

Value of Combined Cytomorphological Parameters in Improving Diagnostic Accuracy of Papillary Thyroid Carcinoma on Cytology - The Five Dependable Features

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Abstract

Background: Fine-needle aspiration cytology remains the preliminary test for diagnosing papillary thyroid carcinoma (PTC). Numerous features are established to arrive at the diagnosis. However, few cases pose a challenge to correctly diagnose PTC. Our study aims to elicit the combination of features to aid in the diagnosis of such cases. **Materials and Methods:** Cytology smears of histologically proven cases of PTC and benign diagnoses were included as case (n = 36) and control group (n = 38), respectively. Features including papillae with cores, 3-D caps, nuclear grooves (NG), intranuclear cytoplasmic inclusions (INCI), giant cells, macrophages, cellular swirls, psammoma bodies, pale chromatin, nuclear overlapping, nuclear enlargement, and metaplastic cells were assessed. Statistic tests including Independent t test/Mann-Whitney Test and Chi-Square test/Fisher's Exact test were used. Receiver operating characteristic curve was used to assess the cut-off point of many cytological features to predict PTC. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of cytological features was calculated to predict PTC. **Results:** Presence of five or more cytological features (papillae with cores, cellular swirls, NG, INCI, and psammoma bodies) together could diagnose PTC (PPV) in 78.95% of the cases, with a NPV of 83.33%. Diagnostic accuracy of these five features combined was 81.08%. Papillae with cores and nuclear grooving were the most sensitive cytological features, whereas INCI followed by cellular swirls and NG were the most specific features. **Conclusion:** Relying on a combination of the most sensitive and specific features rather than any one cytological feature can help reduce the misdiagnoses in PTC.

Keywords: Cellular swirls, papillae, papillary thyroid carcinoma, PTC

INTRODUCTION

Thyroid carcinoma is the most common malignancy of endocrine origin.^[1] Papillary thyroid carcinoma (PTC) represents the most common thyroid gland malignancy accounting for 80%–90% of all thyroid cancers.^[2] In the evaluation of thyroid swellings, fine-needle cytology (FNC)/fine-needle aspiration cytology (FNAC) forms the preliminary test for diagnosis. Owing to its fairly high sensitivity, specificity, cost-effectiveness, and simplicity, FNC/FNAC is a promising and efficient means of distinguishing patients who require therapeutic surgical intervention from those who may require just long-term follow-up.

There are precise cytological features of PTC as recognized by Synopsis of National cancer institute (NCI), Thyroid Fine-Needle Aspiration State of the Science Conference.^[3] However, few cases still pose problems during cytological

evaluation, and in up to one-quarter of the cases, they are misclassified as lesions other than PTC.^[4] These cases with overlapping features or lacking clear-cut morphology are difficult to recognize as PTC. It results in bothersome rates of false-positive and false-negative cytology reports with serious implications in patient care and management. False-positive cytology report for PTC is due to shared cytological features with other benign and malignant entities in the thyroid. Absence

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or infrequent presence of these features, scant cellularity, and degenerative changes can result in a false-negative diagnosis, at times, render diagnoses like possibility of PTC/rule out PTC/suspicious of PTC, which often creates a diagnostic dilemma in the clinician's mind regarding the management protocol for these cases.^[5] Thus, this study aimed to determine the reliability of different cytological features individually and in combinations to identify any individual/set of cytological features carrying the maximum ability to correctly diagnose PTC and distinguish it from its benign mimickers as both have very different management protocols.

MATERIALS AND METHODS

After obtaining approval from the institute's ethics committee, an observational study was carried out in a tertiary care institute in Rishikesh, Uttarakhand. Cytology and histopathology slides of patients who underwent surgical thyroid resection (hemithyroidectomy/total thyroidectomy) between January 2018 and June 2020 with preoperative FNAC were screened.

Inclusion criteria

All histopathologically proven cases of PTC were taken out and their FNAC slides were reviewed for assessing cytology features.

Exclusion criteria

Histopathologically proven cases of PTC for which FNAC slides were not available or were of poor staining quality or contained inadequate cellularity were excluded from the study.

All cases included in our study were divided into the following two groups.

Group 1: This study group included 36 cases whose diagnoses were confirmed as PTC on histopathology. In cytology, these cases were diagnosed as PTC (20 cases), suspicious of PTC (5 cases), possibility of PTC cannot be ruled out (1 case), follicular neoplasm (2 cases), atypia of undetermined significance (AUS) (2 cases), adenomatous goiter (5 cases), and lymphocytic thyroiditis (1 case).

