ORIGINAL ARTICLE

Clinical significance of serial measurement of serum anti thyroglobulin antibodies in the follow up of differentiated thyroid carcinoma

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ABSTRACT

Background: Despite the excellent prognosis, recurrence rate of differentiated thyroid carcinoma (DTC) is 20%–40%, hence long-term follow-up is needed. Thyroglobulin (Tg) measurement is important for follow up and assessment of recurrence in DTC but in the presence of antiTg autoantibody (ATgAb), a negative Tg result may be false negative. Recent guidelines recommend assessing ATgAb, along with measurement of serum Tg, every 6–12 months post-surgery. Persistence of ATgAb after the treatment or increasing concentrations indicates persistent or recurrent DTC.

Methods: A total of 90 patients of DTC who underwent total thyroidectomy along with I-131 ablation, with TSH stimulated Tg < 2 ng/ml were included in this study. Serial assessment of Tg and ATgAb level was done in these patients. Conclusion were extracted after the comparison of ATgAb level with available imaging modalities, i.e., whole body scan, ultrasound, chest X-ray, bone scintigraphy, CT, and *magnetic resonance imaging* and response to therapy.

Results: Out of total 90 patients, 43% had increased ATgAb. There was no significant difference in gender ($p < 0.48$) or multifocality ($p < 0.04$) between ATgAb positive and negative groups. Compared with ATgAb negative group, a greater number of ATgAb positive patients had lymph nodal metastasis ($p < 0.004$) and extrathyroidal extension ($p < 0.002$). Raised ATgAb levels and disease status are very well correlated $p < 0.05$. Out of 39 patients, 17.98% with positive ATgAb showed recurrence, whereas only 3.92% of 51 patients with negative ATgAb had recurrence during the follow up ($p < 0.028$). Recurrence rate was (0%) in group I, (10%) in group II, and (45%) in group III.

Conclusion: ATgAb is also a tumor marker, rising when tumor is present and falling when it has been destroyed. There is a statistically significant correlation between the complete disappearance of thyroid tissue and that of ATgAb so serial measurement of ATgAb levels in the follow up of patients of DTC is as important as the measurement of Tg level.

Keywords: Thyroid cancer, thyroglobulin, anti-thyroglobulin.

INTRODUCTION

Carcinoma of thyroid gland is an uncommon cancer but is the most common malignancy of the endocrine system. The treatment of well-differentiated thyroid cancer is the surgery supplemented by radioiodine ablative therapy followed by thyroid hormone suppression. Regular follow up is must for the early detection of recurrence or metastasis. Thyroglobulin (Tg) is a known tumor marker of Ca thyroid. The quantitative amount of circulating thyroglobulin usually correlates with the extent of disease and the amount of residual or recurrent tissue, enhancing the clinical usefulness of the assay even more [1,2–4]. Thyroglobulin is a protein with numerous antigenic epitopes many of which can produce antibodies, e.g., antithyroglobulin antibodies (ATgAb) [5]. AntiThyroglobulin antibody (ATgAb) is a class G immunoglobulin and an established marker for thyroid autoimmunity. ATgAb are the major limitation of thyroglobulin immunoassays. Thus supporting the concept that continued antibody production depends on the persistence of auto antigen therefore, it is recommended that ATgAb are measured on the same serum sample, in the same laboratory and using the same assay as Tg to assess the accuracy of the thyroglobulin measurement, a topic that is receiving increased attention over the last few years. Several studies have correlated the disappearance of ATgAb with decreased tumor burden [6]. The prevalence of ATgAb is approximately 1.5-fold higher in patients with DTC than in the general population with benign nodules (30.8% *vs.* 19.6%) [7].

