

## ORIGINAL RESEARCH



## Hepatitis C and Oral Lichen Planus: Evaluation of their Correlation and Risk Factors in a Longitudinal Clinical Study

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### ABSTRACT

**Objective:** The aim of this study is to evaluate the correlation between hepatitis C virus (HCV) infection and oral lichen planus (OLP), and further examine the relationship between age, sex, systemic diseases and drugs with the presence of HCV infection or OLP.

**Material and methods:** A longitudinal clinical study was carried out from March 2010 to December 2013 with 51 individuals, of whom 33 had been presented with HCV (HCV-positive group) and 18 had OLP (OLP-positive group), in Passo Fundo, RS, Brazil. Hepatitis C virus-positive individuals who presented lesions compatible with OLP were subjected to an intraoral biopsy for histopathological diagnosis, while OLP-positive individuals underwent anti-HCV serological test for diagnosis of HCV infection. Data on age, sex, systemic diseases and drugs used were recorded for later analysis. The data were analyzed using descriptive statistics of frequency and by Pearson's Chi-square test, with a 5% significance level ( $p < 0.05$ ).

**Results:** Out of the 33 HCV-positive individuals, only one was clinically and pathologically positive for OLP, demonstrating a significant relationship between the presence of HCV infection and the manifestation of OLP (Chi-square test  $-46.852$ ,  $p = 7.65 \times 10^{-12}$ ). None of the individuals in OLP-positive group had HCV infection. The most common systemic diseases were hypertension and diabetes, and the most commonly used drugs were antihypertensives. However, there was no significant relationship between these factors and the presence of OLP or HCV infection ( $p > 0.05$ ).

**Conclusion:** There was a significant relationship between HCV infection and manifestation of OLP. Age, sex, systemic diseases

and drugs were not identified as risk factors for the development of these diseases.

**Clinical significance:** The OLP could serve as an indicative of HCV infection in asymptomatic patients, thus enabling early diagnosis and treatment of hepatitis and hence, a better prognosis.

**Keywords:** Early diagnosis, Hepatitis C, Longitudinal studies, Oral lichen planus, Oral mucosa, Risk factors.

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### INTRODUCTION

Hepatitis C virus (HCV) infection is considered a public health problem with significant morbidity and mortality rates.<sup>1</sup> The extrahepatic manifestations of hepatitis C, such as oral lichen planus (OLP), should be well known by physicians and dentists, thereby favoring an early diagnosis and treatment.<sup>2-5</sup>

The first study indicating an association between chronic liver disease and lichen planus was published in 1978.<sup>6</sup> After this, studies have reported the coexistence of chronic hepatitis C and lichen planus, particularly OLP.<sup>1,4,5</sup> However, differences in the populations, study designs and potential confounder factors are critical biases that can lead to erroneous conclusions.<sup>7</sup>

Several clinical studies have shown an association between HCV infection and OLP.<sup>1,4,5,8,9</sup> However, this relationship remains controversial,<sup>3,7,10</sup> as these diseases may occur independently in patients aged 50 years or older.<sup>11</sup> The influence of geographical location should also

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be considered, given that the association between HCV and OLP seems to be more prevalent in Japan, United States of America and Southern Europe.<sup>12</sup>

Some studies have also suggested risk factors for HCV infection and manifestation of OLP, with no consensus though.<sup>11-19</sup> Longitudinal clinical studies resulting in the identification the risk factors associated with these diseases are fundamental for the development of surveillance measures and implementation of preventive measures targeted at HCV infection and onset of OLP.

This study aimed to evaluate a possible correlation between individuals HCV infection and the presence of OLP. In addition, the relationship between the age, sex, systemic diseases and use of drugs by these individuals with HCV infection or OLP was also analyzed.

## MATERIALS AND METHODS

This study was approved by the Research Ethics Committee of the University of Passo Fundo, Brazil (protocol no. 050/2009), ensuring that all ethical and legal principles were followed.

### Study Design

An observational, longitudinal clinical study was carried out, involving individuals infected with the HCV (HCV-positive group) and individuals with OLP (OLP-positive group).

### Sample

The sample consisted of two groups of subjects (HCV-positive and OLP-positive) belonging to the macro-region of the 6th Regional Coordination of Health in Rio Grande do Sul State, located in the city of Passo Fundo, southern Brazil, which includes a total of 58 municipalities. In both groups, the sample was selected by convenience.

In HCV-positive group, we selected 33 out of 61 subjects diagnosed with hepatitis C at São Vicente de Paulo Hospital (Passo Fundo, RS, Brazil) from January to March 2010. The study included patients with hepatitis C infection confirmed by enzyme-linked immunosorbent assay (ELISA) method and by quantification of ribonucleic acid of the HCV (HCV-RNA), without prior treatment with interferon and ribavirin ('untreated'), and with no blood conditions (thrombocytes counts above 50,000/mm<sup>3</sup> blood).

