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Clinical–patient studies

Giant invasive pituitary prolactinoma with falsely low serum prolactin: the significance of 'hook effect'

Maria Fleseriu[1], Michael Lee[2], Maria M. Pineyro[1], Mario Skugor[1], Sethu K. Reddy[1], Elias S. Siraj[1] and Amir H. Hamrahian[1]
[1]*Department of Endocrinology, Diabetes and Metabolism Cleveland Clinic Foundation, Cleveland, Ohio, USA;*
[2]*Department of Ophthalmology Cleveland Clinic Foundation, Cleveland, Ohio, USA*

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Summary

The authors report a case of a patient with giant, invasive skull base tumor extending to the parasellar area discovered incidentally during the work-up for decreased memory. The patient's neurological exam was otherwise unremarkable. Endocrine evaluation performed at a local hospital showed a moderate hyperprolactinemia 103 ng/ml (normal up to 20 ng/ml). Given the large size of the tumor, the elevated prolactin (PRL) was interpreted to be secondary to stalk effect and patient underwent debulking surgery through a transcranial approach. Immunostaining of the excised tumor tissue was strongly positive for prolactin. His prolactin was found to be 13,144 ng/ml in our lab after surgery confirming the diagnosis of invasive giant prolactinoma. The patient developed a complete right third, fourth and sixth nerve palsy postoperatively. He was started on Cabergoline with normalization of his prolactin level and more than 50% decrease in residual tumor size over 9 months periods. There has been no clinically significant improvement in his right eye ophthalmoplegia since surgery. This case highlights the importance of 'Hook Effect' resulting in falsely low prolactin level, which may have significant therapeutic implication.

Introduction

The differential diagnosis of skull base tumors includes pituitary adenomas, meningiomas, gliomas, craniopharyngiomas, metastatic carcinomas, chordomas and rarely other tumors. Prolactinomas represent the most common secretory pituitary adenoma, up to 50% in some series. Macroprolactinomas (≥1 cm) are readily diagnosed by a prolactin in excess of 200 ng/ml [1,2]. The initial therapy of choice for large pituitary macroprolactinomas frequently involves dopamine agonists. Surgery is usually reserved for debulking the tumor and alleviating neurological deficit in cases where the tumor is resistant to dopamine agonists or if the patient is intolerant of them.

Most clinical laboratories measure prolactin using immunoradiometric assay (IRMA) or chemiluminometric assay (ICMA) [3,4]. These new methods are rapid, accurate and specific but they may sometimes also result in a grossly inaccurate low measurement. We present a case of invasive giant prolactinoma, which was misdiagnosed due to a falsely low prolactin level. A debulking procedure resulted in permanent neurological deficits. The data about this case report has been extracted from pituitary database approved by Institutional Review Board at the Cleveland Clinic Foundation.

Case report

A forty-seven-year old man with past medical history significant for hypertension, hyperlipidemia and depression complained of short-term memory loss. Head CT showed a large sellar mass. The review of system was significant for 40 pound weight gain, fatigue, increased sleepiness, occasional blurry vision and intermittent bilateral eye pain. He denied diplopia, headaches, polyuria, nocturia or any sexual dysfunction. His only medication was Venlafaxine. Physical examination revealed an overweight patient with an otherwise normal neurological exam including extraocular motility.

Preoperative endocrine evaluation performed in an outside hospital was significant for a prolactin level of 103 ng/ml (normal less than 20 ng/ml), hypothyroidism and low normal testosterone, FSH and LH levels. His corticotropin axis was normal and he had normal age and sex matched IGF-1 level. MRI of the brain revealed a $9\times8.2\times6.8$ cm mass in the anterior skull base (Figure 1a, b). The lesion was well circumscribed, lobulated, homogenously enhancing after gadolinium and it invaded the ethmoid, sphenoid and cavernous sinuses and the clivus. The optic chiasm was substantially elevated and displaced. Visual field testing preoperatively was normal.

