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Laboratory investigation of the association between oral lichen planus and Hashimoto's thyroiditis

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Abstract

Background Previous studies have shown some relationship between oral lichen planus (OLP) and certain systemic comorbidities. The aim of this study was to investigate laboratory parameters between cases of Hashimoto's thyroiditis (HT) concomitant with OLP and cases of HT only.

Methods This case–control study comprised 59 HT patients with OLP and 76 without OLP, all of whom had 5 serum thyroid-related indicators, including thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TGAb), thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4).

Results Compared to cases of HT only, female predominance, presence of thyroid nodules, positive TGAb, and higher FT3/FT4 ratio were mainly observed in cases of HT concomitant with OLP (all $P < 0.05$). Multivariate regression analysis revealed that presence of thyroid nodules (odds ratio [OR], 10.328; 95% confidence interval [CI], 2.564–41.604), positive TGAb (OR, 6.936; 95%CI, 2.024–23.765), and higher FT3/FT4 ratio (OR, 2.577; 95%CI, 1.377–4.823) were associated significantly (all $P < 0.005$) with higher risk of OLP occurrence in 135 HT patients. Notably, these significant associations were not found among 30 male patients but did among 105 female patients in regression analysis.

Conclusion This retrospective study revealed that presence of thyroid nodule, positive TGAb, and high FT3/FT4 ratio as risk factors were significantly associated with OLP occurrence risk in female patients with HT. This suggests that female patients suffering from HT, particularly who presented with the risk factors, should be informed about the risk of OLP development and the need for oral mucosal examination to screen for lichen lesions.

Keywords Female patients, Hashimoto's thyroiditis, Oral lichen planus, Thyroid autoantibodies, Thyroid nodule

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Introduction

Oral lichen planus (OLP) is a relatively common chronic inflammatory mucocutaneous disease mainly affecting women [1]. Clinical presentation of OLP ranges from asymptomatic reticular white OLP to symptomatic erosive OLP with symptoms of burning, irritation, and pain [1]. Although the etiology and pathogenesis of OLP remain unclear, it has been reported to be associated with several systemic comorbidities, particularly hepatitis C and thyroid diseases (TDs) [2, 3]. In the Chinese ethnic patients, the correlation between OLP and TDs has been investigated in the previous studies by Tang et al. [4] and Zhou et al. [5]. Among various types of TDs, Hashimoto's thyroiditis (HT) is further demonstrated to be the most prevalent disease in OLP patients by a comprehensive systematic review and meta-analysis [6]. Interestingly, a significant association between OLP and HT was reported [7], mainly OLP patients are more likely to be affected by HT compared to healthy individuals [7, 8]. Conversely, whether HT patients are more likely to be affected by OLP remain unclear [9, 10].

HT is the most common autoimmune TD also mainly affecting women [11]. The diagnosis of HT is based on detection of serum antibodies against thyroglobulin (TGAb) and thyroid peroxidase (TPOAb), and thyroid ultrasonography [12]. HT often causes abnormal thyroid function, which is regulated by thyroid hormones. Thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) are the main thyroid function indicators. FT3/FT4 ratio is employed to evaluate peripheral sensitivity to thyroid hormones [13–15]. Currently, the evidence on the reciprocal association between OLP and HT based on laboratory analyses by thyroid antibodies and thyroid function tests is inadequate. Therefore, we hypothesized that there might be association of OLP condition with abnormal thyroid antibodies and function indicators in HT patients. Thus, we conducted a retrospective case–control study to compare the clinical and laboratory indicators between cases of HT concomitant with OLP and cases of HT only, so as to better elucidate the reciprocal association between OLP and HT.

