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Case Report

Cushing's Disease as a Result of Two ACTH-Secreting Pituitary Tumors

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ABSTRACT

Objective: Our objective is to present a case of Cushing's disease (CD) with 2 adrenocorticotrophic hormone (ACTH)-secreting pituitary tumors. Multiple monohormonal pituitary tumors are rare. This case supports a consideration of repeat transsphenoidal surgery (TSS) in patients with initial surgical failure. **Methods:** Salivary, 24-h urine, serum cortisol testing, and magnetic resonance imaging (MRI) were used to diagnose CD. Treatment included TSS and postoperative hydrocortisone.

Results: A 36-year-old woman followed for hypothyroidism presented with a new left supraclavicular fossa swelling and underwent Cushing's syndrome screening. The levels of late-night salivary cortisol were 0.636 and 0.316 µg/dL, 24-h urine cortisol was 162 µg/24 h, cortisol after 1-mg dexamethasone suppression was 14.0 µg/dL, and serum morning cortisol was 26.4 µg/dL with ACTH of 66.7 pg/mL. A 7-mm hypoenhancing anterior pituitary lesion was noted on pituitary MRI. The cortisol level was 2.7 µg/dL after an 8-mg dexamethasone suppression. She underwent TSS, and her histopathology read as pituitary adenoma staining positive for ACTH. No residual tumor was seen intraoperatively. Postoperative morning serum cortisol was 17.9 µg/dL, and ACTH level was 79 pg/mL. Repeat TSS revealed a second adenoma previously unseen on MRI, which also stained positive for ACTH. Postoperative morning cortisol was 0.7 µg/dL, and ACTH was <9 pg/mL. Hydrocortisone, which was started for her central adrenal insufficiency, was tapered and stopped 1 year postoperatively. Late-night salivary cortisol levels were 0.016 and 0.012 µg/dL.

Conclusion: We conclude that surgical failure in CD after initial TSS should warrant the consideration of a second ACTH-secreting pituitary adenoma and possible repeat TSS.

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Introduction

Cushing's disease (CD) is a pathologic hypercortisolism caused by an adrenocorticotrophic hormone (ACTH)-secreting pituitary adenoma.^{1,2} It accounts for 70% to 80% of endogenous Cushing's syndrome cases.^{3,4} It causes weight gain, hyperglycemia, hypertension, an increased risk for nephrolithiasis, and clinical features, such as moon facies, supraclavicular and dorsal fat deposition, increased infection, violaceous striae, psychological changes, hirsutism, and amenorrhea.^{2,5} Patients with Cushing's syndrome have a higher mortality rate related to cardiovascular disease, venous thrombosis, and infection.¹ When CD and its comorbidities are successfully treated, the mortality rate improves.¹ A total of 80% to

90% of Cushing's disease cases arise from microadenomas and approximately 40% cannot be visualized on magnetic resonance imaging (MRI).³ The initial treatment of CD per guidelines is pituitary tumor resection,¹ most commonly via transsphenoidal surgery (TSS).² The goal of therapy is complete adenoma resection with pituitary gland function preservation.³ Complete adenoma resection is not always possible; therefore, surgical failure is a common issue with TSS.³ The surgical failure can include cases of persistent hypercortisolism after initial surgery or recurrence of CD after initially achieving remission.³

We describe a case of CD that was not cured with initial TSS, although cured with repeat TSS when a second ACTH-secreting pituitary adenoma was found.

Case Report

The patient is a 36-year-old woman with a history of hypothyroidism, nephrolithiasis, and pulmonary embolism 4 years prior to this evaluation. She was being followed by endocrinology for her

Abbreviations: ACTH, adrenocorticotrophic hormone; CD, Cushing's disease; MRI, magnetic resonance imaging; TSS, transsphenoidal surgery.

