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Case Report

Case Report

Giant Prolactinoma Presenting With Facial Nerve Palsy and Hemiparesis

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Abbreviations: CAB, cabergoline; GP, giant prolactinoma; MRI, magnetic resonance imaging; PRL, prolactin.

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Abstract

Background: Giant prolactinomas are an exceedingly uncommon type of pituitary adenomas that usually occur in men, and cause extremely high prolactin levels and mass-related symptoms. Rarely, patients may experience neurological deficits resembling ischemic events.

Methods: We describe an unusual case of a young man who presented with stroke-like symptoms and was found to have a giant prolactinoma.

Clinical Case: A 25-year-old man presented with left facial droop and gradually progressing upper and lower extremity weakness for evaluation of stroke. He reported recent weight gain and erectile dysfunction. Physical examination revealed left homonymous hemianopsia, left VII nerve palsy, and left hemiparesis. Magnetic resonance imaging of the brain showed an enormous mass in the sella turcica, which invaded the sphenoid sinus and right side of the skull base. Prolactin level was elevated at 13 580 ng/mL, and the testosterone level was low. The patient was started on cabergoline and had marked improvement in his symptoms in a few months. Fifteen months after starting treatment, he has had more than 90% reduction in tumor volume and a 93% reduction in prolactin level.

Conclusion: Giant prolactinomas are uncommon and present with compressive symptoms that can be mistaken for a stroke. Our case is a unique report of a facial nerve palsy and hemiparesis secondary to giant prolactinoma in the absence of stroke or pituitary apoplexy.

Key Words: Giant prolactinoma, facial palsy, hyperprolactinemia, hemiparesis

Lactotroph adenomas are the most common pituitary adenomas and can cause infertility and menstrual irregularities in women, and hypogonadism and gynecomastia in men [1-3]. Most prolactinomas are described as microadenomas with a diameter of less than 10 mm and are more prevalent in women [1]. Giant prolactinomas (GPs) are a subset of

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pituitary macroadenomas with limited literature on their management. GPs occur more commonly in men, and, by definition, grow to more than 4 cm in diameter and produce prolactin (PRL) levels above 1000 ng/mL [4].

Symptoms from GPs are usually due to mass effect on surrounding tissue and significant elevation in PRL, causing hypogonadotropic hypogonadism. Dopamine agonists (bromocriptine and cabergoline [CAB]) are considered first-line therapy in GP treatment; however, a surgical approach may be necessary if the tumor continues to cause mass effect and impending visual threat [5, 6]. Although palsies of cranial nerves III-VI have been reported, facial nerve palsy and hemiparesis are relatively unique presentations [4].

We describe an unusual case of a young man who presented with symptoms of motor weakness in the upper and lower extremities with concern for stroke, who on evaluation was noted to have a large multilobular mass in the region of the right cavernous sinus. He was subsequently diagnosed with a giant prolactinoma based on an elevated PRL level. He was started on medical therapy with CAB with complete resolution of the motor deficits over the next few months.

Case Description

A 25-year-old previously healthy, dominant left-hand man presented to the walk-in clinic for an evaluation of stroke with longstanding left-sided facial asymmetry, and new weakness of the left arm and leg.

His symptoms started several months prior to the presentation when he returned from a summer camp and noticed a left-sided facial droop. He presented to his primary care office, where he tested negative for Lyme disease and was thought to have Bell's palsy. Six months later, he noted a new weakness in the left upper and lower extremity, which affected his gait. Due to worsening symptoms and concern about a possible stroke, a magnetic resonance imaging (MRI) of the brain was ordered, and once the mass was identified, he was advised to report to the emergency department for admission.

At the time of admission, his symptoms included facial asymmetry and left-sided weakness. He reported occasional nausea and vomiting but denied having headaches, visual changes, loss of sensation, rhinorrhea, or ear discharge. He did report unknowingly bumping into things in the last few weeks. He noted a weight gain of 50 pounds in the last 6 months due to increased appetite. History was also positive for decreased libido and loss of morning erections. Family history was negative for brain tumors.

On physical examination, the patient was alert and oriented. He demonstrated right eye proptosis and loss of nasolabial fold on the left. He was able to close his left eye, forehead, and eyebrow movements were preserved consistent with central facial nerve palsy. Pupils were round, equal, reactive, and extraocular movements were intact. The ophthalmic examination showed normal fundus, unremarkable visual acuity with left-sided temporal visual field deficit. Left upper and lower extremity weakness was noted. Sensory testing was normal. There was no ataxia or dysmetria, and the gait was normal. Galactorrhea or gynecomastia was not appreciated, and testicular size was normal.

