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SHORT COMMUNICATION

Possible link between Hashimoto's thyroiditis and oral lichen planus: a novel association found

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Abstract
Objectives Hashimoto's thyroiditis as well as lichen planus has been associated to a number of disorders, generally of auto-immune origin. A novel possible association between oral lichen planus (OLP) and Hashimoto's thyroiditis (HT) is here proposed on the basis of a cross-sectional survey.
Materials and methods One hundred and five unrelated OLP patients were considered. Diagnosis of HT was based on positive serum anti-TPO, anti-Tg, TSH levels and the typical ultrasound pattern of the thyroid gland.
Results In the present survey, the prevalence of HT in the OLP group was 14.3 % whereas the prevalence of HT-related hypothyroidism in the general population was reported to be equal to 1 %. By Fisher's exact test, it was revealed that the difference between our data and historical prevalence of HT was found statistically significant.
Conclusion Actually, there is no definitive hypothesis that could explain the coexistence of OLP and HT. However, considering the onset timing of HT followed by OLP in 93.3 % of our series, we suspected a causal or predisposing role for HT. Specifically, we believe that in HT 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.
Clinical relevance Because of the large number of cases of asymptomatic chronic auto-immune thyroiditis, it would be useful that women over 40 years of age affected by OLP were screened for thyroid dysfunction, particularly HT.

Keywords Hashimoto's thyroiditis · Oral lichen planus · Autoimmunity · Circulating thyroid antibodies

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Introduction

A novel possible association between oral lichen planus (OLP) and Hashimoto's thyroiditis (HT) is here proposed on the basis of a cross-sectional survey. Lichen planus has been associated to a number of disorders, generally of auto-immune origin: myasthenia gravis, Sjogren's syndrome, ulcerative colitis, psoriasis, thymoma, lupus erythematous, coeliac disease [1]. Likewise, Sjogren's syndrome, lupus erythematous, type 1 diabetes, pernicious anaemia, surrenal deficiency and Grave's disease were considered as HT-associated disorders [2]. To the best of our knowledge, no one reported so far the association between OLP and HT.

Patients and methods

Between May 2005 and April 2010, within a series of 105 unrelated OLP patients, we observed 15 cases (14.3 %) with coexistence of HT (Table 1). Diagnosis of OLP was confirmed clinically and histologically in all cases, according to

Table 1 The most important clinical findings in a series of 15 OLP patients with HT

Number	Sex	Age	Thyroid function[a]		Thyroid nodules[b]	TSH[c]	Anti-TG[d]	Anti-TPO[d]	Oral lichen planus
			Initial	Now					
1	F	44	↓	↓	2	↑	++	+	Reticular/plaque
2	F	46	↓	↓	Multiple	↑	++++	++++	Reticular/plaque
3	F	61	↑	↓	2	↑	++	++	Reticular
4	F	46	↓	↓	3	↑	++	+	Reticular/plaque
5	F	47	↓	↓	Multiple	↑	++	++	Reticular/plaque
6	F	35	↓	↓	Multiple	↑	++	++	Reticular/plaque
7	F	42	↑	↓	Goitre	↑	+	+	Reticular/plaque
8	F	49	↓	↓	2	↑	++++	++++	Plaque
9	F	38	↑	↓	3	↑	++	++	Reticular
10	F	61	↓	↓	Multiple	↑	+++	+++	Plaque
11	F	63	↓	↓	1	↑	++++	++++	Reticular
12	F	51	↑	↓	Multiple	↑	++	++	Plaque
13	F	33	↓	↓	Multiple	↑	++	+	Reticular/plaque
14	F	41	↓	↓	Multiple	↑	++	++	Reticular/plaque
15	M	62	↓	↓	1	↑	++++	++++	Reticular

↑ Elevated with respect to the range values, ↓ diminished with respect to the range values

[a] In our laboratory, the following normal ranges were established: T4, 5.5 to 12.0 g/dL; T3, 60 to 190 ng/dL

[b] Thyroid nodules evident by echography

[c] In our laboratory, the following normal range was established: TSH, 0.4 to 4.5 IU/mL

[d] Values of antithyroid autoantibodies higher than 10 IU/mL were considered positive

most recent diagnostic criteria [3]. All patients were screened for the presence of IgG anti-HCV antibodies by third-generation ELISA, and positive results were confirmed by means of second-generation RIBA. As exclusion criteria, patients suspected to have drug- or dental restoration-related oral lichenoid lesions were not considered in the present survey as well as patients who were HCV positive and/or undertaking interferon therapy.

HT is, by strict criteria, a histologic diagnosis; however, in clinical practice, expression of TPOAb and a hypoechoic thyroid ultrasound (US) pattern are clinical criteria for the diagnosis of HT [4]. In the present series, diagnosis of HT was based on positive serum anti-TPO, anti-Tg, TSH levels and typical US pattern of the thyroid gland.

Results

Fifteen patients out of 105 fulfilling the inclusion criteria had HT. In the majority of cases (14 out of 15), thyroiditis has preceded the onset of OLP, while only in one case was thyroid dysfunction diagnosed after OLP.

