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RESEARCH

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Comparative study on clinicopathological characteristics of functional and non-functional subtypes in pituitary adenomas

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Abstract

Background Pituitary adenomas comprise clinical and pathological characteristics of functional and non-functional subtypes. To enhance our understanding of diagnostic presentations, our study aimed to know the clinicopathological characteristics of pituitary adenomas of both functional and non-functional subtypes. The purpose of our study was to investigate the clinicopathological characteristics of pituitary adenomas, including demographic characteristics, clinical presentations, hormone secretion patterns, invasiveness, and cellular characteristics.

Methods A total of 41 cases of pituitary adenomas were analyzed, with 63.4% classified as non-functional adenomas (NFPA) and 36.6% as functional adenomas (FPA). Clinical presentations vary, with vision loss and headaches commonly occurring in both NFPA and FPA. In FPAs, serum hormone levels varied and were categorized into growth hormone-secreting (53.3%), ACTH-secreting (26.7%), PRL-secreting (13.3%), and FSH-secreting (6.7%) subtypes. Moreover, clinical presentations in FPA included diplopia, giddiness, vomiting, ptosis, and limb weakness. Clinical features varied across subtypes, with acromegaly in growth hormone-secreting adenomas, moon facies and weight gain in ACTH-secreting adenomas, poor facial growth in PRL-secreting adenomas, and vision loss in FSH-secreting adenomas. Meanwhile, NFPA were predominantly macroadenomas (88.5%) and exhibited various morphological patterns.

Results The proliferation index is higher in functional adenomas (mean 1.32) as compared to non-functional (mean 0.91). Clinical presentations varied across functional and non-functional adenomas. Growth hormone-secreting adenomas were the most common functional subtype, while LH and null cell adenomas were common non-functional subtypes. Two cases were invasive adenomas with a low Ki67 index. Sheets were the most common morphological pattern. PCA analysis revealed significant differences between the two groups, with PC 1 explaining 92.111% of the variance.

Conclusions Our study elucidates the clinicopathological characteristics of pituitary adenomas, highlighting significant differences between functional and non-functional subtypes. These findings underscore the importance of tailored diagnostic and management strategies to optimize outcomes for patients with pituitary adenomas.

Keywords Pituitary adenomas, Functional adenomas, Non-functional adenomas, Clinicopathological features of adenomas, Diagnostic presentations of adenomas

Background

Pituitary adenomas were neoplastic growths originating from the pituitary gland, encompassing a diverse spectrum of functional (FPA) and non-functional (NFPA) subtypes (Melmed et al. 2022). These tumors could give rise to a wide range of clinical manifestations, making accurate diagnosis and appropriate management crucial

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for patient care (Land et al. 2019). Understanding the clinicopathological features of these tumors was essential for accurate diagnosis and appropriate management. The clinicopathological features of pituitary adenomas could vary significantly, depending on their functional status. Growth hormone-secreting adenomas often presented with acromegaly, characterized by enlarged hands, feet, and facial features, whereas ACTH-secreting adenomas led to Cushing's disease, which presented with weight gain, moon facies, and hypertension (Brue and Castinetti 2016). NFPA did not secrete hormones, often causing symptoms due to mass effect or compression of surrounding structures (Chanson and Wolf 2021). Investigating the clinicopathological features of both FPA and NFPA provided valuable insights into their distinct characteristics (Drummond et al. 2019). Various parameters contributed to the characterization of pituitary adenomas, including their morphological patterns, tumor size, location, cellular features, growth rates, and associated hormonal abnormalities. In a different domain, Yekta et al. (2011) investigated the demographic and clinical factors influencing health-related quality of life in patients with diabetic foot ulcers, providing valuable insights for optimizing patient care in this population. Furthermore, demographic parameters, such as age and gender, may also have influenced clinical presentation and management considerations. By studying the clinicopathological features of pituitary adenomas, researchers and clinicians could enhance their understanding of the underlying mechanisms driving tumor development and progression. Moreover, Zhang et al. (2022) undertook an ambitious endeavor to characterize pituitary neuroendocrine tumors across major histological types through integrated proteogenomic analysis. The acquisition of this knowledge served as a foundation for the enhancement of diagnostic precision and the tailoring of individualized therapeutic methodologies, resulting in improved patient outcomes. Furthermore, it facilitated precise categorization, prognostication, and the formulation of suitable treatment modalities for afflicted patients. Through the comprehensive exploration outlined herein, we envisaged the expansion of our understanding and a deeper insight into the intricacies of this multifaceted ailment. It is noteworthy that, heretofore, no investigations had been undertaken to explore the potential advantages of examining the clinicopathological attributes of pituitary adenomas, particularly in light of their functional variations. Consequently, the present study endeavored to undertake a thorough investigation into the clinicopathological characteristics of pituitary adenomas, encompassing both functional and non-functional subtypes.

Methods

Patient selection and data collection

In this study, a sample size of 41 subjects diagnosed with pituitary adenoma at the institute (JIPMER), Pondicherry, India, was included to conduct the research. Furthermore, authorization was acquired from the Head of the Department of Pathology to access previous medical records, tissue blocks, and microscopic slides. Tissue sections, measuring approximately 2 to 3 microns in thickness, were meticulously excised from the tissue blocks. Subsequently, these sections were subjected to H&E staining, in strict accordance with the established standard operating protocol as outlined in the work of Snower et al. (1991).