MATERIALS AND METHODS

Study protocol for I-131 administration [diagnostic/ therapeutic whole body scan (WBS)]

Total data of 90 patients were collected during this study between 2007 and 2011. Among them, 72 were female and 18 were male. All patients were selected from Nuclear Medicine, Oncology& Radiotherapy

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Institute Hospital Islamabad. Only known patients of differentiated thyroid carcinoma were included. Only those patients were selected who had undergone sub-total, total thyroidectomy followed by I-131 ablation after surgery and their Tg level was <2 ng/ml. We excluded the patients with incomplete data (Tg, ATgAb, or WBS) data from the time of ablation and/or 6–12 months thereafter and the patients having irregular follow-up. Pregnant/lactating mothers were also excluded because of their irregular follow up, as their disease status cannot be ascertained properly. The Local Ethics Committee approved the retrospective review protocol.

Study protocol for I-131 administration (diagnostic/ therapeutic WBS)

According to the study protocol, all the patients had to stop thyroxine replacement for about 4 weeks. These patients were also instructed for avoidance of iodine rich foodstuff and medications for at least seven days before and after the I-131. In every follow-up patient of DTC the measurement of serum Tg, ATgAb, TSH, T3, and T4 before any scanning procedure was initiated. The measurement range of IRMA for Tg was 0.3–600 ng/ml with an analytical sensitivity of 0.3 ng/ml while measurement range of IRMA for ATgAb was 5–3,000 ng/ml with an analytical sensitivity of 5 IU/ml and functional sensitivity of 19.7 IU/ml. The samples collected for Tg and ATgAb measurement were processed and the results were obtained. Only those patients were included in the study who were Tg negative, i.e., < 2 ng/ml (*n*= 90). We considered those patients as ATgAb positive (*n* = 39) who had their ATgAb (*i*) (*i* = at the time of first ablation) value > 20 mIU/ml, while patients having their ATgAb (*i*) value <20 mIU/ml are considered as ATgAb negative (*n* = 51). The data of all the 90 patients is analyzed demographically to see any correlation between gender, multifocality, lymph node metastasis and extrathyroidal extension between ATgAb positive and ATgAb negative groups.

Those patients were considered as being disease positive who were either Tg positive, WBS positive, WBS along with Tg positive or WBS and Tg negative but they have evidence of disease on any other imaging modality, e.g., ultrasound neck, bone scintigraphy, Chest X-ray (CXR), CT, or *magnetic resonance imaging (*MRI) as shown in Table 1.

The changes in ATgAb values between the time of remnant ablation, i.e., ATgAb (*i*), (*i* = initial) and 6–12 months thereafter ATgAb *f* (*f* = final) were evaluated. Thirty nine patients with positive ATgAb (*f*) were again subdivided into three groups according to changes in ATgAb concentration between ATgAb (*i*) and ATgAb (*f*). Group I consists of those patients whose ATgAb decreased more than 50% after I-131 ablation. Group II consists of those patients whose ATgAb decreased less than 50% after I-131 ablation while group III consists of those patients whose ATgAb increased even after I-131 ablation. These three groups are again analyzed to see any association between the level of ATgAb and gender, multifocality, lymph node metastasis, or extrathyroidal extension. Odds ratios were also calculated to see the overall risk association of positive ATgAb with concurrent malignant thyroid disease.

Data Processing and Analysis

Data were processed to see the correlation between different variables, disease status and the level of ATgAb. Serial assessment of ATgAb before and after treatment was done. Associations between variables were analyzed using contingency tables. Chi square and Fisher's exact test, where appropriate are used at the significance level of $p < 0.05$. $p < 0.05$ was considered as statistically significant. Various calculations were made and results were deduced. These results were graphically plotted where needed.

Table 1. Criteria of disease positivity.

Tg	I-131 WBS	Any Imaging Modality	Disease Status
Positive	Negative	-	Positive
Negative	Positive	-	Positive
Positive	Positive	-	Positive
Negative	Negative	Positive	Positive

RESULTS

A total of 90 patients (18 males and 72 females) with TSH stimulated Tg < 2 ng/ml were included in this study as shown in Figure 1. Their mean age was 46.67 years.

Histopathological types were distributed as 63.3% (57 out of 90) having papillary carcinoma and 36.7% (33 out of 90) having follicular carcinoma as shown in Figure 2.

Among the 90 patients, 39 (43%) had ATgAb(s) values greater than 20 U/ml after first ablative dose (so were ATgAb positive), as shown in Table 2. There were no differences in gender between the ATgAb positive and ATgAb negative groups ($p = 0.48$, respectively) as shown in Table 2 and Figure 3.

