

# Papillary thyroid carcinoma, a diagnostic approach in fine needle aspiration: Review of literature

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## ABSTRACT

**Background:** Despite well-defined cytology features of papillary thyroid carcinoma (PTC) in fine needle aspiration (FNA), diagnostic difficulties do exist while making decision in respect to papillary thyroid carcinoma (PTC) cases. **Aims:** The aim of this study is to clarify diagnostic significance of various cytology features of PTC and to identify possible diagnostic pitfalls. **Materials and Methods:** FNA cytology (FNAC) features and clinical findings of 17 PTC cases diagnosed on histology were retrieved. A retrospective review of these cases was performed. **Results:** The frequency and number of papillary formations, intranuclear cytoplasmic inclusions (INCI), and nuclear grooves (NG) was more in PTC cases as compared to suggestive/suspicious of (S/O) and rule out (R/O) PTC cases. Cyst macrophages forming clusters were seen in six cases. Multinucleated giant cells (MGC) were seen in seven cases. Large MGC with dense cytoplasm and more nuclei were seen in four PTC and one S/O PTC cases. **Conclusion:** FNAC features of PTC in FNA smears are neither constant nor specific. All the cytology features of PTC should be reported in proper context which allows endocrine specialist to treat and urgent histological verification.

**Key words:** Fine needle aspiration, intranuclear cytoplasmic inclusions, nuclear grooves, papillary thyroid carcinoma

## INTRODUCTION

Thyroid neoplasms are divided into three major categories depending on the cell types involved. 1: Tumors exhibiting follicular cell differentiation which accounts for more than 95% of cases. 2: Tumors exhibiting C-cell differentiation. 3: Tumors exhibiting follicular and C-cell differentiation. PTC shows follicular cell differentiation and is the most common carcinoma in the thyroid gland. It occurs more commonly in the age group of 20-50 years with female to male ratio of 4:1 and 50% cases have regional lymph node metastasis at the time of surgery and 10% cases show distant metastasis to lungs and bone.<sup>[1]</sup> Since 1970, when pioneer work on thyroid cytopathology formulated the first diagnostic

criteria of papillary thyroid carcinoma(PTC).<sup>[2,3]</sup> Fine needle aspiration cytology (FNAC) diagnosis has made a great progress<sup>[4-9]</sup> and has extended significantly in relation to newly described PTC variants.<sup>[10-16]</sup> Though well-defined fine needle aspiration (FNA) cytology features of PTC are established according to the synopsis of National Cancer Institute (NCI), Thyroid Fine Needle Aspiration State of the Science Conference, a large number of PTC cases are diagnosed as suggestive/suspicious of (S/O) PTC or it is suggested that PTC be rule out (R/O) in FNA.<sup>[17]</sup> There are also cases with one or more cytological features of PTC which are diagnosed as benign lesions.<sup>[18]</sup> These diagnosis creates a dilemma in clinician's mind while planning the management strategy. In the present study, we review cytology features of 17 PTC cases diagnosed on histology.

## MATERIALS AND METHODS

During the period of 3 years (May 2008 to June 2012), 17 cases of PTC were diagnosed on histopathology. After prior consent of the patient, FNA was performed with aseptic precautions by using a 10 cm<sup>3</sup> syringe and 23-24 gauge needle. Smears were air dried and stained with

