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DOES THE ENIGMA OF THE THREE STATES OF MATTER (RADIOLOGIC, BIOCHEMICAL AND CYTOLOGIC FINDINGS) IN THYROID SWELLINGS MATTER?

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ABSTRACT

The presence of thyroid nodules is a commonly encountered clinical scenario and about 42 million people in India suffer from thyroid diseases. This study attempted to correlate the results of FNAC with TFT, USG and Histopathologic findings where possible. A total of 70 cases were analyzed for FNAC, TFT and USG of thyroid. We concluded a significant correlation of FNAC with Ultrasound, but a significant correlation was missing between FNAC and TFT results. Histopathological confirmation was available for 17 patients. FNAC proved to have a high sensitivity, specificity and accuracy when compared with the corresponding histopathological reports.

KEYWORDS: FNAC, TFT, Ultrasonography, Cyto-histopathologic correlation, Thyroid.

INTRODUCTION

The presence of thyroid nodules is a commonly encountered clinical scenario. The prevalence of these thyroid nodules in the common population is 4%–5%.[1] Thyroid diseases are among the most common endocrine disorders worldwide including India. It has been estimated that about 42 million people in India suffer from thyroid diseases.[2]

The development of goiter is a matter of concern to both the patient and the clinician because of the risk of malignancy. Goiter is usually benign, and even in solitary nodules, malignancy is found in only around 10% of cases.[3] Exposure to ionizing radiation in childhood and adolescence increases the risk of solitary thyroid nodule and thyroid carcinoma.[4]

Thyroid sonography was first introduced in 1966-1967. It has been widely practiced since the 1970 and is now one of the most popular radiological methods of diagnosing thyroid disease. Sonography is commonly the first imaging modality after clinical examination.[5]

Ultrasound examination of the thyroid is also a useful adjunct to clinical assessment, and nodule characteristics that carry a high risk of malignancy include hypoechogenicity, microcalcifications, irregular margins, solid composition, and single nodularity.[6]

The basic morphologic unit of the thyroid gland is the follicle, composed of follicular cells which produce the hormones triiodothyronine (T3) and thyroxin (T4), which are in turn regulated by thyroid stimulating hormone (TSH), produced by the anterior pituitary gland. The levels of T3, T4 and TSH are assessed and thyroid lesions are categorized as hypothyroid, euthyroid or hyperthyroid conditions accordingly.[7]

Fine needle aspiration cytology (FNAC) of thyroid is a well established outpatient department procedure used in primary diagnosis of thyroid swellings. It often bridges the gap between clinical findings and laboratory test to give a definite diagnosis and subsequently reduces the need of surgery. Fine needle aspiration cytology is simple, cost effective, accurate, readily repeatable and quick to perform procedure in the outpatient department with excellent patient compliance. An important factor for the satisfactory test includes representative specimen from the swelling. It is often used as the initial screening test for diagnosis of thyroid nodule.[8]

This study was undertaken to study the spectrum of different thyroid lesions with cytological, biochemical, radiological and histopathological correlation of lesions of thyroid gland.

AIMS AND OBJECTIVES

- To correlate the cytomorphological features of palpable thyroid nodules using fine needle aspiration cytology (FNAC) with thyroid hormonal profile, radiological and histopathologic findings where possible.
- The study also tried to assess the sensitivity and specificity of FNAC as an initial diagnostic modality for thyroid lesions using histopathology as gold standard.

MATERIALS AND METHODS

This retrospective observational study was conducted in the Department of Pathology, Sri Siddhartha Medical College, Tumkur from October 2017 to October 2018. A total of 70 cases were analyzed during this period. The study included all the patients, irrespective of age and gender who presented to the cytology section with a referral for thyroid fine needle aspiration cytology. The patients who presented for a repeat FNAC due to any cause were excluded from the study. At the time of presentation to the Department, history was obtained and clinical examination of the thyroid lesion was performed and these findings were recorded along with the reports of TFT and Ultrasound.

