



## Immunohistochemistry in 169 Cases of Pituitary Adenoma

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### Aims and Objectives

To study the morphological and immunohistochemical profile of Pituitary Adenomas in relation to determination of cell differentiation & classification, clinical features, radiological features and biochemical data.

### Introduction

The Human Pituitary Gland, despite being a small bean-shaped organ, is the commander of the major endocrine glands in the body. It exerts control over virtually every system and is located intracranially, close to areas of higher function of the Central Nervous System.

It is therefore, not surprising, for a Pituitary Adenoma, the most common tumour arising from it, to present with a wide range of symptoms that challenge clinicians of various specialties, who must assemble all the information they can obtain, with an open mind, to arrive at the diagnosis.

### Materials and Methods

The study was performed in the Department of Histopathology, Apollo Specialty Hospital, Chennai. 172 cases of Pituitary Adenoma was collected over a period of three years (1<sup>st</sup> January 2007 to 31<sup>st</sup> December 2009). Of these, 169 cases were included in our study.

Year	Number of cases studied
2007	47
2008	56
2009	66
Total number of cases studied = 169	

Clinical, biochemical and radiological data were obtained for as many cases as possible.

### Criteria for Exclusion

Biopsies showing extensive infarction.

### Histology

Tissue sections from formalin-fixed Paraffin-Embedded blocks were stained by Haematoxylin and Eosin and observed by Light Microscopy.

### Immunohistochemistry

4 – micrometre thick paraffin sections were collected on Triaminopropylethoxysilane-coated glass slides and subjected to Immunohistochemistry using the Streptavidin-Biotin Complex Immunoperoxidase method, with the following Antibodies:

- CK - Dako - Mouse Monoclonal (1/200 dilution)
- HGH - Dako - Mouse Monoclonal (Prediluted)
- TSH - Biogenex - Mouse Monoclonal (Prediluted)
- ACTH - OSB - Rabbit Polyclonal (Prediluted)
- FSH - Biogenex - Mouse Monoclonal (Prediluted)
- LH - Biogenex - Mouse Monoclonal (Prediluted)
- PRL - Biogenex - Mouse monoclonal (Prediluted)

Positive Controls were employed for the Antibodies as below.

S. No.	Antibody	Positive Control
1.	CK	Colonic Mucosa
2.	FSH	Pituitary, K/c/o Gonadotroph Adenoma
3.	PRL	Pituitary, K/c/o Prolactinoma
4.	HGH	Normal Pituitary
5.	TSH	Normal Pituitary
6.	LH	Normal Pituitary
7.	ACTH	Normal Pituitary

Immunostaining was evaluated in the fields consisting of regions of the tumour having the greatest number of immunoreactive cells, as assessed qualitatively at low-power examination. Cytoplasmic staining, in > 10% of cells was regarded as positive.

### Review of Literature

The Adenohypophysis, is composed of five pituitary-specific cell lineages that produce six trophic hormones<sup>1</sup>.

Immunohistochemistry of Pituitary Adenoma identifies the cell-type and enables a functional classification.<sup>2</sup>

### Epidemiology

Pituitary Adenomas form 10 –15% of Intracranial Neoplasms. They occur in adults, with 2% of cases being children. PRL-producing adenomas are the most common hormone-producing tumours in both adults and children. ACTH-producing adenomas are more common in children.<sup>3</sup>

### Clinical Features

Clinically, they present with signs and symptoms of Intracranial mass, visual field disturbances, hormone excess, deficiency of hormones from the normal portions of the gland or failure of target-organ (thyroid, gonad or adrenal). Mild Hyperprolactinemia (<200 ng/ml) may occur, due to pituitary stalk compression, called ‘Stalk-Section Effect’<sup>3, 20</sup>. Visual disturbance progresses from Superior Quadrantopia, to Bitemporal Hemianopia and eventually blindness. Sometimes, they may show suprasellar extension, or extension into paranasal sinuses and cavernous sinuses to compress cranial nerves, causing ophthalmoplegias.<sup>3</sup> Pituitary Apoplexy may cause sudden enlargement of an adenoma, resulting in visual disturbance.<sup>6</sup>

### Imaging

With its multiplanar capability and dramatic soft tissue contrast, M. R. I. is the radiological investigation of choice. 3 mm T1-weighted coronal images and sagittal images are studied, before and after administration of Gadolinium contrast. Computerised Tomography has less sensitivity and specificity. M. R. I. helps to study the size, location and extent of tumour. Most

Pituitary Adenomas produce Suprasellar Extension. Post-operative Radiological follow-up is also of use to look for residual or recurrent tumor.<sup>3,19</sup>

### Histopathology

Macroscopically, they have a soft, pudding-like consistency, with calcification seen only in Prolactinomas.

Microscopically, they display patternless sheets of uniform cells, with intervening capillary network. At perivascular areas, they display columnar shape, regimentation, tapering ends and polarization of nuclei. Pseudorosettes and papillae may be seen. The cells stain uniformly. Nuclei are round to oval and may show 'salt and pepper chromatin'.

### Classification

A number of attempts have been made, to classify pituitary Adenomas. The two main groups are "Clinically Functioning Adenomas" and "Clinically Non-functioning Adenomas", according to whether or not an endocrine syndrome is present. Two thirds are clinically functioning.<sup>5</sup> Non-functioning adenomas are known to produce Gonadotropin subunits.<sup>1</sup>

According to Tumour size and gross anatomic features, pituitary adenomas are divided into microadenomas (<1cm in diameter) and macroadenomas (>1cm in diameter). Rarely Giant Adenomas occur (>4cm in diameter)<sup>3</sup>. Macroadenomas show an increased tendency toward suprasellar extension, gross invasion and recurrence.<sup>5</sup>

Rarely, Ectopic Adenomas may arise from the sphenoid sinus, oral mucoperiosteum, nasal cavity, suprasellar region, or third ventricle. Pituitary Adenoma may also be a component of an ovarian teratoma.<sup>6</sup>

Morphological classification of Pituitary Adenomas depended on the staining characteristics of the tumour cells. Thus they were designated as Acidophilic, Basophilic or Chromophobic. But this classification did not provide information

about the specific adenoma type.<sup>5</sup> The eosinophilic adenomas once considered solely GH-producing may manufacture GH, PRL, or both. Alternatively, they may lack hormone immunoreactivity altogether. Although basophilic adenomas are PAS-positive and they are usually associated with Cushing disease, weakly PAS-reactive tumors may also produce FSH, LH, or TSH. Lastly, chromophobic adenomas may either lack hormone staining or may contain the full range of pituitary hormones.<sup>7</sup>

Pituitary Adenomas have a variety of growth patterns (diffuse, papillary, trabecular, etc) that may be present in any adenoma type. Although these histological features are of no prognostic significance, they may be considered in the differential diagnosis of Pituitary Adenomas.<sup>5</sup> Reticulin stain helps to distinguish normal Pituitary tissue from adenomatous tissue<sup>10</sup> (Images 3,4)

Immunohistochemistry serves to assess the hormone content of the various Pituitary Adenomas, but does not discriminate specific subtypes, which are of prognostic importance. In such situations, ultrastructural information becomes necessary.<sup>5</sup>

Based on Immunohistochemical and Ultrastructural features, the Pituitary Adenomas have been classified in the W.H.O. CLASSIFICATION (2004)<sup>3</sup>.

