



Association between oral lichen planus and hepatitis C: retrospective study and case report

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ABSTRACT. Oral Lichen Planus (OLP), a chronic inflammatory disease of unknown etiology, which affects the skin and/or mucosal tissues, is an autoimmune disease (pathology) of special interest to dentists due to its oral manifestations and its possible association with Hepatitis C virus (HCV). Although a possible association has been extensively discussed in the literature, the results have been controversial. So that the relationship between Oral Lichen Planus (OLP) and infection by HCV (OLP-HCV) may be investigated, current study conducted an epidemiological survey of all OLP cases diagnosed in two reference projects, with regard to diagnosis, treatment and epidemiology of oral lesions in Maringá, Paraná, Brazil. In addition, the clinical case of a patient with HCV and the clinical manifestation of severe OLP will be provided. A total of 3,488 clinical records of biopsies performed between 1994 and 2014 and 85 cases of OLP were selected for the present study. The reticular type of OLP showed significant prevalence but only 2.3% of OLP cases revealed any association with HCV.

Palavras-chave: líquen plano, hepatite C, epidemiologia.

Associação entre líquen plano oral e hepatite C: estudo retrospectivo e relato de caso

RESUMO. Líquen Plano (LP) é uma doença inflamatória crônica de etiologia desconhecida, que acomete pele e/ou mucosas. Esta doença autoimune é de especial interesse para o cirurgião-dentista pelo fato de apresentar manifestações bucais e pode estar associado ao vírus da hepatite C (VHC). Esta possível associação tem sido muito discutida na literatura, apresentando resultados controversos. Com o intuito de investigar a relação entre o Líquen Plano Oral (LPO) e a infecção pelo VHC (LPO-VHC), o presente trabalho objetivou conduzir um levantamento de todos os casos de LPO diagnosticados em dois projetos de referência quanto a diagnóstico, tratamento e epidemiologia de lesões bucais na cidade de Maringá, Paraná, Brasil. Adicionalmente, um caso clínico de um paciente portador do VHC com manifestação clínica severa de líquen plano será apresentado. Foram selecionados para o presente estudo um total de 3.488 prontuários de biópsias realizadas entre os anos de 1994 e 2014 e 85 casos de LPO. O LPO do tipo reticular apresentou prevalência estatisticamente significante e apenas 2.3% dos casos de LPO apresentaram associação com o VHC.

Keywords: lichen planus, hepatitis C, epidemiology.

Introduction

Lichen Planus (LP) is a chronic inflammatory and immunological disease which affects the mucosa and epidermis, where auto-antibodies are directed against the basal layer of the epithelium, causing lesions with several clinical aspects (Lodi et al., 2005). Some studies have shown that LP affects between 0.5 and 2.0% of the population in general, although there is no consensus on its true prevalence (Chainani-Wu, Lozada-Nur, & Terrault, 2004).

Many patients affected by Oral Lichen Planus (OLP) are middle-aged adults (Gümrü, 2013; Budimir et al., 2014). The lesion is rare in children,

featuring only 0.03% of cases (Gunashekhar et al., 2010), but studies in different countries reveal that females are more affected than males (Gümrü, 2013; Budimir et al., 2014).

According to Eisen, Carrozzo, Sebastian and Thogprasom (2005), OLP has distinct and easily identifiable clinical characteristics with two main forms, namely, reticular and erosive, although the bullous and papular forms of the disease are not rare (Edwards & Kelsch, 2002). The reticular form, characterized by interlaced white lines, known as Wickham striae, is the most common. In most cases, this form of OLP affects the posterior jugal mucosa bilaterally and is generally asymptomatic. The

involvement of other areas, such as the dorsum and lateral section of the tongue, gingivae and palate, may occur simultaneously (Edwards & Kelsch, 2002; Mollaoglu, 2000). Erosive LP is clinically manifested by atrophic and erythematous areas. However, in more severe cases, separation of the epithelium may occur and result in an infrequent form of the disease known as bullous LP (Edwards & Kelsch, 2002).