Plan of Data Analysis

- Cytological assessment along with biochemical and radiologic correlation was carried out.
- FNAC reports were correlated with final histopathology reports where available.

Statistical analysis

Data collected was entered in MS Excel 2007. The data was exported into a statistical software package SPSS 20 and a statistical analysis was done after defining of variables.

True positivity(TP) was considered when the lesion was found to be malignant on both FNAC and histopathology. False positive (FP) were those cases wherein cytology was reported as malignant but benign on histopathology. True negative (TN) were benign on both cytology and histopathology. False negative (FN) were negative on cytology but positive for malignancy on histopathology. Sensitivity was a measure of detection of thyroid cancer by FNAC when it is actually present. Specificity was the ability of FNAC to exclude malignancy when it is actually absent, that is, benign lesions. Diagnostic accuracy was calculated by using sensitivity and specificity. The statistical formulae used were as follows :

- Sensitivity = TP / (TP + FN) x 100
- Specificity = TN / (TN + FP) x 100
- Accuracy = TP + TN / Total No. of Patients x 100

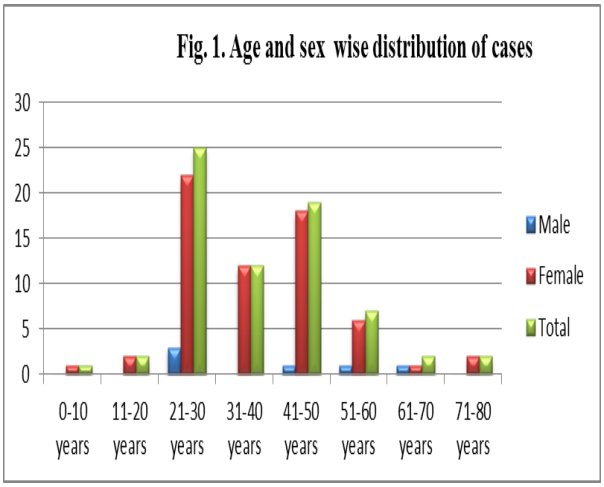
P value was used to assess the significance.[9]

RESULTS

The study included 70 patients with palpable thyroid lesions, of which, total number of females were 64 (91%) and males were 6 (9%). Female to male ratio was 10:1. [Table/ Fig.1].

Table 1: Age and sex wise distribution of cases.

Age (Years)	Male	Female	Total
0-10	-	1	1
11-20	-	2	2
21-30	3	22	25
31-40	-	12	12
41-50	1	18	19
51-60	1	6	7
61-70	1	1	2
71-80	-	2	2
Total	6	64	70

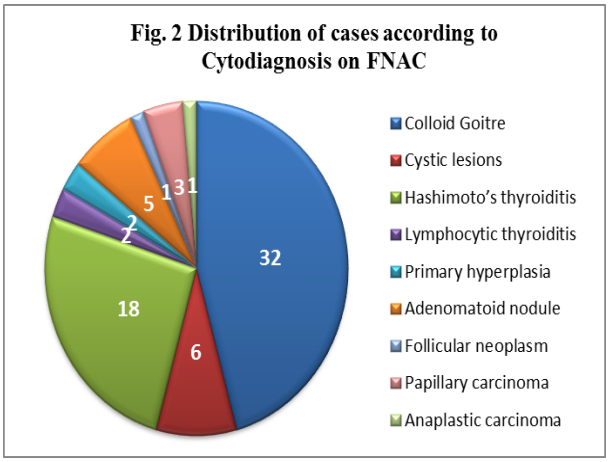


The age of the patients in the study ranged from 7 years to 75 years. Most of the patients belonged to the age group of 21years- 30 years (36%). FNAC was performed on all the 70 patients. The results were as follows.

The non-neoplastic lesions were more common (65/70, 93%), with colloid goitre (32/65; 49%) being the commonest diagnosis followed by Hashimoto's thyroiditis (18/65; 28%), Cystic lesions (6/65, 9%), adenomatoid nodule (5/65, 8%), Lymphocytic thyroiditis (2/65, 3%), and primary hyperplasia (2/65, 3%) in decreasing order of frequency. Among the neoplastic lesions (5/70, 7%), papillary carcinoma (3/5, 60%) was predominant followed by one case each of follicular neoplasm and anaplastic carcinoma (1/5, 20% each) [Table 2/ Fig. 2].