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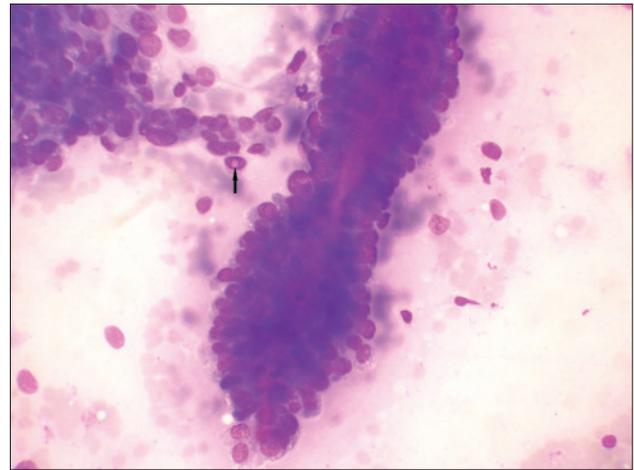
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Leishman's stain. Cytology diagnosis in these cases was given as PTC ( $n = 10$ ), S/O PTC ( $n = 4$ ), R/O PTC ( $n = 1$ ), and multinodular goiter (MNG). ( $n = 2$ ) Ages of cases ranged from 20 to 65 years with maximum number of cases ( $n = 15$ ) in the age group of 20-40 years. Male to female ratio was 1: 4.7 [Table 1]. Clinically, 14 cases presented with solitary thyroid nodules (SN), two with multinodular goiter and one with thyroglossal duct cyst (TDC). Out of 17 cases, six had enlarged cervical lymph nodes. Imaging findings were available in ten cases at the time of FNA and revealed SN in seven cases, MNG in two cases, and TDC in one case. Thyroid function was normal in all cases. Cytology features of all 17 cases were reviewed and compared in respect to the frequency of six features of PTC-papillary formations, nuclear grooves (NG), intranuclear cytoplasmic inclusions (INCI), fine nuclear chromatin (FNC), psammoma bodies (PB), and cellular swirls. Other cytological features as mentioned in many original reports and cytology textbooks were also reviewed. Further, NG was semiquantitatively assessed under three divisions; many/frequent throughout the smear, frequent in occasional groups of cells, and occasional throughout the smear. INCI were assessed as many, few, rare, and absent.

## RESULTS

Table 1 shows detailed age, sex, FNA diagnosis, and cytology features in 17 PTC cases diagnosed on histology. There was no significant difference in sex distribution and clinical presentation. PTC diagnosed within MNG ( $n = 2$ ) had higher age of 65 years and 48 years as compared to solitary PTC nodules ( $n = 14$ ) in which ages ranged from 20 to 40 years. Cytology features were analyzed. The number and frequency of papillary formations [Figure 1],

NG [Figure 2], INCI [inset Figure 2], and FNC in PTC cases were higher as compared to S/O PTC and R/O PTC cases [Table 1]. PB and cellular swirls were present only in one case each. Viscous, stringy (Bubble gum) colloid was present in four cases of PTC. Thin colloid was present in two cases of MNG and PTC each and one case of S/O PTC. Multinucleated giant cells (MGC) were present in four cases of PTC, one case of S/O PTC, and two cases of MNG. MGC in MNG were smaller, ovoid having pale/foamy cytoplasm and few nuclei [Figure 3, thin arrow]. In contrast, MGC in PTC cases were of two types: 1 MNG like MGC and 2 larger MGC of diverse shape, more nuclei, and dense cytoplasm [Figure 3, thick arrow]. Cyst macrophages were seen in total eight cases out of which five PTC, and one S/O PTC cases showed clustering [Figure 4]. Microfollicles were seen in two PTC and one MNG cases. Vacuoles in cytoplasm and cells

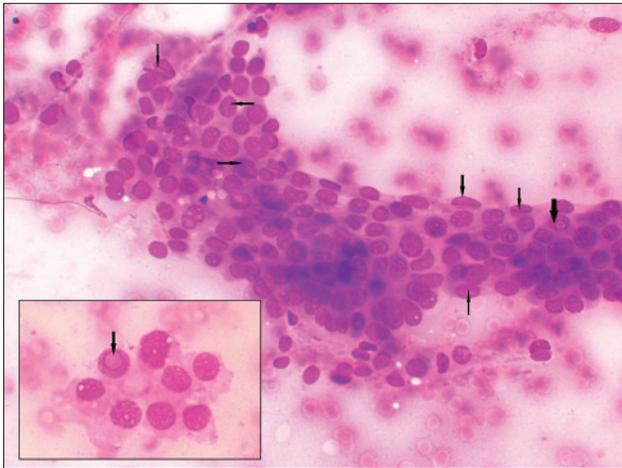


**Figure 1:** Fine needle aspiration smear showing papilla and intranuclear cytoplasmic inclusions (arrow; Leishman's stain,  $\times 400$ )

