Diagnostic significance of various cytomorphological features and their quantification for the diagnosis of papillary carcinoma thyroid on fine needle aspiration cytology

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Abstract

Introduction: The relative reliability of the morphological features for making a diagnosis of PTC when considered independently is debatable. Quantification of morphological features has been attempted to improve the diagnostic efficacy of FNA thyroid, but universal acceptance is lacking.

Aim: This study was aimed to analyze the independent diagnostic significance of the four common morphological features- Nuclear grooves (NG), Intra-nuclear cytoplasmic inclusions (INCI), Papillary Fragments and Metaplastic Cytoplasm, in thyroid swellings using a quantitative approach.

Materials and Methods: This is a retrospective study including all the thyroid FNA cases which had corresponding histopathology report. Eighty six cases had at least one of the four morphological features mentioned. The cases with NG were categorized into three groups: >/= 20%; 10-19% and <10%. Cases with INCI categorized as: frequent (≥5%), infrequent (<5%) and absent. Presence or absence of papillary fragments and metaplastic cytoplasm was recorded. The sensitivity, specificity, positive and negative predictive values were calculated.

Results: The sensitivity, specificity, PPV and NPV of NG ≥ 20% for PTC was 53.3%, 98.2%, 94.1% and 79.7% respectively and the same with NG > 10% was 66.7%, 75%, 58.8% and 80.8% respectively. Specificity and sensitivity of 'Frequent' INCI were 100% and 36.67% respectively.

Conclusion: Typical morphological features of PTC can be seen in non-malignant conditions as well. Occurrence of NG >20% and INCI >5% are highly specific for the diagnosis of PTC. Cases with NG between 10-19% should be considered as 'suspicious for malignancy' and pathologist should cautiously look for other morphological features.

Keywords: Papillary carcinoma thyroid (PTC), FNAC, Cytology, Morphology, Quantification.

Introduction

Fine Needle Aspiration Cytology (FNAC) is the first-line diagnostic test for evaluation of swellings of thyroid gland and an efficient method of deciding surgical treatment owing to its simplicity, low cost, high sensitivity and specificity.[1-5] The morphological diagnostic features for the commonest thyroid cancer, papillary carcinoma (PTC), on FNA are well established. These include: nuclear grooves (NG) [Fig. 1A], intra nuclear cytoplasmic inclusions (INCI) [Fig. 1A], metaplastic cytoplasm [Fig. 1B], papillae [Fig. 1C], tridimensional fragments, monolayered sheets of cells, psammoma bodies, cytoplasmic vacuoles, multi-nucleated giant cells, anisonucleosis, powdery chromatin, scant colloid, autolysis, spindle cells, and macrophages.[6-9]

Despite these advantages, FNAC has pitfalls.[9-11] The relative reliability of each of the known morphological features for making a diagnosis of PTC when considered independently is debatable. Cytologists provide a diagnosis of PTC based on combination of these morphological features. Moreover, the cytomorphological features suggestive of PTC can also be seen in non-neoplastic conditions of thyroid [Fig 2]. Quantification of some of morphological features has been attempted to improve the diagnostic efficacy of FNA thyroid,[12-15] but universal acceptance is lacking.

This study was aimed to analyze the independent diagnostic significance of each of the morphological features in all thyroid swellings using a quantitative approach. The morphological features which were quantified and analysed included the four common features of PTC: Nuclear Grooves (NG), Pseudo-inclusions or Intra Nuclear Cytoplasmic Inclusion (INCI), papillary fragments and metaplastic cytoplasm.

