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Morphological and immunohistochemical evaluation of interface lesions between chronic lymphocytic thyroiditis and papillary thyroid cancers

Pınar Celepli[1], İrem Bigat[2], Salih Celepli[3], Sema Hücümenoğlu[1]

[1]Ankara Training and Research Hospital, Department of Pathology, Ankara, Turkey
[2]TOBB University of Economics and Technology, Department of Biomedical Engineering, Ankara, Turkey
[3]Gülhane Training and Research Hospital, Department of General Surgery, Ankara, Turkey

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ABSTRACT

Objective: To evaluate the expression of papillary thyroid carcinoma-associated tumor markers in reactive and dysplastic changes showing papillary thyroid carcinoma-like nuclear features in chronic lymphocytic thyroiditis cases.

Material and Method: In this study, we retrospectively analyzed 84 cases diagnosed with chronic lymphocytic thyroiditis based on the analysis of thyroidectomy specimens in our center over the last five years. We classified them as normal, reactive and dysplastic changes and performed an immunohistochemical analysis using HBME-1, Galectin-3, Cytokeratin 19, and Cyclin D1.

Results: The mean age of the patients was 45.5 years, and 68 were female and 16 were male. According to the morphological features, 42.9% of the were classified to have normal morphology, 44.0% reactive atypia, and 13.1% follicular epithelial dysplasia (FED). Of the chronic lymphocytic thyroiditis cases, 42.9% were associated with malignancy, with the most common accompanying malignancy being papillary thyroid cancer (36.9%). Immunohistochemically: for HBME-1, FED (72.7%) was higher ($p<0.05$) than normal and reactive atypia (0.0%); for Galectin-3, FED (63.6%) was higher ($p<0.05$) than normal and reactive atypia (0.0%); for Cytokeratin 19, Reactive atypia (75.7%) and FED (90.9%) were higher than normal (44.4%); and for Cyclin-D1, Reactive atypia (62.2%) and FED (81.8%) were higher than normal (33.3%).

Conclusions: We consider that reactive and dysplastic changes including papillary thyroid carcinoma-like nuclear changes may support preneoplastic changes in terms of morphology and immunoprofile in chronic lymphocytic thyroiditis cases.

Keywords: Thyroid cancer, follicular epithelial dysplasia, chronic lymphocytic thyroiditis

INTRODUCTION

Thyroid cancer is the most common type of endocrine cancer with the highest incidence and prevalence worldwide (1). The precursor lesions of thyroid neoplasms may originate from C cells or follicular cells. The role of C-cell hyperplasia as a precursor lesion of medullary thyroid carcinoma has been extensively explored. Despite the common of follicular epithelial cell-derived neoplasms, the precursor lesions of follicular epithelial cell origin were not elucidated until the Chernobyl nuclear power plant accident, and dysplastic or preneoplastic follicular lesions were not well defined (2).

The detection of precursor lesions is the most effective approach to improve the treatment of tumors and reduce their morbidity. The recognition of precursor lesions in the uterine cervix allows for the development of successful screening programs. Similarly, while progress has been made in other organs, including the breast, colon, and urinary tract, an important limitation remains in identifying precursor lesions in the thyroid. Dysplasia as an interface between normal histology and carcinoma in the thyroid gland is still a controversial issue (3).

Due to several epidemiological similarities between chronic lymphocytic thyroiditis and papillary thyroid carcinoma (PTC), it has been suggested that chronic lymphocytic thyroiditis is an endogenous carcinogen for thyroid cancer (4). In chronic lymphocytic thyroiditis, follicular epithelial cells may show histomorphologically nuclear features resembling PTC. The term follicular epithelial dysplasia (FED) was first used by Chui et

Corresponding Author: Pınar Celepli, pcelepli@yahoo.com
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al. (5), who defined it as a putative precursor lesion of papillary carcinoma in chronic lymphocytic thyroiditis. FED lesions are defined as atypical cell foci that differ from the surrounding parenchyma, are smaller than 1 mm, and have moderate cytological atypia and architectural distortion. Atypical cells consist of irregular membranes, mild to moderate nuclear enlargement and clearing, a groove, and crowded nuclei with chromatin margination. These lesions are distinguished from papillary microcarcinoma by their infiltrative growth pattern, absence of stromal desmoplasia and intranuclear pseudoinclusions, and the presence of surrounding intense lymphocytic inflammation (5).