Materials and methods

This study was conducted according to the guidelines of the Declaration of Helsinki, and was approved by the Ethics Committee of Shanghai Ninth People's Hospital. The current study was designed based on our previous cross-sectional study, which was conducted to investigate the prevalence of TDs in patients with OLP [4]. The diagnoses of TDs including HT, hypothyroidism, hyperthyroidism, and thyroid nodules were performed based on our previous study [4]. Based on our previous study [4], we enrolled 59 OLP patients concomitant with HT from Department of Oral Mucosal Diseases in our hospital between June 2017 and April 2018. The detailed inclusion and exclusion criteria of case group were as follows. Inclusion criteria: (i) diagnosis of HT determined by the presence of TPOAb and TGAb and reduced echogenicity on thyroid sonography of patients with clinical feature [12], (ii) diagnosis of OLP according to the clinical and histological definition of the World Health Organization modifications [16], (iii) age > 18 years; (iv) tested for thyroid autoantibodies (TPOAb, TGAb) and thyroid function indexes (FT3, FT4, TSH). Exclusion criteria: (i) history or current diagnosis of other mucosal diseases, such as oral lichenoid lesions, oral leukoplakia, oral erythema, oral submucous fibrosis, discoid lupus erythematosus, or recurrent aphthous stomatitis; (ii) history of other systemic diseases and autoimmune diseases, and related medication history; (iii) current pregnancy or lactation.

As for control group, there were 76 HT patients without OLP condition enrolled from Department of Endocrinology in our hospital between June 2017 and August 2019. The exclusion criteria of control group as follows: (i) The clinical diagnosis of OLP and its related oral disorders, which were performed by oral medicine specialists through oral examination; (ii) history of other systemic diseases and autoimmune diseases, and related medication history; (iii) current pregnancy or lactation. All the subjects underwent B-scan ultrasonography of the thyroid gland. The information on demographic and clinical data on the other TDs including hypothyroidism, hyperthyroidism, and thyroid nodules were recorded. All the participates in case and control group underwent serologic testing for all the 5 thyroid-related indicators (TGAb, TPOAb, TSH, FT3, and FT4). All the indicators were measured with chemiluminescence immunoassays, which were conducted by technicians at the Clinical Laboratory of our hospital. As references, the normal serum levels of TOPAb, TGAb, TSH, FT3, and FT4 are 0–9 IU/mL, 0–115 IU/mL, 0.34–5.6 μIU/mL, 2.5–3.9 pg/mL, and 0.58–1.64 ng/dL, respectively. The diagnosis of HT was performed by endocrinology specialists based on the criteria described previously [12]. The HT patients included in the current study was the presence of positive detection of TPOAb or TGAb needed to be diagnosed of HT, when these patients enrolled in this study. But the medical history of these patients was of the diagnosis of HT performed by endocrinology specialists.

Statistical analysis was carried out with the chi-square test or Fisher's exact test among qualitative variables and the Student's *t*-test among quantitative variables. If quantitative variables did not follow a Gaussian distribution, the differences between 2

Table 1 Comparative and logistic regression analysis of OLP occurrence in 135 HT patients

