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Case Report

Combined treatment of invasive giant prolactinoma with surgical excision, low-dose gamma knife radiosurgery, and a dopamine agonist—Report of two cases

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ABSTRACT

Although most prolactinomas are benign, some are invasive or aggressive. The management of invasive giant prolactinomas (IGPs) has been an area of controversy. The present study reports the combined treatment of IGP with surgical excision, low-dose gamma knife radiosurgery (GKRS), and a dopamine agonist. An enhancing mass at the pituitary fossa with suprasellar extension and invasion of the cavernous sinus was identified in two patients. The blood prolactin level was more than 1000 ng/mL in both patients before treatment. Trans-sphenoidal removal of the tumors was done to reduce tumor compression on the optic apparatus. Low-dose GKRS was then used to treat the residual tumor with invasion to the caversinous sinus. The marginal dose was set at 12 and 14 Gy at the 50% and 42% isodose lines, respectively. A dopamine agonist, cabergoline, was used after GKRS. The tumors were markedly reduced and hard to be seen in magnetic resonance images. After a follow-up period of more than 3 years, the blood prolactin level returned to normal in one patient without the use of the dopamine agonist and was nearly normal in the other patient with continuing use of the dopamine agonist. Treatment combining surgical excision, GKRS, and a dopamine agonist may be a good treatment for IGPs. To make sure the remission of the disease, the longer follow-up is needed.

1. Introduction

A prolactin-secreting pituitary adenoma, the most common type of hyperfunctioning pituitary adenoma, accounts for approximately 50–60% of all functional pituitary tumors [1]. Significant advances in the last few decades have contributed to the effective management of prolactinomas, including pharmacological therapies, microsurgical and endoscopic techniques, and stereotactic radiosurgery. Giant prolactinomas with cavernous sinus invasion are a subcategory of prolactinomas. The giant tumor associated with characteristics of hyperprolactinemia and invasive growth remains one of the greatest challenges in neurosurgery. Although they are generally benign, marcroadenomas are locally aggressive. Tumors can invade the surrounding structures such as the cavernous sinus, sphenoid sinus, and suprasellar optic apparatus. Dopamine agonists were reported to be able to reduce the tumor size and to normalize prolactin levels [2–9]. However, some prolactinomas are refractory medically, and a mass effect may compromise the optic apparatus, resulting in visual impairment [6,8]. Therefore, combination therapy with surgical excision to decompress the mass effect followed by focalized radiosurgery and a low-dose dopamine agonist may be ideal to control a giant prolactinoma. We report successful results in two patients with this combined treatment.

2. Case reports

2.1. Case 1

A 26-year-old man presented with a 3-month history of headache and dizziness with blurred vision for 1 month. He underwent

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brain magnetic resonance imaging, which revealed a homogenously enhancing mass at the pituitary fossa with suprasellar extension and compression of the optic chiasm (vertical diameter 4.0 cm, lateral diameter 3.2 cm, and anterioposterior diameter 2.4 cm). The tumor invaded the sphenoid sinus and the bilateral cavernous sinus with encasement of the internal carotid arteries. Trans-sphenoidal decompression surgery with partial removal of the tumor was done. The pathology showed a benign prolactinoma. The blood prolactin level was greater than 1000 ng/mL before and after this operation. The patient was referred for gamma knife radiosurgery (GKRS) 3 months after surgery. A combination of multiple 8-mm and 4-mm isocenters was used to deliver a dose to the tumor margin of 12 Gy and a maximal dose of 24 Gy. The treated tumor volume was 21.5 cm^3. To avoid the interfere of radiosurgical effect, a dopamine agonist was not used at least 2 weeks before GKRS. However, cabergoline (Dostinex) 0.5 mg once per week was given after GKRS. We checked the prolactin level every 3 months and the dostinex was used if prolactin level is higher than the normal range. Now, 66 months after radiosurgery, he has no new clinical symptoms and the prolactin level has decreased to 3.58 ng/mL without the use of the dopamine agonist. The tumor has almost disappeared (Fig. 1). The patient continues to undergo periodic imaging and hormone survey during follow-up.

