

Lack of Association between Oral Lichen Planus and Hepatitis B and C Virus Infection - a Report from Southeast Iran

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Abstract

Background: Oral lichen planus (OLP) is a chronic autoimmune disease with an unknown etiology. Dentists are usually the first medical practitioners to diagnose this condition although it also affects body parts other than the oral mucosa. Several studies have reported an association between the OLP and hepatitis B and C infections. This study aimed to determine the prevalence of hepatitis B virus (HBV) antigen and hepatitis C virus (HCV) antibodies in patients with OLP compared with healthy controls. **Methods:** In this case-control study, 50 patients with clinical and histopathological characteristics of OLP, and 50 age- and sex-matched healthy controls supplied serum samples (5 mL) for evaluation by ELISA. Data were analyzed using SPSS Software, version 21. Chi-square test was applied as appropriate. **Results:** In this study, the 50 patients with OLP (33 females and 17 males) had a mean age of 42.0 ± 14.5 years, and the 50 healthy subjects (33 females and 17 males) a mean age of 41.9 ± 13.7 years. None demonstrated any evidence of HBV antigen or HCV antibodies. **Discussion:** We could not detect any association between OLP and viral hepatitis. This could be attributed to a lower prevalence of hepatitis viruses compared to other countries or genotypic variation or other etiological factors contributing in our cases.

Keywords: Oral Lichen Planus- Hepatitis C- Hepatitis B

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Introduction

Lichen planus (LP) is a chronic common mucocutaneous inflammatory disorder of uncertain etiology (Gheorghe et al., 2014). With characteristic clinical and pathological features affecting the skin, nails, and hair (Mohd Hanafiah et al., 2013). The prevalence of LP seen in the general population varies according to different studies, but it is estimated to be 0.9–1.2% (Glick, 2014), occurs predominantly in females with a female: male ratio of 1.4:1 and in the age group of third to seventh decade of life, mostly noticed in buccal mucosa, gingiva and tongue. They are present bilaterally in most cases (Rajendran, 2009). Classically present as six types clinically: Reticular (fine white striae cross each other in the lesion), Atrophic (areas of erythematous lesion surrounded by reticular components), papular type, bullous type, plaque type, erosive or ulcerative type. The reticular type of oral lichen planus is often asymptotically can be seen clinically. Ulcerative type in which erythematous areas are seen surrounded by reticular elements (Ingafou et al., 2006).

Although the etiopathogenic mechanism of oral lichen planus is not fully elucidated, recent research suggests that immunological mechanisms play an important role, this disease being considered as having auto-immune

nature, mediated by T CD 8 + cells, macrophages and Langerhans cells. Langerhans cells and macrophages in the basal epithelial layer provide antigenic information for T CD 8 + cells activated against basal layer (Glick, 2014).

During recent years, an association between OLP and hepatitis C virus (HCV) has been described in populations from Japan and some Mediterranean countries such a correlation has not been reported in Northern or American countries. Nor has it been reported in countries like Egypt and Nigeria, which have a high prevalence rate of HCV infection. Such correlation might be possibly attributed to genetic variations in different countries (Glick, 2014).

OLP has been reported to be associated with a variety of totally unrelated disorders like malignancies, gastrointestinal diseases, ulcerative colitis, diabetes mellitus, lupus erythematosus, primary biliary cirrhosis, and chronic active hepatitis (Romero et al., 2002).

Hepatitis B virus (HBV) is a type of hepadnavirus. An association between LP and HBV infection has been suggested as hepatitis B surface antigen (HBsAg)-positive patients may have double the risk of developing LP compared with HBsAg-negative patients. In addition, there are reports of anti-HBV antibodies in LP patients of lichenoid eruption following administration of different HBV vaccines (Jayavelu and Sambandan, 2012).

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Hepatitis C virus (HCV) is one of the major causes of chronic hepatic disease worldwide (Gheorghe et al., 2014). It has been estimated that HCV-infected patients have at least twice the risk of developing LP than the general population. The reports associating LP with HCV reveal marked geographic variation (Gheorghe et al., 2014). The association seems to be strong in Japanese and Mediterranean population, probably due to the higher prevalence of HCV infections (Glick, 2014).

Several studies have also reported epi-demiological and genotypic data on hepatitis C virus in Iran, indicating that 1a, 3a and 1b were the most prevalent genotypes in Shiraz city, while there was a high prevalence of HCV infection amongst hemophilic patients in Isfahan city (MaziarMojtabavi et al., 2007; Alavian et al., 2012; Jamalidoust et al., 2014).

