Relationship of Oral Lichen Planus to Hepatitis C Virus in Southern Taiwan

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Oral lichen planus (OLP) is a relatively common skin and oral disease that manifests as a mucous reaction to a variety of etiologic factors, including autoimmune disease, drug reaction, diabetes mellitus (DM), hypertension, hepatitis C virus (HCV), urolithiasis, psychogenic factors, and bacterial infection. The purpose of this study was to investigate the relationship between HCV infection and OLP as there is a high prevalence of HCV infection in Taiwan. A total of 1,075 subjects aged at least 15 years participated in the study. The total prevalence of OLP was 3% (32/1,075). OLP was significantly associated with DM (odds ratio, OR, 3.09) and HCV (OR, 2.05). Atrophic-erosive OLP (13/32) and reticular OLP (21/32) were significantly associated with HCV and DM, respectively. Logistic regression analysis showed that elevation of alanine aminotransferase (ALT) significantly increased the risk of atrophic-erosive OLP. We concluded that OLP is significantly associated with HCV and DM in southern Taiwan, particularly in HCV patients with elevated serum ALT levels and atrophic-erosive OLP.

Key Words: oral lichen planus, prevalence, hepatitis C virus, diabetes mellitus

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Oral lichen planus (OLP) is a common benign disease in many countries [1]. The overall prevalence of OLP varies in different studies from 0.02% to 1.9% [2,3]. OLP represents a mucous reaction seen in a variety of conditions such as diabetes mellitus (DM), hypertension, rheumatic-collagen disease, urolithiasis, chronic liver disease, exposure to idiosyncratic drugs, chemicals or dental restorations, and betel quid chewing [1,4]. In 1978, the controversial relationship between lichen planus and chronic liver disease was first reported [5]. In 1988, Cottoni et al reported that 28 of 62 lichen planus cases were associated with other diseases, including 16 cases of chronic liver disease and five cases of DM [6]. In 1994, Jubert et al described six cases of lichen planus associated with chronic active hepatitis and actively replicating hepatitis C virus (HCV) [7]. Recently, van der Meij and van der Waal stated that the 18 published studies on HCV infection and OLP suggest that HCV is the main cause of liver disease in patients with OLP and could be involved in the development of OLP [8]. Thus, geographic differences in the prevalence of OLP associated with HCV infection might simply reflect overall differences in HCV epidemiology.

A community survey revealed a 2.5% prevalence of HCV infection among 1,500 subjects in a northern county in Taiwan [9]. In another study conducted in eastern Taiwan, the prevalence was 3.6% in some villages and 20% to 30% in others [10]. The significant difference in the prevalence of HCV infection among the villages was suspected to be associated with OLP. The association between HCV and OLP has not been thoroughly investigated in Taiwan. The

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purpose of this study was to identify the association between HCV and OLP in southern Taiwan.

Materials and Methods

A community-based sample was chosen for this study. Using high hepatoma mortality and high average alanine aminotransferase (ALT) levels as the criteria for high HCV prevalence, two villages with high prevalence and three villages with low prevalence were selected using the Taiwan Cancer Mortality Map and ALT data from local health bureaus in Tainan and Kaohsiung prefectures in southern Taiwan. Between September 1998 and April 1999, participants aged at least 15 years were clinically examined.

Oral examination and diagnosis of oral mucous lesions

The diagnostic criteria for OLP were based on the recommendation of the World Health Organization in 1980 [11] and the Scully classification [1]. Reticular OLP was defined by the presence of slender white lines (Wickham's striae) radiating from the plaque, atrophic OLP by a diffuse red area and whitish Wickham's striae of the oral mucosa, and erosive OLP by lesions of atrophic type with ulcers. Participants were divided into two groups according to the clinical type of lesion observed: reticular OLP (group 1) and atrophic-erosive OLP (group 2).

Serum sample collection and analysis

Blood (10 mL) was drawn from each subject and serum samples were stored at –20°C. Anti-HCV antibodies to HCV-encoded antigens (c100-3, c33, c22) were assayed using a third-generation HCV enzyme immunosorbent assay (ELISA) system according to the manufacturer's instructions (Abbott 3.0 Anti-HCV EIA; Abbott Laboratories, Abbott Park, IL, USA). Samples with optical densities above the cutoff value were considered positive. Reactive samples were retested and were considered positive if both tests were reactive. Serum ALT and aspartate aminotransferase (AST) levels were determined using a kinetic assay with commercial reagents (dry chemistry multi-film; Eastman Kodak Company, Rochester, NY, USA) in a Kodak Ektachem 700XR Analyzer C Series (Eastman Kodak Company). ALT levels of more than 55 U/L and AST levels of more than 45 U/L were considered abnormal.

