

PARATHYROID CYTOLOGY: A DIAGNOSTIC DILEMMA*Naval Kishore Bajaj¹, Shrinivas Somalwar², Akhtar Mohammad³, Ezhil Arasi Nagamuthu⁴*¹Associate Professor, Department of Pathology, Osmania Medical College, Hyderabad.²Assistant Professor, Department of Pathology, Osmania Medical College, Hyderabad.³Junior Resident, Department of Pathology, Osmania Medical College, Hyderabad.⁴Professor & HOD, Department of Pathology, Osmania Medical College, Hyderabad.**ABSTRACT****INTRODUCTION**

Neck nodules are common in clinical practice which are accessible to Fine needle aspiration cytology (FNAC). Thyroid being the commonest organ to present as the nodular lesions. Parathyroid lesions can be incidentally encountered during FNA of a thyroid nodule. Fine needle aspiration cytology is a safe economical and leading investigation in the diagnosis of neck nodules. Thyroid and parathyroid nodules are indistinguishable clinically. An attempt is made to familiarise the pathologist about the cytomorphological features of parathyroid nodules and simple approach to differentiate from thyroid nodules.

MATERIALS AND METHODS

It is a retrospective study conducted over a period of 5 years from 2011-2016. Twelve cases of histologically proven parathyroidal lesions are the subjects of study of which 4 cases were diagnosed as parathyroidal cyst and rest as parathyroid adenoma. All the cases underwent fine needle aspiration cytology under ultrasound guidance, smears were made, stained by H & E and PAP staining method, the slides were reviewed by two cytopathologists. Biochemical and radiological findings were evaluated before giving definitive cytological diagnosis.

RESULTS

A total number of 12 cases which were histologically proven as parathyroidal lesion. Out of which 4 were cystic lesions which were excluded from the study. Rest of the 8 cases confirmed as parathyroid adenoma which had FNAC were evaluated. 5 cases had positive cytohistological correlation. Three out of 8 cases were diagnosed as papillary carcinoma of thyroid, Toxic nodular goitre and Hurthle cell neoplasm due to varied cytomorphology.

CONCLUSION

Parathyroidal lesions has got low sensitivity and specificity in cytology. The confident diagnosis of parathyroid neoplasm was made in conjunction with biochemical and advanced radiological imaging. In neck nodules which are asymptomatic and at abnormal locations, FNAC through its cytomorphological features has an edge in diagnosis.

KEYWORDS

Parathyroid, Thyroid, FNAC.

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INTRODUCTION: Neck nodules are common in clinical practice which are accessible to Fine needle aspiration cytology (FNAC). Thyroid being the commonest organ to present as the nodular lesions. Parathyroid lesions can be incidentally encountered during FNA of a thyroid nodule.^[1] Superior and inferior parathyroid glands embryologically develop from IV and III pharyngeal pouches respectively.^[2] It is difficult to distinguish thyroid nodules from parathyroid nodules clinically especially if it is intrathyroidal/subcapsular location.^[3] Due to advancement in imaging technologies, localisation of parathyroid glands and their enlargement can

be assessed by various radiological techniques using TC99 Sestamibi Scintigraphy and Single Photon Emission Computed Tomography (SPECT) and can be detected elsewhere at abnormal location in the retrosternal, mediastinum.^[4] However, it still poses a diagnostic difficulty as sensitivity is up to 90%^[5] which can be solved by using fine needle aspiration. The lesions associated with parathyroid glands are parathyroid adenoma, hyperplasia and carcinoma responsible for primary hyperparathyroidism.^[6] However, functional parathyroid lesions are not common.^[7] The cytomorphological features of parathyroid gland overlap with that of thyroid lesions hence ancillary techniques using immunocytochemistry along with clinical, radiological and biochemical correlation is necessary. However, there are certain cytological features which makes it possible to differentiate parathyroid from thyroid lesions. The purpose of the study is to understand and make cytopathologist familiarise with the cytomorphological features of Parathyroid and its distinction

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from thyroidal lesions to avoid misdiagnosis and unnecessary major surgery to the patient. Only histologically proven cases of parathyroid lesions which underwent FNAC are the subjects of study.

