Cytohistological Concordance of Papillary Carcinoma of Thyroid and Its Variants

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ABSTRACT

BACKGROUND

Papillary thyroid carcinoma is the most common malignancy of the thyroid gland. Fine Needle Aspiration Cytology (FNAC) is a rapid, safe and economic procedure, and has a sensitivity approaching of 93.5 % and specificity close to 90 % for diagnosing papillary thyroid carcinomas. This study aims at correlating the cytological and histological diagnosis to arrive at the rate of concordance and discordance, identify variants of papillary thyroid carcinoma (PTC) on cytology and discuss the cytological mimics of PTC.

METHODS

Data from cases was collected over a period of three years (2015 - 2018). A descriptive study was done. Cases from Osmania General Hospital representing histologically proven cases of papillary carcinoma thyroid along with their corresponding cytological findings were analysed. Cytosmears were obtained from fine needle aspiration of thyroid lesions using a 26-gauge needle, stained with haematoxylin and eosin (H&E). Thyroidectomy specimens were fixed in 10 % buffered formalin, grossed and paraffin embedded. After processing, sections obtained by microtomy were stained with H & E for histopathologic evaluation.

RESULTS

The institute received a total of 258 thyroid specimens for histopathology and 686 cases for thyroid FNAC over a period of three years. This study includes 70 cases which had both cytology and histopathology correlation at our institution. 65 cases were diagnosed as PTC on histopathology and correct diagnosis was made on cytology with 73.8 % concordance (48 / 65 cases) and discordance was seen in 26.1 % (17 / 65 cases). 5 cases were misdiagnosed on cytology as PTC, and on histopathological examination were diagnosed as non-PTC.

CONCLUSIONS

Fine needle aspiration shows variable accuracy for PTC, ranging from 65 % to 90 %. The architectural arrangement of cells in papillary fragments and presence of nuclear features in majority of cells is diagnostic of the conventional variant of PTC. The other variants however, pose a diagnostic dilemma on account of their architectural variation, altered cytomorphology and the scant presence of nuclear features. An increase in the awareness of cytomorphology of variants and also of the mimics of PTC helps improve the diagnostic accuracy on FNAC.

KEYWORDS

Papillary Thyroid Carcinoma, Variants of PTC, Cytohistopathological Correlation

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DOI: 10.18410/jebmh/2021/41

How to Cite This Article:
Saleem N, Bajaj NK, Nagamuthu EA. Cytohistological concordance of papillary carcinoma of thyroid and its variants. J Evid Based Med Healthc 2021;8(04):213-218. DOI: 10.18410/jebmh/2021/41

Submission 06-10-2020,
Peer Review 20-10-2020,
Acceptance 07-12-2020,
Published 25-01-2021.

BACKGROUND

Thyroid cancer is the most common endocrine malignancy of the human body, accounting for approximately 2 % of the cancers worldwide.[1] Broadly the thyroid cancers are of the following histological types: follicular, papillary, anaplastic and medullary. Of these, papillary thyroid cancer (PTC) is the most common histological type (80 - 85 %).[2] Women have approximately a threefold to fourfold higher incidence of thyroid cancer than men, a ratio consistently observed across countries and which has remained constant over time.[3] This difference is particularly pronounced for PTC compared with other major thyroid cancer histological subtypes. The median age at diagnosis is younger for thyroid cancer than for most other major types of cancer, with a median age at diagnosis of 49 years for women and 54 years for men.[4]

Over the past years, there has been a steep increase in the incidence of thyroid cancers, notably papillary thyroid cancer.[5] The rise in incidence seems to be attributable both to the growing use of diagnostic imaging and fine-needle aspiration biopsy (which has led to enhanced detection and diagnosis of subclinical thyroid cancers) and environmental factors.[6]

The utility of fine needle aspiration cytology, in conjunction with ultrasound and biochemical testing of thyroid hormone status has tremendously impacted the management of thyroid lesions, especially thyroid nodules. FNAC is a rapid, safe and economic procedure, and has a sensitivity approaching 93.5 % and specificity close to 75 % for diagnosing thyroid lesions.[7] This data, coupled with its safe, inexpensive and simple technique, has firmly put FNAC as the first step towards the diagnosis and management of thyroid neoplasms.

