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Markedly elevated thyroglobulin levels in the preoperative thyroidectomy patient correlates with metastatic burden

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Abstract

Background—Thyroglobulin (Tg) is a marker of tumor recurrence during thyroid cancer follow-up. While helpful in the postoperative setting, the clinical significance of preoperative Tg measurements remains unclear. The aim of the study was to determine if preoperative Tg levels are indicative of underlying malignancy or burden of metastatic disease.

Methods—A retrospective review of a prospectively collected database at an academic medical center of all thyroidectomy patients with a measured preoperative Tg level was conducted. Patients were grouped by Tg level into quartiles for initial univariate analysis, followed by multivariable analysis of variance.

Results—Between 2007 and 2012, 611 patients met criteria. Quartile breakdown was as follows: 19 ng/mL, 19.1–54 ng/mL, 54.1–151 ng/mL, and >151 ng/mL. Patients' age and gender were equivalent. Hashimoto's thyroiditis was most common in the lowest Tg group (24% *versus* 11%–12%, $P < 0.01$). While cancer was more common in the low Tg, metastatic disease was most common in the high Tg group. Specimen weight increased with increasing Tg levels ($P < 0.01$). Body mass index, gland weight, cancer, and Hashimoto's and metastatic disease were entered into a multivariable analysis. Only gland weight and metastatic disease correlated with Tg levels (both $P < 0.001$). All patients with Tg > 5000 ng/mL had metastatic disease ($n = 6$).

Conclusions—Although preoperative Tg levels are not associated with a diagnosis of cancer, they are associated with the presence of metastatic disease. All patients with a Tg > 5000 ng/mL had significant disease burden. In patients with concern for metastatic disease, preoperative serum Tg may be a useful marker to aid decision making.

Keywords

Thyroid cancer; Thyroidectomy; Thyroglobulin; Thyroiditis; Multi-nodular goiter; Hashimoto's thyroiditis; Metastatic disease; Metastatic burden

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1. Introduction

Thyroglobulin (Tg) is a glycoprotein produced specifically by the follicular cells of the thyroid, regardless if those cells are benign or malignant in nature [1]. This association with thyroid follicular cells allows for postoperative monitoring of patients with well-differentiated thyroid cancer, but the utility of serum Tg in the preoperative setting is less clear [2–8]. Theoretically, any disease process associated with increased mass of follicular cells (goiter, cancer, and thyroiditis) could potential result in an increase in the serum Tg level, whereas immunoglobulins associated with autoimmune mediated forms of thyroiditis may alter the detection of Tg in the serum [9,10].

With the 2009 American Thyroid Association management guidelines, routine use of serum Tg during the work up of a thyroid nodule was given an F rating, and during the work up of a well-differentiated thyroid cancer was given an E rating, indicating the panelists recommended against it [11]. Previous studies that have evaluated the use of preoperative serum Tg levels have focused on populations with homogenous thyroid pathology and have not looked at a mixed demographic where other thyroid pathologies may influence results [6,7,12–14]. The purpose of this study was to determine if preoperative elevation of serum Tg in the context of other preoperative known variables may be predictive of a diagnosis of cancer or disease burden in patients with metastatic disease. The hypothesis of this study is that significant serum Tg elevation in the preoperative period is indicative of a diagnosis of cancer and/or metastatic disease burden.

2. Methods

After approval by the local institutional review board, a retrospective review was performed of a prospectively maintained database of all thyroidectomy patients at a large academic medical center. As of 2007, preoperative serum Tg was routinely collected on all patients before thyroid surgery. Only patients with preoperative serum Tg levels were included in the study. Patients undergoing total thyroidectomy or thyroid lobectomy without previous thyroid surgery were included. When lobectomy patients went on to completion thyroidectomy, combined total gland weight was used, and those patients were included in the total thyroidectomy classification. Those patients with previous thyroidectomy and undergoing lymph node dissection only were excluded. Preoperative laboratories, operative reports, and imaging and pathology reports were reviewed. Reduced Tg levels were defined as <2.4 ng/mL [6]. To assess the degree of lymph node involvement for those patients with a diagnosis of thyroid cancer, lymph node ratios were calculated for all patients with at least four lymph nodes removed with the thyroid specimen [15,16]. Distant metastatic disease was defined based on the presence of extra cervical activities on whole-body uptake scan after radioactive iodine treatment, or by positive pathology from an extra cervical location. A diagnosis of cancer includes those patients with papillary microcarcinoma.