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Table
Preoperative Hypercortisolism Evaluation

Late-night salivary cortisol levels (normal range, <0.010-0.090 µg/dL)	0.636 µg/dL	0.316 µg/dL
24-h urine cortisol (normal range, 0-50 µg/24 hr)	162 µg/24 hr	
1-mg dexamethasone suppression test (µg/dL)	14 µg/dL	

Preoperative testing for hypercortisolism, including 2 late-night salivary cortisol levels on 2 separate nights, 24-h urine cortisol, and 1-mg dexamethasone suppression test.

hypothyroidism and noted a new left supraclavicular fossa swelling at a follow-up visit. She did not have moon facies, violaceous striae, or easy bruising or bleeding. She was screened for Cushing's syndrome. Late-night salivary cortisol levels were 0.636 and 0.316 (normal range, <0.010-0.090) µg/dL. Her 24-h urine cortisol was 162 (0-50) µg/24 h. Cortisol was 14.0 µg/dL after a 1-mg dexamethasone suppression (Table). Serum morning cortisol was 26.4 µg/dL with a corresponding ACTH of 66.7 (7.2-63.3) pg/mL. Serum dexamethasone level was 606 (140-295) ng/dL after a 1-mg dexamethasone administered the previous evening. A 7-mm relatively hypoenhancing lesion in the right anterior pituitary was noted on pituitary MRI (Fig. 1). Cortisol level was 2.7 µg/dL after an 8-mg dexamethasone suppression.

She underwent TSS, and the pituitary adenoma was resected with clean margins achieved. The sella was explored; no dural or cavernous sinus invasion was observed. Histopathology revealed a pituitary adenoma, which stained positive for ACTH. On postoperative day 1, morning serum cortisol was 17.9 µg/dL and ACTH 79 pg/mL (9-46 pg/mL) (Fig. 2). Due to her history of pulmonary embolism, repeat TSS was recommended. A second pituitary adenoma was noted on repeat TSS which was not previously visualized on MRI. Histopathology revealed a pituitary adenoma, which stained positive for ACTH. On postoperative day 1 after the second TSS, morning cortisol was 0.7 µg/dL, and ACTH was <9 (9-46) pg/mL (Fig. 2). She developed tachycardia and dyspnea secondary to phlebitis and pulmonary embolism postoperatively requiring anticoagulation. Hydrocortisone 30 mg in the morning and 15 mg in the afternoon was started for her central adrenal insufficiency. Within 6 to 8 weeks, her dose was tapered to hydrocortisone 20 mg in the morning and 10 mg in the afternoon. She was tapered off from the hydrocortisone replacement just over 1 year postoperatively. Off hydrocortisone, her serum morning cortisol was 7.7

µg/dL, ACTH was 28.4 (7.2-63.3) pg/mL, and late-night salivary cortisol levels were 0.016 and 0.012 (<0.010-0.090) µg/dL.

Discussion

The patient we presented had hypercortisolism with a known pituitary source, with an elevated ACTH, an MRI noting pituitary adenoma, and a high-dose dexamethasone suppression test with a suppressed but detectable cortisol level. Despite adenoma resection confirmed on histopathology, hypercortisolism persisted after initial TSS. The repeat TSS noted a second pituitary adenoma, which stained for ACTH on histopathology, and hypercortisolism resolved after tumor resection. This case emphasizes the significance of the consideration of a repeat TSS if the initial TSS does not resolve hypercortisolism.

Cushing's disease results from an ACTH-secreting pituitary tumor causing hypercortisolism.^{1,2} Its complications and the high mortality rate necessitate treatment, and the first-line therapy is TSS.¹ Some cases result in surgical failure due to incomplete resection, presence of an invasive tumor, hyperplasia mistaken for an adenoma, a presumed ectopic source of ACTH, misdiagnosis, atypical tumor, or recurrence of disease after remission.⁶ Sometimes, an incomplete resection of corticotroph adenomas occur due to a profuse local bleeding that may prevent adequate gland exposure, a pituitary adenoma may be located above the sella or ectopic in the sphenoid sinus, or an inadequate sphenoidal pneumatization may prevent an adequate sellar exploration. The most common reason for an incomplete resection is difficulty visualizing small adenomas.⁷ If TSS is initially successful but later hypercortisolism recurs, it may be that a residual corticotroph adenoma progressed.⁷ The residual corticotroph tumor may be suspected if there was technical difficulty during the procedure, inability to identify the adenoma, or unanticipated dural invasion.⁷