MRI of the brain was performed, and results were consistent with an enormous extra-axial multilobulated mass arising in the region of the right cavernous sinus invaginating deep into the base of the right cerebral hemisphere and producing a mass effect on the pons, right-sided midbrain, right temporal lobe, and right basal nuclei. In overall dimensions, the mass measured 60 mm × 55 mm × 75 mm (anteroposterior, transverse, and craniocaudal, respectively) without ischemic findings (Fig. 1). The tumor was enhanced homogeneously except for cystic and hemorrhagic areas. The patient underwent a computed tomography angiogram, which demonstrated displacement of the

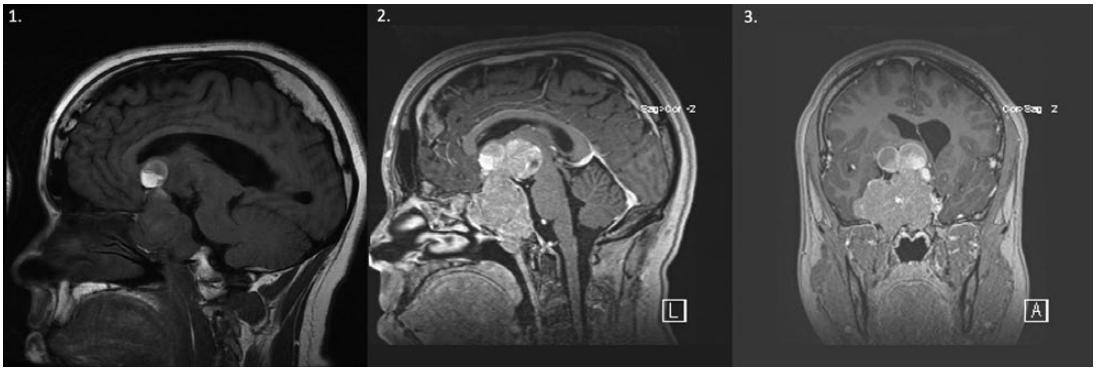

Figure 1. Initial MRI of the brain: sagittal T1 precontrast (1), sagittal T1 postcontrast (2), and coronal T1 postcontrast view (3) demonstrating enormous sellar mass.

right internal carotid artery and anterior displacement of the right middle and anterior cerebral artery. There was no significant vascular stenosis, and the mass demonstrated moderate vascularity. Magnetic resonance venography confirmed the invasion of cavernous sinuses and the right petrosal sinus without thrombosis.

Initial laboratory testing revealed a serum PRL level of 13 580 ng/mL (ref: 2.64-13.13 ng/mL). Further workup demonstrated a thyroid stimulating hormone of 1.71 µU/mL (ref: 0.35-4.94 µU/mL) with a free thyroxine of 0.6 ng/dL (ref: 0.61-1.82 ng/dL), a morning cortisol of 4.8 µg/dL (ref: 7-23 µg/dL), an adrenocorticotropic hormone of 18 pg/mL (ref: 7-69 pg/mL), an insulin-like growth factor 1 of 112 ng/mL (ref: 99-283 ng/mL), and a growth hormone level of <0.05 ng/mL (ref: 0.05-3.00 ng/mL). A cosyntropin stimulation test demonstrated a normal cortisol levels at 30 and 60 minutes. Gonadal panel showed a luteinizing hormone of 0.31 mIU/mL (ref: 1.24-8.62 mIU/mL), a follicle stimulating hormone of 0.9 mIU/mL (ref: 1.27-19.26 mIU/mL), a sex hormone binding globulin of 15 nmol/L (ref: 11-80 nmol/L), and a testosterone level of 42 ng/dL (ref: 300-1080 ng/dL) with free testosterone of 10 pg/mL (ref: 47-224 pg/mL), which was consistent with hypogonadotropic hypogonadism. Hemoglobin A1c was 5.6%. His basic metabolic panel revealed only mild hyponatremia with a serum sodium of 133 mmol/L.