However, FNAC does come with its diagnostic dilemmas, and this study is an attempt to correlate the FNAC diagnosis with the final histopathological diagnosis of the lesion to arrive at the rates of concordance and discordance, with special attention given to the variants of PTC-15 variants have been officially listed in the latest WHO classification of the thyroid gland.[8]

The variants of PTC present with altered cytomorphology and architecture, which is reflected in the cytosmears. Therefore, this study also attempts to review and streamline the diagnostic criteria for variants on cytology. This is of paramount importance when dealing with rare variants and variants with an adverse prognosis. A timely, correct diagnosis with FNAC can help in guiding the surgeon for total thyroidectomy, avoid unnecessary follow up surgeries and prevent spread of the disease.

METHODS

Descriptive study was done, using data from cases amassed over a period of three years (2015 - 2018). Cases from Osmania General Hospital that were reported as PTC on either histopathology or cytology were included. Total 70 cases taken up for review, which included 65 cases of histopathological proven PTC along with corresponding cytosmears studied preoperatively and 5 cases falsely diagnosed as PTC on cytology along with their histopathological sections.

Cytosmears were obtained, after consent of patient, from fine needle aspiration of thyroid lesions using a 26-gauge needle. Smears were alcohol fixed, stained with H & E and Pap and mounted for cytological evaluation. Only smears that were satisfactory for cytological evaluation, as per Bethesda criteria were taken for the study. Thyroidectomy specimens were fixed in 10 % buffered formalin, grossed and paraffin embedded. Gross findings were noted, including cystic areas with solid nodules, of papillary excrescences. After processing, 5 micron thick sections were obtained by microtomy and stained with H & E for histopathologic evaluation. For cases representing diagnostic difficulty on H & E sections, immunohistochemistry (IHC) was done using cytokeratin 19 (CK 19) (DAKO-Monoclonal Mouse Anti-Human CK19, RCK108) and CD 56 (DAKO Monoclonal Mouse Anti-Human CD56, 123C3).

Inclusion Criteria

All cases diagnosed as PTC on either histopathology or cytology, along with their corresponding cytology and histopathology diagnosis respectively.

Exclusion Criteria

Any case with diagnosis of PTC that did not have slides available for review due to damage / loss / taken by patient to other institute.

RESULTS

The study population showed a female predominance, with a M : F ratio of 1 : 3.8. The maximum number of patients were in the 3rd decade of life, with the youngest being 19 years of age and the oldest was 60 years. 65 cases were diagnosed as PTC on histopathology and cytohistological concordance was seen in 73.8 % (48 / 65 cases) and discordance was seen in 26.1 % (17 / 65 cases) 5 cases were misdiagnosed on cytology as PTC, and on histopathological examination were diagnosed as non-PTC.

The final histopathological diagnosis of the 65 PTC cases was as follows: 51 conventional PTC, 8 follicular variants of PTC, 2 oncocytic variant of PTC, 2 cystic metastasis of PTC, 1 tall cell variant of PTC and 1 macrofollicular variant of PTC. Of the total 65 PTC cases, 16 (25.3 %) were observed in a background of Hashimoto's thyroiditis.

All concordant cases were categorized as either Bethesda V–suspicious for PTC, or Bethesda VI–PTC. Of the 48 concordant cases (74 %), there were 3 follicular variants of PTC, 2 oncocytic variants of PTC, 1 tall cell variant of PTC and 42 conventional PTC. 2 follicular variants of PTC and both oncocytic variants were identified correctly as such on cytology. The tall cell variant was classified as suspicious for PTC.