Hormonal, histomorphological assessment and immunophenotyping

Serum levels of ACTH, GH, FSH, TSH, and PRL were assessed using Human Pituitary LINCOplex kits provided by Linco/Millipore Research in Billerica, MA. Thin sections (2–3 μm) were prepared from all blocks and stained with H&E using standard procedures. H&E sections were examined to assess histomorphology in prospective cases. Immunophenotyping was performed on tissue sections from pituitary adenoma cases using a panel of antibodies, including GH, LH, FSH, TSH, ACTH, PRL, p53, and Ki67, along with appropriate positive controls. Archived H&E sections were reviewed to assess histomorphology. The patterns of immunohistochemistry panel positivity were analyzed (Paek et al. 2005). To ensure control, two sections were stained on a single silane-coated slide. H&E slides and available IHC slides were screened for each case. Two sections were taken on one slide for immunohistochemical staining to minimize the use of silane-coated slides and act as a technical control for other sections. Antibodies from Pathnsitu Biotechnologies, Hyderabad, India, with various catalog numbers, namely GH-PR192, LH-M217, FSH-PR191, TSH-PR218, ACTH-PM205, PRL-PR193, p53-PM101, and Ki67-PR314, were employed in the analytical procedures. Tonsil tissue served as the control for Ki67, breast cancer tissue for p53, and normal pituitary tissues were taken as the control for all hormonal markers. These antibodies were selected based on specificity and established use in previous studies. The choice of control tissues aimed to provide a baseline for comparison and ensure the reliability and accuracy of immunohistochemical staining results in our study. For this study, we utilized a microscope with the model number MX21i LEDFS11, manufactured by Magnus Opto Systems. India. We considered microadenomas and macroadenomas in

our study. Microadenomas refer to tumors smaller than 10 mm, while macroadenomas, describing tumors larger than 10 mm, were included in the study (Russ et al. 2023).

Results

Demographic patterns were assessed in all 41 cases. Among them, there were 15 males and 11 females, totaling 26 cases of NFPA, with the remaining cases being FPA, as presented in Table 1. There was an age range from 23 to 74 years, with a mean age of 47.0 ± 15.7 years. Among the cohort, 15 were male (57.7%), and 11 were female (42.3%). Regarding invasiveness, among the 15 FPA, 2 (13.3%) demonstrated invasiveness, while the remaining 13 (86.7%) were classified as non-invasive. The majority of FPA exhibited a macroadenoma phenotype (73.3%), with a smaller proportion manifesting as microadenomas (26.7%). Morphological patterns within FPA, as analyzed in 15 cases, revealed 80% to be sheets, 13.3% papillary, and 6.7% lobules. NFPA presented with various clinical presentations attributed to mass effect, including loss of vision (88.4%), headache (69.2%), diplopia (7.6%), giddiness (7.6%), vomiting (3.8%), ptosis (3.8%), and weakness of both limbs (3.8%). Subtype distribution among the 26 NFPA cases included LH (15.4%), PRL (11.5%), ACTH (7.6%), FSH (3.8%), LH + FSH (3.8%), GH + ACTH (3.8%), and null cell adenomas (53.8%). Clinicopathological features of these 26 NFPA indicated a mean age of 47.0 ± 15.7 years, with 57.7% being male. The study revealed that the mean age of patients afflicted with NFPA was 47.0 ± 15.7 years, with 57.7% of them being male. The most prevalent symptom observed was loss of vision (88.4%), followed by headache (69.2%). In terms of invasiveness, only 7.7% of NFPA exhibited invasiveness, with the majority (88.5%) classified as macroadenomas. Detailed clinical presentations related to endocrine effects among FPA are presented in Table 2. This subset included 15 cases of FPA, with an age range spanning 17 to 60 years and a mean age of 33.73 ± 12.25 years. Among these cases, 10 were female (66.7%), while 5 were male (33.3%). The most common symptoms among FPA were loss of vision (40%) and headache (27%). Concerning subtypes of FPA, out of the 15 cases, 8 exhibited growth hormone-secreting adenomas (53.3%), 4 were identified as ACTH-secreting adenomas (26.7%), 2 had PRL-secreting adenomas (13.3%), and 1 featured an FSH-secreting adenoma (6.7%). The invasiveness evaluation of NFPA within the 26 cases demonstrated that 7.7% were invasive, while 92.3% were non-invasive. Among these cases, 23 were classified as macroadenomas (88.5%), and 3 were microadenomas (11.5%). Morphological patterns within the 26 NFPA included 65.3% sheets, 15.4% cords and papillary each, and 3.9% lobules. The Ki67 was assessed for FPA and NFPA, revealing values of 1.3 ± 1.25% and 0.91 ± 0.77%, respectively. It is noteworthy that the study observed differences in cell growth rates among these

Table 1 Clinicopathological features of the non-functional pituitary adenomas

Feature	Value
Number	26
Age range	23–74 years
Mean age (in years) ± SD	47.0 ± 15.7
Male	15 (57.7)
Female	11 (42.3)
M:F	1.4:1
Loss of vision($n=26$)	23 (88.4%)
Headache ($n=26$)	18 (69.2%)
Diplopia ($n=26$)	2 (7.6%)
Giddiness ($n=26$)	2 (7.6%)
Vomiting ($n=26$)	1 (3.8%)
Ptosis ($n=26$)	1 (3.8%)
Weakness of both limbs	1 (3.8%)
Invasive	2/26 (7.7%)
Non-invasive	24/26 (92.3%)
Macroadenomas	23/26 (88.5%)
Microadenomas	3/26 (11.5%)
Sheets	17/26 (65.3%)
cords	4/26 (15.4%)
Papillary	4/26 (15.4%)
Lobules	1/26 (3.9%)

Table 2 Clinical presentations due to endocrine effects among functional pituitary adenomas

Symptoms	Number*	Percentage
Coarse facial feature	7	47%
Knuckle hyper pigmentation	5	33.3%
Thickening of lips	4	27%
Prominent supraorbital ridges	4	27%
Hirsutism	3	20%
Macroglossia	3	20%
Amenorrhoea	2	13.3%
Weight gain	2	13.3%
Striae marks	2	13.3%
Acanthosis	2	13.3%
Moon facies	2	13.3%
Buffalo hump	2	13.3%
Increase heel pad thickness	1	7%
Poor facial growth	1	7%

