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Original Article

Oral lichen planus among patients suffering from diabetes mellitus and type C hepatitis

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Abstract

The main goal of this observational retrospective study is to discover the common clinical features of the oral lichen planus among patients suffering from both, diabetes mellitus and type C hepatitis. Several 551 observation sheets of patients suffering from oral lichen planus were analyzed. We created 4 subgroups of patients with oral lesions of lichen planus: with no diabetes and hepatitis (1), with diabetes or hepatitis only (2 and 3), and with both diseases (4). Information about patients' data, medical history, smoking status, oral lichen planus clinical forms and symptoms, and how it started were collected. The main finding of our study was that patients who have diabetes had a worse clinical evolution of the oral lesions of lichen planus ($p<0.05$). The results showed the need for closer supervision when oral lichen planus and general conditions coexist. Screening for diabetes or type C hepatitis in patients with oral lichen planus is also useful.

Keywords: oral disorders, oral lichen planus, diabetes, type C hepatitis.

Introduction

Diabetes mellitus (DM) is a metabolic, chronic and high worldwide spread disease. According to the World Health Organization (WHO) reports, almost 422 million people have diabetes all over the world, and 1.5 million deaths are directly linked to DM [1].

Type C hepatitis (TCH) is an inflammation of the liver due to a viral infection caused by the hepatitis C virus (VHC). WHO estimated that 55 million people suffer from TCH worldwide, with a 1.5 million infection rate and 290.000 deaths per year [2].

Sometimes, we can find patients who suffer from both diseases because they are linked somehow. For example, it was found that patients already infected with TCH are at a high risk for DM, and the risk increases with the duration of exposure to TCH. Moreover, eradication of TCH leads, in some cases, to better insulin sensitivity and to a decreased risk of DM for these patients [3]. On the other hand, DM makes TCH worse, including leading to a high risk of cirrhosis [4].

Oral disorders are common among patients suffering from DM, such as periodontal disease, xerostomia, root caries, candidiasis, lichen planus, taste disturbance and burn mouth syndrome [5, 6]. Some oral disorders are also expressed by patients infected with HCV, like oral lichen planus (OPL), Sjogren-like sialadenitis, oral squamous cell carcinoma, paraneoplastic

pemphigus and pemphigus vulgaris, and Behcet's disease [7].

The main objective of this study is to make a comparative and descriptive analysis of the demographic, clinical and progressive characteristics of OLP in a group of patients who suffered from TCH and DM. Moreover, we searched for some strong statistical links between clinical variables. These objectives are important in assessing how TCH can influence the features, clinical forms, evolution, and prognosis of OLP.

Material and methods

This retrospective study analyzed 551 observation sheets of patients suffering from OLP between 2007 and 2014.

The patients were selected from the Department of Oral Pathology of UMF Carol Davila, School of Dentistry, Bucharest, Romania. The study protocol was approved by the Ethics Committee of the UMF Carol Davila (no. 29/09.08.2014).

Diagnosis of OLP followed the clinical and histopathological criteria developed by the WHO in 1978 [8] and modified by van der Meij *et al.* (2003) [9]. These criteria are based on a bilateral reticular keratosis on the buccal mucosa, a chronic inflammatory infiltrate "band-like" pattern, and a lack of dysplasia. We also used Andreasen's clinical classification to point out the clinical form of OLP. So, we considered four clinical forms of OLP: keratotic, atrophic, erosive and bullous form [10].

The criteria for diagnosis of DM provided by the American Diabetes Association (ADA) are HbA1c ≥6.5%, Fasting blood glucose ≥126 mg/dl, 2-hour blood glucose ≥200 mg/dl and Occasional blood glucose ≥200 mg/dl in patients who also have polyuria, polydipsia and weight loss. In our study, the diagnosis of DM was based on what they declared about their case history and on a fasting blood glucose value above 126 mg/dl. DM may be type 1, more common in children and young people, caused by insufficient insulin secretion; type 2, due to insulin resistance (most commonly found); gestational diabetes; and others [11].

