REVIEW ARTICLE

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Pituitary-Tumor Endocrinopathies

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Pituitary adenomas account for approximately 15% of intracranial tumors.[1] Management of these benign tumors requires diagnosis of the specific intrasellar disease and comprehensive, multidisciplinary treatment of local mass effects and peripheral endocrinopathies.[2] Since tumors can produce different hormones, their consequences and management vary widely.

PATHOGENESIS

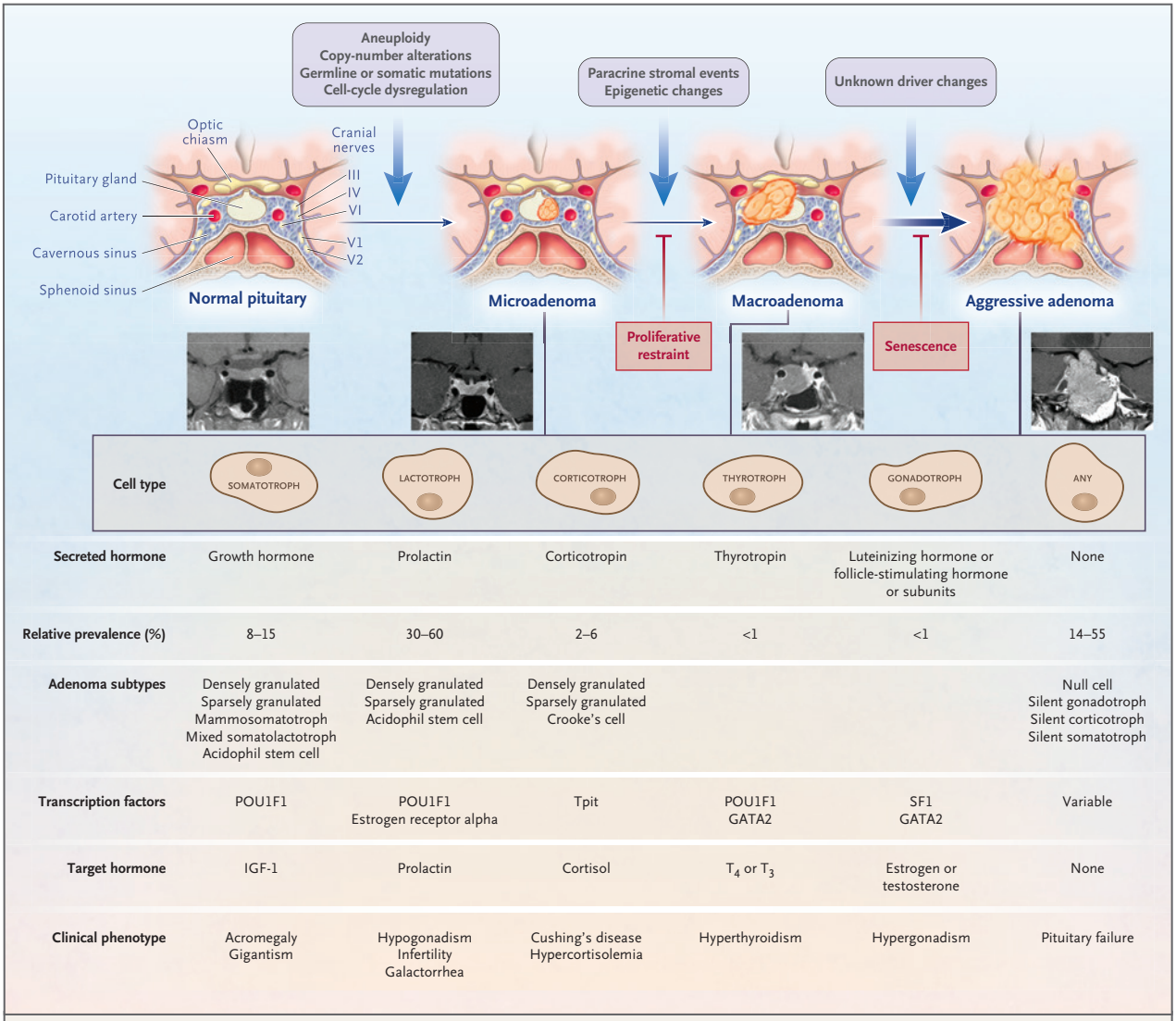
Differentiated, hormone-expressing pituitary cell lineages may give rise to adenomas, often coupled with autonomous hormone hypersecretion. Distinct hypersecretory syndromes depend on the cell of origin: corticotropin-secreting corticotroph adenomas result in Cushing's disease, growth hormone–secreting somatotroph adenomas result in acromegaly, prolactin-secreting lactotroph adenomas result in hyperprolactinemia, and thyrotropin-secreting thyrotroph adenomas result in hyperthyroidism. Gonadotroph adenomas, which are typically nonsecreting, lead to hypogonadism and often manifest incidentally as a sellar mass[3-5] (Fig. 1).

Permissive hypothalamic hormone and paracrine proliferative signals lead to a dysregulated pituitary cell cycle, with aneuploidy, chromosomal copy-number variation, and cellular senescence restraining malignant transformation.[6-8] Although mutations in *GNAS* (the gene for the stimulatory alpha subunit of a guanine nucleotide–binding protein [G-protein] that stimulates adenylate cyclase) and *USP8* (the gene for ubiquitin carboxyl terminal hydrolase 8, a ubiquitin-specific protease) occur in a subgroup of nonfamilial growth hormone–secreting tumors and corticotropin-secreting tumors, respectively,[9] genetic evaluation of sporadic adenomas is rarely helpful for management.

