Clinical Oral Medicine

Oral lichen planus and hepatitis C virus infection

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OBJECTIVE: This investigation was conducted to determine the possible association between oral lichen planus (OLP) and hepatitis C virus infection (HCV) in the population of São Paulo (Brazil).

MATERIALS AND METHODS: Three groups of patients were studied: group 1 was composed of 68 patients with OLP lesions; group 2 had 126 patients with HCV infection; and the control group consisted of 898 individuals seeking dental treatment at our school, used to determine the prevalence of lichen planus in the general population. The prevalence of HCV in group 1 was determined and compared with that of the population of São Paulo (Focaccia et al 1998 Brazilian J Infec Dis 2: 269), while the prevalence of OLP in group 2 was determined and compared with that of the control group.

RESULTS: The results showed that the frequency of HCV in OLP patients was 8.8%, significantly higher than in the general population of São Paulo, which is 1.4% (P 0.002), and the frequency of OLP in HCV patients (4.7%) was also significantly higher (P 0.0003) than that of the control group (0.6%).

CONCLUSION: These data suggest that, at least in São Paulo, there is an association between OLP and HCV infection.

Oral Diseases (2002) 8, 42–46

Keywords: lichen planus; oral; liver disease; hepatitis C infection

Introduction

Many reports have described the association of lichen planus (LP) and chronic liver disease, especially hepatitis C virus (HCV) infection (Rebora and Rongioletti, 1984; Ayala et al, 1986; GISED, 1990; Gandolfo et al, 1994; Nigao et al, 1995; Carrozzi et al, 1996; Sánchez-Pérez et al, 1996; Bagán et al, 1998; Mignogna et al, 1998). It appears interesting that in most of these reports the prevalent location of LP when associated with HCV is the oral mucosa. The possible etiopathogenic mechanism that may link the two diseases remains unclear.

Other studies, however, have failed to show a significant association between LP and liver disease (Scully et al, 1985; El-Kabir et al, 1993; Cribier et al, 1994) or to detect any serological abnormalities of liver disease in oral lichen planus (OLP) patients (Ingafou et al, 1998; van der Meij and van der Waal, 2000). Why studies have contradicted one another remains an answered question. One explanation is that geographic variation in the prevalence pattern of HCV infection could account for these contradictory data (El-Kabir et al, 1993; Roy and Bagg, 1999; Lodi et al, 2000; van der Meij and van der Waal, 2000).

The aim of the present investigation was to verify the possible association between OLP and HCV infection among the population of the city of São Paulo, Brazil.

Materials and methods

The experimental design of this study involved three main groups: group 1 consisted of OLP patients who were tested to determine their frequency of liver abnormalities and, subsequently, to investigate the underlying liver disease in those patients with altered liver function test; group 2 consisted of HCV patients who were examined to determine their frequency of LP/OLP lesions. In group 3, people attending for dental treatment were examined for the frequency of LP/OLP lesions. HCV infection in the general population was obtained from published studies. Details of each group are provided as follows:

Group 1 comprised 68 individuals (23 males and 45 females) with OLP, five with concomitant skin lesions of LP, examined at oral clinics of the University of São Paulo. The mean age was 49.2 years (range, 17–77). Clinical diagnosis of OLP was confirmed by histologic...
examination. Histologic hallmarks used as diagnostic criteria for OLP cases were based on the following signs presented on biopsy specimens obtained from the oral mucosa, such as hyperorthokeratosis/hyperparakeratosis or parakeratosis, acanthosis, liquefactive degeneration of the basal cell layer and subepithelial band-like infiltrate of inflammatory cells consisting mainly of lymphocytes. These findings were in accordance with the criteria defined by WHO (1978). Medical history of the patients revealed that eight were diabetics, 16 had arterial hypertension, and 34 were taking systemic medication, most of whom had presented with the OLP lesions previously to the initial use of the drug. Most of the OLP patients, regardless whether or not they were taking medications, had multiple site involvement with symmetrical distribution of lesions. Such symmetry would not be expected in the case of lichenoid drug reaction. Moreover, in no cases were amalgam restorations associated with the OLP lesions, thus eliminating the possibility of contact lichenoid reaction. No patient presented clinical or histologic signs that raised a suspicion of lupus erythematosus; nor were the histologic findings consistent with either cicatricial pemphigoid or linear IgA disease. Eight patients had alcohol habits. None of the patients were excluded from the study. All the patients were tested for aminotransferases, γ-glutamyl-transpeptidase, alkaline phosphatase, total and direct bilirubin. In any case where liver abnormalities were suspected by elevation of at least one of these enzymes, the patient was referred to the Clinical Hepatology Branch of the University of São Paulo for further evaluation.

