# Clinical Hematology and Oncology

## Presentation, Diagnosis, and Treatment


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# Chapter 111
# Pituitary Tumors

*Robert D. Utiger*

Pituitary tumors are identified because the patient has symptoms of a pituitary mass, clinical manifestations of pituitary hormone excess or deficiency, or both. Among patients with a pituitary mass, approximately 90% have a pituitary adenoma, 8% have a craniopharyngioma or other cell-rest tumor (Rathke's pouch cyst, epidermoid cyst), and 2% have other masses, including metastatic tumors, aneurysms, and inflammatory masses.

## Pituitary Adenoma

Pituitary adenomas are benign, slow-growing monoclonal adenomas of the different types of cells present in the normal anterior pituitary gland. They are rare, occurring with an estimated frequency of 10 cases per 1,000,000 people per year, mostly in older adults. Genetic abnormalities in signal transduction systems or the receptors for the hormones that inhibit the production and secretion of particular pituitary hormones have been identified in some adenomas. Pituitary adenomas occur in approximately 40% of patients with multiple endocrine neoplasia type 1; the other components are parathyroid adenomas and pancreatic islet cell adenomas. Small, incidental pituitary adenomas are found in up to 10% of people at autopsy.

### Clinical Presentations

Pituitary adenomas are classified according to size—as microadenomas (tumor diameter less than 1 cm) or macroadenomas (tumor diameter 1 cm or greater)—and according to their secretory products.

#### Nonsecretory Microadenomas

Nonsecretory microadenomas do not cause symptoms and rarely cause hormonal deficiencies. They are usually detected incidentally by imaging in patients who are being evaluated for unrelated problems.

#### Nonsecretory Macroadenomas

Nonsecretory macroadenomas may also be detected incidentally, but they can cause mass effects as they enlarge and extend superiorly from the sella turcica toward the hypothalamus or laterally toward the cavernous sinuses. The major symptoms are headaches and visual difficulties. The headaches may be frontal, bitemporal, or occipital and are often relieved by minor analgesic drugs. The characteristic visual abnormality is bitemporal hemianopsia, but some patients have quadrant defects, decreased visual acuity, scotomas, or third or sixth nerve palsies.

Nonsecretory macroadenomas may cause deficiency of any pituitary hormone, including vasopressin. The most common deficiency is that of gonadotropins (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]), which is present in approximately 80% of patients, followed by growth hormone (GH) deficiency (60%), thyrotropin (TSH) deficiency (40%), corticotropin (ACTH) deficiency (25%), and vasopressin deficiency (5%). Any of these can occur as an isolated deficiency or as one of multiple deficiencies.

The hypogonadism that results from gonadotropin deficiency is easily detected in young women by the presence of amenorrhea, but it is not as easily detected in men because of the unwillingness of many men to describe loss of libido and other symptoms of hypogonadism (or the unwillingness of the physician to ask). Many of the symptoms of growth hormone, thyrotropin, and corticotropin deficiency are nonspecific, for example, muscle weakness, mental fatigue, and anorexia, and the presence of more specific symptoms, such as cold intolerance and weight loss, may go unnoticed because their onset is so gradual.

Some nonsecretory macroadenomas produce and secrete no hormones or hormonal components, but many produce the common alpha subunit of follicle-stimulating hormone and luteinizing hormone (and thyrotropin), the beta subunits of follicle-stimulating hormone or luteinizing hormone, or intact follicle-

stimulating hormone or luteinizing hormone, as detected by mRNA and immunohistochemical analyses of tumor tissue. These tumors often secrete one or both subunits, which lack biologic activity, but only rarely do they secrete excess amounts of intact follicle-stimulating hormone or luteinizing hormone. Therefore, they are in fact gonadotroph adenomas.

### Secretory Microadenomas and Macroadenomas

The majority of secretory pituitary adenomas are microadenomas.

Among the secretory tumors, lactotroph adenomas (prolactinomas) are the most common (Table 111-1). In young women, even moderate hyperprolactinemia inhibits pituitary-gonadal function, causing infertility, oligomenorrhea or amenorrhea, and, less often, galactorrhea. Most of these women have microadenomas. In contrast, postmenopausal women and men usually present with headaches or visual problems and have macroadenomas. Hyperprolactinemia also inhibits pituitary-gonadal function in men, causing hypogonadism and rarely galactorrhea. Hyperprolactinemia does not necessarily indicate the presence of a lactotroph adenoma. It also can result from loss of tonic hypothalamic inhibition of prolactin secretion, for example, by interruption of hypothalamic-pituitary blood flow.