2.2. Case 2

A 54-year-old woman was referred from another hospital for a residual pituitary adenoma after two trans-sphenoidal operations. She had a history of hyperprolactinemia for 20 years and had irregularly received the dopamine agonist with bromocriptin. She had presented with a 4-month history of dizziness and blurring of vision before the first trans-sphenoidal surgery. The prolactin levels were 13,500 ng/mL before and 24,000 ng/mL after the first trans-sphenoidal removal of tumor. After the second operation 11 months later, the prolactin level decreased to 7143 ng/mL. Other pituitary hormone levels were normal. Clinical examination revealed a right temporal hemianopsia. Magnetic resonance imaging showed residual tumor with a vertical diameter of 5.5 cm, lateral diameter 3.7 cm, and anterioposterior diameter 2.5 cm. The tumor invaded the right cavernous sinus with encasement of the internal carotid artery and extension of the suprasellar portion, which slightly compressed the optic chiasm (Fig. 2). In GKRS, a combination of four 14-mm, nineteen 8-mm, and twenty-six 4-mm isocenters were used to deliver a dose of 14 Gy to the tumor margin at the isodose line of 42% (Fig. 2). The maximal dose was 33 Gy, and the total treated volume was 28 cm^3. Because we consider the possibility of interfering effect by the dopamine agonist, the dopamine agonist was not used 1 month before GKRS and we started using cabergoline 0.5 mg twice a week 1 month after GKRS. The blood prolactin level decreased from more than 1000 ng/mL to 621 ng/mL. After a 3-year follow-up, it became normal. The tumor was markedly reduced and hard to be seen in the following magnetic resonance study (Fig. 3).

3. Discussion

The diagnostic criteria for invasive giant prolactinomas (IGPs) include (1) tumor diameter larger than 4 cm with invasion of the cavernous sinus corresponding to Grade III or IV [2,10,11], in the classification system of Knosp and associates; (2) serum prolactin level greater than 200 ng/mL; and (3) clinical neurological symptoms of hyperprolactinemia and mass effect. In our patients, the tumor size, aggressive invasion of the cavernous sinus, and high prolactin level fit the criteria for IGPs. However, this pattern is not the malignant form of a prolactinoma, the aggressive behavior seems to be an another entity of prolactinoma. Our second patient had a 20-year history of prolactinemia and microadenoma, which seems to indicate a tendency to progression. However, in the report of Ciccarelli et al, the risk of progression from a microadenoma to a macroadenoma was estimated to be only about 4–7% and most observations suggest that aggressive macroadenoma may represent a distinct entity [12–15]. At present, there

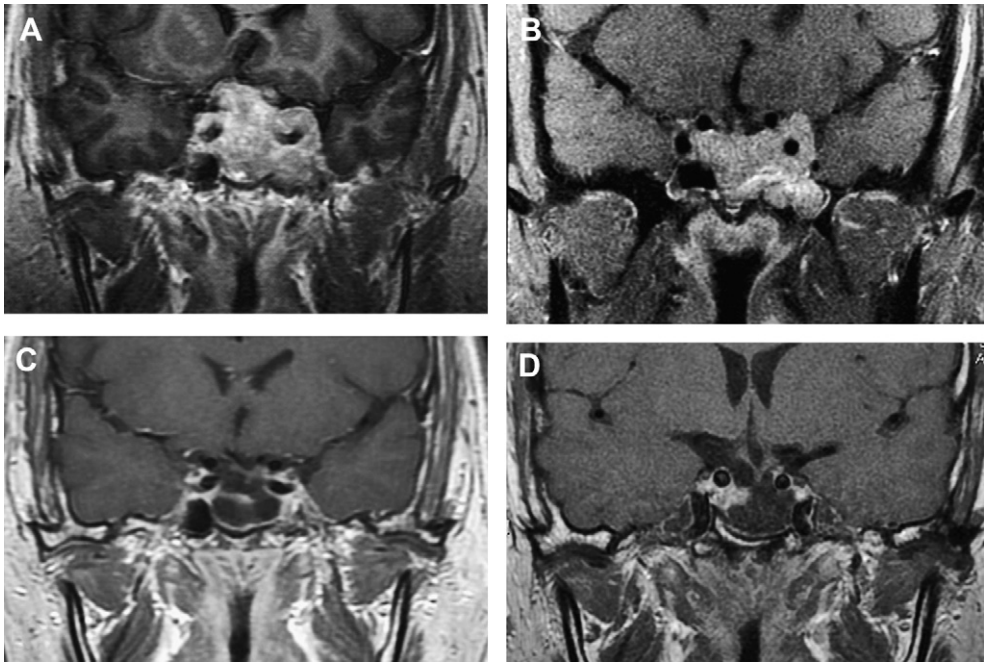

Fig. 1. Case 1. Coronal magnetic resonance images with contrast enhancement obtained in a 26-year-old man. (A) Post-operative, pre-gamma knife radiosurgery image demonstrating a giant sellar tumor with suprasellar extension and invasion of the cavernous sinus. (B–D) Post-gamma knife radiosurgery magnetic resonance images at 6 months (B), 32 months (C), and 51 months (D), demonstrating reduction and near eradication of the tumor.