The diagnosis of TCH was based on the patients' history and presence of anti-HCV antibodies detected by generation II of the ELISA test (MONOLISA anti-HCV PLUS), which was confirmed by a recombinant immunoblot reaction (RIBA-type).

The following data were analyzed from the assessment papers: general data (age, gender), smoking type (smoker/non-smoker/former smoker), patient medical and surgical history, clinical features and the evolution of OLP, blood tests (sugar, transaminases, serological markers of HCV).

Study design and patients

OLP patients who met the criteria were divided into 4 subgroups as follows:

- Subgroup 1 – no DM and no TCH (DM - & TCH -): N=373;
- Subgroup 2 – DM but no TCH (DM + & TCH -): N=46;
- Subgroup 3 – no DM but TCH (DM - & TCH +): N=109;
- Subgroup 4 – DM and TCH (DM + & TCH +): N=23.

Statistical analysis

The data were entered into a computer and analyzed using SPPS – Statistical Package for the Social Sciences, version 13 for Windows. Statistical tests (Pearson chi-square and cross-tabulation) were performed considering $p<0.05$ and a 95% confidence interval. A value of p between 0.05 and 0.09 was considered marginally statistically significant.

Results

The study group consisted of 432 women (78.4%) and 119 men (21.6%) with a mean age of 57 years (SD=14) (Figures 1 and 2)

In each subgroup, variables such as gender, age, smoking status and clinical features of the oral diseases were analyzed. We noticed how the general pathology influenced these variables. Thus, DM, TCH, arterial hypertension, thyroid pathology or dyslipidemia were more frequently found in the patients' history with OLP. We selected only conditions for which we had solid documentation about the association with OLP.

All these subgroups presented a higher prevalence among women, independent in some ways from the association with DM or HCV. The average age was higher in subgroup no. 2–4. The subgroup's characteristics are presented in Table 1. Most of the patients from our study were non-smokers (Table 2)

Patients with DM and TCH visited the dentist approximately 12 months after the oral lesions (OLP) came up (Table 3).

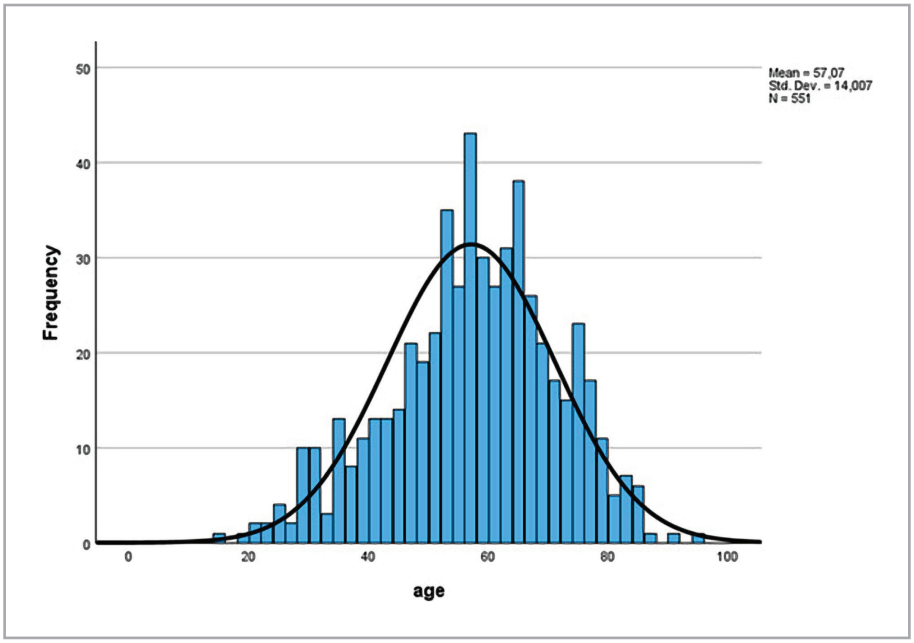

Figure 1: The mean age of the study group.

