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A case of giant prolactinoma and pituitary hemorrhage with the late recovery of pituitary function: A case report

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Abstract

Hypogonadotropic hypogonadism is a common finding in patients who are diagnosed with a prolactinoma. It can be accompanied by the presence of other pituitary hormone deficits, including secondary adrenal insufficiency and central hypothyroidism. While the proportion of improvement in endocrine deficits over the short term is well characterized, there is not enough literature about the recovery of pituitary function over the longer term. We present the case of a 23-year-old man with a giant prolactinoma who initially presented with pituitary hemorrhage and panhypopituitarism. He underwent decompression of the pituitary tumor followed by treatment with cabergoline. Over a 9-year follow-up period, we noted that the hypogonadotropic hypogonadism resolved after 4 years and the secondary adrenal insufficiency resolved after 8 years. This case suggests that partial or complete recovery of the pituitary function is possible over the long-term even in patients with a giant prolactinoma.

Keywords

Prolactinoma, pituitary hemorrhage, cabergoline, hypogonadotropic hypogonadism, adrenal insufficiency

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Introduction

Pituitary apoplexy (PA) is a rare complication of pituitary adenomas which results from hemorrhage or infarction of the tumor.[1] The presenting feature of PA is sudden onset of headache which can be accompanied by the presence of visual field impairment and oculomotor palsies. Incidental radiological appearance of pituitary hemorrhage without the associated clinical features of PA can occur, which has a prevalence of 20.3% in macroprolactinomas.[2] Cabergoline therapy has been noted to be a precipitating factor for PA in patients with prolactinoma but PA can also occur in the absence of any precipitating factors.[3] It can lead to the development of multiple pituitary hormone deficits, which are typically permanent. We report the case of a 23-year-old man with a giant prolactinoma and pituitary hemorrhage who had panhypopituitarism at diagnosis. He underwent surgical resection of the macroprolactinoma and treatment with cabergoline, hydrocortisone, and levothyroxine. Recovery of pituitary function was noted over a 9-year follow-up period.

Case presentation

A 23-year-old man with no chronic medical problems was admitted to the hospital for further investigation of a newly diagnosed sellar mass. The sellar mass was discovered when he had a CT scan of his head done at a local emergency room after he reported a 2–3-month history of progressively worsening headaches and vision loss. On examination following admission to the hospital, blood pressure was 96/69 mm Hg, pulse was 48, and body mass index was 35.44 kg/m^2. Bitemporal hemianopsia was noted. He had gynecomastia with a breast bud of approximately 9 cm bilaterally. His testicular volume was 10 mL bilaterally and his pubic hair was consistent with Tanner stage IV. Thus, puberty had been halted before completion. X-ray to assess bone was considered but was unfortunately not obtained. Laboratory evaluation revealed an elevated prolactin level of 4130.43 ng/dL (reference range: 2.64–13.13 ng/dL) (Table 1). His thyroid stimulating hormone was normal at 1.33 µIU/mL (reference

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Table 1. Serial laboratory results.

Lab test	October 2014	May 2015	October 2016	October 2017	April 2018	April 2019	August 2020	September 2022
Prolactin (2.64–13.13 ng/dL)	4130 ng/dL	290.40 ng/dL	60.76 ng/dL	22.82 ng/dL	12.68 ng/dL	8.87 ng/dL	2.09 ng/dL	0.64 ng/dL
FSH (1.27–19.26 mIU/mL)	5.06 mIU/mL	1.49 mIU/mL	3.41 mIU/mL	—	4.68 mIU/mL	—	3.64 mIU/mL	1.93 mIU/mL
Testosterone (260.0–1000.0 ng/dL)	28.9 ng/dL	15.1 ng/dL	53.6 ng/dL	69.3 ng/dL	86.6 ng/dL	166.1 ng/dL	304.1 ng/dL	269.5 ng/dL
ACTH (7–69 pg/mL)	<5 pg/mL	—	<5 pg/mL	—	<5 pg/mL	8 pg/mL	3.7 pg/mL	20 pg/mL
Cortisol (AM: 5–23 µg/dL)	0.6 µg/dL	—	—	—	—	—	3.4 µg/mL	7.2 µg/mL
TSH (0.34–5.60 µIU/mL)	1.33 µIU/mL	0.12 µIU/mL	0.12 µIU/mL	0.02 µIU/mL	<0.02 µIU/mL	<0.02 µIU/mL	<0.02 µIU/mL	7.56 µIU/mL
Free T4 (0.58–1.64 ng/dL)	0.54 ng/dL	1.35 ng/dL	1.22 ng/dL	1.29 ng/dL	1.27 ng/dL	1.44 ng/dL	1.33 ng/dL	0.55 ng/dL
IGF-1 (90–262 ng/mL)	160 ng/mL	163.2 ng/mL	—	—	302 ng/mL	320 ng/mL	281 ng/mL	199 ng/mL