* Number of patients out of total 15 functioning functional pituitary adenomas with symptoms

adenoma types. Importantly, none of the cases exhibited P53 positivity in the study. Table 4 presents cellular characteristics of FPA, comparing different hormone-producing adenomas based on cytoplasm, nuclear chromatin, nucleoli, and monomorphism/pleomorphism. Among the 15 cases analyzed, 8 were growth hormone-secreting adenomas, 4 were ACTH-secreting adenomas, 2 were PRL-secreting adenomas, and 1 was an FSH-secreting adenoma. Table 5 and Fig. 9 provide comprehensive information regarding eigenvalues, PCA variable loadings, PCA case scores, and the proportion of characteristics between two groups, FPA and NFPA, utilizing two principal components, PC 1 and PC 2. Eigenvalues were used to assess the variance explained by each principal component. PC 1 exhibited an eigenvalue of 4.69, accounting for 92.11% of the total variance, while PC 2 had an eigenvalue of 0.402, explaining 7.889% of the total variance. The cumulative percentage represented the combined proportion of total characteristics explained by each principal component, with PC 1 accounting for 92.111% of the variance and PC 2 explaining the remaining 7.889%, leading to a cumulative percentage of 100% for PC 2.

Discussion

The research findings provide valuable insights into the clinicopathological features of pituitary adenomas, specifically focusing on both FPA and NFPA. This distribution highlights the importance of considering both types of tumors in clinical practice and research (Andereggen et al. 2023). The most common symptoms observed among FPA were loss of vision (40%) and headache (27%). These findings associated with the known clinical manifestations with these tumors and emphasize the importance of thorough evaluation of visual disturbances and headaches in patients. FPA Herein, FPA exhibited a higher proliferation index of 1.32 compared to 0.91 in NFPA, suggesting a potentially more active cellular growth and division in functional tumors. These differences in cell growth rates between FPA and NFPA suggest variations in their biological behavior and potential implications for disease progression and treatment response (Vaughan et al. 1985; Chacko et al. 2010). This distinction may have implications for the aggressiveness and clinical behavior of these tumors (Prieto-Fernández et al. 2022). Among the FPA, clinical presentations due to mass effect were assessed. Loss of vision was the most common symptom observed in 40% of cases, followed by headache in 27% and vomiting in 6%. These findings highlight the importance of recognizing these symptoms as potential indicators of FPA and emphasize the need for prompt evaluation and management to prevent further complications associated with mass effects. The occurrence of subtypes within FPA revealed that growth hormone-secreting adenomas were the most prevalent, followed by ACTH-secreting adenomas. PRL-secreting adenomas accounted for 13.3% of cases, and FSH-secreting adenomas represented 6.7% of the FPA. These findings support Cooper and Melmed (2012) who discussed subclinical hyperfunctioning pituitary adenomas, emphasizing the importance of recognizing these silent tumors and the need to consider specific hormone-secreting subtypes when diagnosing and managing these tumors. The most common symptom observed in NFPA was loss of vision, followed by headache. In terms of invasiveness, only 7.7% of NFPA were classified as invasive, while the majority were macroadenomas. This indicates that NFPA tend to be non-invasive and predominantly of a larger size and findings have implications for treatment planning and surgical considerations (Li et al. 2023). The research findings also include information on the morphological patterns of NFPA, the majority (65.3%) exhibited a sheet pattern, while 15.4% showed cord and papillary patterns, and 3.9% displayed a lobular pattern. These morphological patterns provide additional insights into the histopathological characteristics of NFPA (Serioli et al. 2019). Our study for NFPA reveals that loss of vision is the most common symptom, observed in 88.4% of cases, followed by headache in 69.2% of cases. Findings showed the importance of recognizing visual disturbances as a significant clinical feature in NFPA and emphasize the need for prompt evaluation and management to prevent vision loss (Chang et al. 2008). In terms of invasiveness, only 7.7% of NFPA were classified as invasive, while the majority (88.5%) were macroadenomas. This suggests that most NFPA tend to grow and exert mass effects locally, without significant invasion into surrounding structures (Hagiwara et al. 2003). The predominance of macroadenomas underscores the need for careful evaluation and management of these larger tumors to prevent complications and optimize patient outcomes. These clinical features are often associated with excess hormone production and can aid in the clinical suspicion and diagnosis of FPA (Antsiferov et al. 2021). Recognizing these characteristic features can guide further diagnostic workup and appropriate management strategies (Jaursch-Hancke et al. 2021). These adenomas were primarily associated with acromegaly, a condition characterized by the excessive secretion of growth hormone. Table 3 highlights the heterogeneity in

Table 3 Subtype of functional adenomas with their predominant clinical features

Secreting	Number of case	Age Range (years)	M: F	Clinical features	Serum hormone levels
Growth hormone (Men: < 5 ng/mL; Women: < 10 ng/mL)	8	23–50	1:3	Acromegaly	0.28–81.6 ng/ml *
ACTH (0–46) pg/ml	4	17–60	1:3	Moon facies and weight gain	44.7–80.5 pg/ml
PRL (4.79–23.3) ng/ml	2	23 & 35	2 males	poor facial growth	200 and 16,560 ng/ml
FSH 11.47 mIU/ml	1	45	Female	Vision loss	23.01 mIU/ml