Although immunological factors, neurological alterations, genetic predisposition, viral origin, association with chronic hepatic diseases and psychogenic alterations have been indicated, OLP's etiology and pathogenesis remain uncertain (Scully, Eisen, & Carrozzo, 2000; Romero, Seoane, Varela-Centelles, Diz-Dios, & Otero, 2002).

There are reports of patients with OLP who have been infected by Hepatitis C virus. This association is, however, still controversial and the mechanism connecting the two diseases is not etiologically clear (Lodi et al., 2000). Various investigators have suggested that the concomitance may be due to genetic, environmental and geographical factors.

The Hepatitis C virus is an RNA virus and causes acute and chronic hepatitis, both of which are currently serious public health issues. Contagion mainly occurs by parenteral exposure to infected materials, such as blood transfusions, or by direct contact with contaminated needles. Among infected patients, illicit drug users who share needles and health professionals are considered to be at high risk. Chronic Hepatitis C develops in approximately 75% of infected persons. Acute hepatitis C and the chronic type are asymptomatic in most patients. Nevertheless, chronic hepatitis is a slow progression disease which results in severe morbidity in 20% - 30% of cases, and is associated with various extra-hepatic manifestations (Bonkovsky & Mehta, 2001).

Current investigation comprises an epidemiological survey of all the cases of LP diagnosed in two reference projects, with regard to diagnosis, treatment and epidemiology of oral lesions in Maringá, PR, Brazil. In addition, a clinical case of a patient with HCV and the clinical manifestation of severe LP will be presented.

Material and methods

In order to conduct a retrospective observational study, a survey was carried out on the clinical charts of adult patients attended to in two health institutions in Maringá, Paraná State, Brazil (Departments of Dentistry of Unicesumar and State University of Maringá, UEM), quantifying the cases diagnosed with OLP

between 2004 and 2014. All patients with clinical and/or microscopic LP diagnosed were selected. The cases of OLP were divided according to the following clinical classification: (1) *reticular*: presence of white striae; (2) *erosive*: presence of erosive/atrophic areas; (3) *reticular/erosive*: when white striae and erosive areas were present concomitantly; (4) *papular*: presence of small white papules; and (5) *bullous*: presence of blisters associated with the aforementioned lesions.

After the clinical record charts were selected, a survey was made of the data, taking into consideration the variables: gender, age, systemic disease, hepatitis, type of infection, time of development of the disease, association with candidiasis, smoking, skin lesions, biopsy, region affected, symptoms, follow-up and treatment.

A database on the variables was organized for tabulation and statistical analysis by means of the non-parametric chi-square test. The level of significance was set at 5% for all tests and software Pacotico v.0.5, Microsoft Visual FoxPro, was used.

The study involved no risks to patients, as only the data contained in the record charts of biopsied patients were used. Current study was approved by the Committee for Ethics in Research involving Human Beings of Unicesumar (Protocol N. 380.201) and UEM (Protocol N. 458,301).

Results

A selection of 786 clinical charts from Unicesumar and 2,702 record charts from UEM were analyzed, totaling 3,488 record charts of patients submitted to biopsy. Further, 85 (2.4%) were charts of patients who had some type of OLP. Only four patients presented skin lesions (4.7%). As regard to age, six individuals (7%) were between 20-30 years of age; 19 (22.4%) between 31-40 years; 28 (32.9%) between 41-50 years; 17 (20%) between 51-60 years; 13 (15.3%) >60 years; two patients (2.4%) failed to provide this information (Figure 1).

With regard to patients' gender, 68 (80%) were females and 17 (20%) were males. Seventeen patients (20%) admitted they were smokers (20%). With reference to the types of Lichen Planus, 65 (76.5%) patients were affected by the reticular type ($p < 0.001$); 12 (14.1%) by the erosive type; six (7%) by the reticular/erosive type; one (1.2%) by the papular type (1.2%) and one (1.2%) by the bullous type (Figure 2). Association with Candidiasis occurred in four patients (4.7%).

