Combined surgical and medical treatment of giant prolactinoma: case report

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Abstract: The operative management of giant pituitary prolactinoma represents a significant challenge for neurosurgeons, due to the degree of local tumor infiltration into adjacent structures such as cavernous sinus. The degree of parasellar tumor extension can be classified according to the Knosp grading system' while suprasellar extension is qualified in accordance with the modified Hardys classification system. This report describes the case of a male patient with a giant pituitary prolactinoma in which a partial tumor resection via a subfrontal approach was achieved. Typically, resection rates of less than 50% have been reported following surgery on giant pituitary adenomas. Prolactin levels were very high, consistent with invasive giant prolactinoma. Our patient was treated with Cabergoline which eventually normalized the prolactin level and significantly reduced the size of the residual tumor. This case serves to illustrate that in the presence of significant suprasellar and parasellar extension, multi-modal treatment strategies with surgery and dopamine agonist, is the gold standard in the management of locally aggressive pituitary prolactinomas.

Introduction

Pituitary adenomas are considered to be benign tumors and account for about 15% of primary intracranial tumors (14). Tumors exceeding 10 mm are defined as macroadenomas, and those smaller than 10 mm are termed microadenomas (14). While microadenomas are located within the sella and do not cause visual loss, macroadenomas extend beyond the limits of the sella and may cause neuro-ophthalmologic manifestations by compression of adjoining structures (3). Giant pituitary adenomas, defined as tumors 4 cm or greater in maximum diameter, account for 5%-14% of adenomas in surgical series (12, 18, 20).

Prolactinomas account for approximately 30% of pituitary adenomas and 50 to 60% of functional pituitary tumors (25). They are the most common type of functioning pituitary tumor and are second in frequency to nonfunctioning adenomas in overall incidence. Men tend to present with a larger, more invasive and rapid growth prolactinomas than women, possibly because hypogonadism features are less evident (6).

The degree of radical resection of giant adenomas is restricted to less than 50% in every published surgical study and is associated with a higher complication rate compared with non-giant pituitary adenomas (12, 18, 20). The most common surgical approaches used for the treatment of giant pituitary prolactinomas are the microscopic transsphenoidal or various frontal and frontotemporal transcranial routes (12, 17, 18, 20). Additional therapies are usually necessary to obtain long-term control of tumor growth (18, 20). Current recommendations suggest Dopamine agonists as the treatment of choice for prolactinomas, including giant and invasive types as these drugs suppresses prolactin (PRL) secretion and synthesis as well as lactotrope cell proliferation (24).

We presented the case of a giant pituitary prolactinoma, which infiltrate the dura and cavernous sinus. We performed a subtotal resection through a subfrontal approach followed by dopamine agonist treatment. This combined treatment was very effective in normalizing serum PRL levels and shrinking the tumor size.

Case presentation

We presented the case of a 61 years old male patient, admitted in our clinic with a one year history of a reduction in his peripheral visual field. This was associated with a shorter history of gradual loss of movements and poor vision in the right eye, frontal headache and unsteady gait. Prior to his admission he consulted an ophthalmologist with complaint of double vision. Ophthalmological examination revealed important loss of visual acuity, especially in the right eye, a bilateral superior temporal quadrantanopsia and medial convergent squint due to the right sixth cranial nerve palsy. As his psychic was concerned, the patient was alert and oriented.

A subsequent cerebral magnetic resonance imaging (MRI) scan showed a giant (28/43mm.) enhancing tumor expanding in the pituitary fossa and extending into the suprasellar cistern (Figure 1). The tumor, which demonstrated a relative homogenous enhancement, encased the right optic nerve and showed a lobular extension into the right sylvian fissure, invasion of the right cavernous sinus enclosing the cavernous carotid artery. The tumor elevated the floor of the third ventricle, extended to the perimesencephalic cisterns and contacted the right pons. The anterior vascular arcade (both A1 segments of the anterior cerebral arteries and anterior communicating artery) were displaced posteriorly.