The cases in Bethesda – VI PTC showed the following cytomorphological features: enlarged elongated nuclei (93.7 %), nuclear membrane irregularities / grooves / nuclear pseudo inclusions. (100 %) and pale enlarged nuclei (83.3 %). In addition to the cytomorphological features of PTC, the following were also noted: psammoma bodies (5 / 48), chewing gum colloid (2 / 48) and foreign body giant cells (7 / 48)

Histopathological Diagnosis	Bethesda Grade VI Malignancy PTC	Bethesda Grade V Suspicious for PTC	Bethesda Grade IV Follicular Neoplasm	Bethesda Grade III Atypia of Undetermined Significance	Bethesda Grade II Benign Lesion: NG/ HT	Bethesda Grade I Inadequate Smear/ Cystic Fluid	Total Cases
Conventional PTC	27	15	-	1	8	-	51
Follicular variant of PTC	3	-	5	-	-	-	8
Oncocytic variant of PTC	2	-	-	-	-	-	2
Tall cell variant of PTC		1	-	-	-	-	1
Macrofollicular variant of PTC	-	-	-	-	1	-	1
Cystic PTC	-	-	-	-	-	2	2
Total Cases	**32**	**16**	**5**	**1**	**9**	**2**	**65**

Table 1. Cytological Diagnosis in 65 Cases Proven as PTC on Histopathology

Features	No. of Cases	Percentage
Elongated nuclei	45 / 48	93.7 %
Nuclear membrane irregularities	48 / 48	100 %
Pale nuclei	40 / 48	83.3 %
Psammoma bodies	5 / 48	10.4 %
Chewing gum colloid	2 / 48	4 %
Foreign body giant cells	7 / 48	14.5 %

Table 2. Nuclear and Cytological Features Seen in Concordant Cases

Cytological Diagnosis	No. of Cases	Bethesda Grade	Histopathological Diagnosis
Suspicious for PTC	1	V	Hyperplastic nodular goitre
Follicular variant of PTC	1	VI	Follicular adenoma
Suspicious for PTC	1	V	Hashimoto's thyroiditis
Oncocytic variant of PTC	1	VI	Hurthle cell adenoma
PTC	1	VI	Hyalinising trabecular tumour
Branchial cyst	2	I	Cystic metastasis of PTC
Follicular neoplasm	5	IV	FVPTC
Nodular goitre	3	II	(i) PTC in background of Nodular Goitre and (ii) Macrofollicular variant of PTC
Nodular goitre with Hashimoto's thyroiditis	6	II	PTC in a background of Hashimoto's thyroiditis
Atypia of undetermined significance	1	III	PTC

Table 3. Discordant False Positive and False Negative Cases on Cytology with Their Corresponding Histopathology Diagnosis

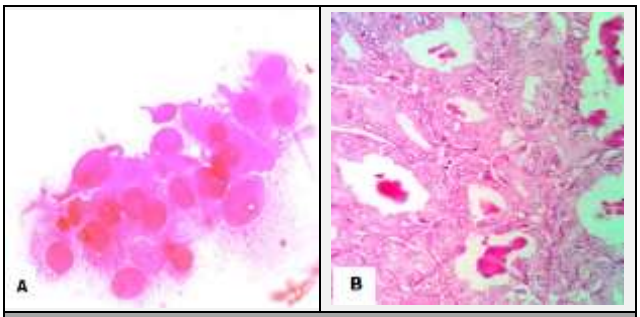

Figure 1 A) Cells with Abundant Granular Eosinophilic Cytoplasm, Cytology 100x H &E (Left) B) Histopathology, 40x, H & E (Right)