In order to have a complete "picture" of the OLP features in patients suffering from DM and TCH, we took fresh photographs, as can be seen in the collages below (Figures 3 and 4):

The clinical forms and sites of OLP are shown in Tables 4 and 5.

Analyzing the oral lesions of OLP, we observed that in most cases, they had a favorable or stationary evolution, except for subgroup no. 4, which associates DM and HCV. They presented an exacerbation of symptoms at the last check-up (Table 6).

The results were statistically significant (Table 7): biological gender and smoking status (p=0.001), biological gender and symptoms (p=0.02), gender and clinical form (p=0.021), age and the presence of symptoms (0.029), and DM and evolution (p=0.002).

Discussion

A recent meta-analysis showed a 1.01% worldwide prevalence of OLP but also an important geographical

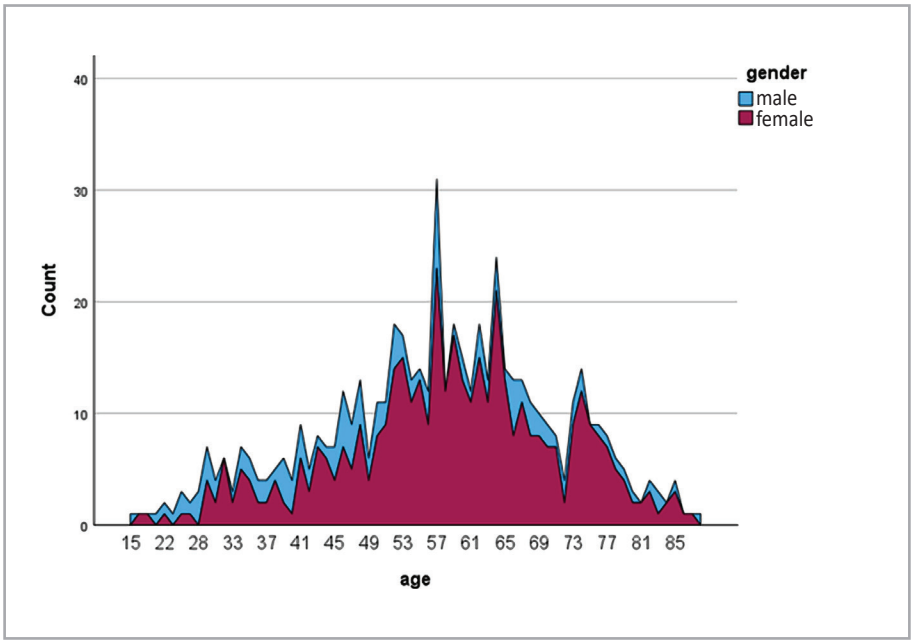

Figure 2: Age and gender distribution of the study group.

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Table 1: The age and gender in the four subgroups.

Subgroup	N	Gender N (%)	Age (year): Mean±SD	Minimum/Maximum
1	373	F*: 275 (73.7) M**: 98 (26.3)	F: 55.68 (13.515) M: 49.48 (16.157)	15/95 19/85
2	46	F: 35 (76.1) M: 11 (23.9)	F: 64.97(10.436) M: 55.91 (10.025)	31/82 45/72
3	109	F: 95 (87.2) M: 14 (12.8)	F: 63.36 (10.354) M: 66.57 (10.588)	31–90 48-85
4	23	F: 20 (87) M: 3 (13)	F: 62.40 (8.702) M: 65.33 (18.566)	46–79 46–83

Note: *– F: female; ** – M: male.

Table 2: Patients smoking status.

Gender	Non-smokers	Smokers	Former smokers	Total
Female	304	67	54	425
Male	63	28	35	126
Total	367	95	89	551

spread. Thus, the highest prevalence of OLP was observed in Europe (1.43%). Also, a progressive increase was found over the age of 40, especially among women [12]. A multicenter study conducted by Jiaxin Liu *et al.* showed a higher frequency of women with OLP (61.4%), the average age of their group being 49.2±13.3 years [13]. In a study conducted in the south of India, OLP was also found more often in women than men (ratio 2/1) [14]. The average age of patients from our study is close to that from other reports, as well as the gender distribution (Figure 2).

