	6.7	60	0[a]	0
Turkey	Ilter *et al* (1998)	72	0	NA	75	0[c]	NA
	Kirtak *et al* (2000)	73	6.8	NA	73	1.4[a]	NA
	Erkek *et al* (2001)	54	12.9	9.3	54	3.7[c]	NA
	Harman *et al* (2004)	128	6.25	NA	128	0.78[a]	NA
	Karavelioglu *et al* (2004)	41	4.8	NA	360	2.5[c]	NA
	Denli *et al* (2004)	140	5	NA	280	1.4[a]	NA
UK	Ingafou *et al* (1998)	55[b]	0	NA	110	0	NA
	Tucker and Coulson (1999)	45	0	NA	32	3[c]	NA
USA	Bellman *et al* (1995)	30	23	16	41	4.8[a]	NA
	Chuang *et al* (1999)	22	55	NA	40	25[a]	NA
	Beaird *et al* (2001)	24	17	NA	20	5[a]	NA

NA, not available.
[a]Significantly different with the control groups.
[b]100% had oral lesions
[c]No significant difference with the control groups
[d]Prevalence data taken from the general population of São Paulo
[e]The prevalence of HCV infection was compared with that in the general population estimated by the Brazilian Hepatology Society
[f]Only 19 patients were tested
[g]As a controls were used 2 cohort of subjects from the general population of the same regions in which the OLP patients were resident and previously published (see the text)

HCV-infected patients increased significantly as the subjects grew older (Nagao *et al*, 2007) suggesting that the patients are very likely first infected with HCV and only developed LP later. This prospective study suggests also that the duration of the infection should be a potential source of heterogeneity in the published studies (Nagao *et al*, 2007). Moreover, in countries where the prevalence among the LP-free subjects is low, the spread of the virus might be recent and not yet produced full consequences on LP development.

Table 2 Uncontrolled studies analyzing the prevalence of hepatitis C virus infections in patients affected by lichen planus (LP)

Country	*Reference*	*Study group*		
		LP (n)	*HCV serology (%)*	*HCV-RNA (%)*
France	Dupond *et al* (1998)	28[a]	29	18
Germany	Grote *et al* (1998)	24	4.2	4.2
India	Narayan *et al* (1998)	75	0	0
	Prabhu *et al* (2002)	65	0	0
	Khaja *et al* (2006)	52	40	44
Iran	Ghodsi *et al* (2004)	146[b]	4.8	NA
Italy	Divano *et al* (1992)	46	14	NA
	Gandolfo *et al* (1994)	105[a,d]	9.5	NA
	Schmitt *et al* (1995)	32	34.7	34.7
	Rossi and Colasanto (2000)	100	13	NA
Japan	Nagao *et al* (1995a)	45	44	NA
Netherlands	van der Meij and van der Waal (2000)	55	0	0
Pakistan	Mahboob *et al* (2003)	184	23.4	NA
Spain	del Olmo *et al* (2000)	169	21.3	NA
UK	Roy *et al* (2000)	27[e]	0	0
	Kirtschig *et al* (2005)	38[c]	0	NA
USA	Egan and Zone (1997)	29	13.8	NA
	Chainani-Wu *et al* (2001)	31	45	NA
	Eisen (2002)	195	0	NA

NA, not available.
[a]100% had oral lesions
[b]41% of the patients had mucous membrane involvement
[c]All having vulval lichen planus,68% with a jointly OLP.
[d]Only patients with severe liver disease were tested.
[e]22% of the patients had OLP, 78% had lichenoid reactions.

Table 3 Prevalence of oral lichen planus (OLP) in patients with chronic HCV infection

Country	*References*	*N*	*Prevalence of OLP in patients with HCV infection (%)*
Australia	Coates *et al* (2000)	87	7.9
Brazil	Figueiredo *et al* (2002)	126	4.7[a]
	Cunha *et al* (2005)	134	1.5[b]
France	Pawlotsky *et al* (1994)	61	5
Germany	Grote *et al* (1998)	127	2.4
Italy	Mignogna *et al* (2001)	300	1.6
	Paoletti *et al* (2002)	96	2.1
	Campisi *et al* (2004a,b)	104	4.8
	Giuliani *et al* (2007)	165	5.5[c]
Japan	Nagao *et al* (1997c)	685	4.8[a,e]
	Nagao *et al* (2000a)	190	12.5[a,e]
	Nagao *et al* (2002)	90	8.5
Poland	Sulka *et al* (2006)	39	2.6[b]
Spain	Bagan *et al* (1998)	505	3.4[a]
	Mico-Llorens *et al* (2004)	87	0[d]
UK	Henderson *et al* (2001)	40	20
USA	El-Serag *et al* (2002)	34 204	0.3[a,f]

[a]Significantly different with the control group.
[b]No significantly different with the control group.
[c]Only two of the eight patients had a final, histologically proven diagnosis of OLP.
[d]Both the patients and controls were all HCV negative.
[e]Diagnosis of HCV infection confirmed by HCV-RNA.
[f]The patients had a no more specified diagnosis of LP.