Group 2: This control group included 38 cases with postoperative confirmed benign histopathological diagnosis of adenomatous goiter/hyperplastic nodule/lymphocytic thyroiditis, and in cytology, they were diagnosed as adenomatous goiter (25 cases), lymphocytic thyroiditis (6 cases), follicular neoplasm (4 cases), possibility of PTC (1 case), and AUS (2 cases).

Stained cytology slides of all cases of groups 1 and 2 were taken out from the archive and assessed by three pathologists together (NK, TK, AM). Four slides, two each of May-Grunwald Giemsa (MGG) stained and two of Papanicolaou (Pap) stained slides were reviewed as per Bethesda system of reporting and assessed for 12 cytological features of PTC in each case.^[5] The two groups were then compared with respect to demographic profile and cytology features.

Parameters taken into consideration included all the major as well as minor diagnostic cytological features of PTC as established by NCI FNA Science Conference State.^[3] Cytological features assessed included the following:

- (i) Papillae with central fibrovascular cores, 3-D caps, nuclear grooves (NG), intranuclear cytoplasmic inclusions (INCI), giant cells, cystic macrophages, cellular swirls, psammoma bodies, pale chromatin, nuclear overlapping, nuclear enlargement/irregularity, and metaplastic cells.
- (ii) NG and INCI were semi-quantitatively assessed based on their frequency in the smears and graded as Grade I- many/frequent throughout the smear, Grade II- frequent in occasional groups of cells, and Grade III- occasional throughout the smear/absent.
- (iii) Nuclear enlargement was described as being absent or present based on a subjective assessment of the nuclear size. All other features were also graded as present or absent.

Statistical analysis

Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean \pm SD and median. Normality of data was tested using Kolmogorov-Smirnov test. If the normality was rejected, then a nonparametric test was used.

Statistical tests were applied as follows:

1. Quantitative variables were compared using Independent t test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups.
2. Qualitative variables were compared using Chi-Square test/Fisher's Exact test.
3. Receiver operating characteristic curve was used to find out the cut-off point of several cytological features to predict PTC.
4. Sensitivity, specificity, PPV, and NPV of cytological features were calculated to predict PTC.

$P < 0.05$ was considered statistically significant.

The data was entered in an MS Excel spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS

This study included 74 cases distributed in group 1 or group 2 with a median age of 34 and 35 years, respectively [Table 1]. Overall, there were 60 females and 14 males. Significant difference was observed between the two patient groups for gender ratio but not for age [Table 1].

Distribution of cases as per Bethesda categories is depicted in [Table 2] and [Figure 1]. Comparison of various cytological features between study group 1 and control group 2 is featured in Table 3. In group 1, 55.5% (20/36) of the cases were diagnosed as PTC on cytology, 16.6% (6/36) were labelled as suspicious/suggestive of PTC, whereas in 27.7% (10/36) cases

Table 1: Comparison of demographic characteristics between groups 1 and 2

Demographic characteristics	Group 1 (n=36)	Group 2 (n=38)	Total	P	Test performed
Age (years)					
Mean±SD	38±15.65	36.05±12.43	37±14.02	0.554	t test; 0.594
Median (IQR)	34 (25-50)	35 (28-42.75)	35 (25.25-44)		
Range	20-75	7-67	7-75		
Gender					
Female	24 (66.67%)	36 (94.74%)	60 (81.08%)	0.003	Fisher's Exact test
Male	12 (33.33%)	2 (5.26%)	14 (18.92%)		

Table 2: Categorization of groups 1 and 2 based on Bethesda system of thyroid reporting

Bethesda category	Group 1 (n=36)	Group 2 (n=38)	Total	P	Test performed
II	6 (16.67%)	31 (81.58%)	37 (50%)	<0.0001	Fisher's Exact test
III	4 (11.11%)	3 (7.89%)	7 (9.46%)		
IV	1 (2.78%)	4 (10.53%)	5 (6.76%)		
V	2 (5.56%)	0 (0%)	2 (2.70%)		
VI	23 (63.89%)	0 (0%)	23 (31.08%)		
Total	36 (100%)	38 (100%)	74 (100%)		