FSH: follicle-stimulating hormone; ACTH: adrenocorticotropic hormone; TSH: thyroid stimulating hormone; Free T4: free thyroxine; IGF-1: insulin-like growth factor-1.
Lab results over an 8-year follow-up after the pituitary adenoma resection. There is normalization of the prolactin level, resolution of the hypogonadotropic hypogonadism, and normalization of the ACTH over serial follow-up. Persistence of central hypothyroidism is noted on the most recent labs. IGF-1 level was normal postoperatively, showed a transient rise around the time that the prolactin level normalized in April 2018, and then returned to baseline by September 2022. "—" Indicates that the data are unavailable.

range: 0.34–5.60 µIU/mL) with low free T4 of 0.54 ng/dL (reference range: 0.58–1.64 ng/dL), consistent with central hypothyroidism. His follicle-stimulating hormone was inappropriately normal at 5.06 mIU/mL (reference range: 1.27–19.26 mIU/mL) with a low LH of 0.74 mIU/mL (reference range: 1.24–8.62 mIU/mL) and low total testosterone of 28.9 (reference range: 260.0–1000.0 ng/dL). A random cortisol level was low at 0.6 µg/dL, but this was after the patient had received dexamethasone 8 mg IV. The insulin-like growth factor-1 level was in the normal range at 160 ng/mL (reference range: 155–432 ng/mL). He was diagnosed with prolactinoma and presumed panhypopituitarism. He was started on treatment with cabergoline 0.25 mg twice a week, hydrocortisone 20 mg twice a day, and levothyroxine 200 mcg daily. Magnetic resonance imaging (MRI) of the brain showed a 5.3 cm sellar mass with an upward deviation of the optic chiasm and effacement of the ventricles without obvious hydrocephalus (Figure 1). There was a fluid-fluid level consistent with hemorrhage (Figure 2). Humphrey Visual Field test by ophthalmology showed bitemporal hemianopsia with left inferior nasal quadrantanopia. He was evaluated by neurosurgery, which cleared the patient for discharge with plans for surgical resection on an urgent basis.

One week later, the patient underwent right frontal supraorbital craniotomy for drainage of the suprasellar hemorrhage and decompression of the optic chiasm. He was given hydrocortisone 100 mg IV (Intravenous) prior to the surgery and the postoperative day 1 AM cortisol was 2.1 mcg/mL (reference range: 5–23 mcg/mL). Pathology revealed a

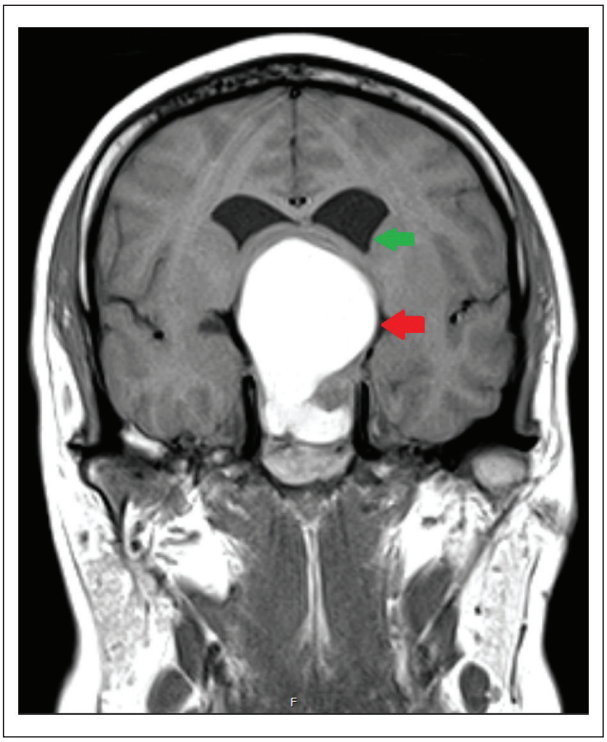

Figure 1. Preoperative MRI pituitary showed a large precontrast T1 hyperintense sellar-suprasellar cystic and solid mass lesion causing mass effect (red arrow) and upward deviation of the optic chiasm. There is effacement of the lateral ventricles without obvious hydrocephalus (green arrow).
MRI: magnetic resonance imaging.