Nine patients received Eutirox® (L-thyroxine) 50 mg/daily, five patients were given 100 mg/day and the others have not yet started any therapy for thyroiditis. Even if one case of lichenoid lesions with Eutirox® (by thyroxine overassumption) has been reported in literature [5], it does not seem to matter in our series.

Of the 15 cases of histologically confirmed OLP with the coexistence of HT, all but one were female, consistent with the major incidence of auto-immune disorders in the female gender.

In the present survey, the prevalence of HT in the OLP group was 14.3 % whereas the prevalence of HT-related hypothyroidism in the general population was reported to be equal to 1 % [6]. By Fisher's exact test, it was revealed that the difference between our data and historical prevalence of HT was found statistically significant ($p<0.0003$, OR=14.29, 95 % CI=1.9, 106.2).

Discussion

Although the fortuitous coexistence of OLP and HT is properly taken into account by us, prevalence of HT in OLP patients was found to be higher than in the general population (1 % from iodine-sufficient regions) [6], and a certain immuno-pathogenetic similarity had to be considered.

The onset of auto-immune diseases, specifically endocrinopathies, is multifactorial in character and includes genetic predisposition, external etiological factors and microenvironment alterations in target organs. Actually, the genetic predisposition is of great value. The most important genetic factor seems to be the polymorphism of the major histocompatibility complex [7]. Data on HLA haplotypes in HT showed an association of goitrous HT with HLA-DR5 and atrophic HT with DR3. The association of HT with HLA-DR3 in Caucasians has been confirmed, and the association of HT with HLA-DQw7 has also been reported [6]. Genetic control has been also considered to play a role in OLP development even if immunogenetic studies have given controversial results [8]. Indeed, cutaneous idiopathic LP is frequently associated with the HLA-DR1 allele, whereas

idiopathic OLP is not [9]. However, a linkage disequilibrium of the –308A TNF-α promoter polymorphism with HLA-DR3 has reported in Caucasians [10].

Recently, the gene for cytotoxic T lymphocyte antigen 4 (CTLA-4) has been identified, able to confer the susceptibility to HT [6]. CTLA-4 is a co-stimulatory molecule expressed on the surface of activated T cells, and it participates in their interaction with antigen-presenting cells (APC) [6, 11]. Several lines of evidence have confirmed that the presence of CTLA-4 downregulates T cell activation [11]. This inhibitory effect have raised the possibility that gene polymorphism or mutations altering CTLA-4 expression and/or function could result in an exaggerated T cell activation, and since CTLA-4 is a non-specific molecule, it is expected to confer susceptibility to autoimmunity in general [6, 11]. Thus, in a predisposed subject, an imbalance in CTLA-4 function can lead to T cell proliferation and cytokine production. Since it has been recognized that the immune system is controlled by Th1/Th2 balance, both HT and OLP are considered to be a Th1-type diseases [12, 13].

Actually, there is no definitive hypothesis that could explain the coexistence of OLP and HT. However, considering the onset timing of HT followed by OLP in 93.3 % of our series, we suspected a causal or predisposing role for HT. Specifically, we believe that in HT 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. This could be also likely to happen in cases where OLP precedes the onset of thyroid dysfunction, since a significant proportion of subjects have asymptomatic chronic auto-immune thyroiditis with circulating thyroid antibodies [14].

Our suggestion, although speculative, seems to be supported by several findings: as the skin is commonly affected in thyroid diseases, we hypothesize that in HT patients, circulating thyroid antibodies could target also oral/skin keratinocytes. Since it has been proved that keratinocytes may express the TSH receptor as well as thyroglobulin gene but not thyroid peroxidase one [15], anti-TGab may target keratinocytes expressing thyroglobulin on their cell surface. However, given that in HT, TPOAb are likely to be of greater pathogenetic importance than anti-TG autoantibodies for a number of reasons [4], it could be also postulated that circulating anti-TPOab may cross react with an unknown keratinocyte membranous protein.

Once the link between thyroid antibodies and the target on the keratinocyte surface took place, several options would have been possible. One possibility is that Ig-thyroid antibodies could trigger CD95 (Fas/Apo-1)-mediated apoptosis in keratinocytes as Ig autoantibodies do in pemphigus vulgaris [16]. Then, the apoptotic bodies could be internalised and processed by surrounding keratinocytes or APC cells leading to subsequent T cell activation.

However, we suggest also the possibility that thyroid antibodies could have the ability to unmask epitopes in keratinocytes, exposing the so-called “lichen planus antigen”. Indeed, Sugerman proposed that, at the lesion site, keratinocytes express a lichen planus antigen and that known (e.g. systemic drugs, dental restorative materials, mechanical trauma or bacterial or viral infection) or unidentified agents could induce keratinocyte antigen expression [13]. Subsequently, CD8+ cytotoxic T cells recognize the lichen planus antigen associated with MHC class I on lesional keratinocytes and trigger keratinocyte apoptosis [13]. All the same, thyroid antibodies linked on the keratinocyte surface may be directly recognized as target antigens by cytotoxic T cells.