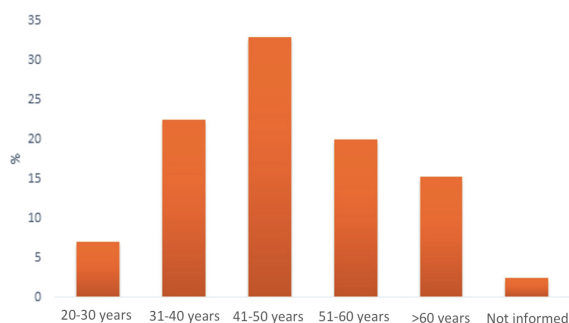


Figure 1. Distribution of patients according to age ($p > 0.05$).

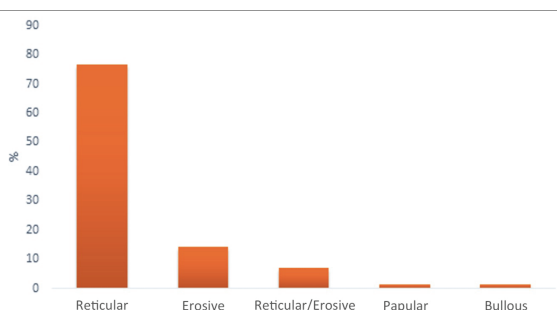


Figure 2. Distribution of patients according to types of OLP ($p < 0.001$).

With regard to the diagnosis, biopsy was performed in all cases, with 77 (90.6%) being of the incisional type; six (7%) of the excisional type, one (1.2%) of the incisional type, followed by excisional biopsy; in one case (1.2%) this information was not stated on the record chart. Forty-one (48.2%) patients reported some type of symptoms, such as pain and burning.

Two patients (2.3%) admitted being carriers of Hepatitis C virus infection; three patients (3.5%) reported positive serology for hepatitis A; three (3.5%) for hepatitis B and four (4.6%) were unable to inform the type. There was no statistically significant difference ($p > 0.05$) with reference to those with Hepatitis C; there was one case of a male with Reticular LP and another of a female with Erosive LP.

Treatment was performed by referral to a doctor/dermatologist in 16 cases (18.8%); for 23 patients (27.1%) local/systemic medication was prescribed, while seven patients (8.2%) were referred and also received administration of the same medication. Surgical removal was performed in two cases (2.4%); there was follow-up in 34 patients (40%) and in three cases (3.5%) the information was not stated on the record chart.

Case report

A 52-year old Caucasian female presented herself to the Department of Dentistry of UEM,

complaining of a burning sensation in the mouth and sores on the tongue. When she was physically examined, several diffuse, erythematous, extremely painful ulcerations circumscribed by Wickham striae were observed. They were located on the dorsum of the tongue, retromolar region and bottom lip (Figure 3). Skin lesions, characterized by itchy papules, were observed in the flexor regions.



Figure 3. Erythematous ulcers on the dorsum of the tongue.

The patient reported that the oral lesions appeared nine months before and that the pain increased during meals. Systemically compromised, she was a Hepatitis C carrier; she had diabetes type 2, with gastritis and arterial hypertension. Based on the clinical aspect of the mucus-cutaneous lesions, in addition to the patient's history, the presumptive diagnosis was erosive LP. The patient was submitted to incisional biopsy on the retromolar region and on the dorsum of the tongue. Microscopic exam confirmed the diagnosis of Erosive LP (Figure 4).

Initially the patient received medication therapy with topical corticosteroids (Dexametasone - Elixir 0.1 mg mL⁻¹, four times a day) and systemic medication (Deflazacort 30mg, for 15 days). On the 21st day of follow-up, the patient presented pseudomembranous candidiasis, possibly due to corticotherapy. At this time, Nystatin 100,000 UI mL⁻¹ in an oral suspension was prescribed. Due to the persistence of the painful symptoms, the option taken was for the oral administration of 20mg Prednisone for 10 days, associated with Hexomedine spray. After 30 days, the patient presented glycemic decompensation, which led to the need for withdrawing the systemic medication. It is important to point out that, in all the steps, the patient was also being followed up by a doctor.

