Clinical Application of Pathology

BRAIN TUMOURS VI – Pineal, Sellar region and Pituitary tumours

System: Nervous

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Introduction: this module discusses tumours of the pineal and non-pituitary tumours in the sella region, as well as tumours of the pituitary gland itself.

The 2016 World Health Organisation Classification of Brain Tumours now incorporates genetic mutations, as well as the traditional histopathology and immunochemistry.

In the case of the hormonally active pituitary tumours, classification is assisted by the use of transcription factors to more closely identify a particular tumour. These hormonal tumours of the pituitary are dealt with in the WHO Classification of Endocrine tumours, an update of that document is expected in May 2017. For that reason, the table on the next screen does not show a WHO grade for those tumours. Instead they have been grouped according to their transcription factor. This is identified with hormonal immunohistochemistry.

There is a large spectrum of chromosomal alterations in pituitary tumours. Chromosomal imbalances are present in 50% of sporadic pituitary tumours, both functioning and non-functioning (Null cell adenoma).

Gains of genetic material have been identified on several chromosomes including X, 22, 19, 17, 12, 9, 8, 7 and 5.

Loss of chromosome 11 is the most common loss in pituitary tumours.

Not all centres have the facilities to undertake molecular pathology, so they rely on histopathology and immunohistochemistry.

A further simplistic classification used is resort to the International Classification of Disease for Oncology (ICD-O) which divides adenomas into Typical pituitary adenoma (8272/0) and Atypical pituitary adenoma (8272/1).

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TABLE of CONTENTS

<table>
<thead>
<tr>
<th>Pineal Tumours</th>
<th>WHO grade I</th>
<th>WHO grade II</th>
<th>WHO grade III</th>
<th>WHO grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pineocytoma</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pineoblastoma</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pineal parenchymal T of intermediate differentn</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Papillary T of pineal region</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tumours of Sella region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General overview of pituitary adenomas.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumours of Posterior Pituitary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granular cell tumour</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituicytoma</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumours of Anterior Pituitary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spindle cell oncocyctoma</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pit-1 (GH/PRL/TSH)adenomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tpit (ACTH) adenoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-1 (Gonadotroph) adenomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymorphous plurihormonal adenoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plurihormonal adenoma, Silent subtype III.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Null cell adenoma (chromophobe adenoma)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PINEAL TUMOURS

Pineal tumours represent a rare and heterogeneous group of primary central nervous system neoplasms, which include:

1. pineal parenchymal tumours (pineocytomas, pineal parenchymal tumours of intermediate differentiation, and pineoblastomas)
2. germ cell tumours and
3. neuroepithelial tumours, such as astrocytomas, ependymomas and papillary tumour of the pineal region.

Introduction: The pineal gland develops during the second month of gestation as a diverticulum in the diencephalic roof of the third ventricle. It is flanked by the posterior and habenular commissures in the rostral portion of the midbrain directly below the splenium of the corpus callosum. The pineal reaches adult size by the age of 12 months.

Pineal tumours comprise 1% of adult CNS tumours and 3-8% of paediatric CNS tumours. Pineal parenchymal tumours comprise 14-27% of tumours in the pineal. [Germinomas account for 40%.

There is a variety of neoplasms in the pineal which reflects the different cell types in the gland. Pineal parenchymal tumours arise from the specialized neurosecretory elements of the mature gland. Gliomas are thought to arise from pineal glial cells or from other glial cells in the vicinity of the pineal gland. Benign pineal cysts also occur and are usually asymptomatic, unless haemorrhage occurs into the cyst but the cyst must be distinguished from pineal tumours.

The pineal parenchymal cells – pineocytes – have large nuclei. The pinocyte is a specialized neuron related to retinal rods and cones. The pinocyte is surrounded by a stroma of fibrillary astrocytes, which interact with adjoining blood vessels to form part of the blood-brain barrier. The pinocyte has a club-shaped process which are few in number and not fully developed before the age of 8 years. The gland contains few typical ganglion cells, but is innervated by sympathetic nerve fibres originating from the superior cervical ganglia. These fibres control the production and secretion of melatonin by pinealocytes, from circulating tryptophan, the synthesis taking place at night. The endogenous rhythm of secretion is generated by the hypothalamic suprachiasmatic nuclei and activated by the light/dark cycle.

Immunohistochemistry: pineocytes stain intensely for synaptophysin and neurofilaments. Chromogranin A can sometimes be detected and a small number of cells express rhodopsin and S-antigen. The interstitial cells express glial fibrillary acidic protein and S-100 protein.

Ultrastructural level: the normal pineal gland has a juxtaposition of clear and dark cells with numerous organelles, and with long zonulae adherents and deeply indented eccentric nuclei. Cytoplasmic melanin granules are rarely observed. The cells of the normal pineal have the features of paraneurons and show neurosensorial and neuroendocrine differentiation.

PINEAL CYSTS are non-neoplastic. Pineal cysts are often misdiagnosed as a pineocytoma or pilocytic astrocytoma, and it is critical the pathologist accurately recognize the non-neoplastic nature of this lesion, and not confuse it with a neoplasm of the pineal region.
**Incidence:** Reported in 40% of autopsy series.

**Size:** 1 – 3 cm diameter and round or oval shape. More frequent in women. Haemorrhage may occur into these cysts and increase in size exerts pressure on the aqueduct of Sylvius and the tectal plate.

**Age:** Most frequently seen in young adults.

**Microscopic:** The cysts are unilocular, containing a proteinaceous fluid, and the wall has a trilaminar structure; an inner gliotic, astrocytic layer, fibrillary in character, and may contain Rosenthal fibres, eosinophilic granular bodies and/or haemosiderophages. A middle layer with columns of pineal parenchyma which may have calcification which is often somewhat disordered and external to this is an outer thin fibrous leptomeningeal layer.

The next image below shows the trilaminar structure of a pineal cyst. The inner lining is astrocytic and fibrillary in character and may contain Rosenthal fibres, eosinophilic granular bodies and/or haemosiderophages (top of image). External to this is a variably calcified layer of pineal parenchymal tissue, which is often somewhat disordered and disorganized (bottom) and external to this is a thin and often incomplete layer of fibrous tissue.
Differential diagnosis:

In intact and well oriented excision specimens the diagnosis of pineal cyst is usually straightforward. Misdiagnosis however is not infrequent, - errors may occur if the histological samples are small or poorly oriented and particularly if careful attention is not paid to the neuroimaging studies. When seen in small fragments, or if cut en face , the compressed and distorted layer of pineal tissue may be erroneously interpreted as a pineal parenchymal tumour. Similarly, the glial lining, with its combination of reactive astrocytic atypia, Rosenthal fibres and eosinophilic granular bodies may lead to confusion with pilocytic and/or fibrillary astrocytoma. The distorted pineal parenchyma lacks pineocytomatous rosettes, and contains scattered calcification. When piloid in character, the glial lining lacks the classical biphasic architecture (particularly the microcystic pattern) of pilocytic astrocytoma and its characteristic hyalinised vessels.

The correct identification is important as the patient may be incorrectly given radiation therapy.

Immunohistochemistry can assist the diagnosis as neurofilaments and synaptophysin are intensely expressed in the residual normal pineal parenchyma. The glial lining and the reactive glial processes that infiltrate the residual pineal parenchyma show strong expression of GFAP.

**PINEOCYTOMA – 9361/1 - WHO grade I**

**Definition:** A tumour arising in the pineal gland that resembles normal pineal parenchyma.

**Age:** 10 – 65 years, mean 45 years.

**Gender:** no sex predilection.

**Clinical Presentation:** is mainly from obstructive hydrocephalus secondary to compression of the tectum of the midbrain and obstruction of the aqueduct. Compression of the superior colliculi can also lead to a characteristic gaze palsy, known as Parinaud syndrome.

**Macroscopic:** Typically pineocytomas are slow growing and well-circumscribed tumours (compared to pineoblastomas that tend to be larger, and less well circumscribed). They tend to be solid, although focal areas of cystic change, or haemorrhage do occur. When the cystic component is large, distinguishing them from pineal cysts can be difficult,

**Imaging:** Pineocytomas do not have a well-formed blood brain barrier so enhance vividly.

CT demonstrates the mass to be of intermediate density, similar to the adjacent brain. Pineal calcifications tend to be dispersed peripherally – see below. This is the same pattern seen in other pineal parenchymal tumours, distinguishing these tumours from pineal germinomas that tend to ‘engulf’ pineal calcification. Image courtesy of John Hegde and Gillian Lieberman, Beth Israel Deaconness Medical Centre, Oct/Nov 2010.
MRI is the modality of choice for examining tumours of the pineal region.

- **T1**: hypo to isointense to brain parenchyma
- **T2**
  - solid components are isointense to brain parenchyma
  - areas of cystic change are common
  - sometimes the majority of the tumour is cystic
- **T1 C+ (Gd)**: solid components vividly enhance

MRI images courtesy of Associate Professor Frank Gaillard, Radiopaedia.org, rID : 2647 and 4068

**Microscopic**: Pineocytoma demonstrates a relatively uniform population of closely aggregated cells with rounded and relatively uniform nuclei. The rounded eosinophilic and fibrillary areas are nuclei-free and represent distinctive pineocytomatous rosettes.

**Immunohistochemistry**: Pineocytomas express several types of neuronal markers. Strong expression of Neurofilament and Synaptophysin is seen in the fibrillary pineocytomatous rosettes of typical pineocytomas or in the gangliocytic processes. Tumour cells may also express class III β-tubulin, microtubule-associated protein 2 (MAP2), crystalline, and ubiquitin C-terminal hydrolase (PGP9.5). The tumour cells express proteins related to the photosensory organ, including S-Ag and rhodopsin. Also can express serotonin and TPOH implicated in melatonin synthesis. The interstitial cells are usually GFAP- and S-100P-positive.

**Molecular pathology**: common changes reported include monosomy and loss of all, or part of chromosome 22, partial deletion or loss of chromosomes 1 and 11, deletion in the distal 12Q region.

**Biochemistry**: no evidence to show an increase or decrease in the production of melatonin.

**Treatment**: Pineocytomas are treated surgically and have an excellent prognosis when a complete resection is achieved.
**Prognosis:** A 5-year survival of 86% has been reported. Average survival is 7 years. Local recurrence and even CSF metastases are reported, but rare.

**PINEOBLASTOMAS:**

**Age:** usually occur within the first 2 decades of life but patients have been reported as old as 44 yrs.

**Gender:** slight male predilection.

**Clinical presentation:** symptoms and signs of a rapidly expanding mass.

**Associated conditions:** in children pineoblastoma has been associated with bilateral retinoblastoma – condition referred to as trilateral retinoblastoma due to RB1 mutation.

