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Is Chronic Lymphocytic Thyroiditis Associated with Aggressive Differentiated Thyroid Cancer in a Predominantly Hispanic Pediatric Population?

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Abstract

Background: The risk of developing Papillary Thyroid Carcinoma (PTC) appears to be increased among patients with Chronic Lymphocytic Thyroiditis (CLT). Studies in adults have shown that the presence of CLT is associated with less aggressive PTC; however, this correlation is unclear in pediatric patients.

Objective: The purpose of this study is to determine the correlation between CLT and markers of aggressive behavior, using histopathological findings, tumor size, lymph node involvement, and molecular analysis, among patients with Differentiated Thyroid Carcinoma (DTC) in a predominantly Hispanic population.

Methods: After obtaining Institutional Review Board approval, we performed a retrospective chart review from 2012-2022 of 55 patients with a final diagnosis of DTC. We analyzed markers of aggressive behavior in patients with and without CLT. Statistical analysis was performed using t-tests and chi-squared tests.

Results: Patients' age ranged between 8 and 20 years. Forty-nine (89.1%) patients identified as Hispanic, and 41 (74.6%) were female. Twenty-five (45.5%) patients had a diagnosis of CLT; 19 (76%) of these patients had classic PTC, 3 (12%) had the follicular variant of PTC, and 3 (12%) had another variant of PTC. Patients with CLT had significantly smaller tumor size (1.8 vs. 2.5 cm) (p=0.048). Of the 36 patients with lymph node involvement, 20 (55.6%) had CLT. Of the 19 patients without lymph node involvement, 5 (26.3%) had CLT. The association between the presence of CLT and lymph node involvement was significant (p=0.038). BRAF-V600E and RET-PTC mutations were significantly more common in patients with CLT compared to those without it.

Conclusions: Our study, conducted within a predominantly Hispanic population, identified that patients with CLT had a significantly higher prevalence of the classic variant of PTC, a higher frequency of lymph node involvement and molecular findings indicative of more aggressive behavior. Of note, these patients had a smaller tumor size, likely due to earlier detection of thyroid nodule via frequent clinical evaluations. More studies with the pediatric populations are needed to clarify the different behavior of DTC among patients with and without CLT.

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Keywords: Chronic lymphocytic Thyroiditis, Differentiated thyroid carcinoma, Hispanic population

Introduction

Thyroid cancer is the second most common cancer among patients aged 15-19 years with a 5 and 10-year survival rate of 98% [1]. Over the past four decades, a significant increase in the diagnosis of differentiated thyroid carcinoma has been observed. Although some authors consider this finding secondary to the widespread use of imaging studies involving the neck, population-based studies have found an increased trend for larger tumors, determining that the increased incidence is real [2].

CLT is an autoimmune condition with prevalence in the pediatric population of 1-2%. It is more common among females, Caucasians, and in areas of iodine deficiency [3]. CLT is the most common cause of hypothyroidism in the pediatric population of western countries. This condition is often diagnosed when thyroid enlargement is noted. The diagnosis is confirmed by the presence of thyroid peroxidase and/or thyroglobulin antibodies. Although it is not recommended to order thyroid ultrasounds for patients with Chronic Lymphocytic Thyroiditis (CLT) unless a nodule is palpated, there is asymmetry of the thyroid gland, or the thyroid gland is significantly large [3], these studies are frequently ordered when patients have a mild abnormality on the thyroid function tests. Often, small nodules that otherwise would not have been detected are being found, and thyroid nodules in the pediatric population are more likely to be malignant than among adults. The easy access to imaging studies, including thyroid ultrasounds, is considered one of the reasons why thyroid cancer has been more frequently diagnosed, especially among children, over the past decades.

The association of differentiated thyroid carcinoma and CLT has been reported. A recent meta-analysis involving 76,281 patients, of which 12,476 had thyroid cancer, reported an overall odds ratio (OR) of 2.12 (95% confidence interval [CI]: 1.78-2.52) for PTC in patients with CLT [4].

