

Coexistence of Craniopharyngioma and Cranial Fibrous Dysplasia: A Clinicopathological Study of 5 Cases and Literature Review

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Research Article

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Abstract

Background:

Craniopharyngioma (CP) and cranial fibrous dysplasia (CFD) are both rare embryonic benign cranial diseases that most commonly present during childhood or adolescence. Co-existence of CP and CFD is extremely rare, which has never been reported before.

Methods:

We retrospectively reviewed the data of 5 patients coexisted with CP and CFD in Beijing Tiantan Hospital from January 2003 to January 2021. Their clinicopathological features, treatment modalities, and outcomes were summarized. Moreover, a comprehensive literature review was conducted, and in order to explore the potential connection leading to this coexistence, the CFD characteristic GNAS gene and corresponding Gsa protein were tested in the CP

Results:

There were 4 males and 1 female (median age, 39 years) in the present series. The symptoms mainly included headache, dizziness, fatigue, polyuria/polydipsia, hypogonadism and blurred vision. Sphenoidal bone is the most common involved bone by CFD (n =4). Four patients had undergone surgery to remove the CP (1 transsphenoid and 3 transcranial). Complete and subtotal resection were achieved in 2 cases respectively. The tumor subtypes were 3 adamantinomatous, 1 unknown subtype. The common postoperative complications are pan-hypopituitarism, diabetes insipidus, and hypothyroidism. The mean follow-up time was 57.2 months. Postoperative hormone replacement was required in 2 patients. 3 patients underwent a genetic study of tumor specimens. GNAS mutations were not detected, but they were positive for Gsa protein.

Conclusions:

Though the definite causative relationship has not been proved, the coexistence of CP and CFD should not completely be excluded potential interplay or atypical FD course for the uncommon manifestations of CPs. Prompt diagnosis and appropriate treatment are more challenging than for solitary CPs for the deformations of skull base, as of now, management strategies are aimed at surgical treating the CP and regularly monitoring the CFD.

1. Introduction

Craniopharyngiomas (CPs) are rare epithelial tumors arising along the path of the craniopharyngeal duct and account for 2–5% of all the primary intracranial neoplasms [1, 2]. There are two major histological subtypes of CP, adamantinomatous craniopharyngioma (ACP) and papillary craniopharyngioma (PCP), differ in their genesis and age distribution [3, 4]. Although the histological grade of CP is usually low, the patient's prognosis and outcome are significantly related to morbidity and mortality, making CP one of the most challenging tumors to treat.

Fibrous dysplasia (FD) is a benign skeletal disorder caused by somatic GNAS activating mutations [5]. It may account for 7 % of benign bone tumors and the craniofacial sites are the most common involved regions [6, 7]. Patients may exhibit involvement of one bone (monostotic FD; MFD), multiple bones (polyostotic FD; PFD) or they may have McCune-Albright syndrome (MAS), which has been classically defined by the triad of PFD, café-au-lait skin macules and endocrinopathies [8].

Disfigurement and thickening of cranial bone caused by coexistent CFD make the treatment of CPs more complicated and limited studies could be referred. In addition, the pathogenesis of such coexistence remains unclear. In this study, we present our experience with successful treatment of five CPs patients with CFD, with a discussion of the optimal therapeutic strategy and possible potential links of such association.

2. Materials And Methods

2.1 Patients

We retrieved the medical records of patients who were diagnosed as CP with CFD in Department of neurosurgery, Beijing Tiantan Hospital, Capital Medical University from January 2003 to November 2021. A total of 5 patients were diagnosed with the coexistence of CP and CFD at the same time. Their demographic data, clinical manifestations, physical examination, surgery and treatment procedures and outcomes were verified in the clinical medical report. Patient follow-up data come from our outpatient and telephone follow-up. Endocrine data were measured by laboratory examination of hormone levels and their radiological data were screened from PACS in our hospital. All patients underwent contrast-enhanced magnetic resonance (MR) imaging and computed tomography (CT) before and after treatment. This study was approved by the hospital ethics committee and informed consent was obtained from individual patient at the follow-up.