A meta-analysis conducted by Mozafari *et al.* showed a higher value of the average age in patients with OLP and DM (51 *vs.* 47.7). This may also be a consequence of DM and TCH being more common in older ages, age being practically a risk factor for OLP [15]. Similar results were reported in a recent study by Rodriguez-Fonseca L. *et al.*, who found an average age of 59.60±12.18 years in their group [16].

Most studies pointed out that smoking is not so often associated with OLP. However, chronic smoking can be correlated with some clinical changes of OLP and with a high frequency of dense keratotic plaques [17]. Although the association of smoking or chronic alcoholism with OLP does not have quite a significant value, patients with OLP mustn't smoke to increase the possible risk of carcinoma (OLP having a malignant transformation potential).

Most studies on the clinical form of OLP reported keratotic lesions as the most common, followed by atrophic and erosive [14]. We found keratotic forms present most in subgroup 1 and with no association with the general pathology. However, a higher frequency of erosive form was observed in patients from subgroups 3 (DM - and TCH +) and 4 (DM + and TCH +). These results are similar to other studies that considered age, the evolution of more than 1 year and the association with some general conditions as risk factors

Table 3: When OLP came up about the first visit to the dentist.

Subgroup	Unknown N (%)	< one month N (%)	1–6 months N (%)	6–12 months N (%)	12–60 months N (%)	>60 months N (%)
1	27 (7.2)	53 (14.2)	108 (29)	84 (22.5)	78 (20.9)	23 (6.2)
2	5 (10.9)	7 (15.2)	12 (26.1)	11 (23.9)	5 (10.9)	6 (13)
3	12 (11)	14 (12.8)	32 (29.4)	21 (19.3)	20 (18.3)	10 (9.2)
4	2 (8.7)	3 (13)	4 (17.4)	9 (39.1)	3 (13)	2 (8.7)