Interview

Trained research assistants or public health nurses interviewed study subjects using a structured questionnaire. The questionnaire gathered data on age, gender, education years, and medical history. Subjects were considered to have drug or food allergies, DM, kidney/urinary tract stone, or hypertension if this had been diagnosed by physicians before the study or if they were currently taking medication for the disease.

Statistical analysis

Oral examination results and information from the questionnaires were analyzed using the SAS statistical software package, version 8.0 (SAS Institute Inc, Cary, NC, USA). Associations between OLP and each variable in the questionnaire were tested using the Chi-squared or Fisher's exact test. Relationships between two categorical variables were tested using the Chi-squared test. However, for tables with more than 20% of expected cell sizes less than 5, Fisher's exact test was used. Logistic regression analysis was used to investigate the associations of HCV, serum ALT and serum AST with OLP. Results were considered statistically significant if the p value was less than 0.05.

Results

A total of 1,075 subjects participated in the study. The average age was 49.81 ± 17.34 years (mean ± standard deviation). The total prevalence of OLP was 3% (32/1,075). The associations of OLP with gender, age, educational level, medical history, and serum ALT and AST levels are shown in Table 1. The prevalence among men (3.61%) was higher than among women (2.37%); the highest prevalence was found in patients aged at least 65 years (5.00%), but this was not statistically significant. The occurrence of OLP was significantly associated with DM (OR, 3.09; $p = 0.019$) and HCV (OR, 2.05; $p = 0.044$).

OLP was divided into only two subtypes, reticular and atrophic-erosive, because the appearance of erosive OLP is similar to that of atrophic OLP but it is very rare. Of the 32 patients with OLP, 21 (65.6%) had reticular OLP and 13 (40.6%) had atrophic-erosive OLP; two patients had mixed type in their oral cavity. The associations of OLP subtype with DM, HCV and ALT and AST levels are shown in Tables 2 and 3. Reticular OLP was significantly associated with DM (OR, 3.90; $p = 0.032$) and atrophic-erosive OLP was significantly associated with HCV (OR, 3.05; $p = 0.037$) and a serum ALT of more than 55 U/L (OR, 3.65; $p = 0.014$).

In the serum analysis, we found that OLP was not associated with AST (OR, 1.01; $p = 0.989$) or ALT levels (OR, 1.94; $p = 0.084$)

Table 1. Association of oral lichen planus (OLP) prevalence with demographic data and medical history

	OLP				
	Yes, *n* (%)	No, *n* (%)	OR	*p**	95% CI
Gender					
Male	19 (3.61)	507 (96.39)	0.65	0.230	0.32, 1.32
Female	13 (2.37)	536 (97.63)	1.00		
Age (yr)					
15–24	2 (1.74)	113 (98.26)	1.00		
25–34	4 (3.45)	112 (96.55)	2.02	0.683†	0.36, 11.24
35–44	4 (2.12)	185 (97.88)	1.22	1.000†	0.22, 6.78
45–54	0 (0.00)	183 (100.00)	0.12	0.148†	0.01, 2.60
55–64	10 (4.31)	222 (95.69)	2.55	0.350†	0.55, 11.81
≥ 65	12 (5.00)	228 (95.00)	2.97	0.242†	0.65, 13.51
Education (yr)					
≤ 9	29 (2.91)	967 (97.09)	0.76	0.506†	0.23, 2.55
> 9	3 (3.80)	76 (96.20)	1.00		
Allergy					
Yes	6 (4.44)	129 (95.56)	1.64	0.283	0.67, 4.05
No	26 (2.77)	914 (97.23)	1.00		
Diabetes mellitus					
Yes	5 (7.81)	59 (92.19)	3.09	0.019	1.15, 8.31
No	27 (2.67)	984 (97.33)	1.00		
Hypertension					
Yes	5 (3.13)	155 (96.88)	1.06	0.905	0.40, 2.80
No	27 (2.95)	888 (97.05)	1.00		
Stone					
Yes	1 (1.72)	57 (98.28)	0.56	1.000†	0.08, 4.16
No	31 (3.05)	986 (96.95)	1.00		
Hepatitis C virus					
Yes	14 (4.65)	287 (95.35)	2.05	0.044	1.01, 4.18
No	18 (2.33)	756 (97.67)	1.00		
Aspartate aminotransferase					
> 45 U/L	5 (2.99)	162 (97.01)	1.01	0.989	0.38, 2.66
≤ 45 U/L	27 (2.97)	881 (97.03)	1.00		
Alanine aminotransferase					
> 55 U/L	10 (4.81)	198 (95.19)	1.94	0.084	0.92, 4.11
≤ 55 U/L	22 (2.54)	845 (97.46)	1.00		

*χ^2 or †Fisher's exact test. OR = odds ratio; 95% CI = 95% confidence interval.

