Published in final edited form as:

Pituitary. 2017 August ; 20(4): 485–487. doi:10.1007/s11102-017-0796-8.

The Longest Stalk: Preserved Pituitary Function after Regression of a Giant Prolactinoma

Jessica A. Lundgren, Edward H. Oldfield, and John C. Marshall

University of Virginia Health System, Charlottesville, Virginia

Key Terms

Giant prolactinoma; macroadenoma; pituitary stalk; hypopituitarism

Clinical History

In December 2007, a 44-year-old male living in the Middle East was diagnosed with meningitis. At that time, CT identified a nasopharyngeal mass (7.5×4.5 cm) involving the clivus and extending to the suprasellar region. Biopsy reportedly was consistent with nasopharyngeal carcinoma. He underwent 5 cycles of cisplatin and 5-fluorouracil. Subsequent MRIs in June and September 2008 showed an unchanged mass. He then relocated to the United States.

In October 2008, he presented upon referral to the University of Virginia Pituitary Clinic, where he reported low libido and daily frontotemporal headache. He denied galactorrhea and had no evidence of hypogonadism, Cushing's, or acromegaly.

Our initial imaging in September 2008 (Fig. 1) showed a mass ($3.7 \times 3.1 \times 5.5$ cm) centered within the sella, clivus, and sphenoid sinus, invading the cavernous sinuses, elevating the optic chiasm, and extending into the nasopharynx. His baseline morning pituitary evaluation showed prolactin $>164,000$ ng/mL (<20), cortisol 8.7 ug/dL, total testosterone 173 pg/mL (310-1010), SHBG 29 nmol/L (13-71), free testosterone 35.1 pg/mL (47-244), LH 4.0 mIU/mL, FSH 11.5 mIU/mL, free T4 1.1 ng/dL (0.7-1.5), TSH 0.71 mIU/L (0.45-4.5), and IGF-1 87 ng/mL (87-267). Macroprolactin was not detected.

Cabergoline was initiated at 0.25 mg twice weekly. He underwent repeat biopsy of the nasopharyngeal mass, confirming a neuroendocrine tumor with prolactin immunoreactivity.

After 4 weeks of cabergoline, prolactin was 129 ng/mL, with markedly low morning cortisol 0.5 ug/dL, total testosterone 46 pg/mL, SHBG 16 nmol/L, free testosterone 11.9 pg/mL, LH

Corresponding author and person to whom reprint requests should be addressed: Jessica A. Lundgren, M.D., Division of Endocrinology and Metabolism, Department of Internal Medicine, Box 801408, University of Virginia Health System, Charlottesville, Virginia, 22908, jlundgren@virginia.edu, Telephone: (434) 924-1825.

Compliance with Ethical Standards

Conflict of Interest: Dr. Jessica Lundgren declares that she has no conflict of interest. Dr. Edward Oldfield declares that he has no conflict of interest. Dr. John Marshall declares that he has no conflict of interest.

Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

4.2 mIU/mL, and FSH 14.1 mIU/mL. For presumed secondary adrenal insufficiency, hydrocortisone was initiated. After 12 weeks of cabergoline, prolactin was 23.8 ng/mL, and total testosterone remained below normal (218 ng/dL) with LH 4.5 mIU/mL and FSH 11.8 mIU/mL. In August 2010, after withholding hydrocortisone for >24 hours, early morning testing showed cortisol 20.9 ug/dL, total testosterone 139 ng/dL, SHBG 19 nmol/L, free testosterone 34.4 pg/mL, LH 4.6 mIU/mL, FSH 12.6 mIU/mL, and free T4 1.05 ng/dL. At that time, he was instructed to discontinue hydrocortisone. Over the next several years, the testosterone level increased to the low-normal range.

MRIs from January 2009 through April 2014 (Fig. 1) showed progressive reduction in adenoma size. This revealed an essentially empty sella with a small, inferiorly located residual pituitary gland and a markedly thin stalk lengthened to 30 mm, the longest pituitary stalk that we have seen. Presumably, the stalk stretched over such a prolonged time period (at least 5 years) that its elongation did not result in persistent hormonal dysfunction.

Discussion

Giant prolactinomas generally are defined by a diameter >4 cm, and they represent <5% of pituitary lesions [1]. While prolactinomas overall are diagnosed most frequently in reproductive-aged females, giant prolactinomas are diagnosed predominantly in middle-aged males.

Several aspects of this case are of interest. Despite the marked elevation of prolactin, gonadotropin levels were not suppressed. Considering that hyperprolactinemia should suppress GnRH secretion, this may reflect impaired bioactivity of the tumor prolactin. Alternatively, his prior chemotherapy may have resulted in testicular damage, leading to gonadotropin elevation due to inadequate sex steroid negative feedback. Additionally, while pituitary function initially was preserved, transient partial hypopituitarism occurred within a month of initiating cabergoline, with subsequent spontaneous recovery—although 5 years passed before restoration of hypothalamic-pituitary-gonadal function.

We hypothesize that the transient hormonal deficiencies could reflect compression and/or too-rapid elongation of the pituitary stalk during the initial tumor shrinkage, temporarily impairing stalk blood flow before subsequent recovery.

While replacement of cortisol or thyroxine for deficient patients is critical, we tend not to initiate sex hormone replacement within the early years of treatment, because gonadal function eventually returns for many of these patients. In a series of 50 patients with giant prolactinomas, 87% had hypogonadotropic hypogonadism at diagnosis, with 32% recovering gonadal function after cabergoline treatment [2]. The series also reported initial incidence of central hypothyroidism (55%), GH deficiency (28%), and hypocortisolism (7%), however, rates of recovery were not noted. In comparing pituitary dysfunction in men presenting with giant prolactinomas (n=26) versus smaller macroprolactinomas (n=55), Tirosch et al [3] observed central hypothyroidism and/or hypocortisolism with 42.9% of giant prolactinomas compared to 17.9% of smaller macroadenomas; these deficiencies persisted post-cabergoline in 34.8% versus 9.1% of patients respectively.

Because dopamine agonist therapy is usually lifelong for patients with macroadenomas, we suggest that hormonal replacement should be withdrawn periodically to assess for recovery of pituitary function.

Acknowledgments

This study received no funding.

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Fig. 1.
Giant prolactinoma. **A** Large tumor prior to cabergoline therapy. **B** Initial tumor shrinkage with pituitary stalk revealed. **C–F** Progressive tumor regression and stalk elongation.