Somatotroph (GH) Adenomas

12

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12.1 Epidemiology and Clinical Presentation

- Growth hormone (GH)–secreting pituitary adenomas (GH adenomas) result in the clinical syndromes of gigantism and acromegaly.
- More than 90 % of patients with acromegaly have a pituitary adenoma [1].
- GH adenomas comprise approximately 15 % of surgically resected pituitary adenomas [2–4].
- The annual incidence of acromegaly has been calculated to be 3–4 cases per 1 million people, with a prevalence of 40–60 cases per million people [5].
- Increased GH secretion results in increased liver production of insulin-like growth factor-1 (IGF-I), which mediates the systemic effects of GH.
- Acromegaly is associated with multiple physical features and symptoms, including increased soft tissue edema, enlargement of the hands and feet, frontal bossing, coarse facial features, prognathism, acral growth, skin tags, snoring, and hyperhidrosis.
- Among the associated medical conditions are hypertension, diabetes mellitus, carpal tunnel syndrome, arthropathy, osteoarthritis, obstructive sleep apnea, colon polyps/cancer, cardiac hypertrophy, cardiomyopathy, and pulmonary disease.
- The clinical presentation may be more subtle in older patients [6].
- Uncontrolled acromegaly is a life-threatening condition that has been associated with decreased survival. Of deaths related to acromegaly, 60 % are accounted for by cardiovascular disease, 25 % by respiratory disease, and 15 % by malignancies [7–9].

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12.2 Diagnosis

12.2.1 Endocrinological Diagnosis

- An initial screening test consists of a serum GH and IGF-I level.
- The serum IGF-I level provides better correlation of the disease state in acromegaly, and early normalization of IGF-I correlates with restoration of a normal life expectancy [5, 10].
- IGF-I levels are age and sex specific, requiring appropriate correlation with the particular laboratory's normal ranges.
- An oral glucose tolerance test (OGTT) is the gold standard test used to confirm the diagnosis or its remission. An oral glucose load of 75 g is given and serum GH levels are subsequently monitored for up to 120 min afterward. A nadir GH level greater than 1 ng/L during an OGTT is generally consistent with a diagnosis of acromegaly.

12.2.2 Imaging

- GH adenomas typically originate in the lateral aspect of the gland and are likely to demonstrate patterns of infrasellar extension with invasion of the sellar floor and clivus (Figs. 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 12.10, 12.11, 12.12, and 12.13) [11, 12].
- A variety of bone and soft tissue changes are commonly identified in acromegalic patients, including hypertrophic nasal turbinates, conchae bullosae, enlarged (hyperpneumatized) paranasal sinuses, and thickened bony anatomy [13].
- GH adenomas are typically isointense on T1- and T2-weighted MR imaging [11].
- Most GH adenomas (86 %) are macroadenomas at the time of diagnosis [2].
- Acromegalic patients often have tortuous or ectatic internal carotid arteries with increased caliber, making their identification during surgical treatment of paramount importance [13].

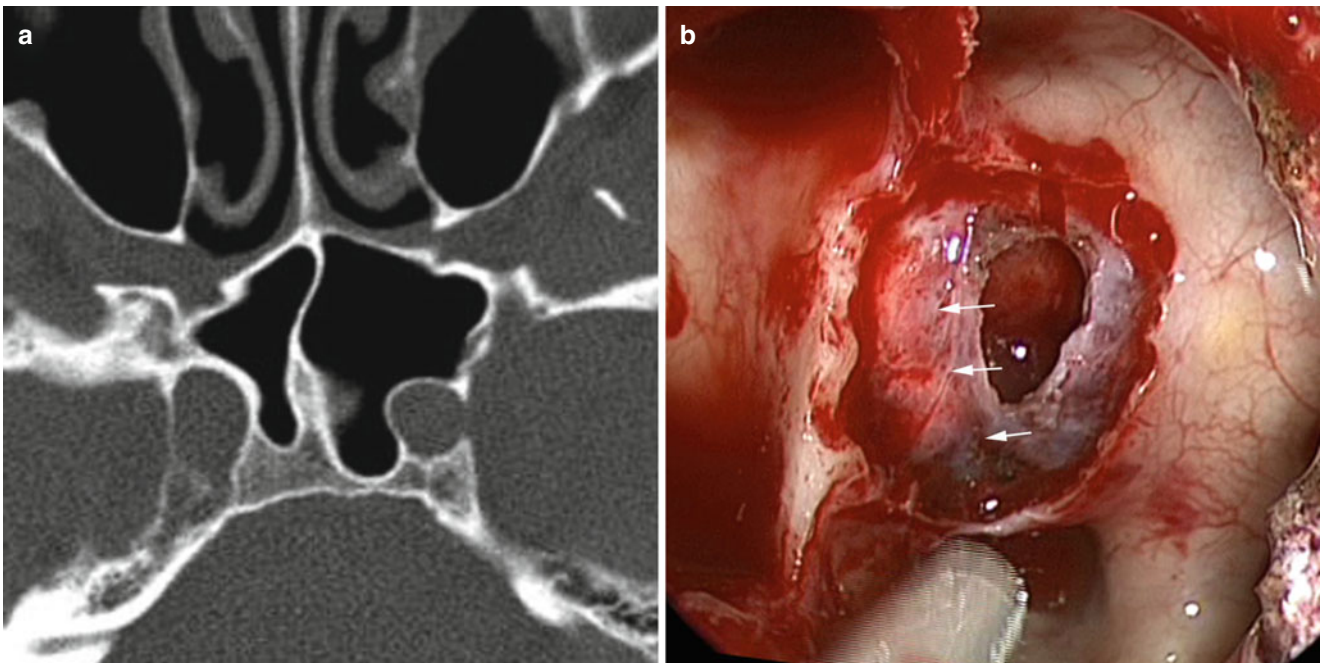

Fig. 12.1 Growth hormone (GH)–secreting adenoma. (**a**) Axial noncontrast CT scan with bony windowing. (**b**) Intraoperative endoscopic photo. The CT scan shows the large caliber and prominence of the internal carotid arteries, which demonstrate ectasia and tortuosity with extension into the sella (*white arrows*). Adapted from Zada et al. with permission [13]