Given the discrepancies in the results from different parts of the world and the geographical codependency between these two disease entities, the present study was undertaken to evaluate the prevalence of HBV antigen and HCV antibody in patients with OLP in Iran.

Materials and Methods

A total of 100 subjects who referred to the department of oral medicine of Zahedan University of Medical Sciences were examined from January 2013 to March 2014. Simple sample selection method was used to collect samples. Subjects were sub-grouped into two groups: Group 1: Study group: 50 patients with OLP were included in this group. OLP is diagnosed by clinical findings and pathologic appearance. Clinical features of OLP include 2 parts: red and white that accompanying different surface characteristics of the lesion contributes to classification of OLP. The white and red components of the lesion can have the following surface characteristics: network (reticular), papules, plaque-like, bullous, erythematous, and wounded. To distinguish the OLP the reticular and papules components should be present. The histopathologic characteristics of OLP are including zones of hyperparakeratosis or hyperorthokeratosis normally with a thickening of the granular cell layer and a saw-toothed appearance to the rete pegs; liquefaction degeneration or necrosis of the basal cell layer; and an eosinophilic band which can be seen under the basement membrane which is called eosinophilic coagulum. The patients were diagnosed on the basis of typical clinical and histological features by a dental specialist. Group 2: Control group: 50 age- and sex-matched healthy subjects with no history of oral or skin lesions were included in this group. The study was approved by the Ethical Committee of Zahedan University of Medical Sciences. Prior to entering the study, patients signed an informed consent form.

Exclusion criteria: For Group 1: Patients who are on antiviral therapy for any other systemic conditions, patients, patients below 13 years of age, having a history of skin or genital lesions, a history of malignant neoplasm, having undergone radiotherapy or chemotherapy, autoimmune disease such as lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, metabolic diseases such as diabetes,

taking any systemic medication within the preceding 30 days (including benzodiazepines, antidepressants, anabolic steroids, OCP, and corticosteroids that suppress the immune system), smokers, IV drug abusers, and lichenoid reactions. For Group 2 patients having systemic disease, patients below 13 years of age, patients who are on antiviral therapy for any other systemic conditions.

We also excluded patients with Lichenoid contact reactions, Lichenoid drug eruptions, and Lichenoid reactions of graft-versus-host disease. Is normally seen in buccal and margin of tongue and its occurrence is limited but oral lichen planus usually shows a more general conflict. Lichenoid drug eruptions are distinguished from OLP through the history of disease. OLP does not start with medication and we have excluded people who used medicine. Lichenoid reactions of graft-versus-host disease is a generalized lesion and have different symptoms from OLP. We excluded patients with systematic disorders.

Procedure

Following aseptic procedures, 5 ml of intravenous blood of the patient was drawn using 22-gauge sterile needle and syringe (Soha Co., Tehran, Iran) from median forearm vein. The blood was allowed to clot in a test tube and serum was separated by centrifugation for 10 min at 5000 rpm. Serum was separated and transferred into a sterile sample storage vial (Pouyanteb, Iran) and was stored in deep freezer at -20°C till further tests were carried out. The serum levels of Hepatitis B Surface antigen (HBS-Ag) (Pishtaz Teb, Iran) and Hepatitis C Viral Antibody (HCV-Ab) (Pishtaz Teb, Iran) were determined by enzyme-linked immunosorbent assay (ELISA) using third generation ELISA kit. For HBS-Ag serum was added to the well which was antibody coated together with enzyme conjugated polyclonal antibodies. In case of presence of HBsAg an antibody-HBsAg antibody-enzyme complex was made. Then the plate was washed to remove unbound material. Then the substrate was added and incubated. A blue color will appear according to the amount of HBsAg. The result was visualized at the wavelength of 450 nm. For HCV-Ab, serum was added to the Ag-coated wells. After 1 h the wells were washed by washing solution. Then the enzyme conjugate was added. After 30 minutes the chromogen/substrate was added to each well. After adding stop solution the result was determined at 450 nm wavelength.

Statistical Analysis

To compare relative frequencies in cases and controls, the chi-square test was used. Using the SPSS software version 21. For data with normal distribution, independent samples t-test was used to compare mean differences. Corresponding P-values were considered significant at values < 0.05. Other data, such as gender, types and locations of the OLP lesions, were expressed as percentages.