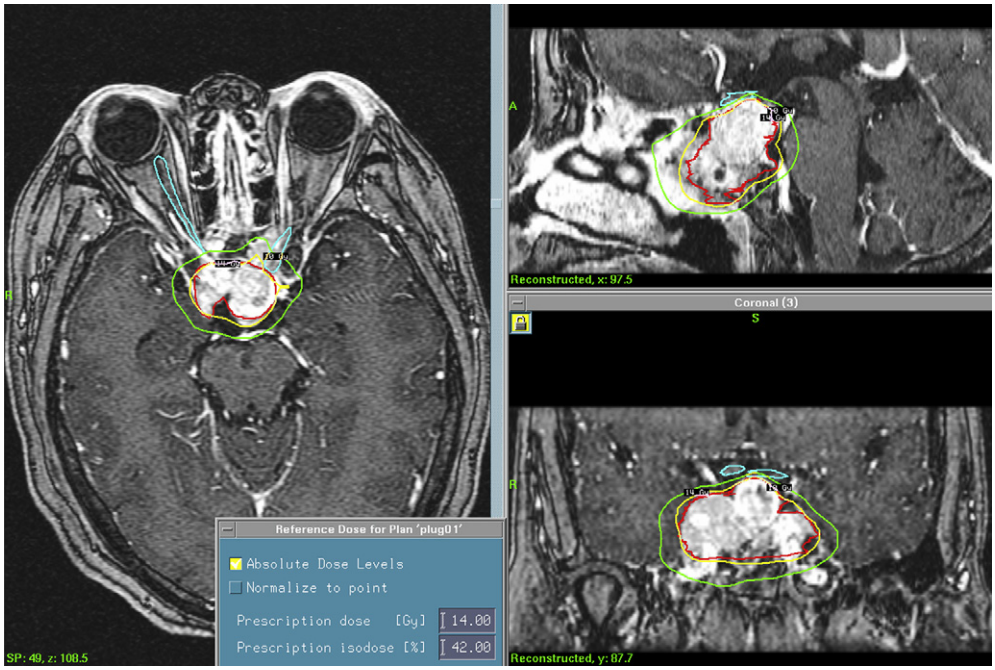

Fig. 2. Case 2. Axial contrast magnetic resonance images with coronal and sagittal reconstruction demonstrating a giant prolactinoma in a 54-year-old woman. The radiosurgical dose plan is also shown. Four 14-mm, nineteen 8-mm, and twenty-six 4-mm isocenters were used. The 42% isodose line with a 14 Gy margin dose was targeted to the tumor. The red line is the tumor margin, the yellow line is the 42% isodose line for 14 Gy and the green line is the isodose line for 10 Gy.

are no clear-cut criteria to predict the biological behavior of prolactinomas [16,17].

The treatment goals of IGPs are as follows: (1) eradication of the tumor, (2) preservation of normal pituitary function, (3) reduction of the prolactin level to normal, and (4) prevention of damage to the regional optic apparatus and hypothalamus. Administration of a dopamine agonist has shown efficacy and safety in therapy for this tumor and some reports even suggest it as the first line treatment for IGPs [2–9]. However, 10–20% of patients are refractory to medical therapies despite increasing doses. They cannot tolerate side effects such as nausea, headache, fatigue, orthostatic hypotension, and depression [6,8]. Although the total removal of the tumor is not possible after invasion of the cavernous sinus, surgical decompression with a trans-sphenoidal procedure is

