

Serum Thyroglobulin Antibody as a Tumor Marker in Differentiated Thyroid Carcinoma and its Correlation with FNAC and Histopathology

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Abstract

Original Research Article

Background: This longitudinal descriptive study was conducted for the first time in the department of Pathology, Rajshahi Medical College in order to evaluate the prognostic significance of serum TgAb as a tumor marker for differentiated thyroid carcinoma. **Objective:** The aim of this study to detect the antibody positive differentiated thyroid carcinoma using serum TgAb and compare with the FNAC and histopathological findings. **Method:** A total forty patients of clinically, radiologically and by FNAC diagnosed as differentiated thyroid carcinoma were selected attending in the department of Otolaryngology, Rajshahi Medical College Hospital from January 2010 to December 2011. Preoperative serum TgAb level (TgAb1) was measured in all patients taking cut off value as 40 IU/ml. Biopsy material were examined for histopathological diagnosis. 3-6 months after thyroidectomy postoperative serum TgAb level (TgAb2) was measured in those patients only who were TgAb1 positive. **Result:** The correlation, association and statistical analysis of preoperative and postoperative serum TgAb level were computed against histopathological diagnosis. Out of forty cases, 35 were papillary and 5 were follicular carcinoma. Mean age was 25.48+9.70 years and Male: Female was 1:6. In this study, 9 cases (22.5%) were TgAb positive preoperatively and 2 cases showed highest level 3000 and 2200 IU/ml. Post operative TgAb level of 9 cases showed significant reduction. Statistical analysis demonstrates significant correlation ($P < 0.01$) and association ($P < 0.05$) between preoperative and postoperative TgAb level. **Conclusion:** So, it is concluded that serum TgAb level can be used as a tumor marker in antibody positive differentiated thyroid carcinoma.

Keywords: Differentiated thyroid carcinoma. Serum TgAb, Tumor marker.

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INTRODUCTION

Thyroid carcinoma is the most common endocrine malignancy. The incidence of thyroid cancer accounts for approximately 37,200 cases in USA for 2009. Now it is the sixth most common cancer in women and second most common cancer in women under 40 years of age (Grogan *et al.*, 2010) and 14th ranking in male [1]. The US thyroid cancer prevalence reflecting patients living with their disease is even higher, an estimated 388, 386 cases at the end of 2006, approximately 3.5% of all living cancer patients [1]. Although death attributed to thyroid cancer is only 0.29% of all cancer death [2].

In Bangladesh, total number of new adult thyroid cancer patients attending radiotherapy department of Chittagong Medical College Hospital is

24 (0.81%) and in pediatric group 03(3.33%) in 2007 [3].

According to National Institute of Cancer Research and Hospital (NICRH) Dhaka report among 1.1% endocrine malignancy, 0.7% is of thyroid origin [4].

Differentiated thyroid carcinoma includes papillary and follicular carcinoma are among the most curable cancers. The overall survival rate at 10 years for middle aged adults with thyroid carcinoma is about 80% to 95% [5]. Thyroid cancer has therefore become a prime example of malignancy that presents as a long-term chronic disease rather than an immediate threat to life. Hence the key challenge in thyroid cancer management is to provide the least invasive and most cost-effective follow that allows identification of

recurrent or progressive disease. Recurrences usually detected during the early years of follow up but may be detected later. Therefore, follow up is necessary throughout the patient's life. At the same time, it is important to minimize the number of extensive diagnostic workups, most of which will prove unnecessary, costly and potentially harmful.

