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Prevalence and Clinical Significance of Preoperative Thyroglobulin Antibodies in Differentiated Thyroid Cancer Patients

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Abstract

Thyroglobulin antibody (TgAb) has been used as a surrogate tumor marker of differentiated thyroid carcinoma (DTC) patients. Preoperative TgAb (PreopTgAb) is thought to affect the prevalence, disease severity, and outcome of DTC. The objective of the present study was to retrospectively analyze the prevalence of PreopTgAb in patients diagnosed with DTC and its relation to thyroid cancer characteristics, staging, and disease outcome. A retrospective analysis of 109 DTC patients with reports of PreopTgAb was carried out. Clinicopathological parameters, including patient demographics (age and gender), TNM staging, histopathologic characteristics (type of pathology, vascular invasion, extrathyroid extension, carcinoma variant, multifocality), treatment (surgery, radioactive iodine), and outcome were recorded. The association of PreopTgAb was compared with the study variables and outcome of the disease using the Chi-square test and Mann-Whitney tests. The prevalence of PreopTgAb was 59.6%. Among the 54 PreopTgAb positive patients, 34 patients had an excellent response and 15 patients had an indeterminate response, while biochemically and structurally incomplete response was observed in 3 and 2 patients, respectively. PreopTgAb was not significantly associated with age ($p = 0.919$), sex ($p = 0.650$), pathology ($p = 0.079$), stage at diagnosis ($p = 0.513$), vascular invasion ($p = 0.211$), extra thyroid extension ($p = 0.734$), histologic variant ($p = 0.877$), multifocality ($p = 0.361$), and outcome ($p = 0.360$). Although we did not find a significant association between positive PreopTgAb and clinical characteristics and outcome of DTC, it can still be considered as a surrogate marker of DTC during follow-up.

Keywords

Differentiated Thyroid Carcinoma, Preoperative TgAb, Treatment Outcome, Surrogate Marker

1. Introduction

Thyroid cancer is one of the most common cancers of the endocrine system, with a rising incidence in recent years. Among them, differentiated thyroid cancer (DTC) accounts for more than 90% of thyroid malignancies. Total thyroidectomy is the treatment of choice followed by thyroid hormone replacement and radioactive iodine for remnant ablation. Factors such as age, gender, tumor size, multifocality, capsular invasion, extra thyroid extension, and lymph node metastasis are related to the surgical outcome and prognosis. Additionally, dynamic disease stratification beginning from the initial diagnosis helps to predict the treatment approach, mortality, risk of recurrence, and response to initial therapy and assess the relapse of DTC [1] [2] [3] [4]. Patients with DTC have a good prognosis with a recurrence rate ranging from 0.6% - 2.8% in low-risk patients, which mandates lifelong surveillance in such patients [5].

Thyroglobulin (Tg), a thyroid-specific protein, is considered a serologic tumor marker for surveillance of DTC as it is produced only in normal cells or in cancer tissue. Because many differentiated thyroid cancers produce Tg, measurement of serum Tg can detect thyroid cancer recurrence or progression and is, therefore, an important element of long-term surveillance in patients with thyroid cancer [6]. However, the clinical utility of Tg is limited in the presence of antithyroglobulin antibodies (10% - 30% patients with DTC) [7] [8], which interferes with Tg measurement [9]. TgAb, therefore, represents a significant clinical issue in thyroid cancer monitoring [7]. After surgical treatment, there is a substantial decrease in the Tg as well as TgAb levels, and it reduces progressively and becomes undetectable. The increase in TgAb values post-therapy is suggestive of either presence of a residual tumor, immune response to it, or suggestive of recurrence [10]. Persistent or rising TgAb titers have been associated with disease recurrence, whereas early clearance of TgAb may be associated with decreased risk of recurrence [11]-[17]. Therefore, it is considered a valuable surrogate tumor marker for longitudinal monitoring in DTC-treated patients.

