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Case Report

Decrease of Proliferative Potential and Vascular Density of Giant Prolactinoma in Patients Treated with Cabergoline

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Abstract

Introduction: Currently, cabergoline therapy is the main treatment for prolactinomas. The use of the drug in most cases leads to regression of the tumor, normalization of prolactin (PRL) levels, and restoration of gonadotropic function. The mechanism of its action in tumor cells "*in vivo*" tracked in dynamics in the same human tumor is of considerable interest. **Materials and Methods:** A 30-year-old male was admitted to N.N. Burdenko National Medical Research Center of Neurosurgery. An magnetic resonance imaging (MRI) revealed a giant pituitary adenoma. The level of PRL was more than 5000 mU/l (30-360) (serum dilution was not used to determine PRL). Transcranial microsurgical removal of the tumor was performed. He was treated by cabergoline after surgery. Endoscopic transsphenoidal approach was repeated with subtotal removal of the rest of the tumor. Morphological and immunohistochemical studies of the tumor were done. **Results:** A morphological study revealed PRL-positive tumor with a Ki-67 LI of 8% with a distinctive expression of D2R, CD31, and CD34 markers. Control MRI in 3 months after surgery revealed remnants of a tumor of endoinfrasellar localization, the tumor remainders were found in endoinfrasellar localization. The tumor retained pronounced immunopositivity to PRL and D2R and a decrease in the Ki-67 to 2% and in the expression of CD31 and CD34. Subsequent therapy with cabergoline resulted in persistent normoprolactinemia, restoration of androgenic function, and absence of tumor recurrence during the 10-year follow-up period. **Conclusions:** Cabergoline is an effective treatment for prolactinoma, which leads to tumor regression. One of its mechanisms is the reduction of the proliferative index and tumor angiogenesis.

Keywords: *Aggressive pituitary adenoma, cabergoline, giant prolactinoma, Ki-67, male prolactinoma, proliferative potential*

Introduction

Prolactinomas account for about 40% of all pituitary tumors.[1] Dominant among them is pituitary microadenomas, which are detected mainly in women. Macroprolactinomas are much less common and less studied.[2] This group of adenomas is heterogeneous in its composition and differs in the size of tumors, their growth rates, and clinical symptoms. Small tumors of endosellar localization can be characterized only by hyperprolactinemia and are more often detected in women, whereas giant prolactinomas are prone to rapid and infiltrative growth; often have a multinodular nature; and penetrate into the ventricles of the brain, cavernous sinuses, main sinus, and nasopharynx, causing neurological and optic neuropathy and described mainly in men. They are the most difficult group to treat, of all prolactin (PRL) secreting tumors.[3-5] Until the emergence of dopamine agonist, surgical treatment was the main treatment method used. The successes of modern pharmacology allowed an alternative solution to this problem. Currently, cabergoline therapy is the main method of treatment with prolactinoma, which leads to a reduction in the size of the tumor, normalization of PRL in most patients.[6-8] For the first time in literature, the reduction of pituitary tumors during treatment with dopamine agonists was described in the early seventies.[9] In subsequent numerous *in vitro* studies in laboratory animals as well as in humans, it was shown that the drug selectively activates dopamine 2 receptors, which is accompanied by a decrease in tumor size, as well as a decrease in the synthesis and secretion of

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PRL. It was shown that tumor regression can be caused by various mechanisms, including a decrease in cell size,[10-12] induction of apoptosis, and tumor necrosis,[13,14] as well as inhibition of cell proliferation.[15] However, studying the effects of cabergoline *in vivo* directly on the cellular structures of the same human pituitary tumor is of considerable interest.

Materials and Methods

A 30-year-old male was admitted to N. N. Burdenko National Medical Research Center of Neurosurgery in November 2004 with complaints of visual impairment and headaches. From the medical history, within 3 years, an increase in weight by 20 kg was noticed, an increase in blood pressure to 150/100 mmHg, decreased libido, impaired erectile function, and complaints of visual impairment.

