First Report of Coexistence of Two Ectopic Pituitary Tumors: Rathke Cleft Cyst and Silent Adrenocorticotropic Hormone Adenoma

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Key words
- ACTH pituitary adenoma
- Clival invasion
- Ectopic pituitary adenoma
- Rathke cleft cyst
- Sphenoid sinus tumor

Abbreviations and Acronyms
ACTH: Adrenocorticotropic hormone
MRI: Magnetic resonance imaging
PA: Pituitary adenoma
RCC: Rathke cleft cyst
ST: Sella turcica

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BACKGROUND: **Rathke cleft cysts (RCCs) and pituitary adenomas (PAs) are thought to have a common embryonic ancestry; however, PAs with a concomitant RCC inside the sella turcica are rarely observed. Ectopic pituitary tumors are also rare.**

CASE DESCRIPTION: **We present the case of a 65-year-old woman with an ectopic RCC in the sphenoid sinus and outside the sella turcica concomitant with an adrenocorticotropic hormone (ACTH)-staining, clinically silent PA. The patient had headache but no endocrine or visual disturbances. Preoperative magnetic resonance imaging revealed infrasellar cystic lesion in the sphenoid sinus with erosion of the clivus and intact sellar floor. The patient underwent gross total microsurgical resection through the transnasal route with an uneventful postoperative course.**

CONCLUSIONS: **To our knowledge, this is the first reported ectopic RCC located outside the sella turcica with a concomitant ACTH-staining PA. This also appears to be the first ACTH-staining adenoma concomitant with RCC reported in the literature, regardless of location, not presenting with Cushing disease. This case shows that we can now include pituitary adenoma with or without a concomitant RCC in the differential diagnosis of processes in the sphenoid sinus. As both PAs and RCCs are benign sellar lesions, surgical management of a concomitant occurrence of these tumors mainly depends on the size of the lesions and their clinical manifestations. For patients with PA and concomitant RCC, surgical resection should be considered, as there is an approximatrely 20% recurrence rate of the cyst after resection and the possibility of future clival erosion, if left untreated.**

INTRODUCTION

The Rathke pouch gives rise to the anterior pituitary lobe via proliferation of its anterior wall, and the anterior pituitary lobe gives rise to pituitary adenomas through clonal expansion.[1] Both Rathke cleft cysts (RCCs) and pituitary adenomas (PAs) are thought to have a common embryonic ancestry. Despite this common origin, however, PAs with concomitant RCCs inside the sella turcica (ST) have been observed only rarely.[2] Furthermore, ectopic PAs—and in particular, ectopic adrenocorticotropic hormone (ACTH)-PAs—are rare, with only 42 cases of ectopic ACTH-PAs described in the literature[3] and only 4 cases of ectopic RCCs.[4]

We present the case of a 65-year-old woman with 2 concomitant ectopic pituitary tumors: a Rathke cleft cyst and an ACTH-PA. To our knowledge, this is the first case of a concomitant ectopic Rathke cleft cyst and ACTH-PA outside the ST. Furthermore, this is the first described case of a concomitant asymptomatic corticotrophic adenoma without Cushing disease and RCC regardless of the location (sellar or extrasellar). This double tumor invaded and eroded the clivus, which is also unusual. In addition to case materials, we discuss the histologic findings, clinical presentation, and management of these combined tumors and review the literature of existing cases.

CASE REPORT

A 65-year-old woman with no significant medical history came to our neurosurgical clinic on referral from her primary care physician. The patient stated that she experienced headache and nasal stuffiness in the previous weeks. Physical examination revealed no neurologic deficit. Noncontrast computed tomography of the head showed a mass in the sphenoid sinus with bony erosion of the clivus, but with an intact sellar floor and dura. Magnetic resonance imaging (MRI) with and without contrast revealed a heterogeneously enhancing infrasellar mass with a nonenhancing cystlike portion in the sphenoid

