CASE REPORT

Cabergoline-induced fibrosis of prolactinomas: a neurosurgical perspective

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SUMMARY

Presently, the standard of care for prolactinomas, a type of pituitary adenoma, is dopaminergic agents such as bromocriptine and cabergoline. However, dopaminergic agents may induce fibrosis of cardiac valves leading to valvular insufficiency, necessitating surgical treatment of prolactinoma. Fibrosis of prolactinoma can be induced by prolonged medical treatment with bromocriptine, and this usually occurs after years of treatment. In comparison to bromocriptine, there have been no reports of cabergoline-induced fibrosis of prolactinoma. There is a potential for greater emphasis to be placed on assessing the tumour consistency from preoperative MRI scans, or even preoperative contrast-enhanced 3D Fast Imaging Employing Steady-state Acquisition imaging to allow better planning of the surgery. We report a rare case of fibrosis of prolactinoma after cabergoline treatment resulting in its subsequent difficult surgical removal. This patient had early MRI changes of fibrosis of prolactinoma after a short period of 6 months of cabergoline treatment.

BACKGROUND

This case report is an interesting addition to medical literature as fibrosis of prolactinoma usually occurs after treatment with bromocriptine, and even then, it is after years of treatment with bromocriptine. There have been no reports of fibrosis of prolactinomas linked to treatment with cabergoline.¹ In this case report, our patient who was diagnosed with prolactinoma was only initially treated with cabergoline for a short period of 6 months, and had early MRI changes of fibrosis of prolactinoma.

Additionally, this case report serves as a springboard from which other studies could be done to shed light on the possibility of using surgical findings of tumour fibrosis to prognosticate biochemical remission postsurgical intervention and whether or not we should cease medical therapy a few months prior to the surgical removal of prolactinoma, so as to improve the current management of neurosurgical patients with prolactinomas.

Finally, while routine MRI scans are often done preoperatively, there has been little emphasis to assess the nature and consistency of the pituitary macroadenomas such as prolactinomas from these MRI scans in the past. This case report aims to point out the potential importance of the assessment of nature and consistency of the prolactinomas preoperatively, using MRI scans or contrast-enhanced 3D Fast Imaging Employing Steady-state Acquisition

(FIESTA). Assessment of the nature and consistency of prolactinomas prior to surgeries could allow for better planning and preparation for the neurosurgeries, and further large-scale prospective studies could be conducted in the near future to explore the benefits that could be accrued from such a new surgical practice.

CASE PRESENTATION

A 27-year-old man presented with reduced secondary sexual characteristics. He never had facial nor underarm hair. He reported that his height remained stagnant over the years and he did not experience any growth spurt during puberty. His voice did not deepen. At the age of 19 years, he was found to have low testosterone level during his previous medical check-up. On initial presentation, the patient did not experience any headaches or any visual field defects. However, he reported cold intolerance.

The patient had no family history of any pituitary macroadenomas. His parents had normal growth and development. His younger sister and maternal aunt have systemic lupus erythematosus (SLE). His maternal aunt passed away in her early 30s. His sister was diagnosed with SLE at the age of 17 years.

On general examination, his height was measured at 1.58 m (fourth percentile of the population). On genitalia examination, the patient was found to be stage III on the Tanner Staging Scale. Both testes were found to be descended in scrotum. Pubic hair was sparse and limited in distribution to only the genitals with no extension to the abdominal region and lower limbs. The prostate was not enlarged and was smooth in nature. He was also noted to have slight gynaecomastia.

INVESTIGATIONS

Initial investigations done were significant for a low testosterone level of 7.88 nmol/L (reference interval: 9.90–27.80 nmol/L) and an elevated prolactin level of 14 952 mIU/L (reference interval: 72–320 mIU/L). (Refer to [table 1](#) for an overview of the blood hormones that were trended from when the patient first presented to the postoperative period.) MRI of the brain revealed a homogeneously enhancing intrasellar mass with suprasellar component abutting the intracisternal segments of the optic nerves and optic chiasm ([figure 1A,B](#)). It measured 1.5 × 1.6 × 1.6 cm.