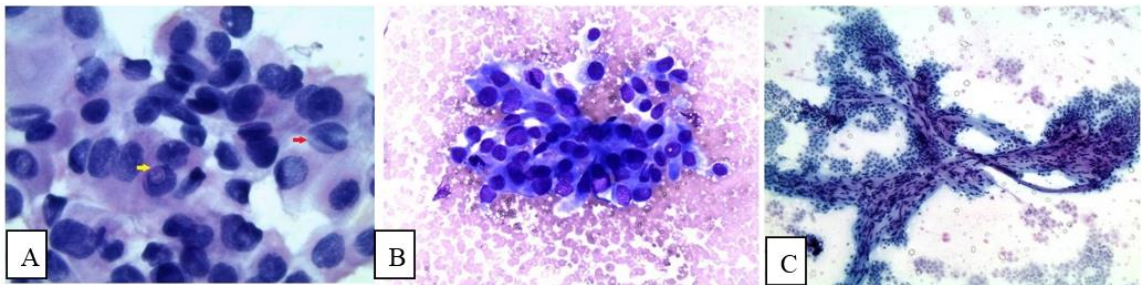

Fig. 1: Typical features of papillary carcinoma thyroid; A): MGG stain showing nuclear grooves (Red arrow) and intra-nuclear cytoplasmic inclusions (Yellow arrow) in a case of papillary thyroid carcinoma (X1000); B): MGG stain showing metaplastic cytoplasm in a case of papillary thyroid carcinoma (X400); C): Papanicolaou stain showing papillary fragments in a case of papillary thyroid carcinoma (X40)

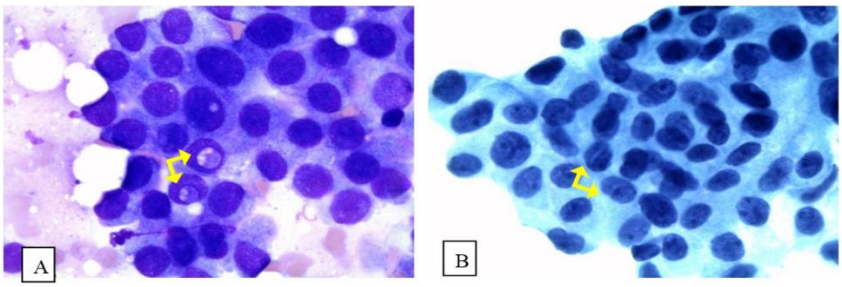

Fig. 2: Non-PTC lesions showing features typical of PTC; A): MGG stain showing INCI (arrow) in a case of nodular colloid goitre (X1000); B): Papanicolaou stain showing nuclear grooves (arrow) in a case of adenomatous goitre (X1000)

Materials and Methods

All the thyroid FNA cases, during the period of January 2010–December 2012, which had corresponding histopathological report available, were included in this retrospective review. The cytology slides of the study population were retrieved and reviewed for presence of the four cytomorphological features of PTC i.e. NG, INCI, papillary fragments and metaplastic cytoplasm. All the cases with presence of any of these four features were included in the study. Hypo-cellular and ill-preserved smears were excluded.

The cases with NG or INCI were further reviewed to quantify these features. We followed a quantitative method by counting 500 cells and then divided the cases into three groups based on the percentage of cells showing NG: ≥ 20%; 10 – 19%and < 10%. Cases with INCI were divided in three groups based on the percentage of cells showing INCI: frequent (≥5%), infrequent (<5%) and absent INCI. Presence or absence of papillary fragments and metaplastic cytoplasm was recorded.

These quantified cytology reports were compared with the corresponding histopathology reports (HPE) and the sensitivity and specificity of each of these four features for a precise diagnosis of PTC were calculated.

Results

A total of 556 thyroid FNAs had been done in the specified study period. Out of these, 86 cases had at least one of the four cytological features included in this study and formed the study group. The cytology diagnoses in 86 cases were: PTC in 12 cases; suspicious for PTC in 6 cases; follicular neoplasm in 16 cases; non-neoplastic lesions in 52 cases (adenomatous goitre-37 cases; colloid goitre-12 cases; cystic lesion- 2 cases; Hashimotos thyroiditis- 1case) (Table 1). Among these 30/86 cases which were diagnosed as PTC on HPE: 22 were conventional PTC, 7 follicular variant of PTC (FVPTC) and 1 was oncocytic variant of PTC.

The diagnostic specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) of NG, INCIs, papillary fragments and metaplastic cytoplasm for the diagnosis of PTC were determined by statistical analysis.

Nuclear Grooves (NG): Quantification of NG can be done in many ways. Based on the percentage of cells showing NG we categorised the cases as:≥ 20%, 10–19% and < 10%. (Table 2-3). Data from table 2 shows that all FNAs with ≥ 20%NG were diagnosed as PTC on HPE, except one which was follicular carcinoma. All the 7 cases of FVPTC showed NG between 10-19% (Table 3), none showed ≥ 20% NG (table 2). One case of oncocytic variant of PTC also showed NG to be between 10 and 19% (Table 3).

