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Sustained Clinical Improvement After Discontinuation of Mifepristone: Unexpected Remission of Hypercortisolism

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INTRODUCTION

- Endogenous hypercortisolism (Cushing syndrome) is associated with increased mortality and substantial morbidity[1-5]
- The clinical signs and symptoms of hypercortisolism are often nonspecific and overlap with commonly encountered conditions, including impaired glucose tolerance/diabetes, obesity, hypertension, psychiatric disorders, and osteoporosis[1]
- Knowing when to suspect hypercortisolism is especially challenging in patients without overt cushingoid features (eg, proximal muscle weakness, bruising, plethora, purple striae), particularly when the source is unknown
- Mifepristone (Korlym®, Corcept Therapeutics, Menlo Park, CA) is a competitive glucocorticoid receptor antagonist approved to treat endogenous hypercortisolism of all etiologies
- In patients treated with mifepristone, symptoms of hypercortisolism (eg, hyperglycemia, weight gain, or psychiatric symptoms) can return within several weeks of discontinuation
- Here we describe a patient who experienced clinical improvement in symptoms attributed to excess cortisol after treatment with mifepristone and whose symptoms did not recur after discontinuation of mifepristone

CASE HISTORY AND PRESENTATION

- A 39-year-old female patient presented with persistent weight gain 20 months after diagnosis and successful treatment of thyroid cancer (total thyroidectomy and iodine ablation)
 - Her thyroid function was currently normal with administration of Synthroid 137 μg and Cytomel 10 μg daily
- The patient's chief complaint was "stress" resulting from an inability to lose weight or sleep through the night, fatigue, and recent onset of migraine with vomiting
- No significant weight loss was noted despite diet and exercise; phentermine 15 mg prescribed by her healthcare provider was increased to 37.5 mg
- She had a history of regular but heavy menses and displayed no overt cushingoid features at clinical presentation
- Despite diet, exercise, and phentermine, she lost only 8 lbs in 2 months

WORK-UP FOR SUSPECTED HYPERCORTISOLISM

- Given her difficulty losing weight, poor sleep, migraines, and history of "stress," hypercortisolism was suspected
- Lab results indicated abnormal fasting blood glucose (FBG), low serum potassium (K+) levels, and an abnormal AM cortisol and dexamethasone suppression test (DST), as shown in **Table 1**

Table 1. Baseline Biochemical and Clinical Examination

Parameter	Value
AM cortisol (μg/dL)	29.3 (high)
DST (μg/dL)	2.6 (high)
ACTH (pg/mL)	19
K+ (mEq/L)	3.4 (low), 4.3[a]
FBG (mg/dL)	119, 118[a]
Blood pressure (mm Hg)	130/84, 126/90[a]
Weight (lbs)	200, 192[a]
BMI (kg/m²)	33.2, 31.9[a]

[a]Repeat assessment 2 months later.
ACTH, adrenocorticotropic hormone; BMI, body mass index; DST, dexamethasone suppression test; FBG, fasting blood glucose.

- Imaging of pituitary and adrenals was ordered but the patient declined these tests

MEDICAL THERAPY

- Because of the abnormal biochemical results, a trial of mifepristone 300 mg and spironolactone 25 mg was initiated; at Month 2, the mifepristone dose was increased to 600 mg (**Figure 1**)

Figure 1. Timeline of Treatment and Patient Response

Synthroid 137 μg + Cytomel 10 μg (doses reduced to 112 μg + 7.5 μg at Month 6)
Phentermine 37.5 mg
Mifepristone 300 mg (dose increased to 600 mg at Month 2)
Spironolactone 25 mg (except Months 2-4)
K+ 40 mEq twice-daily supplementation