A diagnosis of prolactinoma was made, and the patient was advised to start on oral cabergoline

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Table 1 Overview of the blood hormones that were trended from when the patient first presented to the postoperative period

	Pre-operative bloods							Post-operative bloods		
Blood investigations	Initial bloods	1 month	3 months	6 months	12 months	Preoperative		1 month	6 months	1 year
Prolactin (reference interval: 72–320 mIU/L)	14952	10462	6053	5179	1859	1964	Operation (~18 months)	182	219	278
Free thyroxine (reference interval: 8.0–20.0 pmol/L)	8.7	7.3	7.9	11.0	10.5	11.1		14.3	13.6	14.1
Testosterone (reference interval: 9.90–27.80 nmol/L)	7.88	8.45	NA	NA	6.95	8.26		9.28	7.96	10.73

Other initial bloods (at point of diagnosis): 8:00 am cortisol (reference interval: 123–626 nmol/L): 232 nmol/L; thyroid-stimulating hormone (reference interval: 0.45–4.50 mIU/L): 2.06 mIU/L; corrected calcium (reference interval: 2.15–2.55 mmol/L): 2.42 mmol/L; insulin-like growth factor-1 (reference interval: 128–336 µg/L): 161 µg/L.

0.25 mg once every week (to be taken at bedtime). Approximately 27 days later, testosterone levels were still low at 8.45 nmol/L (reference interval: 9.90–27.80 nmol/L), prolactin levels went down to 10 462 mIU/L (reference interval: 72–320 mIU/L) and free thyroxine levels were again measured and found to be low at 7.3 pmol/L (reference interval: 8.0–20.0 pmol/L). Synacthen test done in the same setting was normal, showing no evidence of hypocortisolism. The impression was that of macroprolactinoma with secondary hypogonadism and secondary hypothyroidism. The dose of cabergoline was increased to 0.5 mg once every week for 1 month, then 0.5 mg two times per week. Small dose of thyroxine 25 µg once every morning was also started. He was compliant to medical treatment.

When our patient was first started on cabergoline, he experienced occasional headaches when moving from a sitting to a standing position, as well as when he tried to bend down. While headaches are common side effects of cabergoline, positional headaches are not classical of cabergoline, and are instead likely due to the prolactinoma. Our patient did not experience any gastrointestinal side effects such as nausea and vomiting, nor did he experience any other neurological side effects such as drowsiness, dizziness and weakness. No psychiatric side effects such as psychosis, anxiety and depression were noted.

Patient was referred for ophthalmology review and Humphrey's visual fields test revealed right incongruous homonymous hemianopia. Although the serial prolactin levels came down with treatment, the prolactin levels were still elevated beyond the normal ranges, hence the dosage of cabergoline was increased to 1.5 mg every week (to take 1 mg on Tuesday and 0.5 mg on Friday). In view of low free thyroxine levels, the dosage of thyroxine was increased to 50 µg per day.

With the increase in dosage of cabergoline to 1.5 mg every week, the prolactin levels consistently came down but was still elevated beyond the normal ranges. Cabergoline dosage was increased to 1.0 mg two times per week for 2 weeks, then 1.5 mg two times per week. Thyroxine was kept at 50 µg per day. Over time, as prolactin levels were persistently above the normal ranges, cabergoline was increased to 2 mg two times per week. Even with the increase in dosage of cabergoline, prolactin levels did not normalise. Concurrently, free thyroxine levels were only within the low end of normal range.

The decrease in prolactinoma size can, in many patients, be detected by imaging within 6 weeks after initiation of treatment.² A follow-up MRI scan of the brain done 6 months after the onset of medical treatment with cabergoline showed that the tumour was found to have mildly shrunk in size, with an increased signal on the T2-weighted coronal (figure 2A) section and reduced central enhancement on the T1 postcontrast sagittal (figure 2B) section. Interestingly, despite the mild reduction in size of the tumour centrally, there was persistent tethering at the dural margins and persistent suprasellar tumour seen insinuating around the optic chiasm and anterior cerebral artery. These findings were persistent even on the repeat MRI scan that was subsequently obtained 12 months after the onset of medical treatment with cabergoline.

In view that 6 months from the onset of medical therapy with cabergoline, prolactin levels were not normalised yet, and MRI scan revealed that tumour size had only shrunk mildly, patient not having experienced any significant side effects, and ophthalmology follow-up revealing possible early bitemporal hemianopia, the cabergoline dosage was increased to 2.5 mg two times per week. Concurrently, the thyroxine dosage was increased to 75 µg in view that the thyroxine levels were only

Figure 1 Before medical treatment: (A) and (B) show the coronal (T2-weighted) and sagittal (T1-weighted postcontrast) views respectively of the MRI scans obtained at the onset of medical treatment.

