The Effect of Preoperative Cabergoline on Prolactinoma Fibrosis: A Case Series

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Abstract

Introduction Prolactinomas are a common intracranial neoplasm and constitute most pituitary tumors. Although patients can present with variable hormone dysregulation and symptom severity, the use of dopamine agonists remains a first-line treatment. While bromocriptine has been found to increase tumor fibrosis, the effect of cabergoline on collagen deposition has been disputed. The aim of this article is to understand the influence of cabergoline on tumor fibrosis prior to resection.

Case Presentations Four male patients who underwent prolactinoma resection were included in this report. The average age was 39.8 years (range: 26–52 years). Pretreatment prolactin levels ranged from 957.8 to 16,487.4 ng/mL. Three patients received cabergoline for at least 1 month prior to surgery (treatment range: 1–6 months). One patient had surgery without prior cabergoline use. Pathology reports confirmed each tumor to be of lactotroph origin. For each sample, Masson's trichrome staining was performed and the percentage of sample fibrosis was quantified using an artificial intelligence imaging software. Among those who received preoperative cabergoline, the extent of tumor fibrosis was in the range of 50 to 70%. In contrast, specimen fibrosis was approximately 15% without cabergoline use.

Conclusion This report demonstrates that a short duration of preoperative cabergoline can cause significant prolactinoma fibrosis. Understanding the effect of cabergoline on tumor consistency prior to surgery is essential as increased fibrosis can lead to more difficult tumor removal, reduce the extent of resection, and increase surgical complications. Considering these effects, further studies regarding the use of surgery prior to cabergoline for prolactinoma management are warranted.

Keywords
► cabergoline
► pituitary neuroendocrine tumors
► prolactinoma
► neurosurgery
► neuroendocrinology

Introduction

Pituitary neuroendocrine tumors (PitNETs) are a commonly identified tumor of the skull base, with most being of lactotroph lineage and causing prolactin hypersecretion. Such tumors, referred to as prolactinomas, account for approximately 50% of all PitNETs with an incidence of three to five cases/100,000/year.[1,2] Without treatment, prolactinomas can result in amenorrhea, diminished libido, galactorrhea, erectile dysfunction, infertility, gynecomastia, and decreased bone mass.[3,4] Additionally, patients may develop symptoms of hypopituitarism, visual field deficits, cranial nerve dysfunction, and seizures as a result of the mass effect that large tumors may impose on nearby intracranial structures.[4]

Currently, the preferred initial treatment of prolactinomas consists of medical management with dopamine agonists (DA), such as cabergoline. Use of this medication has proven effective at normalizing prolactin levels and reducing tumor volume in a majority of patients, with notable improvement in clinical symptoms.[5] While previous reports have documented bromocriptine use with increased tumor fibrosis, limited data exists on the relationship between cabergoline and pituitary tumor collagen content. In this report, we present three cases of prolactinomas treated with cabergoline prior to surgery, resulting in significant tumor fibrosis. Given that increased amounts of fibrotic tissue can increase the risk of surgical complications and reduce the potential for complete resection, understanding the effects of preoperative cabergoline use on tumor consistency is imperative for surgical planning and future patient management.

Case Presentations

Case 1

A 51-year-old male with a past medical history of hyperlipidemia and hypertension presented with sudden-onset headaches, bilateral blurry vision, photophobia, and diminished libido and spontaneous erections. He denied galactorrhea, breast engorgement, heat/cold intolerance, change in ring or shoe size, fatigue, fractures, polyuria, polydipsia, weakness, or weight changes. On initial physical exam, pupils were equal and reactive to light and extraocular movements were intact; however, inferotemporal field loss in the right eye and supertemporal field loss in the left eye were present. His strength, reflexes, coordination, and gait were all normal. The remaining physical exam was unremarkable. Optical coherence tomography (OCT) revealed diminished retinal nerve fiber layer (RNFL) thickness, with a value of 70 and 71μ in the right and left eye, respectively.

