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Clinical Aggressiveness and Long-Term Outcome in Patients with Papillary Thyroid Cancer and Circulating Anti-Thyroglobulin Autoantibodies

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Objective: The association between papillary thyroid cancer (PTC) and Hashimoto's thyroiditis is widely recognized, but less is known about the possible link between circulating anti-thyroglobulin antibody (TgAb) titers and PTC aggressiveness. To shed light on this issue, we retrospectively examined a large series of PTC patients with and without positive TgAb.

Methods: Data on 220 TgAb-positive PTC patients (study cohort) were retrospectively collected in 10 hospital-based referral centers. All the patients had undergone near-total thyroidectomy with or without radioiodine remnant ablation. Tumor characteristics and long-term outcomes (follow-up range: 2.5–24.8 years) were compared with those recently reported in 1020 TgAb-negative PTC patients with similar demographic characteristics. We also assessed the impact on clinical outcome of early titer disappearance in the TgAb-positive group.

Results: At baseline, the study cohort (mean age 45.9 years, range 12.5–84.1 years; 85% female) had a significantly higher prevalence of high-risk patients (6.9% vs. 3.2%, $p < 0.05$) and extrathyroidal tumor extension (28.2% vs. 24%; $p < 0.0001$) than TgAb-negative controls. Study cohort patients were also more likely than controls to have persistent disease at the 1-year visit (13.6% vs. 7.0%, $p = 0.001$) or recurrence during subsequent follow-up (5.8% vs. 1.4%, $p = 0.0001$). At the final follow-up visit, the percentage of patients with either persistent or recurrent disease in the two cohorts was significantly different (6.4% of TgAb-positive patients vs. 1.7% in the TgAb-negative group, $p < 0.0001$). At the 1-year visit, titer normalization was observed in 85 of the 220 TgAb-positive individuals. These patients had a significantly lower rate of persistent disease than those who were still TgAb positive (8.2% vs. 17.3%. $p = 0.05$), and no relapses were observed among patients with no evidence of disease during subsequent follow-up.

Conclusions: PTC patients with positive serum TgAb titer during the first year after primary treatment were more likely to have persistent/recurrent disease than those who were consistently TgAb-negative. Negative titers at 1 year may be associated with more favorable outcomes.

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Introduction

DIFFERENTIATED THYROID CANCER (DTC) is the most common of the endocrine cancers. With annual incidence rates ranging from 1 to 10 cases per 100,000, it accounts for 1.7% of all malignancies in the United States (0.85% of those in men, 2.6% in women) (1). Serum thyroglobulin (Tg) assays and neck ultrasonography (US) are currently the mainstays of postoperative surveillance in patients with DTC (2). The former, however, yields unreliable results in the presence of circulating anti-thyroglobulin antibodies (TgAbs) (2,3), which are present in about 20% of patients with DTC (3). In these cases, the current American Thyroid Association (ATA) guidelines recommend simultaneous measurement of TgAb titers and serum Tg levels every 6–12 months (2). Destruction of follicular thyrocytes (normal and neoplastic) should markedly reduce the levels or even eliminate these antibodies by removing the antigenic stimulus that drives their production. Stable or increasing serum TgAb levels during the follow-up of DTC patients are thus regarded as markers of recurrent/persistent disease. This correlation has been demonstrated in a number of studies (4–8), but there are exceptions (9,10).

Moreover, the incidence of positive TgAb and/or antithyroid peroxidase antibody titers in DTC patients is approximately twofold higher than that of the general population (3). This finding suggests an association between autoimmune thyroid disease and papillary thyroid cancer (PTC), although the nature and prognostic significance of this link has yet to be defined (3,11–15). Indeed, several groups have examined the association between PTC aggressiveness and histologically confirmed thyroiditis or circulating TgAb, but the results that have emerged have been discordant (5–7,9,15–20).

