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ORIGINAL ARTICLE

ANALYZING THE 'GRAY ZONE' IN FOLLICULAR LESIONS OF THYROID

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ABSTRACT: BACKGROUND: Fine needle aspiration (FNA) is used as a gold standard for diagnosis of thyroid nodules. But, diagnostic efficacy of FNA declines sharply when follicular patterned lesions of thyroid are considered. Hence these lesions form a "gray zone" where a definite diagnosis on FNA is difficult. This article discusses the umbrella diagnosis of 'follicular lesions' on cytology, which largely comprises of four entities i.e., adenomatous goiter, follicular adenoma, follicular carcinoma, and the follicular variant of papillary thyroid carcinoma. **AIMS:** To assess the accuracy of FNAC in differentiating benign and malignant follicular patterned lesions so as to contribute to better patient care. **MATERIALS AND METHODS:** A retrospective analysis was conducted between 2009 and 2014 at our institution. Sixty two cases with diagnosis of 'follicular lesion' and 'follicular lesion with atypical cells' on FNA were included in the study. The cytological features were correlated with histopathology and the results tabulated. **RESULTS:** Sixty two cases with a FNA diagnosis of 'follicular lesion' or 'follicular lesion with atypical cells' was analyzed in the present study. The diagnosis of 'Follicular lesion' was noted in 46 cases and 'follicular lesion with atypical cells' in 16 cases. The histopathology diagnosis was adenomatous goiter in 35 cases, follicular adenoma in 16 cases, follicular carcinoma in four cases, and follicular variant of papillary carcinoma of thyroid (PTC) in seven cases. The malignancy rate in follicular pattern lesions (N=62) was 17.7% and neoplasia rate was 43.5%. In atypical or suspicious cases (N=16) the malignancy rate was 43.7% and the neoplasia rate was 68.7%. **CONCLUSION:** Follicular-patterned thyroid lesions remain a 'gray zone' and a challenge for cytopathologist. High malignancy rate in these patients supports the concept of giving an umbrella diagnosis of "follicular lesion" and advising excision of the nodule for histopathology to confirm the diagnosis or maintain close follow up.

KEYWORDS: Cytology, Gray zone, Follicular lesions thyroid.

INTRODUCTION: Fine-needle aspiration (FNA) has been widely accepted as an accurate and reliable screening method to differentiate between 'benign' and 'malignant' thyroid nodules.[1,2] However, the diagnostic efficacy of FNA declines sharply when follicular patterned lesions of thyroid are considered. The differential diagnosis of a follicular lesion/neoplasm in thyroid FNA specimens includes hyperplasic/adenomatoid nodule, follicular adenoma (FA) and carcinoma (FC), and follicular variant of papillary thyroid carcinoma (FVPTC).[3] Most of these cases are diagnosed as follicular lesion/neoplasm on cytology and surgical excision followed by histopathologic examination is recommended for definite diagnosis.[3,4,5]

The malignancy rate in cases diagnosed as follicular lesion/neoplasm is approximately 20%.[5,6,7,8] Large numbers of benign lesions undergo surgery because FNA cannot distinguish between, adenomatous goiter, follicular adenoma and carcinoma on the basis of cyto-morphology. This is due to the fact that the basis of rendering a diagnosis of malignancy in a follicular lesion/neoplasm is capsular and vascular invasion which can be made out only on histopathological examination.[3,9] Similar challenges have been encountered with FVPTC due to follicular pattern and paucity of characteristic nuclear features in this entity.[10,11,12,13]

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Further, the limitation and difficulty to confidently categorize 'follicular lesions' has undoubtedly lead to the use of terms such as "atypical", "indeterminate", "suspicious" etc, which adds to the dilemma faced by the clinician in providing correct treatment to the patient.[14]

We therefore, decided to do this study, so as to throw some light on the clinical implication of using various cytology diagnoses. This study analyzes the efficacy of FNAC in differentiating benign and malignant follicular lesions with eventual aim to improve our cytological analysis of these lesions. We hope our efforts eventually will contribute to better patient care.