(Table 1), but atrophic-erosive OLP was significantly associated with ALT level (OR, 3.65; $p = 0.014$) (Table 3). Logistic regression analysis for participants with atrophic-erosive OLP with HCV infection showed that ALT had a significant synergistic effect (Table 4). The prevalence of atrophic-erosive OLP among subjects with HCV infection and elevated ALT was 20.1-fold higher (95% confidence interval, 95% CI, 4.48–89.85) than in healthy subjects. The prevalence among participants who only had HCV infection without elevated ALT was 1.6-fold higher (95% CI, 0.31–8.49) than in healthy participants.

Table 2. Relationship between prevalence of reticular oral lichen planus (OLP) and diabetes mellitus, hepatitis C virus, and levels of aspartate aminotransferase and alanine aminotransferase

	Reticular OLP				
	Yes, *n* (%)	No, *n* (%)	OR	*p**	95% CI
Diabetes mellitus					
Yes	4 (6.25)	60 (93.75)	3.90	0.032†	1.38, 11.05
No	17 (1.68)	994 (98.32)	1.00		
Hepatitis C virus					
Yes	8 (2.66)	293 (97.34)	1.60	0.298	0.66, 3.87
No	13 (1.68)	761 (98.32)	1.00		
Aspartate aminotransferase					
> 45 U/L	3 (1.80)	164 (98.20)	0.90	1.000†	0.26, 3.11
≤ 45 U/L	18 (1.98)	890 (98.02)	1.00		
Alanine aminotransferase					
> 55 U/L	5 (2.40)	203 (97.60)	1.31	0.601	0.48, 3.61
≤ 55 U/L	16 (1.85)	851 (98.15)	1.00		

*χ^2 or †Fisher's exact test. OR = odds ratio; 95% CI = 95% confidence interval.

Table 3. Association between the prevalence of atrophic-erosive oral lichen planus (OLP) and diabetes mellitus, hepatitis C virus, and levels of aspartate aminotransferase and alanine aminotransferase

	Atrophic-erosive OLP				
	Yes, *n* (%)	No, *n* (%)	OR	*p**	95% CI
Diabetes mellitus					
Yes	2 (3.13)	62 (96.88)	2.93	0.179†	0.68, 12.62
No	11 (1.09)	1,000 (98.91)	1.00		
Hepatitis C virus					
Yes	7 (2.33)	294 (97.67)	3.05	0.037	1.07, 8.68
No	6 (0.78)	768 (99.22)	1.00		
Aspartate aminotransferase					
> 45 U/L	2 (1.20)	165 (98.80)	0.99	1.000†	0.22, 4.50
≤ 45 U/L	11 (1.21)	897 (98.80)	1.00		
Alanine aminotransferase					
> 55 U/L	6 (2.88)	202 (97.12)	3.65	0.014	1.30, 10.23
≤ 55 U/L	7 (0.81)	860 (99.19)	1.00		

*χ^2 or †Fisher's exact test. OR = odds ratio; 95% CI = 95% confidence interval.

Discussion

Demographic analysis in this study showed that OLP is a disease of adulthood occurring at ages ranging from 30 to 70 years and afflicting both sexes, although some surveys have found that 60% to 65% of patients are female [1]. We also found that there was a greater prevalence of OLP in males older than 65 years with a higher education level, but the difference was not significant.

