Chapter 3
Nonfunctioning Pituitary Adenoma: Management

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Case Presentation

A 65-year-old man was referred to the neuroendocrine clinic after failing a cosyntropin stimulation test and being diagnosed with central adrenal insufficiency during a hospital admission for fatigue and hypotension. Pituitary MRI during that admission demonstrated a 10 mm sellar lesion approaching, but not impinging, on the optic chiasm. His review of symptoms was otherwise negative, including no headaches, vision changes, low libido, erectile dysfunction, or galactorrhea. His other anterior pituitary hormones included serum TSH 0.54 uIU/mL (0.35–5.5), Free T4 (fT4) 1.29 ng/dL (0.8–1.9), 8 AM total testosterone 258 ng/dL, IGF-1 66 ng/mL (20–176), and prolactin 9.8 ng/mL (0–15). His medications included prednisone 5 mg QAM for adrenal insufficiency and levothyroxine 100 mcg QAM for a prior diagnosis of primary hypothyroidism. He was referred to a neuro-ophthalmologist, and visual field and visual acuity testing was normal. Repeat pituitary MRI in 6 months demonstrated that the mass had increased in size to 12 mm in the largest dimension, but was not impinging on the optic chiasm. Pituitary hormone testing, as well as visual field and visual acuity testing, at that time was stable. Pituitary MRI another 6 months thereafter demonstrated that the

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L. B. Nachtigall (ed.), *Pituitary Tumors*,
https://doi.org/10.1007/978-3-319-90909-7_3

sellar lesion was now 14 mm in the largest dimension and close to impinging on the optic chiasm. Pituitary hormone testing, as well as visual field and visual acuity testing, was again stable.

My Management

1. Observe for tumor growth with serial MRI's.
2. Refer to neurosurgeon for transsphenoidal surgery.
3. Initiate therapy with stress dose steroids perioperatively, given adrenal insufficiency.
4. Postoperative monitoring of sodium and anterior pituitary function.

Assessment and Diagnosis

Pituitary adenomas are characterized by their size (microadenomas < 1 cm, macroadenomas ≥ 1 cm) and cell of origin (lactotroph, somatotroph, corticotroph, gonadotroph, and thyrotroph). Most adenomas (approximately 70%) are functioning tumors that secrete an excess amount of hormone and cause a clinical syndrome [1]. The remaining 30% of pituitary adenomas are considered clinically nonfunctioning, although 80–90% do produce intact gonadotropins or their subunits. However, clinical syndromes due to excess gonadotropin secretion are rare because gonadotroph adenomas are usually poorly differentiated and rarely cause elevated sex steroid levels [2].

Since nonfunctioning pituitary adenomas do not present with a clinical syndrome of pituitary hormone excess, the presentation may instead include the following:

1. Neurologic symptoms, such as visual impairment and/or headache. Most commonly this is visual field loss due to the adenoma's suprasellar extension resulting in optic chiasm compression and bitemporal hemianopsia. When the optic chiasm is severely compressed, decreased visual acuity may occur. Compression of the oculomotor nerve due to cavernous sinus invasion of the adenoma may result in diplopia. Headaches are a less common

presentation, but a new excruciating headache with new visual impairment must raise concern for pituitary apoplexy, which may be life-threatening due to acute secondary adrenal insufficiency [3].

2. Pituitary hormone deficiency due to mass effect from the adenoma. Symptoms of pituitary hormone deficiency are often nonspecific and may therefore go undiagnosed for some time. In a series of patients with nonfunctioning pituitary adenomas, 37–85% of patients had laboratory evidence of at least one pituitary hormone deficiency [4, 5], whereas panhypopituitarism was noted in 6–29% of patients [6, 7].
3. An incidental sellar mass on an imaging study not performed for pituitary disease. Given the prevalence of pituitary adenomas on autopsy series (10.6%), this is not an uncommon presentation of a nonfunctioning pituitary adenoma [8].