The degree of parasellar tumor extension was classified according to the Knosp grading system (grade 4), while suprasellar extension

was qualified in accordance to the Hardys classification system (grade C).

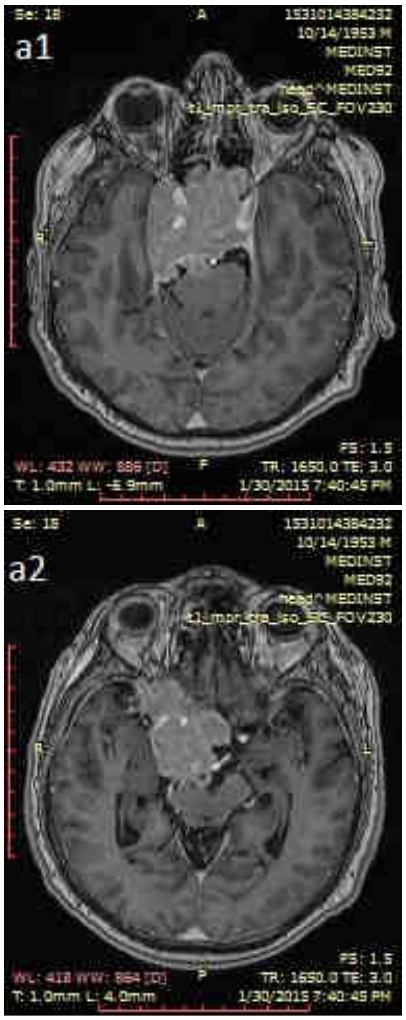
Because of the irregular shape of the tumor and its extension into the subfrontal region, retrochiasmatic area and sylvian fissure we chose to perform a transcranial approach for this case. The patient underwent a subtotal tumor resection via a right subfrontal approach, achieving an approximately 30% reduction in tumor bulk, with focus on right optic nerve decompression.

Postoperatively, the patient's bilateral superior quadrantanopsia improved and his headache resolved, but he developed diabetes insipidus. There were no other operative complications. The histopathological exam revealed a pituitary prolactinoma.

Preoperatively, laboratory studies revealed prolactin 4700 ng/ml (4.60-21.40), cortisol 1.64 μg/dl (6.2-19.4), testosterone 0.025 ng/ml (1.93-7.40), TSH 0.097uUI/ml (0.27-4.20), low free thyroxine (fT4) 0.617 μg/dl (0.93-1.7). After surgery, beside the substitutional hormonal therapy, the patient started medical treatment with Cabergoline (Dostinex), a dopamine agonist, 0.25 mg twice per week, with gradual increase in the dose to 1 mg twice a week. After 3 weeks of endocrine treatment, laboratory studies revealed an important decrease in prolactin level to value of 343.50 ng/ml.

After his discharge from hospital, the patient continued his treatment with Cabergoline, which eventually normalized the prolactine level and significantly reduce the size of the tumor rest.

MRI images, obtained 5 months after surgery, showed important reduction of the tumor's size. The right pons, the right temporal lobe and the floor of the third ventricle were completely decompressed (Figure 2). There is still residual tumor in the right cavernous sinus. The visual symptoms were improved and the follow-up MRI, 10 months after surgery, demonstrated that residual tumor has continued to collapse and minimize, under dopamine agonist therapy (Figure 3).