Figure 2 After medical treatment: (A) and (B) show the corresponding MRI scans obtained 6 months after the onset of medical treatment.

Figure 3 Pituitary adenoma. (A) Nests of polygonal tumour cells with uniform nuclear features. (H&E, original magnification $\times 200$) Diffuse prolactin reactivity in tumour cells (inset). (B) Dense tumorous fibrosis with diminution of tumour cell size. (H&E, original magnification $\times 200$) Persistent reactivity for prolactin in dense fibrocollagenous areas (inset).

within the low end of normal range. Patients with prolactinomas who do not respond to typical dosages of dopamine agonists (as evidenced by the serum prolactin concentration not normalising) may respond if higher dosages of dopamine agonists were used.³ This should only be done provided that no significant side effects have been experienced by the patient.³ Higher dosages may be associated with higher risk of valvular heart disease,³ and hence, in the case of our patient, a 2D-echocardiogram was arranged for the patient to monitor for valvular heart disease. Full blood count results, including haemoglobin, were within the normal limits throughout the course of medical treatment with cabergoline.

Approximately 9 months after the onset of medical treatment with cabergoline, the patient developed significant tricuspid valve regurgitation which was moderately severe on 2D-echocardiogram done as a screening tool in view of higher dosages of cabergoline used on the patient. Patient, however, was free from symptoms such as shortness of breath. Further worsening of the tricuspid regurgitation could potentially have led to adverse outcomes including open heart valve intervention. A cardiology consult was made. Even though our patient developed valvular disease at 9 months after the onset of treatment, cabergoline was continued at 1.0 mg, two times per week. This was because of deteriorating visual fields suggested by early bitemporal hemianopia. Moreover, cabergoline dosage was reduced to a low dose, and the overall cumulative dosage was also low. In addition, cabergoline dosage was continued because a further cardiac MRI was done and showed only mild tricuspid valve regurgitation. In addition, left ventricular ejection fraction was normal in our patient. Moreover, studies including that of Kars *et al*⁴ have shown that it would be the cumulative dose of cabergoline that would predispose patients to significant valvular abnormalities; and in our case report, the cumulative dose was relatively much lower.

The dosage of thyroxine was increased to 100 μ g once every morning in view that the free thyroxine levels were in the low end of the normal range. The patient was promptly referred to the neurosurgical team for discussion of resection of the pituitary tumour.

TREATMENT

Cabergoline was discontinued 1 day prior to the neurosurgery. At approximately 18 months after the onset of medical treatment with cabergoline, the patient subsequently underwent endoscopic transnasal transsphenoidal resection of the pituitary tumour. Neuronavigation system (Medtronic) was used for image guidance. During removal of the lesion, the tumour was found to be tough and fibrous. It was very adherent to the medial wall of the cavernous sinus wall and dura of the sella turcica. The tumour was carefully removed piecemeal using curettes and

pituitary rongeurs. The tumour was completely removed, but there was an inadvertent breach at the diaphragm sellae which was repaired using a nasal septal flap. Intraoperatively, there was cerebrospinal fluid (CSF) leak which resolved.

OUTCOME AND FOLLOW-UP

The pituitary adenoma was composed of nests of polygonal cells with uniform round nuclei, fine nuclear chromatin and moderate amounts of amphophilic to finely vacuolated cytoplasm (figure 3). The tumour cells lacked significant nuclear atypia and did not exhibit an increase in mitotic activity or necrosis. Dense tumorous fibrosis was present. In the areas with significant interstitial and perivascular fibrocollagenous deposition, the tumour cells showed diminution of cell size and condensation of nuclei. The tumour cells showed diffuse expression for prolactin. Reactivity for prolactin immunohistochemistry in the tumour cells in dense fibrocollagenous areas persisted.

