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Case Report

A Second Look at Cushing Disease: Hypercortisolism Recurrence From Another Gland

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Abstract

Cushing disease (CD) is the most common form of adrenocorticotropin (ACTH)-dependent Cushing syndrome (CS), whereas unilateral adrenal adenoma is the most common cause of ACTH-independent CS. However, the occurrence of different subtypes of CS in a single individual is very rare. We present a case of a 44-year-old woman with distant histories of left adrenalectomy for an adrenal adenoma and total thyroidectomy following the diagnosis of papillary thyroid carcinoma. She was later diagnosed with CD, achieving disease remission after pituitary surgery, but subsequently developed adrenal CS from the remaining right adrenal gland. After discussing the potential advantages and drawbacks of another adrenalectomy to remove her right adrenal gland, the patient declined surgery and opted for medical management. After 7 years of imaging follow-up studies, her right adrenal adenoma has remained stable in size and she is biochemically controlled on low-dose osilodrostat therapy. Our case emphasizes the importance of recognizing the rare occurrence of successfully treated CD followed by the recurrence of CS from a different gland, and the adoption of management strategies tailored to each individual patient's preferences.

Key Words: refractory Cushing syndrome, corticotroph adenoma, adrenal adenoma, transsphenoidal resection, adrenalectomy

Abbreviations: ACTH, adrenocorticotropin; CD, Cushing disease; CS, Cushing syndrome; CT, computed tomography; MEN, multiple endocrine neoplasia; RR, reference range.

Introduction

Cushing syndrome (CS) arising from either pituitary or adrenal lesions is generally a rare condition, with an estimated prevalence of 10 to 15 cases per million individuals [1]. The majority of cases of endogenous CS are adrenocorticotropin (ACTH) dependent, accounting for 80% to 85% of cases. Among these cases, approximately 75% to 80% are attributed to pituitary corticotroph adenomas [2, 3], whereas ACTH-independent CS constitutes 15% to 20% of cases, with 90% of such cases caused by unilateral adrenal adenomas [4]. Surgery is the preferred first-line treatment option for all cases of CS; however, approximately 20% cases may recur following surgical resection that necessitates second-line treatments, such as medical therapy, adrenalectomy, and radiation therapy [5, 6].

Bilateral adrenalectomy may be considered for some Cushing disease (CD) patients, such as patients with persistent or recurrent disease following pituitary surgery, medication intolerance, nonadherent or unresponsive to medical therapy, or in situations where rapid normalization of life-threatening hypercortisolism is required. However, this procedure carries the risk of development of Nelson syndrome and lifelong use of glucocorticoid and mineralocorticoid replacement therapies [7]. Consequently, the role of bilateral adrenalectomy in patients with CS still remains a subject of debate and medical therapy is increasingly preferred [8]. Additionally, there is accumulating evidence affirming the effectiveness, safety, and tolerability of medical therapies leading to its increased use in the treatment of CS, subsequently allowing a more personalized approach for these patients [9].

We hereby present a case of a patient with distant histories of left adrenalectomy for an adrenal adenoma and total thyroidectomy for papillary thyroid carcinoma, who later developed CD that required transsphenoidal resection. After 6 years of disease remission following her transsphenoidal resection, the patient sought medical guidance for recurrence of her hypercortisolemic symptoms leading to the discovery of a right cortisol-secreting adrenal adenoma and the subsequent diagnosis of adrenal CS.

Case Presentation

A 44-year-old African American woman presented to our clinic in 2017 for worsening headaches, joint and muscle pains, muscle weakness, facial acne, facial roundness, facial plethora, pink abdominal striae, easy skin bruising, hair loss, and weight gain of 7 kg over 6 months. Her past surgical history included a left adrenalectomy for an adrenal adenoma in 2009, transsphenoidal resection of a corticotroph adenoma in 2011, and total thyroidectomy for papillary thyroid

