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Association of Oral Lichen Planus with Autoimmune Diseases in A Northern Serbia Population: Matched Case-Control Study and Literature Review

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Abstract

Oral lichen planus (OLP) is a still poorly understood and relatively common chronic inflammatory disease of oral mucosa. A connection between OLP and certain diseases have been reported in the past, such as diabetes, hypertension, hepatitis C infection (HCV), thyroid disease, and malignant diseases. There is some controversial about mentioned link with OLP. The study objective was to investigate association between autoimmune diseases and OLP in Northern Serbian province. A total of 48 patients (33 females and 15 males, ranged 29-84 years, mean age 59.8 ± 13.0) with clinical and histopathological proven OLP, along with 71 matched controls without oral mucosa lesions were included in the study. This was a retrospective case-control study conducted in patients who were treated at the Dental Clinic, Faculty of Medicine, University of Novi Sad, between January 2010 and Jun 2016. Clinical characteristics of OLP lesions, other oral mucosal diseases, presence of cutaneous LP, medical and family history with special regard to their autoimmune diseases with medication intake were recorded. Association regarding total of autoimmune diseases was found significant especially in prevalence of thyroid gland diseases. This study indicates connection between thyroid gland disorders (Hashimoto thyroiditis) and OLP. There is a need for further investigations such a screening for asymptomatic OLP in woman over the 40 years old suffering from thyroid gland disorders, particularly hypothyroidism.

Keywords: Oral lichen planus, Clinical features, Autoimmune disease, Thyroid gland, Hashimoto thyroiditis, Rheumatoid arthritis.

Introduction

Oral lichen planus (OLP) seems to be unique but common oral mucosa inflammatory disease that clinician is likely meeting in practice. Mucosal lesions in OLP are chronic, considered to be a potentially premalignant, hardly ever undergo spontaneous remission and frequently impair patient's wellbeing [1]. Recent epidemiological studies have shown varying prevalence of 0.1-4% cases; mostly without distinguish between the OLP and oral lichenoid lesions (OLL) [2]. From the clinicians aspects a recent study proposed that OLP should be primarily considered and taken care of as a systemic disease and not as isolated oral and/or genital lichen [3]. To gain better understanding of OLP nature, systemic associations with disease is more than welcome. A positive connection between OLP and certain systemic diseases have been reported in the past, such as diabetes [4,5], arterial hypertension [6], infection with hepatitis C (HCV) [7], and malignant diseases [8].The association between OLP and other autoimmune diseases has been a subject of ongoing research, although studies qualify these associations with scarce. Furthermore, over the last 5 years in various populations a novel possible association between OLP and thyroid diseases has been described [9-13]. Previous research has also produced some evidence of a higher frequency of some diseases, generally of autoimmune origin among OLP patients than among the general population (myasthenia gravis, vitiligo, alopecia areata, thymoma, ulcerative colitis, psoriasis, celiac disease, Sjögren's syndrome and rheumatoid arthritis). However this association might be merely accidental rather than linked to autoimmune pathogenesis [14-20]. So, there is some controversial about mentioned links with OLP. The study objective was to investigate association between autoimmune diseases and OLP in Northern Serbian province. Also we try to explore some potential influence of different geographic origin in these associations by reviewing the literature.

Materials and Methods

Study population

The study was designed as a cross-sectional, retrospective case-control clinical study. All patients with clinical and histopathological proven OLP who have been treated at the Oral Medicine Section of the Dental Clinic, Faculty of Medicine, Novi Sad, Serbia in the period from January 2010 to Jun 2016 were included in the study. The sample comprised 48 of these patients (33 females and 15 males, ranged 29-84 years, mean age

59.8 ± 13.0). All the study patients underwent biopsy. The biopsy was fixed in formalin, embedded in paraffin, and processed for routine histopathology examination. After getting acquainted with the procedure, patients gave written consent. The diagnosis of OLP was based upon both clinical and histological findings in according to the well-accepted diagnostic criteria proposed by World Health Organization (WHO) [21] and van der Meij and van der Waal [22]. Patients with OLL were excluded.