Initial endocrine workup revealed a significantly elevated prolactin of 4,053.2 ng/mL (ref. range: <15 ng/mL). Other laboratory results showed thyroid stimulating hormone (TSH)—1.94 mIU/mL (ref. range: 0.3–4.2 mIU/mL), free thyroxine (FT4)—less than 0.4 ng/dL (ref. range: 0.6–1.5 ng/dL), follicle-stimulating hormone (FSH)—0.5 mIU/mL (ref. range: <15 mIU/mL for adult male), luteinizing hormone (LH)—0.2 mIU/mL (ref. range: <10 mIU/mL for adult male), testosterone—1 ng/dL (ref. range: 250–1100 ng/dL), cortisol—less than

1.0 ug/dL (ref. range: 4–20 ug/dL), and insulin-like growth factor-1 (IGF-1)—18 ng/mL (ref. range: 50–317 ng/mL). Magnetic resonance imaging (MRI) of the brain demonstrated a heterogeneously enhancing sellar mass elevating the optic chiasm and bilateral inferomedial frontal lobes with invasion into the left cavernous sinus. The lesion measured 5.4 cm (craniocaudal [CC]) × 2.9 cm (transverse [TV]) × 3.7 cm (anterior–posterior [AP]).

Treatment with cabergoline was initiated at 0.5 mg, twice weekly. Additionally, the patient received hydrocortisone (2x/day; dose 15/10 mg) and levothyroxine (50 ug daily). The patient noted improvement in his headaches after a few days but opted for surgical intervention after 1 month of treatment, despite decreasing tumor size on MRI, due to concerns of continued blurry vision and visual field deficits (►Fig. 1).

The patient underwent an unremarkable endoscopic transnasal transsphenoidal resection of the pituitary tumor. Pathology of the resected tissue revealed a lactotroph tumor with neoplastic cells arranged in sheets, exhibiting round to oval nuclei with speckled chromatin and scant amounts of amphophilic cell cytoplasm. Significant perivascular fibrosis was present. Quantification of overall specimen fibrosis after Masson's trichrome stain revealed a level of 60 to 70% on ImageJ (►Fig. 2).

Postoperatively, his prolactin levels normalized (<5.0 ng/mL) and cabergoline use was discontinued. Postoperative MRI at 1-month confirmed that gross total resection was achieved. By his 3-month follow-up visit, the patient reported significant improvement in his prior visual field deficits and resolution of headaches. Endocrine laboratories were not completed at this time and the patient was lost to follow-up (►Table 1).

Case 2

A 30-year-old male with no significant past medical history presented with 8 months of peripheral visual field loss, blurry vision, headaches, and decreased libido. He denied gynecomastia, galactorrhea, change in hair distribution, polyuria, polydipsia, change in ring or shoe size, fatigue, heat/cold intolerance, weight changes, or weakness. Physical exam was unremarkable aside from left-sided visual field deficits. Laboratory workup revealed a prolactin level of 2,624 ng/mL, TSH of 2.5 mIU/mL, FT4 of 0.7 ng/dL, LH of 1.8 mIU/mL, FSH of 3.5 mIU/mL, testosterone of 33 ng/dL, adrenocorticotropic hormone of 78 pg/mL (ref. range: 6–50 pg/mL), cortisol of 1.8 μg/dL, growth hormone of 0.1 ng/mL (ref. range: ≤7.1 ng/mL), and IGF-1 of 95 ng/mL. MRI of the brain from an outside institution showed a 2.5 × 3.5 cm sellar mass.

