

## Hepatitis B Virus Infection and Oral Lichen Planus: A Report from Northeast of Iran

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### Abstract

**Introduction:** Lichen planus is a chronic inflammatory disease in oral mucosa and skin. Recently, reports have demonstrated a possible relationship between lichen planus and liver diseases. During the past decade, there has been a hypothesis regarding viral etiological agents that have been found to be in association with hepatotropic viruses known as Hepatitis B and C with LP. This research was studied in Mashhad, northeast of Iran, to find a relationship between OLP and HBV infection.

**Methods:** Age and gender of 134 patients (with OLP) and 134 controls (without OLP) were not matched and their serum samples were respectively screened for HBsAg by ELISA (third generation) and polymerase chain reaction (PCR) for HBV-DNA. **Results:** Tests were positive (for both HBsAg and HBV-DNA) for 9 patients (6.71%) with OLP and 2 healthy individuals (1.49%) infected with HBV ( $P=0.03$ ). **Conclusion:** There was a relationship between HBV and OLP in our population. Based on our findings, it is recommended that viral serology for Hepatitis B and OLP patients be conducted as a routine screening process.

**Keywords:** Hepatitis B, Viral Infections, Lichen Planus, Oral, Epidemiology, Iran.

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## Introduction

Oral lichen planus is a chronic inflammatory dermal and mucosal disease (1). The prevalence of lichen planus is between 0.1% and 2.2% (2). Some of the contributing co-factors are high blood pressure, diabetes, hepatitis C, blow and increase in drug and metal allergy (1). Recently, a considerable attention has been given to the influence of viruses on neoplasms and premalignant lesions. Human malignancies which appear to be directly related to viral infections have been estimated to be approximately 10% to 20% (2). The investigations have shown that CD8 (+) T cells are activated in lichen planus and substitute keratinocytes. On the other hand, CD8 (+) cytotoxic T cells induce apoptosis in virally infected cells. Therefore, viral infections in oral mucosa may play an important role in oral lichen planus (3). Oral lichen planus has been reported along with other systemic diseases such as ulcerative colitis, diabetes mellitus, candidiasis, syphilis, AIDS, amoebiasis, acute dermatomyositis, herpes simplex virus type 2, chronic bladder infection and various liver diseases (4-6). The association between erosive OLP and liver cirrhosis has been reported by Rebora et al. (7) in 1978. Since then, this relation has been demonstrated by a number of authors (8-15), however, pathogenesis of LP is still unclear (16). The association of primary biliary cirrhosis and chronic active hepatitis with lichen planus has been mentioned by many studies (12,17-19). According to these studies, the highest prevalence of hepatitis B has been observed in Italy and Spain.

Daramola OO et al. found a higher prevalence of HBsAg in patients with lichen planus when compared with patients with other cutaneous dermatoses or with apparently normal individuals (20). The association of hepatitis B with lichen planus was reported in a research done by Ayala *et al.* to be 4.7%(21), in the study of a group of dermatologists as 4.8% (22), in the study of Korkij *et al.* as 4.2%(13) and in Robera *et al.* research as 11.3%. According to the study by Bagan *et al.* from 187 oral lichen planus patients, 40 individuals (21.39%) showed an abnormally elevated liver enzymes as well as hepatitis; Hepatitis C was detected in 28 patients (15%) and the rest had hepatitis B(23). In a research by Del Almo *et al.* (14) in Spain, of 65 oral lichen planus patients, 22 (33.8%) demonstrated clinical symptoms of chronic liver diseases. High prevalence of active chronic hepatitis has also been observed among the lichen planus patients in USA, Sweden and England (15,24,25). Garg *et al.* in Nepal (26) and Ibrahim *et al.* in Egypt (27), showed the prevalence of HBsAg to be the same as the control group. According to the research by Banihashemi and Daneshmandrakhi, in Zahedan (south east of Iran), the

prevalence of HBsAg positive cases among lichen planus patients was significantly higher compared with the general population (28). Hepatitis B is one of the major public health problems in Iran. According to a study carried out by Meshkat *et al.* 1% of population in the city of Mashhad were HBsAg positive, (29). As previous studies have shown a relationship between hepatitis B and OLP, and since the prevalence of HBsAg is greatly influenced by the geographical location, we aimed to distinguish the relationship between OLP and hepatitis B in Mashhad, northeast of Iran.