**Imaging:** CT and MRI show a large poorly demarcated heterogeneous mass.

This tumour has a tendency to involve directly adjacent brain structures, which helps distinguish it from other pineal tumours that tend to be better circumscribed.

**CT:** The solid component tends to be slightly hyperdense compared to the adjacent brain due to high cellularity. This is a characteristic shared by other small round blue cell tumours such as medulloblastoma.

Classically, they are described as having peripherally dispersed or "exploded" calcification, similar to pineocytomas. In contrast, pineal germinomas tend to engulf pineal calcification – see images in pineocytoma.

**MRI:** Pineoblastomas tend to appear as sizable (>4 cm) irregular masses often with evidence of invasion into adjacent brain. Typical signal characteristics include:

- T1: isointense to hypointense to adjacent brain
- T2
  - isointense to adjacent brain
  - areas of cyst formation or necrosis may be present
- T1 C+ (Gd): vivid heterogeneous enhancement
- DWI/ADC: restricted diffusion due to dense cellular packing. ADC ~ 400-800 mm²/s

Central necrosis is sometimes present which can make the mass appear centrally cystic and thus can roughly mimic a pineal cyst, although the latter should have a smooth, thin wall. Image below is courtesy of Associate Professor Frank Gaillard, Radiopaedia.org, rID 22620.
**Macroscopic:** pink or gray, focally haemorrhagic, necrotic, friable neoplasms. The tumour may spread to the leptomeninges and third ventricle frequently. CSF seeding is present in 15% of patients at the time of diagnosis. Image below courtesy of Associate Professor Frank Gaillard, Radiopaedia.org, rID: 27617.

![Image](image-url)

**Microscopic:** Histologically the cells are indistinguishable from cerebellar medulloblastoma.

In contrast to pineocytomas, pineoblastomas are poorly differentiated, malignant W.H.O. grade IV tumours of tightly packed small cells with scant cytoplasm, dense chromatin, and irregular or round nuclei. Mitotic figures are typically observed, and the MIB-1 index is high. See image below.

While neuroblastic Homer-Wright rosettes may be detected, larger pineocytomatous structures are not present.

![Image](image-url)

**Immunohistochemistry:** Neurofilament proteins and markers of melanocytic or mesenchymal components may be expressed. As in pineocytomas, immunostaining is positive for synaptophysin. NSE and Syn immunolabelling at a lower intensity than in other pineal parenchymal tumours can be observed in pineoblastoma. Labeling for NF, Chrg A, S-Ag, class III β-tubulin and sometimes GFAP is restricted to cell subsets.

**Ultrastructure:** pineoblastomas’ poorly differentiated neuroectodermal cells have elongated, polygonal or round nuclei and scanty cytoplasm. Cell processes and cell junctions are rarely seen.

**Molecular pathology/genetics:** Monosomy for chromosomes 20 and 22 and trisomy for chromosome 14 have been described.

The most frequently involved chromosome in structural rearrangements is chromosome 1. The short arm was involved in some cases; in others, the anomaly was in the long arm. There may be unbalanced gain of chromosome 17q, e.g. i(17)(q10). These factors illustrate the complex karyotypic nature of this tumour type.
Comparative genomic hybridization (CGH) has identified chromosomal gains and losses in pineoblastomas.

**Treatment:** is usually a combination of surgery, chemotherapy and radiation

**Prognosis:** Despite treatment, the prognosis is poor, with a 5-year survival of only 58%. Most important factors for a favourable outcome are early detection and treatment with at least chemotherapy, preferably a high dose regime with stem cell rescue.

**PINEAL PARENCHYMAL TUMOUR OF INTERMEDIATE DIFFERENTIATION – 9362/3 – PPT int**

Can be WHO grade II or III.

This tumour falls between pineocytoma (well differentiated, WHO grade I) and pineoblastomas (poorly differentiated, WHO grade IV)

**Age:** commonly middle aged adults but has been reported between 5 and 65 years

**Gender:** males and females affected equally.

**Imaging:** no specific features differentiate PPT int from other pineal region lesions.

**Macroscopic:** They may invade adjacent structures and also spread along CSF pathways.

**Microscopic:** they do not demonstrate the highly differentiated appearance of pineocytomas, but also lack the malignant small blue cell appearance of a pineoblastoma.

However, 4 different morphological subtypes have been described. In the first 2 subtypes there is a lobular form with an endocrine-like vascularity and a diffuse form mimicking oligodendroglioma or neurocytoma with the tumour cells containing a round nucleus with stippled chromatin surrounded by a variable amount of cytoplasm.

The 3rd subtype is a transitional form with lobulated and/or diffuse areas associated with other areas containing pineocytomatous rosettes and occasionally giant cells or ganglionic cells. The 4th type has a biphasic pattern including areas of typical pineocytoma and piloblastoma also called mixed PC/PB.

There is variability in mitotic activity. Microvascular proliferation and limited foci of necrosis may be present.

The example is composed of a moderately pleomorphic population of cells with rounded nuclei. The stroma lacks the well formed pineocytomatous rosettes of pineocytoma. Here is focal necrosis but the appearances are not those of a malignant small cell lesion such as the pineoblastoma.
**Immunohistochemistry:** strong immunolabelling for NSE and Syn can be seen in the well-differentiated areas of PPT int. Some tumours express NF, ChrgA and S-Ag. GFAP and S-100P staining is seen in interstitial cells.

**Ultrastructure:** frequently see neuronal, neuroendocrine and/or neurosensory differentiation.

**Prognosis:** local recurrence and rare spinal metastasis may occur with WHO grade II PPT int. The 5 year event-free survival is 85%.

Grade 3 PPT int (and piloblastoma WHO grade 4 ) can recur locally and metastasize. The 5 year event-free survival being 65%.

**PAPILLARY TUMOUR OF THE PINEAL REGION – 9395/3 – WHO grade II or III.**

First described in 2007.

Thought to arise from specialised ependymocytes of the subcommissural organ located in the lining of the posterior commissure rather than from the pineal gland itself.

**Age:** reported from 5 – 65 years of age.

**Clinical presentation:** is mainly from obstructive hydrocephalus, secondary to compression of the tectum of the midbrain and obstruction of the aqueduct. Compression of the superior colliculi can also lead to a characteristic gaze palsy, known as Parinaud syndrome.

**Imaging:** MRI - intrinsic high T1 signal attributed to secretory inclusions is a relatively specific finding when other causes of T1 shortening are excluded (e.g fat in teratomas / lipomas; melanoma or haemorrhagic metastases; thrombosed aneurysms). Contrast enhancement is moderate and cystic regions common. Screening of the entire neural axis is required as CSF dissemination has been reported in up to 7% of cases.

The example below is courtesy of Shakir HJ, Qiu J, Prasad D, Mechtler LL, Fenstermaker RA. Papillary tumor of the pineal region with extended clinical and radiologic follow-up. Surg Neurol Int 2015, 07-Oct;6:

Preoperative T1-weighted axial, coronal, and sagittal images with gadolinium contrast enhancement (left panels, in clockwise direction), and corresponding T1-weighted axial, coronal, and sagittal images obtained on day of gamma knife treatment (right panels, in clockwise direction)
**Microscopic:** Microscopic examination reveals the distinctive papillary growth pattern, but in addition, there are also intervening solid aggregates of neoplastic cells. Within the papillary foci, thick and well-formed fibrovascular stromal cores are lined by neoplastic epithelium, and these papillary structures form arborizing arrangements. The solid cellular aggregates lining between the papillary structures may contain small ependymal-type rosettes, intracytoplasmic lumina, and perivascular pseudorosettes.

The stratified epithelium lining the papillae varies in thickness and is formed by a mixture of cuboidal and columnar cells. This population generally demonstrates little in the way of pleomorphism, though occasional pleomorphic nuclei may be present. Mitotic activity is variable, but often sparse. The nuclei of the epithelial-cell population are generally relatively monomorphic in appearance, in both solid and papillary areas, with ovoid or slightly polygonal outlines, and occasional small individual nucleoli, though occasional pleomorphism may be observed.

The stromal cores may contain patchy, mixed chronic inflammatory infiltrates. Free-lying necrotic cellular and inflammatory debris is often found between the epithelial lined surfaces of the papillary structures.
The tumour is quite densely cellular with frequent areas of necrosis. There is an epithelial-like growth pattern in which the vessels are covered by a layer of tumour cells. In papillary areas, the neoplastic cells are large and columnar or cuboidal with a clear cytoplasm and a round or infolded nucleus.


**Immunohistochemistry:** tumour cells express cytokeratin, S-100 P, NSE and vimentin but only show weak expression of EMA and GFAP.

**Differential diagnosis:** The tumour may resemble papillary pineocytomas or choroid plexus papillomas, which can occur in the pineal region.

Also could be mistaken for metastatic carcinomas. However, the high expression of cytokeratin and EMA in carcinomas is rarely associated with immunostaining for other proteins such as vimentin, S-100 P and NSE, so the correct diagnosis can be made using immunohistochemistry.

**Treatment:** surgery and radiation therapy. Bevacizumab is effective for recurrent papillary tumour of the pineal region. It is an antibody against vascular endothelial growth factor.

**Prognosis:** These tumors are characterized by frequent local recurrence. Five-year estimates of overall and progression-free survival have been set at 73% and 27%, respectively. Incomplete resection and a mitotic index higher than five per 10 high power fields correlates with decreased survival and increased recurrence. Gross total resection is the only clinical factor strongly associated with overall survival and recurrence.

**TUMOURS of the SELLA REGION**

**CRANIOPHARYNGIOMA – 9350/1 – WHO grade I**

**Development:** Craniopharyngiomas are thought to arise from remnants of Rathke’s pouch. The latter originates during the 4th week of embryonic life, when the roof of the primitive oral cavity (stomatodeum) forms an upward evagination lined by epithelial cells of ectodermal origin. The superior extension gives origin to the cells of the anterior pituitary and pars tuberalis. The path between the uppermost aspect of the primitive adenohypophysis and the stomatodeum is the craniopharyngeal duct. This duct involutes but any remnant ectoblastic epithelial rests can be sequestrated along the path of the duct, and can be especially dense in the region of the pars tuberalis. The path of the distribution of those cell rests corresponds to the distribution of craniopharyngiomas.
Types: adamantinomatous (90%) and papillary

Incidence: account for 3% of intracranial tumours.

Age: can develop in utero presenting as large masses in the newborn. However, there are 2 peaks; paediatric and young adults and during the 5th and 6th decades. Children most commonly diagnosed between the ages of 5 and 10 years.

Site: intrasellar (20%), suprasellar (infundibular-tuberian), and dumb-bell shaped tumour (sellar and suprasellar). Suprasellar growth may be impeded by the diaphragmatic aperture, producing a dumb-bell outline. 80% are in a suprasellar location but some of these will also have an intrasellar component.

Rare sites are wholly within the 3rd ventricle, the optic chiasm, sphenoid bone, pharynx, pineal and cerebellopontine angle.

