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Thyroglobulin antibody resolution after total thyroidectomy for cancer

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ABSTRACT

Background: Thyroglobulin antibodies (TgAb) are produced by 10%–25% of thyroid cancer patients and interfere with thyroglobulin measurement, a marker of residual or recurrent cancer after surgery. Our purpose was to describe the TgAb resolution time course and the significance of persistent antibody elevation after thyroidectomy.

Methods: A database of 247 consecutive patients with TgAb measured preoperatively who underwent thyroidectomy for differentiated thyroid cancer between January 2007 and May 2013 was reviewed. Patients were stratified by TgAb status (positive or negative) and recurrence (defined as biopsy proven disease or unplanned second surgery). Survival and regression analysis was used to determine TgAb resolution time course. Log-rank was used to determine an association between persistent antibody elevation and recurrence.

Results: Of 247 patients (77% women, 23% men; mean 45.7 ± 1.0 y) with TgAb measured preoperatively, 34 (14%) were TgAb+ (≥20 IU/mL; mean 298.1 ± 99.2 IU/mL). Median time to TgAb resolution was 11.0 ± 2.3 mo, and the majority resolved by 32.4 mo. Regression analysis of patients with antibody resolution yielded an average decline of −11% IU/mL per month ± 2.2%. Disease-free survival was equivalent between TgAb-positive and TgAb-negative groups ($P = 0.8$). In 9 of 34 patients, antibodies had not resolved at the last follow-up and imaging could not identify recurrent disease.

Conclusions: TgAb are common in patients with thyroid cancer but resolve after treatment at approximately −11% IU/mL per month from preoperative levels with median resolution at 11.0 mo. Persistently elevated levels after thyroidectomy were not associated with disease recurrence in our series.

1. Introduction

The thyroid produces thyroglobulin (Tg) in its follicles as a precursor to the active T3 and T4 forms of thyroid hormone. Tg is produced by thyroid tissue in both benign and malignant states. In differentiated thyroid cancer (DTC), the thyroid is usually removed, but residual tissue can continue to synthesize and secrete Tg in the presence of high thyroid stimulating hormone concentrations. Tg levels can be used postoperatively as a tumor marker to identify residual or recurrent thyroid cancer after surgical treatment. Antibodies to thyroglobulin (TgAb), however, are produced in 10%–25% of

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patients and can interfere with Tg measurement [1]. TgAb interfere with both immunometric and radioimmunometric (RIA) assays. Although radioimmunometric is less susceptible to interference by TgAb and immunometric usually underestimates Tg, patient characteristics can also affect Tg measurement both positively and negatively. Therefore, reliable detection of TgAb is necessary before evaluating the validity of a given Tg measurement [2].

If Tg cannot be measured as a tumor marker because of TgAb interference, then it may be possible to use TgAb as a surrogate marker of Tg levels, but that link is not well established. It is thought that TgAb are produced by lymphocytes within the thyroid, therefore, if all thyroid is removed one would anticipate resolution of TgAb as well, but TgAb may persist even after total thyroidectomy. This could indicate that cervical lymph nodes possibly promulgate the response or Tg persist in antigen producing cells [2]. Other studies show that the disappearance of TgAb is related to the disappearance of auto-antigen or thyroid tissue; however, the literature is equivocal about the link between TgAb and recurrent cancer. Some cross-sectional studies and longitudinal studies report a higher frequency of cancer recurrence in TgAb-positive patients and inversely a lower frequency of cancer recurrence in TgAb-negative patients [1,3], but other researchers did not find the same results [4–7].

To further investigate, we sought first to understand how TgAb resolve and then to determine the relationship between TgAb-positive patients and recurrent cancer. Although the current standard of care is to measure serum Tg and TgAb postoperatively [8], preoperative data have also been collected at our institution, which provide a useful baseline measurement that could be used to identify TgAb-positive patients and to establish a time course for postoperative TgAb resolution [1]. The three aims of this study were to describe the time course of TgAb resolution, determine if recurrent cancer is more common in patients with positive preoperative TgAb, and determine if recurrent cancer is more common in patients with persistently elevated antibody levels.

2. Methods

A retrospective review of a prospectively collected thyroid database was conducted. Patients undergoing surgical treatment for DTC between January 2007 and May 2013 were included. Only patients treated with a total thyroidectomy or completion thyroidectomy were included. Patients without preoperative TgAb measurement were excluded. In the end, 247 consecutive patients with preoperative TgAb measurement who underwent surgical treatment were reviewed.

TgAb was measured using Beckman Coulter Access Dxl (Beckman Coulter, Brea, CA) method and Siemens Immulite 2000 (Siemens, Munich, Germany). Since 2011, testing has been performed at ARUP, a national reference laboratory (Salt Lake City, UT). The currently used TgAb assay, which has only been used since 2012, uses a cutoff of <4 IU/mL to define negative antibodies, but the version used before 2012 used a cutoff of <20 IU/mL. For consistency, positive TgAb status was defined as a preoperative measurement ≥20 IU/mL. TgAb resolution in those patients was defined as postoperative levels <20 IU/mL. If TgAb resolved temporarily, recurred, then resolved again, the later date of resolution was used. Recurrent disease was defined by biopsy-proven disease or unplanned second surgery. Patients who underwent completion thyroidectomies were not considered to have unplanned second surgery.

Survival and regression analysis was used to determine the time course of TgAb resolution. Log-rank (Mantel–Cox) was used to determine an association between positive preoperative TgAb levels and cancer recurrence. Fisher exact test was used to determine an association between persistently elevated TgAb levels and cancer recurrence. SPSS version 21 statistical software was used for analysis (IBM, Armonk, NY).

3. Results

Our cohort consisted of 247 patients with TgAb measured preoperatively who underwent a total ($n = 188$) or completion ($n = 59$) thyroidectomy for DTC. The mean age of the patients was 45.7 ± 1.0 y, and 77% were women. Preoperative TgAb were positive (mean 298.1 ± 99.2 IU/mL) in 34 patients (14%). The average tumor size was 1.8 ± 0.2 cm, and lymph-node involvement was seen in 8.9% of patients. Extrathyroidal extension was present in 5.3% of patients. There was a significant difference in the proportion of autoimmune thyroid disease between the TgAb+ and TgAb− groups (35.3% *versus* 15.5%, $P = 0.01$). Subgroup analysis also showed a significant

Table – Cohort demographics.

Metric	Total, $N = 247$	TgAb−, $n = 213$	TgAb+, $n = 34$	P values
Sex, %	77.3 women, 22.7 men	75.6 women, 24.4 men	85.3 women, 14.7 men	0.28
Age (y)	45.7 ± 1.0	46.2 ± 1.1	43.0 ± 2.5	0.28
Tumor size (cm)	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.3	0.99
Histopathologic subtypes, %	96.0 PTC	95.3 PTC	100 PTC	0.37
	4.0 FTC	4.7 FTC		
Autoimmune thyroid disease, %	16.6 HT	14.6 HT	29.4 HT	0.05
	1.6 GD	0.9 GD	5.9 GD	0.09
	18.2 total	15.5 total	35.3 total	0.01
Lymph node involvement, %	8.9	8.5	11.8	0.75
Extrathyroidal extension, %	5.3	5.1	5.9	0.70
Surgery type, %	76.2 total	75.1 total	85.3 total	0.28
	23.8 completion	24.9 completion	14.7 completion	

FTC = Follicular Thyroid Cancer; GD = Graves Disease; HT = Hashimotos Thyroiditis; PTC = Papillary Thyroid Cancer.