In OLP-positive group, we selected 18 out of the 31 individuals with reticular or plaque-like lichen planus, diagnosed at the Clinic of Stomatology, School of Dentistry, University of Passo Fundo (Passo Fundo, RS, Brazil), between January and March 2010. The study included only patients with OLP who had a clinical diagnosis

confirmed histopathologically. Individuals with metallic dental restorations or using medications that could trigger lichenoid lesions were not included in the sample.

## Methodology

Individuals in HCV-positive group (n=33) underwent a clinical interview (anamnesis) and three annual intra and extraoral physical examinations from March 2010 to December 2013. In case these individuals presented lesions compatible with OLP on one of those appointments, an intraoral biopsy for histopathological diagnosis of lesions was performed.

In OLP-positive group (n=18), the individuals underwent a clinical interview, anti-HCV serological test and three annual clinical intra and extraoral physical examinations, also from March 2010 to December 2013. Data on age, sex, systemic diseases and drugs used of all individuals were recorded for subsequent analysis. The clinical and histological analyses of the OLP lesions were performed based on the criteria proposed by Krutchkoff et al<sup>20</sup> and van der Meij and van der Waal.<sup>21</sup> A light microscope (Olympus® BX 50, Olympus Corporation of the Americas, Center Valley, PA, USA) was used to analyze the tissue specimens stained with hematoxylin-eosin (HE).

## Statistic Analysis

The data obtained were analyzed using descriptive statistics of frequency and Pearson's Chi-square test, with a significance level of 5% (p < 0.05), on SPSS version 13.0.

## RESULTS

During clinical follow-up, only one individual in HCV-positive group showed OLP at baseline. Still, there was a significant relationship between the presence of HCV infection and the manifestation of OLP (Pearson's Chi-square test -46.852, p = 7.65 × 10<sup>-12</sup>).

In OLP-positive group, none of the individuals had HCV infection. It was noted that 16 individuals had the same clinical features of OLP lesions observed at baseline, and that two others had complete remission of their lesions 12 months after the diagnosis, although they were not using drugs to treat the OLP lesions.

Table 1 summarizes the epidemiological data for both groups. There was no significant relationship between sex and the presence of HCV infection or OLP (Pearson's

**Table 1:** Epidemiological data

Variable	HCV <sup>+</sup> (n=33)		OLP <sup>+</sup> (n=18)		Total (n=51)	
	F	M	F	M	F	M
Sex	21	12	12	06	33	18
Mean age (± SD)	52.21 (±13.48)		53.72 (±16.73)		52.97 (±14.56)	

Chi-square test  $-0.047$  and  $0.183$ ,  $p=0.829$  and  $0.669$  for HCV-positive and OLP-positive groups, respectively).

Individuals aged between 43 and 60 years were the most affected by HCV infection (HCV-positive,  $SD \pm 4.99$  years) and OLP (OLP-positive group,  $SD \pm 4.55$  years) (Table 2). Nevertheless, no significant relationship was found between age and the presence of HCV infection or OLP (Pearson's Chi-square test  $-0.127$  and  $0.158$ ,  $p=0.938$  and  $0.924$  for HCV-positive and OLP-positive groups respectively).

According to Table 2, hypertension and diabetes were the most common systemic diseases in individuals from both groups. There was no significant relationship between systemic diseases and the presence of HCV or OLP though (Pearson's Chi-square test  $-6.250$  and  $6.975$ ,  $p=0.856$  and  $0.801$  for HCV-positive and OLP-positive groups respectively).

Antihypertensives were the most commonly used drugs in both groups (Table 2). However, there was no significant relationship between the use of drugs and the presence of HCV or OLP (Pearson's Chi-square test  $-14.145$  and  $13.772$ ,  $p=0.225$  and  $0.246$  for HCV-positive and OLP-positive groups respectively).

## DISCUSSION

This study evaluated a group of 33 individuals infected with HCV and 18 presented with OLP in three different times throughout a 46-month period. Only HCV-positive subjects who did not undergo treatment with interferon and ribavirin were included, in order to determine whether HCV infection influences the onset of OLP.

**Table 2:** Number of individuals with HCV or OLP based on age, systemic diseases and drugs used

Factors	HCV <sup>+</sup>	OLP <sup>+</sup>	Total
Age range			
22–42 years	6	4	10
43–60 years	17	9	26
61–84 years	10	5	15
Systemic diseases			
None	8	5	13
Hypertension	13	7	20
Diabetes	6	3	9
HIV	2	0	2
Cirrhosis	3	0	3
Hepatitis B	1	0	1
Drugs			
None	14	7	21
Anti-hypertensives	12	5	17
Anxiolytics /Antidepressants	10	1	11
Antidiabetics	5	0	5
NSAIDs	3	1	4
Corticoids	1	4	5

Based on the study sample and clinical follow-up of patients, we observed that in the macro-region of the 6th Coordination of Health of Rio Grande do Sul in Passo Fundo, southern Brazil, there was no statistical relationship between HCV infection and the occurrence of OLP, although a single case in HCV-positive group (3.03%) had oral lesions of lichen planus. This rate suggests that the HCV-positive population in this research had a higher prevalence of OLP than that uninfected, which corroborates a study by Grossmann et al<sup>8</sup> and Birkenfeld et al,<sup>4</sup> showing prevalence rates ranging from 0.1 to 2%.