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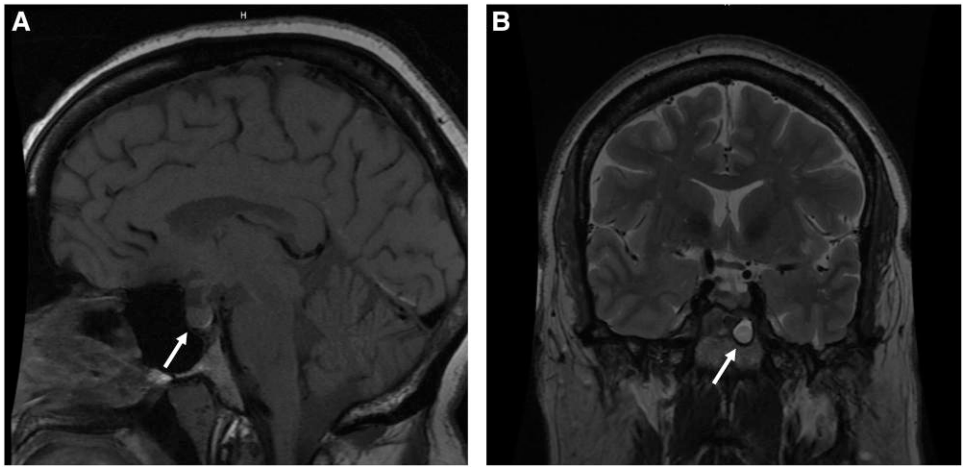

Figure 1. Nonenhancing cystic foci in the left lateral aspect of the pituitary gland (A: sagittal view; B: coronal view).

carcinoma in 2016. The left adrenalectomy was undertaken due to worsening hypertension and mildly elevated plasma metanephrines and catecholamines; however, the pathology revealed an adrenal cortical adenoma and not pheochromocytoma characteristics, demonstrating clear and eosinophilic cytoplasm, low mitotic activity, no significant atypia, and no vascular invasion, while immunohistochemistry was positive for inhibin, calretinin, and Melan-A. Genetic studies, including multiple endocrine neoplasia (MEN) 1 testing, were performed and were negative. Her past medical history included long-standing type 2 diabetes mellitus, metabolic dysfunction–associated steatohepatitis, and osteoporosis with compression fractures on her lumbar 4 to 5 vertebral bodies of her spine. The patient reported no known family history of endocrine disorders.

Diagnostic Assessment

Further testing at this clinic visit revealed elevated 24-hour urine cortisol levels of 49.3 µg/24 hours (135.73 nmol/24 hours) (reference range [RR] <45 µg/24 hours; <124.40 nmol/24 hours), unsuppressed overnight 1-mg dexamethasone suppression test with a postdexamethasone cortisol level of 15.8 µg/dL (435.88 nmol/L) (RR <5 µg/dL; <138 nmol/L), a low dehydroepiandrosterone sulfate level of 14 µg/dL (0.38 µmol/L) (RR: 32-240 µg/dL; 0.86-6.49 µmol/L), and normal 24-hour urine metanephrine levels. These findings, in conjunction with the patient's clinical symptoms, raised concerns of recurrence of CS, especially considering a recent magnetic resonance imaging scan that had revealed some residual tissue in the sella described as a nonenhancing cystic foci in the left lateral aspect of the pituitary gland (Fig. 1).

Follow-up laboratory testing revealed plasma morning ACTH of less than .1 pg/mL (<23.98 pmol/L) (RR: 7-63 pg/mL; 152.6-1373.4 pmol/L), whereas 24-hour urinary free cortisol and serum morning cortisol levels were within the normal range at 47 mcg/24 hours (129.98 nmol/24 hours) and 14.8 mcg/dL (408.67 nmol/L) (RR <45 µg/24 hours; 124.40 nmol/24 hours). Due to the low plasma morning ACTH level, an abdominal magnetic resonance imaging scan was performed that revealed a right adrenal adenoma measuring 6.3 × 3.5 cm. Additionally, her insulin-like growth factor 1 was elevated at 316 ng/mL (41.28 nmol/L) (RR: 7.44-25.44 nmol/L), while her prolactin levels were normal. Based on her elevated insulin-like growth factor 1 level, an oral glucose tolerance test for growth hormone suppression was performed that ruled out acromegaly, with a nadir growth hormone level of 0.20 ng/mL (0.61 mIU/L) (RR <1 ng/mL; <3.03 mIU/L) [10].