The control group consisted of 71 (56 females and 15 males, ranged 26-89 years, mean age 64.1 ± 10.9) subjects manually selected by other investigator from the medical records of the patients who had visited the Dental Clinic, Faculty of Medicine, Novi Sad, for general dental care or treated because of subjective symptoms (burning mouth syndrome and dysguesia) without oral mucosa lesions. Selected control subject was the next possible patient found in the medical documentation which was of the same sex, residence and without difference in age for more than 2 years compared to case subject. The exclusion criterion was that the selected control patient had a history of OLP/OLL or other oral mucosa lesion except the presence of the variations in morphology and appearance of healthy oral mucosa (lingua plicata, leukoedem, linea alba and Fordyce spots). The study was approved by our Ethics Committee of the Faculty and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2008.

Interview and clinical examination

Data on sex, age, smoking, alcohol consumption, presence of systemic diseases, regular and periodical intake of medications were collected by means of a questionnaire. The patients' medical conditions were recorded on the basis of their medical histories, noting the presence of the following autoimmune diseases: Hashimoto's disease, Graves' disease, Crohn's disease, rheumatoid arthritis (RA), ulcerative colitis, type 1 diabetes mellitus, alopecia areata, haemolyticanaemia, giant cell arteritis, multiple sclerosis, systemic lupus erythematosus (LE), vitiligo, psoriasis, chronic glomerulonephritis, pulmonary fibrosis, Sjögren's syndrome, Addison's disease, immune thrombocytopenia, chronic urticaria, coeliac disease, primary biliary cirrhosis, and systemic sclerosis. All subjects were interviewed by one investigator in order to minimize possible variations in the data gathering.

Visual Intraoral examination was carried out by single oral medicine specialist experience in the field to determine the presence, number, and location of OLP lesions and their clinical form. Erosive, atrophic, bullous, plaque, and papular-type lesions are accepted in the presence of reticular lesions elsewhere in the oral mucosa. If the patient had reticular and erosive lesions, the OLP was classified as erosive because of the more severe clinical course of this form. We also investigated other body parts involvement with lichen planus as reported by patients themselves and when indicated confirmed by dermatologists.

Reviw of literature

To identify existing evidence about OLP association with autoimmune diseases or thyroid gland diseases, we conducted a systematic review of the literature up to Jun 2016 by searching PubMed and Scopus using the following terms: 'oral lichen planus AND thyroid', 'oral lichen planus AND autoimmune disease' and 'patients with oral lichen planus' in all fields or all text for clinical or epidemiological studies. The search was conducted without language limits, but was restricted to humans and excluded the following publication types_Editorial, Letter, Review, Case Reports, and Comment.

Statistical analysis

The commercial statistical program "SPSS 21 for Windows" was used for statistical analysis. Attributive features were shown as absolute and relative numbers, while numerical features through mean value and measures of variability. Univariate analyses were applied by Chi-square test for the testing of the differences between the two groups for categorical data and Student's t-test for numeric features. If univariate analyses showed a p-value <0.05 for the group difference the variable was selected for binary logistic regression. To calculate odds ratios (OR) with 95% confidence intervals (CI) for bivariate associations of the different systemic conditions with the presence of OLP (presence=1, absence=0), adjusting for the matching factors age and sex, direct logistic regression was used. The value $P<0.05$ was considered to be statistically significant.

Results

In the OLP group, there was clear female predominance. There were 33 (68.8%) females and 15 (31.3%) males. The mean age was 59.8 ± 13.0 in OLP group and 64.1 ± 10.9 in controls. In relation to the gender and average age of the patients there was no significant difference between the groups ($P>0.05$). There was also no difference related to incidence of smokers or the alcohol consumption between the groups ($P>0.05$). The distribution of OLP patients according to socio-professional level was: high level (15.2%), average level (23.1%) and housewife/unemployed or retired with low income (61.7%), with no difference in related to controls. Table 1 showed no differences between the characteristics of participants in the study groups, which implicate high homogeneity of tested samples.

The most common clinical form of OLP lesions was the reticular (54.2%). Lesions involving the buccal mucosa only were present in 20.8% of the patients. More than third of the cases the lesions were located buccally and lingually (35.5%) and in the rest of the patients (43.7%) the lesions were located in multiple regions. The skin involved was recorded in 12 OLP patients. Eighteen patients showed no symptoms, 27 manifested oral discomfort, burning sensation or mild pain and the only 3 patients experienced strong burning and pain. All clinical features of OLP group are presented in Table 2.

A history of autoimmune thyroid gland disorders was recorded in 16.7% (n=8) of the OLP patients and in 2.8% (n=2) of control subjects (p=0.020). All patients were under medicament therapy: in OLP group 6 patients use levothiroxyne, one use levothiroxyne-natrium, one methimazole; and in control group both use levothiroxyne-natrium. All cases in OLP group with thyroid gland disorders were women mean age 65.0 ± 10.5 years old.