MATERIALS AND METHODS: It is a retrospective study conducted over a period of 5 years from 2011-2016. Twelve cases of histologically proven parathyroidal lesions are the subjects of study of which 4 cases were diagnosed as parathyroidal cyst and rest as parathyroid adenoma. All the cases underwent fine needle aspiration cytology, smears were made, stained by H & E and PAP staining method, the slides were reviewed by two cytopathologists. PTH levels were evaluated before giving cytological opinion. In cases of cystic lesions of Parathyroid, aspirated fluid was subjected to cellblock for further evaluation which often give better results. A detailed cytomorphological evaluation was done keeping thyroid and parathyroidal lesions in mind. The architectural pattern, nuclear and cytoplasmic features with the background material were assessed. That includes cellularity, dispersion of cells singly, loose aggregates, tight clusters, papillaroid formation, bare nuclei, follicular pattern, presence of vascular proliferation, anisocytosis, anisonucleosis, intranuclear cytoplasmic pseudo inclusions, nuclei with stippled chromatin, Oncocytic change, mitotic figures, cytoplasmic granularity and vacuolations, plasmacytoid appearance, lymphocytes, macrophages, background colloid like substance. Biochemical and ultrasound findings were also considered which includes

serum calcium, Parathyroid hormone (PTH), alkaline phosphatase and Vitamin D.

Estimation of preoperative and postoperative PTH along with serum calcium levels was done to assess the efficacy of the surgical treatment.

RESULTS: A total number of 12 cases were studied out of which four cases were diagnosed as parathyroid cyst, remaining 8 cases as parathyroid adenomas on cytology. Most of them were females, 08/12 patients. Age ranged from 14 yrs. to 60 years. Out of 12, 10 cases were presented as neck nodules and two cases as mediastinal lesion. All cases had aspiration cytology under ultrasound guidance. Most of the cases had clinical suspicion and few had incidental diagnosis. 8 out of 12 cases had PTH levels done before FNAC with clinical suspicion. Three were in normal range and rest of the 5 cases had raised PTH levels, all proven as Parathyroid adenoma. Serum calcium levels were raised in 2/8 cases. Thyroid aspirates in general shows monolayered sheets, clusters of follicular cells in acinar pattern, scattered and bare nuclei and colloid in the background. In our series, cytological features of 8 cases which were proven histologically as parathyroid adenoma were studied in detail show cells in tight clusters, acinar pattern, papillaroid pattern and dispersed cell and bare nuclei. 3 out of 8 cases which were subjected to FNAC were misdiagnosed each as papillary carcinoma of Thyroid, toxic nodular goitre and follicular neoplasm.

Case No.	Age in Years	Sex	History	Cytological diagnosis	Histopathological diagnosis
1.	56	F	Nodule in Neck (raised PTH)?Parathyroid	Parathyroid neoplasm	Parathyroid adenoma
2.	38	M	Suspicious of papillary carcinoma of thyroid.	Papillary carcinoma	Parathyroid adenoma
3.	43	F	Known case of Hashimoto's thyroiditis, Thyroxine intake+	Toxic nodular goitre	Parathyroid adenoma
4.	60	M	Left palpable Thyroid nodule of 2x2 cm, PTH normal.	Parathyroid neoplasm	Atypical adenoma
5.	49	F	Palpable right thyroid nodule. PTH normal	Follicular neoplasm-Hurthle cell variant	Parathyroid adenoma
6.	42	F	? Parathyroid nodule on ultrasound	Parathyroid neoplasm	Parathyroid adenoma
7.	14	F	Genu valgum, Raised PTH, incidental finding of neck nodule.	Parathyroid neoplasm	Parathyroid adenoma
8.	50	F	Thyroid nodule, Marginally raised PTH.	Parathyroid neoplasm	Parathyroid adenoma

Table 1: Showing age, sex, and clinical history with Cytological and Histological Diagnosis in total 8 Cases

