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Case Report

Successful Multimodal Management of an Aggressive Functional Gonadotropic Pituitary Macroadenoma

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ABSTRACT

Background/Objective: Although most gonadotroph cell–derived pituitary adenomas (PAs) give rise to nonfunctional PAs, hormonally active functional gonadotroph adenomas (FGAs) are exceedingly rare. We present a case of a giant and invasive functional gonadotropic pituitary macroadenoma treated with endoscopic transsphenoidal surgery and subsequent postoperative radiotherapy.
Case Report: A 54-year-old man presented with gradually worsening vision over 1 year. Magnetic resonance imaging demonstrated a 5.2-cm sellar and suprasellar mass with cavernous sinus invasion, mass effect on the optic chiasm, and extension into the sphenoid sinus, nasal cavity, and clivus. Preoperative workup was remarkable for erythrocytosis without sleep apnea and increased levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, and testosterone. Immunohistochemistry results following endoscopic transsphenoidal resection confirmed dominant staining for steroidogenic factor-1, FSH, and LH. Postoperatively, the patient's FSH level decreased, whereas the LH level normalized within 1 week. The free testosterone level normalized at 9 months. The patient underwent radiotherapy for a small amount of residual tumor in the right cavernous sinus and has demonstrated no evidence of disease or hormonal progression.
Discussion: There is no consensus on FGA-specific management that differs from the management of nonfunctional PAs; surgery is recommended when vision is impacted. The invasive nature of the tumor presented in this case is rare and limited safe gross total resection, requiring adjuvant radiotherapy.
Conclusion: FGAs are rare, and those of similar size and extent of invasion as in our case are even more so. In addition to surgical resection, consideration of adjunct therapies including radiation and multidisciplinary physician involvement are vital in achieving clinical improvement and remission while preventing possible progression and recurrence.

Introduction

Functional gonadotroph adenomas (FGAs) are exceedingly rare tumors, with the overall prevalence unknown and limited primarily to case studies. They typically present as macroadenomas with headaches and visual field defects secondary to mass effect of the tumor on the optic chiasm.[1] Although surgery is a first-line

Abbreviations: FGA, functional gonadotroph adenoma; FSH, follicle-stimulating hormone; LH, luteinizing hormone; NFPA, nonfunctional pituitary adenoma; PA, pituitary adenoma; POD, postoperative day; PRL, prolactin; SF-1, steroidogenic factor-1.

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treatment for these symptomatic patients, a multidisciplinary approach is often necessary for large and invasive FGAs. Here, we present a case of a male patient with erythrocytosis and increased levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and free and total testosterone in the setting of a highly invasive pituitary macroadenoma who underwent transsphenoidal surgery for resection with adjunct radiation therapy.

Case Report

Initial Presentation

A 54-year-old man presented as a referral to our tertiary care hospital. The patient had a past medical history of chronic sinusitis, hyperlipidemia, and obesity (body mass index, 30 kg/m^2) with no prior operations and first reported gradual decline in visual acuity worse in the right eye that progressed to also having bitemporal hemianopsia over the course of 1 year. The patient denied headaches, fatigue, nausea/vomiting, changes in libido, sexual activity, mood disturbance, or increased frequency of shaving and previously had no difficulty of conceiving as a father of 2 children. Ophthalmology evaluation prompted magnetic resonance imaging of the head, which revealed a large 5.1 × 4.0 × 5.2−cm (anteroposterior × transverse × craniocaudal) mass occupying the nasal cavity and ethmoid and sphenoid sinuses, with extension down to the clivus (Fig. 1). This mass also showed suprasellar extension that displaced the optic nerves and chiasm superiorly and encased the right more than left cavernous internal carotid artery (Knosp grade 4 pituitary adenoma [PA]).[2] On physical examination, the patient demonstrated bitemporal hemianopsia without diplopia. There were no stigmata of acromegaly or Cushing disease and no abnormal hirsutism, facial plethora, or acne. Pubic and axillary hair distributions were age-appropriate. The patient was found to have slight macroorchidism with homogeneously enlarged testicles approximately 25 cm^3 in size. Preoperative hormone panel was remarkable for increased levels of FSH at 166.8 mIU/mL (normal range, 1.6-8 mIU/mL), LH at 15.1 mIU/mL (1.5-9.3 mIU/mL), prolactin (PRL) at 60.6 ng/mL (2.5-17.4 ng/mL), and free and total testosterone (Quest Diagnostics; 348.4 pg/mL [35-155 pg/mL] and; 1,103 ng/dL [250-1100 ng/dL], respectively) (Figs. 2 and 3). The patient had evidence of central hypothyroidism with an inappropriately normal thyroid-stimulating hormone level at 3.66 mIU/L (normal range, 0.4-4.5 mIU/L) and low free thyroxine level at 0.77 ng/dL (0.8-1.8 ng/dL) and was started on 125-mcg levothyroxine supplementation. Other hormones were within relative age- and sex-adjusted normal limits.