In PTC, HBME-1, Cytokeratin 19, and Galectin-3 have been proven to be the most promising immune markers due to their high sensitivity and specificity (6,7). Cyclin D1, which is involved in the regulation of the cell cycle, has been reported to be overexpressed in PTC (8).

In this study, we evaluated the morphological and immunohistochemical features of FED with markers used in PTC in chronic lymphocytic thyroiditis samples diagnosed in our center over the last five years.

MATERIAL AND METHOD

The study was carried out with the permission of the Turkish Ministry of Health Ankara Training and Research Hospital Clinical Researches Ethics Committee (Date: 20.10.2021, Decision No: 769-2021). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 120 patients who underwent total thyroidectomy/lobectomy in our center and were diagnosed with chronic lymphocytic thyroiditis over the last five years were retrospectively analyzed. Thirty-six cases whose specimens could not be reached, whose immunostained sections were lost, or who had tissue shedding due to technical reasons were excluded from the study. In the remaining 84 cases, thyroid follicle epithelial cells in the inflammation areas consisting of lymphocytes in the thyroid parenchyma were evaluated morphologically.

The diagnosis of chronic lymphocytic thyroiditis was based on the presence of lymphoplasmacytic infiltration between thyroid follicles with or without a germinal center. Inflammation was evaluated as mild if the inflammation is focally in groups among the follicular, and intense if it is widespread in the parenchyma with prominent germinal centers.

The parenchyma was divided into 3 groups using the criteria described by Chui et al. and evaluating the structurally/cytological appearance; normal parenchyma, reactive atypia and FED (5).

Normal parenchyma (**Figure 1A**): Structurally and cytological preserved normal-appearing thyroid follicle epithelial cells adjacent to lymphocytic inflammation.

Reactive atypia (**Figure 1B**): Structurally; Follicles that do not contain papillary structures and vary slightly in size and shape. Cytological; Round slightly enlarged nuclei slight nuclear membrane. irregularity, rare grooves, nuclear clearing, and cells showing slight crowding/overlapping.

FED (**Figure 1C**): Structurally; Irregularly shaped follicles, trabecular, solid sockets without papillary structure. Cytological; Cells containing grooves, often showing nuclear clearing, nuclear membrane irregularity, and overlapping, slightly to moderately enlarged, lost nuclear roundness.

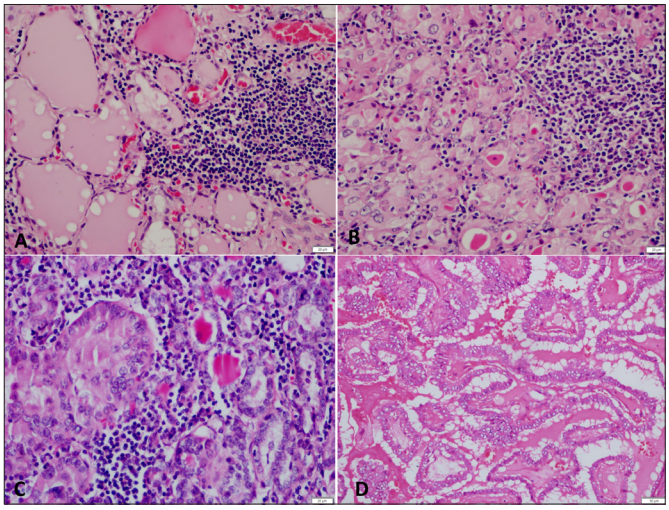

Figure 1. Morphological spectrum of atypical follicular epithelial lesions in chronic lymphocytic thyroiditis. (A) normal morphology (H&E, x40), (B) reactive atypia (H&E, x40), (C) follicular epithelial dysplasia (H&E, x40), (D) papillary thyroid carcinoma (H&E, x200).

Formalin-fixed, paraffin-embedded tissue sections of 4 micron were prepared using the Leica HRP conjugated compact polymer system detection dab kit (Leica DS9800, New Castle, UK) on the Leica bond max automated IHC/ISH system. HBME-1 (clone HBME1, Dako), Galectin-3 (clone 9c4, Leica), Cytokeratin 19 (clone b170, Leica), and Cyclin-D1 (clone EP12, Leica) were immunohistochemically applied.