Table 2: Distribution of cases according to Cytodiagnosis on FNAC.

Non-neoplastic	No. of cases, n(%)	Neoplastic	No. of cases, n(%) 1
Colloid Goitre	32	Follicular neoplasm	1
Cystic lesions	6	Papillary carcinoma	3
Hashimoto's thyroiditis	18	Anaplastic carcinoma	1
Lymphocytic thyroiditis	2		
Primary hyperplasia	2		
Adenomatoid nodule	5		



Thyroid hormone profile was done in all patients, of which majority of patients (43 cases, 61%) were in euthyroid state, followed by hypothyroid state (21 cases, 30%) and least in hyperthyroid state (6 cases, 9%). [Table 3] There was no significant correlation between thyroid hormonal profile and FNAC. Radiological examination was done for all patients. 67 cases (96%) were given benign and 3 cases (4%) were malignant. There was a statistically positive significant correlation between FNAC findings and radiological features for different thyroid lesions with P<0.001.

Table 3: Distribution of cases according to hormonal status.

Cytodiagnosis	Euthyroid, n	Hyperthyroid, n	Hypothyroid, n
Colloid Goitre	25	3	4
Cystic lesions	6	-	-
Hashimoto's thyroiditis	3	-	15
Lymphocytic thyroiditis	-	-	
Primary hyperplasia	1	1	-
Adenomatoid nodule	3	2	-
Follicular neoplasm	1	-	-
Papillary carcinoma	1	-	2
Anaplastic carcinoma	1	-	-

In the present study, out of the 70 patients, surgical intervention was conducted on 17 patients. Among these, non-neoplastic lesions (11/17, 65%) were more common than neoplastic lesions (6/17; 35%). Among the neoplastic lesions, 1 was of follicular adenoma with goiter, 1 was anaplastic carcinoma, 2 were papillary carcinoma, 1 was papillary carcinoma with colloid goiter and 01 was papillary carcinoma with Hashimoto's thyroiditis. In the neoplastic lesions, cytology correlated positively in follicular neoplasm, anaplastic carcinoma and 3 cases of papillary carcinoma. One case of papillary carcinoma with Hashimoto's thyroiditis was diagnosed as Hashimoto's thyroidtis on cytology. Cytology correlated positively in all 11 cases of non-neoplastic lesions (07-colloid goitre, 04-hashimoto's thyroiditis) [Table 4].

Table 4: Comparison of FNAC and Histopathology diagnosis.

FNAC	HPE	No. of cases
Follicular neoplasm	Follicular adenoma with goitre	1
Anaplastic carcinoma	Anaplastic carcinoma	1
Papillary carcinoma	Papillary carcinoma	2
Papillary carcinoma	Papillary carcinoma with colloid goitre	1
Hashimoto's thyroiditis	Papillary carcinoma with Hashimoto's thyroiditis	1
Colloid goitre	Colloid goitre	7
Hashimoto's thyroiditis	Hashimoto's thyroiditis	4

Thus, the sensitivity of FNAC in the present study was 80%, specificity was 100%, positive predictive value (PPV) was 100% and negative predictive value (NPV) was 91.7%. The diagnostic accuracy of FNAC in diagnosing thyroid lesions was 88.2% [Table 5].

Table 5: Cyto-histopathologic concordance.

FNAC	HPE		Total
	Malignant	Benign	
Malignant	4	0	4
Benign	1	65	66
Total	5	65	70

DISCUSSION

In our study, 70 patients with palpable thyroid mass was included. Of these, majority were females (91%), which correlate with similar studies done by Makhwana et al[10], Raniwala et al.,[10] and Poudel et al.,[12] The age of the patients in the study ranged from 7 years to 75years. Most of the patients were in the age group of 21 to 30 years which is similar to the study by Karki et al.[13] Sheela et al.,[14] and Gupta R et al.,[15] on the other hand have reported maximum cases in the combined group of 20-40 years.