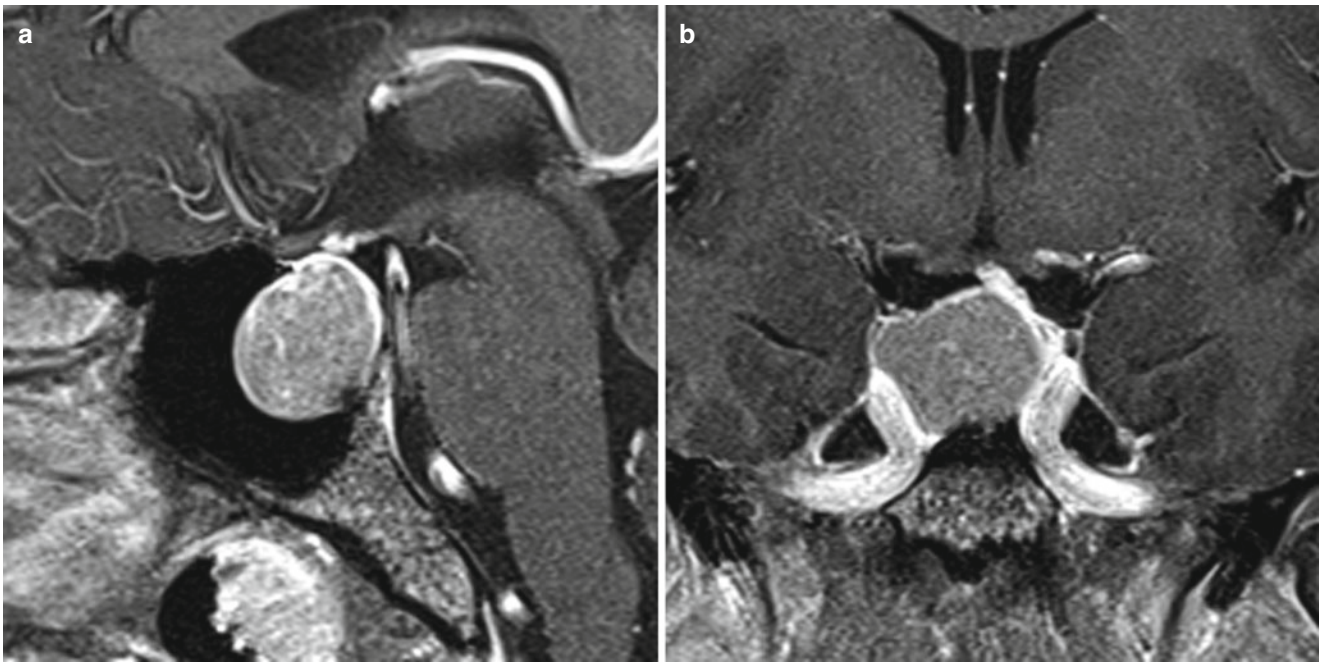

Fig. 12.2 GH adenoma. (**a**) Sagittal T1-weighted post-gadolinium image. (**b**) Coronal T1-weighted post-gadolinium image. An expansile sellar/suprasellar mass abuts the right cavernous internal carotid artery, and there is remodeling of the sellar floor. The pituitary stalk is elevated and deviated to the left

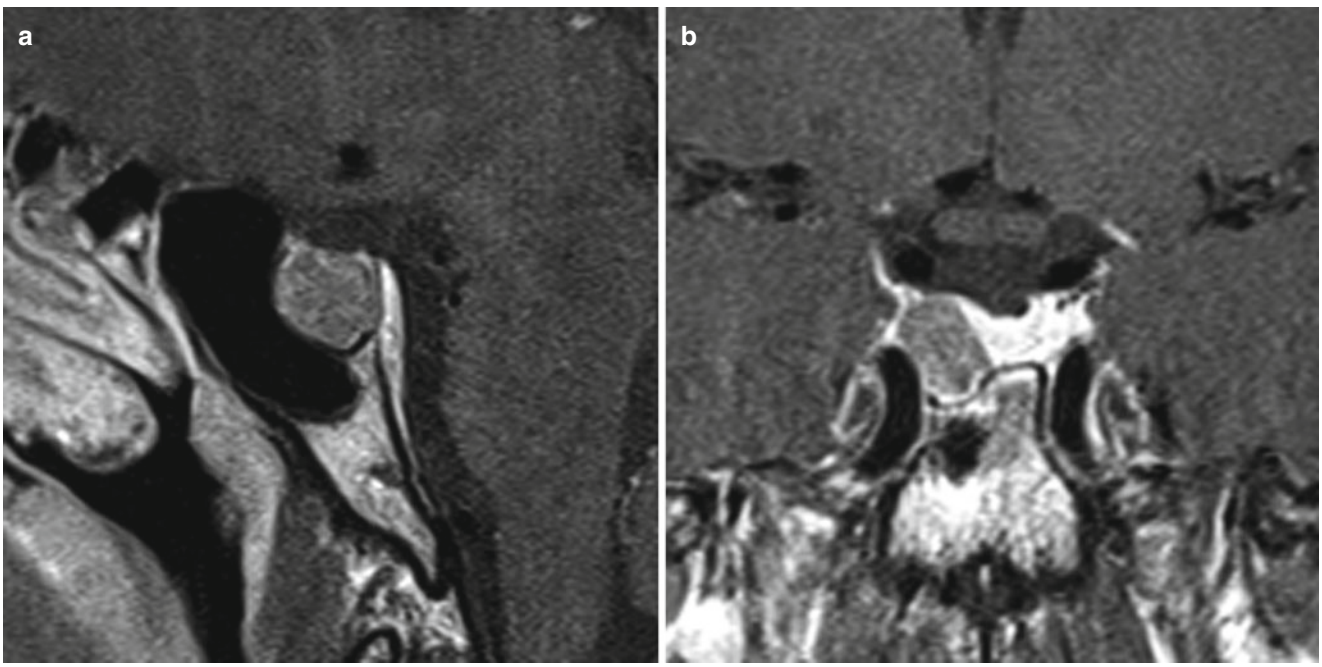

Fig. 12.3 GH adenoma. (**a**) Sagittal T1-weighted post-gadolinium image. (**b**) Coronal T1-weighted post-gadolinium image. A hypoenhancing mass presents in the *right* aspect of the sella abutting the right cavernous internal carotid artery without encasement. There is erosion of the right sellar floor

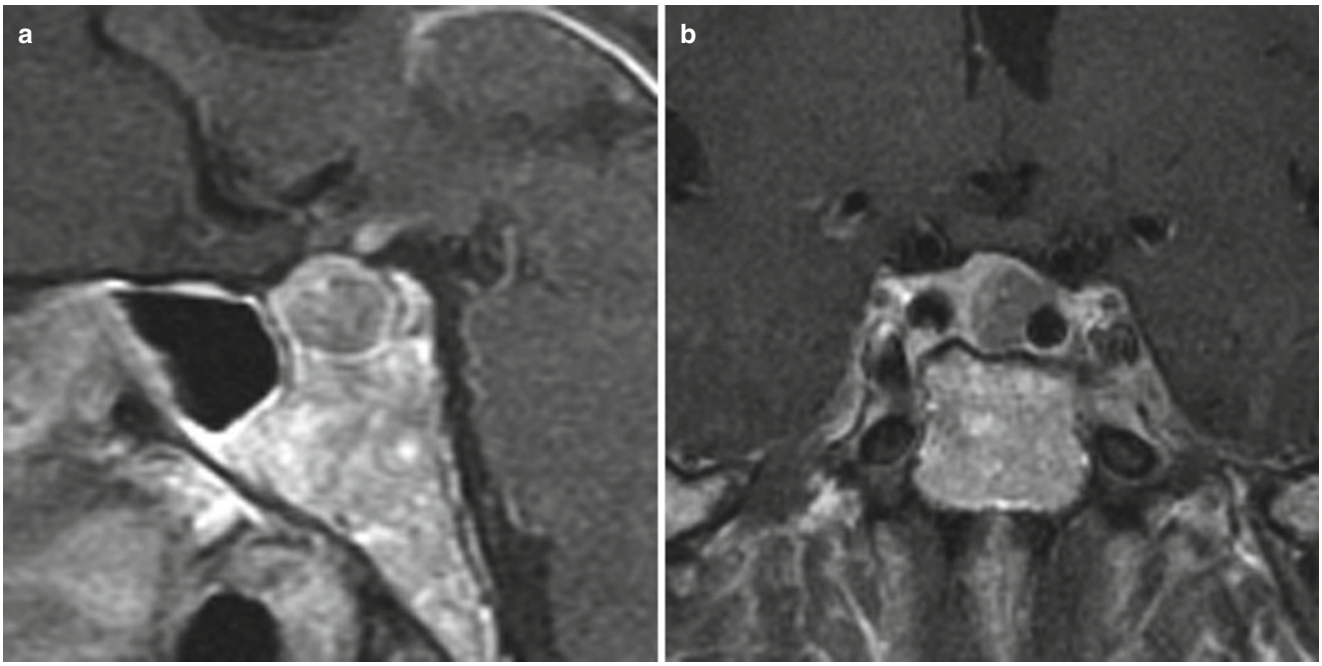

Fig. 12.4 GH adenoma. (**a**) Sagittal T1-weighted post-gadolinium image. (**b**) Coronal T1-weighted post-gadolinium image. A hypoenhancing mass is located in the left aspect of the sella, abutting the left cavernous internal carotid artery without encasement