*In these cases, IGF-1 level were also high (> 300 ng/ml)

hormone production and secretion among these tumors. Our study found a wide range of serum growth hormone levels (0.28–81.6 ng/ml) in patients with growth hormone-secreting adenomas. ACTH-secreting adenomas were the second most common functional subtype, representing 26.7% of cases. Clinical features commonly observed in patients with ACTH-secreting adenomas included moon facies and weight gain. Serum hormone levels in these cases ranged from 44.7 to 80.5 pg/ml. PRL-secreting adenomas accounted for 11.5% of cases and were primarily associated with poor facial growth. FSH-secreting adenomas were relatively rare, with only one case identified, and the associated clinical feature was vision loss. Table 4 provides a comparison of different hormone-producing adenomas based on their cellular characteristics, such as cytoplasm, nuclear chromatin, nucleoli, and monomorphism/pleomorphism. This comparison allows for a better understanding of the histopathological variations among these adenomas and their potential implications for diagnosis and management. Our study contributes to the existing literature by offering a comparative analysis of clinicopathological characteristics between functional and non-functional pituitary adenomas, integrating principal component analysis (PCA) to discern significant differences. While previous studies have explored aspects of either functional or non-functional adenomas separately, our research uniquely combines both subtypes, providing a comprehensive understanding of their distinctions. In comparison with existing literature, our findings corroborate trends such as the predominance of growth hormone-secreting adenomas among functional subtypes and the prevalence of macroadenomas among non-functional adenomas. However, our study offers novel insights, particularly through the use of PCA, which reveals previously unexplored clinicopathological variations between these subtypes. Additionally, our quantitative assessment of the proliferation index and identification of rare adenoma subtypes such as LH and adenomas among non-functional adenomas add further depth to the literature. Overall, these results provide insights into the relationship between the characteristics and the groups, FPA and NFPA, in the context of two principal components. PC 1 appears to capture important differences between the groups, while PC 2 contributes to a lesser extent. By examining the variable loadings and case scores, it is possible to understand which characteristics are most strongly associated with each principal component and how they differentiate between the two groups (Guerreiro et al. 2023). The presence of ACTH-secreting pituitary macroadenoma is depicted in Fig. 1A–F. Microscopic observation revealed sheets of cells with abundant cytoplasm and focal calcification. The cells showed moderate pleomorphism, prominent nucleoli, and giant cells. Additionally, ACTH

Table 4 Cellular characteristics of functional adenomas

Hormone	Cytoplasm			Nuclear chromatin			Nucleoli		Monomorphism/Pleomorphism	
	Scant	Moderate	Abundant	Open	Stippled	Clumped	Prominent	Inconspicuous	Monomorphism	Pleomorphism
GH(8)	–	7	1	–	8	–	5	3	7	1
ACTH(4)	–	2	2	–	3	1	2	2	4	–
PRL(2)	–	1	1	–	2	–	–	2	2	–
FSH(1)	–	1	–	–	1	–	–	1	–	1

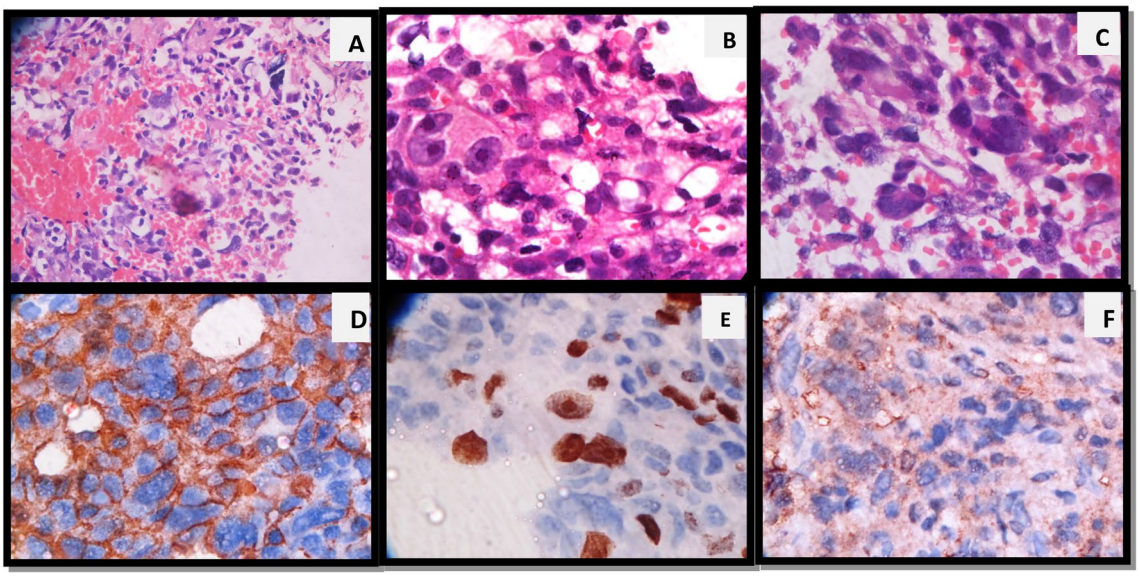

Fig. 1 **A–F: A:** ACTH-secreting pituitary macroadenoma (H&Ex400); **B:** cells with moderate pleomorphism, prominent nucleoli (H&Ex400) **C:** ACTH-secreting pituitary macroadenoma, moderately pleomorphic with giant cells (H&Ex400). **D:** cytoplasmic positivity of ACTH stain (×400). **E:** Ki67 (nuclear positivity) > 3%. (×400). **F:** P53 negative stain (×400)

