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Rathke cleft cyst with squamous metaplasia and activating mutations of mitogen-activated protein kinase signaling: illustrative case

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BACKGROUND Rathke cleft cysts (RCCs) are benign sellar/suprasellar lesions that result from mucin-secreting vestigial remnants within the pars intermedia of the pituitary gland. When symptomatic, they can present with retro-orbital headaches, visual field defects, and/or pituitary dysfunction.

OBSERVATIONS A 35-year-old female presented with subacute retro-orbital headache, right ptosis, and blurred vision. Workup revealed panhypopituitarism with central hypothyroidism and adrenal insufficiency. Imaging demonstrated a sellar/suprasellar mass with subacute intralesional hemorrhage, which was thought to represent chronic pituitary apoplexy. The patient underwent an endoscopic endonasal approach in which the initial intraoperative frozen section suggested papillary craniopharyngioma. Subsequent specimens suggested RCC, thus presenting a surgical management conundrum. Hemihypophysectomy with lesionectomy was performed. Final histopathology demonstrated RCC with squamous metaplasia (RCC-SM), rupture, and hemorrhage. *BRAF V600E* was not detected. However, activating mutations in *KRAS* and *MAP2K1* were identified.

LESSONS RCC can undergo SM and rupture, leading to a hemorrhagic-appearing cystic sellar/suprasellar mass associated with cranial nerve palsies and hypopituitarism that mimics pituitary apoplexy. Intraoperative frozen sections can be ambiguous due to overlapping histopathological features with craniopharyngioma, complicating surgical decision-making. The authors hypothesize that RCC-SM may represent a transitional state between RCC and craniopharyngioma. Neurosurgeons should be mindful of this transitional entity and be prepared to modify their surgical strategy accordingly.

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KEYWORDS apoplexy; craniopharyngioma; pituitary; Rathke cleft cyst; squamous metaplasia

Rathke cleft cysts (RCCs) arise from remnants of the Rathke pouch or diverticulum and consist of a single layer of ciliated cuboidal or columnar epithelium including goblet cells from which they secrete mucus into the cyst.[1] Management typically includes partial cystectomy and aspiration of the mucus, followed by marsupialization to the sphenoid sinus, achieving remission in 90% of the cases.[2] Craniopharyngioma also arises from the Rathke pouch. However, in contrast to RCC, these tumors consist of nonkeratinizing stratified squamous epithelium. A disease spectrum has been postulated from RCC to craniopharyngioma wherein there is a metaplastic transition from cuboidal or columnar epithelium to squamous and/or stratified squamous epithelium with goblet cells in craniopharyngioma.[3] Consistent with this, patients in the middle of the spectrum having RCC with squamous metaplasia (RCC-SM) have a 3-fold increased rate of cyst recurrence, implying that RCC-SM is a more aggressive entity than typical RCC. These histological variations are therefore crucial to consider during surgical decision-making, histopathological assessment, and patient counseling.[4,5]

Here, we present the unusual case of a 35-year-old female who presented with retro-orbital headaches, ptosis, visual field defects, and hypopituitarism in the setting of a sellar mass with suprasellar extension and intralesional necrosis, believed to represent chronic pituitary apoplexy. Histopathological analysis demonstrated a ruptured RCC with extensive SM, highly resembling papillary craniopharyngioma, although the *BRAF V600E* mutation, a molecular alteration present in 95%–100% of such tumors, was negative on immunohistochemistry and next-generation sequencing. However, activating mutations were identified in *KRAS* and *MAP2K1* (also known as *MEK1*), members

ABBREVIATIONS CT = computed tomography; ED = emergency department; EEA = endoscopic endonasal approach; MAPK = mitogen-activated protein kinase; MRI = magnetic resonance imaging; RCC = Rathke cleft cyst; SHA = superior hypophyseal artery; SM = squamous metaplasia.

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of the mitogen-activated protein kinase (MAPK) signaling cascade that includes *BRAF*. This suggests a clonal process with neoplasia arising from SM within an RCC. At the time of manuscript writing, these molecular alterations had not been previously reported in RCC, RCC-SM, or craniopharyngioma.

