No Postoperative Adrenal Insufficiency in a Patient with Unilateral Cortisol-Secreting Adenomas Treated with Mifepristone Before Surgery

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ABSTRACT

BACKGROUND: Glucocorticoid replacement is commonly required to treat secondary adrenal insufficiency after surgical resection of unilateral cortisol-secreting adrenocortical adenomas. Here, we describe a patient with unilateral cortisol-secreting adenomas in which the preoperative use of mifepristone therapy was associated with recovery of the hypothalamic–pituitary–adrenal (HPA) axis, eliminating the need for postoperative glucocorticoid replacement.

CASE PRESENTATION: A 66-year-old Caucasian man with type 2 diabetes mellitus, hyperlipidemia, hypertension, and obesity was hospitalized for Fournier's gangrene and methicillin-resistant *Staphylococcus aureus* sepsis. Abdominal computed tomography scan revealed three left adrenal adenomas measuring 1.4, 2.1, and 1.2 cm and an atrophic right adrenal gland. Twenty-four-hour urinary free cortisol level was elevated (237 µg/24 hours, reference range 0–50 µg/24 hours). Hormonal evaluation after resolution of the infection showed an abnormal 8 mg overnight dexamethasone suppression test (cortisol postdexamethasone 14.5 µg/dL), suppressed adrenocorticotropic hormone (ACTH; <5 pg/mL, reference range 7.2–63.3 pg/mL), and low-normal dehydroepiandrosterone sulfate (50.5 µg/dL, male reference range 30.9–295.6 µg/dL). Because of his poor medical condition and uncontrolled diabetes, his Cushing's syndrome was treated with medical therapy before surgery. Mifepristone therapy was started and, within five months, his diabetes was controlled and insulin discontinued. The previously suppressed ACTH increased to above normal range accompanied by an increase in dehydroepiandrosterone sulfate levels, indicating recovery of the HPA axis and atrophic contralateral adrenal gland. The patient received one precautionary intraoperative dose of hydrocortisone and none thereafter. Two days postoperatively, ACTH (843 pg/mL) and cortisol levels (44.8 µg/dL) were significantly elevated, reflecting an appropriate HPA axis response to the stress of surgery, and two weeks postoperatively, ACTH was within normal range and a repeat dexamethasone suppression test was normal. Six months postoperatively, ACTH was within normal limits and cortisol was approaching normal. The patient has exhibited no postoperative signs or symptoms of adrenal insufficiency in 12 months.

CONCLUSION: Preoperative mifepristone therapy was associated with apparent recovery of the HPA axis prior to unilateral adrenalectomy in a patient with unilateral adrenal adenomas. Postoperatively, the patient experienced no signs or symptoms of adrenal insufficiency and no glucocorticoid replacement was required.

KEYWORDS: mifepristone, Cushing's syndrome, cortisol, adrenal adenoma, adrenalectomy, adrenal insufficiency, adrenocorticotropic hormone

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Background

Cushing's syndrome (CS) is caused by prolonged and increased exposure to excess cortisol and is associated with significant morbidity (eg, cardiovascular disease, diabetes, infection, psychiatric disorders, and osteoporosis) and increased mortality.[1,2] Approximately 20% of patients with endogenous CS have adrenocorticotropic hormone (ACTH)-independent CS due to excess cortisol secretion by an adrenal adenoma or carcinoma, or less commonly due to adrenal hyperplasia.[1,3] The true prevalence, however, may be higher as imaging technology improves and clinical awareness and screening increases.

Unilateral adrenalectomy is the treatment of choice for patients with CS caused by a cortisol-secreting adenoma.[4] Postoperative adrenal insufficiency occurs in almost all patients with overt CS (99.7%)[5] because of suppression of the hypothalamic–pituitary–adrenal (HPA) axis from excess cortisol and subsequent atrophic changes of the contralateral adrenal gland. As a result, postoperative treatment with glucocorticoid replacement therapy is required to prevent secondary adrenal insufficiency as the HPA axis recovers. The time frame for HPA axis recovery following unilateral adrenalectomy for adrenal CS varies significantly in many patient series and depends on the severity of CS and the postoperative glucocorticoid replacement dosing regimen. Recent studies showed that the recovery of the HPA axis can be prolonged, with only 38% of patients with adrenal CS recovering within five years,[6]