Among OLP patients, the presence of coexisting autoimmune diseases was 33.3% (16/48) of patients: 7 with Hashimoto thyroiditis; one Graves disease, 6 rheumatoid arthritis, two diabetes type 1, one presented psoriasis; one colitis ulcerosa, and one vitiligo. Three OLP patients presented two coexisting autoimmune

Table 1: Characteristics of participants in the study

Variables	OLP group N =48 (%)	Control group N=71 (%)	p[1]
Age (Mean±SD)	59.8±13.0	64.1±10.9	0.212
Blood glucose			0.521
normal value 4.6-6.2 mmol/l	43 (89.6)	62 (87.3)	
above normal value	5 (10.4)	9 (12.7)	
Antihypertensive drugs			0.151
Yes	18 (37.5)	32 (45.0)	
Anxiolytics			0.112
Yes	6 (12.5)	13 (18.3)	
Smoking			0.243
Yes	9 (18.8)	16 (22.5)	
Alcohol			0.588
Yes	9 (18.8)	15 (21.1)	

p[1] significance for chi-square (Yates correction) test and Student t-test (age)

Table 2: Clinical features of patients with OLP

	N=48 (%)
Clinical type	
Reticular	26 (54.2)
Erosive	10 (20.8)
Atrophic erithemtouse	9 (18.8)
Plack	3 (6.3)
Localization	
Buccal only	10 (20.8)
Buccal and lingual	17 (35.4)
Gingival, buccal and lingual (multiple regions)	21 (43.7)
Coexistent with cutaneous LP	12 (25.0)
Presentation	
Unilateral	3 (6.3)
Bilateral	45 (93.7)
Symptoms	
No symptoms	18 (37.5)
Oral discomfort, burning or mild pain	27 (56.3)
Strong pain	3 (6.3)
Treatment	
Topical steroids	15 (31.3)
Systemic steroid	1 (2.1)
No treatment	32 (66.6)

diseases. In the control group autoimmune diseases was identified in 5/71 (7.0%) of subjects: two presented Hashimoto thyroiditis; two rheumatoid arthritis and one diabetes type 1. There was significant difference between the group (p=0.001). No significant differences were found between non-erosive and erosive clinical form of OLP in relation to thyroid gland disorders and autoimmune diseases.

Table 3: Distribution (numbers and percentages) of autoimmune diseases in the patients with OLP and controls

Autoimmune diseases	OLP group N =48 (%)	Control group N=71 (%)	p[1]
Thyroid gland disorders			
Yes	8 (16.7)	2 (2.8)	0.020
Hashimoto thyroiditis	7 (14.6)	2 (2.8)	
Graves disease	1 (2.1)	0 (0)	0.084
Rheumatoid arthritis	6 (12.8)	2 (2.8)	
Autoimmune diseases total per patient			
Yes	16 (33.3)	5 (7.0)	0.001

p[1] significance for chi-square (Yates correction) test

Table 4: All presented autoimmune diseases in the patients with OLP or in them family history

Autoimmune diseases in OLP group	Present in patient	Present in family histotry
Vitiligo	1	1
Hashimoto thyroiditis	7	5
Graves disease	1	1
Rheumatoid arthritis	6	8
Diabetes type 1	2	6
Multiple sclerosis	0	2
Psoriatic disease	1	3
Alopetiaareata	0	1
Crohn's disease	0	1
Colitis ulcerosa	1	0

The results of logistic regression analysis indicate that only thyroid gland disorders (OR=5.04, 95% CI 1.61 to 9.06) were significantly associated with OLP. P - value of Hosmer Lemeshow test shows that the model describes well the original data (0.427> 0.05). The overall success of prediction is 80.5%. According to the Wald criteria, thyroid gland disorders significantly ($p<0.05$) contributes to the prediction of disease. Assuming that other variables remain unchanged, ratio of the probability which is 5.04 shows us those patients with thyroid gland disorders have 5 times more likely to get OLP.