Apart from the Pituitary Hormones, these tumours may show staining for Synaptophysin and Chromogranin<sup>15</sup>. Proliferating rates may be assessed using Ki-67 or Proliferating Cell Nuclear Antigen.<sup>9</sup> Matrix Metalloproteinase-9 is significantly increased in Invasive Pituitary Adenomas.<sup>11</sup> Immunostaining studies are not of use in infarcted tissue.<sup>6</sup>

Cell biology studies have provided abundant data regarding the nature and behavior of pituitary adenomas. For instance, X-chromosome inactivation studies have shown that they are clonal lesions. DNA ploidy analysis, despite reports to the contrary, is of limited use in identifying invasive and aggressive lesions.

Silver-staining nucleolar organizing region (AgNOR) analysis is not much more promising. On the other hand, cell proliferation studies using flow cytometry (S-phase analysis, as well as Ki67 and bromodeoxyuridine labeling, show a correlation between elevated indices and the capacity of a tumor to invade and to metastasize. The same is true of mitotic indices and p53 protein immunoreactivity. In situ hybridization permits the identification of hormone mRNA expression, a modality useful in the study of so-called silent adenomas. The degree of secretory activity exhibited by pituitary adenomas shows little correlation with indicators of cell proliferation<sup>3</sup>. The hemolytic plaque assay has provided useful information regarding rates of hormone secretion, but it and the more conventional tissue culture methods remain experimental modalities.<sup>7</sup>

### Aetiology

Inherited Genetic abnormalities seen are:

- MEN-1 with involvement of 11q13
- Carney Complex with involvement of 2p16 and 17q
- Familial acromegaly with involvement of 11q13 and other loci
- McCune-Albright syndrome with involvement of 20q13.2

Increased production of the hypothalamic releasing hormones can give rise to pituitary adenomas.

Abnormal hormone receptors in the pituitary gland and abnormal signal-transduction can also lead to pituitary adenomas.<sup>3</sup>

### Molecular Pathogenesis

Point mutations in the  $\alpha$ -subunit of the stimulatory G-protein ( $G_{\alpha}$ ), leads to the oncogene *gsp*, which encodes for a constitutively active form of  $G_{\alpha}$ , leading to elevated levels of cyclicAMP. This mutation is seen in 40% of somatotroph adenomas and a few non-functional and corticotroph

adenomas. Hypermethylation of p16 in gonadotroph and null-cell adenomas.

Mutations in the  $\alpha$ -subunit of the inhibitory GTP-binding protein,  $G_{i2\alpha}$ , resulting in the oncogene *gip2*, is also seen in some tumours.<sup>8</sup>

Silencing of the RB1 promoter is seen, by means of methylation at a CpG island.

There is reduced p27 expression in ACTH producing adenomas.

A truncated kinase-containing variant of Fibroblast Growth Factor Receptor, bearing an alternative initiation site, (known as 'Pituitary-derived Kinase' or ptd-FGFR4) is expressed in most tumours.

Other factors involved are oncogenes *PTTG* and *Cyclin D1*.

The transcription factor PIT-1 is found within cells of the acidophil cell line, which are somatotrophs, lactotrophs and thyrotrophs. This may explain the presence of these cells in plurihormonal adenomas.

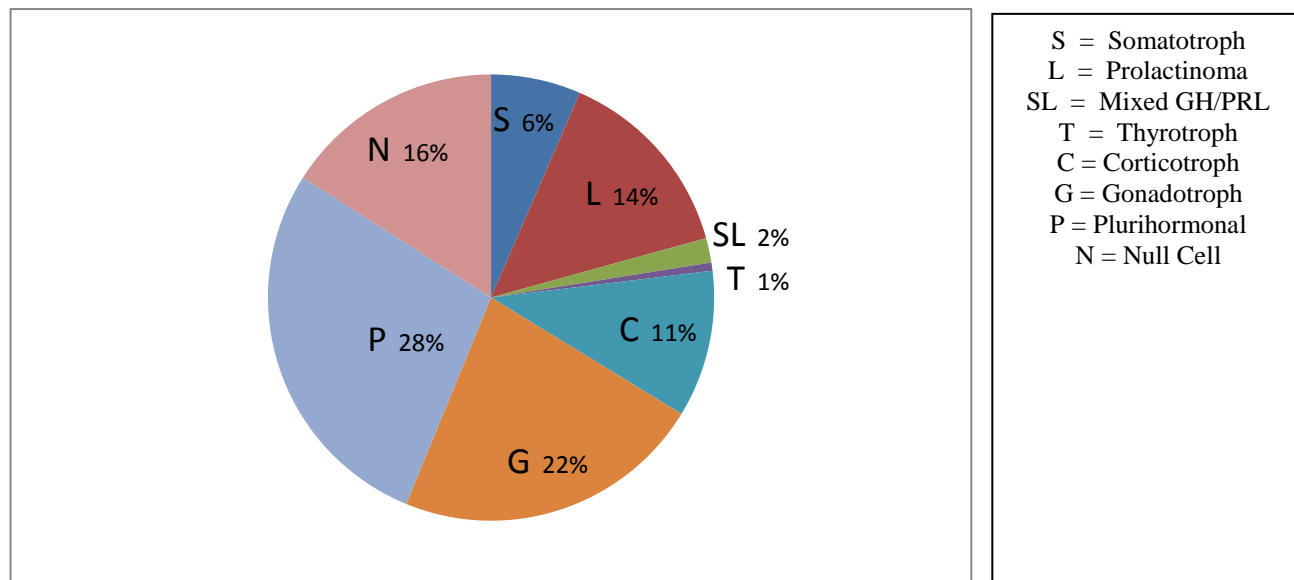
### Therapy

Surgery is the main modality of the treatment, and is necessary to relieve the pressure-effects of the tumour. The usual approach is trans-sphenoidal minimally-invasive procedure. Medical therapy is used initially, for patients with GH-producing and PRL-producing adenomas. Radiation therapy used to be performed before the trans-sphenoidal route was in vogue, but its side-effects are hypopituitarism and radiation-induced glioma and sarcoma.<sup>3, 18</sup> Gamma knife stereotactic surgery may have a role in recurrent or residual disease and in pituitary carcinomas.<sup>3</sup>

### Results, Observations & Analysis

#### Proportion of Each Tumour Type

The distribution of cases in each tumour category as classified by Immunohistochemistry is as given in Figure 1.



**Figure 1 - Proportion of Each Tumour Type**

**Age**  
 Despite a wide age range (16 - 77), the maximum incidence was noted in the fourth to sixth decade. The mean age at diagnosis of each individual tumour type was studied. The Kruskal-Wallis test showed a highly significant statistical difference with a P value of <0.00001. Cases of Prolactinoma, Somatotroph Adenoma and Corticotroph Adenoma showed a significant lower mean age compared to Gonadotroph Adenoma, Plurihormonal Adenoma and Null Cell Adenoma.