The evaluation of immunostaining was performed by an independent pathologist blinded to the clinical and pathological data. The presence of cytoplasmic staining with Galectin-3, cytoplasmic/membranous staining with Cytokeratin 19, apical staining with HBME-1, and nuclear staining with Cyclin-D1 was evaluated. Staining intensity: 0; negative, 1; weak, 2; medium, 3; strong; as a percentage of staining, more than 10% was considered positive 5. Normal thyroid tissue was focally positive for Cyclin D1 and Cytokeratin 19, and negative for HBME-1 and Galectin-3.

Statistical Analysis

Data were analyzed using SPSS software package (version 22.0; SPSS, Inc., Chicago, IL, USA) and expressed as number, percentage and mean±standard deviation values as applicable. The Pearson chi-square analysis was performed to evaluate the relations between the groups. In cases where the expected value is less than 5 in more than 20% of the sections, the Fisher Exact Test was applied instead of Pearson Chi-Square. A p value of less than 0.05 was considered statistically significant.

RESULTS

The age of the patients with chronic lymphocytic thyroiditis ranged from 17 to 73 years, and the mean age was 45.4±13.16 years. 81 % (n=68) of the cases were female and 19% (16) were male. Seventy-six (90.5%) samples were total thyroidectomy and the remaining cases were lobectomy.

In chronic lymphocytic thyroiditis samples, relatively normal follicles were found in areas of mild inflammation, while atypia findings were observed in follicle epithelial cells adjacent to lymphoid aggregates. According to morphological features, 42.9% (n=36) of the patients were classified to have normal morphology, 44.0% (n=37) reactive atypia, and 13.1% (n=11) FED (**Figure 1**). No statistically significant difference was observed between the lesions and accompanying malignancy. (p=0.346). Two or more foci were detected in 32.2% of the cases with reactive atypia and 6.8% of those with FED. The size of the reactive atypia foci was 0.1mm-3.6 mm, and that of the FED foci was 0.1 mm-2.4 mm. The FED size did not significantly differ between the groups (p=0.367), and there was no statistical relationship between multifocality and concomitant neoplastic pathology (p=0.051).

The lesions observed adjacent to chronic lymphocytic thyroiditis and the accompanying benign and malignant lesions were compared. In cases of chronic lymphocytic thyroiditis, malignancy association was found at a rate of 42.85%, and the most common accompanying malignancy was PTC at a rate of 36.9%. A PTC association was present in 40.5% of the samples containing reactive atypia and 36.4% of those containing FED. PTC in reactive atypia; NIFTP and FTC in FED accompanied Chronic lymphocytic thyroiditis more than other groups (p<0.05) (**Table 1**). In a total of 31 cases, PTC was associated with chronic lymphocytic thyroiditis. The staining profiles of these cases with HBME-1, Galectin-3, Cytokeratin 19 and Cyclin D1 are summarized in **Table 2** and presented as an image in **Figure 2.**

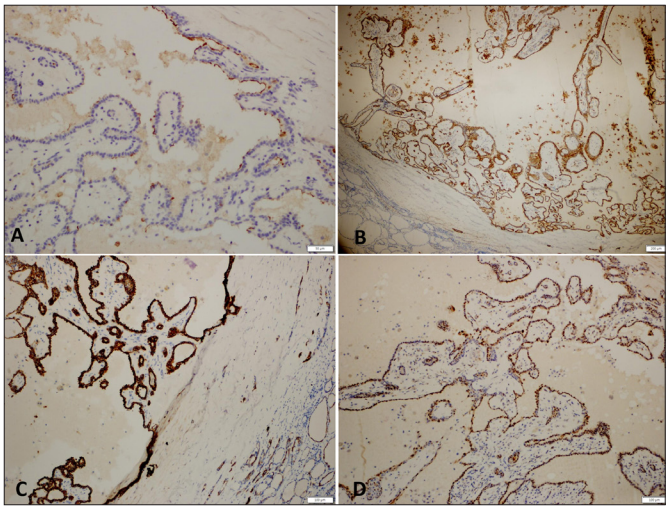

Figure 2. Papillary thyroid carcinoma. (A) HBME-1, x200 (B) Galectin-3, x40 (C) Cytokeratin 19, x100 (D) Cyclin D1, x100.