and some patients may be unable to taper off of glucocorticoids and will require lifelong replacement therapy.[7] Glucocorticoid replacement therapy, however, does not mimic physiological cortisol release.[8] For this reason, maintaining adequate treatment of adrenal insufficiency with glucocorticoid replacement therapy while also minimizing excessive long-term glucocorticoid exposure is challenging and can contribute to increased morbidity and decreased life expectancy and quality of life in patients with adrenal insufficiency.[9] Acute adrenal crisis is a significant concern, occurring in approximately 35% of patients with secondary adrenal insufficiency as reported by Hahner et al.[10] Patients currently receiving or recently discontinuing glucocorticoid replacement therapy must be carefully educated and monitored, as physiologic stressors or illness will require an empiric increase in adrenal steroid doses to avoid adrenal crisis.

The glucocorticoid receptor antagonist, mifepristone, is approved by the US Food and Drug Administration for patients with CS and hyperglycemia who have failed surgery or are not a surgical candidate.[11]

Here, we describe a case of a 66-year-old male patient with diabetes who was diagnosed with adrenal CS due to multiple unilateral left adrenal adenomas and who was treated with mifepristone for five months prior to unilateral adrenalectomy. In addition to clinical and metabolic improvement, the use of mifepristone was associated with recovery of the HPA axis, eliminating the need for postoperative glucocorticoid replacement therapy.

Case Presentation

The patient is a 66-year-old Caucasian man with a past medical history significant for type 2 diabetes mellitus, proteinuria, hyperlipidemia, hypertension, obesity, prostate cancer, depression, and hypogonadism. The patient was hospitalized for Fournier's gangrene and sepsis, which required multiple perineal soft-tissue debridements and rounds of intravenous antibiotics. Concurrent with the episode of Fournier's gangrene, the patient was treated for a right axillary abscess that was methicillin-resistant *S. aureus* positive. A computed tomography (CT) scan of the abdomen revealed three lipid-rich adenomas measuring 1.4, 2.1, and 1.2 cm on the left adrenal gland and an atrophic right adrenal gland (Fig. 1). Hormonal work-up was negative for pheochromocytoma and primary aldosteronism, but revealed an elevated urinary free cortisol (UFC) level (237 µg/24 hours, reference range 0–50 µg/24 hours; Table 1).

The patient was seen six weeks after hospital discharge, for continued work-up of his adrenal mass. His clinical presentation included central obesity, facial plethora, and bilateral midclavicular fat pads. Additional hormonal analysis revealed unsuppressed cortisol after an 8 mg overnight dexamethasone suppression test (DST), suppressed ACTH, and low-normal dehydroepiandrosterone sulfate (DHEA-S; Table 1). The patient's glycemic control, which had been relatively stable

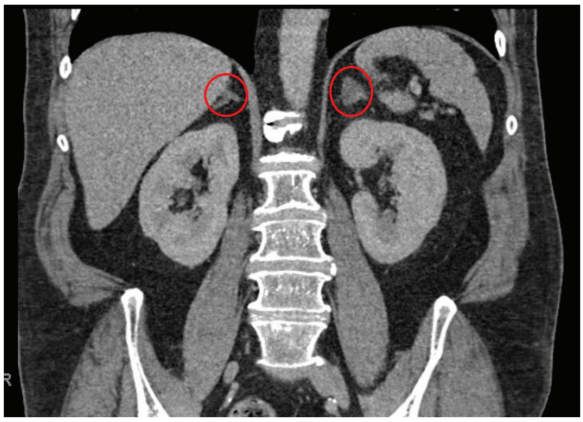


Figure 1. Adrenal CT scan revealing left adrenal adenomas and atrophic right adrenal gland.

over the past two years (HbA1c < 7%), had worsened prior to his hospitalization (HbA1c 8.03%). The patient's medication list is provided in Table 2. A review of the patient's laboratory history also revealed elevated white blood cell counts in the $10.8–16.0 \times 10^3$ range over several years. The patient was diagnosed with CS on the basis of abnormal hormonal testing (eg, abnormal DST, suppressed ACTH, and elevated UFCs) and clinical stigmata of CS and was referred for surgical evaluation for unilateral adrenalectomy.