**Table 1 - Age Distribution**

Diagnosis	Age Range	Mean Age	Median Age
Somatotroph Adenoma	28-62	38.9	35.0
Prolactinoma	18-67	38.0	34.5
Mixed GH-PRL Adenoma	35-44	38.0	35.0
Thyrotroph Adenoma	48	48.0	48.0
Corticotroph Adenoma	16-53	35.8	36.5
Gonadotroph Adenoma	23-77	49.9	50.5
Plurihormonal Adenoma	16-72	49.5	54.0
Null-Cell Adenoma	21-65	43.2	43.0
<b>ALL</b>	<b>16-77</b>	<b>44.5</b>	<b>43.0</b>

**Table 2 - Incidence in Age Groups**

Age Group	Total	Male	Female	L	S	SL	T	C	G	P	N
≤19	3	1	2	1	-	-	-	1	-	1	-
20-29	21	11	10	8	1	-	-	4	2	4	2
30-39	43	20	23	4	7	2	-	8	10	6	6
40-49	37	19	18	4	1	1	1	2	6	9	13
50-59	37	26	11	6	1	-	-	3	9	13	5
60-69	22	14	8	1	1	-	-	-	6	13	1
≥70	6	5	1	-	-	-	-	-	5	1	-

L = Prolactinoma, S = Somatotroph, SL = Mixed GH/PRL, T = Thyrotroph, C = Corticotroph, G = Gonadotroph, P = Plurihormonal, N = Null Cell

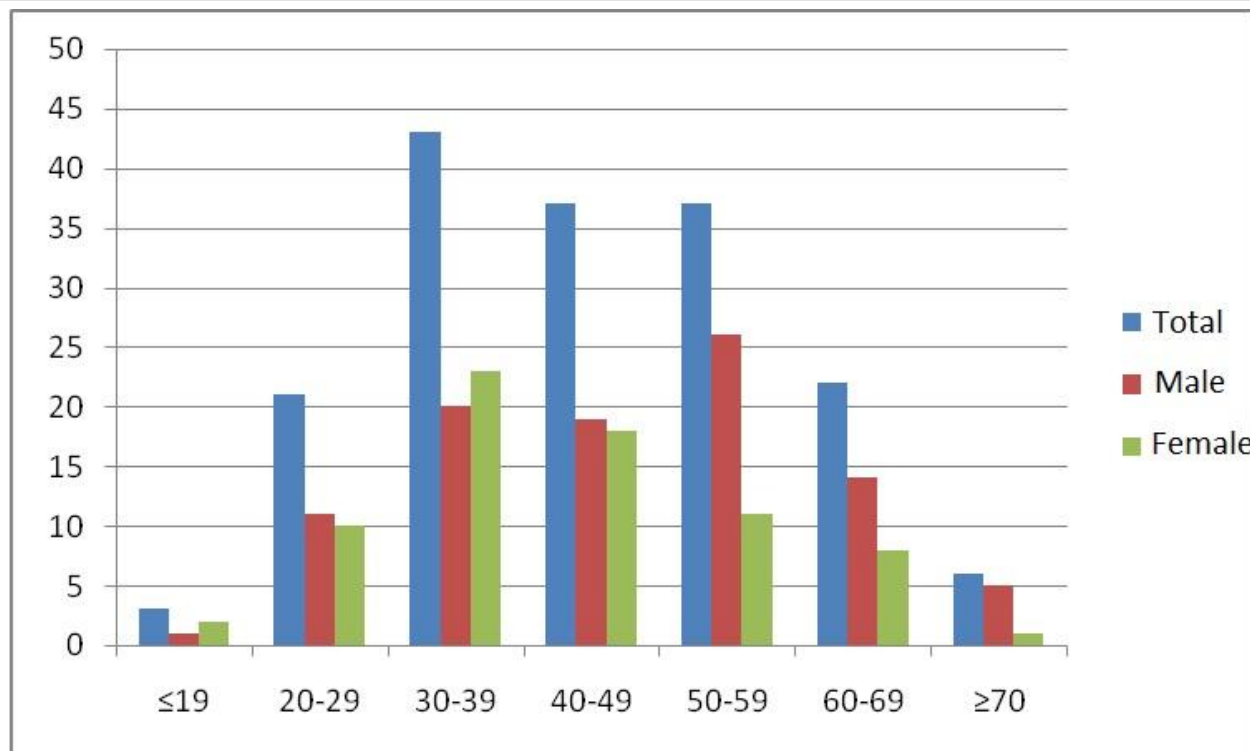


Figure 2 – Incidence in Age Groups

Of the 169 cases of Pituitary Adenoma studied, 96 were male and 73 were female. All tumour categories occurred in both sexes, with slightly higher occurrence in males (Table - 3) (57%). Among the individual categories, Prolactinoma and Plurihormonal Adenomas showed higher occurrence in males. However

the difference was statistically significant only in Plurihormonal Adenomas (P value = 0.0373). Corticotroph Adenomas showed a female preponderance, compared to the rest and this association was statistically significant (P value = 0.0022).

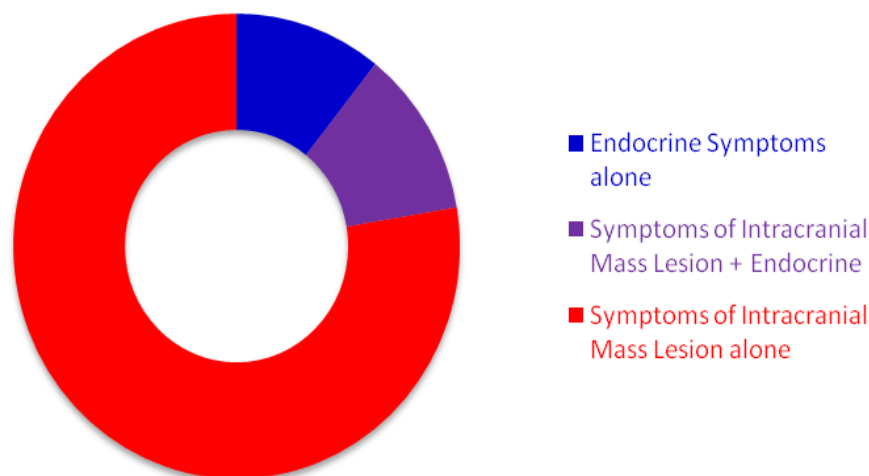
Table – 3 Gender distribution Incidence

Diagnosis	No. of Cases	Male	Female
Somatotroph Adenoma	11	6 (54%)	5 (46%)
Prolactinoma	24	17 (71%)	7 (29%)
Mixed GH-PRL Adenoma	3	2 (67%)	1 (33%)
Thyrotroph Adenoma	1	-	1
Corticotroph Adenoma	18	4 (22%)	14 (78%)
Gonadotroph Adenoma	38	23 (61%)	15 (39%)
Plurihormonal Adenoma	47	33 (70%)	14 (30%)
Null-Cell Adenoma	27	11 (41%)	16 (59%)
<b>TOTAL</b>	<b>169</b>	<b>96</b>	<b>73</b>

**Duration**

Details on duration of symptoms was available in 103 cases. It was highly variable, ranging from days to years. Patients presented with symptoms of either intracranial mass lesion, hormonal symptoms, or both. Symptoms due to intracranial mass lesion were Headache, visual field defects notably Bitemporal Hemianopia, Vomiting or Giddiness and

patients with these symptoms presented earlier than those with hormonal symptoms. Patients with acromegalic features presented with a mean duration of 45.2 months, while patients with hypothyroid, or lactational symptoms presented within the first year of onset. On studying the duration of symptoms for each tumour type, the overall variation was not statistically significant.