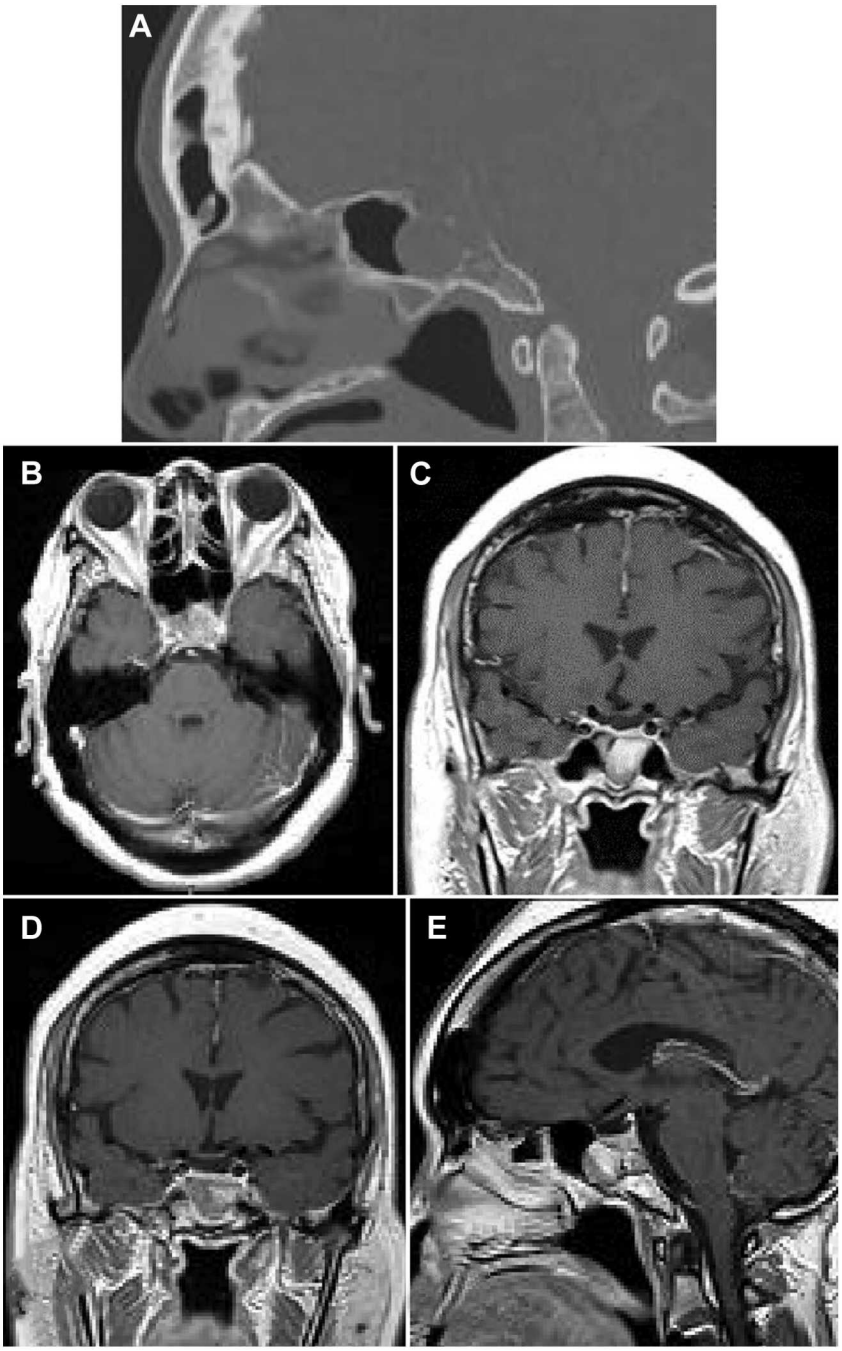

Figure 1. Imaging studies reveal a cystic lesion in the sphenoid sinus with nonhomogeneous contrast enhancement. (**A**) Sagittal computed tomography without contrast. (**B**) Axial, (**C**, **D**) coronal, and (**E**) sagittal T1-weighted postcontrast magnetic resonance imaging.