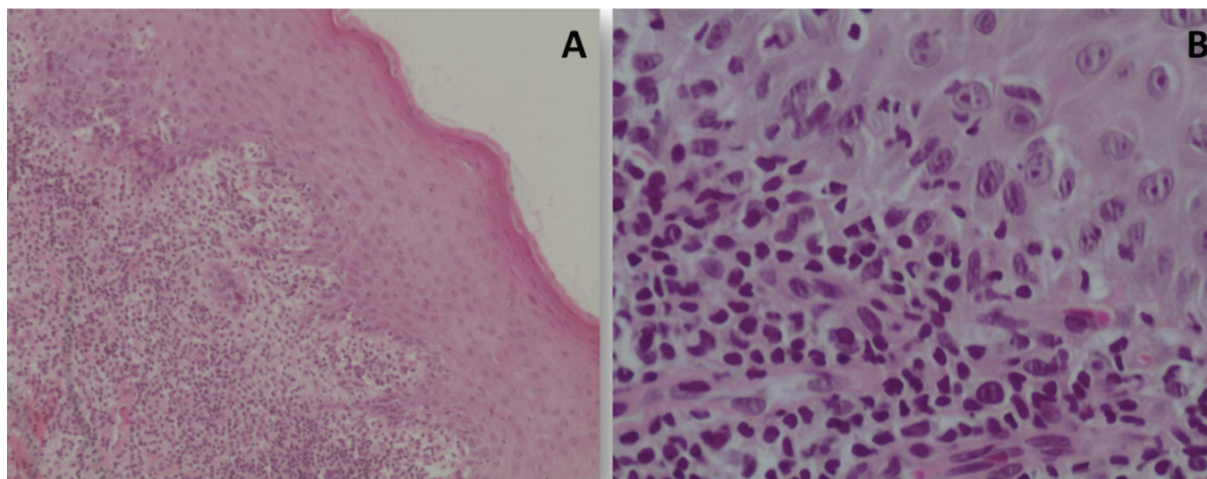


Figure 4. Photomicrographs of biopsy samples.

After three months of follow-up the patient presented controlled glycaemia, albeit without treatment for Hepatitis C. With the pause in systemic treatment, although the topical medication had been maintained, the ulceration on the dorsum of the tongue increased and lesions on the lip and skin were identified. At this time, the patient was in a highly emotionally unbalanced state, with persistent painful symptoms, being followed up by doctors and awaiting consultation with a hepatologist.

Discussion

OLP is commonly present in two forms: reticular and erosive. The most common form in current study was the reticular type with 65 cases (76.5%). Preponderance of the reticular type occurred in a recent study by Budimir et al. (2014), in which 64.8% of the 563 cases of OLP were of the reticular type. Although the erosive form is not so common, it is more significant for the patient, because it is symptomatic and may vary from simple discomfort to intense pain, with consequent difficulty in chewing. Unilateral or bilateral involvement of the jugal mucosa was present in 63 cases (74.1%), corroborating reports by Mollaoglu (2000). The jugal lesions in current study were commonly associated with other sites, such as the tongue, retromolar area and palate, also registered in the study by Eisen (2002).

Results revealed that OLP more frequently affects females at a male/female ratio of 1:4. The age-bracket most involved lay between 41-50 years (32.9%), followed by the 31-40 years group bracket (22.4%), which reinforces the preference for middle-aged women, as reported (Gümrü, 2013;

Budimir et al., 2014; Eisen, 2002). Budimir et al. (2014) registered that females had more complaints of symptoms associated with OLP (59.6%) when compared with males (45.2%), with 48.2% of all the patients reporting some type of symptoms. This prevalence may be even higher, as shown by Gümrü (2013) in a study with 370 patients, of whom 83% had complaints associated with the lesion.

In spite of the etiology of OLP being unknown, various studies (McCartan; Lamey, 2000; Birkenfeld, Dreier, Weitzman, & Cohen, 2011; Nagao, & Sata, 2012) have pointed out a strong statistical relationship with HCV infection. In 1990, one year after the discovery of the virus, and by available serologies, the HCV infection started to be considered a possible etiologic agent (Rebora, 2011). The association between LP and HCV (OLP-HCV) was reported for the first time in 1991 (Mokni et al., 1991), whereas the first cases of OLP possibly linked to HCV were published in 1994 (Gandolfo, Carbone, Carrozzo, & Gallo, 1994).