Gender: equal in the sexes.

Clinical presentation: In children there is short stature, diabetes insipidus and delayed sexual development. In adults there may be visual complaints due to compression of the optic chiasm, hypopituitarism and pituitary stalk effects of pituitary insufficiency.

Macroscopic: 50% are cystic, 15% are solid and 35% are mixed. Blood supply to the tumour comes from perforating branches of the anterior communicating artery to the anterior wall of the tumour and from the posterior communicating artery to supply the lateral walls of the tumour.

In the paediatric population, the adamantinomatous type is most frequent and these tend to be cystic or mixed and calcify (90% of cases calcify). Only a few are purely solid lesions.

In adults, the papillary craniopharyngioma is dominant and these are more often solid and rarely have calcification. Consists of metaplastic squamous cells.

The free surfaces of the tumour are smooth, lobulated and vary from a thin diaphanous, translucent membrane that envelops the cystic portion to the grayish white opacity of the firm, calcified type. There is no restraining capsule to craniopharyngiomas so these can adhere to neural and vascular structures in the vicinity.

The cystic components have a mixture of cholesterol crystals and calcified desquamated debris which appears dark greenish brown.

The solid type contains minute cysts, cholesteatomatous deposits and foci of calculi or actual bone.

Microscopy: adamantinomatous – 9351/1 Consists of keratinous whorls and micro cystic formation and calcification.
Microscopy of papillary variants – 9352/1. Are well-differentiated squamous neoplasms. Numerous squamous-lined papillae are seen in cross section, each supported by a central fibrovascular core. There are no microcystic changes, peripheral palisading, wet keratin whorls or cholesterol clefts which are the hallmark of the adamantinomatous variant.

Immunohistochemistry: β-Catenin gene mutations were found in all of the adamantinomatous and none of the papillary craniopharyngiomas. Immunohistochemically, all cases of adamantinomatous craniopharyngioma showed cytoplasmic and nuclear expression of β-catenin. In contrast, papillary craniopharyngiomas showed exclusively membranous expression.

Imaging: Adamantinomatous variant

CT

- cysts
  - near CSF density
  - typically large and a dominant feature
  - present 90% of the time
- solid component
  - soft tissue density
  - enhancement in 90%
- calcification
  - seen in 90%
  - typically stippled and often peripheral in location

In the CT non contrast image below, courtesy of Dr Ruslan Esodov, Radiopaedia.org, rID: 10606 see the huge central low attenuation mass with a calcified perimeter – arrow.
MRI

- cysts: variable but 80% are mostly or partly T2 hyperintense
  - T1: iso- to hyperintense to brain (due to high protein content machinery oil cysts)
- solid component
  - T1 C+ (Gd): vivid enhancement
  - T2: variable or mixed
- calcification
  - difficult to appreciate on conventional imaging
  - susceptible sequences may better demonstrate calcification

The MRI T1W sagittal image, courtesy of Dr Hani Al Salam, Radiopaedia.org, rID 9276. The longer white arrows are indicating the perimeter of a huge suprasellar mass. The small arrows show the tumour within the sella as well.

The MRI T2W image, courtesy of Assoc Professor Frank Gaillard, Radiopaedia.org, rID 33751. The arrows indicate the cystic fluid in the pituitary fossa and suprasellar extension. Also extension has occurred down the back of the clivus – lower arrow.
MRI T1W coronal view with contrast, coronal view, courtesy of Dr Roberto Schubert, Radiopaedia.org, rID 14101. The arrow indicates the enhancing solid part of the tumour.

- **MR angiography**: may show displacement of the A1 segment of the anterior cerebral artery
- **MR spectroscopy**: cyst contents may show a broad lipid spectrum, with an otherwise flat baseline

**Papillary variant**

Papillary craniopharyngiomas tend to be more spherical in outline and usually lack the prominent cystic component; most are either solid or contain a few smaller cysts. **Calcification is uncommon or even rare** in the papillary subtype.

These tumours tend to **displace adjacent structures**.

**CT**

- Cysts – small, insignificant and near CSF density.
- solid component – has soft tissue density and vividly enhances after contrast.
- calcification – uncommon, even rare

CT non contrast image courtesy of Assoc. Professor Frank Gaillard, Radiopaedia.org, rID: 16791. Arrow indicates the non-calcified, spherical suprasellar mass.
MRI
- cysts – if present vary in signal
  85% are hypointense on T1W images
- solid component
  - T1: iso- to slightly hypointense to brain
  - T1 C+: vivid enhancement
  - T2: variable/mixed

Image courtesy of Assoc. Professor Frank Gaillard. Radiopaedia.org, rID 4722 is a T1W sagittal image with contrast. Long arrow indicates enhancement of the normal pituitary gland; short arrow is enhancement in the solid part of the craniopharyngioma.

- MR spectroscopy: cyst contents does not show a broad lipid spectrum as they are filled with water fluid

Treatment and prognosis

Treatment is usually surgical with radiotherapy especially useful for incomplete resection. Surgical approach depends on the size and sellar vs. suprasellar extent. Some lesions can be accessed via a transphenoidal approach, whereas others require a craniotomy.

Benign local recurrence is seen in up to a third of patients.

Differential diagnosis:

General imaging differential considerations include:
- Rathke cleft cyst
  - no solid or enhancing component
  - calcification is rare
  - unilocular
  - the majority are completely or mostly intrasellar
- pituitary macroadenoma (with cystic degeneration or necrosis)
- can look very similar
- usually has intrasellar epicentre with pituitary fossa enlargement rather than suprasellar epicentre
- despite occasional presence of T1 bright cystic regions, calcification in these cases is often absent (whereas most adamantinomatous craniopharyngiomas are calcified)
- intracranial teratoma
  - presence of fat is helpful, but requires fat saturated sequences or CT to confirm fat.

**PITUITARY ADENOMAS - OVERVIEW**

The WHO allocated a code of 8272/0 in the International Classification of Disease for Oncology (ICD-O) to a “typical pituitary adenoma” and 8272/1 to an “atypical pituitary adenoma”. Pituitary carcinoma was given 8272/3.

Clinical classification divides the adenomas into functioning and non-functioning.

A simple classification based on size is also used: microadenomas are less than 10 mm in size and are often functioning; macroadenoma are larger than 10 mm and frequently have both intrasellar and suprasellar components and have a propensity for invasion and recurrence.

A more recent classification of pituitary adenomas has been drawn up taking into account the hormone the tumour produces and the accompanying Transcription Factor. Thus each of the hormone families is dealt with separately, based on this hormonal immunohistochemistry.

In the next classification of pituitary adenomas from WHO, expected to be released in May 2017, it is expected that genetic mutations may be included to further refine diagnosis in reporting.

**Genetic:** Hereditary conditions associated with development of pituitary adenomas include:

- Multiple endocrine neoplasia type 1 (MEN-1), linked to somatic mutations of the MEN-1 gene
- Carney complex, linked to mutations of the tumour suppressor gene PRKAR1A
- McCune-Albright syndrome, linked to activating mutation of the gsp oncogene

A few other rare familial syndromes are also associated with pituitary adenomas:

- Pituitary adenoma predisposition (PAP), associated with a germline mutation of the AIP (aryl hydrocarbon receptor-interacting protein) gene
- Isolated familial somatotrophinoma (IFS), associated with a loss of heterozygosity at the 11q13 locus but not with the MEN-1 gene
- Familial isolated pituitary adenoma (FIPA), for which a single genetic alteration has not been characterized, although mutations of the AIP gene have been reported to occur in about 15% of families.

In the majority of sporadic adenomas, however, the primary genetic defect remains unknown. A number of oncogenes and tumour suppressor genes have been recognized as potential participants in the tumorigenesis of pituitary adenomas.

The most commonly found genetic alteration in sporadic tumors is an activating mutation of the gsp gene, an oncogene mostly identified in GH-cell adenomas. The gsp mutation has been identified in about 40% of GH-secreting adenomas, but it is rare in other pituitary tumour subtypes, occurring in only 10% of clinically nonfunctioning pituitary adenomas and 5% of corticotroph adenomas.
Other oncogenes and tumour suppressor genes that have been shown to be linked to pituitary tumorigenesis include the oncogene PTTG (pituitary tumor-transforming gene), the proto-oncogene H-ras, and the tumour suppressor genes RB and TP53. These genes are not directly associated with pituitary adenoma tumorigenesis but may play a role during the progression and malignant transformation of these tumors.

**Legend:** GH growth hormone, ACTH – adrenocorticotropic hormone, PRL prolactin, FSH follicle stimulating hormone, LH luteinizing hormone, TSH thyroid-stimulating hormone, Pit-1 pituitary-specific transcription factor 1, Tpit is T-box transcription factor TBX19, GATA-2 is GATA binding protein 2, ER-α Oestrogen receptor alpha, SF1 steroidogenic factor 1.

*Transcription factor* – a protein that binds to DNA and regulates gene expression by promoting or suppressing transcription which is the process of making RNA from a DNA template by RNA polymerase.

**Macroscopic:** image courtesy of library.med.utah.

**Diagnosis summary:**

1. the most important routine stain for diagnosis of pituitary adenomas, using histopathology is the haematoxylin and eosin (H and E) preparation.

Features of an adenoma include cytologic monomorphism, uniform cytoplasmic staining quality, occasional multinucleate or pleomorphic cells, prominent nucleoli or mitotic figures. The disruption of the normal acinar pattern is shown using silver stains to show reticulin fibres.

Normal pituitary tissue shows a mixture of different cell types arranged in a well-organized acinar pattern.

The normal pituitary has multiple cell types – basophilic, eosinophilic and chromophobic.

Images courtesy of M B S Lopes. Medscape Nov 17, 2015,
2. The next step in classification of tumour type is based on immunohistochemistry and electron microscopy. A standard immunohistochemical battery includes immunoreactions for prolactin, growth hormone, ACTH, luteinizing hormone, follicle stimulating hormone, thyroid stimulating hormone and the glycoprotein hormone α-subunit.

3. Pituitary adenomas are also immunoreactive for neuroendocrine markers including synaptophysin, neuronal-specific enolase and chromogranin.

4. Ultrastructure features which are used to distinguish normal pituitary from adenoma and to classify the adenomas are:- cell size, cell shape, nuclear morphology, as well as the distribution and morphology of secretory granules; rough endoplasmic reticulum; Golgi apparatus and intermediate filament accumulation.

Hence basic diagnosis of pituitary adenomas, uses light and electron microscopy and hormone immunohistochemistry.

Microscopic of pituitary adenoma: The growth pattern can be diffuse, trabecular, pseudo-acinar or pseudo-papillary. This example below is a trabecular pattern. Courtesy of PathPedia.com.