Considering the tumor size, the elevated prolactin level was interpreted to be secondary to stalk effect ± the effect of his antidepressant therapy. He underwent debulking surgery through a right frontal craniotomy approach with the presurgical diagnosis of invasive nonfunctional pituitary macroadenoma. MRI of the brain 3 days after the surgery is shown in Figure 1c, d. Postoperatively he noted diplopia secondary to complete right 3rd, 4th and 6th nerve palsies.

The excised tumor tissue showed a strong positive immunostaining for prolactin but negative for other

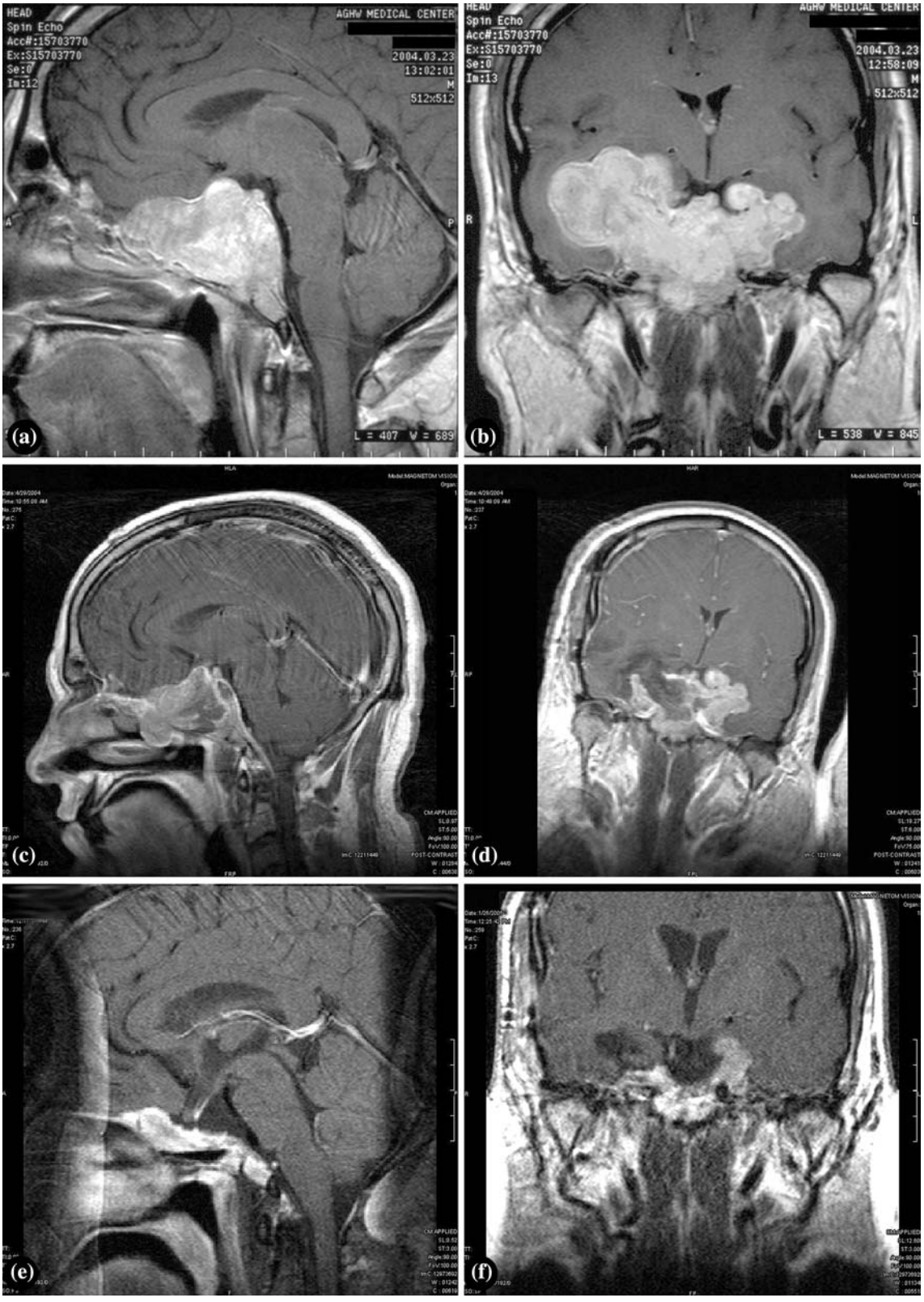

Figure 1. Sagittal and Coronal T1 weighted MR image of giant skull base tumor with suprasellar extension prior to surgery (a, b), postop (c, d) and 9 months after therapy with Cabergoline (e, f).

