AntiThyroglobulin Antibody as a Prognostic Factor to Evaluate the Recurrence and Metastases of Differentiated Thyroid Carcinoma following Radioactive Iodine Ablation

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ABSTRACT

Objectives: Patients with Differentiated Thyroid Carcinoma (DTC) are usually treated with thyroidectomy followed by radioactive iodine ablation (RAIA). After treatment, during their follow up period, serum thyroglobulin (Tg) estimation and diagnostic whole body ^{131}I scan (DxWBS) are established modalities to observe recurrence. The aim of this study was to evaluate the clinical significance of TgAb levels for possible use as a prognostic factor of recurrence and metastases of disease.

Patients & Methods: An observational Cohort study was conducted in total 48 diagnosed DTC patients who underwent total thyroidectomy followed by RAIA during July, 2016 to June, 2017 at National Institute of Nuclear Medicine & Allied Sciences (NINMAS). Among them, 24 patients with high TgAb level (>40 IU/ml) were considered as group I and 24 DTC patients with low TgAb level (<40 IU/ml) was considered as group-II. Detail history, clinical examination, Tg & anti TgAb levels were assessed and DxWBS were done in all patients. Fine needle aspiration cytology (FNAC) of enlarged lymphnodes and ^{18}Fluorine- fluorodeoxyglucose positron emission tomography-Computed Tomography (^{18F}-FDG PET-CT) were done in patients with negative DxWBS but having high anti TgAb. Demographic and clinicopathological characteristics were compared between two groups and recurrence and metastases were observed. Statistical analysis was done.

Results: Among 24 patients of Group-I, 6 patients showed either metastases or recurrences and no patient of group-II showed metastasis or recurrence. The difference was statically significant ($p<0.05$) between two groups. Relative risk (RR) was found 2.33 in group-I in comparison to group-II, suggesting the patients at higher risk of metastases or recurrence in group-I than group-II who had high anti TgAb.

Conclusion: Among DTC with high TgAb patients, papillary carcinoma was more common. Recurrence and metastases were evaluated in 6(25%) patients who had high antiTgAb level and 0% with low anti TgAb levels. This may be concluded that, high TgAb levels in patients with DTC could be considered as a marker to evaluate recurrence and metastases after RAIA. Patients of DTC with high TgAb are at risk of recurrence and metastases during follow up period as the RR was found 2.33.

Key words: **Differentiated thyroid carcinoma (DTC), radioactive iodine ablation (RAIA), Thyroglobulin (Tg), Thyroglobulin antibodies (TgAb)**

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INTRODUCTION

Thyroglobulin (Tg) is a protein made only by thyroid cells, both normal persons and thyroid cancer. When all thyroid tissue is destroyed in patients with differentiated thyroid carcinoma (DTC) after surgery and radioactive iodine ablation (RAIA), Tg can be used as a thyroid cancer marker. Persistent levels of Tg indicate that, there are still thyroid cells in the body and rising Tg levels indicate recurrence of the thyroid cancer, most commonly after spread of the cancer to the lymph nodes in the neck. Undetectable Tg levels usually indicate remission of the thyroid cancer. However, antibodies to Tg exist up to 25% of these patients and can interfere with the measurement of Tg in the blood (1). Measurement of Tg levels could be made difficult in the presence of Thyroglobulin antibodies (TgAb) and it should be checked. Estimation of TgAbs revealed that these are more prevalent in thyroid cancer patients than in the general population. TgAbs may interfere with Tg estimation, sensitive assays can detect low serum levels of Tg in presence of TgAbs (2,3). Diagnosis and treatment of residual or relapsing DTC may be influenced with the interaction of TgAb with Tg in the patient's blood. The measurement of TgAb is not widely accepted as the

prognostic factor of DTC. In controversy, some authors suggested TgAb may be an alternative tumor marker (4). The persistence of detectable circulating TgAb, particularly if at high levels, may suggest the presence of metastatic tissue in some patients and Tg measurement in these patients may be lowered because of the presence of TgAb. In these cases, patients with DTC with persistent circulating TgAb after treatment should be considered at risk. These patients should be followed until the disappearance of circulating TgAb after therapy, which seems to represent an important favorable prognostic factor. TgAb determination appears useful during follow-up of the patients with DTC, not only to validate the Tg assay but because TgAb themselves may provide additional clinical information for the follow-up of DTC patients (5).