Variate, n (%)	HT with OLP *n* = 59	HT without OLP *n* = 76	*P* value	Univariate analysis OR (95% CI)	*P* value	Multivariate analysis Adjusted OR (95% CI)	*P* value
Gender			0.038				
Male	8 (13.6)	22 (28.9)		1.00 (ref)		1.00 (ref)	
Female	51 (86.4)	54 (71.1)		2.597 (1.061–6.357)	0.037	2.720 (0.692–10.688)	> 0.05
Age, y			0.002				
Mean (SD)	51.66 (13.525)	58.67 (1.988)		0.954 (0.927–0.983)	0.002	0.982 (0.944–1.021)	> 0.05
Range	24–72	25–85					
Smoking history			> 0.05				
No	50 (84.7)	54 (71.1)		1.00 (ref)			
Yes	9 (15.3)	22 (28.9)		0.442 (0.186–1.050)	> 0.05		
Hyperthyroidism			> 0.05				
No	55 (93.2)	75 (98.7)		1.00 (ref)			
Yes	4 (6.8)	1 (1.3)		5.455 (0.593–50.159)	> 0.05		
Hypothyroidism			> 0.05				
No	48 (81.4)	61 (80.3)		1.00 (ref)			
Yes	11 (18.6)	15 (19.7)		0.932 (0.392–2.214)	> 0.05		
Thyroid nodule			< 0.001				
No	35 (59.3)	72 (94.7)		1.00 (ref)		1.00 (ref)	
Yes	24 (40.7)	4 (5.3)		12.343 (3.975–38.321)	< 0.001	10.328 (2.564–41.604)	0.001
TGAb			0.002				
Negative	12 (20.3)	35 (46.1)		1.00 (ref)		1.00 (ref)	
Positive	47 (79.9)	41 (53.9)		3.343 (1.536–7.279)	0.002	6.936 (2.024–23.765)	0.002
TPOAb			> 0.05				
Negative	10 (16.9)	9 (11.8)		1.00 (ref)			
Positive	49 (83.1)	67 (88.2)		0.658 (0.249–1.742)	> 0.05		
TSH (μIU/mL)			> 0.05				
Median (IQR)	2.85 (2.80)	3.19 (2.92)		0.935 (0.840–1.040)	> 0.05		
FT3 (pg/mL)			< 0.001				
Median (IQR)	3.455 (1.33)	4.46 (0.68)		0.475 (0.310–0.726)	0.001	0.695 (0.392–1.231)	> 0.05
FT4 (ng/dL)							
Median (IQR)	0.965 (10.19)	14.915 (4.84)	< 0.001	0.867 (0.820–0.917)	< 0.001	1.067 (0.910–1.250)	> 0.05
FT3/FT4 ratio							
Median (IQR)	3.065 (3.77)	0.2954 (0.10)	< 0.001	2.248 (1.686–2.996)	< 0.001	2.577 (1.377–4.823)	0.003

HT Hashimoto's thyroiditis, *OLP* Oral lichen planus, *IQR* Interquartile range, *OR* Odds ratio, *CI* Confidence interval, *TPOAb* Thyroid peroxidase antibody, *TGAb* Thyroglobulin antibody, *TSH* Thyroid stimulating hormone, *FT3* Free triiodothyronine, *FT4* Free thyroxine. The (ref) indicates that one variate (e.g. male) of the dichotomous variates refers the other one (e.g. female) in logistic analysis

groups were calculated using the non-parametric test. Logistic regression analysis was applied to evaluate odds ratios (OR) with 95% confidence intervals (CI) and the associations among variables. The significant variables in the univariate logistic analysis were included in the multivariate analysis. Statistical analysis was performed using SPSS for Windows (version 23.0; SPSS Inc.). All the tests were two-sided, and *P* values < 0.05 were considered statistically significant.

Results

Occurrence risk of OLP in HT patients

As presented in Table 1, a comparative analysis was preformed to examine the differences in the parameters between 59 HT patients with OLP and 76 without OLP. Significant differences in gender, mean age, thyroid nodule, TGAb, FT3, FT4, and FT3/FT4 ratio (all $P < 0.05$) were observed between 2 groups. HT concomitant with OLP affected female (86.4%) was more ($P = 0.038$) than HT without OLP affected female (71.1%). The occurrence (40.7%) of thyroid nodule in HT patients concomitant with OLP was higher ($P < 0.001$) than that (5.3%)

in HT without OLP. The positive proportion (79.9%) of TGAb in HT patients concomitant with OLP was higher ($P=0.002$) than that (53.9%) in HT without OLP. The median of FT3/FT4 ratio in HT patients concomitant with OLP was significantly higher than that in HT without OLP. The levels of FT3, FT4, and FT3/FT4 ratio between 2 groups are quantitatively illustrated in Fig. 1A. Multivariate regression analysis revealed that thyroid nodule, positive TGAb, and higher FT3/FT4 ratio (all $P<0.005$) were associated significantly with higher risk of OLP occurrence in 135 HT patients. The presence of thyroid nodule (OR, 10.328; 95%CI=2.564–41.604; $P=0.001$), positive TGAb (OR, 6.936; 95%CI=2.024–23.765; $P=0.002$), and elevated FT3/FT4 ratio (OR, 2.577; 95%CI=1.377–4.823; $P=0.003$) were associated with a significantly increased risk of OLP occurrence in HT patients.

