Consecutive resections of double pituitary adenoma for resolution of Cushing disease: illustrative case

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BACKGROUND Double pituitary adenomas are rare presentations of two distinct adenohypophyseal lesions seen in <1% of surgical cases. Increased rates of recurrence or persistence are reported in the resection of Cushing microadenomas and are attributed to the small tumor size and localization difficulties. The authors report a case of surgical treatment failure of Cushing disease because of the presence of a secondary pituitary adenoma.

OBSERVATIONS A 32-year-old woman with a history of prolactin excess and pituitary lesion presented with oligomenorrhea, weight gain, facial fullness, and hirsutism. Urinary and nighttime salivary cortisol elevation were elevated. Magnetic resonance imaging confirmed a 4-mm3 pituitary lesion. Inferior petrosal sinus sampling was diagnostic for Cushing disease. Primary endoscopic endonasal transsphenoidal resection was performed to remove what was determined to be a lactotroph-secreting tumor on immunohistochemistry with persistent hypercortisolism. Repeat resection yielded a corticotroph-secreting tumor and postoperative hypoadrenalism followed by long-term normalization of the hypothalamic-pituitary-adrenal axis.

LESSONS This case demonstrates the importance of multidisciplinary management and postoperative hormonal follow-up in patients with Cushing disease. Improved strategies for localization of the active tumor in double pituitary adenomas are essential for primary surgical success and resolution of endocrinopathies.

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KEYWORDS pituitary neuroendocrine tumor; PitNET; pituitary adenoma; Cushing disease; prolactinoma; transssphenoidal

Pituitary adenomas are adenohypophyseal tumors that can cause endocrinopathies, such as pituitary hormone hypersecretion or anterior hypopituitarism. Cell lineages are used to classify these tumors on the basis of immunohistochemical (IHC) staining of transcription factors, hormones, and other biomarkers.1 Pituitary adenomas differentiate from pluripotent stem cells along one of three lineage pathways, depending on the following active transcription factors (TFs): pituitary transcription factor 1 (PIT-1), T-box transcription factor (TPIT), or steroidogenic factor-1 (SF-1). Rarely, two or more discrete pituitary adenomas from different lineages are identified in patients; however, the etiology remains unclear.2 The incidence of multiple pituitary adenomas has been reported to be 1%–2% of all resected pituitary adenomas but is likely underestimated based on data from large autopsy series.1–4 Pluri-hormonal adenomas are also rare entities in which a single tumor contains multiple TF lineages with one or more hormonal excesses.1–3 Preoperative recognition of multiple or pluri-hormonal pituitary adenomas is rare, and most tumors are discovered incidentally upon autopsy, intraoperatively, or on histological analysis.2,3,5 In cases of multiple synchronous pituitary adenomas, only one hormone excess syndrome is most frequently evident on clinical presentation and endocrine workup. Silent pituitary tumors positive for prolactin on immunohistochemistry are the most prevalent additional, incidentally found tumor in cases of multiple pituitary adenomas.5 This is particularly true in Cushing disease.6,7 It is important to recognize the presence of multiple pituitary adenomas especially in the
setting of hormonally active pituitary adenomas to provide optimal management for this subset of patients. Complete resection is curative for Cushing disease with the standard of care achieved through a transsphenoidal approach. Localization of the tumor presents a challenge because of suboptimal sensitivity of magnetic resonance imaging (MRI) in demonstrating microadenomas, the inconsistency of lateralization with inferior petrosal sinus sampling (IPSS), and delays in pathological analysis.\(^1,8,9\) Additionally, the presence of an additional pituitary adenoma can obscure the microtumor through its large size and mass effect and can act as a “decoy lesion” during MRI, IPSS, and resection.\(^5\)

Consideration of multiple pituitary tumors is necessary for successful resection. In a patient with a biochemical picture of Cushing disease, the demonstration of an adenoma with negative adrenocorticotropic hormone (ACTH) immunostaining and the absence of postoperative hypoadrenalism may indicate the existence of a double adenoma. Few cases have described a lack of remission of an endocrinopathy after transsphenoidal resection due to the presence of an additional adenoma,\(^2,6,10\) and even less so in the instance of the persistence of Cushing disease.\(^6\) We present a rare case of double pituitary adenomas in a patient presenting with Cushing disease who underwent two endoscopic endonasal transsphenoidal resections and immunostaining for prolactin and ACTH, respectively, with long-term normalization of her hypothalamic-pituitary-adrenal (HPA) axis.

