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The Prevalence of Hepatitis C Virus Infection in Oral Lichen Planus in an Ethnic Chinese Cohort of 232 Patients

Yu Zhou[1], Lu Jiang[1], Jie Liu[2], Xin Zeng[1]*, Qian-ming Chen[1]*

[1]State Key Laboratory of Oral Diseases, West China College of Stomatology, Sichuan University, Chengdu, China

[2]Section of Oral Biology, College of Dentistry, the Ohio State University, Columbus, USA

Abstract

Aim Oral lichen planush (OLP) is a chronic inflammatory disease, and has been reported to have a correlation with hepatitis C virus (HCV) infection in some regional investigations. In this study, we investigated the prevalence of HCV in patients with oral lichen planus in an ethnic Chinese cohort.

Methodology The antibody of HCV infection was detected by using enzyme-linked immunosorbent assay. Moreover, the clinical characteristics of whole the cohort have also been studied, such as the gender, age, clinical type, habits and social factors.

Results Of all 232 patients, the antibody of HCV infection was detected positive in 4 patients (1.72%) using enzyme-linked immunosorbent assay. It was lower than that in control group of 2.5%, but not significant (P=0.309). The positive rate of HCV antibody in the erosive type ones (4.2%) was higher than that in the reticular type ones (1.0%), but this difference was proved to be not significant (P=0.389). The clinical characteristics of whole cohort, such as the gender, age, clinical type, habits and social factors, showed the outcome obtained in the present study were similar to thao of our previous study.

Conclusion HCV may play no etiological role in oral lichen planus in ethnic Chinese OLP patients**.**

Keywords hepatitis C virus, oral lichen planus, epidemiology, Chinese cohort

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Introduction

Lichen planus (LP) is a chronic inflammatory disease that affects skin and mucous membranes of squamous cell origin. The oral form of lichen planus (OLP) seems more common, chronic, and recalcitrant than the cutaneous type, with prevelance ranging from 0.5% to 2% in the general population (Edwards and Kelch, 2002), persisting up to more than 20 years without spontaneous remission (Miles and Howard, 1996). OLP causes bilateral white striations, papules, or plaques on the buccal mucosa, tongue, and gingivae. Erythema, erosions, and blisters may or may not be present (Bermejo-Fenoll and López-Jornet, 2006). Since the characteristics of persistence and anxiety eruption (aching and maligant transformation), OLP remarkably cut down the patient's quality of life.

However, the etiology of OLP is still undefined. To date, some scholars advocate that the central role may be accredited to T lymphocytes, mast cells, intercellular adhesion molecule-1 (ICAM-1) and major histocompatibility complex class Ⅱ antigens (Dissemond, 2004). The factor of psychosomatic disorders has also been involved. Ivanovski *et al*. showed that prolonged stress evidenced by hypochondriasis, depression, and hysteria may contribute to psychosomatization in the OLP subjects (Ivanovski *et al*., 2005). Other authors prefer genetic predisposition by demonstrating that OLP affected families have an increased frequency of HLA-B7 (De Moura Castro Jacques *et al.*, 2003). Moreover, several studies

have shown that hepatitis C virus (HCV) infection is supposed to be a potential factor increasing the OLP susceptibility, and OLP has been reported as an extra-hepatic manifestation of HCV infection (Campisi *et al*., 2004). However, it is controversial since the incidence of the coexistence of OLP and HCV varies remarkably in different geographic regions (Al Robaee and Al Zolibani, 2006).

In China, the studies of prevalence of HCV in OLP patients in the last 10 years consistently demonstranted that HCV was significantly associated with OLP, with prevalence ranging from 11.7% to 29.3% (Zhang *et al*., 1998; Huang, 1999; Wu, 2000; Huang *et al*., 2000; Zhang and Wang, 2000). However, the size of the studied group (from 31 to 80) in these studies seems too small to be completely convincing. To counteract, we conduct this larger-scale study to determine whether the correlation between HCV infection and OLP exists or not in ethnic Chinese population. Meanwhile, the clinical and epidemic characteristics of the OLP patients have also been recorded and analysed.

Patients and methods

Subjects

This study was held in West China Hospital of Stomatology, Sichuan University, and ratified by the Committee for the Use of Human Subjects in Research, Sichuan University. A total of 232 consecutive patients with OLP were enlisted in from January 2005 to December 2006. Meanwhile, 240 gender and age-matched patients with other oral mucosal diseases (recurrent aphthous ulcer, burning mouth syndrome, fissured tongue, geographic glossitis, chronic cheilitis) were recruited as the control group. All the recruits voluntarily provided signed written informed consent. Based on the definition of OLP by World Health Organization (Kramer *et al.*, 1978) and other recent report (van der Meij *et al.*, 2003), the patients were all clinically and partially pathologically confirmed when necessary by proficient specialists in oral medicine and oral pathology with more than 10 years experience. The typical clinical pictures were shown (Figures 1, 2 and 3).