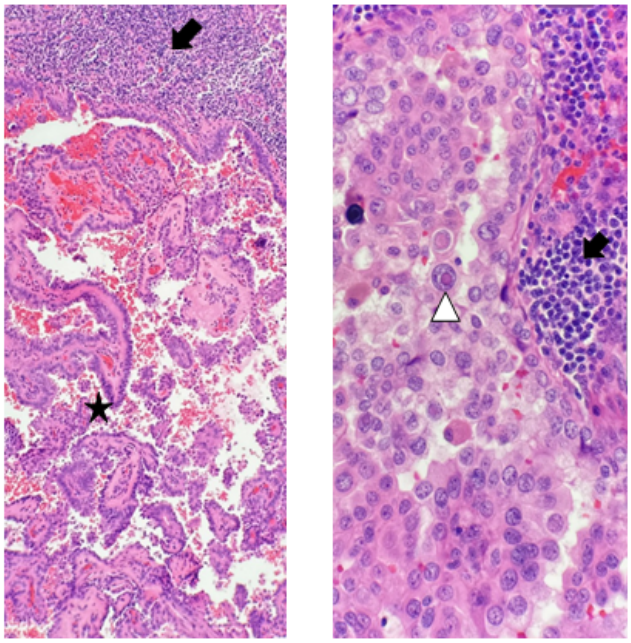

Figure1: Papillary Thyroid Carcinoma (PTC) arising in the setting of chronic lymphocytic thyroiditis. Low power magnification demonstrating the papillae ⬋ and the lymphoid infiltrate ★ (a). Higher magnification demonstrating pseudonuclear inclusions of the PTC △ (b).

Mutation	CLT	Without CLT	Aggressiveness
BRAF-V600E	10	3	High
RET-PTC	4	3	High
PAX8-PPARG		1	Low
RAS		1	Low
PTEN		1	Low
EML4-ALK		1	High
RET-TRIM 27		1	High
TSHr		1	High

Table1: Molecular findings and aggressiveness in patients with and without CLT.

The goal of this study was to determine the correlation between CLT and markers of aggressive behavior, using histopathological findings, tumor size, lymph node involvement, and molecular analysis, among patients with Differentiated Thyroid Carcinoma (DTC) in a predominantly Hispanic population.

Methods

After obtaining Institutional Review Board approval, we performed a retrospective chart review from 2012-2022 of 55 patients with a final diagnosis of DTC. Demographic information included age, sex, and ethnicity. Primary outcome was to determine the correlation between CLT and markers of aggressive behavior in patients with DTC. Diagnosis of CLT was established by the presence of TPO and Thyroglobulin antibodies or findings in pathology consistent with CLT. Markers of aggressiveness included histopathological categories, tumor size, invasion, distant metastasis, and molecular markers when available. Statistical analysis was performed using t-tests and chi-squared tests.

Results

A total of 55 patients aged 8 to 20 years were included in our study. Forty-nine (89.1%) patients identified as Hispanic, and 41 (74.6%) were female. Twenty-five (45.5%) patients had a diagnosis of CLT; 19 (76%) of these patients had pathological findings classic of PTC (Figure 1), 3 (12%) had the follicular variant of PTC, and 3 (12%) had another variant of PTC. Of the 30 (54%) patients who did not have CLT, 13 (43.3%) had findings classic of PTC, 10 (33.3%) had the follicular variant of PTC, and 7 (23.3%) had another variant of PTC. The distribution of the histopathological findings was significant (p=0.048). This finding aligns with adult studies suggesting increased aggressiveness of these lesions when compared to the follicular variant.

Patients with CLT had a significantly smaller tumor size (1.8 *vs.* 2.5 cm) (p=0.048). Of the 36 patients with lymph node involvement, 20 (55.6%) had CLT. Of the 19 patients without lymph node involvement, 5 (26.3%) had CLT. The association between the presence of CLT and lymph node involvement was significant (p=0.038).

Molecular analysis was available in 26 patients, fourteen of which had CLT. Ten harbored BRAF-V600E rearrangements and 4 RET-PTC mutations, both associated with a higher level of aggressive thyroid cancer. In contrast, the 12 patients without CLT displayed a more diverse mutational landscape with 6 mutations associated with high aggressive behavior and 3 with low (Table 1).