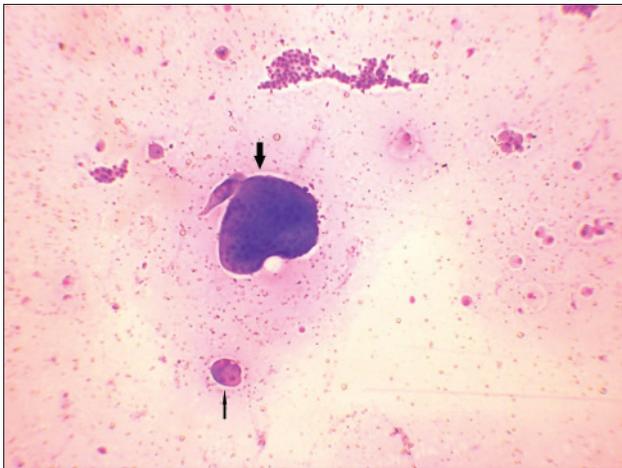
**Table 1: Age, sex, FNA diagnosis and cytology features of 17 PTC cases**

Age/sex	FNA diagnosis	FNA cytology features, (+) present and (-) absent							
		Papillae	INCL	NG	FNC	CM/CMC	MGC	Cellular swirls	PB
35/F	PTC	+	Many	-	-	-/-	-	-	-
29/F	PTC	+	Many	-	-	+/+	+	-	-
30/F	S/O PTC	-	Few	FOG	-	-/-	-	-	-
20/F	S/O PTC	+	-	FOG	-	-/-	-	-	-
40/F	PTC	-	Many	OTS	+	-/-	-	-	-
38/F	PTC	+	Few	-	-	-/-	+	-	-
32/F	PTC	+	Many	-	+	-/-	-	-	+
65/F	MNG	-	Rare	-	-	+/-	+	-	-
23/F	TDC and R/O PTC	-	Rare	OTS	-	-/-	-	-	-
48/F	MNG	+	-	OTS	-	+/-	+	-	-
26/F	PTC	-	Few	FOG	+	+/+	+	-	-
38/M	PTC	+	-	OTS	-	+/+	-	+	-
39/M	S/O PTC	-	Few	Many	-	+/+	+	-	-
34/F	PTC	+	Many	-	+	+/+	+	-	-
38/F	S/O PTC	-	Few	Many	-	-/-	-	-	-
28/F	PTC	+	Many	FOG	-	+/+	-	-	-
32/M	PTC	-	Many	FOG	-	-/-	-	-	-

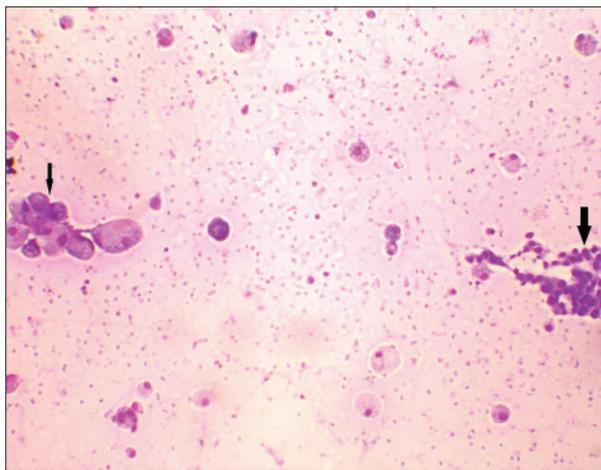
FNA: Fine needle aspiration, INCI: Intranuclear cytoplasm inclusion, NG: Nuclear grooves, FNC: Fine nuclear chromatin, CM: Cyst macrophages, CMC: Cyst macrophages clusters, MGC: Multinucleated giant cells, PB: Psammoma bodies, TDS: Thyroglossal duct cyst, PTC: Papillary thyroid carcinoma, FOG: Frequent in occasional groups, OTS: Occasional throughout smear, F: Female, M: Male, MNG: Multinodular goiter