However, specific experimental studies should address the herein proposed hypotheses. In conclusion, our aim was to report this novel possible association, inviting colleagues to investigate about the coexistence of HT and OLP, especially in terms of confirmation of epidemiological datum and respective immuno-pathogenetic rationale. On this base, it would be useful that OLP women over 40 years of age are screened for thyroid dysfunction, particularly HT, because of the important number of cases of asymptomatic chronic auto-immune thyroiditis [14]. Furthermore, in the presence of evidence of our suggestion, patients suffering from HT should be informed about the risk of developing OLP lesions.

Conflict of interest The authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

References

1. Romero MA, Seoane J, Varela-Centelles P, Diz-Dios P, Otero XL (2002) Clinical and pathological characteristics of oral lichen planus in hepatitis C-positive and -negative patients. Clin Otolaryngol Allied Sci 27:22–26
2. Szyper-Kravitz M, Marai I, Shoenfeld Y (2005) Coexistence of thyroid autoimmunity with other autoimmune diseases: friend or foe? Additional aspects on the mosaic of autoimmunity. Autoimmunity 38:247–255. doi:10.1080/08916930500050194
3. van der Meij EH, van der Waal I (2003) Lack of clinicopathologic correlation in the diagnosis of oral lichen planus based on the presently available diagnostic criteria and suggestions for modifications. J Oral Pathol Med 32:507–512
4. Karanikas G, Schuetz M, Wahl K, Paul M, Kontur S, Pietschmann P, Kletter K, Dudczak R, Willheim M (2005) Relation of anti-TPO autoantibody titre and T-lymphocyte cytokine production patterns in Hashimoto's thyroiditis. Clin Endocrinol (Oxford) 63:191–196. doi:10.1111/j.1365-2265.2005.02324.x
5. Kaur S, Bhalla M, Thami GP (2003) Subacute lichenoid eruption due to L-thyroxine overdosage. Dermatology 206:346–347. doi:10.1159/000069952
6. Tomer Y, Davies TF (2003) Searching for the autoimmune thyroid disease susceptibility genes: from gene mapping to gene function. Endocr Rev 24:694–717

7. Wucherpfennig KW, Strominger JL (1995) Selective binding of self peptides to disease-associated major histocompatibility complex (MHC) molecules: a mechanism for MHC-linked susceptibility to human autoimmune diseases. J Exp Med 181:1597–1601
8. Carrozzo M, Francia Di Celle P, Gandolfo S, Carbone M, Conrotto D, Fasano ME, Roggero S, Rendine S, Ghisetti V (2001) Increased frequency of HLA-DR6 allele in Italian patients with hepatitis C virus-associated oral lichen planus. Br J Dermatol 144:803–808
9. La Nasa G, Cottoni F, Mulargia M, Carcassi C, Vacca A, Pizzati A, Ledda A, Montesu MA, Cerimele D, Contu L (1995) HLA antigen distribution in different clinical subgroups demonstrates genetic heterogeneity in lichen planus. Br J Dermatol 132:897–900
10. Carrozzo M, Uboldi de Capei M, Dametto E, Fasano ME, Arduino P, Broccoletti R, Vezza D, Rendine S, Curtoni ES, Gandolfo S (2004) Tumor necrosis factor-alpha and interferon-gamma polymorphisms contribute to susceptibility to oral lichen planus. J Invest Dermatol 122:87–94. doi:10.1046/j.0022-202X.2003.22108.x
11. Vaidya B, Pearce S (2004) The emerging role of the CTLA-4 gene in autoimmune endocrinopathies. Eur J Endocrinol 150:619–626
12. Stassi G, Di Liberto D, Todaro M, Zeuner A, Ricci-Vitiani L, Stoppacciaro A, Ruco L, Farina F, Zummo G, De Maria R (2000) Control of target cell survival in thyroid autoimmunity by T helper cytokines via regulation of apoptotic proteins. Nat Immunol 1:483–488. doi:10.1038/82725
13. Sugerman PB, Savage NW, Walsh LJ, Zhao ZZ, Zhou XJ, Khan A, Seymour GJ, Bigby M (2002) The pathogenesis of oral lichen planus. Crit Rev Oral Biol Med 13:350–365
14. Vanderpump MP, Tunbridge WM (2002) Epidemiology and prevention of clinical and subclinical hypothyroidism. Thyroid 12:839–847. doi:10.1089/105072502761016458
15. Slominski A, Wortsman J, Kohn L, Ain KB, Venkataraman GM, Pisarchik A, Chung JH, Giuliani C, Thornton M, Slugocki G, Tobin DJ (2002) Expression of hypothalamic-pituitary-thyroid axis related genes in the human skin. J Invest Dermatol 119:1449–1455. doi:10.1046/j.1523-1747.2002.19617.x
16. Wang X, Bregegere F, Frusic-Zlotkin M, Feinmesser M, Michel B, Milner Y (2004) Possible apoptotic mechanism in epidermal cell acantholysis induced by pemphigus vulgaris autoimmunoglobulins. Apoptosis 9:131–143. doi:10.1023/B:APPT.0000018795.05766.1f