Genetic differences among different populations should be also taken into account. Indeed, it has been reported that PCT susceptibility is different in British and Italian patients, being correlated with mutation in the human leukocyte antigen (HLA)-linked hemochromatosis gene C 282Y in the former and to the H63D gene and HCV in the latter (Elder and Worwood, 1998). HCV-related OLP appears associated mainly with the HLA-DR6 allele in Italy (Carrozzo *et al*, 2001) whereas it does not appear to be so in UK (Carrozzo *et al*, 2005) and this could partially explain the peculiar geographic heterogeneity in the association between HCV and LP.

Despite some concerns (Mignogna *et al*, 2000; Romero *et al*, 2002) mainly mucocutaneous and erosive LP may be linked to HCV infection (Bertolusso *et al*, 2004) but the findings are equivocal and further data on this issue are needed.

Pathogenesis of HCV-related LP

Apparently, there are no significant differences in the histopathological characteristics specific to LP or in the ratio of T and B cells among infiltrating lymphocytes regardless of the presence or absence of HCV infection (Nagao *et al*, 2000b; Kirby *et al*, 1998; Mega *et al*, 2001). However, the proportion of CD8+ T cells in the lamina propria appears to be higher in HCV-related OLP compared with idiopathic OLP.

Molecular mimicry between the HCV and host epitopes is unlikely to be active in LP (Fleishmann *et al*, 1996; Lodi *et al*, 1997a; Carrozzo *et al*, 1999) and neither are viral factors such as genotype or viral load (Pawlotsky *et al*, 1995b; Nagao *et al*, 1996a; Lodi *et al*, 1997b).

The presence of HCV in LP lesional tissue has been the object of several investigations (Table 4). Both *in situ* hybridization and extractive polymerase chain reaction (PCR) techniques revealed the presence of replicative intermediate HCV-RNA in skin and oral LP

Table 4 Hepatitis C virus (HCV) detection in lichen planus lesional tissue (modified from Lodi *et al*, 2005)

Country	*Reference*	*Patients with oral lesions*	*Detection of HCV in specimens of lichen planus N (%)*	*Tecnique*	*HCV antigens*	*Oral mucosa/*skin HCV RNA	
						Genomic strand N (%)	*Negative strand N (%)*
Italy	Sansonno *et al* (1995)	NA	0/7 (0)[a]	IP	c22, c23, c100-3	–	–
	Mangia *et al* (1999)	0/19	0/19 (0)	PCR	–	–	–
	Carrozzo *et al* (2002)	12/12	10/12 (83.3)	PCR, SA, PhA	–	10 (83.3)	4 (33.3)
	Pilli *et al* (2002)	4/4	3/4 (75)	PCR	–	3 (75)	0 (0)
	Femiano and Scully (2005)	25/25	0/25 (0)	PCR	–	0 (0)	0 (0)
Japan	Nagao *et al* (2000c)	14/14	13/14 (93)	PCR, SA	–	13 (93)	3 (21.4)
	Kurokawa *et al* (2003)	2/3	3/3 (100)	PCR	–	3 (100)	3 (100)
Spain	Arrieta *et al* (2000)	23/23	23/23 (100)	ISH	–	23 (100)	23 (100)
	Lazaro *et al* (2002)	0/5	5/5 (100)	ISH, IP	core	5 (100)	5 (100)
Turkey	Erkek *et al* (2001)	4/5	5/5 (100)	PCR	–	5 (100)	NA
UK	Roy *et al* (2000)	27/27[a]	0/27 (0)	PCR	–	0 (0)	NA
USA	Boyd *et al* (1998)	NA	0/25 (0)[b]	IP	NA	–	–
	Harden *et al* (2003)	1/4	0/0 [c]	PCR	–	0 (0)	0 (0)

NA, not available; IP, immunoperoxidase; PCR, polymerase chain reactions; ISH, *in situ* hybridization; SA, sequence analysis; PhA, phylogenetic analysis.
[a]All the patients were HCV seronegative.
[b]All but of two of the patients were HCV seronegative.
[c]All formalin-fixed, paraffin-embedded skin biopsy specimens were used.

specimens (Table 4). Positive and negative strands were detected by PCR in 75–100% and 21–100% of LP tissue specimens respectively (Arrieta *et al*, 2000; Nagao *et al*, 2000c; Carrozzo *et al*, 2002; Lazaro *et al*, 2002; Pilli *et al*, 2002; Kurokawa *et al*, 2003), even if there were some studies reporting complete negative results (Roy *et al*, 2000; Harden *et al*, 2003; Femiano and Scully, 2005). However, some of the studies had evident methodological biases such as the use of formalin-fixed, paraffin-embedded skin biopsy specimens rather than frozen or fresh sections (Harden *et al*, 2003). Similarly, two studies failed to detect HCV antigens in sections of cutaneous LP using various immunohistochemical techniques but all but two of samples studied were from non-HCV-infected persons (Sansonno *et al*,1995; Boyd *et al*, 1998).