Table 1. Benign and malignant lesions accompanying chronic lymphocytic thyroiditis

Chronic lymphocytic thyroiditis (n=84)	Coexistence of benign and malignant lesions	Total, n (%)
Normal morphology, n=36		
	Benign lesions (FA/HCA/NH)	24 (66.7%)[a]
	NIFTP	0 (0%)[a]
	PTC	12 (33.3%)[a]
	FTC	0 (0%)[a]
Reactive atypia, n=37		
	Benign lesions (FA/HCA/NH)	19 (51.4%)[a]
	NIFTP	1 (2.7%)[a]
	PTC	15 (40.5%)[b]
	FTC	2 (5.4%)[a]
FED, n=11		
	Benign lesions (FA/HCA/NH)	4 (36.4%)[a]
	NIFTP	2 (18.2%)[b]
	PTC	4 (36.4%)[a]
	FTC	1 (9.1%)[b]

Each subscript letter denotes a subset of "Coexistence of benign and malignant lesions" categories whose column proportions do not differ significantly from each other at the ,05 level. FED: Follicular epithelial dysplasia. FA: Follicular adenoma. HCA: Hurthle cell adenoma. NH: Nodular hyperplasia NIFTP: non-invasive follicular thyroid neoplasm with papillary-like nuclear features. PTC: Papillary thyroid carcinoma. FTC: Follicular thyroid carcinoma.

Table 2. Results of the immunohistochemical analysis of papillary thyroid carcinomas

Immunostaining	Positive (n, % of evaluated cases)
HBME-1	25/31 (80.6%)
Galectin-3	24/31 (77.4%)
Cytokeratin 19	29/31 (93.5%)
Cyclin-D1	27/31 (87.1%)

We also analyzed Cytokeratin 19, galectin-3, HBME-1 and Cyclin D1 that are markers known to be associated with PTC and lesions observed in chronic lymphocytic thyroiditis. The Immunohistochemical profiles of chronic lymphocytic thyroiditis lesions are summarized in **Table 3**. A statistically significant difference was observed in HBME-1, Galectin-3, Cytokeratin 19 and Cyclin D1 according to the presence of FED (**Figure 3**). While there was medium (+2) staining with Galectin-3 in FED lesions, more intense (+3) staining was detected with HBME-1, Cytokeratin 19, and Cyclin D1. Mild staining with Cyclin D1 was observed in 62.2% of the reactive atypia lesions and moderate staining with Cytokeratin 19 in 75.7%. No staining with HBME-1 and Galectin-3 was detected in reactive atypia lesions (**Figure 4**). Mild staining with Cytokeratin 19 and Cyclin D1 was detected in thyroid follicle epithelial cells with normal morphology at a rate of 44.4% and 33.3%, respectively. No staining was observed with HBME-1 and Galectin-3.

In brief, FED foci observed in chronic lymphocytic thyroiditis tissues shared similar morphologies and immune phenotypes with PTC.

Table 3. Results of the immunohistochemical analysis of chronic lymphocytic thyroiditis

Lesion	HBME-1	Galectin-3	Cytokeratin 19	Cyclin-D1
Normal morphology, n=36	0/36 (0%)[a] 0	0/36 (0%)[a] 0	16/36 (44.4%)[a] +1 (15/16) +2 (1/16)	12/36 (33.3%)[a] +1 (12/12)
Reactive atypia, n=37	0/37 (0%)[a] 0	0/37 (0%)[a] 0	28/37 (75.7%)[b] +1 (4/37) +2 (24/37)	23/37 (62.2%)[b] +1 (19/23) +3 (4/23)
FED, n=11	8/11 (72,7%)[b] +2 (2/8) +3 (6/8)	7/11 (63.6%)[b] +1 (2/7) +2 (5/7)	10/11 (90.9%) [b] +2 (2/10) +3 (8/10)	9/11 (81.8%)[b] +2 (1/9) +3 (8/9)
p value	0.001	0.001	0.003	0.005

Each subscript letter denotes a subset of "Lesions" categories whose column proportions do not differ significantly from each other at the ,05 level. FED: Follicular epithelial dysplasia.

