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Cytomorphology (FNAC) Of Thyroid Nodules and Their Relation with Thyroid Function Tests and Anti-Thyroid Peroxidase Antibody

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Abstract:
Background*: FNAC is a simple and cost-effective diagnostic modality for thyroid lesions with high specificity and accuracy. Cytological analysis in conjunction with thyroid hormone profile and Anti-Thyroid Peroxidase antibodies helps clinicians determine the course of therapy in effective management of patients with thyroid lesions. The present study aimed at to describe the cytomorphological features of Thyroid swellings and correlate with thyroid hormone status in patients presented with diffuse swelling/solitary nodule of thyroid.*
Materials and Methods*: A cross sectional study conducted at Department of Pathology, in collaboration with Microbiology & Otorhinolaryngology Dept, AGMC during 2020-2022 year among thyroid cases where cytomorphological (FNAC) examination, thyroid hormone profile and Anti-Thyroid peroxide antibodies were checked, and all information were collected in a case record form (CRF).*
Results*: The study findings showed 71.4% of the thyroid swelling among the participants were diffuse, 16.7% were solitary nodules, and 11.9% were multi-nodular type. The cytomorphological (FNAC) findings of the thyroid swelling and nodules showed that most of the nodule was lymphocytic thyroiditis (35.7%). Granulomatous thyroiditis has shown highest imbalance of thyroid hormone than other nodules. Anti-TPO antibody level was highest in lymphocytic thyroiditis (83.80+43.49 IU/mL), followed by granulomatous thyroiditis (64.35+40.41 IU/mL).*
Conclusion: *Lymphocytic thyroiditis was the major cytomorphological findings among thyroid nodules lesions. However, Granulomatous thyroiditis has shown higher variation to thyroid profile, but anti-thyroid peroxide antibody was more in lymphatic thyroiditis.*
Keyword: *FNAC, Thyroid Nodules, thyroiditis, Thyroid Function Tests, Anti-Thyroid Peroxidase*

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I. Introduction

Thyroid Peroxidase (TPO) is an enzyme present in the thyrocyte membrane, which catalyses oxidation reaction of iodine on tyrosine residue in thyroglobulin to produce triiodothyronine and thyroxin. Anti-TPO antibodies produced against the TPO enzyme are cytotoxic that damage the thyroid cells by complement activation and antibody dependent cell toxicity. Previous researchers had proved that assays of anti-TPO antibody were considered to have high specificity, sensitivity and accuracy in detecting autoimmune thyroiditis like Hashimoto's thyroiditis (HT).[1] The first line of investigation for thyroid swelling is the thyroid function test, which is the estimation of serum T3, T4, free T3, free T4 and TSH.[2] These estimations of the hormonal levels categorize the thyroid swelling cases as euthyroid, hyperthyroid, hypothyroid, subclinical hyperthyroidism and subclinical hypothyroidism.[3]

Thyroid fine needle aspiration cytology (FNAC) has been used over a prolonged period and is over 50 years old.[4] FNAC is a cost-effective, simple, quick, and safe procedure without any known significant complications.[5] Therefore, it has been superior to other modalities of investigations and most practitioners depend on FNAC alone for the diagnosis of thyroid nodules at first attempt.[3]

Thyroid lesions can be classified as hypothyroid, euthyroid, or hyperthyroid, based on T3, T4, and TSH levels. Individuals are labelled as euthyroid if the TSH level is within the reference level. Individuals with TSH concentrations greater than the reference range and normal free T4 (FT4) concentrations, are labelled as having

subclinical hypothyroidism or subclinical hyperthyroidism if the TSH concentration is below the reference range.[6] In iodine-deficient geographic areas around the world, iodine deficiency is the most common cause of primary hypothyroidism. In the iodine-sufficient regions, autoimmune thyroid diseases are usually the most common cause of hypothyroidism. Grave's disease and toxic multinodular goitre are the most common cause of hyperthyroidism.[7] Thyroid peroxidise (TPO) is the thyroid enzyme that helps in thyroid hormone synthesis by iodination and coupling of tyrosine residues in thyroglobulin. Raised anti-TPO antibodies are found in about 90 to 95 % of autoimmune thyroid disease (AITD) patients and about 15 % in non-AITD patients. Anti-TPO antibodies from AITD patients can destroy follicular cells and inhibit enzymatic activity. Anti-TPO antibody is considered a sensitive marker of AITD. However, raised level of anti-TPO antibodies can also be found in 5 to 27 % of general population.[8]

However, there is a scarcity of research on the cytomorphology of thyroid swelling and nodules in relation to thyroid enzymes in northeast India. Therefore, this study was conducted in Tripura to find out the causes of thyroid swelling cases in Northeast India population and to determine the relation of levels of anti-TPO antibody and thyroid hormones with cytomorphology of thyroid nodules to help in the management of thyroid diseases by the physicians and avoid unnecessary thyroidectomy.

