



Association between Thyroiditis and Multifocality in Papillary Thyroid Carcinoma

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Abstract

Introduction Hashimoto thyroiditis (HT) shares many characteristics with papillary thyroid carcinoma (PTC), and some studies show that, when associated, PTC is diagnosed mostly with smaller lesions and multifocal pattern.

Objective To evaluate the relationship between HT and PTC.

Methods A retrospective study of 155 patients who underwent total thyroidectomy from 2009 to 2015. Demographical, clinical and ultrasonographical data, as well as anatomopathological findings were evaluated.

Results There were signs of thyroiditis in 35 patients, and 114 patients had a unifocal disease. There was no statistical significance between the variables studied and thyroiditis. However, when compared with the occurrence of unifocal or multifocal lesions, there was statistical significance regarding age ($p = 0.038$) and mass ($p = 0.031$). There was no direct relationship between thyroiditis and multifocality ($p = 0.325$) nor between thyroiditis and cervical extension of the disease ($p = 0.300$ e $p = 0.434$).

Conclusion There was no relationship between thyroiditis and multifocality in cases of PTC.

Keywords

- ▶ thyroiditis
- ▶ thyroid cancer
- ▶ papillary thyroid carcinoma

Introduction

Hashimoto thyroiditis (HT) was first described in 1912 by the Japanese surgeon Hakaru Hashimoto, in Berlin, Germany.¹ It is the most common disease in the thyroid gland, and it occurs mainly in women.² It is an inflammatory autoimmune disease with diffuse infiltration of the gland by lymphocytes,

leading to fibrosis and atrophy, and is the most common cause of hypothyroidism.^{3–5} Papillary thyroid carcinoma (PTC) is the most common thyroid cancer, responsible for ~ 70% to 80% of cases of this tumor.

The first causal association between both conditions was proposed in 1955 by Dailey et al.⁶ However, some

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controversy still remains. Some papers suggest a strong relationship between them,⁷⁻⁹ whereas others do not.^{1,10,11}

Hashimoto thyroiditis shares many characteristics with PTC, such as similar morphology, immunohistochemical pattern, and molecular profile, suggesting that it could be a predisposing factor for PTC.¹⁰ Thus, some papers show that, in patients with HT, there is an increase of ~ 30% in cases of PTC. When associated with HT, PTC is diagnosed mostly in young women, with smaller lesions, in an early and multifocal pattern, and with better prognosis.^{3,5,7,8,12}

The objective of the present study was to evaluate the relationship between these diseases.

Methods

The present study was approved by the Ethics and Research Committee of the institution in which it was performed under number 83977318.4.0000.5509.

It is a retrospective study to evaluate the medical records of patients treated in a tertiary reference facility. In total, 155 patients treated between 2009 and 2015 were evaluated. They underwent total thyroidectomy, with or without neck dissection and radioiodine therapy, according to the protocol of the institution.

Demographical data (gender and age), clinical and ultrasonographic data, as well as anatomopathological findings (presence of chronic thyroiditis, size and multicentricity of the lesions and staging of the neck) were evaluated. All histopathological data was reviewed by the same pathologist. Based on the histopathological findings, the possible risk factors for multicentricity, including the presence of chronic thyroiditis, were evaluated.

Frequency distribution was used to describe the categorical variables, (number of cases and percentage) the central measurement tendencies (average and median) and dispersion measurements. The Student *t*-test was used to check the association between the numerical variables, and the Fisher exact test was employed to compare the categorical variables. A significance level of 5% was used for all statistical tests.

Results

In total, 155 files of patients were evaluated after the anatomopathological analysis of the surgical specimens: 120

Table 1 Patient distribution ($n = 155$)

Aspect	With thyroiditis ($n = 35$)	Without thyroiditis ($n = 120$)	Total
Men	6 (17.1%)	13 (10.9%)	19
Women	29 (82.9%)	107 (89.1%)	136
Unifocal	28 (80%)	86 (71.6%)	114
Multifocal	7 (20%)	36 (28.4%)	41
N0	34 (97.1%)	109 (90.8%)	143
N1a	1 (2.9%)	8 (6.6%)	9
N1b	0	3 (2.6%)	3

Table 2 Average characteristics of the patients according to the presence of thyroiditis

	Without thyroiditis	With thyroiditis	<i>p</i> -value
Age (years)	50.37	52.71	0.434
Mass (grams)	26.91	25.20	0.795
Measurement of the higher focus (mm)	12.77	12.26	0.737

showed no signs of thyroiditis, 114 showed unifocal disease, and 143 didn't developed regional metastasis (► **Table 1**).

After the evaluation and comparison of the results, the main variables were age, size of the largest focus and glandular mass. There was no statistical significance when these variables were related to the presence of thyroiditis (► **Table 2**). However, when compared with the occurrence of unifocal or multifocal lesions, there was statistical significance for age ($p = 0.038$) and mass ($p = 0.031$) (► **Table 3**). Nevertheless, the tests did not show the same results for multifocality and uni/bilaterality (► **Tables 4**).

There was no direct relationship between thyroiditis and multifocality ($p = 0.325$) nor between thyroiditis and cervical extension of the disease ($p = 0.300$ and $p = 0.434$) (► **Table 5**).