As shown in Figure 4, multifocality of the tumor was found to be slightly more common in the ATgAb positive group (29 *vs.* 25%; $p = 0.04$).

Lymph node metastasis is present in 25 (27.7%) patients of ATgAb positive group while 16 (17.7%) of ATgAb negative patients ($p = 0.004$), respectively, and was more common than in ATgAb negative patients as shown in Figure 5.

Extrathyroidal extension is noted in 28 (31%) and 19 (21%) patients of the ATgAb (*f*) positive and ATgAb (*f*)-negative groups, respectively ($p = 0.002$) as shown in Figure 6.

The correlation of ATgAb with disease status was calculated and the results are graphically plotted as show in Table 3 and Figure 7. p value of <0.05 shows significant correlation between the presence of ATgAb and disease status.

In same set of patients Radioactive I-131 therapeutic dose was given and

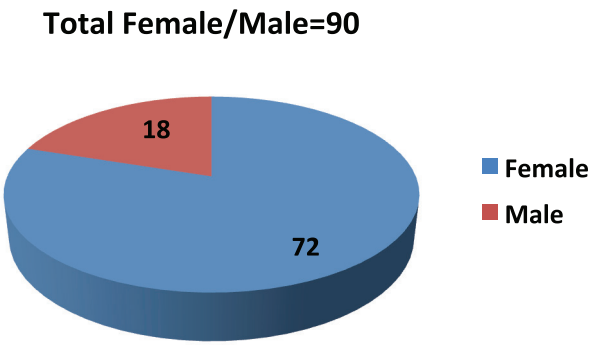

Figure 1. *Percentage of male and females patients.*

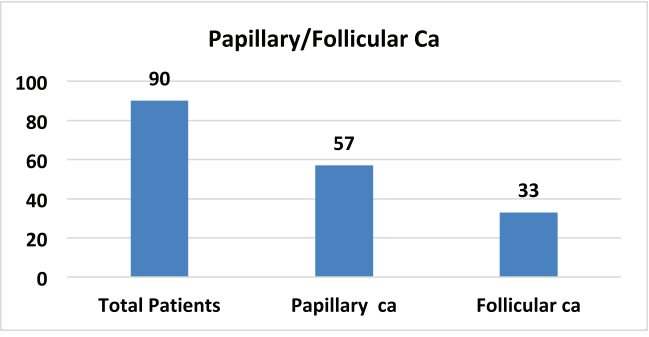

Figure 2. *Histopathological distribution of Ca thyroid.*

Table 2. Correlation of gender with ATg (positive and negative) groups.

		ATG group		Total
		Positive	Negative	
Gender	Male	06	12	18
	Female	33	39	72
	Total	39	51	90

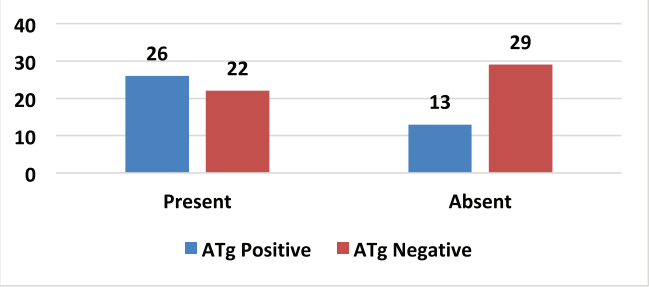

Figure 3. *Gender distributions in ATg (positive and negative) groups.*

the level of ATgAb was correlated, post treatment, with the status of the disease, evaluated with diagnostic WBS, CXR, bone scan, ultrasonography, CT, and MRI. The correlation between disease status and the level of ATgAb at the time was done at the significance level of $p < 0.05$. The calculated p value was 0.028 signifying that disease status was well correlating with ATgAb levels as shown in Figure 8, 7 of 39 (17.98%) patients with positive ATgAb(*i*) had recurrence while only 2 of 51 (3.92%) patients with negative ATgAb(*i*) has recurrence during subsequent follow up.