The purpose of this study is to assess thyroglobulin antibody level as a prognostic factor to evaluate the recurrence and metastases of DTC patients after RAIA.

PATIENTS AND METHODS

This observational cohort type of study was carried out among the patients with DTC after total thyroidectomy and RAIA during the follow-up period at Thyroid division, National Institute of Nuclear Medicine & Allied Sciences (NINMAS) from July 2016 to June 2017. Before commencement of this study, approval was taken from the Institutional Medical Research Ethics Committee (MREC), NINMAS, and human research ethics certificate of approval (ref no:39.01.2675.252.099.26.2013/22) was obtained. Informed written consents were obtained. Proper permission was also taken from the concerned divisional heads.

A total of 24 patients of DTC with high TgAb during follow-up period at Thyroid division, NINMAS, were included in group-I and 24 patients of DTC with normal TgAb during follow up period was obtained as control (Group-II). Pregnant patients, patients with poorly differentiated thyroid carcinoma, anaplastic thyroid carcinoma, known immune-compromised DTC patients were excluded from the study. Sampling technique was purposive sampling. Details of the history, histopathological report, clinical examination were taken and noted on the structured questionnaire in both case and control groups.

The results of the routine investigations, TSH, Tg (>10 ng/ml were considered as high in case of DTC patient), and TgAb (>40 IU/ml was considered as high) were recorded. TgAb assay was performed according to the chemiluminescent technique by IMMULITE, DPC, USA, and recorded in a structured questionnaire in both groups and statistically compared. Assessment of the persistent or recurrent disease was confirmed by the imaging modalities available. Diagnostic whole-body scan (DxWBS) was done in all patients and FNAC of enlarged lymph nodes/mass or PET-CT scan was done in Dx-WBS negative patients and all data were recorded. Statistical analysis was done between two groups.

Statistical analyses were carried out by using the Statistical Package for Social Sciences version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). A descriptive analysis was performed for all data. The mean values were calculated for continuous variables. The quantitative observations were indicated by frequencies and percentages. Unpaired t- test used to compare continuous variables between high TgAb was considered as case and normal TgAb was considered as control. Chi-square test and fisher's exact test was used to compare categorical data like clinical signs and symptoms. Results were summarized as odds-ratios (RR) and their respective 95% confidence interval (CI). A "p" value <0.05 was considered as significant.

RESULTS

In this study, the level of TgAb ≥ 40 IU/mL was considered as high. It was observed that the mean TgAb level was 330.2 ± 238.8 IU/ml with range from 41.8 to 1000 IU/ml in group I and 15.27±4.84 IU/ml with ranged from 1.15 to 30.8 IU/ml in group II. The mean TgAb level was significantly (P<0.05) higher in group I.

Table 1 shows distribution of the study patients by age, it was observed that majority (45.8%) patients belonged to age 31-40 years in group-I and 12(50.0%) patients belonged to 41-50 years in group-II. Different types of DTC in group-I are shown in Figure 1.

Table 1: Distribution of the study patients by age (n=48)

Age (in years)	Group-I (n=24)		Group-II (n=24)		p value
	n	%	n	%	
≤30	8	33.3	0	0.0	
31-40	11	45.8	3	12.5	
41-50	2	8.3	12	50.0	
51-60	0	0.0	3	12.5	
>60	3	12.5	6	25.0	
Mean ± SD Range (min, max)	35.6 ± 15.0 (15,70)		39.67 ± 12.49 (21,65)		0.312^{ns}

Group-I = DTC patients with **high** TgAb was considered as exposed group.
Group-II = DTC patients with **Normal** TgAb was considered as unexposed group. ns-not significant

Table 2: Distribution of the study patients by gender (n=48).

Gender	Group-I (n=24)		Group-II (n=24)		p value
	n	%	n	%	
Male	3	12.5	5	20.8	0.438^{ns}
Female	21	87.5	19	79.2	

ns = not significant
p-value obtained from chi-square test

It was observed that the majority (87.5%) of patients were female in both groups. There were no significant differences in age and sex distribution between the two groups (p >0.05) (Table 2)

