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*Case Report*

# Rathke's cleft cysts causing Cushing's disease: Two unique cases and review of the literature

Krisna Maddy[1], Evan Luther[1], Katherine Berry[1], Victor M. Lu[1], Ashish Shah[1], Michael E. Ivan[2], Ricardo J. Komotar[1]

Departments of [1]Neurosurgery and [2]Neurological Surgery, University of Miami Miller School of Medicine, Miami, Florida, United States.

E-mail: *Krisna Maddy - ksm129@med.miami.edu; Evan Luther - evanluthermd@gmail.com; Katherine Berry - kmb239@miami.edu; Victor M. Lu - vml43@med.miami.edu; Ashish Shah - ashah@med.miami.edu; Michael E. Ivan - mivan@med.miami.edu; Ricardo J. Komotar - rkomotar@med.miami.edu

***Corresponding author:**
Krisna Maddy,
Department of Neurosurgery, University of Miami Miller School of Medicine, Miami, Florida, United States.

ksm129@med.miami.edu

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## ABSTRACT

**Background:** The presentation of isolated Rathke's cleft cysts (RCC) without any associated pituitary adenoma in patients with symptoms consistent with Cushing's disease (CD) remains exceedingly rare. As such, we aim to present two cases of RCC presenting with CD with a resultant resolution of their CD following surgical resection.

**Case Description:** Here, we present two cases of RCCs presenting with symptoms suggestive of CD. A functional pituitary microadenoma was the presumed diagnosis based on initial clinical presentation and diagnostic imaging suggesting a pituitary lesion. However, pathology results demonstrated no evidence of adenoma but cysts lined with columnar epithelia consistent with RCC. Complete surgical resection was achieved in both patients through endoscopic endonasal pituitary resection with postoperative symptomatic resolution and normalization of cortisol levels. In addition, we discuss the literature on this rare presentation and suggest a pathological mechanism for this unique presentation of RCC-causing CD.

**Conclusion:** Surgical resection of RCC may provide a "biochemical cure" for patients presenting with CD, as demonstrated by these two unique cases. The clinical features, histological findings, and possible pathological mechanisms for this unique presentation of RCC causing CD discussed lay the groundwork for future studies into the pathophysiology of RCC and CD.

**Keywords:** Cushing's disease, Neurosurgery, Pituitary adenoma, Rathke's cleft cyst

## INTRODUCTION

Rathke's cleft cysts (RCC) arise from the epithelial remnants of Rathke's pouch, which persists in adult life between the pars anterior and pars posterior of the pituitary.[5] These cysts are benign sellar and suprasellar lesions with a peak incidence at 30–50 years of age.[8] Most RCCs are between 10 mm and 20 mm in diameter and contain mucoid or gelatinous material encapsulated in a thin cyst wall of simple or pseudostratified cuboidal or columnar epithelium.[8] RCCs are usually found incidentally in adults, with an incidence of about 12–33% in autopsy cases.[6] Functionally, these cysts are mostly asymptomatic. Progressive enlargement can result in compression of the optic chiasm, pituitary stalk, and gland, resulting in symptomatic visual disturbances, and endocrinopathies.[6] Cushing's disease (CD) is an endocrinopathy defined by autonomous/dysregulated secretion of adrenocorticotropic hormone (ACTH) and excess cortisol production.[7] It is primarily caused by pituitary ACTH-secreting tumors, namely pituitary adenomas.

The presence of RCC concurrently with pituitary adenoma is rare, however reported in the literature.[12,21] One study reported that RCC was associated with 1.7% pituitary adenoma cases.[13] However, minimal data exist discussing isolated RCCs without any associated pituitary adenoma causing CD.[17] Here, we present two cases of RCCs presenting symptoms suggestive of CD. We discuss the clinical features and histological findings and suggest a pathological mechanism for this unique presentation of RCC-causing CD.

## CASE PRESENTATION #1

A 72-year-old male with a history of growth hormone deficiency symptomatic for generalized fatigue and weakness and on somatropin replacement therapy (1 mg daily) had an incidentally found pituitary lesion identified two decades prior on magnetic resonance imaging (MRI) following hospitalization for stroke. His comorbidities included obesity (body mass index, BMI 30) and diabetes. At that time, the lesion was assumed to be a microadenoma measuring 1.0 cm and abutting the optic chiasm. At the time, he had no visual deficits and was managed conservatively. In 2021, he presented to his outside endocrinologist with an elevated cortisol level of 2.3 mcg/dL from a normal value one year prior and the absence of overt changes in clinical features, suggesting subclinical CD. In addition, the low-dose (1 mg) dexamethasone suppression study did not suppress cortisol levels, indicating CD versus Cushing's syndrome. Repeat imaging demonstrated the growth of the lesion, now measuring 1.3 cm, with no compression of the optic apparatus [Figure 1].