MATERIALS AND METHODS: This is a retrospective analysis conducted between 2009 and 2014 at our institution. Data was collected from the hospital database and recorded. It included all the cases that underwent FNAC and surgical excision of thyroid at our institution. Information gathered was age and sex of the patient, cytology and histopathology diagnosis. 62 cases with follicular pattern on FNA formed the study group. Cases with FNAC or histopathology done elsewhere were excluded from the study.

RESULTS: The search of the institution data base from 2009-2014, revealed 1135 cases of thyroid which had undergone both FNAC and histopathological examination. The occurrence of thyroid lesions was commonly noted between the age group of 3rd and 5thdecade (Chart 1). Females were more commonly affected and comprised 83% of study population in comparison to males accounting only for 17% of the study population (Chart 2). Out of total of 1135 cases; 528 cases were nodular colloid goiter, 321 were Hashimotos thyroiditis, 72 were papillary thyroid carcinoma, 70 were cystic lesions and 62 were follicular lesions. In 70 cases FNA smears were inadequate for evaluation (Chart 3).

There were 62 cases with a follicular pattern on FNA with a reported diagnosis of 'follicular lesion' or 'follicular lesion with atypical cells'. These were analyzed in the present review. The diagnosis of 'Follicular lesion' was noted in 46 cases and 'follicular lesion with atypical cells' in 16 cases. The histopathology diagnosis in these cases was adenomatous goiter in 35 cases, follicular adenoma in 16 cases, follicular carcinoma in four cases and follicular variant of papillary carcinoma of thyroid (PTC) in seven cases [Table 1 and Chart 4].

The malignancy rate in follicular pattern lesions (N=62) was 17.7% and neoplasia rate was 43.5%. In atypical or suspicious cases (N=16) the malignancy rate was 43.7% and the neoplasia rate was 68.7% (Table 2).

Statistical analysis was done for all 62 cases to assess the value of FNAC in differentiating benign and malignant follicular lesions of thyroid. The results were as follows: false positive and false negative rates were 17.6% and 36.4% respectively. The sensitivity and specificity were 63.6% and 82.4% respectively. The positive predictive value was 43.75% and negative predictive value was 91. 3%. The accuracy of FNA in predicting a malignancy in follicular lesions of thyroid was 79%.

DISCUSSION: Fine needle aspiration (FNA) has proven to be an effective tool in management of patients with thyroid nodules. However, Fine needle Aspiration has some limitations like specimen inadequacy, sampling techniques and WHAFFT changes.[15] The diagnosis of follicular patterned lesions can be challenging because of overlapping features between benign and malignant lesions and is considered as a 'gray zone'.[5,14,16]

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The use of diagnostic categories is central to the practice of cytopathology, but in the case of follicular lesions of the thyroid, such categories are poorly standardized.[17,18] Use of various terms, including "atypical", indeterminate, favor, cannot exclude, possible, or probable and suspicious by pathologists often creates confusion for the clinicians.[14]

The large number of benign thyroid nodules relative to the small number of malignant ones creates a clinical dilemma. The 'follicular-patterned lesion' is a commonly encountered type of thyroid FNA specimen and includes adenomatous nodules, follicular adenomas, follicular carcinomas, and the follicular variant of papillary thyroid carcinoma.[1]

In our study of a total of 62 cases with follicular pattern, 46 were reported as 'follicular lesions' and 16 as "follicular lesion with atypical cells". Out of 46 cases reported as 'follicular lesions', 42(91.3%) proved to be benign on HPE and reflected the fact that majority of follicular lesions are benign. The term "follicular lesion with atypical cells" was reported in 16 cases where the pathologist noticed the possibility of a malignant lesion. Out of these, 7 cases (44%) were malignant and 9(56%) were benign. There is high disparity between the cytology and histology diagnosis in this group.

In our study, 11 cases out of 62 follicular pattern lesions were malignant and amounted to a malignancy rate of 17.74% as compared to 30% by Greaves et al,[19] and 23% by Ersöz et al.[20] The reported malignancy rates in literature range from <10% up to 30%.[14] This wide variation may reflect the lack of standardized diagnostic terminology, especially within the gray zone of thyroid FNA, and, consequently, the ability to draw good comparisons between these studies is limited.