The prevalence of pituitary adenomas has increased to 115 cases per 100,000 population over the past several decades, probably as a result of enhanced awareness and improved diagnostic imaging and hormone assays.[10] The relative prevalence of prolactinomas (54 cases per 100,000 population) and nonfunctioning adenomas (42 per 100,000) may reflect a reporting bias with respect to surgical versus nonsurgical series, since most prolactinomas are treated medically and are not captured in reports of surgical diagnoses.

CLASSIFICATION

Microadenomas are less than 10 mm in diameter. Regardless of the cell origin, macroadenomas (≥10 mm) may impinge on critical parasellar vascular and neural structures, with resultant visual-field defects, including bitemporal hemianopia and decreased acuity, and headaches.[5] Immunocytochemical evaluation of differentiated, cell-specific pituitary transcription factors and hormones,[11] as well as clear biochemical, imaging, and clinical phenotypes, define tumor characteristics



Secreted hormone	Growth hormone	Prolactin	Corticotropin	Thyrotropin	Luteinizing hormone or follicle-stimulating hormone or subunits	None
Relative prevalence (%)	8–15	30–60	2–6	<1	<1	14–55
Adenoma subtypes	Densely granulated Sparsely granulated Mammosomatotroph Mixed somatolactotroph Acidophil stem cell	Densely granulated Sparsely granulated Acidophil stem cell	Densely granulated Sparsely granulated Crooke's cell			Null cell Silent gonadotroph Silent corticotroph Silent somatotroph
Transcription factors	POU1F1	POU1F1 Estrogen receptor alpha	Tpit	POU1F1 GATA2	SF1 GATA2	Variable
Target hormone	IGF-1	Prolactin	Cortisol	T_4 or T_3	Estrogen or testosterone	None
Clinical phenotype	Acromegaly Gigantism	Hypogonadism Infertility Galactorrhea	Cushing's disease Hypercortisolemia	Hyperthyroidism	Hypergonadism	Pituitary failure

Figure 1. Pathogenesis of Pituitary Tumors.

Pituitary adenomas arise from a differentiated hormone-expressing cell or from a null cell. Clinical phenotype is determined by the cell of origin and the presence or absence of autonomous, specific hormone hypersecretion. The prevalence data are estimates. IGF-1 denotes insulin-like growth factor receptor 1, SF1 steroidogenic factor 1, and Tpit T-box factor, pituitary.

and endocrine syndromes, allowing for individualized treatment[5,12] (Table 1).

Evaluation of a pituitary mass should include magnetic resonance imaging (MRI) and visual-field examination for accurate tumor localization and assessment of local compressive mass effects. Hormone hypersecretion should be assessed to distinguish nonsecretory from secretory tumors[13] (Table 2), and pituitary-reserve function should be tested.[14]

Approximately 30% of surgically resected adenomas have persistent or progressive postoperative growth for up to four decades or even longer, with local invasion and an increased percentage of cells positive for Ki-67.[11,15] In one study, more than 40% of 50 aggressive pituitary adenomas showed cavernous sinus invasion.[16] Tumors particularly prone to invasive growth and recurrence include those arising from sparsely granulated somatotrophs, silent corticotrophs, corticotroph Crooke's cells (CK20-positive nonneoplastic cells with a prominent

Table 1. Individualized Approach to Pituitary Adenoma Management.*

Characteristic	Finding or Outcome
Patient	
Age	
<30 yr	More aggressive growth and recurrence, florid hormone phenotype (growth hormone)
>60 yr	Less aggressive features, smaller tumor (growth hormone), larger tumor (prolactin)
Sex	
Female	More microadenomas (prolactin and corticotropin)
Male	More macroadenomas, higher hormone levels (prolactin)
Tumor	
MRI findings	
Size	Larger tumors are more resistant to treatment
Invasiveness	Invasive tumors are more likely to recur
Intensity on T2-weighted images	Intensity determines somatostatin receptor ligand responsiveness (growth hormone)
Histologic features	
Dense granules	Indolent course, responsive to somatostatin receptor ligand (growth hormone)
Sparse granules	Florid course, resistant to somatostatin receptor ligand (growth hormone)
Receptor expression	
Positive for SST2	Likely to respond to octreotide or lanreotide (growth hormone)
Positive for SST5	Likely to respond to pasireotide (corticotropin and growth hormone)
Positive for D2	Likely to respond to dopamine agonist (prolactin)
Negative for SST2, SST5, and D2	Likely to be treatment-resistant
Ki-67 cell-cycle marker	Recurrence less likely if <3%; recurrence more likely if ≥3%
GSP mutation	Likely to respond to somatostatin receptor ligand (growth hormone)
Treatment	
Transsphenoidal surgical resection	Advantages: rapid hormone and symptom remission, one-time cost, potential for cure, decompression of vital parasellar structures, tumor debulking may enhance adjuvant therapy Disadvantages: persistent tumor remnant, postoperative hypopituitarism requiring lifelong replacement therapy, some patients are not candidates for surgery Risks: diabetes insipidus, electrolyte abnormalities, neurologic deficits, CSF rhinorrhea, death from anesthetic agent (rarely); other risks include resection performed by low-volume surgeons, as well as coexisting cardiac disease, cerebrovascular disease, or diabetes
Radiation therapy	Advantages: permanent results, one-time cost, long-term treatment not required, no drug-related adverse events Disadvantages: very slow efficacy onset, medical therapy required until effects are evident Risks: hypopituitarism, visual disturbances, stroke; rarely, CNS damage, brain tumor
Pituitary-directed medical therapy	Advantages: hormone control and symptom relief (prolactin, growth hormone, corticotropin, thyrotropin), no hypopituitarism, tumor-mass control Disadvantages: cure not permanent, long-term sustained treatment required, ongoing cost, injection adherence required Risks regarding somatostatin receptor ligand: gallstones or sludge, diarrhea, nausea, hyperglycemia, sinus bradycardia, alopecia, injection-site pain, headache Risks regarding D2 agonist: depression, nausea, vasospasm

* Hormones in parentheses are those secreted by the adenoma. CNS denotes central nervous system, CSF cerebrospinal fluid, and SST2 and SST5 somatostatin receptor subtype 2 and subtype 5, respectively.