The aim of this retrospective multicenter study was to compare two large cohorts of PTC patients with and without positive serum TgAb titers after primary treatment, to assess the impact of TgAb positivity on the long-term clinical outcome. The secondary aim was to evaluate the prognostic significant of early postoperative titer decreases.

Subjects and Methods

Patients

The protocol for this multicenter retrospective study was preapproved by the local ethics committee of each participating center. The requirement for written informed consent was waived in view of the exclusively observational nature of the study. The study cohort was selected from the population of patients consecutively diagnosed with PTC between January 1990 and June 2009 in 10 hospital-based referral centers for thyroid disease management in Italy. The inclusion criteria were as follows: 1) a positive serum TgAb titer at the first postoperative assay (1–12 months after primary treatment); 2) complete follow-up data for the 1-year postoperative visit; and 3) all follow-up data collected at the participating referral center. The control cohort consisted of 1020 patients with PTC and TgAb titers that were consistently negative for the duration of the postoperative follow-up. These patients, who were analyzed in a previous study by our group (21), came from 8 of the 10 referral centers providing data on the study cohort (TgAb-positive) patients. In both cohorts, the TgAb status was classified on the basis of the specific assay and cut-off values used in the center caring for the patient.

Treatment and postoperative follow-up

The primary treatment consisted of total or near-total thyroidectomy plus (depending on local policies at the time of treatment) cervical lymph node dissection (in 51.3% of the patients) and/or radioiodine remnant ablation (RRA) (83.6%). The outcome of the primary treatment was assessed at the 1-year visit in all patients (including those who had also been evaluated earlier during the first year). Patients were defined as being without evidence of disease if they did not show residual tumor tissue detected by neck US or additional imaging studies. The latter included computed tomography (CT), magnetic resonance imaging (MRI), or diagnostic ^{131}I whole-body scans (dxWBS) and were performed as needed according to clinical evaluation (i.e., aggressive histology and/or detectable basal serum Tg levels, increasing AbTg values). Subsequent follow-up visits were scheduled approximately once a year. Each visit included measurement of basal and/or stimulated serum Tg levels (immunoradiometric assays with functional sensitivities ranging from 0.2 to 1 ng/mL), Tg antibody radioimmunoassays, or immunometric assays (with cut-offs for negativity that varied from center to center), and a Doppler ultrasound examination of the neck performed with multifrequency probes (7.5–12 MHz). The latter examinations were done by endocrinologists with specific training and experience in cervical US. Suspicious neck lesions were confirmed by positive findings on fine-needle aspiration cytology (FNAC) (i.e., cytological features of malignancy and/or detectable levels of Tg in the needle washout fluid). Patients with persistent or recurrent disease were referred for additional treatment (surgery, radioiodine, or external-beam radiation, depending on the site of involvement).

Data collection and analysis

Clinical data collected at each site were retrospectively transferred to a standard electronic case report form. They included patient demographics; tumor characteristics (histological features, baseline tumor stage, and risk for persistent/recurrent disease as defined by the 2009 ATA Management Guidelines for Differentiated Thyroid Cancer); treatments (surgery, RRA, any other intervention); findings (results of laboratory tests, neck US, and any functional or cross-sectional imaging study) and disease status at each follow-up visit; and final outcome (disease status, vital status, cause of death if applicable).

For the purposes of patient enrollment and the analyses performed in this study, the results of each TgAb assay were recorded simply as ''positive'' or ''negative'' based on a titer above or below the cut-off of the specific assay used in the center where the patient was being followed. Disease status was defined as ''persistent'' or ''recurrent'' only when measurable lesions were documented by imaging studies (distant metastases) or by US plus FNAC (thyroid bed or lymph node disease). The term ''persistent'' was used exclusively to refer to disease diagnosed at the 1-year postoperative visit; disease observed later in the follow-up was classified as ''recurrence'' only in patients found to have no evidence of disease at the 1-year visit. Patients with

detectable serum Tg values without structural correlates were considered as being without evidence of disease, unless they had significant increases (i.e., ≥50%) in serum Tg levels with respect to the previous visit(s), or they developed structural disease during follow-up. In these cases, they were retrospectively scored as having persistent disease.