A magnetic resonance imaging (MRI) revealed a giant tumor of endo-supra-latero-infrasellar localization, 6.7 cm in diameter [Figure 1a and b], visual impairment in the form of bitemporal hemianopsy, and reduction of visual acuity of the right eye (VIS OD = 0.4), VIS OS = 1.0, small right-sided exophthalmos in 1.5 mm (height OD = 18 mm, OS = 16.5 mm). The level of PRL was more than 5000 mU/l (30–360) (serum dilution was not used to determine PRL), testosterone – 2.3 (8–35) nmol/l, thyroid-stimulating hormone (TSH) – 1.3 (0.4–4.0) IU/l, free T4 – 12 (9-22) nmol/l, and cortisol – 398 (260–720) nmol/l.

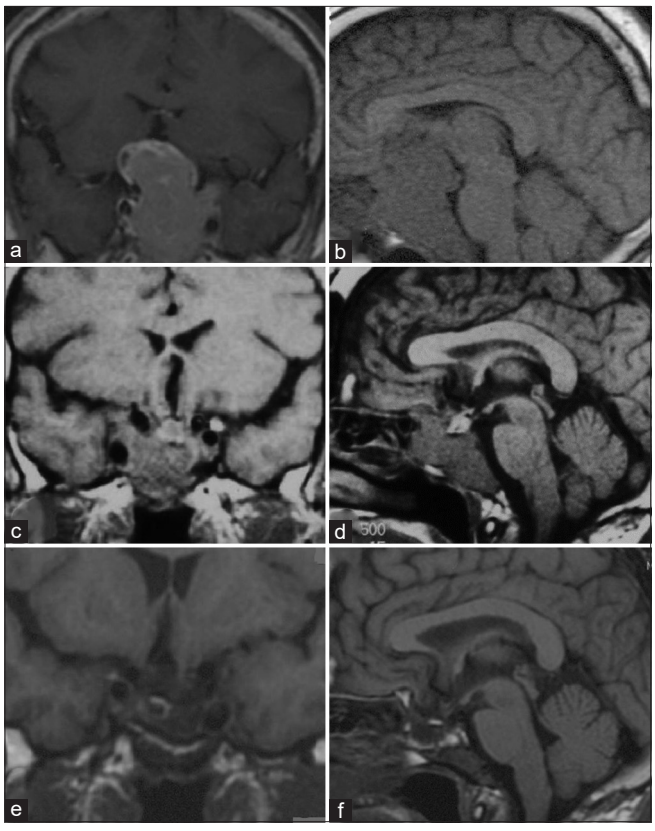

Figure 1: Magnetic resonance imaging of pituitary adenoma. (a and b) Before the first stage of surgical treatment (removal by transcranial approach). A giant pituitary adenoma of endo-supra-latero-infrasellar localization is visualized. (c and d) 3 months after tumor removal via transcranial approach and cabergoline treatment before the second stage of surgical treatment (removal with transsphenoidal approach). The remainder of the tumor in endo-latero-infrasellar localization is visualized. (e and f) 10 years after the removal of the tumor during therapy with cabergoline. Regression of the tumor size and the empty sella

Transcranial microsurgical removal of the tumor was performed. He was treated by cabergoline after surgery. Endoscopic transsphenoidal approach was repeated with subtotal removal of the rest of the tumor. Morphological and immunohistochemical studies (with antibodies to PRL, thyroid-stimulating, somatotropin, adrenocorticotropic, luteinizing, and follicle-stimulating hormone, Ki-67, dopamine 2 receptors, and vascular endothelium markers CD31 and CD34) of the tumor were done.

Results

Considering the giant size of the tumor, the distinctive reduction in visual functions, as well as neurosurgical treatment of giant tumors being the priority treatment of choice at the time, regardless of hormonal activity (before the active implementation of cabergoline), a two-step procedure was applied (transcranial and transsphenoidal approaches with an interval of 3 months between surgeries). In November 2004, a surgery with a transcranial approach was performed, resulting in the removal of the suprasellar part of the tumor. After the surgery, there was a deterioration in the vision of the right eye until amaurosis, at the same time, right-sided ptosis and restriction in the range of movements of the right eyeball (gross paresis of the third nerve on the right). The PRL level after surgery remained higher than 5000 mU/l (30–360).