As a result of these findings, surgery was recommended. He underwent endoscopic endonasal transsphenoidal resection of the lesion without issue, and postoperative MRI demonstrated no residual mass [Figure 2]. Postoperative AM serum cortisol was 12.4 mcg/dL one day after surgery and 1.7 mcg/dL two days after surgery. At one year follow-up, the patient's insulin-like growth factor 1 level was decreased to 181 ng/mL from 281 ng/mL prior. Complete postoperative endocrinological laboratory results for patient 1 are unavailable due to reliance on endocrinological workup from an external hospital, despite efforts to access the records. Pathology demonstrated multiple fragments of the pituitary gland with normal nesting growth patterns. In addition, pituitary transcription factors, including growth hormone factor 1 (Pit-1), T-box transcription factor Tpit, and steroidogenic factor-1 (SF-1) showed normal distribution patterns in the parenchyma. Adjacent to these fragments was a colloid nodule and epithelium suggestive of RCC. The patient's postoperative course was uneventful with his RCC resection. Approximately one week after surgery, for symptoms of nausea, fatigue, and muscle weakness, his workup was benign aside from hyponatremia, which was corrected during his hospitalization. One month postoperatively, the patient exhibited excellent recovery and no complications from the operation. On a longer-term follow-up with endocrinology, the patient reported improved fatigue and generalized muscle weakness.

## CASE PRESENTATION #2

A 61-year-old female initially presented in 2015 to her physician with a several-year history of symptoms of hirsutism, proximal muscle weakness, thinning skin, and easy bruising. Her comorbidities included obesity (BMI 37.6), diabetes, and hypertension. In June 2018, the patient's serum ACTH was elevated at 77 pg/mL, and in February 2019, the patient's urine-free cortisol was elevated at 134 mcg/dL. The patient reported a trial of mifepristone for several months but could not tolerate the medication. MRI in 2019 showed a 5 mm hypoenhancing lesion in the pituitary gland, presumed to be a pituitary microadenoma measuring approximately 3.5 mm [Figure 3].

The patient underwent endoscopic endonasal transsphenoidal resection of the lesion, and postoperative

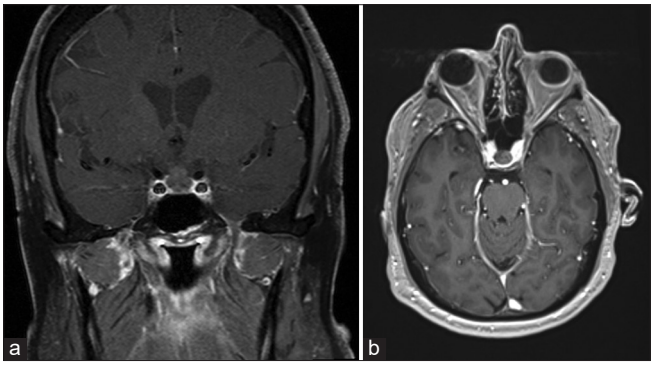


**Figure 1:** (a and b) Patient 1 preoperative imaging demonstrating solid appearing, hypo-enhancing suprasellar mass immediately anterior to midline pituitary stalk with abutment of the undersurface of the optic chiasm.

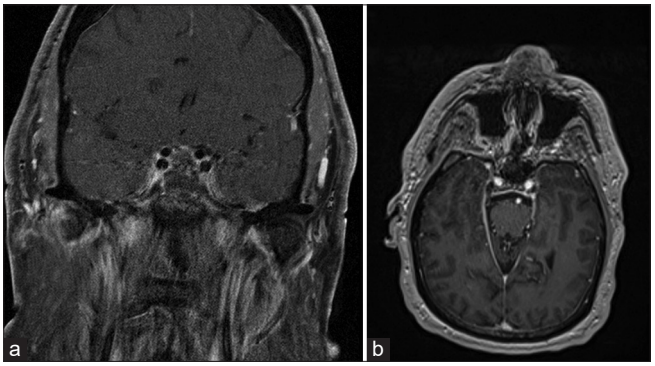


**Figure 2:** (a and b) Patient 1 postoperative imaging demonstrating cyst removal.

MRI showed resection of the nodule in the mid-left superior adenohypophysis [Figure 4]. Postoperative AM serum cortisol was 4.3 mcg/dL one day after surgery.