Illustrative Case

History and Presentation

A 32-year-old female, gravida 0 para 0, with a history of a pituitary lesion and hyperprolactinemia presented to our institution for the evaluation for Cushing disease. Ten years earlier, the patient had presented to a gynecologist with hirsutism, galactorrhea, and oligomenorrhea. Her endocrine workup was remarkable for an elevated prolactin at 33.8 ng/mL (2.3–23.3 ng/mL), while follicle-stimulating hormone (FSH), luteinizing hormone (LH), and thyroid-stimulating hormone (TSH) levels were normal. No ACTH or cortisol levels were available. MRI demonstrated a 5 × 6 × 5-mm T1-weighted isointense pituitary lesion protruding into the suprasellar cistern due to a small sella size. She was started on bromocriptine 2.5 mg daily for 5 years, with normalization of her prolactin level. Subsequent MRI demonstrated a stable lesion size and T1 and T2 hyperintensity in the region of the known pituitary lesion, considered to be posttreatment cystic change with proteinaceous contents and blood. After the normalization of her prolactin levels, she continued to have oligomenorrhea and abnormal hair growth. Polycystic ovaries were not visualized on ultrasound. She was started on oral contraceptives and then switched to the etonorgestrel implant.

A decade after initial presentation, she presented to endocrinology at our institution with 3 years of weight gain, hirsutism, and potential oligomenorrhea. Vital signs were stable (blood pressure: 122/86; heart rate: 72 beats/min), and facial fullness and striae on her bilateral breasts were appreciated on physical examination. She was taking isoniazid and pyridoxine for a recent diagnosis of latent tuberculosis and had discontinued bromocriptine 5 years earlier. Her weight was 66.3 kg and body mass index (BMI) was 23.9 kg/m\(^2\). She reported that her maternal uncle had a pituitary tumor. Laboratory analysis was positive for elevated urinary free cortisol (UFC) of 109 µg per 24 hours (2.5–45 µg/24 h; Table 1) and nighttime salivary cortisol of 142 ng/mL (<100 ng/dL) with high-normal prolactin of 22.8 ng/mL (2.3–23.3 ng/dL) and normal FSH, LH, TSH, and thyroxine (T4). Dehydroepiandrosterone sulfate (DHEA-S) was 128 µg/dL (98.8–340.0 µg/dL). Imaging demonstrated a 4 × 4 × 4-mm pituitary lesion with decreased T1-weighted and increased central T2-weighted signal intensity in the left lateral pituitary (Fig. 1A–C). Desmopressin (Ferring Pharmaceuticals DDAVP) stimulation increased a basal ACTH of 49.9 pg/mL to ACTH of 91.2 pg/mL, and cortisol increased from 13.7 µg/dL to 21.2 µg/dL, consistent with neoplastic hypercortisolism. IPSS was performed, which showed a right-sided, central-to-peripheral ACTH gradient (Table 2). The patient elected to undergo endoscopic endonasal resection with the initial target as the left-lateral pituitary mass to achieve a cure for Cushing disease.

Primary Resection and Outcomes

During the primary resection, abnormal tissue was immediately visible after a linear incision along the bottom of the dura, with an excellent plane of dissection. The inferomedial adenoma was distinct from the known left lateral lesion, and the resection was considered complete by the primary neurosurgeon. Subsequently, the left-sided adenoma was not pursued because of the historical prolactinoma diagnosis and an assumption that the newly discovered adenoma was the cause of ACTH hypersecretion. However, pathology of the inferomedial tumor was strongly and diffusely positive for prolactin (Fig. 2B), synaptophysin, and cytokeratin, with a Mindbomb Homolog-1 (MIB-1) proliferative index of 2.4%. ACTH, growth hormone (GH), FSH, LH, and TSH immunostaining were negative. TF immunohistochemistry was not available. On postoperative day (POD) 1, pituitary MRI was performed and demonstrated the unchanged 4-mm\(^3\) T1-weighted hypointense lesion with small central T2-weighted hyperintensity in the left lateral gland (Fig. 1D–F). Cortisol levels ranged from 9.7 to 76.2 µg/dL (4.8–19.5 µg/dL), and ACTH was 19.5 pg/mL (7.2–63.3 pg/mL) on POD 1.