Illustrative Case

History and Examination

A 35-year-old female presented to the emergency department (ED) with a 3-day history of bifrontal retro-orbital headache for which she was taking aspirin and over-the-counter nonsteroidal anti-inflammatory drugs without relief. Of note, the patient was also taking omega-3 fish oil supplements daily. On initial examination, she was neurologically intact, with full visual fields on confrontation. Laboratory evaluation was unremarkable except for mild leukocytosis. Initial computed tomography (CT) scanning of the head demonstrated a 1.9-cm sellar mass with suprasellar extension, without acute intralesional hemorrhage (Fig. 1). The patient was discharged home but returned to the ED 2 weeks later with persistent headache, mild right ptosis, subjective right peripheral vision loss, and severe fatigue. Neurological examination confirmed trace right ptosis, but visual fields were full on confrontation. Upon further workup, the patient was found to have severe hypopituitarism with undetectable free thyroxine and undetectable cortisol (Table 1). She was started on pituitary hormone replacement, with marked improvement in her symptoms. Magnetic resonance imaging (MRI) demonstrated a 2-cm lobulated sellar/suprasellar mass with a radiographic signature consistent with subacute to chronic hemorrhage, and there was elevation and compression of the optic apparatus (Fig. 2). On automated perimetry, there was mild bitemporal superior quadrantanopia, more conspicuous on the right (data not shown). Given the working diagnosis of subacute pituitary apoplexy with mass effect on the optic chiasm and referable neurological defects, expedited surgery was indicated. The patient was taken to surgery the next morning, 4 days following her second presentation to the ED and 3 weeks following symptom onset.

Operation

A standard transellar transsphenoidal endoscopic endonasal approach (EEA) was performed. Upon dural opening, careful extracapsular dissection revealed an encapsulated heterogeneous mass with firm yellow fibrous material and cystic cavities containing grayish viscous material and chronic hemorrhage. The initial frozen section diagnosis was suggestive of papillary craniopharyngioma, although this was inconsistent with the gross intraoperative appearance (Fig. 3). Intraoperative images and video were unavailable due to a technical difficulty during the early stages of the COVID-19 pandemic that could not be repaired due to restrictions allowing only "essential personnel" to enter the hospital. A second, larger frozen section specimen demonstrated inflammatory necrosis with fibrosis and histiocytes as well as elements of an RCC. No pituitary adenoma was identified. The subdiaphragmatic plane was developed, and the pituitary gland

TABLE 1. Endocrine laboratory values

Test (reference range)	Initial Presentation	1.5 Yrs Postop	2 Yrs Postop
Na (136–145 mmol/L)	130	141*	141*
TSH (0.27–4.20 μIU/mL)	0.27	0.57	0.65
Free T4 (0.93–1.70 ng/dL)	<0.11	1.20†	1.33†
ACTH (7.2–63.3 pg/mL)	15.1		
Cortisol (2.7–10.5 μg/dL)	<0.2	6.1‡	6.6
Prolactin (4.8–23.3 ng/mL)	63.6		
FSH (1.7–21.5 mIU/mL)	<1.0		4.2
LH (14.0–95.6 mIU/mL)	1.2	1.8	4.8
GH (0.05–8.00 ng/mL)	2.2		
IGF-1 (81–278 ng/mL)	0.2	99	

ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; GH = growth hormone; IGF-1 = insulin-like growth factor–1; LH = luteinizing hormone; T4 = thyroxine; TSH = thyroid-stimulating hormone.
* Taking DDAVP 200/100/200 μg 3 times daily.
† Taking levothyroxine 88 μg daily.
‡ No longer taking hydrocortisone; cosyntropin stimulation test 16.5 μg/dL.

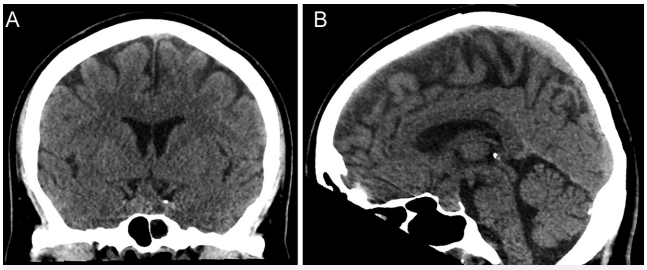

FIG. 1. Preoperative coronal (**A**) and sagittal (**B**) noncontrast CT images demonstrated a mixed isointense and hypointense sellar mass with suprasellar extension without evidence of acute hemorrhage of mineralization. There was retrosellar pneumatization without thinning of the sellar bone.