Among the 56/86 non-PTC cases, 1 (2%) case showed NG ≥ 20%, 13 (23%) cases had NG 10-19% and 42 (75%) cases showed < 10% NG [Fig. 3].

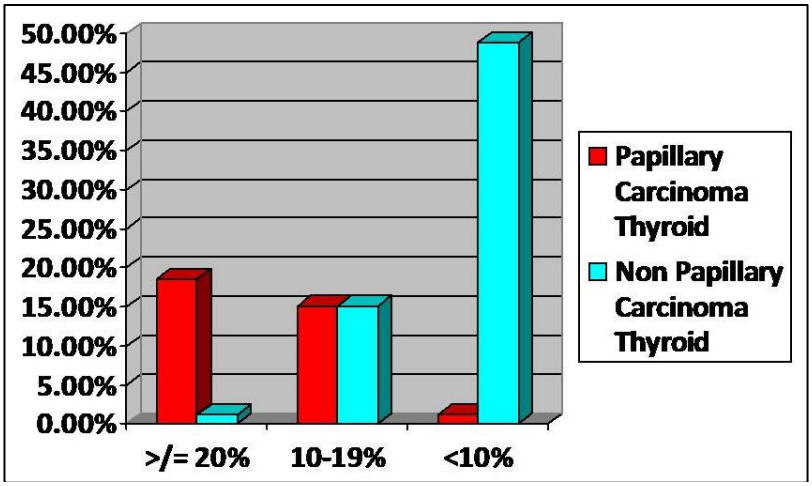

Fig. 3: Distribution of papillary carcinoma and non-papillary carcinoma cases based on percentage of nuclear grooves

The sensitivity and specificity of NG for PTC in the category of ≥ 20% was 53.3% and 98.2% respectively and the same in the category of > 10% were 66.7% and 75% respectively. The PPV and NPV for PTC in the category of ≥ 20% was 94.1% and 79.7% respectively and the same in the category of > 10% were 58.8% and 80.8% respectively.

In the category of 10-19% NG, there were total of 26 cases, out of which only 13 (50%) were PTC on histopathology and others were non-papillary carcinomas. In <10 category only one case was found to be PTC on histopathology.

Intranuclear Cytoplasmic Inclusions (INCI): In our study, we followed a quantitative approach to assess the frequency of INCI and categorized the cases in three groups based on the percentage of the cells showing INCI: frequent (≥5%), infrequent (<5%) and absent INCI.

In the 30 cases of histologically proven PTC, 11 (37%) cases showed 'frequent' INCI, 12 (40%) cases showed infrequent and 7 (23%) cases showed absence of INCI. Out of the 11 cases with 'frequent' INCI which were diagnosed as PTC on HPE, nine had a cytological diagnosis of PTC, one was follicular neoplasm and one was adenomatous nodule. It is to be noted that 'frequent' INCI were not seen in any of the non-PTC cases and their specificity and sensitivity for PTC were 100% and 36.67% respectively.

Papillary Fragments: Among the 30 cases with a confirmed diagnosis of PTC on HPE, papillary fragments were present only in 16 (53%) cases. Only one case other than PTC showed papillary fragments which was diagnosed as follicular adenoma with papillary hyperplasia on HPE. The specificity and sensitivity of papillary fragments for PTC were 98.21 % and 53.33 % respectively.

Metaplastic Cytoplasm: Among the 30 cases of histologically proven PTC, metaplastic cytoplasm was seen in 21 (70%) cases. One case of follicular carcinoma and a case of colloid goitre also showed metaplastic cytoplasm. The specificity and sensitivity of metaplastic cytoplasm for PTC were 96.43% and 70 % respectively.

