Epidemiological Relationship of Oral Lichen Planus to Hepatitis C Virus in an Indian Population

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Abstract

Aim: The relationship between the hepatitis C virus (HCV) and oral lichen planus (OLP) remains a controversial subject for clinicians. Many studies aimed at studying the association between HCV and OLP have been conducted over the years. Geographical variations have been shown to be a major factor influencing this association. This study aimed at determining whether such an epidemiological relationship exists in an Indian population.

Methods: One hundred and thirty clinically and histopathologically confirmed OLP patients (46 males and 84 females, mean age 43.47±10.48 years) and 130 age- and gender matched controls were examined for serological evidence of chronic hepatic disease, hepatitis B surface antigen (HBsAg), and anti-HCV seropositivity. The blood samples were collected from both the groups and subjected to biochemical analysis for total bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase enzymes using a semi-automated biochemistry analyser. HBsAg and antibody to HCV were tested by ELISA. Statistical analysis was calculated using Levene's test and the independent *t*-test.

Results: No significant difference between serum levels of total bilirubin, alanine aminotransferase, alkaline phosphatase and aspartate aminotransferase was observed between both groups. All patients with OLP had normal liver function. None of the patients with OLP or the control subjects had antigens for HBsAg and HCV.

Conclusion: Patients with OLP did not have any evidence of chronic liver disease or HBV or HCV infection. The exact mechanism that exists between the association of HCV and OLP still remains unclear and this study rejects the hypothesis that established a co-relation between OLP and HCV infection.

Key Words: Hepatitis C Virus, Indian Population, Oral Lichen Planus

Introduction

The relationship between the hepatitis C virus (HCV) and oral lichen planus (OLP) remains a controversial subject. Lichen planus (LP) is a chronic, mucocutaneous, immunologically mediated disease of unknown aetiology. Associated factors include stress, trauma, malnutrition, infection, diabetes and hypertension. OLP is predominantly seen in middle-aged females. Clinically, the OLP has six variants: papular, reticular, plaque-like, atrophic, erosive and bullous. Symptoms can range from none to severe discomfort [1].

HCV is a single-stranded, positive ribonucleic acid (RNA) virus. It is a blood-borne pathogen, and transmits mainly through blood transfusion, percutaneous exposure from contaminated needles, and occupational exposure to blood. After acute HCV infection, the proportion of patients who may remain chronically infected is estimated to be as high as 85-90% [2]. A large proportion of these chronically infected individuals are asymptomatic carriers, unaware of their infected state.

An association between LP and chronic active hepatitis (CAH) has been noted after first being reported in 1978 [3]. High prevalence of HCV infection in patients with LP was first documented in 1991 [4]. The prevalence rate of CAH in patients with LP ranged from 4.0% to 13.5% and the prevalence of anti-HCV antibodies and patients with LP ranged from 3.8 to 65%. An increased frequency of hepatic cirrhosis was also seen in patients with LP [5].

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A number of studies have investigated the relationship between HCV and LP in the last two decades with variable results. Geographical heterogeneity of the association between HCV and LP has been clearly noted. Studies from Southern Europe, Japan, USA, Brazil, Thailand and Pakistan have shown a high prevalence of antibodies in patients with LP. This might be related to the fact that the general populations in these countries have a high prevalence of HCV infection. No serological evidence was seen in the studies from the countries where the prevalence of HCV infection was low, such as UK, Serbia, and Netherlands. Two studies from Germany showed conflicting results in comparison to the above observations [6]. Bias in terms of selection of the study samples and genetic predisposition in relation to immune responsiveness have also been proposed as the reason for the varying results of the studies carried out to date [2].

Aim

Considering all the previous observations, this study was carried out to investigate the possible epidemiological relationship between the prevalence of increased hepatic disease, HCV infection in particular, in patients with OLP in the Indian population.

Methods

A cross-sectional case-controlled study was carried out after approval by the Ethical Committee of Jodhpur National University (Faculty of Medicine and Health). The patients were informed beforehand about the purpose and methods of the study. Written consent was obtained from each subject.

One hundred and thirty consecutive patients (46 males and 84 females) attending the Department of Oral Medicine, Jodhpur National University, India, were included in the study. The patients were diagnosed with OLP based on characteristic clinical findings and later confirmed histopathologically [7]. The control group consisted of 130 patients who had been hospitalised in the oral and maxillofacial trauma ward and had been tested for HCV and had no OLP lesions. The age and gender of the control group was matched with the OLP patients. The study was of three years' duration.