All 70 cases of palpable thyroid nodules underwent FNAC by aspiration. The cases were broadly classified as neoplastic and non-neoplastic. The non-neoplastic lesions were more predomiant (93%) compared to neoplastic lesions. Among the non-neoplastic lesions, colloid goitre (49%) was the commonest diagnosis followed by Hashimoto's thyroiditis (28%) whereas among the neoplastic lesions, papillary carcinoma was most common (60%). These findings are consistent with studies by Devi et al[8], Hirachand et al[16] and Chandanwale.[17]

Thyroid function tests was performed in all patients and most patients were euthyroid (61%). Among the non-neoplastic lesions, TFT was mostly euthyroid (58%) followed by hypothyroid (29%) and hyperthyroid (18%). Colloid goiter cases showed mostly euthyroid (78%), followed by hyperthyroid (13%) and hypothyroid (9%) status. Hashimoto's thyroiditis most commonly presented as hypothyroid (83%) with a few cases being euthyroid (17%). These findings are similar to the findings by Siddegowda et al.[9] Goiter, the enlargement of thyroid gland, is caused by inadequate synthesis of thyroid hormone as a result of iodine deficiency, leading to increased TSH levels. This high level of TSH stimulates the thyroid follicular cells which results in compensatory hypertrophy and hyperplasia, and presents as gross enlargement of the gland. This further causes increased hormonal production and results in an euthyroid status in most of the individuals. Hashimoto's thyroiditis presents as painless thyromegaly in middle aged woman. It commonly presents over a period of time to subclinical and then clinically overt hypothyroidism. However, in some cases, it may be preceded by a transient hyperthyroid state (hashitoxicosis) due to destruction of follicles and subsequently elevated free T3 and T4, low TSH and diminished radioactive iodine uptake.[9] All the neoplastic cases n our study were euthyroid. In the studies done by Poudel et al[12] and Devi et al,[8] the neoplastic thyroid lesions were more commonly seen associated with euthyroidism. There was no significant correlation between thyroid hormonal profile and FNAC as is the case seen with the study by Poudel et al.[7]

Sonologic analysis was carried out for all patients. The nodules were assessed on the basis of echogenicity, calcification, internal vascularity, cystic areas, lymphadenopathy and background thyroid changes.[18] Of these, 67 cases (96%) were given benign and 3 cases (4%) were malignant. The malignant cases included 1 anaplastic carcinoma and 2 cases of papillary carcinoma and was consistent with the respective cytology67 cases (96%) were given benign and 3 cases (4%) were malignant.. A case of goiter diagnosed on USG turned out to be Papillary carcinoma on FNAC. There was a statistically significant connection between ultrasound and results of cytological exam with $p<0.001$. Similar results were obtained by Sehovic et al.[19] [Fig. 3]