Group 2 involved 126 patients (56 males and 70 females) with HCV infection diagnosed by means of second-generation enzyme-linked immunosorbent assay (Cobas Core Anti-HCV EIA, Laboratory Roche, Basel, Switzerland). In all patients, confirmatory diagnosis was made by detection of serum HCV RNA by means of reverse transcription-polymerase chain reaction (Cobas Amplicor HCV Monitor™ test, version 2.0, Roche Diagnostic Systems, NJ, USA). The patients were referred by physicians of the Clinical Hepatology Branch at the University of São Paulo who did not know the nature of our study, and none of them were rejected. The mean age of the patients was 48.5 years (range, 22–79). Sixty-five of these patients had become infected as a result of blood transfusion, nine were intravenous drug users, three had been infected by sexual intercourse. For the remaining 49 patients the mechanism of infection could not be established. Liver biopsy was carried out in 76 patients who agreed to undergo this procedure. Histologic findings of the liver biopsies revealed 49 with active chronic hepatitis and 16 with liver cirrhosis. All 126 patients were questioned and submitted to oral and skin examinations to investigate the presence of LP lesions or any other mucocutaneous disease. Oral or skin biopsy was performed for any lesion that required histologic examination for confirmation of a clinical diagnosis.

Group 3 was designed as a control to establish the prevalence of LP lesions in the general population. This group was composed of 898 individuals (267 males and 631 females), mean age 44.0 years (range, 30–73) that came to our school for dental treatment. The individuals were accepted into the study as they appeared for treatment, the only rejecting criterion being an age less than 30 years. In these patients an oral examination was carried out, and they were also questioned regarding any present or past history of skin lesions. Biopsy was performed in cases with clinical evidence of oral or cutaneous lesions.

For the control group to establish the rate of HCV in the general population, rather than composing a group of individuals from our clinic, we made use of a preexisting study conducted by Focaccia et al (1998). This study, based on 1055 randomly selected São Paulo residents, estimated the prevalence of viral hepatitis in the general population of São Paulo. The population sample was composed of individuals of 2 years or older. They were stratified by different socio-economic levels as to assure a representative profile of São Paulo population. The prevalence found for HCV was 1.4% with no difference for male or female individuals. The highest rate for HCV was found among those of lower educational level and unemployed, followed by housewives and individuals with odd jobs. The pertinent results of this study are presented in Table 1.

Table 1: Age distribution for HCV infection in the population of the city of São Paulo (Focaccia et al, 1998; n = 726) and in group 1 (OLP patients; n = 68) of our study

<table>
<thead>
<tr>
<th>Age range</th>
<th>18–29</th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
<th>60 or plus</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Focaccia et al (1998)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>726</td>
<td></td>
<td></td>
<td>250</td>
<td>182</td>
<td>123</td>
</tr>
<tr>
<td>HCV</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>Group 1 (OLP patients)</strong></td>
<td>68</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>68</td>
<td></td>
<td></td>
<td>2</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>HCV</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

n = number of patients
*Significant: Chi-squared with Yate’s correction = 8.93; P = 0.002
*Four women, two men
Data were analysed using Chi-squared and Fischer tests with the aid of the EpiInfo software. Significance was set at $P \leq 0.05$.

**Results**

The results showed that for the 68 patients in the OLP group the liver function tests were elevated in 10 patients (14.7%), six of whom presented HCV infection (8.8%), three alcoholic hepatitis (4.4%) and one cryptogenic liver cirrhosis (1.4%). In the six patients with HCV infection reticular lesions were the most prevalent form of OLP (four cases), the buccal mucosa being the most affected site. None of these six patients presented any other systemic disease or were using topical or systemic medication.

Among the 126 patients of the group with HCV infection, six had OLP (4.7%), all of them being confirmed by histologic examination. Only one of these six exhibited cutaneous LP lesions as well. The atrophic and reticular forms were seen in equal frequency in these OLP patients, and the tongue was the most affected site. Liver biopsy of these six patients showed that all of them had active chronic hepatitis; two were being treated with $\alpha$-interferon and one was taking an immunosuppressive drug. Other oral mucosal diseases found in the remaining patients were one case each of geographic tongue, erythematous candidiasis, hyperplastic candidiasis, leukoplakia, recurrent aphthous stomatitis, and Darier’s disease.

To determine the significance of these results two comparisons were made: the frequency of HCV infection in the group of OLP patients was compared with the control frequency of HCV in the population of São Paulo established by Focaccia et al in 1998 (Table 1); while the frequency of OLP in the group of HCV patients was compared with the frequency of OLP determined by our study of the 898 individuals in the control group. Six of these control group patients (all females) presented oral lesions clinically consistent with OLP, which were subsequently confirmed by histologic examination. Of these six cases, three were of the reticular type, two were atrophic and one erosive; none of them were taking any medication nor suffering from any systemic disease. No skin lesions of LP were found or reported by any of these six patients nor, for that matter, by any of the other patients in the control group. The prevalence of OLP in this group was 0.6% (Table 2).

Statistical analysis showed that the prevalence rate of HCV infection in the OLP group (8.8%) was significantly higher ($P = 0.002$) than that of the general population of São Paulo, which is 1.4% (Focaccia et al., 1998).

Statistical analysis of the frequency of OLP in the HCV group (4.7%) was significantly higher ($P = 0.0003$) as compared with the frequency of OLP in our control group (0.6%).