Treatment Course

Because of the patient's recent multiple infections and worsening glycemic profile, preoperative medical treatment was recommended to improve his surgical candidacy. At the time of hospital discharge, the patient's diabetes regimen included insulin glargine 20 units daily, canagliflozin 100 mg daily, liraglutide 1.8 mg daily, and metformin 1000 mg twice daily. His glycemic profile continued to worsen and the decision was made to initiate medical therapy for CS. He was started on mifepristone 300 mg by mouth daily and the dose was

Table 1. Adrenal adenoma hormonal evaluation.

TEST (NORMAL RANGE)	RESULT
24-hr urinary metanephrine (0–1000 µg/24 hr)	67 µg/24 hr
Normetanephrine (138–521 µg/24 hr)	290 µg/24 hr
Vanillylmandelic acid (1.9–9.8 mg/24 hr)	2.3 mg/24 hr
24-hr urine free cortisol (0–50 µg/24 hr)	237 µg/24 hr
Random cortisol (6.2–19.4 µg/dL)	19.5 µg/dL
Random ACTH (7.2–63.3 pg/mL)	4.0 pg/mL
DHEA-S (male: 30.9–295.6 µg/dL)	50.5 µg/dL
1 mg DST (<1.7 µg/dL)	5.56 µg/dL
8 mg DST (<1.7 µg/dL)	14.5 µg/dL

Abbreviations: UFC, urinary free cortisol; ACTH, adrenocorticotropic hormone; DHEA-S, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test.

Table 2. Patient's medication list at the time of initial hormonal evaluation.

MEDICATION	DOSE/ROUTE/FREQUENCY
Liraglutide	1.8 mg SQ daily
Insulin glargine	10 units SQ every evening
Metformin	1000 mg PO twice daily
Canagliflozin	100 mg PO daily
Atorvastatin	80 mg PO daily
Fenofibric acid	135 mg PO daily
Icosapent ethyl	1 g PO daily
Amlodipine/valsartan	5 mg/325 mg PO daily
Metoprolol tartrate	50 mg PO twice daily

Abbreviations: PO, by mouth; SQ, subcutaneously.

increased by 300 mg every three weeks based on clinical signs of efficacy and tolerability.

Soon after the initiation of mifepristone, his glycemic profile improved dramatically, as evidenced by a decrease in HbA1c (Fig. 2). Ten weeks after starting mifepristone, insulin was discontinued. Glycemic control was achieved after 18 weeks of mifepristone therapy. The patient remained on liraglutide 1.8 mg daily, metformin 1000 mg twice daily, and canagliflozin was increased to 300 mg daily until surgery.

Clinical improvement was also associated with hormonal changes indicative of HPA axis recovery. Specifically, at 18 weeks of mifepristone therapy, his ACTH level increased to 22.5 pg/mL (previously suppressed). Further increases of ACTH were noted with increasing doses of mifepristone (Fig. 3). The rise in ACTH was accompanied by an increase in DHEA-S levels, indicating recovery of the atrophic adrenal tissue. After five months of treatment with mifepristone, levels of ACTH, DHEA-S, and a random cortisol two days prior to surgery were 85.5 pg/mL, 94.9 µg/dL, and 63.4 µg/dL, respectively (Fig. 3). Mild cortisol withdrawal symptoms were reported early in the course of therapy with mifepristone that resolved with ongoing therapy. No hypokalemia was noted during therapy with mifepristone. In addition, the patient's weight decreased by 4.8% (from a baseline of 105 kg) and he exhibited less facial ruddiness. Mifepristone was discontinued one week prior to surgery.