## Materials and Methods

This study was approved by the Ethic Committee of Mashhad University of Medical Science. 134 patients with OLP who referred to the Oral Medicine Department of Mashhad Dental School were participated in the research. All cases were clinically diagnosed in the Oral Medicine Department of Mashhad Dental School. Standard histopathological evaluation and investigation of the biopsy specimens were performed by direct immunofluorescence for suspected cases. Diagnostic criteria, as explained by WHO in 1978, were the basis for clinical and histopathological diagnosis. Patients likely to have developed oral lichenoid reaction, in response to drugs and dental restorative materials, were excluded from this study. The control group consisted of 134 patients that were clinically examined by two dentists to ensure the absence of OLP. Furthermore, patients with suspicious lesions were excluded. Medical histories of study groups were evaluated and all available data on viral hepatitis, risk factors for liver diseases e.g. episodes of jaundice, liver dysfunction, blood transfusion, previous surgery, smoking habits, intravenous drug abuse, alcohol consumption and other risks of HBsAg infection such as family history of liver disorders were recorded. After signing the consent form, a 5 mL blood sample was obtained from each participant in order to measure levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and bilirubin in serum by standard biochemical methods. Third-generation enzyme-linked immunosorbent assay (ELISA) was used to perform HBsAg tests. Chi-square test, Student's t test and nonparametric tests were used for statistical analysis to compare the groups. A significance level of less than 0.05 was considered significant.

## Results

Demographic information of OLP patients and the control group is listed in table 1 (30). The average age of patients was  $51.60 \pm 12.03$  and that of the controls was  $45.61 \pm 17.51$ . The prominent type of OLP lesions was reticular (31.3 %), which is usually observed in buccal mucosa (76.9%). In addition, liver function tests

(LFT) were abnormal in 24.6% of patients and 31.34% of the control group (30). Prevalence of HBsAg in patients with lichen planus was 6.71% which is significantly higher than that of the control group (1.49%) ( $P=0.03$ ).

**Table 1.** Demographic Data of the study groups (adapted from 30).

| Characteristics                     | Patients with Oral Lichen Planus | Control group       | P Value  |
|-------------------------------------|----------------------------------|---------------------|----------|
| Male:Female                         | 41 : 93                          | 58 : 76             | 0.031    |
| Age , year                          | $51.60 \pm 12.03$                | $45.61 \pm 17.51$   | 0.003    |
| Dermatologic Disorder               | 8 (5.97)                         | 0 (0)               | 0.004    |
| Allergy                             | 7 (5.22)                         | 1 (0.74)            | 0.03     |
| Diabetes                            | 29 (21.67)                       | 27 (20.14)          | 0.76     |
| Hypertension                        | 30 (22.38)                       | 26 (19.40)          | 0.55     |
| Heart Disease                       | 16 (11.94)                       | 9 (6.71)            | 0.14     |
| Anemia                              | 15 (11.19)                       | 13 (9.70)           | 0.7      |
| Kidney Disease                      | 2 (1.49)                         | 8 (5.97)            | 0.052    |
| Lung Disease                        | 4 (2.98)                         | 1 (0.74)            | 0.18     |
| Arthritis                           | 6 (4.47)                         | 2 (1.49)            | 0.15     |
| Addiction                           | 3 (2.23)                         | 0 (0)               | 0.08     |
| Smoking                             | 3 (2.23)                         | 2 (1.49)            | 0.65     |
| Alcohol consumption                 | 2 (1.49)                         | 0 (0)               | 0.16     |
| Blood Transfusion                   | 8 (5.97)                         | 2 (1.49)            | 0.053    |
| Previous Surgery                    | 33 (24.62)                       | 9 (6.71)            | < 0.0001 |
| Family history of Liver Disorder    | 8 (5.97)                         | 1 (0.74)            | 0.02     |
| Jaundice                            | 2 (1.49)                         | 0 (0)               | 0.15     |
| Liver Dysfunction                   | 5 (3.73)                         | 1 (0.74)            | 0.1      |
| Organ transplant                    | 0 (0)                            | 6 (4.47)            | 0.01     |
| AST, U l <sup>-1</sup>              | $20.67 \pm 13.27$                | $22.25 \pm 7.55$    | < 0.001  |
| ALT, U l <sup>-1</sup>              | $19.77 \pm 6.97$                 | $21.03 \pm 18.13$   | < 0.0001 |
| ALP, U l <sup>-1</sup>              | $209.86 \pm 67.95$               | $239.37 \pm 121.62$ | 0.08     |
| Direct Bilirubin, U l <sup>-1</sup> | $1.63 \pm 0.73$                  | $1.44 \pm 0.65$     | 0.02     |
| Total Bilirubin, U l <sup>-1</sup>  | $0.69 \pm 0.34$                  | $0.59 \pm 0.25$     | 0.008    |

