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Does the Association of Hashimoto's Thyroiditis with Differentiated Thyroid Cancer Really Have a Protective Role?

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ABSTRACT

The study is an investigation of aggressive tumor features, prognosis, and disease-specific mortality rates of differentiated thyroid cancer (DTC) in the presence of concomitant Hashimoto's Thyroiditis (HT). The data of patients with DTC followed in our tertiary care center between 2000–2022 were analyzed. Variables such as patient age, gender, preoperative serum autoantibody levels, tumor characteristics, and treatment modalities were obtained from medical records. The diagnosis of HT was based either on the presence of a positive result in the pathological examination and/or on antibody positivity. A total of 637 patients [mean ± SD age, 44.9 ± 13.5 years; 485 women [76.1 %)] were included in the analysis. The overall prevalence of coexistent HT was 22.9 % (n = 146). The disease-specific mortality associated with DTC was 2.9 %. DTC patients with HT compared to those without; have more positive lymphovascular invasion ($p < 0.001$), and lymph node metastases ($p < 0.001$). According to the Kaplan–Meier curves, disease-specific survival rates among DTC patients without HT were significantly higher than patients with HT (log-rank $p = 0.002$). The disease-specific mortality rate was 4.79 % in DTC patients with HT, it was 1.43 % in those without HT. Hashimoto thyroiditis was not associated with a 10-year recurrence-free survival ($p = 0.059$). Differentiated thyroid cancers with concomitant HT are associated with some aggressive tumor features (such as lymphovascular invasion and nodal metastasis) and lower survival. In staging systems based on tumor risk factors, it may be useful to evaluate the presence of concomitant HT as a prognostic factor.

Introduction

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy and is treated with total or near-total thyroidectomy, and if necessary followed by ablation of the remaining tissue with radioiodine (RAI) therapy [1]. Most DTCs are associated with an indolent disease course and have a favorable prognosis even after low-intensity therapy [1]. Therefore, the main clinical challenge is classifying patients according to the risk of mortality or relapse and determining the scope of treatment. According to our current accepted knowledge, several clinicopathological features are associated with an unfavorable prognosis, including advanced age, large primary tumor size, extrathyroidal extension, lymph node metastasis, and distant metastasis [1–3]. For this reason, patients with these risk factors require aggressive treatment, while low-intensity therapy may be sufficient for patients without these risk factors [1–4].

Hashimoto's Thyroiditis (HT) is the most common form of autoimmune thyroid disease [5]. Hashimoto's Thyroiditis may coexist with DTC, particularly the papillary histotype (PTC), but its relationship's effect is still controversial [6–9]. Previous literature argues that the prognosis of DTCs arising from the background of HT is better than other DTCs [10–14]. But, while some researchers reported conflicting results about the lack of positive prognostic effects of HT, they argued that it has negative effects on DTC prognosis, especially central lymph node metastases [15–18]. In addition, few results were found from the above-mentioned studies regarding the association of HT with DTC-related mortality.

This study aimed to evaluate the relationship presence of concomitant HT with the aggressive features of DTC at presentation, disease recurrence, and disease-related mortality.

Materials and Methods

This single-center, retrospective study was conducted in a tertiary care university hospital. The study was approved by the Research Ethics Committee of Istanbul University-Cerrahpaşa. The study fully adheres to the Declaration of Helsinki. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for observational studies. Patient data were coded and stored anonymously.

Subjects and procedure

All medical records of 855 thyroid cancer patients treated in Cerrahpaşa Faculty of Medicine, Department of Endocrinology between 2000–2022 were reviewed. Inclusion criteria were: (i) clear pathological diagnosis of differentiated thyroid cancer; (ii) thyroid autoantibody levels were measured perioperatively; (iii) non-cancerous areas of thyroidectomy material have been evaluated for chronic lymphocytic thyroiditis; (iv) be over 18 years of age; (v) patients with at least 12 months of regular follow-up. Exclusion criteria were; (i) patients with medullary thyroid cancer or other thyroid malignant neoplasms; (ii) a history of cancer other than thyroid; (iii) insufficient follow-up data (≤ 12 months since initial treatment).

