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Hypothyroidism and oral lichen

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Evidence of earlier thyroid dysfunction in newly diagnosed oral lichen planus patients: a hint for endocrinologists

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Abstract

The association between oral lichen planus (OLP) and hypothyroidism has been debated with conflicting results: some authors detected a statistically significant association between these two, while others did not confirm it. The aim of this study was to evaluate the thyroid status in patients with newly diagnosed OLP to test the null hypothesis that thyroid disease is not associated with an increased incidence of oral lesions, with a prospective case-control approach. A total of 549 patients have been evaluated, of whom 355 were female. Odds ratio (OR) and 95% confidence intervals (CIs) were obtained. Patients suffering from thyroid diseases were associated with an almost 3-fold increased odds of having OLP (OR 2.85, 95% CI: 1.65–4.94), after adjusting this analysis for age, gender, body mass index, smoking status, diabetes, hypertension and hepatitis C infection. It would be appropriate to further investigate the possible concomitance of OLP among patients with thyroid disorder; endocrinologists should be aware of this association, especially because OLP is considered a potentially malignant oral disorder.

Introduction

Oral lichen planus (OLP) is a common immune-mediated mucocutaneous disorder, usually described among females between the fifth and the sixth decades; the estimated worldwide prevalence is reported between 0.22 and 5%, with an average value of 1–2% (1). The exact aetiology still remains unknown, although immune dysregulation seems to play a critical role in the development and progression of OLP, with such disease being the ultimate outcome of interaction between the immune system and a varied range of extrinsic antigens and/or altered self-antigens (2).

The OLP clinical forms are usually classified as follows: (a) white lichen (WL), which included the papular, reticular and plaque forms; (b) red lichen (RL), which included all the atrophic or erosive forms, irrespective of a contemporaneous presence of a white form (1). It has been supposed that these different clinical manifestations may be related to dissimilar biological events; furthermore, a significant involvement of specific classes of T-lymphocytes, responsible of marked tissue damage, could determine the development of erosive lesions (3).

In the last decade, some authors have reported a statistically significant association between OLP and hypothyroidism (4, 5, 6) or Hashimoto's thyroiditis (7), while other studies denied it (8).

Considering all the previous deliberations, in such a discordant context, we decided to assess the association of OLP with some comorbidities, focusing our attention on thyroid diseases, with a case-control approach.

Study design and methods

Our study is a prospective analysis, conducted on a comprehensive sample collected from the Caucasian population residing in Piedmont, Northwest Italy; only patients older than 18 years were selected, while pregnant or breast-feeding women were excluded.

The case group consisted of 307 OLP patients attending the Oral Medicine Unit, C.I.R. Dental School, between January 2015 and May 2017. According to accepted standards (1), the diagnosis of OLP was based on the following criteria: (a) presence of characteristic bilateral clinical signs (papular and/or reticular lesions alone or in association with atrophic or erosive lesions); (b) histological confirmation of clinical diagnosis through incisional biopsy demonstrating the presence of a well-defined band-like zone of cellular infiltration, consisting mainly of lymphocytes, confined to the superficial part of the connective tissue and signs of 'liquefaction degeneration' in the basal cell layer; (c) absence of signs of epithelial dysplasia at the moment of first diagnosis; (d) and absence of suspicion that oral lesions may be related to any drug or oral restoration.

In the same period, a sample of 242 healthy controls with no clinically detectable oral lesions, unrelated to the cases, were recruited from the population attending two dental private practices in need of an oral implant rehabilitation.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the ethical committee of the CIR-Dental School. Consent was obtained after full explanation of the purpose and nature of all procedures used.

At baseline, anamnestic data were collected, focusing on pre-existing or coexisting systemic diseases and daily medications. In particular, the prevalence of diabetes, hepatitis C (HCV) infection, hypertension and thyroid disease was thoroughly detailed. Moreover, thyroid function tests (free thyroxin (fT_4) and thyroid-stimulating hormone (TSH)) were required after the baseline examination of the oral cavity. The reference ranges, to consider normal function of the thyroid gland, were between 9.0 and 25.0 pmol/L for fT_4, and between 0.4 and 4.0 milliunits per litre (U/L) for TSH. Patients with the abnormal test were referred to an endocrinologist. Levothyroxine was the most commonly reported prescribed medication in our sample.