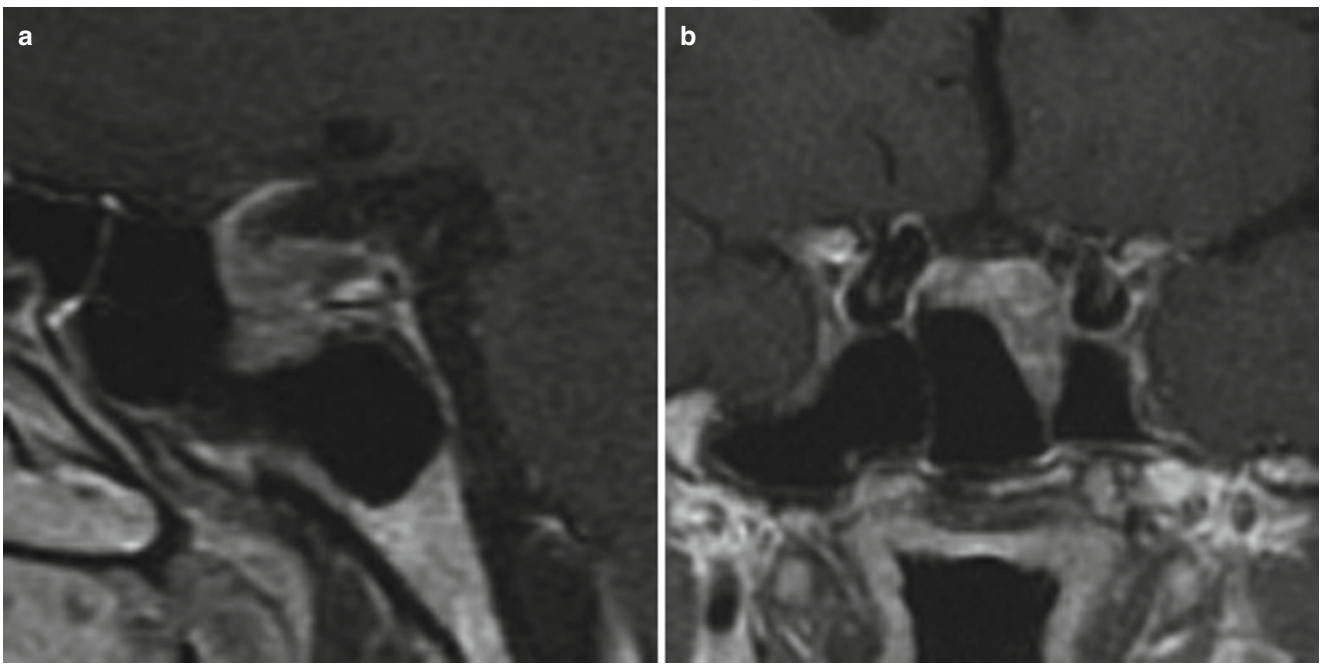

Fig. 12.5 GH adenoma. (**a**) Sagittal T1-weighted post-gadolinium image. (**b**) Coronal T1-weighted post-gadolinium image. Within the sella there is a heterogeneous, predominantly hypoenhancing mass causing erosion of the sellar floor. The mass contacts the left cavernous internal carotid artery without evidence of invasion

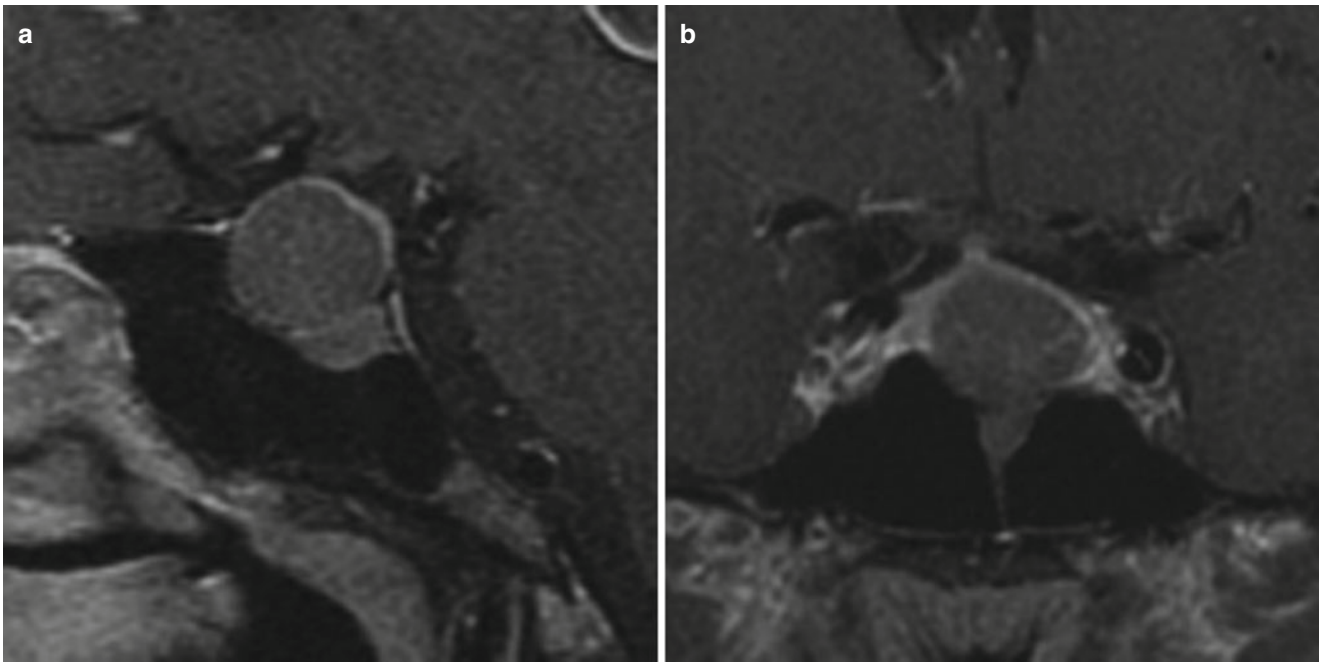

Fig. 12.6 GH adenoma. (**a**) Sagittal T1-weighted post-gadolinium image. (**b**) Coronal T1-weighted post-gadolinium image. There is a hypoenhancing mass in the sella causing erosion of the sellar floor and suprasellar extension without contacting the optic chiasm