**Figure 2:** FNA smear showing many nuclear grooves (NG) (thin arrow), thick arrow and inset showing INCI (Leishman's stain, ×400)



**Figure 3:** FNA smear showing small multinucleated giant cells (MGC) (thin arrow) and large MGC with many nuclei, dense cytoplasm (thick arrow) (Leishman' stain, ×400)



**Figure 4:** FNA smear showing cyst macrophage cluster (thin arrow) in vicinity of follicular sheets (thick arrow) (Leishman stain, ×400)

with metaplastic cytoplasm were present in one case of PTC each.

## DISCUSSION

PTC resembles a type of cancer with favorable prognosis.<sup>[19]</sup> Some of them even regress spontaneously to the level of micro carcinoma.<sup>[20]</sup> But distant metastasis is well known. Thus an early diagnosis and treatment is desirable. Number of cytology features for diagnosis of PTC varies in different studies. Kini *et al.*,<sup>[9]</sup> described six parameters for PTC: Papillary tissue fragments, monolayer sheets of follicular cells, INCI, NG, tissue fragments with or without a follicular pattern, and large multinucleated foreign body-type of giant cells in the absence of degenerative changes. According to Wu *et al.*,<sup>[21]</sup> the most commonly cited cytology criteria for PTC were flat syncytial sheets, nuclear enlargement, fine chromatin, NG, INCI, and some amount of colloid. Castro-Gomez *et al.*,<sup>[22]</sup> described 15 cytology features of PTC in FNA smears of thyroid: Tridimensional fragments, papillae, anisonucleosis, nuclear bars (grooves), INCI, powdery chromatin, vacuolated cytoplasm, metaplastic cytoplasm, PB, autolysis, multinucleated giant cells, spindle cells, colloid, monolayer lamina, and macrophages. Kumar *et al.*,<sup>[16]</sup> suggested cellular swirls in cytology smears are highly specific for PTC. Despite these well-defined cytology features, diagnostic difficulties do exist in FNA smears while making decision in respect to PTC cases. This can be appreciated from the number of cytology diagnosis offered in 17 PTC cases which were diagnosed on histology. FNA diagnosis of PTC ( $n = 10$ ), S/O PTC ( $n = 4$ ), R/O PTC ( $n = 1$ ), and MNG ( $n = 2$ ) were given.

In our study, we observed higher age group in PTC cases diagnosed within MNG. Das *et al.*,<sup>[18]</sup> and Cheng *et al.*,<sup>[23]</sup> observed similar findings in their studies. The number and frequency of four cytological features viz., papillary formation, INCI, NG, and FNC were significantly higher in PTC cases as compared to S/O PTC and R/O PTC cases [Table 1]. Lesser number of NG in our cases can be attributed to the following reasons: NG are usually identified in isolated cells and in monolayer clusters and are difficult to recognize in tissue fragments because of nuclear overlap. Although NG are more constant than INCI,<sup>[9,24]</sup> they have been reported with much less frequency. They have been also been reported in follicular adenoma/carcinoma, nodular goiter, Hashimoto's thyroiditis, medullary carcinoma, and metastatic tumors.<sup>[25,26]</sup> FNC was seen in only four PTC cases. Reason can be Leishman staining of cytology smears in our study. FNC are best seen in papanicolaou preparation.<sup>[27]</sup> PB is almost diagnostic of PTC, but are seen only in 11-35% of PTC cases in FNA.<sup>[28]</sup> In our study, PB was seen in only one PTC case. One PTC case showed cellular swirls. These are concentrically arranged follicular cells with peripheral neoplastic cells having their axis perpendicular to the radius of swirl and were described first by Szoporn. Kumar *et al.*,<sup>[16]</sup> found cellular