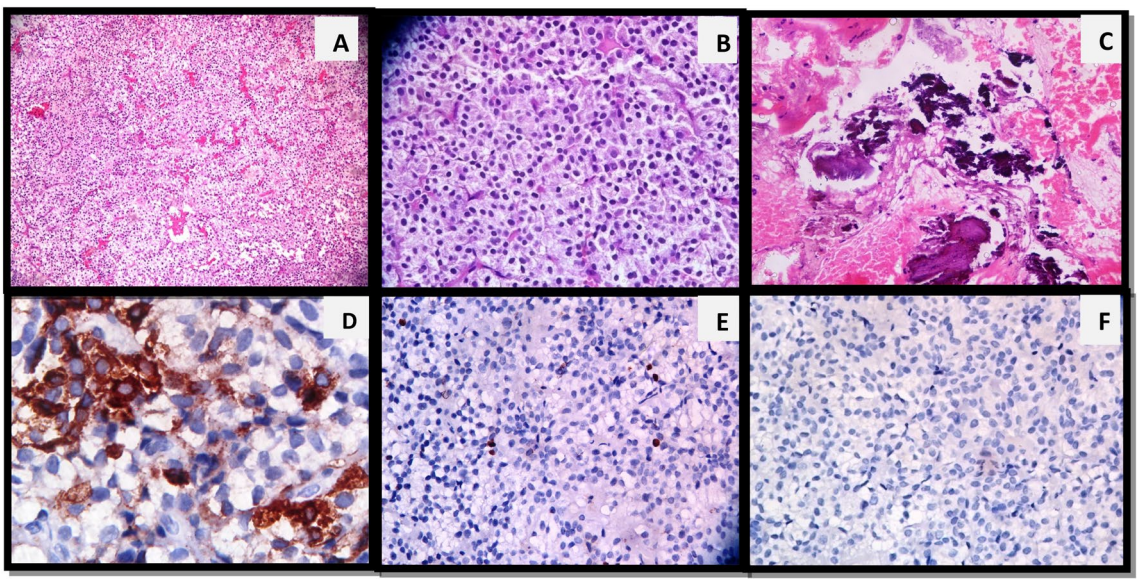

Fig. 2 **A–F:** FSH-secreting adenoma; **A:** tumor cells arranged in sheets, round to oval nuclei, inconspicuous nucleoli, clear to eosinophilic cytoplasm(H&Ex100). **B:** tumor cells arranged in sheets, clear cytoplasm (H&Ex400). **C:** FSH-secreting adenoma with calcification (H&Ex400); **D:** cytoplasmic positivity of FSH (×400). **E:** nuclear positivity of Ki67 (×400). **F:** P53 negative stain (×400)

staining was positive, indicating the presence of ACTH hormone in the cells. The Ki67staining showed nuclear positivity in more than 3% of the cells, indicating a moderately high proliferation index. The P53 protein staining was negative. These findings suggest the presence of an ACTH-secreting pituitary macroadenoma with distinct clinicopathological features (Burcea et al. 2021).

Figure 2A–F illustrates an FSH-secreting adenoma. Tumor cells are observed arranged in sheets with round to oval nuclei, inconspicuous nucleoli, and clear to eosinophilic cytoplasm. The H&E stain also reveals clear cytoplasmic arrangement of tumor cells and areas of calcification within the adenoma. Furthermore, the FSH stain demonstrates cytoplasmic positivity, indicating the

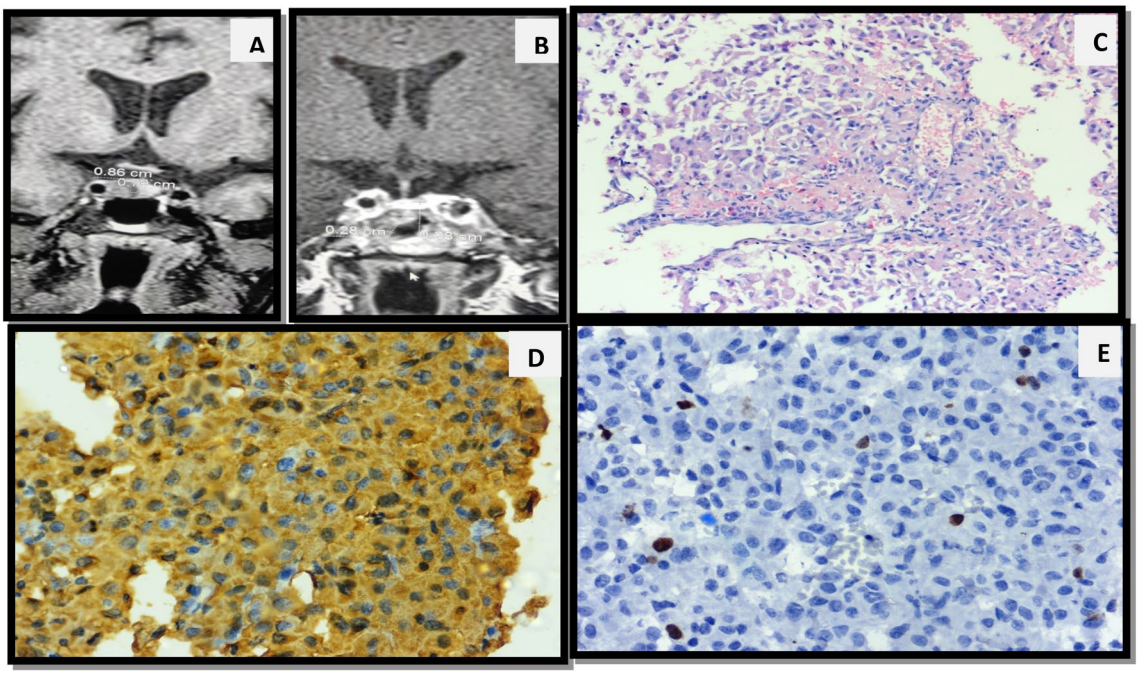

Fig. 3 **A–E:** ACTH-secreting microadenoma; **A:** CECT in PA; **B:** recurrence of tumor; **C:** Sheets of monomorphic, moderate amount of chromophobic cytoplasm, stippled nuclear chromatin, inconspicuous nucleoli (H&Ex100). **D**: cytoplasmic positivity of ACTH (×400). **E:** nuclear positivity of Ki67 > 3% (×400)