II. Material And Methods

A descriptive cross-sectional study was conducted in the Department of Pathology, Agartala Government Medical College (AGMC), Agartala, Tripura, in collaboration with the Departments of Microbiology and Otorhinolaryngology, AGMC, Agartala during 2020-2022. All thyroid swelling cases attending the Department of Pathology, AGMC for cytomorphological examination, were included in the study population. Patients on treatment for either hypothyroidism or hyperthyroidism was excluded from the study. All cases were selected conveniently among those who reported for FNAC during the study period. As study tool predesigned proforma, VIDAS Biomeriuex auto-analyzer for TFT, ELISA machine, Binocular light microscope was used to accumulate the data. Fine Needle Aspiration Cytology, staining of smears by Papanicolaou staining method and Leishman staining method, Thyroid Function Test by VIDAS auto-analyzer and Anti-TPO antibody estimation by ELISA were performed under strict protocol. Before data collection participants were explained about the purpose and procedure of the test and written informed consent were taken. All relevant personal data were collected in the pre-designed proforma. Collected data were checked for consistency and completeness. Data were entered in Microsoft Excel data sheet for analysis. Data were organized and presented using the principles of descriptive statistics in the form of tables and diagrams. Diagrams were done in Microsoft Excel software. Categorical data were expressed in proportions and mean, and standard deviations were calculated for continuous data. IBM statistical package for Social Sciences (SPSS) version 21.0 was used for data analysis.

III. Result

During the reference period of two years, a total of 84 eligible participants were included in the study. The Mean age of the participants was 45.2 ± 7.6 years ranges from 16 years to 71 years. Among the study participants 89.3% were females and 10.7% were males. Out of 84 participants, the majority (27.4%) belonged to 40-49 years age group, followed by 25% in 30-39 years age group, 17.8% in 20-29 years group, 8.3% (7 out of 84) was in ≥ 60 years and least (4.8%) in < 20 years age group. Among the study participants 89.3% were females and 10.7% were males.

Table 1: Distribution the study participants by thyroid nodule types (N=84)

Types of thyroid swelling and nodules	Frequency	Percentage
Diffuse	60	71.4
Solitary	14	16.7
Multi-nodular	10	11.9

The study findings showed 71.4% of the thyroid swelling among the participants were diffuse, 16.7% were solitary nodules, and 11.9% were multi-nodular type (Table 1).

Table 2: Distribution of thyroid nodules according to the Bethesda system for reporting thyroid cytopathology (n = 84)

Bethesda Diagnostic Category	Frequency	Percentage
Bethesda Diagnostic Category I	0	0.0
Bethesda Diagnostic Category II	75	89.3
Bethesda Diagnostic Category III	0	0.0
Bethesda Diagnostic Category IV	6	7.1
Bethesda Diagnostic Category V	0	0.0
Bethesda Diagnostic Category VI	3	3.6

Among the cytomorphology of thyroid swelling and nodules, 89.3% belonged to Bethesda system category II, 7.1% were category IV and 3.6% belonged to category VI (Table 2). According to Bethesda category II, most of the nodules (40%) were lymphocytic thyroiditis, followed by 33.3% were colloid goitre, 14.7% granulomatous thyroiditis, 6.7% were colloid goitre with cystic degeneration and 5.3% were follicular hyperplastic nodule.

The FNAC diagnosis of the thyroid swelling and nodules showed that most of the nodules were lymphocytic thyroiditis (35.7%) followed by colloid goitre (29.7%), granulomatous thyroiditis (13.1%), colloid goiter with cystic degeneration (5.9%), follicular hyperplastic nodule (4.8%), papillary thyroid carcinoma (3.6%), follicular neoplasm 3.6% and 3.6% were Hurthle cell neoplasm (Table 3).