Statistical analysis

Continuous variables are reported as median values and ranges, while categorical variables are reported as absolute numbers and percentages. Intergroup differences were assessed with the independent-samples *t*-test (continuous variables) or the χ^2 statistic and Fisher exact test (categorical variables). *p*-Values <0.05 were considered statistically significant. All analyses were performed with StatView® 5.0.1 software (SAS Institute Inc., Cary, NC).

Results

Baseline cohort characteristics

Table 1 shows the characteristics of the study cohort (TgAb positive at the first postoperative visit) and the control cohort (TgAb negative throughout follow-up) at the time of primary treatment. The percentage of patients in the study cohort who were classified as high risk was approximately twice as high as that of the controls. Although the study cohort patients had smaller primaries at baseline, they were also more likely to have gross extrathyroidal disease extension at baseline. Distant metastasis rates were appreciably but not significantly higher in the study cohort. These rates reflect only lesions that were confirmed by ^{131}I WBS following RRA, which, although not reaching the statistical significance, was performed more frequently in control patients (902 out of 1020; 88.4%) than those of the study cohort (184 out of 220; 83.6%, $p = 0.055$).

Persistent disease

As shown in Table 2, the percentage of study cohort patients with persistent disease at the 1-year follow-up visit was approximately twice as high as that observed among controls ($p = 0.002$). A similar ratio was observed when the analysis was focused only on patients who had undergone RRA, being the percentage of persistent disease of 17% in the study cohort, and 8.4% in controls ($p = 0.002$). In 24 (80%) of the 30 patients in the study cohort, the persistent disease was confined to the thyroid bed or cervical lymph nodes. The other six also had metastases to the lung, mediastinum, and/or bones. While TgAb-positive patients were more frequently submitted to dxWBS (48% vs. 29%, $p < 0.0001$), most of the residual tumor foci that persisted after primary treatment were detected by cervical US with comparable rates between the two groups (78% vs. 67%, respectively).

In both cohorts, the prevalence of persistent disease increased with the ATA risk category ($p < 0.0001$ for both), but in the study cohort, persistence rate among the low-risk subgroup was significantly higher (7.6% vs. 2.5%, $p < 0.0038$). Most of study cohort patients (25/30; 83.3%) and all 72 controls with persistent disease were retreated (surgery, RRA, or chemoembolization, depending on the site of involvement) and subsequently re-entered the surveillance program. At the end of follow-up, 7 out of 30 (23.3%) of TgAb-positive patients and 14 out of 72 (19.4%) of TgAb-negative patients still had persistent disease.

Table 1. Characteristics of the Study and Control Cohorts at the Time of Primary Treatment

Characteristic[a]	*Study cohort (n = 220)*	*Controls (n = 1020)*
Sex		
Male	33 (15)	207 (20.3)
Female	187 (85)	813 (79.7)
Median age at diagnosis, years (range)	45.9 (12.5–84.1)	44.0 (13.0–78.0)
Median tumor size, mm (range)	12 (0.5–50)*	15 (0.3–90)
Tumor foci[b]		
Unifocal	140 (63.6)	656 (64.3)
Multifocal	80 (36.4)	364 (35.7)
Unilateral	162 (75.7)	765 (75)
Bilateral	52 (24.3)	255 (25)
Extrathyroidal extension, %		
No	158 (71.8)	776 (76)
Microscopic	53 (24.1)	244 (24)
Macroscopic	9 (4.1)**	0 (0)
Lymph node metastases[c]		
No	157 (71.4)	766 (75)
Yes	63 (28.6)	254 (25)
Distant metastases[d]		
No	175 (95.1)	869 (96.3)
Yes	9 (4.9)	33 (3.7)
Stage		
I	160 (72.7)	753 (73.8)
II	18 (8.2)	82 (8)
III	21 (9.6)	117 (11.4)
IVa	10 (4.5)	41 (4)
IVc	4 (1.8)	15 (1.4)
Unknown	7 (3.2)	12 (1.2)
ATA risk		
Low	131 (59.5)	625 (61.3)
Intermediate	74 (33.6)	362 (35.5)
High	15 (6.9)*	33 (3.2)
Radioiodine ablation		
Yes	184 (83.6)	902 (88.4)
No	36 (16.4)	118 (11.6)