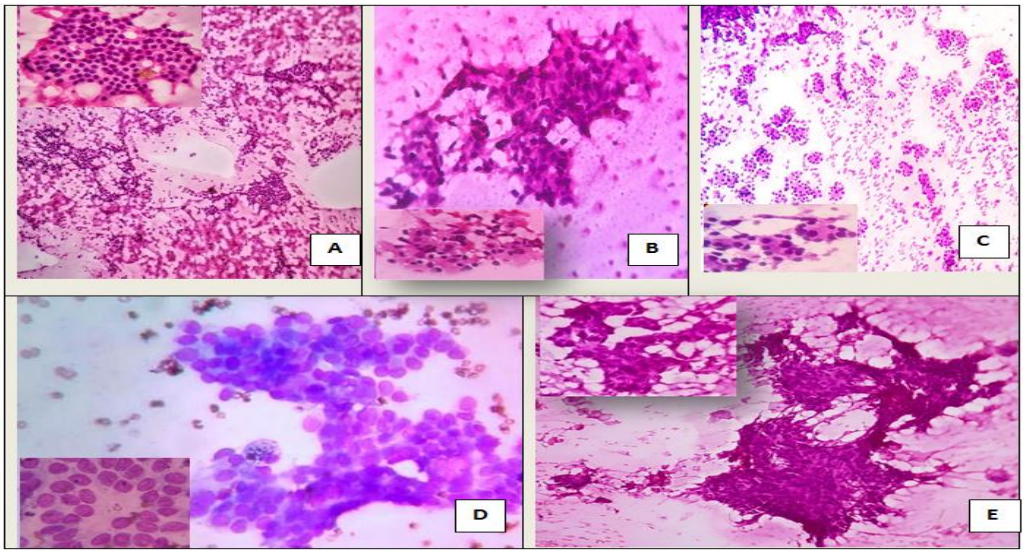


Fig. 3. Cytology of thyroid swellings. A. Colloid goiter. Clusters of benign follicular cells against a background of thin colloid with inset showing cluster of benign follicular cells. B Hashimoto's thyroiditis. Lymphocytic

impingement of follicular cells with inset (40x) showing foci of Huthle cells and lymphocytes. (10x, H&E). C. Follicular neoplasm. Repetitive follicles seen (10x) and inset showing higher magnification of follicles (40x). D. Papillary thyroid carcinoma. Tumor cells arranged in papillary pattern (10x) with inset showing nuclear grooving of cells. (40x) (H&E). E. Anaplastic Carcinoma (10x) with inset (40x) showing cluster of highly pleomorphic tumor cells *(H&E)*.

In the present study, histopathological correlation was available in 17 cases, of which 6 were neoplastic and 11 were non-neoplastic lesions. Among the neoplastic lesions, positive cyto-histological correlation was observed in 5 cases. One case of Hasimoto's thyroiditis with papillary carcinoma was diagnosed on cytology as Hashimoto's thyroiditis [Table 4]. Hashimoto's thyroiditis (HT), also known as chronic lymphocytic or autoimmune thyroiditis, is a part of the spectrum of autoimmune thyroid diseases (AITD). The association of HT with papillary thyroid cancer (PTC) was first reported by Dailey in 1955. The chronic inflammation associated with HT was postulated to be a source of carcinogensis. Occasionaly, HT exhibits cytological alterations and nuclear modifications like RET/PTC rearrangements and BRAF mutations which are also seen in PTC, suggesting that the neoplastic and autoimmune disease share the same basis of molecular pathogenesis. Immune mediated receptors like TLRs and DNA repairing genes like ATM, hOGG mutations may accumulate as aberrant genetic changes in long standing HT, which serves as a precursor lesion of PTC. Elevated levels of TSH found in HT with hypothyroid status may stimulate follicular epithelial proliferation, and eventually lead to development of PTC.[20] The pitfall in misdiagnosing Papillary thyroid carcinoma in our patient could be attributed to sampling error where the site of FNA was away from the foci of the carcinoma, and hence only picked up cells from the area of HT. Hence, one must exercise great caution while sampling the cytology of Hashimoto's thyroiditis to avoid missing a possible occult carcinoma. Among the non-neoplastic lesions, positive correlation was observed in all 11 cases. Siddegowda et al reported similar findings.[9]

In this study, we demostrate a high sensitivity, specificity and and accuracy of FNAC in diagnosing the thyroid lesions, which is in agreement to similar studies conducted previously.[21,22,23] One of the major diagnostic challenges faced with FNAC of thyroid lesions is the inability to distinguish follicular adenoma from follicular carcinoma. [Fig. 4]

