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Original Research Article

Analyzing the relationship between differentiated thyroid cancer and thyroid autoimmunity: an exploratory study from tertiary care center in South India

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ABSTRACT

Background: Differentiated thyroid cancer (DTC) is the most common endocrine malignancy. There is a rising incidence of DTC over the past few decades. This dramatic increase in incidence may be due to increased detection rate or because of factors like thyroid stimulating hormone (TSH) or thyroid autoantibodies which remains unclear. Our study aims to analyze the association between DTC and thyroid autoimmunity.
Methods: This was a retrospective study over 1 year conducted at the department of endocrine surgery, Madras medical college, a tertiary care center in South India. During the study period, 364 total thyroidectomies were performed which includes 292 benign and 72 malignant cases. Among malignancies, 15 non-DTC cases were excluded from the study. Finally, we included 57 patients with DTC and 114 patients with benign disease (randomly chosen age and sex-matched controls) for analysis. Demographic data, TSH levels, antithyroglobulin (anti-TG), and anti-thyroid peroxidase (anti-TPO) antibody levels, histopathology were recorded and analyzed.
Results: Histopathological examination revealed 47.4% of DTC and 63.2% of benign cases has associated thyroiditis. In our study elevated anti-TPO and anti-TG antibodies were not significantly associated with DTC (anti-TPO positivity 75.4% in DTC group vs. 74.6% in benign group, p=0.90, anti-TG antibody positivity 66.7% in DTC vs. 67.5% in benign group, p=0.90). Also, no significant association established between elevated TSH and DTC.
Conclusions: Association between thyroid autoantibodies and DTC has been evaluated in several studies with inconsistent results. The present study did not show any significant associations between elevated thyroid autoantibodies, TSH levels, and DTC.

Keywords: Anti-thyroglobulin, Thyroid peroxidase, TSH, Thyroid cancer, Thyroiditis

INTRODUCTION

Differentiated thyroid cancers (DTC) are the most common thyroid malignancy. There has been a rising incidence of DTC reported over the last few years. A high prevalence of thyroiditis in patients with DTC has also been reported in various pathological studies.[1-3] Hashimoto's thyroiditis (HT), characterized by destruction of thyroid follicles by T-lymphocytes and fibrosis of the gland, results in a hypothyroid state with elevated thyroid stimulating hormone (TSH) levels. It has been hypothesized that the high antibody titers in HT and higher TSH levels secondary to hypothyroidism are the key factors in the development of DTC in patients with thyroiditis.[4] This association between HT and DTC was first proposed by Dailey et al.[1] Since then there have been several studies published on this association but with inconsistent results.[2,3,5] Our region being an iodine

sufficient zone together with the high prevalence of HT, inspired us to study and evaluate this association between elevated thyroid autoantibodies, higher TSH levels, and DTC.

METHODS

Ours is a retrospective study conducted at the Endocrine surgery department, Madras medical college for 1 year from 2017 to 2018. During the study period, 364 total thyroidectomies were performed. Based on the histopathology report; patients diagnosed with either DTC or benign thyroid disease were both included in the study. The patient's demographic data, TSH levels, anti-thyroglobulin (anti-TG), and anti-thyroid peroxidase (anti-TPO) antibody levels, histopathology reports were obtained from the medical records department. Serum TSH and thyroid autoantibodies levels were measured by the automated enzyme-linked fluorescent assay. Biomerieux mini-Vidas hormonal analyzer was used to measure the hormone levels using the manufacturer's reagents and calibrators. The normal reference range of serum TSH in our laboratory is between 0.35 and 5.5 mIU/L. The TSH levels were further subdivided into 4 categories (<0.35, 0.35 to 2.5, 2.5 to 5.5, >5.5) for analysis. The reference ranges for anti-TPO and anti-TG antibodies were less than 2 and 7 IU/ml respectively. The data were analyzed using IBM.SPSS statistics software 23.0 version. To describe the data, percentage analysis was used for categorical variables and the mean and S.D was used for continuous variables. For the significance of association, the Chi-Square test and Fisher's Exact test were used. The probability value of 0.05 was taken as a significant level.

RESULTS

Among 364 total thyroidectomies, there were 292 benign and 72 malignant thyroid cases. In the malignancy group, there were 15 non-DTC cases (2 medullary thyroid cancers, 6 anaplastic, and 7 poorly differentiated carcinomas) which were excluded from the study. For each patient diagnosed with DTC, randomly chosen two benign age and sex-matched controls were included for analysis. The final study population included 57 patients with DTC and 114 benign thyroid cases.

Majority of the patients were females (94.7%) and most of them were in the age group of 22 to 55 years. With regards to patients with malignancy, 31.6% had elevated TSH levels (>5.5), 66.7% had elevated anti-TG antibody levels and 75.4% had elevated anti-TPO antibody levels. In the control group, 28.1% had elevated TSH levels (>5.5), 66.5% had elevated anti-TG antibody levels and 75.6% had elevated anti-TPO antibody levels. Histopathological examination revealed that 47.4% of patients diagnosed with DTC and 63.2% of benign thyroid cases had associated thyroiditis.