2.2 Immunohistochemistry and genetic analysis

Immunohistochemistry was performed to detect protein expression of Gsa in CPs specimens. The tissue sections were incubated with primary antibody, Gsa (1:100, sc-365855, Santa Cruz). Each stained slide was individually reviewed and scored by two independent neuropathologists.

Genomic DNA was extracted from paraffin-embedded CPs specimens using the Wizard Genomic DNA Purification kit following the manufacturer's instructions (Promega, Madison, WI).

3. Results

3.1 Patient characteristics

The clinical, therapeutic, pathological and prognostic characteristics of 5 patients were shown in Table 1. There were 4 males and 1 female (median age, 39 years; range, 29-55 years) in the present series. The mean follow-up time was 57.2 (6-98) months. The preoperative symptoms included headache (n=2), dizziness (n=2), polyuria/polydipsia (n=2), fatigue (n=2), visual deterioration (n=1) and hypogonadism (n=1). One patients were given diagnoses incidentally during a physical check-up (case 5). The duration of symptoms ranged from 1.0 to 24.0 months with a mean length of 8.2 months. None of the patients received previous radiotherapy or surgery. Sphenoidal bones (n =4) are the most common involved bones by FD and no patients had FD diagnosed before.

3.2 Radiographic characteristics

Table 2 summarized the radiological characteristics of all included 5 patients. And preoperative MRI, CT and MRI of 3-month follow-up were shown in Figure 1. The CPs were mainly located in the sellar/suprasellar region (n=5). Four tumors were suprasellar with extension to the third ventricle (case 1, 2, 3, and 4), 1 tumor was purely suprasellar (case 3), and 2 tumors had extension into the sella (case 1, 2). Different from the general adult CP, the CP coexisting with CFD is mainly cystic in our study (n = 5). The CPs of cases 1, 2 and 4 showed hyperintensity on T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI). The CPs of cases 2 and 5 showed isointensity on T1WI and hyperintensity on T2WI. After Gd-DTPA administration, the tumors showed inhomogeneous nodular and ring enhancement (n=3), ring enhancement (n=2) in contrast-enhanced T1-weighted imaging (CE-T1WI). Additionally, hydrocephalus was found in 1 patient (case 4).The CFDs were mainly located in the sphenoid bones (n=4), and maxilla (n=1), appears thickening of skull bone with mixed signal (n=4). As shown in **Figure. 2**, calcifications were found in all 5 patient by CT scan, including cyst wall (n=3), intrasella (n=1) and intratumours (n=1). CT scans showed typical CFD in all included 5 patients, with 4 mixed radiolucent and 1 “ground-glass” manifestations. Sphenoidal bone is the most common involved bone by FD (n =4), followed with maxilla (n=2), ethmoid (n=1) and clivus (n=1).

Table 2
Radiological characteristics of all included five patients in our study

No.	CP							FD		
	Location	Pattern	Size (cm)	MRI	CT	Hydrocephalus	Calcification	Location	MRI	CT
Case.1	Intra/suprasellar/third ventricle	Cystic	3.3x3.3x3.2	T1WI, high; T2WI, high;CET1WI, INRE	Low	No	Cyst wall	Sphenoid wing; Zygomatic process of the maxilla (L)	Mixed; CET1WI, NE	Mix
Case.2	Intra/suprasellar/third ventricle	Cystic	2.4x2.6x3.7	T1WI, high; T2WI, high; CET1WI, INRE	Low	No	Intrasella	Sphenoid body; Ethmoid	Mixed; CET1WI, NE	Mix
Case.3	suprasellar	Cystic	2.0x2.2x2.2	T1WI, iso; T2WI, high;CET1WI, IRE	High	No	Cyst wall	Sphenoid wing (R)	T1WI, iso; T2WI Hypo; CET1WI, NE	Groi glas
Case.4	suprasellar/third ventricle	Cystic	3.3x2.8x4.0	T1WI, high; T2WI, high;CET1WI, INRE	Mixed	Yes	Intratumours	Maxilla (R)	Mixed; CET1WI, NE	Mix
Case.5	suprasellar/third ventricle	Cystic	1.7x2.0x2.2	T1WI, iso; T2WI, high;CET1WI, IRE	Low	No	Cyst wall	Sphenoid body and wing (L) ; Clivus,	Mixed; CET1WI, NE	Mix