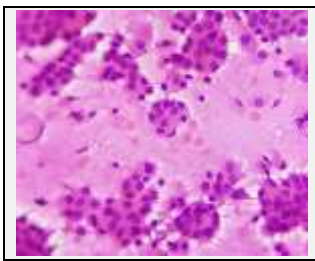

Figure 1C. Follicular Variant of PTC, 100x, Cytology, H & E

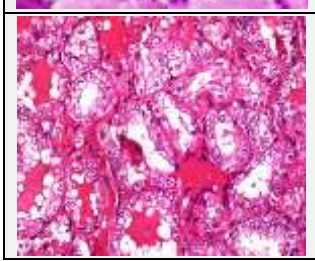

Figure 1D. Follicular Variant of PTC, 40x, Histopathology, H & E

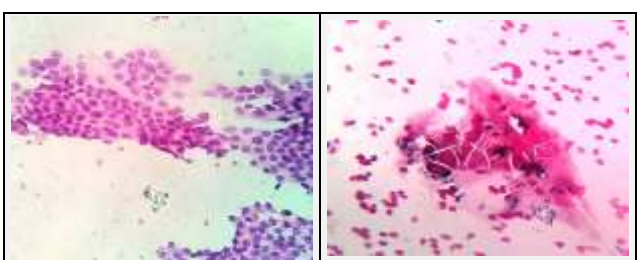

Figure 2A) Macrofollicular Variant, Cytology

Single cell with pseudo inclusion (Left), Variable amounts of thick colloid (Right), 40X, H & E

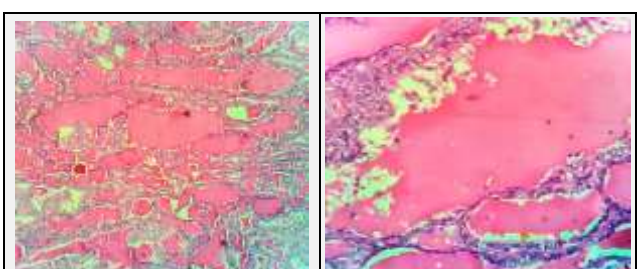

Figure 2B. Macrofollicular Variant of PTC, with Abundant Colloid, Follicles Lined by Cells with Classic PTC Nuclei, Histopathology 10x (Left) and 40x (Right), H & E

In addition to the cytomorphological features of PTC, the following were also noted: psammoma bodies (5 / 48), chewing gum colloid (2 / 48) and foreign body giant cells (7 / 48). This study had an overall discordant rate of 31.4 % (22 out of 70 cases) and the discordant cases were further subdivided as: false positives 7.1 % (5 out of 70) and false negatives 24.2 % (17 out of 70). False positives were cases

diagnosed on cytology as suspicious for PTC or malignancy-PTC only to be revealed as non PTC lesions on histopathology. False negatives were cases of PTC that were missed on cytosmears.

DISCUSSION

The cytological diagnosis of PTC, being reliable enough to dictate further surgical management, depends entirely on certain cytomorphological features distinctive to PTC. However, these cellular features can occur in other thyroid lesions as well, both benign and malignant. Also, follicular and papillary patterns are often overlapping between benign and malignant lesions. For these reasons, diagnostic pitfalls may be noted.[9] According to the literature, even variants of PTC can lead to diagnostic errors, and the follicular variant of papillary carcinoma (FVPTC) is thought to be one of the most common causes of false negative cytologic diagnosis of PTC.[10] Other factors that impact FNAC reporting are specimen inadequacy, incorrect sampling techniques, and worrisome histologic alterations following fine-needle aspiration of the thyroid (WHAFFT) changes.[11]

The present study shows a peak incidence in the third decade of life, which is comparable to the studies done by S. Gupta et al. [12] and C. Sharmaetal.[13] Overall the present study showed a positive cytohistological correlation in 68.5 % cases of PTC (48 / 70 cases). M. Nair et al.[14] had a positive cytohistological correlation of 75 % (93 / 124 cases) and S. Gupta et al.[12] had a concordance of 80.4 % (112 / 139 cases). C Sharma et al.[13] reported a cytohistological concordance of 81.9 % (59 / 72 cases). The lower correlation in this study can be attributed to the small number of cases reviewed and the inclusion of false positive cytology cases in the study, which both Nair et al. and Gupta et al. did not consider in their studies.

