



## Patterns of Thyroid Disorders Diagnosed on Cytology with Histopathological Correlation in A Tertiary Care Hospital in South India- A Retrospective Study

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**ABSTRACT**

**BACKGROUND:** Fine needle aspiration cytology (FNAC) is a well established, simple, safe and outpatient procedure used in diagnosis of thyroid swelling.

**OBJECTIVE:** To study the profile of thyroid lesions as diagnosed on FNAC at our hospital, to assess the diagnostic role of FNAC in goitre patients and to correlate cytology and histopathology findings wherever possible.

**MATERIALS AND METHODS:** A retrospective study of 231 consecutive patients was conducted from January, 2014 to December 2015 in pathology department of our hospital. Aspiration was taken after detailed clinical history, physical examination and thyroid function test. FNAC results were compared with final histopathological diagnosis, wherever patient underwent surgical excision.

**RESULTS:** FNA results were classified as inadequate material, Benign, Follicular Neoplasms, and Malignant lesions. FNA analysis showed 89.17% (206 cases) non-neoplastic lesions, 5.19% (12 cases) malignant lesions. Follicular lesions were a gray zone on cytology, where we didn't classify them as adenoma or carcinoma, and they accounted 13 cases (5.62%). The most common benign entity diagnosed was Hashimoto's thyroiditis accounting to 87 cases (37.6%) in females. The most common malignancy diagnosed on FNAC was Papillary carcinoma accounting to 8 cases (3.46%) with male predominance.

**CONCLUSION:** The study definitely resulted in helping the clinicians in better patient care and management. FNAC gives a reliable pre-operative cytological diagnosis based on which surgical procedures can be confidently executed. It helps to filter out cases which can be successfully treated by conservative methods and thus reduce unnecessary thyroid surgery.

**KEYWORDS**

Thyroid, FNAC, Histopathology, Correlation.

**Introduction:**

Thyroid disorders are amongst the most common endocrine diseases in India.<sup>1</sup> The total burden of thyroid disorders in India is 42 million.<sup>2</sup> There is increasing prevalence of endemic goitre among people living in coastal areas.<sup>3</sup> Biopsy by aspiration, also known as fine needle aspiration cytology (FNAC), has become an important diagnostic technique, replacing to some extent and complementing tissue pathology in many clinical situations.<sup>4</sup> Many of the benign thyroid diseases with classical clinical and hormonal setting are easy to diagnose and FNAC serves mainly to confirm the diagnoses. However living in a society concerned with containment of medical costs, where the hormonal profile and antibody titres are not available or unaffordable, the diagnosis rest on FNAC which is a simple, easy and cost effective test. Thyroid cytology is far more accurate for the selection of patients with nodules for diagnostic lobectomy and is much cheaper than any combination of non-invasive tests. Its use has halved the number of operations prescribed and has doubled the number of cancers identified per 100 surgical removals<sup>5</sup>. Cutting surgical and hospital bills for the management of nodules in half is a worthwhile achievement. The purpose of the study would be to assess the various patterns of thyroid disorders in a clinical setting with high prevalence of goitre and the role of cytology with histopathology correlation (in patients who underwent surgery) in arriving at an appropriate diagnosis.

- To study the profile of thyroid lesions as diagnosed on FNAC at our hospital.
- To assess the diagnostic role of FNAC in goitre patients.
- To correlate cytology and histopathology findings wherever possible.

**Methodology:**

The study was carried out in the department of Pathology, after obtaining Institutional Ethics Committee (IEC) approval. We started our study by collecting data of all cases referred for FNAC from general surgery and ENT departments during the study period of two years. The medical records were collected regarding clinical examination findings, radiological findings and thyroid function test (TFT) results. The aspiration technique was the standard one described in literature.

Surgical removal of the lesion was done at the discretion of the surgeons. Whenever the excised specimen was received in the department, it was routinely processed to obtain paraffin sections which were stained by Hematoxylin and Eosin. Histopathological study was done independently. Results of cytological and histopathological studies were later correlated to evaluate the efficacy of FNAC.

Cytological interpretation / Fine needle aspiration cytology diagnoses were placed in four categories:

1. Benign: this category includes benign follicular lesions

**Objectives:**

- such as multinodular goitre/ adenomatous hyperplasias, colloid nodules, thyroiditis (lymphocytic/Hashimoto).
- 2. Malignant: Meaning aspirates suggestive of papillary, medullary or anaplastic carcinoma.
- 3. Follicular neoplasms: This includes suspicious, meaning findings suggestive of but not definitive for malignancy. Both follicular adenomas and carcinomas, including Hurthle cell neoplasms are included in this category.
- 4. In-adequate means inadequate material for diagnosis.
- 5. It was descriptive record review study by retrospective data collection.