Somma J et al suggested that in addition to malignancy rate studies should also focus on neoplasia rates as cytology cannot distinguish between follicular adenoma and carcinoma.[14] In our study 27 of 62 cases were found to be neoplasms on HPE and the neoplasia rate was 43.55%. Literature review reveals the neoplasia rate of around 50%.[14,18,21] Our study showed a malignancy rate of 43.75% and neoplasia rate of 68.75% in suspicious cases.

According to study done by Baloch ZW et al, two major factors were identified as causes for discrepant diagnosis between cytological and histological specimens, overlapping cytological features among follicular-derived lesions and inadequate/suboptimal specimens.[22] The cytological features of follicular variant of papillary carcinoma were found to overlap with those of hyperplasic /adenomatous nodules and follicular neoplasms due to the presence of abundant thin colloid, monolayer sheets of follicular cells and subtle nuclear features of papillary carcinoma.

Application of FNA to distinguish benign follicular nodules from follicular carcinomas is problematic because the criteria to distinguish between them are based upon histologic evidence of transcapsular or vascular invasion which cannot be assessed on cytology.[1] The cytologic criteria to distinguish benign from suspicious thyroid lesions includes the follicular group architecture, smear cellularity, amount of colloid, and cytologic atypia.[23] The most important criteria is cytoarchitecture.[24,25] Macrofollicular architecture in a background of moderate abundant colloid is indicative of benign pathology, whereas, microfollicles and three dimensional clusters are a feature of follicular carcinomas as well as some adenomas. These aspirates are diagnosed as ''suspicious for a follicular neoplasm'' and it is this group of patients for whom thyroid lobectomy is generally considered warranted.[1]

The follicular variant of papillary thyroid carcinoma is the most common subtype of papillary thyroid carcinomas.[26] In FNA specimens, it can pose a diagnostic challenge due to the abundance of microfollicles or monolayer tissue fragments mimicking a follicular neoplasm.

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Over 30% of cases diagnosed as ''suspicious for a follicular neoplasm'' were identified as FVPTC on histologic follow-up.[3,27] Studies in past have highlighted the fact that in FVPTC, the nuclear features essential for a cytological diagnosis of PTC are infrequent.[18,28,29,30] One of the most common and clinically significant pitfalls in the assessment of an aspirate of a follicular lesion is the failure to recognize the nuclear features of the FVPTC.[23] In our study, 4(25%) cases of the suspicious cases were FVPTC on HPE. But, 3 of 46(6.5%) follicular lesions, where a suspicion of malignancy was not given by pathologist, turned out to be FVPTC. This data reflects the probability of malignancy being missed on FNA and therefore enforces the need for surgical excision followed by HPE for accurate categorization of follicular lesions.

In our study, 9 out of 16 cases were diagnosed as suspicious but actually came out to be benign on HPE (5 were adenomatous goiter and 4 follicular adenoma). The data points to the fact that FNA can lead to a false suspicion of malignancy in follicular lesions owing to its limitation in this particular category. This could be explained better in view of the existing studies in literature which state that the characteristic features diagnostic of PTC like nuclear grooves; nuclear pseudo-inclusions etc. can also be seen in benign conditions of thyroid like adenomatous goiter, hashimotos thyroiditis, nodular goiter, follicular neoplasm etc.[31,32] However, studies have stated that occurrence of these features in benign lesions is very infrequent as compared to PTC.[33] Hence, presence of frequent nuclear features in follicular lesions should alert the pathologist of the possibility of FVPTC.

In our study false positive and false negative rates were 17.6% and 36.4% respectively. The sensitivity and specificity were 63.6% and 82.4% respectively. The positive predictive value was 43.75% and negative predictive value was 91.3%. The accuracy of FNA in predicting a malignancy in follicular lesions of thyroid was 79%. In our study we observed that FNAC is not reliable to detect malignancy in follicular pattern lesions as clearly indicated by a high false negative rate of 36.4% and low sensitivity of 63.6%. However, FNA still stands as a good screening method for follicular lesions of thyroid, which subsequently need to undergo surgical excision followed by HPE for a definite diagnosis.