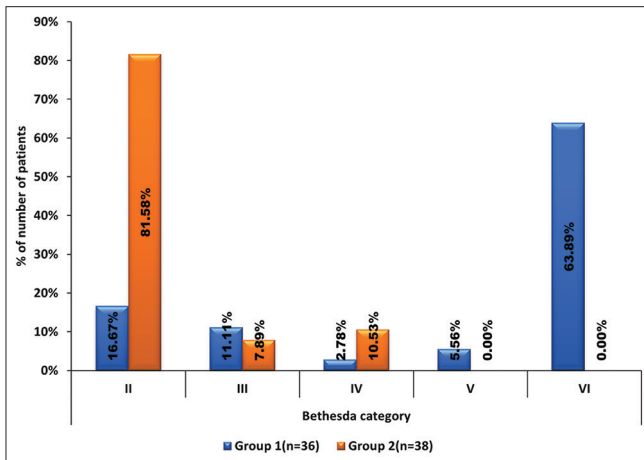


Figure 1: Comparison between groups 1 and 2 based on Bethesda category

the possibility of PTC was not suggested. Of these 27.7% cases, 11.11% cases were diagnosed as either follicular neoplasm or AUS and 16.6% were given a benign diagnosis [Table 3].

The cytological features that showed statistically significant differences between group 1 and group 2 were papillae with cores, 3D-caps, cellular swirls, nature of colloid, NG, INCI, squamous metaplastic cells, and cytoplasmic vacuolations [Table 3]. Cystic/foamy macrophages, nuclear overlapping and psammoma bodies did not differ significantly between groups 1 and 2 [Table 3]. Receiver operating characteristic curve analysis to predict PTC revealed that the presence of ≥ 5 cytological features, namely papillae with cores, cellular swirls, NG, INCI, and psammoma bodies, when found together in a case could diagnose PTC on cytology correctly (PPV) in 78.95% of the cases, with a negative predictive value of 83.33% [Table 4 and Figure 2].

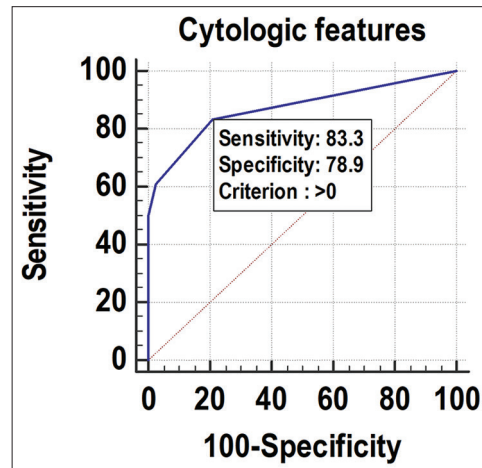


Figure 2: Receiver operating characteristic curve on combining five cytological features to predict PTC

Diagnostic accuracy of these five features combined was 81.08% [Table 5]. Papillae with cores and nuclear grooving were the most sensitive cytological features (sensitivity: 61.1%) whereas INCI followed by cellular swirls and NG (100%, 97.3%, and 97.3%, respectively) were the most specific features to diagnose PTC [Table 5]. Psammoma bodies had high specificity but very low sensitivity to detect PTC on cytology. Table 5 shows the sensitivity, specificity, PPV, and NPV of five cytological features to predict PTC.

Multinucleated giant cells (MGC) in benign condition were small ovoids having pale/foamy cytoplasm and few nuclei [Figure 3]. In contrast, MGC found in PTC cases were of two types: MGC as found in benign and MGC that appeared larger with varying shape, more nuclei, and dense cytoplasm. Clinical and histopathological parameters of group 1 are described in Table 6.