Table 2. Testing to Diagnose Hormone-Secreting Pituitary Tumors.*

Tumor or Disease	Test	Results Requiring Further Evaluation
Prolactinoma	Serum prolactin level measurement	Prolactin level elevated
Acromegaly	Serum IGF-1 level	Age-adjusted IGF-1 level elevated
	Oral glucose-tolerance test (75 g of glucose) with growth hormone measured at 0, 30, and 60 min	Growth hormone level >0.4 μg/liter with the use of an ultrasensitive assay
Cushing's disease	24-hr urinary free cortisol measurement	Elevated urinary free cortisol level on at least two tests
	Midnight salivary cortisol measurement	Elevated free salivary cortisol level
	Plasma cortisol measurement at 8 a.m., after administration of dexamethasone (1 mg) at 11 p.m.	Failure to suppress cortisol level to <1.8 μg/dl
	Serum corticotropin measurement	Low corticotropin level suggests adrenal adenoma; very high level may indicate ectopic corticotropin source
Thyrotropin-secreting tumor	Serum thyrotropin measurement, free T_4 measurement	Normal or increased free T_4 level with measurable thyrotropin may suggest thyrotropin-secreting tumor

* IGF-1 denotes insulin-like growth factor 1.

cytoplasmic hyaline ring that displaces the normal basophilic granules of corticotropic cells), and lactotrophs in middle-aged or older men.[17]

Pituitary carcinomas are exceedingly rare. They account for less than 0.5% of pituitary tumors and respond inconsistently to temozolomide.[5]

MANAGEMENT

Comprehensive management of a pituitary adenoma includes transsphenoidal surgical resection, irradiation, and medical therapy, each with advantages and disadvantages that are specific to the type of adenoma (Table 1). Serial or combined approaches may be required.

Surgery is generally indicated for masses that are 10 mm or more in diameter and those that have extrasellar extension or central compressive features, as well as for persistent tumor growth, especially if vision is compromised or threatened.[18] Resection may alleviate compression of vital structures and reverse compromised pituitary hormone secretion. Predictors of remission include experience of the surgeon, relatively low levels of secreted hormone (if the level is elevated at all), and small tumors. Postoperatively, hypopituitarism may develop, as may diabetes insipidus and cerebrospinal fluid leaks. Approximately 10% of patients have a recurrence over a period of 10 years after surgery. Persistent tumor postoperatively may reflect incomplete resection, inaccessible cavernous sinus tumor tissue, or dural nesting of hormone-secreting tumor cells.

Radiation therapy, administered by means of conventional external-beam or proton-beam techniques, or stereotactic radiosurgery requires local expertise and is generally reserved for tumors that are resistant to medical treatment or are not controlled by surgery. Tumor growth is usually arrested over a period of several years, and adenoma-derived hormone hypersecretion may persist during the initial years.[19] In most patients, pituitary failure develops within 10 years after radiation therapy, and lifelong hormone replacement is required. Deterioration in vision and new cranial-nerve palsies are rarely observed.[19] Mortality from cerebrovascular causes is increased by a factor of 4.42 (95% confidence interval [CI], 2.71 to 7.22) after conventional pituitary irradiation, with 16 observed deaths versus 3.6 expected deaths.[20]

GENETIC SYNDROMES

Pituitary adenomas may occur in association with several very rare genetic syndromes. Multiple endocrine neoplasia type 1 is associated with pituitary adenomas as well as parathyroid and pancreatic-islet tumors and, less commonly, carcinoid, thyroid, and adrenal tumors. The McCune–Albright syndrome is characterized by polyostotic fibrous dysplasia and cutaneous pigmentation, with sexual precocity, hyperthyroidism, hypercor-