Occurrence risk of OLP in HT patients only associated with the female

Since significant difference in gender were observed between HT patients with OLP and without OLP, we speculated that there were different clinical and laboratory parameters among female and male patients,

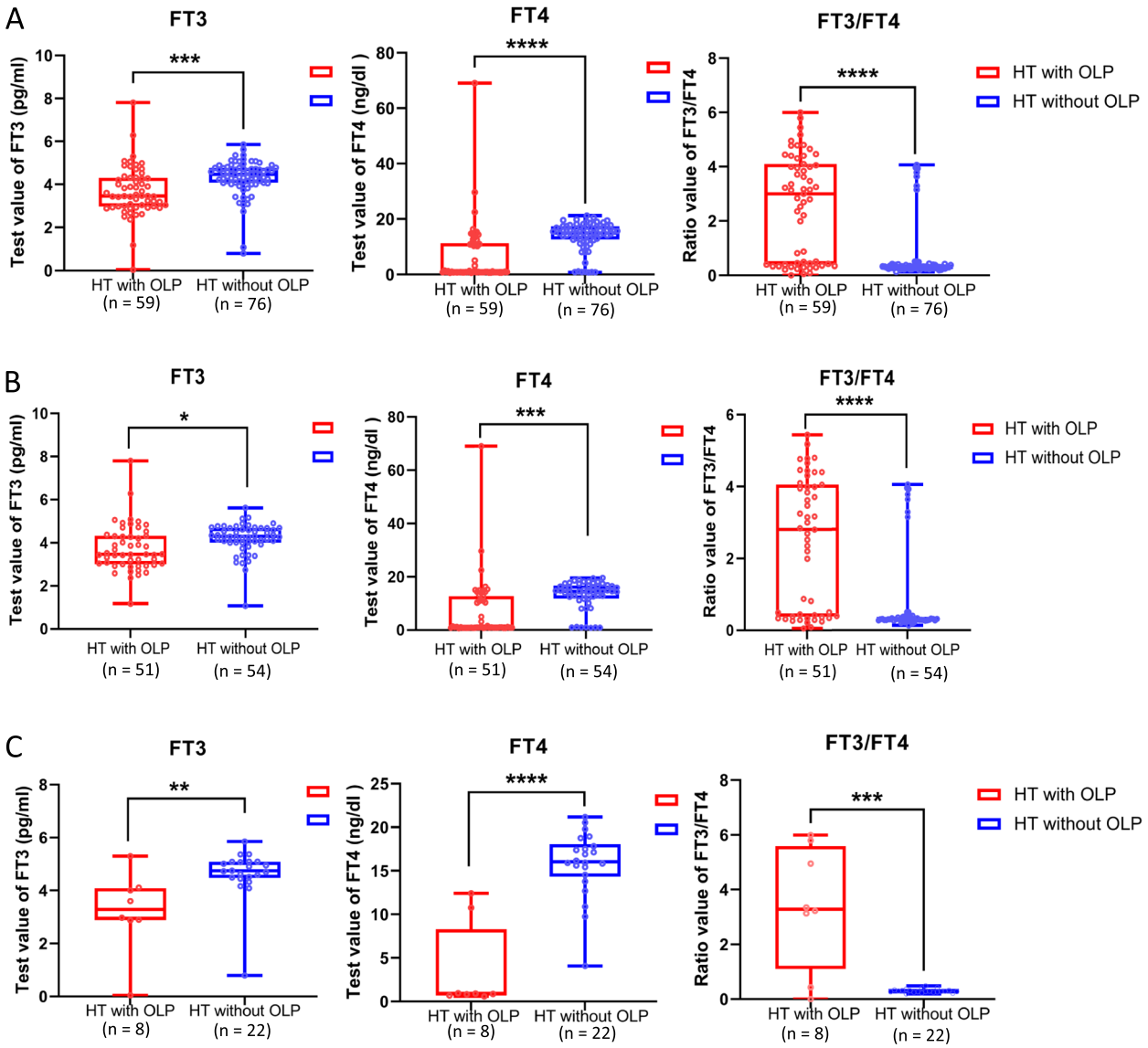

Fig. 1 The levels of FT3, FT4, and FT3/FT4 ratio (**A**) between Hashimoto's thyroiditis (HT) patients concomitant with and without oral lichen planus (OLP), (**B**) between female HT patients with and without OLP, and (**C**) between male HT patients with and without OLP. *$P<0.05$; **$P<0.01$; ***$P<0.001$; ****$P<0.0001$

Table 2 Comparative and logistic regression analysis of OLP occurrence in 105 female HT patients

Variate, n (%)	HT with OLP	HT without OLP		Univariate analysis		Multivariate analysis	
	n = 51	*n* = 54	*P* value	OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age, y			> 0.05				
Mean (SD)	52.12 (13.65)	56.87 (12.04)		0.974 (0.942–1.002)	> 0.05		
Range	24–72	25–85					
Smoking history			> 0.05		> 0.05		
No	50 (98.0)	53 (98.1)		1.00 (ref)			
Yes	1 (2.0)	1 (1.9)		1.060 (0.065–17.407)			
Hyperthyroidism			> 0.05				
No	48 (94.1)	54 (100.0)					
Yes	3 (5.9)	0 (0.0)					
Hypothyroidism			> 0.05				
No	41 (80.4)	44 (81.5)		1.00 (ref)			
Yes	10 (19.6)	10 (18.5)		1.073 (0.405–20.843)	> 0.05		