DISCUSSION

In 1863, German pathologist Rudolf Virchow suggested the presence of lymphocytes in neoplastic tissues and indicated a relationship between cancer and inflammation (9). Chronic inflammation is considered to contribute to approximately 25% of all malignancies (10). Although many epidemiological studies have reported that the risk of PTC is increased with chronic lymphocytic thyroiditis, the relationship between chronic lymphocytic thyroiditis and PTC is still debated due to many conflicting results (11,12). The epidemiological association of chronic lymphocytic thyroiditis and PTC has been reported with a frequency of up to 38% with no evidence (12,13). Consistent with the literature, in our study, up to 43% of the chronic lymphocytic thyroiditis cases were associated with malignancy, with the most common accompanying malignancy being determined as PTC at a rate of 36.9%. It has been suggested that due to the relative prevalence of both diseases, this may be an accidental association or chronic inflammation may lead to the development of neoplastic transformation (4,14). In addition, it is still controversial whether there is an immunological link between the two diseases based on their simultaneous developments. Uncertainties remain in the development of papillary carcinoma concerning the immune escape mechanism, target-specific immune response, or cross-reacting antitumor immunity (15). Recent gene expression experiments have also demonstrated a strong correlation between the expression of immune lymphocytic infiltrates in the thyroid and error-prone DNA repair (16). In the study of Kholova et al., the size of FED lesions ranged from 0.1 to 3.5 mm, and it was frequently found to be multifocal in 45.1% of the samples (17). In our study, the size of FED foci were in the range of 0.1-2.4mm, and 2 or more

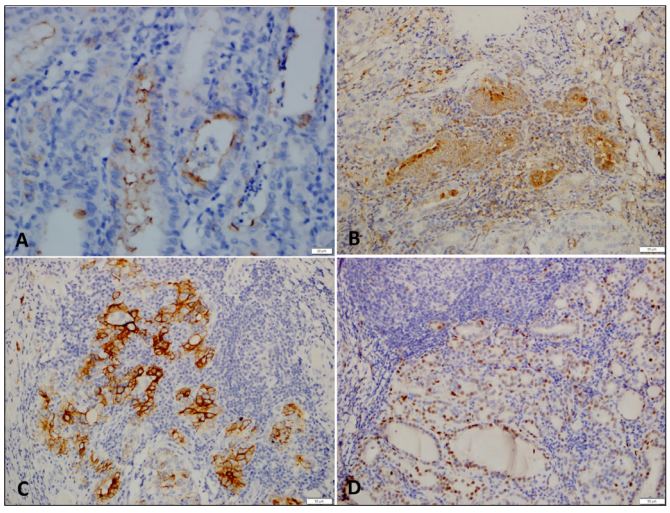

Figure 3. Follicular epithelial dysplasia. (A) HBME-1, x400 (B) Galectin-3, x200 (C) Cytokeratin 19, x200 (D) Cyclin D1, x200.

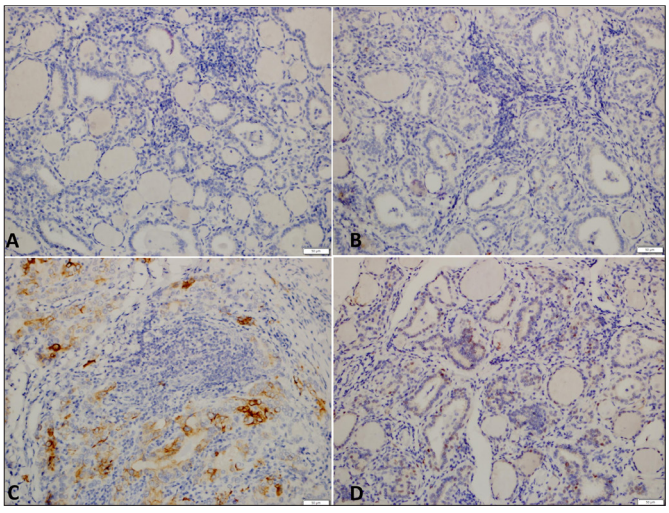

Figure 4. Reactive atypia. (A) HBME-1, x200 (B) Galectin-3, x200 (C) Cytokeratin 19, x200 (D) Cyclin D1, x200.

foci were detected in 6.8%. Although it was similar in size to the literature, a lower rate was observed in terms of multifocality. It may be due to the small number of FED lesions in the study group.