Variables such as patient age, gender, preoperative serum autoantibody levels, tumor characteristics, and treatment modalities were obtained from medical records. The diagnosis of HT was based either on the presence of a positive result in the pathological examination and/or on thyroid antibody positivity. A positive pathology result was defined as diffuse lymphocytic and plasma cell infiltrate, oxyphilic cells, lymphoid follicle formation, and the presence of reactive germinal centers. The infiltrate must have been found in a normal region of the thyroid gland, distinct from the site of the DTC. A peritumoral inflammatory response was not considered to be evidence of HT. Measurements of serum antithyroglobulin and antithyroid peroxidase levels using the immuno-electrochemiluminescence method before or up to 30 days after surgery were accepted, and results were considered positive when these levels exceeded 115 IU/ml and 34 IU/ml, respectively.

Primary tumor size, extrathyroidal extension, tumor capsule invasion, thyroid capsule invasion, lymphovascular invasion, and nodal metastasis were defined by postoperative pathologic examination. Lymph node metastasis was considered to be absent if no lymph nodes were examined. Surgical procedures for primary tumors included lobectomy and total thyroidectomy; therapeutic neck dissection was performed in patients with standard indications. Standard pathologic diagnoses were based on World Health Organization criteria. Postoperative treatments included conventional thyrotropin suppression at appropriate levels and if necessary RAI ablation. Survival outcomes were determined by medical records in combination with telephone follow-up. Local and regional recurrences were defined as structural diseases as determined by either a cytologist or a pathologist. Distant metastasis was defined using computed tomography (CT) or emission-computed tomography (PET-CT). Whole-body scans (with or without SPECT/CT) were used for disease staging after ablation or treatment of remnant thyroid tissue with RAI. ^{18}F-FDG-PET scanning was generally used in high-risk DTC patients with negative RAI imaging but high serum thyroglobulin (usually > 10 ng/ml). Finally, all patients were staged according to the eighth edition of the American Joint Committee on Cancer (AJCC) preparation guide in terms of standardization of the pathological and clinical staging of the patients.

Differentiated thyroid cancer patients were divided into two groups according to the presence or absence of accompanying Hashimoto's thyroiditis. The two groups were compared in terms of analyzed variants, aggressive tumor characteristics, tumor recurrence, and disease-related mortality.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 21.0). Data were first analyzed for normality using the Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± standard deviation (SD) and/or medians (interquartile range [IQR]). Student's *t*-tests or analysis of variance (ANOVA) were used to compare means between groups with normal data distributions. Medians were compared using the Mann–Whitney U-test and the Kruskal–Wallis test. Spearman's rank order test and Pearson's correlation test were used to calculate the correlation coefficients between continuous variables. Frequencies were compared using Pearson's and Fisher's exact tests. Logistic regression was performed to assess the association between HT and aggressive characteristics at the presenta-

tion of DTC (primary tumor size ≥ 4 cm, extrathyroidal extension, nodal metastasis, thyroid capsule invasion, lymphovascular invasion, and distant metastasis) with and without adjustment for related factors. Kaplan–Meier survival curves, log-rank tests censoring patients at the last follow-up, and Cox proportional hazards regression analyses were used to compare DTC-related mortality by presence or absence of coexistent HT. Cox proportional hazards regression models were adjusted for age and sex, and a second model was used to additionally adjust for other known prognostic factors (primary tumor size, extrathyroidal extension, nodal metastasis, distant metastasis, extent of surgery, and RAI ablation). Adjusted survival curves were created based on multivariate models and focused on the presence of HT. The results were evaluated at a 95 % confidence interval, and a p-value < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 637 patients were included in the study. The mean age of the patients was 44.9 ± 13.5 years and 76.1 % (n = 485) of the patients were females. The overall prevalence of coexistent HT was 22.9 % (n = 146). Demographic, clinical, and pathological characteristics of DTC patients according to the presence or absence of concomitant HT are compared in ▶ **Table 1**. The frequency of follicular thyroid cancer was significantly lower in patients with DTC accompanied by HT (p = 0.042, ▶ **Table 1**). Preoperative thyroid ultrasound data of 146 patients with DTC accompanied by HT were analyzed. The number of patients with sonographic findings consistent with HT, such as hypoechogenicity, heterogeneity, and pseudonodular hypoechoic infiltration, was 88 (60.3 %). There was no finding suggestive of HT in the sonography report of 58 patients (39.7 %).