In accordance with the Endocrine Society Clinical Practice Guidelines on Pituitary Incidentalomas, the evaluation of a newly diagnosed sellar mass >1 cm in size should include a detailed history and physical exam, a dedicated pituitary MRI, biochemical evaluation of pituitary hormone excess and deficiency, and visual field and visual acuity testing if clinically indicated [9]. Visual testing may not be required if the pituitary MRI clearly shows no evidence of optic chiasm or cranial nerve involvement, the patient has no new visual symptoms, and the patient is being followed closely by MRI. Although pituitary adenomas are the most common cause of a sellar mass >1 cm, the differential diagnosis is large and includes craniopharyngioma, meningioma, metastatic tumors, Rathke's cleft cyst, and hypophysitis, which is why a thorough evaluation is prudent [10]. Biochemical evaluation for pituitary hormone excess may include serum prolactin, insulin-like growth factor 1 (IGF-1), TSH and FT4, and 24 hour (24-h) urine free cortisol and/or late-night salivary cortisol. Hyperprolactinemia may be consequent to pituitary stalk compression by a sellar mass or due to a pituitary lactotroph adenoma. Hyperprolactinemia secondary to stalk compression is due to obstruction of normal hypothalamic dopamine inhibition on pituitary lactotroph cells and typically results in serum prolactin levels <100 ng/mL, which can be used as a cutoff to help distinguish between a nonfunctioning

pituitary macroadenoma with stalk compression and a pituitary lactotroph macroadenoma, the latter of which typically has serum prolactin levels >100 ng/mL [11]. In patients with pituitary macroadenomas, the laboratory should measure serum prolactin levels in dilution to ensure that levels are not falsely lowered by a hook effect in the assay. Biochemical evaluation for pituitary hormone deficiency may include a serum 8AM cortisol ± cosyntropin stimulation test, IGF-1, TSH and FT4, and LH/FSH/testosterone in men (or LH/FSH/estradiol in women who are not menstruating regularly).

Management

The primary indication for more urgent surgical resection of a nonfunctioning pituitary adenoma is neurologic symptoms, including vision impairment. Transsphenoidal surgery may also be considered in cases of high risk of visual impairment (including a tumor close to the optic chiasm with plans for pregnancy), clinically significant tumor growth, and/or hypopituitarism. *Preoperatively*, hormone replacement for hypothyroidism, and especially for adrenal insufficiency, must be undertaken if present. *Perioperatively*, patients should be treated with stress dose glucocorticoids at the induction of anesthesia to cover the possibility of adrenal insufficiency should normal corticotroph cells be damaged during surgery. *Postoperatively*, monitoring for adrenal insufficiency, diabetes insipidus, and syndrome of inappropriate antidiuretic hormone (SIADH) is required. Patients should be treated with physiologic glucocorticoid replacement until adrenal insufficiency can be ruled out with an AM serum cortisol or a cosyntropin stimulation tests 6 weeks postoperatively. Postoperatively, patients should have their thirst, fluid intake and output, and serum sodium monitored in order to appropriately diagnose and treat diabetes insipidus and SIAD. This is typically done with serial serum sodiums on several days within the first two weeks after surgery. Patients may be seen back in clinic for repeat pituitary hormone evaluation 6 weeks postoperatively and repeat pituitary MRI scan 3–6 months postoperatively. Postoperative visual field and visual acuity testing

should be scheduled for patients who had evidence of visual impairment preoperatively.

Transsphenoidal surgery is typically successful in reducing tumor volume and improving vision and is less successful in reversing hypopituitarism. One prospective observational cohort study and multiple retrospective studies have demonstrated residual tumor volume in 10–36% of patients, improved visual function in 75–91% of patients, and improved hypopituitarism in 35–50% of patients [12–14]. Even if there is little or no residual adenoma on pituitary MRI, the patient should still be monitored with serial pituitary MRI scans because approximately 20% of adenomas recur after transsphenoidal surgery [15], although the risk of recurrence is lower if there is no radiologic evidence of residual adenoma after surgery. If there is significant residual adenoma on pituitary MRI or progressive adenoma regrowth in the months or years after surgery, postoperative radiation therapy may be considered. When administered for adenoma regrowth, conventional radiation therapy results in 10-year control rates, defined as lack of clinical or radiologic progression, of approximately 80% [16]. However, patients who receive radiation therapy are at risk of developing hypopituitarism [17] and thus require long-term biochemical pituitary hormone monitoring. Currently, there are no approved pharmacologic treatment options for nonfunctioning pituitary adenomas. However, one historical cohort analysis suggested that dopamine agonist therapy in nonfunctioning pituitary adnenomas may be associated with decreased risk of tumor enlargement after transsphenoidal surgery [18]. This is biologically plausible given that most nonfunctioning pituitary adenomas express dopamine receptors.