The patient was started on cabergoline 0.5 mg, twice weekly, which was taken for 1 month before discontinuation by the patient per his preference. He reported improvement in vision loss and prolactin levels decreased to 369.6 ng/mL. Ophthalmologic evaluation at this time revealed complete temporal hemianopsia on the left and superior temporal vision defect on the right, with diminished RNFL thickness of 79 and 65μ in the right and left eye, respectively. After
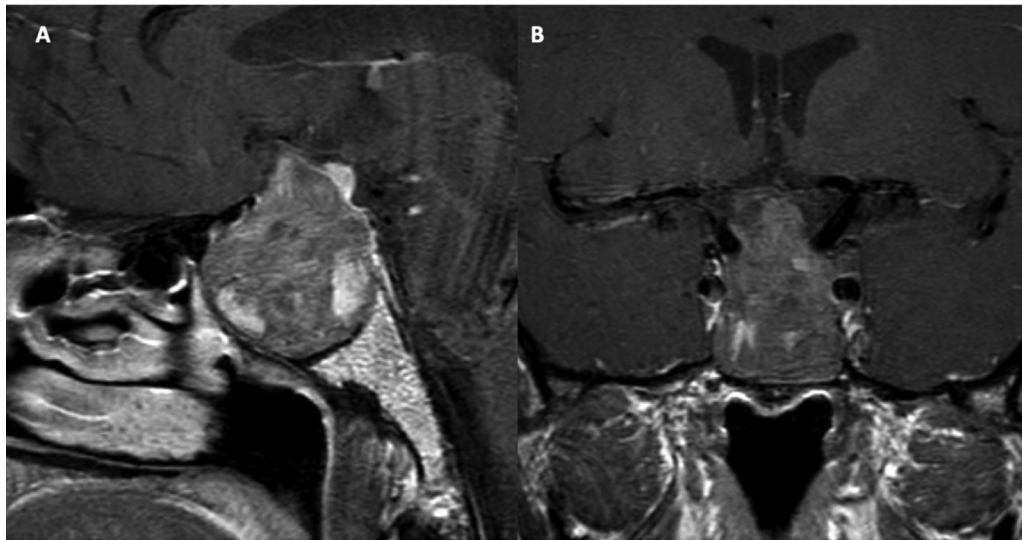
Fig. 1 Patient number 1. Preoperative imaging after cabergoline treatment: (**A**) and (**B**) The sagittal and coronal T1-weighted magnetic resonance imaging postcontrast.
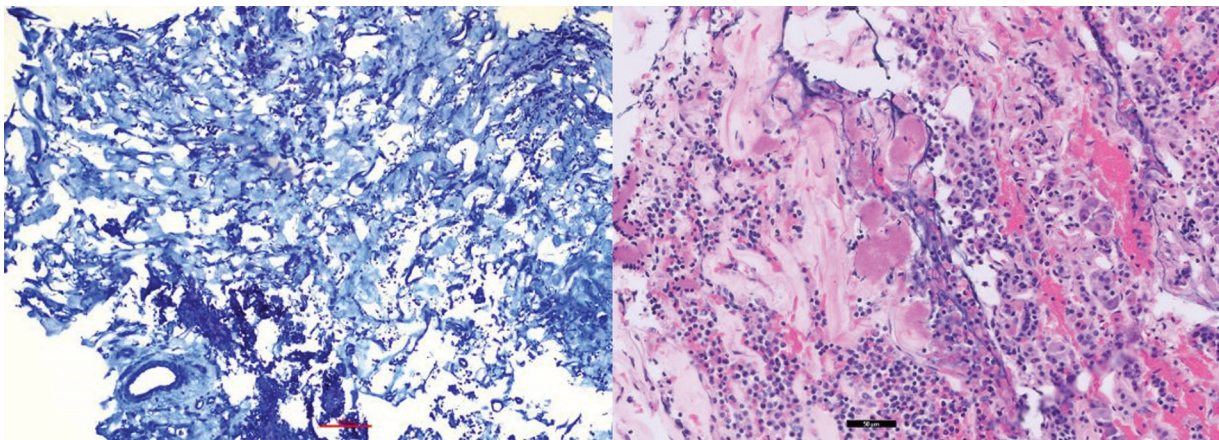

Fig. 2 Patient number 1. Cabergoline use for 1 month before surgery. Overall specimen fibrosis 60 to 70% (left: Masson's trichrome stain, 200x; right: hematoxylin and eosin stain, 200x).

1 month of no cabergoline therapy, the patient was restarted on 0.5 mg, three times per week. The patient continued the medication for an additional 5 months, with improvement in prolactin levels to less than 5.0 ng/mL. MRI showed tumor shrinkage (2.6 cm [AP] × 3.0 cm [TV] × 3.3 cm [CC]); however, the patient did not notice any visual improvements (►**Fig. 3**). Repeat OCT values were 77μ for the right and 61μ for the left eye.

The patient underwent an uncomplicated transnasal transsphenoidal pituitary tumor resection due to progressively worsening visual field loss on cabergoline therapy. Pathology report detailed a PitNET staining positive for prolactin and growth hormone, with features of a mixed sparsely granulated lactotroph (predominant component) and somatotroph tumor (relatively minor component). The neoplastic cells were arranged in nests and exhibited round to oval nuclei with speckled chromatin and small amounts of chromophobic to faintly eosinophilic cell cytoplasm. Significant mitotic figures were not identified. Masson's trichrome

staining revealed an overall specimen fibrosis of 50 to 60% (►**Fig. 4**).

The patient experienced no postoperative complications and was discharged without continued cabergoline treatment. At his 3-month follow-up appointment, he reported decreased headaches with minimal vision improvement. MRI revealed subtotal resection of the tumor with a small portion of residual tumor invading into the right cavernous sinus, surrounding the internal carotid artery. The patient was subsequently lost to follow-up.