Table 3: Distribution of the study participants according to cytomorphology of the thyroid Swelling and nodules (N=84)

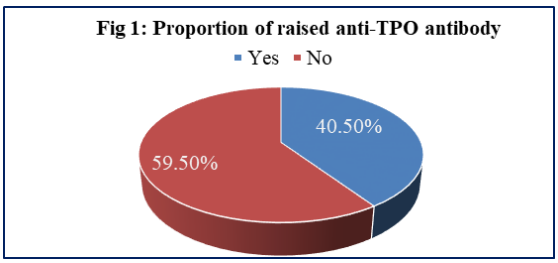
Cytomorphology of thyroid swelling and nodules	Frequency	Percentage
Colloid goiter with cystic degeneration	5	5.9
Colloid goitre	25	29.7
Lymphocytic thyroiditis	30	35.7
Granulomatous thyroiditis	11	13.1
Papillary thyroid carcinoma	3	3.6
Follicular neoplasm	3	3.6
Follicular hyperplastic nodule	4	4.8
Hurthle cell neoplasm	3	3.6

Table 4 is showing comparison of thyroid profile in relation to the FNAC findings of thyroid nodule where thyroid stimulating hormone is more in lymphocytic thyroiditis (4.68uIU/ml), T3 is more in Granulomatous thyroiditis (2.89nmol/L), T4 is more Granulomatous thyroiditis (136.55nmol/L) comparatively to other types of thyroid nodules.

Table 4: FNAC findings of thyroid nodules in relation with thyroid function test parameters (n=84)

Cytomorphology of thyroid swelling and nodules (Mean, SD)	TSH [uIU/ml]	T3 [nmol/L]	T4 [nmol/L]	FT3 [pmol/L]	FT4 [pmol/L]
Colloid goiter with cystic degeneration	3.36 (1.59)	1.61 (0.53)	89.89 (19.02)	6.11 (1.18)	13.93 (2.83)
Colloid goitre	1.95 (0.74)	1.61 (0.40)	92.59 (17.89)	6.31 (1.07)	14.52 (0.91)
Lymphocytic thyroiditis	**4.68** (2.40)	1.65 (1.01)	85.63 (40.14)	5.26 (1.70)	13.20 (4.11)
Granulomatous thyroiditis	2.40 (2.10)	**2.89** (2.15)	**136.55** (87.51)	6.9 (1.9)	**14.94** (5.09)
Papillary thyroid carcinoma	2.70 (1.21)	1.83 (0.41)	82.60 (13.61)	5.03 (0.76)	2.66 (1.89)
Follicular neoplasm	3.78 (1.15)	1.60 (0.26)	83.86 (22.20)	5.00 (0.43)	13.20 (2.29)
Follicular hyperplastic nodule	1.36 (1.46)	2.12 (1.30)	93.90 (28.95)	**7.66** (1.52)	14.35 (4.08)
Hurthle cell neoplasm	2.77 (1.07)	1.79 (0.46)	66.30 (3.66)	5.43 (1.15)	12.70 (2.29)

The study also revealed that 40.5% of the participants had raised anti-TPO antibody while 59.5% had normal anti-TPO antibody on serological examination (Figure 1).

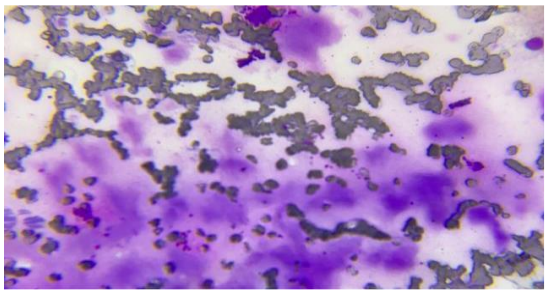


The study showed the anti-TPO profile of the participants according to the cytomorphological diagnosis. Anti-TPO antibody level was highest in lymphocytic thyroiditis (83.80+43.49 IU/mL), followed by

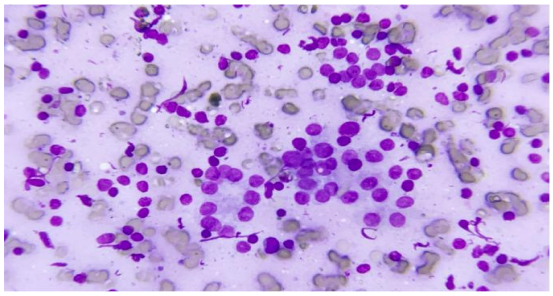
granulomatous thyroiditis (64.35+40.41 IU/mL), follicular hyperplastic nodule (56. 82+30.92 IU/mL), Hurthle cell neoplasm (34.30+11.91 IU/mL), Colloid goitre with cystic degeneration (34.10+37.18 IU/mL), Colloid goitre (25.38+25.95 IU/mL), Follicular neoplasm (15.33+9.57 IU/mL) and papillary thyroid cancer (15.33+9.56 IU/mL) (table 5).