Patients in both the study and control group were asked about their medical history. Exclusion factors included previous history of viral hepatitis, alcoholism, hepatotoxic drugs, history of blood transfusions, intravenous drug abuse, tattooing, unprotected sexual activity and smoking habits.

Laboratory procedure

The blood samples were collected from both groups and subjected to biochemical analysis for total bilirubin (TBIL), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) enzymes using semi-automated biochemistry analyser. HBsAg and antibody to HCV were tested by ELISA.

Information of the each patient was recorded on specially designed data-collection form (*Figure 1*).

Statistical analysis

An independent *t*-test was used to statistically test the data from the two groups. Levene's test for equality of variances was carried out to compare relative frequency between the study groups. A *P*-value of lower than 0.05 was considered to be significant.

Results

Table 1 shows the demographic data of the OLP patients and control group. The mean age of the patients was 43.47±10.48 years. The type of the lesion and the site involved are shown in *Table 2*. The reticular type was the most commonly seen lesion (43.07%), followed by erosive type (38.46%) and the buccal mucosa was the most commonly involved site. No statistically significant difference was noted between both the groups regarding mean age, sex, surgical treatment, blood transfusion, alcohol consumption, smoking and various other risk factors. In both the experimental and control group, no biochemical features of chronic hepatitis were noted. None of the patients or control subjects had abnormal liver function tests. No statistically significant difference ($P>0.05$) in the hepatic serological marker between both groups was seen. None of the patients with OLP or the control group showed the presence of HBsAg or HCV seropositivity (*Table 3*).

Discussion

Bilirubin is a byproduct of the routine destruction of red blood cells occurring in the liver and is released as bile in the faeces. Elevation of the bilirubin can suggest liver dysfunction. Bilirubin increases in both cholestatic and hepatotoxic liver disease. AST and ALT are the most useful measures for liver cell injury and considered as sensitive

DATA COLLECTION FORM

Patient Details: ***Record No. _ _ _ _ _***

Patient Name		Age – years	Sex – Male /Female
Address			

Clinical Details:

Oral Lichen Planus		Others
Site		
Clinical Types		

Personal History:

	Type	Amount	Frequency
Tobacco Chewing / Smoking			
Alcohol			

Medical History (Please tick in block):

Jaundice		Blood transfusions	
Previous surgeries		Other risk factor if any	
Details if any			

Laboratory investigations:

Total bilirubin (μmol l^{-1})	ALT (I.U. l^{-1})	AST (I.U. l^{-1})
ALP (μkat l^{-1})	HBsAg	anti-HCV

Histopathological Diagnosis:

Observer's Signature

Figure 1. *Data collection form.*

Table 1. *Demographic data*

		No of individuals (n)	Age range (years)	Age (in years) Mean ± SD
OLP group	Male	46	22-60	41.78±10.72
	Female	84	22-76	44.04±10.29
	Total	130	22-76	43.47±10.48
Control group	Male	46	22-58	41.52±10.76
	Female	84	22-76	44.26±10.32
	Total	130	22-76	43.29±10.52

Table 2. *Clinical types and intra-oral distribution of lesion in OLP group*

LP types	**Nos.**	**Percentage**
Reticular	56	43.07
Atrophic/erosive	50	38.46
Pigmented	14	10.76
Papular	6	04.61
Bullous	4	03.07
Total	**130**	**100.00**

Oral sites	Nos.
Buccal mucosa	104
Gingiva	68
Tongue	52
Mucobuccal fold	48
Palate	38
Lips	30
Floor of the mouth	16
Total lesions	**356**

indicators of liver damage or injury from various diseases. Elevated AST levels may also be seen in acute cardiac or skeletal muscle injury. Disproportionate elevation of the AST and ALT levels, when compared to alkaline phosphatase levels, are seen in the diseases that primarily affect hepatocytes, such as viral hepatitis. In viral hepatitis and other forms of disease associated with hepatic necrosis, blood levels of AST and ALT are elevated even before the appearance clinical signs and symptoms. The AST and ALT levels show a variable increase during the prodromal phase of acute viral hepatitis and precede the rise in bilirubin level. Specific antigens and antibodies help to establish the diagnosis of viral hepatitis. ALP is a heterogeneous group of enzymes found mainly in liver and bone cells. Hepatic ALP levels are usually evaluated along with other tests for liver disease. In some forms of liver disease, such as hepatitis, ALP is usually much less elevated than AST and ALT. Hence in the present study the levels of bilirubin, AST, ALT and ALP were measured as an