The relationship between DM and OLP was suggested by Grinspan et al [12], and since then, many investigators have studied the problem. The prevalence of OLP in patients with DM varies from 0% to 5.7% (Table 5) [12–21]. A match-pair study by Van Dis and Parks showed no association

Table 4. Logistic regression analysis for oral lichen planus (OLP) with hepatitis C virus (HCV) and levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT)

Variable	Parameter estimate	SE	Wald χ^2	*p*	OR	Confidence limit		OLP	
						Lower	Upper	*n*/Total	%
Total									
Intercept	–3.78	0.26	209.85	0.0001					
HCV+ALT+AST	0.34	0.64	0.28	0.5986	1.40	0.40	4.94	3/97	3.09
HCV+ALT	2.22	0.61	13.35	0.0003	9.25	2.80	30.51	4/23	17.39
ALT+AST	0.76	0.77	0.98	0.3221	2.14	0.47	9.69	2/43	4.65
HCV	0.66	0.47	2.00	0.1571	1.93	0.78	4.82	7/166	4.22
ALT	0.00	1.04	0.00	0.9988	1.00	0.13	7.73	1/45	2.22
Reticular OLP									
Intercept	–4.10	0.30	181.79	0.0001					
HCV+ALT+AST	–0.47	1.05	0.20	0.6576	0.63	0.08	4.92	1/97	1.03
HCV+ALT	1.75	0.80	4.77	0.0289	5.74	1.20	27.54	2/23	8.70
ALT+AST	1.08	0.79	1.89	0.1697	2.94	0.63	13.71	2/43	4.65
HCV	0.63	0.55	1.32	0.2513	1.87	0.64	5.46	5/166	3.01
Atrophic-erosive OLP									
Intercept	–4.90	0.45	118.98	0.0001					
HCV+ALT+AST	1.04	0.84	1.51	0.2197	2.82	0.54	14.72	2/97	2.06
HCV+ALT	3.00	0.76	15.38	0.0001	20.07	4.48	89.85	3/23	13.04
HCV	0.49	0.84	0.34	0.5605	1.63	0.31	8.49	2/166	1.20
ALT	1.11	1.11	1.01	0.3148	3.04	0.35	26.60	1/45	2.22

SE = standard error; OR = odds ratio.

Table 5. Studies of oral lichen planus (OLP) prevalence in patients with diabetes mellitus (DM)

Study	DM, *n*	OLP, *n*	%
Grinspan et al 1965 [12]	70	4	5.71
Martinez Pena 1982 [13]	100	0	0
Lozada-Nur et al 1985 [14]	119	2	1.68
Borghelli et al 1987 [15]	240	1	0.42
Borghelli et al 1988 [16]	584	1	0.17
Albrecht et al 1992 [17]	1,600 (621)	17 (0)	1 (0)
Borghelli et al 1993 [18]	729 (676)	4 (6)	0.55 (0.7)
Van Dis and Parks 1995 [19]	161 (161)	11 (8)	4 (3)
Petrou-Amerikanou et al 1998 [20]	492 (274)	18 (5)	4.2 (1.82)
Guggenheimer et al 2000 [21]	405 (268)	2 (2)	0.5 (0.7)
Chung et al 2004 [present study]	64 (1,011)	5 (27)	7.8 (2.67)

Numbers in parentheses = control group.

between DM and OLP [19]. The prevalence of DM in patients with OLP varies from 1.6% to 38.9% [13,14,22–29] (Table 6). The variation in prevalence is due to differences in criteria for DM. Bagan et al showed that atrophic-erosive lesions are common in patients with OLP associated with DM [29]. The present study showed that the prevalence of OLP among participants with DM was 7.8%, 3.09-fold higher than in normal subjects. Reticular OLP was associated with DM (OR, 3.90; 95% CI, 1.38–11.05). This result is not compatible with that of Bagan et al's study and requires more participants for further analysis.

The relationship between OLP and HCV infection remains controversial. Table 7 summarizes the 11 studies of the relationship between OLP and HCV infection with

Table 6. Studies of diabetes mellitus (DM) prevalence in patients with oral lichen planus (OLP)

Study	OLP, *n*	DM, *n*	%
Grinspan et al 1966 [22]	61	23	37.7
Howell and Rick 1973 [23]	316	41	12.9
Kovesi and Banoczy 1973 [24]	326	17	5.2
Christensen et al 1977 [25]	123	2 (18)	1.6 (10.56)
Hornstein et al 1980 [26]	92	17	8.4
Lundstrom 1983 [27]	40	11	28.0
Silverman et al 1985 [28]	570	33	5.8
Bagan et al 1993 [29]	72	28	38.9
Chung et al 2004 [present study]	32	5	15.6

Numbers in parentheses = DM according to World Health Organization criteria.