Case 3

A 52-year-old male with no significant past medical history presented with headaches, decreased libido, and lack of spontaneous erections. He did not have galactorrhea, gynecomastia, weight changes, vision deficits, fatigue, change in ring or shoe size, weakness, polydipsia, polyuria, or heat/cold intolerance. Physical exam was unremarkable aside from a right eye temporal visual field defect. Initial
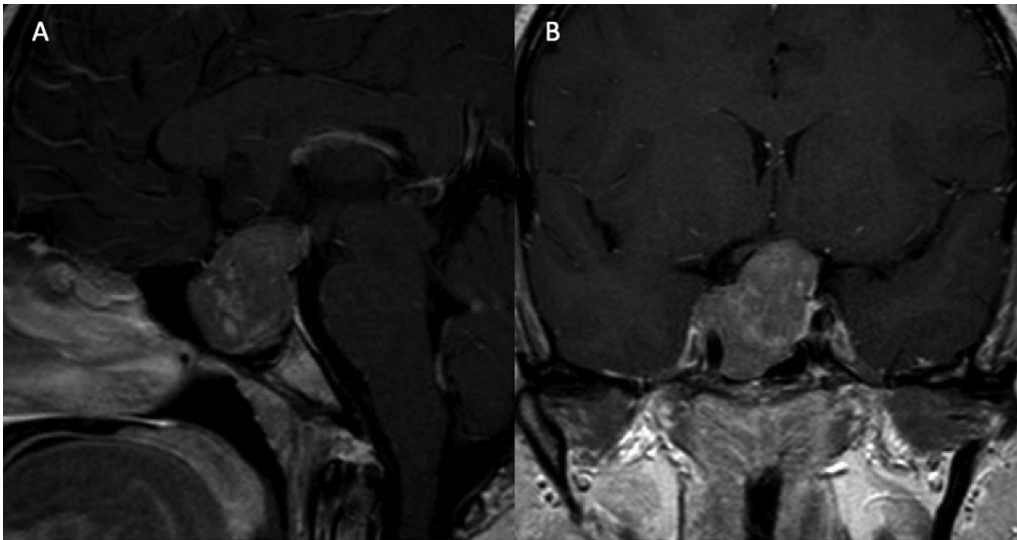
Fig. 3 Patient number 2. Preoperative imaging after cabergoline treatment: (**A**) and (**B**) The sagittal and coronal T1-weighted magnetic resonance imaging postcontrast.
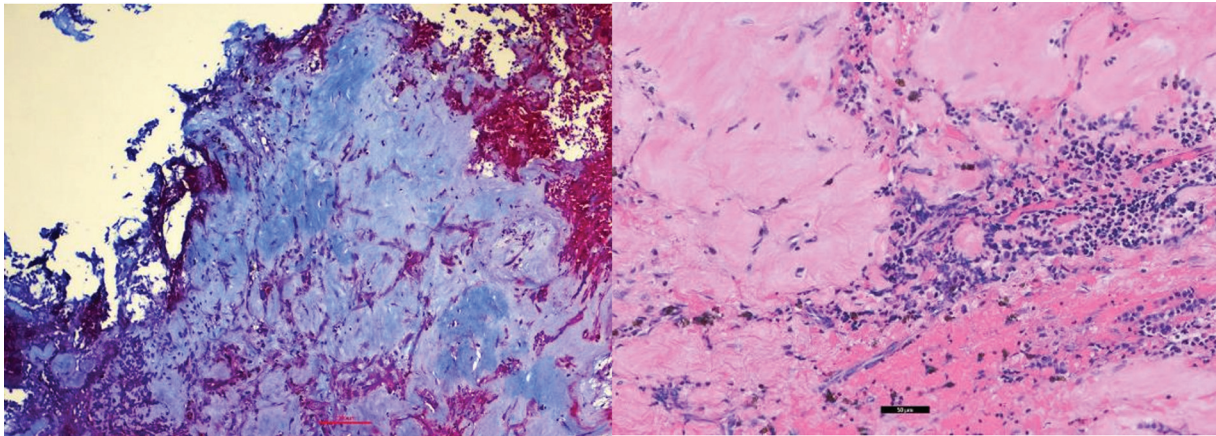

Fig. 4 Patient number 2. Cabergoline use for 6 months prior to surgery. Overall specimen fibrosis 50 to 60% (left: Masson's trichrome stain, 200x; right: hematoxylin and eosin stain, 200x).

endocrine workup revealed a prolactin level of 16,487.4 ng/mL, TSH of 1.11 mIU/mL, FT4 of 0.7 ng/dL, LH of 0.8 mIU/mL, FSH of 2.0 mIU/mL, total testosterone of 64 ng/dL, and IGF-1 57 of ng/mL. MRI of the brain from an outside institution demonstrated a large intra and suprasellar mass measuring 4.8 cm (TV) × 5.2 cm (CC) × 4.5 cm (AP) that extended into the bilateral cavernous sinuses, right middle cranial fossa, and inferiorly to the clivus. Significant optic chiasm compression and involvement of the inferomedial bilateral frontal lobes were noted.