In the present study, we came across a unique case of a 14-year-old female child, presented with genu valgum with clinical suspicion of primary hyperparathyroidism. Biochemical investigations revealed Serum calcium 11.8 mg/dL (Normal value 8.0-10.8 mg/dL), Serum Phosphorous 4.5 mg/dL (Normal value: 2.5-4.8 mg/dL), Serum alkaline

Phosphatase 1272 U/L (Normal value: 35-129 U/L), Serum Parathyroid hormone 1943 pg/mL (Normal value: 15-65 pg/mL), 25 hydroxyl Vitamin D 13.4 ng/mL (Normal value: 30-80 ng/mL). Ultrasonography revealed hypoechoic nodule measuring 2.2x1.9 cm at inferior pole of right lobe of thyroid suspected to be Right thyroid adenoma and the same

considered in CT scan. Tumour Scintigraphy with Tc99m MIBI scan showed increased uptake in the right lobe of thyroid found to be Parathyroid adenoma. FNAC done which revealed clusters of follicular cells in acinar pattern with mild anisonucleosis, nuclei smaller in size, stippled chromatin, and few clusters showed salt and pepper chromatin, moderate eosinophilic cytoplasm with occasional vacuolated cytoplasm. Background showed many bare nuclei and blood elements with absence of colloid. Negative immune expression of TTF1 ruled out thyroid follicular cells (Figure

1). Postoperative serum PTH, calcium and Vitamin D levels were in normal state. In correlation with biochemical, radiological and cytological findings, parathyroid adenoma was considered which was confirmed with Intraoperative squash cytology and Histopathological examination. Chief cell adenoma was the final diagnosis. To the best of our knowledge, parathyroid adenoma in a child presenting as genu valgum is very rare and only 11 cases reported worldwide till now.

Cytological features	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Architectural features								
Monolayered sheet	+	-	+	+	-	+	-	+
Follicular pattern	+	+	-	+	+	-	-	+
Papillaroid pattern with vascular core	+	+	-	-	-	+	+	+
Loose clusters	+	-	+	+	+	-	+	-
Tight clusters	-	+	+	-	+	-	+	+
Dispersed cells	+	-	+	+	+	-	-	+
Nuclear features								
Anisonucleosis	+	+	+	++	-	-	+	+
Salt and pepper chromatin	-	+	-	+	-	+	-	-
Stippled chromatin	+	+	+	+	+	+	+	+
Eccentric nuclei	-	-	+	+	-	-	+	+
Prominent nucleoli	-	-	+	+	-	-	-	-
Intranuclear pseudo inclusions	-	++	-	-	-	+	-	-
Nuclear grooving	-	+	-	-	-	+	-	-
Mitotic figures	-	-	-	+	-	-	-	-
Cytoplasmic features								
Granularity	+	-	+	-	++	-	+	-
Vacuolations	++	++	++	++	-	++	++	+
Background								
Colloid like material	-	+	-	-	+	+	-	-
Colloid	-	-	-	-	+	-	+	+
Lymphocytes	+	-	+	+	+	-	-	-
Macrophages	-	-	+	-	+	-	+	-
Bare nuclei	+	+	+	-	+	+	+	+

Table 2: Showing various Cytomorphological Features of 8 cases of Parathyroid Adenomas

DISCUSSION: Thyroid and Parathyroid lesions presenting as neck nodule are clinically indistinguishable. It is important to distinguish parathyroid lesions from thyroid lesions by FNAC for the management and quality of life of the patients. Biochemical, radiological as well as clinical correlation with cytomorphology increases the accuracy of diagnosis.^[8] FNAC in parathyroid has got utility when they occur as cystic lesion and as an incidentaloma without any symptoms at an abnormal location. Ultrasound and Scintigraphy with TC99 along with clinical evidence of hyperparathyroidism are useful in localising the parathyroid lesion. So that minimal invasive surgery can be performed whereas thyroidal lesions require extensive resection.^[9]

Parathyroid lesions in FNAC most often confused with adenomatous thyroid nodules,^[10] Hurthle cell adenomas,^[11] lymphocytic thyroiditis and sometimes with papillary^[12] and

follicular neoplasms.^[10,12,13] Presence of tissue fragments with papillary architecture, epithelial cells in micro follicular pattern, colloid like material in the background, oxyphilic cells resembling Hurthle cells are the most commonly encountered cytomorphological overlapping features often confusing between thyroid and parathyroid lesions.