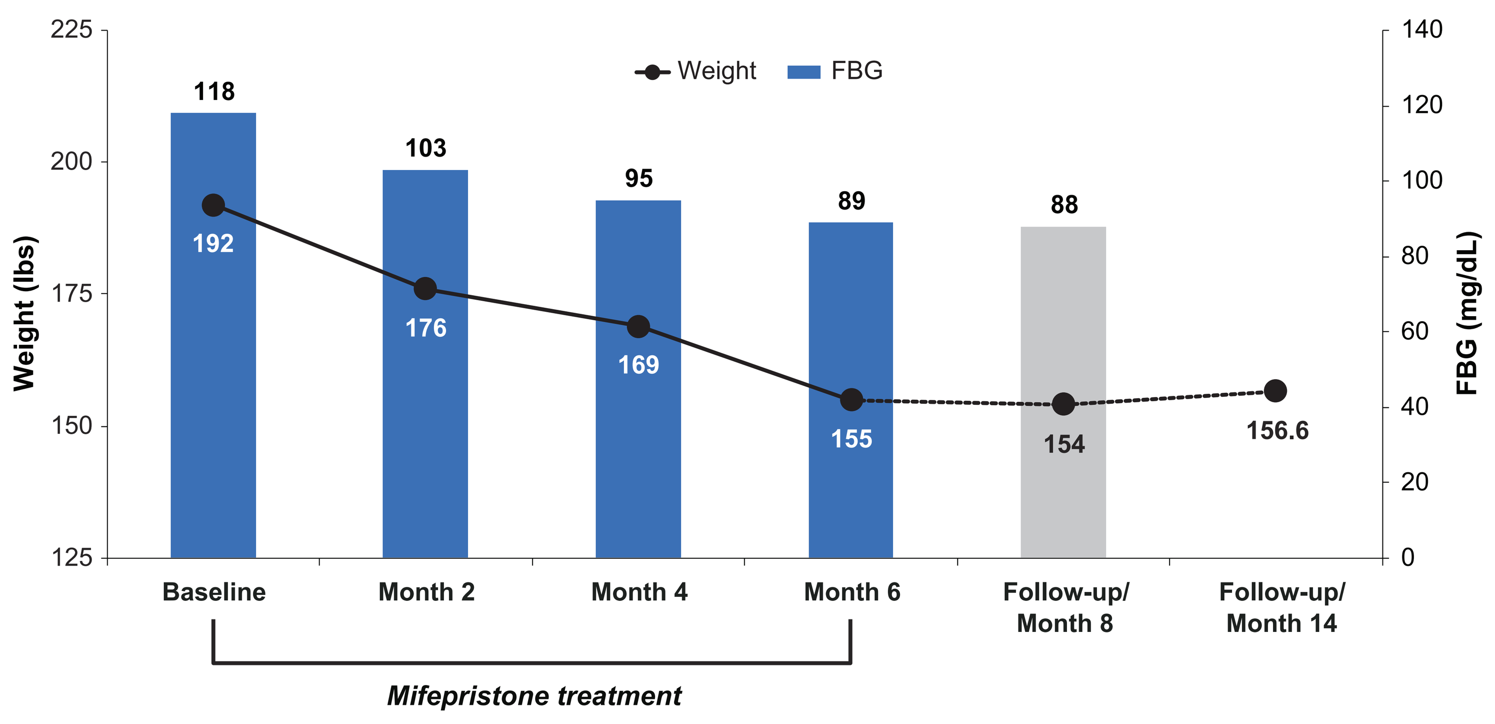
Patient History	Mifepristone Start	Month 2	Month 4	Month 6	Off Mifepristone/ Follow-up
• Persistent weight gain 20 months after successful treatment for thyroid cancer • Poor sleep • Migraines with vomiting • History of "stress"	• DST: 2.6 μg/dL • FBG: 119 mg/dL • Patient declines imaging tests for suspected hypercortisolism • Trial of mifepristone and spironolactone initiated	• Sleep improves • Edema develops • Blood pressure elevated • Amenorrhea develops • Patient not taking spironolactone	• Low K+ • Elevated blood pressure • Patient resumes spironolactone	• Migraines, edema, and fatigue resolved • Mifepristone, phentermine, spironolactone, K+ stopped	• Repeat DST: 0.4 μg/dL • Thyroid function tests normal • Weight and FBG remain normal • Sleep remains improved • Regular menses resume

DST, dexamethasone suppression test; FBG, fasting blood glucose.

