Original Research Article

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Preoperative serum thyroglobulin levels as a predictor of thyroid carcinoma

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ABSTRACT

Background: Incidence of thyroid nodules varies according to the methods of diagnosis, 4-7% by palpation and 17-67% by high resolution ultrasound. The gold standard of diagnosis for thyroid nodules is fine needle aspiration (FNA); however, fine needle aspiration cytology (FNAC) alone is insufficient to detect cancer because of inadequate cytology (5-15%) and in cases of follicular neoplasm (15-25%) where only surgery is diagnostically conclusive. Therefore, other factors in addition to FNA should be considered to predict malignancy. This study was done to evaluate the association between elevated pre-operative thyroglobulin levels and histopathologically proven thyroid carcinoma.

Methods: This retrospective study was conducted in Bowring and Lady Curzon Hospital, from December 2017 to November 2018. All patients above 18 years, undergoing total thyroidectomy, with normal antithyroglobulin levels and with indeterminate thyroid nodules or disease on FNAC were included. Patients proven to have malignancy by FNAC, who underwent hemithyroidectomy and patients with thyroglossal cyst or ectopic thyroid swellings were excluded.

Results: A total of 50 patients were included. The Fischer's exact test shows significant value of 0.037 and also the two-tailed test showed a p value <0.05, hence it is significant to conclude that the mean value of thyroglobulin levels among histopathologically proven malignant thyroid cancers is significantly higher compared to the benign thyroid disease.

Conclusions: In addition to thyroid-stimulating hormone, thyroid nodules with elevated thyroglobulin levels were independently associated with the presence of thyroid cancer; therefore, the evaluation of pre-operative thyroglobulin level in patients with indeterminate FNAC might give additional information to predict malignancy.

Keywords: Thyroid carcinoma, Elevated thyroglobulin levels, Histopathological analysis

INTRODUCTION

Thyroid nodules are frequently found in clinical practice but their incidence varies according to the methods of diagnosis, 4-7% by palpation and 17-67% by high resolution ultrasound. ¹⁻⁴ Although the malignancy rates among usual thyroid nodules is relatively low, precise diagnosis is quite important as the incidence rate among thyroid nodules is progressively increasing because of

early detection of nonpalpable nodule using high resolution ultrasound.⁵⁻⁷

The gold standard of diagnosis for thyroid nodules is fine needle aspiration. However, fine needle aspiration (FNA) alone is insufficient to detect cancer not only because of inadequate cytology but also because of cases of follicular neoplasm in which only surgery is diagnostically conclusive.⁸ Therefore, other factors in

addition to FNA should be considered to predict malignancy preoperatively. Traditionally, clinical factors such as age, gender, nodule size and radiation history are considered meaningful for predicting thyroid malignancy.⁹

Metabolism of thyroglobulin occurs in the liver and via thyroid gland and recycling of the protein takes place. Circulating thyroglobulin features a half lifetime of 65 hours. Following thyroidectomy, it will take many weeks before thyroglobulin levels become undetectable. After thyroglobulin levels become undetectable (following thyroidectomy), levels are often serially monitored. A subsequent elevation of the thyroglobulin level is an indicator of recurrence of papillary or follicular thyroid carcinoma. Hence, thyroglobulin levels in the blood are mainly used as a tumor marker for certain kinds of thyroid cancer (particularly papillary or follicular thyroid cancer). Thyroglobulin is not produced by medullary or anaplastic carcinoma.

Therefore, this study tries to evaluate the association between the preoperative thyroglobulin levels and thyroid carcinoma proven by post-operative histopathology.

METHODS

This retrospective study was conducted in Bowring and Lady Curzon Hospital, a tertiary care centre from December 2017 to November 2018. Inclusion criteria included all patients above the age of 18 years, patients undergoing total thyroidectomy, patients with normal antithyroglobulin levels and all patients indeterminate thyroid nodules or disease on fine needle aspiration cytology (FNAC). Patients excluded were those who were proven to have malignancy by FNAC, Patients who underwent hemithyroidectomy and patients with thyroglossal cyst or ectopic thyroid swellings. Therefore, the pre-operative thyroglobulin levels were measured and its association with post-operative histopathology was studied.

Preoperatively serum thyroglobulin levels were measured and ultrasound of the thyroid gland was done. Patients also underwent FNAC of the thyroid nodule to establish a diagnosis and following which patients underwent total thyroidectomy. Following thyroidectomy the specimen was sent for histopathological analysis and the reports were correlated to the preoperative serum thyroglobulin

levels and FNAC. The final diagnosis of benign or malignant nodules was determined using combined results of FNAC and postoperative histopathology.