Baloch ZW et al suggested that awareness of variable cytological features in follicular lesions (Especially in follicular variant of papillary carcinoma); following strict criteria of specimen adequacy in thyroid FNA, and clinicopathological correlation can markedly reduce false-negative results.[22] Advances in molecular testing for genetic mutations may soon allow for preoperative differentiation of follicular carcinoma from follicular adenoma. Until then, a patient with a follicular neoplasm should undergo a diagnostic thyroid lobectomy, which is definitive treatment for a benign follicular adenoma or a minimally invasive follicular cancer.[34]

CONCLUSION: Follicular-patterned thyroid lesions are a common and challenging area of cytopathology. Follicular pattern in cytology is not characteristic of a particular diagnosis and constitutes a 'gray zone'. It can represent any of the four pathologies i.e., adenomatous goiter, follicular adenoma, follicular carcinoma, and the follicular variant of papillary thyroid carcinoma as seen in our histopathology correlated study. Even though various morphological parameters have been suggested in literature to differentiate among these entities, none of them is full proof. The patients with cytology diagnosis of 'follicular lesion' along with riders like 'atypical' or 'suspicious' are usually considered by surgeons for surgical excision. But, even those follicular lesions where the probability of an existing malignancy has not been suggested should be under close follow-up and probably should undergo lobectomy, because of the well-known fact that definite diagnosis of

follicular adenoma or carcinoma is possible only on HPE. Similarly for FVPTC also surgical excision followed by HPE is necessary. High malignancy rate in these patients supports the concept of giving an umbrella diagnosis of "follicular lesion" and advising excision of the nodule for histopathology to confirm the diagnosis or maintain close follow up.

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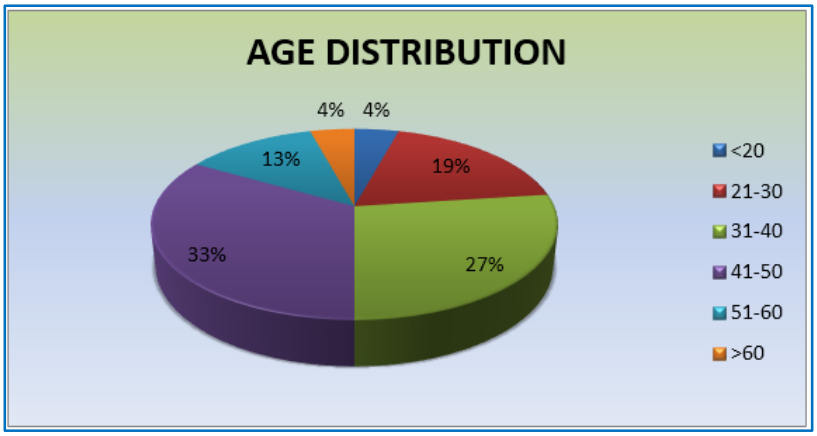