The primary aim of this study was to describe the thyroid status both in patients with OLP and healthy controls to test the null hypothesis according to which OLP is not associated with an increased incidence of thyroid disease.

Quantitative variables were described via means, standard deviations (s.d.), medians, first and third quartiles (Q1 and Q3), qualitative ones via frequencies and percentages. The Gaussian distributions of the continuous variables were verified via Kolmogorov–Smirnov tests. Due to the non-Gaussian distribution of the medians, their differences were tested using Kruskal–Wallis tests. Chi-squared tests were performed to evaluate differences in qualitative variables; meanwhile, if the values were expected to be less than 5, Fisher's exact tests were performed. Then, odds ratios (ORs) and their 95% confidence intervals (95% CIs) were obtained computing two multivariable logistic regression models. The first one was adjusted for age, gender, body mass index (BMI) and smoking status; the second one was adjusted for diabetes, hypertension and HCV infection. All statistical analyses were performed using SAS-ver.9.3, and a 2-tailed *P*-value less than 0.05 was considered statistically significant.

Results

A total of 549 patients have been evaluated, of whom 355 were female (f/m = 1.83/1). Table 1 summarises the main characteristics of cases and controls. On the one hand, the two groups were similar for age, gender and habit of smoking: average age was 58 years for both samples, with s.d. = 13.5 for cases and s.d. = 10.5 for controls. Furthermore, 14.9% of the cases were smokers, with a mean of nine cigarettes per day, while in the control group, 18.7% smoked an average of thirteen cigarettes per day. On the other hand, prevalence of overweight, diabetes, hypertension and thyroid diseases was statistically higher in cases than controls (Table 1).

Table 2 reports thyroid disorders and evaluation of serological analyses between cases and controls. At the

Table 1 Demographical and clinical characteristics of the studied groups (OLP: oral lichen planus).

	OLP patients no. 307 (100%)	Control patients no. 242 (100%)
Gender		
Male	104 (33.9%)	90 (37.2%)
Female	203 (66.1%)	152 (62.8%)
P-value§=0.40		
Age		
Mean (s.d.)	58.3 (13.5)	58.0 (10.5)
Median (Range)	59 (50; 68)	59.0 (52; 66)
P-valueç=0.50		
Concomitant extra-oral manifestation due to lichen planus		
Skin	23 (7.5%)	–
Genital	20 (6.5%)	–
Scalp	3 (1%)	–
Nail	1 (0.3%)	–
Body mass index		
Mean (s.d.)	25.7 (4.4)	24.2 (4.2)
Median (Range)	25.0 (22.6; 28.3)	23.8 (21.1; 26.6)
P-value§=0.0001		
Smoking status		
No	261 (85%)	197 (81.4%)
P-value§=0.26		
Hypertension		
Yes	117 (38.1%)	65 (26.9%)
P-value§=0.005		
Diabetes		
Yes	36 (11.7%)	14 (5.8%)
P-value§=0.02		
Hepatitis C infection		
Yes	8 (2.6%)	2 (0.8%)
P-value*=0.12		
Thyroid diseases		
Yes	71 (23.1%)	22 (9.1%)
P-value§=0.0001		

P-value: *Fisher's test; §chi-squared test; çKruskall–Wallis test.

Table 2 Description of reported thyroid problems and evaluation of serological analyses (OLP: oral lichen planus; P-value: Fisher's test).

	OLP patients no. 307 (100%)	Control patients no. 242 (100%)
TSH		
Normal	291 (94.8%)	229 (94.6%)
Low	3 (1.0%)	1 (0.4%)
Elevated	13 (4.2%)	12 (5.0%)
P-value=0.78		
fT$_4$		
Normal	303 (98.7%)	241 (99.6%)
Low	4 (1.3%)	0 (0%)
Elevated	0 (0%)	1 (0.4%)
P-value=0.08		
Thyroid disease positive patients		
	No. 71 (/307)	No. 22 (/242)
Nodular thyroid diseases	9 (12.7%)	3 (13.6%)
Hyperthyroidism	4 (5.6%)	1 (4.6%)
Autoimmune hypothyroidism	30 (42.3%)	11 (50%)
Not autoimmune hypothyroidism	28 (39.4%)	7 (31.8%)
P-value=0.91		
Patients on active treatment for hypothyroidism at baseline		
	No. 51 (/64)	No. 18 (/22)
P-value=>0.99		