[a]Unless otherwise stated, results are reported as numbers (%) of patients in the study and control cohorts (TgAb-positive and TgAb-negative, respectively, at the first [1–12 month] posttreatment visit).

[b]Primary tumor laterality was unknown for six TgAb-positive patients.

[c]The group without evidence of lymph node metastases includes both patients who underwent neck dissection with no metastastic nodes at histology report (pN0) and patients who did not undergo neck dissection and who had no evidence of lymph node involvement at neck ultrasonography (cN0).

[d]Data reported only for patients who had post-RRA ^{131}I whole-body scan to assess distant sites (184/220 study patients, 902/1020 controls). N.B. All patients excluded from the analysis were classified as low risk, and none had clinically signs suggestive of extrathyroidal tumor spread.

*$p < 0.05$.

**$p < 0.0001$.

ATA, American Thyroid Association; RRA, radioiodine remnant ablation; TgAb, anti-thyroglobulin antibody.

Table 2. Final Disease Status in Study and Control Cohort Subsets with Diagnoses of Persistent or Recurrent Disease During Follow-Up

	Study cohort (n = 220)	*Controls (n = 1020)*	p-*Value*
Subsets with persistent disease[a]	30 (13.6)	72 (7.1)	0.002
Final disease status[b]			ns
No imaging-documented disease	20 (66.7)	58 (80.6)	
Imaging-documented disease	7 (23.3)	14 (19.4)	
Unknown[c]	3 (10)	0 (0)	
Subset with disease recurrence[d]	11 (5.8)	13 (1.4)	0.0003
Final disease status[b]			ns
No imaging-documented disease	8 (72.7)	9 (69.2)	
Imaging-documented disease	3 (27.3)	3 (23.1)	
Unknown[e]	0 (0)	1 (7.7)	
Subset with disease at final follow-up[f]	10 (4.5)	17 (1.7)	0.017

Results are reported as numbers (%) of patients in the study and control cohorts (TgAb-positive and TgAb-negative, respectively, at the first [1–12 month] post-treatment visit).

[a]Persistent disease: disease documented at the 1-year visit; assessed in all 220 study patients and 1020 controls.

[b]Based on findings at last follow-up visit.

[c]Lost to follow-up immediately after the 1-year visit.

[d]Disease recurrence: disease documented at any time during follow-up in one of the 190 study patients and 948 controls with no evidence of persistent disease at 1 year.

[e]Lost to follow-up immediately after recurrent disease was diagnosed.

[f]Disease at final follow-up: imaging-documented disease at last follow-up visit.

ns, not significant.

Recurrent disease

During the follow-up (median: 5.3 years [range 2.5–24.8] for the study population, 8.5 years [range 2.7–21.4] for the controls), recurrences were identified in 11 (5.8%) of the 190 study cohort patients who had been considered without evidence of disease at 1 year. The median time of recurrence was 1.6 years (range 0.7–3.2) after the 1-year visit. Eight of the 11 patients had undergone RRA. Recurrence rates increased with the baseline ATA risk score (2.3% in the low-risk group, 6.7% in those with intermediate risk, 20% in the high-risk group, $p = 0.008$). In nine cases (81.8%), the recurrences were confined to the thyroid bed or cervical lymph nodes, and in eight of these, the lesions were diagnosed by US. In the ninth patient, the US examination was negative, but the previously stable serum Tg levels had increased. For this reason, a dxWBS was ordered, and it confirmed the presence of cytologically confirmed tumor tissue regrowth in the thyroid bed without any lymph-node involvement. The two patients with distant metastases (pulmonary in both cases) had both been classified as high risk at baseline, and the lung lesions were disclosed by CT. In one of the two patients, the CT had been ordered because locoregional metastases had been detected at the same visit by US. The second patient had undergone total thyroidectomy with cervical lymph-node dissection, and the cervical US examination was negative. In this case, the CT study had been ordered because of increasing serum TgAb levels. All 11 patients with recurrent disease were treated with RRA and/or surgery, and six (55%) were found to have no evidence of disease at the last follow-up visit.