There is insufficient evidence to make a recommendation regarding the primary treatment strategy for asymptomatic nonfunctioning pituitary adenomas. For those patients with nonfunctioning pituitary adenomas who do not undergo surgical resection, interval pituitary MRI imaging and biochemical evaluations should be performed. For some macroadenomas, pituitary MRI scan and biochemical evaluation for hypopituitarism may be repeated in 6 months and then 12 months thereafter if stability is demonstrated. For some microadenomas, pituitary MRI scan may be repeated in

12 months and then 12–24 months later if stability is demonstrated. Repeat biochemical evaluation for hypopituitarism may not be required for microadenomas if the patient's symptoms and MRI do not change over time. However, limited data are available on the natural history of nonfunctioning pituitary macroadenomas because most patients undergo surgery; studies suggest that approximately 40–50% of patients experience adenoma growth and 21–28.5% of patients eventually require surgery [19, 20].

Outcome

This patient has a nonfunctioning pituitary macroadenoma that was diagnosed in the setting of pituitary hormone deficiency (central adrenal insufficiency). As he did not meet criteria for more urgent transsphenoidal surgery (i.e., neurological symptoms), he was monitored with serial pituitary MRI scans, visual field and visual acuity testing, and pituitary hormone biochemical evaluation. Over the course of 12 months, his sellar mass enlarged and came close to impinging on the optic chiasm. Given the time course of enlargement, the decision was made between the neurosurgeon, endocrinologist, and patient to undergo transsphenoidal surgery. The patient received stress dose glucocorticoids perioperatively. Pathology was consistent with a nonfunctioning pituitary adenoma. Postoperatively, the patient was discharged on physiologic glucocorticoid replacement and was monitored for the development of diabetes insipidus and/or SIADH, neither of which occurred. He will be seen in the neuroendocrine clinic for his 6-week postoperative visit.

Clinical Pearls and Pitfalls

- The most common presentations of nonfunctioning pituitary adenomas include neurologic symptoms (such as visual impairment), pituitary hormone deficiency due to mass effect from the adenoma, and an incidental sellar mass on an imaging study.

- In accordance with the Endocrine Society Clinical Practice Guidelines on Pituitary Incidentalomas, the evaluation of a newly diagnosed sellar mass >1 cm in size should include a detailed history and physical exam, a dedicated pituitary MRI, biochemical evaluation of pituitary hormone excess and deficiency, and visual field and visual acuity testing if clinically indicated.
- Although pituitary adenomas are the most common cause of a sellar mass >1 cm, the differential diagnosis is large and includes craniopharyngioma, meningioma, metastatic tumors, Rathke's cleft cyst, and hypophysitis, which is why a thorough evaluation is prudent.
- Hyperprolactinemia may be consequent to pituitary stalk compression by a sellar mass or due to a prolactinoma. In the former case, serum prolactin levels are typically <100 ng/mL, which can be used as a cutoff to help distinguish between stalk compression and a macroprolactinoma, the latter of which typically has serum prolactin levels >100 ng/mL. In patients with macroadenomas, the laboratory should measure serum prolactin levels in dilution to ensure that levels are not falsely lowered by a hook effect in the assay.
- Vision impairment due to optic chiasm compression is a clear indication for transsphenoidal surgery. Transsphenoidal surgery may also be considered in cases of high risk of visual impairment, clinically significant tumor growth, and/or hypopituitarism.
- Transsphenoidal surgery is typically successful in reducing tumor volume and improving vision and is less successful in reversing hypopituitarism. Even if there is little or no residual adenoma on pituitary MRI, the patient should still be monitored for recurrence with serial pituitary MRI scans. If there is significant residual adenoma on pituitary MRI or progressive adenoma regrowth after surgery, postoperative radiation therapy may be considered.

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