The pathology report of the specimen suggested RCC with Crooke's hyaline changes. Noted on histology were several islands of eosinophilic acellular material, strips of ciliated epithelium with adjacent intact native pituitary parenchyma with all hormonal markers in a nonneoplastic distribution with no evidence of adenoma. The patient's postoperative course was uneventful. One month postoperatively, the patient exhibited excellent recovery and no complications from the operation. On longer-term follow-up with endocrinology, the patient reported improvement in hirsutism and proximal muscle weakness.

## DISCUSSION

To our knowledge, these are the first reported cases of RCC causing CD without concurrent pituitary adenoma or pituitary hyperplasia, as confirmed on histology. RCCs are considered embryological remnants of Rathke's pouch, presenting typically as asymptomatic benign lesions.[16] They rarely present in association with pituitary adenomas

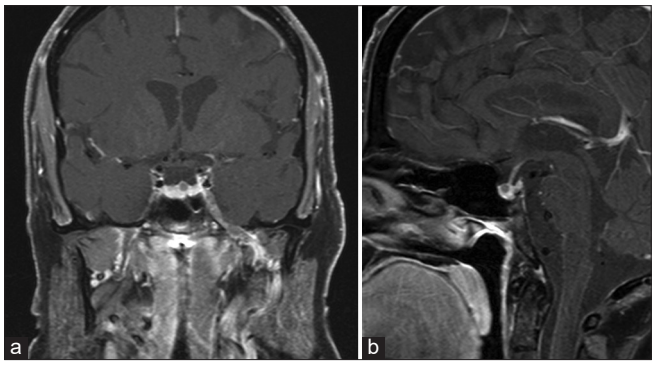


**Figure 3:** (a and b) Patient 2 preoperative imaging demonstrating ovoid, hypo-enhancing lesion in the superior aspect of the pituitary gland just to the left of midline.

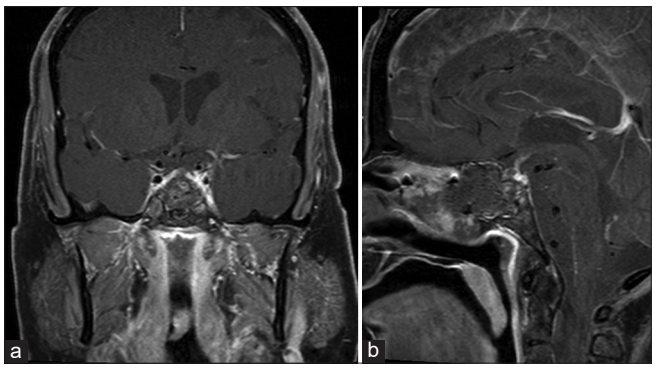


**Figure 4:** (a and b) Patient 2 postoperative imaging demonstrating cyst removal.

in patients presenting with CD. In the literature, to date, there are several reported cases of pituitary adenoma and hyperplasia presenting in association with RCC.[2,17,21] These typically present as nonfunctional pituitary adenomas and prolactinomas coexisting with RCC in patients presenting with endocrinological imbalances and compressive effects, which resolved after transsphenoidal resection.[21] Even more rare is the presentation of RCC causing similar endocrinological symptomology without evidence of concurrent pituitary adenoma on histology. We present two cases where histology demonstrated completely benign adjacent pituitary tissue to the RCC in these patients with symptomatic CD.

Typically, RCCs present on MRI as well-demarcated homogeneous lesions with a variable intensity highly dependent on cyst contents, ranging from clear cerebrospinal fluid-like fluid to thick mucoid material.[6] They are typically hypointense on T1-weighted images and hyperintense on T2-weighted images (serous) or hyperintense on T1-weighted images and isointense on T2-weighted images (mucoid).[4] A small area of hypo- or iso intensity may indicate the thickening of the cyst wall or aggregation of cellular debris. In our patients, the lesions were presumed to be pituitary microadenomas. Given the clinical correlation with the presenting symptoms, this is not unusual.

RCCs are typically thought to not have functional disturbances compared to pituitary microadenomas; thus, the radiological correlation will suggest the latter's presentation in a syndromic CD patient. Typically, an ACTH-producing adenoma would be suspected. The shared component of MRI presentation in both of our patients was the hypoenhanced/non-enhancing presentation of the lesion. Pituitary microadenomas also typically present as relatively hypointense lesions within an intensely enhanced pituitary gland.[3] Given the similarity of presentation on MRI, the diagnosis of RCC in our patients relied on histological findings.