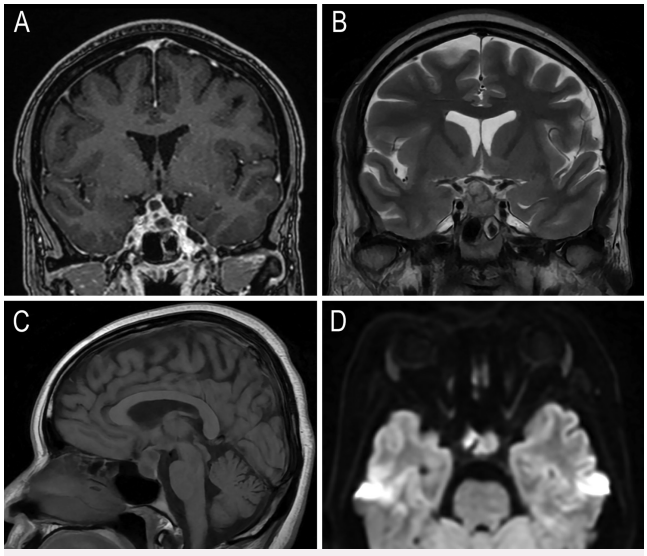

FIG. 2. Preoperative coronal postcontrast T1-weighted (**A**) and T2-weighted (**B**) MRI demonstrated an enhancing multilobulated sellar mass with surprasellar extension and compression of the optic apparatus, eccentric to the right. The lesion had mixed iso- to hypointensity on noncontrast T1-weighted imaging (**C**), and there was restricted diffusion within the lesion (**D**). The radiographic characteristics were most consistent with chronic intralesional hemorrhage.

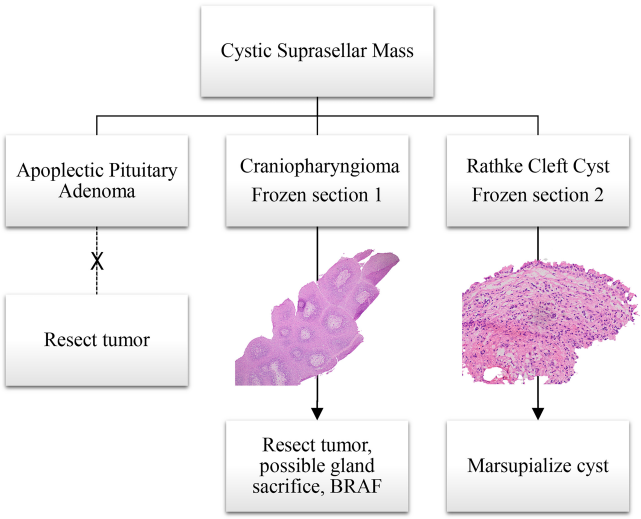

FIG. 3. Schematic demonstrating intraoperative data and decision-making. The lesion was initially thought to represent an apoplectic pituitary adenoma. The gross intraoperative appearance strongly refuted this diagnosis. The first frozen section suggested papillary craniopharyngioma, but this diagnosis was also rejected by the neurosurgeon based on the gross appearance (intraoperative imaging not available). A second frozen section suggested RCC. Given thrombosis of the left SHA and infraction of the left hemiphypophysis, left hemihypophysectomy was performed to decompress the optic apparatus and provide an adequate specimen for definitive histomolecular characterization.