The patient was initially scheduled for surgical resection; however, surgery was delayed due to a nasal septal perforation in the setting of cocaine use. In the interim, he was started on cabergoline 0.5 mg, twice weekly. After 1 month of treatment, prolactin levels decreased to 13.1 ng/mL. After 2 months of treatment, the patient had significant improvement in his temporal visual field in the right eye; however, OCT report demonstrated diminished RNFL thickness (78μ right eye, 73μ left eye). At this time, he developed severe headaches. MRI showed heterogeneous internal signal enhancement of the lesion, suggestive of hemorrhage, with persistent invasion into the cavernous sinus, sphenoid sinus, and central skull base (►**Fig. 5**). As a result, surgical resection of the tumor was completed without any complications. The pathology report revealed a sparsely granulated lactotroph tumor, with neoplastic cells arranged in clusters within fibrotic tissue. Overall specimen fibrosis on Masson's trichrome staining was 50 to 60% (►**Fig. 6**).

The patient had an uncomplicated postoperative course and was discharged without cabergoline. Follow-up endocrine laboratories 2 weeks after surgery revealed a prolactin level of 14.3 ng/mL and a persistently low total testosterone level of 35 ng/dL. Humphrey visual field testing demonstrated grossly full vision in both eyes and the patient reported only occasional headaches. Repeat prolactin levels 2-months after surgery showed an increase to 589.7 ng/mL. Cabergoline treatment was recommended at this time; however, the patient was lost to follow-up. As a result, postoperative imaging was not obtained.
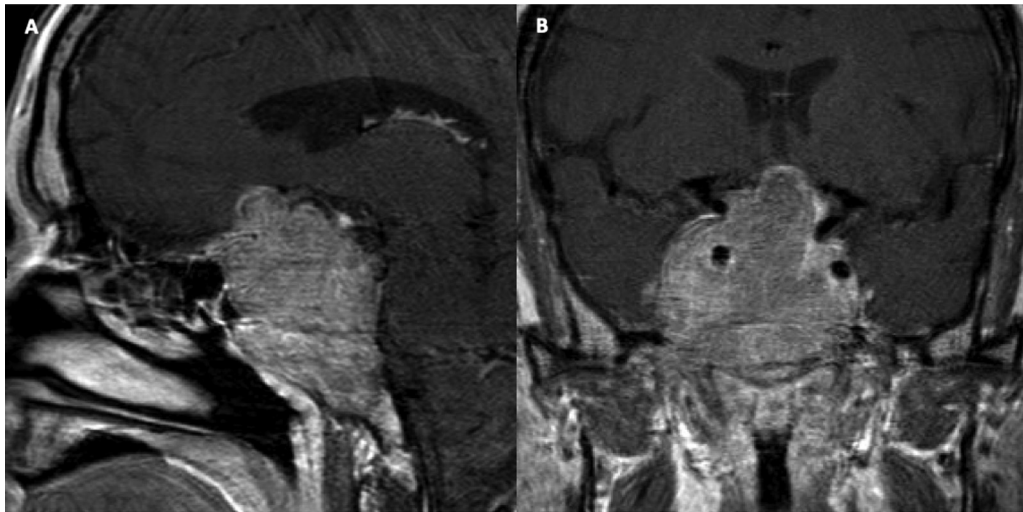
Fig. 5 Patient number 3. Preoperative imaging after cabergoline treatment: (**A**) and (**B**) he sagittal and coronal T1-weighted magnetic resonance imaging postcontrast.
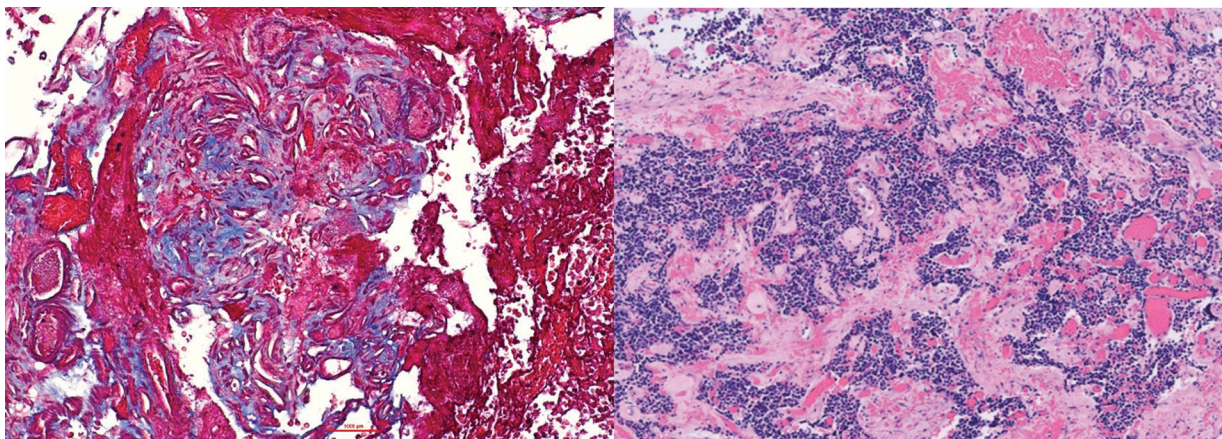

