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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.

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].

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Table 1 – Demographics by serum Tg quartile.

	Serum Tg quartiles				P Value
	≤19 ng/mL	19.1–54 ng/mL	54.1–151 ng/mL	>151 ng/mL	
N	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.

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 ± 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/m^2. 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/m^2 *versus* 29 kg/m^2 in the remaining quartiles ($P < 0.01$). Pathologic breakdown noted an increased percentage of Hashimoto's