Differentiated thyroid carcinoma, like normal thyroid produce thyroglobulin that can be measured in peripheral blood by sensitive radioimmunoassay [6]. Thyroglobulin is a large glycoprotein molecule containing about 70 tyrosine amino acids and 14C-sialic acid in the form of both CMP (cytidine 5' monophosphate) activated and non-activated N-acetylneuraminic acid. In papillary thyroid carcinoma, CMP activated 14C-sialic acid is greater than in thyroglobulin of normal thyroid tissue [7]. Thyroglobulin is an established serum tumour marker for differentiated thyroid carcinoma which accounts for approximately 97% of thyroid cancer. But its measurement is one of the most difficult biochemical test for a laboratory to maintain a high level of precision and reliability. Thyroglobulin antibody (TgAb) interference is highly common (Haapala *et al.*, 1995, Pedro *et al.*, 2004) and the most serious specificity problem affecting serum thyroglobulin measurement [8-11]. In the presence of thyroglobulin antibody, a negative thyroglobulin immunometric assay result is most likely a false negative presumably because the endogenous thyroglobulin complexed with thyroglobulin antibody cannot participate in the reaction. Circulating antibodies directed against thyroglobulin are principally of the IgG isotype. Among the four IgG subclasses, IgG4 is the dominant one in patients with thyroid carcinoma.

Underestimation of serum thyroglobulin positive patient is more problematic for both the patient and physician than interference causing over-estimation and concomitant unnecessary imaging studies [12, 13]. 1998, Spencer *et al.*, studied 15 TgAb positive differentiated thyroid carcinoma patients with serial serum TgAb and Tg RIA measurement [12]. 6 patients were considered to be clinically free of cancer after an average follow up of 37.2 months. Rest of 9 patients had clinical or radiographic evidence of persistent or recurrent disease after follow up averaging 68.9 months. He found that serum TgAb and Tg concentration declined to low or undetectable level on or before the second postoperative year in the disease free group. In contrast, all patients with persistent or recurrent disease retained detectable serum TgAb and Tg concentrations throughout the follow up period. Serum TgAb measurements appeared to produce more consistent and reproducible results than the serum Tg RIA in this group of patients.

According to Rubello *et al.*, (1992) for many years, TgAb determination had been utilized to verify the diagnostic accuracy of serum thyroglobulin assay

[14]. The presence of circulating TgAb may distort serum thyroglobulin values in RIA resulting in either over or underestimation. All patients in whom circulating thyroglobulin antibody become undetectable after therapy is considered tumour free. Thus disappearance of circulating thyroglobulin antibody after therapy seems to represent an important favourable prognostic factor. TgAb determination appears useful in the follow up of patients with differentiated thyroid carcinoma not only to validate the serum thyroglobulin assay but because TgAb themselves may provide additional clinical information for the follow up of patients.

High titre of TgAb were found in differentiated thyroid cancer patients 20%, 25% and 26.4% [15, 16, 12]. Median serum half life of TgAb in treated patients is 10 weeks. TgAb=<50 U/ml is considered as negative in Haemagglutination method. In chemiluminescent method, cut off value is >40 IU/ml. So if the source of thyroglobulin were completely removed the TgAb concentration would decrease rapidly within 6-12 months and changing level of TgAb may be used as a prognostic indicator [17]. There is no known broad based study regarding TgAb in Bangladesh. The proposed study is aimed to evaluate the TgAb as a tumour marker and the data obtained from the study may add further on to the existing information.

OBJECTIVES

General Objective

To detect the antibody positive differentiated thyroid carcinoma using serum TgAb and compare with the FNAC and histopathological findings.

Specific Objectives

1. To estimate the serum TgAb level in patients with differentiated thyroid carcinoma before and after thyroidectomy.
2. To correlate FNAC with histopathological findings.
3. To correlate TgAb level with histopathological findings.

MATERIALS AND METHODS

Type of study

This was a longitudinal descriptive type of study

Study place

Department of Pathology, Rajshahi medical college and Department of Otolaryngology, Rajshahi Medical College Hospital (RMCH), Rajshahi.

Study period

January 2010 to December 2011.

Study population

Clinically suspected and diagnosed by FNAC patients of differentiated thyroid carcinoma attending

outpatient and inpatient department of Otolaryngology, RMCH and in private clinics who fulfill the inclusion criteria constituted the study population for present research.

Sample size: By Cochran's formula, sample size was 40.