A clear cut distinguishing features were not mentioned anywhere to differentiate parathyroid from thyroid lesions. Presence of one or more cytological features were recorded in individual cases. Parathyroid lesions do not have a distinct diagnostic criterion, but rather a combination of cytomorphological features should be considered.^[12] An attempt is made to explain the cytomorphological features of parathyroid by studying various cases and comparing with the literatures.

In the present study, the most consistent features in most of the parathyroidal lesions were Papillaroid fragments with fibro vascular core (5/8 cases), micro follicular pattern and mono layered sheets (5/8 cases), intracytoplasmic multiple vacuolations (7/8 cases) as well as granularity (4/8 cases), nuclei were smaller when compared to thyroid follicular cells, many bare nuclei (7/8 cases) with stippled chromatin were noticed. Rest of the findings were presence of dispersed cells, clusters, plasmacytoid and cells resembling Hurthle cells were observed. (Figure 2 and 3). In one of our cases, intranuclear cytoplasmic pseudo inclusions and papillaroid pattern with occasional colloid like material mislead us for papillary carcinoma of Thyroid. So intranuclear inclusions are not specific to papillary carcinoma of Thyroid but can be seen in parathyroid lesions, medullary carcinoma of thyroid, etc.^[6] Hurthle cell neoplasm was one of the misdiagnosis in one of our case in which sheets of follicular cells with dense eosinophilic cytoplasm and mild anisonucleosis mimicking Hurthle cells were misinterpreted. Plasmacytoid and oval cells in smears sometimes can be misinterpreted as medullary carcinoma of thyroid as both will have stippled chromatin nuclei;^[14] however, Calcitonin immunocytochemistry was done to rule out medullary carcinoma of thyroid which found to be negative in one of our case study. Follicular cells in acinar pattern with intracytoplasmic vacuolations in a background of thin colloid, with raised T3, T4 and equivocal TSH was another pitfall in one of our cases labelled as toxic nodule in cytology. Parathyroidal cells usually demonstrate uniform smaller nuclei with hyper chromatic nuclei as opposed to granular

chromatin with fine nucleoli in thyroid cells. All the 3 cases mentioned above had normal PTH levels. A confident cytological diagnosis of parathyroid lesion was made, when biochemical and radiological evidence in favour of Parathyroid was considered. Cytological smears can show colloid substance which is obtained while doing aspiration from parathyroidal lesion which should not mislead the diagnosis. In our study, we observed cells with moderate anisonucleosis with indistinct nucleoli was turned out to be atypical parathyroid adenoma on histology. In cases with clinical suspicion of parathyroid carcinoma, FNAC should be avoided as needle tract seeding of carcinoma can occur as reported by Tseng et al^[15] and Kumari N et al.^[10]

However with the past experience of discordant cases 3 out of 6 cases, recently 2 cases of parathyroidal lesions back to back were reported with positive histological correlation. Getting ourselves familiarized with the parathyroid cytology an insight for learning parathyroid lesions.

CONCLUSION: Parathyroidal lesions has got low sensitivity and specificity in cytology. The distinction between parathyroid hyperplasia, adenoma and carcinoma are difficult on cytology and were designated as parathyroidal lesions. The confident diagnosis of parathyroid neoplasm were made in conjunction with biochemical and advanced radiological imaging. Neck nodules which are asymptomatic and at abnormal locations, FNAC through its cytomorphological features has an edge in diagnosis.