Fig. 6 Patient number 3. Cabergoline use for 2 months prior to surgery. Overall specimen fibrosis 50 to 60%. (left: Masson's trichrome stain, 200x; right: hematoxylin and eosin stain, 200x).

Case 4

A 26-year-old male with no significant past medical history presented to the emergency department with 1.5 months of progressive vision loss in the left eye and daily headaches. Aside from fatigue and decreased libido, further review of systems was negative. Physical exam was notable for decreased visual acuity in the left eye, diffuse left peripheral vision loss, and right superotemporal field loss. OCT values were within normal limits. Initial MRI of the brain showed a large sella and suprasellar mass measuring 3.4 cm (CC) × 2.2 cm (TV) × 2 cm (AP). The lesion elevated and compressed the optic chiasm with areas of hypointensity and fluid levels, likely secondary to underlying hemorrhage. Laboratory workup revealed a prolactin level of 957.8 ng/mL, TSH of 1.02 mIU/mL, FT4 of 0.2 ng/dL, LH of 0.6 mIU/mL, FSH of 1.5 mIU/mL, total testosterone of 2 ng/dL, IGF-1 74 of ng/mL, and cortisol of 2.1 µg/dL.

Due to imaging evidence of hemorrhage and concern for apoplexy, transnasal transsphenoidal removal of the tumor was performed (►**Fig. 7**). Surgical resection was uncomplicated and pathology report revealed a sparsely granulated lactotroph tumor. The neoplastic cells were arranged in solid clusters and exhibited irregularly shaped nuclei with speckled chromatin and prominent nucleoli. Cellular cytoplasm showed a juxtanuclear eosinophilic region and a basophilic peripheral zone. Ki67 immunohistochemical staining was focally elevated up to 11%. Overall specimen fibrosis was 15% on Masson's trichrome staining (►**Fig. 8**).