Sampling technique

Patients were selected by purposive sampling

Inclusion criteria

Patients of differentiated thyroid carcinoma diagnosed clinically and by FNAC.

Exclusion criteria

Patients with thyroid tumors other than differentiated thyroid carcinoma.

Methods of data collection

A pretested questionnaire was used to collect data from all the cases including

1. Informed written consent was taken
2. Complete history

Duration of illness, family history, history of prior irradiation during childhood.

Data collection instrument

Pre-designed data sheet (Appendix-1) was used for recording all relevant information and

laboratory results regarding patients. The data were recorded methodically and meticulously.

Data processing and analysis

First the clinical informations regarding patients were recorded separately. Serum TgAb was then estimated from the collected 1st set serum samples of the patients. After operation histological diagnosis was made based on H & E stain. Then 2nd set serum sample (which are TgAb positive in 1 set sample) were tested for estimation of TgAb after 3-6 months of thyroidectomy. The collected data was compiled in a master sheet. Data were analyzed by using SPSS-15 (Statistical Package for Social Science) software program of computer and where necessary manually. Mean and standard deviation were done for continuous data and percentage done for categorical data. Paired t test analysis was done between preoperative and postoperative TgAb level. Fisher's exact test was applied to detect any association between sex and presence of TgAb in differentiated thyroid carcinoma (Park and Park Jr; 2007; Rashid et al, 2004).

RESULTS AND OBSERVATIONS

Blood from the all patients were collected for estimation of serum TgAb level both preoperatively and postoperatively within 3-6 months. After operation biopsy materials were collected from all cases and examined for histopathological diagnosis. The laboratory findings and other statistical data collected from each case have been presented in tabulated form and they are shown below.

Table 1: Age and sex distribution of differentiated thyroid carcinoma patients (n=40)

Age groups (years)	Sex		Total No (%)
	Male No (%)	Female No (%)	
<20	1(50%)	1(50%)	2(5%)
20-40	4(11.1%)	32 (88.8%)	36(90%)
>40	0(00%)	2(100%)	2(5%)
Total	5(12.5%)	35(87.5%)	40(100%)

Mean + SD =25.48 +9.70 years

Among the 40 patients studied, the age ranged from 17 to 74 years. Mean age was 25.48+9.70 years. Majority of the patients were in the age group 20 to 40

years. 35 cases (87.5%) were female and 5(12.5%) cases were male.

Table 2: FNAC and histopathological distribution of differentiated thyroid carcinoma patients (n=40)

Findings	No. of cases of FNAC No (%)	No. of cases of Histopathology No (%)
Papillary carcinoma (classic)	33(82.5%)	32(80%)
Follicular variant of papillary carcinoma	01(2.5%)	03(7.5%)
Follicular lesion/ Follicular carcinoma	5(12.5%)	5(12.5%)
Nodular goitre	1(2.5%)	0(00%)
Total	40(100%)	40(100%)

Among 40 cases of FNAC findings, 33 cases (82.5%) were classic papillary carcinoma, 01(2.5%)

case was follicular variant of papillary carcinoma, 5 cases (12.5%) were follicular lesion and 01(2.5%) case

was nodular goitre. Among 40 cases of histopathological findings, 32(80%) cases were classic papillary carcinoma, 03(7.5%) were follicular variant of papillary carcinoma and 5 cases were follicular carcinoma. In histopathological findings none of them

was nodular goitre. So, all FNAC findings were consistent with histopathological findings except nodular goitre which was diagnosed as classic papillary carcinoma in histopathology.

Table 3: Preoperative TgAb level (TgAb1) distribution in differentiated thyroid carcinoma patients (n=40)

TgAb1 level (IU/ml)	No. of cases	Percent
21-39	31	77.59%
40-4000	9	22.5%
Total	40	100%

Mean +SD = 329.22-t660.56

Among 40 cases, preoperative 1gAb level of 31 (77.5%) cases were within 20 JU/ml and 9 (22.5%) cases were within 40-4000 IU/ml. Mean +SD 21-3 was

329.22-660.56. Table 4.7 showed the preoperative TgAb level (TgAb1) distribution.