The changes in ATgAb values between the time of remnant ablation and 6–12 months thereafter were evaluated. Thirty nine patients with positive ATgAb were further divided into three groups according to the changes in ATgAb concentration between ATgAb (*i*) and ATgAb(*f*) as shown Table 4.

ATgAb concentration decreased more than 50% in 16 patients (group 1) and decreased less than 50% in 10 patients (group 2).The ATgAb concentration increased over the 6–12 months period in 13 patients (group 3).There were no significant differences in age, gender, multifocality, lymph node metastasis, or extrathyroidal extension between these three groups.

The correlation of female and male with ATgAb positive groups were assessed and the p value came out to be 1.0 (statistically insignificant).

The correlation of multifocality with ATgAb was calculated and the resultant p value signifies less association between the two as shown in Figure 9, with p value = 0.583 (statistically insignificant).

The correlation of lymph node metastases with ATgAb positive groups is also calculated and the p value came out to be more than 0.05 as shown in Figure 10, with p value = 0.458 (statistically insignificant).

The correlation of extrathyroidal extension with ATgAb positive groups was calculated and the p value came out to be more than 0.05 as shown in Figure 11, with p value = 0.843 (statistically insignificant).

In those 39 ATgAb positive patients which were further divided in three groups based on the response of ATgAb level as described above, none of 16 patients (0%), 1 of 10 patients (10%), and 6 of 13 patients (45%) had recurrent/ persistent disease in group 1, group 2, and group 3, respectively ($p = 0.002$), as shown in Figure 12. Among the 39 patients with positive ATgAb(*f*), 7 patients(17%) were confirmed to have recurrent/persistent disease during the median 73.6 months of follow-up, whereas only 2 of 51 patients (3.9%) in the ATgAb (*f*) negative group had recurrent/ persistent disease ($p = 0.028$).

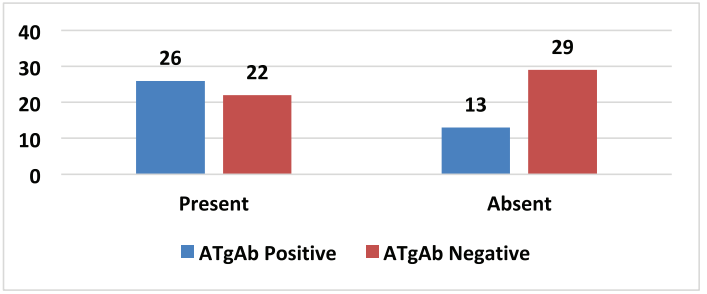

Figure 4. *Correlation of multifocality with ATgAb (positive and negative) groups.*

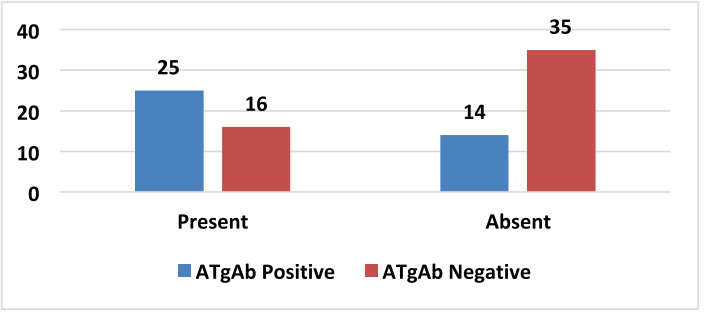

Figure 5. *Correlation of lymph node metastasis with ATg (positive and negative) groups.*

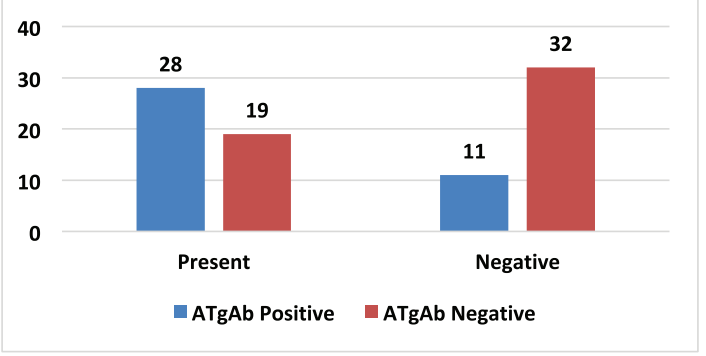

Figure 6. *Correlation of extrathyroidal extension with ATgAb (positive and negative) groups.*