Table 3: Comparison of cytologic features between groups 1 and 2

Cytologic features	Group 1 (n=36)	Group 2 (n=38)	Total	P	Test performed
Papillae with cores					
Absent	14 (38.89%)	32 (84.21%)	46 (62.16%)	<0.0001	Chi-square test, 16.144
Present	22 (61.11%)	6 (15.79%)	28 (37.84%)		
3D caps					
Absent	18 (50%)	34 (89.47%)	52 (70.27%)	0.0003	Fisher's Exact test
Present	18 (50%)	4 (10.53%)	22 (29.73%)		
Cellular swirls					
Absent	17 (47.22%)	38 (100%)	55 (74.3%)	<0.0001	Fisher's Exact test
Present	19 (52.78%)	0 (0%)	19 (25.6%)		
Colloid					
Absent	10 (27.78%)	3 (7.89%)	13 (17.57%)	0.0002	Fisher's Exact test
Thick	16 (44.44%)	6 (15.79%)	22 (29.73%)		
Thick and thin	0 (0%)	4 (10.53%)	4 (5.41%)		
Thin	10 (27.78%)	25 (65.79%)	35 (47.30%)		
Giant cells					
Absent	16 (44.44%)	26 (68.42%)	42 (56.76%)	0.037	Chi-square test, 4.33
Present	20 (55.56%)	12 (31.58%)	32 (43.24%)		
Cyst macrophages					
Absent	16 (44.44%)	11 (28.95%)	27 (36.49%)	0.166	Chi square test, 1.916
Present	20 (55.56%)	27 (71.05%)	47 (63.51%)		
Nuclear grooves					
Many/frequent throughout the smear	22 (61.11%)	1 (2.63%)	23 (31.08%)	<0.0001	Chi-square test, 40.873
Frequent in occasional groups of cells	7 (19.44%)	4 (10.53%)	11 (14.86%)		
Occasional throughout the smear	5 (13.89%)	7 (18.42%)	12 (16.22%)		
Absent	2 (5.56%)	26 (68.42%)	28 (37.84%)		
Nuclear grooves (present/absent)					
Absent	2 (5.56%)	26 (68.42%)	28 (37.84%)	<0.0001	Fisher's Exact test
Present	34 (94.44%)	12 (31.58%)	46 (62.16%)		
Frequent Nuclear grooves (positive/negative)					
Negative	14 (38.89%)	37 (97.37%)	51 (68.92%)	<0.0001	Fisher's Exact test
Positive	22 (61.11%)	1 (2.63%)	23 (31.08%)		
Intra-nuclear cytoplasmic inclusion					
Many/frequent throughout the smear	11 (30.56%)	0 (0%)	11 (14.86%)	<0.0001	Fisher's Exact test
Frequent in occasional groups of cells	8 (22.22%)	0 (0%)	8 (10.81%)		
Occasional throughout the smear	4 (11.11%)	2 (5.26%)	6 (8.10%)		
Absent	13 (36.11%)	36 (94.73%)	49 (63.51%)		
Intra-nuclear cytoplasmic inclusion (present/absent)					
Absent	13 (36.11%)	36 (94.73%)	49 (66.21%)	<0.0001	Fisher's Exact test
Present	23 (63.89%)	2 (5.26%)	25 (33.78%)		
Frequent Intra-nuclear cytoplasmic inclusion (positive/negative)					
Negative	25 (69.44%)	38 (100%)	63 (85.14%)	0.0001	Fisher's Exact test
Positive	11 (30.56%)	0 (0%)	11 (14.86%)		
Powdery chromatin					
Absent	16 (44.44%)	30 (78.95%)	46 (62.16%)	0.002	Chi-square test, 9.357
Present	20 (55.56%)	8 (21.05%)	28 (37.84%)		
Psammoma body					
Absent	31 (86.11%)	37 (97.37%)	68 (91.89%)	0.103	Fisher's Exact test
Present	5 (13.89%)	1 (2.63%)	6 (8.11%)		
Nuclear overlapping					
Absent	10 (27.78%)	18 (47.37%)	28 (37.84%)	0.082	Chi-square test, 3.016
Present	26 (72.22%)	20 (52.63%)	46 (62.16%)		
Cytoplasmic Vacuoles					
Absent	26 (72.22%)	35 (92.11%)	61 (82.43%)	0.033	Fisher's Exact test
Present	10 (27.78%)	3 (7.89%)	13 (17.57%)		

Contd...

Table 3: Contd...

Cytologic features	Group 1 (n=36)	Group 2 (n=38)	Total	P	Test performed
Squamous Metaplastic cells					
Absent	18 (50%)	31 (81.58%)	49 (66.22%)	0.004	Chi-square test, 8.241
Present	18 (50%)	7 (18.42%)	25 (33.78%)		
Nuclear atypia/enlargement					
Present	25 (69.44%)	8 (21.05%)	27 (36.49%)	0.020	Chi-square test, 5.3667
Absent	11 (30.5%)	30 (31.58%)	12 (16.22%)		
Number of nuclei in giant cells					
Mean±SD	10.25±15.14	3.32±5.28	6.69±11.67	0.039	Mann-Whitney test; 510.5
Median (IQR)	4.5 (0-11.25)	0 (0-7.25)	0 (0-10)		
Range	0-55	0-20	0-55		

Table 4: Receiver operating characteristic curve with a combination of five cytological features to predict PTC

PTC	Cytologic features
Area under the ROC curve (AUC)	0.871
Standard Error	0.0398
95% Confidence interval	0.773-0.938
P	<0.0001
Cut-off	>0
Sensitivity (95% CI)	83.33% (67.2%-93.6%)
Specificity (95% CI)	78.95% (62.7%-90.4%)
PPV (95% CI)	78.9% (62.7%-90.4%)
NPV (95% CI)	83.3% (67.2%-93.6%)
Diagnostic accuracy	81.08%

