ORIGINAL ARTICLE

Hepatitis C virus infection in patients with oral lichen planus

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Abstract

Background: Lichen planus (LP) is a chronic mucocutaneous disease of uncertain etiology. Recent reports suggest that LP is an extrahepatic manifestation of Hepatitis C infection.
Objective: To determine the association of Hepatitis C virus (HCV) infection with oral LP and to study the tests of liver function in patients with oral LP.
Study Design: A cross-sectional case-control study was carried out on 25 patients with oral LP and an equal number of controls. The study was conducted in the outpatient department of a dental college for a period of six months between January and June 2008. The sera of the patients and controls were tested for HCV ribonucleic acid (RNA) using reverse transcription primed-polymerase chain reaction and liver function tests (bilirubin, transaminases, and alkaline phosphatase).
Results: Of the 25 patients with LP, three (12%) had HCV infection. None of the controls had HCV RNA positivity ($P = 0.2347$). Oral LP patients had higher serum bilirubin and transaminases when compared with controls ($P < 0.05$). However, there was no significant difference in alkaline phosphatase. HCV-positive and -negative patients did not differ significantly in liver function tests.
Conclusions: An increased prevalence of HCV infection was seen in oral LP patients. Our findings support a possible etiological association between these two diseases.

Key words: Hepatitis C virus infection, liver disease, oral lichen planus

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Introduction

Lichen planus (LP) is a chronic mucocutaneous disease of uncertain etiology. Stress, anxiety, genetic predisposition, and altered cell-mediated immune response have been considered as possible etiological factors.[1] LP was earlier considered to be associated with systemic diseases like diabetes mellitus, hypertension, myasthenia gravis, ulcerative colitis, and systemic lupus erythematosus, but a consistent association has not been demonstrated.[2,3] An increased association of LP with chronic liver disease (CLD) was found in the past.[4,5] Recent reports suggest an association between hepatitis C virus (HCV)-related CLD and oral lichen planus (OLP).[6,7] HCV is a hepatotropic, single-stranded ribonucleic acid (RNA) virus and has been associated with extrahepatic manifestations and autoimmune diseases, like LP, polyarteritis nodosa, and erythema nodosum.[8] The prevalence of HCV infection among general population in various states of India ranges between 0.1 and 7.9%.[9] Previous published studies from our country showed no correlation between HCV infection and OLP.[10,11] Hence, we conducted this study to determine the association of OLP and its clinical types with HCV infection.

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Materials and Methods

This study was conducted in the outpatient department of a dental college for a period of six months between January and June 2008. A total of 25 consecutive, newly diagnosed OLP patients were selected as study population. OLP patients receiving treatment were excluded from the study. OLP was diagnosed based on clinical features and histopathological findings of overlying keratinization, lymphocytic infiltration into underlying connective tissue, and liquefaction degeneration of basal cell layer. The patients were divided into the following clinical types:[12]

Erosive
Erosion or ulceration covered with fibrous plaque or pseudoexudate.

Reticular
Symmetrical, fine, white striae (Wickham's Striae).

Atrophic
Diffuse red lesion; and

Mixed
Presence of two or more types in the same patient.

A total of 25 age- and sex-matched healthy controls were selected from the friends and relatives attending the hospital outpatient department along with the patients. All participants (study subjects and controls) were asked a detailed history including drug intake like thiazides, beta blockers, chloroquine, etc. A detailed clinical examination was carried out to identify the lesions of LP and other associated hepatic/systemic diseases such as liver cirrhosis, diabetes mellitus, systemic lupus erythematosus, and ulcerative colitis. They also had their blood samples taken for the detection of HCV RNA, serum total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP). Serum total bilirubin was estimated by Van den Bergh reaction,[13] transaminases by colorimetric method,[14] and ALP by King Angstrom method, respectively.[15] The normal range of the laboratory assays were serum bilirubin (3.42-17 μmol/l), AST (0-50 IU/l), ALT (0-60 IU/l), and ALP (0.7-1.9 μkat/l). Detection of HCV RNA was conducted by reverse transcription primed - polymerase chain reaction (RT-PCR) method after RNA isolation by Guanidine isothiocyanate-acid phenol method.[16] HCV antibody was not tested in study participants. All participants gave informed consent and the study protocol was approved by the institutional ethics committee.

The continuous data were presented as mean with standard deviation. Chi-square test and Student's *t* test was used for statistical analysis to compare between the groups. A significance level of less than 0.05 was considered significant.

Results

There were 15 females and 10 males in the study group with their age ranging between 9 to 65 years. The average age in men and women was 33.1 years and 47.1 years, respectively. The commonest type of OLP was the reticular form, although the erosive form was exclusively seen in two patients. Mixed pattern was seen in 11 patients and the details are shown in Table 1. Cutaneous involvement was found in only two patients, with the skin lesions preceding the oral lesions by 8 to 12 months.

Three of 25 (12%) patients with OLP tested positive for HCV infection and none of the controls were positive ($P = 0.2347$). All three HCV-positive patients had reticular lesions and one patient had a mixed pattern including erosive component. Two of three HCV-positive patients with OLP had elevated transaminases, as seen in Table 2.