3.3 Endocrinal abnormalities

Preoperative endocrinological deficits were found in 3 patients, including hypothyroidism (n=2), hypogonadism (n=1). Hyperprolactins was found in case 2 and 3, which was thought for stimulated of the pituitary stalk. Postoperative hormone deficits included panhypopituitarism (n=2), hypothyroidism (n=2). Transient and permanent diabetes insipidus were observed in 1 patients, respectively.

3.4 Surgical approaches and complications

Four of five patients were performed surgical resection of CPs (3 transcranial and 1 transsphenoidal). Case 5 refused surgical treatment for it is founded incidentally without any discomfort, and the patient is still under close observation and regular follow-up. Case 4 was performed ventriculo-peritoneal (VP) shunt before tumor resection for hydrocephalus. Case 3 underwent FD resection with optic nerve decompression, his preoperative vision was normal, but his postoperative vision was still impaired even after surgical repair. Extent of resection was confirmed both by intraoperative impression and immediate postoperative imaging in all cases. The extent of resection was considered gross total in 2 patients and subtotal in 2 patients respectively.

Postoperative complications included panhypopituitarism (n=2), diabetes insipidus (n=2), visual loss (n=1), and hypothyroidism (n=2), meningitis (n=1), hypernatremia (n=1), central fever (n=1), thrombus of lower extremity veins (n=1). All the patients didn't receive any adjuvant therapy postoperatively.

3.5 Histopathologic Findings

Regarding the subtypes of craniopharyngiomas, there were 3 ACPs and 1 unidentified (Figure.3). DNA sequencing was performed on the CPs specimens of cases 2 and 3 to detect GNAS mutations, and no GNAS mutations were detected (Supplementary Figure 1). However, the immunohistochemical results found a strong positive Gsa expression (Figure.4).

3.6 Follow-up and outcome

The median follow-up period was 57.2 months (range, 6-98 months). During the follow-up period radiological recurrence occurred in 1 patient (case 1). And long-term hormone replacement therapy was given in case 1 for permanent panhypopituitarism. The CP of case 4 was obviously calcified, closely related to blood vessels, and pathologically showed brain invasion (Figure.5). Therefore, the patient's operation is very difficult. After the operation, the patient's hypothalamic/pituitary function is severely damaged, causing water and electrolyte imbalance, lower limb vein formation, and dying of pulmonary embolism caused by thrombosis 6 months after the operation.

4. Discussion

To the best of our knowledge, this is the first cases report of coexistence of CP and CFD that highlights the diagnostic and management challenges. In addition to summarize the clinicopathologic features, treatment modalities, and outcomes of the cases, we also review the existing literature on analogous event and discussed possible links of this coexistence by genetic mutation detecting and immunohistochemical study.

The incidence of coexistence of primary brain tumors of different pathologies is low and the most common association is meningioma and glioma, followed by meningioma and pituitary, for that these are the most common primary intracranial tumors [9]. The definite pathogenesis of this coexistence remains unknown, except familial or hereditary diseases such as neurofibromatosis type 2 or multiple endocrine neoplasia 1. Several hypotheses have been advocated to explain this phenomenon including purely coincidence, surgical trauma, radiation and/or chemical exposure, and genetic predisposition, but all in debating [10–12].