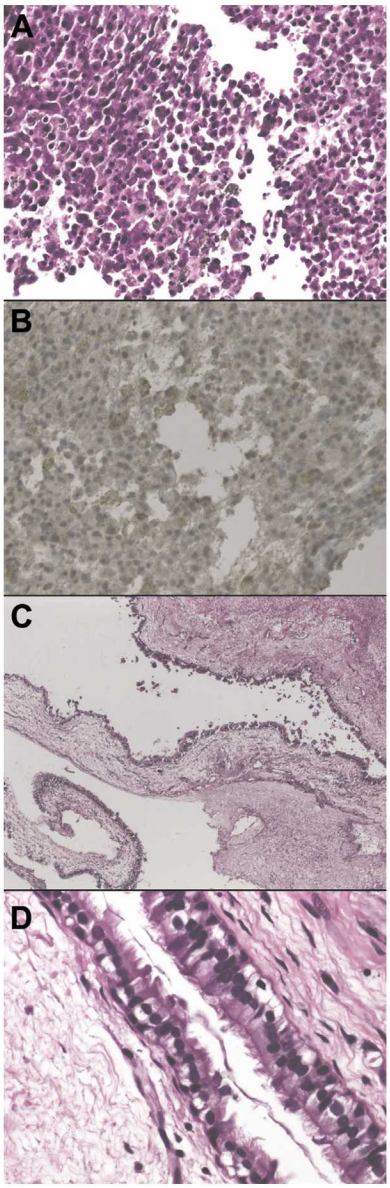

Figure 2. (**A**) The specimen contained a monotonous population of cells with amphophilic to basophilic cytoplasm, indicating a pituitary adenoma (hematoxylin and eosin [H&E] staining, original magnification ×20). (**B**) Immunostaining for adrenocorticotropic hormone was positive in tumor cells (moderate and cytoplastic; original magnification ×40). (**C**) In addition, there was ciliated columnar epithelium (H&E staining, original magnification ×20X). (**D**) Higher-power magnification showing the RCC and cilia (H&E staining, original magnification ×40). The histopathologic findings were of a pituitary (corticotroph) adenoma with an adjacent Rathke cleft cyst.

sinus. The mass also extended posteriorly, partially eroding the clivus. In the cystlike part, it showed isointense signal on T1-weighted MRI and homogenous enhancement in its posterior part near the sellar floor (Figure 1). The differential

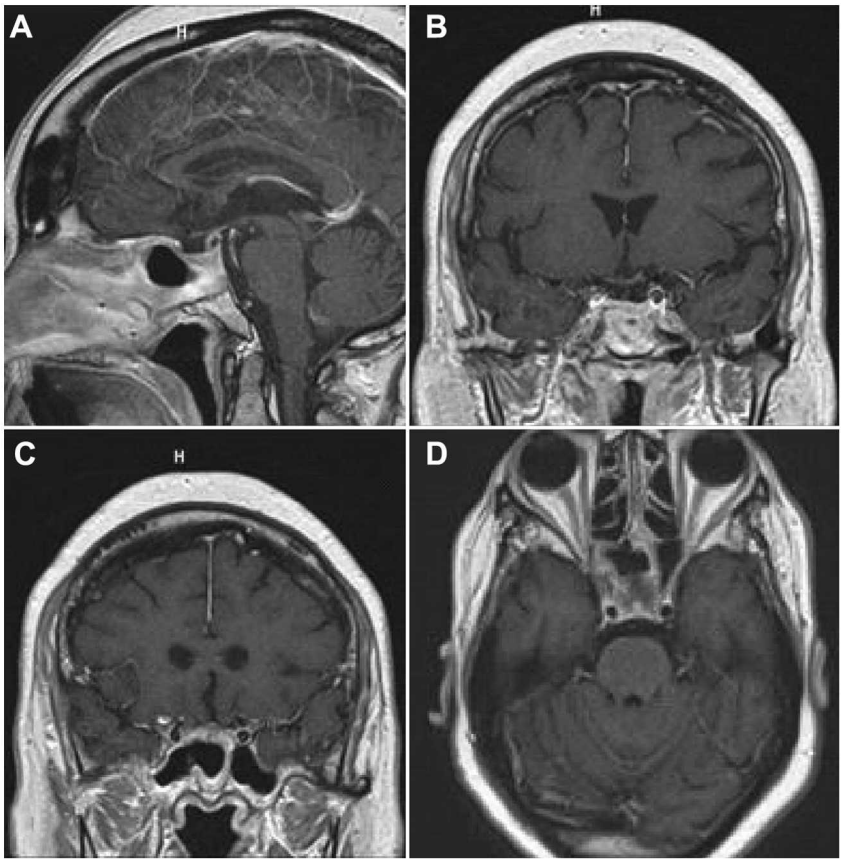

Figure 3. Postoperative postcontrast magnetic resonance imaging studies verifying gross total resection of the tumor: (**A**) sagittal, (**B**, **C**) coronal, and (**D**) axial views.

diagnosis included mucocele, sphenoiditis, sphenoidal polyps, fibrous dysplasia, squamous cell carcinoma, chordoma, chondrosarcoma, and metastasis. Surgery was indicated for diagnostic and therapeutic purposes, particularly because of severe headaches and the erosion of the clivus.