The total number of discordant cases in this study was 22 of 70 cases reviewed (31.4 %). The number of discordant false negatives in this study was 17 (24.2 %) and the number of discordant false positives was 5 (7.1 %). A similar study was done by C Sharma et al.[13] over a period of six years amassing 72 cases. The total number of discordant cases in the study was 13 / 72 (18 %), with 9 false negative cases (12.5 %) and 4 false positive cases (5.5 %) S. Gupta et al.[12] had a very low false negative rate of 6 out of 139 cases (4 %) reviewed over a period of 10 years. M. Nairetal[14] had a false negative rate of 31 of 124 cases (25 %) reviewed over a 16-year period, which was comparable with the present study.

In the present study, the possible reasons for discordance include: non-representative sampling, sampling of the non-neoplastic background lesion and presence of variants with paucity of characteristic nuclear features on FNAC

The classic nuclear features described in literature that were noted in this study: elongated nuclei (n = 54), nuclear grooves and intranuclear cytoplasmic inclusions (n = 48), and pale nuclei with powdery chromatin (n = 40). The pattern of cell arrangement in the conventional PTC was either papillary fronds or syncytial sheets with focal nuclear overlapping and overcrowding. Other features noted were psammoma bodies (n = 5), chewing gum colloid (n = 2), and foreign body giant cells (n = 7)

The nine conventional PTCs that were misdiagnosed included one case that was graded as Bethesda Category III (atypia of undetermined significance) and eight cases were graded as Bethesda Category II (benign lesions)

The single case of atypia of undetermined significance was taken for a repeat FNAC after two months, and the repeat FNAC was inconclusive due to lack of material. An intraoperative squash cytology was done, which showed abundant material with papillary fronds with typical PTC nuclei. Total thyroidectomy was done for the patient.

The eight cases diagnosed as benign lesions were attributed to non-representative sampling, as histopathology sections showed multifocal PTC in the background of the same benign lesion, i.e., nodular goitre (n = 3) and Hashimoto's thyroiditis (n = 5) The presence of PTC in a background of Hashimoto's thyroiditis has been researched extensively. A meta-analysis done by Lee, Kim and Choi et al.[15] showed that PTC is significantly associated with pathologically confirmed Hashimoto's thyroiditis (HT). PTC patients with HT have favourable clinic pathologic characteristics compared with PTCs without HT. In the present study, 16 of the 63 PTC cases were associated with a background of Hashimoto's thyroiditis, i.e., 26 % of the total cases, which is comparable to Cipolla et al.[16] These findings reflect research that show that rearranged during transfection (RET) / PTC gene rearrangement that is seen in PTC occurs in HT too[17]. This association perhaps points to a continuum in the spectrum of disease, which is not yet proved.[18]

The two cases reported as branchial / neck cysts on cytology are classic examples of the notorious micro carcinoma presenting itself as an occult PTC, with cystic nodal metastasis. Though an uncommon occurrence, all lateral neck cysts should undergo ultrasound of the neck, to detect occult PTC.

The most common variant encountered in this study was conventional or classical variant (n = 51, 78.4 %) followed by the follicular variant (n = 8, 12.3 %). Other variants noted were the oncocytic, (n = 2, 3 %), tall cell (n = 1, 1.5 %) and macrofollicular variant (n = 1, 1.5 %).

Amongst the discordant cytological smears, it was found that follicular variant of PTC (FVPTC) had the maximum number of misdiagnosis of cytology, in this study as well as in literature, with the lesion reported as either a benign nodular lesion or a follicular neoplasm.[19]

The presence of a follicular pattern of cell arrangement, coupled with infrequent nuclear featured suggestive of PTC make this variant problematic on FNAC reporting. The morphological heterogeneity of FVPTC on histopathology explains the high false negative rate of diagnosis on cytology.