It is evident that the incidence of preoperative TgAb (PreopTgAb) is higher in patients with DTC, suggesting a potential predictive role of TgAb in DTC; however, the association between TgAb and DTC is controversial [18]. In addition to the prognostic marker role of postoperative TgAb role, few authors have studied the role of preopTgAb in DTC and suggested that the presence of TgAb is associated with aggrieve DTC characterized by extrathyroidal extension, Lymph node metastasis [11]. Although authors have tried to correlate the presence of preopTgAb with clinical characteristics and prognosis, the results are inconclusive and, the mere presence of TgAb does not conclusively determine the severity and prognosis [19] [20] [21] [22]. Given the clinical relevance of TgAb and the extended duration of monitoring required in thyroid cancer patients, the present study was carried out to determine the prevalence of preopTgAb in patients diagnosed with DTC and to evaluate its significance to thyroid cancer characteristics, staging, and disease outcome.

2. Material and Methods

This hospital-based retrospective study was conducted in the Department of Medicine, King Abdulaziz University Hospital (KAUH), Saudi Arabia. The research proposal was approved by the biomedical ethics research committee, King Abdulaziz University (Ref no. 695-20 dated 28 December 2020). We retrieved medical records of all patients diagnosed with differentiated thyroid carcinoma and underwent treatment in the last sixteen years (from 2004 to 2020). All patients with records of preopTgAb test reports (n = 109) were included in the study, and those patients with no records of preopTgAb were excluded. Clinicopathological parameters, including patient demographics (age and gender), Tumor, Nodal involvement and metastasis (TNM) Classification of Malignant Tumors staging, histopathologic characteristics (type of pathology, vascular invasion, extrathyroid extension (ETE), carcinoma variant, multifocality), treatment(surgery, radioactive iron treatment (RIA)), and treatment outcome were retrieved from the medical records.

ARCHITECT Anti-Tg, a Chemiluminescent Microparticle Immunoassay (CMIA) was used to measure TgAb values. Baseline or preopTgAb was obtained one month to <12 months before surgery. Serum TgAb cut-off value was set at 10 UI/mL. Serum TgAb > 10 UI/mL was considered positive, while serum TgAb < 10 UI/mL was considered negative. Response rate or outcome was categorized based on the 2015 ATA DTC guidelines at one-year post-surgery or RAI [6].

The following criteria were used to categorize treatment responses. Negative postoperative thyroglobulin and TgAb were considered as Excellent response, positive thyroglobulin or TgAb with an increase in concentration was considered an incomplete biochemical response, unchanged thyroglobulin or TgAb status was considered indeterminate, and highly suspicious status regardless of TgAb was considered incomplete structural response [23] [24].

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2010) and then exported to the data editor page of IBM SPSS version 22.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were calculated. The association of PreopTgAb was compared with the study variables and outcome of the disease using the Chi-square test and Mann-Whitney tests. For all tests, the confidence interval and p-value were set at 95% and ≤0.05, respectively.

3. Results

In our study, out of 109 patients, 65 (59.6%) patients had positive preopTgAB while 44 (40.4%) patients had negative preopTgAb. The mean age of the patients in our study cohort was 41.28 ± 13.59 years; the mean age of patients did not differ between TgAb positive and negative patients (p = 0.919). The majority of patients (88.1%) were females; gender had no relation to the preopTgAb positivity (p = 0.650). The mean weight (kg), height (cm) and BMI (kg/m^2) of the study population were 71.57 ± 14.71, 161.88 ± 8.28 and 27.12 ± 4.66 respectively. Al-

most all patients (93.6%) were categorized as TNM stage I; among them, 59.8% of patients were TgAb positive. No significant difference was observed between the distribution of patients based on TNM staging and preopTgAb positivity (p = 0.513) (Table 1).

Table 1. Comparative assessment of preoperative TgAb with clinicopathologic characteristics of differentiated thyroid carcinoma.