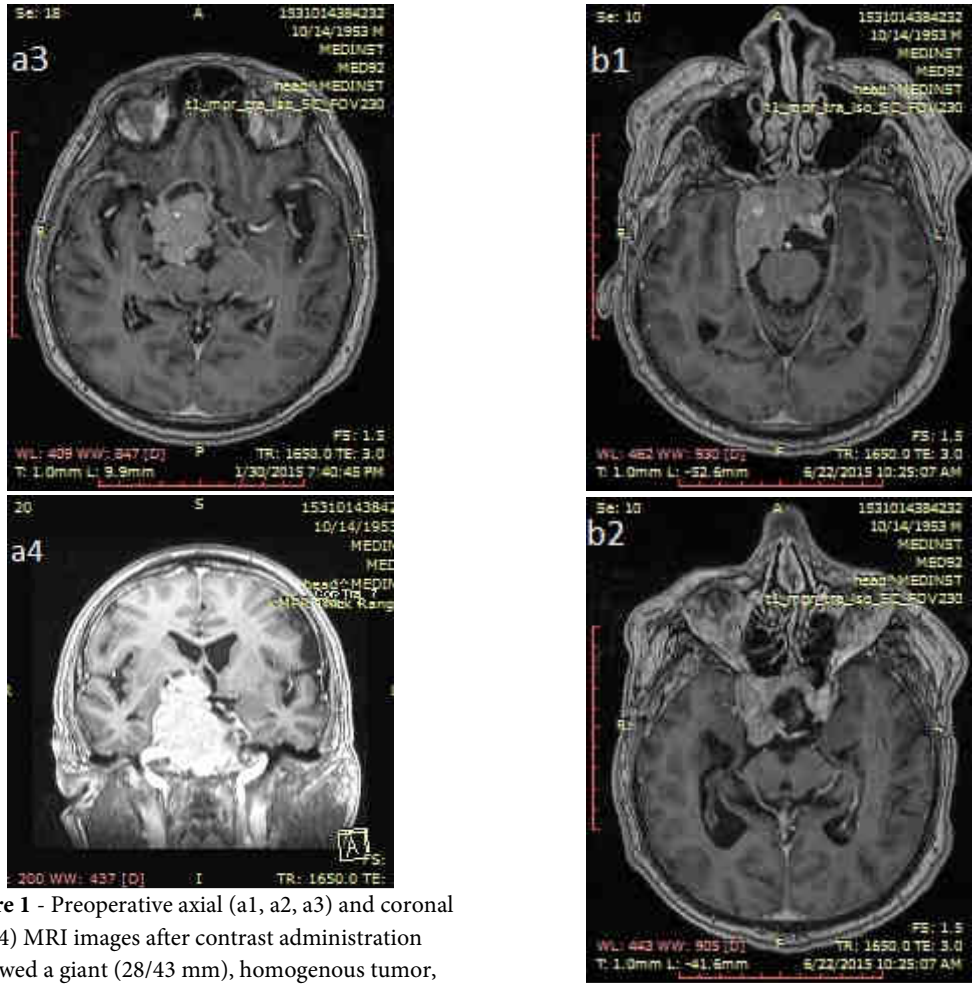


Figure 1 - Preoperative axial (a1, a2, a3) and coronal (a4) MRI images after contrast administration showed a giant (28/43 mm), homogenous tumor, which invaded the right cavernous sinus, extended over the upper clivus and in the temporal lobe, and elevated the floor of the third ventricle

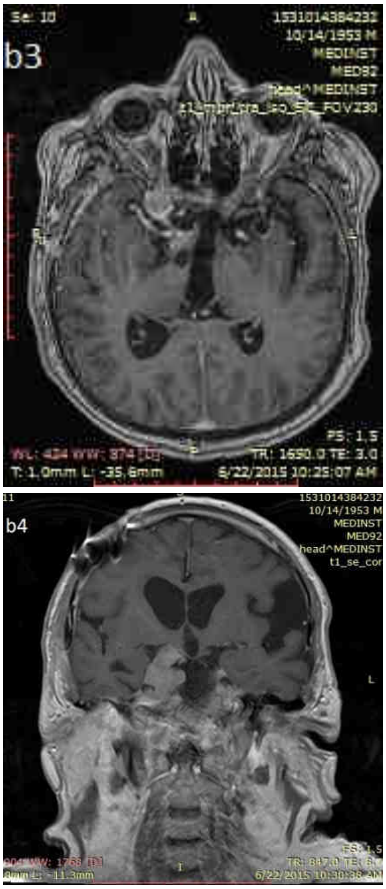


Figure 2 - Images obtained 5 months after surgery and cabergoline treatment. Axial (b1, b2, b3) and coronal (b4) MRI images showed important reduction of the tumor's size. The right pons, the right temporal lobe and the floor of the third ventricle were completely decompressed