In a morphological study, the distant tumor was characterized by growths of predominantly rounded cells with bright cytoplasm, hyperchromic nuclei, and isolated mitoses. In the tumor tissue, increased vascularization was observed [Table 1], and tumor cells were located between numerous vessels with an expanded lumen and thickened fibrous walls [Figure 2a]. The immunohistochemical study revealed a pronounced positive expression of PRL, as well as distinct expression of D2R receptors, increased proliferative activity of tumor cells, Ki-67 LI to 8% [Figure 3a], and high expression of CD34 [Figure 4a]. The tumor was immunonegative for TSH, human growth hormone, luteinizing hormone, follicle-stimulating hormone, and adrenocorticotropic hormone.

After the surgery, cabergoline therapy was prescribed at a dose of 0.5 mg with a gradual increase in dose to 1.5 mg/week; against this background, a decrease in the level of PRL to 3800 mU/l (30–360) was noted. At a 3-month follow-up, the paresis of the right oculomotor nerve regressed, but blindness remained in the right eye. MRI scans [Figure 1c and d] revealed the remainder of the tumor

Table 1: The morphological and immunohistochemical characteristics of giant prolactinoma before and after the treatment with cabergoline in a 30-year-old patient

Morphology	At the time of the first surgery (before cabergoline therapy was started)	At the time of the second surgery (after treatment with cabergoline)
Light microscopy	Cellular complexes are separated by numerous vessels with an expanded lumen and thickened walls	Solid tumor with thin-walled sinusoidal vessels
Mitoses	Detected	Absent
Vascularization of the tumor	High	Low
Immunohistochemical characteristics of the tumor		
PRL expression	++	++
D2R expression	++	++
Ki-67 expression (%)	8	2
CD 31 expression	++	+
CD 34 expression	++	+

+ – Weak expression; ++ – Strong expression

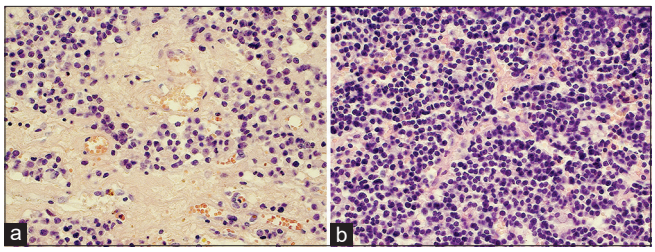

Figure 2: Morphological characteristics of pituitary adenoma before and after the treatment. (a) Pituitary adenoma, operated before cabergoline therapy: tumor cells are located between the vessels with thickened walls (H and E, ×400). (b) Pituitary adenoma of solid structure with thin-walled sinusoidal vessels operated after cabergoline treatment (H and E, ×200)

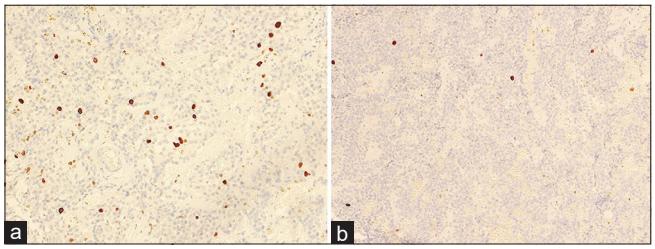

Figure 3: Immunohistochemical characteristics of giant prolactinoma before and after the treatment with cabergoline. (a) Nuclear immunoexpression of Ki-67: Ki-67 proliferation inde × 8%, ×200. Operated before cabergoline therapy. (b) Nuclear immunoexpression of Ki-67: Ki-67 proliferation 2%, ×200. Operated after cabergoline therapy