Nevertheless, it is important to consider that data of epidemiological studies vary considerably according to the geographical region. In Japan,<sup>22</sup> Italy,<sup>23</sup> Nigeria and Thailand,<sup>11,24</sup> for instance, the prevalence of HCV infection in patients with OLP ranged from 8.33 to 60%, with significant differences compared with the respective controls. Paradoxically, this could not be confirmed in the Netherlands,<sup>25</sup> Germany,<sup>26</sup> Serbia<sup>27</sup> and Southeastern Brazil,<sup>28</sup> where there was no difference in HCV infection rates between individuals with OLP and the general population.

Carrozzo<sup>10</sup> reported that HCV-positive individuals develop late OLP lesions possibly due to an immunological condition; however, this remains poorly understood. In this regard, one of the shortcomings of this study was the inability to determine the time of HCV infection, as study participants were asymptomatic and became aware of their positivity for HCV in routine examinations.

A systematic review with a meta-analysis by Carrozzo and Scally<sup>29</sup> showed that epidemiological findings support the association between OLP and HCV, and that the HCV may be implicated in the pathogenesis of OLP, as this virus can replicate in the oral mucosa and attract virus-specific T-lymphocytes.

Oral lichen planus is an inflammatory chronic disease whose definitive and complete cure rates range from 2.5 to 17%.<sup>30</sup> This seems to explain the findings of this study, given that at 46 months follow-up, 2 out of 18 individuals in OLP-positive group had complete remission of their lesions. On the contrary, 32 out of 33 subjects in HCV-positive group showed no clinical signs of OLP during follow-up.

The results of this study are similar to those of Bermejo-Fenoll et al,<sup>9</sup> who found a mean age of 56.35 years for patients with OLP. Similarly, with regard to HCV infection, the Brazilian Ministry of Health informs that in 2009, the diagnosis was more frequent in patients aged 50–59 years.<sup>31</sup> Lodi et al<sup>11</sup> reported in their study that many patients with OLP were 50 years or older and that the high frequency of seropositivity for HCV found in groups of patients with OLP was just a coincidence,

given that both diseases significantly affect patients in this range age, with no causal relationship.

According to Eisen,<sup>13</sup> predisposing factors such as stress, spicy foods, dental procedures, systemic diseases, drugs and poor oral hygiene may result in exacerbation of OLP. Previous studies have suggested that individuals with lichen planus also have diabetes more often than the general population.<sup>14,15</sup> In this study, the most common systemic illnesses reported by individuals in both groups were hypertension and diabetes. However, there was no significant association between systemic diseases and the presence of OLP or HCV infection, which is in agreement with Jing-Ling et al.<sup>16</sup>

Antihypertensives were the class of drugs mostly used in both groups, but there was no significant relationship between the use of drugs and the presence of HCV or OLP. In agreement with this, only one individual who had OLP in HCV-positive group did not use drugs, excluding the hypothesis that the injury was caused by drugs.

According to the literature, there are a few drugs classically known to induce OLP, such as nonsteroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors.<sup>17</sup> There is also sufficient evidence that  $\beta$ -blockers and other drugs play a significant role in the development of OLP.<sup>12,18</sup>

Li et al<sup>32</sup> investigated the incidence of skin adverse events during the treatment of chronic hepatitis C in 152 patients, and found 14 (9.2%) patients with eczematous reactions, two (1.3%) patients with lichenoid eruption and a single case of OLP, among other lesions. The authors concluded that the treatment of HCV with interferon-alpha/ribavirin contributes to the occurrence of dermatological reactions involving the skin, mucous membranes, nails and hair. Such a comparison could not be performed in this study, as the analyzed HCV-positive patients had not undergone treatment with any of these drugs.

For Ben Salem et al,<sup>19</sup> the exact mechanism of the pathogenesis of drug-induced lichen planus is uncertain. A suggested mechanism is the antigenic formation theory, by which drugs may induce damage to keratinocytes with exposure of basal membrane (not previously exposed), leading to the formation of antibodies.

Although a relationship between OLP and HCV infection has been statistically verified in the population of Passo Fundo, RS, southern Brazil, based on a 46-month clinical follow-up, further evidence is required to prove this assumption. Studies with longer follow-up are needed to confirm more precisely the findings of our study.

## CONCLUSION

Individuals with OLP should be screened for the presence of HCV infection, as there was a significant

relationship between the presence of HCV infection and the manifestation of OLP. Age, sex, systemic diseases and drugs used by patients were not identified as risk factors for development of these diseases, as no significant relationship was found between these factors and HCV infection or the presence of OLP.

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