Early reoperation was discussed with the patient based on the pathology and persistent hypercortisolism; however, she elected to pursue conservative management with close follow-up. Postoperative cortisol nadir was 4.8 µg/dL (4.8–19.5 µg/dL) on POD 2 during her 4-day hospital stay. DHEA-S was significantly decreased from baseline at 22.3 µg/dL (98.8–340.0 µg/dL) and a prolactin level of 3.4 ng/mL (2.3–23.3 ng/dL) was low-normal. No glucocorticoids were administered during her hospital course. There was no clinical evidence of vasopressin deficiency while she was an inpatient.

Three months postoperatively, the patient reported insomnia, poor hair quality, fatigue, nocturnal sweating, and continued increasing weight gain with fat accumulation in the supraclavicular and dorsal cervical area. She had one spontaneous menstrual period despite the

| TABLE 1. Urinary free cortisol at baseline and 3, 5, and 7 months after the primary resection |
|---------------------------------|-----|-----|-----|-----|
| Variable                        | Baseline | 3 Mos | 5 Mos | 7 Mos on Osilodrostat |
| Urinary free cortisol (4–50 µg/24 hrs) | 109 | 134.2 | 125.4 | 40.3 |
| Urinary creatinine (0.5–2.5 g/24 hrs)  | 0.995 | 1.17 | 1.42 | 1.11 |
| Urinary vol (mL)                | 1950 | 2300 | 2100 | 2125 |
use of etonogestrel implant. UFC was increased at 134.2 μg/24 hours (4–50 μg/24 h; Table 1). The 8:00 am serum cortisol was 10.2 μg/dL (5.0–25.0 μg/dL). She was started on osilodrostat 2 mg twice daily for her persistent hypercortisolism, and she reported some clinical improvement; however, she had continued elevation in her late-night salivary cortisol levels up to 7.0 nmol/L. Other endocrine lab work was normal, with a prolactin of 13.5 ng/mL (2.8–23.3 ng/mL) and TSH of 3.67 mIU/mL (0.4–4.0 mIU/mL). Her weight had increased by 4.9 kg to 71.2 kg with a BMI of 25.3 kg/m². Approximately 6 months postoperatively, she was amenable to a secondary resection targeting the remaining left lateral pituitary adenoma.

Secondary Resection and Outcomes

After obtaining adequate exposure for the secondary resection, the lesion in the left lateral aspect of the pituitary was targeted. The tumor was clearly identified and completely resected without intraoperative complication. IHC staining was diffusely positive for ACTH (Fig. 2E), synaptophysin, and cytokeratin with decreased reticulin and an MIB-1 index of 3.3%. Prolactin, GH, TSH, LH, and FSH immunostaining were negative. Postoperative cortisol monitoring demonstrated decreased levels, with a nadir of 2.0 μg/dL on POD 0. Levels of ACTH and DHEA-S were decreased at 4.4 pg/mL (7.2–63.3 pg/mL) and 13.3 μg/dL (98.8–340 μg/dL), respectively, on POD 1. Prolactin remained within the normal range at 8.2 ng/mL (2.8–23.3 ng/mL). The patient was started on intravenous hydrocortisone 50 mg every 8 hours for adrenal insufficiency. Postoperative symptoms of nausea, headache, and muscle weakness resolved with hydrocortisone administration. She was discharged on hydrocortisone 60 mg daily in divided doses for adrenal insufficiency and had no signs of vasopressin deficiency during her 2-day hospital course.

By 3 months, the patient reported decreased fatigue, myalgia, and insomnia and improved overall well-being and physical appearance. She was weaned down to a total daily dose of 20 mg of hydrocortisone and had lost 5.2 kg. Her menstruation returned while having an etonogestrel implant. Rapid ACTH stimulation was abnormal, with decreased cortisol at 30 minutes of 4.1 μg/dL (7.2–63.3 pg/mL) demonstrating continued adrenal insufficiency. Follow-up MRI demonstrated miniscule remaining left pituitary adenoma (Fig. 3). Seven months after her second surgery, she was started on 50 mg levothyroxine for primary hypothyroidism in the setting of slightly elevated TSH of 4.1 μIU/mL (0.4–4.0 μIU/mL) and a low-normal T4 of 0.8 ng/dL (0.7–1.5 ng/dL).

Two years after the second resection, the patient lost 10.1 kg (weight, 61.1 kg; BMI, 21.76 kg/m²). Her ACTH stimulation test

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ACTH or prolactin ratio = inferior petrosal sinus ACTH or prolactin/peripheral blood ACTH or prolactin.
became normal, and hydrocortisone therapy was discontinued. At the 2-year time point, the patient and her husband successfully conceived a child.