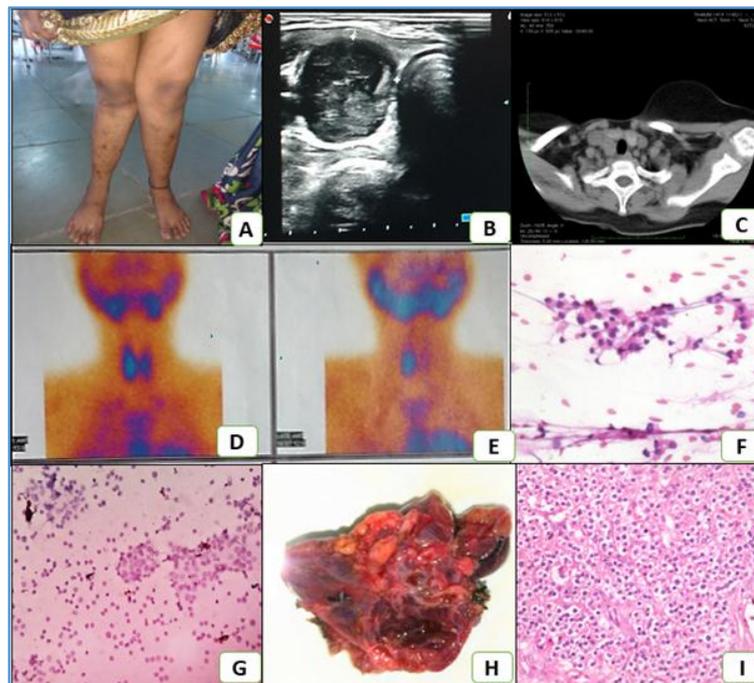


Figure 1A, B, C, D, E, F, G, H & I

Figure 1: **A** shows Genu valgum, **B** showing hypo echoic intrathyroidal mass measuring 2.2×1.9 cm ultrasonographically. **C** CT scan showing hyperechoic mass within the lower pole of right lobe of thyroid. **D** and **E** showing Tc99M scintigraphy early and delayed scan showing retention of tracer in the right thyroid confirming intrathyroidal parathyroid lesion. **F** showing clusters of follicular cells with intracytoplasmic vacuolations, smaller nuclei. **G** showing TTF1 negative immune expression. **H** showing tan grey brown nodular lesion along with adjacent thyroid tissue. **I** represents histopathological section of Parathyroid adenoma.