Suspecting recurrence of CS, her serum cortisol and ACTH levels were closely monitored over the course of a year (Table 1). During this period, her 24-hour urinary free cortisol levels were either mildly elevated or within the normal range at 47, 39, and 32 mcg/24 hours (129.74, 107.63, and 88.14 nmol/day, respectively) (RR <45 µg/24 hours; <124.40 nmol/24 hours), prompting further evaluation with late-night salivary cortisol measurements on 4 separate occasions that were consistently elevated at 0.154, 0.218, 0.298, and 0.109 µg/dL (4.24, 6.01, 8.21, and 3.01 nmol/L, respectively) (RR: <0.010-0.090 µg/dL; <0.28-2.48 nmol/L). The persistent suppression of ACTH levels supported the diagnosis of adrenal CS, and an abdominal computed tomography (CT) scan revealed a lipid-rich adenoma that was stable in size measuring 6.6 × 3.5 cm (Fig. 2).

Treatment

Because our patient was biochemically in remission following her pituitary surgery for CD for 6 years before the current presentation and now has biochemical evidence of recurrence of hypercortisolism due to adrenal CS, treatment options were discussed with the patient, including medical therapy and right adrenalectomy. The patient opted against a right adrenalectomy due to concerns about the need for lifelong hydrocortisone and fludrocortisone, and decided to commence medical therapy. The patient was offered the option to start either ketoconazole or a glucocorticoid receptor antagonist (mifepristone). The patient declined being treated with ketoconazole and mifepristone, as she was concerned about the side-effect profile of liver function test derangements due to her history of metabolic dysfunction–associated steatohepatitis and hypokalemia, respectively. Hence, she decided to start osilodrostat therapy and began a low dose of 1 mg twice daily.

Outcome and Follow-up

Annual follow-up CT imaging studies of the patient's adrenal gland for the next 7 years after the current presentation have

Table 1. Comparison of hormonal parameters over time

Hormone tested	Initial consult	Post adrenal adenoma findings[a]	Post osilodrostat (1 y)[b]	Reference range
8 AM ACTH	<1.1 pg/mL (<0.24 pmol/L)	<1.1 pg/mL (<0.24 pmol/L)	3.5 pg/mL (0.76 pmol/L)	7.2-63.3 pg/mL (1.6-13.9 pmol/L)
8 AM serum cortisol	14.8 µg/dL (408.67 nmol/L)	16.3 µg/dL (448.1 nmol/L)	4.2 µg/dL (115.8 nmol/L)	6.2-19.4 µg/dL (171.1-534.41 nmol/L)

Reported in conventional units (SI units).
Abbreviation: ACTH, adrenocorticotropin.
[a]One year after initial consult.
[b]Two years and 9 months after initial consult.

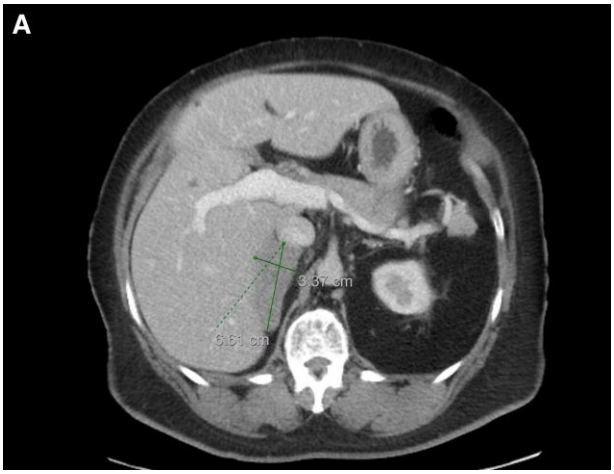

Figure 2. Abdominal computed tomography images demonstrating adrenal adenoma in the right adrenal gland measuring 6.6 × 3.5 cm.