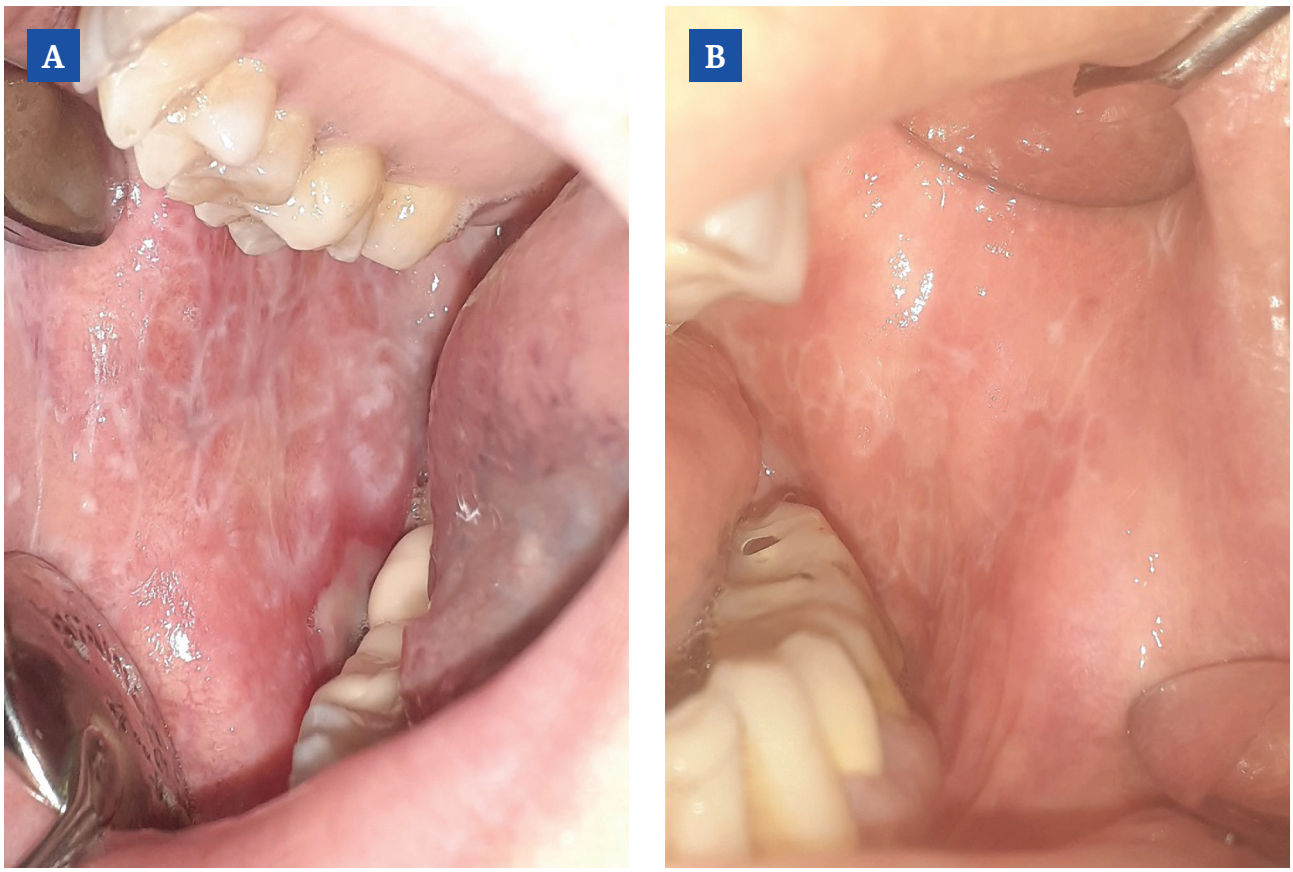

Figure 3: A – Reticular keratosis and central atrophy on the jugal mucosa; B – Reticular keratosis.