Results

The present study was conducted among the subjects attending the Department of Oral Medicine. The study

Table 1. Demographic Features of the Participants

Age, y	Mean ± SD	Range
OLP Group (n = 50)	42 ± 14.51	
Male	43.37 ± 13.88	31-76
Female	41.95 ± 14.79	18-73
Healthy Group (n = 50)	41.86 ± 13.71	
Male	40.48 ± 13.78	15-93
Female	41.18 ± 13.03	18-69

population was divided into two groups: Group 1 consisted of 50 OLP patients and Group 2 consisted of 50 healthy subjects. The average age of the patients was 42 ± 14.51 years and the average age of the controls was 41.86 ± 13.71 years (Table 1). Most lesions were reticular (66 %), which are usually observed in buccal mucosa (%66.4) (Table 2).

Out of 50 patients with OLP, 33 were female (66%) and 17 were male (34%). The patients with OLP had suffered from the condition for at least 1 and at most 72 months, with mean affliction duration of 10 months. None of the patients had cutaneous or genital lichen planus.

The study participants had come with various chief complaints. The most common complaint was burning sensation of buccal mucosa or gingival (66%). Few patients (23%) complained of burning sensation, with other complaints like white patch, white lines, and roughness of the mucosa. Rest of them (10%) had no

Table 2. Types and Sites of the Lesion in the OLP Patients

Variables	Values, No. (%)
Atrophic-erosive	9 (%18)
Reticular	33 (%66)
Papular	6 (%12)
Pigmented	4 (%8)
Bullous	0 (0)
Atrophic-erosive-Reticular	42 (%84)
Pigmented-Atrophic-erosive	13 (%26)
Pigmented-Reticular	37 (%74)
Pigmented-Atrophic-erosive-Reticular	13 (%26)
Sites Buccal mucosa	33 (%66)
Mucobuccal fold	11 (%22)
Gingiva	1 (%2)
Lips	2 (%4)
Tongue	1 (%2)
Floor of the mouth	0 (0)

Table 3. Distribution of Study Subjects According to HBsAg Status among the Cases and Control Group

Group HBsAg Test	Positive		Negative	
	No.	%	No.	%
Control	0	0	50	100
Cases	0	0	50	100

Table 4. Distribution of Study Subjects According to HCV-Ab Status among the Cases and Control Group

Anti-HCV Test	Positive		Negative	
	No.	%	No.	%
Control	0	0	50	100
Cases	0	0	50	100

complaint of OLP. The serum of the entire study sample was tested for both hepatitis C antibodies and HBsAg with the ELISA test (using the third generation kit). It was found negative for both HBsAg (Table 3) and hepatitis C antibodies (Table 4).

Discussion

Lichen planus (LP) is a chronic common mucocutaneous inflammatory disorder of uncertain etiology (Glick, 2014). HCV and HBV infection is a health problem worldwide. Several extrahepatic diseases have been reported to be associated with HCV and HBV infection among these extrahepatic manifestations, LP is well known to be associated with chronic liver diseases, although its association with HCV infection is still a debated issue, appearing to be proven only in some geographic areas, such as Japan and Southern Europe (Pilli et al., 2002).

In the 50 patients with OLP evaluated in the present study, the most common lesion locations were the buccal mucosa (66%) and the Mucobuccal fold (22%). The minimum and maximum duration of affliction with the condition was 1 month and 72 months, respectively, with a mean of 10 months.

The prevalence of hepatitis B virus and hepatitis c has been reported as %1.9-3.3% and %0.27-0.9% respectively among the population of Zahedan (South-east of Iran) (Ansari-Moghaddam et al., 2012).

Prevalence of OLP has been reported to be 0.5% among textile workers in Iran (Jahanbani, 2003). The prevalence of hepatitis C in patients with LP has been reported to be highly variable in different countries, ranging from 8.3% in France to 62% in Japan. Several studies have shown that 2.4–8% of patients with chronic hepatic diseases (related to hepatitis C) have LP, too (16; 15; 14) with different infection rates in different countries (Denli et al., 2004; Lodi et al., 2010; Jayavelu and Sambandan, 2012; Nagao and Sata, 2012).