DISCUSSION

Worldwide, thyroid cancer ranks ninth in incidence and is three times more common in women than in men.^[6] It is the most common type of thyroid cancer accounting for 70%–80% of all thyroid malignancies and compared to other thyroid cancers carries the best prognosis.^[7] Since 1980, incidence of thyroid carcinoma has shown an increase in trend throughout the world, which may be attributed to increased detection of PTC through improved diagnosis and changing prevalence of risk factors or possibly may be an impact of overdiagnosis.^[8,9] However, as over the same duration, death rate due to PTC has not shown any significant change, one pertinent question which comes to mind is whether the rise in PTC cases is actually true or it is an overdiagnosis.

Cytological evaluation is a well-established diagnostic modality and a variable number of cytological features have been used by different studies to diagnose PTC on FNAC. In the study conducted by Chandanwale *et al.*,^[10] frequency of papillae, NG, and INCI were significantly higher in PTC cases compared to those that were diagnosed as suggestive of PTC. Wu *et al.*^[11] reported nuclear enlargement, fine chromatin, NG, INCI, flat syncytial sheets, and some amount of thick colloid as the most common cytological features of PTC. Castro-Gomez *et al.*^[12] reported the presence of tridimensional fragments, anisonucleosis, nuclear bars, powdery chromatin, cytoplasmic

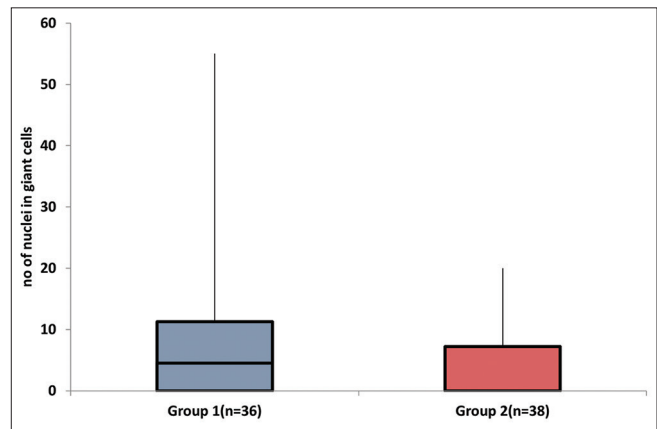


Figure 3: Comparison of the number of nuclei in giant cells between groups 1 and 2 (nonparametric variable, Box whisker plot)

vacuoles, metaplastic cytoplasm, and autolysis as cytological features that occurred significantly higher in the PTC group as compared to the benign thyroid lesions. Castro-Gomez *et al.*^[12] noted that papillae, psammoma bodies, multinucleated giant cells, spindle cells, colloid, and macrophages did not show any statistically significant between the benign and PTC groups.

Kumar *et al.*^[13] reported powdery chromatin, nuclear inclusions, nuclear grooves, and cellular swirls as the most consistent features present in all their cases of PTC, with nuclear grooves being more abundant than nuclear inclusion; 14% of their cases showed frequent nuclear grooves (>60%/10HPF), and 64% of the cases showed 2+ nuclear grooves (i.e., 31%–60%/10HPF), whereas INCI were infrequently identified (0%–30%/10HPF) in 93% of their cases. The majority of our cases (61%) showed frequent nuclear grooves throughout the smear while 30% showed frequent INCI [Figure 4].

Das *et al.*^[14] observed that the presence of ≥3 of the following features—psammoma bodies, papillae, inclusions, nuclear grooves, and granular chromatin—facilitate cytological diagnosis of papillary carcinoma of thyroid, with frequent grooves and inclusions being the most dependable. Miller *et al.*^[15] studied logistic regression analysis of the cytological variables and found that a combination of intranuclear

Table 5: Sensitivity, specificity, PPV, and NPV of cytological features to predict PTC