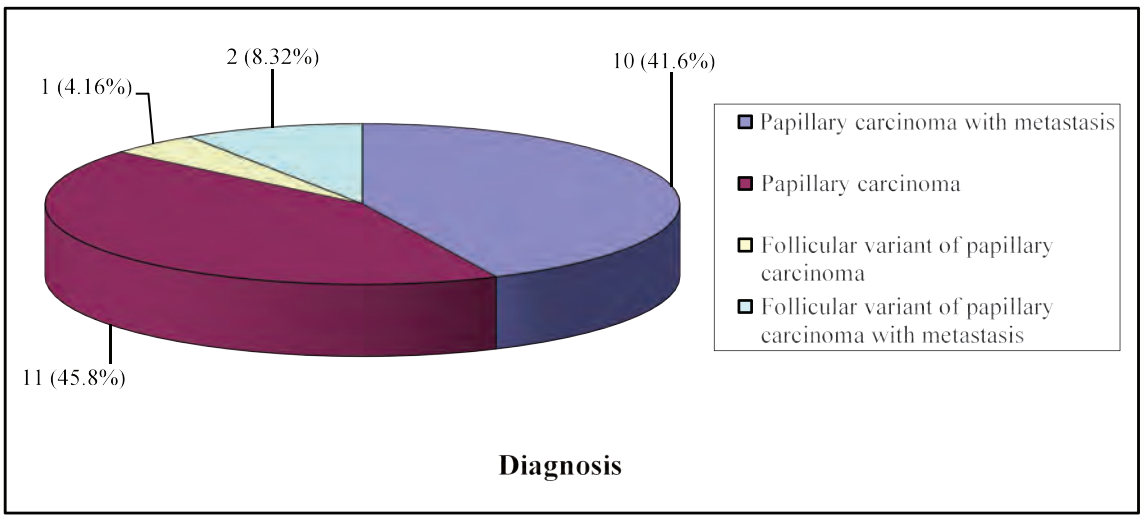

Figure 1: Pie chart shows types of DTC patients with high TgAb.

Table 3: Diagnostic Whole body scan findings in group I (n=24).

Diagnostic WBS	Number of patients	Percentage
Positive	3	12.5
Negative	21	87.5

DxWBS reports of the group-I patients was found positive in 3(12.5%) and negative in 21(87.5%). FNAC was done in 18 patients with enlarged neck lymph nodes and PET-CT was done in 3 patients. Among the 21 patients with negative DxWBS reports, two patients showed metastases of enlarged lymph nodes in cytology and one patient showed metastases in PET-CT scan (Table 3).

Table 4: Presence of recurrence and metastases in patients diagnosed by ultrasound imaging, whole body scan, PET scan and confirmed by FNAC.

	Group I (n=24)		Group II (n=24)		RR	95% CI (Lower-Upper)	P value
	N	%	n	%			
Recurrence	2		0	0.0			
Metastases	4	25.0			2.33	1.65-3.31	0.022[s]
Negative for recurrence or metastases	18	75.0	24	100.0			

s = significant
p-value obtained from chi Square test

Recurrence rate in group I is shown in Table 4, where 2.5% (6/24) showed disease recurrence and the rate was 2.33 times increased than the control group (II). The difference was statistically significant ($p < 0.05$)

DISCUSSION

DTC may affect people of all age groups from childhood to extremely old patients (6). A total of 48 patients with DTC were analyzed in this study. It was observed that the majority (45.8%) of patients belong to 31-40 years in group-I and 50.0% of patients belong to 41-50 years in group-II. The mean age was found 35.6 ± 15.0 years ranging from 15 – 70 years in group-I and 39.67±12.49 years ranging from 21 to 65 years in group II. The mean age difference was statistically not significant ($P>0.05$) between two groups. Asli et al. (2014) (7) observed the mean age of their study patients was 40 ± 15 years and 40.1 ±17.2 years respectively, which are comparable with the current study. On the other hand, Toubeau et al. (2004) (8) found ≥45 years as predominant (57.0%) age group in their study patients with a mean age of 47.0 ± 15.0 years, which appears older than the current study populations. Geographical variations, race, ethnic differences, genetic cause, and patient selection methods may be the underlying influencing factors.

The majority of patients (87.5%) were female in group I and 79.2% patients in group II; female predominance was found in patients with DTC. Asli et al. (2014) and Toubeau et al. (2004)

also found similar trends and the number of female patients were 83% and 87.4% respectively (7, 8). The majority of patients with high TgAb had papillary carcinoma (63.64%), with or without metastases. Whereas, follicular carcinoma was detected in 20.77% (9).

