J Dent Sci 2009;4(4):191–197

ELSEVIER

ORIGINAL ARTICLE

Increased oral lichen planus in a chronic hepatitis patient associated with elevated transaminase levels before and after interferon/ribavirin therapy

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Received: Sep 14, 2009
Accepted: Nov 19, 2009

KEY WORDS:
hepatitis C;
interferon;
oral lichen planus;
ribavirin

Background/purpose: Oral lichen planus (OLP) is the most frequent oral lesion found in patients with hepatitis C virus (HCV) infection. The aims of this study were to investigate the prevalence of OLP among chronic hepatitis C patients, to clarify the role of HCV in the pathogenesis of OLP, and to assess its relationship to transaminase levels.
Materials and methods: Two groups of subjects were studied; 277 hepatitis C patients were examined for OLP (Group 1) and 5273 outpatients seeking dental care within 1 year were used as a control (Group 2) to determine the prevalence of OLP in the general population. The dental and hepatic records were collected and analyzed.
Results: The prevalences of OLP were 4.7% (n=13) in Group 1 and 2.0% (n=104) in Group 2 and significantly differed (P=0.002). All 13 OLP cases occurred in hepatitis C patients who had experienced elevated alanine transaminase levels of >80 IU/L within the 2 previous years, regardless of whether they were treated with interferon-ribavirin combination therapy or not. There was a strong association between elevated transaminase levels and the development of HCV-related OLP lesions (P=0.014). Of the 13 OLP patients, two were in the group with a sustained virologic response (SVR) to HCV therapy, two were in the group without an SVR, and nine were in the non-therapy group. The incidence of OLP in hepatitis C patients did not significantly differ between those who showed an SVR to HCV therapy and those who did not respond or did not receive therapy (P=0.560).
Conclusion: We concluded that: (1) elevation of transaminase levels is associated with the detection of HCV-related OLP, and (2) HCV-related OLP can remain unchanged for years after an SVR to HCV therapy. The findings revealed that the role of HCV in OLP pathogenesis is due to host factors induced by HCV rather than a direct cytopathic effect of HCV.

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Introduction

Oral lichen planus (OLP) is frequently seen in patients with chronic hepatitis C virus (HCV) infection and was reported to be an extrahepatic manifestation of HCV.[1–3] Many studies associated OLP with HCV, especially in HCV-endemic areas such as southern Europe and Japan, although the mechanisms of HCV in OLP pathogenesis are unclear.[1,4–9]

HCV RNA was detected in the saliva and oral mucosa of patients with chronic hepatitis C. Persistent HCV infection of the oral epithelium may trigger a host immune response and result in HCV-related OLP. However, the underlying mechanism remains unclear.[1,9–11] Chung et al.[12] found that elevation of transaminase levels significantly increased the risk of atrophic-erosive OLP, particularly in HCV patients. Ali and Suresh[13] reported a strong association between elevated transaminase levels and detection of erosive OLP, but no correlation between OLP and HCV infection was determined in their study. Nagao et al.[8,14] observed HCV-related OLP in patients with severe liver dysfunction and also in patients without it. Further, there were no significant differences in serum HCV RNA levels and HCV genotypes between the HCV with OLP group and the HCV without OLP group. Arrieta et al.[15] detected HCV replicates in epithelial cells of anti-HCV-positive patients with and without OLP. Those reports suggest that host factors induced by HCV infection are more important than viral factors in the pathogenesis of HCV-related OLP.

Combination therapy with interferon (IFN) and ribavirin is the current standard treatment for chronic HCV infections. Some reported the therapeutic effects of IFN on OLP lesions, but others reported that OLP can be aggravated or triggered by IFN.[16,17]

There is no report describing the therapeutic effect of IFN and ribavirin for HCV-related OLP in chronic hepatitis C patients. Also, controversy and uncertainty regarding the association of the activity of HCV in OLP led us to conduct this study. The aims of this study were to investigate the prevalence of OLP among patients with chronic hepatitis C in southern Taiwan, to clarify the role of HCV in the pathogenesis of OLP by investigating the progression and occurrence of OLP in HCV patients treated with IFN plus ribavirin, and to assess the possible association of transaminase levels in OLP. We conducted oral examinations of chronic hepatitis C patients with the investigators blinded to their HCV status.