presence of FSH hormone in the cells. Nuclear positivity of Ki67 stain is observed, indicating a moderate proliferation index within the adenoma. The P53 protein stain shows a negative result. These findings collectively suggest the presence of an FSH-secreting adenoma with distinct clinicopathological features (Lania et al. 2002). Figure 3A–E focuses on an ACTH-secreting microadenoma. The CT scan shows the presence of a pituitary adenoma before the patient underwent surgery at an outside hospital. Microscopic examination reveals sheets of monomorphic cells with moderate amounts of chromophobic cytoplasm, stippled nuclear chromatin, and inconspicuous nucleoli. The ACTH stain exhibits cytoplasmic positivity, indicating the presence of ACTH hormone in the cells. Additionally, in our follow-up study of 41 pituitary adenomas, two cases of recurrent adenomas, both secreting ACTH, were observed. Additionally, in our follow-up study of 41 pituitary adenomas, we observed two cases of recurrent adenomas, both secreting ACTH. In both instances, Ki67 was > 3%. These findings suggest the presence of an ACTH-secreting microadenoma with characteristic clinicopathological features (Picó et al. 2021). In Fig. 4A–B, a growth hormone-secreting adenoma with apoplexy is depicted. The

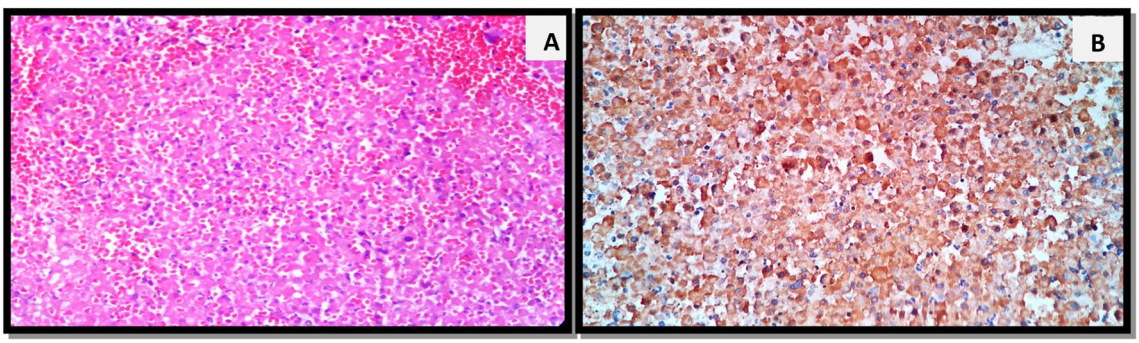

Fig. 4 GH-secreting adenoma with apoplexy **A:** areas of hemorrhagic infarction admixed with focal clusters of viable cells (H&E × 100). **B:** cytoplasmic positivity of GH stain at 1000 x

H&E stain reveals large areas of hemorrhagic infarction mixed with focal clusters of viable cells. Further our study on GH stain confirms cytoplasmic positivity, confirming the presence of GH hormone in the cells and supports the findings of Kim et al. (2008) of apoplexy in a GH-secreting adenoma, characterized by areas of hemorrhagic infarction and viable cell clusters. Figure 5A–B represents an LH subtype of a non-functioning pituitary macroadenoma. The H&E stain at 100×magnification shows monomorphic cells arranged in cords, some of which exhibit perivascular pseudorosette formation. The cells display round to oval nuclei, fine chromatin, and

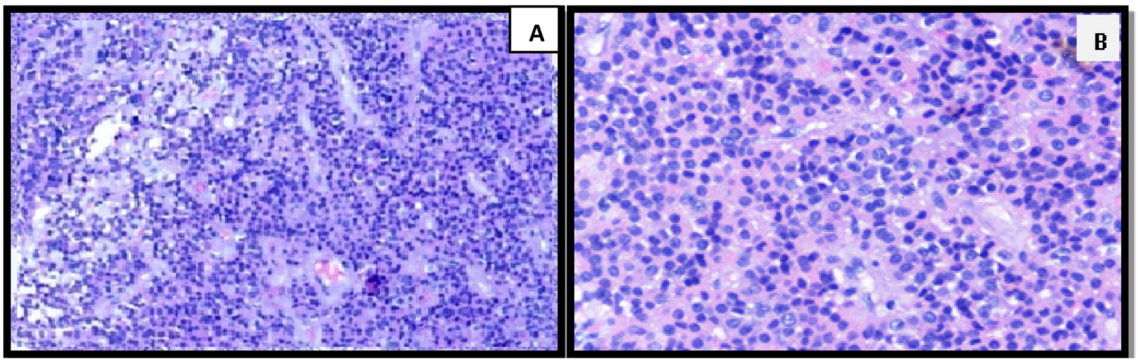

Fig. 5 **A–B:** NFPA macroadenoma (LH subtype) of monomorphic cells arranged in cords, with perivascular pseudorosette formation, round to oval nuclei, fine chromatin, chromophobic cytoplasm **A:** (H&Ex100); **B:** (×400) with cytoplasmic positivity of LH stain

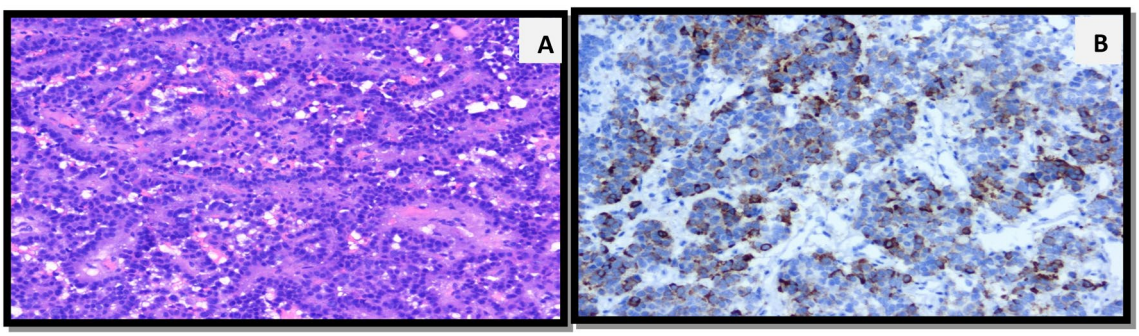

Fig. 6 **A–B: A:** NFPA macroadenoma (FSH subtype) with monomorphic cells arranged in papillae, round to oval nuclei, fine chromatin, chromophobic cytoplasm (×100). **B:** NFPA macroadenoma (FSH subtype) with cytoplasmic positivity of FSH stain (H&Ex400) and nuclear positivity of Ki67