Highlights

- Hormonal monitoring before and after surgery should be standard in pituitary adenomas
- Functional gonadotroph adenomas in men may cause hypogonadism, large testes, or vision loss
- Aggressive gonadotroph adenomas need surgery plus multidisciplinary adjuvant treatments

Clinical Relevance

Functional gonadotroph adenomas, especially in males, are rare, and those with similar size and extent of invasion as in our case even more so. Surgical resection and consideration of adjunct therapies including radiation and multidisciplinary physician involvement are vital in achieving clinical improvement and remission while preventing possible progression and recurrence.

The patient reported a history of intermittent asymptomatic erythrocytosis that was first noted 3 years prior without a history of sleep apnea. The hemoglobin level on admission increased at 18.4 g/dL (normal range, 13.3-17.7 g/dL). Given the patient's large tumor causing visual field deficits and need for diagnosis and decompression, surgery was offered. An endoscopic endonasal transsphenoidal approach was selected.

Surgical Resection and Pathology Results

The patient underwent elective surgery the same week. It was noted intraoperatively that the tumor had occupied the entire sphenoid sinus and invaded the clivus. The tumor had a firm consistency; therefore, an extracapsular approach was performed for the intracranial component. A small amount of residual tumor was left within the right cavernous sinus given its adherence to and encasement of the internal carotid artery. There was no intraoperative or postoperative cerebrospinal fluid leak. Surgical pathology with immunohistochemistry showed dominant staining for steroidogenic factor-1 (SF-1), FSH, LH, and alpha subunit. The Ki-67 labeling index was <3%. These results confirmed our initial suspicion for a functional gonadotroph PA (functional SF-1 PitNET tumor).

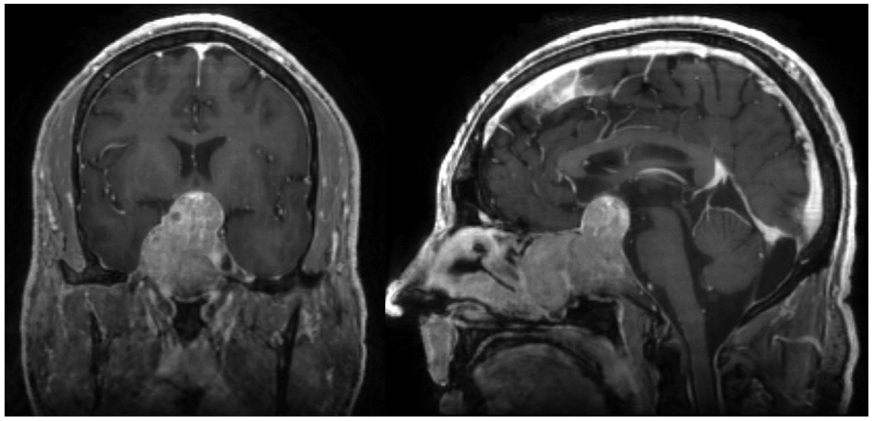

Fig. 1. Preoperative T1-weighed postcontrast magnetic resonance imaging demonstrated the extent of invasion of the macroadenoma into the nasal cavity, ethmoid and maxillary sinuses, sellar and suprasellar spaces, and clivus.

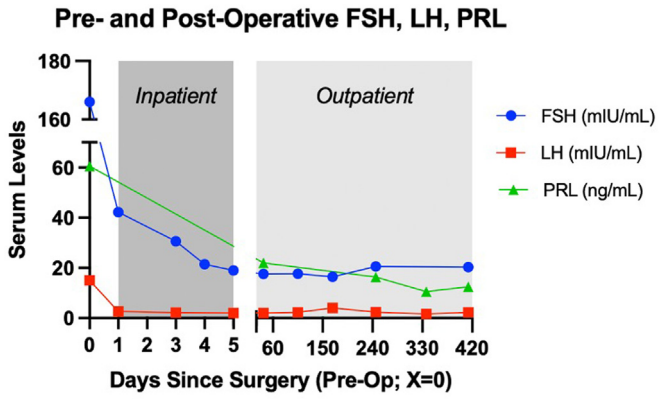

Fig. 2. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin (PRL) trends across the patient course, separated by the preoperative baseline, postoperative inpatient course, and long-term outpatient monitoring.