Association of HT with aggressive tumor features

Regression analysis showed that HT was positively associated with frequencies of nodal metastasis [odds ratio (OR), 1.92; 95 % CI, 1.089–3.396; p = 0.024], and lymphovascular invasion (OR, 2.12; 95 % CI, 1.046–4.287; p = 0.037). There was no association with primary tumor size of 4 cm or greater, thyroid capsule invasion, extrathyroidal extension, and distant metastasis (p > 0.05 for all, ▶ **Table 2**).

The study included 146 patients with DTC accompanied by HT. Of these, 106 patients had positive anti-TPO and anti-TG antibodies. Concomitant HT was detected in 40 patients according to the pathology preparations. In 24 of these patients, antibody levels were not measured or results could not be reached. There are 16 patients whose antibody was measured and found to be negative, but whose pathology was positive. When we compared 16 pathology-positive and antibody-negative patients with 106 antibody-positive patients, there was no difference between the two groups in terms of lymphovascular invasion, extrathyroidal spread, T stage, and M stage (p > 0.05 for all, **Supplementary Table**). Only the frequency of N1 disease was statistically significantly lower (p = 0.013) in the pathology-positive and antibody-negative patient group (n = 2, 12.5 %) compared to the antibody-positive patients (n = 25, 23.6 %, **Supplementary Table**).

Association between HT and DTC-related mortality

The median follow-up period for the whole cohort was 58 months (range, 12–466 months), and no significant difference in follow-up time was observed between patients with and without HT [median, 56 months (range, 12–400 months) vs. 59 months (range, 12–466 months); p = 0.059]. DTC-related mortality occurred in a total of 14 patients. The overall mortality rate associated with DTC was 2.1 %. While the DTC-related mortality rate was 4.79 % (n = 7) in DTC patients with HT, this rate was 1.43 % (n = 7) in DTC patients without HT. According to the Kaplan–Meier curves, unadjusted 10-year disease-specific survival rates among DTC patients without HT were significantly higher than those among DTC patients with HT (log-rank p = 0.002, ▶ **Fig. 1a**). According to Cox proportional hazards regression models, HT was associated with increased DTC-related mortality after adjusting for sex and age [hazard ratio (HR), 8.149; 95 % CI, 2.533–26.216; p < 0.001, ▶ **Fig. 1b** and after adjusting for sex, age, primary tumor size, extrathyroidal extension, nodal metastasis, distant metastasis, the extent of surgery, and RAI ablation (HR, 4.073; 95 % CI, 1.816–20.336; p = 0.047, ▶ **Fig. 1c**).

According to Kaplan–Meier curves, unadjusted 10-year disease-specific survival rates in antibody-negative and pathology-positive differentiated thyroid cancer patients were not significantly different from those in antibody-positive patients (log-rank p = 0.935, **Supplementary Figure**).

Association between HT and structural recurrence

Structural tumor recurrence was detected in a total of 8.95 % of patients during follow-up (n = 57). This rate was 8.90 % (n = 13) in DTC patients with HT, and 8.96 % (n = 44) in DTC patients without HT. In the presence of concomitant HT wasn't associated with 10-year recurrence-free survival (91.0 % vs. 91.1 %; log-rank p = 0.125, ▶ **Fig. 2a**); there was no association after adjusting for sex and age (HR, 1.856; 95 % CI, 0.978–3.522; p = 0.059, ▶ **Fig. 2b**).

Discussion

The prevalence of concomitant Hashimoto's thyroiditis (HT) in patients with differentiated thyroid cancer (DTC) was 22.9 %. In the presence of concomitant HT, DTCs were associated with more aggressive tumor features and lower survival. Lymphovascular invasion and lymph node metastasis were significantly higher in DTCs with HT. The overall mortality associated with DTC was 2.9 %. While this rate was 4.79 % in DTCs with HT, it was 1.43 % in DTCs without HT. On the other hand, we did not find a relationship between structural recurrence risk factors such as extrathyroidal extension and the frequency of structural recurrence in follow-up in DTCs with HT.