Most investigators reported that papillary thyroid carcinoma (PTC) or follicular thyroid carcinoma (FTC) are common variety which together represents more than 90% of all thyroid malignancies (10-12). Asli et al. (2014) (7) mentioned that 93.0% patients diagnosed with the papillary type of DTC, and 7.0% cases had follicular type of DTC.

In this study, the level of TgAb ≥ 40 IU/mL was considered high. It was observed that the mean TgAb level was 330.2 ± 238.8 IU/ml, ranging from 41.8 to 1000 IU/ml in group I and 15.27 ± 4.84 IU/ml ranging from 1.15 to 30.8 IU/ml in group II. The mean TgAb level was significantly higher in group I ($P<0.05$). Asli et al. (2014) also observed a TgAb level of 250 ± 893 U/mL with a range of 0-9000 U/mL. Among them, 34.9% had TgAb levels higher than 100 U/mL. In another study, the authors observed that patients with intra-thyroidal tumor had higher TgAb levels (445.0 ±250.6U/ml) and patients with lymph node metastases and lung metastases had 418.4 ± 236.1 U/ml, and 473.7 ± 277.2 U/ml respectively (5). TgAb levels were significantly higher in patients with persistent disease in comparison to disease free ($p<0.01$) patients. The above findings are comparable with the current study. Serum Tg measurements have been a major tool for detecting recurrence of DTC in the absence of TgAb (10-12). Diagnosis and treatment of residual or relapsing DTC may be influenced by the interaction of TgAb with Tg. The measurement of TgAb is not widely accepted as the prognostic factor of DTC. In controversy, some authors suggested TgAb may be an alternative tumor marker (4).

All patients of group-I underwent high resolution neck ultrasound (HRUS) and DxWBS. FNAC was done in 18 patients and PET-CT imaging in 3 patients after a negative DxWBS. Among them, three (3/18) were cytology positive and three (3/3) were PET scan positive. More data suggested disease progression with high anti TgAb in 9.0% of patients (8). HRUS was a useful tool to evaluate thyroid bed recurrence and cervical lymph node metastases.

DxWBS was done in 24 cases, out of the 12.5% of patients had a positive diagnosis in patients with DTC having high TgAb (7). Asli et al. (2014) observed 14.0% cases with metastasis, with or without thyroid bed or lymph node involvement on RxWBS (7). Serum Tg level of 10 ng/ml was considered as a cut-off point for metastases. A Tg level above 10 ng/mL is highly predictive of recurrences considered by many investigators because of such levels (13-18). This value of Tg has been considered even when simultaneous DxWBS was negative (18, 19).

It was observed that 6 (25%) DTC patients had recurrence and metastasis who had high TgAb in group I, the difference was statistically significant ($p<0.05$) between two groups, where relative risk was 2.33 times with 95% CI, 1.65-3.31%. Spencer (2011) observed that TgAb is a more specific marker than thyroid peroxidase antibodies (TPOAb) and approximately 20% of DTC patients had high antiTgAb. He explained that TgAb concentrations respond to changes in Tg-secreting thyroid tissue (11).

TgAb are moe frequently found in patients with Hashimoto's thyroiditis and may have a higher risk for PTC. In another study, Gorges et al. (2005) (4), observed evidence of more circulating TgAb in patients with DTC. The prevalence of TgAb was 29.0% with a median level of 130 U/ml initially. Trauseiut ice TgAb levels wewe abserved in one tenth of their study subjects. After 3 years, the prevalence of demonstrable TgAb decreased to <10%. Serum TgAb reduced Tg values by up to 32% by invitro dilution assay. The course or further increment of TgAb levels in DTC patients cannot be predicted by initial or residual tumour volume, TgAb or Tg levels. Tg underestimation may be occured in the presence of TgAb, even in low concentrations (4).

The study population comprised of patients from one selected hospital in Dhaka city, so the results of the study may not reflect the exact scenario of the whole country. Present study was conducted at a very short period with. Small sample size. In future further study may be done with large imoliving more beuter sample size.

CONCLUSION

This study was undertaken to assess the role of TgAb as a marker to evaluate the recurrence and metastases of DTC

following RAIA. Most of the patients were in fourth and fifth decade with female predominance. High TgAb was more commonly found in PTC with or without metastases. Recurrence and metastases were found in 25% patients having high TgAb level. This may be concluded that, high TgAb levels in patients with DTC could be a marker to evaluate recurrence and metastases after RAIA significantly. Patients of DTC with high TgAb are at risk of recurrence and metastases during follow up period as the RR was found 2.33.

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