Laparoscopic left adrenalectomy was performed. The patient received one standard intraoperative intravenous dose of hydrocortisone 100 mg. As the patient exhibited no signs or symptoms of adrenal insufficiency, the typical postoperative use of glucocorticoid replacement therapy was not ordered, and the patient was closely monitored. Two days after surgery, the patient had an ACTH level of 843 pg/mL and a cortisol level of 44.8 µg/dL (not shown in Fig. 3), indicating an appropriate HPA axis response to the stress of surgery. Four weeks postoperatively, an overnight DST was normal, and six months after surgery, his ACTH levels were within normal limits and serum cortisol was approaching normal. Twelve months postoperatively, the patient had not experienced any signs or symptoms of recurrent CS and his HbA1c level was 7.54%. The patient's diabetes medications at that time included liraglutide 1.8 mg daily, canagliflozin/metformin 150/1000 twice daily, and insulin glargine 4 units daily (which was previously discontinued while taking mifepristone).

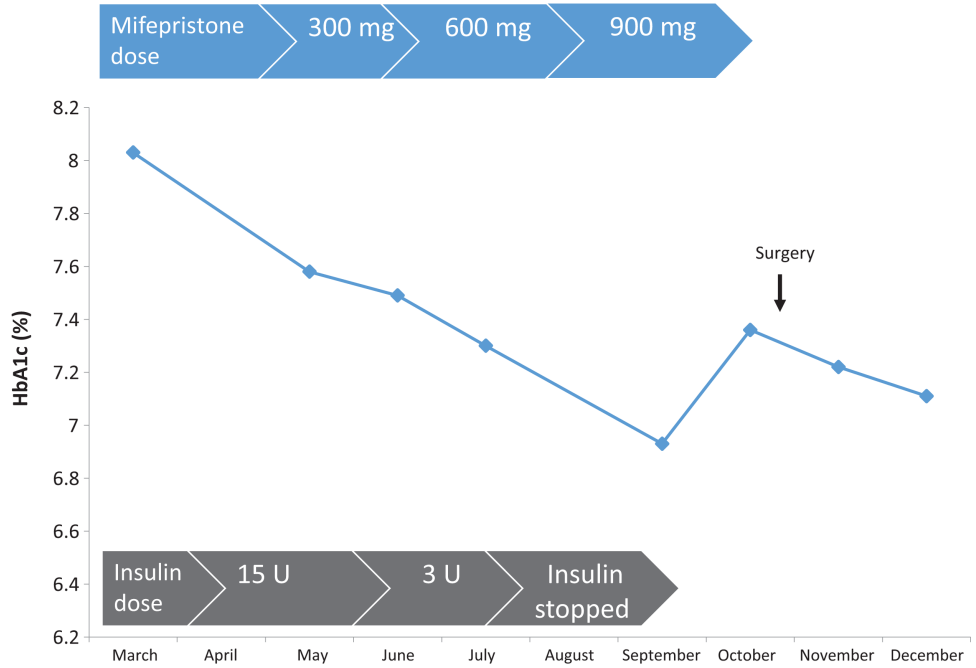
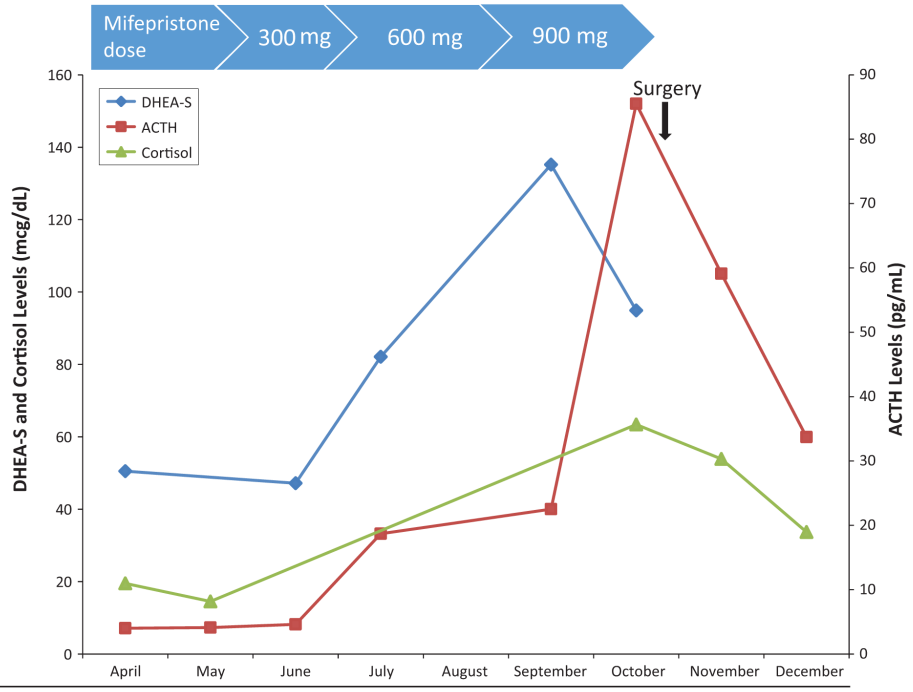