Sequence analysis suggested a possible compartmentalization of HCV in the oral mucosa (Carrozzo *et al*, 2002). However, HCV is unlikely to cause direct damage to epithelial cells in OLP lesions, as it was also found in normal mucosa (Arrieta *et al*, 2000). The lymphomononuclear infiltrate typically found in oral lichen lesions suggests that the progressive destruction of the oral mucosa lining is on account of local immune aggression. A recent study showed that HCV-specific CD4+ and/or CD8+ T lymphocytes can be found in the oral mucosa of patients with chronic hepatitis C and LP (Pilli *et al*, 2002). CD4+ polyclonal T-cell lines were generated more efficiently from lichen-infiltrating lympho-mononuclear cells than from peripheral blood mononuclear cells from the same patients, suggesting a higher frequency of HCV-specific T cells in the oral compartment (Pilli *et al*, 2002). However, T-cell clones present in the oral mucosa showed a different TCR (T-Cell Receptor)-Vβ chain usage than those circulating in the peripheral blood, suggesting a specific compartmentalization at the site of the LP lesions (Pilli *et al*, 2002). Furthermore, HCV-specific CD8+ T cells were present with higher frequency in mucosa tissue than in the blood and produced gamma interferon upon peptide stimulation (Pilli *et al*, 2002). Notably, HBV-specific T cells could not be found in the oral mucosa of patients with LP and chronic HBV infection even if they were detectable in the peripheral blood. This suggests that HCV-specific T cells among the lichen-infiltrating lymphocytes were not recruited as a result of inflammation and irrespective of HCV replication and viral antigen expression. In view of the already mentioned demonstration of both forms of HCV-RNA in LP lesions, these results strongly suggest that HCV-specific T cells may play a role in the pathogenesis of OLP. The characteristic band-like lymphocytic infiltrate in OLP might thus be directed towards HCV-infected cells. Interestingly, plasmacytoid dendritic cell recruitment with IFN-α and antiviral protein MxA production have been described in OLP patients with HCV infection (Santoro *et al*, 2005). It is possible that oral cell damage is the result of a direct immune aggression of epithelial cells expressing HCV antigens, possibly sustained by a cytokine environment favorable to trigger and maintain the lichenoid reactions. Alternatively, neo-antigens expressed on infected cells by HCV could lead to lichenoid inflammation. Because evidences similar to the above are not completely available for skin LP, it should be questioned whether cutaneous lesions of LP also might be triggered by HCV and further specific studies on skin LP are clearly warranted.

Very recently, it has been reported that OLP patients with and without HCV infection show a different genetic cytokine background. Indeed, in the idiopathic form of OLP, the increased production of tumor necrosis factor-alpha (TNF-α) and IFN-γ is the result of genetic dysregulation of the immune response (Carrozzo *et al*, 2004) whereas OLP patients with HCV infection have a

Th1 cytokine bias, possibly secondary to an abnormal immune-response to the virus (Carrozzo *et al*, 2007). Significantly, an excessive TNF-α response characterizes HCV-infected patients who developed type-2 diabetes mellitus, another putative extra-hepatic manifestation of HCV infection (Carrozzo *et al*, 2007).

OLP and anti-HCV therapy

Interventional studies may potentially give us important information for or against a causal link between HCV and LP but the available data are scanty and inconclusive. For unknown reasons, the effect of α-IFN therapy on HCV-associated LP differs markedly from case to case. IFN-α has been reported to have no influence (Pawlotsky *et al*, 1995a), to ameliorate (Doutre *et al*, 1992, 1996; Strumia *et al*, 1993; Hildebrand *et al*, 1995; Pedersen, 1998; Nagao *et al*, 1999), or to trigger or worsen LP lesions (d'Agay-Abensour *et al*, 1992; Agner *et al*, 1992; Cayla *et al*, 1993; Protzer *et al*, 1993; Sassigneux *et al*, 1993; Heintges *et al*, 1994; Papini *et al*, 1994; Perreard *et al*, 1994; Barreca *et al*, 1995; Fornaciari *et al*, 1995; Nunez *et al*, 1995; Areias *et al*, 1996; Nagao *et al*, 1996b; Schlesinger *et al*, 1997; Dalekos *et al*, 1998; Varela *et al*, 2000; Guijarro Guijarro *et al*, 2001). Multiple *de novo* cases of LP were described in patients with sustained viral responses (Berk *et al*, 2007) and from 4.4% to 16.7% of the patients under IFN-α treatment for chronic hepatitis C developed LP, mainly OLP (Nagao *et al*, 1996b; Dalekos *et al*, 1998). Notably, several patients had circulating anti-nuclear antibodies before the initiation of IFN-α therapy suggesting an epitope-spreading phenomenon (Dalekos *et al*, 1998). In a small series of four OLP patients on long-term follow-up after IFN-α treatment, a clinical and histological improvement of the oral lesions was noted after 3 years, similar to what was observed in the liver of patients responding to the anti-viral therapy (Nagao *et al*, 1999).