The histopathological intricacies in patients with other sellar lesions are also worth noting, as this is pivotal for accurate diagnosis, treatment planning, and prognostication, underscoring the significance of ongoing research efforts in this domain. Pituitary adenomas, the most prevalent sellar lesions, exhibit diverse histological patterns, as highlighted by the comprehensive classification by the World Health Organization, using markers of cytodifferentiation as the principal classifier.[9] Furthermore, craniopharyngiomas present characteristic histopathological features such as keratinized epithelium and surrounding fibrovascular stroma.[18] They are categorized as adamantinomatous, characterized by mutations in the β-catenin gene as a specific molecular pathogenic mechanism, and papillary.[1]The complexity of sellar lesions extends beyond these common

entities, encompassing rare pathologies such as sellar chordomas, which are characterized by large, vacuolated cells known as "physaliphorous" cells enclosed within a mucinous matrix. These cells are arranged in interconnected cords or sheets, occasionally exhibiting mitotic activity. Tumors express specific markers, including S100, low-molecular-weight keratins, and epithelial membrane antigens. Brachyury, or transcription factor T,[20] and of interest to the discussion on the presented cases, RCC is characterized by a monolayer of cuboidal cells with microvilli, scattered columnar, and goblet cells. The cyst contents typically comprise amorphous eosinophilic material. Squamous metaplasia, a transformation of the lining epithelium, is frequent and may pose a diagnostic challenge, resembling craniopharyngioma. In addition, xanthogranulomas with chronic inflammation and cholesterol crystals may be present in this context.[19]

Understanding the histological presentation of RCCs may elucidate the pathophysiological mechanisms by which these lesions may have led to CD in our patients. CD typically occurs from a pituitary gland tumor or pituitary hyperplasia, resulting in the overproduction of ACTH and resultant overproduction of cortisol by the adrenal glands.[10] One report of a patient presenting with CD and pituitary microadenoma also demonstrated Crooke's changes in pituitary cells on histology.[2] In one case of CD in a female patient in her 3rd decade, corticotroph cell hyperplasia/ACTH-positive cells penetrating the wall of the RCC were seen on histology.[17] Findings demonstrated an RCC, numerous ACTH+ cells, and, to a lesser extent, thyroid-stimulating hormone (TSH)+ cells.[17] In our patients, biopsy demonstrated unremarkable pituitary tissue with adjacent islands of eosinophilic acellular material and strips of ciliated epithelium, a colloid nodule, and a fibrous membrane/wall. Biopsy findings in our second patient described Crooke's hyaline changes. In 75–80% of patients with chronic hypercortisolism of any etiology, the normal corticotrophs undergo changes in which the cytoplasmic granules are replaced with homogeneous hyaline material, known as Crooke's changes.[14] The absence of these changes does not confirm the absence of CD; however, the presence of these changes is associated with the degree of hypercortisolism in the patient.[14]

Laboratory values reflecting endocrine dysfunction presented similarities and differences between these two cases [Table 1]. First, patient two presented with elevated ACTH preoperatively at 60.4 pg/mL with associated symptoms of CD. Patient 1, however, presented with low ACTH levels at 4.1 pg/mL. This patient had a long-reported history of growth hormone deficiency and symptoms consistent with CD, but given the low ACTH value preoperatively, his disease likely was cyclical. Both patients presented with markedly elevated insulin-like growth factor 1 levels, 281 ng/mL and 245 ng/mL, respectively. Prolactin, follicle-stimulating hormone, TSH, and free T4 levels were within normal limits for both patients. Interestingly, the growth hormone in our first case was elevated at 22.5 ng/mL but low in the second patient at 0.1 ng/mL. Another report of a patient presenting with CD secondary to concurrent pituitary microadenoma and RCC found a similar resolution of elevated ACTH levels following complete resection, normalization of blood cortisol levels, and improved CD symptomatic presentation.[2]

In measuring pre- and postoperative cortisol changes in both patients, we measured the degree of improvement that surgical resection of the RCC provided [Table 2]. Our first patient with a PM cortisol level of 2.3 mcg/dL preoperatively, an AM cortisol of 12.4 mcg/dL on postoperative day 1, and an AM cortisol of 1.7 mcg/dL on postoperative day 2, an overall downward trend in cortisol levels. Our second patient presented with an elevated PM cortisol level at 22.8 mcg/dL. Postoperatively, her AM cortisol was 4.3 mcg/dL on postoperative day 1, and an AM cortisol of 5.6 mcg/dL on postoperative day 2, an overall downward trend in cortisol levels. This decline in cortisol levels following RCC resection led us to consider this a biochemical cure to the hormone imbalance causing this CD.