Laboratory findings, including endocrine studies, showed normal values; the ACTH level was normal at 26 pg/mL (normal range, 3–52 morning, 4–32 pg/mL afternoon), cortisol level was 5.09 μg/dL (normal range, 3–22 μg/dL morning). Glucose and hemoglobin A1C were in normal range. The patient underwent complete transsphenoidal microsurgical resection by the senior author (K.I.A.). There were no signs of tumor intrusion into the sella or erosion of the sellar floor, and the patient had no postoperative deficits. Postoperative laboratory findings were normal, and there was no need for hormonal substitution therapy. Histopathologic evaluation revealed 2 lesions—an ACTH-staining corticotrophic PA and an adjacent RCC (Figure 2). The specimen contained a monotonous population of cells with amphophilic to basophilic cytoplasm, indicating a pituitary adenoma. Immunostaining for ACTH was positive in tumor cells (moderate and cytoplastic). In addition, there was ciliated columnar epithelium. Higher-power magnification showed the RCC and cilia. The histopathologic findings were of a pituitary (corticotroph) adenoma with an adjacent Rathke cleft cyst. Follow-up MRI with and without contrast (Figure 3) showed no residual tumor at the 6-month evaluation. Laboratory findings—including ACTH and cortisol levels—remained in the normal range at follow-up. In addition, midnight salivary cortisol was analyzed for 3 consecutive nights postoperatively, and values were normal.

DISCUSSION

Concomitant Intrasellar PA and RCC

A review of all the English-language publications in Medline/PubMed and the Cochrane Database of Systematic Reviews of the Cochrane Library showed that until recently (with a prospective study of Ikeda et al.[5]), a concomitant RCC with a PA inside the ST was considered to be rare.[1,2,6-29] RCC was associated with only 1.7% of PAs in a large series of 464 patients.[1] The link between PA and RCC stems from the fact that PAs occasionally contain elements of both the fetal Rathke pouch and differential adenohypophyseal cells. These tumors have been believed to derive from "transitional" cells between the lining of Rathke cleft and the glandular cells of the anterior pituitary.[6,30,31]

The literature contains 33 reports of concomitant RCC and PA inside the ST, with a total of 175 cases. Of those, 5 reports refer to an ACTH-PA,[16,17,23,24,32] with a total of 8 cases associated with RCC, and another 2 reports describe a plurihormonal PA with ACTH expression concomitant with the RCC.[10,14] Overall, 37 cases of concomitant RCC and ACTH or plurihormonal PAs with ACTH expression have been described. Furthermore, all previously described ACTH-only PAs concomitant with RCC were symptomatic in patients with Cushing disease. Details of the literature reports are presented in Table 1. Most of the adenomas associated with ruptured RCCs were plurihormonal (97 patients, of which 37 had ACTH predominance)[5,14,39] followed by prolactin adenomas (35 patients), growth hormone adenomas (15 patients), ACTH adenomas (8 patients), and 1 patient with a follicle-stimulating hormone adenoma.

Clinically Silent ACTH Adenomas

Our case was a unique, ectopic, concomitant RCC with an ACTH-staining but clinically silent adenoma outside the ST. This type of adenoma is commonly referred to as a *silent corticotrophinoma*—an ACTH-immunopositive tumor that is not accompanied by physical or biochemical signs of cortisol excess.[39-41] The combination of hematoxylin and eosin staining with immunostaining for pituitary hormones allows subclassification of adenomas; it

Table 1. Characteristics and Clinical Presentation of Patients with Concomitant Pituitary Adenoma and Rathke Cleft Cyst