RESULTS WITH MIFEPRISTONE

- A diagnosis of hypercortisolism was supported by the improvement in FBG and weight (**Figure 2**)

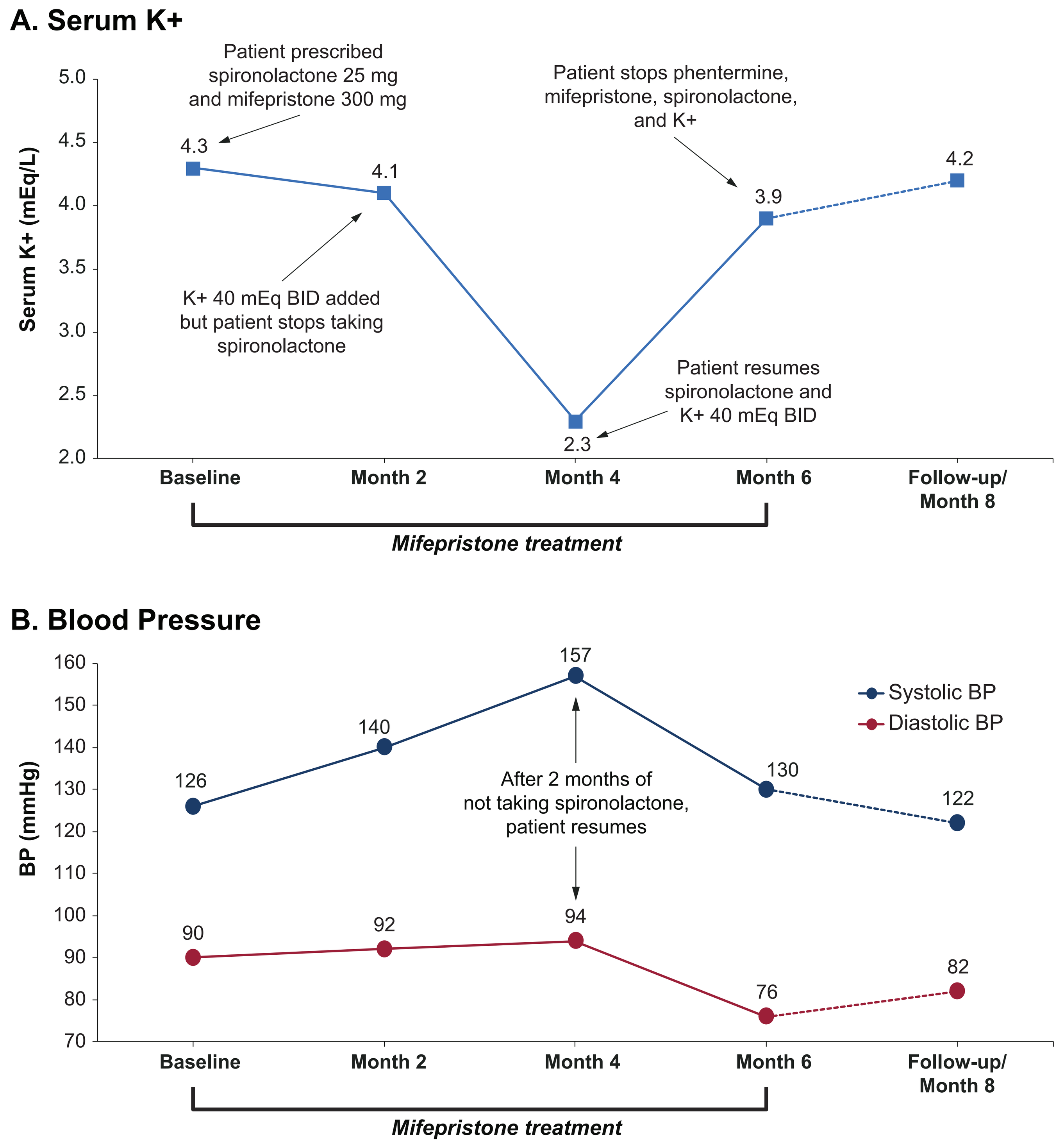
Figure 2. Patient Weight and FBG During the Observation Period