Somatotroph adenomas cause acromegaly, with acral enlargement, macroglossia, skin thickening, excessive perspiration, arthralgia, sleep apnea, hypertension, and cardiomyopathy. Somatotroph adenomas are extremely slow-growing tumors. At the time of diagnosis, many patients have had changes attributable to growth hormone excess for many years, and the majority have macroadenomas. Many somatotroph adenomas also hypersecrete prolactin.

Corticotroph adenomas cause Cushing's disease and account for approximately 70% of cases of Cushing's syndrome. The major clinical findings are moon facies, plethora, central obesity, hypertension, myopathy, psychological disturbances, and osteoporosis. Most of the tumors are microadenomas, and in some patients, the tumor is so small that it cannot be detected by imaging.

Thyrotroph adenomas are rare and are far less common than Graves' disease, nodular goiter, and thyroiditis as a cause of hyperthyroidism. In addition to hyperthyroidism, the patients have a diffuse goiter, but they do not have Graves' ophthalmopathy. Most of the adenomas are macroadenomas, and approximately 40% secrete prolactin or other pituitary hormones.

Gonadotroph adenomas may secrete sufficient follicle-stimulating hormone or luteinizing hormone to have clinical effects. In young women, follicle-stimulating hormone hypersecretion can cause ovarian hyperstimulation with multiple ovarian cysts and oligomenorrhea or amenorrhea. In men, excess luteinizing hormone secretion causes high serum testosterone concentrations, but this has little clinical effect in normal men. The adenomas are nearly always macroadenomas.

### Pituitary Apoplexy

Occasional patients, most of whom have macroadenomas, present with pituitary apoplexy. It is characterized by the sudden onset of severe headache; visual field deficits; third, fourth, or sixth cranial nerve palsies; nausea and vomiting; and decline in mental status. It is caused by hemorrhagic infarction of the adenoma.

**Table 111-1 ■ Types and Relative Frequency of Pituitary Adenomas**

| Type of Adenoma | Frequency |
|---|---|
| Nonsecretory adenoma | 35% |
| Lactotroph (prolactinoma) adenoma | 30% |
| Somatotroph (GH-secreting) adenoma | 15% |
| Corticotroph (ACTH-secreting) adenoma | 15% |
| Other (thyrotroph [TSH-secreting] adenoma, gonadotroph [FSH- or LH-secreting]) adenoma | <5% |

## Clinical Evaluation

All patients who are suspected of having a pituitary adenoma or other pituitary disease should undergo magnetic resonance imaging (MRI), with special attention given to the region of the sella turcica (Figure 111-1). Magnetic resonance imaging provides better resolution of the anatomy of this region and reveals more microadenomas than does computed tomography. Visual field testing should be done if there is clinical or radiologic evidence of compression of the optic chiasm or optic tracts.

### Hormonal Deficiencies

The possible deficiency of corticotropin, follicle-stimulating hormone and luteinizing hormone, or thyrotropin in a patient with a pituitary tumor should be assessed by simultaneous measurements of the particular pituitary hormone and its respective target gland hormone (cortisol, estradiol or testosterone, or thyroxine) in serum (Table 111-2). Pituitary hormone deficiency is characterized by a normal or low serum pituitary hormone concentration in the presence of a low serum concentration of the target gland hormone.