Statistical analysis was performed using IBM SPSS Statistics, version 20 (Armonk, NY). For initial analysis, patients were grouped by preoperative serum Tg into quartiles. Univariate analysis was performed comparing demographic and pathologic variables among the Tg quartiles with χ^2 , analysis of variance, and Kruskal-Wallis, as appropriate. If a

variable was noted to be significant ($P < 0.05$) on univariate analysis, it was included in a multivariable analysis. A Pearson correlation of >0.3 was concerning for confounding variables, and further χ^2 analysis was performed. For the multivariable analysis of variance, Tg was treated as a continuous variable and was log transformed to ensure the normal distribution required based on analysis assumptions. A P value of <0.05 was determined to be significant. Data are expressed as mean $\pm$ standard error of the mean, or as count (percentage) unless otherwise stated.

3. Results

Between 2007 and 2012, a total of 1014 patients underwent thyroidectomy and would meet study criteria. A total of 611 patients (60%) had preoperative serum Tg levels for review. The average age was 49 ± 1 y, and 484 patients (79%) were female. Average body mass index (BMI) was 29.6 ± 0.3 kg/m². The most common postoperative diagnoses included goiter (193, 32%), cancer (174, 29%), Graves' disease (66, 11%), and Hashimoto's thyroiditis (87, 14%). Based on preoperative serum Tg levels, patients were sorted into equal quartiles; 19 ng/mL, 19.1–54 ng/mL, 54.1–151 ng/mL, and >151 ng/mL.

On univariate analysis, the serum Tg quartiles did not differ by patients' age or gender (Table 1). BMI differed, with a higher BMI present in the third quartile at 32 kg/m² *versus* 29 kg/m² in the remaining quartiles ($P < 0.01$). Pathologic breakdown noted an increased percentage of Hashimoto's thyroiditis in the lowest Tg quartile ($P < 0.01$) [10]. Presence of multinodular goiter demonstrated a trend of increased frequency as Tg quartile increased, however, it did not reach significance ($P = 0.06$). However, total gland weight measured in grams was significantly greater in the higher Tg groups ($P < 0.001$).

Surprisingly, the greatest percentage of cancer was found in the lowest Tg group (36%), and incidence was decreased in the subsequent quartiles (28%, 21%, and 29%, respectively, $P = 0.03$). To determine if this was because of dedifferentiated tumors with reduced Tg production, patients were also defined as having reduced Tg levels. Thirty-nine patients were found to have reduced (<2.4 ng/mL) Tg levels, of which 16 patients had cancer [6]. Tg antibody levels were available in nine of the cancer patients with reduced Tg levels, of which only five (55%) had detectable antibodies.

Although the diagnosis of cancer was not associated with higher Tg levels, presence of metastatic disease was almost exclusively seen in the highest Tg quartile (Table 2, $P < 0.001$). Further univariate analysis of cancer pathology demonstrated a greater incidence of follicular carcinoma, Hurthle cell carcinoma, and anaplastic cancer in the highest Tg group ($P = 0.03$). To evaluate the lymph node involvement, frequency of therapeutic neck dissection (central and/or lateral) was tallied, and determined to be equivalent between the Tg quartiles ($P = 0.20$). Lymph node ratios were also similar between the groups ($P = 0.52$).

A Pearson correlation was calculated for all variables. A diagnosis of cancer and multinodular goiter had a Pearson correlation of -0.366 , with only 4% of goiter patients having a concomitant thyroid cancer *versus* 40% of nonmultinodular goiter patients ($P < 0.001$). Gland weight and multinodular goiter had a Pearson correlation of 0.315 , ($P <$

0.001), whereas metastatic disease and Tg level had the strongest correlation of 0.674 ($P < 0.001$).

A multivariable analysis of variance was performed using preoperative Tg levels as the dependent variable. To assure normal distribution assumed by the test, serum Tg levels were log transformed. BMI, gland weight in grams, diagnosis of cancer, Hashimoto's thyroiditis, and metastatic disease were all included as variables in the model (Table 3). A diagnosis of multinodular goiter was excluded because of the strong correlation with gland weight. Only gland weight ($P < 0.001$) and presence of metastatic disease ($P < 0.001$) were noted to still be significant. Adjusted $R^2 = 0.149$.

Of note, when looking at the distribution of the serum Tg levels, patients with marked elevation of preoperative Tg levels >5000 ng/mL, all had cancer with a significant metastatic disease burden. This consisted of six patients or 1% of the entire cohort. The details of these patients are listed in Table 4.