Weight
FBG
Weight (lbs)
FBG (mg/dL)
225
200
175
150
125
140
120
100
80
60
40
20
0
118
103
95
89
88
192
176
169
155
154
156.6
Baseline
Month 2
Month 4
Month 6
Follow-up/ Month 8
Follow-up/ Month 14
Mifepristone treatment

FBG, fasting blood glucose.

- Within 4 months, K+ levels decreased, BP increased, and edema developed, indicating that mifepristone may have increased cortisol levels and mineralocorticoid receptor activation (**Figure 3**)

Figure 3. Serum K+ (A) and Blood Pressure (B) During the Observation Period


A. Serum K+
Serum K+ (mEq/L)
Patient prescribed spironolactone 25 mg and mifepristone 300 mg
Patient stops phentermine, mifepristone, spironolactone, and K+
K+ 40 mEq BID added but patient stops taking spironolactone
Patient resumes spironolactone and K+ 40 mEq BID
4.3
4.1
2.3
3.9
4.2
Baseline
Month 2
Month 4
Month 6
Follow-up/ Month 8
Mifepristone treatment
B. Blood Pressure
BP (mmHg)
Systolic BP
Diastolic BP
126
140
157
130
122
90
92
94
76
82
After 2 months of not taking spironolactone, patient resumes
Baseline
Month 2
Month 4
Month 6
Follow-up/ Month 8
Mifepristone treatment

BID, twice daily; BP, blood pressure.

- When the mineralocorticoid receptor antagonist spironolactone was added, both K+ and BP improved significantly, supporting the presence of excess cortisol levels
- At Month 6, her migraines, edema, and fatigue resolved; she discontinued mifepristone, spironolactone, and K+ supplementation; and her Synthroid and Cytomel doses were reduced
- At Month 8, thyroid function and FBG were normal, weight and sleep improvements continued, and regular heavy menses resumed
- By Month 8, she had lost 38 lbs from baseline (a 19.8% reduction) and her FBG decreased by 30 mg/dL (a 25% reduction)
- By Month 14, her weight continues to be maintained (156.6 lbs) and her blood pressure assessments are consistently between 120-130/70-80 mmHg
- Images of the patient before and after treatment with mifepristone are shown in **Figure 4**

Figure 4. The Patient Before and After Treatment With Mifepristone


Before
AFTER

CONCLUSIONS

- This report details a patient with hypercortisolism who was treated with mifepristone for 6 months
- Hypercortisolism was suspected because of worsening clinical parameters (despite lifestyle and therapeutic interventions) and biochemical testing; however, the patient declined to undergo further diagnostic imaging work-up
- A trial of mifepristone was initiated because of its intracellular mechanism of action and the uncertainty of disease etiology
- The clinical and metabolic improvements noted while on therapy support the diagnosis of hypercortisolism
- We hypothesize that these findings, which are consistent with those observed in patients with more overt hypercortisolism,[6] may be indicative of a "reset" of the HPA axis
- Unexpectedly, the patient's improvements have been maintained up to 6 months after treatment discontinuation
- We postulate that the patient's history of stress and obesity might have contributed to autonomous non-neoplastic hypercortisolemia[7]
- These results suggest that a therapeutic trial of mifepristone can be useful in diagnosing and treating patients with suspected hypercortisolism when surgery is not warranted

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DISCLOSURES

RA: Consultant and speaker, Corcept Therapeutics
NP: Employee, Corcept Therapeutics.
AK: Nothing to disclose.

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