Because the sellar region has complex embryonic development, it is easy to coexist with primary intracranial tumors of different cell types at the same time. However, CPs coexisting with other central nervous system neoplasms is extremely rare. To the best of knowledge, a few cases have been reported, and the most common coexisted tumors are pituitary adenomas and meningiomas. According to a latest review reported, only 22 CP patients (median age 47.0 years; 15 males 7 females) were reported associated with pituitary adenoma and 19 out of 22 were ACPs [13]. Guofang Liu et al reported there were 8 patients (median age 62.0 years; 5 males 3females) with coexistence of CP and meningioma, and 5 out of 8 were ACPs [14]. Similarly, in our 5 cases (median age 39 years; 5 males 1females), 3 out of 4 operative patients were ACPs. It is found that such coexistence are more likely to occur in adults and type of ACPs, with an obvious male predominance. This is obviously different from the ACP that occurs alone, which has no gender orientation and is more common in adolescents [15]. It is indicated that there is some underlying reason for CPs coexistence with other CNS diseases rather than purely by chance and some factors may stimulate ACP cells to induce a secondary tumor formation which is quite different from PCPs.

On the other hand, FD could also occur in association with other primary brain tumors, which is in two different conditions. The first was purely accidental and coexisted with the most common brain tumor-meningiomas, of which only a few cases were reported [16, 17]. The second, coexistence with PA, which might be in accord with McCune-Albright syndrome (MAS), and there were dozens of cases had been reported. As a postzygotic disease, clinical spectrum and severity of FD varied depending on the timing of the mutation [18]. In addition to the classic triad, there could be a broad spectrum or atypical presentations of the MAS [19]. Furthermore, MAS may be associated with gastrointestinal disease and breast cancer [20, 21]. Though, no GNAS mutations were detected in the CPs specimens in our cases. Their co-occurrence should not be completely excluded the possibility of atypical FD/MAS course, for immunohistochemistry staining were high expression of Gsa protein in the 3 specimens. Further studies are needed to clarify this issue.

Based on the typical clinical symptoms and imaging features, most CPs or CFDs could be diagnosed correctly. However, it is difficult to diagnose the coexistence of CP and CFD accurately and promptly before operation because the imaging features of FDs and CPs are variable and mutual influenced [22, 23]. Deformation and thickening of the skull base might make the situation more confused, especially when the two lesions adjacent to each other. However, it is important when devising a treatment strategy preoperatively to confirm which one was responsible for the clinical symptoms. In fact, in our present cases, 4 cases that underwent surgical treatment were diagnosed accurately preoperatively.

Treatment strategies for CP coexisting with CFD have yet to be established. The current standard of treatment in CP is surgical resection via a transcranial or extended endonasal endoscopic approach followed by adjuvant radiation therapy, if required for residual tumor [24]. Given the benign nature of CFD, and all the cases were adults, observation is considered adequate for asymptomatic quiescent FD [25]. On the other hand, all the primary symptoms such as headaches, fatigue, polydipsia and polyuria, visual impairment were diagnosed caused by CPs in all cases in our study, at present, management strategies are aimed at surgical resect the CP and regular monitoring of FD. With the progress of microsurgery and endoscope technology, the surgical obstacles and risks

caused by skull hyperplasia and deformation caused by FD will be gradually reduced. Our results also show that there were no complications directly related to surgery except vision deteriorate in case 3 for preventive decompression of optic canal encased by FD. It should also be noted that FD radiotherapy may produce side effects of malignant transformation [26].

The prognosis of collision tumors composed of CP and PA were undefined for the small number of cases. From our experience, it is similar to sporadic CPs and long-term morbidity is associated with tumor and treatment related risk factors. Our study has some limitations. As an extremely rare condition, the total number of cases is small and more cases are needed to strengthen the reliability of data. Secondly, the deep mechanism of the coexistence of CP and CFD still needs to be further explored and verified

5. Conclusion

In summary, we report a very rare case series of coexistence CP and CFD presented with clinicopathological features, treatment, and prognosis in detail. It is warranted comprehensive assess of this rare complicated situation and to decide the appropriate treatment strategy. Based on the clinical course of our case, the best choice of an individual treatment plan for CP or PA is certain and can lead to good prognosis. Meanwhile, the pathogenesis responsible for the coexistence of the two tumor types is still undefined, further studies should be required.