Independent variables		TgAb Negative n (%)/Mean ± SD	TgAb Positive n (%)/Mean ± SD	Total	p-value
Age (years)@		41.36 ± 13.88	41.23 ± 13.49	41.28 ± 13.59	0.919
Sex#					
Male		6 (46.2)	7 (53.8)	13 (11.9)	0.650
Female		38 (39.6)	58 (60.4)	96 (88.1)	
Stage at diagnosis#					
0		1 (100)	0	1 (0.9)	
I		41 (40.2)	61 (59.8)	102 (93.6)	
II		2 (50)	2 (50)	4 (3.7)	0.513
III		0	1 (100)	1 (0.9)	
Stage IV b			1 (100)	1 (0.9)	
Pathology#					
Papillary		36 (37.1)	61 (62.9)	97 (89)	
Follicular		5 (83.3)	1 (16.7)	6 (5.5)	
Poorly Differentiated		1 (25)	3 (75)	4 (3.7)	0.079
Hurthle cell cancer		1 (100)	0	1 (0.9)	
NIFTP		1 (100)	0	1 (0.9)	
Variant#					
Classical PTC		13 (52)	12 (48)	25 (22.9)	
Follicular PTC		8 (42.1)	11 (57.9)	19 (17.4)	
Tall cell variant		0	1 (100)	1 (0.9)	0.510
Columnar		0	1 (100)	1 (0.9)	
Papillary microcarcinoma		14 (38.9)	22 (61.1)	36 (33)	
Follicular cancers and others		7 (63.6)	4 (36.4)	11 (10.1)	
Vascular invasion#					
Papillary	None	34 (38.6)	54 (61.4)	88 (80.7)	
	Present	3 (30)	7 (70)	10 (9.2)	
Follicular	Minimally invasive	2 (100)	0	2 (1.8)	0.211
	Encapsulated angioinvasive	2 (66.7)	1 (33.3)	3 (2.8)	
	Widely invasive	1 (100)	0	1 (0.9)	

Continued

Extrathyroid extension#				
None	40 (42.1)	55 (57.9)	95 (87.2)	
Minimal	3 (30)	7 (70)	10 (9.2)	0.734
Extensive	1 (33.3)	2 (66.7)	3 (2.8)	
Multifocality#				
Absent/Unifocal	21 (36.2)	37 (63.8)	58 (53.2)	0.361
Present	22 (44.9)	27 (55.1)	49 (45)	

Test applied: @Mann Whitney test, #Chi square test.

Papillary thyroid carcinoma (PTC) was seen in 97 (89%) patients, followed by follicular carcinoma (5.5%), poorly differentiated (3.7%), Hurthe cell carcinoma, and NIFTP was seen in 1 (0.9%) patient each. PreopTgAb was positive in 62.9% of patients with papillary carcinoma; however, it did not have a significant association with the type of pathology (p = 0.079). Among the histologic variants, papillary microcarcinoma (33%) was the most common variant, followed by classical PTC (22.9%) and follicular PTC variant (17.4%). No significant association was observed between the histologic variant and preopTgAb status (p = 0.510). Vascular invasion was present in 10 (9.2%) patients, among whom 7 (70%) patients were preopTgAb positive. However, the association between vascular invasion and preopTgAb was not significant (p = 0.211). Minimal ETE was present in 10 (9.2%) patients, while 3 (2.8) patients had extensive ETE. In preopTgAb positive patients, minimal and extensive ETE was observed in 7 (70%) and 2 (66.7%) patients, respectively; however, preopTgAb did not affect the ETE in our study population (p = 0.734). Multifocality was observed in 49 (45%) patients; the mean size of the largest focus was 2.04 ± 1.61 mm. Among them, 27 (55.1) were TgAb positive and 22 (44.9) were TgAb negative (p = 0.361) (Table 1). Similarly, no significant association between preopTgAb and Capsule invasion (p = 0.402) and margin involvement (p = 0.611).