Discussion

Giant macroadenomas are defined as lesions greater than 4cm in diameter and represent till 14-15% of all pituitary adenomas (20). Since the original description of this pathological entity by Jefferson in the 1940s, surgical treatment of giant pituitary adenomas has been extremely challenging (13). Postoperative mortality rates as high as 35% has been reported (13, 19). Giant pituitary adenomas can be extremely challenging to manage using surgery alone. In case of giant prolactinoma, the use of medical therapy and, possibly, radiation therapy, is crucial for achieving long-term tumor control.

The main goals of surgery for giant pituitary adenomas are visual improvement, recovery from endocrinological and neurological symptoms, and maximal tumor resection (25). Surgery, either transcranial or transsphenoidal approaches, is the first-line treatment in tumors with compression upon optic structures and visual impairment. The complexity of surgery for giant pituitary adenomas relate to the degree and direction of perisellar spread, because they tend to extend in either a suprasellar or parasellar trajectory (19). The degree of suprasellar tumor extension can be classified according to the modified Hardys classification system, while parasellar extension is qualified in accordance with the Knosp grading system (23). The completeness of microsurgical resection is inversely related to both the Hardys and Knosp grade of the tumor. In fact, true cavernous sinus invasion typically prohibits complete tumor resection (10, 18). It is generally accepted that the goal of surgical treatment for giant pituitary adenomas must be maximal tumor resection with minimal associated morbidity (9).

Total resection rate of giant pituitary adenoma vary between different series and the surgical approach used. On a large series, Mortini et al (18) showed that total resection rate was 14.7%., while Goel et al. (12) showed

a total resection rate of 29.65%. Koutourousiou (15) presented a near-total resection rate of 66.7%. The rate of gross and near-total tumor removal, in cases of giant pituitary adenomas, after transsphenoidal, transcranial or combined procedures range from 14.7% to 74% (12, 15, 18). With recent advances in the expended endoscopic endonasal approach and the associated benefits of improve panoramic visualization afforded, these resection rates will improve. The limitation of endoscopic endonasal approach is invasion of the lateral wall of the cavernous sinus and extension of the tumor to the temporal lobe. But, despite all this, as in our case, an open craniotomy may still be indicated in patients with dumbbell tumors extending far into the anterior cranial fossa, middle fossa or retro-chiasmatic space (13). Safe complete resection of a giant pituitary adenoma lateral to the carotid artery remains nearly impossible with no regards to the surgical corridor used (8, 21). Gross-total resection of giant pituitary adenomas was dependent on multiple factors, and the overall low resection rates confirm the difficulty in their management.

In our opinion, even in case of giant pituitary prolactinoma, surgery could improve vision and its improvement is related with tumor resection rate. Additionally, surgery could significantly improve the symptoms of headache and dizziness. However, surgery may not be effective for declined sexual function and amenorrhea (26). It is also believed that visual acuity improvement is significant during the first two postoperative weeks, with no further significant improvement after this period, while visual field defects significantly improve during the first two weeks postoperatively and continue to improve for the first three months but no later than that (21). Maximum visual improvement after pituitary surgery is at three months postoperatively (4). Although postoperative visual improvement varies among published series, it is more likely after transsphenoidal than transcranial surgery, with rates of approximately 80% (5, 15, 18). Postoperative improvement of hypopituitarism after surgery for giant pituitary adenomas has not been studied in detail. The reported hormonal improvement rates of 35%-50% after transsphenoidal surgery are in reference to macroadenomas and cannot be applied to giant pituitary adenomas, in which hypopituitarism is usually long-standing and more difficult to be corrected after surgery (11).

Postoperative MRI performed at different time points after surgery may affect the accuracy of tumor volume calculation. For example, MRI performed within the first postoperative week may measure the volume of the hematoma while MRI performed after 2 months or later may measure the adenoma recurrence.