In the immediate postoperative period, patient recovered well with only mild giddiness, but there was no headaches, no nausea nor vomiting, no postnasal drip and no visual field defects. The cabergoline remained withheld in the postoperative period. Intravenous hydrocortisone was given preoperatively and slowly tapered down postoperatively. Thyroxine was continued at 100 μ g once every morning (premeal). In postoperative day 1, patient complained of episodes of polyuria overnight which resolved spontaneously. Diabetes insipidus workup (serum Na, serum osmolality, urine osmolality) was done, and diabetes insipidus was ruled out subsequently. Otherwise, our patient had no other complications and was haemodynamically stable. MRI brain done on postoperative day 1 revealed that patient's status was post-transsphenoidal hypophysectomy nasal septectomy and grafting with nasal packing and haemorrhagic material seen filling the posterior nasal cavity and sphenoid sinus. There is interval debulking of the pituitary mass, with non-enhancing haemorrhagic debris within the surgical cavity. The margin again abuts the bilateral cavernous internal carotid arteries (ICA) and optic chiasm. The enhancement along the surgical margin and pachymeninges is probably postsurgical.

Ear, nose and throat (ENT) specialists were also involved in the management of this patient and they noted no episodes of CSF rhinorrhoea and removed the nasal packs on the postoperative day 4. Patient was discharged medically fit and well on postoperative day 7 with no further complications. ENT review 1 week postdischarge revealed on examination that there was a small synechiae at right inferior turbinate and septum suggestive of a break. No CSF rhinorrhoea or leak was noted. There was crusting at the area of the nasal septal flap. Neurosurgery review 1 week postdischarge revealed that patient was well. Patient did not complain of any visual problems or headaches. There was no galactorrhoea. Endocrinologist review 2 months postdischarge revealed that patient was well, clinically euthyroid without goitre, did not have visual problems nor headaches, no galactorrhoea nor problems with libido. A repeat MRI brain to look in particular at the pituitary gland was arranged 8 months later postoperatively, postponed 2 months later on patient's request secondary to financial constraints.

Ophthalmology review revealed that Humphrey's visual fields were stable and within normal limits. Cardiology review revealed that patient did not have chest pain nor shortness of breath, no orthopnoea, no paroxysmal nocturnal dyspnoea, no swellings of the extremities to suggest heart failure. There was no giddiness nor palpitations. Their main concern was that of moderate tricuspid regurgitation secondary to cabergoline-induced valvulopathy. A

repeat transthoracic echocardiography was arranged 18 months later to evaluate the heart function. Meanwhile, cabergoline has been stopped since the day of the operation.

MRI brain done 8 months postoperatively revealed normal enhancement of nasoseptal flap and no residual tumour seen. Neurosurgeons reviewed the patient and deemed him well to be followed-up in 1 year's time. Our patient went into successful biochemical remission postoperatively.

DISCUSSION

We have described a case of a patient with prolactinoma complicated by secondary hypogonadism and secondary hypothyroidism who had good biochemical response to cabergoline but subsequently, developed moderately severe tricuspid regurgitation and in view of potential cardiac complications coupled with deteriorating visual fields, was surgically managed subsequently.

It is unusual for patients being treated with cabergoline to develop fibrosis of prolactinomas. As compared with tumours exposed to cabergoline, prolactinomas that were initially managed with bromocriptine have greater chances of becoming fibrous.^{1 5–10} In literature, fibrosis of prolactinomas occur after a prolonged period of treatment with bromocriptine, involving many years.⁶ Interestingly, our patient developed this fibrous change of prolactinoma detected via MRI scan of the brain after a mere 6 months of medical therapy with cabergoline, and intraoperatively the tumour was found to be harder to remove as well.

As a consequence of a wide array of pharmacological actions at multiple receptors, dopamine agonists such as bromocriptine and cabergoline have multiple side effects that could broadly be classified into three major categories: (1) side effects related to the gastrointestinal system (most commonly, nausea, vomiting, abdominal pain and constipation), (2) side effects related to the cardiovascular system (including that of fibrosis of cardiac valves) and (3) side effects related to the neurological system (most commonly, headaches, drowsiness, dizziness and weakness).^{10–12} An important side effect to note is that of psychosis which occurs less frequently, and is fully reversible with the cessation of usage of dopamine agonists.¹² Other psychiatric side effects such as anxiety and depression occur more commonly, yet are not easily picked up clinically.¹² Side effects are dose related, and patients who are susceptible usually present at the initial stages of medical treatment with dopamine agonists.^{11 12} Approximately 9 months after the onset of medical treatment, the patient developed significant tricuspid valve regurgitation which was moderately severe on 2D-echocardiogram. In view of potential adverse cardiac outcomes that might require open heart valve intervention, the patient was surgically managed subsequently. Apart from fibrosis of his cardiac valves, the patient did not experience any other adverse effects from his medical treatment with cabergoline.