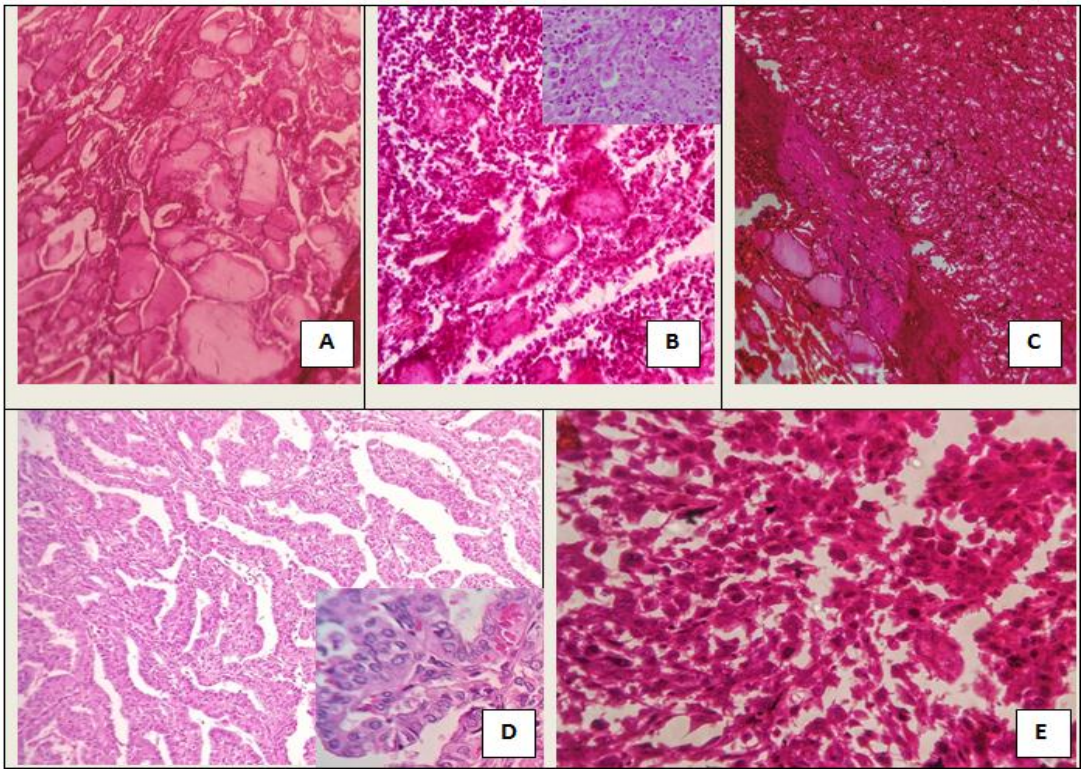


Fig.4. Histopathology of thyroid swellings. A. Colloid goiter. Colloid filled follicles of varying size and shape lined by benign follicular cells. (10x, H&E). B. Hashimoto's thyroiditis. Lymphocytic destruction of follicles with inset (40x) showing foci of Huthle cells and lymphocytes. (10x, H&E). C. Well encapsulated follicular adenoma (right) with colloid goiter (left). No capsular invasion seen. (10x, H&E). D. Papillary thyroid carcinoma. Tumor cells arranged in papillary pattern (10x) with inset showing papillae with fibrovascular core and lined by tumor cells with Orphan Annie eye nuclei.. (40x) (H&E). E. Anaplastic Carcinoma showing highly pleomorphic tumor cells (40x,H&E).

CONCLUSION

FNAC is a simple, easy to perform, quick, safe and cost effective minimally invasive technique used as part of the initial evaluation of thyroid lesions.

In this study, we concluded a significant correlation of FNAC with Ultrasound, but a significant correlation was missing between FNAC and TFT results.

FNAC proved to have a high sensitivity, specificity and accuracy when compared with the available histopathological reports. Hence, it is particularly useful in developing countries like India.

We faced diagnostic dilemmas in two cases with regard to FNAC - One of a follicular neoplasm where FNAC fails to distinguish adenoma from carcinoma and the other case of Papillary carcinoma with Hashimoto's thyroiditis which was missed due to sampling error and was reported as Hashimoto's thyroiditis.

Thus, FNAC of thyroid, used in conjunction with TFT and USG results can help clinicians in planning the course of treatment and management of patients with thyroid lesions and also avoid unnecessary surgeries in case of benign lesions.

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