Table 7. Studies of hepatitis C virus (HCV) infection in subjects with oral lichen planus (OLP)

Study	Country	HCV prevalence*, %	HCV seropositive OLP	HCV seropositive control
Cribier et al 1994 [30]	France	1.15	3.8% (2/52)	2.6% (3/112)
Bellman et al 1995 [31]	USA	1.80	23% (7/30)†	4.8% (2/41)
Tanei et al 1995 [32]	Japan	2.30	37.8% (17/45)†	6.7% (3/45)
Carrozzo et al 1996 [33]	Italy	0.48	27.1% (19/70)†	4.3% (3/70)
Sanchez-Perez et al 1996 [34]	Spain	0.74	20% (16/78)†	2.4% (2/82)
Dupin et al 1997 [35]	France	1.15	4.9% (5/102)	4.5% (14/306)
Imhof et al 1997 [36]	Germany	0.12	16% (13/84)†	1.1% (1/87)
Bagan et al 1998 [37]	Spain	0.74	23% (23/100)†	5% (5/100)
Mignogna et al 1998 [38]	Italy	0.48	28.8% (76/263)†	3% (3/100)
Ingafou et al 1998 [39]	UK	0.02	0% (0/55)	0% (0/110)
Chuang et al 1999 [40]	USA	1.80	55% (12/22)†	25% (10/40)
Chung et al 2004 [present study]	Taiwan	1.60	43.8% (14/32)†	27.5% (287/1,043)

*World Health Organization, 1999 [41]; †statistically significant difference.

control groups published between 1994 and 1999 [30–40]. Significant associations were found in southern European countries [33,34,37,38], the USA [31,40], Germany [36], and Japan [32]. On the other hand, no significant association was found in the UK [39], France [30,35], or the Netherlands [8]. Geographic differences in the association of OLP with HCV infection might simply reflect overall differences in HCV prevalence. These were mostly hospital-based studies. Nine showed that OLP was significant in HCV infection. The present community-based study found a significant association between OLP and HCV infection in southern Taiwan. The prevalence of atrophic-erosive OLP among participants with HCV infection was three-fold higher than in healthy people. This result is compatible with the Sanchez-Perez et al study [34]. We also noted the synergistic effect of ALT, but not AST, elevation on the prevalence of atrophic-erosive OLP. Among participants with HCV infection and elevated ALT, the prevalence of atrophic-erosive OLP was 20-fold higher than in healthy people. On the other hand, among participants with HCV infection but no elevation of ALT, the prevalence was 1.63-fold. This suggests that the host effect is a more important factor than the viral effect in the relationship between OLP and HCV.

OLP represents a mucous reaction seen in a variety of conditions such as DM, hypertension, rheumatic-collagen disease, urolithiasis, chronic liver disease, and exposure to idiosyncratic drugs and chemicals. This study showed that OLP is associated with HCV infection and DM in southern Taiwan.

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南台灣口腔扁平苔癬和C型肝炎病毒之間的關係

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扁平苔癬是常侵犯皮膚和口腔黏膜的疾病，其確實原因目前並不知道，但常常和下列疾病同時產生：自體免疫疾病、目前服用某些藥物、糖尿病、高血壓、C型肝炎、尿結石、精神方面疾病和某些細菌感染有關。而台灣是屬於C型肝炎高盛行率的地區，所以本研究是探討南台灣口腔扁平苔癬和C型肝炎之間的關係。本篇論文的結果：在1,075位大於15歲以上的南台灣居民，口腔扁平苔癬盛行率為3% (32/1,075)。利用Chi-squared檢定 ($p < 0.05$) 探討口腔扁平苔癬和各全身疾病間的關係，得知糖尿病 ($p = 0.019$；OR = 3.09) 和C型肝炎 ($p = 0.044$；OR = 2.05) 有顯著統計上相關；其中具有C型肝炎病毒的民眾和萎靡型(atrophic-erosive)口腔扁平苔癬有顯著統計上相關，而糖尿病的患者和網狀型 (reticular) 口腔扁平苔癬有顯著統計上相關。在迴歸分析的研究，具有C型肝炎病毒的民眾若同時具有血清 alanine aminotransferase (ALT) 升高則對其患萎靡型口腔扁平苔癬有明顯加成性 (OR = 9.25)。本論文所獲得的結論：南台灣居民口腔扁平苔癬和糖尿病與C型肝炎病毒有顯著統計上相關性；且當血液中有C型肝炎病毒若同時具有血清ALT升高則更易患萎靡型口腔扁平苔癬。

關鍵詞：口腔扁平苔癬，C型肝炎，盛行率，糖尿病

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