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Original Article

Pharmacology Section

Various Cytomorphological Cell Patterns Analysis in Thyroid Swelling on Adequate Smears

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ABSTRACT

Introduction: Fine Needle Aspiration Cytology (FNAC) is considered as an independent and accurate diagnostic test for the different types of thyroid swelling. Adequacy is dependent on the technique and nature of the lesion.

Aim: To study the various cell patterns of thyroid aspiration and evaluation of the concordance between FNAC and Histopathology findings.

Materials and Methods: A prospective study was conducted during a period of September 2015 to November 2017. Correlation of FNAC and histology findings has been interpreted. FNAC of 502 patients presented with features of enlarged thyroid gland was analysed. All the relevant details about age, sex, duration of swelling and thyroid profile were taken. The diagnosis of lesions were made based on the presence of primary dominant cell pattern and included macro/normofollicular, microfollicular, papillary, syncytial, dispersed, cystic pattern and degenerated plus granulomas pattern. Total 203 specimens were examined for histology and compared with FNAC findings. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy were evaluated.

Results: A total of 502 thyroid swellings were studied, out of which, 6 cases were inadequate and revealed blood only. On the basis of primary dominant cell pattern, the macro/normofollicular pattern was noted in 189 (38.10%) cases, microfollicular pattern in 79 (15.93%) cases, papillary pattern in 18 (03.63%) cases, syncytial pattern in 80 (16.13%) cases, dispersed pattern in 33(06.65%) cases, cystic pattern in 87 (17.54%) cases granulomas in 10 (2.02%) cases. Normo/macrofollicular (35.28%) and cystic pattern (14.51%) were common in colloid goiter which was also a common finding in FNAC (52.02%) and in histology (55.66%). In Hashimoto thyroiditis, frequent pattern noted were syncytial (13%) and dispersed (03.42%). Microfollicular (09.6%) and papillary pattern (03.62%) were common in follicular and papillary carcinoma respectively. FNAC and histology concordant were noted in 195/203 (96%) cases. 5 of 8 discordant cases were malignant and 3 /8 were benign. Overall the sensitivity, specificity, positive predictive value and negative predictive value were 93.54%, 98.59%, 98.30% and 97.91% respectively. Diagnostic accuracy of FNAC was 97.22%.

CONCLUSION: FNAC is a microinvasive, inexpensive and important tool for the evaluation of patients with thyroid swellings. Differential diagnosis can be encountered on the basis of various cellular patterns that can be narrowed by histopathological examination.

Keywords: Fine needle aspiration cytology, Follicular epithelial cells figure, Histopathology

INTRODUCTION

Thyroid FNAC was first used by Martin and Ellis in New York in 1930 but it was first commonly used in Sweden during the 1950s and 1960s [1]. It is the most simple, accurate, fast and economical, reliable method to distinguish a benign lesion from a malignant one, that dramatically reduced the unnecessary surgeries [2,3]. It is also a preoperative screening method of choice worldwide. Other specific indications of FNAC are evaluation of diffuse goiter, follow-up of individuals after irradiation of head and neck and therapeutic drainage of cystic lesions. Adequacy of FNAC is satisfied by the presence of 5-6 groups of well-preserved follicular epithelial cells with each group containing 10 or more cells on at least two slides [1]. Despite iodine supplementation colloid goiter is a common clinical presentation with a prevalence rate of 4-7% in the general population [4]. Many architectural patterns of follicular epithelial cells analysed were intact macrofollicular, microfollicular, papillary fronds, isolated cell pattern (dispersed), cystic and multinucleated giant cell. In this study cytological diagnosis were encountered on the basis of first predominant cellular pattern that were compared with histopathological examination, whenever possible.