When groups 1, 2 and 3 were compared for mean age, significant differences were seen among the three groups ($P \leq 0.05$), the mean ages being 49.2, 48.5 and 44.0 years, respectively. In terms of gender, a significant difference was seen only between groups 2 and 3 ($P = 0.001$), the percentages being 56 and 70% females, respectively. In the study by Focaccia et al (1998) the prevalence rate for HCV infection was the same for male and female subjects, being slightly more predominant in individuals between 40 and 60 years.

**Discussion**

The discrepancy among the findings of the various studies for the relation between OLP and HCV has been a subject of speculation among authors. Besides variation in a possible etiopathogenic factor, which has not yet been established between OLP and HCV infection, various researchers have suggested that relation between the two diseases could be the result of genetic, environmental, geographic, or other factors (El-Kabir et al., 1993; Scully et al., 1998; Roy and Bagg, 1999; Lodi et al., 2000; van der Meij and van der Waal, 2000).

With respect to a common etiopathogenic basis for the two diseases, two recent studies regarding the presence of HCV in the oral mucosal tissues are of note. These studies (Arrieta et al., 2000; Nagao et al., 2000) detected the presence of HCV RNA in the oral mucosa biopsies from HCV-positive patients, but in none of HCV-negative patients. It is interesting that in both studies HCV RNA was detected in the oral mucosa of HCV patients independently of having OLP or not.

**Table 2**  Age distribution for OLP lesions in the HCV patients (group 2) and in control group (group 3)

<table>
<thead>
<tr>
<th>Group</th>
<th>18–29</th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
<th>60 or plus</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2 (HCV patients)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>19</td>
<td>38</td>
<td>29</td>
<td>34</td>
<td>126</td>
</tr>
<tr>
<td>OLP</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>6*</td>
</tr>
<tr>
<td>Group 3 (control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>–</td>
<td>378</td>
<td>283</td>
<td>142</td>
<td>95</td>
<td>898</td>
</tr>
<tr>
<td>OLP</td>
<td>–</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

$n =$ number of patients
HCV patients with OLP lesions = two men and four women
Control group with OLP lesions = six women

*Significant: Chi-squared with Yates’s correction = 12.65; $P = 0.0003$
This finding may be taken to suggest that HCV is not sufficient in itself as a causative agent in the development of OLP lesions, and that host factors play an important role in the pathogenesis of HCV-related OLP. Another study, dealing with HLA-typing in Italian patients with OLP (Carrozzo et al., 2001), showed that OLP patients with HCV infection had a statistically significant higher frequency of HLA-DR6 than did OLP patients without HCV infection. This result suggests that HCV positive patients with HLA-DR6 are more susceptible to develop OLP lesions. According to the authors, the higher frequency of HLA-DR6 in OLP patients seems to be a characteristic of the Italian population, and cannot be extrapolated world-wide.

These above-mentioned studies and others (Nagao et al., 1996; Lodi et al., 1997) seem to support the current view that host immune response rather than the viral factors is of greater importance in determining the development of OLP lesions in HCV infected patients. The role of environmental or geographical factors, however, is less clear in the pathogenesis of HCV-related OLP. It has been suggested that geographical variation in the prevalence of HCV infection would be the explanation for the association between HCV and OLP, and that a higher frequency of HCV infection within countries would increase the chance of patient with OLP also be infected with HCV. In this view, the coexistence of the two diseases would not be linked by any common pathogenesis basis but by patient selection. However, in case-control studies (Bellman, Reddy and Falanga, 1995; Carrozzo et al., 1996; Imhof et al., 1996; Bagán et al., 1998) HCV infection was significantly higher in OLP patients than in control subjects, thus opposing the view that the relation is based merely on higher HCV rates in the population studied.

Other studies have gone in depth into the question of idiosyncratic or environmental issues which may be linked with OLP. Of note is the review Update on Oral Lichen Planus: Etiopathogenesis and Management (Scully et al., 1998). Whether such factors play a role or not in the development of OLP is a question not addressed by our study, which was designed to determine the statistical correlation between OLP and liver disease among our patients.

The statistically significant difference in respect to mean age among the groups of this study is explained simply by how the groups were formed. Groups 1 and 2 were formed on a walk-in basis, with no selection criteria except that of presenting with the disease. The control group 3 was similarly formed, the only criteria for rejection being if the patient was less than 30 years, and women showed up in greater numbers than men, which is the norm for our clinic.

In conclusion, the analysis of our data shows that among OLP patients the rate of HCV infection is six-fold higher; and among HCV patients the rate of OLP is eight-fold higher. In practical terms, on average, one person in 72 in São Paulo has HCV; with OLP this figure rises to one in 12. As this contrasts with findings of other studies, it should be taken as applying to the São Paulo area.

Thus, our findings suggest that at least in São Paulo the presence of OLP lesions can be used by clinicians for the purpose of screening patients regarding the possibility of concomitant liver disease, especially HCV infection.

References