Author, year	Cases (N)	Age (years)	Sex	Hormone Production	Symptoms
Duffy, 1920[33]	1	50	Male	NS	Visual disturbance
Shuangshoti et al, 1970[34]	1	64	Female	NS	Decreased vision
Kepes, 1978[30]	1	79	Female	NS	NS
Trokoudes, 1978[35]	1	38	Female	Prolactin	Amenorrhea
Matsumori et al., 1984[18]	1	28	Female	Prolactin	Bitemporal hemianopsia, galactorrhea, amenorrhea
Swanson et al., 1985[25]	1	34	Female	None	Headache, visual disturbance, amenorrhea
Hiyama, 1986[36]	1	35	Female	Prolactin	Bitemporal hemianopsia, galactorrhea, amenorrhea
Nishio et al., 1987[1]	9	21	Female	Prolactin	Headache, amenorrhea, galactorrhea
		23	Female	Prolactin	Amenorrhea, galactorrhea
		24	Female	Prolactin	Amenorrhea, galactorrhea
		25	Female	Prolactin	Amenorrhea, galactorrhea
		29	Female	Prolactin	Irregular menses
		30	Female	Prolactin	Amenorrhea, galactorrhea
		31	Female	Prolactin	Headache, amenorrhea, galactorrhea
		31	Male	Prolactin	Galactorrhea, decreased libido
		34	Female	Prolactin	Amenorrhea, galactorrhea, lethargy
Ikeda et al., 1987[10]	1	31	Female	Prolactin	Visual disturbances, amenorrhea, galactorrhea
Nakasu, 1989[37]	1	21	Female	Prolactin	Amenorrhea
Ikeda et al., 1992[11]	1	50	Male	GH	LU temporal quadrantopsia, acromegaly, loss of libido
Miyagi et al., 1993[19]	1	44	Male	None	None
Nishio et al., 1995[21]	2	44	Male	GH	Acromegaly, loss of libido
		35	Female	GH	Enlargement of blind spot, menstrual irregularity
Sumida et al., 2001[24]	8	67	Female	GH	Acromegaly
		42	Male	ACTH*	Cushing disease*
		44	Female	GH	Acromegaly
		18	Male	GH	Gigantism
		46	Male	GH	Acromegaly
		56	Female	GH	Acromegaly
		39	Male	ACTH*	Cushing disease*
		48	Male	GH	Acromegaly
Bader, 2004[38]	1	47	Female	GH	Headache, binasal field defect, acromegaly, carpal tunnel
Kaku et al., 2005[12]	1	42	Male	None	Headache, bitemporal hemianopsia
Vancura et al., 2006[27]	1	70	Male	None	Diplopia
Noh et al., 2007[2]	1	62	Female	GH	Acromegaly
Karavitaki et al., 2008[16]	1	54	Male	ACTH*	Cushing disease*

NS, not specified; GH, growth hormone; LU, left upper; ACTH, adrenocorticotropic hormone.
*Indicates ACTH and Cushing disease tumors.

Continues

Table 1. Continued

Author, year	Cases (N)	Age (years)	Sex	Hormone Production	Symptoms
Radhakrishnan et al., 2011[22]	1	16	Female	None	Bitemporal hemianopsia, amenorrhea
Koutourousiou et al., 2010[17]	2	42	Female	ACTH*	Cushing disease*
		76	Male	None	None
Gessler et al., 2011[8]	2	76	Female	None	Headache, double vision, third nerve palsy; pituitary apoplexy
		67	Male	None	Headache, pituitary apoplexy
Zhou et al., 2012[23]	2	38	Female	ACTH*	Cushing disease,* headache, exophthalmus
		38	Female	None	Visual disturbance
Wang et al., 2012[15]	1	42	Female	None	Headache
You et al., 2012[9]	1	46	Female	GH	Visual field deficits, acromegaly
Babu et al., 2013[6]	1	39	Male	None	Horizontal nystagmus
Sarmiento et al., 2013[14]	2	65	Male	None	Blurred vision, decreased libido
		45	Female	Plurihormonal: prolactin + ACTH*	Headache, vomiting, diplopia
Tamura et al., 2015[26]	1	53	Male	GH	Acromegaly
Ikeda and Ohhashi, 2015[5]	106	NS	—	111 adenomas in 106 patients; 5 double adenomas; 14 prolactin, 1 ACTH* 96 plurihormonal*: 40 GH predominance, 36 ACTH predominance*	Periodic headache and dizziness; Cushing disease* (number of cases=NS)
Guo et al., 2015[32]	18	NS	—	4 none, 3 NS, 7 prolactin, 2 GH, 2 ACTH*	15 symptomatic with headache, dizziness, visual disturbances, paramenia, acromegalia; 2 Cushing disease*
Yip et al., 2016[29]	1	66	Male	Follicle-stimulating hormone	Bitemporal hemianopsia
Wu and Wang, 2016[28]	1	22	Female	None	Headache
Gao et al., 2016[7]	1	26	Female	None	Bitemporal hemianopsia
Pojskic et al., 2017 (this case)	1	65	Female	ACTH*	Headache, nasal stuffiness

NS, not specified; GH, growth hormone; LU, left upper; ACTH, adrenocorticotropic hormone.
*Indicates ACTH and Cushing disease tumors.