In the next image, courtesy of M B S Lopes. Medscape Nov 17, 2015, the normal pituitary with a delicate acinar pattern is shown on the left. On the right is the adenoma with disruption of the normal reticulin framework.
GRANULAR CELL TUMOUR – 9582/0 – (known as Abrikosoff tumours) – WHO grade I

**Definition:** are soft-tissue neoplasms probably derived from Schwann cells.

**Frequency:** rare tumours, especially in the central nervous system.

**Site:** They are usually located in the dermis or subcutis and less frequently in the submucosa, smooth muscle, or striated muscle. Granular cell tumours are also found in the internal organs, particularly in the upper digestive tract where 40% are found in the tongue. In the CNS cases have been reported in the posterior pituitary gland, the sellar region, the spinal canal, the cerebral hemisphere, parasellar-nasal communicating, and one was combined with an enterogenous cyst at the ventral aspect of the medulla oblongata.

**Pathology:** most are benign although 2% may be locally aggressive and these are associated with a poor prognosis, being difficult to treat. Granularity of the cells in these tumours is due to the accumulation of secondary lysosomes in the cytoplasm. This change is nonspecific and can be observed in many non-neural tumours, including those arising from smooth muscle, connective tissue, neuroglia, endothelial, and epithelial cells. 10% of patients with GCT have multiple lesions.

**Size:** are typically solitary and smaller than 3 cm.

**Gender:** slight female predominance, M: F = 3 : 2.

**Demographic:** more common in black persons who also commonly have multiple lesions.

**Age:** any age, peak in 4th – 6th decades.

**Clinical presentation:** varies depending upon location of the tumour.

**Imaging:** tend to be homogeneous and well defined on radiological images. Parasellar-nasal communicating tumour showed destruction of the skull base and a cystic component in the sphenoid sinus.

In the block of MRI images below, courtesy of Soo Jeong Park, Youn Hyuk Chang, Na-Rae Yang, and Eui Kyo Seo. Brain Tumor Res Treat. 2015 Apr; 3(1): 60–63 these show a homogeneous enhanced mass, on axial T1W Gd, T1W Gd coronal- see pituitary stalk –arrow), TIW Gd coronal (see mass) and axial T2W – arrow on mass of low signal.
**Microscopic:** features are uniform, regardless of the site. Granular cell tumours are distinguished by the presence of eosinophilic cytoplasmic granules and small round nuclei with dense chromatin. 50% of all granular cell tumors have poorly defined or infiltrative margins. The nodules are composed of large polyhedral cells arranged in sheets, nests, lobules, or trabeculae and are surrounded by variable stroma. A reticulin framework may be around individual cells or small groups of cells. Occasionally, granular cell tumours are extensively collagenized.

Images courtesy of the same authors as MRI. See also single image before the 3 images

Images next screen (a) shows large polygonal cells with ample granular cytoplasm and small oval, eccentric nuclei
(b) fibrocollagenous tissue mixed with granular cell nests.
(c) immunohistochemistry staining for S-100 has diffuse weak to strong positivity.

**Immunohistochemical findings:** Granular cell tumors have an uncertain histogenesis. Many immunohistochemical and ultrastructural studies suggest a Schwann cell origin.

The tumour cells stain positively for S-100 protein, neuron-specific enolase, and NK1-C3 in almost all cases. Positivity with stains for myelin-associated P0 and P2 proteins, myelin basic protein, and Leu-7 is less consistent.
The tumour cells are non-immuno-reactive for epithelial, muscle, endothelial, and glial cell markers. This is useful for differentiating a granular cell tumour from other diagnostic possibilities and negative for epithelial, melanocytic, smooth muscle, dendritic cell, and endothelial markers.

**Ultrastructural findings** with granular cell tumours are highly characteristic. Pleomorphic secondary lysosomes are observed within the cytoplasm of tumour cells.

Features that may be present are those indicating neural derivation of granular cell tumours (eg, myelin residues, long-spacing collagen, arrays of neuritic processes among tumour cells).

Malignancy may be indicated by the following:

- Locally destructive changes (e.g., ulceration, necrosis, haemorrhage)
- Infiltrative activity at the edges
- Frequent mitoses
- Vesicular nuclei with prominent nucleoli

**Differential diagnosis:** Intracranial granular cell tumours especially the posterior pituitary granular cell tumour, may be mistaken for granular variants of glial tumors but can be differentiated based on their negativity for glial fibrillary acid protein (GFAP).

**Treatment:** With benign granular cell tumours, local surgical excision is usually curative.

If complete resection is achieved; recurrence is still possible even with clear margins. Wide excision is recommended for malignant lesions.

Radiation and chemotherapy are not needed for benign lesions and are not effective for malignant lesions. However, case reports describe response to pazopanib in patients with metastatic disease.

**Pazopanib** (trade name Votrient) is a potent and selective multi-targeted receptor tyrosine kinase inhibitor that blocks tumour growth and inhibits angiogenesis.

**Prognosis.**

- In benign lesions, recurrence rates are 2-8%, even when the resection margins are deemed free of tumour infiltration but are around 20% when the margins are positive for tumour.
- Malignant lesions are aggressive and difficult to eradicate with surgery. Local recurrences are as high as 32%, and metastases were reported in 50%. Metastases are usually detected within 2 years.
- Of patients with malignant granular cell tumors, 39% die of the disease within 3 years after detection of the primary tumour.
- Ki-67 immunoreactivity of 10% or more tumour cells is an adverse prognostic factor.

**PITUITARY TUMOUR – 9432/1 (astrocytoma of the neurohypophysis)**

**Definition:** is a very rare tumour arising from pituicytes, a specialised glial cell in the neurohypophysis and infundibulum of the pituitary gland. It is thus a low grade astrocytoma and resembles pilocytic astrocytomas in the CNS. Often mistaken for a pituitary adenoma.

**Frequency:** only 50 cases reported by 2015.

**Age:** mean is 48 years and none less than 20 years.
**Gender:**  \( M : F = 1 : 2 \)

**Size:** a few mms to a few cms.

**Clinical:** varies but headaches, visual difficulties, hypothalamic dysfunction, diabetes insipidis and hydrocephalus may occur.

**Macrosopic:** these tumours are well circumscribed, soft to medium consistency with a gray to yellow homogeneous or granular cut surface. Necrosis and cystic degeneration are uncommon.

**Microscopy:** Pituicytomas consist of solid sheets and/or fascicles of relatively monomorphic bipolar spindle cells, often dispersed in short curvilinear, storiform, and perivascular arrangements. The neoplastic cells have oval-to-elongate nuclei with slightly fibrillary cytoplasm which lacks granular or oncocytic features. Mitotic activity is by the rare or entirely lacking, and MIB-1 determined proliferation indices are low. Immunohistochemically pituicytoma demonstrates strong and diffuse vimentin and S100 protein positivity together with variable GFAP positivity. Variable EMA positivity is observed. A number of neoplasms which may involve the sellar and suprasellar region may need to be considered in the differential diagnosis of pituicytoma. These include granular cell tumour, spindle cell oncocytoma (SCO) – (see below), pilocytic astrocytoma, pituitary adenoma, fibroblastic meningioma and schwannoma. Morphological and immunohistochemical studies usually resolve these difficulties.

Image of pituicytoma courtesy of Wikipedia.

![Image of pituicytoma](https://via.placeholder.com/150)

**Immunohistochemistry:** They stain diffusely for S-100 and vimentin. GFAP and EMA are variably positive. \( \text{Ki-67} \) is usually less than 2%.

Others may lack the compact and microcystic pattern, Rosenthal fibres accumulation and eosinophilic granular bodies that typify the classic pilocytic type.

**Ultrastructure:** shows intermediate filaments.

**Imaging:** CT – masses are homogeneously enhancing, either within the pituitary fossa or in the suprasellar region.
MRI - **T1**: isointense solid mass; posterior pituitary bright spot often absent

*(Note: posterior pituitary bright spot* is a MRI feature of the normal pituitary gland. It refers to the intrinsically high T1 signal of the posterior pituitary thought to be from the storage of vasopressin, which has a T1-shortening effect.)*

- It is important to note that a posterior pituitary bright spot is not identified in all patients, seen between 50-100%
- **T1 C+ (Gd)**: bright contrast enhancement
- **T2**: heterogeneous, hypointense to isointense

See the sagittal and coronal images below, both T1W post contrast, courtesy of Dr Natalie Yang, Radiopaedia.org, rID: 2650. Both images show a normal sized pituitary gland in the pituitary fossa and above this, arising in the stalk, is the tumour.

![Sagittal and coronal images of the pituitary gland](image_url)

**Differential diagnosis:** is essentially that of a solid and enhancing pituitary region mass, which includes:

- granular cell tumour of the pituitary
- pilocytic astrocytoma of the neurohypophysis
- ectopic posterior pituitary
- pituitary adenoma
- lymphocytic hypophysitis
- pituitary hyperplasia
- pituitary metastasis
- meningioma
- optic nerve glioma
- neurosarcomatosis

**DSA:** Pituicytomas have a rich capillary network, accounting for their usual contrast enhancement and propensity to bleed at surgery. They receive their blood supply from the normal and extensive supply to the pituitary gland, including the meningohypophyseal trunk and superior hypophyseal arteries. Angiogram below and legend is courtesy of Gibbs WN, Monuki ES, Linskey ME, Hasso AN. AJNR 2006, 27 : 1639-1642.
Selective bilateral internal carotid artery (ICA) angiograms. A, Early arterial lateral, (B) late arterial anteroposterior (AP), and (C) venous lateral magnified views of the left ICA injection. There are numerous vascular pedicles arising from the suprACLinoid portion of the ICA that represent the various inferior and superior hypophyseal branches (arrows, A and B) that supply the neurohypophysis and hypothalamus. The meningohypophyseal trunk, which supplies the inferior hypophyseal artery as well as the dorsal meningeal artery, is also visible, arising from the posterior genu of the cavernous ICA (arrowheads). During the venous phase (C), the tumour stain is apparent, extending from the suprasellar region upwards in a “dumbbell” or “mushroom” pattern. There is a prominent portal vein draining into the dural venous sinus (arrow). D, Late venous phase of the lateral injection of the right ICA. The shape of the tumour stain is well seen with a caudad extension along the enlarged pituitary stalk and cephalad extension into the hypothalamus. The delayed tumour stain and prominence of the meningohypophyseal trunk initially suggest a meningioma of the diaphragma sella and suprasellar region.

**Treatment:** As the tumours are benign and slow growing, if asymptomatic and a chance finding, then expectant management is sufficient. If mass effect is present then resection may be required if the mass is accessible.

**Complications:** These tumours are highly vascular which may lead to difficulties with a routine transphenoidal approach.

