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Hashimoto's Thyroiditis and Nodular Pathology: A Prospective Study in 227 Subjects

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Abstract

The association between Hashimoto's Thyroiditis (HT) and Papillary Thyroid Carcinoma (PTC) remains controversial. The aim of this prospective study is to determine if there is a risk to develop a thyroid carcinoma in subjects affected by nodular pathology and HT.

Methods: 227 subjects (192 females and 35 males) affected by thyroid nodular pathology were submitted to FNAB (Fine Needle Agobiopsy) to define the cytology of the nodules. TSH, and serum anti-thyroid antibodies were measured.

If they had positive serum anti-thyroglobulin (Ab anti-TG) and/or anti-thyroperoxidase (Ab anti-TPO) antibodies and had a TSH <4 uUml were included in the study and they were defined as patient affected by autoimmune thyroiditis (HT) in euthyroidism. No patients assumed substitutive therapy with l-thyroxine. All patients gave their informed consent to the study.

The patients were classified in 2 groups: Group A: 103 patients (mean age 55.2 ± 13.2 years, 91.3% females, 8.7% males) affected by HT and Group B: 124 patients (mean age 59.3 ± 13.3 years, 79% females and 21% males) without thyroiditis.

Results: The nodular pathology is more represented, as attended, in females (91,3% vs. 8,7% in Group A and 79% vs. 21% in Group B). TSH levels were different between Group A and Group B (2.9 vs. 1.5 μUI/ml, p<0.001) but they were similar in patients with or without thyroid carcinoma (3.1 vs. 2.3, p=0.3). The benign pathology was diagnosed in the 94.2% in the Group A and in the 96% in the Group B whereas the malignant nodular pathology was present in the 5.8% in the group A and in the 4% in the Group B without any significant statistical difference.

Conclusion: Our study suggests that the associationof HT and nodular pathology do not represent a risk to develop a thyroid carcinoma.

Keywords: Hashimoto's thyroiditis; Pathology; Papillary thyroid carcinoma

Introduction

The association between Hashimoto's Thyroiditis (HT) and Papillary Thyroid Carcinoma (PTC) remains controversial in medical bibliography. Both HT and PTC share some epidemiological and molecular features. In fact, thyroid lymphocytic inflammatory reaction has been observed in association with PTC at variable frequency, although the precise relationship between the two diseases is still debated.

The mitogen-activated protein kinase (MAPK) signaling pathway is a foremost event in the carcinogenesis of the PTC. Affected elements include RET/PTC rearrangements and point mutations of the *RAS* and *BRAF* genes. Mutations in these genes are found in over 70% of PTC [1]. Several authors have found RET/PTC rearrangements in non-neoplastic thyroid lesions, such as HT [2-4]. In addition, Muzza et al. [5] found RET/PTC1 being more represented in PTCs associated with autoimmunity than in PTC without autoimmunity, suggesting that the association between RET/PTC1 and thyroiditis points to a critical role of this oncoprotein in the modulation of the autoimmune response [5]. However, different mechanisms could also explain the association between HT and RET/PTC rearrangement. Chronic inflammation might facilitate the rearrangement: the production of free radicals, cytokine secretion, cellular proliferation, and other phenomena correlated with inflammation might predispose to the rearrangement in follicular cells [6].

A series of reports indicate a close association between the presence of antithyroid antibodies and malignancy [7,8] even if this result is not confirmed in other reports [9,10] and recently a study confirmed the risk to develop thyroid cancer in patients affected by HT [11].

It remains a matter of debate whether the association with a HT or even an autoimmune disorder could affect the prognosis of PTC [12]. In fact, a worse prognosis was reported in a few series [13], whereas most of the studies showed either a protective effect of thyroid autoimmunity [14-16] or a similar behavior between cancer with and without associated thyroiditis [5].

The favorable clinical outcome in PTC patients with concurrent autoimmunity strongly suggests that a thyroid autoimmune response may enhance or even provide an antitumor attack.

Some but not all reports, particularly those of a retrospective nature, have noted an increased risk of carcinoma in thyroid nodules in

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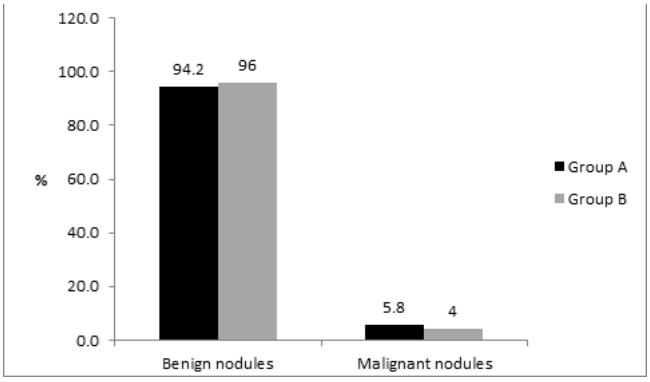

Figure 1: Histological diagnosis of the 227 patients submitted to FNAB (Group A 94, 2% versus Group B 96% benign pathology, Group A 5, 8% versus Group B 4% malignant pathology) No statistical difference.