swirls as novel findings and when present in cytological smears, are highly specific for PTC. Out of two cases of PTC which were misdiagnosed as MNG in FNA smears, one case showed papillary formations and occasional NG throughout the smear and rare INCI in one case. Abundant thin colloid was seen in both the cases. No other definitive cytology features of PTC were seen in these cases. Both the patients subsequently underwent subtotal thyroidectomy for pressure symptoms. Histopathological examination in both cases showed PTC with MNG. Multicentric papillary hyperplasia is known in MNG. INCI and NG can be found in variety of lesions such as medullary thyroid carcinoma, follicular adenoma, hyalinizing trabecular adenoma, and colloid goiter.<sup>[25,26,29]</sup> Thus, due to lack of adequate numbers of cytology features of PTC in FNA, diagnosis of MNG was offered in both cases. Some authors believe that more than three INCI in enlarged nuclei on a single aspirate is pathognomic of PTC.<sup>[30]</sup> Some even believe INCI are such characteristics that even if they are seen in an aspirate with no other features of PTC, surgical excision should be considered.<sup>[31]</sup> One case of TDC in which cytodiagnosis of R/O PTC was given, showed suboptimal smears. Occasional thyroid follicular cells show NG and INCI which prompted us to give the diagnosis of R/O PTC. The case was operated by Sistrunk procedure and subsequently confirmed the diagnosis of PTC arising in TDC on histology. Incidence of malignancy in TDC is less than 1%.<sup>[32]</sup>

Amongst other cytological features, we observed cyst macrophages in eight cases out of which 6 cases showed clustering of cyst macrophages (PTC = 5 and S/O PTC = 1). In a study conducted by Hamburger *et al.*,<sup>[33]</sup> they observed up to 25% of the papillary carcinomas showed cystic change and/or hemorrhage. Cusick *et al.*,<sup>[34]</sup> observed 23% of malignant neoplasms as cystic. Some authors suggest tumor size more than 3 cm and fluid rich cyst macrophages forming clusters in FNA smears, tumor must be suspected.<sup>[1]</sup> Traditionally, multinucleate vacuolated or pigment laden histiocytes have been considered of little diagnostic value.<sup>[35]</sup> Tsou *et al.*,<sup>[6]</sup> studied 100 cases each of PTC and benign nodular goiter. They observed most MGC in benign nodular goiter tended to be smaller, ovoid, and have foamy cytoplasm and few nuclei. In contrast MGC in PTC cases were more diverse in terms of size, shape, cytoplasm, and number of nuclei. They are larger, ovoid/irregular, and have many nuclei with dense cytoplasm. However, similar MGC can be seen in chronic thyroiditis. They concluded large MGC with dense cytoplasm and many nuclei together with other pertinent information in FNA of thyroid nodule should prompt a careful appraisal for associative PTC. Similar findings were observed in our study. Inadequacy or suboptimal sample due to cystic change and microscopic/occult PTC alone cannot be blamed for diagnostic pitfalls in PTC. It may be very difficult to sample the small lesion

without imaging guidance and even with ultrasound guidance, adequate neoplastic cells may not be aspirated resulting in false negative cytodiagnosis. Even when the FNA sample is adequate, none of the features described for PTC in various literatures are pathognomic and may be seen in other benign and malignant conditions.

## CONCLUSION

We conclude papillary formations, INCI, NG, and FNC are important features on FNA smears in diagnosis of PTC. Though nuclear changes and other cytological features are neither constant nor specific, they should be reported in proper context. Cyst macrophages forming clusters in thyroid aspirate, tumor must be suspected. Presence of large multinucleated giant cells with abundant cytoplasm and many nuclei in FNA of thyroid nodule along with other pertinent information should prompt a careful appraisal for associated PTC. A cautious approach is to be adopted in PTC and even slight suspicion should be mentioned which allows the endocrine specialists to determine the treatment and urgency of histological verification.

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