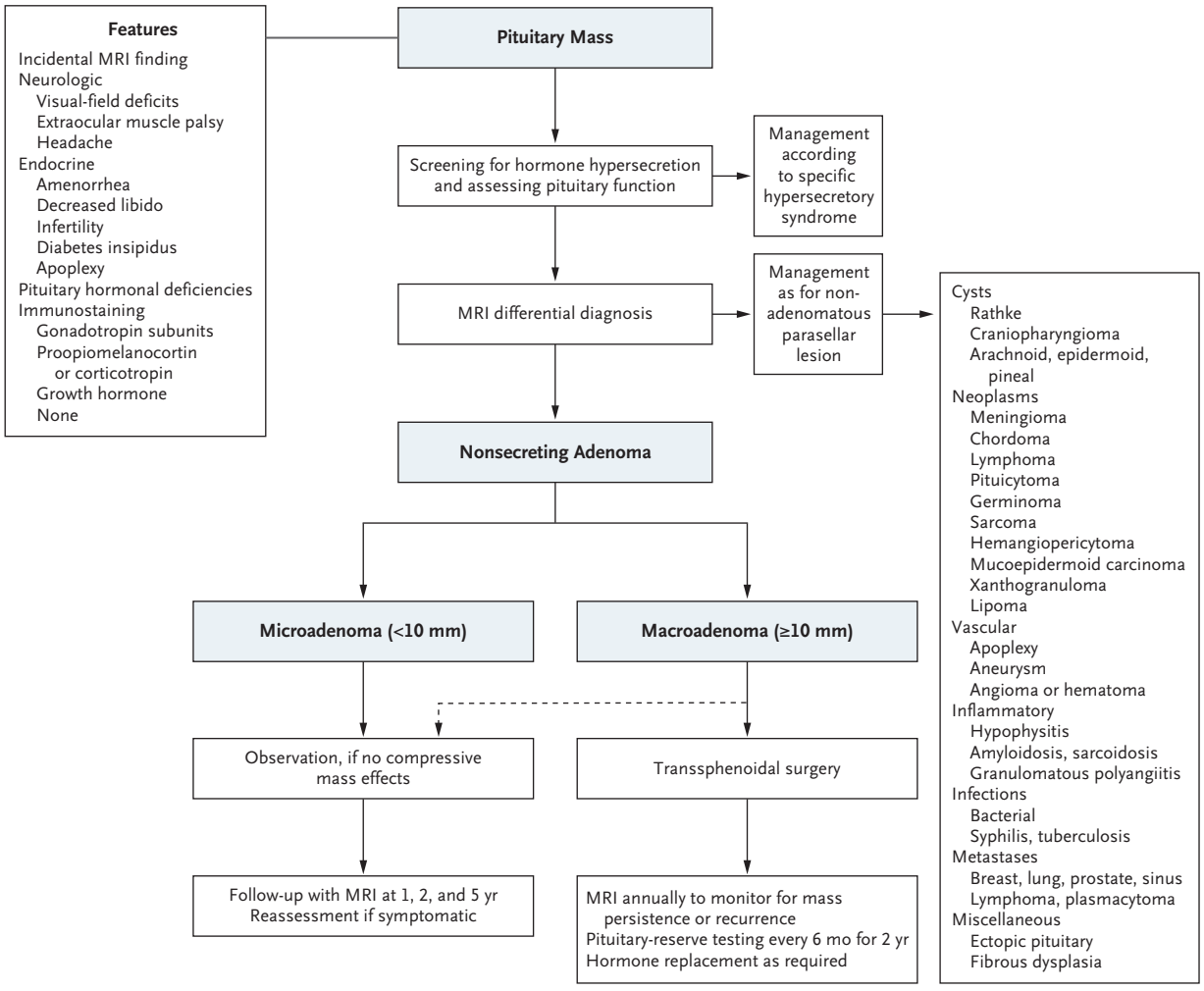


Figure 2. Approach to Patients Presenting with a Nonsecreting Pituitary Mass.

The main diagnostic consideration is to distinguish a nonsecreting or secreting adenoma from a nonadenomatous lesion. The treatment approach is determined by the specific diagnosis. The dashed line indicates an option that may be considered under some circumstances.

tisolism, hyperprolactinemia, and acromegaly. Rare cases of familial pituitary adenomas have been reported in families with a predisposition for somatotroph tumors in childhood or young adulthood, and about 25% of these tumors have been linked to germline mutations in *AIP* (the gene for aryl hydrocarbon receptor–interacting protein),[21] which are not commonly encountered with sporadic adenomas. The Carney complex includes pituitary adenomas with benign cardiac myxomas, schwannomas, thyroid adenomas, and pigmented skin spots.[22]

NONSECRETING ADENOMAS

Although several lesions may present as nonsecreting sellar masses[23] (Fig. 2), most are nonsecreting adenomas of gonadotroph lineage. These adenomas express differentiated hormone products and cell-specific transcription factors, but since the respective peripheral-blood hormone levels are not elevated, the adenomas are not associated with systemic syndrome phenotypes.[24] True null-cell adenomas express no hormone gene product.