MATERIALS AND METHODS

A prospective study was done in the department of Pathology, Lala Lajpat Rai Memorial Medical College, Uttar Pradesh,

during the period of September 2015 to November 2017. This study was approved by hospital Ethical committee. All patients (male and female, any age group) those who had thyroid swelling, willingness for participation and were advised for FNAC were included in the study. Patients those who had psychiatric illness, surgical illness, taking medicine affecting thyroid profile and were unwilling for FNAC excluded from this study. Consent of all the patients were taken after the explaining the purpose and importance of FNAC. Total of 502 patients presenting with features of thyroid swelling were thoroughly examined clinically after taking all the relevant clinical history and data related to thyroid swelling. FNAC was done in 502 willing patients using a 23 to 24 gauge needle and 20 mL syringe under aseptic precautions. Repeat FNAC was done if necessary. At least 1-2 Giemsa stain and one Papanicolaou's stain per case were applied. Papanicolaou's stained slides were analysed because it increases the sensitivity to detection of nuclear features. All the thyroid FNAC cases were reported according to the predominant cell pattern, nuclear features and background. Out of the 502 cases, respectively 203 surgically removed and formalin fixed thyroid specimens were received from Surgery Department of our institute and evaluated for histopathological examination. At last concordance of respective diagnosis made by FNAC and histology was done [Table/Fig-1].

STATISTICAL ANALYSIS

Overall Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were analysed using the SPSS version 18.0 these were 93.54%, 98.59%, 98.30% and 97.91 % respectively. The diagnostic accuracy of FNAC was 97.22%.

RESULT

A total of 502 thyroid FNAC cases were reported in the study tenure. The common age group of thyroid swellings was between 31-40 years comprising 274 cases (54.58%) in total. Females (91.43%) were commonly involved with M: F ratio of 1:10. Out of 502 cases, most common presentation of swelling was solitary nodule (57.37%) followed by diffuse swelling (36.25%) and multinodular (6.37%) goiter. Right lobe (52.79%) of thyroid was commonly affected. 6 cases (1.2%) were inadequate and showed only blood. Out of 496 cases the non neoplastic and neoplastic lesions were 82.66% and 17.34% respectively.

Cytohistomorphological Correlation				
Cases		n	Concordance	Discordance
Colloid goiter (117)	Macrofollicular	72	70	02- papillary carcinoma
	Microfollicular	02	01	01- follicular adenoma
	Cystic	43	42	01 – papillary carcinoma
Colloid cyst (02)	Cystic	02	02	-
Hashimoto thyroiditis (16)	Microfollicular	03	03	-
	Syncytial	11	11	
	Dispersed	02	02	
Granulomatous thyroiditis (01)	Gedenerated + granuloma	01	01	-
Graves disease (08)	Macrofollicular	01	01	-
	Syncytial	01	01	-
	Dispersed	06	05	01 – Multinodular goiter
Follicular neoplasm (37)	Macrofollicular	01	01	-
	Microfollicular	35	33	02- papillary carcinoma
	Cystic	01	01	
Papillary carcinoma (20)	Microfollicular	02	02	-
	Papillary	15	15	
	Syncytial	02	02	
	Dispersed	01	01	
Medullary carcinoma (01)	Syncytial	01	-	01- Hyalinised trabecular tumour
NHL (01)	Dispersed	01	01	-
Total		203	195	08

[Table/Fig-1]: Histopathological concordane and discordance.

Follicular epithelial cells of thyroid revealed various cytomorphological pattern, including-

1. Macrofollicular pattern, defined as flat sheets and clusters of evenly spaced follicular cells [5] [Table/Fig-2].

2. Microfollicles are small circles of follicular cells [5] [Table/Fig-3].

3. Papillary pattern are nipple like projection with fibrovascular core consisting of follicular epithelial cells [5] [Table/Fig-4].

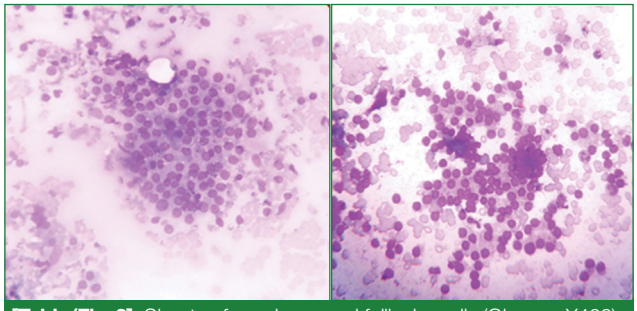
4. Isolated cell pattern referred to as loosely cohesive clusters and lying singly follicular epithelial cells [6] [Table/Fig-5].