PTC	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	PPV (95% CI)	NPV (95% CI)	Diagnostic accuracy
Papillae with cores	61.11% (43.46%-76.86%)	84.21% (68.75%-93.98%)	0.73 (0.61-0.82)	78.57% (59.05%-91.70%)	69.57% (54.25%-82.26%)	72.97%
Cellular swirls	52.78% (35.49%-69.59%)	100% (90.9%-100%)	0.75 (0.64-0.84)	100.00% (75.13%-100%)	69.09% (56.45%-82.48%)	77.02%
Nuclear grooves (positive/negative)	61.11% (43.46%-76.86%)	97.37% (86.19%-99.93%)	0.79 (0.68-0.88)	95.65% (78.05%-99.89%)	72.55% (58.26%-84.11%)	79.73%
Intra-nuclear cytoplasmic inclusion (positive/negative)	30.56% (16.35%-48.11%)	100.00% (90.75%-100.00%)	0.65 (0.53-0.76)	100.00% (71.51%-100.00%)	60.32% (47.20%-72.43%)	66.22%
Psammoma body	13.89% (4.67%-29.50%)	97.37% (86.19%-99.93%)	0.56 (0.44-0.67)	83.33% (35.88%-99.58%)	54.41% (41.88%-66.55%)	56.76%
Combined five Cytologic features	83.33% (67.19%-93.63%)	78.95% (62.68%-90.45%)	0.81 (0.70-0.89)	78.95% (62.68%-90.45%)	83.33% (67.19%-93.63%)	81.08%

PPV: Positive predictive value; NPV: Negative predictive value CI: Confidence Interval

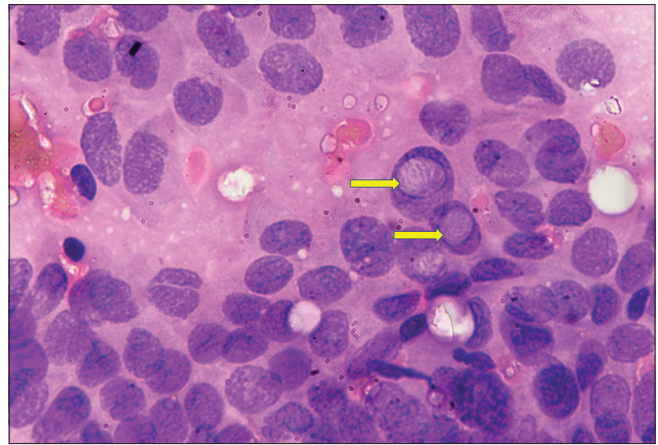


Figure 4: Microphotograph showing intracytoplasmic inclusion (arrow) (May Grunwald Giemsa, ×400)

cytoplasmic pseudo inclusion, papillary structure without adherent blood vessels, and dense metaplastic cytoplasm were the most important variables with 100% predictive value when a combination of any of these two was found. In the current study, by using the logistic regression analysis, we found that combination of five cytological features, namely papillae with cores, cellular swirls, NG, INCI, and psammoma bodies, had a diagnostic accuracy of 81% and could correctly diagnose (PPV) PTC in 78.9% of cases [Table 7]. PPV for cellular swirls and INCI was 100%, and it exceeded 95% when cellular swirls, NG, and INCI were present together.

Cytological features of PTC are not specific as they are also seen in other malignant and benign lesions of the thyroid. Nuclear grooves can be seen in medullary thyroid cancer, follicular cancer, follicular adenoma, lymphocytic thyroiditis, and nodular goiter.^[16,17] Certain studies have shown that quantification of intranuclear grooves can be helpful as PTC tends to have a greater number of cells with intranuclear grooves in comparison to other thyroid lesions and widespread pattern of NG can be a useful criterion.^[18,19] It has also been noted that in benign entities, usually, nuclear grooves are thin and/or incomplete, whereas they are thick longitudinal and accompanied by other cytological features in cases of PTC.^[18] INCI can be seen in medullary carcinoma, insular carcinoma, hyalinizing trabecular adenoma, Hashimoto’s thyroiditis, and multinodular goiter.^[16,19] In the present study, 10 cases of PTC that were incorrectly diagnosed on cytology as adenomatous goiter, AUS, or follicular neoplasm showed nuclear grooves in nine cases, while INCI was not seen in any of these cases. On further scrutiny of cytospreads, three of the nine cases showed frequent NG (Grade 1), a feature that could have helped in favoring the diagnosis of PTC in these cases. Seven cases showed infrequent/paucity of NG and all 10 cases showed absence of INCI, thereby posing diagnostic difficulty.

Similar observations were made by Renshaw *et al.*^[20] who compared the cytological features of PTC between two groups, group that performed well versus one that performed poorly in the College of American Pathologists (CAP) cytology program.

They reported that the group that performed poorly or were difficult to recognize as PTC were significantly more likely to lack nuclear enlargement, intranuclear inclusions, and pale chromatin, whereas nuclear crowding, nuclear overlapping, colloid, cellularity, Hurthle cell changes, and type of staining did not differ significantly between their two study groups.