Serum bilirubin was elevated in three of 25 (12%), ALT in two

Table 1: Demographic data and clinical types of study population

Clinical type	Number	Male	Female	Age range (years)	Mean age (years)
Reticular	12	6	6	9-62	33.75
Erosive	2	1	1	52-60	56
Atrophic	-	-	-	-	-
Reticular + Erosive	5	2	3	45-65	56
Reticular + Atrophic	6	1	5	25-51	40.17
Atrophic + Erosive	-	-	-	-	-

Table 2: Details of HCV-positive patients

Patient	Age	Sex	Type	Sites involved	Bilirubin μmol/l	ALT iu/l	AST iu/l	ALP (μkat/l)
A	62	F	Reticular	Buccal mucosa	13.68	69	66	0.95.1
B	65	M	Reticular + Erosive	Labial and buccal mucosa, tongue, gingiva, palate, skin	10.26	30	22	0.7.8
C	17	M	Reticular	Labial and buccal mucosa	20.52	70	66	1.18.4

Table 3: Liver function test results in patients and controls

Parameter	Patients ($N = 25$)	Controls ($N = 25$)	*P* value
S. bilirubin (μmol/l)	14.19 ± 3.42	11.8 ± 2.22	0.006
AST (IU/l)	73.8 ± 36.7	53 ± 12.8	0.01
ALT (IU/l)	55.12 ± 19.2	45.7 ± 9.8	0.033
ALP (μkat/l)	1.18 ± 0.58	0.97 ± 0.23	0.266

Data are Mean ± S. D values

Table 4: Liver function test results in HCV-positive and -negative patients

Parameter	HCV positive ($N = 03$)	HCV negative ($N = 22$)	*P* value
S. bilirubin (μmol/l)	14.88 ± 5.3	13.85 ± 3.42	0.6497
AST (IU/l)	51.33 ± 25.4	71.4 ± 28.2	0.2556
ALT (IU/l)	56.33 ± 22.8	51.7 ± 22.3	0.7394
ALP (μkat/l)	0.95 ± 0.24	1.03 ± 0.45	0.76

Data are Mean ± S. D values

(8%), AST in four (16%), and ALP in two (8%) patients with OLP. Serum bilirubin, ALT, and AST showed a significant rise in patients with OLP when compared with controls, but ALP did not differ significantly, as shown in Table 3. The mean values of serum bilirubin and ALT of HCV-positive patients were comparable with HCV-negative patients, though mean AST levels of HCV-positive patients was lower [Table 4].

When correlated with the clinical type, the mean values of serum bilirubin and transaminases were lower and ALP was higher in the erosive group (data not shown since there were only two patients with exclusive erosive LP). Patients with atrophic LP had the highest mean transaminase values but not that of ALP. However, when subjected to statistical analysis, the correlation between clinical types and liver function test alterations was not significant.

Discussion

From our study, 12% of patients with OLP were positive for HCV infection. None of the controls had HCV infection. Bagan *et al*. found that 14.9% of patients with OLP had antibodies to HCV in a study population of 187 patients.[17] Several authors have reported an increased prevalence of CLD in patients with LP and association with Hepatitis C.[4-7] However, studies from our country and other parts of South Asia did not find an association of LP with HCV infection.[18,19] Our findings showed an association between patients with OLP and HCV infection, which could be due to differences in genetic, environmental, geographic, or other host factors as described earlier.[20] In our study, we tested for the presence of HCV infection by doing RT-PCR, whereas most of the previous studies used antibodies to HCV as a diagnostic marker of HCV infection.[10,11] Some studies have detected the presence of positive and negative strands of HCV in the normal as well as lesional mucosa by RT-PCR and in situ hybridization.[21,22] However, in a study by Femiano and Scully, HCV RNA could not be demonstrated in the lesional or normal mucosa in 25 HCV-positive Italian patients.[23]

In our study, 44% of patients showed alteration in liver function tests, whereas previous studies reported alterations in 7 to 60% patients.[5,24] Patients with reticular form of OLP mostly had elevated transaminases in our study. Several authors found a statistically significant association between erosive LP and liver function abnormality.[25,26] This observed discrepancy could be explained as reticular form was the predominant type of LP in our study. HCV infection was seen to be associated more commonly with both erosive and reticular forms.[25-27] The mean values of bilirubin and ALT of HCV-positive patients were comparable with HCV-negative patients with OLP, though the mean AST levels of HCV-positive patients were lower. This may be due to the frequent fluctuations in biochemical abnormalities in HCV-infected patients.

There are various theories to explain the association between LP and HCV infection. First, alteration in epidermal antigenicity induced by HCV infection leading to proliferation of keratinocytes and second, cytopathic replication of HCV eliciting an autoimmune process.[18] Mega *et al*.[28] noted a deeper lymphocytic infiltration in the lamina propria and a significant rise in CD-8 cells in cases of HCV-associated LP than idiopathic LP, thereby suggesting that probably HCV acts through the modulation of the quality of the immunologic response.

Our study, though suggest a possible association between OLP and HCV infection, is limited by the small sample size. It also showed elevated transaminases in patients with OLP. Further studies involving larger number of patients are required to validate this association. We recommend routine screening of patients with LP with liver function tests to detect symptomless hepatopathies.

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