We found no significant association between DTC, elevated anti-TPO and anti-TG antibody levels (p=0.90) in our patients. Despite higher TSH levels in our patients with DTC than in the benign group, no significant association could be established between the TSH levels and DTC (p=0.9). The results were illustrated in Table 1.

Table 1: Comparison of preoperative serum TSH and thyroid autoantibody values, between benign versus malignant thyroid disease.

		Malignant	Benign	P value
		N (%)	N (%)	
TSH	<0.35	12 (21.1)	27 (23.7)	0.90
	0.35 to 2.5	12 (21.1)	28 (24.6)	
	2.5 to 5.5	15 (26.3)	27 (23.7)	
	>5.5	18 (31.6)	32 (28.1)	
Elevated anti-TPO Ab		43 (75.4)	85 (74.6)	0.901
Elevated anti-Tg Ab		38 (66.7)	77 (67.5)	0.908

Table 2: Clinicopathological characteristics of patients with DTC.

		DTC with HT (n=27)	DTC without HT (n=30)
		N (%)	N (%)
Tumor variant	Classical	25 (92.6)	24 (80)
	FVPTC	2 (7.4)	2 (6.7)
	Tall cell	-	4 (13.3)
Extra thyroidal extension		1 (3.7)	7 (23.3)
Multifocality		2 (7.4)	18 (60)
Lymph node metastasis		1 (3.7)	11 (36.7)
Distant metastasis		-	3 (10)
Recurrence rate		-	2 (6.7)

DISCUSSION

The most common thyroid malignancy is DTC which accounts for 80% of all thyroid cancers.[6] The overall prevalence of thyroid malignancy in our study population was 19.8% of which 79% of the patients had DTC. Several risk factors for DTC exists such as male gender, younger age, history of radiation and family history of thyroid cancer. Since the implementation of universal salt iodization, certain areas have become iodine excess zone leading to thyroid autoimmunity. Whether this factor could be attributed to the rising incidence of DTC remains unclear.

HT is characterized by lymphocytic infiltration of the thyroid gland and production of thyroid-specific antibodies due to the humoral immune response. The prevalence of coexisting of HT and DTC in thyroidectomy specimen ranges between 9.4 to 36%.[7-9] In

our study, 47.4% of patients with DTC had associated HT. The mechanism behind this association is poorly understood. It may be due to the tumorigenic effect of the anti-Tg antibody or due to inflammatory response secondary to HT. The association between elevated thyroid autoantibodies with DTC has been demonstrated in several studies.[5,10,11]

In contrary to this positive association, several other studies suggested that HT plays a protective role against the progression of DTC.[12-15] The more specific marker for HT is the anti-TPO antibody which protects against thyroid tumorigenesis.[10] Souza et al reported that thyroid autoantibodies have a protective effect for DTC.[16] In our study, we found that patients with elevated thyroid autoantibodies were not significantly associated with DTC. Similar to our study, Smooke-Praw et al also reported that anti-Tg antibody levels do not predict disease status in DTC.[17]

TSH is required for the normal growth of thyrocytes and physiological function of the thyroid gland. It is being postulated that chronic TSH stimulation of the thyroid follicles leads to increased growth and an increased propensity for malignant transformation. Based on this principle, TSH suppressive therapy is being employed in patients with DTC following thyroidectomy.

Boelaert et al first reported a significant increase in malignancy risk and serum TSH levels in his prospective study of 1183 patients.[4] Since then, several authors have demonstrated a positive association between higher TSH levels and risk of DTC. But in our study, we did not observe any statistically significant association between higher TSH levels and risk of DTC despite the higher TSH levels in our malignancy group (31.6%). Similar to our study, Kim et al and Castro et al found no significant association between higher TSH level and DTC.[2,18]

We also found that the tumor characteristics and prognosis among the patients in DTC and HT were less aggressive than those without HT (Table 2). All patients with PTC and HT in our study population were low grade, classical PTC and none of them had distant metastasis or tumor recurrence. This milder behavior of the disease could be due to the protective effect of thyroid autoantibodies. Certain genetic mutations like BRAF V600E which have been associated with aggressive variants of papillary thyroid cancer (PTC) are seen less frequently encountered in patients diagnosed as having both DTC and HT.[16,19] We did not perform any genetic testing in our patients because of limited resources in our center.

The high rate of HT in patients with DTC in our study may be due to the high prevalence of HT in our population. The limitation of this study is that this is a retrospective study and could be subjected to selection bias. A prospective study with a large sample size is further needed to evaluate this association and to come to a definite conclusion.

CONCLUSION

Association between thyroid autoantibodies and DTC has been evaluated in several studies with inconsistent results. The present study did not show any significant associations between elevated thyroid autoantibodies, TSH levels, and DTC. Based on our results, elevated thyroid autoantibodies and higher TSH cannot be taken as a surrogate marker for the development of DTC.

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