Table 1: The Cytological and corresponding histopathological diagnosis in 86 cases of thyroid swellings

Cytology Diagnosis	Total 86 cases	Histopathology Diagnosis	Total 86 cases
PTC	14 cases	PTC (Conventional PTC-14)	14 cases
Suspicious for PTC	6 cases	PTC (Conventional PTC-4, FVPTC- 2)	6 cases
Follicular neoplasm	14 cases	PTC (FVPTC- 3, oncocytic variant of PTC- 1 cases)	4 cases
		Follicular adenoma	6 cases
		Follicular carcinoma	3 cases
		Adenomatous goitre	1 case
Non-Neoplastic	52 cases	Adenomatous goitre	26 cases
		Hashimotos thyroiditis	9 cases
		Colloid goitre	11 cases
		PTC (Conventional PTC-4; FVPTC- 2)	6 cases

Table 2: Cytology diagnosis with corresponding histopathology diagnosis in cases with ≥ 20% nuclear grooves

Cytology Diagnosis	Histopathology Report	
	Papillary Carcinoma	**Non-Papillary Carcinoma**
Papillary Carcinoma (N=12)	12 (Conventional PTC-12)	0
Suspicious of Papillary Carcinoma (N=4)	4 (Conventional PTC-4)	0
Follicular Neoplasm (N=1)	0	1

Table 3: Cytology diagnosis with corresponding histopathology diagnosis in cases with 10-19% nuclear grooves

Cytology Diagnosis	Histopathology Report	
	Papillary Carcinoma	**Non-papillary Carcinoma**
PTC (N=2)	2 (Conventional PTC- 2)	0
Suspicious of Papillary Carcinoma (N=6)	2 (FVPTC-2)	4
Follicular Neoplasm (N=6)	4 (FVPTC-3, oncocytic variant-1)	2
Cystic Lesion Thyroid (N=2)	2 (FVPTC-1, conventional PTC-1)	0
Hashimotos Thyroiditis (N=1)	1 (Conventional PTC-1)	0
Colloid Goitre (N=9)	2 (FVPTC-1, conventional PTC-1)	7

Discussion

The morphological diagnostic features for papillary carcinoma (PTC), on FNA are well established but the relative reliability of each of the known morphological features for making a diagnosis of PTC is debatable and generally a combination of these morphological features is used to provide a diagnosis.[16] Moreover, the cytomorphological features suggestive of PTC can also be seen in non-neoplastic conditions of thyroid.[17-20] Quantification of some of morphological features has been attempted to improve the diagnostic efficacy of FNA thyroid but universal acceptance is lacking. We analyzed the diagnostic significance of quantification of four of the common features of PTC: Nuclear Grooves (NG), Intra-Nuclear Cytoplasmic Inclusion (INCI), Papillary Fragments and Metaplastic Cytoplasm.

Studies in literature have mentioned as many as 15 cyto-morphological features for PTC.[7] Kini et al found six diagnostically useful findings as: monolayered sheets of cells, INCI, papillary structure, presence of follicular pattern, foreign body type multi-nucleated giant cells and absence of degenerative changes.[8] Amongst the various features of PTC, nuclear grooves (NG) are recognized as essential diagnostic criteria, ever since their identification in 1986.[21] Miller et al in their step-wise logistic regression analysis found that the three most important variables in making prediction of PTC were INCI, papillary structures without vessels and cells with metaplastic cytoplasm.[22]

Inspite of having many well described features of PTC, difficulty in diagnosis still persists. In the present study only 20out of 30 histologically proven PTC, were diagnosed so on cytology. Das and Sharma in their study evaluating the constraints in cytology of PTC studied five cyto-morphological features such as NG, INCIs, papillary fragments, fine chromatin pattern and psammoma bodies.[16] They concluded that the diagnosis of PTC can be more accurate, if ≥ 3 out of 5 above mentioned features are present. When the number of cytologic features are < 3, the most dependable nuclear features in favour of PTC are NG and INCI.[16]

In our study we analysed and quantified four nuclear features namely NG, INCI, papillae and metaplastic cytoplasm for their significance to independently diagnose PTC.

Nuclear Grooves (NG): NG occur due to in folding of the nuclear membrane and are usually oriented parallel to the long axis of the oval shaped nuclei giving a coffee bean appearance.[21,23,24] These are easily appreciated in ethanol fixed and papanicolaou stained smears.