**Prognosis:** Complete resection can be difficult due to the structures involved and local recurrence is common.
TUMOURS of the ANTERIOR PITUITARY GLAND

SPINDLE CELL ONCOCYTOMA (SCO) – 8291/0 – WHO grade I

First described in 2002 by Roncaroli et al with 5 cases. Only 16 cases have so far been reported in the literature. It is a non-endocrine neoplasm of the anterior pituitary that occurs in adults and usually follows a benign clinical course.

**Age:** average age is 60 years.

**Gender:** M : F = 5 : 8 i.e. 60% have been females.

**Clinical:** SCO typically presents with visual disturbance, panhypopituitarism, and headache. Panhypopituitarism seems to be more common with SCO than either pituicytoma or GCT. This discrepancy may possibly be explained by SCO's exclusive derivation from the adenohypophysis. There are no reported cases of SCO presenting with diabetes insipidus so neither pituicytoma, SCO, nor granular cell tumour should be considered for patients who present with diabetes insipidus, prolactinemia, or galactorrhea.


![Coronal and sagittal T1W with contrast shows a heterogeneous enhancement in a suprasellar infiltrating pituitary lesion. The lack of an intrasellar component is unusual.](image)

All 13 cases pathologically documented SCOs presented as combined intra- and suprasellar lesions. Thus it is unlikely that a lesion presenting as a purely intra- or suprasellar mass on imaging is a SCO but this case was one.

**Spindle cell oncocytoma arise from the adenohypophysis whereas pituicytoma and GCT derive from the neurohypophysis.** Therefore, if imaging localizes a tumour to the neurohypophysis, the diagnosis of SCO may be excluded. All cases of SCO were infiltrating and none could be seen separately from the pituitary gland itself. It is therefore not possible to distinguish SCOs from more common lesions such as pituitary adenoma or lymphocytic hypophysitis on the basis of imaging features alone.
**Microscopic:** Histologically, SCO comprises mitochondria rich spindle and epithelioid and polygonal cells, arranged in cellular nests or fascicles, separated by fibrous stroma which might contain lymphohistiocytic infiltrates. The nuclei of the neoplastic cells are generally mildly pleomorphic, with granular or slightly dispersed chromatin and small eosinophilic nucleoli. Scattered single cells may have particularly large pleomorphic nuclei. The cytoplasm is eosinophilic and granular in quality, reflecting the large number of intracytoplasmic mitochondria. There is generally no evidence of necrosis or significant mitotic activity, though increased mitotic activity has been described in a recurrent lesion.


(a) Mitotic figures are rare.

Immunostains for (b) transcription factor 1, (c) epithelial membrane antigen (EMA), (d) and mitochondria are positive.

**Immunohistochemistry:**

The tumour cells exhibit immunoreactivity for S-100 protein, galectin-3, vimentin and epithelial membrane antigen but are negative for GFAP, anterior pituitary neuroendocrine markers (prolactin, growth hormone, TSH, ACTH, FSH, LH), chromogranin, synaptophysin, cytokeratin CK (AE1/AE3), smooth muscle actin, desmin, CD34 and CD68. MIB1 labeling index does not usually exceed 10%.

**Ultrastructurally,** the tumour cells are rich in mitochondria with lamellar cristae. Spindle cell oncocytoma of the anterior pituitary is often a misdiagnosed entity of uncertain histogenesis. It should be considered in the differential diagnosis of various sellar-region lesions of oncocytic morphology.

**Treatment:** The inability to distinguish the lesions of GCT, pituicytoma and SCO from entities such as pituitary adenoma is important because these tumors, unlike pituitary adenomas, tend to be very vascular and are prone to heavy bleeding during surgical resection. This has often resulted in the need to stabilize the patient, abort the surgery, and consider reoperation at a later date, potentially
after embolization of tumour vasculature. If reoperation does not occur, symptomatic recurrence is common.

**Prognosis:** all the recurrent cases had received an incomplete resection due to tumour tissue adhering to vital structures.

**ADENOMAS producing GROWTH HORMONE (GH)**

– all have the Pit-1 (pituitary-specific transcription factor)

**Function of Pit-1**

PIT1 is a pituitary-specific transcription factor responsible for pituitary development and hormone expression and is a member of the POU family of transcription factors that regulate mammalian development. The POU family is so named because the first 3 members identified were PIT1 and OCT1 (MIM 164175) of mammals, and Unc-86 of C. elegans (Herr et al., 1988).

PIT1 contains 2 protein domains, termed POU-specific and POU-homeo, which are both necessary for high affinity DNA binding on genes encoding growth hormone (GH; MIM 139250) and prolactin (PRL; MIM 176760). PIT1 is also important for regulation of the genes encoding prolactin and thyroid-stimulating hormone beta subunit (TSHB; MIM 188540) by thyrotropin-releasing hormone (TRH; MIM 257120) and cyclic AMP.[supplied by OMIM]. MIM is the gene symbol and its description is P-loop containing nucleoside triphosphate hydrolases superfamily protein and its function is protein coding.

**SOMATOTROPH ADENOMAS –**

A growth-hormone-secreting tumour of the anterior pituitary that causes acromegaly or gigantism.

**Types:** Densely granulated containing GH hormone and α-subunits

Sparsely granulated – hormone GH (weak)

**Incidence:** the pituitary somatotroph adenoma accounts for 90% of all somatotroph adenomas. Other non-pituitary somatotroph adenomas occur in the pancreas, lung and adrenals.

* all somatotroph adenomas can cause acromegaly and gigantism

**Imaging:** MRI courtesy of Thawani JP, Bailey RL, Burns CM and Lee JYK. Surg Neurol Int 2014; 5 :149

**Under physiological conditions,** alpha- and beta-chain synthesis and secretions are tightly coupled, and only small amounts of monomeric subunits are secreted.
Some pituitary adenomas may overproduce **alpha-subunits** which may disturb the coordinated production of intact glycoprotein hormones and disproportionate quantities of free alpha-subunits are secreted.

In particular, although most commonly associated with gonadotroph- or thyrotroph-derived tumors, alpha-subunit secretion has also been observed in corticotroph, lactotroph, and somatotroph pituitary adenomas.

Overall, depending on cell type and tumour size, between 5% to 30% of pituitary adenomas will produce sufficient free alpha-subunits to result in elevated serum levels, which usually fall with successful treatment.

Stimulation testing with hypothalamic releasing factors (e.g., gonadotropin releasing hormone [GnRH] or thyrotropin-releasing hormone [TRH]) may result in further elevations, disproportionate to those seen in individuals without tumours.

**Molecular pathology:**  *Gsp* oncogene mutation is one of the major intrinsic defects in the pathogenesis of growth hormone-secreting pituitary tumours and is found in 40% so the identification of *gsp* mutation can be a reference for classification and prognosis of GH tumors.

**Clinical:**  In children, there is excessive growth in height and appendages. In adults, there is overgrowth of the nose, mouth and tongue. The patient may complain of headaches, joint pain, excessive sweating, thickening of the skin and back pain. Carpal tunnel syndrome, hypertension, cardiomyopathy, visual field defects (due to pressure on the optic chiasm) may also be present. It has been reported that there is an increased risk of small intestine and colo-rectal cancer.

Women may experience irregular periods and hirsuitism.

**Microscopic:**  The images below, courtesy of M B S Lopes. Medscape Nov 17, 2015, is a growth hormone secreting adenoma, densely granulated type.

**Growth hormone (GH)-secreting adenoma.** Top left: **Densely granulated GH-secreting adenomas** show large cells with an eosinophilic, granular cytoplasm and a central nucleus with prominent nucleoli (hematoxylin-eosin stain). Top right: The tumor shows intense and diffuse immunostain for GH (GH-immunohistochemistry [IHC] stain). Bottom left: The ultrastructure exhibits well-developed organelles and abundant large secretory granules. Bottom right: A strong immunostain for transcription factor Pit-1 is typically seen in these adenomas (Pit-1-IHC stain).
Growth hormone (GH)-secreting adenoma. Top left: Sparsely granulated GH-cell adenomas are characteristically more chromophobic than densely granulated ones (H and E). Top right: The immunostain for GH is heterogeneous and less prominent than with densely granulated adenomas (GH-immunohistochemistry [IHC] stain).

Bottom left: Cytokeratin immunostaining highlights fibrous bodies (FBs) typically seen in these sparsely granulated tumors (cytokeratin-IHC stain). Bottom right: The ultrastructure of sparsely granulated GH cells displays sparse neurosecretory granules and typical FBs.

Complications of GH tumours: Diabetes type 2.

Tests: fasting GH blood test, oral glucose tolerance test, IGF-1 (insulin-like growth factors) level in blood and either a CT scan or MRI.

Treatment:

Sparsely granulated GH adenomas exhibit more aggressive biologic behavior than densely granulated tumors do. The response of tumours to adjuvant medical treatment also differs according to the subtype of GH cell adenoma.

Surgery: is often able to be undertaken by the trans-sphenoidal route. If all tumour cannot be removed the patient may have post-operative medical therapy.

Medical therapy for acromegaly with somatostatin receptor ligands, mainly octreotide, is common practice in endocrinology. The drug can interfere with the excessive secretion of GH by the pituitary gland, and thus produce rapid decline in GH levels. However, in treated GH cell
adenomas, significant reduction of tumour cell size is not commonly seen; the most common changes are varying degrees of perivascular and interstitial fibrosis.

**Radiation therapy:** may be required for residual tumour. However, it may take 10 years for the full effect of the treatment to be noticeable on the GH levels and the symptoms. For more focussed radiation, using the Stereotactic Gamma Knife, the effect of reducing the GH levels may be obvious in 5 years.

Follow-up care may be needed for life.

**MAMMOSOMATOTROPH ADENOMAS – hormone GH, PRL, α-subunit.**

This tumour is associated with gigantism and acromegaly.

is rare, - 2% of all pituitary adenomas and about 8% of tumours associated with acromegaly. Like mixed GH cell/PRL cell adenomas, these tumours are associated with elevated circulating GH levels and acromegaly; hyperprolactinemia is less common.

Histologically, these adenomas are acidophilic on H&E staining, and immunohistochemistry demonstrates the presence of GH and PRL in the cytoplasm of the same tumour cell.

Ultrastructural analysis demonstrates a well-differentiated adenoma composed of a monomorphous cell population that contains features of GH and PRL cells. The tumour cells are mostly similar to densely granulated GH cells, but with irregular secretory granules of variable sizes (200–2000 nm) and containing granule extrusions and extracellular deposits of secretory material, a feature consistent with PRL cell differentiation

The ultrastructure of mixed growth hormone (GH)-/prolactin (PRL)-secreting adenoma shows a monomorphous cell population exhibiting large secretory granules and granular extrusion.

**MIXED GH-PRL ADENOMAS – GH, PRL, α-subunit**

Constitute 8% of pituitary adenomas.