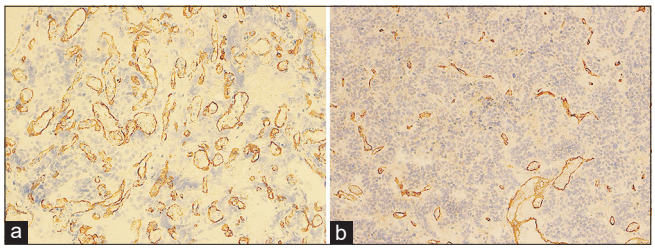

Figure 4: Immunoexpression of CD34 of giant prolactinoma before and after the treatment with cabergoline. (a) Immunoexpression of CD34 in the vascular endothelium of the tumor shows rich vascular network, ×200. Operated before cabergoline therapy. (b) Immunoexpression of CD34 in the vascular endothelium of the tumor shows more rare small vessels with thin walls by compared with primary tumor, ×100. Operated after cabergoline therapy

of endoinfrasellar localization. In February 2005, a subtotal removal of an intrainfrasellar tumor residue was carried out via transsphenoidal access. When neuro-ophthalmological examination was done after the surgery, visual impairments remained unchanged. The level of PRL in the blood after surgery decreased to 1304 mU/l (30–360). In the morphological study, the change in the structure of the tumor was observed, expressing an increase in the solid component with perivascular structures and a decrease in the number of vessels, which were mainly the sinusoidal vessels with a narrow lumen.

Figures of the mitotic division were not detected [Figure 2b]. At the same time, the tumor retained the same expression of immunopositivity for PRL and D2R as in the first biopsy. The proliferative potential of the tumor was significantly lower, Ki-67 LI was about 2% [Figure 3b], and a decrease in the number of vessels estimated using CD34 expression was also observed [Figure 4b]. The morphological and immunohistochemical characteristics of giant prolactinoma before and after the treatment with cabergoline are presented in Table 1.

After the operation, therapy with cabergoline was continued, which led to persistent normoprolactinemia, restoration of androgenic status, and absence of tumor recurrence during the next 10-year observation period [Figure 1e and f]. Three years after the surgery, the patient's wife became pregnant, and pregnancy resulted in her having a healthy baby.

Discussion

Until the implementation of cabergoline, surgical treatment remained the main treatment for giant pituitary adenomas, regardless of hormonal activity. At the same time, one of the methods for the removal of tumors with distinctive suprasellar growth and massive invasion into the structures of the base of the skull was surgery performed in two stages, when transcranial and transsphenoidal access to different parts of the tumor were introduced, penetrating both into the cavity and the structures of the base of the skull.[16,17]

From the moment of the active introduction (beginning of the 2000s) of cabergoline, which has proven to be an effective and safe drug.[1,2] It has become the priority treatment for PRL secreting tumors. Numerous studies *in vitro*, as well as in laboratory animals, have shown that the drug selectively activates type 2 dopamine receptors on the cell surface (D2R), which leads to the suppression of transcription and expression of the PRL gene, as well as a decrease in the synthesis and secretion of PRL.[18-23] Various studies have shown that tumor regression is caused by the suppression of cell proliferation.[15] One of the most reliable markers of cell proliferation is Ki-67, being widely recognized in the world. Overexpression of Ki-67 reflects aggressive characteristics and is an indicator of tumor recurrence.[24,25] There are few studies assessing Ki-67 in human adenomas treated with dopamine agonists.[2,22,26] Two groups of patients without the prior drug treatment having prolactinoma were studied and operated, having preoperative treatment with dopamine agonists. Dopamine agonist therapy has demonstrated leading to a significant decrease in Ki-67 LI.[22,26] However, in these studies, proliferative potential was evaluated in different groups of patients. Subsequent studies were performed mainly in patients with resistant prolactinomas.[27,28] There are almost no research data on the effect of cabergoline on the proliferative potential of tumors with good sensitivity to *in vivo* therapy. Indeed, at present, the first and main treatment method for prolactinoma is cabergoline therapy. Considering the background of a positive adenoma response to treatment in the form of reducing its size and reducing the level of PRL, this treatment is continued until complete regression of the tumor and normalization of the level of PRL. Such patients do not need surgical treatment, and therefore, obtaining histological material is not possible. Surgical treatment mainly involves cabergoline-resistant prolactinomas, as well as adenomas, the treatment of which is accompanied by the development of complications, mainly cerebrospinal fluid rhinorrhea.[2,29]

Therefore, it is almost impossible to assess the effect of cabergoline on the proliferative index of a tumor that is also sensitive to therapy *in vivo*.