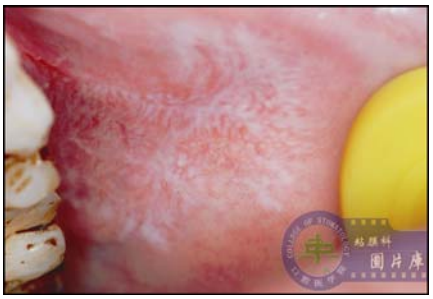

Figure 1 Reticular fom of oral lichen planus: white striations on the buccal mucosa

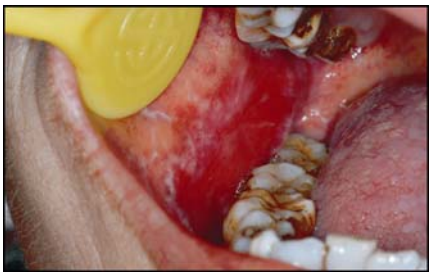

Figure 2 Atrophic/erythematous fom of oral lichen planus: erythematous mucosa with white striations

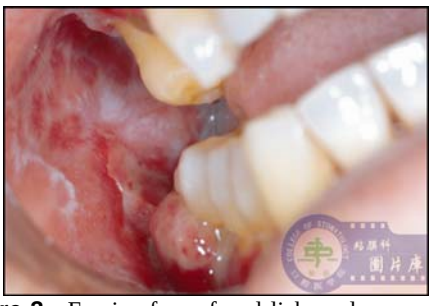

Figure 3 Erosive fom of oral lichen planus: combination of ulceration, erythematous, and keratosis

Serologic examination

The sera of the patients were screened for the anti-HCV antibodies by using the third generation enzyme-linked immunosorbent assay (ELISA Ⅲ; Shanghai Kehua Biotechnology Co., Ltd, China) according to the manufacturer's instructions. Briefly, first, place 100 μL sample dilution plus 10 μL patient's serum into the testing well, 100 μL HCV^+ serum into 2 wells for positive control, 100 μL HCV^- serum into 2 wells for negative control, and 100 μL sample dilution into 1 well for blank control, then incubate at 37℃ for 30 minutes. Second, discard the solution and then wash all the wells 5 times. Third, place 100 μL enzyme-compound into each well, and incubate the plate at 37℃ for 30 minutes again, then discard the solu-

tion and wash the wells as before. Subsequently, add chromogenic reagent A and B 50 μL respectively into each well, after the incubation at 37℃ for 30 minutes, place a stop buffer of 50 μL into each well. Finally, assess the value of optical density (OD value) at a wave length of 450 nm within 10 minutes. The blank control is used for zero setting, and samples were judged to be positive when the OD value were equal to or larger than COV (COV=0.1* mean OD valve of positive control + mean OD value of negative control), and others were considered to be negative.

The latest largest-scale investigation (assuming ELISA assessment) of HCV-antibody screening in general population (Liu and Wei, 2007) was used as the control. In this study, the rate of HCV infection in the general population had been demonstrated as 2.5%.

Questionnaire survey

The questionnaire comprised various topics. These were: gender, age, illness course, complaint, educational level, occupation, living condition, smoking, drinking, eating habits, lesion form, lesion site, lesion surrounding (dental cusp, oral hygiene), malignant transformation, as well as the presence of systemic disease, and skin involvement. As to the classification of the lesion, we categorized OLP into 3 clinical forms based on the literature (Silverman *et al*., 1985; Chainani-Wu *et al*., 2001; Xue *et al*., 2005). These are reticular, atrophic/erythematous, and erosive. If the patient had more than one lesion at the point of examination, this would be ranked as the most severe form.

Statistical analysis

Data analysis was performed with the Statistical Package for the Social Science (Windows 10.0, SPSS Inc., USA). The Chi square test was used to compare lesion forms according to symptoms as well as HCV affection rate in reticular and erosive lesion type. The Rank-sum test was used to compare the lesion form according to gender, occupation, inhabitation, dental margin, smoking and alcohol consumption, systematic disease, and eating habits. Rank-correlation test was used to compare the lesion form according to age, educational level and oral hygiene. A probability of 0.05 or less was considered significant.