In chronic lymphocytic thyroiditis, atypia of the follicular epithelium, which has similar appearance to PTC nuclear features, is common, especially in areas of intense inflammation (18). Some authors have suggested that these atypical cells may represent the precursor lesion of PTC (5,19). Dysplasia and/or precursor lesions in the background of thyroiditis have been described as FED (5). FED lesions and PTC immunoprofile have also been found to be similar in various studies. Chui et al. (5) showed that these atypical proliferations exhibited an immunohistochemical profile similar to PTC with strong staining with HBME-1, galectin-3, CK19 and Cyclin D1 and supported the presence of a premalignant lesion. In another study, Ma et al. (20) revealed the increased expression of PTC-related markers, such as CK19, galectin-3, HBME-1, CD56, claudin 1, and NGAL in atypical follicular epithelial foci in Hashimoto's thyroiditis cases compared to peritumoral benign thyroid tissues. In a similar study, Prasad et al. (21) reported an increased expression of Galectin-3, fibronectin-1, CITED-1, HBME1 and cytokeratin-19 in follicle epithelial cells with papillary-like nuclei in chronic lymphocytic thyroiditis (21). Kholová et al. (17) found a high expression of Cyclin D1, Galectin-3, Cytokeratin 19 and HBME-1 in FED foci and noted the presence of a significant relationship between Cyclin D1 and FED accompanied by PTC.

In our study, there was more frequent staining with Cytokeratin 19 and Cyclin D1 in patients with reactive atypia and FED. In FED lesions, staining with HBME-1 and Galectin-3 was similar to the PTC cases. The staining pattern of the FED lesions was similar to PTC. Our findings support the idea that follicular epithelial cells with normal morphology and reactive atypia and FED lesions may represent a neoplastic spectrum during PTC development and, as previously suggested (5), FED may be a precancerous lesion in terms of morphology and immune profile.

Molecular and immunohistochemical studies to detect specific gene profiles and related proteins in thyroid cancer have been extensively reported in the literature. Nasr et al. (22) suggested that atypical cells found in Hashimoto's thyroiditis showed HBME1 and CK19 expressions but could not be considered preneoplastic because they did not harbor BRAF mutations.

The earliest molecular event in PTC is RET/ PTC gene rearrangement, which is a common finding in encapsulated papillary thyroid carcinoma, papillary thyroid microcarcinoma, and Hashimoto's thyroiditis. RET/PTC gene rearrangement is highly specific for PTC and associated with the characteristic nuclear features seen in this disease (23). However, low-level RET-PTC recombination has also been demonstrated in hyperplastic thyroid nodules (24,25). A study in the PTC series showed that RET/PTC rearrangement was more common in autoimmunity-associated PTC, whereas the BRAFV600E mutation was more common only in PTC. There was an overlap in the molecular profile of PTC and Hashimoto's thyroiditis, as well as similarities in morphological features and immunohistochemical staining patterns (26–28). One of the main limitations of the study is that the tissues are exposed to fixation and follow-up methods in different time periods due to their retrospective nature. Therefore, due to the small size of the lesions during the immunohistochemical examination, problems such as shedding of the tissue and disappearance in the section were experienced due to technical reasons. This has resulted in fewer cases. Another limitation is the lack of molecular data on patients. Papillary thyroid carcinoma is diagnosed definitively by detecting the BRAFV600E mutation combination, which is known to be associated with malignancy, together with morphological examination. It is also important to look for the BRAFV600E mutation for possible precursor lesions of PTC.

We consider that normal-reactive-dysplastic changes observed in patients with chronic lymphocytic thyroiditis may also support molecular changes in the PTC spectrum in terms of their morphology and immune profile.

CONCLUSION

The relationship between chronic lymphocytic thyroiditis and papillary thyroid carcinoma, and the concept of 'follicular epithelial dysplasia' as a possible precursor lesion are very controversial among researchers. Chronic inflammation can be a risk factor for the development of PTC. Due to the similarity of the morphological and immunohistochemical features of FED to PTC, the former can be considered as an interface or a precancerous lesion between chronic lymphocytic thyroiditis and PTC.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Turkish Ministry of Health Ankara Training and Research Hospital Clinical Researches Ethics Committee (Date: 20.10.2021, Decision No: 769-2021).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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