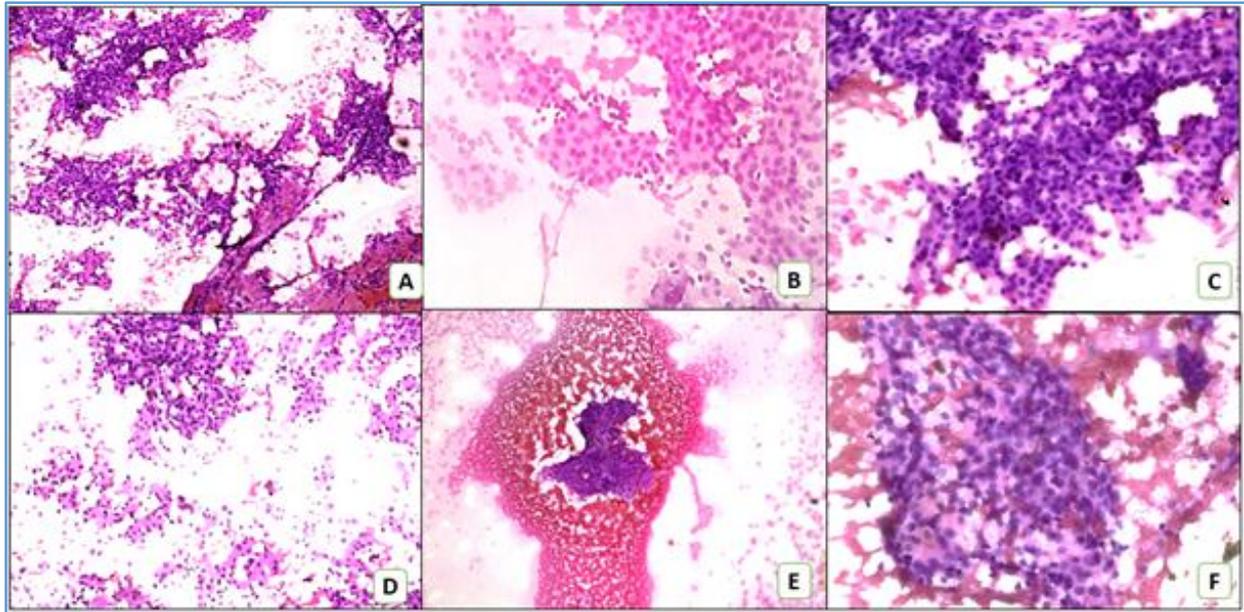


Figure 2A, B, C, D, E & F

Figure 2: **A** showing papillary fragments with fibrovascular core, **B** showing cells in follicular pattern **C** showing sheets of cells 3 three dimensional pattern, **D** showing microfollicles with smaller hyper chromatic nuclei, **E** showing tight clusters and **F** showing characteristic intracytoplasmic vacuolations.

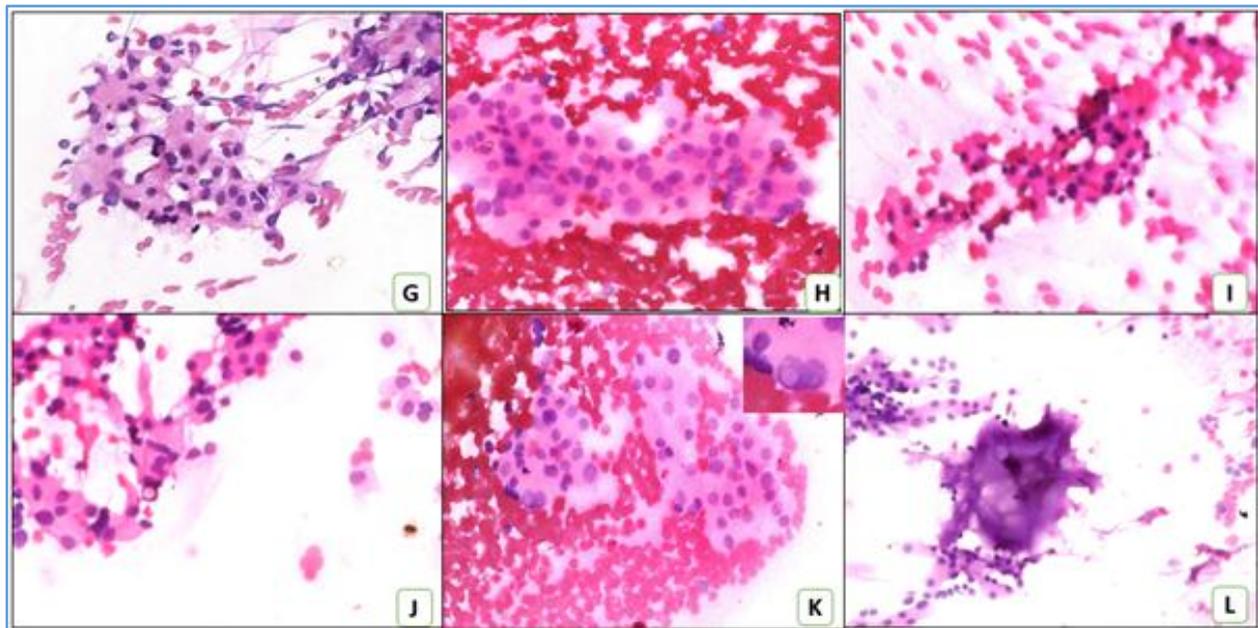


Figure 2G, H, I, J, K, L

Figure 3: **G** shows intracytoplasmic vacuolations and granular cells. **H** showing anisonucleosis, **I** showing clusters of cells with abundant granular eosinophilic cytoplasm resembling Hurthle cells, **J** showing large polygonal cells with abundant cytoplasm with plasmacytoid appearance, **K** showing intracytoplasmic pseudo inclusions, **L** showing thick colloid.

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