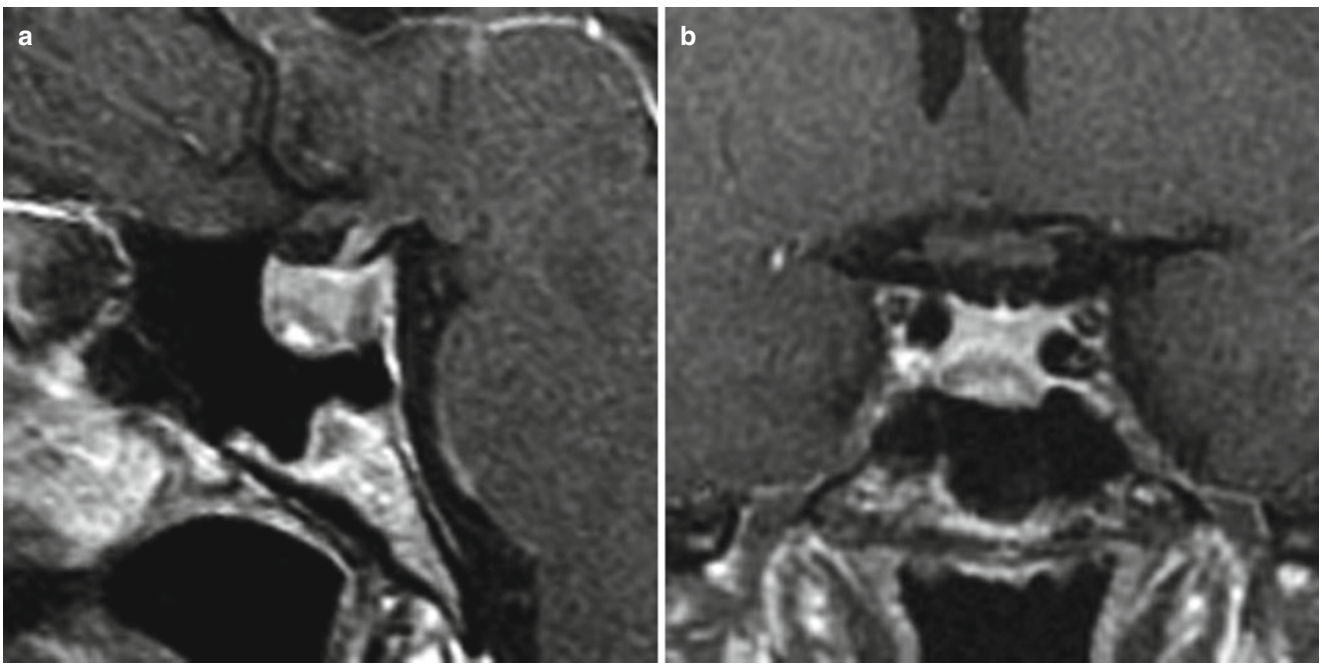

Fig. 12.7 GH adenoma. (**a**) Sagittal T1-weighted post-gadolinium image. (**b**) Coronal T1-weighted post-gadolinium image. A small, hypoenhancing mass is seen in the inferior anterior aspect of the sella, causing mild erosion of the sellar floor

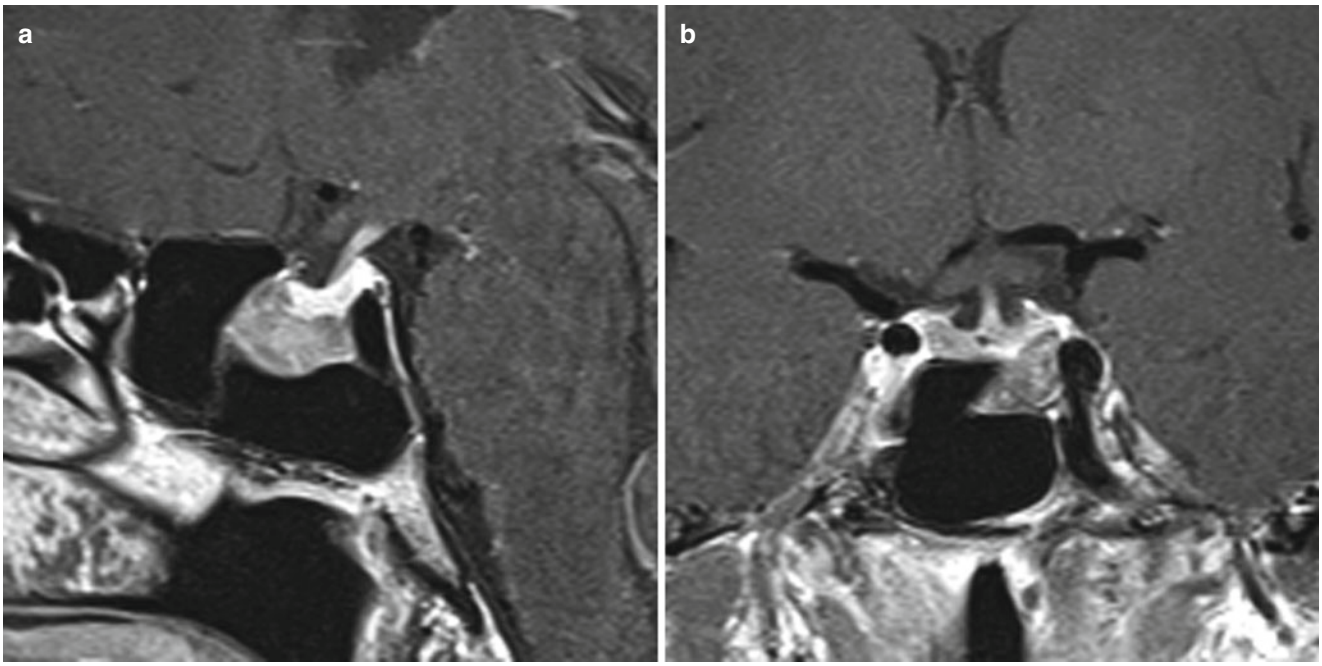

Fig. 12.8 GH adenoma. (**a**) Sagittal T1-weighted post-gadolinium image. (**b**) Coronal T1-weighted post-gadolinium image. There is a hypoenhancing mass in the left inferior aspect of the sella, causing erosion of the sellar floor. The mass contacts the left cavernous internal carotid artery without evidence of invasion of the left cavernous sinus