Several research studies have reported a relationship between LP and hepatitis B and C. A study in Iran on 134 patients showed that 2.23% of patients with OLP were positive for HCV antibody (Gerayli et al., 2015). Another study in Italy on 263 OLP patients showed HCV antibody positivity in 28.6% of the subjects (Mignogna et al., 1998). Similar studies in other countries in this region, too, have reported similar findings. Studies in Pakistan (Mahboob et al., 2003) and Saudi Arabia (Asaad and Samdani, 2005) too, have reported a relationship between LP and hepatitis C; however, a study in Turkey did not report such a relationship (Karavelioglu et al., 2004). In Taiwan, Chung et al., (2004) reported a significant relationship between OLP and hepatitis C. In Iran, two studies in Kerman (Rahnama et al., 2005) and Hamadan (Ansar et

al., 2011) showed no association between LP and hepatitis C. Another study in Shiraz showed no relation between HCV infection and OLP (Ghodsai et al., 2004). In a study in Tehran in 1997–1998, 146 people with LP were investigated for HCV antibody. Seven cases (4.8%) were reported to be positive, indicating a significant relationship between these two entities (Tucker and Coulson, 1999).

Similar studies have also been carried out in other parts of the world. A study on 47 LP patients in England showed that none of the patients were positive for HCV and it was concluded that it was not necessary to assess HCV antibody in England (Luis-Montoya et al., 2005). In a study by Strada da Silva et al., (2017) only 2.3% of OLP cases revealed any association with HCV. A study evaluated HCV in 36 LP patients in Spain and demonstrated only one (2.77%) positive case for HCV antibody, indicating no significant relationship between LP and hepatitis C (Daramola et al., 2002). In Donempudi et al study there was no relation of oral lichen planus with HCV and HBsAg. Though, there was a minor increase in the occurrence of HCV in OLP when compared with control group (Donempudi et al., 2016). In a study in Nigeria on 57 patients with LP, one positive case was discovered for HCV antibody; a much lower prevalence rate of hepatitis C was reported in patients with LP compared to those with dermatosis, which in turn was higher than healthy individuals. Therefore, no relationship was reported between LP and hepatitis C (de Mattos Camargo Grossmann et al., 2007).

The results of the present study revealed a non-significant relationship between OLP and hepatitis B and C. The true association between LP and HCV might be attributed to heterogeneity. The differences in heterogeneity in different geographic locations in relation to the association between LP and HCV are difficult to explain, but there are speculations that they result from differences in genetic factors, including differences in human leukocyte antigen types (Carrozzo et al., 2004).

Hepatitis B and C might be attributed to the following reasons. First, geographic differences might explain differences in genetic susceptibilities of the hosts. Differences in the genetic make up of different populations might be responsible for OLP presentation. For example, interferon- γ genetic polymorphism and TNF- α variations might affect the incidence of OLP (Carrozzo et al., 2001; Bai et al., 2008). Second, differences in the prevalence rates of HCV infection in LP patients with geographic and ethnic variations might be attributed to immunological factors, such as HLA-DR6 allele, which is particularly prevalent in some countries (Carrozzo et al., 2001; Carrozzo et al., 2005). This allele is prevalent in Italian patients suffering from OLP and hepatitis C. Given these variations, concurrent incidence of LP and hepatitis C is high in Japan and Italy; however, it has been reported to be low in America and Germany. Therefore, variations in the incidence of hepatitis C might explain the differences in the incidence of this disease in patients with LP (Nagao and Sata, 2012). Third, differences in the prevalence rates of the two disease entities in different regions might explain differences in

coincidence or relationship between these two conditions. A high prevalence rate of hepatitis C in Italy might have affected this relationship. Fourth, differences in the criteria used for the diagnosis of OLP can affect the results. In our study clinical and histopathological evidence was used to confirm OLP diagnosis. Last, some lichenoid reaction cases might be mistaken for OLP, affecting the real frequency of OLP. We excluded these cases from our study.

Different reasons have been suggested for these variations based on the geographic area, including the prevalence of HBV and HCV, the prevalence of other etiologic factors for OLP, differences in genetic susceptibility to HCV-induced OLP, differences in the genotypes of HCV and cytotoxic reactions to keratinocytes expressing HBsAg.

No association was established between OLP and hepatitis B and/or hepatitis C virus in the present study. There were some limitations in the present study, the most important of which was small sample size. This sample size might not be representative of the whole population. Therefore, a study with a larger sample size is recommended to determine whether there is association between OLP and hepatitis B and/or hepatitis C virus.

We could not demonstrate any association between OLP and viral hepatitis. This could be attributed to lower prevalence of hepatitis viruses compared to the countries hyper endemic for these viruses or genotypic variation of the viruses or other etiological factors contributing for the present group of patients. It is recommended that future studies should be performed with a larger sample size to have more valid results.

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Conflict of interest

We declare that there is no conflict of interest.

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