**Patient Informed Consent**

The necessary patient informed consent was obtained in this study.

**Discussion**

Double or multiple pituitary adenomas are discovered in 0.37%–2.6% of resected pituitary lesions. A majority of multiple pituitary adenomas are not suspected before surgery with an inconclusive clinical presentation or endocrine laboratory workup. The presentation of multiple synchronous neoplasms is thought to be more common than having a single neoplasm with multiple lineages. Studies have shown that additional pituitary adenomas are seen at a rate of 1.6%–3.3% in Cushing disease in studies including both contiguous and noncontiguous double pituitary adenomas. Additional pituitary adenomas that are hormonally active make up 40% of resected double pituitary adenomas, with most staining for gonadotroph adenoma. Overall, the most common incidental pituitary adenoma is prolactinoma, which occurs most frequently with GH or ACTH adenomas. In very rare instances, Cushing cases can present with hyperprolactinemia and Cushing synchronously. Hormonal secretion and clinical presentation are variable, with the pathology most often attributed to only one component of double pituitary adenoma. The multiple-hit theory is the most common hypothesis for double pituitary adenoma etiology with coincidental monoclonal expansion of two or more lineages, which present with separate pseudo-capsules for each lesion.

**Observations**

On presenting with Cushing disease, the differential diagnosis before the initial operation considered that the known left lateral pituitary adenoma could be a mixed tumor with both prolactin and ACTH lineages. The presentation of multiple synchronous neoplasms is thought to be more common than having a single neoplasm with multiple lineages. Studies have shown that additional pituitary adenomas are seen at a rate of 1.6%–3.3% in Cushing disease in studies including both contiguous and noncontiguous double pituitary adenomas. Additional pituitary adenomas that are hormonally active make up 40% of resected double pituitary adenomas, with most staining for gonadotroph adenoma. Overall, the most common incidental pituitary adenoma is prolactinoma, which occurs most frequently with GH or ACTH adenomas. In very rare instances, Cushing cases can present with hyperprolactinemia and Cushing synchronously. Hormonal secretion and clinical presentation are variable, with the pathology most often attributed to only one component of double pituitary adenoma. The multiple-hit theory is the most common hypothesis for double pituitary adenoma etiology with coincidental monoclonal expansion of two or more lineages, which present with separate pseudo-capsules for each lesion.

**FIG. 2.** Histological examination of surgical specimens from the inferomedial (A–C) and left lateral (D–F) lesions. The initial resection (hematoxylin and eosin [H&E], A) was strongly and diffusely positive for prolactin (B) with normal reticulin levels (C) indicating a lactotrophic pituitary adenoma. The second operation (H&E, D) was diagnostic for a corticotropic pituitary adenoma with diffusely positive adrenocorticotrophic hormone (ACTH) (E) and decreased reticulin (F). Original magnification × 100.

**FIG. 3.** Postoperative imaging 3 months after the second operation demonstrates near gross-total resection (yellow arrows: surgical cavity) of the left lateral pituitary adenoma on coronal precontrast (A) and postcontrast T1-weighted (B) and T2-weighted (C) MRI.
incidental pituitary tumors that look like the hormonally active adenoma and encourage resection of it, leaving the primary pituitary adenoma behind. It has been reported that these “decoy lesions” can cause surgical failure and require secondary operations. Intraoperative localization and confirmation of the adenoma classification may have also been helpful during the case, including tissue-based ACTH antibody assay, plasma ACTH measurements with an immunochemiluminometric method, or intraoperative ultrasound.

The inferomedial second tumor was not appreciated or reported throughout her serial MRI studies from 2010 to 2020. Interestingly, imaging did demonstrate the left pituitary adenoma that was medically treated as a prolactinoma, although it was later diagnosed as an ACTH-secreting lesion on IHC staining. Preoperative visualization of a pituitary adenoma in Cushing disease is reported to be limited, with a reported 50% incidence with negative MRI with standard 1.5 T. MRI technical refinements in magnet strength, slice thickness, or enhanced spin sequences have increased sensitivity, but one-third of patients with Cushing disease still have negative scans. Small prolactinomas, especially those near the cavernous sinus, are also notoriously difficult to visualize on MRI, although recent advances using co-registration of 11C-methionine positron emission tomography–computed tomography with MRI (Met-PET/MRI) may prove useful. Difficulty with preoperative visualization complicates a diagnosis of multiple adenomas, with or without multiple endocrinopathies, and negatively affects surgical planning. In a single-institution retrospective review of MRI in all cases of double pituitary tumors, only one of eight patients (12.5%) over 16 years of age had a positive MRI for double pituitary tumors and was diagnosed preoperatively.