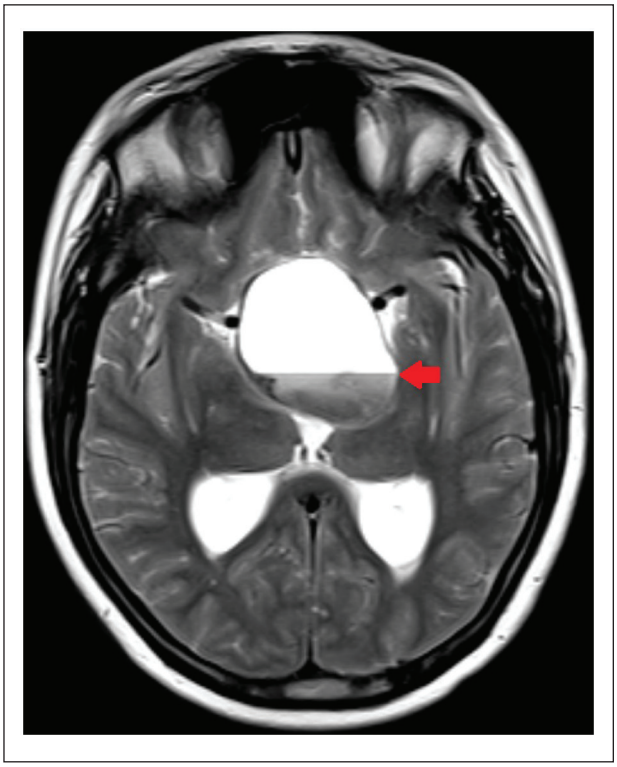

Figure 2. The cystic component of the sellar-suprasellar mass demonstrated a fluid-fluid level (red arrow) with a homogenously hyperintense material on T2, layering over a less intense dependent fluid component.

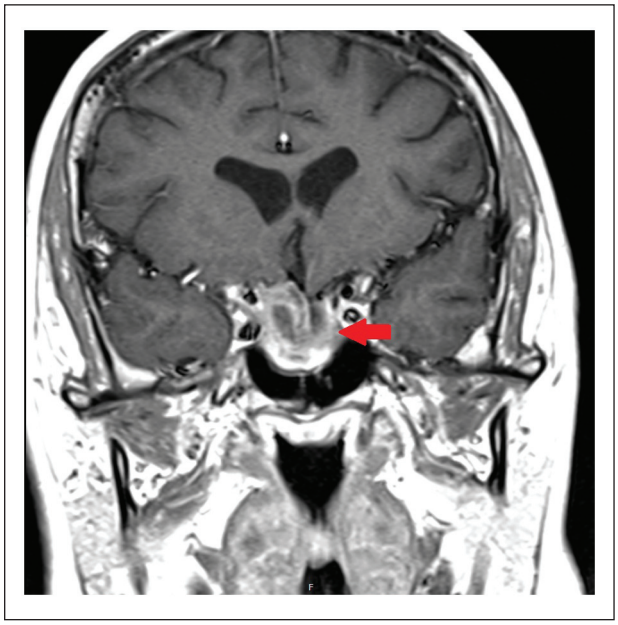

Figure 3. Residual mass lesion within the sellar and suprasellar region (red arrow). The center of the lesion is cystic, and the periphery shows nodular enhancement. The optic chiasm is elevated, and the mass lesion reaches up to the floor of the third ventricle.

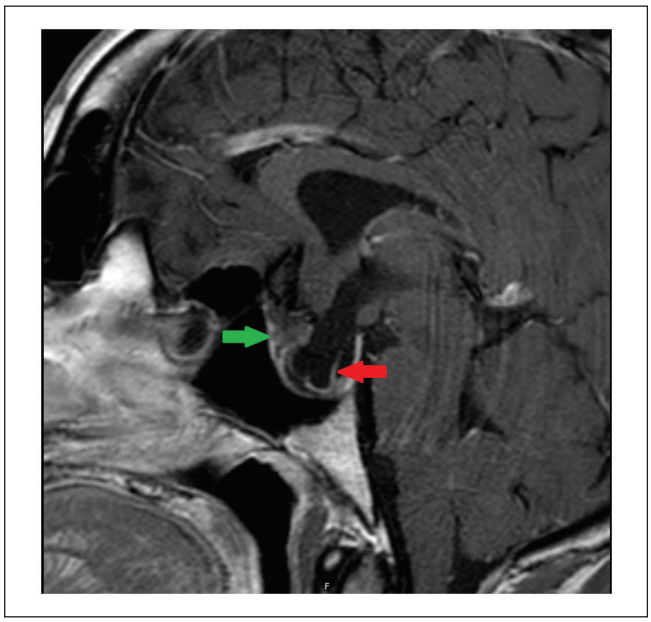

Figure 4. The sella is expanded and there is herniation of the floor of the third ventricle into the floor of the sella (red arrow). A 1 cm soft tissue is noted along the right anterior superior sella which represents the residual pituitary tissue (green arrow).