Declarations

Ethic approval and consent to participate

This study was approved by Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University. Due to the retrospective nature of our study, the board waived the need for written consent.

Consent for publication

All the patients included signed the consent for publication.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to individual privacy of the patients included but are available from the corresponding author on reasonable request

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No.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YHF analyzed and interpreted the patient data and was a major contributor in writing the manuscript. LZ designed the study and revised the manuscript. All authors read and approved the final manuscript.

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Not applicable

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Tables

Table 1 is available in the Supplementary Files section.

Figures

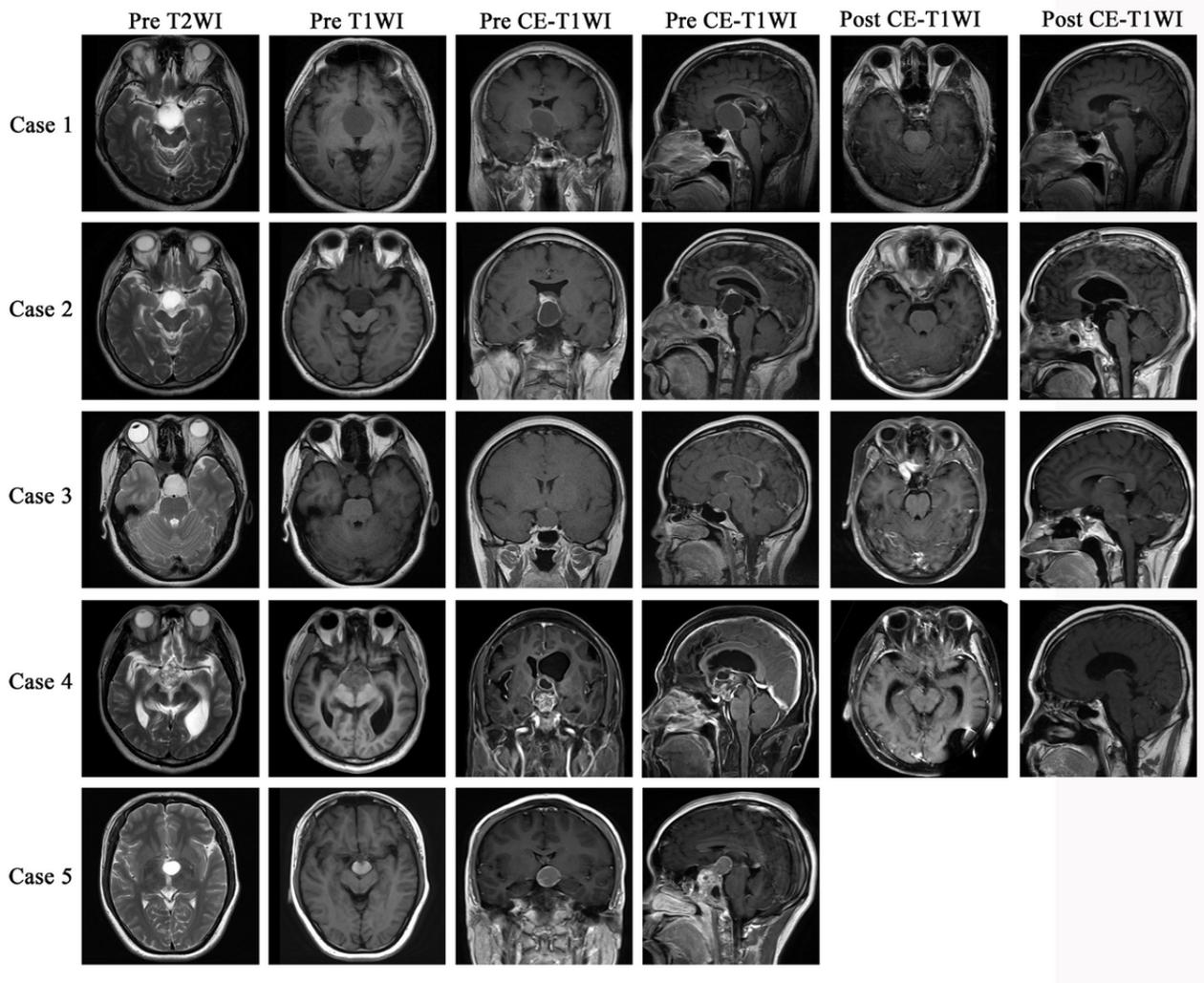


Figure 1
 Preoperative and postoperative MRI imaging findings of all included five cases. The first, second, third and fourth columns were the preoperative axial position T2-weighted imaging, axial position T1-weighted imaging, coronal position contrast-enhanced T1-weighted imaging (CE-T1WI), and sagittal position CE-T1WI MRI sequences, respectively. The fifth and sixth columns were the axial and sagittal position CE-T1WI MRI image reviewed in 3 months after surgery. Because case 5 did not undergo surgery, this is blank.