Another less commonly reported cytological feature as a diagnostic clue for PTC are cellular swirls [Figure 5]. Cellular swirls are concentrically arranged follicular cells with peripheral neoplastic cells whose axis is perpendicular to the radius of the swirl.^[21] Cellular swirls have been reported as highly specific for PTC when found in cytological smears.^[13,22,23] We also found similar results as the presence of cellular swirls was limited to cases of PTC and none of the cases in group 2 showed cellular swirling. Cellular swirls may be confused with the spherules or whorl-like structures structure, which consists of cells with prominent nuclear changes such as enlarged nuclei and thickened nuclear membranes, and is seen in cases of the cribriform-morular variant of PTC.^[24] In contrast, nuclear features in cellular swirls are bland.

One case in group 2 was falsely diagnosed as PTC on cytology and turned out to be nodular goiter with lymphocytic thyroiditis on histopathology showing few nuclear grooves (grade 2) and rare INCI (grade 3).

Results of our study and revelations by various studies highlight the fact that cytological features in PTC may vary in some cases, causing diagnostic dilemmas in them owing to either limited morphology or overlapping cytological findings. False-positive and false-negative cytology results in overdiagnosis and underdiagnosis and may misguide the clinician. Thus, it is essential that such focused studies be carried out on a larger scale, and a systematic review and meta-analysis may be helpful in defining precise criteria to identify PTC on cytosmears.

CONCLUSION

The majority of the cytological features of PTC are neither specific nor constant. Incorrect diagnoses on FNAC in

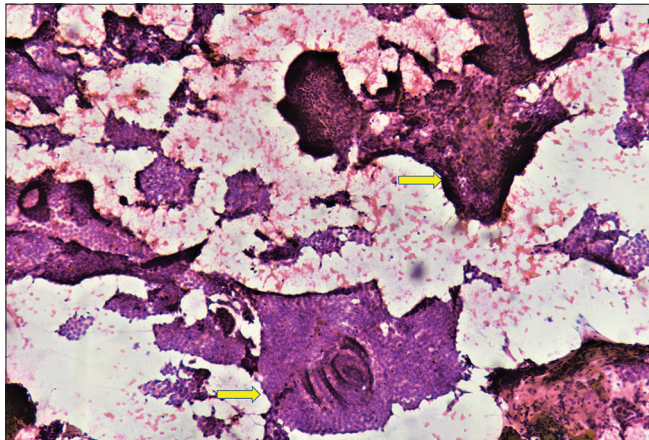


Figure 5: Microphotograph showing cellular swirls (arrow) (May Grunwald Giemsa, ×400)

suspected cases of papillary carcinoma of thyroid can be minimized if the pathologist is aware of these pitfalls. Relying on a combination of most sensitive features like nuclear grooves and papillae and specific features such as cellular swirls and intranuclear cytoplasmic inclusions rather than on any one single cytological feature alone can help in reducing the false-positive/false-negative diagnoses in papillary thyroid carcinoma.

Table 6: Clinical and histological details of PTC cases included in the study

Characteristics	Frequency	Percentage
Type of surgery		
HT	8	22.22%
TT	28	77.78%
Laterality		
Bilateral	9	25.00%
Isthmus	2	5.56%
Left	12	33.33%
Right	11	30.56%
Right + Isthmus	2	5.56%
Focality		
Multifocal	12	33.33%
Unifocal	24	66.67%
LVI		
Absent	32	88.89%
Present	4	11.11%
PNI		
Absent	35	97.22%
Present	1	2.78%
Angioinvasion		
Absent	36	100.00%
T staging		
T1a	2	5.71%
T1b	9	25.71%
T2	11	31.43%
T3a	7	20.00%
T3b	1	2.86%
T4a	5	14.29%
N staging		
0	7	29.17%
1	1	4.17%
1a	4	16.67%
1b	12	50.00%
M staging		
0	4	66.67%
1	2	33.33%

LVI: lymphovascular invasion; PNI: Perineural invasion; T: Tumor; N: Node; M: Metastasis

Table 7: The Pentad of Cytological Features

- Papillae with cores
- Cellular swirls
- Nuclear grooves
- Intra-nuclear cytoplasmic inclusion
- Psammoma body