In terms of both side effects and effectiveness, the more selective dopamine agonist, cabergoline, has consistently fared better than bromocriptine.^{11 12} Furthermore, with a longer half-life, cabergoline needs to be taken only once or two times weekly. By contrast, bromocriptine needs to be taken two times or three times a day, because of a shorter half-life. Thus, patients' compliance is enhanced with the usage of cabergoline.^{10 12} In spite of all these benefits that come with the usage of cabergoline, there have been rare reports of cabergoline-induced severe immune haemolytic anaemia.¹² While it is a rare occurrence, severe immune haemolytic anaemia is life-threatening and hence should be taken into serious consideration, especially when using cabergoline in

the medical treatment of prolactinomas in children and adolescents.¹² This rare phenomenon was also taken into consideration in the care of the patient, with regular full blood counts revealing that there was no signs of anaemia, with the haemoglobin levels consistently within the normal limits, throughout the course of his medical treatment with cabergoline. Nevertheless, in spite of cabergoline generally being better tolerated in terms of side effects, in the case of our patient, fibrosis of his cardiac valves still occurred, which led to tricuspid valve regurgitation. This adverse cardiac side effect was also potentially life-threatening, and together with his deteriorating visual fields, a neurosurgical intervention was crucial.

Endoscopic transnasal transsphenoidal resection of the pituitary tumour involves operating through small channels via the nose and removing the tumour via a small opening in the sellar floor. Most pituitary tumours are soft and easily suctioned, rendering this form of surgery appropriate. However, if the tumour becomes tough and fibrotic, it would be very difficult and potentially dangerous to attempt to suction the tumour completely, due to the fact that there are vital structures such as the cavernous sinus and ICA and anteriorly the optic chiasm, just next to the sellar floor. Our neurosurgeons found that the pituitary tumour was significantly harder to remove as compared with other cases they have encountered.

There are three schools of thought on the effects of tumour fibrosis on surgical treatment of prolactinomas.¹³ At one end of the spectrum, some studies have shown that fibrous tumours are more difficult to remove surgically, and this might result in a higher incidence of intraoperative complications such as CSF leak and postoperative complications like hypopituitarism and diabetes insipidus.^{14–17} At the other end of the spectrum, other studies reported that the initial management of prolactinomas with dopamine agonists could improve rates of success of the surgery, through reducing the size of the tumour preoperatively, and that outweighed the impact of tumour fibrosis on surgical outcomes.^{18–20} Menucci *et al*¹ concluded that regardless of the nature of the tumour—be it fibrous or non-fibrous—patients' outcomes in terms of intraoperative and postoperative complications aforementioned, did not vary significantly. Postoperatively, our patient did not experience major complications such as that of hypopituitarism and diabetes insipidus. Septal perforations and upper dental anaesthesia are frequent complications of the standard surgical approaches.^{21 22} Our patient did not experience upper dental anaesthesia postoperatively. However, septal perforation occurred.

Menucci *et al*¹ observed that fibrous tumours had a smaller chance of going into biochemical remission postsurgery than non-fibrous tumours (0% vs 37%). This trend had actually been reported before by Landolt *et al*²³ during the time when the first reported instance of fibrosis of prolactinoma after dopamine agonist therapy was noted. Landolt *et al*²³ went on to postulate that due to bromocriptine induced fibrosis, there was a loss of distinction between adenoma and normal pituitary tissue. This, in turn, lowered the chances of effective removal of the actual tumour, and hence prolactin levels were harder to normalise postoperatively. This explanation was supported by Esiri *et al*.⁶ However, an alternative perspective was that initial medical management with dopamine agonists could shrink the tumour and this eased the process of effective surgical dissection of the tumour, and subsequently, resulted in better normalisation of prolactin levels.¹⁹ One study done by Faglia *et al*²⁴ suggested the possibility of reversing bromocriptine-induced tumour fibrosis by halting dopamine agonists' usage a few months prior to the actual surgery. In the case of our patient, after the fibrous

tumour was removed via the neurosurgery, our patient went into successful biochemical remission. This is in spite of the fact that cabergoline was only stopped 1 day prior to the neurosurgery.