The patient was diagnosed with a giant prolactinoma and was managed by a multidisciplinary team, including endocrinology, ophthalmology, and neurosurgery. Given his very high PRL level, he was started on high-dose CAB, 0.5 mg daily, with close monitoring by neurosurgery and ophthalmology. After being on CAB 0.5 mg daily for a week, there was a 74% reduction in his serum PRL level to 3515 ng/mL. Repeat MRI showed stability of the pituitary mass after 1 week and CAB dose was decreased to every other day after 2 weeks of the treatment as the PRL level began to decline further. Repeat MRI of the brain 6 weeks after initiation of dopamine agonist therapy, showed a significant reduction (57%) in the tumor size to 60 mm × 38 mm × 47 mm, and volume (decreased from 247 cm^3 to 107 cm^3) (volume calculated using equation $V = abc$ using the 3-dimensional MRI measurements [anteroposterior, transverse, and craniocaudal]. The left-sided weakness and facial asymmetry resolved a few months after treatment initiation, followed by resolution of the visual field deficits. At the 7-month follow-up visit, the patient reported full resolution of symptoms with normal neurological and visual function. He resumed normal erections, although testosterone level was still below normal. The prolactinoma size decreased to 63 mm × 13 mm × 38 mm (31 cm^3), corresponding to an 87.5% total volume reduction after 12 months. The gonadotropic axis remained suppressed, although consistent recovery was noted, with total testosterone levels of 185 ng/dL (from 42 ng/dL) and free testosterone of 42 ng/dL (from 18 ng/dL) at his 15-month follow-up (Fig. 2). Simultaneously, follow-up MRI revealed approximately 91% total volume mass reduction since the

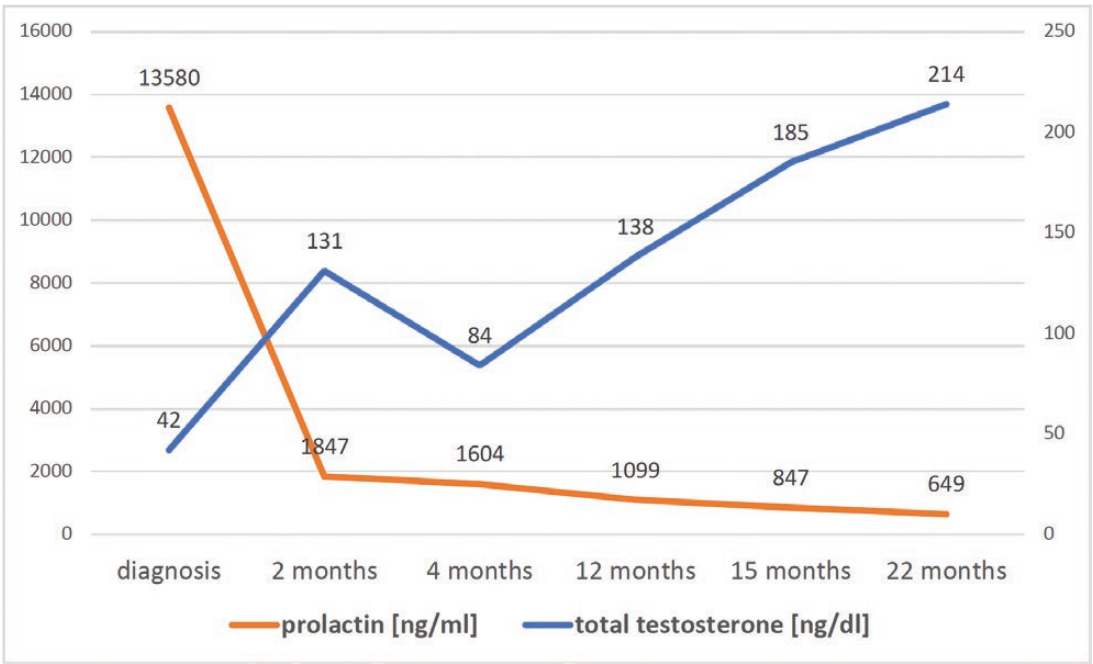

Figure 2. Trend line of prolactin (nanogram/millimeter, ng/mL) and total testosterone (nanogram/deciliter, ng/dL) level from the diagnosis until 22-month follow-up.