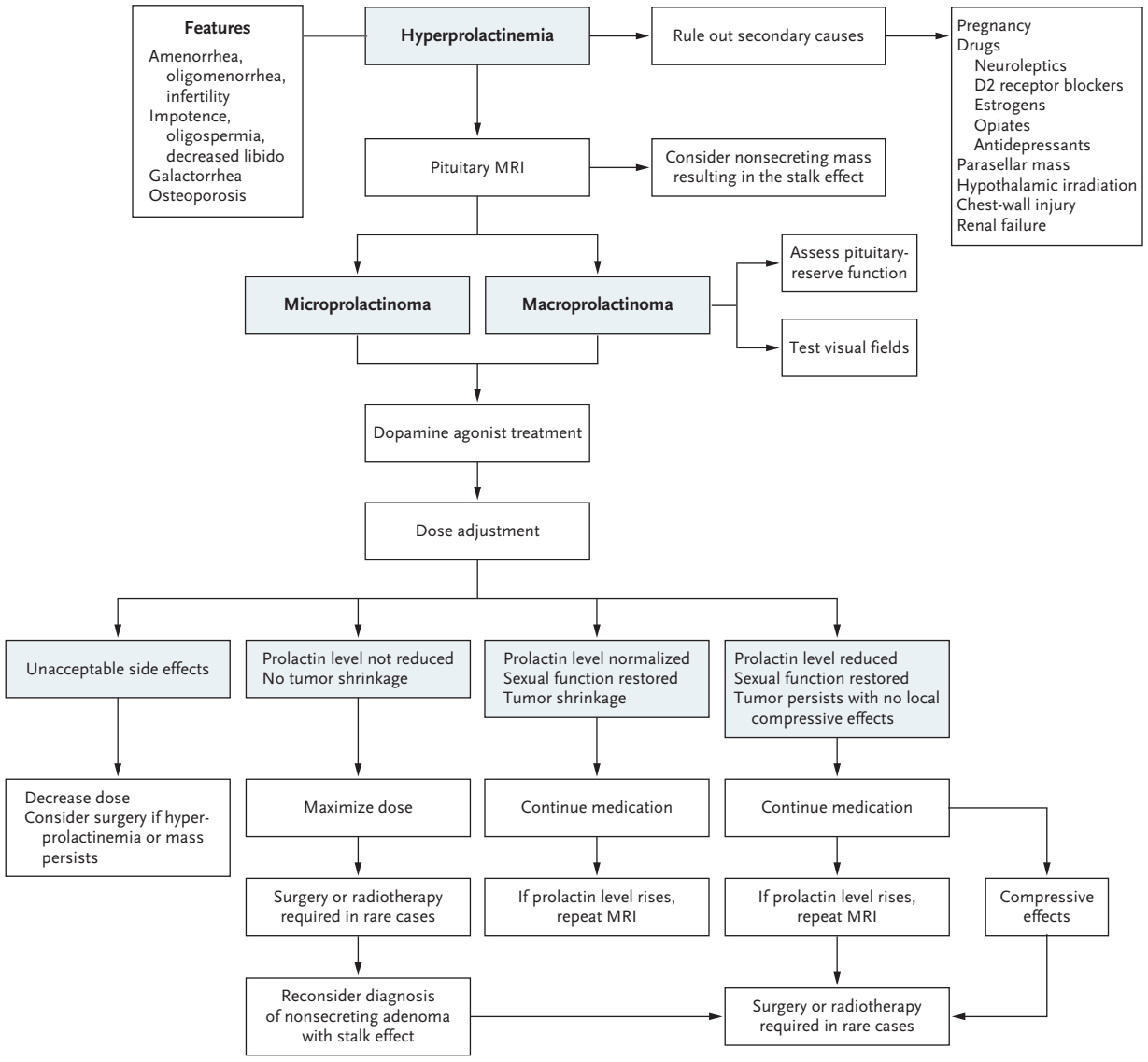


Figure 3. Approach to Patients Presenting with Hyperprolactinemia.

In patients with hyperprolactinemia, the clinical challenge is to rule out a secondary, nonpituitary cause before embarking on comprehensive pituitary imaging and testing. The stalk effect is compression of the pituitary stalk due to a nonsecreting sellar mass that interrupts delivery of inhibitory dopamine from the hypothalamus to the prolactin-secreting cells of the pituitary.

CLINICAL FEATURES AND DIAGNOSIS

Nonsecreting adenomas may be unrecognized for years and are usually diagnosed because of local mass effects or hypogonadism or are detected incidentally. Chiasmal compression causes gradual, progressive deficits in vision, and about two thirds of patients have decreased gonadotropin levels and hypogonadism.[25] In a study involving 385 consecutive patients with nonsecreting adenomas, 289 had macroadenomas and 66 had giant adenomas (>4 cm in diameter), with most of the patients presenting with headache or disturbances in vision.[26] Approximately 10% of patients with nonsecreting adenomas present with pituitary apoplexy (characterized by the abrupt onset of retroorbital pain, altered consciousness,

ophthalmoplegia, and ultimately, loss of vision from pituitary hemorrhage or infarction).

Very rarely, circulating gonadotropin levels are elevated, resulting in ovarian hyperstimulation or increased testicular volumes. Paradoxically, however, high gonadotropin levels more commonly down-regulate the gonadal axis.

Clinically silent tumors expressing nonsecreted corticotropin or growth hormone account for up to 20% of nonsecreting tumors. They are usually resected after a nonsecreting macroadenoma has been diagnosed, with the diagnosis subsequently confirmed by histologic assessment with appropriate immunostaining. These silent tumors grow aggressively, with no apparent features of hypercortisolism or acromegaly, although their morphologic features may be indistinguishable from those of secretory adenomas. A systematic review of 14 studies with a total of 297 patients who underwent surgical treatment for silent corticotroph adenomas showed that 31% of the adenomas recurred during a follow-up period of more than 5 years.[17]

TREATMENT

Complete resection of a nonsecreting macroadenoma is achieved in approximately 65% of patients, with visual function restored in up to 80% of the patients and hypopituitarism, when present, reversed in approximately 50%.[26,27] Preoperative tumor invasiveness largely determines the risk of postoperative persistent or recurrent tumor requiring adjuvant irradiation and reoperation. Radiosurgery was associated with high rates of tumor control in a multicenter analysis involving 512 patients followed for a median of 36 months, and pituitary failure developed in 21% of the patients.[28] In a retrospective analysis of tumor growth rates among 237 patients who were followed for a median of 5.9 years, 36% of the patients had a recurrence after surgery alone, whereas 13% had a recurrence after surgery and adjuvant radiotherapy.[29]

Guidelines[13] recommend follow-up with periodic pituitary MRI, vision evaluations, and pituitary-function testing, and prophylactic radiotherapy to prevent postoperative tumor recurrence or progression has been suggested. Of 648 incidentally discovered pituitary adenomas, 10% of the 229 microadenomas and 20% of the 419 macroadenomas increased in size during up to 8 years of follow-up.[30] Accordingly, expectant observation is recommended for the management of stable, nonsecreting microadenomas and small macroadenomas. Preoperative or newly manifested postoperative pituitary failure may be insidious. In a study involving 2795 patients, pituitary failure, especially with corticotropin deficiency, was associated with excess overall mortality (standardized mortality ratio, 4.35; 95% CI, 1.99 to 8.26), on the basis of 2.1 expected deaths versus 9 observed deaths ($P<0.001$).[31]

PROLACTIN-SECRETING ADENOMAS

Prolactinomas are the most common secretory tumor, accounting for up to 60% of all pituitary adenomas and more than 75% of pituitary adenomas in women.[32] Microprolactinomas, which have a female:male ratio of 20:1, are usually stable and slow-growing, with continued growth after diagnosis in less than 15% of cases.[33]

CLINICAL FEATURES

Most patients with a pituitary mass and a serum prolactin level exceeding 150 ng per milliliter (reference range, <20) are found to have a prolactinoma (Fig. 3). A prolactin level of more than 250 ng per milliliter is usually diagnostic of a macroprolactinoma, and the tumor mass usually correlates with the serum prolactin level.[34] Large prolactinomas (>10 mm in diameter) that are aggressive account for less than 5% of tumors and are characterized by very high prolactin levels (>1000 ng per milliliter) and a male:female ratio of 9:1. In a study involving 45 men and 51 women with prolactinomas, the tumors in the men were larger than those in the women (mean [±SD] diameter, 26±2 mm vs. 10±1 mm) and grew more aggressively, with a mean serum prolactin level of 2789±572 ng per milliliter in men versus 292±74 ng per milliliter in women.[35]

Persistently elevated prolactin levels suppress gonadotropin, leading to amenorrhea, oligomenorrhea, or a short luteal phase associated with infertility in women and low libido, impotence, oligospermia, or azoospermia in men. About 50% of women and 35% of men have galactorrhea, and both women and men have reduced bone density, often associated with sex steroid hormone deficiency and an increased risk of vertebral fractures.