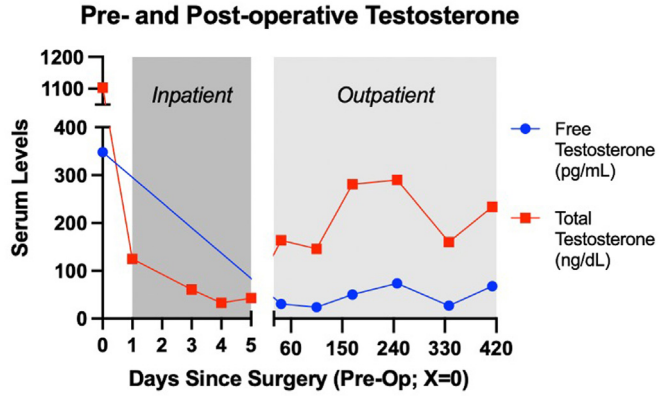

Fig. 3. Free and total testosterone trends across the patient course, separated by the preoperative baseline, postoperative inpatient course, and long-term outpatient monitoring.

Inpatient Postoperative Course

The patient was subsequently transferred to the neurointensive care unit in stable condition. On postoperative day (POD)1, the patient's gonadotroph hormone values were noted to have immediately decreased: (1) FSH level, 166.8 to 42.2 mIU/mL; (2) LH level, 15.1 to 2.7 mIU/mL; and (3) total testosterone level, 1103 to 125 ng/dL (Figs. 2 and 3). The morning cortisol level on POD1 was sufficient at 25.8 mcg/dL, indicating normal pituitary adrenocorticotropic hormone secretion and an intact hypothalamic-pituitary-adrenal axis. The patient experienced postoperative polydipsia and polyuria consistent with vasopressin deficiency with 5.6 L of oral intake and 5.7 L of urine output over 24 hours. The sodium level reached a peak of 145 mmol/L on POD2 and a nadir of 133 mmol/L when desmopressin was held on POD6. Over several days, the patient's FSH, LH, and total testosterone levels decreased with no reported changes in libido or energy level. Because vasopressin deficiency failed to resolve 72 hours postoperatively, the patient was started on 0.1-mg oral tablets of DDAVP twice daily to be continued upon discharge to home on POD7.

Outpatient Postoperative Course and Radiation Therapy

The patient's vision had improved significantly on 2-week postoperative evaluation in a neurosurgery clinic. The free and total testosterone levels were 30.8 pg/mL and 164 ng/dL, respectively. The patient continued to take the same dose of levothyroxine and DDAVP after hospital discharge and symptoms of polyuria and polydipsia improved. Three months postoperatively, the free and total testosterone levels were still low. Testosterone replacement was deferred at this point, whereas the serum gonadotropin and testosterone levels were monitored as tumor markers.

Given the patient's young age and invasive nature of the residual tumor (Fig. 4) noted on 3-month postoperative magnetic resonance imaging, a multidisciplinary tumor board recommended intensity-modulated radiation therapy. The patient underwent a total dose of 54 to 60 Gy in 30 fractions with volumetric modulated arc therapy completed 7 months postoperatively. After treatment, the FSH, LH, PRL, free thyroxine, and thyroid-stimulating hormone levels were 20.6 mIU/mL, 2.4 mIU/mL, 16.4 ng/mL, 1.4 ng/dL, and 0.01 mIU/L, respectively. Side effects of the patient's radiation treatment included fatigue, nasal congestion, and mild right-sided blurry vision, which improved to baseline a month later. The patient was able to return to full activity. At 1 year, there were no imaging signs of progression and no substantial changes in symptoms with regard to testosterone secretion. The patient's free and total testosterone levels have gradually increased (97.4 pg/mL and 464 ng/dL, respectively). It is unclear whether this is due to the effect of residual tumor or normalization of pituitary function. The patient continues to be on DDAVP at a reduced dose of 0.1 mg and levothyroxine at 125 mcg and is followed by otolaryngology, radiation oncology, neurosurgery, and endocrinology physicians at our institution.