pituitary adenoma that was diffusely positive for prolactin and had an extensive hemorrhage. Scant mitotic figures were present. The gross specimen consisted of multiple fragments that measured $3.5 \times 3.0 \times 0.8$ cm in aggregate. The cabergoline, levothyroxine, and hydrocortisone were continued at their previous doses on discharge.

On his first clinic follow-up after 3 months, he was noted to have an improvement in the prolactin level to 946.60 ng/mL, and cabergoline was continued. His hydrocortisone was reduced to 15 mg in the morning and 10 mg in the afternoon to provide more physiological dosing. His levothyroxine dose was left unchanged at 200 mcg per day given that his free T4 level was 1.22 ng/dL. His total testosterone was low at 31 ng/dL. Testosterone replacement therapy was not initiated due to the anticipated improvement in testosterone levels with the control of hyperprolactinemia. The initial postoperative MRI showed a residual mass lesion within the sellar and suprasellar region that measured 2.4×1.8 cm in size and caused elevation of the optic chiasm (Figure 3). There was a significant decrease in the hemorrhage and the bilateral cavernous sinuses did not show the presence of any mass lesion. The patient did not tolerate dose escalation of the cabergoline beyond 0.5 mg two times a week due to which he was maintained on cabergoline 0.5 mg two times a week over the long-term. Annual pituitary MRIs were obtained over the next 6 years which showed resolution of the pituitary hemorrhage and stable expansion of the sella. On the MRI obtained 2.5 years post-surgery, no residual tumor was seen. The residual pituitary tissue measured 1 cm in size and was located along the right anterior superior sella (Figure 4). Annual visual field tests were obtained which

showed resolution of the left inferior nasal quadrantanopsia but he had persistent bitemporal hemianopsia.

His prolactin level normalized 3.5 years after the pituitary surgery but his testosterone level remained low at 86.6 ng/mL (Table 1). He was offered testosterone replacement therapy but refused due to the cost of the medication. His testosterone level displayed progressive improvement and he had normalization of the testosterone level 16 months after he was first noted to have a normal prolactin level. The adrenocorticotrophic hormone (ACTH) level was low at 3.7 pg/mL with concurrent cortisol of 3.4 mcg/mL which was indicative of ongoing secondary adrenal insufficiency. He displayed an increase in facial and body hair, regression of the gynecomastia, and had gained 1 inch in height. He did not consent to a repeat genital examination due to which Tanner's stage could not be reassessed.

The patient was then lost to follow-up for 2 years. He then returned to the endocrinology clinic and was noted to have discontinued his prescription medications without any apparent symptoms or signs of adrenal insufficiency. The reason for discontinuation of medications was a lack of insurance and financial difficulties. Labs showed normal prolactin level, normal testosterone, normal ACTH, and an appropriate rise of cortisol to 18 mcg/dL following a cosyntropin stimulation test (a normal response is peak cortisol of 18 mcg/dL or higher).[4] Central hypothyroidism persisted due to which levothyroxine 75 mcg daily was restarted. MRI pituitary did not reveal a recurrence of the pituitary adenoma. Cabergoline was not resumed but he continued to maintain normal prolactin and testosterone levels on serial observation.

Discussion

Our case highlights that pituitary hormone deficits that develop in patients with prolactinoma can resolve over long-term follow-up. Our patient's prolactin level normalized 3.5 years after starting cabergoline therapy followed by a resolution of hypogonadotropic hypogonadism after an additional 16 months. He was noted to have a resolution of secondary adrenal insufficiency 8 years after his pituitary surgery as evidenced by a normal ACTH level and normal cosyntropin stimulation test. Although his central hypothyroidism persisted, he displayed a reduction in his levothyroxine dose requirement from 200 mcg daily at the initial visit to 75 mcg daily at the last appointment.