Table 5: Anti-TPO profile of the participants according to the cytomorphological diagnosis of thyroid swelling and nodules (n=84)

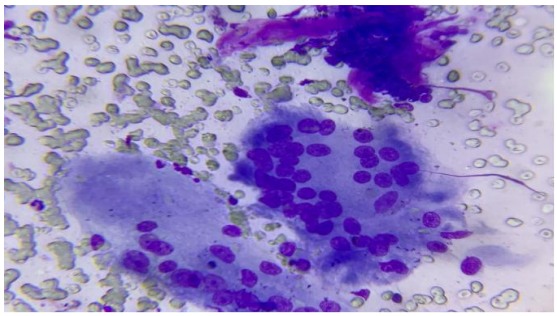
Cytomorphology of thyroid swelling and nodules (Mean, SD)	Anti-TPO [uIU/ml]
Colloid goiter with cystic degeneration	25.38 (25.95)
Colloid goitre	34.10 (37.18)
Lymphocytic thyroiditis	**83.80 (43.49)**
Granulomatous thyroiditis	64.35 (40.41)
Papillary thyroid carcinoma	15.33 (9.56)
Follicular neoplasm	15.33 (9.57)
Follicular hyperplastic nodule	56. 82 (30.92)
Hurthle cell neoplasm	34.30 (11.91)



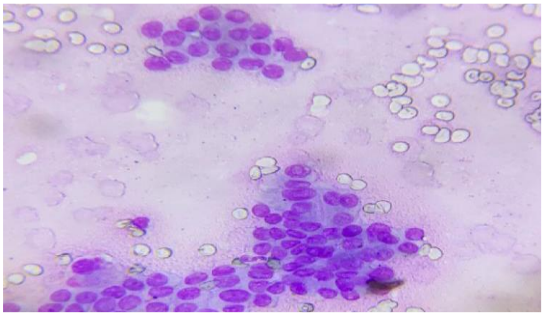
Photomicrograph 1: Colloid goitre (10x40)



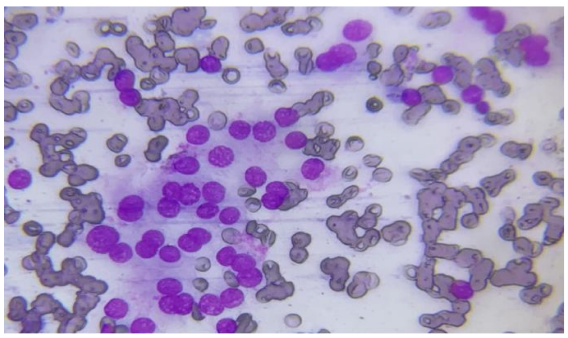
Photomicrograph 2: Lymphocytic thyroiditis (10x40)



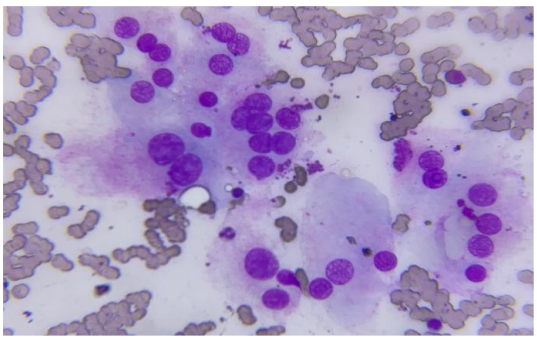
Photomicrograph 3: Granulomatous thyroiditis (10x40)



Photomicrograph 4: Papillary thyroid Ca (10x40)



Photomicrograph 5: Follicular neoplasm (10x40)



Photomicrograph 6: Hurthle cell neoplasm (10x40)

IV. Discussion

The present study aimed at finding out the causes of thyroid swelling cases in Northeast India population and to determine the relation of levels of anti-TPO antibody and thyroid hormones with cytomorphology findings.