As indications of the replication of the RNA of HCV may be detected within the OLP lesions and the presence of damage to the basal layer is clear in these patients, there may be a very probable etiological link between OLP and the immune response mediated by cells against HCV. Pilli et al. (2002) showed a specific response by lymphocytes T directed to HCV in the OLP lesions, strongly suggesting its role in the pathogenesis of the damage. The proportion of T CD8+ cells in the lamina propria appears to be higher in cases of OLP-HCV, when compared with cases of idiopathic OLP (Carrozzo, 2008).

According to Arrieta et al. (2000), HCV replicates itself in the epithelial cells of individuals with or without OLP, in spite of no microscopic

changes, or even without any inflammatory infiltrate around the infected cells being observed. Mega, Jiang and Takagi (2001) reported that the infiltration of lymphocytes into the lamina propria is deeper in patients with OLP-HCV. Moreover, the more extensive and aggressive infiltration of lymphocytes may be associated with the erosive manifestation of OLP, as illustrated in the present case, in which the patient with HCV featured the erosive type of OLP.

Some studies, however, contest this association (Garg, Karki, Agrawal, & Gupta, 2002; Daramola, George, & Ogunbiyi, 2002; Nagao & Sata, 2004; Patil, Khandelwal, Rahman, Kaswan, & Tipu, 2012). Patil et al. (2012) analyzed 130 patients with clinical and histopathological confirmation of OLP with regard to serologic evidence of chronic liver disease. The authors concluded that there was no evidence of association between OLP and infection by hepatitis B or C virus. According to Nagao and Sata (2004), the prevalence of HCV in patients with LP varies from region to region since it depends on the virulence of the HCV in the country, with no consistent relationship between the two diseases.

A large number of patients with OLP in current analysis were observed carrying Hepatitis A and B virus, rather than the Hepatitis C virus, corresponding to 50% of the total number of hepatopathic patients. However, there is no evidence of the relationship between these types of hepatitis and OLP (Patil et al., 2012). The prevalence of patients with positive serology for HCV with cutaneous lichen planus and with OLP ranges between 3.8 and 65% (Bagan et al., 1998; Carrozzo, 2001). In the present study, only two patients (2.3%) stated having positive serology for HCV: a male and a female respectively with reticular and erosive OLP.

Another study by Mignogna et al. (2000) analyzed OLP in patients with and without associated HCV to evaluate possible differences in the clinical characteristics between the two groups of patients. The authors reported a statistically significant difference between the patients of the two groups, and this variability may strengthen the hypothesis of the participation of HCV in the etiology of OLP, probably via modulation of the qualitative aspects of the inflammatory infiltrate.

In a recent study by Gorouhi, Davari and Fazel (2014), a meta-analysis was conducted to find a possible association between LP and HCV. Important previously published meta-analyses were also included, such as those by Lodi et al. (2004), Shengyuan et al. (2009), Lodi, Pellicano and Carrozzo (2010), among others (Birkenfeld et al., 2011; Lin, Lu, & Lu, 2010; Halawani, Balbisi, Alotaibi, Alsaif, & Bakir, 2010; Zhou, Jiang, Liu,

Zeng, & Chen, 2010; Rübsam et al., 2011). Analysis of 64 articles detected that patients with OLP had 5.58 times more chances of having a concomitant infection by HCV when compared to control population (Gorouhi et al., 2014).

The low prevalence of cases with an association between OLP and hepatitis C in the present study may be explained by the fact that current research were foregrounded on data from record charts, and not on confirmatory serology. It is also probable that various individuals did not know the type of hepatitis, or even the presence of infection. In spite of the association not being proved, the severe manifestation of OLP in the case reported seems to show the relationship and that treatment is more complex in patients infected by the HCV. Furthermore, OLP may be the first manifestation of the infection by HCV and it is highly relevant that dental practitioners actively investigate this possibility.

Conclusion

The relationship between OLP and HCV is still highly controversial. In current study, the prevalence of HCV in patients with OLP was only 2.3%. However, the clinical case reported may illustrate the possibility of this concomitance to justify further exposure of clinical cases refractory to treatment.

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