Material and methods

Two hundred and seventy-seven consecutive patients (152 women and 125 men), aged 34–87 years (mean, 60.5±10.7 years) with a diagnosis of chronic HCV infection and who had been followed up for at least 2 years at the Division of Hepato-Gastroenterology of Kaohsiung Chang Gung Memorial Hospital, were examined for OLP (Group 1), and 5273 outpatients seeking dental treatment at the Department of Oral Pathology and Family Dentistry within 1 year were used as the control group (Group 2) to determine the prevalence of OLP in the general population. All patients enrolled in the study came from the same general population in southern Taiwan. With the investigators blinded to a patient's medical history including his/her HCV status and whether he/she had received HCV treatment, OLP was observed through a clinical examination by a well-trained family dentist, and then double-checked by an oral medicine specialist. The study was conducted from August 2007 to March 2009. A diagnosis of OLP was made on the basis of the recognized typical clinical features; in suspicious cases, a diagnosis was confirmed by a biopsy. Reticular OLP was defined by the presence of a lace-like network of grayish-white lines (Wickham's striae). Atrophic, erosive and bullous types of OLP lesions were accepted as a subtype only in the presence of reticular OLP elsewhere.[18–20] Participants were divided into a reticular OLP group and an atrophic-erosive OLP group according to the clinical type of lesions observed. Patients suspected of graft-to-host disease, or areca nut use or drug-induced lichenoid eruptions were excluded. Demographic data such as age, sex, past medical history, type of OLP lesion, and its duration were collected using a checklist after receiving a patient's consent.

HCV infection was diagnosed by detecting antibodies against HCV (anti-HCV, with microparticle enzyme immunoassay (AxSYM HCV version 3.0; Abbott Diagnostics, Chicago, IL, USA). HCV RNA by qualitative polymerase chain reaction (COBAS AMPLICOR HCV test version 2.0; Roche Diagnostics, Basel, Switzerland; with a lower limit of detection of 50 IU/mL) was detected when needed. Liver function tests including serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were measured, and serum AST and ALT levels of <40 IU/L were assumed to be normal. AST and ALT levels were estimated in all cases in Group 1 from several weeks to several months. A sustained virologic response (SVR) was defined by the absence of HCV RNA at 24 weeks after completion of HCV therapy. The goal of treatment for chronic HCV infection is an SVR accompanied by improvement in the liver damage. In this study, a therapeutic response was judged after IFN-ribavirin combination therapy to be a complete responder if there was an SVR with normalization of serum ALT

levels, and an incomplete responder if there was neither an SVR nor a return to normal transaminase levels. The incidences of OLP in the hepatitis C patients (Group 1) were compared between those with elevated transaminase levels of >80 IU/L (double the normal limits of the value of ALT) and those whose ALT levels never exceeded 80 IU/L and between those who showed an SVR to HCV therapy and those who did not respond (non-SVR) or did not receive therapy. An ultrasonographic scoring system consisting of the liver surface, parenchyma, vascular structure and splenic size was used to describe the severity of hepatic parenchymal damage.[21] In the scoring system, a score of 4 indicates a normal situation, scores of 5–7 indicate hepatic fibrosis, a score of 8 indicates early cirrhosis, and scores of 9 and higher indicate cirrhosis. The intraobserver reproducibility of our gastroenterologist was documented.[22] In this study, we defined scores of 4–6 as normal or mild hepatic fibrosis, while scores of 7 and higher were defined as definite and advanced hepatic fibrosis. The ultrasonographic evaluation of 277 HCV patients by this scoring system was used to investigate the correlation between the prevalence of OLP and the degree of liver abnormalities.

All collected data were analyzed by the computer package SPSS version 15.0 software (SPSS, Chicago, IL, USA). Chi-squared and Fisher's exact tests were used to analyze the association between qualitative variables. In all analyses, $P<0.05$ was considered statistically significant. The study was approved by the institutional review board of Chang Gung Memorial Hospital.

Results

OLP was the most prevalent oral lesion in hepatitis C patients (Group 1) with 13 cases (9 females and 4 males, 4.7%; Table 1). The remaining lesions consisted of leukoplakia in five cases (1.8%), aphthous stomatitis in three (1.1%), oral candidosis in two (0.7%), and cheilitis in two (0.7%) (Table 2). No abnormalities of the oral mucosa were found in the remaining 252 cases (91.0%). In the 13 HCV-related OLP patients, the painless reticular form of OLP was the most common oral lesion ($n=10$, 76.9%); only three showed atrophic-erosive OLP (23.1%), with the buccal mucosa being the most-often affected site. On the contrary, of the 104 OLP patients in Group 2, the most prevalent OLP lesion was the painful erosive type ($n=90$, 86.5%) and 14 patients (13.5%) showed reticular OLP. The clinical features of OLP between HCV patients (Group 1) and dental outpatients (Group 2) statistically differed ($P<0.0001$).