Previous studies have reported varying rates of the coexistence of DTC and HT. Kebebew et al. reported the frequency of accompanying chronic lymphocytic thyroiditis as 30 % in their study on 136 patients with papillary thyroid cancer. Anti-TG positivity was reported in 65 % of these patients. However, the HT ratio was not given in the general DTC [9]. Zhang et al. Found the prevalence of PTC to be 29.4 % in patients with HT who had undergone thyroid-

▶ **Table 1** Demographic, clinical, and pathological features according to the presence or absence of Hashimoto's thyroiditis (HT).

Characteristics	Patients (n = 637)		p-Value
	HT presents	HT absent	
	(n = 146, 22.9 %)	(n = 491, 77.1 %)	
Age (year), mean ± SD	44.18 ± 13.27	45.14 ± 13.58	0.973
Sex, Female, n (%)	122 (83.6)	363 (73.9)	**< 0.001**
Follow-up time (month), median [IQR]	56.19 [12–400]	59.84 [12–466]	0.059
Primary tumor size (mm), mean ± SD	18.59 ± 12.79	19.70 ± 13.50	0.278
Tumor histology, n (%)			**0.042**
Papillary thyroid cancer	138 (94.5)	436 (88.8)	
Follicular thyroid cancer	8 (5.5)	55 (11.2)	
Multifocality, n (%)			0.243
Present	47 (32.2)	151 (30.8)	
Absent	99 (67.8)	340 (69.2)	
Lymphovascular invasion, n (%)			**< 0.001**
Present	25 (17.1)	40 (8.1)	
Absent	121 (82.9)	451 (91.9)	
Extrathyroidal extension, n (%)			0.855
Present	28 (19.2)	92 (18.7)	
Absent	118 (80.8)	399 (81.3)	
T stage, n (%)			0.499
TX–T3	144 (98.6)	483 (98.4)	
T4	2 (1.4)	8 (1.6)	
N stage, n (%)			**< 0.001**
NX–N0	117 (80.1)	433 (88.2)	
N1	29 (19.9)	58 (11.8)	
M stage, n (%)			**0.024**
MX–M0	140 (95.9)	480 (97.7)	
M1	6 (4.1)	11 (2.2)	
Clinical Stage, n (%)			0.565
I	80 (54.8)	453 (92.2)	
II	59 (40.4)	34 (6.9)	
III	7 (4.8)	2 (0.4)	
IV	–	2 (0.4)	
Radioiodine treatment, n (%)			0.345
Present	40 (27.4)	151 (30.8)	
Absent	106 (72.6)	340 (69.2)	
ATA risk score, n (%)			0.264
I	80 (54.8)	324 (65.9)	
II	59 (40.4)	146 (29.7)	
III	7 (4.8)	21 (4.3)	
The extent of surgery, n (%)			0.055
Total thyroidectomy	136 (93.2)	448 (91.3)	
Subtotal thyroidectomy	10 (6.8)	43 (8.8)	

$p < 0.05$ suggested statistical significance. T: Tumor; N: Nodal; M: Metastasis; ATA: American thyroid association.

ectomy [18]. In this study, unlike the others, the prevalence of HT in generally differentiated thyroid cancers was examined and it was found to be 22.9 %.

▶ **Table 2** Regression analysis of the association of the presence of Hashimoto's thyroiditis with aggressive tumor features.