5. Syncytial pattern defined as sheets of follicular cells without discernible cell membrane [6] [Table/Fig-6].

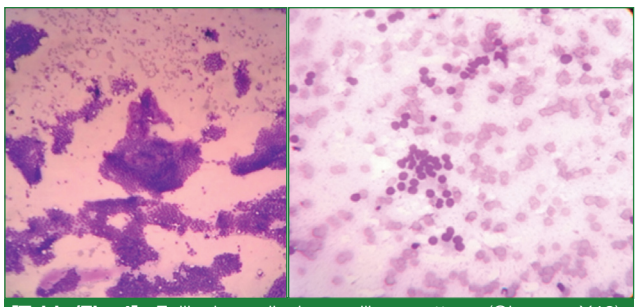
6. Scattered foamy and haemosiderin laden macrophages in a proteinaceous background defined the cystic pattern [6] [Table/Fig-7].

7. Granuloma is defined as clusters of epithelioid histiocytes [7] [Table/Fig-8].

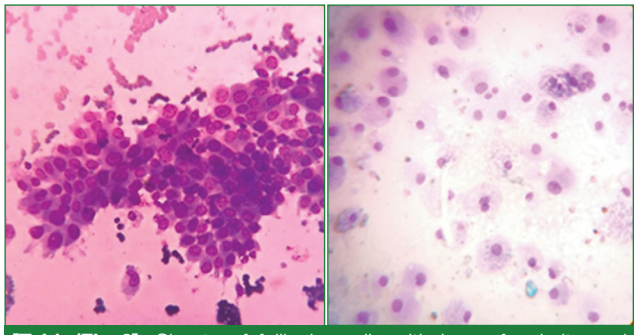
Cytology showed common non-neoplastic lesions was colloid goitre (n=258/496; 52.02%) followed by Hashimoto thyroiditis (n=94/496; 18.95%) and least common was granulomatous thyroiditis. The common neoplastic lesion on FNAC was found to be follicular neoplasm (n=52/496; 10.49%) followed by papillary carcinoma (n=29/496; 05.85%). The macro/normofollicular pattern was noted in 189/496 (38.10%) cases, microfollicular pattern in 79/496 (15.93%) cases, papillary pattern in 18/496 (03.63%) cases, syncytial pattern in 80/496 (16.13%) cases, dispersed pattern in 33/496 (06.65%) cases, Cystic pattern in 87/496 (17.54%) cases and granuloma in 10 /496 (2.02%) cases. Colloid goiter revealed mostly macrofollicular pattern in 175/258(67.83%) cases and cystic in 72/258(27.90%) cases. In Hashimoto thyroiditis, frequent pattern noted were syncytial (13%) and dispersed (03.42%). Microfollicular (09.6%) and papillary pattern (03.62%) were common in follicular and papillary carcinoma respectively. Degenerated granulomas were seen in 100% cases of granulomatous thyroiditis.



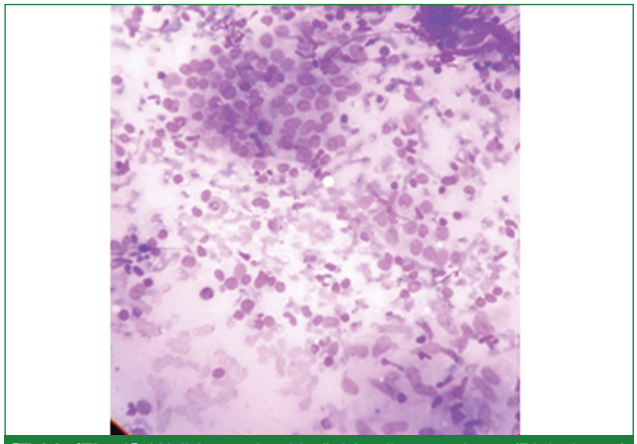
[Table/Fig-2]: Sheets of evenly spaced follicular cells (Giemsa, X400). **[Table/Fig-3]:** Small circles of follicular cells (Giemsa, X400).