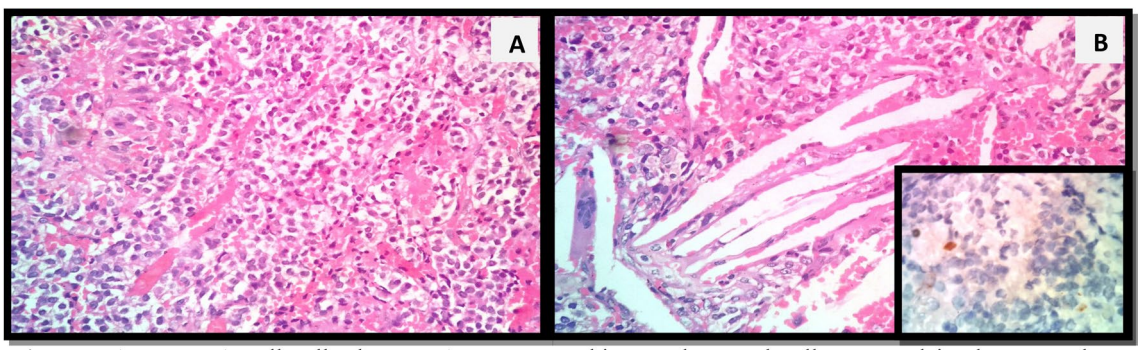

Fig. 7 **A–B:** NFPA null cell adenoma **A:** monomorphic round to oval cells arranged in sheets, moderate amount of chromophobic cytoplasm, fine granular chromatin, inconspicuous nucleoli (H&Ex400); **B:** cholesterol clefts and foamy macrophages (H&Ex400). Inset shows Ki67; labeling index < 1%

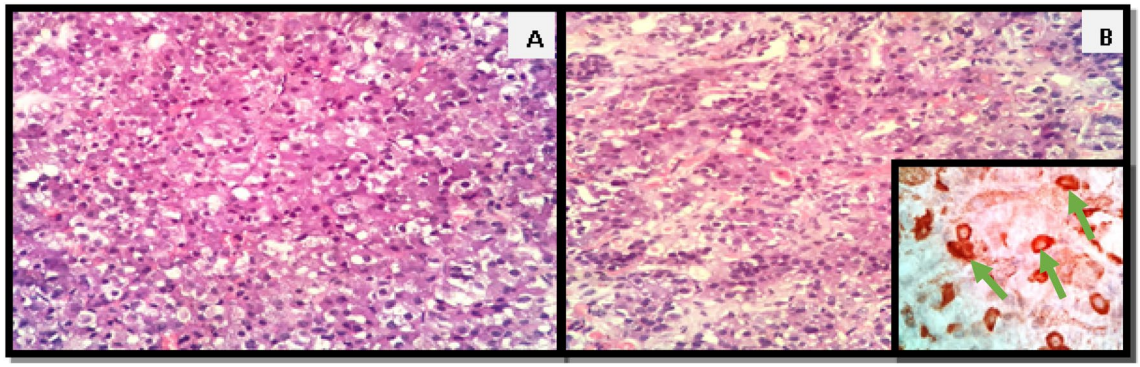

Fig. 8 **A–B:** Growth hormone-secreting pituitary macroadenoma**. A:** sections shows lobules of monomorphic cells with of eccentrically placed oval nuclei and eosinophilic cytoplasm(H&Ex400); **B:** microscopic focus from the same case highlighting similar features (H&Ex400) and inset with green arrows show cytoplasmic positivity of GH stain (H&Ex400)

chromophobic cytoplasm. The inset shows cytoplasmic positivity of LH stain, indicating the presence of LH hormone in the cells. These observations suggest the presence of an LH subtype of a non-functioning pituitary macroadenoma, characterized by specific histopathological features (Melmed et al. 2022). Figure 6A–B shows NFPA of the FSH subtype, which displays monomorphic cells arranged in papillae with round to oval nuclei, fine chromatin, and chromophobic cytoplasm, demonstrating cytoplasmic positivity of FSH stain, indicating the presence of FSH hormone in the cells. The nuclear positivity of Ki67stains, suggesting cellular proliferation within the tumor (Ntali et al. 2014). In Fig. 7A–B, a null cell adenoma of the NFPA subtype is depicted, showing monomorphic round to oval cells arranged in sheets with a moderate amount of chromophobic cytoplasm, fine granular chromatin, and inconspicuous nucleoli with the presence of cholesterol clefts and foamy macrophages.

Table 5 Eigenvalues, PCA variable loadings, PCA case scores and proportion of total characteristics between FPA and NFPA at two principal components

Eigenvalues principle components	**PC 1**	**PC 2**
Eigenvalues	4.69	0.402
Percentage	92.111	7.889
Cum. percentage	92.111	100
PCA variable loadings	**PC 1**	**PC 2**
FPA	−0.659	0.752
NFPA	0.752	0.659
Characteristic	**PC 1**	**PC 2**
PCA case scores		
Coarse facial feature	−0.519	0.169
Knuckle hyper pigmentation	−0.477	0.121
Thickening of Lips	−0.452	0.092
Prominent supraorbital ridges	−0.452	0.092
Hirsutism	−0.416	0.051
Macroglossia	−0.416	0.051
Amenorrhoea	−0.368	−0.003
Weight gain	−0.368	−0.003

Table 5 (continued)