is the best method for determining correlations to clinical hyperfunction and for determining the sensitivity of drug therapies.[41] The staining intensity correlates with the amount of secretory granules, which is characteristic of the periodic acid-Schiff positivity of densely and sparsely granulated ACTH adenomas. Tumors that are both clinically silent and associated with Cushing disease show a varying extent of immunoreactivity.[41] Silent corticotroph pituitary adenomas account for 1.1%–6% of surgically removed pituitary adenomas. In surgical series, most tumors are macroadenomas with suprasellar extension (87%–100%). This is in contrast to Cushing disease, which is mostly attributed to microadenomas.[42] The shift from an ACTH-silent to a functioning adenoma was observed in 9% of the ACTH-silent adenomas in 1 series of 44 cases.[43] These tumors do not recur more often than ACTH immunonegative tumors do, but they show a more aggressive course when they regrow.[44] The ACTH-only adenomas concomitant with RCC described in the literature were all symptomatic in patients with Cushing disease (Table 1).

The diagnosis and subtyping of plurihormonal adenomas can be performed only with immunohistochemistry.[5] In a prospective study by Ikeda et al.,[5] there were 36 plurihormonal adenomas with ACTH predominance, and only 1 case of preclinical Cushing disease was specified.[5] This study included 308 cases of RCC diagnosed through both radiologic and intraoperative findings. Pathologic examination confirmed 111 PAs in 106 patients with a ruptured RCC, a coincidence rate of 34%. Most of the PAs were detected only on 11C-methionine positron-emission computed tomography scans and MRI as standard diagnostic tools proved powerless to detect adenomas associated with RCC.[5] The literature also has 1 case of a spontaneous PA occurring after resection of an RCC.[45]

Ectopic PA and RCC (Occurring Separately)

Ectopic PAs are rare; the current literature has only about 100 descriptions of these tumors, most of which originated in the sphenoid sinus.[46,47] Among these reports, there were 42 cases of ectopic ACTH-PA, 19 of which appeared in the sphenoid sinus.[3] Ectopic ACTH-PAs are

an important cause of therapy-resistant Cushings disease. Furthermore, only 4 cases of ectopic RCC in the sphenoid sinus appear in the literature.[4,31] To our knowledge, a concomitant RCC with a PA in the sphenoid sinus and outside the ST has not been described previously and has not been included in the differential diagnosis of lesions of the sphenoid sinus.

Ectopic PAs are thought to arise from residual cells along the migration tract of the pharyngeal pituitary as it travels from the Rathke pouch to the ST.[48] Ectopically deposited cells can develop into adenomas anywhere along this tract and, concomitant with remnants of the RCC, can form a collision lesion. This is the most probable pathophysiologic mechanism that led to the formation of the double tumor described here.

Kepes et al.[30] described a transitional cell tumor composed of a PA and an RCC. Nishio et al.[1] observed positive staining for S-100 protein in lining cells in 2 of 9 cases.[1] Nishio et al.[1] suggested the possibility that both PAs and associated RCCs arise from folliculostellate cells or marginal cell.

PA Eroding the Clivus

Another item of note in our case is that the tumors invaded and eroded the clivus below the ST. Large PAs can be invasive and can infiltrate the surrounding dura, bone, and sinuses with suprasellar, infrasellar, lateral, or anterior directions of invasion, but posterior-inferior invasion into the clivus is rare.[49,50] In a recent retrospective study of 390 patients with surgically treated pituitary macroadenomas, clival invasion was detected in 8.21% of patients on computed tomography,[49] whereas female sex, large tumor volume, and null-cell type were the most important risk factors. The differential diagnosis for tumors eroding a clivus below ST includes chordoma, chondrosarcoma, plasmocytoma, and clival metastases,[51] and—rarely—meningioma, astrocytoma, craniopharyngioma, germ cell tumor, non-Hodgkin lymphoma, and PA.[50] There are fewer than 20 reported cases of ectopic clival PAs with erosion of the clivus; most of these produced hormones, and 2 were ACTH-adenomas.[46]

CONCLUSION

To our knowledge, this is the first case of an ectopic concomitant RCC with PA in the sphenoid sinus and outside the ST. Furthermore, it is the first ACTH-staining PA that does not include laboratory and clinical findings of Cushing disease associated with PA at any location. Another unusual characteristic is the erosion of the clivus below the ST (without erosion of the sellar floor), which is highly uncommon in pituitary tumors. This case also shows that the differential diagnosis of processes in the sphenoid sinus and eroding the clivus should now include a PA with or without a concomitant RCC.

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