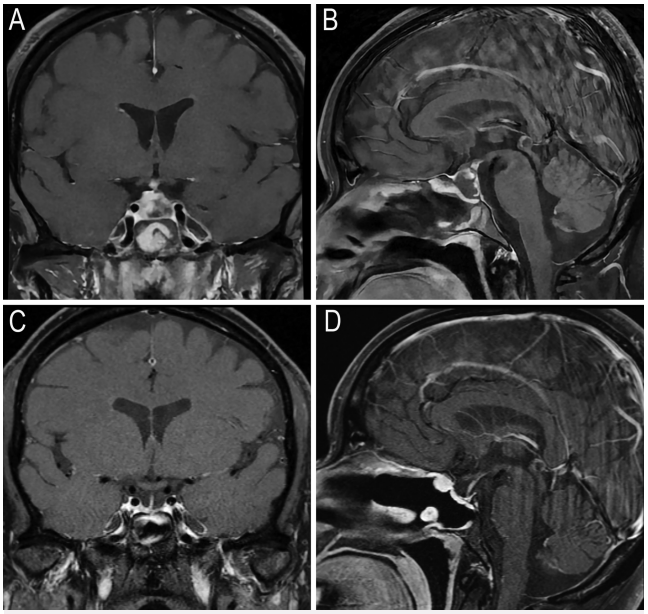

FIG. 4. Postoperative coronal (**A**) and sagittal (**B**) postcontrast MRI sequences demonstrated left hemihypophysectomy with decompression of the optic apparatus and cavernous sinuses. The pituitary stalk and gland demonstrated avid contrast enhancement, and the nasoseptal flap was well perfused. Similar imaging (**C and D**) 2 years postoperatively was without evidence of recurrence and demonstrated physiological enhancement of the pituitary stalk and gland. The suprasellar cistern remained widely patent.

and stalk were carefully explored. The pituitary stalk appeared to be viable. However, the left superior hypophyseal artery (SHA) was gray and appeared thrombosed, while flow appeared to be preserved in the right SHA. This pattern was also seen in the pituitary gland where the left hemihypophysis appeared pale gray and nonviable. The right pituitary gland appeared reddish-yellow and well perfused. The neurohypophysis was also identified and preserved surgically. After consideration of the available data, left hemihypophysectomy/lesionectomy was performed to decompress the optic chiasm and provide tissue for definitive histomolecular diagnosis. Given that the left gland was nonviable, hemihypophysectomy was not expected to result in additional patient morbidity. Having created a moderate flow cerebrospinal fluid leak from the suprasellar cistern, reconstruction was performed with an imbricated Duragen Plus inlay graft (Integra Corp.) in a "soft gasket seal" fashion, followed by a pedicled nasoseptal flap.[6] This was buttressed in place with Gelfoam, followed by Nasopore (Stryker).

Postoperative Course

Postoperative MRI demonstrated left hemihypophysectomy with decompression of the optic apparatus (Fig. 4A and B). The patient developed new diabetes insipidus postoperatively and was started on desmopressin. Her headache and visual symptoms rapidly improved, and she was discharged home on postoperative day 2 with levothyroxine, hydrocortisone, and desmopressin replacement, under the care of the endocrinology team. At the 4-month postoperative visit, the patient had complete symptom resolution and had returned to work, but she continued to have hypopituitarism requiring hormone replacement. She subsequently weaned off hydrocortisone 17 months following surgery and had a normal cosyntropin stimulation test. At the 2-year postoperative follow-up, the patient was neurologically intact with full visual fields. She remained headache free and was pleased to once again have regular menses. At the time of manuscript writing, she continued taking levothyroxine 100 µg, desmopressin 200/100/200 µg 3 times daily, and progesterone and estradiol, with regular progesterone-dependent menses. Surveillance imaging demonstrated an atrophic-appearing pituitary gland with wide patency of the suprasellar cistern (Fig. 4C and D). The pituitary stalk and gland demonstrated physiological contrast enhancement, and the nasoseptal flap remained well perfused.

Pathology

Sections of the resection specimen revealed portions of adenohypophysis encircling a central cystic structure (Fig. 5A). The gland exhibited retained acinar architecture indicative of normal adenohypophysis, with marked infiltration by inflammatory cells, including lymphocytes, plasma cells, and aggregated foamy macrophages associated with fibrin and granulation tissue. Other portions of the specimen showed papillary arrangements of stratified nonkeratinizing squamous epithelium supported by fibrovascular cores reminiscent of papillary craniopharyngioma, as seen in the first frozen section (Fig. 5B). The central cyst lining varied from strictly stratified nonkeratinizing squamous epithelium (Fig. 5C) to more slender squamous epithelial ribbons overlain by ciliated columnar epithelium with goblet cells (Fig. 5D), indicative of SM arising in an RCC. In other regions of the cyst wall, a transition to frank SM was observed (Fig. 5E). *BRAF V600E* immunohistochemical stain was negative (data not shown). Next-generation sequencing of the cyst wall confirmed *BRAF* wildtype