DIAGNOSIS

Hyperprolactinemia is caused mainly by pregnancy, prolactinomas, medications, chest-wall injury, and functional or mechanical interruption of pituitary-stalk dopamine transport. Prolactin levels are elevated in approximately 30% of patients with acromegaly.[36]

Prolactin levels should be measured in all patients with a sellar mass; conversely, hyperprolactinemia not explained by pregnancy or exposure to neuroleptic drugs should prompt pituitary imaging to rule out a pituitary mass. In patients with hyperprolactinemia and a pituitary mass, failure to achieve tumor shrinkage with dopamine agonists may suggest compression of the pituitary stalk due to a nonsecreting sellar mass that interrupts delivery of inhibitory dopamine from the hypothalamus, resulting in disruption of prolactin control; this is known as the stalk effect.

TREATMENT

Prolactin levels should be normalized, with sexual function and fertility restored, galactorrhea halted, and the tumor mass eliminated or reduced, while pituitary function is retained. Low bone density should be addressed.

Prolactinomas are ideally managed with a dopamine agonist,[33] which should lower prolactin levels and shrink the tumor mass. Bromocriptine is rarely used, since it requires daily dosing. One study showed that cabergoline, administered at a dose of 0.5 to 1 mg once or twice weekly, lowered prolactin levels in 83% of 459 women with hyperprolactinemia,[37] and this agent restores ovulatory cycles and fertility with few side effects. In approximately 65% of patients with macroprolactinomas, treatment normalizes prolactin levels and reduces the tumor mass.[38] Up to 15% of patients do not have a response to maximal dopaminergic doses (i.e., prolactin levels are not normalized, and tumor shrinkage is <50%). Patients with normalized prolactin levels but inadequate tumor shrinkage may require surgery or radiotherapy.

Hyperprolactinemia remits in up to 20% of patients after dose tapering and discontinuation of cabergoline, which can be attempted after more than 2 years of therapy and only when the possibility of tumor invasion has been rigorously ruled out.[39]

Adverse effects of cabergoline, reported in up to 50% of patients, include nausea, nasal stuffiness, depression, digital vasospasm, postural hypotension, and in rare cases, cerebrospinal fluid leak. Mood disorders, exacerbation of psychosis, and poor impulse control are additional rare effects.[40] The low doses of cabergoline used for the treatment of prolactinomas do not appear to place patients at risk for clinically significant cardiac valve disease, and valvulopathy was not observed in 192 patients who were followed for 34 months in a cross-sectional study.[41] Because asymptomatic, mild tricuspid regurgitation was reported in 20% of patients, those treated with cabergoline in whom a cardiac murmur develops should undergo cardiac evaluation.

In 31 surgical series involving a total of 1224 patients with microprolactinomas, transsphenoidal resection resulted in normal prolactin levels in 71% of the patients, and initial cure rates may exceed 90% when resection is performed by high-volume surgeons.[42] About 50% of macroprolactinomas remit, and persistent, postoperative hyperprolactinemia arises from tumor remnants.[42] The efficacy of treatment with dopamine agonists and the long-term risk of postoperative recurrence have discouraged clinicians from choosing surgery as a primary treatment for macroprolactinomas. Invasive, dopamine agonist–resistant prolactinomas may require more than one surgery, with continued administration of high-dose cabergoline.[43] Radiation therapy is reserved for patients with treatment-resistant macroprolactinomas.

During pregnancy, pituitary expansion, especially in the case of macroprolactinomas, may threaten the visual fields.[44] Prophylactic transsphenoidal resection should be considered when vision is threatened. Dopamine agonist therapy should be discontinued when pregnancy is confirmed.

ACROMEGALY

Acromegaly, with an incidence of approximately 10 cases per 1 million persons,[32,45] is caused by a growth hormone–secreting somatotroph tumor. High growth hormone and insulin-like growth factor 1 (IGF-1) levels are associated with striking somatic and metabolic dysfunction. Densely granulated somatotroph adenomas arise insidiously, whereas sparsely granulated subtypes, which develop in younger patients, are character-

ized by aggressive growth and florid disease.[12] In very rare cases, extrapituitary acromegaly is caused by neuroendocrine tumor production of growth hormone or growth hormone–releasing hormone.[46,47]

CLINICAL FEATURES

Approximately 70% of patients with acromegaly have an invasive macroadenoma at diagnosis. Coexisting conditions include headache and insidious acral and soft-tissue changes. The diagnosis of acromegaly can be delayed by a mean of approximately 10 years after the onset of symptoms.[48] Patients may first seek dental, orthopedic, rheumatologic, or cardiac care. In one study, approximately 20% of 324 patients sought care because of an altered facial appearance, enlarged extremities, or both.[49] Other features include increased shoe or ring size, voice deepening, the carpal tunnel syndrome, hyperhidrosis, and frontal-skull bossing and coarse oily skin. Prognathism leads to incisor separation and jaw malocclusion. Obstructive sleep apnea and excessive snoring are hallmarks of uncontrolled acromegaly. Arthropathy is reported in approximately 70% of patients, with polyarticular arthritis, osteophytosis, dorsal kyphosis, and vertebral fractures.[48] Coexisting cardiovascular conditions include hypertension, arrhythmias, and left ventricular dysfunction, with an increased aortic-root diameter.[50] Despite biochemical control, cardiovascular disorders may persist.[51] Growth hormone induces insulin resistance, with glucose intolerance,[52] and patients with acromegaly have an increased risk of diabetes, as compared with a control cohort from the general population (hazard ratio, 4.0 [95% CI, 2.7 to 5.8]; rate per 1000 persons, 12.1 cases [95% CI, 9.0 to 16.4] vs. 3.4 cases [95% CI, 2.9 to 4.1]).[53] About 30% of patients have high prolactin levels, often with galactorrhea.