Further, the association of the postoperative outcome of DTC patients and preopTgAb is summarized in Table 2. Records of only 90 patients (preopTgAb+ve = 54; preopTgAb-ve = 36) were available for analysis. Among the 54 preopTgAb positive patients, 34 patients had an excellent response and 15 patients had an indeterminate response, while the biochemically incomplete and structurally incomplete response was observed in 3 and 2 patients, respectively. Preoperative TgAb had no effect on the outcome response in our study population (p = 0.360).

4. Discussion

Despite treatment, mortality associated with DTC is 10%, with a considerably higher incidence of recurrences [1]. Therefore, it is important to identify the clinicopathological predictors of DTC to plan an appropriate treatment strategy.

Table 2. Effect of Preoperative TgAb on treatment outcome in DTC patients.

Outcome response	TgAb-ve (N = 36)	TgAb+ve (n = 54)	Total (n = 90)	P value
Excellent response	21 (38.2%)	34 (61.8%)	55 (50.5%)	0.362
Indetermined response	7 (31.8%)	15 (68.2%)	22 (20.2%)	
Biochemically incomplete	5 (62.5%)	3 (37.5%)	8 (7.3%)	
Structurally incomplete	3 (60%)	2 (40%)	5 (4.6%)	

Test applied: Chi-square test; For all tests, confidence interval and p-value were set at 95% and ≤0.05, respectively.

Over the years, many researchers have focused on analyzing the predictive factors of thyroid cancer and its relation to the disease outcome. Factors such as age, gender, tumor size and extension, lymph node involvement, and metastasis have been identified as predictors of DTC, its treatment response, and prognosis [1]. Along with demographic and pathological factors, Tg and its antibodies have gained attention. TgAbis an intrafollicular antibody that binds to immune cells and antigens in the presence of Major T cell epitomes on Tg [3]. Kim *et al.* [13], Jia *et al.* [18], Qin *et al.* [20], McLeod *et al.* [25], Rago *et al.* [26], He *et al.* [27], Hosseini *et al.* [28], and Grani *et al.* [29] have identified positive TgAb as an independent predictor of thyroid malignancy.

In our study, out of 109 patients, 65 (59.6%) patients had positive preopTgAb while 44 (40.4%) patients were negative. Prevalence of positive TgAB was much higher than 10.9% reported by Kim *et al.* [5], 19.9% by Jia *et al.* [18], 35.2% by Morbelli *et al.* [19], 35% by Gholve *et al.* [30], and 38.2% by Vasileiadis *et al.* [31]. The difference in the prevalence rates observed in various studies can be due to the variability in the measurements obtained by using different commercially available methods as well as the use of different cutoff points in studies as per the institutional and study protocol [25]. Moreover, TgAb measurement before surgery is correlated with the degree of lymphocytic infiltration, being higher in cases with massive infiltration and lower in those with no infiltration. TgAb found in DTC could be a consequence associated with lymphocytic infiltrate or immune reaction to thyroid cancer [32].

The mean age of the patients in our study population was 41.28 ± 13.59 years which is in accordance with studies by Giannoula *et al.* [1] and Kim *et al.* [13]. Rago *et al.* [26] observed a higher prevalence of preopTgAb in females as compared to males. On the contrary, a higher prevalence of preopTgAb in males (7.7%) as compared to females (2.4%) was observed by Jia *et al.* [18]. In our study, since the majority of patients (88.1%) were females, the preopTgAb positivity was also higher in females. Although demographic factors such as age and sex are predictors of DTC, similar to the results by Chung *et al.* [12], Kim *et al.* [13], and Trimboli *et al.* [22], we did not observe any correlation between preopTgAb and demographic characteristics in DTC patients. In our study, almost all patients (93.6%) were categorized as TNM stage I. Among them, 59.8%

of patients were TgAb positive. According to Chung *et al.* [12], McLeoid *et al.* [25], Jia *et al.* [18] Qin *et al.* [20], preopTgAb was not independently associated with the tumor stage. Similarly, no significant difference was observed between the distribution of patients based on TNM staging and preopTgAb positivity in our study.