Ribavirin was reported to increase the risk of adverse cutaneous reactions, often of a lichenoid type (Sookoian *et al*, 1999), and it apparently both worsened and improved LP (Manjón-Haces *et al*, 2001; Harden *et al*, 2003; Nagao *et al*, 2005) but there are no large studies evaluating in details the impact of therapy for HCV infection on LP.

Oral carcinoma

An increased prevalence of HCV infection in patients with oral squamous cell carcinoma (SCC) was reported by Nagao *et al* (1995b). Recently, an uncontrolled study from USA reported that 21% of 99 patients with head and neck SCC had HCV infection (Nobles *et al*, 2004) although HCV did not affect patients' disease-free survival (Hunt *et al*, 2005). In another study from Japan evaluating the prevalence of HCV in a large population requiring oral surgery (Takata *et al*, 2002), the authors found an increased frequency of HCV antibody in patients with oral cancer, but this difference disappeared when the data were adjusted for age. Oral verrucous and squamous cell carcinomas have been reported in HCV-infected patients with OLP (Nagao *et al*, 1995b, 1996c; Carrozzo *et al*, 1997; Porter *et al*, 1997; Cervoni, 1998; Lo Muzio *et al*, 1998) and positive and negative HCV-RNA strands have been detected both in oral cancer tissues (Nagao *et al*, 2000c). Some HCV proteins, namely the core and the non-structural 3 protein, may deregulate the cell cycle *in vitro* (Siavoshian *et al*, 2004). In a retrospective study on 402 OLP patients, the role of HCV infection on OLP outcome was analyzed (Gandolfo *et al*, 2004). Although 44% of the patients who developed an oral cancer were HCV-infected, the risk was not significantly increased, possibly because of low statistical power. However, HCV is a common cause of liver cirrhosis which may represent itself an independent risk factor for the development of oral cancer (Sorensen *et al*, 1998). On the other hand, potentially oral premalignant lesions such as leukoplakia and oral epithelial dysplasia are not associated with HCV infection (Carrozzo *et al*, 1996; Jaber *et al*, 2003; Bokor-Bratic,2006).

Other diseases

Two cases of pemphigus [1 pemphigus vulgaris [PV] and 1 paraneoplastic) associated with chronic HCV infection and involving the oral cavity have been published (Marinho *et al*, 2001: Nanda *et al*,2007). The PV case was supposed to be caused by IFN therapy but this is a very rare occurrence according to the available data.

The possibility that Behcet's disease (BD) is an HCV-associated disorder was first suggested in 1995 (Munke *et al*, 1995). However, since then, there has been no convincing evidence supporting a triggering or aggravating role of HCV in BD and almost all the studies published report negative results (Oguz *et al*, 1995; Aksu *et al*, 1999; Ilter *et al*, 2000; Sonmezoglu *et al*, 2004; Erkek and Ayaslioglu, 2005; Farajzadeh *et al*, 2005).

Conclusions

Epidemiological data suggest that LP may be significantly associated with HCV infection, mainly in Southern Europe and Japan. However, given the retrospective design of most of the case–control studies published, it is impossible to establish whether the HCV exposure occurred earlier to or after the onset of disease. Thus, HCV-infected patients may have increased risk of developing LP or alternatively, patients with LP have an enhanced risk of HCV infection. More prospective well-designed studies are necessary to clarify definitively the above issue. However, recent experimental and epidemiological data suggest that the patients are very likely first infected with HCV and only later develop LP, probably *via* an immunological pathway possibly driven by HCV but still to be defined. It should be important to establish whether the lymphocyte response is directed against neo-antigens expressed on infected cells by HCV or against viral proteins able to induce a specific T-cell response. Interventional studies may potentially give us important information for or against a causal link between HCV and LP but little attention has been paid to the variable effect of IFN-α (with and without ribavirin) therapy on LP. Specific trials analyzing the

effect of treatment eradicating HCV infection on LP are clearly warranted. Conversely, the link between oral carcinoma and HCV is weak and possibly influenced by the presence of liver cirrhosis while other oral diseases as PV and BD are unlikely to have been triggered by HCV.

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