shown stability in the size of her right adrenal adenoma. Her blood pressure is well controlled with a single antihypertensive medication (amlodipine), and her glycated hemoglobin has remained in the nondiabetic range. Additionally, she has been experiencing increased energy levels and improvement in peripheral edema. While on osilodrostat therapy, she continues to be biochemically well controlled and has had only a single episode of adrenal insufficiency. A chronological overview of clinical events is displayed in Fig. 3. Because her morning serum cortisol level was relatively low (5.6 µg/dL [154.5 nmol/L]), her osilodrostat dose was further decreased to 1 mg in the evening in December 2024 and she was educated on the proper timing and administration of rescue oral hydrocortisone therapy of 5 to 10 mg, as needed, whenever she developed symptoms of adrenal insufficiency.

Discussion

While previous reports have documented the coexistence of CD with a solitary adrenal adenoma [9], the unique aspect of our case lies in the development of a right adrenal adenoma after a distant history of surgical resection of a left adrenal adenoma and the achievement of disease remission following transsphenoidal resection of a pituitary corticotroph adenoma [4]. Several molecular studies have been performed to elucidate the pathogenesis of recurrent and refractory endocrine tumors, revealing links to genetic factors. The majority of previously reported cases of pituitary adenomas coexisting with adrenal adenoma are seen in patients with MEN syndromes [11]. The genetic testing for MEN 1 syndrome conducted on our patient yielded negative results. However, while MEN 1 was ruled out in our patient, it is possible that other, yet-unidentified genetic factors may contribute to this pattern of tumor formation, including Carney complex and McCune-Albright syndrome, that can be associated with adrenal adenomas and will need to be tested in our patient. Notably, our patient does not report any family history of endocrine tumor syndromes, and corticotroph adenomas are primarily sporadic monoclonal neoplasms that are rarely found in genetic syndromes [12].

In assessing our patient, we also noted a discrepancy between the overt cushingoid features in our patient and the marginal elevations in 24-hour urine free cortisol levels, underscoring the complexities in diagnosing and characterizing the severity of hypercortisolemic states. While 24-hour urine free cortisol remains an important screening test, its limitations must be acknowledged, including variability in 24-hour cortisol secretion, renal clearance differences, and the potential for episodic hypercortisolism that may not be fully captured in a single 24-hour urine collection measurement [13]. These factors have been substantiated by Petersenn et al [14], who reported significant intrapatient variability in 24-hour urinary free cortisol measurements, with a coefficient of variation of approximately 50%, highlighting the need for multiple sample collections to improve the reliability of assessments. These fluctuations, along with individual differences in cortisol sensitivity and metabolism, may account for the presence of varying phenotypic features that are not correlated with the degree of urinary hypercortisolism [15]. In our patient's case, her clinical phenotype, imaging data, and the associated comorbidities are more useful in assessing the severity of CS, highlighting the importance of thorough and comprehensive clinical and biochemical assessments for CS patients.

Another aspect contributing to the complexity of our case included the treatment options that we could offer to our patient. She opted to avoid a second adrenalectomy, which has the potential of causing Nelson syndrome [9]. Initially, we offered the patient to start treatment with a steroidogenesis inhibitor such as ketoconazole, which has been used to treat hypercortisolism for more than 30 years with an average remission rate of 71.1% [9]. Another alternative was mifepristone, a glucocorticoid receptor antagonist used in the treatment of hyperglycemic patients with underlying CS [16]. However, our patient decided against being treated with ketoconazole and mifepristone due to the side-effect profiles of liver function test derangements and hypokalemia, respectively. Hence, she was offered osilodrostat treatment, to which she has responded well symptomatically, and her disease currently remains well-controlled in remission.