**Clinical:** have signs and symptoms of acromegaly and hyperprolactinaemia

**Types:** 1) mixed GH cell/PRL cell adenoma, (2), acidophilic stem cell adenoma

Mammosomatotroph cell adenoma was previously placed in this group but is now a separate entity – see previous screens.

The mixed are more aggressive than pure GH – secreting adenomas and the surgical cure rate is less.

Images courtesy of M B S Lopes. Medscape Nov 17, 2015,
Mixed growth hormone (GH)-/prolactin (PRL)-secreting adenoma. Top left and right: Morphologically, mixed GH-/PRL-secreting adenoma may be indistinguishable from GH adenoma (hematoxylin-eosin stain). Bottom left and right: Immunohistochemistry (IHC) shows intensive reaction for GH (bottom left: GH-IHC stain) and dotlike PRL immunostain (bottom right: PRL-IHC stain).

The ultrastructure of mixed GH-/PRL-secreting adenoma shows a bimorphous cell population with densely granulated GH cells and PRL cells.

PLURIHORMONAL GH-PRODUCING ADENOMAS – hormone GH, PRL, α-subunit, β-TSH

Represent 10 – 15% of all adenomas. Comprise 50% of those adenomas in the clinical setting of acromegaly. 8% are associated with multiple endocrine neoplasia, type I.

Age: more frequent in children and adolescents than in adults.

Clinical: The most common variant produces growth hormone, prolactin, and one or more glycoprotein hormones, the most common being TSH. Clinical effects most often reflect the presence of growth hormone, and to a lesser extent, prolactin cells; expression of glycoprotein hormone production is rare.

Macroscopic: 80% are macroadenomas and 20% microadenomas. Gross invasion is seen in 50%.

Plurihormonal adenomas may be ultrastructurally monomorphous, bimorphous, or trimorphous; that is one morphologic cell type may elaborate several hormones.
ADENOMAS PRODUCING PROLACTIN

All have Pit-1 (pituitary-specific transcription factor)

Account for 50% of all pituitary adenomas.

**Macroscopic:** the majority are microadenomas during the reproductive age period. In men and elderly women, prolactinomas are usually macroadenomas.

**Clinical:** microadenomas present with oligomenorhoea or amenorrhoea, galactorrhoea and infertility.

The macroadenomas present most frequently with symptoms of a tumour mass – headaches, neurologic defects and visual loss. In males the common symptoms are impotence and decreased libido.

**Diagnosis** of a prolactinoma is confirmed by sustained hyperprolactinemia and neuroradiologic evidence of a pituitary tumour.

**Types:** sparsely granulated – produce prolactin, α-subunit and the densely granulated produces prolactin.

**Imaging:** courtesy Royal Melbourne Hospital, Radiopaedia.org, rID 14820. MRI T2W of the pituitary demonstrates a 11 x 12 x 9 mm mass in the left pituitary gland – see arrow. There is remodelling of the sellar floor, which slopes to the left. There is displacement of the infundibulum and normal pitutary tissue to the right. There is slight tilting of the chiasm, but without chiasmal contact. While the mass abuts the left cavernous carotid, there are no specific signs for cavernous sinus invasion.

MRI of Microadenoma – T1 + contrast. Courtesy of Dr Chris O’Donnell, Radiopaedia.org, rID 19664
**Microscopic:**

Prolactinomas are composed of medium-sized cells with chromophobic or slightly acidophilic cytoplasm and a central, oval nucleus; small nucleoli can be present. Approximately 10-20% of cases show microcalcifications.

Images courtesy of M B S Lopes. Medscape Nov 17, 2015,

Prolactin (PRL)-secreting adenoma. Left: The cells show chromophobic cytoplasm and central nuclei (hematoxylin-eosin stain). Right: Immunohistochemistry (IHC) shows reactivity for PRL in a characteristic dotlike staining pattern located near the nucleus (PRL-IHC stain).

Immunohistochemistry (IHC) shows reactivity for PRL in a very characteristic pattern of staining, with localization near the nucleus in a dotlike pattern, also known as a Golgi pattern. On ultrastructural analysis, prolactinomas may be divided into densely and sparsely granulated variants, although the clinical significance of this distinction is uncertain.

Sparsely granulated PRL cell adenomas are the most common tumors, and their cells resemble actively secreting lactotrophs of the normal pituitary gland. The adenoma cells are characterized by a prominent rough endoplasmic reticulum (RER) network, conspicuous Golgi complexes, and a sparse number of small (150-300 nm) secretory granules. Misplaced exocytosis (ie, granule extrusions on the lateral cell surfaces) is typical of these tumours.

**Treatment:** dopamine agonists e.g. cabergoline. This drug induces atrophy of lactotrophs with resultant tumor shrinkage.

**ACIDOPHILIC STEM CELL ADENOMA** – secrete prolactin and growth hormone.

Very rare, representing only a small minority of GH-/PRL-producing tumors. Most patients present with symptoms of hyperprolactinemia; acromegaly is uncommon, and GH levels are often normal.

**Macroscopic:** are rapidly growing macroadenomas with invasive features. Because most of the patients have clinical features of hyperprolactinemia, the diagnosis is of clinical importance in that these tumours may be mistaken for the more benign prolactinomas.
By light microscopy, acidophilic stem cell adenomas are chromophobic, with focal oncocyctic changes of the cytoplasm. Immunoreactivity for PRL and, to a lesser extent, GH is present in the cytoplasm of the same tumour cells.

Electron microscopy is necessary for precise identification of these adenomas. They are composed of a single population of immature cells exhibiting features reminiscent of both sparsely granulated GH cells and PRL cells. Oncocytic change, with the presence of giant mitochondria, is characteristic of these adenomas.

ADENOMAS producing THYROID STIMULATING HORMONE (TSH)

Transcription factors Pit-1 and GATA-2 (GATA binding protein)

Hormones:  β-TSH, α-subunit.

Incidence:  0.5 – 3% of the functioning pituitary adenomas. It is found in 1% of patients presenting with hyperthyroidism.

Pathophysiology: Most TSH-secreting adenomas secrete only TSH. However, 20 to 25 percent of the adenomas secrete one or more other pituitary hormones, predominantly growth hormone or prolactin. There have been no reported instances of co-secretion of adrenocorticotropic hormone (ACTH) and TSH.

Gender:  Adenomas secreting TSH and growth hormone are equally common in men and women, whereas co-secretion of TSH and prolactin is about five times more common in women than in men.

Hyperprolactinemia is not always due to tumour secretion of prolactin; in some patients, it is caused by compression of the pituitary stalk and interruption of tonic hypothalamic inhibition of prolactin secretion.

Age:  occurs in the 4th and 5th decade of life most commonly.

Clinical:  Patients may present with inappropriately elevated TSH levels and hyperthyroidism. However may also arise in the setting of hypothyroidism or in clinically euthyroid patients. Patients typically present with signs and symptoms of hyperthyroidism; sweating, heat intolerance, tremor, palpitations, nervousness, increased stool frequency, weight loss, poor sleep quality and irregular periods. In addition they may have headache, visual disturbance, an enlarged thyroid and galactorrhoea. Early diagnosis and correct treatment may prevent pituitary and heart complications.

Macroscopic:  70% of TSH-secreting adenoma are macroadenomas. 30% are microadenomas.

The tumour is very fibrous and sometimes called a ‘pituitary stone’. These show localized or diffuse invasiveness into the surrounding structures, especially into the dura mater and bone. Extrasellar extension in the supra- and/or parasellar direction is present in the majority of cases. The occurrence of invasive macroadenomas is particularly high among patients with previous thyroid ablation by surgery or radioiodine.

Microscopic: thyrrotroph cell adenomas are frequently chromophobic by light microscopy and are composed of elongated, angular, or irregular cells. Have a slightly firm consistency.

Immunohistochemistry:  Immunostains reveal variable β-TSH positivity. IHC is also commonly positive for the α- subunit of the glycoproteins.
Ultrastructure level: the cells are moderately differentiated, with scant RER network and Golgi complexes. Secretory granules are small (100–200 nm), spherical, and evenly electron dense, and they are typically lined up along the cytoplasmic membrane.

Diagnosis of TSH-secreting adenoma can be difficult. If the clinical presentation and TSH immunoreactivity are not convincing, electron microscopy is mandatory for appropriate diagnosis.

Diagnosis: involves measuring blood thyroid hormone and thyroid stimulating hormone (TSH) levels. Further blood tests are taken to measure the levels of other hormones produced by the pituitary gland.

Similar biochemical findings to the above tests may also be found in patients with a related condition called 'resistance to thyroid hormone.'

Note: Thyroid hormone resistance (sometimes called Refetoff syndrome) describes a rare syndrome in which the thyroid hormone levels are elevated but the thyroid stimulating hormone (TSH) level is not suppressed, or not completely suppressed as would be expected.

Imaging of the pituitary is required. Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) of the pituitary is used to image the pituitary and look for a mass and evidence of invasion.

On CT imaging pituitary adenomas usually present as a solid tumour with an attenuation similar to brain (30-40 HU) and demonstrate moderate contrast enhancement.

MRI, they are isointense to the grey matter both on T1 and T2-weighted images. However attenuation and signal characteristics can significantly vary depending on tumour components such as haemorrhage, cystic transformation or necrosis.

Micro: courtesy of Mingqiang Song, Haijing Wang, Li Song, Haiye Tian, Quanxu Ge, Jun Li, Yan Zhu, Jizhou Li, Runzhen Zhao, and Hong-Long Ji. 2014, BMC Cancer; 14: 544. Upper left shows tumour tissue invasive growth involving the submucosa. Upper right shows cytoplasm is filled with fine granules in tumour cells. The lower left side is immunohistochemistry, with tumour cells expressing TSH (brown) and the right side is expression of growth hormone in the cells.
**Treatment:** The most common initial therapy for patients with a TSH-secreting pituitary adenoma is transphenoidal (via the nose) resection of the tumour. Transcranial resection of the tumour may be performed for very large tumour vision. If surgery is not advisable or does not work, radiation to the pituitary and/or medical treatment with somatostatin analogs (Octreotide, Lanotite) can be used.

Anti-thyroid therapy of any type such as radioiodine or anti-thyroid medications (eg carbimazole or propylthiouracil) are not used to treat patients with TSH-secreting pituitary adenomas as these would be expected to increase thyroid stimulating hormone secretion and stimulate tumour growth.

**Complications/ prognosis:**

The surgery may cause hypopituitarism, either partially or completely. Assessment of pituitary function to measure the amount of hormones the pituitary is producing should be undertaken soon after surgery. Appropriate hormone replacement may be required.

Patients on somatostatin analogs may also experience side-effects particularly related to gastrointestinal disturbance as well as gall stone formation and occasionally diabetes mellitus. Radiotherapy can lead to failure of the normal pituitary gland tissue over the following years, again resulting in hypopituitarism. Patients with long-term hypopituitarism as a result of surgery will need to take daily medication for life and will require regular checks with an endocrinologist to monitor pituitary and thyroid hormone levels. Hypopituitarism is associated with an increased risk of heart disease and strokes. Appropriate pituitary hormone replacement therapy can reduce all these risks.