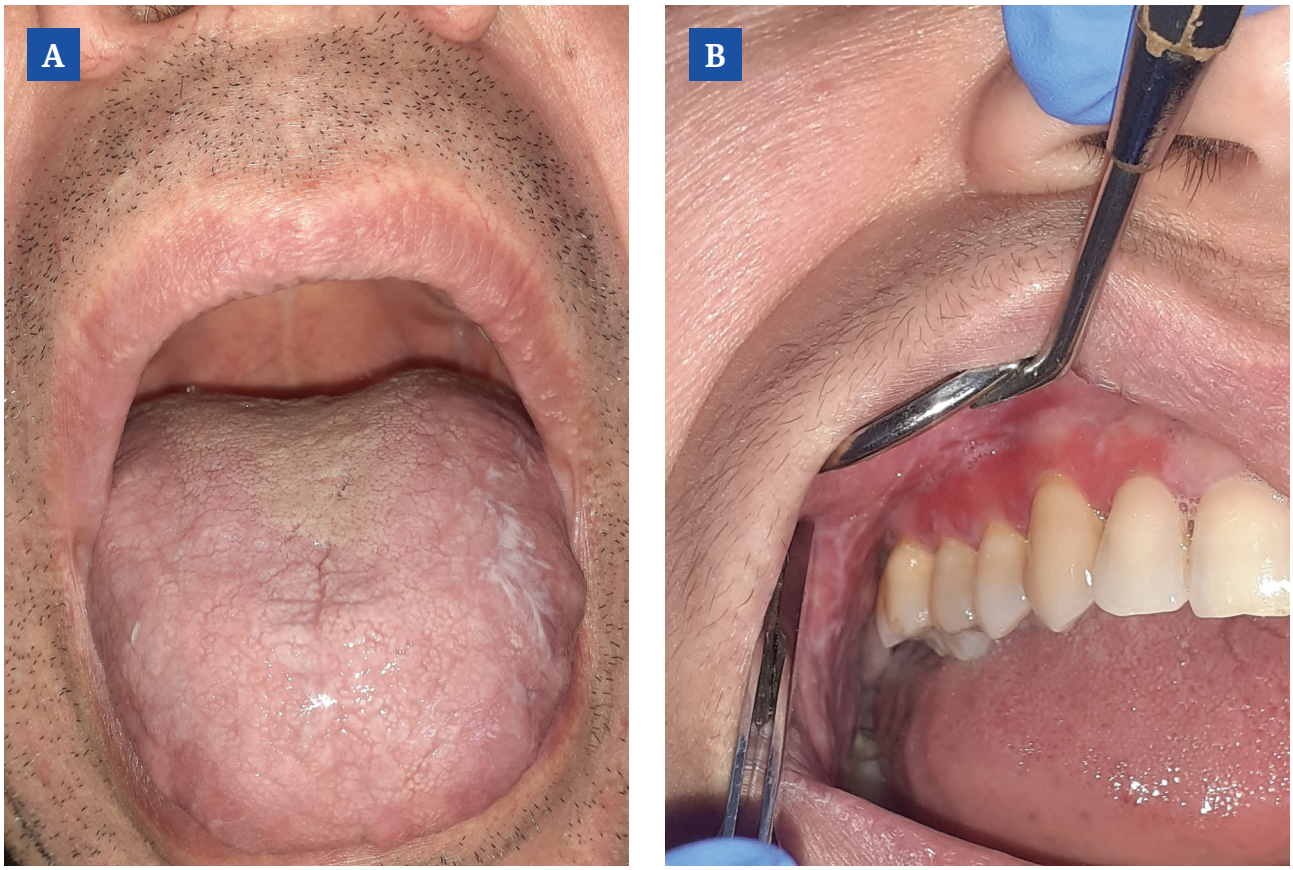

Figure 4: A – Keratotic plaque on the tongue; B – Gingival OLP.

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Table 4: OLP clinical forms and symptoms.

Subgroups	Symptoms N (%)		OLP clinical forms N (%)			
	Asymptomatic	Symptomatic	Keratotic	Atrophic	Erosive	Bullous
1	107 (28.7)	266 (71.3)	92 (86)	7 (6.5)	8 (7.5)	-
2	10 (21.7)	36 (78.3)	13 (36.1)	12 (33.3)	8 (8.3)	3 (8.3)
3	12 (11)	97 (89)	22 (22.7)	13 (13.4)	55 (56.7)	7 (7.2)
4	3 (13)	20 (87)	7 (35)	2 (10)	10 (50)	1 (5)

Table 5: Sites of OLP lesions.

Subgroup	Jugal N (%)	Tongue N (%)	Gingiva N (%)	Jugal + Tongue N (%)	Jugal + Gingiva N (%)	Jugal + Gingiva + Tongue N (%)	Tongue + Gingiva N (%)
1	134 (35.9)	12 (3.5)	12 (3.2)	111 (29.8)	56 (15)	41 (11)	6 (1.6)
2	6 (16.7)	-	1 (2.8)	12 (33.3)	7 (19.4)	9 (25)	1 (2.8)
3	24 (24.7)	-	-	42 (43.3)	10 (10.3)	20 (20.6)	1 (1)
4	7 (35)	-	-	6 (30)	2 (10)	5 (25)	-

Table 6: Evolution of OLP in study groups.

Subgroup	No clinical follow-up N (%)	No lesions N (%)	Improve N (%)	Stationary N (%)	Worse N (%)
1	76 (20.4)	71 (19)	118 (31.6)	76 (20.4)	32 (8.6)
2	4 (8.7)	3 (6.5)	21 (45.7)	14 (30.4)	4 (8.7)
3	40 (36.7)	16 (14.7)	34 (31.2)	9 (8.3)	10 (9.2)
4	6 (26.1)	1 (4.3)	6 (26.1)	0	10 (43.5)

