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PITFALLS OF PITNETs – A THREE YEAR STUDY

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ABSTRACT **Introduction:** Anterior lobe is the origin for pituitary neuroendocrine tumors (pitNETs). Radiologically and clinically pitNETs are mimicked by germinoma, craniopharyngiomas and pituicytoma. Histopathology is the gold standard for definitive diagnosis of pitNET. **Material and methods:** A retrospective observational study was conducted over three years at a tertiary health care center. Patient demographic, clinic-radiologic and microscopic details were retrieved from histopathology records. **Results:** Total 26 cases of microscopically proven pitNET were found during January 2020 to February 2023. There was female preponderance (17, 65%). Mean age was 41 years (range 25 - 61). Mean duration of symptoms was 14.5 months. Commonest non-hormonal and hormonal symptom was reduced vision (n 24, 92%) and amenorrhea (n 5, 19%) respectively. On imaging the mean tumor size was 33 mm. The commonest pattern on histopathology was papillary (61.5%). 8/26 cases showed nuclear pleomorphism. Commonest Ki67 index was 3-9 % (46%). **Conclusion:** Newer insights highlight the assessment of invasive status and histological subtypes to identify aggressive pitNETs. Clinical follow up and immunohistochemistry using lineage-specific hormonal and transcription factors are essential for global evaluation of pitNETs.

KEYWORDS : pitNET, Histopathology, Hormones, Pituitary Adenoma, Ki67

INTRODUCTION:

Adenomas of anterior pituitary origin are now termed as Pituitary Neuroendocrine tumors (PitNETs) as per CNS WHO 2022 &WHO Endo 5th edition. Radiologically and clinically germinoma, craniopharyngiomas and pituicytoma can mimic PitNETs. Histopathology is the gold standard for definitive diagnosis. PitNETs do not have WHO grading or staging system unlike other neuroendocrine tumors. Subtyping PitNETs depends upon hormone specific IHC markers & Transcription factors (PIT1, TPIT, SF1). [1,2]

OBJECTIVES:

To study clinico-radiological and histomorphological spectrum of PitNETs and evaluate correlation between Ki67, nuclear pleomorphism, tumor size, and tumor invasion.

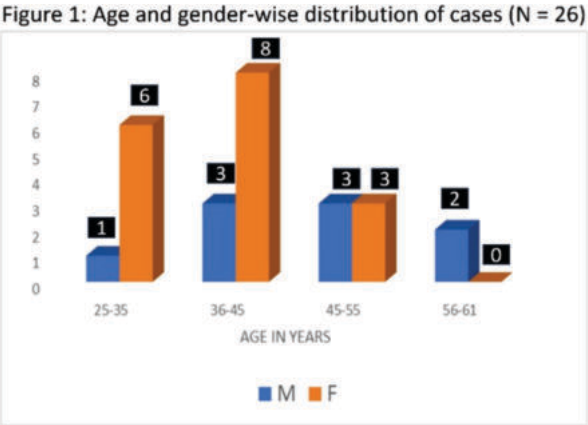
MATERIALS AND METHODS:

A retrospective observational study was conducted from January 2020 to February 2023 at the surgical histopathology section of tertiary health care center. Surgically proven cases of PitNETs were included, while non-PitNET and autopsy pituitary lesions were excluded. Patient demographic, clinico-radiologic and microscopic details were retrieved from histopathology archives. Cases were stained with Hematoxylin & Eosin stain. Whenever available or relevant, special stains and Ki67 were done.

RESULTS:

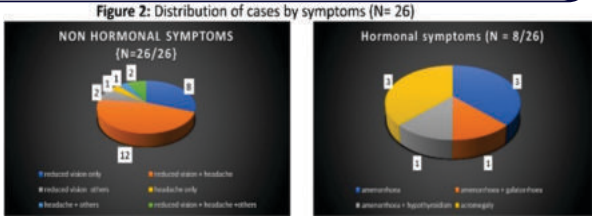
Thirty-three cases of pituitary lesions were received while seven cases of craniopharyngioma were excluded. The final study sample was 26 cases.

Figure 1: Age and gender-wise distribution of cases (N = 26)



Female preponderance below 45 yrs (17, 65%) and male predominance above 55 yrs was noted. Majority cases were in 36-45 age group (11, 42%). Mean age was 41 years, range 25 – 61 **(Figure 1).**

Figure 2: Distribution of cases by symptoms (N= 26)



Mean duration of symptoms was 14.5 months (range 7 days - 96 months). Commonest non-hormonal and hormonal symptom was reduced vision (n 24, 92%) and amenorrhea (n 5, 19%) respectively. Sixteen cases had raised prolactin levels, manifesting as amenorrhoaea (06) and asymptomatic (10). Three cases with raised growth hormone showed acromegaly. **(Figure 2)**

On Magnetic Resonance Imaging (MRI), the mean tumor size was 33.16 mm (14 - 65 mm). Majority were non-invasive (n 15,58%) and macroadenoma (21,80.8%).