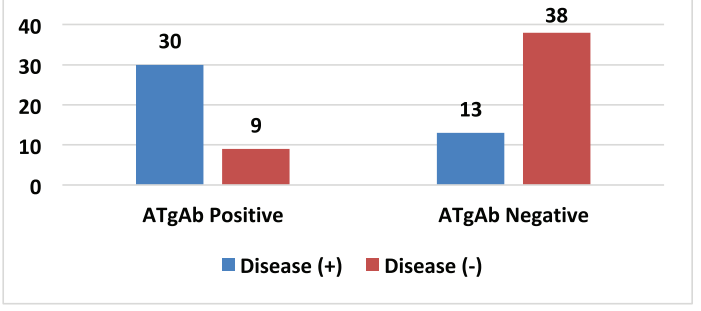

Figure 7. *Correlation of ATgAb with disease.*

DISCUSSION

Differentiated thyroid carcinoma is the most common malignancy of endocrine system and it requires a long-term follow-up. Since 1975 it was confirmed that Thyroglobulin (Tg) measurement could be used as a tumor marker for residual or metastatic thyroid carcinoma [4]. But among the different conditions in which Tg cannot be used as the only marker of thyroid cancer recurrence, one is ATgAb [8–14]. The interference from ATgAb may lead to falsely high or low serum Tg values depending on the method used for the measurement of serum Tg and ATgAb [8,9,14–16]. The frequency of these ATgAb in patients with differentiated thyroid carcinoma is relatively high as compared to general population [8,9,10,17], and these can also be used as markers for the determination of the absence or persistence of the disease [8,9,11–14]. The positive predictive value of Tg when it is measured off thyroxine is 42% when Tg cut off value is taken as 5 ng/ml and 50% when taken as 10 ng/ml [18]. But in those patients who have ATgAb in their serum, they show almost blunted response of Tg even when it is measured after thyroid hormone withdrawal. Thus, persistently elevated ATgAb level appears to serve as a useful marker for recurrent or persistent disease in the follow up of patients of DTC in which the serum thyroglobulin level is undetectable [17].

We conducted this retrospective study on this premise that in the absence of Tg or in cases where the Tg levels are false negative, in such patients ATgAb can be used as a surrogate marker. We retrospectively analyzed data of 90 patients. Among them 72 patients were female and rest of them were males. The female preponderance in our study population is in accordance with the established fact that differentiated thyroid cancer is more prevalent in the females as compared to males and bears better prognosis in comparison to males [19,20]. Out of total population, 63.3% patients were having Papillary Ca thyroid and rest (36.7%) were of follicular variety.