4. Discussion

In this report of 611 consecutive patients undergoing thyroidectomy, elevated preoperative Tg levels were associated with increased gland weight and the presence of metastatic disease. Although elevated Tg was associated with metastatic disease, it did not correlate with the mere presence or absence of malignancy. The observation of significant Tg elevation in the setting of distant metastatic disease has been previously made, although in series much smaller than the one presented here [14]. Increased Tg levels in the setting of follicular carcinoma and Hurthle cell carcinoma has also been described [14,17]. Our observations of the highest Tg level group containing a larger percentage of follicular carcinoma and Hurthle cell carcinoma are in keeping with this.

Previous studies have attempted to narrow study design to patients with a particular suspected pathology based on fine needle aspiration results and determine if within that select cohort if preoperative Tg held diagnostic or prognostic value. Besic *et al.* [7] reviewed 327 patients with follicular neoplasm that went onto surgery because of suspicion of carcinoma. A cut off of 300 ng/mL was used to define elevation of Tg pre-operatively. In conjunction with other clinical parameters (age and tumor diameter), they concluded that elevated Tg levels (>300 ng/mL) along with younger age and tumors >4 cm in size were higher risk for cancer, and should be offered total thyroidectomy. This model, however, only had a sensitivity of 57% and specificity of 61%, and Tg in isolation of the other parameters was not helpful. Petric *et al.* [14] added to the previous series with an additional 61 patients accrued over an additional 5 y. With the additional patients, now 388 in total, they again looked only at follicular neoplasms and found that a Tg level of >400 ng/mL had an odds ratio of 2.36 for malignancy, although there was an overlap of Tg levels between the benign and malignant patients.

Additional studies evaluated the utility of preoperative Tg for patients with thyroid nodules. Guarino *et al.* [18] looked at preoperative Tg measurements in patients with malignant or benign thyroid nodules. They found that Tg levels correlated to thyroid volume from

ultrasound measurements, regardless of whether the nodule was benign or malignant. They also looked at the patients with malignant nodules and did not see any difference in rates of metastatic disease or disease persistence between those patients with high *versus* low pre-operative Tg levels. They concluded preoperative serum Tg levels held neither diagnostic nor prognostic value in their series. Early work by Christensen *et al.* [19] also looked at the use of serum Tg in the preoperative setting for solitary thyroid nodules, along with physical examination findings, none-image-guided fine needle biopsy, and thyroid scan. They observed that patients with malignant tumor had significantly higher Tg levels, but there was an overlap between benign and malignant patients, making elevated Tg levels (defined as >40 mcg/L) not very specific. Only five patients in their series of 100 patients had Tg levels >500 mcg/L, of which three had papillary thyroid cancer and two had thyrotoxicosis.

Tg holds a critical role in the postoperative and long-term follow-up of patients with the most thyroid malignancies [3,8,11,20,21]. However, it is important to realize that not all patients have Tg producing tumors [6,22,23]. Giovanella *et al.* [6] evaluated 436 patients with differentiated thyroid cancer, and found that as many as 5.1% of patients had undetectable or reduced preoperative serum Tg levels. Within our study, 16 cancer patients (9.2%) out of 174 had undetectable or reduced preoperative Tg levels, suggesting this incidence of this phenomenon may be higher. This obviously changes the strategy used to follow these patients long-term and the utility of Tg levels in the postoperative period to guide treatment decisions. Ibrahimpasic *et al.* [24] have recommended using Tg levels immediately after thyroidectomy as a way to determine need in low to intermediate risk patients for radioactive iodine therapy. Patients with tumors that do not produce Tg may be incorrectly assumed to have had a complete resection without need for additional therapy, or would not have further imaging work up prompted, if neck ultrasound is unremarkable. While a small percentage of patients, if Tg is not measured when cancer is suspected preoperatively, there is no way to know if lack of detection after surgery is truly due to cure or merely nonproduction by the tumor.

As this study is retrospective in nature, it has the inherent limitations and biases of this particular study design. For purposes of this study, the presence of serum Tg antibodies did not result in patient exclusion. This was intentionally done, as positive antibodies can be present with varying incidence based on the primary pathology, and patients may often have more than one pathologic diagnosis or process within the thyroid [20]. Tg antibody can affect the measurement of serum Tg [9,10]. The data appear to demonstrate this indirectly, as the incidence of Hashimoto's thyroiditis in the lowest Tg quartile was more than double the incidence seen in the other quartiles [10]. Papillary microcarcinoma was included as a cancer diagnosis, and this may skew the data in regards to the incidence of well-differentiated cancer within each Tg quartile. As this dataset includes patients undergoing lobectomy, total thyroidectomy and completion, only those patients with a total gland weight available ($n = 419$, 69%) were included for multivariable analysis and relationship to Tg levels.