The patient’s preoperative IPSS demonstrated a right central-to-lateral gradient. This was incongruent with the MRI demonstrating the single left-sided tumor. While IPSS is useful in confirming Cushing disease, its sensitivity for lateralization has been reported at only 59%–71%. With this in mind and a known left-sided adenoma on MRI, exploration of the right side of the pituitary was not originally planned. Ultimately, the left-sided adenoma was the source of ACTH hypersecretion, which remains incongruent with preoperative IPSS. It has been suggested that multiple pituitary adenomas in Cushing disease could further decrease its accuracy.

The patient’s initial historical prolactin levels (33.8 ng/dL) were lower than reported levels of 100–250 ng/dL for microadenoma and >250 ng/dL in cases of macroadenoma. Normally, in active single prolactinoma, prolactin secretion is correlated to size. We do not suspect that the presence of more than one pituitary adenoma would affect the level of prolactin hypersecretion. Slight elevations in prolactin can be attributed to causes such as pituitary stalk effect, medications, and physiological stimulation. During the 5 years of bromocriptine therapy, the effect on the inferomedial prolactinoma was unknown, as it was not appreciated on MRI. There are reports of prolactinomas being less responsive to dopaminergic agonist therapy in cases of double adenomas. Upon resection of the inferomedial prolactinoma during the initial operation, there was no further change in the patient’s prolactin levels, which could most likely be attributed to prior dopaminergic therapy. Unfortunately, the initial endocrine laboratory workup did not include levels of ACTH or cortisol. In addition to hyperprolactinemia, Cushing disease can also present with changes in menstruation. After the secondary resection and removal of the ACTH-secreting pituitary adenoma, the patient’s oligomenorrhea resolved and she achieved pregnancy. Retrospectively, it remains unclear if the prolactinoma was once truly active hormonally.

Lessons
The rare presence of two pituitary adenomas can complicate the diagnosis, medical and surgical management, and long-term outcomes for patients. A complete endocrine workup is essential when a pituitary adenoma is suspected and can help screen for plurihormonal and multiple pituitary adenomas. In our patient, it is unknown when the onset of hypercortisolism was with the limited initial hormonal workup.

Currently, localizing and resecting the hormonally active adenoma in double or multiple pituitary adenomas remain a challenge, with limitations in preoperative imaging and intraoperative measures. After encountering the additional inferomedial lesion during surgery, resection of both adenomas during the initial surgery may have been prudent to ensure the resolution of Cushing disease. Although exploration for additional pituitary adenomas is not usually recommended, it could be considered in cases of multiple pituitary adenomas and uncertainty of the culprit of Cushing disease.

The current characterization of pituitary tumors by the World Health Organization includes immunohistochemistry for both transcription factors and pituitary hormones, with clinical usefulness to be determined by future studies. Multiple lineages can occur mixed in a single pituitary adenoma or across different noncontiguous adenomas and can only be determined by TF immunostaining. The left ACTH-staining lesion in our patient had some shrinkage and MRI changes, which may have been a response to dopaminergic therapy. Full characterization of the tumor cell lineages in this case remains undetermined without staining for TFs.

In conclusion, we report a rare case of Cushing disease concurrent with a prolactinoma leading to the need for repeat resection. This is one of the few reported cases of a double pituitary adenoma leading to a lack of biochemical remission of hypercortisolism after the initial surgery. Strategies for localization of the active tumor in double pituitary adenomas are essential for primary surgical success and the resolution of endocrinopathies.

References


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

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Analysis and interpretation of data: Zwagerman, Armstrong, Tavakoli, Shah, Coss, Ioachimescu, Findling.

Drafting of the article: Zwagerman, Armstrong, Shah.

Critically revising the article: Zwagerman, Armstrong, Tavakoli, Shah, Ioachimescu, Findling.

Reviewed submitted version of the manuscript: Zwagerman, Armstrong, Tavakoli, Shah, Laing, Ioachimescu, Findling.

Approved the final version of the manuscript on behalf of all authors: Zwagerman.


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