[Table/Fig-4]: Follicular cells in papillary pattern (Giemsa, X40). **[Table/Fig-5]:** Loosely cohesive clusters and lying singly follicular epithelial cells (Giemsa, X400].



[Table/Fig-6]: Sheets of follicular cells with loss of polarity and lack of distinct cell borders (Giemsa, X400). **[Table/Fig-7]:** Many haemosiderin laden macrophages in a granular background (Giemsa, X400).



[Table/Fig-8]: Well formed epithelioid cells granuloma (Right lower) along with clusters of follicular cells (Left upper) (Giemsa, X400).

Total 203/496 (40.93%) specimens were analysed for histopathological examination. Out of these 144 (70.94%) cases were nonneoplastic and 59 (29.06%) were neoplastic. In present study on cyto histopathological correlation of 203 cases, FNAC concordance were noted in 195 (96.05%) cases. Discordance were noted in four cases of colloid goiter, among them three cases revealed papillary carcinoma and one as follicular adenoma. The predominant cell pattern observed in cytology was macrofollicular architecture. One case of graves disease was diagnosed as multinodular goiter in histology. Two cases diagnosed as follicular neoplasm cytologically were diagnosed as papillary carcinoma on histopathology [Table/Fig-9].

S.no	Cytology	Architecture of Follicular Epithelial Cells							
	496	Normo/ Macro-follicular	Micro-follicular	Papillary	Syncytial	Dispersed	Cystic	Degeneration + Granulomas	Total
1.	Colloid goiter	175 (67.83%)	11 (4.26%)	-	-	-	72 (27.90%)	-	258
2.	Colloid cyst	-	-	-	-	-	12 (100%)	-	12
3.	Hashimoto thyroiditis	-	16 (17.02%)	-	61 (64.90%)	17 (18.08%)	-	-	94
4.	Granulomatous thyroiditis	-	-	-	-	-	-	10 (100%)	10
5.	Graves disease	12 (33.33%)	-	-	09 (25%)	15 (41.67%)	-	-	36
6.	Follicular neoplasm	02 (3.84%)	48 (92.30%)	-	-	-	02 (3.84%)	-	52
7.	Papillary carcinoma	-	04 (13.80%)	18 (62.07%)	06 (20.69%)	-	01 (3.44%)	-	29
8.	Medullary carcinoma	-	-	-	02 (100%)	-	-	-	02
9.	Anaplastic carcinoma	-	-	-	01 (100%)	-	-	-	01
10.	Metastatic carcinoma	-	-	-	01 (100%)		-	-	01
11	NHL	-	-	-	-	01 (100%)	-	-	01
		189 (38.10%)	79 (15.93%)	18 (3.63%)	80 (16.13%)	33 (6.65%)	87 (17.54%)	10 (2.02%)	496

[Table/Fig-9]: Various type of follicular epithelial cell pattern in thyroid disease.

One case of medullary carcinoma cytologically had syncytial cell pattern showed features of hyalinised trabecular tumour in histology. All the cases of thyroiditis, colloid cyst, and papillary carcinoma were confirmed histopathologically with diagnostic accuracy of 100%.

DISCUSSION

Due to easiness and cost effective technique of FNAC, it is the choice of investigation in any type and size of thyroid swelling along with ultrasonography, hormonal assay and antibody levels. Prepared slide after FNAC can show many pattern of follicular epithelial cells that can revealed false positive and false negative diagnosis. Correlation of FNAC and histology findings revealed that FNAC has high efficacy rate in the diagnosis of thyroid lesions either benign or malignant on the basis of morphological pattern [8].

First, the evaluation of thyroid FNAC slides should be done under scanning magnification to study the adequacy and arrangement of cells. High power magnification should be used to evaluate the morphology of cells including nuclear detail and background elements like colloid and macrophages [9].