5. Conclusions

Routine use of preoperative use of serum Tg has limited utility in thyroidectomy patients, and based on these data the authors recommend against routine preoperative testing of all patients scheduled for thyroidectomy. The subset of patients in which additional study is warranted, are patients with a preoperative diagnosis of thyroid cancer, or when thyroid cancer is strongly suspected as high preoperative values are associated with metastatic disease. If preoperative serum Tg levels return >5000 ng/mL, based on the data from this series, a diagnosis of cancer with the presence of metastatic disease can be assumed and the patient can undergo total thyroidectomy and be promptly referred for radioactive iodine. Patients with a preoperative diagnosis of thyroid cancer and an undetectable preoperative Tg can have long-term follow-up tailored accordingly, with reliance on imaging modalities for disease detection [6].

Although this series represents a large cohort of thyroidectomy patients with both benign and malignant disease, only a small subset of patients had markedly elevated Tg levels (1%). A multi-institutional study may allow for the collection of a larger patient population to see if this trend of markedly elevated Tg levels indicating metastatic disease is consistent.

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Table 1

Demographics by serum Tg quartile.

	Serum Tg quartiles				<i>P</i> Value
	19 ng/mL	19.1–54 ng/mL	54.1–151 ng/mL	>151 ng/mL	
<i>N</i>	153	152	154	152	
Age (Y)	47 ± 1	49 ± 1	49 ± 1	49 ± 1	0.58
Female	122 (80%)	123 (81%)	126 (82%)	113 (74%)	0.373
BMI (kg/m ²)	29 ± 0.6	29 ± 0.6	32 ± 0.8	29 ± 0.5	<0.01
Main pathology					
Goiter	35 (23%)	51 (34%)	54 (35%)	53 (35%)	0.06
Graves	16 (11%)	11 (7%)	16 (10%)	23 (15%)	0.171
Hashimotos' thyroiditis	37 (24%)	16 (11%)	18 (12%)	16 (11%)	<0.01
Cancer [*]	55 (36%)	42 (28%)	32 (21%)	45 (29%)	0.03
Thyroid gland weight (g)	31 ± 4	33 ± 3	39 ± 3	59 ± 5	<0.01

Data are expressed as mean ± standard error of the mean, or as *N*(%).

* Includes patients with papillary microcarcinoma.

Table 2

Cancer diagnosis by serum Tg quartile.

	Serum Tg quartiles				<i>P</i> Value
	19 ng/mL	19.1–54 ng/mL	54.1–51 ng/mL	>151 ng/mL	
<i>N</i>	55	42	32	45	0.03
Type of thyroid cancer					0.03
Papillary	51 (93%)	40 (95%)	31 (97%)	34 (74%)	
Follicular	3 (6%)	1 (2%)	1 (3%)	5 (11%)	
Medullary	1 (2%)	0	0	0	
Hurthle cell	0	1 (2%)	0	6 (13%)	
Anaplastic	0	0	0	1 (2%)	
Metastatic disease	0	2 (5%)	0	8 (18%)	<0.01
Lymph node dissection	6 (11%)	4 (10%)	8 (25%)	8 (18%)	0.20
Lymph node ratio	0.25 (0.39)	0.45 (0.78)	0.30 (0.25)	0.87 (1)	0.52

Data are expressed as *N*(%) or median (interquartile range).

Table 3

Linear regression multivariable analysis of variance. Log transformation of serum Tg as dependent variable.

	B	95 % Confidence interval		P Value
		Lower bound	Upper bound	
BMI	−0.003	−0.012	0.007	0.55
Gland weight (gm)	0.005	0.003	0.007	<0.001
Cancer *	−0.004	−0.58	0.57	0.99
Hashimoto's	−0.29	−0.84	0.26	0.30
Metastatic disease	1.703	1.154	2.252	<0.001

* Includes patients with papillary microcarcinoma.

Table 4

BPatients with marked Tg elevation (>5000 ng/mL).

Patient	Age (Y)	Gender	Tg (ng/mL)	Tg antibody	Pathology	Gland weight (gm)	Metastatic disease location
1	61	F	5001	Neg	FV PTC	10.2	Lung, acetabulum
2	32	M	6000	N/A	PTC	N/A	Extensive lateral cervical disease
3	65	F	6361	58	FV PTC	79	Lung
4	78	M	17,473	Neg	FTC	20	Lung, spine, chest wall
5	50	M	22,930	Neg	FTC	56	Ischium
6	69	F	24,139	Neg	FTC	14	Spine, epidural space, chest wall

F = female; FTC = follicular thyroid cancer; FV PTC = follicular variant papillary thyroid cancer; M = male; N/A = data not available; PTC = papillary thyroid cancer.