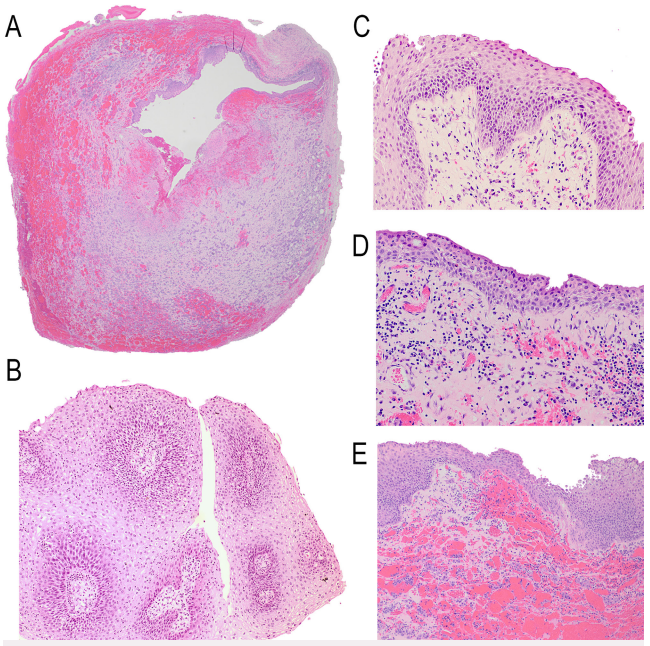

FIG. 5. Low magnification shows adenohypophysis encircling a central cyst lined by a focally interrupted layer of nonkeratinizing squamous epithelium (**A**). Focal papillary arrangements of stratified nonkeratinizing squamous epithelium supported by fibrovascular cores are reminiscent of papillary craniopharyngioma (**B**). The cyst wall varied from purely stratified nonkeratinizing squamous epithelium (**C**) to more slender squamous epithelial ribbons overlaid by ciliated columnar epithelium with goblet cells (**D**), indicative of SM arising in an RCC. At lower magnification, the transition from columnar epithelium to thickened SM was observed (**E**). Hematoxylin and eosin, original magnification ×12.5 (A), ×100 (B and E), and ×200 (C and D).

but also demonstrated activating mutations of *KRAS* (p.G12D) and *MAP2K1* (p.E203K, p.I111N), members of the MAPK cascade. Both mutations were present with a 30% allele fraction. There were also mutations in the methylcytosine dioxygenase *TET2* and the DNA topoisomerase *TOP1*, both with a 50% allele fraction. The clinical relevance of these mutations remains unclear. There were no other mutations or copy number alterations noted.

Informed Consent

The necessary informed consent was obtained in this study.

Discussion

Here, we present the unusual case of a young woman who presented with pituitary infarction in the setting of a ruptured hemorrhagic RCC with extensive SM, highly resembling a papillary craniopharyngioma on histopathology. Given severe retro-orbital headache, mass effect on the optic chiasm, and mild bitemporal quadrantanopia along with a new oculomotor nerve palsy, the patient was taken to surgery for apparent subacute pituitary apoplexy. The unusual gross appearance at surgery, together with the uncertain intraoperative histological diagnosis on frozen section, required critical intraoperative decision-making to optimize the patient outcome (Fig. 3). While the absence of pituitary adenoma was immediately clear at surgery, it remained unclear whether the lesion represented a papillary craniopharyngioma, as indicated by the first frozen section, or RCC, as indicated by the second frozen section. The intraoperative appearance of a firm, pseudoencapsulated cystic mass with paste-like xanthomatous internal contents created further uncertainty. The distinction between the two potential pathological entities was critical, given that the surgical strategy to address them is significantly different. For RCCs, EEA for marsupialization is the primary surgical strategy. The cyst wall is widely opened along the ventral surface to allow drainage into the sphenoid sinus and decompression of the diaphragma sellae while minimizing the risk of pituitary dysfunction.[4] This allows the internal secretory mucosa to evert and drain into the sphenoid. On the other hand, for craniopharyngioma, complete resection is the goal, with internal decompression followed by sharp extracapsular dissection and even sacrifice of the pituitary stalk if this would allow definitive gross-total resection.[7] More recently, less aggressive approaches have been advocated for papillary craniophyarngiomas, as clinical trials of *BRAF/MEK* inhibition have demonstrated significant tumor shrinkage and durable control of growth.[8,9] For adamantinomatous craniopharyngiomas, however, there are presently no targeted therapies available despite frequent mutations in beta-catenin (*CTNNB1*). Thus, stalk sacrifice is often necessary to achieve definitive gross-total resection for Stamm/Kassam type 2 adamantinomatous tumors.[7]