The patient was discharged home on hydrocortisone (20 mg, twice daily) and levothyroxine (50µg daily). Three weeks after surgery, prolactin levels declined to 77.3 ng/mL, cortisol improved to 10.1 µg/dL, and testosterone continued to be low at a total level of 15 ng/dL. TSH was 0.52 mIU/mL and FT4 was 0.7 ng/dL. He reported his vision was fully restored, headaches were resolved, and there was an improvement in his libido with increased morning erections. Two months after surgery, prolactin remained elevated at 80.1 ng/mL and the patient was initiated on cabergoline 0.25mg, twice weekly. MRI at 3 months revealed gross total resection, with persistently elevated prolactin to 225.3 ng/mL. Treatment with cabergoline was increased to 0.5mg, twice weekly, while use of hydrocortisone and
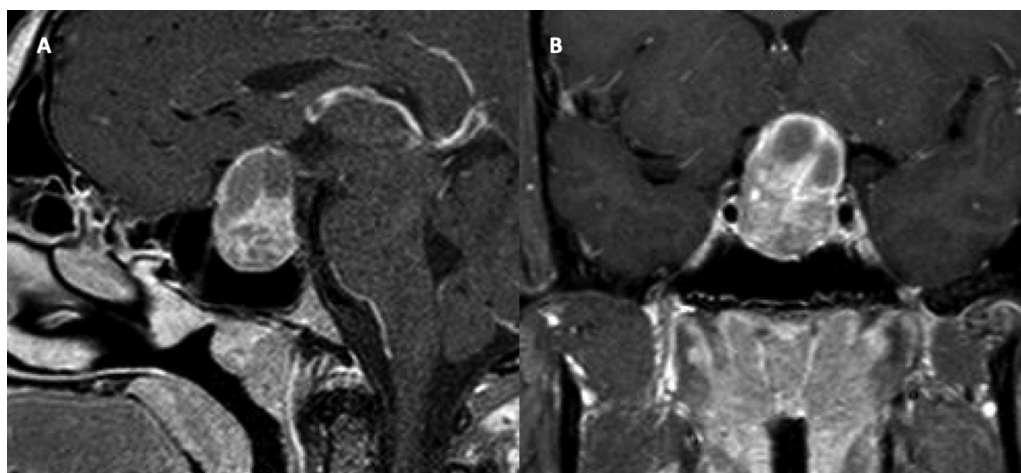
Fig. 7 Patient number 4. Preoperative magnetic resonance imaging (MRI) without prior cabergoline use. (**A**) and (**B**) The sagittal and coronal T1-weighted MRI postcontrast.
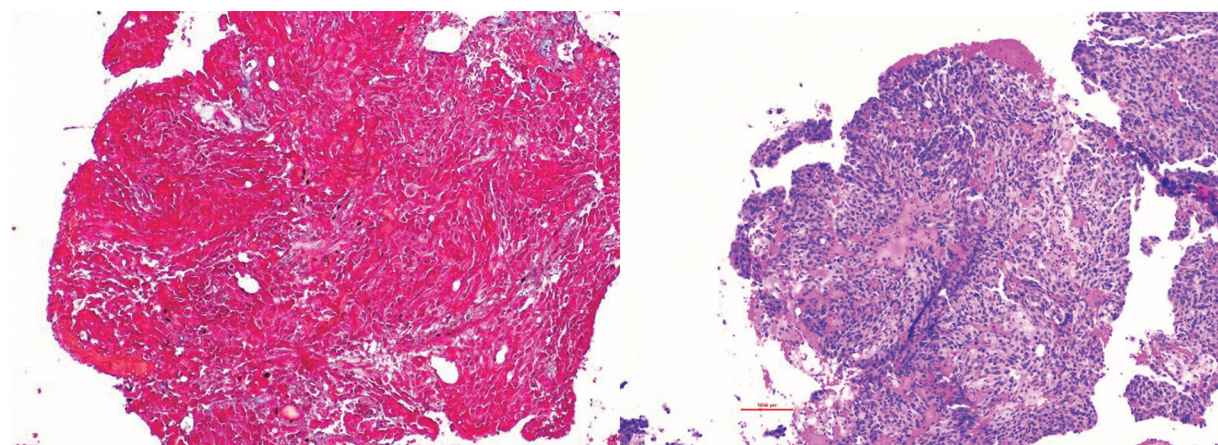

Fig. 8 Patient number 4. No cabergoline use prior to surgical resection. Overall specimen fibrosis 15% (left: Masson's trichrome stain, 200x; right: hematoxylin and eosin stain, 200x).

levothyroxine was tapered off due to normalization of hormone levels. Follow-up imaging 6 months later demonstrated tumor along the posterior and left aspects of the pituitary. After this time, the patient was lost to follow-up with no additional endocrine laboratories obtained.

Discussion

In this report, we describe three cases of prolactinomas treated with cabergoline therapy, resulting in significantly increased tumor fibrosis prior to surgical resection. Preoperative medical treatment with DA has remained the standard of care for prolactin-secreting PitNETs, demonstrating efficacy in reducing prolactin levels and markedly decreasing tumor size.[6] However, the use of medical therapy has been shown to result in significant side effects within the gastrointestinal, neurological, and cardiovascular systems.[7,8] Bromocriptine use, in particular, has been found to result in substantial tumor, cardiac valve, and retroperitoneal fibrosis, yet patients treated with cabergoline have been found to be less likely to experience such effects.[9,10] Additionally, the fibrotic effects of DA therapy have been most commonly observed after several years of treatment.[11] Surprisingly, in this report, cabergoline use was associated with increased tumor fibrosis after 6 months of treatment or less.

Despite understanding the potential for DA therapy to increase collagen deposition within tumors, there has been debate regarding the effects of fibrosis on clinical outcomes. While some may argue that preoperative medical therapy results in improved patient outcomes by allowing for greater tumor resection, other reports have documented that increased tumor fibrosis is associated with more difficult tumor removal and decreased ability to achieve gross total resection.[12,13] Not only can fibrosis create a more challenging surgical case, it may also elevate the risk of intra- or postoperative complications. Prior studies have demonstrated that preoperative radiation therapy leads to a higher rate of surgical morbidity, such as cerebrospinal fluid leaks, postulated to be due to radiation-induced tissue fibrosis.[14,15] The effect of cabergoline therapy on fibrosis has thus been thought to result in similar operative complications.