anterior pituitary hormones. After surgery his serum prolactin level was reported as 13,144 ng/ml in our assay. Patient began Cabergoline with gradual increase to 4 tablets per week. At 9 months postoperatively, his prolactin level normalized at 14.4 ng/ml with a significant decrease in tumor size (Figure 1e, f). He had partial recovery of his third nerve palsy, but continues to have diplopia with complete 4th and 6th nerve palsies.

Discussion

Giant prolactinomas (> 4 cm) are rare skull base tumors associated with high serum prolactin levels that may exceed 100,000 ng/ml. Their large size usually prohibits complete surgical resection without high surgical morbidity. Dopamine agonists effectively lower serum prolactin and significantly reduce tumor size in most cases. For these reasons a correct diagnosis is very important in such patients.

The introduction of the two-site monoclonal 'sandwich' assays, IRMA and ICMA (chemiluminescent assays), has been associated with more rapid and accurate hormone measurement [5]. In these assays two different antibodies, one attached to a solid surface (capture antibody) and the other added with patient's serum sample (signal antibody) labels the hormone (antigen) with a substance such as radioactive tracer. After the unbound signal antibodies are washed away, the remaining tracer detected correlates to the 'level' of prolactin hormone. However if antigen outnumbers capture and signal antibodies, the excess soluble antigen binds separately to each antibody. This prevents the formation of a 'sandwich,' which leads to much lower levels of antigen detected. This is called high dose 'hook effect' or 'prozone phenomenon.'

The presence of a high dose hook effect for prolactin in two automated immunoassays was described in 1992 [6]. Comtois et al. [7] reported the first patient in whom hook effect lead to misdiagnosis of a giant prolactinoma. The high-dose hook effect has also been reported for other laboratory tests such as ferritin [8], human chorionic gonadotropin, growth hormone [9], thyroglobulin [10], myoglobin, prostate specific antigen [11], gonadotropins, and carcinoembryonic antigen. St-Jean et al. [12] described a prevalence of 5.8% (4/69) and 26% (4/15) for hook effect in patients with pituitary macroadenomas and macroprolactinomas, respectively, who were referred for transsphenoidal pituitary surgery over a 5-year period. All four patients with hook effect were male with their tumor measuring 3.3–6.0 cm in size. The absolute prolactin levels above which hook effect occurs seems to depend on the particular assay used, but may appear in patients with prolactin concentration as low as 1320 ng/ml [13].

Some institutions like ours have switched to two-step process that eliminates hook effect. The laboratory washes away excess antigen before adding the signal antibody to the capture antibody–antigen complex. The disadvantage is that it is time consuming and thus more costly. Laboratories using a one-step process should perform a 1/100 dilution to avoid hook effect [3,14,15].

It is easy to see why a giant prolactin-secreting macroadenoma was misdiagnosed as a nonfunctional pituitary tumor in our patient. Unfortunately, he suffered significant morbidity following surgical debulking. Dopamine agonist therapy normalized our patient's prolactin level and significantly decreased the tumor size. Physicians should keep a high index of suspicion for giant prolactinomas in the setting of large pituitary adenomas and mild to moderate hyperprolactinemia, which may otherwise be attributed to stalk effect. The hook effect can be avoided in monoclonal sandwich assays by using two-step processing or perform serial dilution in the one step processing.

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Address for offprints: Amir H. Hamrahian, Department of Endocrinology, Diabetes and Metabolism Cleveland Clinic Foundation, Desk A53, 9500 Euclid Avenue, Cleveland, Ohio, 44195, USA; Tel.: +1-216-445-8538; Fax.: +1-216-445-1565; E-mail: hamraha@ccf.org