**Figure 3 - Symptomatology**

**Table 4 – Duration of Symptoms**

(Data Available = 84)

S. No.	Tumour Type	No. of Cases	Duration (months)		
			Range	Mean	Median
1.	Prolactinoma	11	1 – 120	22.6	12
2.	Somatotroph	4	2 – 60	33.5	36
3.	Mixed GH/PRL	1	12	12.0	12
4.	Corticotroph	6	1 – 144	31.7	8
5.	Gonadotroph	21	1 – 48	9.8	6
6.	Plurihormonal	26	1 – 120	30.9	9
7.	Null Cell Adenoma	15	1 – 48	12.7	6
ALL		<b>84</b>	<b>1 – 144</b>	<b>21.25</b>	<b>6</b>

**Radiology**

Radiological information on tumour size was available in 66 cases (Table - 5). Most of the tumours were Macroadenomas. Of the 5 Giant Adenomas seen, 4 were Plurihormonal Adenomas and 1 was Prolactinoma.

**Table 5 - Radiological Classification**  
(Data Available = 66)

S. No.	Size	No. of Cases
1.	Microadenoma	1
2.	Macroadenoma	60
3.	Giant Adenoma	5

The most common pattern of tumour extent was Suprasellar (seen in 62% of cases with available data). 31% showed involvement of Optic Chiasma.

Details on Radiological follow-up was available in 29 cases, of which 5 cases showed residual/recurrent lesion. In this category, 4 were Plurihormonal Adenomas, and one was Gonadotroph Adenoma..

**Biochemical Studies**

Serum Prolactin levels were mildly elevated in tumours other than Prolactinomas, in keeping with the Stalk-Section Effect. Serum HGH or IGF were elevated in 3 cases of Somatotroph Adenoma and 3 cases of Plurihormonal Adenoma.

Most of the patients underwent Endoscopic Transnasal Transsphenoidal Surgery.

**Microscopy**

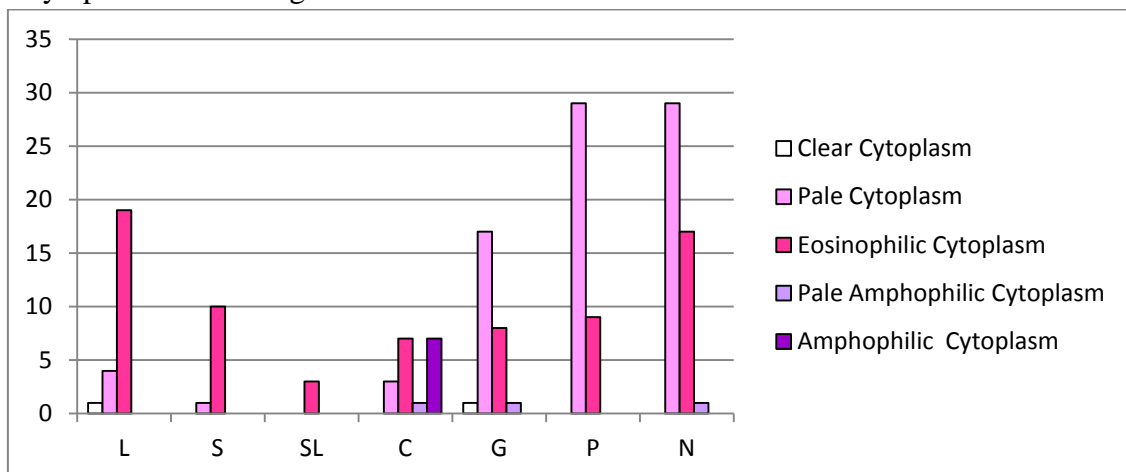
On H & E stained sections, the architectural pattern of most tumours were predominantly sinusoidal . Gonadotroph, Plurihormonal and Null Cell Adenomas showed sinusoidal or Papillary Pattern, with Pseudorosettes also. Corticotroph Adenomas had arrangement of cells in sinusoids as well as diffuse sheets. Few Prolactinomas showed Amyloid and Calcospherites also.

Cytoplasmic Staining was observed as below (Table 6, Figure 4).

**Table 6 - Cytoplasmic Staining Properties**

Cytoplasm	Prolactinoma	Somatotroph	Mixed GH/PRL	Corticotroph	Gonadotroph	Plurihormonal	Null Cell
Clear	1	0	0	0	0	0	1
Pale	4	1	0	3	29	29	17
Eosinophilic	19	10	3	7	9	17	8
Pale Amphophilic	0	0	0	1	0	1	1
Amphophilic	0	0	0	7	0	0	0

**Figure 4 - Cytoplasmic Staining**





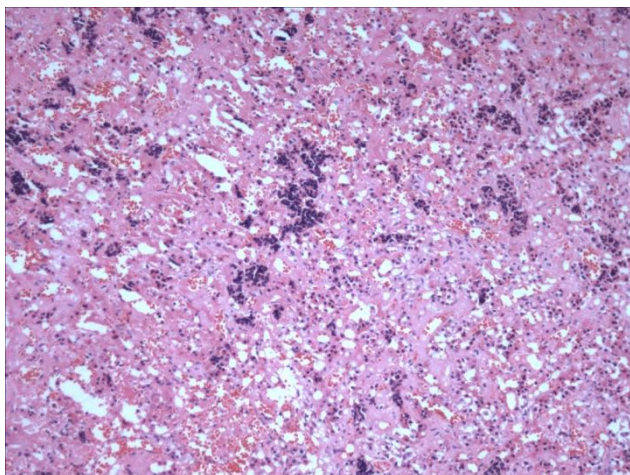
Nuclei were mostly uniform, with mild pleomorphism and prominent nucleoli being noted in Prolactinomas and Somatotroph Adenomas.

Of the 24 Prolactinomas, 8 had biochemical correlation with serum PRL level. Seven of these had elevated levels, with 6 of them, in excess of 100 ng/dl and 5 above 200 ng/dl. All these 7 cases showed strong immunopositivity for PRL in >60% of tumour cells. Two of these cases also showed significant drop in PRL levels after surgery.

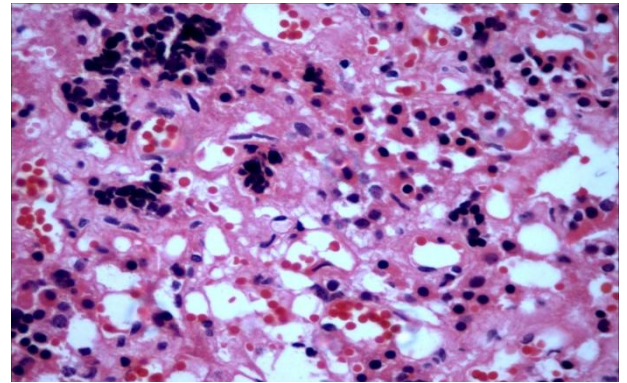
Of the 11 Somatotroph Adenomas, 4 showed acromegalic features. Biochemical correlation with serum levels of HGH was available in 4 cases, 3 of whom showed raised levels of HGH, with one of them showing elevated serum IGF level also.

Of the Plurihormonal Adenomas, the commonest combination of hormone immunopositivity was FSH, LH and TSH, which was seen in 26 cases (55%). 18 cases had FSH and PRL positivity (38%).