Discussion

Thyroid cancer is one of the most common cancers, with approximately 1.2% of people in the USA being diagnosed with this condition during their lifespan [5]. CLT, the most common autoimmune condition, increases the risk of developing DTC [4]. In our analysis of predominantly Hispanic patients diagnosed with differentiated thyroid cancer (DTC), we observed an association between chronic lymphocytic thyroiditis (CLT) and more aggressive cancer behavior, as evidenced by lymph node involvement, pathological features, and molecular mutations. While previous studies have linked CLT in adults to less aggressive papillary thyroid cancer (PTC), our findings suggest a different trend in our patient cohort.

The findings of this study contribute to the growing body of literature on the association between Chronic Lymphocytic Thyroiditis (CLT) and differentiated thyroid cancer (DTC) in a pediatric population. Our observation that 45.5% of patients with DTC also had CLT aligns with the reported range in the literature for pediatric patients, where the frequency of CLT in those with PTC ranged from 6.3% to 44% [6-11].

Given the limited size of our patient cohort, definitive conclusions cannot be drawn; however, our observations suggest a potential divergence in the behavior of DTC between patients with and without CLT. Notably, we observed a tendency towards smaller tumor sizes among patients with DTC, a trend likely attributed to the routine ordering of thyroid ultrasounds in this population, despite such practice not being universally recommended [3].

The literature reflects a complex relationship between HT and DTC, particularly in children. Unlike most adult studies that suggest a protective role of HT against DTC aggressiveness [12,13], pediatric studies, including ours, paint a less clear picture. Previous studies reported more aggressive features of DTC in pediatric patients with HT, such as increased thyroid parenchyma infiltration, familial PTC associations, and links between thyroglobulin autoantibodies and lymph node metastases [9,14]. These findings resonate with our observation of increased aggressiveness based on lymph node involvement and molecular markers in CLT patients. One biological rationale for our observed increased aggressiveness, as proposed in Kamma H, et al.'s study [15], links heightened lymphocytic infiltration in CLT patients with cancer aggressiveness, as increased infiltration correlated with carcinoma extension. In our cohort, despite smaller nodules in CLT patients, the observed aggressive behavior suggests that other factors, possibly genetic or immunological [16], significantly influence disease progression.

Specifically, among patients with CLT, we identified two molecular markers—BRAF-600E and RET-PTC fusion—both recognized for their association with higher-risk cancer profiles. Conversely, patients without CLT exhibited a broader spectrum of molecular findings, including BRAF-600E, RET-PTC mutations, and six other molecular alterations (Table 1).

We reviewed the mutations found in our group of patients and searched the literature to determine the association with aggressive behavior. BRAF V600E and RET-PTC mutations have been associated with a more aggressive clinical course [17-19]. In addition, other reports of aggressive behavior of PTC were found in the literature with EML4-ALK [20,21], a putative gain-of-function mutation of TSHR L272V has been associated with aggressive clear cell follicular carcinoma [22], and the patient with a TSHR mutation in our group had a PTC with aggressive behavior. Distant metastasis to lung and recurrence was reported on a patient with TRIM27-RET fusion with histologic diagnosis of PTC with diffuse sclerosing variant [23].

Conversely, mutations associated with a less aggressive behavior include RAS mutations [18] and PAX8/PPARG rearrangements which behave more as follicular thyroid carcinoma (FTC) [24]. PTEN mutations are often found in patients with FTC. However, occasionally are reported in PTC. In pediatrics, differentiated thyroid carcinomas (DTC) with PTEN mutations have less aggressive behavior [25].

Conclusion

DTC appears to have more aggressive features among patients with CLT in our cohort of predominantly Hispanic patients. Though the tumor size was smaller among patients with CLT, their cancer has more aggressive behavior in terms of lymph node involvement, pathological features, and molecular findings. Studies with larger populations, preferably multicenter studies, are needed to clarify this finding. Although routine ultrasonography evaluation in adults with CLT is not recommended due to the chances of finding nodules and thyroid carcinoma that otherwise would not be life-threatening and would not justify treatment, in children, this may be different due to the long lifespan and uncertainty about the long-term progression of smaller thyroid nodules with cancer.

Our study has some limitations. Number of patients is relatively small, and a significant patient percentage did not have molecular analysis. We do not have long-term follow-up of these patients to determine their outcomes.

Founding Sources

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Conflicts of Interest

All authors of the manuscript declare no conflicts of interest.

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