Among the several subtypes of DTC, PTC is the most common and accounts for 85% of all cases; follicular thyroid cancers and Hurthle cell variants comprise 12% of DTC, while poorly differentiated cancer account for less than 3% of cases [33]. In our study, PTC was seen in 89% of patients, followed by follicular carcinoma (5.5%), poorly differentiated (3.7%) and, Hurthe cell carcinoma and NIFTP were seen in 1 (0.9%) patient each. Among the histologic variants, papillary microcarcinoma (33%) was the most common variant, followed by classical PTC (22.9%) and follicular PTC variant (17.4%). It is evident that the frequency of preopTgAb is higher in PTC than in follicular carcinoma [3]. An increase in preopTgAb positivity with PTC could be due to the difference in antigenic expression in different types of carcinomas [34]. Similarly, preopTgAb was positive in 62.9% of patients of PTC. Interestingly, our study population consisted of tall cell or columnar variants in one patient each, and both were TgAb positive. Similar to the report by Chung *et al.* [12] and Trimboli *et al.* [22], the histopathology of DTC was independent of preopTgAb values.

DTC is associated with ETE, vascular invasion, multifocality, and distant metastasis with corresponds to high recurrence rates and poor prognosis [35]. According to Kim *et al.* [13], Matrone *et al.* [36], and Jo *et al.* [37], positive preopTgAb is common in the aggressive form of DTC. It is believed that metastasis or invasion resulting from the primary tumor will induce a cancer-specific immune response resulting in positive TgAb [3]. In a study by Kim *et al.*, multifocality (48%), ETE (69%), central lymph node metastasis (57%), and lateral cervical LN metastasis (23%) were common in TgAb positive patients. In our study, the vascular invasion was present in 10 (9.2%) patients, among whom 7 (70%) patients were preopTgAb positive. In preopTgAb positive patients, minimal and extensive ETE was observed in 7 (70%) and 2 (66.7%) patients, respectively, and multifocality was observed in 49 (45%) patients. However, no correlation between preopTgAb and disease severity was noted, which is in accordance with the observation by Durante *et al.* [11], Kim *et al.* [13], Jia *et al.* [18], and Jo *et al.* [37].

In the present study, total thyroidectomy/subtotal thyroidectomy was performed in 98 (89.9) patients, while 61.5% were given at least one dose of RAI. Theoretically, the complete elimination of follicular cells during thyroidectomy, followed by ablation, will stop the antigenic stimuli, resulting in the decline and disappearance of TgAb. Following surgery, due to decreased formation of Tg and increased metabolic clearance of Tg-TgAb complexes, there is a transient decline in TgAblevels [8]. However, it takes up to a median of 3 years for the complete disappearance of TgAb [25], and hence, it is considered as a surrogate marker for DTC recurrence [32]. Rising levels of TgAb after initial treatment is a

biochemical incomplete response. This new appearance of TgAb/rising values is associated with the risk of recurrence/persistent disease [35]. Hsieh *et al.* [14] conferred that persistently high TgAb levels (incomplete biochemical response) are a predictor of poor prognosis. Therefore, such patients need to be monitored for disease recurrence. It could be because of the immune reaction phenomenon explained above.

On the other hand, non-decreasing TgAb (indeterminate response) and the persistence of TgAb concentration for a long period after therapy is an indicator of persistent disease or recurrence [13]. This could be a result of residual normal thyroid tissue, the coexistence of autoimmune thyroiditis, or antibody production by memory cells [18]. "Indeterminate response" may also occur as a result of inaccurate Tg values due to interference of TgAb in the clinical assessment of DTC. In such cases, alternate methods such as neck ultrasound or image explorations are sought [35]. Postoperatively, a reduction of >50% TgAb from the baseline value is indicative of a better prognosis [38]. A slow and steady decrease in the TgAb levels post-treatment suggests a good prognosis; while an increase TgAb indicates a poor prognosis [32]. On the contrary, patients with positive preopTgAb, who become negative postoperatively and subsequently become positive, are at a higher risk of recurrence [35].