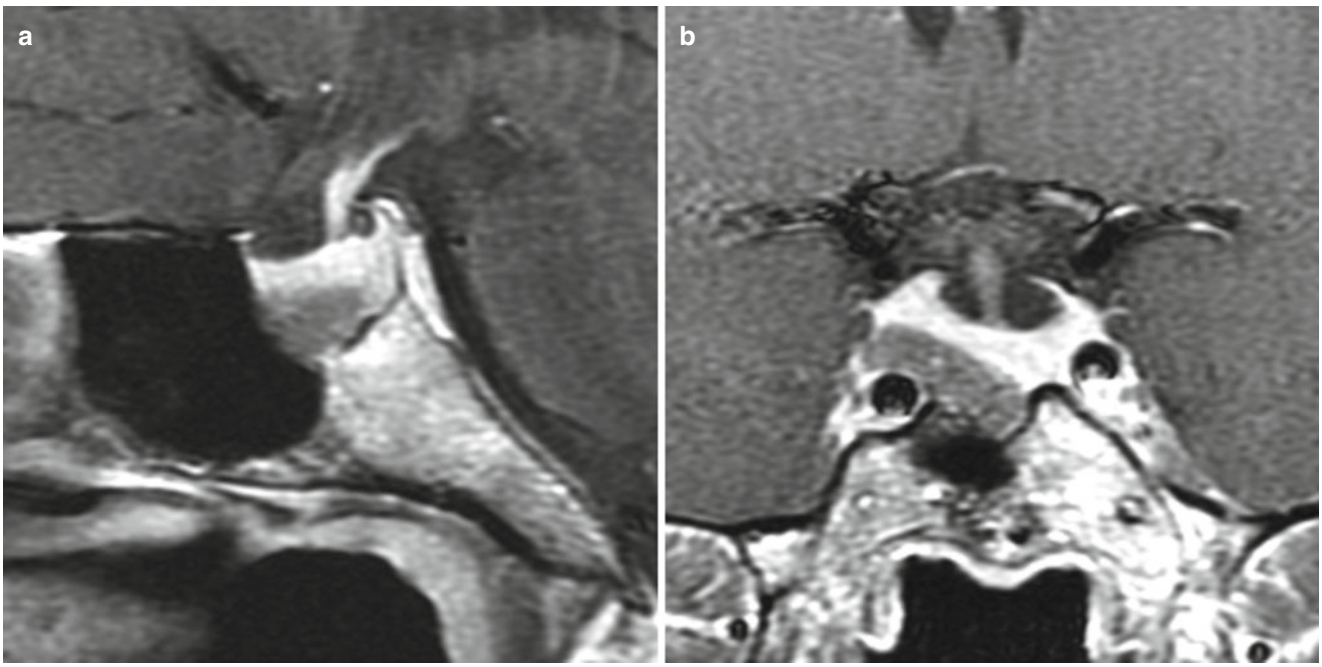

Fig. 12.9 GH adenoma. (**a**) Sagittal T1-weighted post-gadolinium image. (**b**) Coronal T1-weighted post-gadolinium image. There is a hypoenhancing mass located in the right inferior aspect of the sella, causing erosion of the sellar floor. The mass abuts the right cavernous internal carotid artery without evidence of encasement

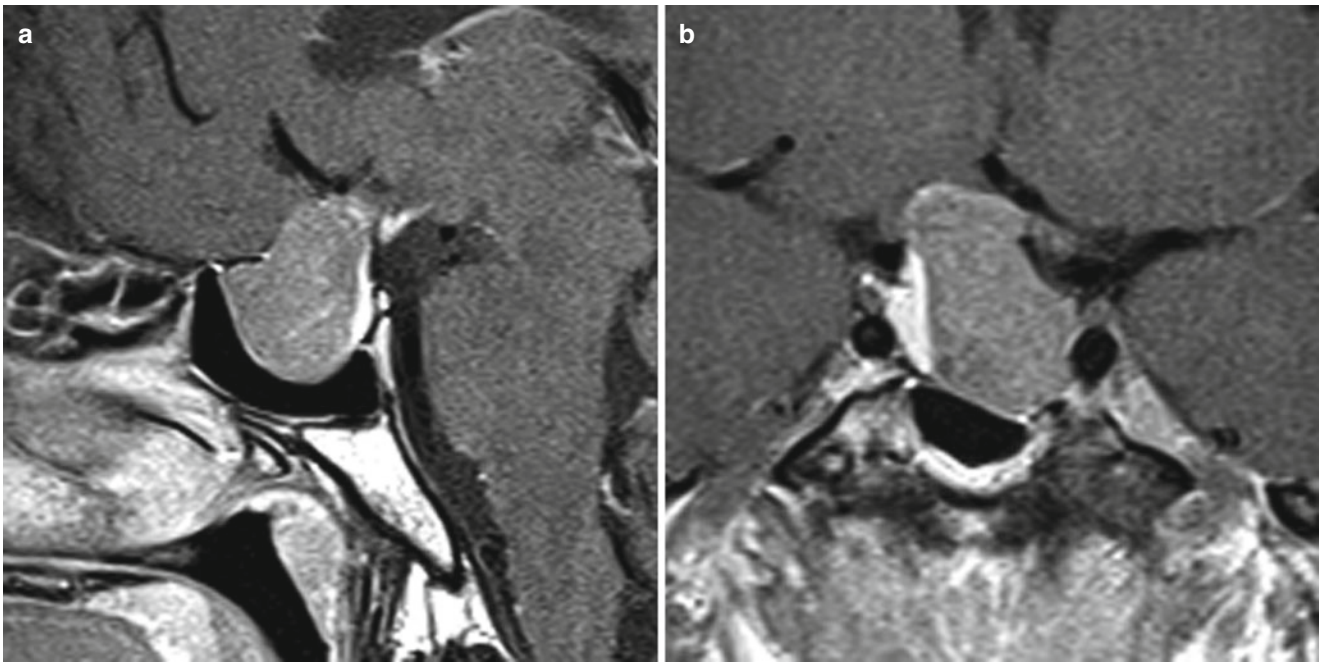

Fig. 12.10 GH adenoma. (**a**) Sagittal T1-weighted post-gadolinium image. (**b**) Coronal T1-weighted post-gadolinium image. There is a heterogeneously enhancing sellar mass with suprasellar extension. The mass abuts the left cavernous internal carotid artery without definite invasion of the left cavernous sinus. There is erosion of the left sellar floor. Superiorly, the mass abuts the right hypothalamus. Normal pituitary glandular tissue is seen along the right aspect of the sella