The prevalences of OLP were 4.7% in Group 1 and 2.0% in Group 2 with a significant difference ($P=0.002$). In total, 125 hepatitis C patients completed HCV therapy with IFN or peginterferon and ribavirin; 83 (66.4%) of them showed an SVR with a return to normal ALT levels, and 42 patients (33.6%) showed a non-SVR with elevated ALT levels. Because the hepatitis C status did not reach the therapeutic requirements of health insurance of Taiwan (a persistent ALT level of >80 IU/L and significant hepatic fibrosis), adverse effects from IFN, or financial problems, the other 152 hepatitis C patients did not receive HCV therapy or failed to complete therapy. Of the 13 HCV-related OLP patients, nine were in the non-therapy group (69.2%), two were in the non-SVR group (15.4%), and two were in the SVR group (15.4%). The OLP prevalence in the SVR group ($n=2$, 2.4%) was lower than that of the non-SVR group plus the non-therapy group ($n=11$, 5.7%). However, no significant difference was found ($P=0.240$; Table 3). The HCV-related OLP in two patients developed before HCV therapy and persisted after an SVR to therapy for several months to 1 year. All 13 OLP patients were hepatitis C patients who had experienced elevated ALT

Table 1. Age and sex distribution of 277 hepatitis C patients with oral lichen planus (OLP) lesions in Group 1

	Patients with OLP		
	Male	Female	Total
Age (yr)			
30–39	0/6	1/5	1/11
40–49	0/15	0/15	0/30
50–59	2/38	2/52	4/90
≥60	2/66	6/80	8/146
Total	4/125	9/152	13/277 (4.7%)

Table 2. Distribution of oral mucosal lesions in 277 hepatitis C patients (Group 1)

Oral mucosa condition	*n* (%)
Oral lichen planus	13 (4.7)
Leukoplakia	5 (1.8)
Aphthous ulcers	3 (1.1)
Oral candidosis	2 (0.7)
Cheilitis	2 (0.7)
Normal mucosa	252 (91.0)
Total	277 (100)

levels of >80 IU/L within the past 2 years, regardless of whether they were treated with HCV therapy or not. Elevated transaminase levels of >80 IU/L were significantly related to the development of OLP (P=0.014; Table 4).

Ultrasonographic scores of 7–9 indicating definite to advanced hepatic fibrosis were detected in eight of 13 HCV-related OLP patients, and scores of 4–6 indicating normal to mild hepatic fibrosis were found in the other five HCV-related OLP patients. When possible differences in OLP prevalence with respect to the degree of liver damage by the ultrasonographic scoring system between the advanced hepatic fibrosis group and the normal to mild hepatic fibrosis group were investigated, a significant difference between the groups was not found (P=0.566; Table 5).

Discussion

According to our study, the prevalence of OLP in southern Taiwanese patients with hepatitis C was 4.7%. This was significantly higher than the prevalence of OLP in the general population (2.0%), which was used as a control in our study (P=0.002). The prevalence of OLP in 277 hepatitis C patients (4.7%) was quite similar to the results of other authors, such as Figueiredo et al.[23] who reported a 4.7% incidence of OLP among 126 patients with HCV infection in Brazil, Nagao et al.[24] who reported a 4.8% incidence of OLP among 84 patients with HCV infection in Japan, and Pawlotsky et al.[25] who reported a 5% incidence of OLP among 61 patients with HCV infection in France. To avoid investigator bias, the two investigators who investigated all of the HCV patients were blinded to their hepatitis C activity. If patients with known HCV therapy or transaminase levels were more likely to be overdiagnosed or underdiagnosed with OLP, this would have resulted in arbitrary statistics. We did not find a higher OLP prevalence in hepatitis C patients treated with IFN and ribavirin, in contrast to reports of OLP being triggered or aggravated by IFN by other authors.[16,26–28] Furthermore, HCV-related OLP was observed to be more common in the non-therapy group (69.2%) than in the IFN-ribavirin combination therapy group (30.8%). However there was no significant difference (P=0.287). To our knowledge, this is the first report to investigate the prevalence of OLP among chronic hepatitis C patients in southern Taiwan, and it describes the effect of IFN-ribavirin combination therapy for chronic hepatitis C patients with HCV-related OLP.