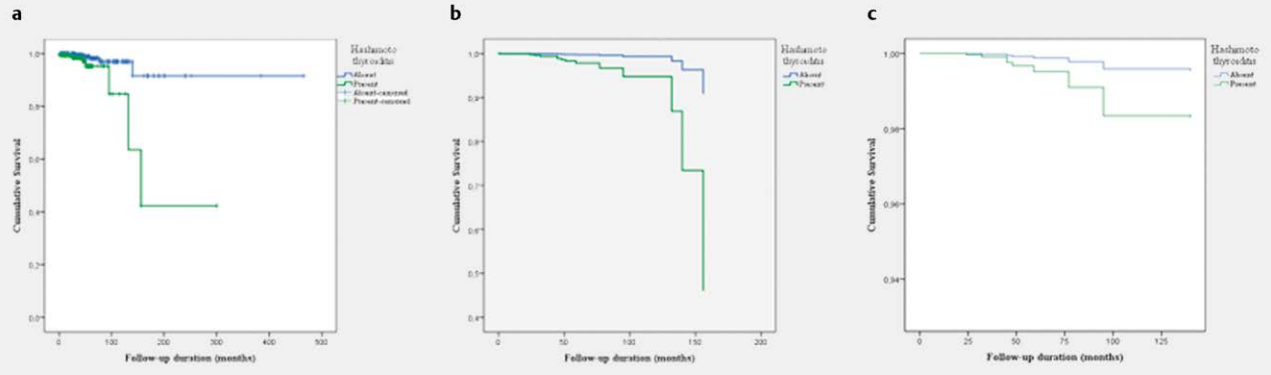
Characteristics	OR	95 % CI	p-Value
Primary tumor size ≥ 4 cm	0.261	0.025–2.689	0.259
Lymphovascular invasion	2.118	1.046–4.287	**0.037**
Thyroid capsule invasion	0.786	0.345–1.792	0.567
Extrathyroidal extension	0.839	0.364–1.931	0.680
Lymph node metastasis	1.923	1.089–3.396	**0.024**
Distant metastasis	0.732	0.164–3.265	0.683

p< 0.05 suggested statistical significance. CI: Confidence interval; OR: Odds ratio.

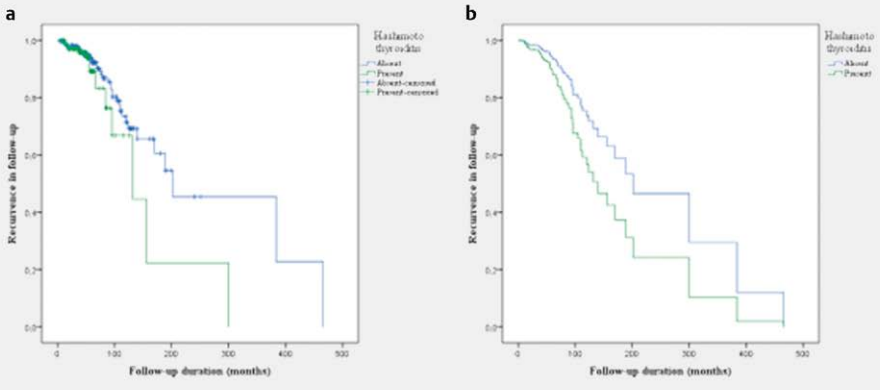
Papillary thyroid cancer histology was significantly higher than follicular thyroid cancer histology in DTC patients with HT. These results were in agreement with the literature [19].

Data on the frequency of lymph node metastases in DTCs in the presence of concomitant HT are conflicting. Zhu et al. reviewed 763 PTC patients retrospectively. A total of 277 patients had concomitant HT. They found the frequency of lymph node metastasis to be lower in the group with HT than in the group without HT [20]. Similarly, Dvorkin et al. reviewed 753 DTC patients retrospectively. 107 patients had concomitant HT. They found the frequency of lymph node metastasis to be lower in the group with HT than in the group without HT [12]. On the contrary, Vasileiadis et al. stated that Anti-TG positivity was associated with an increase in the frequency of lymph node metastasis [15]. Shen et al. also stated that in their series of 1126 patients, HT was a risk factor for more metastatic cervical lymph nodes [16]. Our findings support the view that lymph node metastasis is more common in the presence of concomitant HT.

In the literature, there are data related to a lower incidence of DTC-related mortality in the presence of HT [11–14]. These results



▶ **Fig. 1** **a**: According to the Kaplan–Meier curves, unadjusted 10-year disease-specific survival rates among DTC patients without HT were significantly higher than those among patients with HT (log-rank p = 0.002). **b**: According to Cox proportional hazards regression models, HT was associated with increased DTC-related mortality after adjusting for sex and age [hazard ratio (HR), 8.149; 95 % CI, 2.533–26.216; p < 0.001]. **c**: According to Cox proportional hazards regression models, HT was associated with increased DTC-related mortality after adjusting for sex, age, primary tumor size, ETE, LNM, distant metastasis, the extent of surgery, and RAI ablation (HR, 4.073; 95 % CI, 1.816–20.336; p = 0.047).