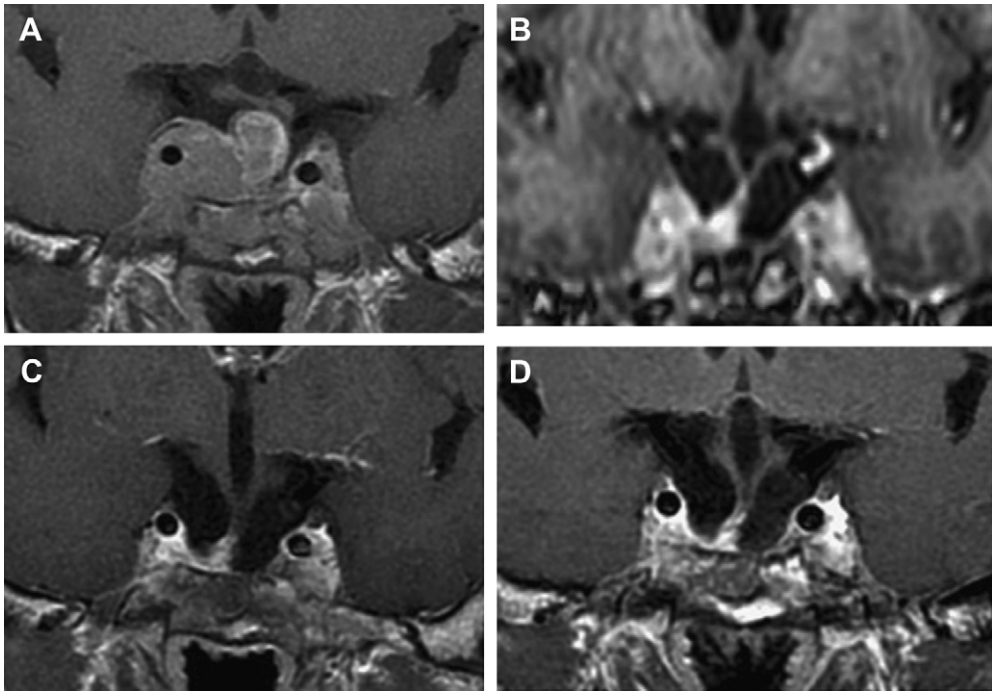

Fig. 3. Case 2. Coronal magnetic resonance images with contrast enhancement obtained in a 54-year-old woman. (A) Post-operative, pre-gamma knife radiosurgery image demonstrating a giant sellar tumor with suprasellar extension and bilateral invasion of the cavernous sinus. (B–D) Magnetic resonance imaging at 6 months (B), 22 months (C), and 30 months (D) after gamma knife radiosurgery, demonstrating reduction and near eradication of the tumor.

mandatory for normal visual function in the early stage of visual field impairment. To avoid the damage to the vision in radiosurgery, it is necessary to have a gap between tumor mass and the optic apparatus. This surgical decompression is used not only for restoration of visual function but also to avoid the possibility of damage to the optic apparatus from high marginal dose radiosurgery. In Pourantan et al's report, a distance of at least 5 mm between the tumor margin and the optic apparatus was considered for GKRS [18]. With such a large gap, a high margin dose, for example 25 Gy, can be used in some relatively small tumors. Because we used low margin doses (12–14 Gy) to treat IGPs in our study, the gap clearance could be set as low as 2 mm to limit the dose to the optic apparatus to 8 Gy. No further vision changes were identified in our two patients during follow-up.

In this report, we treated large giant prolactinomas (21.5 cm^3 and 28 cm^3) with low-dose radiosurgery and maintained a low but effective dose of a dopamine agonist to control the prolactin level. We did not use the dopamine agonist at the time of GKRS. We hypothesized that the higher activity of the prolactin-secreting tumor cells may have conferred sensitivity to radiosurgery. Landolt et al and Pouratian et al reported low remission rates in patients who were on a dopamine agonist at the time of GKRS [18,19]. A dopamine agonist not only reduces prolactin synthesis and secretion, but also reduces the metabolism and cell cycling of prolactinomas, which may render them less susceptible to radiation. In contrast, high prolactin levels in IGPs indicate that metabolism and cell cycling are high and these tumors may be more susceptible to a dopamine agonist or even radiation than small prolactinomas. However, with these treatments, it is difficult to ascertain the contribution of antisecretory medications to the observed volumetric tumor control. The continued antisecretory medication therapy for the duration of follow-up undoubtedly contributed in part to the long-term volumetric changes observed in these two cases. Furthermore, it is known that the effects of radiosurgery are delayed. Lim et al reported a series of 19 patients with prolactinomas [20]. They found that approximately 1.5 years was needed to achieve a significant decrease in tumor volume and volume reduction could continue beyond 2 years. This study supports the notion that a volumetric response in prolactinomas can continue for years after GKRS. This study shows that combined therapy, including low-dose GKRS and a dopamine agonist, should be considered to achieve volumetric tumor control.

There are reasons why we used low marginal doses (12–14 Gy) to treat IGPs. The tumors were large, 21.5 cm^3 in Case 1 and 28 cm^3 in Case 2. It is difficult to render a high margin dose in a tumor mass without involving the adjacent optic apparatus in the high dose. A radiosurgery dose less than 8 Gy to the optic nerves and chiasm is generally recommended, although some studies indicate that small sections of the optic nerve chiasm can tolerate doses of 10–12 Gy with a very low risk of optic injury [21–26]. We hypothesized that the higher activity of the prolactin-secreting tumor cells may have indicated higher sensitivity of the tumor to radiosurgery. Low-dose radiosurgery may be good enough to shrink these giant tumors.

In this report, a dopamine agonist was not used at the time of GKRS for not reducing the prolactin-secreting activity, but after GKRS it was re-started and found effective in the tumor shrinkage. IGPs are tumors invading the cavernous sinus. Although higher doses such as 25 Gy or more for the margin dose are suggested to reach a functional remission of hormone levels, radiation injury to the cranial nerves has been reported. Furthermore, higher doses might also lead to a greater risk of radiation-induced hypopituitarism [18]. In our cases, we used low-dose radiosurgery and a low-dose dopamine agonist to reach a volumetric reduction, and no cranial neuropathy was found. We conclude that a multidisciplinary approach that includes low-dose radiosurgery and a low-dose dopamine agonist may benefit patients when extirpation is not possible.

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