The oncocytic variant is characterized by abundant dense eosinophilic cytoplasm with focal presence of PTC nuclei. It is not uncommon for the oncocytic variant of PTC to be diagnosed as a Hurthle cell neoplasm.[20]

To diagnose a carcinoma as a macrofollicular PTC, more than 50 % of the cross-sectional area of the tumour must

be formed by macrofollicles, with a mean diameter of at least 200 µm and at least some of lining cells of the follicles must show the nuclear features characteristics of PTC. This is a rare variant and has prognosis similar to conventional PTC. The differential diagnosis includes macrofollicular adenoma, a hyperplastic macrofollicular nodule in a nodular goitre, and a macrofollicular variant of follicular thyroid carcinoma.[21] the single case of macrofollicular variant in this study was misdiagnosed on cytology as a nodular goitre due to the presence of abundant colloid and lack of PTC nuclei.

The tall cell variant of PTC is an important subtype with a potentially aggressive clinical course. It usually affects the elderly population, and often presents as a large and bulky tumour with extra thyroidal extension and metastases.[22] The characteristic description of the tumour cell is a cell which has height three times more than its width, abundant dense eosinophilic cytoplasm and a central round to elongated nucleus with multiple intranuclear cytoplasmic invaginations (INCIs), imparting a soap bubble appearance to the nucleus in almost 30 % of the cells. These cells constitute more than 50 % of tumour volume.

The present study had only a single case of tall cell variant, which was identified as suspicious for PTC on cytology.

The false positive cases in this study accounted for 7 % (5 / 70 cases). In all false positive cases, the presence of PTC like nuclear features led to misdiagnosis. Though much has been said about the characteristic nuclear features of PTC, it is universally known that similar nuclear features, especially the presence of nuclear grooves and inclusions are seen in other conditions[11], including air drying artefacts, FNAC induced changes, chronic lymphocytic thyroiditis, benign papillary proliferations, ultimo brachial body cell rests and hyalinising trabecular neoplasms.

This is also the reason why one stresses on assessing nuclei based on all nuclear criteria, i.e., shape, size, overcrowding, overlapping, chromatin, grooves and inclusions before concluding a lesion as a PTC.

Hyperplastic nodules of the thyroid closely mimic PTC, even on histopathology. However, the nuclei have pseudo-inclusions that lack a clear demarcation.[23] The presence of PTC like nuclear features aren't uncommon in Hashimoto's thyroiditis, and the presence of such cells along with a sparse lymphocytic infiltrate can lead to the misdiagnosis of PTC.

Follicular neoplasms are also confused with the follicular variant of PTC. The misdiagnosis is due to high cellularity, along with nuclear features of PTC.

The nuclear features of PTC along with presence of Hurthle cells point towards an oncocytic variant of PTC. However, scant nuclear features and an overwhelming majority of oncocytic cells are more in favour of a Hurthle cell neoplasm,[24] like the case in this study, which was confirmed as a Hurthle cell adenoma on histopathology.

Hyalinising trabecular tumours are rare neoplasms that also possess the RET / PTC gene rearrangements characteristic of PTC.[25] These can be misdiagnosed on cytology as PTC, due to the presence of PTC like nuclei[26], as in this study.

In the concordant cases, the identification of the variants did not bear much importance as they were all identified as PTC, in either Bethesda category V or VI, which ultimately have the same surgical outcome. However, in the discordant cases, a definite change in outcome is observed. This is because the management guidelines as per Bethesda system of thyroid reporting vary vastly for benign lesions, follicular neoplasms and malignancies including PTC.

CONCLUSIONS

Cytology in conjunction with ultrasound has improved the overall diagnosis of PTC. The variants, however, pose a diagnostic dilemma due to their architectural variation, altered cytomorphology and the scant presence of nuclear features. A thorough knowledge of the variants and a keen eye can help pick up the PTCs that would have otherwise been misdiagnosed. Ultimately, an increased diagnostic accuracy of PTC on cytology translates into single sitting total thyroidectomy, obviating multiple surgeries and spread of carcinoma.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.
The authors would like to thank the technical staff at OMC for their help.

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