Results

The situation of HCV infection in OLP patients

Four patients (1.72%) demonstrated positive antibodies against HCV, which was lower than the prevalence of 2.5% in control group, but not significant (P=0.791>0.05). Among the 4 HCV infected patients, 2 were detected liver cirrhosis, and the other 2 were chronic hepatitis C.

The clinical characteristics of the HCV positive OLP patients

As shown in Table 1, in the present study, one

Table 1 Pheromone of HCV infected OLP patients

Case No	1	2	3	4
Gender/age(year)	Male/44	Female/42	Female/52	Female/59
Liver disease	chronic hepatitis C	chronic hepatitis C	liver cirrhosis	liver cirrhosis
Occupation	Yes/brain worker	Yes/brain worker	Yes/brain worker	Retired/brain orker
Education experience (year)	15	15	15	12
Inhabit condition	City/cohabiting	City/cohabiting	City/cohabiting	City/alone
Smoking/drinking	Nil/nil	Nil/nil	Nil/nil	Nil/nil
Eating habit	Spicy	Spicy	Spicy	mild
Skin involvement	No	No	No	No
Systemic disease		rheumatism		
Malignant transformation	No	No	No	No
Lesion type	erosive	erosive	reticular	erosive
Lesion site	Lip	Buccal	Buccal	Buccal/tongue/lip
Course of disease (month)	5	24	9	61

male and three female patients were detected positive antibody against HCV. These were all in 40–59 years group, had endured OLP from 5 to 61 months, with a mean of 25 months. Of the four HCV infected OLP patients in our study, three had sharp dental cusps around the lesion, and two were in poor oral hygiene, three patients favored spicy diet, consumed no cigarettes or alcohol. All the four HCV infected OLP patients were urban brain workers with education experience from 12 to 15 years, one case had retired and lived alone. Of the four HCV infected OLP patients, one suffered rheumatism except for HCV infection and OLP, and none were found with skin involved or malignant transformed. Three of the four HCV infected OLP patients presented erosive lesion, and the other one manifested reticular lesion, and all complianed of soreness. The infection rate of HCV in the erosive type OLP patients (4.2%) was higher than that in the reticular type ones (1.0%), but this difference was proved to be not significant (P= 0.389>0.05).

The clinical characteristics of the total studied OLP patients

Apart from HCV detection, we also analyzed the epidemic characteristics of OLP, especially the correlation between precipitating factors (such as educational level, occupation, living conditions, smoking, drinking, eating habits, lesion surrounding) and lesion form (Tables 2–5).

Table 2 Lesion profiles in different age and gender

	Lesion type *n* (%)			Total
	Reticular	Atrophic/ erythematous	Erosive	
	100 (43.1)	61 (26.3)	71 (30.6)	232 (100)
Age group (years)*				
18–19	2 (2.0)	1 (1.6)	1 (1.4)	4 (1.7)
20–29	9 (9.0)	4 (6.6)	4 (5.6)	17 (7.3)
30–39	27 (27.0)	14 (21.4)	18 (25.4)	59 (25.4)
40–49	29 (29.0)	11 (23.0)	20 (28.2)	60 (25.9)
50–59	23 (23.0)	22 (46.0)	19 (26.7)	64 (27.6)
60–	10 (10.0)	9 (14.8)	9 (12.7)	28 (12.1)
Gender				
male	23 (23.0)	15 (24.6)	26 (36.6)	64 (27.6)
female	77 (77.0)	46 (75.4)	45 (63.4)	168 (62.4)

*P=0.000, **P=0.16.

Table 3 Incidence of site involvement in each lesion form of OLP

Site	Total	Reticular	Atrophic/erythematous	Erosive
	n (%, *N*=232)*	*n* (%, *N*=100)	*n* (%, *N*=61)	*n* (%, *N*=71)
Buccal	185 (79.8)	75 (75.0)	48 (78.7)	62 (87.3)
Dorsal tongue	50 (21.6)	28 (28.0)	8 (13.1)	14 (19.7)
Floor of mouth and ventral tongue	33 (14.2)	15 (15.0)	4 (6.5)	14 (19.7)
Gingiva	31 (13.4)	16 (16.0)	10 (16.4)	5 (7.0)
Vestivular groove	30 (14.9)	13 (13.0)	11 (18.0)	6 (8.5)
Lower lip	16 (12.9)	9 (9.0)	5 (8.2)	2 (2.8)
Upper lip	2 (0.8)	1 (1.0)	1 (16.4)	0 (0)
Palate	3 (1.3)	3 (3.0)	0 (0)	0 (0)

*% of subgroup.