Discussion

Some controversy in the literature still remains about the relationship between HT and PTC. Some papers^{3-5,12} suggest a strong positive relationship between them, as well as a cause and effect relation in which the inflammatory process

Table 3 Average characteristics of the patients according to multifocality

	Unilateral multifocal lesions	Bilateral lesions	<i>p</i> -value
Age (years)	48	46	0.707
Mass (grams)	28.16	19.37	0.53
Measurement of the higher focus (mm)	15	16.48	0.99

Table 4 Comparison between unifocal and multifocal lesions

	Unifocal lesion	Multifocal lesions	<i>p</i> -value
Age (years)	52.45	46.59	0.038
Mass (grams)	28.17	21.95	0.031
Measurement of the higher focus (mm)	11.43	16.05	0.104

Table 5 Relationship between thyroiditis and multifocality and neck staging

	With thyroiditis (n = 35)	Without thyroiditis (n = 120)	Total	p-value
Unifocal	28 (80%)	86 (71.7%)	114 (100%)	0.325
Multifocal	7 (20%)	34 (28.3%)	41 (100%)	0.325
N0	34 (97.1%)	109 (90.8%)	143 (92.3%)	0.300
N1a	1 (2.9%)	8 (6.7%)	9 (5.8%)	0.434
N1b	0	3 (2.5%)	3 (1.9%)	0.434
N+	1 (2.9%)	11 (9.2%)	12 (7.7%)	0.300

from the thyroiditis could lead to malignant transformation. This chronic inflammatory response could induce several damages in the DNA through the development of free radicals, resulting in mutations that could promote the transformation to PTC. On the other hand, other studies^{1,2} suggest this is just an accidental finding in the samples. As a result, it is difficult to determine if HT is a predisposing factor for PTC or if it is only a response of the organism to the development of PTC.¹²

Epidemiological and histological data show that PTC often occurs in the context of thyroiditis, and is often infiltrated by inflammatory-immune cells. In spite of the fact that an elevated level of serum thyroglobulin antibody (TgAb) is an independent predictor for PTC, the level of serum thyroid peroxidase antibody (TPOAb) was not present in the univariate and multivariate analyses. Some studies failed to identify this relationship probably due to the high diversity of the TgAb assay.¹³ The mechanism of such an association is unknown. It is possible that TgAb has a tumorigenic effect or is strongly associated with a specific tumorigenic inflammatory response. Changed processing or mutation in the molecular structure of thyroglobulin can increase its antigenicity. On the other hand, the TPOAb does not present an apparent relationship with PTC. Maybe the tumorigenic effect of thyroid inflammation can be avoided by its cytotoxic effect.¹⁴

The main indications for thyroidectomy used to be a lack of response to the pharmacological therapy for hyperthyroidism, compressive symptoms, suspicious or inconclusive cytology and history, or a physical examination that demanded investigation/treatment for cancer (vocal-fold paralysis, pain or increase in the size of cervical lymph nodes).^{15,16} However, most patients with thyroiditis do not need the surgical procedure.

In samples obtained from fine needle aspiration (FNA), an important difference in the prevalence and hazard ratio was found between PTC when compared with specimens obtained after thyroidectomy. The prevalence of PTC in specimens after FNA biopsy in patients with thyroiditis was of 1.2%, whereas in surgical specimens it was of 27.56%. This variability could be the result of different methods when obtaining samples and the heterogeneity of the population in distinct studies.¹²

The use of FNA for the diagnosis of PTC in patients with thyroiditis shows a sensitivity of 90% and negative predictive values of 96%.^{17,18} However, the diagnostic accuracy is diminished in follicular lesions and Hürthle-cell neoplasm, which could lead to false-positives and negatives in some cases.¹⁷⁻²¹ Despite some disadvantages, FNA is indicated as an initial method of investigation of PTC before other more invasive procedures are performed.

An important association between thyroiditis and PTC was found, mainly when associated with multifocality, early tumors and small lesions,¹² which corroborates the hypothesis that the immune response plays a fundamental role in the development of malignant thyroid neoplasms. Nevertheless, our study showed no statistical significance for these variables. In 155 specimens analyzed, 22.58% showed thyroiditis associated with PTC, a percentage lower than that of some findings from the literature, which report percentages of ~ 37.2%.^{22,23} The main hypothesis for that association would be a result of the changes in the glandular stroma.^{24,25} The articles are controversial, suggesting that the association between HT and PTC would be related to a better prognosis with a smaller recurrence.²⁶ Meanwhile, other studies show that this association will not change the aggressiveness of the disease.²⁷ A meta-analysis⁷ gathered 38 studies including 10,648 PTC patients. Histologically-confirmed thyroiditis was identified in 2,471 (23.2%) cases of PTC, which was significantly related to multifocal diseases (odds ratio [OR] = 1.5; $p = 0.010$). A total of 12 studies addressed the frequencies of thyroiditis in uni- and multifocal cancers, including 1,378 cases with multifocal PTC and 2,549 cases with unifocal PTC. Thyroiditis was more frequently observed in multifocal PTC than in the unifocal disease; however, a significant statistical heterogeneity was verified in the studies.⁷

Our study showed positive and statistical significance between multifocality, age and glandular mass. Some articles²⁸⁻³⁰ in the literature remain controversial on this point. In spite of the fact that the age of the patients is similar in the studies, some^{28,29} point out that there is no relationship or difference in age and glandular mass with unifocal or multifocal lesions, whereas others³⁰ show a positive relationship between these variables. It is possible that more studies, with a larger number of patients enrolled, would be necessary in order to reach a definitive conclusion.

We did not find statistical significance in the analysis of cervical extension (neck metastasis) when compared with multifocality and thyroiditis when associated, just like many studies.³¹⁻³³ However, other studies show that multifocality is an independent risk factor for the occurrence of neck metastasis, mainly in the central neck³⁴⁻⁴¹ and regarding young male patients.²⁹

Conclusion

There was no relationship between thyroiditis and the occurrence of multifocality in cases of PTC. However, we found statistical significance between multifocality, glandular mass and the age of the patients in the study.

Conflict of Interests

The authors have no conflict of interests to declare.

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