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CASE REPORT
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Hormonally Active, Aggressive Gonadotropinoma with Increased Testicular Size: A Rare Case Report

ABSTRACT

We present a case report of a 32-year male who presented with pituitary macroadenoma with initial presentation of visual disturbances in the form of decreased vision in the left eye followed by the right eye with no features suggestive of acromegaly, Cushing's syndrome, and hypogonadism. Preoperative hormonal evaluation revealed high follicle-stimulating hormone, luteinizing hormone, and testosterone, rest of the hormonal profile was normal. The patient was subjected to craniotomy with tumor decompression which was complicated by transient Diabetes Insipidus (DI), central hypothyroidism, and hypocortisolism started on hormonal replacement, but there was little improvement in symptoms after surgery. The patient presented with deterioration of visual symptoms, and repeated magnetic resonance imaging revealed a similar lesion; the patient was again subjected to Transnasal transphenoidal surgery (TNTS) and radiotherapy. Immunohistochemistry of the tumor revealed positive staining for follicle-stimulating hormone and negative staining for adrenocorticotropic hormone and growth hormone.

Keywords: Pituitary, pituitary, surgical endocrinology, thyroid

Introduction

Pituitary tumors constitute around 15.5% of all central nervous system tumors. In the younger age group of 20-30 years, the prevalence of these tumors can go up to 30%.[1] With easy availability and recent advancements in immunohistochemistry, it has been seen that 80%-90% of non-functioning pituitary adenomas (NFPA) are gonadotropin derived, producing either intact gonadotropins or gonadotropin subunits.[2] Most of these tumors are asymptomatic unless the tumor is large enough to present with features of mass effect in the form of headache, visual disturbances, or hypopituitarism as most of these tumors are non-secretory. Functionally active gonadotropinomas secreting intact follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are found to be very rare.[3,4] These tumors are most common in middle-aged males than females, the reason being that LH and FSH levels are already high in peri-menopausal and post-menopausal women making diagnosis difficult in females.[5] These tumors are rarely found in children.[6] Surgical treatment of pituitary macroadenomas often fails because of tumor recurrence after the operation. The causes of tumor recurrence are complex, but one of them may be the high growth potential of the adenoma. It is found that the adenomas undergoing the early recurrence have lower expressions of somatostatin receptors (SSTR) 2A and 3 in comparison to those which did not recur. On the other hand, the recurrent tumors show higher expression of SSTR 1, 2A, 3, and 5 subtypes than their primary counterparts. So, it is hypothesized that SSTR may, at least in part, counteract adenoma recurrence.[7]

Case Presentation

We present a 32-year-old man, married with 2 live kids with a 3-month history of decreased vision in the left eye which was insidious in onset and progressive. In due course of time, the vision of the right eye was also compromised. It was associated with a mild headache on and off especially during morning hours. There was no history of fever, vomiting, abnormal body movements, or weakness of any body part. Ophthalmologic examination revealed mild papilledema and bitemporal hemianopia. The magnetic resonance imaging of the brain showed a large, well-defined, lobulated, altered signal intensity mass lesion measuring approximately 5.4 × 4.9 × 4.8 cm that is isointense on T1W1 and mildly hyperintense on T2W1 showing moderate homogenous enhancement on post-contrast images which is seen centered in the sellar region extending superiorly into suprasellar cistern causing significant compression of optic chiasma and hypothalamus resulting in partial effacement of the third ventricle. The anterior

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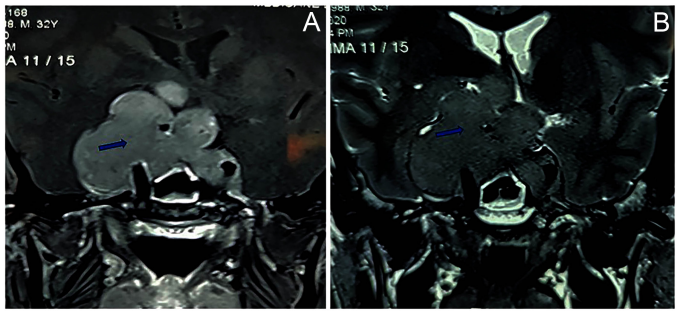

Figure 1. (A) Coronal T1W hypointense lesion with gadolinium enhancement. (B) Coronal T2W mildly hyperintense lesion with enhancing.