time of OLP diagnosis, 64 patients reported a positive anamnestic record of pre-existing thyroid disease, whereas only 7 were later found to have irregular thyroid function tests, and consequently referred to a specific unit in order to make the proper diagnosis. Conversely, none of the control group was diagnosed with any kind of thyroid condition after the enrolment. Comparing these data, OLP patients were found to be statistically more exposed to a thyroid disease underdiagnosed at baseline (P=0.003 with Fisher's test) than controls.

Seventy-one (23.1%) OLP patients were finally found to have a specific thyroid problem, in comparison to only 22 (9.1%) control patients. In detail for OLP patients, twenty-eight (39.4%) of them had a diagnosis of hypothyroidism, which was iatrogenic in nine patients – due to either thyroidectomy or treatment with I-131 – post-infectious in two cases, not otherwise specified in the remaining seventeen individuals. Thirty patients reported

a previously diagnosed Hashimoto's thyroiditis (HT). Nine cases suffered from nodular thyroid disease, such as diffused goitre (no. 5), single nodule (no. 3) or multiple nodules (no. 1). Finally, 3 patients had Graves–Basedow disease, whilst 1 had a non-specified hyperthyroidism. Concerning the distribution of these specific disorders, no differences were detected between cases and controls (Table 2). Moreover, no statistical differences were found in terms of serological thyroid values or reported therapy with levothyroxine as prescribed by the specialist (Table 2).

Figure 1 and Table 3 describe the multivariable model used to make the logistic regression, by means of the 2 models previously explained. When compared with controls, patients with thyroid problems were associated with an almost 3-fold increased odds of having OLP (regarding the types); the difference was indeed statistically significant if adjusted for age, gender, BMI and smoke (OR 2.71, 95% CI: 1.58–4.65), and also if adjusted for diabetes, hypertension and HCV infection (OR 2.85, 95% CI: 1.65–4.94). Similar data have also been detected if considering patients with only hyperkeratotic lesions (WL); moreover, if considering only RL patients, this risk was found to be even higher. Otherwise, no difference in risk was assessed between patients with RL and those with WL.
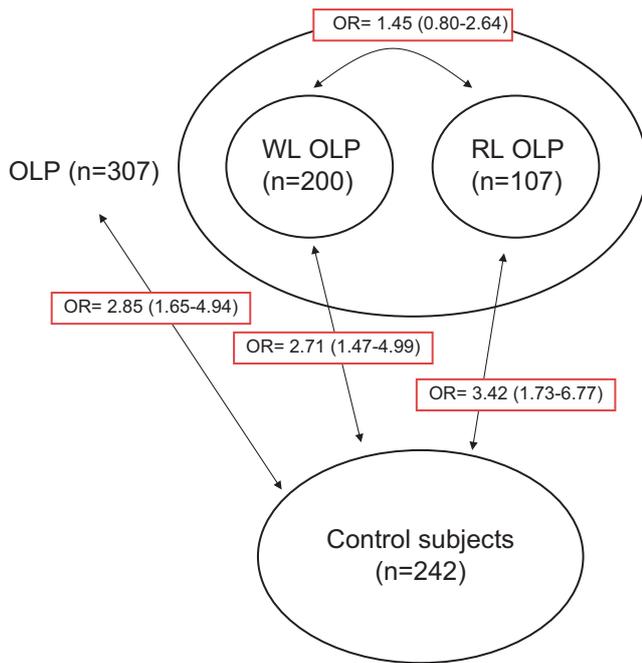
Figure 1
Analysis between differences in thyroid disease positivity for OLP patients vs patients with no oral lesions, adjusted for age, gender, BMI, smoke, diabetes, hypertension and HCV infection.

Discussion

To the best of our knowledge, this is the largest prospective study ever published reporting the possible positive relationship between OLP and thyroid diseases.