**Study population: Inclusion criteria:** All cases with goitre referred to cytology lab for FNAC from 1<sup>st</sup> January 2014 to 31<sup>st</sup> December 2015 (2 years duration) were included in the study irrespective of age and sex of the patient. Ultrasound (USG) guided FNAC were also included in the study. **Exclusion criteria:** Cases other than goitre and inadequate material with no conclusion on cytology have been excluded from the study.

Data regarding age and sex of the patient, clinical diagnoses, cytological diagnoses and final histopathological diagnoses were collected from cytology and histopathology registers and correlation of the diagnoses was done, if the cases had underwent surgery. The data was entered and analyzed using SPSS software.

**Results:**

In the year 2014 we got 117 cases requested for thyroid FNAC and 139 cases in the year 2015. Out of 117 in the year 2014, FNAC was inconclusive in 8 cases, and out of 139 cases in the year 2015, 17 cases were inconclusive. The main reason for inconclusive FNAC was absence of diagnostic follicular epithelial cells or/ and when smears showed only hemorrhage mixed with scant colloid. So these 25 cases constituted 4<sup>th</sup> "In-adequate category" have been removed from the study. Finally, total number of cases for our two year study design was 231.

The results and observations of our study are depicted as follows:

**Age Incidence:** Age of the patient was ranged from 7 to 87 years with mean age of presentation being 37.6 years. Most of the patients in our study were in the age group of 21-40 yrs and accounted for 46.32% of the patients. Least number of patients (0.43 %) were in the age group of 81-100 years followed by 61-80 years (6.45%).

**Sex Incidence:**

Out of 231 patients, 89.6% of the patients (207 cases) in our study were females and the rest 10.4% of the patients were males (24 cases). Female to male ratio was 9:1.

In our study, females had 84.41% benign swellings and 0.86% of the swellings were malignant; whereas 4.76% of male patients had benign swellings and 4.32% had malignant tumors of the thyroid gland.

**Table 1: List of diagnoses offered in Cytology.**

Category		Total cases	Males	Females
Benign	MNG	65	4	61
	Colloid Nodule	48	2	46
	Thyroiditis	89	2	87
Follicular lesions	Hyperplastic nodule of MNG	4	3	1
	Follicular lesion	12	2	10
	Hurthle cell lesion	1	1	0
Malignant	Papillary carcinoma	8	6	2

	Follicular variant of Papillary Carcinoma	2	2	0
	Medullary carcinoma	1	1	0
	Anaplastic carcinoma	1	1	0
	Total	231	24	207

The most common disorder of thyroid diagnosed on FNAC were benign constituting 206 cases (89.17%), whereas malignancies accounted for only 12cases (5.19%). Follicular lesions were a gray zone on cytology, where we didn't classify them as adenoma or carcinoma, and they accounted 13 cases (5.62%). The most common benign entity diagnosed was Hashimoto's thyroiditis accounting to 87 cases (37.6%) in females. The most common malignancy diagnosed on FNAC was Papillary carcinoma accounting to 8 cases (3.46%) with male predominance.

After collecting FNAC results we collected reports from histopathology section to know, how many of these patients underwent surgical excision during the study period. Only 31 patients (13.4%) were underwent surgical intervention and the rest were under medical line of treatment or under observation. Some patients with malignancy report on cytology didn't underwent surgical intervention at our hospital during study period. Probably, they might have selected some other premier institutes for further management according to their willingness and convenience. Hence we didn't got their histopathology reports and lost the followup. Excising all thyroid nodules is impractical, as most thyroid nodules are benign and thyroid surgery is not without risks. Table 4 shows histopathology results.