Table 4: Post operative TgAb level (TgAb2) distribution in differentiated thyroid carcinoma patients (n=9)

TgAb2 level (IU/ml)	No. of cases	Percent
150-300	5	55.6%
400-700	4	44.4%
Total	9	100%

Mean SD = 345.11+176.46

Among 40 cases, preoperative TgAb level were estimated in all the patients of differentiated thyroid carcinoma. But postoperative TgAb level were estimated in 9 patients only who were TgAb positive (>40 IU/ml). Table 4.8 showed the postoperative TgAb

level (TgAb2) distribution. Among 9 cases, postoperative TgAb level of 5 cases (55.6%) were within 150-300 IU/ml and 4 cases (44.4%) were within 400-700 IU/ml. Mean SD was 345.11+176.46.

Table 5: Correlation between preoperative and postoperative TgAb level at a cut off value of >40 IU/ml (n=9)

No of cases	Mean	Mean difference	t	95% Confidence Interval	Significance
Preoperative 9	1073.89	728.78	2.465	47.119-1410437	0.039
Postoperative 9	345.11				

Table showed that, mean of preoperative TgAb level and postoperative TgAb level were 1073.89 and 345.11 respectively. Mean difference was 728.78. By t

test analysis, finding of the study showed that there was significant correlation and association between preoperative and postoperative TgAb level (p=<0.05).

Table 6: Association between lymph node status and presence of TgAb in differentiated thyroid carcinoma patients (n=40)

Lymph node status	TgAb positive N=9	TgAb negative N=31
No lymph node metastasis	7	29
Lymph node metastasis	2	2

$\chi^2=0.016, df=1, P>0.05$

Table showed that among 40 cases, 29 cases without lymph node metastasis were TgAb negative and 7 cases without lymph node metastasis were TgAb positive. Rest of the 4 cases, all are with lymph node

metastasis, but 2 were TgAb positive and 2 were TgAb negative. Finding of this study showed that there was no association between lymph node status and presence or absence of TgAb.

Table 7: Association between sex and presence of TgAb in differentiated thyroid carcinoma patients (n=40)

Sex	TgAb positive	TgAb negative	Total
Male	1	4	5
Female	8	27	35
Total	9	31	40

Fisher's Exact test=0.020, df=1, P=1.

Table showed that among 40 cases, 5 cases were male, 4 were IgAD negative and 1 was TgAb positive. Among 35 female cases, 27 cases were TgAb negative and 8 cases were TgAb positive. By Fisher's Exact test, finding of this study showed that there was no association between sex and presence or absence of TgAb ($p>0.05$).

DISCUSSION

Thyroid malignancy accounts for only 1.2% of all new cancers in the On States annually. There will be almost 26000 new cases of thyroid cancer the USA-19,190 in women and 6,500 in men and an estimated 1,500 people are expected to die of thyroid cancer in 2005. While rare, thyroid cancer is actually one of the few cancers that are becoming more common in the past several years with a rate of 3 per 100,000 people each year. Survival rates are high with 95% of all thyroid cancer patients achieving what would be considered a case of long term survival without recurrence. Differentiated thyroid carcinoma is a malignancy with favourable prognosis but it can also be aggressive, leading to recurrent disease or death and needs life long monitoring. The present study was undertaken with the aim to diagnose TgAb positive differentiated thyroid carcinoma patients by measuring serum TgAb level and to correlate with FNAC and histopathological findings. Total 40 patients of differentiated thyroid carcinoma attending department of Otolaryngology, Rajshahi Medical College Hospital and also in private clinics were included purposively in this study. It is focused on the histopathological distribution of differentiated thyroid carcinoma with their correlation to age, sex, clinical presentations. USG findings, FNAC and preoperative and postoperative serum TgAb level were correlated.