The importance of fibrosis of prolactinoma to a neurosurgeon is a widely debated and controversial issue. At one end of the spectrum, it is difficult to distinguish normal from abnormal pituitary tissues secondary to cabergoline-induced fibrosis. At the other end of the spectrum, the tumour may enlarge if cabergoline is stopped for long periods of time preoperatively. Nevertheless, more studies are required to shed light on the possibility of using surgical findings of tumour fibrosis to prognosticate biochemical remission postsurgical intervention, and whether or not we should cease medical therapy a few months prior to the surgical removal of prolactinoma.

Fibrous tumours were reflected as being isointense to hyperintense on T2-weighted images on MRI, and ranges from low intensity to isointensity to high intensity on T1-weighted images on MRI.^{25 26} Correspondingly, in our patient, a MRI scan done 6 months after the onset of medical treatment showed that the tumour was found to have shrunk in size, with an increased signal on the T2-weighted coronal (figure 2A) section and reduced central enhancement on the T1 postcontrast sagittal (figure 2B) section. Interestingly, it was also noted that despite the reduction in size of the tumour centrally, there was persistent tethering at the dural margins and persistent suprasellar tumour seen insinuating around the optic chiasm and anterior cerebral artery, an indication of the surgical challenge in removing the tumour in its entirety.

Yamamoto *et al*²⁷ suggested that tumour consistency of pituitary macroadenomas could be predicted accurately by contrast-enhanced 3D FIESTA than do conventional MRI imaging techniques such as contrast-enhanced T1-weighted and T2-weighted MRI imaging. Nevertheless, in Singapore, contrast-enhanced 3D FIESTA is not routinely used in clinical practice.

The transsphenoidal approach is efficacious in removing pituitary adenomas in normal circumstances. However, this procedure becomes more complicated when fibrous tumours are met. Fibrous pituitary adenomas are generally harder to remove in one-stage operations, particularly if the tumours are large.^{15 26} Such cases involving larger fibrous macroadenomas may require two-stage operations.²⁶

Learning points

- Fibrosis of prolactinoma can occur with usage of cabergoline.
- In the care of patients undergoing medical treatment with dopamine agonists, both the common and the life-threatening adverse effects of dopamine agonists need to be taken into consideration.
- More studies are required to find out whether tumour fibrosis could be used to prognosticate biochemical remission postsurgical intervention.
- Further research could also be done to explore whether or not medical therapy should be ceased a few months prior to the surgical removal of prolactinoma.
- Greater emphasis could potentially be placed on assessing the consistency of pituitary macroadenomas via routine preoperative MRI scans or preoperative contrast-enhanced 3D Fast Imaging Employing Steady-state Acquisition to determine its fibrosity, allowing better planning of the neurosurgery.

While Yamamoto *et al*²⁷ excluded patients who underwent prior surgery or any other forms of prior medical therapy for the pituitary macroadenomas, assessing the consistency of pituitary macroadenomas which have been initially treated with dopaminergic agents through contrast-enhanced 3D FIESTA is certainly a prospect to be further explored in the future. This could potentially change neurosurgical practice and benefits could be accrued in terms of better planning of the surgery from the neurosurgeons' end, and also better preparation of the patient for a possibility of a second surgery, should the tumour be predicted to be fibrous preoperatively.

Contributors NM and CYY were actively involved in the literature review and conceptualisation of this case report, as well as the writing and editing of the entire manuscript. NM and CYY were also involved in coordinating the team, taking charge of the administrative aspects of this case report. GGH has provided the team with the pathology images and has written up the pathology section of the manuscript. He also contributed to the overall editing of the manuscript. ET has provided the team with the radiology images and has written up the radiology section of the manuscript. He also contributed to the overall editing of the manuscript. KT has written up the surgical treatment section of the manuscript as he was the neurosurgeon in charge of the patient's neurosurgery and care. He also contributed to the conceptualisation and overall editing of the manuscript. TTY contributed to the conceptualisation and overall editing of the manuscript. He also provided invaluable advice and insight into the technicalities of the neurosurgical aspect of this case report.

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