While histologically benign, craniopharyngiomas arise from the infundibulum and/or pituitary stalk and typically cause compression of the optic apparatus and pituitary gland. When large, tumors can extend into the third ventricle and cause compression of the hypothalamus and obstructive hydrocephalus. Craniopharyngiomas are often relentlessly adherent to surrounding neurovascular structures and require meticulous extracapsular sharp dissection, with early identification and preservation of the SHAs and their distal branches to the pituitary axis and optic apparatus. Similarly, it is also critically important for the surgeon to have a clear appreciation that overly aggressive attempts at removing a firmly implanted cyst wall from critical neurovascular structures such as the hypothalamus, optic apparatus, and supraclinoid internal carotid arteries carry a significant risk of permanent hypothalamic injury, vision loss, and catastrophic vascular injury. Although transcranial approaches have historically been performed for the resection of craniopharyngiomas, over the past 2 decades the expanded EEA has become the standard for Kassam type I–III tumors, as it offers a comparable extent of resection with superior visual and endocrinological outcomes as well as reduced complications.[7]

Observations

There are a few large cohorts of RCCs with immunohistochemical analysis in the literature suggesting that SM can be seen in 25%–40% of all RCC cases.[10–12] In one case series, the postoperative recurrence of a sellar mass with genetic markers of craniopharyngiomas was seen in half of RCCs-SM.[13] Another case series used the presence of *BRAF V600E* to reclassify 2 histologically diagnosed RCCs that contained SM and were found to harbor the *BRAF V600E* mutation.[5,14] In addition, a pediatric case of RCC-SM has been reported that was positive for the *BRAF V600E* mutation, in further support of a continuum between RCC-SM and the development of papillary craniopharyngioma.[15] However, another recent study concluded that there was no disease spectrum from RCC to craniopharyngioma based on the absence of *BRAF V600E* immunoreactivity in any of the 12 RCCs studied, while all 20 papillary craniopharyngiomas studied harbored the mutation.[11] Interestingly, the study also demonstrated that the myeloid surface antigen TREM1 was expressed in the squamous epithelium of all "mixed-type" papillary craniopharyngiomas (expression of both *CTNNB1* and *BRAF V600E*), as well as in all RCCs-SM, but not in

pure papillary craniopharyngiomas or RCCs without SM. In our case, the lack of *BRAF V600E* was inconsistent with a diagnosis of papillary craniopharyngioma. However, the presence of activating mutations in both *KRAS* and *MAP2K1*, members of the MAPK cascade that includes *BRAF*, suggests an alternative driver of neoplasia that is well described in several solid organ cancers. The *KRAS G12D* mutation identified in this case is present in 20%–50% of *KRAS*-mutated solid tumors.[16,17] This raises the exciting possibility of adjuvant treatment of patients with RCC-SM using *KRAS* and/or *MEK* inhibitors.[18,19]

Lessons

RCC can undergo SM and rupture, leading to a hemorrhagic-appearing, cystic sellar/suprasellar mass that clinically and radiographically mimics pituitary apoplexy. Intraoperative frozen sections can be difficult to interpret due to overlapping histopathological features with craniopharyngioma. This can complicate surgical decision-making, as these 2 distinct pathologies require markedly different surgical strategies. While gross-total resection is the surgical goal for craniopharyngiomas, for RCCs, typically only marsupialization is required. If there does exist a continuum of metaplastic progression from RCC to RCC-SM to papillary craniopharyngioma, the identification of clinical and radiological determinants of this potential transitional entity will be important for guiding appropriate surgical management. In the interim, neurosurgeons should be keenly aware of RCC-SM and remain ready to modify their surgical strategy to optimize patient outcomes.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Beaumont. Acquisition of data: Beaumont, Halaoui, Yan, Goodwill. Analysis and interpretation of data: Beaumont, Halaoui, Goodwill. Drafting the article: Beaumont, Halaoui, Estrella. Critically revising the article: Beaumont, Halaoui, Yan, Goodwill. Reviewed submitted version of manuscript: Beaumont, Halaoui, Yan, Goodwill. Approved the final version of the manuscript on behalf of all authors: Beaumont. Administrative/technical/material support: Halaoui, Yan. Study supervision: Beaumont.

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