Table 4 Features of each subtype of oral lichen planus

	Reticular	Atrophic/erythematous	Erosive	Total	*P*
	100 (43.1)	61 (26.3)	71 (30.6)	232 (100)	
Symptom					0.002
Yes	9 (9.0)	34 (55.7)	61 (85.9)	104 (44.8)	
No	91 (91.0)	27 (44.3)	10 (14.1)	128 (55.2)	
Occupation					0.009
Brain worker	26 (26.0)	20 (32.8)	27 (38.0)	73 (31.5)	
Manual worker	38 (38.0)	26 (42.7)	27 (38.0)	91 (39.2)	
Retiring and unemployment	36 (36.0)	15 (24.5)	17 (24.0)	68 (29.3)	
Educational level					0.000
0–6	17 (17.0)	14 (23.0)	19 (26.8)	50 (21.6)	
7–9	22 (22.0)	16 (26.3)	17 (23.9)	55 (23.7)	
10–12	18 (18.0)	15 (25.0)	15 (21.1)	48 (20.7)	
13–15	22 (22.0)	10 (16.4)	14 (19.7)	46 (19.8)	
16–-	21 (21.0)	6 (9.8)	6 (8.5)	33 (14.2)	
Inhabited condition					0.076
Living alone	5 (5.0)	4 (6.6)	4 (5.6)	12 (5.1)	
Cohabiting	95 (95.0)	57 (93.4)	67 (94.4)	220 (94.9)	
Inhabited place					0.532
City	72 (72.0)	43 (70.5)	45 (63.3)	160 (69.0)	
Suburb	8 (8.0)	10 (16.4)	7 (9.9)	25 (10.8)	
Country	20 (20.0)	8 (13.1)	19 (26.8)	47 (20.2)	
Amount of calculus[#]					0.301
0	17 (17.0)	8 (13.1)	8 (11.3)	33 (14.2)	
1	38 (38.0)	31 (50.8)	30 (42.3)	99 (42.7)	
2	24 (24.0)	10 (16.4)	14 (19.7)	48 (20.7)	
3	21 (21.0)	12 (19.7)	19 (26.7)	52 (22.4)	
Dental margin					0.011
Sharp	32 (32.0)	22 (36.1)	33 (46.5)	87 (37.5)	
Mutic	68 (68.0)	39 (63.9)	38 (53.5)	145 (62.5)	
Eating habit					0.000
Spicy	50 (50.0)	47 (77.5)	46 (64.8)	143 (61.6)	
Bland	50 (50.0)	14 (22.5)	25 (35.2)	89 (38.4)	
Smoking					0.04
Yes	26 (26.0)	7 (11.4)	12 (16.9)	45 (19.4)	
No	74 (74.0)	54 (88.6)	59 (83.1)	187 (80.6)	
Drinking					0.197
Yes	25 (25.0)	9 (14.7)	15 (21.1)	49 (21.1)	
No	75 (75.0)	52 (85.3)	56 (78.9)	183 (88.9)	
Systematic disease					0.005
Yes	22 (22.0)	20 (32.8)	26 (36.6)	72 (31.0)	
No	78 (78.0)	41 (67.2)	41 (63.4)	160 (69.0)	

Data given as *n* (%). # oral hygiene was evaluated by the amount of calculus as follow: (0) No calculus present. (1) Supragingival calculus covering not more than third of the exposed tooth surface. (2) Supragingival calculus covering more than one third but not more than two thirds of the exposed tooth surface or the presence of individual flecks of subgingival calculus around the cervical portion of the tooth or both. (3) Supragingival calculus covering more than two third of the exposed tooth surface or a continuos heavy band of subgingival calculus around the cervical portion of the tooth or both.

Table 5 Profiles of the two OLP patients with Malignant transformation

Case	Age /year	Gender	Site	Clinical type at the point of transformation	Smoking	Drinking	Course /month	Systemic diseases
1	52	male	Dorsum of tongue	erosive	yes	yes	180	hepatitis B
2	66	male	lower lip	erosive	no	yes	38	gastric ulcer

The mean age of patients was (45.9 ± 13.3) years, with end points of 18 and 76. The majority (53.4%) of patients were aged 40 to 59 years, and females were more than males in the ratio of 2.6:1. Reticular form was the most common (43.3%), followed by atrophic/erythematous (26.4%) and erosive (30.3%). Two male patients (0.86%) with erosive lesion were recorded with malignant transformation, which was significantly higher than the prevalence in general male population, which is reported to be about 8.7/100 000 (Guo and Zhang, 2003) (P=0.000 0). Age, educational level, occupation, smoking, systematic disease, sharp dental margin around lesions as well as the eating habit had statistically significant correlations with the lesion form (P<0.05). In contrast, the lesion form was unrelated to gender, alcohol consumption, living conditions and poor oral hygiene (P>0.05). In the results, no remarkable difference was found from that of our former study in 767 Chinese OLP patients (Chen *et al*., 2008).