The remission rates of CD after initial TSS range from 76.0% to 85.5%.^{8,9} Reported remission after TSS is higher in patients with microadenomas or positive-ACTH tumor histology,⁸ although this was not the case for the patient we presented. She experienced surgical failure, but her persistent hypercortisolism was related to the presence of a second pituitary adenoma that was not visualized on MRI and not noted or resected during the initial surgery. On autopsy, single and double or multiple pituitary adenomas are found with a prevalence of 1.5% to 27% and 1%, respectively.¹⁰ In surgical series, double or multiple pituitary adenomas are

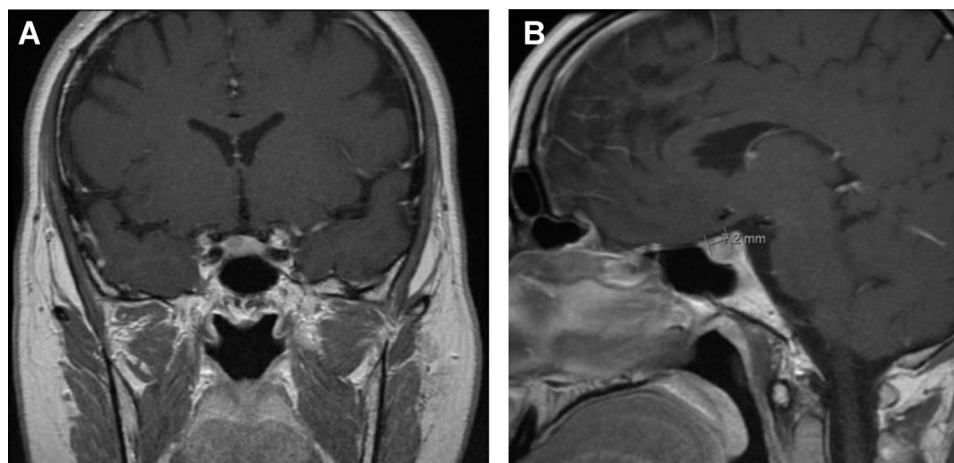


Fig. 1. Brain MRI with and without contrast with attention to the sella notes a microadenoma. It measures 6 × 4 mm in coronal dimension and 7 mm in AP dimension. A, coronal view and B, sagittal view

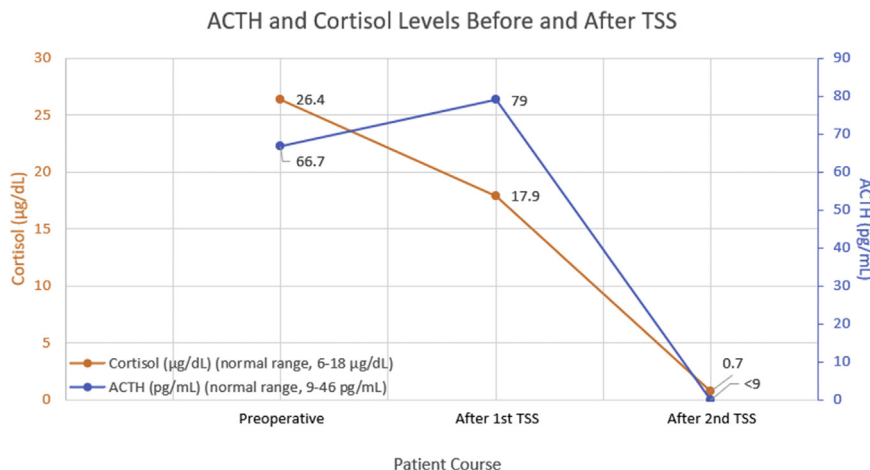


Fig. 2. ACTH and cortisol levels before and after first and second TSS. Adrenocorticotropic hormone (ACTH) (pg/mL, normal range, 9–46 pg/mL), cortisol (µg/dL), transsphenoidal surgery (TSS)