▶ **Fig. 2** **a**: Hashimoto thyroiditis was not associated with 10-year recurrence-free survival (91.0 % vs. 91.1 %; log-rank p = 0.125). **b**: Hashimoto thyroiditis was not associated with 10-year recurrence-free survival after adjusting for sex and age (HR, 1.856; 95 % CI, 0.978–3.522; p = 0.059).

are interesting. Because the relationship between lymph node metastasis and increased mortality in DTC in those older than 45 years has been well defined [1]. There is also data on increased mortality risk in those younger than 45 years [21]. It is contradictory that mortality is lower even in studies where the frequency of lymph node metastasis increases in the presence of HT. Our findings suggest that disease-related mortality increases in DTCs in the presence of concomitant HT. Although our findings are self-consistent, they differ from the literature. The underlying cause of this condition is unclear, but potential causes may include differences in histological examination level, criteria for the definition of autoimmunity, patient selection, environmental factors (radiation exposure history, etc.), genetic differences, and geographic factors (eg, amount of iodine intake).

Extrathyroidal extension of the tumor is a risk factor for tumor recurrence. In previous studies, it was stated that the frequency of extrathyroidal extension in DTCs does not increase in the presence of concomitant HT [9, 22–26]. Our findings are consistent with the literature on extrathyroidal extension. Our finding that the structural tumor recurrence risk is not affected by the presence of HT is consistent in terms of results.

The situation underlying this conflicting information remains unclear. Whether infiltrative lymphocytes are beneficial (anti-tumorigenic or protective) or harmful (pro-tumorigenic) in thyroid cancer may depend on their phenotype. Thus, it can be argued that the immune response plays a protective role in some patients, but promotes cancer development and progression in other patients, explaining inconsistent data on the effect of thyroid autoimmunity on cancer characteristics and progression [27]. Conflicting literature results reporting that HT has a positive, negative, or neutral effect on DTC survival may be due to differences in the diagnosis of HT, patient selection criteria, studies in different ethnic groups and genetics, number of patients, and selection biases. In addition, it should be considered that HT patients are followed more frequently, TSH suppression is performed with L-Thyroxine replacement, and more frequent ultrasound follow-up is performed for nodules. It can be predicted that studies showing the relationship between DTC patients with HT and smaller tumor size and less aggressive tumor characteristics have reached this conclusion because of earlier diagnosis in patient groups. However, this study did not examine DTC patients developed on the basis of HT. The presence of HT concurrent with DTC was investigated. The previous HT diagnoses and treatments of the patients are unknown. This may be one of the reasons for our different results from the literature.

One of the strengths of our study is that pathological data, antibody measurements, and recurrence evaluation are standard since all patients were evaluated by a single center. On the other hand, the study's retrospective design was a limitation. The time elapsed between the first diagnosis of HT and the detection of DTC, and whether the patients received l-Thyroxine replacement is unknown. Therefore, our inability to further comment on the etiopathogenesis of the relationship between HT and DTC is one of the limitations of our study. In addition, when the preoperative sonographic data of DTC patients accompanied by HT were examined, the sonographic findings of HT were not mentioned in 40 % of the patients. There were mostly reports of suspicious nodule presence and description. However, we think that this situation is due to the fact that the nodule is given more importance by the sonographer and the structure of the gland remains in the background. Due to the retrospective nature of the study, we cannot provide more precise information.

Conclusion

This study showed that DTCs concomitant with HT are associated with some aggressive tumor characteristics and lower survival. Lymphovascular invasion and nodal metastasis were significantly higher in DTC patients with HT. We recommend preoperative measurement of thyroid antibodies in patients diagnosed with DTC. We think that it is important to evaluate the non-tumor parts of the thyroidectomy material of the operated patients in terms of chronic lymphocytic thyroiditis. In staging systems based on tumor risk factors, it may be useful to evaluate the presence of concomitant HT as a prognostic factor. In addition, we think it is important to carefully monitor nodules' presence in HT patients. Prospective and long-term studies are needed to make stronger recommendations regarding the relationship between HT and DTC prognosis.

Conflict of Interest

The authors declare that they have no conflict of interest.

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