Discussion

We describe a case of a 54-year-old man diagnosed with an FGA after presenting with loss of visual acuity and/or field defects secondary to optic chiasm compression.[3] The patient underwent transsphenoidal surgery,[4] which significantly improved vision, and adjunct radiation therapy to limit the risk of residual tumor progression and hormonal nonremission.[5,6] Surgical pathology confirmed the diagnosis with tissue samples staining strongly for SF-1, FSH, and LH in the context of a preoperative hormone panel that demonstrated increased serum FSH, LH, and testosterone levels. The increased PRL level on the initial preoperative panel was likely caused by tumor compression of the infundibulum (stalk effect).[7] The patient did not present with any symptoms of hyperprolactinemia or increased testosterone level, although he had a history of erythrocytosis and was noted to have slight macroorchidism on physical examination. It is important for clinicians to distinguish this pathology[8-11] from nonfunctional PAs (NFPAs), which may present in a similar fashion.

NFPAs are often clinically silent and grow insidiously.[12] On pathologic examination, NFPA tissues staining positive for FSH and LH on immunohistochemistry do not necessarily actively secrete these hormones; these are termed silent gonadotrophs.[3] The first-line treatment for symptomatic silent gonadotrophs, which represent 73% of NFPAs,[13] is surgery. In this case, it was felt that a more aggressive course of adjuvant radiation therapy following surgery was appropriate in the setting of the patient's dramatic presentation with visual disturbance.

FGAs, are characterized by increased serum levels of FSH, LH, and testosterone in men and estradiol in women. Existing literature on FGAs has been limited to reviews and case series or reports over the past decade. The overall prevalence is unknown, and clinical presentation is variable.[8,10,11] Women most commonly present with ovarian hyperstimulation, ovarian cysts, and menstrual irregularities,[9,11,14,15] and men most commonly present with testicular

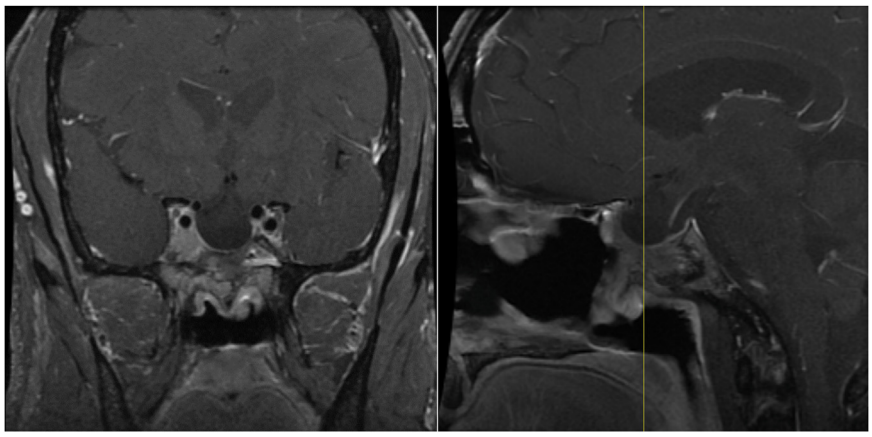

Fig. 4. Nine-month postoperative T1-weighted postcontrast magnetic resonance imaging demonstrated area of hypoenhancement that corresponds with residual tumor along the right cavernous sinus in coronal view (left) and relative position (yellow line) of the sella in the sagittal view, which also demonstrated the extent of tumor resection achieved with surgery.

enlargement and sexual dysfunction.[10] *Polycythemia* is a rare and often unrecognized manifestation of an FGA.[16] Asymptomatic presentation has also been reported.[8] There is no consensus for treatment of this type of adenoma aside from surgical management.[1] This case of FGA presented an increased risk of the following: (1) hormonal nonremission given the persistent increase in the FSH, LH, and testosterone levels and (2) tumor progression and recurrence given its invasion into the bone and dura, which prompted adjunct radiation therapy.[1,6] Clinical characteristics need to be factored in the natural course of the residual tumor. That the patient presented with known vision disturbance may be more clinically significant than tumor markers themselves.[17] We, therefore, took a measured multimodal and multidisciplinary approach to address these risk factors with this patient's tumor.

Conclusion

This case highlights the key steps in the diagnosis, management, and treatment of a rare, giant, invasive functional gonadotroph pituitary macroadenoma. Adjunct radiotherapy was administered to residual tumor and resection cavity following surgery with significant recovery of visual acuity. Persistently increased FSH levels with normalizing testosterone levels likely represent known residual disease. In conclusion, we demonstrate the importance of involving a multidisciplinary team of physicians and a combination of surgery, radiation, and hormonal treatments to successfully manage a complex FGA.

Informed Consent

The authors attest that this submission is in compliance with Section E, "Protection of Research Participants," of the ICMJE Recommendations. Patient information was deidentified.

Disclosure

The authors have no conflicts of interest to disclose.

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