Also evaluated was the age, sex, nodule size, singularity, thyroid autoimmunity and thyroid-stimulating hormone (TSH) in both benign and malignant groups.

Data analysis

Data analysis was based on descriptive statistics to determine the general population characteristics. The one-way ANOVA, paired student's test and the chi-square test were employed to establish the statistical significance of the differences between groups.

Statistical significance was determined with a p<0.05. Sensitivity, specificity, positive predictive value and negative predictive value was calculated at various cut off levels of serum thyroglobulin levels.

RESULTS

A total of 50 patients were included in our study. The age of the patients ranged from 18 to 60 years. The mean age of the patient was 39.88±11.01 years. The Fischer's exact test applied shows significant value of 0.037 (p<0.05=95% confidence interval), hence we can infer that the high thyroglobulin levels lead to more chance of malignant thyroid cases. The two tailed test applied also showed a p<0.05, hence, it is significant to conclude that the mean value of thyroglobulin levels among histopathologically proven malignant thyroid cancers is significantly higher compared to the benign thyroid disease.

Table 1: Statistical analysis based on age, TSH levels and pre-op thyroglobulin levels.

	Age (in years)	TSH	Preop thyroglobulin
N valid	50	50	50
Missing	0	0	0
Mean	39.880	2.90772	183.74
Std error of mean	1.5583	0.234035	20.387
Std deviation	11.0188	1.654880	144.154

Table 2: Crosstabulation of benign and malignant cases and their corresponding pre-op thyroglobulin levels.

		Benign report	Malignant report	Total
	<40 count	9	1	10
	% within category	90.0	10.0	100.0
	% within report	30.0	5.0	20.0
Preop thyroglobulin	% of total	18.0	2.0	20.0
levels	>40 count	21	19	40
	% within category	52.5	47.5	100.0
	% within report	70.0	95.0	80.0
	% of total	42.0	38.0	80.0

Continued.

	Benign report	Malignant report	Total
Total count	30	20	50
% within category	60.0	40.0	100.0
% within report	100.0	100.0	100.0
% of total	60.0	40.0	100.0

This crosstabulation is based on the total number of benign and malignant cases and their corresponding preoperative serum thyroglobulin levels.

DISCUSSION

In humans, thyroglobulin has only four to six epitopes that are recognized by B cells among the 40 known epitopes. ¹⁰ Recently, thyroglobulin produced by thyroid cancer was demonstrated to have epitopes different from those involved with autoimmune thyroid disease (AIT) auto antibodies. ¹¹

Previous studies have used preoperative serum thyroglobulin levels (Tg) for differential diagnosis of differentiated thyroid carcinoma (DTC). Petric et al, differentiated between follicular adenoma and carcinoma, and between follicular carcinoma and Hurthle cell carcinoma using preoperative serum Tg.14,15 Sarah et al showed that preoperative serum Tg concentration was significantly higher with initial diabetes mellitus. However, a cut off for serum Tg was not presented. 16,17 Some studies found that preoperative serum Tg concentrations are not useful for differential diagnosis of DTC.^{18,19} The reason for this may be the many factors that affect preoperative serum Tg concentration.²⁰ Therefore, in this study, we analyzed preoperative serum thyroglobulin level as one of the main predictor of thyroid carcinoma and found significant p value which suggest serum thyroglobulin levels as to be included in preoperative investigation in all thyroid swelling.

A study conducted by Kim et al suggested that no sex difference was observed in their study however our study showed increased incidence of thyroid disease in females when compared to males.²¹

Therefore, it is possible that occult thyroid cancer that develops in normal thyroid or AIT stimulates chronic immunologic responses and produces new or more TgAb against thyroglobulin released by increased tumour cell mass in proportion to TSH levels.

A study conducted by Kim et al showed that positive TgAb in thyroid nodules could predict thyroid cancer independent of TSH levels.²¹

Concerning TSH, its role of prediction for malignancy was also apparent in our study

The reason why TSH acts as a predictive factor for malignancy is not ascertained, but it has been proposed that TSH might cause tumor growth through the TSH

receptor in well-differentiated thyroid carcinoma as in normal thyroid tissue, which results in occult cancer progression into overt cancer. 12,13

Here the significance (2 tailed) shows value p<0.05, hence it is significant to conclude that mean value of thyroglobulin levels among histo-pathologically proven malignant. Thyroid cancers is significantly higher compared to the benign thyroid disease.

CONCLUSION

In addition to TSH, thyroid nodules with elevated thyroglobulin levels were independently associated with the presence of thyroid cancer; therefore, the evaluation of pre-operative thyroglobulin level in patients with indeterminate FNAC might give additional information to predict malignancy in conjunction with clinical risk factors and TSH levels.

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Institutional Ethics Committee

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