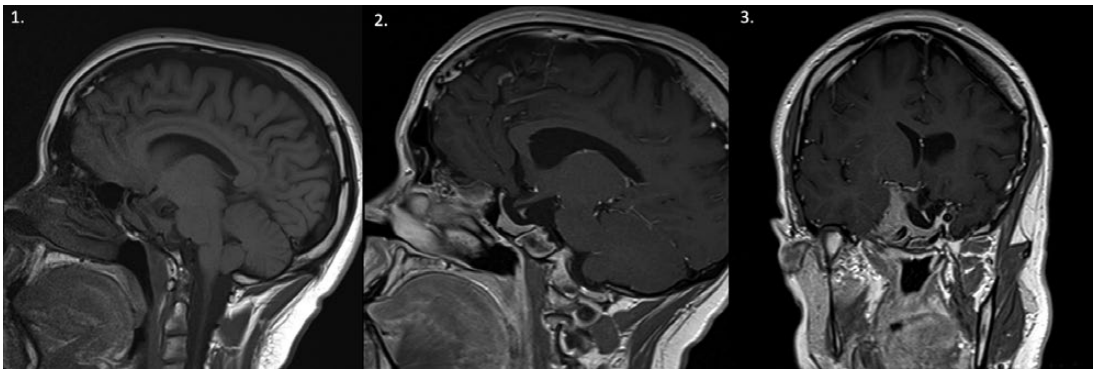

Figure 3. MRI of the brain at 15-month follow-up: sagittal T1 precontrast (1), sagittal T1 postcontrast (2), and coronal T1 postcontrast view (3) demonstrating significant reduction in the size of the tumor.

diagnosis, with 57 mm × 11 mm × 35 mm measurements (Fig. 3). Subsequent labs at 22 months showed further improvement of total testosterone to 214 ng/dL and free testosterone of 45 ng/dL, while PRL levels decreased to 649 ng/mL on continued dopamine agonist therapy (CAB 0.5 mg every other day) (Fig. 2).

Discussion

Giant prolactinomas are relatively rare pituitary tumors and management of these patients can be quite challenging. Clinical presentation can be misleading, mimicking other intracranial tumors or neurological disorders. Giant prolactinomas usually cause mass effect, compressing surrounding tissues and the optic chiasm [6]. The most common symptoms are vision changes (54.9%) and headaches (42.3%). Hormonal derangements are frequent, the most common one being low testosterone levels with hypogonadotropic hypogonadism, causing decreased libido and erectile dysfunction [6-9]. Less common presentations include cranial nerve palsy, seizures, cognitive decline, and psychiatric disturbances and pituitary apoplexy has been described in up to 9.8% of cases [6]. These patients have been reported to present with cranial nerves III, IV, V, and VI palsies [4]. Our patient is unique in that he presented with facial nerve palsy that reversed after CAB was started. Hemiparesis has rarely been reported with large pituitary adenomas in the setting of concurrent stroke or apoplexy was diagnosed [10]. In our case, we suspect that the enormous prolactinoma and its mass effect resulted in distortion of critical brain motor pathways and the corticobulbar fibers of the VII nerve, causing impaired motor function and weakness. These findings resolved with the reduction in size of the tumor with CAB therapy.

Giant prolactinoma can present with very high PRL level [6, 7, 9]. However, no consistent correlation has been reported between PRL level and tumor size [5, 6, 9, 11, 12]. Dopamine agonists, including bromocriptine and CAB, are effective first-line therapy and generally well tolerated. CAB, a long-acting D2-agonists, is favored over bromocriptine as it causes a greater decline in PRL levels [8, 13]. Surgical management is sometimes needed to rapidly decompress the optic chiasm due to visual impairment [14, 15] or can be a part of multimodal therapy due to continued growth and worsening symptoms despite dopamine agonist therapy or medication intolerance [6, 15]. Long-term dopamine agonist therapy is usually necessary for management [14-16]. Due to concern about the neurological symptoms at presentation, the treating team decided to start the patient on a higher dose of CAB to see if the neurological symptoms improve and surgical intervention can be avoided. This was done with close observation and understanding that such large tumors have increased risk of apoplexy because of their large size, which can sometimes be precipitated by CAB treatment. The patient was followed closely and a follow up MRI of the brain a week after starting CAB, confirmed tumor shrinkage and lack of apoplexy. Hence, CAB dose was reduced to 0.5 mg every other day, on which he has been maintained.