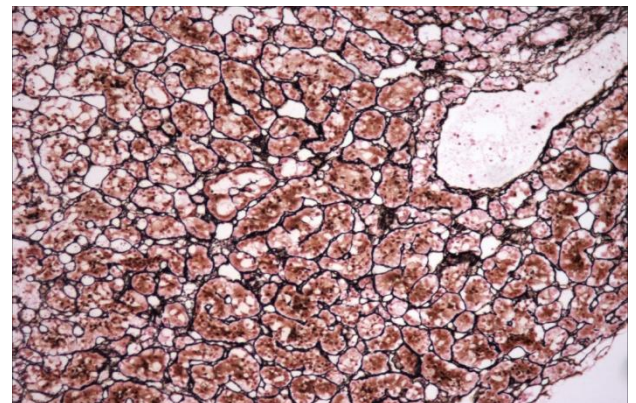
Seven cases of our study were recurrent cases, of which 4 were Pluihormonal Adenomas.



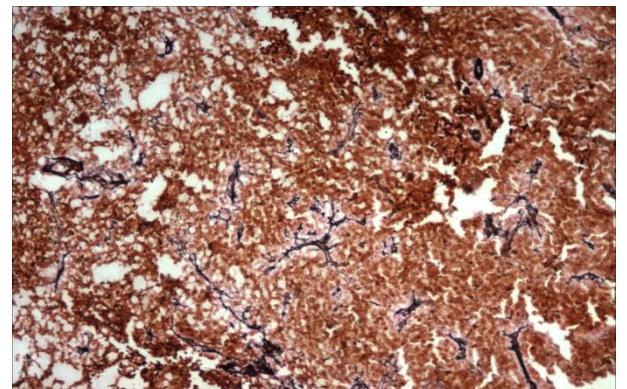
**Image 1.** The normal Pituitary Gland, H & E 10x



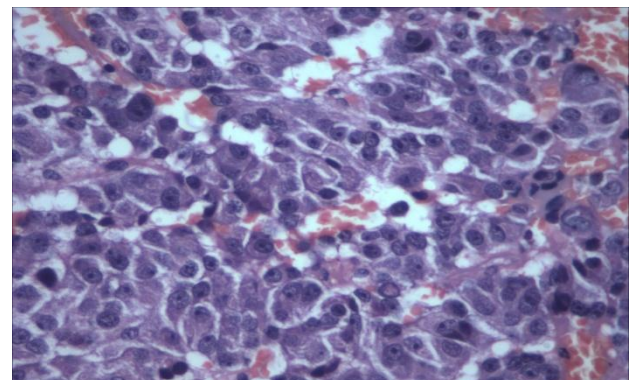
**Image 2.** The Normal Pituitary Gland. Multiplicity of cell-types is appreciated. H & E, 40x



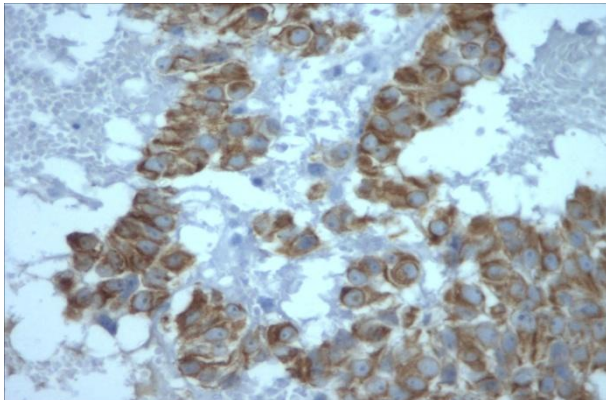
**Image 3.** Normal Pituitary Gland Reticulin Stain 10x



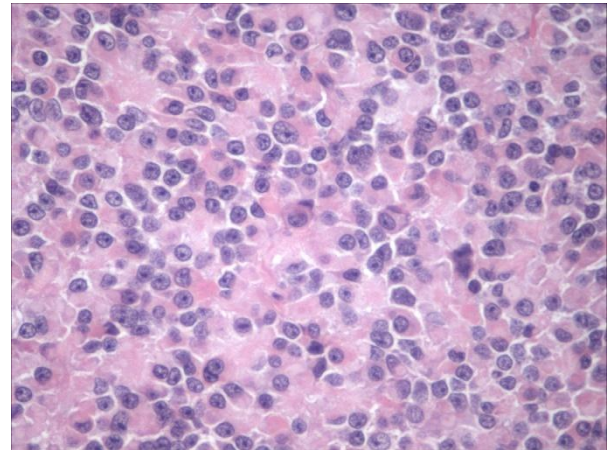
**Image 4.** Pituitary Adenoma Reticulin Stain 10x



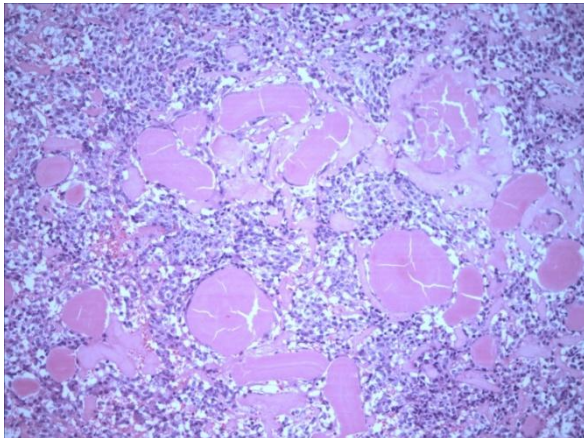
**Image 5.** Prolactinoma H & E, 40x



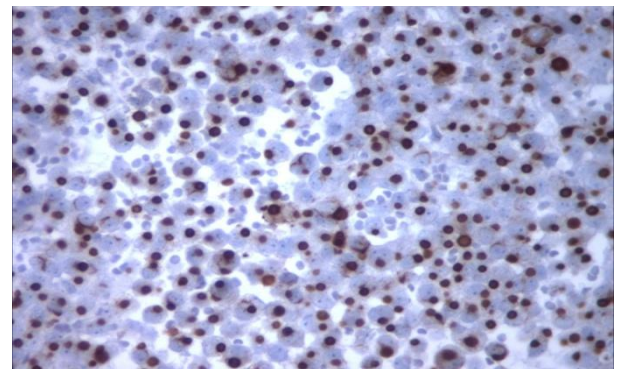
**Image 6.** Prolactinoma, PRL, 40x



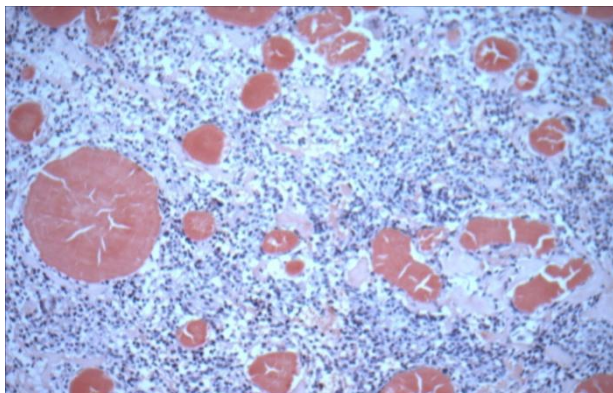
**Image 10.** Somatotroph Adenoma H & E, 40x



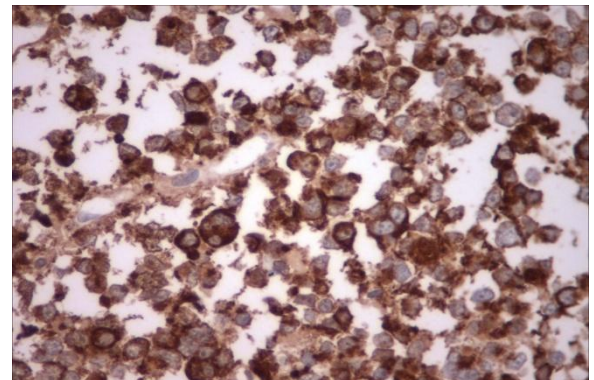
**Image 7.** Prolactinoma - Amyloid H & E, 10x