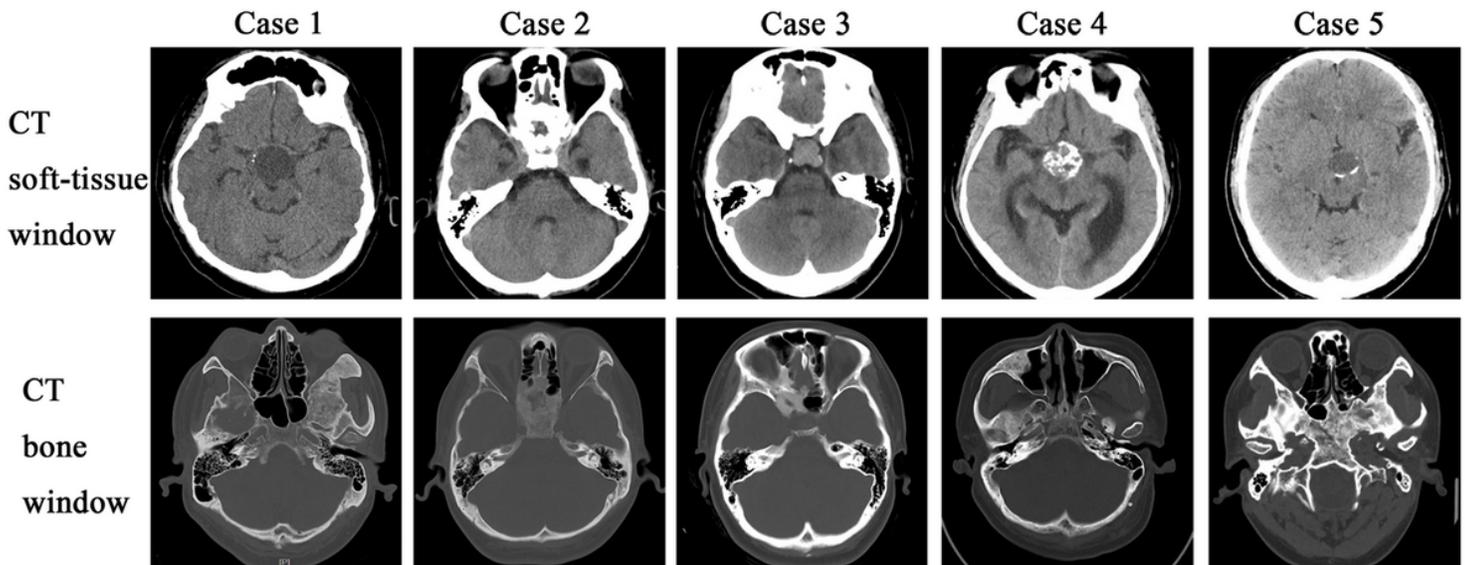


Figure 2

Preoperative CT imaging findings of five cases. The first line is the patient's head CT soft tissue window scan, showing low-density mass shadow in the sellar region, accompanied by varying degrees of calcification. The second line is the patient's head CT bone window scan, showing significant abnormal skull fibrous dysplasia.



Figure 3

Pathological hematoxylin-eosin staining analysis of patient's tumor specimen in case 1-4. The results showed that three were adamantinomatous craniopharyngioma (ACP) and one was craniopharyngioma without accurate subtype. (A) Histopathological studies revealed an ACP characterized by squamous epithelium arranged in a trabecular pattern as well as nodules of wet keratin in Case 1. (B) Postoperative pathology was ACP