The prevalence of thyroid dysfunction could differ within different populations and countries, occurring most frequently in ageing women (9, 10), but recent epidemiological data from our territory have been collected, reporting an overall crude prevalence of 31.1/1000 (2.3/1000 for iatrogenic hypothyroidism) and an overall crude incidence of 7/1000 (11). Our data reported an incidence of thyroid disease of 23% which is unconfutably higher also considering those values.

The idea of a possible association between OLP and thyroid diseases has originated from previous reports of patients who were found to be affected by OLP as well as thyroid diseases.

Usually, patients with any kind of autoimmune disease are more susceptible to other types of autoimmune disorders; however, such tendency varies according to many factors, such as the prevalence and incidence of that disease (8). Due to its immune-mediated pathogenesis, the possibility of an association between OLP and concurrent autoimmune conditions, such as thyroid diseases, can be speculated. In our series, almost half of thyroid pathologies among OLP patients had an autoimmune aetiology (i.e. HT and Graves–Basedow disease). Immune-mediated diseases, such as OLP, have multifactorial aetiology, including genetic predisposition; it has been reported that some common alleles may be involved in the development of OLP as well as HT (7). To this date, there is no conclusive hypothesis that could explain the coexistence of OLP and HT. However, recently Lo Muzio and co-workers suspected a causal or predisposing role of HT in OLP patients, by suggesting that circulating thyroid antibodies could contribute to trigger an organ-specific autoimmune response also in the oral mucosa or skin, leading to the development of LP lesions. In contrast, other authors found no relationship between HT and OLP (8), but those data arose from a retrospective study in which the diagnosis of OLP was not always performed histologically; moreover, that study was conducted

Table 3 Logistic regression models to analyse differences in thyroid disease positivity for oral lichen planus (OLP) patients and negative control cases (OLP patients also divided in those with white lesions (WL) or red lesions (RL)).

	Model 1 OR (95% IC)	**Model 2 OR** (95% IC)
Patients with OLP vs patients without OLP (307 vs 242)		
Negative thyroid disease (236 vs 220)	Ref.	Ref.
Positive thyroid disease (71 vs 22)	2.71 (1.58–4.65)	2.85 (1.65–4.94)
Patients with WL OLP vs patients without OLP (200 vs 242)		
Negative thyroid disease (159 vs 220)	Ref.	Ref.
Positive thyroid disease (41 vs 22)	2.44 (1.35–4.40)	2.71 (1.47–4.99)
Patients with RL OLP vs patients without OLP (107 vs 242)		
Negative thyroid disease (77 vs 220)	Ref.	Ref.
Positive thyroid disease (30 vs 22)	3.32 (1.72–6.42)	3.42 (1.73–6.77)
Patients with RL OLP vs patients with WL OLP (107 vs 200)		
Negative thyroid disease (77 vs 159)	Ref.	Ref.
Positive thyroid disease (30 vs 41)	1.40 (0.78–2.53)	1.45 (0.80–2.64)

*Model 1: adjusted for age, gender, BMI, and smoke. Model 2: adjusted also for diabetes, hypertension, and HCV infection.

in an Iranian sample, where genetic and ethnical idiosyncrasies might have played a role in the outcomes, as well.

Some authors have suggested that the association between OLP and hypothyroidism could be linked to an unidentified common immune-mediated process, justifying the need for further studies regarding such intriguing theory (6). Differently, nodular thyroid diseases have no autoimmune aetiology; yet, immunological alterations such as an increased number of dendritic cells, an increased number of circulating lymphocytes and production of inflammatory mediators like IL-6 and TNF-α, also involved in OLP pathogenesis, have been detected (5).

In light of the above, we decided to consider thyroid diseases as a whole: concerning this matter, we did not find statistically significant differences in the incidence of OLP lesions between autoimmune and nodular thyroid disorders (data not shown; *P*-value>0.05). Similar data have also been obtained in a recent prospective case-control study, even though no case of autoimmune thyroid disorder has been reported; however, also based on the findings of the present study, it is likely to assume that patients with OLP could suffer from thyroid disease more frequently than the general population, particularly from hypothyroidism (4).

Considering these results, especially among Caucasian Northern Italian patients diagnosed with thyroid diseases, it would be appropriate to investigate the possible coexistence of OLP, through specialist counselling. Endocrinologists should be aware of this association, mainly because OLP should be considered as an oral potentially malignant disorder that requires regular follow-up over time (12).

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