Table 3. *Serum parameters and statistical analysis of both study groups*

Serum parameter	OLP group (n = 130)	Control group (n = 130)	Levene's test for equality of variances		*t*-test for equality of means	
			F	*P*-value	df	Significance (2-tailed)
TBIL (µmol/l)	10.013±1.064	10.038±1.094	.143	>0.7 NS	258	.853
ALT (IU/l)	20.553±1.431	20.566±1.410	.043	>0.8 NS	258	.944
ALP (µkat/l)	65.906±10.555	65.841±10.570	.004	>0.9 NS	258	.961
AST (IU/l)	20.943±1.501	20.938±1.491	.016	>0.8 NS	258	.980
HBsAg	0	0	-	-	-	-
anti-HCV	0	0	-	-	-	-

NS = not significant

indicator of liver disease using blood samples of OLP patients and controls [8].

HCV infection is often asymptomatic or shows no specific manifestation in the acute phase, and it is rarely recognised and largely under-diagnosed, leading to chronic hepatitis C [9]. Whereas in the majority of cases cutaneous lesions of lichen planus are self-limiting and cause itching, oral lesions in OLP are chronic, rarely undergo spontaneous remission, are potentially premalignant and are often a source of morbidity. Although the specific pathogenesis of OLP is unknown, it is recognised as a T-cell-mediated immune disease, and several studies have been performed regarding its association with chronic hepatitis C [1,10].

OLP is an extra-hepatic manifestation of chronic liver disease and the HCV infection acts somehow to increase keratinocyte, targeting the immune system. It is postulated that HCV may mimic a structural component of the keratinocyte, resulting in autoantibody production [11]. Another possibility is that HCV may infect the keratinocyte directly resulting in altered antigenicity and subsequent T-cell activation and targeting. Others have found no correlation at all between HCV infection and OLP. Thus the specific role played by HCV in the development and/or progression of OLP remains to be clearly defined [12,13]. The pathogenesis of OLP induced by HCV is uncertain, but two hypotheses have been raised to explain the mechanism of the triggering of OLP by HCV. The first hypothesis suggests that virus replication is associated with the oral epithelium and thus contributes directly to the development of lesions. The second hypothesis proposes that the high mutation rate of the virus results in repeated activation of immune cells, increasing the probability of cross-reaction with its own tissue and, consequently, the risk of autoimmune disease. In certain genotypes, cross-reactivity that activates immune cells against epithelial cells is favoured [14]. One group of researchers has suggested that HCV infection is not a direct causal factor of OLP because replication of HCV was observed in mucosa both with and without OLP. In addition, the same group found a mononuclear cell infiltrate around the epithelial cells of HCV-seropositive patients with and without OLP. However, they did not rule out the possibility of HCV inducing changes in the host that may have led to an autoimmune response [15].

The purpose of this study was to examine the HCV status in OLP patients and controls. No such association could be established because none of the patients with OLP or the control subjects were HCV seropositive. The apparent lack of association between the two entities parallels other similar studies [6,12]. Michele *et al.* (2007) [16] also found no clear association between OLP and chronic hepatitis C. They postulated that this possible association mainly depends on the frequency of each disease in the population, which would explain the wide geographic variation [16]. However, Del Olmo *et al.* (2000) concluded that HCV plays a role in the aetiopathogenesis of chronic liver diseases documented in patients with OLP and that treatment of the disease with IFN-α, which inhibits virus replication, may lead to the development of a lichenoid reaction to this drug [17].

The HCV-related OLP association is supported by the fact that HCV viral sequences have been found in the serum of patients with OLP, and HCV was shown occasionally to replicate in oral lichen planus tissue, possibly contributing to the pathogenesis of mucosal damage [18-20]. HCV has a single-stranded positive RNA genome and it replicates using the negative strand as a template in the infected tissues. Thus the single-stranded negative RNA present in the tissues is considered to be a marker of HCV replication. Also, recent data have shown that the HCV-specific T-cells can be found in the oral mucosa of patients with chronic HCV and OLP [21].