Characteristic	PC 1	PC 2
Striae marks	−0.368	−0.003
Acanthosis	−0.368	−0.003
Moon facies	−0.368	−0.003
Buffalo hump	−0.368	−0.003
Increase heel pad thickness	−0.296	−0.086
Poor facial growth	−0.296	−0.086
Loss of vision	0.602	0.178
Headache	0.567	0.148
Diplopia	0.269	−0.113
Giddiness	0.269	−0.113
Vomiting	0.186	−0.186
Ptosis	0.186	−0.186
Weakness of both limbs	0.186	−0.186
Invasive	0.27	−0.112
Non-invasive	0.608	0.183
Macroadenomas	0.602	0.178
Microadenomas	0.322	−0.067
Sheets	0.559	0.141
cords	0.361	−0.033
Papillary	0.361	−0.033
Lobules	0.189	−0.184

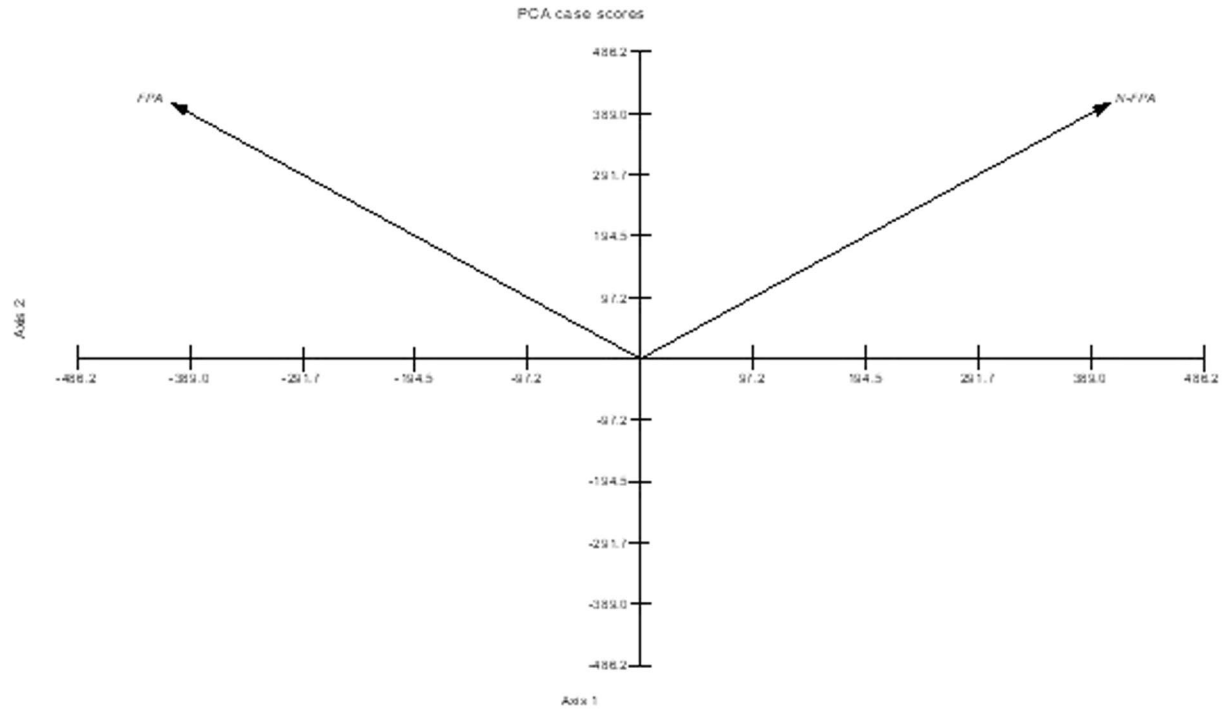

Fig. 9 PCA biplot representing functional and non-functional subtypes in pituitary adenomas and their correlated characteristics with PC1 and PC2 axes

Figure 8A–B focuses on a growth hormone-secreting pituitary macroadenoma, displaying lobules of monomorphic cells composed of eccentrically placed oval nuclei and eosinophilic cytoplasm from the same case emphasizes similar features with cytoplasmic positivity of GH stain, confirming the presence of GH hormone in the cells (Moreno Jiménez et al. 2023) (Table 5).

Conclusions

Our research revealed that when Ki67 expression surpasses 3%, it anticipates the recurrence of pituitary adenoma and sheds light on the clinicopathological features of these tumors, highlighting notable distinctions between functional and non-functional subcategories. Our study introduces novel findings by PCA to discern significant differences between functional and non-functional pituitary adenomas, offering unique insights into their clinicopathological distinctions. Through quantitative assessment of the proliferation index, we reveal a higher rate in functional adenomas, alongside identification of rare subtypes like LH and null cell adenomas among non-functional adenomas. These pioneering advancements contribute to a deeper understanding of pituitary adenomas and inform future diagnostic and management strategies (Fig. 9).

Abbreviations

ACTH	Adrenocorticotropic hormone
PRL	Prolactin
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
PCA	Principle component analysis
H&E	Hematoxylin and eosin
IHC	Immunohistochemistry

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Author contributions

ARS designed and executed the research, overseeing all aspects of the project from conception to implementation. ARS drafted the initial manuscript, summarizing research findings and contributing to the narrative. PK conducted data analysis and compiled the manuscript in writing and revising. Together, ARS and PK's collaborative efforts produced a well-rounded research paper. All authors have read and approved the manuscript.

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Availability of data and materials

All the data generated or analyzed during this study are included in this article.

Declarations

Ethics approval and consent to participate

Clearance from the Research Ethics Committee of the institute was obtained (Letter number: JIP/IEC/SC/2014/8/642). Written informed consent was obtained from all participants involved in this study. The identity of the patients was kept confidential, and data were collected in a de-identified format. No potential conflict of interest was reported by the author(s).

Consent for publication

Consent to publish obtained.

Competing interests

The authors declare that they have no competing interests.

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