**Table 2: Histopathology results after surgical intervention:**

Sl No	FNAC diagnosis	Histopathology diagnosis
1	Nodular goitre	Follicular adenoma
2	Hyperplastic nodule of MNG	Minimally invasive follicular carcinoma
3	Nodular goitre	Nodular goitre with cystic change
4	Multinodular goitre	Papillary carcinoma thyroid with Hashimoto's thyroiditis
5	Nodular goitre with cystic change	Nodular hyperplasia with Hashimoto's thyroiditis
6	Multinodular goitre	Multinodular goitre
7	Multinodular goitre	Nodular goitre
8	Multinodular goitre	Multinodular goitre
9	Multinodular goitre	Nodular goitre
10	Multinodular goitre	Hashimoto's thyroiditis
11	Nodular goitre	Nodular goitre
12	Nodular goitre with cystic change	Nodular goitre with cystic change
13	Nodular goitre with cystic change	Multinodular goitre with cystic change
14	Multinodular goitre	Hashimoto's thyroiditis
15	Colloid goitre	Follicular adenoma
16	Colloid goitre	Multinodular goitre with cystic change
17	Colloid goitre	Colloid goitre
18	Colloid goitre	Colloid goitre
19	Colloid goitre with cystic change	Colloid goitre with cystic change
20	Colloid goitre	Colloid goitre
21	Colloid goitre with cystic change	Multinodular goitre with cystic change
22	Colloid nodule	Follicular adenoma
23	Colloid goitre with cystic change	Papillary carcinoma with cystic change.

24	Colloid goitre	Nodular hyperplasia
25	Colloid goitre	Colloid goitre
26	Hashimoto's thyroiditis	Hashimoto's thyroiditis
27	Hashimoto's thyroiditis	Hashimoto's thyroiditis
28	Papillary ca thyroid	Papillary carcinoma with Hashimoto's thyroiditis
29	Papillary Ca	Papillary carcinoma thyroid with LN metastasis
30	Follicular lesion	Follicular adenoma
31	Follicular lesion	Follicular variant of papillary carcinoma thyroid

Table 2 shows reveals that, patients benign conditions like colloid goitre were also underwent surgical excision probably for "cosmetic reason" or to get relief from the fear of cancer. One case of minimally invasive follicular carcinoma was diagnosed as multinodular goitre in cytology, indicating possibility of sampling error. In one case, papillary carcinoma we diagnosed as multinodular goitre on cytology; review of cytology smears again, revealed occasional follicular epithelial cells showing intranuclear grooves and cytoplasmic inclusions which were missed initially. Two cases diagnosed as colloid goitre on cytology revealed follicular adenoma on histopathology. One case reported as colloid goitre with cystic change revealed Papillary carcinoma with cystic change on histopathology. Review of cytology smears revealed sparse cellularity with very few microfollicles. Re-aspiration was not done, and we felt, it would have reduced the chance of sampling error. Hashimoto's thyroiditis is most common and easiest lesion to diagnose on cytology, provided we get good cellularity with follicular cells showing Hurthle cell metaplasia and background of mononuclear cell infiltrate. Most of these cases will be managed with thyroid hormone supplementation and medical line of management. Cases with cytological diagnosis of follicular neoplasm and Hurthle cell tumors were most challenging as it is not possible to differentiate follicular adenoma (benign) from follicular carcinoma (malignant) based on cytological assessment only. This group of lesions was a gray zone in the field of Thyroid FNAC and we had total of 13 cases (5.6%) during the study period.

#### Discussion:

**FNAC as diagnostic tool:** Fine needle aspiration cytology (FNAC) examination introduced by our Scandinavian Colleagues in the nineteen fifties is a reliable, cost effective and simple procedure.<sup>3</sup> Various pre-operative investigations like ultrasound scan, thyroid function tests, imaging analysis like CT and MRI, and many others sometimes lead the surgeon along a uncertain path towards the diagnosis and thus towards a surgical strategy have proven to be unreliable to a large extent when the final diagnosis of histopathology is obtained, all in spite of the cost the patient incurs. FNAC has stood the vigorous assault of all its critics among both the surgeons and the physicians.<sup>4</sup> It has proved to be the single most important factor in achieving a pre-operative diagnosis there by aiding or altering the surgical strategy or in other forms of management of thyroid pathology.

**Case selection:** From Pathologist point of view, we feel that all the neck swellings sent by clinicians will not be suitable for FNAC. In this study, we had 25 cases that constituted "inadequate" category. In these cases, thyromegaly was minimal and aspiration not yielded adequate material. The true value of FNA lies in patient selection and case identification. Patients with long history of thyroid enlargement, family history of goitre, bilateral lobe affection, have a low probability of malignancy and can be treated conservatively. Silverman et al described aspirations from 309 patients of whom only 60 were treated surgically.<sup>5</sup> Similarly we had 231 cases of which only 31 cases were treated surgically, indicating FNAC is useful diagnostic tool in selecting cases for further line of treatment.