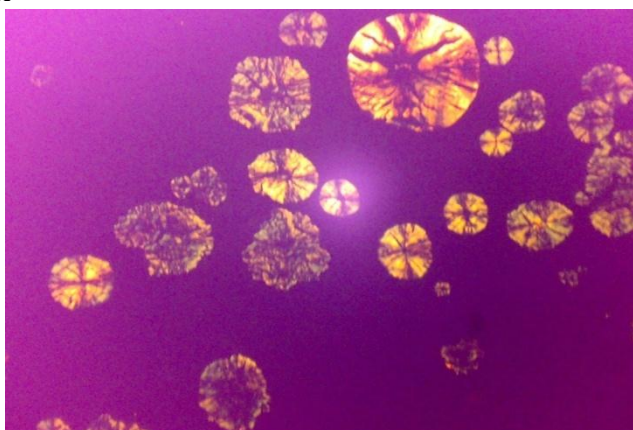
**Image 11.** Somatotroph Adenoma Dot Positivity, CK 40x



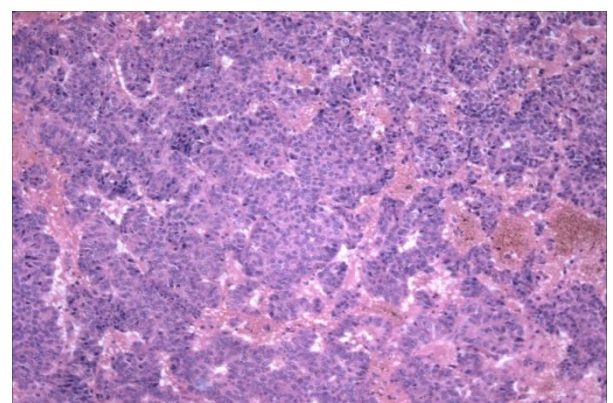
**Image 8.** Prolactinoma, Amyloid, Congo Red, 10x



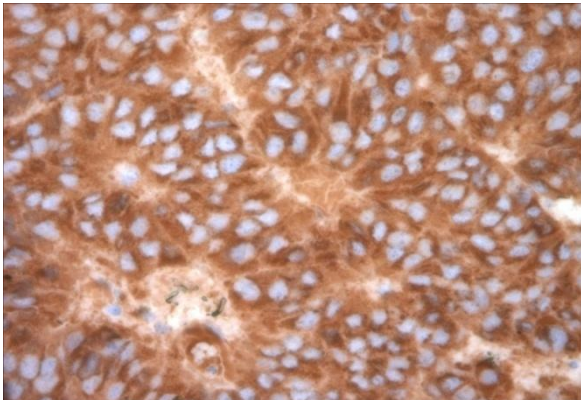
**Image 12.** Somatotroph Adenoma, HGH 40x



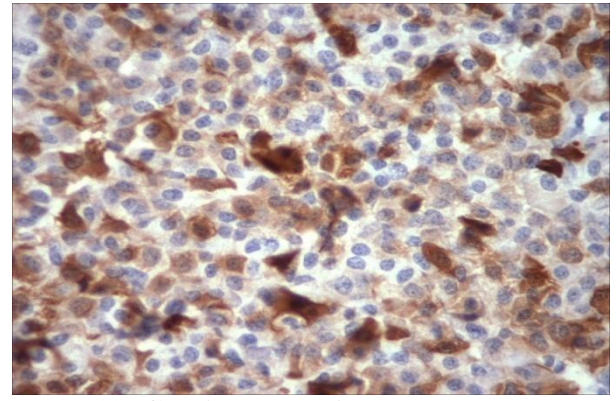
**Image 9.** Prolactinoma Congo Red, Polarized, 10x



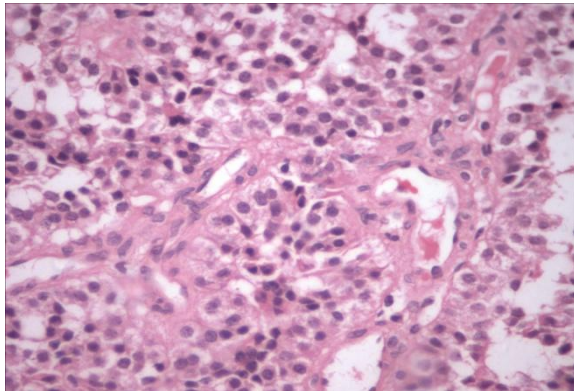
**Image 13.** Mixed GH/PRL Adenoma H & E, 10x



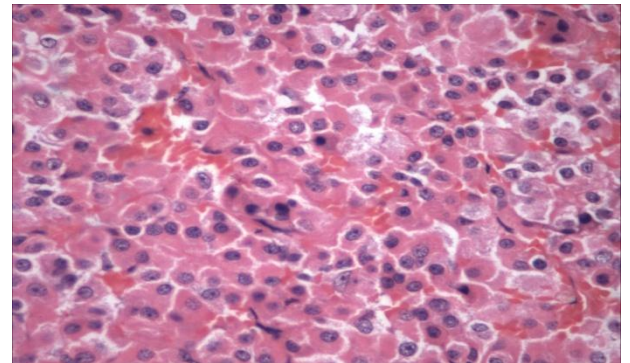
**Image 14.** Mixed GH/PRL Adenoma HGH, 40x



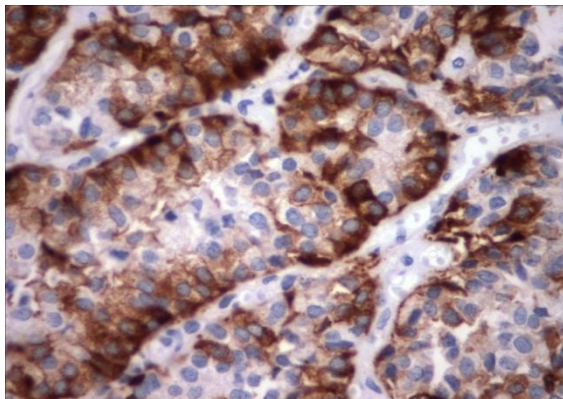
**Image 18.** Corticotroph Adenoma ACTH 40x



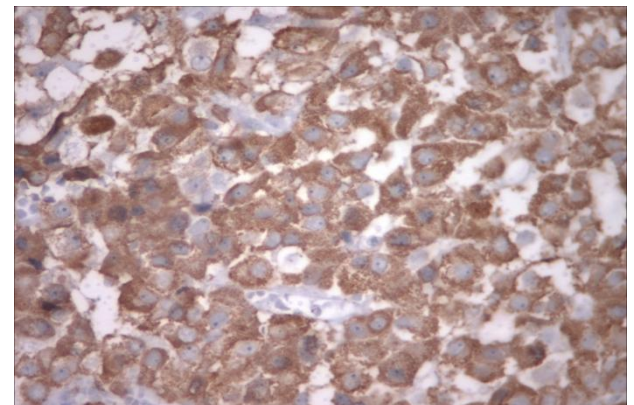
**Image 15.** Gonadotroph Adenoma H & E 40x