Chart 1

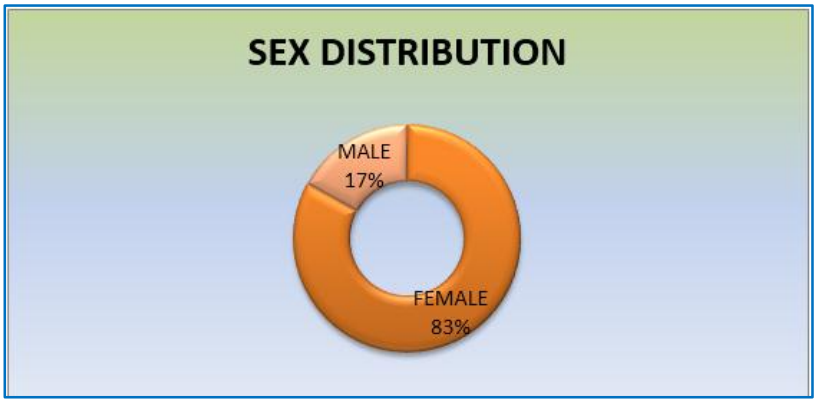

Chart 2

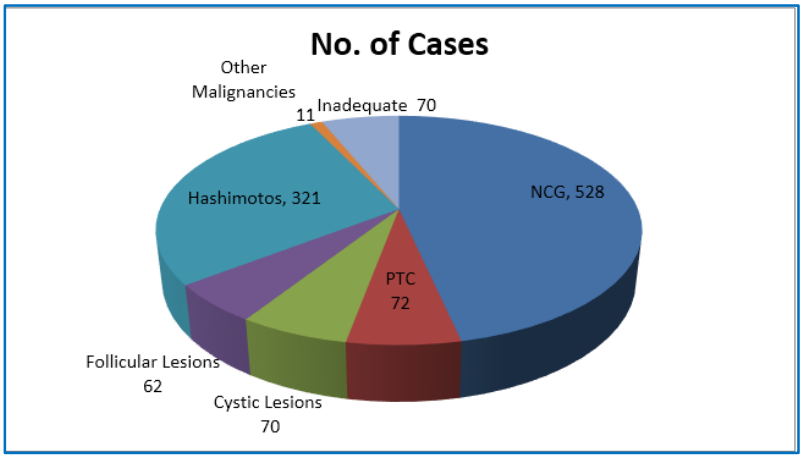

Chart 3: Distribution of Disease in 1135 Cases

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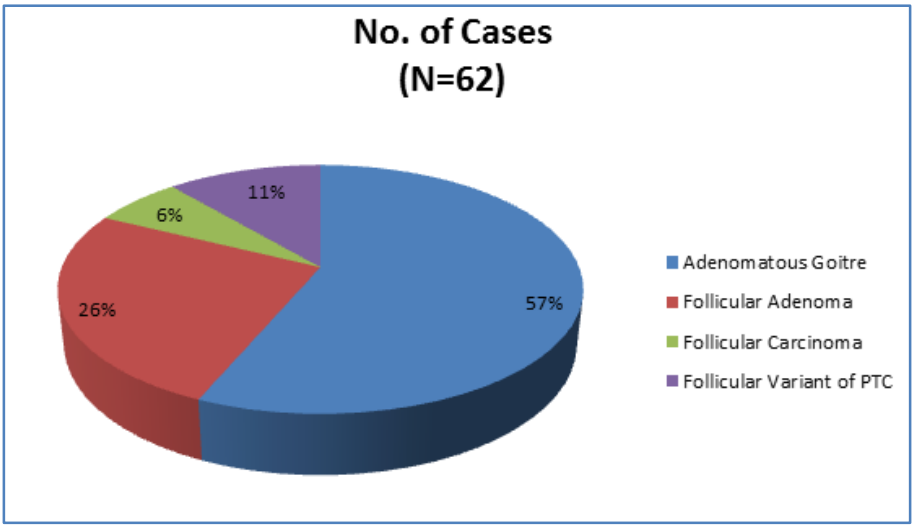

Chart 4: Histopathology Diagnosis in Cases with follicular pattern on FNAC

FNA report	Histopathological Diagnosis				
	Adenomatous Goitre	Follicular Adenoma	Follicular Carcinoma	Follicular Variant of PTC	Total
'Follicular lesion'	z	12 (TN)	1 (FN)	3(FN)	46
'Follicular lesion with atypical cells'	5(FP)	4(FP)	3(TP)	4(TP)	16
	35	16	4	7	62

Table 1: Distribution of the Histopathological Diagnosis of the Follicular Lesions Reported on FNAC

*TN- True Negative; FN- False Negative; FP- False Positive; TP- True Positive.

	Malignancy Rate	Neoplasia Rate
Follicular pattern (n=62)	17.7%	43.5%
Reported as 'follicular lesion' (n=46)	8.7%	34.8%
Reported as 'follicular lesion with atypical cells' (n=16)	43.7%	68.7%

Table 2: Malignancy and Neoplasia Rate in Follicular Pattern Lesions

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