According to the study conducted by Tahlan, NGis not specific for PTC and can be found in non-neoplastic conditions of thyroid. They concluded that NG should be given appropriate weightage for the diagnosis of PTC.[25] Some of the other pathologies which can have nuclear grooving are follicular adenoma, follicular carcinoma, nodular goitre and hashimoto's thyroiditis.[7,26]

According to Yang, a semi-quantitative approach can be helpful in quantifying the NG and thereby indicating the diagnosis of PTC in the absence of other diagnostic features. They concluded that presence of ≥20% NG is virtually diagnostic of a neoplasm, most likely PTC.[12]

Intra Nuclear Cytoplasmic Inclusions (INCI, Pseudo inclusions): INCI are usually present in more than 5% of the cells in 90% of PTC cases.[27-29] INCI are invaginations of cytoplasm into the nucleus. Characteristic cytologic features of INCI are important for their correct identification.[7] INCI are membrane bound, large and occupy more than 50% of the nuclear area. They have tinctorial pattern similar to cytoplasm and are optically clearer than surrounding chromatin. Optically clear artifacts due to staining technique can simulate INCI and care should be taken to differentiate these from true INCI. Other diseases which can have Pseudo-inclusions are anapalstic carcinoma, medullary carcinoma, follicular carcinoma, Hurthle cell Carcinoma, metastatic RCC and Hashimoto's thyroiditis.[7]

Papillary Structure: In cytology, papillae can present with different morphologies and dimensions depending on the aspirate. If papillae are completely aspirated they appear as large fragments with prominent vascular network. If aspirated partially they tend to appear as flat sheets. If only tip of a papilla is aspirated, it gives the appearance of spherical cellular fragments exhibiting palisading and nuclear overlapping.[7]

Metaplastic Cytoplasm: It is the waxy or squamoid quality exhibited by cytoplasm of malignant cells.[7] In 2007, weber suggested that atypical epithelial cells, cannot exclude papillary thyroid carcinoma (AEC-PTC).[17] The author stated that this diagnosis is very controversial and can lead to dilemma in patient management. Conditions where this diagnosis is commonly given are cystic nodule or Hashimoto thyroiditis. Presence of atypical epithelial cells along with nuclear features such as INCI, squamoid cytoplasm and psammoma bodies should alert the pathologist to rule out the possibility of PTC, as occurrence of focal cytological features is strongly associated with PTC in the follow-up resection.[17]

Quantification of Morphological Features: There have been attempts at quantifying the morphological features to improve diagnostic accuracy. NG have been the main focus of quantification but their quantification is still not universally practiced. We have studied and quantified NG and compared our observation with literature. We have also analysed the significance of quantification of INCI and presence of papillae and metaplastic cytoplasm to independently diagnose PTC.

The quantitative approach for NG has been debated over three decades since its discovery in 1986.[21] Quantification in the literature has been done in many ways. Categories like many/frequent; infrequent and occasional are very subjective. Hence we use the criteria adopted by Yang and Demirci where they categorise the cases as ≥ 20% NG; 10-19% NG and <10% NG.[12] Rupp et al. and Gould et al compared the number of NG present in PTC and in benign lesions by evaluating percentage of NG in 30 HPF and 5 HPF respectively. [13,14] Both concluded that occurrence of NG in benign lesions is very less as compared to PTC. Yang and Demirci evaluated percentage of nuclear grooves in 5 HPF and reported that sensitivity of ≥ 10% NG for PTC was 100%, which reduced to 65% for ≥ 20% grooves but specificity increased from 68% to 95% respectively.[12] Francis et al used a different quantitative method of evaluating percentage of NG in 500 cells and concluded that 88% of PTC had NG ≥20%, whereas the frequency of NG was less in other thyroid diseases.[15] In our study we followed a quantitative method by counting 500 cells and calculated the percentage of NG. We subsequently derived the sensitivity and specificity of NG for the diagnosis of PTC.

In our study we observed that, the diagnostic sensitivity was 66.7% when the diagnostic criteria was set at the level of ≥ 10% grooves but the sensitivity was seen to reduce to 53.3% when ≥20% grooves was considered as a diagnostic feature.

Yang and Demirci found that the specificity of ≥ 20% grooves was 95% and it increased to 100% when all other neoplasms were also considered.[12] According to our analysis, the diagnostic specificity of ≥ 20% NG for PTC was 98.2%. Only one case with ≥ 20% of NG turned out to be follicular carcinoma. Similar to their study, the specificity for detecting a neoplasm in our study also was 100%. The above data shows that presence of ≥ 20% grooves is characteristically diagnostic of PTC. The NPV of < 10% NG for PTC was 97.7%. From this, we infer that, when NG constitute< 10% of the cell population, the probability of PTC can be excluded.