Among 13 HCV-related OLP cases, the reticular form of OLP (76.9%) was the most prevalent oral

Table 3. Prevalence of oral lichen planus (OLP) in hepatitis C virus (HCV) patients (Group 1), stratified by a sustained virologic response (SVR) to HCV therapy with interferon and ribavirin and non-SVR to therapy plus the non-therapy group*†

	OLP (−)	OLP (+)‡	Total
SVR	81 (29.2)	2§ (0.7)	83 (30.0)
Others	183 (66.1)	11‖ (4.0)	194 (70.0)
Total	264 (95.3)	13 (4.7)	277 (100)

*Data are presented as *n* (%); †percentages may not add up to total because of rounding; ‡not significant (P=0.240); §2.4% (2/83) with an SVR; ‖5.7% (11/194) with a non-SVR and no therapy.

Table 4. Prevalence of oral lichen planus (OLP) in hepatitis C virus (HCV) patients (Group 1), stratified by alanine transaminase (ALT) levels of >80 IU/L within 2 years of follow-up, by whether they were treated with HCV therapy or not*

	OLP (−)	OLP (+)†	Total
ALT			
<80 IU/L	85 (30.7)	0‡ (0)	85 (30.7)
>80 IU/L	179 (64.6)	13§ (4.7)	192 (69.3)
Total	264 (95.3)	13§ (4.7)	277 (100)

*Data are presented as *n* (%); †significant (P=0.014); ‡0% (0/13) with OLP; §100% (13/13) with OLP.

Table 5. Prevalence of oral lichen planus (OLP) in hepatitis C virus (HCV) patients (Group 1), stratified by the ultrasonographic scoring system*

	OLP (−)	OLP (+)†	Total
Echo score			
4–6 (normal or mild hepatic fibrosis)	123 (44.4)	5‡ (1.8)	128 (46.2)
7–9 (definite or advanced hepatic fibrosis)	141 (50.9)	8§ (2.9)	149 (53.8)
Total	264 (95.3)	13 (4.7)	277 (100)

*Data are presented as *n* (%); †not significant (P=0.566); ‡38.5% (5/13) with OLP; §61.5% (8/13) with OLP.

lesion in hepatitis C patients. This is compatible with the finding of Mignogna et al.[29] that the reticular form is more frequent in HCV-positive patients than in HCV-negative patients. Most hepatitis C patients with reticular OLP do not seek treatment because of the asymptomatic nature of the disease. Variations in OLP symptoms between HCV patients (Group 1) and dental outpatients (Group 2) may have influenced the option of seeing doctors and resulted in the different manifestations of OLP between the two groups. All HCV-related OLP cases among the 13 hepatitis C patients were tolerable. No patient subjectively complained about gross or symptomatic changes, regardless of whether they were treated with IFN-ribavirin combination therapy or not. Three atrophic-erosive OLP and two reticular OLP patients were referred to the dental department of the same hospital for treatment, and showed dramatic remission of signs and symptoms with levamisole and low-dose prednisolone therapy within 2 weeks, and there was no evidence of erosive OLP after 4–6 weeks of treatment. The HCV-related OLP in two cases developed before HCV therapy and remained unchanged after an SVR to therapy. Nevertheless, HCV-related OLP responded to conventional therapy for OLP as well.[30] The beneficial effects of prednisolone plus levamisole on HCV-related OLP also suggest immunopathogenesis.[30] The etiology of OLP is thought to reflect a cell-mediated immune response, although the mechanisms remain to be addressed.[31–33] Leukoplakia was the second most common lesion in hepatitis C patients. Caution should be taken to regularly follow up on the leukoplakia, as with OLP, for possible malignant changes.[1]