Specimens that have obscuring blood, overly thick smears, air drying of alcohol fixed smears, or an inadequate number of follicular cells referred as insufficient for the diagnosis [5]. In our study, inadequate aspirates were obtained in 06 (1.20%) cases due to yield only blood. Adequacy of 98.80% in the current study was similar to several studies showed adequacy of 98.41%, 96.90%, 93.33%, 93.02% and 92.06% respectively [10-14].

Most of the thyroid nodules are benign in nature, but 5-20% are true neoplasm [15]. In this study the percentage of benign and malignant lesions on FNAC were 82.66% and 17.34% respectively. Reddy P et al., 2018, showed 89.20 % had benign lesion and 4.1% had malignancy [16].

Goiter is a common thyroid disorder characterised by an enlarged thyroid gland and the presence of macrofollicular pattern indicate the benign nature of disease [5]. In this study, FNAC results most common non neoplastic lesion consisting of 52.02% cases were colloid goiter followed by colloid cyst, Hashimoto thyroiditis, granulomatos thyroiditis, Graves' disease and the most common neoplastic lesions consisting of follicular neoplasia 37, papillary carcinoma 20, rest were medullary and NHL. These findings were in favour of many studies [17-19].

In this study, the predominant normo/macrofollicular pattern were noted in colloid goiter (72/117), rest of the cases had cystic pattern (43/117) and microfollicualr pattern (02/117). 113/117 cases of colloid goiter were concordant with cytology. In all 3 of 4 discordant cases confirmed as papillary carcinoma and one case confirmed as follicular adenoma. Similar findings were observed in study conducted by Georgescu R et al., that included 122 cases interpreted as benign in FNAC, out of which 118 cases of them were

concordant but rest four cases confirmed as three papillary carcinoma and one as follicular neoplasm [20]. Repetitive pattern of macro or microfollicular pattern and background of colloid would aid in the diagnosis of a goiterus lesions. It has been proposed that risk of follicular neoplasm is inversely related to size of follicle and amount of colloid [21].

Microfollicular pattern is a predominant feature of follicular neoplasm or a follicular variant of papillary carcinoma [5]. In our study, 2/37 cases of follicular neoplasm were discordant as papillary carcinoma. They had microfollicular pattern on cytology. In study of Stelow EB et al., One case of follicular neoplasm showed interobserver bias, it was found that three observers diagnosed a case as follicular neoplasm but at last it was noted that the features were suggestive of papillary carcinoma [22]. Lngegowda JB et al., noted that 2 cases had microfollicular pattern with haemorrhagic background were diagnosed as neoplasm on FNAC which turned out to be follicular variant of papillary carcinoma on histology [23]. The reason of cytology and histology discrepancy and diagnostic misinterpretations could be due to overlapping cytological features and inadequate specimens. Follicular variant of papillary thyroid carcinoma share few cytological features, including presence of abundant thin colloid, monolayer sheets of follicular cells and subtle nuclear features of papillary thyroid carcinoma, that overlap with the features of hyperplastic nodules and follicular neoplasm [24]. So, awareness to variable cytological features in follicular lesions, specimen adequacy and cyto-histopathological correlation reduce the false negative results.

Papillary pattern are highly characteristic of papillary carcinoma [5]. In the present study all 20/203 cases of papillary carcinoma were concordant with cytology. Fifteen out of 20 cases had papillary pattern followed by microfollicular (02), syncytial (02) and dispersed (01). This study was comparable with the study of Ramteke DJ et al., that showed four out of four cases of papillary carcinoma which diagnosed by FNAC were confirmed by histopathology with diagnostic accuracy of 100% [19].

Syncytial patern of follicular cells could be seen in benign and malignant conditions of thyroid, like thyroiditis, grave's disease, papillary thyroid carcinoma, medullary thyroid carcinoma and follicular neoplasm [6]. In our study this pattern were noted more in thyroiditis, followed by grave's disease, papillary carcinoma, medullary carcinoma and metastatic carcinoma. Cytologically diagnosed medullary carcinoma was 100% discordant to the histology. The reason of misinterpretation could be presence of hyalinised material on FNAC [25].