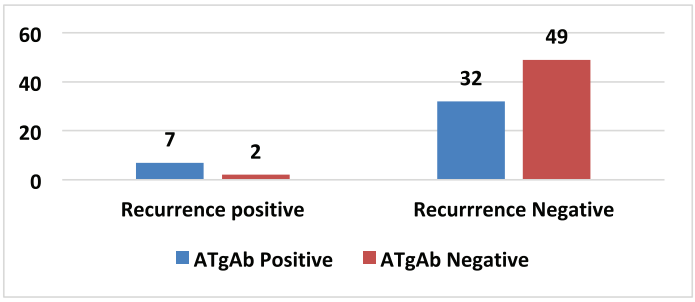

Figure 8. *Correlation of ATgAb with disease after treatment.*

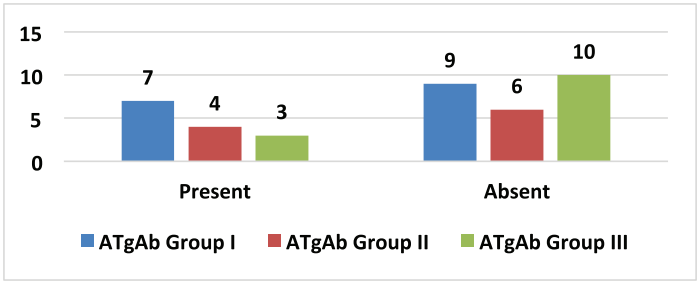

Figure 9. *Correlation of multifocality with ATgAb positive groups.*

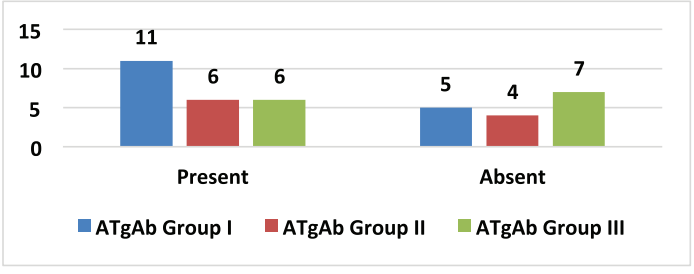

Figure 10. *Correlation of lymph node metastases with ATgAb positive groups.*

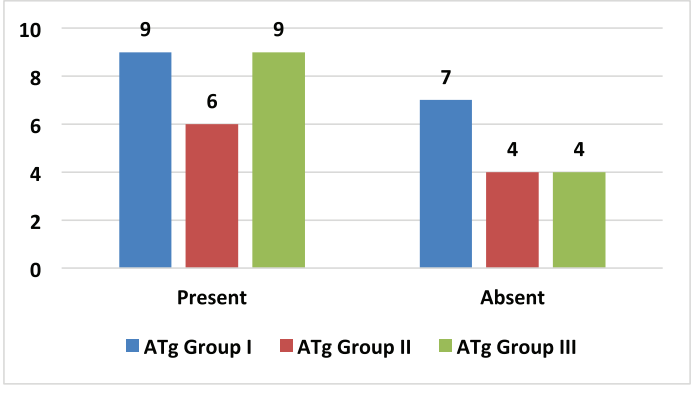

Figure 11. *Correlation of extra thyroidal extension with ATgAb positive groups.*

The reported prevalence of ATgAb in patients with DTC is 10%–25%, which was higher than in the general population [10,12,13,21]. In our study population, the incidence of raised ATgAb was even higher (43%). Although we saw higher prevalence of ATgAb in our study population, it may not be a true reflection of the entire population of thyroid cancer patients because the limited numbers of patients were patients only analyzed.

Based on the clinicopathological data of our study population there was no significant gender difference among the population of ATgAb positive and ATgAb negative groups. The results of our study are in concordance with the published results of Kim et al. [22]. Despite of limited study population in our study comparison with this study, our results are depicting the similar trend. Multifocality of the tumor among our two main groups was more common in ATgAb positive group patients as compared to the ATgAb negative group patient. This finding in our study enhances the impression brought forth by other studies [22,23].

In our study patients, it was also observed that group having raised ATgAb had significantly higher number of regional lymph nodes. Extra-thyroidal extension of the disease was more commonly seen in the group having raised ATgAb values and calculated *p* value among the 0.02 (Figure 6). In our study, we analyzed the data of the patient in whom Tg values were within normal limits (n = 90). Further analysis of ATgAb in these patients showed that 43.3% had raised ATgAb levels as discussed earlier. Correlation between the level of ATgAb and disease status was calculated using Fischer's exact test with null hypothesis that there was no correlation between two entities. The *p* value came out to be 0.00000106 proving that there was significant correlation between disease status and the level of ATgAb. In same set of the patients, we repeated the calculation after giving one therapeutic dose of I-131 and *p* value in this case came out to be 0.028, which again showed statistically significant correlation between the disease status and the level of ATgAb at