In the control cohort, the prevalence of recurrences was significantly lower (1.4%, $p = 0.0001$), and involvement was always confined to cervical lymph nodes or the thyroid bed (21). The percentage of patients with either persistent or recurrent disease at the end of the follow-up was also significantly lower than that observed in the TgAb-positive cohort (1.7% vs. 4.5%, $p < 0.017$). No significant difference in cancer-related mortality rates was observed between the study cohort and the control group (0.4% vs. 0.7%, respectively).

Prognostic role of an early normalization of TgAb titer and clinical outcome

As shown in Table 3, the total number of patients with positive titers at the 1-year visit was only 133 (61%). In the other 85 cases (39%), TgAb titers had become undetectable since the first postoperative assay at 1 or 3 months. These patients had a significantly lower rate of persistent disease than those who were still TgAb positive (8.2% vs. 17.3%. $p = 0.05$).

Furthermore, analysis of data for the 188 patients who were without evidence of disease at the 1-year visit revealed subsequent disease recurrence in 11 (10%) of the 110 who had remained TgAb-positive but none of the 78 whose titers were negative at 1 year (Table 3). On the whole, early post-treatment normalization of TgAb titers (i.e., within the first year after surgery) was associated with a persistent/recurrent disease rate three times lower than that observed when titers were still positive at 1 year (8.2% vs. 25.5%, $p = 0.001$). Early normalization thus displayed a negative predictive value for recurrent disease of 100%, while the positive predictive value of persistent positivity was 9.0% (specificity 41.1%).

Discussion

Our findings clearly indicate that PTC patients with positive serum TgAb titers after primary treatment have more aggressive disease and less favorable long-term outcomes than demographically similar patients without circulating TgAbs (21). The differential aggressiveness could already be observed at the time of primary treatment, when the percentage of high-risk patients in the study cohort was twice as high as that of controls. It was also evident at the 1-year

Table 3. Disease and TgAb Status in the Study Cohort at the 1-Year and Final Follow-Up Visits

	TgAb status		
	Positive	*Negative*	p-*Value*
1-year follow-up visit[a]	$n = 133$ (61.0%)	$n = 85$ (39.0%)	
Persistent disease[b]	23 (17.3)	7 (8.2)	0.05
Recurrent disease[c]	11 (10)	0 (0)	0.003
Persistent/recurrent disease	34 (25.5)	7 (8.2)	0.001
Final follow-up visit[d]	$n = 47$ (21.7)	$n = 168$ (77.4)	
No imaging-documented disease	40 (85.1)	161 (95.8)	0.015
Imaging-documented disease	7 (14.9)	7 (4.2)	

Results are reported as numbers (%) of patients with positive and negative TgAb.
[a]Analysis limited to 218/220 patients with known TgAb status at this time point.
[b]Persistent disease: disease documented at the 1-year visit; assessed in 133 TgAb-positive patients and 85 TgAb-negative patients.
[c]Recurrent disease: disease documented at any time during follow-up in one of the 110 TgAb-positive and 78 TgAb-negative patients with no evidence of persistent disease at 1-year.
[d]Analysis limited to 215/220 patients with known TgAb status at this time point.

follow-up visit, when persistent and recurrent disease rates were approximately two and three times higher, respectively, than those of controls, and at the final follow-up visit, when the disease rate was roughly three times higher than that of the patients who had never presented Tg-Ab positivity. Patients with positive TgAb were more frequently submitted to dxWBS, but the number of US examinations was comparable in the two groups. However, given that most of the persistent and recurrent disease was confined to the neck and was detected by US (78% in TgAb-positive patients and 67% in TgAb-negative patients) rather than dxWBS, the difference in imaging procedures should have not influenced the results. In other words, the higher prevalence of persistent/recurrent disease in TgAb-positive patients is unlikely to depend on the higher number of dxWBS performed.