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Unnikrishnan AG, Menon UV. Thyroid disorders in India: An epidemiological perspective. *Indian J Endocrinol Metab* 2011;15(Suppl 2):S78-81.
- Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, *et al.* 2015 American Thyroid Association Management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 2016;26:1-133.
- Pitman MB, Abele J, Ali SZ, Duick D, Elsheikh TM, Jeffrey RB, *et al.* Techniques for thyroid FNA: A synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. *Diagn Cytopathol* 2008;36:407-24.
- Hall TL, Layfield LJ, Philippe A, Rosenthal DL. Sources of diagnostic error in fine needle aspiration of the thyroid. *Cancer* 1989;63:718-25.
- Ali SZ, Cibas ES. *The Bethesda System for Reporting Thyroid Cytopathology-Definition, Criteria and Explanatory Notes*. New York: Springer; 2010.
- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al.* Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209-49.
- Busnardo B, DeVido D. The epidemiology and etiology of differentiated thyroid carcinoma. *Biomed Pharmacother* 2000;54:322-6.
- Kitahara CM, Schneider AB, Brenner AV. Thyroid cancer. In: Thun MJ, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D, editors. *Cancer Epidemiology and Prevention*. 4th ed. New York: Oxford University Press; 2018. p. 839-60.
- Vaccarella S, Franceschi S, Bray F, Wild CP, Plummer M, Dal Maso L. Worldwide thyroid-cancer epidemic? The increasing impact of overdiagnosis. *N Engl J Med* 2016;375:614-7.
- Chandanwale SS, Kumar H, Buch AC, Vimal SS, Soraisham P. Papillary thyroid carcinoma, a diagnostic approach in fine needle aspiration: Review of literature. *Clin Cancer Investig J* 2013;2:339-43.
- Wu HH, Jones JN, Grzybicki DM, Elsheikh TM. Sensitive cytologic criteria for the identification of follicular variant of papillary thyroid carcinoma in fine-needle aspiration biopsy. *Diagn Cytopathol* 2003;29:262-6.
- Castro-Gomez L, Cordona-Ramirez S, Duarte-Torres R, Alonso de Ruiz P, Hurtado-Lopez LM. Cytologic criteria of cystic papillary carcinoma of the thyroid. *Acta Cytol* 2003;47:590-4.
- Kumar B, Joshi U, Srivastav P, Khetan H. To evaluate the role of cellular swirls in fine needle aspiration cytology diagnosis of papillary carcinoma thyroid. *Indian J Pathol Oncol* 2017;4:18-22.
- Das DK, Sharma PN. Diagnosis of papillary thyroid carcinoma in fine needle aspiration smears: Factor that affect decision making. *Acta Cytol* 2009;53:497-506.
- Miller TR, Bottles K, Holly EA, Friend NF, Abelle JS. A step-wise logistic regression analysis of papillary carcinoma of the thyroid. *Acta Cytol* 1986;30:285-93.
- Deligeorgi-Politi H. Nuclear crease as a cytodiagnostic feature of papillary thyroid carcinoma in fine-needle aspiration biopsies. *Diagn Cytopathol* 1987;3:307-10.
- Chan JK, Saw D. The grooved nucleolus: A useful diagnostic criterion of papillary carcinoma of thyroid. *Am J Surg Pathol* 1986;10:672-9.
- Jing X, Michael CW. Potential pitfalls for false suspicion of papillary thyroid carcinoma: A cytohistologic review of 22 cases. *Diagn Cytopathol* 2012;40(Suppl 1):E74-9.
- Das DK. Intracellular cytoplasmic inclusions in fine-needle aspiration smears of papillary thyroid carcinoma: A study of its morphological forms, association with nuclear grooves, and mode of formation. *Diagn Cytopathol* 2005;32:264-8.
- Renshaw AA, Wang E, Haja J, Wilbur D, Henry MR, Hughes JH, *et al.* Fine-needle aspiration of papillary thyroid carcinoma: Distinguishing between cases that performed well and those that performed poorly in the college of american pathologists nongynecologic cytology program. *Arch Pathol Lab Med* 2006;130:452-5.
- Szpor AH, Yuan S, Wu M, Burstein DE. Cellular swirls in fine needle aspirates of papillary thyroid carcinoma: A new diagnostic criterion. *Modern Pathol* 2006;19:1470-3.
- Yashaswani R, Suresh TN, Kumar MK, Kumar HML. Role of cellular swirls in the cytodagnosis of papillary carcinoma thyroid. *J Dent Med Sci* 2015;14:7-10.
- Kumar S, Singh N, Siddaraju N. Cellular swirls and similar structures on fine needle aspiration cytology as diagnostic clues to papillary thyroid carcinoma: A report of 4 cases. *Acta Cytol* 2010;54:939-42.
- Kuma S, Hirokawa M, Xu B, Miyauchi A, Kukudo K, Sano T. Cribriform-morular variant of papillary thyroid carcinoma. Report of a case showing morules with peculiar nuclear clearing. *Acta Cytol* 2004;48:431-6.