Dispersed arrangement of follicular cells pattern is almost never seen in benign follicular nodules or papillary carcinoma. Instead, it is common in thyroiditis, hyalinising trabecular tumour, medullary thyroid carcinoma, Hürthle cell neoplasms, poorly differentiated carcinoma, anaplastic carcinoma thyroid and lymphoma [5,6]. In our study this pattern was common in Hashimoto thyroiditis followed by Grave's disease and medullary carcinoma.

Presence of haemosiderin laden macrophages in a granular background is a feature of cystic swelling and could be present in colloid goiter, colloid cyst, hyperplastic lesion, papillary carcinoma and follicular neoplasm. In our study this patter was common in colloid goiter and least common in papillary carcinoma. Similar finding was observed by Bommanahalli BP et al., [6].

According to our study the most common pattern noted was normo/mocrofollicular in 175/496 (38.10%) cases. Colloid goiter was the most common lesion that showed macrofollicular pattern as well as cystic pattern. Microfollicular pattern was common in follicular neoplasm. Syncytial pattern and dispersed pattern were common in Hashimoto thyroiditis. Papillary pattern was seen in papillary carcinoma.

Overall the sensitivity, specificity, positive predictive value and negative predictive value were 93.54%, 98.59%, 98.30% and 97.91% respectively. Similar findings were noted in several studies [14, 18].

Despite, high sensitivity and specificity of FNAC thyroid, the assurance should be toughened with awareness of possible diagnostic pitfalls. The intellect of pitfalls can happen at many level including during sampling, clinical evaluation and microscopic evaluation. Clinically, the thyroid nodule can be misguided as parathyroid, lymph nodes and salivary glands [26]. Aspiration of colorless, clear fluid indicate parathyroid cyst, but thyroid cyst is characterised by brownish (colloid) cystic contents [27]. Contamination from surrounding tissues (ciliated cells, squames and lymphoid tissue) may lead to false diagnosis. Cystic changes and degenerative changes in hyperplastic nodules may cause false positive and negative results [28]. Hashimoto's thyroiditis is one of the most common causes of false positive diagnosis. Hurthle's cell nodule may develop in the later phase of hashimoto's thyroiditis. Presence of extensive oncocytic cells, nuclear grooves and even pseudoinclusions in Hashimoto's Thyroiditis (HT) can be interpreted as oncocytic neoplasm and PTC [29]. Risk of lymphoma is increased in HT. So, carefully examination of slide should be done to rule out false positive results [30]. Background should be carefully evaluated if the predominant cell pattern shows microfollicles. Uniform proliferation of microfollicles with scant colloid indicates neoplasms. The pitfalls related to PTC should be analysed in three parts concerning aspirated material, pattern and nuclear features. False negative diagnoses of PTC are sometimes due to the cystic degeneration of the neoplasm and the absence of well preserved neoplastic cells in the smears [26]. Papillary architecture, nuclear inclusion, nuclear grooves and cytoplasmic quality are the features of papillary carcinoma.

However, it should be kept in mind that these features can be seen in other lesions including multinodular goiter, HT, hyalinised trabecular tumour and follicular tumour[26,28]. Medullary carcinoma thyroid have amyloid which mimic thick colloid can cause false positive diagnosis of PTC.

CONCLUSION

FNAC of the thyroid swelling is a simple, easy and cost effective investigation. It is also a reliable and outpatient based first line screening tool to detect if a thyroid swelling is benign, malignant or inflammatory. Adequacy and study of cell pattern is the first step toward the diagnosis. The common reason of false negative and positive findings could be due to presence of various cell patterns in the same slide. Diagnosis of papillary carcinoma requires meticulous examination of smears to know the details of nucleus. A pathologist should be aware of this fact. FNAC is considered as a screening procedure, so attention should be given to minimising false negative diagnosis. This is also less reliable to differentiate follicular neoplasm and follicular variant of PTC. Through cell pattern analysis of thyroid swelling the diagnostic accuracy is very high. The various pitfalls should be kept in mind during the reporting as they help to improve diagnosis, patient treatment and reduce the number of unnecessary thyroidectomies.

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