Discussion

Reviewing the literature among numerous epidemiological and clinical-bases studies in OLP patients we find out 16 who have been reported data about the prevalence, within range of 2.4%-7.7%, 3%-15% (6.7%-10.9%) and (14-15,8%) for all autoimmune, thyroid gland (hypothyroidism) and rheumatological diseases, respectively (Table 5). Eleven of them had histological confirmation of all cases with distinguish between OLP and OLL [1,11,23,25,27-33] and five presented with control group [11,13,24,25,27]. It can be noticed clear difference in reported coexistence of thyroid gland pathosis and OLP between Northern and Central European countries (Finland [11], Czech Republic

Table 5: Geographic origin, sample size and prevalence of autoimmune (Thyroid gland and Rheumatological) diseases in oral lichen planus studies

Study	Place	Sample size	Autoimmune Diseases N(%)	Thyroid diseases N(%)	Hypo-thyroidism N(%)	Hyper-thyroidism N(%)	Rheumatological diseaseN(%)	Hystological examination
Carbone et al. [1]	Italiy	808	19 (2.4)	24 (3.0)				yes[1]
Dreiher et al. [10]	Israel	1477			148 (10.0)			no
Siponen et al. [11]	Finland	152		22 (14.5)	15 (9.9)	2 (1.3)		yes[1]
Robledo-Sierra et al. [13]	Sweden	956		85 (8.9)[2]				no
Thongprasom et al. [23]	Thailand	533				20 (1.1)	20 (1.1)	yes[1]
Kragelund et al. [24]	Denmark	172		7 (4.1)[2]				no
Hirota et al. [25]	Brasil	110			12 (10.9)			yes[1]
Lopez-Jornet et al. [27]	Spain	130	10 (7.7)					yes[1]
Radochová et al. [28]	Cezch Republic	171		25 (14.6)	18 (10.5)		9 (5.2)	yes[1]
Gümrü [29]	Turky	370	16 (4.3)	18 (4.9)				yes[1]
Shen et al. [30]	China	518				4 (0.8)	9 (1.7)	yes[1]
Lauritano et al. [31]	Italy	87		13 (15)				yes[1]
Bermejo-Fenoll et al. [32]	Spain	550					86 (15.8)	yes[1]
Eisen [33]	USA	723					101 (14)	yes[1]
Vučićević Boras et al. [34]	Croatia	163		22 (13.7)				no
Vučićević Boras et al. [34]	Australia	163		15 (9.2)				no
Budimir et al. [51]	Croatia	563			38 (6.7)			no

[1]Histological examination of all cases with distinguish between OLP and OLL

[2]Number of OLP patients who were taking thyroid medication

[28] and Croatia [34]) and Southern Mediterranean countries (Italy [1,26] and Turkey [29]). Although, distinction in thyroid gland diseases prevalence is obvious between the different regions of the same country, reported on different sample size [1,31]. These observation and results of present study suggest that the association of thyroid diseases with OLP may depend on the geographic origin of the patients, similar to HCV association [1,7,35].

A novel possible association between OLP and thyroid gland diseases (Hashimoto's thyroiditis) has been proposed recently on the basis of cross-sectional, case-control studies similar to our [11,12]. A very similar odd ratio estimates were found by Siponen et al. [11] for the associacion of any thyroid diseases and OLP, particularly with hypothyroidism. Except in present study, a higher intake of thyroid medication among patients with OLP has also been found in three additional studies

[24,25,13]. Recent publication by Robledo-Sierra et al. [13] suggested that it is hypothyroidism and not the drug that is associated with OLP. In contrast, some authors based on a cross-sectional study performed in Sicily (West Mediterranean area) have denied an association between OLP and hypothyroidism [26]. Lo Muzio et al. [12] pointed out that there is no definitive hypothesis that could explain the coexistence of OLP and Hashimoto's thyroiditis. However, considering the onset timing of Hashimoto's thyroiditis followed by OLP in 93.3 % of them and in all of our series, Hashimoto's thyroiditis may have trigger or predisposing role. Same authors believe that in Hashimoto's thyroiditis patients, circulating thyroid antibodies could contribute to trigger an organ specific auto-immune response also in the oral mucosa or skin, leading to the development of LP lesions. Another hypothesis proposed that autoimmune thyroid disease might produce nuclear antigens in the damaged thyroid tissue that then activate antigen-specific B cells to produce nuclear antibodies locally as well as in blood circulation of OLP patients, based on significant higher finding of TGA and TMA autoantibodies compared with healthy control subjects [9]. Most of authors agreed in one fact that the futures studies need to include a judicious characterization of the underlying cause of hypothyroidism as well as genetic and immunological analyses of existing OLP lesions.