In general, giant pituitary adenomas have a higher surgical complication rate, highlighting the difficulty of their treatment. In cases of transsphenoidal or endoscopic endonasal approaches the most common complication was postoperative cerebrospinal fluid (CSF) leak (16.7%), necessitating reoperation and/or lumbar drain placement (15). Worsening of pituitary function occurred

in 16.7% of patient after endoscopic endonasal surgery, which is comparable to new endocrinopathy after microscopic transsphenoidal surgery and lower than new pituitary dysfunction after transcranial surgery (5, 18, 20). Diabetes insipidus is also another complication after surgery for giant adenomas. Permanent postoperative diabetes insipidus vary between 8.2% and 10.4% (20). Postoperative visual deterioration is also more common after transcranial than transsphenoidal surgery and can be as high as 22% (9, 18). Postoperative cranial nerve dysfunction is a frequent complication after transcranial surgery for giant tumors involving the cavernous sinus, and it affects the oculomotor nerve most often (7). Other complication such as syndrome of inappropriate antidiuretic hormone, hydrocephalus, pulmonary embolus, or cerebral ischemia may occur after transcranial or transsphenoidal surgery (microscopic or endoscopic) and are not correlated directly with the surgical approach. Mortality rates after surgery are higher in giant pituitary adenomas compared with non-giant adenomas and range from 3.2% to 18.7% (16, 18). One of the leading causes of postoperative death is apoplexy of the residual adenoma.

Remarkable progress has been made with regards to the management of giant prolactionoma. Sometimes, total resection can be achieved with a combined endonasal/transcranial approach or possibly with a staged endoscopic endonasal approach (2). The ultimate goal of a combined treatment (surgery, radiotherapy, endocrine medications) is to achieve eugonadism, euprolactinemia status, and reduction of tumor size (24). While radiotherapy is not the usual preferred treatment because of high complication rates, therapy with dopamine agonists (Bromocriptine, Cabergoline) are consistently promising in regression size of the pituitary prolactinoma, hypogonadal status reversal and prolactin level correction (6,27). Once normalized, serum PRL levels should be monitored annually (1). Bromocriptine is started at 1.25 to 2.5 mg orally once a day and increased during 2 to 3 weeks to 5 to 10 mg daily in divided doses. Cabergoline may be administered at doses ranging between 0.5 and 1.5 mg once or twice per week (1). After normalization of serum PRL levels, bromocriptine can be reduced to the smallest effective dose. Visual examination should be repeated approximately 1 month after initiation of therapy, and MRI should be repeated at 6 weeks and again at 3 months after initiation of treatment (24, 27). Some 10 to 25% of patients are partially or totally resistant to bromocriptine (22) and 5% to 10% of patients are intolerant to bromocriptine because of side effects (3, 22). In patients with giant or invasive prolactinomas, pretreatment with a dopamine agonist may improve the success of subsequent surgery. Long-term treatment with dopamine agonists may alter the consistency of the tumor and make surgery more difficult (22).

Stereotactic radiosurgery is an option for patients with prolactinomas after failed transsphenoidal surgery or failed medical therapy and may be a primary treatment for prolactinomas in patients who are reluctant to undergo long-term medical therapy or surgery

(22). This is not the case for a giant prolactinoma, in which stereotactic radiosurgery is only a postsurgical therapy. There is a risk of hypopituitarism, and there may be a radioprotective effect of dopamine agonist therapy; therefore, these medications should be stopped temporarily during radiosurgical treatment (12, 22, 24).

Conclusions

Prolactinoma is one of the pituitary tumors that significantly respond well to medical therapy. The main goal of surgical treatment of giant pituitary prolactinoma, through transsphenoidal or transcranial approach, is maximum possible tumor extirpation with minimal side effects. In our case, we used the transcranial approach, due to the dimension and extension of the tumor (temporal lobe and cavernous sinus) and the preference and experience of the operating team. Our patient improved significantly after medical treatment, avoiding unnecessary reoperation, and preventing short and long term complications. Multidisciplinary treatments should be applied during long-term follow-up periods for successful care and optimal outcomes.

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