On microscopy, papillary pattern was commonest (17, 65%) followed by nesting and tubulo-acinar patterns. Papillary admixed with nesting pattern was commonest combination (n 6, 38%). Cytoplasmic hue was amphophilic (n12,46%), eosinophilic (n12, 46%) and chromophobic (n2, 8%). Nuclear pleomorphism seen in 8/26 cases (30.8%). **(Figure 3)**

Figure 3: Microscopic features of PitNETs

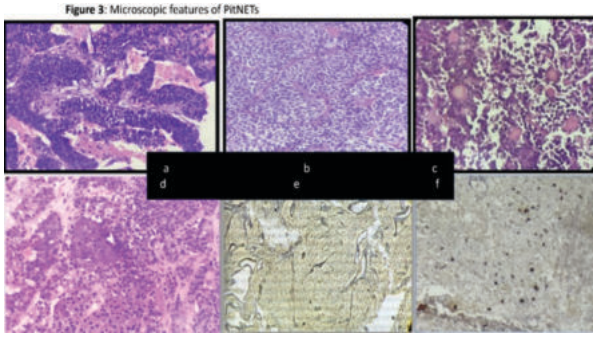


Figure 3: papillary, nesting and tubule-acinar patterns (a-c), nuclear pleomorphism (d), lost Reticulin framework (e), Ki67 nuclear immunohistochemistry (f)

Over 36 months of follow up, 24 cases had no recurrence. Two cases showed relapse [persistent acromegaly & >20 % tumor remnant on post-operative MRI]. Both cases are currently undergoing octreotide therapy.

Rathke's cleft cyst, apoplexy and xanthogranulomatous changes were seen in 4, 5 and 2 cases respectively (**Figure 4).**

Figure 4: Rathke's cleft cyst, apoplexy and xanthogranulomatous change in PiitNET

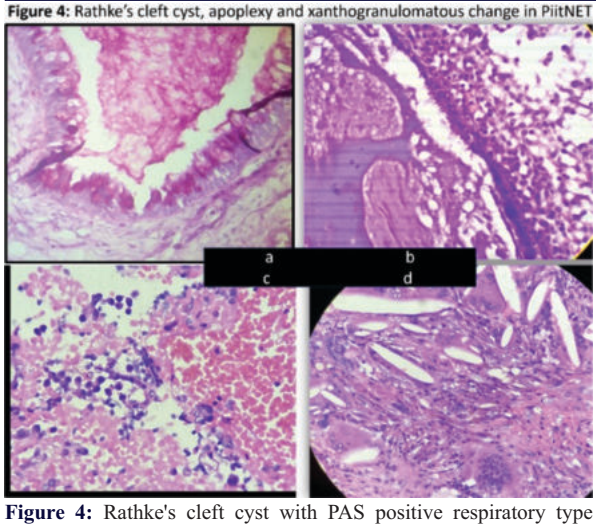


Figure 4: Rathke's cleft cyst with PAS positive respiratory type epithelium and Alcian blue mucinous contents (a-b), apoplexy (c), cholesterol clefts with foreign body giant cells (d).

DISCUSSION:

Commonest age group ranges between 36-45 years. Gender distribution matches our findings. Most adenoma in adults are prolactin secreting while ACTH and prolactin secreting in children. [3,4] Our study also had raised prolactin levels in 16/26 cases. Prolactin adenomas in males carry higher recurrence risk than females[3]

Clinical: Functional PitNETs usually present with acromegaly (somatotropin), amenorrhea-galactorrhea (prolactin) and Cushing's (ACTH)[3,4]. Gonadotroph adenoma (FSH-LH) are usually non-functional. [2, 3] Non-secretory PitNETs can manifest galactorrhea or Cushing's due to pressure 'stalk effect'. Post-operative persistence of symptoms may herald relapse of tumor or presence of multiple PitNETs[3,4,5]

Histology: Usually eosinophilic cells correspond to somatotropin, prolactin or TSH secretion, basophilic cells to ACTH, while chromophobic cells to null cell adenoma with LH-FSH secretion. In our study, raised prolactin levels were associated with eosinophilic or amphophilic cells, while raised GH with clear or amphophilic cells. Thus, cytoplasmic tinge did not correspond to hormonal symptoms. Hormone-specific immunohistochemistry (IHC)is essential to subtype PitNETs.

Prognostic: No grading or staging system exists for PitNETs. Terminology pituitary carcinoma is now replaced by Metastatic PitNETs. Asioli S et al [3] and Trouillas J et al [4] reported that tumor invasion, Ki 67 index >3% and histological type (PRL, Crooke's, FSH-LH and sparsely granulated GH) are independent predictors for worse prognosis and recurrence. Our study found relapse in 2/26 cases, both with raised GH levels. We did not have any case of metastatic PitNET.

Table 1: Correlation between tumor size, tumor invasion & Ki67 index </> 3%

	OUR STUDY	Asioli S et al
Microadenoma(<10mm)	0(0%)	126(22%)
Macroadenoma(>10mm)	26(100%)	440(78%)
Invasive adenoma	11	129
Ki 67 >3%	1 Ratio 1: 4	42 Ratio 1: 2
Ki 67 <3%	4	87
Non invasive adenoma	15	438
Ki 67 >3%	6 Ratio 3:1	59 Ratio 1: 6
Ki 67 <3%	2	389

Thus, Ki67 index did not show significant relation with tumor invasion or tumor size ($p > 0.05$).

CONCLUSION:

Female dominance was observed below 45 yrs while male dominance above 55 yrs. Commonest clinical findings included reduced vision, amenorrhea & raised prolactin levels. The majority were non-invasive macroadenoma. On microscopy papillary pattern, monomorphic nuclei and Ki67 index 3-9% were commonest. Serum hormonal levels corresponded with hormonal symptoms. No statistically significant correlation was observed between cytoplasmic tinge - hormonal symptoms and between Ki67 index/ nuclear pleomorphism/tumor size/ tumor invasion. Multi-disciplinary studies with transcription factors and hormone-specific IHC markers are needed to establish predictive markers of aggression.

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