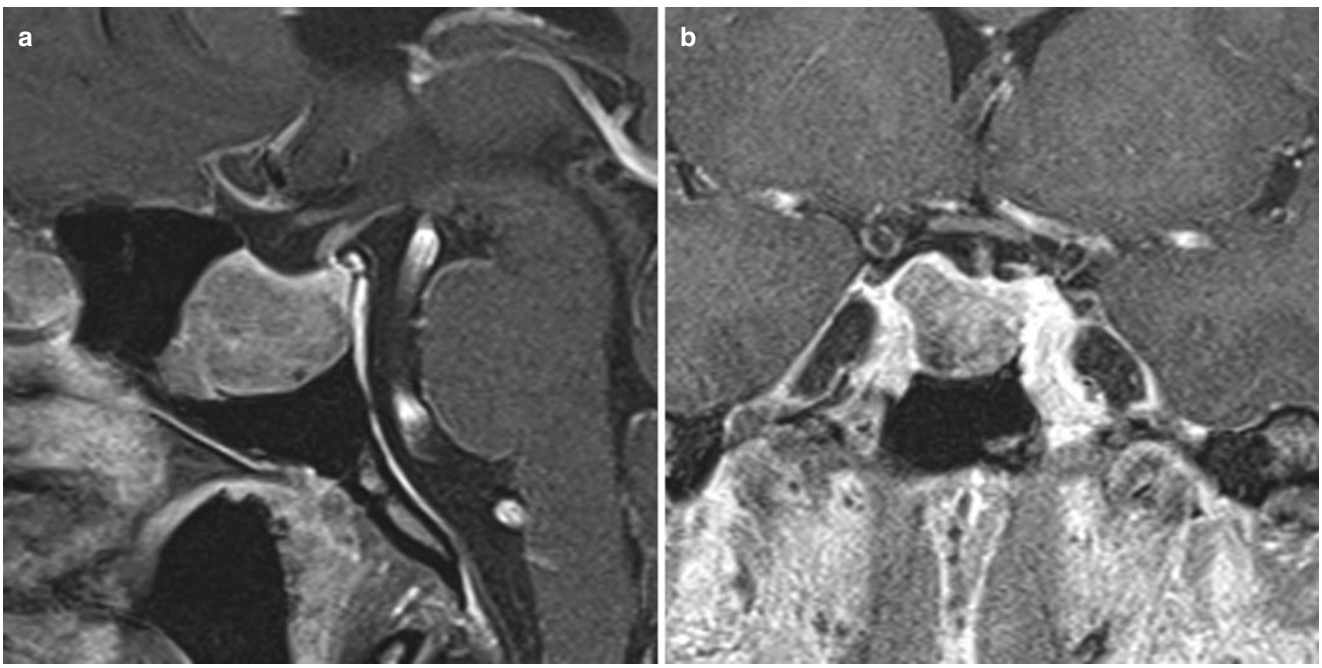

Fig. 12.11 GH adenoma. (**a**) Sagittal T1-weighted post-gadolinium image. (**b**) Coronal T1-weighted post-gadolinium image. There is a hypoenhancing sellar mass with erosion of the sellar floor. The mass abuts the bilateral cavernous internal carotid arteries without encasement

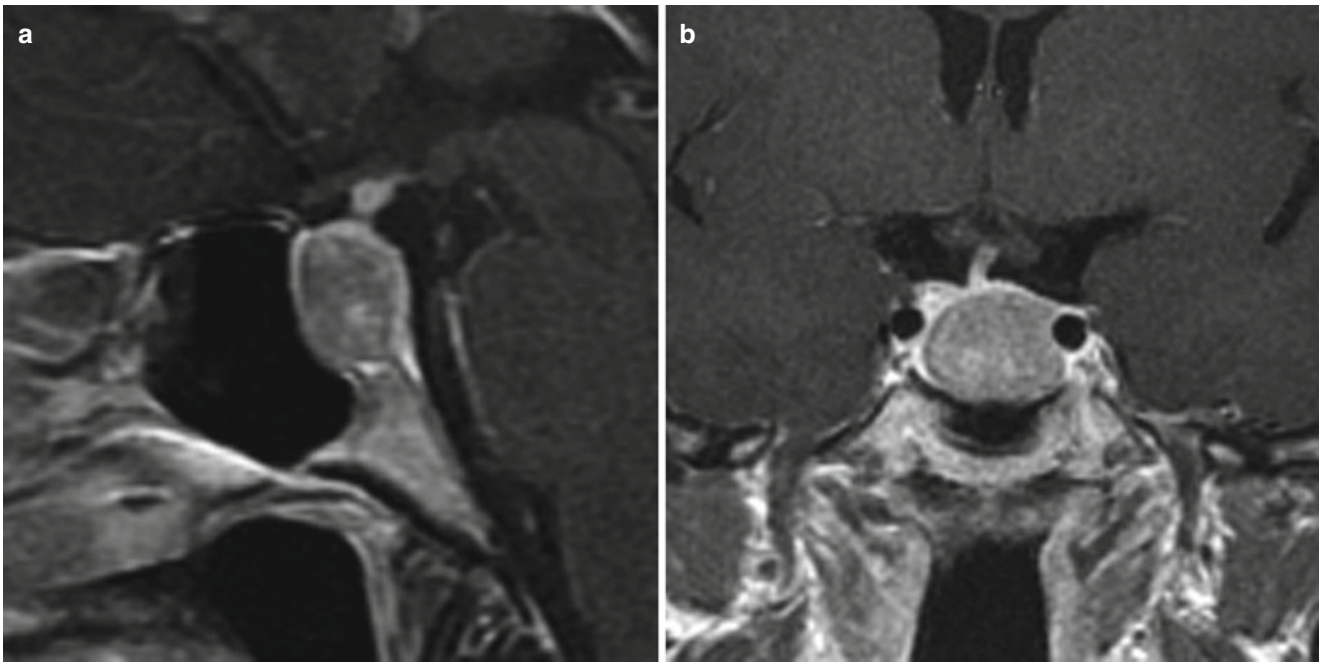

Fig. 12.12 GH adenoma. (**a**) Sagittal T1-weighted post-gadolinium image. (**b**) Coronal T1-weighted post-gadolinium image. A hypoenhancing sellar mass erodes the sellar floor and abuts the left cavernous internal carotid artery without encasement. The pituitary stalk is mildly deviated to the right, with normal gland flattened in the superior right aspect of the sella

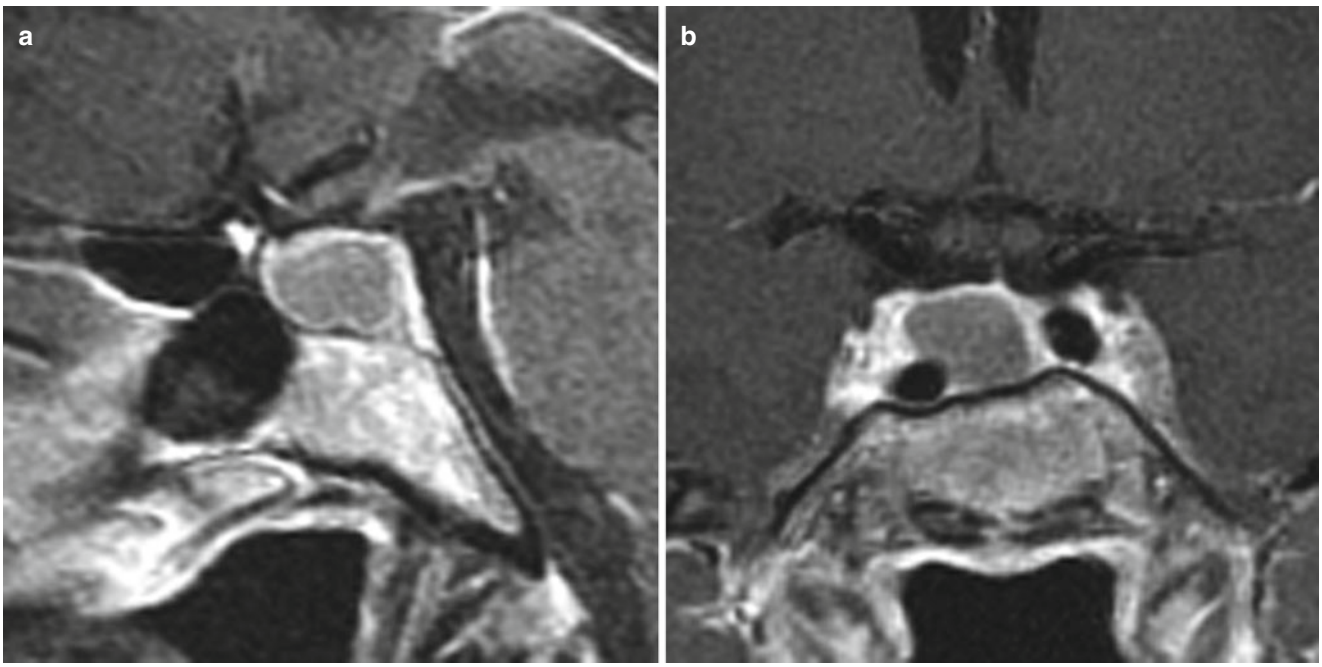

Fig. 12.13 GH adenoma. (**a**) Sagittal T1-weighted post-gadolinium image. (**b**) Coronal T1-weighted post-gadolinium image. There is a hypoenhancing sellar mass in the right aspect of the sella, contacting the right cavernous internal carotid artery without encasement

12.2.3 Histopathology

- Approximately two thirds of GH adenomas are densely granulated adenomas; the other third are sparsely granulated [2, 14].
- Densely granulated GH adenomas are characterized by medium- to large-sized cells with slight pleomorphism and a strong, diffuse staining pattern for GH (Fig. 12.14).
- Sparsely granulated GH adenomas are frequently pleomorphic, with fibrous bodies, a region of perinuclear clearing, and typically weaker immunoreactivity for GH stain (Fig. 12.15) [2]. Fibrous bodies in the cytoplasm can be stained with CAM 5.2 [14].
- Dural invasion has been noted in over 50 % of GH adenomas [2].
- Associated tumor subtypes are those composed of both GH and PRL cells, the mammosomatotroph cell adenoma, and the acidophil stem cell adenoma.
- GH/PRL tumors may be more primitive subtypes; they are more likely to be atypical adenomas than pure GH tumors [15].