Giant prolactinomas are very sensitive to dopamine agonists [17, 18]. Acute symptoms arising from mass effect improve dramatically within days [5, 8]. Other symptoms may resolve later during therapy, which often occurs before PRL levels normalize [5]. Gonadal dysfunction is reversed in 67% to 80% of men in the literature [5, 8]. CAB dosage should be adjusted individually to avoid adverse effects and doses varying from 1.5 mg to 17.5 mg/week have been reported in various series [6, 8]. In resistant giant prolactinomas, PRL level may not normalize despite a fairly high weekly dose of CAB (2.0 mg/day) or bromocriptine (15 mg/day) [19]. Prolactin level may stay elevated in 20% to 40% of patients despite therapy and the nadir of PRL level seen between 10 and 20 months of therapy [5, 6, 16, 19]. Patients with higher initial levels of PRL demonstrated a more significant response to dopamine agonist, suggesting that

highly active tumors are more likely to respond to dopamine agonist monotherapy. The biochemical response does not correlate with tumor size and initial PRL level [6]. Our patient had an excellent response with a significant drop in PRL level just 2 days after starting CAB, suggesting high activity of lactotrophs. Dopamine agonists also facilitate tumor shrinkage and several studies have reported 60% to 80% reduction in tumor size over time [6, 8, 17, 19], with shrinkage in size usually reported at 6 to 20 months after starting treatment [5, 8, 11, 16]. Although our patient has had an incomplete PRL response at 22 months of follow-up, he continues to show gradual improvement in PRL level and gradual shrinkage in the tumor size. Therefore, CAB dose has not yet been increased due to concern about side effects from higher CAB therapy.

Giant prolactinoma require long-term follow-up to monitor for structural response and for possible complications. Prolactin level, pituitary function tests, visual fields, and tumor size need to be followed regularly. Cohort study of massive (larger than 60 mm) and aggressive prolactinomas revealed that 39% of patients did not reach full resolution of hyperprolactinemia (17% reached partial response [PRL < 3 × upper limit of normal]) although most patients reported disappearance or improvement of their symptoms [16]. In our patient, given resolution of symptoms and successive decline in PRL and increase in testosterone, patient was observed clinically with frequent hormonal evaluation and repeat imaging.

Novel pharmacological regimens like pasireotide, a new somatostatin receptor ligand, and temozolomide, an alkylating agent, have been used successfully for aggressive and resistant prolactinomas and may become promising adjuncts [20, 21]. Aggressive giant prolactinomas have been also linked to familial germline mutations including multiple endocrine neoplasia type 1, multiple endocrine neoplasia type 4, Carney complex, familial isolated pituitary adenoma, and mutations in genes encoding succinate dehydrogenase, thus genetic testing may be pursued when there is high clinical suspicion or suggestive family history [22, 23]. Our patient has continued to show gradual improvement both in tumor size and PRL levels. Hormonal testing for calcium level, and parathyroid and thyroid function has been normal and testosterone level continues to improve with full resolution of erectile dysfunction. We are planning to up-titrate CAB therapy as the next step and to pursue genetic evaluation. If the adenoma starts to behave more aggressively, surgical intervention and pasireotide or temozolamide treatments may also be considered.

Dopamine agonists may not prevent tumor re-expansion once they were discontinued [24]. Hence, patients with giant prolactinomas may never be a candidate for dopamine agonist withdrawal [25, 26]. The most important predictors for prolactinoma recurrence are maximum tumor diameter and baseline PRL levels [26]. CAB up-titration should be managed cautiously as rapid shrinkage of the invasive tumor may cause unplugging of the eroded area and induce cerebrospinal fluid leakage [27] and can cause pituitary apoplexy or chiasmal herniation [8, 26]. In our patient, initially high dose CAB (0.5 mg daily) was used due to urgency of the presentation, however patient was monitored closely by Neurosurgery and had repeat brain imaging to assure none of the complications have occurred. Patients on high-dose CAB or long-term therapy should be monitored by echocardiography for a possible valvular adverse effect [28].

Conclusions

Giant prolactinoma is a rare entity that occurs mostly in men and presents with a significant mass effect on surrounding tissue. At diagnosis, clinical features may be mistaken for other neurological conditions like stroke. Giant prolactinoma may present with unique symptoms of facial nerve palsy and hemiparesis. Most giant prolactinomas are sensitive to dopamine agonists; however, PRL normalization may not happen and although the adenoma may shrink in size, it may not disappear. Long-term therapy and surveillance are required to monitor symptoms, decline in PRL, tumor shrinkage, and complications from dopamine agonist therapy.

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Additional Information

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Data Availability:

All data generated or analyzed during this study are included in this published article or in the data repositories listed in References. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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