Hypertrophic colonic mucosal folds and diverticulae can occur in patients with acromegaly.[54,55] In a case–control study, colonic polyps were detected in 32% of 165 patients, with an estimated relative risk of 6.21 (95% CI, 4.08 to 9.48).[56] Studies involving more than 2000 patients showed an increased incidence of cancer, with an overall standardized incidence ratio of 1.5 (95% CI, 1.2 to 1.8), mostly accounted for by colorectal, kidney, and thyroid cancers.[57,58] However, other studies have shown no increase in the incidence of cancer. Nevertheless, colonoscopy should be performed at diagnosis and subsequently, according to published guidelines.[59]

A 20-year study showed higher mortality rates among 333 patients with acromegaly than among 4995 controls (113 deaths [34%] vs. 1334 deaths [27%]; odds ratio 1.6; 95% CI, 1.2 to 2.2).[60] Deaths associated with acromegaly are due to cardiovascular, respiratory, and cerebrovascular disorders, with cancer also reported as a cause of death in more recent years. Persistently elevated growth hormone and IGF-1 levels, diabetes, hypertension, older age, pituitary irradiation, and inadequate treatment of adrenal insufficiency all contribute significantly to mortality.[61]

Gigantism, a rare condition, is due to excessive secretion of growth hormone before epiphyseal closure. The disorder may be associated with germline *AIP* mutations, the McCune–Albright syndrome, or acidophilic stem-cell adenomas; X-linked gigantism is characterized by Xq26.3 chromosomal microduplications, resulting in accelerated gigantism and overexpressed tumor *GPR101* (a gene for a G-protein–coupled receptor).[62] Surgical resection with adjuvant growth hormone suppression is required to maintain remission and prevent long-term tissue exposure to excess growth hormone and IGF-1.[63]

DIAGNOSIS

IGF-1 levels that are elevated for the patient's age are highly specific for acromegaly and also correlate with indexes of disease activity.[64] The pulsatile nature of adenoma growth hormone secretion precludes reliance on a random measurement for diagnosis. Instead, the diagnosis is established by using an ultrasensitive assay to document nadir growth hormone levels of more than 0.4 μg per liter during a 75-g glucose load.[65] Growth hormone levels are log-linearly concordant with IGF-1 levels.[66] Postoperatively, IGF-1 levels may remain elevated for months despite control of growth hormone secretion.

TREATMENT

Comprehensive treatment goals for acromegaly include ablating or controlling the pituitary mass, suppressing growth hormone and IGF-1 hypersecretion, and preventing the development of associated disorders while maintaining anterior pituitary function.[59] In 13 studies involving 1018 patients who underwent surgical resection,

control of growth hormone secretion and IGF-1 levels was achieved in 73% of patients with microadenomas and 61% of patients with macroadenomas.[67-69] However, patients with macroadenomas that invade the cavernous sinus invariably show persistent growth hormone hypersecretion after surgery. In a study involving 371 patients treated with radiosurgery, biochemical remission was reported in 59% of the patients, with a mean time to remission of 38 months and a mean time to recurrence of 17 months.[70]

Dopamine agonists have been proposed for patients with mild disease, and the addition of cabergoline may normalize IGF-1 levels in some patients with disease that is resistant to somatostatin therapy.[71] The somatostatin receptor ligands octreotide and lanreotide bind SST2 (somatostatin receptor subtype 2), inhibiting growth hormone secretion.[72] A meta-analysis of 90 studies involving 4464 patients treated with somatostatin receptor ligands showed overall control of growth hormone secretion and of IGF-1 levels in 56% and 55% of the patients, respectively.[73] In a meta-analysis involving 1685 patients in 41 studies, 53% of patients had a reduction in tumor mass.[74] Efficacy may be enhanced by increasing the dose and injection frequency.[75] Soft-tissue swelling and headache usually resolve, sleep apnea abates, and left ventricular function improves,[48] but hypertension may persist. Tumor SST2 expression, densely granulated tumor, and hypointensity on T2-weighted MRI are important markers of treatment responsiveness.[12,76] Transient gastrointestinal side effects, occurring in approximately 30% of patients, include loose stools and nausea. Gallbladder sludge occurs in up to 25% of patients, although cholecystitis is very rare. Asymptomatic sinus bradycardia also occurs. Octreotide and lanreotide do not generally disrupt glucose homeostasis, but pasireotide, a long-acting hexapeptide somatostatin multireceptor ligand, results in hyperglycemia and new-onset diabetes in about 60% of patients.[77]

Pegvisomant, a growth hormone receptor antagonist that blocks peripheral growth hormone action and subsequent IGF-1 production,[78] is useful for patients with disease that is resistant to somatostatin receptor ligands, as well as patients with hyperglycemia, since the drug enhances insulin sensitivity.[79] A surveillance study showed IGF-1 control in 63% of 1288 patients.[80] Side effects include elevated hepatic aminotransferase levels, injection-site inflammation, and lipodystrophy. Growth hormone axis blockade with growth hormone receptor–directed pegvisomant combined with pituitary-directed somatostatin receptor ligand offers greater efficacy than either drug alone.[81]

Treatment approaches have advantages and disadvantages for individualizing patient care and maximizing growth hormone and IGF-1 control (Table 1).[12] Patients should be monitored for symptoms affecting the quality of life, including anxiety. Management of coexisting conditions, especially high blood pressure, cardiac dysfunction, and sleep apnea, as well as elevated blood sugar levels, is important to reduce the risk of death.