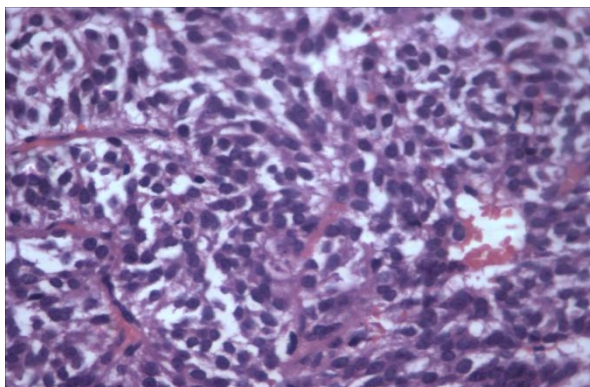
**Image 19.** Plurihormonal Adenoma Sinusoidal Pattern, H & E 40x



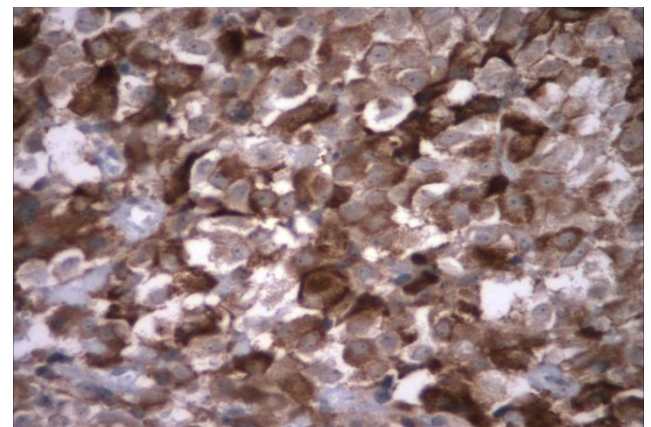
**Image 16.** Gonadotroph Adenoma LH 40x



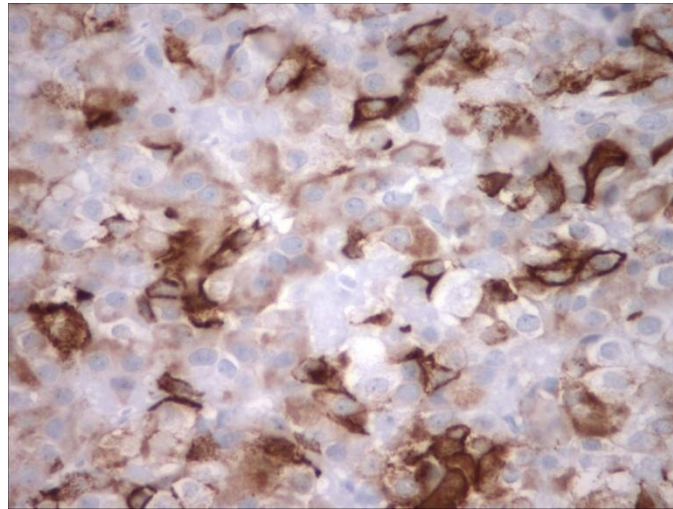
**Image 20.** Plurihormonal Adenoma HGH 10x



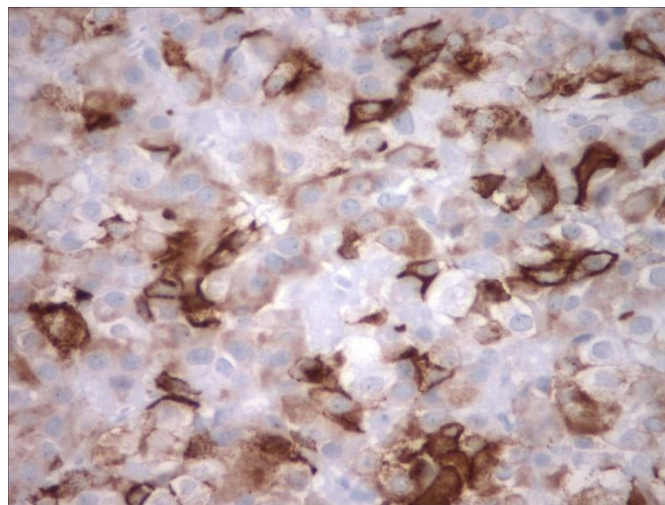
**Image 17.** Corticotroph Adenoma H & E 40x



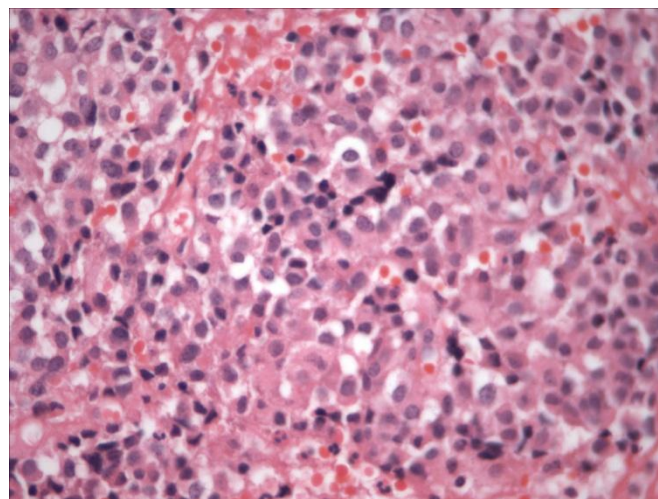
**Image 21.** Plurihormonal Adenoma FSH 40x