If left untreated, in addition to complications of hyperthyroidism, patients may experience neurological complications such as visual field defects due to compression of the optic nerves; hypopituitarism; decrease in sexual function; acromegaly, which can occur in a proportion of tumours that also produce growth hormone; and galactorrhoea, either due to compression of the pituitary stalk, by the tumour, or by direct secretion of prolactin by the TSH-secreting pituitary adenoma.

**PITUITARY ADENOMAS producing ACTH (Cushing’s Disease)**

**Hormones – ACTH**

**Transcription factor Tpit(T-box transcription factor TBX19)**

**Types:** densely granulated, sparsely granulated (rare) and Crooke’s cell adenoma. All produce ACTH.

**Incidence:** account for 10-15% of pituitary adenomas and for 85% of the tumours producing ACTH.

**Peak Age:** between 30 – 40 years. Rare in children and there is a more aggressive clinical course and more difficult to cure.

**Gender:** M : F = 1 : 3.5 in adults but in pre-pubertal children it is the opposite, more common in males.

**Macroscopic:** The majority of ACTH-secreting adenomas are microadenomas, and approximately 15% are invasive at the time of surgery.
**Microscopic:** ACTH-secreting adenomas are usually basophilic on H&E staining and are often strongly positive with periodic acid-Schiff (PAS) staining. The cytoplasm is very granular, and the nucleus is large, with coarse chromatin and a prominent nucleolus. Some degree of nuclear pleomorphism can be present. The cells have very distinct cytoplasmic borders and tend to touch each other in a tilelike arrangement. Papillary formations are very common.


**Ultrastructure:** characterized by well-differentiated cells that resemble normal corticotrophs and contain well-developed organelles, including RER, smooth endoplasmic reticulum (SER), conspicuous Golgi complexes, and numerous large (250–500 nm) secretory granules. The secretory granules are often of different shapes (e.g., spherical or heart-shaped) and vary in electron density. Bundles of intermediate filaments lying adjacent to the nucleus or forming large circles (Crooke's changes) are easily identified.

Ultrastructural analysis of clinically functioning ACTH-cell adenomas is not obligatory; histologic and immunohistochemical studies are sufficient to provide an accurate diagnosis.

**CROOKE CELL ADENOMA** , a particularly rare form of ACTH-producing pituitary gland tumour.

Endocrinologically functional ACTH-producing pituitary adenomas are associated with Cushing disease. Most occur in women, at a mean age of 35 to 44 years, and the majority are microadenomas (75-90%).

Corticotrophs of the anterior pituitary normally contain small numbers of perinuclear cytokeratin filament bundles. Persistently elevated blood cortisol levels causes cytoplasmic accumulation of cytokeratin resulting in a distinctive cellular alteration termed Crooke hyaline change: cell cytoplasm of hyalinized appearance on hematoxylin-eosin and periodic acid–Schiff stains. Rarely this change is seen in corticotroph adenomas, termed Crooke’s cell adenoma.
Crooke’s changes in the anterior pituitary gland of a patient with Cushing disease. Left: Several "target cells" consistent with corticotroph cells with hyaline bundles in the cytoplasm can be seen (hematoxylin-eosin stain). Right: Cytokeratin immunostain highlights Crooke’s changes in corticotroph cells (cytokeratin-immunohistochemistry [IHC] stain)

Production of ACTH occurs in ectopic situations and is responsible for 15% of Cushing’s disease viz:

- lung cancer: bronchial carcinoid; small cell lung cancer
- small cell cancers of the thymus
- pancreatic neuroendocrine tumour
- pheochromocytoma
- benign ovarian tumours

Note: adrenocorticotropic (ACTH)-independent macronodular adrenocortical hyperplasia (AIMAH) is a rare cause of ACTH independent Cushing syndrome.

**Clinical features:** Patients with Cushing syndrome may complain of weight gain, especially in the face, supraclavicular region, upper back, and torso. Frequently, patients notice changes in their skin, including purple stretch marks, easy bruising, and other signs of skin thinning. Because of progressive proximal muscle weakness, patients may have difficulty climbing stairs, getting out of a low chair, and raising their arms.

Menstrual irregularities, amenorrhea, infertility, and decreased libido may occur in women. In men, inhibition of LHRH and FSH/LH function may lead to decreased libido and impotence.

Psychological problems such as depression, cognitive dysfunction, and emotional lability may develop. New-onset or worsening of hypertension and diabetes mellitus, difficulty with wound healing, increased infections, osteopenia, and osteoporotic fractures may occur.

**Biochemistry:** The work up of Cushing syndrome requires measurement both of cortisol as well as ACTH. Measuring cortisol typically needs to be over a 24 hour period because release is intermittent.
**Imaging:** CT or MRI to demonstrate a mass in the anterior pituitary.

ACTH secreting pituitary microadenomas may not be visible on imaging in 40-50% of cases.

If ACTH is elevated but no microadenoma can be identified, and no ectopic source can be found, then inferior petrosal sinus sampling can be undertaken. Petrosal venous sampling allows the surgeon to identify which half of the pituitary gland contains an adenoma. The surgeon then slices the pituitary methodically from one side to the other of that half of the pituitary gland until the adenoma is found and removed.

Petrosal venous sampling with stimulation of corticotropic releasing hormone is nearly 100% accurate in distinguishing pituitary from ectopic ACTH production. Intraoperative ultrasonography of the pituitary gland can aid the neurosurgeon in identifying the pituitary microadenoma. The sensitivity of this technique in patients with negative MR images is 84%, with a specificity of 33%.

The image below is a bilateral petrosal venous sinus venogram, courtesy of Choyke PL and Doppman JL. RSNA Radiology 2000; 214 (1). The arrows are pointing to the inferior petrosal sinus on each side of the sella turcica.

![Image of bilateral petrosal venous sinus venogram](image.png)

Bilateral adrenal hyperplasia is one of the most common findings on abdominal CT in patients with Cushing’s syndrome.

**Treatment:** 2015, the Endocrine Society released new guidelines for Cushing syndrome

- Optimal treatment of Cushing syndrome involves direct surgical removal of the causal tumour, except in cases unlikely to cause a drop in glucocorticoids or in patients who are not candidates for surgery. Second-line therapy should be individualized.
- Other first-line treatments include surgical resection of ectopic ACTH-secreting tumours; transsphenoidal selective adenomectomy; blocking hormone receptors in bilateral micronodular adrenal hyperplasia; and surgical removal in cases of bilateral adrenal disorders.
- The choice of second-line treatments include medication, bilateral adrenalectomy, and radiation therapy (for corticotrope tumours).
- Effective treatment includes the normalization of cortisol levels or action. It also includes the normalization of co-morbidities (eg, hypertension, diabetes) by adjunctive treatments (eg, antihypertensives). Lowering cortisol levels improves hypertension, insulin resistance, dyslipidemia, and obesity.
In cases of benign unilateral adrenal adenoma, adrenalectomy is associated with a high cure rate in both children and adults. Adrenal carcinoma is associated with a poor prognosis; therefore, complete resection, and possibly medical treatment to stabilize cortisol levels, are necessary.

Long-term follow-up is recommended for osteoporosis, cardiovascular disease, and psychiatric conditions.

**Medications** used in the management of Cushing syndrome include the following:

- Somatostatin analogs: Pasireotide
- Adrenal steroid inhibitors: Metyrapone, ketoconazole, etomidate
- Glucocorticoid receptor antagonist: Mifepristone
- Adrenolytic agents: Mitotane

**Surgery:**

The treatment of choice for endogenous Cushing syndrome is surgical resection of the causative tumour. The primary therapy for Cushing disease of the pituitary is transsphenoidal surgery, and the primary therapy for adrenal tumours is adrenalectomy.

Other surgical interventions include the following:

- Bilateral adrenalectomy
- Unilateral adrenalectomy
- Resection of carcinomas

Patients with endogenous Cushing syndrome who undergo resection of pituitary, adrenal, or ectopic tumours should receive stress doses of glucocorticoid in the intraoperative and immediate postoperative period. Typically, hydrocortisone is infused intravenously, either continuously (10 mg/h) or in boluses (80-100 mg q8h) starting prior to surgery and for the first 24 hours afterward. If the patient does well, intravenous glucocorticoid replacement may be tapered over 1-2 days and replaced with an oral formulation. The rate of steroid taper may be slowed if severe preoperative hypercortisolism was present. In the event of pituitary destruction or bilateral adrenalectomy, lifelong glucocorticoid replacement is necessary. Lifelong mineralocorticoid replacement is also necessary in those patients who undergo bilateral adrenalectomy.

**Cushing disease**

**Treatment of choice** is transsphenoidal surgery by a neurosurgeon. The goal of surgery is to remove the adenoma, preserving as much pituitary function as possible.

- The more extensive the mass and the resulting resection, the greater the risk for loss of pituitary function. Successful reduction of hypercortisolism occurs in 60-80% of cases.
- Pituitary irradiation is employed when transsphenoidal surgery is not successful or not possible. The procedure is less successful than surgery in adults, with a 40-50% cure rate in adults and 85% cure rate in children. Late-onset adverse effects include hypopituitarism.
- Bilateral adrenalectomy is an option if transsphenoidal surgery, pituitary irradiation, and medical therapy fail or if rapid normalization of cortisol levels is required. The patient then requires lifelong glucocorticoid and mineralocorticoid therapy.
- Individuals who undergo bilateral adrenalectomy might develop Nelson syndrome, which is symptomatic enlargement of the pituitary gland and adenoma. This may occur in 25 – 50% of adults not treated with pituitary irradiation and in as many as 25% of patients pretreated with radiation therapy.
ADENOMAS producing FSH, LH - Gonadotroph adenomas

Hormones:  β-FSH, β-LH, α-subunit

Transcription factors: SF-1 (steroidogenic factor 1), ER-α (oestrogen receptor alpha), GATA-2 (GATA binding protein 2)

Definition: Gonadotropin-secreting adenomas, or gonadotroph adenomas, are adenomas that secrete the gonadotropins follicle stimulating hormone (FSH) and luteinising hormone (LH). Gonadotroph adenomas do not usually cause a clinical syndrome related to hormone overproduction. The hormonal production from these tumours is inefficient, and the detection of excess hormone levels is difficult.

Incidence: Gonadotroph adenomas account for a large proportion of clinically nonfunctioning adenomas and about 20% of all adenomas.

Age: most frequent in the sixth decade of life and older.

Gender: slight male predominance.

Clinical presentation: Typically, they present as clinically nonfunctioning tumours with symptoms instead related to local mass effects, including visual deficits, hypopituitarism, headaches, and cranial nerve palsies.