Figure 2. HbA1c levels (%) before and after surgery, with corresponding insulin glargine and mifepristone dosing.



	April	May	June	July	August	September	October	November	December
DHEA-S, mcg/dL	50.5	---	47.2	82.1	---	135.2	94.9	---	---
ACTH, pg/mL	4	4.1	4.6	18.7	---	22.5	85.5	59.1	33.7
Cortisol, mcg/dL	19.5	14.5	---	---	---	---	63.4	53.9	33.7

Figure 3. ACTH, cortisol, and DHEA-S levels before and after surgery. Mifepristone dosing is also shown.
Abbreviations: ACTH, adrenocorticotropic hormone; DHEA-S, dehydroepiandrosterone sulfate.

The surgical pathology showed two adrenocortical adenomas measuring $0.7 \times 0.7 \times 0.6$ cm^3 and $1.6 \times 1.5 \times 1.1$ cm^3.

Discussion

Glucocorticoid replacement therapy is generally recommended for patients undergoing surgical treatment for CS in order to prevent postoperative secondary adrenal insufficiency.[4] The rate of postsurgical recovery of the HPA axis depends in part on the etiology of the CS. A retrospective analysis reviewed the postsurgical duration of adrenal insufficiency in 230 patients treated for Cushing's disease, adrenal CS, and ectopic CS.[6] The authors reported that the probability of recovery of adrenal function within a 5-year follow-up period was 82% for ectopic CS, 58% for Cushing's disease, and 38% for unilateral adrenal CS patients, with a median recovery time of 0.6, 1.4, and 2.5 years, respectively. A review of the last four cases of cortisol-secreting adrenal adenoma with a diagnosis of CS that were referred to our institution found a median duration of postoperative glucocorticoid replacement therapy of 14 months (range 10–37 months), which is consistent with the reported literature.[4] Three patients remain on glucocorticoid replacement therapy after a median of 11 months (range 10–17 months) post unilateral adrenalectomy.

Low serum DHEA-S is frequently seen in adrenal CS.[12–15] The elevated cortisol levels lead to atrophic changes of nontumoral adrenocortical tissue (zona fasciculate and reticularis) ipsilateral to the adenoma and in the contralateral adrenal gland, resulting in impaired glucocorticoid and adrenal androgen synthesis.[16]

In contrast to steroidogenesis inhibitors, which inhibit steroidogenesis in both abnormal and normal adrenocortical tissue, mifepristone does not affect adrenal steroidogenesis because it acts at the glucocorticoid receptor level. In addition, by antagonizing the glucocorticoid receptor at the pituitary and the hypothalamus level, mifepristone may significantly expedite the recovery of the HPA axis. Fleseriu et al[17] showed that the use of mifepristone in patients with Cushing's disease was associated with a mean 2.76-fold rise in ACTH from baseline that returned back to baseline within a month upon discontinuation of mifepristone therapy. In patients with Cushing's disease, it is difficult to determine whether the rise in ACTH comes from the tumor or the normal corticotroph cells of the pituitary. In patients with adrenal CS, the rise of ACTH indicates recovery of the suppressed corticotroph pituitary cells that is followed by a rise in DHEA-S levels, indicative of recovery of the atrophic adrenocortical tissue. Case reports in patients with adrenal CS have also documented increases in ACTH and DHEA-S levels following mifepristone treatment.[18,19] In this patient setting, ACTH and DHEA-S could be used, along with clinical measures, as potential biomarkers of response to mifepristone and could possibly serve as markers of HPA axis recovery, eliminating the need for peri- and postoperative steroid use.[18] The rationale for presurgical management would be analogous

to the presurgical treatment of pheochromocytoma with alpha-blockade or presurgical management of hyperaldosteronism with a mineralocorticoid receptor antagonist.