**Image 22. Plurihormonal Adenoma PRL 40x**



**Image 23. Plurihormonal Adenoma PRL 40x**



**Image 24. Null Cell Adenoma Papillary and Pseudorosette Pattern, H & E 40x**

2007

Lab no. IH0	Age	C. F.	Mont hs	Radiology	HGH	IGF	T3	T4	TSH	Cor	ACT	FSH	LH	Tes	PRL	Pred . Pattern	Cyto plas m	Nucl ei	Othe r LM fea tures	CK	HGH	TSH	ACT H	FSH	LH	PRL	Dx
33	56 M	B	36	MA, IS, C,	0.06	52		0.93	1.8	10.7	27.9			0.01	7.5	S	E	U		1	0	0	0	1	1	0	G
79	52 M	E, H	28	MA, SS, V,	0.05			0.8		7				2	400	H	E	M		1	0	0	0	0	0	1	L
85	72 M	D		MA					1							S	E	U		1	0	0	0	1	1	1	P
86	56 M	A	120	SS	49											H	E	M		1	1	0	0	1	0	1	P
109	26 F															S	E	M, N		1	0	0	0	0	0	1	L
124	34 M	H		SS, IS, MA,		456				13.6	54	1.6		3.2		S	E	M, N	calcos pherte	1	0	0	0	0	0	1	L
163	76 F	D, T	18	SS, IS	0.2	25		0.63	2.63				1.8	1		P	P	U		0	0	0	0	1	1	0	G
176	48 F	G, D, T, M			0.61	100		0.8	3.2	23.4	127				51	S	PA	M		1	0	0	1	0	0	0	C
209	53 M	H, D	1	IS				0.7	1	15				0.9	10714	S	E	U		1	0	0	0	0	0	1	L
294	16 M															H	A	U		1	0	0	1	0	0	0	C
322	44 M	A			12			1.6	0.97	10						S	E	U		1	1	0	0	1	0	1	SL
347	56 M	D, H	4	MA,												S	E	M		1	0	0	0	0	0	1	L
375	58 M															S	P	U		1	0	1	0	1	1	1	P
380	40 F															H	PA	M		1 dot	0	0	0	0	0	0	N
432	43 F	A	12	MA		360										H	E	U	Hge	1	1	0	0	1	1	0	P
453	53 M															S	E	U		1	0	0	0	0	0	1	L
535	42 M	G, D		SS												S	E	U		1	0	0	0	0	0	1	L
592	49 F	D		SS, C												P	P	U		1	0	0	0	0	0	0	N
593	53 M															H	P	U		1	0	0	1	0	0	0	C
808	35 F	H	36	SS, IS												S	E	U		1	1	1	1	1	0	1	P
810	61 M															S	E	U, N		1	1	1	0	0	1	0	P
944	43 M															S	E	M		1	0	0	0	0	0	0	N
956	41 M	G, k/c/o hypot		MA, SS, IS, C	0.07					12					17.9	S	P	U		0	0	0	0	1	0	0	G
1076	30 F															S	E	U	Necro	0	0	0	0	0	0	1	L
1191	46 M	D	48	MA,				0.9	1	2.6				0.05	7.6	S	E	U		1	0	0	0	0	0	0	N
1205	34 M															S	E	U		1	0	0	0	1	0	0	G
1217	21 M															S	E	U	Amyloi	0	0	0	0	0	0	1	L
1263	39 F															S	E	U	Necro	1	0	0	1	0	0	0	C
1284	32 M															S	P	U		1	0	0	0	1	0	1	P
1355	29 M															H	E	M, N		1	0	0	0	0	0	1	L
1372	46 M	G		SS, N												S	P	U		1	0	0	0	0	0	0	N
1395	58 M	H, V,	12					0.36							116	S	P	U		1	0	0	0	0	0	4	L
1456	46 M															S	P	U		1	0	0	0	1	0	0	G
1457	41 M	D	6	SS				1.2	2.8	18.8					38.4	P	E	U		1	0	0	1	1	0	0	P
1552	28 F															S	E	M, N		1	1	0	0	0	0	0	S
1554	33 F															S	E	U	Amyloi	1	0	0	0	0	0	5	L
1576	35 M	H, D	1			42	141	0.4	1.5					5.9	1.3	2.7				0	0	0	0	1	1	0	G
1632	35 F	A, M,	12	N												S	E	M		1	1	0	0	0	0	6	SL
1639	42 F	H, M, D, B, k/c/o hypert	48	R	20.2	260		0.94	1.75	10					63.1	S	E	U, N		1	1	0	1	0	0	2	P
1656	46 F	H, D	36	PS,	0.4		62	2.6	1.6						24	P	P	U		0	0	0	0	0	0	0	N
1730	53 F	V	1	MA, SS, PS		34		1.5	1.4					12	11.8	1	8	N	P	U		1	0	0	0	1	G
1757	54 M	B	6	MA,			113	7.4	1.3						9	S	P	U		0	0	0	0	1	1	0	G
1790	37 F	D, H, V	12	MA, SS, C			93	4.4	1.54	17	19.2	3.2	1.5		9.2	S	P	U		1	0	0	0	1	1	0	G
1791	35 M															S	E	U		0	0	0	0	1	1	0	G
1819	20 F															N	E	U	Infarct	1	0	0	1	0	0	0	C
1856	65 F															H	P	U		1	0	0	0	1	1	0	G
1923	45 M															H	P	M		1	0	0	1	1	0	0	P





## Discussion

The ratio of the various tumour types, seen in the study conducted by Osamura, Kajiya and Takei<sup>1</sup> showed a preponderance of Non-Functioning Adenomas, which comprised Null Cell Adenomas and Oncocytomas<sup>1, 19</sup>, which was followed, in order, by Somatotroph Adenomas, Prolactinomas, Corticotroph Adenomas and Gonadotroph Adenomas. Plurihormonal Adenomas were very rare in Western literature<sup>3, 9</sup>. In our study, the commonest tumour was Plurihormonal Adenoma (28%), followed by Gonadotroph Adenoma (22%), Null Cell Adenoma (16%), Prolactinoma (14%) and Corticotroph Adenoma (11%). Plurihormonal Adenomas had a frequency of 36.1% in the study conducted by Pawilowski et al<sup>19</sup> and 31% in the study of Ho et al<sup>21</sup>.

71.5% of cases occurred during the fourth, fifth and sixth decades. Corticotroph Adenomas had a relatively younger mean age of occurrence (35.8), which was in accordance with 30 to 40, mentioned in literature available<sup>3</sup>. The mean age of presentation of Null Cell (43.2), Plurihormonal (49.5) and Gonadotroph Adenomas (49.9) was in accordance with the mean ages described in literature<sup>19, 21, 12</sup>.

All tumours occurred in both sexes, with a slight male preponderance. Plurihormonal Adenomas showed a statistically significant male preponderance. Corticotroph Adenomas were commoner in females, which was in accordance with literature<sup>3</sup>.

In patients for whom clinical history was available, 77% presented with signs and symptoms of symptoms of intracranial mass lesion (Headache, Bitemporal Hemianopia) in comparison with 74% of patients with only visual field defects, in the study conducted by Cury et al.<sup>19</sup>. Patients with these symptoms presented earlier than those with only endocrine symptoms.

In patients with available radiological data, 91% presented with Macroadenoma. Most

cases showed Suprasellar Extension. Involvement of Optic Chiasma, seen in 31% of cases with available data, could account for Visual Field Defects.

Serum PRL levels were available in 60 cases, of which 27 showed elevated values. Values below 200 ng/dl, in non-prolactinomas, could be attributed to the stalk-section effect<sup>3</sup>. Of the 5 cases in our study with values above 200 ng/dl, 4 were Prolactinomas and one was Plurihormonal Adenoma.

Reduction in values of T4 were noted in non-thyrotroph adenomas, explaining the deficiency of hormones produced by the uninvolved Pituitary gland<sup>3</sup>.

Most tumours showed predominantly Sinusoidal Pattern, with Corticotroph Adenomas forming Diffuse sheets and Gonadotroph, Plurihormonal and Null Cell Adenomas<sup>7</sup> showing Papillary and Pseudorosette patterns. Cytoplasmic Staining Properties on H & E were consistent with the Histologic Classification of the various Tumour types<sup>7</sup>.

Only one case of Thyrotroph Adenoma was seen (48/F).

Most Plurihormonal Adenomas expressed FSH hormone immunohistochemically. The commonest combination of hormone immunopositivity seen was FSH, LH and TSH (55%). Plurihormonal Adenomas were the commonest tumour types known to recur, as seen in literature<sup>1</sup>.

## Conclusions

Pituitary Adenomas can be classified immunohistochemically.

Patients with symptoms of Intracranial Mass Lesion present earlier than those with endocrine symptoms.

Plurihormonal Adenoma is the most common type of tumour in our study Population. They are most likely to recur.

The most common combination of hormone immunopositivity in Plurihormonal Adenomas seen in our study is FSH, LH and TSH.



Corticotroph Adenomas are relatively commoner in females and Plurihormonal Adenomas in males.

Radiologic and Biochemical correlation and correlation with H & E stained light microscopy is necessary to explain symptomatology

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