described 0.4% to 1.3% of the time.¹⁰ Other sources cite that double pituitary adenomas account for approximately 1% to 4% of all pituitary adenomas.¹¹ They are sometimes subclassified as adenomas directly visualized separately either on imaging or identified during TSS.¹¹ Multiple pituitary adenomas are defined as concurrent adenomas with recognizable morphological, microscopic, and histological features in a single gland.¹¹ Some reviews report that the most common multiple adenomas are somatotropinomas and prolactinomas,¹¹ and others report that growth hormone-secreting and ACTH-secreting tumors are the most common types of multiple adenomas.¹⁰ ACTH-secreting plurihormonal tumors commonly coexist with prolactinomas and nonfunctional adenomas; however, they have also been seen with growth and gonadotropic hormones.¹¹ In a review by Ratliff JK and Oldfield EH, 13 of 660 CD patients surgically treated had multiple pituitary tumors.¹² With this known clinical entity of multiple adenomas, surgical sellar exploration by an expert neurosurgeon at a high-volume center is needed when treating ACTH-secreting tumors.¹¹ There are not several reported cases of multiple ACTH-secreting pituitary tumors, with the first case reported in 2010.¹³ In the case we presented, this rare condition in the setting of her young age and possible comorbidities related to her hypercortisolism warranted an early repeat TSS to achieve remission.

Although MRI is the best imaging modality to identify pituitary tumors, ACTH-secreting pituitary microadenomas are not identified in 30% to 50% of cases.¹⁴ Several ACTH-secreting tumors are too small to be detected by imaging.¹⁴ The use of MRI with postcontrast FLAIR imaging may be one method to improve the identification of multiple pituitary tumors¹⁵ as well as intraoperative ultrasound during TSS.¹⁶ However, MRI with FLAIR imaging did not note a second adenoma in the patient we presented.

There are varying methods to attempt to prevent persistent CD due to incomplete resection or multiple ACTH-secreting pituitary adenomas. Using the histologic pseudocapsule, a layer of compressed normal anterior lobe, as a surgical capsule during TSS could be an improved method of ensuring complete resection.¹⁷ Moreover, a consideration for whole-sellar stereotactic radiosurgery in cases of invasive adenomas or adenomas that are not clearly defined on imaging may prevent the persistence of CD.¹⁸ Ensuring the patient does not have cyclic or ectopic Cushing's syndrome prior to TSS is also significant to avoid the misdiagnosis of CD.^{1,7} If the preoperative diagnosis of CD is correct, the surgical and pathology findings will be suggestive of a chance of biochemical remission.⁷ If the tumor was laterally visualized and touching the

dura or histopathology notes the tumor was not completely surrounded by a normal pituitary tissue, this may suggest an incomplete resection.^{7,17,18}

In 1994, Ram et al reported that 71% of cases, which had early repeat TSS for persistent CD, had immediate hypercortisolism remission; however, the cases had a high risk of hypopituitarism.¹⁹ This is reiterated in the clinical practice guidelines for CD management.¹ The factors that predicted remission with repeat TSS are evidence of previous incomplete resections, the presence of a pituitary lesion on imaging, and intraoperative tumor detection.¹ Remission is less likely to occur than after the first TSS, although it can be achieved rapidly compared to other treatments.¹ The other treatment options for surgical failure are medical therapy, radiation therapy, or in some cases, bilateral adrenalectomy.^{1,19} Owing to the potential for adverse effects with other treatments, there should be a consideration of repeat pituitary surgery.¹ There can also be a delayed response to initial TSS. One case series reports 2 cases of CD treated with TSS, although cure was only apparent 2 to 6 weeks later.²⁰ The reason for this delayed response to TSS is unknown; however, this suggests that if remission is not achieved after an initial TSS, then a patient should be monitored closely for at least several weeks prior to any other major interventions.²⁰

Conclusion

We conclude that if a patient with CD does not achieve remission with an initial TSS, then there should be a strong consideration of performing a repeat TSS to achieve surgical cure in high-volume centers with an expert pituitary surgeon. Multiple or double pituitary adenomas are a known entity that may respond to a second TSS, if initially, the patient is not cured. A repeat TSS should likely only be considered after attempting to visualize a residual pituitary tumor or second adenoma with pituitary imaging and after ruling out an ectopic ACTH or adrenal source of hypercortisolism.

Disclosure

The authors have no multiplicity of interest to declare.

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