**Adequacy of material:** Smears from non neoplastic nodules as a rule contained much colloid and few cells. In contrast, aspirates from neoplastic lesions there was little colloid

but high cellularity. Hamburger et al suggested that, in the assessment of a thyroid nodule six clusters of benign cells in at least two slides prepared from separate aspirates constitute reasonable minimum material for diagnosing benign lesions.<sup>6</sup> Other authors rely on similar criteria (5-6 groups of cells with more than 10 cells per group). It is believed that abundant clean colloid without altered blood or debris also indicates a benign diagnosis in a STN, but nevertheless the presence of a certain number of intact and well-fixed follicular epithelial cells is obligatory for a smear to be satisfactory. Clearly, the issue is dependent on the type of lesion (cystic or solid) and the skill combined with experience of the performer and it is said that the latter is paramount.

Thyroid cysts can be safely aspirated and aspirate should be examined cytologically after sedimentation or cell block preparation. When we aspirate colloid cysts, swelling usually reduces in size and re-aspiration should be attempted from residual solid area of thyroid tissue. Hamburger et.al, accounted that the distinction between a cellular colloid goiter and a follicular neoplasm may be impossible.<sup>5</sup> In our another case of cystic colloid nodule, histopathology revealed papillary carcinoma thyroid with cystic change (Fig No 1). As it is known fact, that around 30%-40% of papillary carcinoma can have cystic degenerative changes, every solitary nodule of thyroid with cystic change has to be viewed suspiciously.<sup>6</sup> As per Backdahls et al, analysis of DNA content in aspirated cells was found to be helpful in delineating benign from malignant cells.<sup>7</sup> Ultrasound-guided FNAC can then be performed to sample the suspicious solid component. Ultrasound (US) investigation permits direct sampling of the wall and/or the solid portion of the cystic thyroid nodule, thereby increasing the possibility of a representative sample. However, due to difficulties both in obtaining adequate tissue sampling, and in accurately detecting enlargement of the solid portions of these nodules, surgery should be considered for persistent and recurrent complex cystic nodules for both diagnostic and therapeutic reasons. Surgery is indicated especially for cystic thyroid nodules >4 cm, since the risk of malignancy is higher in large cystic lesions.<sup>8-9</sup>

In our study we noted higher incidence of Hashimoto's thyroiditis especially in females of 4<sup>th</sup> and 5<sup>th</sup> decade of life presenting with diffuse thyroid enlargement. In two of the Papillary carcinoma cases, surrounding thyroid tissue showed Hashimoto's thyroiditis, making us to think the association between the two conditions. An unambiguous association between papillary thyroid cancer and Hashimoto thyroiditis was demonstrated for the first time by Dailey et al.<sup>11</sup> in 1955. Presently, the best known form of such alterations in papillary thyroid cancer is the concept of oncogenic RET/PTC1 and RET/PTC3 sequences that are also present in chronic lymphocytic thyroiditis, but with no clinical manifestation of lesions in the thyroid parenchyma. The common transformation path of thyroid cells in papillary thyroid cancer and Hashimoto thyroiditis has been also attempted to be explained by similarities in activation of the metabolic cycle of tyrosine kinases (PI3k/Akt pathway) and overexpression of p63 protein that leads to apoptosis inhibition.<sup>12</sup> Many studies conclude that patients with Hashimoto's thyroiditis may warrant increased attention for the development of clinically relevant thyroid nodules given their higher risk of malignancy.<sup>13-14</sup>

Follicular neoplasm was most misleading entity we encountered in our study accounting to 12 cases. One case we diagnosed as hyperplastic nodule of MNG turned as follicular carcinoma on histopathological examination. The probable reason for misdiagnosis as hyperplastic nodule is presence of high cellularity with predominant microfollicular pattern. The microfollicular pattern is common pattern present in both the conditions, but presence of fire-flare appearance of colloid favors diagnosis of MNG, and microfollicles with very scant colloid favor diagnosis of follicular neoplasm. Two cases of colloid goitre were diagnosed as follicular adenomas on histopathology. One case of follicular variant of papillary carcinoma was misdiagnosed as follicular neoplasm because of high cellularity, predominant follicular pattern and nuclear overlapping. Focal nuclear features like grooving or intranuclear inclusions were ignored in view of predominant follicular pattern



(Fig No 2). Review of cytology slides again revealed our mistake. Diagnosis of this tumor by FNAC and frozen section is notoriously difficult and unreliable. A possible remedy is multiple aspirations from different sites, and many feel that nuclear features in more than 20 cells have a greater risk of papillary carcinoma, and typical nuclear features are always helpful.<sup>13</sup>