Pathophysiology: The diagnosis of a clinically non-functioning adenoma requires appropriate classification for accurate prognosis. The vast majority of these lesions are actually gonadotroph adenomas which very rarely present with clinical or biochemical evidence of hormone excess. They do produce follicle-stimulating hormone (FSH) or luteinising hormone (LH), and they express the transcription factors that prove gonadotroph differentiation – SF-1, ER-α, GATA-2.

Microscopic: Gonadotrophs are composed of chromophobic cells with nuclei displaying a fine chromatin pattern. They have a highly characteristic histological pattern, in which solid sheets, nests and sinusoidal patterns are interrupted by pseudopapillae and striking pseudorosettes around vascular channels. They usually have two types of cell: tall columnar cells line pseudopapillae and rosettes, whereas polygonal cells comprise the bulk of the lesion. Oncocytic change can be observed in all patterns. Image courtesy of Al-Brahim NY Y and Asa SL. J Clin Pathol 2006 Dec; 59(12):1245-1253
**Immunohistochemistry:** Monoclonal antibodies specific to β-FSH, β-LH, and α-SU are used for characterization of gonadotroph adenomas, because these lesions may demonstrate varying degrees of reactivity for one or more of the gonadotropin subunits. They also express steroidogenic factor-1 with strong nuclear reactivity.

Immunoreactive cells may be scattered throughout the adenoma but are often clustered. Immunoreactivity for β-FSH tends to be more frequent, with a stronger and broadly distributed pattern than immunoreactivity for the other glycoproteins.

**Ultrastructurally,** gonadotroph adenomas are characterized by elongated, polar cells containing scant numbers of small (50–200 nm) secretory granules. The secretory granules are distributed unevenly within the cytoplasm or, more commonly, along the cytoplasmic membrane. A sex-linked dichotomy between gonadotroph adenomas of male and female patients has been described. In women, most of the adenomas display a typical vacuolar transformation of the Golgi complex, giving the Golgi apparatus a honeycomb appearance.

Characterization of gonadotroph adenomas by ultrastructural means does not alter clinical patient management. The correlation between β-FSH and β-LH immunoreactivity, degree of ultrastructural differentiation, and clinical symptoms is relatively poor in patients with gonadotroph adenomas.

**Imaging:** MRI with intrasellar and suprasellar mass.


![Gonadotropin producing (cell) adenoma (Gn-oma). Mid-sagittal (a) and coronal (b) MRI image. The tumour cells present macroadenoma type and no evidence of bioactivities of hormone. αSU (c, d; blue), FSHβSU (c; brown) and LHβSU (d; brown) are localized in different tumour cells](image)

**Treatment:** At present, most patients are treated as having a clinically nonfunctioning adenoma, and the therapeutic goals are restoration of visual deficits, preservation of pituitary function, and prevention of recurrence.

**PLURIHORMONAL ADENOMAS – Silent subtype III**

**Hormones:** Multiple

**Transcription factors:** multiple

Plurihormonal adenomas are rare adenomas that have unusual immunoreactivity for multiple pituitary hormones that are not related through the normal cytogenesis and development of the anterior pituitary. Because of their rarity, these tumours do not have a well-characterized clinical
presentation. Most exhibit symptoms of mass effect resulting from the large size of the adenomas at the time of diagnosis.

Plurihormonal adenomas do not have specific histopathologic features.

**Immunohistochemistry:** various combinations of hormones have been described, including FSH with GH as well as PRL with TSH.

Such combinations do not include either (1) GH with PRL and TSH or (2) FSH with LH, because these two combinations are commonly seen in GH-secreting and gonadotroph adenomas, respectively. Rarely, plurihormonal adenomas show immunoreactivity for ACTH.

**SILENT ADENOMAS – general overview**

A certain percentage of clinically nonfunctioning adenomas are tumours that, despite the patient’s lack of clinical syndrome or signs of hormone hypersecretion, have a pattern of IHC staining and an ultrastructural appearance that are consistent with a secreting adenoma.

Although both silent somatotroph and silent lactotroph adenomas have been described, the adenomas with most significant clinical implications are the silent corticotroph adenomas. Silent corticotroph adenomas are characterized by immunoreactivity for ACTH in the absence of either clinical signs of Cushing disease or serum levels reflecting excess ACTH secretion. Most are macroadenomas, and patients present with signs and symptoms of a mass lesion. Characteristically, silent corticotroph adenomas show a high tendency for haemorrhage and apoplexy, which may be the presenting symptoms in about one third of the patients. These tumours tend to arise in patients older than those with Cushing disease.

**Silent subtype III adenomas**

Silent subtype III adenoma is a rare plurihormonal tumour that has a typical ultrastructural appearance characterized by intranuclear inclusions known as spheridia. Therefore, electron microscopy is required for confirmation of the diagnosis. Like other plurihormonal adenomas, these adenomas may exhibit immunoreactivity for pituitary hormones but are clinically nonfunctioning. Silent subtype III adenomas tend to be invasive and generally have a higher rate of recurrence.

**NULL CELL ADENOMAS**

**Hormones – Nil; Transcription factor Nil**

Approximately 20% of adenomas show neither clinical nor IHC evidence of hormone production. The term "null cell adenoma" is given to these tumours, based largely on the absence of ultrastructural features providing specific differentiation.

**Clinical presentation** of null cell adenoma resembles that of gonadotroph adenoma; patients present with signs and symptoms of a mass lesion. Null cell adenomas most commonly arise in postmenopausal females and elderly males, with the great majority macroadenomas at presentation.

**Microscopy:** null cell adenomas are chromophobic on light microscopy, and the tumour cells may be arranged in several neuroendocrine patterns, including trabecular, papillary, and diffuse. Oncocytic change can be seen in a number of cases, and so the designation of oncocytoma (oncocytic variant of null cell adenoma) may be applied to these adenomas.
Null cell adenomas may lack immunoreactivity for any pituitary hormone (so-called immunonegative adenomas), or they may demonstrate focal and weak immunoreactivity for β-FSH, β-LH and α-SU (see the image below). The presence of glycoprotein hormone immunoreactivity in null cell adenomas is corroborated by the occasional expression of glycoprotein hormone genes and the secretion of small quantities of these hormones in culture.

On ultrastructural analysis, null cell adenomas demonstrate poorly developed organelles with only sparse small secretory granules, as depicted in the above image. Large numbers of mitochondria are seen in the tumors, and oncocytic degeneration is visible.

The cytogenesis of null cell adenomas is still unknown. A considerable overlap exists between null cell adenomas and gonadotroph adenomas, as is indicated by the finding that some of these adenomas show focal immunoreactivity for glycoprotein hormones.

Many authors have suggested that these two tumour types are derived from a single progenitor cell that has the capacity to differentiate along a spectrum ranging from the more differentiated gonadotroph cell to a variety of less differentiated cells. In fact, most null cell adenomas express steroidogenic factor–1 (SF-1), a transcription factor whose pituitary expression is specific to the gonadotroph lineage. However, from the viewpoint of patient management, differentiation between these two adenomas has little significant clinical value.

**Null cell adenoma (chromophobe adenoma) below**. Top left, top right, bottom left: These poorly differentiated adenomas may show focal and weak immunoreactivity for glycoprotein hormones, including (top left) follicle-stimulating hormone (FSH) (FHS-immunohistochemistry [IHC] stain), (top right) luteinizing hormone (LH) (LH-IHC stain), and (bottom left) alpha-subunit (alpha-SU) (alpha-SU-IHC stain). Bottom right: The ultrastructure shows poorly developed organelles and sparse small secretory granules.
Conditions that can mimic Pituitary Adenomas:

Inflammatory conditions
- lymphocytic hypophysitis
- granulomatous hypophysitis
- sarcoidosis

Microscopy: courtesy of MBS Lopes. Medscape Nov 17, 2015. Left: Lymphocytic hypophysitis is characterized by dense infiltration of lymphocytes and plasma cells [H&E stain] Right: An example of granulomatous hypophysitis with dense inflammatory infiltrates and a granuloma with a giant cell completely obscuring pituitary parenchyma (H&E stain).

Examples of the non-specific classification into Atypical adenoma and Typical adenoma


Top left and right: A pituitary adenoma shows increased mitotic activity despite lack of cellular pleomorphism (hematoxylin-eosin stain).

Bottom left: Immunohistochemistry (IHC) is strongly positive for prolactin (PRL) (PRL-IHC stain).

Bottom right: Immunostain for Ki67 (MIB-1 antibody) shows a high labeling index (MIB-1-IHC stain).
PITUITARY CARCINOMA

**Site:** can only arise in the anterior pituitary gland.

**Incidence:** very rare – account for less than 1% of all pituitary neoplasms.

**Age:** older adults.

**Pathophysiology:** The majority are endocrinologically functioning tumours.

Prolactin-secreting tumours are the most common, followed by ACTH-secreting tumours.

Non-functioning tumours such as the silent corticotroph, gonadotroph and the rare null cell carcinoma account for 15-20% of the cases.

**Clinical presentation:** varies. Most cases have an initial course indistinguishable from that of a benign pituitary adenoma.

A longer course, when there has been multiple local recurrences, is then followed by metastatic dissemination.

It is rare for patients to present with metastases at the time of the original sellar tumour.

**Diagnosis:** depends on the demonstration of metastatic spread using imaging techniques.

*There are no morphologic criteria to distinguish locally aggressive, or even markedly atypical, adenomas from carcinomas when the tumour is confined to the sella.*

**Microscopic:** Standard morphologic features associated with malignancy: hypercellularity, nuclear and cellular pleomorphism, increased mitotic activity, necrosis, and dural/osseous invasion are commonly present but are not necessarily diagnostic of carcinoma.

**Immunohistochemistry:** Like pituitary adenomas, pituitary carcinomas are immunopositive for neuroendocrine markers, including synaptophysin and chromogranin A. The majority of carcinomas are immunoreactive for PRL or ACTH. A few examples of silent corticotroph carcinomas have also been described. Pituitary carcinomas are only rarely immunoreactive for growth hormone (GH), gonadotropins (ie, luteinizing hormone [LH] or follicle-stimulating hormone [FSH]), or thyroid-stimulating hormone (TSH).

Ki67 labeling indices are quite variable and show considerable overlap with common pituitary adenomas; however, they are often higher in metastatic deposits. Additionally, unlike pituitary adenomas, pituitary carcinomas appear to show overexpression of the p53 protein on immunohistochemistry (IHC).

**Treatment:** Because this tumour is so rare there are no standard guidelines. However, the options will be determined by the size of the tumour, whether it has spread and is it producing hormones. It is often diagnosed late when it has spread.

Treatment options include:

- surgery
- radiation therapy
- chemotherapy
- hormonal medications

**Prognosis:** most patients survive for less than one year and only 20% survive for more than 8 yrs.
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