The main diagnostic dilemma occurs when the NG are between 10%-19%. According to the study conducted by Yang and Demirci, the diagnostic specificity of NG in the debated range falls to 68%.[12] In our study also we noted that there was lot of disparity in this group. Out of 26 cases in this category only 13 (50%) were PTC on histopathology and others were non-papillary carcinomas. We agree with their conclusion that, in the absence of other contributory nuclear features such as INCI, a diagnosis of "suspicious for malignancy" or "atypical cytology" should be given to reduce the false negative diagnosis.[12]

One should always remember that thyroid nodules other than PTC can also show NG but their frequency will be very less. Awareness of pathologists regarding this fact will prevent over diagnosis of PTC and will reduce false positives. In addition, presence of other features such as INCI, papillary fragments and metaplastic cytoplasm, undoubtedly, contributes to a definite diagnosis of PTC.

In contrast to NG, the literature regarding quantification of other morphological features is sparse. Studies considering INCI have analysed only its presence or absence. Yang and Demirci found that INCI had a diagnostic specificity of 100% for PTC but the NPV was only 61%.[12] We followed a quantitative method to find the frequency of INCI. Five HPF were selected and studied. INCI in ≥ 5% cells were considered as frequent and < 5% were called labelled as infrequent.

When INCI were frequent (≥ 5%) all the 11 cases were PTC on histopathology out of which two were not reported so on cytology. The sensitivity for diagnosis of PTC was 81.8% and PPV was 100%. As there were no true negative cases, specificity and NPV could not be calculated. In cases with infrequent (< 5%) INCI sensitivity was 93%, specificity was 33%, PPV was 79.48% and NPV was 66.67%. From the above data it can be inferred that, mere presence of INCI cannot be used as a diagnostic criteria for PTC but when it is frequent (≥ 5%) it strongly suggests a diagnosis of PTC and pathologist should diligently look for presence of other morphological features to prevent misdiagnosis. With infrequent INCI the reliability to diagnose PTC is low (specificity- 33%) because it can be seen in thyroid lesions other than PTC.

In our study, the FVPTC was missed more frequently on cytology. According to separate studies conducted by Perez et al and Yi Jun Yang, frequency of NG and INCI is less in FVPTC.[12,30] In concordance with both their studies, we also had the same impression. In our study 7/86 cases were FVPTC, out of these five cases were missed in cytology due to paucity of features of PTC.

In most of the studies in literature, papillary fragments and metaplastic cytoplasm were not studied as individual features. In our study papillary fragments and metaplastic cytoplasm were seen in 17/86 and 21/86 cases. On analysing these features individually found that PPV and NPV of papillary fragments were 94.12% and 79.71% respectively. PPV and NPV for metaplastic cytoplasm were 91.30% and 85.71% respectively. This reflects that when these features are considered independently, the diagnosis of PTC cannot be considered or excluded based on their presence or absence. Nevertheless, papillary fragments, metaplastic cytoplasm along with other specific features like NG and INCI can be helpful to arrive at a definite diagnosis of PTC.

The pathologists should be aware that the cytomorphological features of PTC can also be seen in other thyroid lesions and hence, care should be taken while reporting such cases. The specificity of NG for PTC is high when its occurrence is ≥20%. The category of cases with NG between 10-19% should be considered as 'suspicious for malignancy'. The presence of other cytomorphologic features such as INCI, papillary fragments or metaplastic cytoplasm in addition can favour the diagnosis of PTC. In "suspicious cases", the presence of frequent INCI should be searched carefully as it strongly indicates a diagnosis of PTC. Mere presence of INCI cannot be used as diagnostic criteria for PTC but when it is frequent (≥ 5% cells) it strongly suggests a diagnosis of PTC and pathologist should diligently look for presence of other morphological features to prevent misdiagnosis. FVPTC is commonly missed on cytology due to paucity of nuclear features of PTC and hence, it is the commonest false negative diagnosis. Papillary fragments and metaplastic cytoplasm are not independently diagnostic for PTC, but, presence of any of these features in addition to frequent NG can favour the diagnosis of PTC.

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