This study found lymphocytic thyroiditis (35.7%) as the most common thyroid lesion among the participants. The next most common diagnosis was colloid goitre (29.7%), followed by granulomatous thyroiditis

(13.1%). The study by Sang et al[9] among 42 patients showed that majority of the patients had nodular goitre and most of them were euthyroid. Another study by Hanushraj R et al[10] showed colloid goitre (30%) was the commonest diagnosis, followed by Hashimoto's thyroiditis (27%). Iodine deficiency is one of the important causes for development of colloid goitre. According to a study conducted in Tripura, there was no biochemical iodine deficiency in the study population, as evidenced by median iodine excretion levels. As common vegetables, a large number of cyanogenic plants (SCN precursors) were used. The current goitre prevalence in the region could be due to a non-uniform adequate iodine supply as well as a high thiocyanate load, according to this study.[11] It was also seen from studies that in iodine-sufficient regions, auto-immune thyroiditis or Hashimoto's thyroiditis was the most common cause of thyroid nodules.[12] In another study by Saha et al[13] showed that 73% of cases were multinodular goitre and only 25% were thyroiditis. In the current study, 71.4% of the participants presented with diffuse swelling of thyroid, 16.7% with solitary nodule, and 11.9% with multinodular goitre. In the study by Zou et al 56.9% patients with thyroid nodules had single nodule and 43.1% had multiple nodules.[14]

The current study showed no significant relation between cytopathological diagnosis and T3, T4 levels and TSH levels. Similarly, Poudel et al[15] and Sang et al[9] in their studies found that there was no significant relation between thyroid function test and diagnosis. Poudel et al[15] and Chaudhary et al[4] found that the hormone levels varied across and within the same group of FNAC diagnosis.

In the present study, anti-TPO antibody titre of lymphocytic thyroiditis was significantly (mean anti-TPO 88.5±44.5) higher than that of other thyroid diagnosis. There was a significant relationship between presence of anti-TPO antibody and lymphocytic thyroiditis in this study. More than 80% of the lymphocytic thyroiditis patients were positive for anti-TPO antibody. This finding was like other studies which showed anti-TPO antibody level was significantly higher in autoimmune thyroiditis group when compared to both non-neoplastic group and the neoplastic group.[1] Similarly Hanushraj R et al in Tamil Nadu reported that anti-TPO antibody titres were elevated consistently in all patients with Hashimoto's thyroiditis and strongly correlated.[10] In another study by Bera et al[16] in 2015 revealed that there was an increase in anti-TPO antibody level in multinodular goiter (Benign & toxic) and papillary carcinoma but no elevation of anti-TPO antibody level in follicular adenoma or follicular carcinoma. In another correlation study by Ravisankar P et al[2] showed that all patients diagnosed as thyroiditis (Hashimoto's) had increased titres of anti-TPO antibodies and anti-TPO antibody estimation can be used as a tool in diagnosing thyroiditis. Significant correlation between lymphoplasmacytic infiltrate, Hurthle cells change, lymphoplasmacytic infiltrate with anti TG antibody and presence of anti-TPO antibody in patients was documented by Ahluwalia et al.[17] Additionally, John et al[18] in his study concluded that anti-TPO antibody level estimation can provide a valuable non-invasive method to rule out Hashimoto's thyroiditis in a patient presenting with hypothyroidism.

Limitation: As this is a hospital-based study, therefore may not represent the actual incidence of a thyroid nodules and swelling in the general population. Though the sample size was calculated statistically, but because of feasibility criteria, the sample size was kept to a minimum. Interpreting cytology slides might introduce an inter-observer variation that might affect the diagnosis. FNAC might induce an iatrogenic change in the thyroid follicles. The nature and size of the target lesion, the calibre of the needle used, the number of passes attempted, and the interval between FNAC and excision surgery are all factors that might influence such changes.

V. Conclusion

In this study of Fine Needle Aspiration Cytology of thyroid nodules and their relationship with thyroid function tests and anti-TPO antibody levels that were studied showed that females had higher preponderance for thyroid lesions. Autoimmune thyroiditis (lymphocytic thyroiditis) was the most common thyroid lesions followed by colloid goitre. Diffuse swelling of the thyroid was the most common clinical presentation in colloid goitre. There was a difference between findings of thyroid status and the cytomorphological diagnosis of the thyroid nodules. However, there was no association between cytomorphological diagnosis of the thyroid nodules and TSH and anti-TPO levels. There was a comparable finding between thyroid nodules and anti-TPO levels.

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