## Discussion

During the past decades, many researches have been conducted on the association of lichen Planus with hepatitis B and C, which have led to different results. This was the motivation of our research. One of the largest researches conducted by a group of Italian epidemiologists which contained 577 lichen planus patients and 1008 controls. This study revealed that the risk of lichen planus in patients with a background of chronic liver disease or HBsAg present in their blood is at least twice more than the ordinary population; this risk evaluation was made without considering other factors such as age, gender and alcohol consumption. In a patient who had been treated by liver biopsy due to liver diseases, the risk of lichen planus would be even 5 times more than the ordinary population (31). An association has been found between oral lichen planus and chronic liver disease in various studies. In the study of Del alma *et al.* conducted on 65 Lichen planus patients in Spain, 22 patients (33.8%) had the clinical and laboratory symptoms of chronic liver disease (14). On the other hand, there are some similarities between lichen planus and chronic liver hepatitis such as the reaction of transplant rejection (infiltration of typical lymphocytes and formation of fibro-sclerotic tissue). This pattern also exists in the primary biliary cirrhosis. It is probable for immunological invasion against keratinocytes to also invade liver cells and destruct hepatocytes. Liver pathological changes observed in erosive oral lichen planus are very severe (21, 32). Therefore, pathogenicity of erosive oral lichen planus, may make a severe invasion toward keratocytes and liver cells as well.

Studies conducted in other places have obtained different results. In the work of Banihashemi and Daneshmandrakhhi (28) done on 80 lichen planus patients in Zahedan, the prevalence of HBsAg in patients was mentioned to be 10% , and 4% in the control group, and the difference between the two groups was statistically significant. In an extensive and comprehensive research in Italy in 1990, which was done on 577 lichen planus patients and 1008 controls, 4.8% were HBsAg positives in patients' group and 2.6% among the control; this difference was significant from the statistical point of view (31). Korkji *et al.* in their case-observation study in 1984, observed abnormal liver function tests among 52% of 73 lichen planus patients and 36% of 193 control cases (13). In another research conducted by Robora and Rongiolatti in Italy, on 44 lichen planus patients, 11.3% had active chronic liver hepatitis and its prevalence in the similar geographic area was 0.25% to 0.5% (33). In the study of Ibrahim *et al.* in 1999 in Egypt, 44 patients were under investigation. The prevalence of HBsAg was 27.9% in the patients' group and 26.7% in the control

group (27). According to the results of Garg *et al.* Essay in 2002 in Nepal on 86 lichen planus patients, HBsAg and hepatitis C were reported to be negative in all of the patients and controls (26). Monk, in 1985, conducted a research on 55 lichen planus patients and 10000 individuals as the control group. He reported the liver disorders to be 5.4% in the patients' group and 5.85% in the control group; this difference was not statistically significant (25). However, according to the statistics derived from the mentioned researches, different results are reported about the association of HBsAg and lichen planus. The reason for such an antithesis could be: 1) The high prevalence of hepatitis B in some parts of the world such as Italy, 2) The unknown epidemiologic and immunologic factors such as especial HLA which makes the person prone to hepatitis virus, 3) Genetic sensitivity of a population to hepatitis infection and 4) The association of hepatitis related chronic liver diseases with lichen planus that is mentioned in most of the reports; while the association of positive HBsAg with lichen planus without liver diseases was rarely reported (4, 15, 17). In the present study, there were significant differences in some demographic parameters such as age and gender. However, it would be better to select participants with similar demographic characteristics between the two groups in future studies.

## Conclusion

According to the results of this study, it seems that the performance of HBsAg seeking tests is required for lichen planus patients, and those patients who had liver problems must be monitored more carefully. It is suggested that further studies in multi-focus forms, along with higher sample volumes be conducted. Also a comparison between lichen planus patients with liver problems and those who do not suffer from this problem be made with more definite comments and judgments.

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