Thyroid nodule			< 0.001				
No	29 (56.9)	51 (94.4)		1.00 (ref)		1.00 (ref)	
Yes	22 (43.1)	3 (5.6)		12.897 (3.552–46.828)	< 0.001	13.964 (3.039–64.16)	0.001
TGAb			< 0.001				
Negative	9 (17.6)	28 (51.9)		1.00 (ref)		1.00 (ref)	
Positive	42 (82.4)	26 (48.1)		5.026 (2.051–12.315)	< 0.001	8.542 (2.328–31.35)	0.001
TPOAb			> 0.05				
Negative	8 (15.7)	4 (7.4)		1.00 (ref)			
Positive	43 (84.3)	50 (92.6)		0.430 (0.121–1.527)	> 0.05		
TSH (μIU/mL)			> 0.05				
Median (IQR)	2.74 (2.73)	3.19 (2.93)		0.942 (0.835–1.063)	> 0.05		
FT3 (pg/mL)			< 0.001				
Median (IQR)	3.46 (1.31)	4.29 (0.68)		0.557 (0.345–0.898)	0.016	0.844 (0.422–1.688)	> 0.05
FT4 (ng/dL)			< 0.001				
Median (IQR)	1.05 (11.83)	14.53 (4.89)		0.902 (0.850–0.957)	0.001	1.046 (0.898–1.219)	> 0.05
FT3/FT4 ratio			< 0.001				
Median (IQR)	2.80 (3.67)	0.30 (0.10)		1.977 (1.472–2.653)	< 0.001	2.258 (1.223–4.169)	0.009

HT Hashimoto's thyroiditis, *OLP* Oral lichen planus, *IQR* Interquartile range, *OR* Odds ratio, *CI* Confidence interval, *TPOAb* Thyroid peroxidase antibody, *TGAb* Thyroglobulin antibody, *TSH* Thyroid stimulating hormone, *FT3* Free triiodothyronine, *FT4* Free thyroxine. The (ref) indicates that one variate (e.g. male) of the dichotomous variates refers the other one (e.g. female) in logistic analysis