Papillary carcinoma FNAC diagnosis was offered in 8 cases. Histopathological confirmation was available in only 2 cases. Powdery nuclear chromatin, papillary fronds, intra-nuclear inclusions and nuclear grooves were common findings. Psammoma bodies are seen rarely. Problems in diagnosing papillary carcinoma include cystic change, marked lymphocytic infiltration and mixed patterns of growth.<sup>14</sup>

One case of medullary carcinoma was diagnosed by FNAC and showed tumor cells having plasmacytoid appearance with moderately pleomorphic nuclei, granular cytoplasm and occasional binucleated forms (Fig No 3). Amyloid was not seen. We diagnosed one case of anaplastic carcinoma on cytology, where smears were highly cellular with marked pleomorphism. Clusters of spindle shaped tumor cells having hyperchromatic nuclei with mitotic figures and occasional binucleate forms favored our diagnosis of spindle cell variant of anaplastic carcinoma. Khan et al, stated that diagnostic reliability is limited, because these cases can be associated with inflammation, necrosis and hemorrhage.<sup>14</sup>We didn't receive histopathological specimen in both these cases, as probably they were referred to some other hospital.

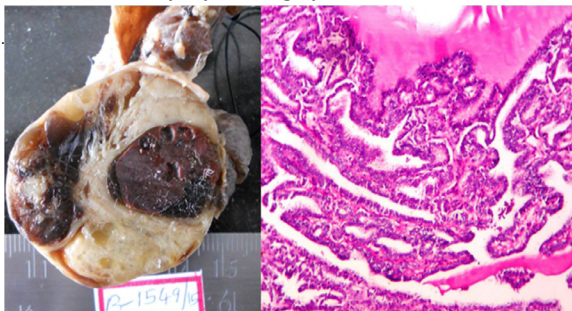
#### Conclusions:

Benign disorders made up the bulk of thyroid disorders, majority of whom respond to medical line of management with follow up in chosen few cases.

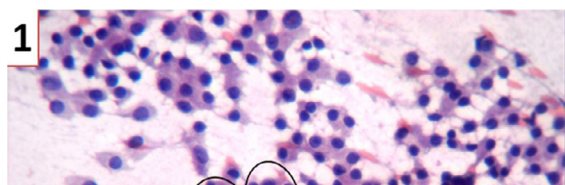
The study thrown light upon the most common form of thyroid disorder in the Pondicherry, a coastal area of South India. Hashimoto's thyroiditis emerged as most common lesion in females.

The misdiagnosis was more with follicular neoplasms compared to other lesions. The scope and limitations of FNAC should be fully realized, especially in the interpretation of adenomatous goiter and follicular neoplasms. We stress the importance of nuclear features in the diagnosis of papillary carcinoma and follicular variant of papillary carcinoma.

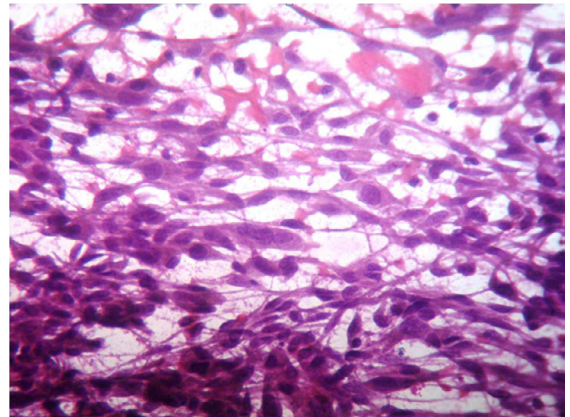
The study definitely resulted in helping the clinicians in better patient care and management. FNAC gives a reliable pre-operative cytological diagnosis based on which surgical procedures can be confidently executed. It helps to filter out cases which can be successfully treated by conservative methods and thus reduce unnecessary thyroid surgery



**Fig No 1: Solitary thyroid nodule diagnosed as cystic colloid nodule. Histopathology revealed papillary carcinoma thyroid with cystic change (H and E, 10 X).**



**Fig No 2: Highly cellular aspirate showing predominant repetitive microfollicular pattern (circles) (Pap stain, 4X). Focal intranuclear inclusions (inset) were ignored in view of predominant follicular pattern (Leischman Stain, 40X). Histopathology revealed follicular variant of Papillary Carcinoma.**



**Fig No 3: Medullary carcinoma diagnosed by FNAC showing tumour cells having plasmacytoid to spindle appearance with moderately pleomorphic nuclei and granular cytoplasm (Pap stain, 20 X)**

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