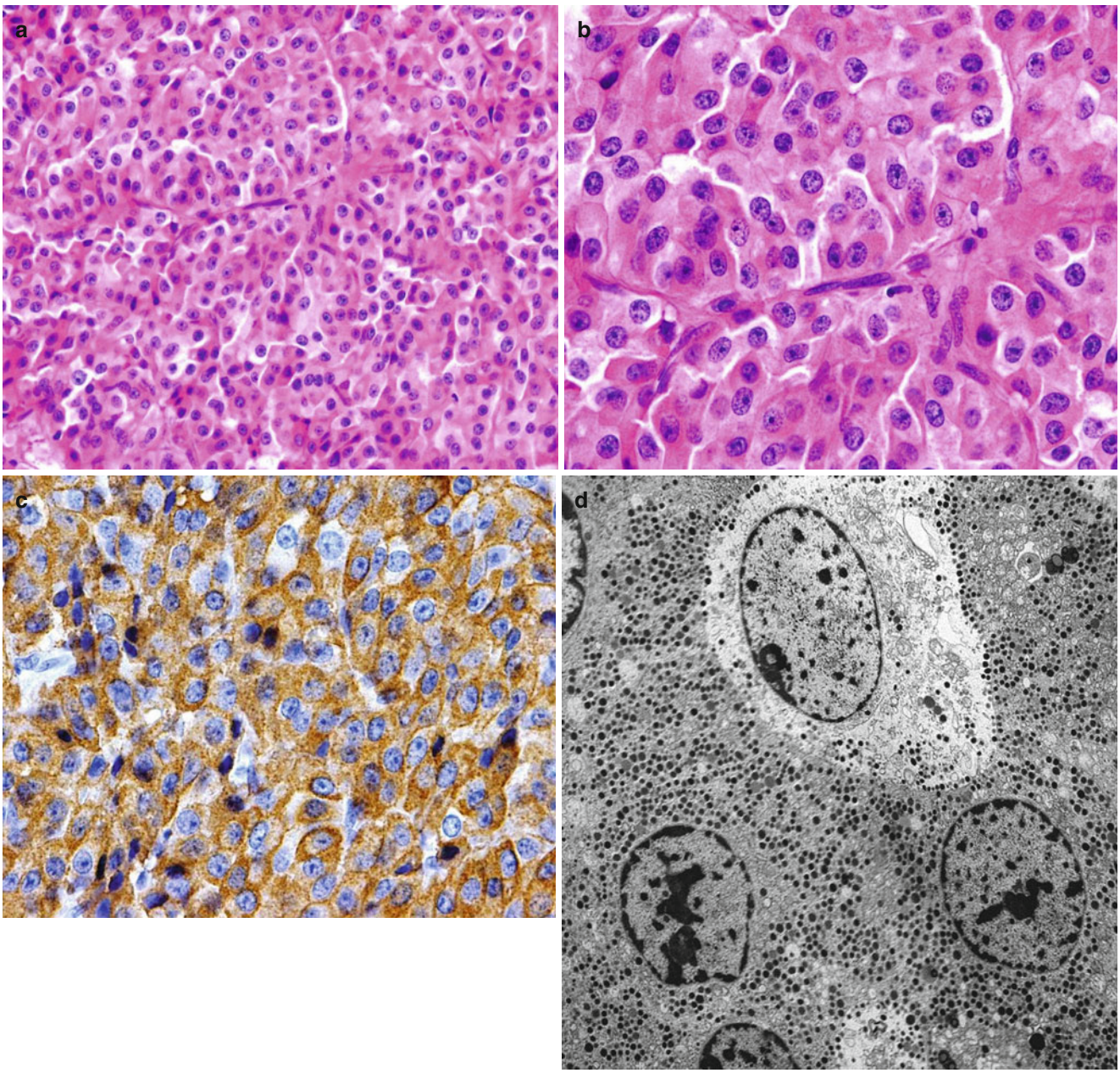

Fig. 12.14 GH adenoma. (**a**, **b**) Densely granulated GH cell adenomas show large cells with eosinophilic, granular cytoplasm and a central nucleus with prominent nucleoli. (**c**) On immunohistochemistry, the tumor shows intense and diffuse staining for GH. (**d**) Densely granulated GH cell adenoma exhibits well-developed organelles and abundant, large secretory granules at the ultrastructural level