respectively. Among 105 female patients, significant differences in thyroid nodule, TGAb, FT3, FT4, and FT3/FT4 ratio (all $P < 0.001$) were observed between 51 HT female concomitant with OLP and 54 without OLP (Table 2). The occurrence (43.1%) of thyroid nodule in HT female concomitant with OLP was higher than that (5.6%) in HT without OLP. The positive proportion (82.4%) of TGAb in HT female concomitant with OLP was higher than that (48.1%) in HT without OLP. The median of FT3/FT4 ratio in HT female concomitant with OLP was significantly higher than that in HT without OLP. The levels of FT3, FT4, and FT3/FT4 ratio between 2 female groups are quantitatively illustrated in Fig. 1B. Multivariate regression analysis revealed that thyroid nodule, positive TGAb, and higher FT3/FT4 ratio (all $P < 0.01$) were associated significantly with higher risk of OLP occurrence in 105 HT female. The presence of thyroid nodule (OR, 13.964; 95%CI = 3.039–64.16; $P = 0.001$), positive TGAb (OR, 8.542; 95%CI = 2.328–31.35; $P = 0.001$), and elevated FT3/FT4 ratio (OR, 2.258; 95%CI = 1.223–4.169; $P = 0.009$) were associated with a significantly increased risk of OLP occurrence in HT patients. Among 30 male patients, the significant differences in these parameters were not found between 2 male groups (supplementary Table S1, Fig. 1C) in the analyses. Besides, no difference in demographic and thyroid-related indicators was observed that between clinical types (non-erosive vs. erosive) of OLP patients (supplementary Table S2).

Discussion

To the best of our knowledge, the previous investigations focused on the association of TDs occurrence in OLP patients [17, 18]. Conversely, there were rare investigations focusing on the association of OLP occurrence in TD or HT patients [9, 10]. Zhou et al. [5] aimed to investigate the prevalence of TDs in OLP patients and association of thyroid disorders among OLP patients, and found that the occurrence risk of both HT and thyroid nodule was significantly increased in OLP patients compared with healthy control. In contrast, we aimed to investigate the association of OLP and thyroid nodule among HT patients, and found that the occurrence risk of thyroid nodule was significantly increased in HT patients concomitant with OLP compared with ones without OLP. These results suggest that there may be some relationship between thyroid nodules and OLP occurrence. Selenium deficiency is a possible connection between OLP and thyroid nodule [19, 20], while further studies are necessary to confirm this connection.

Most previous studies on OLP and HT did not include the level of HT autoantibodies and thyroid dysfunction indicators in the correlation analysis of the two diseases [5]. Vehviläinen et al. [21] examined the expression of TSH and TSH receptor (TSHR) only in 14 OLP patients with hypothyroidism and 14 without hypothyroidism, and found no detection of TSH or TSHR in OLP lesions in patients with or without hypothyroidism. Robledo-Sierra et al. [22] investigated thyroid parameters in 59 TD patients without OLP and 108 with OLP, and found significant differences not in TGAb, TPOAb, and TSH levels but in FT3 and FT4 levels between 2 groups. TPOAb and TGAb are the most common autoantibodies expressed in HT patients. FT3 and FT4 are the main indicators of thyroid dysfunction. FT3 is converted from FT4 by deiodinase in peripheral tissues; thus, FT3/FT4 ratio could be served as not only a proxy of deiodinase activity but also the peripheral sensitivity to thyroid hormones. We found significant differences not in TPOAb and TSH levels but in TGAb, FT3 and FT4 levels, and FT3/FT4 ratio between HT patients with OLP and without OLP. Also, TGAb and FT3/FT4 ratio as laboratory markers could indicate the risk of OLP occurrence in HT patients, mainly in female.