The surgical management of RCC is indicated in symptomatic presentations such as that in our patients. In previous studies

**Table 1:** Pre-operative laboratory results in patients presenting with Cushing's disease.

| | Preoperative | | Postoperative | |
|---|---|---|---|---|
| | Patient 1 | Patient 2 | Patient 1 | Patient 2 |
| TSH (mlu/L) | 0.137 | 0.208 | - | 0.82 |
| FT4 (ng/dL) | 0.84 | 1.16 | - | 1.3 |
| Prolactin (ng/mL) | 7.0 | 14.8 | - | 18.3 |
| LH (mlu/mL) | 1.5 | 33.5 | - | 13 |
| FSH (mlu/mL) | 3 | 57.1 | - | 27.8 |
| ILGF1 (ng/mL) | 281 | 245 | 181 | - |
| Growth hormone (ng/mL) | 22.5 | 0.1 | - | 1.9 |
| ACTH (pg/mL) | 4.1 | 60.4 | - | 25 |

TSH: Thyroid-stimulating hormone, FT4: Free thyroxine, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, ILGF1: Insulin-like growth factor 1, ACTH: adrenocorticotropic hormone

**Table 2:** Trends in cortisol level (mcg/dL) in patients pre and post-operatively.

| | Patient 1 | Patient 2 |
|---|---|---|
| Preoperative | 2.3 (PM) | 22.8 (PM) |
| Postoperative day 1 | 12.4 (AM) | 4.3 (AM) |
| Postoperative day 2 | 1.7 (AM) | 5.6 (AM) |
| One month F/u visit | N/A | 8.9 (AM) |

F/u: Follow-up, N/A: Not available

of cases with overt signs of RCC compression causing symptomatic clinical presentation, there was demonstrated improvement in clinical symptoms after surgery.[6] In particular, transsphenoidal endoscopic surgery is the first choice for surgical treatment of RCC, intending to drain the cyst contents and remove the surrounding capsule.

Suprasellar involvement of RCC can prove to be a neurosurgical challenge. Our first patient case presented with an abutment of the optic chiasm. It has been shown that compared with sellar-based RCCs, RCC's visual dysfunction is more difficult to eliminate, recurs more frequently, and is associated with higher postoperative endocrine morbidity, and their preoperative visual dysfunction and headache less frequently improve with surgery.[15] Avoidance of optic nerve damage due to its location above the surgical corridor through traversing the tuberculum sella and the planum sphenoidale also offers a factor of difficulty to the surgical management of these RCCs.[11] Surgically, both cases presented without any postoperative complications.

What remains to be understood in these cases is the pathophysiological mechanism by which these RCCs resulted in CD presentation, typically resulting from pituitary microadenomas. One possible explanation is that the RCC resulted in an overproduction of ACTH in neighboring cells surrounding the cyst. This suggests an effect of elevated circulating corticosteroids on the anterior pituitary parenchyma, resulting in the presentation of CD. In addition, the resolution of symptoms in both patients, including fatigue and generalized weakness, clinical and reduction of cortisol levels, and improvement in endocrinological laboratories postoperatively, suggests that the surgical removal of the RCC in these patients provided a "biochemical cure."

However, the pathophysiologic mechanism of how the cystic cells resulted in symptomatic CD remains unclear. The absence of a concurrent pituitary microadenoma and benign pituitary tissue leaves no clear explanation of the cellular level changes that may have occurred. Nevertheless, the apparent symptomatic resolution of CD in these patients suggests that neurosurgical intervention was worthwhile. In cases of CD secondary to the presence of RCC, neurosurgical intervention should be considered for symptomatic improvement; however, further research should be undertaken to understand the underlying mechanism of this presentation.

## CONCLUSION

Here, we present two cases of isolated RCCs presenting symptoms suggestive of CD. Based on the initial clinical presentation in these two patients and diagnostic imaging suggesting a pituitary lesion, pituitary microadenoma was the presumed diagnosis. However, there was no evidence of adenoma histopathologically, with findings more consistent with RCC. Maximal surgical resection was achieved in both patients through endoscopic endonasal pituitary resection with postoperative symptomatic resolution and normalization of cortisol levels. The clinical features, histological findings, and possible pathological mechanisms for this unique presentation of RCC-causing CD have been discussed and laid the groundwork for future studies into the pathophysiology of RCC and CD.

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Patients' consent not required as patients' identities were not disclosed or compromised.

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### Conflicts of interest

There are no conflicts of interest.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The author confirms that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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