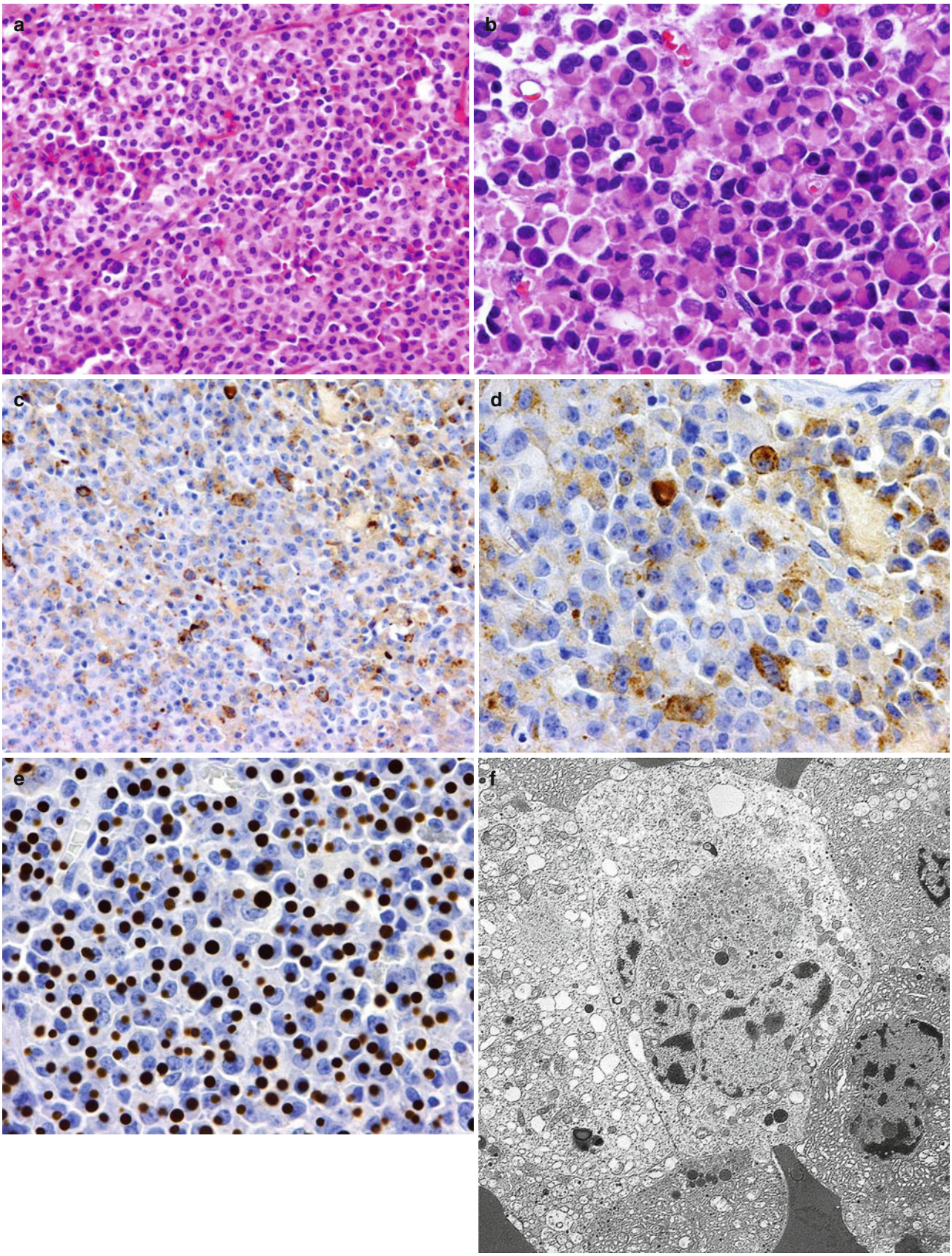

Fig. 12.15 GH adenoma. (**a**) Sparsely granulated GH cell adenomas have a more chromophobic appearance of the cells, with slight granular cytoplasm. (**b**) Characteristically, the tumors have a paranuclear eosinophilic inclusion called "fibrous bodies." (**c**, **d**) Immunohistochemistry for GH shows more focal staining within the cell that is less prominent than in densely granulated adenomas. (**e**) Cytokeratin (CAM 5.2) histochemistry highlights the paranuclear "fibrous body" seen in sparsely granulated GH adenomas. (**f**) At ultrastructure, sparsely granulated GH adenomas display sparse secretory granules and the characteristic "fibrous bodies"

12.3 Clinical Management

- The overall goal of multimodal treatment for acromegaly is the reduction of tumor mass effect and biochemical normalization of IGF-1 and GH levels [8, 16].

12.3.1 Medical Management

- Primary medical treatment typically consists of somatostatin receptor ligands (SRLs), the most notable ones being octreotide and lanreotide.
  - Octreotide has been reported to normalize GH and IGF-I levels in 34–70 % of patients over a 10-year period.
  - Significant tumor volume reduction may occur in 50–75 % of patients [8, 17].
  - Common adverse effects include cramping and diarrhea.
- In patients with refractory GH-secreting adenomas, especially those with mammosomatotroph subtypes, dopamine agonists (DAs) may provide normalization of the IGF-I level in 35–50 % of patients receiving combination therapy (DA and SRL) [17].
- Pegvisomant, a GH receptor antagonist, is a newer agent that acts by inhibiting the production of IGF-I:
  - IGF-1 normalization is reported in 80–97 % of patients [17, 18].
  - Liver dysfunction has occurred in approximately 25 % of patients and requires serial monitoring [8].
  - Infrequently, the size of GH-secreting adenomas has been reported to increase following administration of pegvisomant, owing to a compensatory somatotroph hypertrophy from the reduction of systemic IGF-I in the feedback mechanism [19].
  - Combination therapy using an SRL and pegvisomant has proven to be more effective in many cases [20].
- Routine colonoscopy screening is recommended for all acromegalic patients [21].

12.3.2 Surgical Treatment

- Transsphenoidal surgery is the most common approach for GH adenomas, with excellent resection and safety profiles [4].
- Variations in bony and soft tissue structures, such as thickened bone, boggy nasal mucosa, and excessive nasal polyps, may pose challenges for microscopic or endoscopic transsphenoidal surgery in some patients with severe acromegaly [13].
- Intraoperatively, GH-secreting adenomas tend to have a whiter color and softer consistency than other adenomas (Fig. 12.16).
- The gold standard definition of remission is a normalized IGF-I level obtained 2–3 months following surgery and a GH level less than 1 ng/mL following an OGTT [8, 22].
- A serum GH level less than 2 ng/mL on postoperative day 1 serves as an early marker for long-term remission (98 % predictive) [23].
- More pronounced fluid diuresis in the first 48 h following surgery has been correlated with lower postoperative GH levels [24].
- For GH-secreting tumors confined to the intrasellar space, reported surgical long-term remission rates have ranged from 75 to 95 % [4, 8].
- For invasive GH-secreting macroadenomas, remission rates have been reported to be 40–60 % [3, 4].
- The ability to achieve hormonal remission following transsphenoidal surgery is often limited by tumor size (i.e., macroadenomas $\geq$10 mm in diameter), the degree of extrasellar extension (particularly lateral into the cavernous sinuses), and high preoperative serum GH concentrations ($\geq$45 ng/mL) [3, 25, 26].
- Disease recurrence has been reported in 8–20 % of patients with up to 10 years of follow-up; it was more likely when tumors invaded the parasellar dura or bone [23, 27, 28].

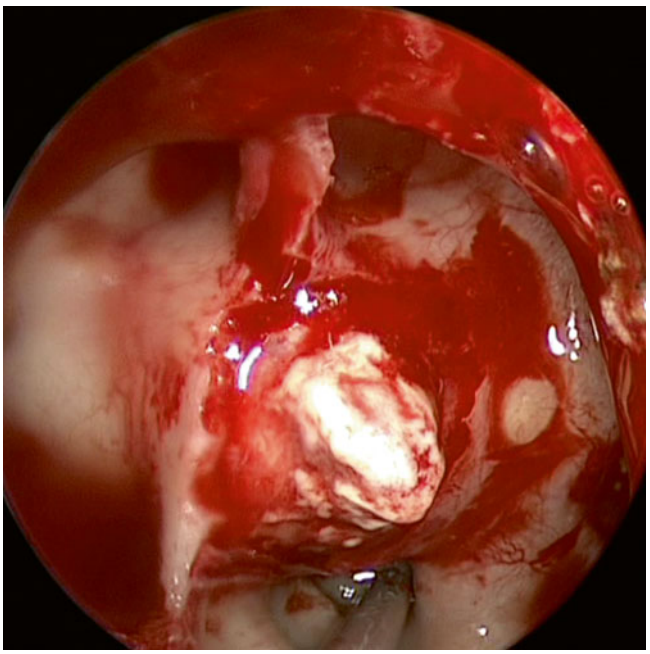

Fig. 12.16 Intraoperative endoscopic photo showing resection of a GH adenoma and its characteristic white color

12.3.3 Radiosurgical Management

- Fractionated or single fraction stereotactic radiosurgery is an effective adjunctive modality for achieving tumor control and potential biochemical remission in patients with residual or recurrent tumor burden.
- Stereotactic radiosurgery has been effective in achieving hormonal remission in approximately 50 % of patients following initial surgical resection, and tumor volume control has been achieved in over 90 % of patients [16, 29].

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