An association between OLP and HCV infection has been reported in the literature. If this is a true association, OLP in certain populations can be used as a marker of HCV infection in asymptomatic patients, leading to diagnosis and early treatment and, possibly, a better prognosis. In addition, identifying extra-hepatic manifestations of HCV infection has important implications for the ongoing care of patients. However, if this is not a true association, the routine testing of patients with OLP for HCV may result in the unnecessary use of medical resources, with increased monetary costs and other harmful effects such as increased anxiety among those tested. Therefore, it is important to determine whether or not there is an association between OLP and HCV infection so that guidelines regarding the routine HCV testing of patients with OLP may be developed for clinicians. In the present study, no definitive relationship between hepatic disease and OLP was established.

Previously, liver function tests were advised in patients with OLP [5,22,23]. In the present study,

total bilirubin value (OLP 10.01±1.06; control 10.04±1.094) was within normal limits and the enzymes' ALT (OLP 20.55±1.43; control 20.57±1.41), ALP (OLP 65.91±10.55; control 65.84±10.57) and AST (OLP 20.94±1.50; control 20.94±1.94) did not show any abnormal levels in patients with OLP. No statistically significant (P>0.05) difference could be drawn from the analysis of these parameters. These results were inconsistent with the previous studies [12,24]. Reports suggested that hepatic diseases might increase the aggressiveness of the oral lesions in patients with LP [5]. This feature was not seen in the present study. The present study did not notice any skin lichenoid eruptions following administration of HBV vaccines, which was in accordance with two previous studies [25,26]. None of the samples from either group was HCV-seropositive. This result was comparable with that from a study in London [12]. Earlier studies suggest that erosive lichen planus patients show increased tendency to have chronic hepatic disease and specifically HCV [5,27]. In the present study, reticular lichen planus (43.07%) was the most common clinical type followed by erosive type (38.46%) with the buccal mucosa being the most commonly involved site. None of the patients with either form showed any evidence of hepatic disease or HCV infection. In contrast to this, a previous study [23] suggested that reticular form of LP is seen more frequently in HCV-positive patients. Another previous study reported ten cases of erosive OLP, six patients were diagnosed with HCV and four with severe hepatic disease with a conclusion of a positive relationship between oral erosive LP and HCV infection [11].

The association of OLP with both HCV infection and liver disease appears to be partially dependent on geographical factors. It has been hypothesised that the differences seen in the association of OLP and HCV in terms of geographical location may be explained by the differences in genetic factors controlling host immune responses. HLA class II allele HLA-DR6 is thought to be associated with HCV-related OLP and this might be the reason for the peculiar geographical heterogeneity of the association between HCV and LP [28]. At present there is not enough information to determine whether HCV genotype plays a role in the development of OLP.

The comparison of the results is limited by the use of different methods. Moreover, inclusion and exclusion criteria also directly influence the published results. Thus, discrepancies observed among studies may well reflect the varied geographical distribution of HCV infection among countries, a selection bias of the populations studied, or a genetic predisposition to immune responsiveness. Although the reports of this association are contradictory and controversial, the present data indicate that OLP patients in India do not have an increased frequency of hepatic disease or evidence of HBV or HCV or any chronic liver disease. Taken together, the findings from this study could not establish an epidemiological relationship between OLP and HCV in the Indian population.

Conclusion

The results from the present study did not show any correlation between hepatic disease and OLP. With the present state of knowledge the following conclusion can be drawn:

- It is difficult to say whether any specific relationship exists between HCV and OLP.
- Further detailed studies are required to explain the relationship between HCV and OLP.
- Important biases, including selection bias or a genetic predisposition associated with immune responsiveness, make it difficult to draw firm conclusions.
- Because chronic HCV is an asymptomatic disease, which in many cases leads to severe consequences, the knowledge of its extra-hepatic manifestations may help to identify asymptomatic patients infected with HCV.
- Further studies focusing on this possible epidemiological relationship should consider these factors in the study.

Funding

No external funds were available for this study.

Contributions of each author

- SP designed the study.
- SKh assisted in data collection.
- FR compiled the clinical data.
- SKa carried out editing of the manuscript.
- ST coordinated all aspects of this study and assisted in proof reading.

Statement of conflict of interest

As far as the authors are aware, there is no conflict of interests

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