IFN with antiviral, antiproliferative and immunomodulatory functions is effective in treating chronic hepatitis C. The rate of response to IFN is enhanced by increasing the IFN dose and extending the treatment duration. The addition of ribavirin to IFN therapy increases the SVR rate in Taiwanese HCV patients by up to approximately 60%.[34–37] In this study, the SVR rate to IFN-ribavirin combination therapy was 66.4%. The long-term benefits of SVR are decreased infectivity, lower risks of developing cirrhosis and hepatocellular carcinoma (HCC), and an improved quality of life. Therapeutic effects of IFN and ribavirin have been confirmed in extrahepatic lesions other than OLP.[38–40] We found that HCV-related OLP in chronic hepatitis C patients with SVR to IFN-ribavirin combination therapy can be persistent. As OLP neither disappeared nor improved but remained unchanged when HCV RNA became negative after HCV therapy, it is unlikely that HCV directly participates in the pathogenesis of OLP lesions. Our data suggest that HCV is not sufficient in itself to be a causative agent for the development of OLP lesions, and that host factors play important roles in the pathogenesis of HCV-related OLP. This was supported by other researchers who reported that the percentages of HCV-infected oral mucosa cells do not correlate with serum viremia levels or the intensity of inflammatory infiltrates in OLP lesions, together with the fact that HCV RNA levels or HCV genotypes in HCV patients with or without OLP did not significantly differ.[14,15,41] Furthermore, Femiano and Scully[42] found that an increase in immunomodulatory cytokines in HCV-positive OLP lesions induced cell-mediated cytotoxicity to basal layer cells and resulted in OLP lesions. Pilli et al.[43] demonstrated that HCV-specific $CD4^+$ and $CD8^+$ T cells were present within intralesional infiltrates in HCV-positive OLP lesions, thus providing strong evidence for the involvement of HCV in the pathogenesis of OLP. Although it is unclear how HCV affects the immune system of hosts, it is thought that the host immune system plays an important role in the development of HCV-related OLP. For further elucidation of the therapeutic effects of IFN-ribavirin combination therapy on HCV-related OLP, an accumulation of more cases and long-term follow-up are needed. Also in this study, nine of 13 HCV-related OLP patients were female; therefore, sex may be related to the occurrence of OLP.

Chronic hepatitis C has peaks and valleys of activity, so most hepatitis C patients have ALT levels that may go up and down or remain stable over time. No HCV-related OLP was found in hepatitis C patients whose ALT levels were always <80 IU/L during 2 years of follow-up, regardless of whether or not they were treated with HCV therapy. Such a finding is quite interesting and corresponds to some earlier reports that there is a close association between transaminase elevation and the development of HCV-related OLP lesions,[8,12,13] although no definite values of elevated ALTs were mentioned in those reports. As far as we know, these ALT numbers do not have a linear relationship with the stage of liver damage in HCV infection. A level of ALT of 160 IU/L is not twice as bad as 80 IU/L, and an ALT value of 95 IU/L and 80 IU/L are essentially the same to a liver specialist. It is not surprising to find that there were no significant differences in OLP prevalence between the advanced hepatic fibrosis group and the normal to mild hepatic fibrosis group according to the ultrasonographic evaluation ($P=0.566$) in the study. However, the prevalence of OLP in the advanced hepatic fibrosis group was higher than that of the normal to mild hepatic fibrosis group. Therefore, further studies are needed to clarify the mechanism of this association between ALT levels of >80 IU/L and the detection of HCV-related OLP.

In conclusion, our data show that among HCV patients, the rate of OLP is twofold higher (4.7% *vs*. 2.0% in the general population); and among OLP patients the rate of HCV infection is 11-fold higher (22.1% *vs*. 2.0% in control subjects of our previous study). We concluded that at least in southern Taiwan, there is a positive association between HCV and OLP and a strong association between elevated transaminase levels of >80 IU/L and the detection of HCV-related OLP. Physicians should be aware that OLP can occur or persist even when serum HCV RNA is negative after IFN-ribavirin combination therapy for hepatitis C patients. These findings contradict the notion that HCV is the direct causal agent of OLP. In other words, HCV together with other factors (either viral or host-related immune responses) may be responsible for some cases of HCV-related OLP.

Acknowledgments

The authors would like to express their gratitude to Drs Kwong-Ming Kee, Wei-Chih Tung and Chuan-Mo Lee of the Division of Hepato-Gastroenterology for their kind referral of chronic hepatitis C patients for our investigation and to Ms Pao-Fei Chen for her kind help with the statistics. This investigation was supported in part by a CMRP research grant (CMRPG870311 to S.Y.L.) from Chang Gung Memorial Hospital, Kaohsiung, Taiwan.

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