Among the 54 preopTgAb positive patients, 34 patients had an excellent response and 15 patients had indeterminate responses, while the biochemically incomplete and structurally incomplete responses were observed in 3 and 2 patients, respectively. In a study by Zavala *et al.* [23], 68.3% showed an indeterminate response followed by an excellent response in 24.4% of patients, biochemical incomplete in 4.9%, and structural incomplete in 1%. Ora *et al.* [38] suggested that high postoperativeTgAb and lateral compartment metastasis are risk factors for the persistence of high TgAb levels and incomplete treatment response in long-term follow-up. They observed an anatomical recurrence in patients with >1000 IU/mL TgAb values on longer follow-ups. Similarly in our study, we observed indeterminate response in four PTC patients with preopTgAb > 1000 IU/mL and two PTC patients with preopTgAb > 4000 IU/mL, and structurally incomplete response in an elderly patient with poorly differentiated cancer with preopTgAb > 1000 IU/mL at one year follow up.

Giannoula *et al.* [1] observed a significant association with treatment response and TgAb. Trimboli *et al.* [23], Kim *et al.* [13], and Seo *et al.* [39] observed that positive preopTgAb was associated with the risk of disease recurrence as compared to preopTgAb negative patients. While Ora *et al.* [38] observed an association between baseline TgAb value and treatment outcome, similar to results by Soyluk *et al.* [18] and Patell *et al.* [40], preopTgAb had no correlation with the outcome response in our study population. According to Ora *et al.* [28], 35.52% and 67.05% recurrence was seen in patients with baseline TgAb of <100 and 500 IU/ml, respectively. Similarly, with a cut-off value of 100 IU/Ml, Kim *et al.* [13] observed a recurrence of 18% and 1% in patients with less than or above the

value, respectively [13]. This indicates the importance of the cut-off value of the TgAbassay.

It is well known that postoperative TgAb is associated with persistent disease and less favorable long-term outcomes; while normalization of TgAb titers within the first year was associated with decreased risk of recurrence [11]. Therefore, the measurement of TgAb over a period of time is a better indicator than cross-sectional TgAb value at one point [21]. Moreover, follow-up of these patients for a longer duration is paramount as these are helpful markers of recurrence, especially in patients with undetectable Tg. However, measurement of TgAb is a challenge as there is no single commercially available immunoassay capable of detecting all the circulating TgAbs as a result of restricted epitope range. Therefore, during annual thyroid surveillance checkups, along with clinical examinations, imaging, and Tg measurements, measurement of TgAb must also be recommended [2]. Furthermore, to avoid variable results, a single immunoassay along with an appropriate cut-off (lower limit of the assay) value must be followed throughout the study period.

Gaps in the available and recorded data are a major limitation of the study. Firstly, since it was a single-center study, the sample size was relatively small. Therefore, the results must be validated by multicentric prospective studies with large sample sizes. Methodological factors impacting TgAb measurements are also a significant barrier to reliable results as inaccurate measurements lead to improper results, hindering the prognostic value of TgAb in DTC. Since TgAb-values are dependent on the type of assay and determined cut-off value [18], selecting an appropriate assay with a specific cut-off value is required to reduce bias in data and subsequent results. We further recommend studies to assess the feasibility of using TgAb as a supportive predictive marker for DTC and understanding the epitome-specific immunological response of TgAb in thyroid cancer.

5. Conclusion

Due to a lack of definitive evidence, formulating a treatment plan and assessing the prognosis of DTC patients remains a major challenge. With an increase in the incidence of thyroid cancer worldwide, there is a need for lifelong surveillance. We recommend screening tests for TgAb at initial appointments in all high-risk patients (higher TNM stage, histologic stage with higher prognosis, recurrent disease). However, clinicians must be knowledgeable of different TgAb assays and cut-off values, as well as their limitations and pitfalls. Furthermore, knowledge of the false positive and false negative measurements is also essential. Although we did not find a significant association between positive preoperative TgAb and clinical characteristics and outcome of DTC, it can be considered as a prognostic marker of DTC during follow-up.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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