in Case 2. (C) The postoperative pathology of case 3 showed craniopharyngioma. After discussing with the pathologist, the specific subtype could not be accurately identified. (D) The case 4 was ACP, which invaded and infiltrated normal brain tissue



Figure 4

Immunohistochemistry analysis of Gsa expression of craniopharyngiomas in case 1-3. The results showed that Gsa was strongly positively expressed in all 3 cases.

Case 4

**Head
CTA**

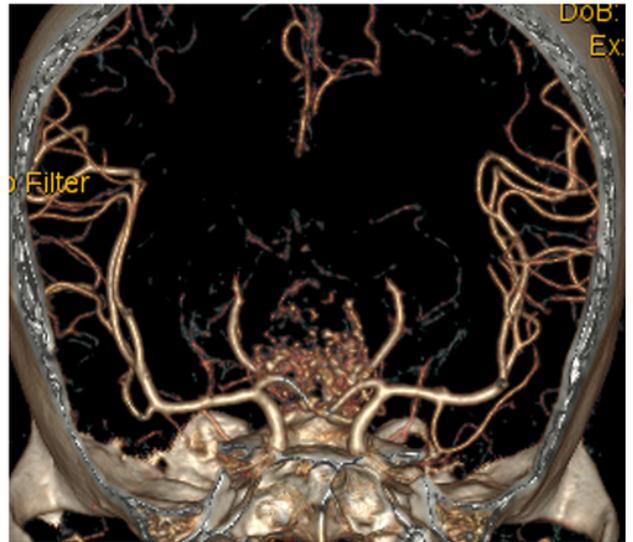
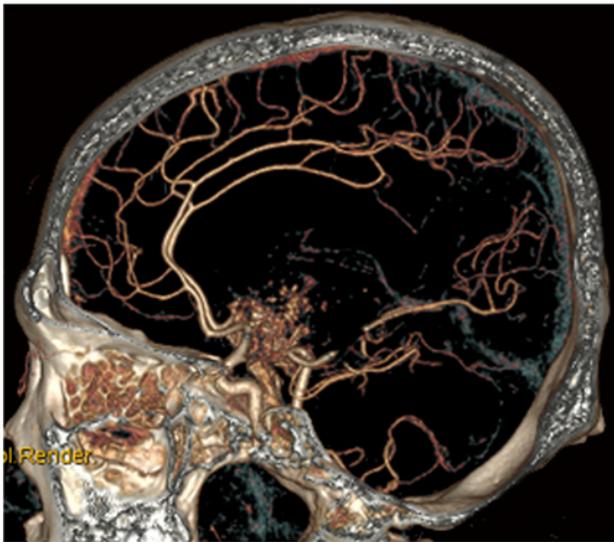


Figure 5

The head computed tomographic angiography (CTA) examination of the patient in case 4 showed that the tumor is closely related to the blood vessel, indicating that the operation is more difficult.

Supplementary Files

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