Use of mifepristone before surgery in this patient was associated with recovery of the HPA axis, as documented by an ACTH increase from 4.0 pg/mL at initial evaluation to 85.5 pg/mL preoperatively and a DHEA-S increase, in parallel with ACTH, from 50.5 µg/dL at baseline to 94.9 µg/dL just prior to surgery. The recovery of the HPA axis is further supported by the post adrenalectomy ACTH and cortisol levels, which were both appropriately elevated, as well as the absence of postoperative symptoms of adrenal insufficiency and avoidance of glucocorticoid replacement therapy.

It is important to recognize in this case that it is unknown how the patient would have responded to adrenal surgery without mifepristone pretreatment, as all patients may not develop adrenal insufficiency. However, adrenal insufficiency is likely to occur after surgery for overt cases of adrenal CS. Important factors to be considered for the development of secondary adrenal insufficiency following surgery in adrenal CS patients undergoing unilateral adrenalectomy include the duration, severity, and histologic subtype of CS. Adrenal CS, in contrast to ACTH-dependent CS, is a slowly evolving disease, in which functional suppression of the otherwise normal contralateral and ipsilateral adrenal occurs in addition to hypothalamic and pituitary suppression.[16] This may be the reason why the HPA axis takes longer to recover in adrenal CS compared to ACTH-dependent causes of CS, although the latter are associated with a significantly higher degree of hypercortisolemia. Regardless of these considerations, the findings in this case are consistent with positive clinical benefits reported in other cases of CS where mifepristone was utilized preoperatively.[18,20] In the case series reported by Moraitis and Auchus,[18] a patient with primary pigmented nodular adrenocortical disease was treated preoperatively with mifepristone for nine months, after which the patient underwent a right total and left partial adrenalectomy. Over the course of mifepristone treatment, the patient experienced a 44 lbs weight loss, resolution of facial plethora and supraclavicular fat pads, as well as improvement in other clinical features including abdominal striae and proximal muscle strength. Postoperative treatment with hydrocortisone was successfully discontinued after one month following a normal cosyntropin stimulation test.[18] In another case report, a patient with CS associated with bilateral adrenal adenomas was treated with mifepristone prior to surgery. By month 4 of mifepristone treatment, she experienced a weight loss of 65 lbs, improvement in hypertension (previously uncontrolled), and complete resolution of chronic leg cellulitis.[20]

It is important to note that patients receiving mifepristone may experience cortisol withdrawal symptoms or symptoms of excessive glucocorticoid receptor antagonism, such as nausea, fatigue, and decreased appetite.[21,22] Acute adrenal crisis does not appear to occur, because mifepristone does not bind to the mineralocorticoid receptor.[23] In cases of excessive glucocorticoid receptor antagonism, dexamethasone can be given to reverse the effect of mifepristone. Because of the long half-life of mifepristone, dexamethasone should be given for two to three days as needed.[11,24] Also hypokalemia is unlikely to occur in patients with adrenal CS who are treated with mifepristone because an increase in cortisol is not noted until the HPA axis recovers. However, hypokalemia might occur upon recovery of the HPA axis, when the ACTH levels increase significantly, stimulating cortisol secretion by both tumoral and nontumoral adrenal tissue.

This case report describes the medical management of a patient with adrenal CS who was treated with mifepristone for five months prior to surgery. In addition to the significant improvement of Cushingoid signs and symptoms, this patient subsequently did not develop signs or symptoms of adrenal insufficiency and required no glucocorticoid replacement therapy postoperatively. Further investigation of mifepristone in the presurgical management of patients with adrenal CS will benefit from a prospective study to evaluate its complete utility.

Consent

The patient provided written informed consent for the publication of this case report and any accompanying images. A copy of the written consent was made available to the journal editor for review. The research was conducted in accordance with the principles of the Declaration of Helsinki.

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Author Contributions

Treated the patient and drafted or critically reviewed the manuscript: RMS, MPK, LR, and RSB. Involved in data collection: RMS and MPK. All the authors conceptualized the case report. Carried out the surgery: LR. All the authors read and approved the final manuscript.

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