for erosive forms [13]. In our study, both keratotic and atrophic forms and also some erosive forms of OLP were observed in DM patients (subgroup 2). There are also other studies that showed that the atrophic and erosive forms are more frequent in patients with OLP and DM (n=177; 64.36%) [16]. The association between OLP and DM is due to an increased risk of inflammation and infection and a poor and slow healing process of oral mucosa. Some studies revealed that metabolic and immunological imbalances lead to this association [15]. Other authors considered oral lesions as a result of treatment with oral antidiabetics. Thus, the Greenspan syndrome, characterized by the triad of DM, arterial hypertension and OLP, was also described. In these patients, the oral lesions may come up in relation to treatment for hypertension or DM (oral antidiabetics) [18]. Rodríguez-Fonseca L. *et al.* reported statistically significant differences in the association between

Table 7: Statistical correlations.

	Debut	Tobacco	Symptoms	Sites	Clinical form	Evolution
Gender	0.074	0.001*	0.02*	0.074	0.021*	0.265
Age	0.427	0.046*	0.029*	0.111	0.510	0.126
DM	0.248	0.265	0.287	0.469	0.614	0.002*

Note: * – $p<0.05$.

the clinical forms and the treatment with oral antidiabetics (p=0.005). They also found the atrophic-erosive forms of OLP more frequently (N=26; 92.9%) than other types (N=2; 7.1%) [16]. Potts [19] and Robertson [20] observed a link between treatment with nonsteroidal anti-inflammatory drugs or antihypertensives and erosive forms of OLP, but they found no association in the case of DM. A meta-analysis of 11 case-control case series also showed a significantly higher prevalence of OLP in patients with DM (OR 1.584 (95% CI 1.013–2.477; P=0.044) [15].

Speaking about liver diseases, there is evidence that HCV can replicate itself in the liver, skin and oral mucosa, and the specific T cells are also involved in the replication mechanism of both diseases, TCH and OLP [21]. Many studies analyzed the connection between OLP and HCV. A cross-sectional study conducted in Italy by Lodi *et al*. proposed to determine the seroprevalence of anti-HCV antibodies in patients with OLP. They observed a significantly higher prevalence of anti-HCV antibodies in patients with OLP compared to the control group. Subgroup analysis of patients associating TCH and OLP showed that prevalence depends more on the geographic area of the patient's residence than on other risk factors such as age [22]. Other studies developed in different geographical areas had opposite results. So, a descriptive study conducted by Taghavi Zenouz in northwest Iran did not report significantly higher results on the prevalence of anti-HCV antibodies in patients with OLP compared to the control group [23].

In our study, we observed that the intensity of symptoms is not influenced by the association to DM or TCH. Other studies have shown that more than half of the OLP clinical forms have symptoms. Moreover, the symptoms are most often correlated with the clinical form and with the pain perception level, which is specific for each patient and depends on the patient's opinion [14].

The oral area of the OLP lesions is directly correlated with severity. We found lesions on bilateral jugal mucosa only if no general pathology was associated. However, in subgroups 2 and 3, the OLP lesions are present on both the jugal and tongue, showing an acute trend (Table 5). Similar results were reported by other studies. They found lesions on the jugal mucosa, tongue, and gingiva [14]. One study reported that half of the patients with OLP and DM would have lesions in two areas (n=139; 50.5%), three or more.

The study conducted by Rodríguez-Fonseca L. *et al*. analyzed the oral distribution of lesions and the number of areas involved among patients with OLP and DM. The results showed the presence of lesions in two areas in half of the cases. Thus, the authors did not find a greater development of the OLP lesions in DM patients [16].

There are some studies which found statistically links such as age over 60 years (p=0.007) and oral antidiabetic treatments (p=0.021) with the atrophic-erosive clinical form; and between the location of OLP lesions (p=0.036) and age [16].

Conclusion

Many previous studies observed the association of OLP with general conditions such as DM, TCH, metabolic syndrome and thyroid dysfunction. Some of them provided evidence about the link between OLP evolution and clinical features. The results showed the need for closer supervision when OLP and general conditions coexist. Screening for DM or TCH in patients with OLP is also useful.

Conflict of interest

The authors declare no conflict of interest.

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