Giant prolactinomas are defined as pituitary tumors more than 4 cm in diameter with significant suprasellar extension and prolactin elevation above 1000 mcg/L with no co-secretion of growth hormone or ACTH.[4] These are rare tumors, accounting for 2–3% of all prolactinomas, and display a male predominance.[5,6] Cabergoline is the first-line treatment option in these tumors and can lead to the normalization of prolactin in 60% of patients. Tumor response, defined as a >30% decrease in tumor diameter or >65% reduction in tumor volume, was seen in 74% of patients.[5] This means that a decrease in the tumor size can occur even in patients whose prolactin level does not normalize with treatment. Our patient underwent decompression of the tumor to preserve his vision. Residual pituitary tumor was left behind after surgery which responded to treatment with cabergoline.

The hormone deficiencies that result from prolactinomas include hypogonadotropic hypogonadism, central hypothyroidism, secondary adrenal insufficiency, and growth hormone deficiency. The presence of three or more pituitary hormone deficits constitutes panhypopituitarism. Pituitary hormone deficits are noted at diagnosis in around 74% of patients with giant prolactinomas.[7] The most common hormone deficit is hypogonadotropic hypogonadism, which can occur by two mechanisms. The first mechanism is the inhibitory effect of prolactin on the pulsatile secretion of follicle-stimulating hormone and luteinizing hormone, in which case the correction of hyperprolactinemia leads to the resolution of the hypogonadism.[8] The second mechanism is the destruction of gonadotroph cells by pressure atrophy from the tumor, in which case the hypogonadism is permanent. Resolution of hypogonadotropic hypogonadism following treatment with cabergoline occurred in 58–67% of men with giant prolactinomas.[7,9] Studies rarely reported the resolution of the other pituitary hormone deficits. This is in contrast to our patient who also had a resolution of secondary adrenal insufficiency.

There is no consensus on the timing of instituting testosterone therapy in patients with prolactinoma who have hypogonadotropic hypogonadism. Italian Association of Clinical Endocrinologists and the International Chapter of Clinical Endocrinology released a position statement that recommends the institution of testosterone therapy within 3–6 months of starting dopamine agonists for the treatment of hypogonadism in men with prolactinoma as long as the prolactin level is decreasing with treatment.[10] Testosterone replacement-induced hyperprolactinemia and tumor growth have been reported. The hypothesis is that the exogenous testosterone is aromatized to estradiol which stimulated the release of prolactin by the anterior pituitary.[11] This hypothesis is supported by the fact that there are case reports that show that treatment with aromatase inhibitors leads to a decrease in the prolactin level and a decrease in the tumor size.[12]

Our patient had radiological evidence of pituitary hemorrhage at the time of the initial presentation. Patients with pituitary hemorrhage may be asymptomatic, report chronic headaches or present with classical features of PA. Pituitary hormone deficits are common in PA and can occur from the destruction of anterior pituitary endocrine cells or the impaired release of pituitary hormones due to the increased intrasellar pressure exerted by the tumor. Secondary adrenal insufficiency is the most common hormone deficit in PA with an incidence of 50–80%, followed by gonadotropin deficiency at 40–75%, and thyrotropin deficiency at 30–70%.[13] One retrospective study that followed patients with PA for a mean duration of 3.7 years revealed that 79% of

patients required long-term glucocorticoid replacement compared to 50% at presentation.[14] Long-term levothyroxine requirement was 67% compared to 50% at presentation. There were no statistically significant differences in the rates of adrenal insufficiency, hypothyroidism, or hypogonadism among the patients who underwent surgery or conservative management of PA.

Our case report has some limitations. The secondary adrenal insufficiency was not confirmed at the initial diagnosis due to the recent administration of dexamethasone. However, the finding of suppressed ACTH on follow-up while the patient was taking a physiological dose of hydrocortisone supported this diagnosis. The patient continues to have central hypothyroidism, so complete recovery of pituitary function has not yet occurred. Delaying testosterone replacement may not be appropriate in patients who are severely symptomatic from hypogonadism. In addition, these findings may not be generalizable to patients who have undergone more extensive pituitary surgery and do not have residual healthy pituitary tissue left behind. Prospective studies looking into the long-term follow-up of patients with prolactinoma are necessary to assess the odds of recovery of pituitary function.

Conclusion

This case highlights the importance of periodic monitoring of pituitary labs to assess for the recovery of pituitary function in patients with panhypopituitarism as a result of hemorrhage into a prolactinoma. Correction of the hyperprolactinemia can lead to the completion of puberty and normalization of the testosterone level in patients who present with stalled puberty in the setting of a prolactinoma.

Author contributions

L.P.M. drafted the first version of the article and was part of the team that took care of the patient. D.E. participated in drafting the article and editing the final version.

Declaration of conflicting interests

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Consent

Written consent was obtained from the patient for the publication of this case report.

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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