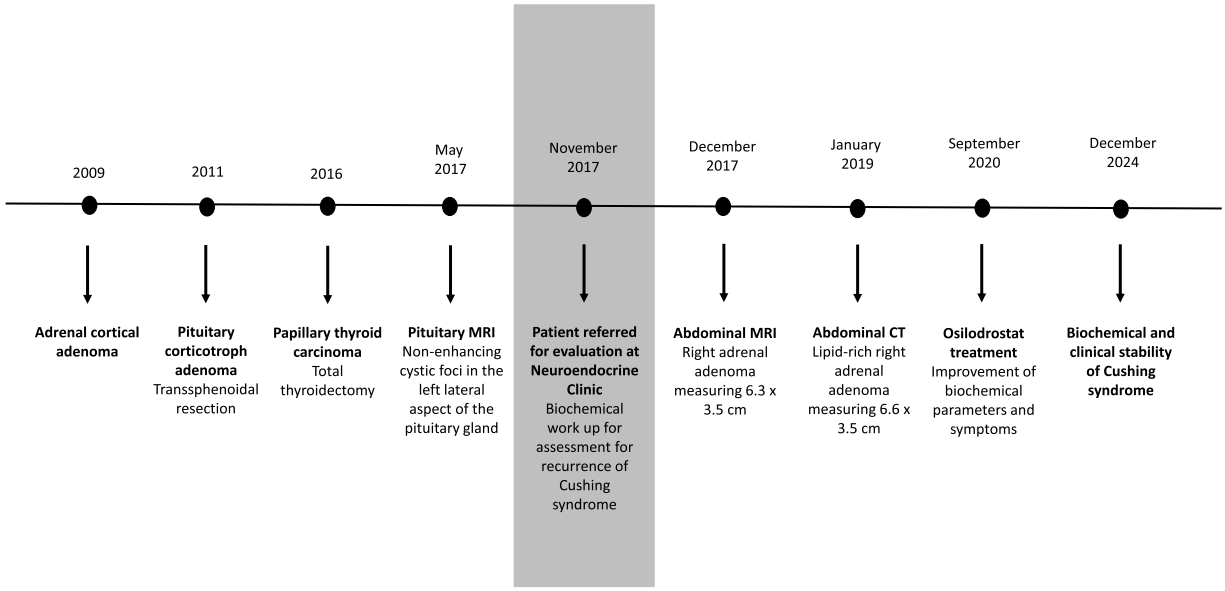

Figure 3. Chronological overview of clinical events.

Because of the effectiveness of osilodrostat, adrenal insufficiency is a side effect that was commonly reported in previous pivotal clinical trials [17, 18]. More recently there have been several publications describing prolonged duration of adrenal insufficiency even after osilodrostat discontinuation that requires close monitoring, a finding that remains mechanistically unclear, especially with its short half-life of approximately 4 hours [19, 20]. Given the emerging reports of prolonged adrenal insufficiency after osilodrostat discontinuation [19, 20], close monitoring of serum cortisol levels and patient education to manage symptoms of adrenal insufficiency are essential for the long-term management of patients on osilodrostat therapy. Finally, eventual recovery of adrenal function has also been recently reported [21], hence clinicians are advised to exercise a low threshold of retesting the adrenal reserve of patients who have discontinued osilodrostat therapy.

Learning Points

- This case highlights an unusual scenario in which a patient with CS presented with both adrenal and pituitary adenomas following prior surgical resections. Physicians should be aware of the rare occurrence of two different etiologies of CS in the same patient and should consider its possibility in patients with recurrent hypercortisolism.
- The patient's hesitation to undergo a second adrenalectomy demonstrates the importance of personalized medicine in individualizing the treatment plan for our patient.
- Recent reports suggest that prolonged adrenal insufficiency after discontinuation of osilodrostat and the eventual recovery of adrenal function can occur in some patients. Clinicians should be aware of this and ensure close monitoring of adrenal function after discontinuing therapy.

Contributors

All authors made individual contributions to authorship. K.C.J.Y. was involved in the diagnosis and management of this case, manuscript review, and text editing. M.M.-G. was involved in manuscript preparation, writing, and submission. Both authors reviewed and approved the final draft.

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Disclosures

None.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the present study.

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