Discussion

Oral lichen planus is a chronic inflammatory mucocutaneous disease, whose etiology is still mysterious. To date, immunologic disorder, mental disease, genetic predisposition, systemic illness and HCV infection *etc* are proved to play important role in OLP pathogensis by some scholars.

As yet, the correlation between HCV and OLP is still controversial. First, some confirmative evidence has been found in laboratory tests. Pilli *et al*. have manifested the HCV-specific T-cell response at the site of the lesion (Pilli *et al*., 2002), and HCV RNA has been detected in epithelial cells from oral lichen planus lesions using *in situ* hybridization through other experiments (Arrieta *et al*., 2000). On the other hand, the outcome of epidemic investigations varies considerably in different geographic regions. In Japan, Italy, Nigeria, Thailand (Nagao *et al*., 1995; Carrozzo *et al*., 1996; Figueiredo *et al*., 2002; Daramola *et al*., 2003; Klanrit *et al*., 2003; Lodi *et al*., 2004), the prevalence of HCV infection in OLP patients ranging from 8.33% to 60% was statistically higher than the controls. However, reports from other areas, such as Holland,Germany, Serbia, Rio de Janeiro (van der Meij *et al*., 2000; Friedrich *et al*., 2003; Bokor-Bratic *et al*., 2004; Cunha *et al*., 2005) showed no difference in the HCV infection rate between the patients with OLP and the common population. In this study, we investigated the prevalence of HCV in 232 ethnic Chinese OLP patients and no association was found between these two diseases. Why does it vary so considerably in different geographic regions? Human leukocyteantigen (HLA) may play a very important role in the variation. OLP had been reported associated with HLA-DRB1*09 and DRB1*07 in Chinese patients (Li *et al*., 2006), HLA-DRB1 *0101 in Mexican patients (Luis-Montoya1 *et al*., 2007), HLA-DR3 in Swedish patients (Homey *et al*., 2000), HLA-DR2 in Israeli Jewish patients (Shai and Halevy, 1992), and HLA-DR9 in Japanese patients (Watanabe *et al*., 1986). Carrozzo *et al*. proposed that HCV-related OLP appears to be associated with the human leukocyteantigen (HLA) class Ⅱ allele HLA-DR6. This could partially explain the particular geographic heterogeneity of the association between HCV and OLP (Carrozzo *et al*., 2001). Excluding the aforementioned standpoint, the difference of study sample size, age and sex structure, as well as sensitivity of the assay methods may also affect the results. Regarding the age structure, HCV peaks dramatically over the fifth decade of age. Therefore, the age of the enrolled ones would affect the result considerably. Concerning assay method, for example, in the Japan study (Nagao *et al*., 1995), polymerase chain reaction (which is more sensitive than ELISA, but with ahigh percentage of false positives) was used for the HCV RNA assay.

Chung *et al*. had reported that, in southern Taiwan, OLP was significantly associated with HCV, particularly atrophic-erosive type (Chung *et al*., 2004), which is consistent with the conclusion which Ghodsi *et al*. had obtained in the Tehran cohort (Ghodsi *et al*., 2004). Similar results were found in our study. The infection rate of HCV in the erosive type of OLP was 4.2%, which was higher than that in the reticular type lesions, however, no significant results were obtained.

Moreover, some other factors, such as smoking, systemic disease, eating habits, as well as sharp dental margin around lesions should have more attention in clinical management. Routine further consultation is necessary for screening malignant transformation.

Conclusion

In conclusion, HCV seems to play no etiologic role in ethnic Chinese OLP patients. To clarify the correlation between OLP and HCV, more active epidemic investigation and penetrating laboratory tests should be carried out.

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*Corresponding authors: Qian-ming Chen, Xin Zeng

Address: State Key Laboratory of Oral Diseases, West China College of Stomatology, Sichuan University, No.14, 3rd Section, Renmin South Road, Chengdu 610041, China

Tel & Fax: 86 28 85405251 E-mail: qmchen@scu.edu.cn, zengxin22@163.com