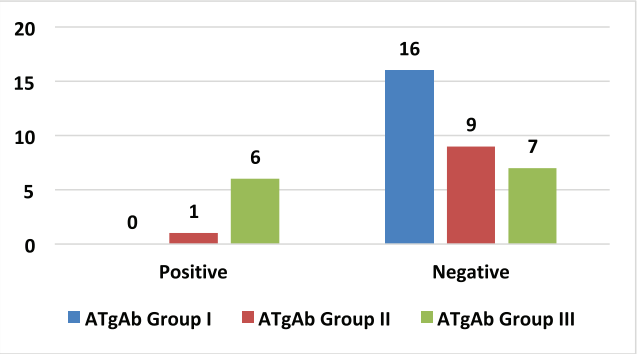

Figure 12. *Correlation of recurrence/progression of disease with ATgAb positive groups.*

that time. Our results are in concordance with various published research in which the disease correlation was observed before and after the treatment with ATgAb values [22–25]. Finally, we further subdivided the patients having raised ATgAb on basis of the response of the ATgAb to therapeutic dose of I-131. Group I consisted of patient which showed more than 50 declines in ATgAb levels after I-131 dose, Group II were patients in which decrease in ATgAb was less than 50 percent and Group III patients were those who showed either static ATgAb or increased in the ATgAb level after I-131 therapeutic dose. When we further analyzed these three sub-groups of patients based on gender, multifocality of tumor, lymph node metastasis and extra-thyroidal extension of disease our null hypothesis was rejected and *p* values for these parameters were 1, 0.583, 0.458, and 0.843, respectively. This signifies that among the patients having raised ATgAb levels there was no significant difference between gender and multifocality of tumor or lymph node metastasis or extrathyroidal extension with respect to their ATgAb levels. Our inference from this statistical outcome was this that ATgAb will be raised in patients whether they have single or multiple disease foci and local or distant disease. Therefore, we can confidently claim that ATgAb can be used as disease indicator irrespective of the clinicopathological presentation of the disease. Although studies focusing on such findings are scarce but our impression is in concordance with the few we came across [22,23]. More detailed and large data analysis will be able to confirm our and findings of others.

In the end, we analyzed the recurrence/presence/progression of disease in correlation with the change in ATgAb status (Figure 2) from the initial reading. We applied Fisher exact test and *p* value came out to be $p \leq 0.002$. This analysis outcome shows the significant correlation between recurrent/persistent disease and ATgAb levels. Calculating odds ratios for ATgAb, it is found that in the face of positive ATgAb titer in an ablated patient of differentiated thyroid carcinoma, there are nine times more chances that the patient might be having residual or metastatic thyroid disease. Our findings are confirming the similar findings seen in the Adil et al study which showed that raised ATG in presence of normal or below normal serum TG increased the relative risk of having recurrent/residual DTC.

Although assays for serum Tg are improving and they are becoming more standardized, the presence of ATgAb is still a problem and it can give either falsely low or falsely high serum Tg measurement. Thus, a largely Tg-based approach in the follow up of patients of DTC may be a problematic at times due to the presence of ATgAb in DTC population.

One small study by Li et al. [26,27] evaluated the protein expression of specific invasion-related genes [BRAF V600E and nuclear factor κB (NF-κB)] in thyroid cancer tissues to test whether TgAb is associated with the expression of these genes. The protein expression levels of BRAFV600E and NF-κB were greater in TgAb-positive patients compared to TgAb-negative patients.

CONCLUSION

Follow-up cases of DTC should be evaluated for ATgAb status because more than one-third of these patients have positive ATgAb titer, which can affect the accuracy of serum Tg level. Positive ATgAb signifies concurrent metastatic or recurrent thyroid disease but still more studies are required to support its overall significance. In conclusion, serum ATgAb levels measured at 6–12 months after high dose I-131 remnant ablation during thyroid hormone with drawl seems to predict recurrent or persistent disease in the follow up patients of DTC.

List of Abbreviations

ATgAb	AntiTg autoantibody
CT	Computerized Tomography
CXR	Chest Xray
DTC	Differentiated thyroid carcinoma
IRMA	Immunoradiometric assay
Tg	Thyroglobulin
WBS	Whole body scan

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent for publication

Written informed consent was taken from all the patients.

Ethical approval

The local ethical committee of hospital approved Research.

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