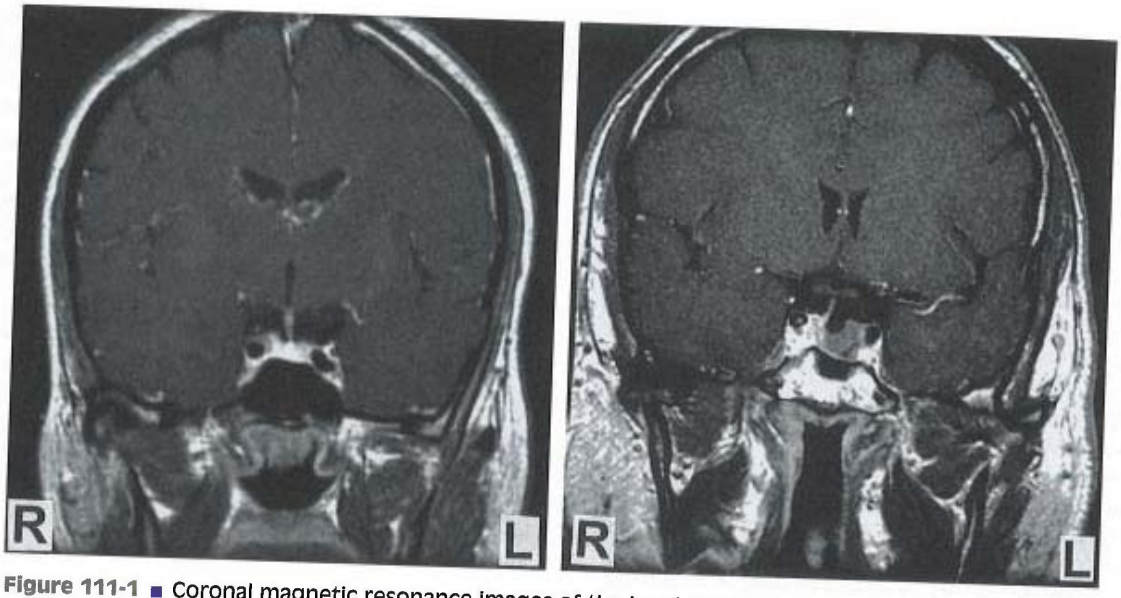


**Figure 111-1** ■ Coronal magnetic resonance images of the head (contrast-enhanced) of a patient with a normal pituitary gland (*left*) and a patient with a pituitary macroadenoma (*right*). The macroadenoma fills the left side of the sella turcica and is hypodense relative to the normal pituitary gland, and it has displaced the pituitary stalk to the right.

Growth hormone secretion need not be assessed. Many stimulation tests have been devised to determine whether secretion of pituitary hormones can be raised, but these tests add little and are rarely indicated.

### Hormonal Excesses

Excess hormonal secretion also can be assessed adequately in most patients by serum measurements of both the pituitary and target gland hormones or the pituitary hormone alone (see Table 111-2), but demonstration of failure of target hormones or other substances to inhibit pituitary hormone secretion is important in some patients. In patients with Cushing's disease, many of whom do not have a radiologically identifiable pituitary tumor, petrosal sinus cannulation and measurements of plasma corticotropin before and after intravenous administration of corticotropin-releasing hormone that reveal high petrosal; peripheral plasma ratios of corticotropin provide strong evidence for the presence of a corticotroph adenoma.

## Treatment

Patients with nonsecretory microadenomas need no treatment but should have repeat magnetic resonance imaging and basal hormone measurements in six and 12 months and then at longer intervals to be sure the adenoma is not enlarging. These adenomas do not often change during follow-up.

Patients with nonsecretory macroadenomas and most patients with secretory microadenomas or macroadenomas should be treated by transsphenoidal resection of the tumor, but drug therapy is appropriate for some patients with secretory adenomas (Table 111-3). Among patients treated by transsphenoidal surgery, the success rate depends on the size of the tumor. Patients with microadenomas are considerably more likely to be cured than are those with macroadenomas (60% to 90% versus 30% to 50%). The operative mortality is very low (less than 1%). Postoperatively, fewer than 20% of patients have new anterior pituitary hormone deficiencies or diabetes insipidus (usually transient), and approximately 1% have bleeding or vascular occlusion, new visual loss, meningitis, sinusitis, third and sixth cranial nerve palsies, or hyponatremia.

Drug therapy, in the form of dopaminergic agonist drugs, is the preferred initial treatment for patients with a prolactinoma, including those with visual impairment. These drugs not only decrease prolactin secretion, but also reduce tumor size. Similarly, long-acting somatostatin analogs are gaining favor as initial treatment for patients with acromegaly.

Patients with pituitary adenomas who are not cured by surgery or do not respond well to drugs may be treated with external-beam radiation, usually in a dose of 50 Gy. This is effective therapy, but its effect is slow; serum hormone concentrations usually fall at a rate of 10% to 20% per year, and it eventually causes

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