Accurate statistical and statistical figures in Bangladesh are not available except some institutional reports. Awal *et al.*, (2009) conducted a survey on cancer of the year 2007 at radiotherapy department of Chittagong Medical registry of College Hospital, Chittagong and showed thyroid cancer was 0.81% among 11 cancer patients [3]. Another report from National Institute of cancer research and Hospital showed that endocrine malignancy was 1.1% and thyroid cancers was 0.70 among 7,516 patients attended the outpatient department in 2005.

In this study the age of study subjects ranged from 17 years to 74 years, most of the patients were in age group of 20-40 years and mean age was 25.48±9.70 years. Kim *et al.*, (2008) showed in their study that age range of the patients were 13-76.4 years, mean age was 46±11 years [18]. In another study done by Pedro *et al.*, (2004) concluded that mean age was 40.1±17.2 years [19]. In Bangladesh, Alam (2005) showed that mean age of papillary carcinoma patients was 32.98 years and age range was 12-68 years [20].

Muzzafar *et al.*, 1998, (cited by Alam 2005) showed that mean age of papillary carcinoma patient was 27 years [21]. Age incidence varies country to country shown in a study of Khan and Eshy carried out in Saudi Arabia (Cited by Alam 2005). So the present study is consistent with others.

In this study, out of 40 cases, USG findings of 25 were available. 11 cases were solid nodule, 3 were diffusely enlarged, 5 were solid and cystic and 6 cases were cystic nodule with irregular margin. This finding was supported by Alam (2005) [20].

In this study, out of 40 cases, FNAC findings showed 33 cases (82.5%) were papillary carcinoma, 5 cases (12.5%) were follicular lesion 1 case (2.5%) was nodular goitre and 1 case (2.5%) was follicular variant of papillary carcinoma.

Among 40 cases of DTC, 35 cases were papillary and 5 were follicular carcinoma. All of TgAb positive cases were papillary carcinoma, which is statistically not significant ($P>0.05$). Kumar *et al.*, (1994) showed that TgAb was more prevalent ($P<0.01$) with the papillary carcinoma than follicular carcinoma [22].

In this study, from all 40 patients of differentiated thyroid carcinoma, blood were collected for estimation of serum TgAb level (TgAbI) preoperatively and correlated with the histopathological variants (Papillary and follicular carcinoma). Cut off value 40 IU/ml was considered as positive (According chemiluminescent method). Kim *et al.*, (2008) found 12.4% TgAb positive among 824 DTC patients [18]. Adil *et al.*, (2003) had done a case control study with 25 DTrC patients and 11 patients were TeAb positive (44%) [23]. This finding was consistent with Spencer *et al.*, (1998) (40%). Chiovato *et al.*, (2003) studied with 182 patients and found 64% TgAb positive cases. 3-6 months after thyroidectomy 2nd blood sample for TgAb2 was taken from the 9 TgAbI positive patients of DTC [24]. All of them were showed decreased level. By t test analysis, it showed that there is significant correlation ($P<0.01$) and association ($P<0.05$) between preoperative and postoperative TgAb level.

In the present study, among 9 TgAb positive patients, 1 was male and 8 were female. By statistical analysis this study showed that there was no association between sex and presence of TgAb. Kumar *et al.*, (1994) reported that prevalence of TgAb in female (21.5%) was significantly higher ($P<0.001$) than that of male among 963 patients with differentiated thyroid carcinoma. These dissimilarities may be due to small sample size [22].

Study showed that among 40 patient of DTC, 4 patients were presented 2h lymph node metastasis, 2 were TgAb positive and 2 were TgAb with negative. By

tive. By Chi-square analysis, this study showed that there was no association between lymph node status and presence or absence of TgAb. This finding was supported by Kumar *et al.*, (1994) [22].

CONCLUSION

This study showed that out of 40 Cases, 9 were TgAb positive preoperatively. During follow up period of 3-6 months after thyroidectomy, all of 9 cases showed significant reduction in TgAb level. So, it is concluded that serum TgAb can be used as a tumor marker in differentiated thyroid carcinoma and 6 month interval TgAb assay may be sufficient for long term follow up.

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