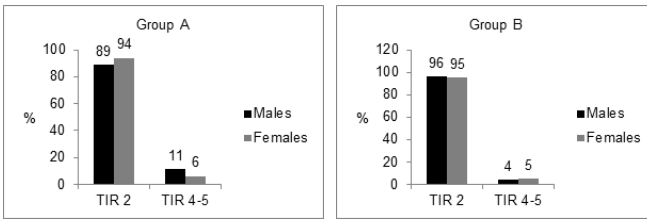

Figure 2: Comparison between males and females with malignant and benign pathology in the the Group A and in the Group B.

	Group A (103 patients with thyroiditis)	**Group B** (124 patients without thyroiditis)	**P**
Age (years)	55.2±13.1	59.3±13.3	<0.005
Sex (%)			<0.005
Female	91.3	79	
Male	8.7	21	
TSH (uU/ml)	2.9	1.4	<0.005
Tir 2	97	119	
Tir 4	2	2	
Tir 5	4	3	

(Significative p<0.05)

Table 1: Clinical characteristics of the 227 patients affected by nodular pathology.

patients with HT [16-23].

Material and Methods

In this study, we included patients at their first observation in our Outpatients Clinic of Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases of the University of Bari Aldo Moro who underwent FNAB of cold thyroid nodules.

All patients with thyroid nodules >1 cm had undergone a diagnostic cytological examination. FNAB results were differentiated in five categories: nondiagnostic, malignant, indeterminate or suspicious, and benign (patients with nondiagnostic, cystic or indeterminate cytology were excluded), TSH, and serum anti-thyroid antibodies were measured. If they had positive serum anti-thyroglobulin (Ab anti-TG) and/or anti-thyroperoxidase (Ab anti-TPO) antibodies and had a TSH <4 uUml were included in the study and they were defined as patient affected by autoimmune thyroiditis (HT) in euthyroidism. No patients assumed substitutive therapy with l-thyroxine. All patients gave their informed consent to the study.

227 subjects (192 females and 35 males) were included: the patients were classified in 2 groups:

Group A: 103 patients (mean age 55,2 ± 13.2 years, 91.3% females, 8.7% males) affected by HT and

Group B: 124 patients (mean age 59.3 ± 13.3 years, 79% females and 21% males) without thyroiditis (Figure 1).

Serum TSH was measured by a sensitive IRMA (Delphia Pharmacia, Turku, Finland - normal values - 0.4 -3.4 μU/ml). TgAbs and TPOAbs were measured by an Automated Immunoassay Assay (AIA) system (AIA-Pack TgAb, and TPOAb, Tosoh, Tokyo, Japan), and are expressed in U/ml. Normal values were <30 U/ml for TgAb and <10 U/ml for TPOAb.

FNAB was performed under echo guidance using a 23-gauge needle attached to a 10-ml syringe. The material was air-dried, stained with Papanicolaou and Giemsa and was interpreted by an experienced cytologist. The adequacy of aspirates was defined according to the guidelines of The Papanicolaou Society of Cytopathology Task Force on Standards of Practice (1996) [24], and the cytological results were classified according to the guideline of the British Thyroid Association [25].

Statistical Analysis

X2, test exact of Fisher and ANOVA one way test were used. The statistical significance was defined as $p \leq 0.05$.

Results

As expected TSH was significantly higher in patients of Group A (2.9 vs. 1.5 μUI/ml, p<0.001 Table 1) Moreover the patients of Group A were younger of patients of Group B: 55.2 ± 13 years, vs. 59.3 ± 13,3 years.

In both groups the thyroiditis is more frequent in the females 91,3% versus 8,7% in the group A e 79% versus 21% di in the group B. The Figure 1 shows that the nodular cytological benign pathology is 94.2% in the Group A e 96% in the Group B, whereas the malignant pathology is 5.8% in the group A and 4% in the group B without any statistical significant difference. Only the patients with a malignant cytological diagnosis were submitted to thyroidectomy and the all were affected by a thyroid papillary carcinoma. If we compare (Figure 2) the males and the females for malignant pathology we are not able to demonstrate any statistical difference.

On the basis of cytopathological an histopatological criteria, thyroid nodules in patients with HT are no more likely to be malignant than in those without HT.

Conclusions

We demonstrated in this prospective study that the rate of malignancy, at least as ascertained by FNAB, was similar in thyroid nodule of patients with HT (5.8.0%) and without HT (2.7%). We know that the limit of this results is that only patients with suspected or malignant cytological results are submitted to thyroidectomy , but certainly, it is likely that those that were missed were less clinically

relevant that the ones that had submitted to FNAB. Nevertheless we have to keep in mind that there is a percentage of malignant tumours [26] in surgically treated patients for benign pathology, although generally they are micro carcinomas.

The linkage between HT, thyroid nodules and thyroid malignancy was first proposed by Dailey [27]. However this topic remains a highly debated and controversial issue. The differences among the studies can be largely attributed to the retrospective analysis of surgical series and the type of study design. The recently revised American Thyroid Association guidelines [28] have reported that the rate of malignancy in nodules of thyroid glands with HT is possibly higher. However it is noteworthy that most of the series that reported increased risk were focused after surgery.

Prospective studies of this nature are few and they lack of the control group. Our prospective study is in line with that of Anil [29] who showed the same results in a study methodologically similar to our study.

In retrospective studies, the prevalence are in favour of a major rate of malignancy in patients having HT [18-22]. The explanation of this result could be attributed to the fact that all patients were surgically treated, however few studies showed no differences between patients with HT and no HT [9,23,30].

In summary, we found in this prospective study that the rate of malignancy in thyroid nodules is similar in patients with or without HT.

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