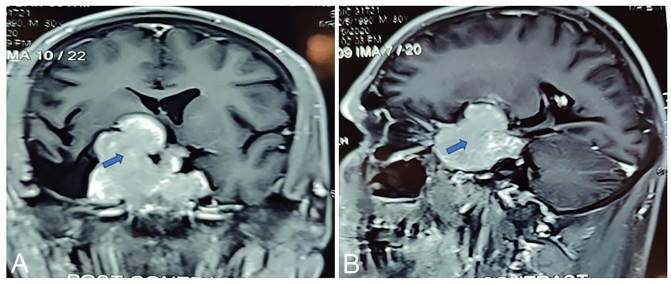

Figure 2. (A) Coronal T1W image with gadolinium enhancement showing recurrent/residual tumor. (B) Sagittal T1W image with enhancement.

pituitary is not seen separately from the mass lesion. Laterally the lesion is seen extending into both cavernous sinuses with complete encasement of both internal carotid arteries (ICA) and right posterior communicating artery. Antero-inferiorly the lesion is seen extending into the sphenoid sinus through the sellar floor. Posteriorly the lesion is bulging into the cranial part of the right cerebellopontine angle (CP) angle cistern indenting the right middle cerebral peduncle. Anteriorly, the lesion is extending into the extra-axial cerebrospinal fluid (CSF) space of right anterior temporal convexity reaching up to the right orbital apex. The prominence of the peri-optic CSF sheath is seen bilaterally (Figure 1). There are no symptoms of hypocortisolism or hypothyroidism. There is no hyperphagia, weight gain, hypothermia, polyuria, or polydipsia. Clinical examination revealed bitemporal hemianopia. No features are suggestive of acromegaly and Cushing's syndrome or hypogonadism (no loss of axillary hair, gynecomastia, and pubic hair). A testicular exam revealed increased testicular volume (25-30 mL B/L) by means of orchidometer and a stretched penile length of 16 cm. Preoperative hormonal profile showed serum total triiodothyronine (T3)—0.96 ng/mL (0.70-2.50), total levothyroxine (T4)—6.6 ug/dL (4-13), thyroid-stimulating hormone (TSH)—1.47 uIU/mL (0.5-6.5), random growth hormone (rGH)—1.19 ng/mL (0-5), 8 AM cortisol—11.6 mcg/dL (10-25), LH >200 IU/mL (3-12), FSH >200 IU/mL (2-10), serum total testosterone (8 AM) >1500 ng/dL (350-750), and mildly elevated serum prolactin of 64.5 ng/mL (0-25) likely because of stalk effect. The patient underwent craniotomy with tumor decompression. The biopsy of the tumor was suggestive of a non-functional pituitary adenoma. Postoperatively there was mild improvement in vision. However, the postoperative period was complicated by secondary hypocortisolism with 8 AM serum cortisol level of 6.0 ug/dL and secondary hypothyroidism with serum T3, T4, and TSH levels of 0.70 ng/mL, 4.1 ug/dL, and 0.19 uIU/mL, respectively. The patient persisted with high serum gonadotropin and testosterone levels. The patient was started on Tab hydrocortisone and thyroxine replacement postoperatively. The postoperative period was also complicated by transient diabetes insipidus which was managed by vasopressin infusion for a few days (3-5 days). Five months later, the patient presented again with deterioration of vision bilaterally and repeat contrast enhanced magnetic resonance imaging (CEMRI) brain identified 6.2 × 5.2 × 5 cm, lobulated, sellar-suprasellar mass with bilateral cavernous sinus invasion with bilateral ICA encasement with compression of the third ventricle (Figure 2). Repeat gonadotropin and testosterone levels were still very high with LH of >254 IU/mL, FSH of 200 IU/mL, and total testosterone of 1318.26 ng/dL. The patient underwent resurgery (TNTS) with the removal of most of the tumor, with repeat biopsy again suggestive of pituitary adenoma, and hormone immunohistochemistry showed positive staining for FSH suggestive of gonadotropinoma; however, staining for LH not done in view of unavailability. Staining for hormones like GH and adrenocorticotrophic hormone (ACTH) was negative (Figure 3). Postoperatively, patients also received 31 cycles of radiotherapy, with meager improvement in underlying symptoms. The patient is

MAIN POINTS

- Non-functional pituitary adenomas are mostly gonadotropinomas; however, they can be functional as well as very aggressive, requiring recurrent surgeries with unsatisfactory prognosis.
- Reports suggest that most of the functional gonadotropinomas in males have normal testicular size.
- Contrary to these findings, we report for the first time a biochemically and pathology-proven gonadotropinoma, with increased testicular size.
- This was an aggressive gonadotropinoma with multiple recurrences requiring multiple surgeries but poor symptom improvement.