The thyroid is so prone to autoimmune thyroid diseases which arise due to the complex interplay of genetic, environmental, and endogenous factors similar to the current etiology of OLP [36]. Onset of autoimmune thyroid diseases and OLP may have a mutual associated risk factor such as stress involvement, that have been reported frequently in the past [37-40]. Furthermore, relationship between autoimmune rheumatic condition, such as systemic lupus erythematosus, rheumatoid arthritis, celiac disease and autoimmune thyroid gland diseases has also been found [41].

All of the OLP patients in the present study with the coexistence of Hashimoto thyroiditis and all but one in recently reported [12] were female gender. Most autoimmune diseases occurs significantly more frequently in women than men, especially Hashimoto's thyroiditis and Grave's disease, with a female to male ratio of 50:1 and 7:1 respectively [42,43]. OLP also affected women more frequently (3-4:1) [23]. This female preponderance for abnormal autoimmune function may help understood a novel possible association between these diseases. Lleo et al. [44] suggest that the pathogenesis of all autoimmune diseases recognizes the necessary role of environmental factors and genetical susceptibility to lead to tolerance breakdown and females seem to be more prone to autoimmune diseases development based on both components. Immune-mediated diseases frequently affected oral mucosa, which may be the first site of their clinical manifestation. Although etiology of these diseases still remains unknown, but recently have been found that some of them share common genes [45].

The various mechanisms hypothesized to play an important role in the pathogenesis of OLP and one of them is autoimmune response. The antigen that triggers the inflammatory immune response in OLP lesion is still unknown. This trigger might be a self-antigen in which case qualifies OLP as a true autoimmune disease. The role of autoimmunity in the disease's pathogenesis is supported by the many autoimmune features of OLP, adult onset, female predilection, association with other autoimmune diseases, occasional tissue-type associations, depressed immune suppressor activity in OLP patients and the presence of autocytotoxic T-cell clones in lichen planus lesions [47,48] and very effectiveness immunosuppressor therapy [49]. Different hypotheses have been proposed implicating autoimmune reaction in OLP: deficient antigen-specific immunosuppression; lack of transforming growth factor-beta 1; breakdown of immune privilege; keratinocyte apoptosis and Langerhans cell maturation; heat shock protein expression [46,47]. Same authors propose that in OLP patients, diverse exogenous agents such as drugs, trauma and infection, stimulate the expression of a common self-molecule by oral mucosal keratinocytes. An autoimmune reaction by cytotoxic T lymphocytes to these activated keratinocytes may result in the tissue destruction which is clinical characteristic of OLP [49]. Several investigators have implicated an association between LP and other immune-mediated diseases sush as psoriasis [16,17], coeliac disease [18,19], rheumatoid arthritis and Sjogren's syndrome [20]. Although, those reports are quite rare and the epidemiological evidence for this is scant. An Italian epidemiologic study has obtained association between LP and alopecia areata and ulcerative colitis, which are considered immune-mediated diseases [15]. Recently there was some case that illustrates diagnosis of Multiple Autoimmune Syndrome which represented coexistence of vulvar, oral and esophageal LP with autoimmune thyroiditis, alopetia and systemic hypertension [50]. Similar to these findings three of our patient's with OLP present vulvar LP, Hashimoto thyroiditis and systemic hypertension.

Finally, limitations of the present study should be taken into consideration. The thyroid gland disorders as a variable tested in this study should be interpreted carefully, because the small number of these cases in the control group may be a simple coincidence. However, we believe that in order to minimize possible variations in the data gathering all patients' complete medical history has been obtained by one investigator.

Considering that present study was conducted on a relatively small sample, which represents only a part of population, any generalization of our outcomes to other populations could not be done. However, an interesting fact is that few other recent studies from different parts of the world have reported similar results that highlight connection between lichen planus and thyroid gland disorders [9-13]. Since many autoimmune diseases showed primary signs in the mouth detailed clinical examination of oral mucosa in asymptomatic patient could be the best opportunity for early diagnosis of autoimmune disease. Further studies may be required in this area to draw a final conclusion does the OLP should be considered and taken care of as a full or partial expressed autoimmune systemic disease and not as an isolated oral condition.

Conclusion

In summary, study proposed a possible strong connection between thyroid gland disorders (especially autoimmune hypothyroidism) and woman with OLP, with dependents on

the geographic origin of the patients. There is a need for further investigations as a screening for asymptomatic OLP in woman over the 40 years old suffering from Hashimoto thyroiditis and rheumatoid arthritis.

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