CUSHING'S DISEASE

Corticotropin-secreting corticotroph adenomas, which account for up to 15% of pituitary tumors, with an incidence of 1.6 cases per 1 million persons,[82] are typically small (approximately 6 mm in diameter) and are 5 to 10 times as common in women as in men. Excessive secretion of corticotropin leads to adrenal hypercortisolemia. Corticotroph adenomas account for approximately 70% of cases of Cushing's syndrome, with iatrogenic hypercortisolism, ectopic corticotropin or corticotropin-releasing hormone production, and cortisol-producing adrenal lesions accounting for the rest.[83]

CLINICAL FEATURES

Typical cushingoid features include plethoric moon facies with thin skin, purple striae, and easy bruising. Central obesity, hypertension, glucose intolerance or diabetes, and, especially in younger women, menstrual disturbances and osteoporosis are observed, as are proximal muscle wasting and weakness, acne, hirsutism, depression, psychoses, and susceptibility to infection.[84]

The disorder may be indolent or clinically florid, with a high mortality rate if inadequately controlled. In a study involving 502 unselected patients, the overall standardized mortality ratio was 2.5 (95% CI, 2.1 to 2.9), with 133 observed deaths versus 54 expected deaths; cardiovascular disease accounted for most of the excess deaths.[85] Mortality was also elevated among the patients with biochemical remission (standardized mortality ratio, 1.9 [95% CI, 1.5 to 2.3]), with 89

observed deaths versus 47 expected deaths. Other causes of death include infections and suicide. Rapid-onset hypercortisolism with skin hyperpigmentation and severe myopathy suggests an ectopic tumor source of corticotropin, often associated with hypertension and hypokalemic alkalosis.[83]

DIAGNOSIS

Accurate diagnosis of Cushing's disease can be challenging.[83] Approximately 40% of corticotropin-secreting corticotroph tumors are not visible on imaging, and at least 10% of persons in the general population have small, clinically silent microadenomas. The disorder may therefore be overdiagnosed, especially since clinical features of hypercortisolemia overlap with other, much more common disorders, including obesity, hypertension, glucose intolerance, and osteoporosis.

The diagnosis of pathologic hypercortisolemia is established on the basis of clinical features of hypercortisolism coupled with reproducible evidence of failure to suppress plasma cortisol at 8 a.m. to a level below 1.8 μg per deciliter after the administration of 1 mg of dexamethasone at 11 p.m. or elevated 24-hour urinary free cortisol levels and midnight salivary cortisol values.[84] Basal corticotropin levels are usually inappropriately high, and suppressibility of corticotropin by glucocorticoids may distinguish a pituitary tumor from an ectopic source.

Since the results of repeated urinary free cortisol and midnight salivary cortisol measurements may vary, bilateral inferior petrosal sinus sampling of corticotropin levels may be required to confirm the diagnosis. A central-to-peripheral corticotropin gradient that exceeds 2 before and after the administration of corticotropin-stimulating hormone definitively localizes a corticotroph tumor source with more than 95% sensitivity.

TREATMENT

Selective transsphenoidal adenomectomy is recommended as initial therapy for Cushing's disease, with remission achieved in approximately 75% of patients and recurrence seen in approximately 10%.[86] Although more radical surgery offers the potential for total adenoma resection, complication rates are higher and pituitary damage is more likely with total resection.[87] Radiation therapy may control the disease,[88] but the efficacy of this treatment is delayed for several years, and approximately 30% of patients have a relapse.

Adrenalectomy may immediately reverse hypercortisolism. However, lifelong replacement of adrenal hormones is challenging. Patients who undergo adrenalectomy are also at risk for adrenal crisis and Nelson's syndrome (pituitary enlargement and development of corticotropin-secreting pituitary adenomas, which often have an invasive growth pattern).

Adrenal-targeted medical therapy may offer clinical and biochemical improvement, but most studies of such treatment have not been rigorously controlled, and the results are often inconsistent.[89] Adrenal steroidogenesis inhibitors block hypercortisolemia but do not target the pituitary tumor. Ketoconazole, an antifungal imidazole, normalizes urinary free cortisol levels in 50% of patients.[90] Side effects include nausea, headache, low testosterone levels, reversible elevated liver enzyme levels, and in rare cases, hepatotoxicity. Metyrapone controls urinary free cortisol levels in about 50% of patients, and accumulated steroid precursors may cause acne, hirsutism, hypertension, and hypokalemia. Mitotane, an adrenolytic agent, is used mainly for adrenal carcinoma. Mifepristone, a glucocorticoid receptor antagonist, is approved for the treatment of hyperglycemia associated with Cushing's syndrome in patients in whom surgery has failed or who are not surgical candidates. Since mifepristone blocks the action of cortisol, corticotropin and urinary free cortisol levels are increased.[91] Adrenal failure, hypokalemia, and excessive vaginal bleeding may limit the use of this agent.

Pituitary-targeted drugs include high-dose cabergoline (up to 1 mg daily), which controls hypercortisolism in up to 30% of patients, although therapeutic efficacy is often not maintained in the long term. Pasireotide blocks adenoma-derived corticotropin secretion, normalizes urinary free cortisol levels in approximately 40% of patients with mild disease, and improves clinical features. Hyperglycemia develops in most patients.[92,93]

THYROTROPIN-SECRETING TUMORS

Accounting for approximately 1% of adenomas, thyrotropin-secreting tumors lead to elevated or inappropriately suppressed thyrotropin levels

with normal or elevated thyroid hormone levels.[94] Resection and adjuvant treatment are required for adequate biochemical outcomes.

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