This case study describes the patient who underwent the surgery at the intersection of the primary surgical and pharmaceutical approaches in treating giant prolactinoma. Therefore, *in vivo*, we were able to assess the effect of cabergoline on the proliferative potential of the same tumor. In the biopsy from the first and second operations, the tumor retained pronounced immunopositivity to PRL and D2R. However, there was a significant decrease in Ki-67 LI from 8% to 2% and a decrease in CD31 and CD34 expression.

Angiogenesis, the process of formation of new blood vessels, is an important link in the pathogenesis of the development of various tumors, including pituitary adenomas. Pituitary tumors are less vascularized compared to nontumor pituitary tissue; it is assumed that the absence of significant angiogenesis underlies the slow growth of pituitary tumors, and the progression of tumor cells should correlate with angiogenesis. The parameter for evaluating angiogenesis is the density of blood vessels in the tumor. It was shown that vascular density is significantly higher in macro in comparison with microprolactinomas; in invasive prolactinomas in comparison with noninvasive as well as in PRL-secreting pituitary carcinomas. In previous studies, it was reported that tumors treated with dopamine agonists have a lower vascular density compared to primary-operated prolactinomas without prior treatment with cabergoline.[5,22] To assess the angiogenesis of adenoma before and during treatment with cabergoline, a study was conducted with antibodies to vascular endothelial markers CD34 and CD31. It was revealed that before treatment with cabergoline, vascular density in adenoma, assessed by the degree of expression of CD34 and CD31, was significantly higher than in the biopsy from the second surgery. In addition, the very structure of the tumor vessels has changed.

In 1982, Landolt *et al*. described the development of perivascular fibrosis in patients with long-term treatment with bromocriptine.[30] With this phenomenon, some authors explained the worst results of surgical treatment of patients with prolactinoma who received bromocriptine.[31] In our clinical observation after a 3-month course of cabergoline, such changes in the tumor were not recorded. On the contrary, if before the treatment the vessels had an expanded lumen and thickened fibrous walls [Figure 3b], then in the biopsy from the second operation they were mainly represented by sinusoidal vessels with thin walls and a narrow lumen [Figure 2b]. The previous (2004-2017) WHO classification of endocrine tumors outlined isolated "typical" and "atypical" pituitary adenoma.

The latter included tumors with clinical signs of infiltrative growth and morphological signs of atypia in the form of an increased mitotic index, p53 overexpression, and an increase in Ki-67 IL of over 3%.[32] When using these criteria, the incidence rates of atypical adenomas, according to various data, vary from 2% to 15%, and the prognostic value of this classification has not yet been established despite its long duration.[33,34] However, according to this classification, it was observed that the original tumor could be interpreted as "atypical," whereas during treatment with cabergoline, the morphological picture began to correspond to the "typical" pituitary adenoma. In the modern WHO morphological classification of endocrine tumors, adopted in 2017, there is no concept of "atypical" pituitary adenoma, instead the term "adenoma with increased proliferative activity" is proposed. In addition, the new classification also identified subtypes of pituitary tumors with a clinically aggressive course, including "prolactinomas in men."[35,36]

Conclusions

In the described case, the treatment with cabergoline

resulted in a significant clinical improvement, confirmed by morphological changes in the tumor tissue, a decrease in cell proliferative potential, which is one of the mechanisms for reducing the tumor size, as well as a decrease in vascular density and vascular structure of the tumor.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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