Our results also tend to confirm the favorable prognostic significance of early normalization of serum TgAb titers reported by several groups (4,5,7). Indeed, at the first control visit the prevalence of persistent disease was half in patients with normalization of TgAb compared to those with titers that were still positive. Moreover, none of the patients with no evidence of disease and early TgAb normalization relapsed as compared to 10% of those with titers that were still positive.

The association between PTC and lymphocytic thyroiditis is widely recognized (3,13,14,22,23), but the impact of Hashimoto's thyroiditis (HT) and circulating TgAb on PTC patients remains a controversial issue (12,15–17,20,23). HT is more frequent in young women, whose age alone is a favorable prognostic factor (in terms of no evidence of disease intervals and mortality) (3,15,17–19). In a recent meta-analysis of 38 studies, PTCs with histologically proven HT (23.8%) were negatively associated with extrathyroidal extension ($p = 0.002$) and lymph node metastasis at baseline ($p = 0.04$) (15). Findings of this type have led some investigators to speculate that the autoimmune response to thyroid-specific antigens in patients with HT enhances the destruction of cancer cells expressing thyroid-specific antigen in PTC, thereby reducing the risk of recurrence and improving survival (3,18,19). In other studies, however, the prognosis for PTC patients with HT was similar to or worse than that of PTC patients without HT (6,12,24–27). A recent study on papillary thyroid microcarcinomas, for example, revealed higher frequencies of bilateral and/or multifocal involvement as well as of lymph node metastases in patients with concomitant lymphocytic thyroiditis (26).

A very recent review of the surgical pathology archives of the Johns Hopkins Hospital showed that recent increases in the incidence of PTC include cases associated with full-blown HT and others associated with a milder form of lymphocytic infiltration known as chronic nonspecific thyroiditis. These findings suggest that PTC and lymphocytic infiltration may not be part of the same causal pathway: instead, neoplastic transformation of the thyrocyte may trigger the lymphocytic response, which may or may not progress to HT (13). Therefore, the clinical implications of cross-talk between the tumor and its inflammatory microenvironment are still poorly understood. In this setting, it is widely recognized that TgAbs are less diagnostic for HT than anti-thyroid peroxidase antibodies and more tumor specific as supported by epitope mapping studies (28). Thus, one should distinguish between a positive TgAb titer associated with underlying HT or one arising as a response to tumorigenesis and associated inflammation. Overall, these findings may explain the controversial results in the scientific literature regarding the impact of thyroid autoimmunity on PTC development and aggressiveness. Given these considerations, the lack of information concerning histological lymphocytic infiltration of thyroid tissue represents a limitation of the current study, although it is multicentric and carried out in a large number of patients. Future studies with closer investigation of the histological features of lymphocytic infiltrates in TgAb-positive patients are warranted.

Several studies have highlighted the link between long-standing TgAb positivity and persistent/recurrent disease in PTC patients (4,5,7,8). Eradication of follicular cells, by eliminating the antigenic stimulus, should in fact lead to a progressive decline in TgAb levels and ultimately their complete disappearance. Persistently positive titers are viewed as evidence of the continued presence of functional thyroid cells, benign or malignant (3,29). Our findings support the view that early disappearance of TgAb titers is a prognostically favorable finding in patients with PTC.

In conclusion, our data indicate that PTC patients with positive postoperative serum TgAb titers are more likely to have persistent/recurrent disease than similar patients who are consistently TgAb negative. Disappearance of TgAb

titers within the first postoperative year seems to be associated with a more favorable prognosis.

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