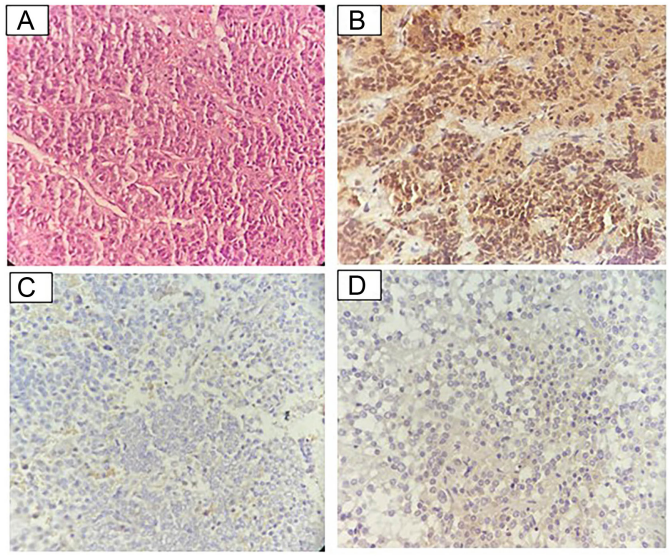

Figure 3. (A) Pituitary macroadenoma. (B) Positive staining for follicle-stimulating hormone. (C) Negative staining for growth hormone. (D) Negative staining for adrenocorticotrophic hormone.

continuing hormone replacement therapy for postoperative panhypopituitarism and is on regular endocrinology and neurosurgery follow-up. Written informed consent was obtained from the patient for this study.

Discussion

Pituitary tumors are the third most common intracranial neoplasm (15%) after meningiomas and gliomas. Due to improvements in imaging techniques, the detection rate of pituitary adenomas has improved and is not considered a rare disease nowadays.[8] The NFPA comprises around 15%-30% among all adenomas.[9] NFPA are the second most common pituitary tumor, being exceeded only by prolactinomas.[10] Gonadotropinoma or gonadotroph adenoma got its proper characterization very late among other pituitary tumors, and it is still yet not properly characterized in view of its mostly non-functional nature. These are identified mainly either by increased production of LH, FSH, or their subunits like alpha glycoprotein subunit, FSH beta (FSH β), and LH beta (LH β) or by immunohistochemical studies.[2] Though these are the most common type of pituitary macroadenomas, their medical attention often gets delayed owing to their non-secretory nature or due to the very low-level secretion of hormones or hormone subunits causing unrecognizable clinical symptoms.[3] We presented a case of giant invasive pituitary tumors which on hormonal evaluation and immunohistochemistry was found to be gonadotropinoma. Even though the patient underwent multiple surgeries and radiotherapy, there was less improvement in symptoms. But in view of its large size and invasiveness, with typical symptoms and signs of mass effect, it was diagnosed at an early stage, though unresponsive to treatment. The most common presentation of gonadotropinoma includes visual field defect, headache, hypogonadism with decreased libido, impotence, or menstrual dysfunction, panhypopituitarism (GH, FSH/LH, TSH, and ACTH deficiency), mild or moderate elevation of prolactin levels (mimicking prolactinoma). This may also present as an incidental finding as asymptomatic micro or macroadenoma when brain imaging is done for other reasons. The rare presentations include ovarian hyperstimulation syndrome, testicular enlargement (macro-orchidia), precocious puberty, pituitary apoplexy, cranial nerve palsy, cavernous sinus syndrome, and CSF rhinorrhea.[2] Five premenopausal women with gonadotropinoma of size 12 mm to huge invasive adenomas in the age range of 10-39 years presented with features of ovarian hyperstimulation syndrome. These patients had high serum FSH levels and variable LH levels ranging from subnormal to supranormal range with elevated serum estradiol levels in all patients.[11,12] Another rare presentation of gonadotropinoma is testicular enlargement with increased serum intact LH and FSH levels and increased testosterone. Though in our patient serum gonadotropin levels and testosterone levels were elevated, testicular size was normal which could not be explained. Two prepubertal boys with rare FSH, LH, and prolactin (PRL) secreting gonadotropinoma presented with precocious puberty.[13,14] Another rare clinical presentation is pituitary apoplexy due to bleeding into the tumor causing severe headache, diplopia, and acute pituitary hormone insufficiency.[15]

Conclusion

NFPA's though initially considered rare due to their non-functional nature are now found to be quite common due to their aggressive nature and recurrence. Increased testicular size associated with gonadotropinoma though quite rare as per literature,however was found in our case.

Informed Consent: Written informed consent was obtained from the patient for this study.

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Declaration of Interests: The authors have no conflict of interest to declare.

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