Aside from the surgical risks that may result from DA use, biochemical dysregulation may be more likely to persist among those treated with preoperative medical therapy.

Table 1 Overview of key information

	Patient 1	Patient 2	Patient 3	Patient 4
Age at diagnosis	51	30	52	26
Sex	Male	Male	Male	Male
Presenting symptoms	Headaches; blurry vision; photophobia; diminished libido/spontaneous erections	Visual field deficits; blurry vision; headaches; diminished libido	Headaches; diminished libido/spontaneous erections	Headaches; vision loss; fatigue; diminished libido
Tumor size at diagnosis (AP x CC x TV) [cm]	$3.7 \times 5.4 \times 2.9$	2.5×3.5[a]	$4.5 \times 5.2 \times 4.8$	$2.0 \times 3.4 \times 2.2$
Tumor size pre-operatively (AP x CC x TV) [cm]	$3.7 \times 4.1 \times 2.7$	$2.6 \times 3.3 \times 3.0$	$4.4 \times 5.6 \times 5.5$	–
Duration of cabergoline treatment (months)	1	6	2	0
Amount of tumor fibrosis (%)	60–70	50–60	50–60	15
Patient outcomes	Symptom improvement; PRL normalization; GTR	Symptom improvement; STR	Symptom improvement; initial PRL normalization, followed by PRL elevation	Symptom improvement; no PRL normalization; GTR
Postoperative cabergoline advised?	No	No	Yes[b]	Yes
Lost to follow-up?	Yes	Yes	Yes	Yes

Abbreviations: AP, anterior–posterior; CC, craniocaudal; GTR, gross total resection; PRL, prolactin; STR, subtotal resection; TV, transverse.
[a]Full dimensions were unavailable as scans were completed at an outside institution.
[b]Patient was lost to follow-up before cabergoline was provided.

Menucci et al demonstrated that PitNETs with increased fibrosis were less likely to exhibit hormone normalization after surgery compared with those that were deemed non-fibrous.[9] Further studies have corroborated these results, finding that even a short duration of preoperative DA treatment decreased the chances of hormonal homeostasis.[16] As a result, those treated with upfront cabergoline treatment may be at higher risk of requiring a significantly prolonged duration of medication use. As a result of the potential consequences of medical treatment prior to surgery, some physicians argue that surgical intervention should be prioritized as a first-line treatment as doing so may optimize long-term patient outcomes and mitigate postoperative complications.

At this time, current indications for the surgical resection of PitNETs include resistance to DA therapy, intolerance to medication side effects, pituitary apoplexy, and patient preference.[16] Resistance to medical therapy has been estimated to occur in 20 to 30% of prolactinomas treated with bromocriptine and 10 to 20% of those treated with cabergoline, with tumor size and invasiveness being predictive factors for resistance.[17] In fact, one surgical series found DA resistance to be one of the most common indications for surgical intervention, accounting for over 64% of cases.[16] DA intolerance, on the other hand, is a less likely cause of surgical intervention. While high rates of cabergoline side effects have been reported, the severity of such effects has not proven to be a common cause of drug discontinuation. One cohort study, for example, documented side effects in 68% of women with hyperprolactinemic amenorrhea treated with cabergoline, with only 3% requiring medication cessation.[18] Given the moderate rates of tumor resistance, the prevalence of undesirable side effects, and the increased chances of long-term postoperative medication use after preoperative cabergoline use, it can be argued that surgical intervention should be considered prior to medical management for many patients, particularly those who present with visual compromise.

In consideration of the negative outcomes that preoperative cabergoline use may impose on patients, it is necessary to determine indications for initial management of prolactinomas with surgical intervention. One retrospective study of patients treated with upfront surgical resection found that micro- or macroprolactinomas with Knosp grade 0 were most likely to not require postoperative DA therapy.[19] However, given the increase in tumor fibrosis associated with cabergoline use, initial surgical management may prove advantageous for patients with large tumors, as well. Therefore, in contrast to current recommendations, patients with both small and large tumors may benefit from surgery prior to medical therapy, especially those experiencing visual deficits.

Conclusion

Prolactinomas treated with preoperative cabergoline for at least 1 month prior to surgical resection exhibit increased

tumor collagen deposition. Given that tumor fibrosis can decrease the ability to achieve gross total resection, increase the risk of operative complications, and result in the need for prolonged DA treatment after surgery, surgery may be the optimal first-line treatment for patients with prolactinomas presenting with visual compromise.

Conflict of Interest
None declared.

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