Since OLP and HT are autoimmune diseases related to T-cell mediated immune responses, they seem to have some common immune triggers and pathogenic processes [23]. Due to a lack of tissue specificity, HT antibodies (TPOAb and TGAb) lead to occasional reports of their extra-thyroid effects. HT autoantibodies and antigens with structure recognize the similar antigens expressed by oral mucosal epithelial cells [23]. Circulating thyroid autoantibodies may target oral keratinocytes or cross-react with proteins on keratinocyte membranes, which stimulate cytotoxic T cells to release cytokines or chemokines to promote the development of lichen lesion and attract more immune cells into developing lesions [23]. The active systemic immune condition during the course of autoimmune diseases is also a possible precipitating factor, which might be also involved in the coexistence of the different autoimmune diseases. Therefore, it is possible to argue that in HT patients, circulating thyroid autoantibodies could contribute to trigger an organ-specific autoimmune response also in the oral mucosa, eventually resulting in more cryptic epitope exposure and OLP development. This could be likely to happen in the cases of HT where OLP precedes the onset of thyroid dysfunction, since a significant proportion of subjects have asymptomatic chronic autoimmune thyroiditis with circulating thyroid autoantibodies [7].

It is well-known that OLP and HT affect more female than male, respectively. Thus, it is reasonable to observe that the cooccurrence incidence of the two diseases in female patients was significantly higher than that in male patients. OLP incidence in patients with HT was related to gender, and that female patients with HT were more likely to suffer from OLP. Indeed, the predilection for women in systemic autoimmune diseases is established. Oral environment is likely to impose a combination of systemic and local factors that ultimately result in the sex bias in autoimmune diseases of the oral cavity. Variations of immune responses, target organ vulnerability, endocrine and genetic factors, sex chromosomes and modes of parental inheritance are potential systemic factors, whereas the oral microbiome, oral tolerance, saliva, and oral epithelial stem cells may account for local contributing factors [24]. The difference in the prevalence of OLP in different sexes of HT patients might be related to these systemic and local factors. Reciprocally, Zhang et al. [8] reported that the HT incidence rate in female patients with OLP was significantly higher than that in male, namely female patients with OLP were more likely to suffer from HT. Besides, the level of HT autoantibodies and thyroid dysfunction indicators in OLP patients were not related to the clinical types of OLP. Further investigations are needed to confirm these findings.

We are aware of the limitations of this study that was a retrospective case–control study and a causal relationship between the two diseases could not be determined. Due to the small sample size of participants and single-center nature, the subjects included could not have accurately represented the general population. In addition, we did not obtain the exact onset time of OLP and HT in the present study. The patients of the case and control groups were not selected from the same department which may show selection bias of the participants.

Moreover, potential confounding effects of changes in thyroid autoantibody levels were not excluded. Given the wide ranges of the 95%CI as for the variables thyroid nodule and positive TGAb, the results should be interpreted with great caution. Considering the limitations of this study, we could not determine and examine the potential mechanism underlying the association between OLP and HT. Large-scale multicenter prospective clinical and laboratory investigations are necessary to demonstrate our findings and search the potential pathophysiologic mechanisms of these two diseases.

Conclusion

In conclusion, this retrospective case–control study revealed that presence of thyroid nodule, positive TGAb, and high FT3/FT4 ratio as risk factors were significantly associated with higher risk of OLP occurrence in female patients with HT. Based on the evidence of our findings, female patients suffering from HT, particularly who presented with the risk factors, should be informed about the risk of OLP development and the need for oral mucosal examination to screen for lichen lesions. The findings could help further elucidate the risk factors involved in the relationship between OLP and HT.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12903-025-05780-2.

Additional file 1. Table S1. Comparative and logistic regression analysis of OLP occurrence in 30 male HT patients. Table S2. Comparative analysis of demographic and thyroid-related indicators of 59 OLP patients

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Authors' contributions
WL and XS designed the study. YT, ZZ and YL extracted, analyzed, and interpreted the data. YL drafted the manuscript. YL and WL revised the manuscript. All authors read and approved the final version of the manuscript.

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Data availability
The study data are available from the corresponding authors.

Declarations

Ethics approval and consent to participate
The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee (No. 2016–201-T145) of Shanghai Ninth People's Hospital with written informed consent obtained from all participating subjects.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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