Mifepristone Use in Hypercortisolism from an Unknown Source: A Case Study

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Conclusions & Takeaways

- Less severe hypercortisolism, eg, from an adrenal source, can cause significant metabolic pathology, even though UFC and LNSC levels may be normal.
- Patients with severe diabetes, resistant hypertension, obesity, and other metabolic disorders, who are outliers in terms of disease management complexity, should be viewed with a high index of suspicion for CS even in the absence of classical physical features.
- Patients with metabolic disease driven by hypercortisolism can derive therapeutic benefit from cortisol-directed medical treatment.
  - Mifepristone was an effective treatment in this patient while the search for the source continued.
- Treatment need not be delayed even if the source of hypercortisolism is not initially apparent.

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Introduction

- Endogenous hypercortisolism (Cushing syndrome, CS) is a complex, multisystem endocrine disorder.
- CS is frequently associated with hypertension and/or hyperglycemia due to excess cortisol activity.[1, 2]
- CS is associated with increased mortality and a plethora of comorbidities, especially if untreated.
  - Comorbidities include visceral obesity, dyslipidemia, osteoporosis, hypercoagulopathy, and neuropsychiatric disorders.

Challenges in the diagnosis of CS

- Clinical features overlap with numerous common disorders
- Imperfect sensitivity and specificity of biochemical tests
- Discordant biochemical findings are common

Diagnosis and management are further complicated if a source of hypercortisolism is not readily apparent.

⇨ We describe the medical management of a patient with suspected CS, whose initial evaluation did not reveal a source of pathologic hypercortisolism.

1 Case History & Presentation

- 76-year-old man
- 18-year history of type 2 diabetes mellitus (T2DM)
  - Well-maintained on metformin monotherapy for the first 13 years

During the last 5 years:

- 23 lbs central weight gain despite dietary control
- Worsening T2DM
- Resistant hypertension

- Except for central obesity, no typical physical features of CS present
- Pheochromocytoma/paraganglioma and hyperaldosteronism were ruled out
  - Normal plasma norepinephrine, plasma epinephrine, dopamine, and normetanephrine
  - Metanephrine <3x ULN, consistent with baseline use of calcium blockers and beta blockers

CS suspected because:

- Control of fasting glucose and HbA1c levels required 4 antidiabetic medications
- Significant postprandial hyperglycemia despite control of fasting glucose
- Blood pressure control required 5 antihypertensive medications plus a diuretic

2 Baseline Lab Results & Imaging

Diabetic control

- Fasting glucose: 116 mg/dL
- HbA1c: 6.8%
- 4-hour post-dinner glucose levels frequently >200 mg/dL, despite dietary carbohydrate control

Biochemical evaluation

- Non-suppressed total cortisol and adequate dexamethasone levels on overnight 1-mg DSTs
- Low DHEA-sulfate, and low-normal ACTH levels
- LNSC and UFC normal
- Aldosterone, renin, and catecholamines unremarkable

Adrenal CT imaging

- Adrenals initially reported as normal in size and appearance
- No adrenal calcifications

⇨ Findings consistent with hypercortisolism due to a primary adrenal source
⇨ ACTH-dependence not demonstrated
⇨ Source not identified

	Baseline	Normal range
Total cortisol (µg/dL)	20; 19	8.0-19
ACTH (pg/mL)	10.4; 12.9	7.2-63.3
1-mg DST; done in duplicate		
Total cortisol (µg/dL)	3.9; 3.5	<1.8
ACTH (pg/mL)	3.1; 3.6	7.2-63.3
Dexamethasone (ng/dL)	471; 583	140-295
Cortisol-binding globulin (mg/dL)	2.0	1.7-3.1
Free cortisol (µg/dL)	6.0	0.2-1.8
DHEA-sulfate (µg/dL)	11	28-175
LNSC (µg/dL); done in triplicate	QNS; 0.054; QNS	<0.010-0.09
24-hour UFC (µg/24-h)	41	5-64
Aldosterone (ng/dL)	10.0	0.0-30.0
Plasma renin activity (ng/mL/h)	0.769	0.167-5.380
Aldosterone/Renin Ratio	13	0.0-30
Creatinine (mg/dL)	1.31	0.76-1.27
eGFR (mL/min/1.73)	53	>59
Potassium (mmol/L)	4.2	3.5-5.2

Purple indicates values outside the normal range.

ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; DST, dexamethasone suppression test; eGFR, estimated glomerular filtration rate; LNSC, late-night salivary cortisol; UFC, urinary free cortisol

3 Diagnosis & Treatment

Diagnosis

- Hypercortisolism was hypothesized to be the probable underlying driver of the metabolic pathophysiology based on clinical condition and biochemical evaluation

Treatment plan

- Patient was dissatisfied with his weight gain and medication burden
- **Mifepristone[3] (Korlym®, Corcept Therapeutics)**
  - Starting dose 300 mg q.d., titrated up to 600 mg q.d. after 2 weeks
  - Since fasting glucose was well controlled, glimepiride was proactively reduced by 50% before starting mifepristone
  - Due to concern of baseline edema and hypokalemia risk, eplerenone 50 mg b.i.d. was proactively started before starting mifepristone
  - Due to declining eGFR attributed to combination RAAS blockade, all RAAS-inhibiting agents were discontinued, including eplerenone, by week 9. A reduced dose of eplerenone was restarted at week 20
  - Furosemide was changed to eplerenone and a potassium supplement was added

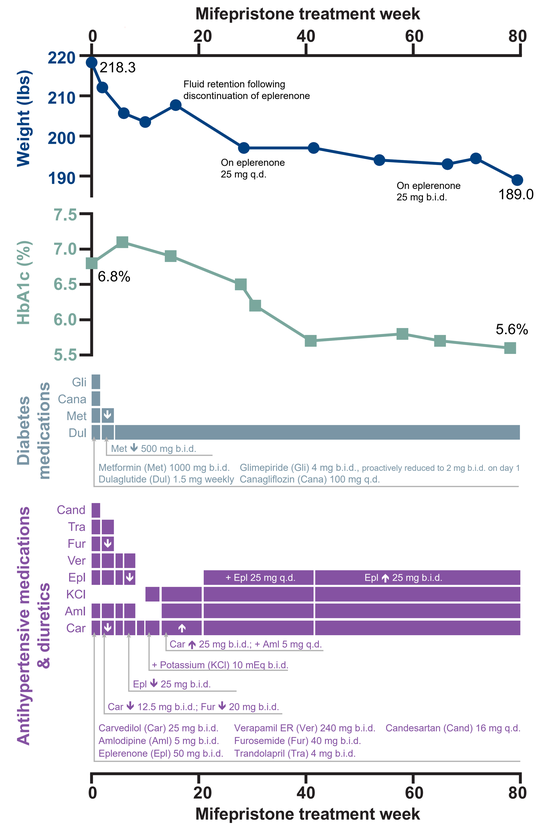
A priori criteria for a favorable treatment response

- Improved glycemic control, including improved postprandial hyperglycemia
- Decreased requirement for antidiabetic medications
- Improved blood pressure control
- Decreased requirement for antihypertensive medications
- Weight loss

Treatment response

- Weight decreased from 218.3 lbs to 189.0 lbs
- HbA1c decreased from 6.8% to 5.6%
  - Despite discontinuation of 3 of 4 antidiabetic medications
- 4-hour post-dinner glucose levels decreased from frequently >200 mg/dL to usually <150 mg/dL
- Typical blood pressure values decreased from 140/92 mmHg to 133/77 mmHg
  - Despite discontinuation of 3 of 5 antihypertensive medications

RAAS, Renin-angiotensin-aldosterone system.



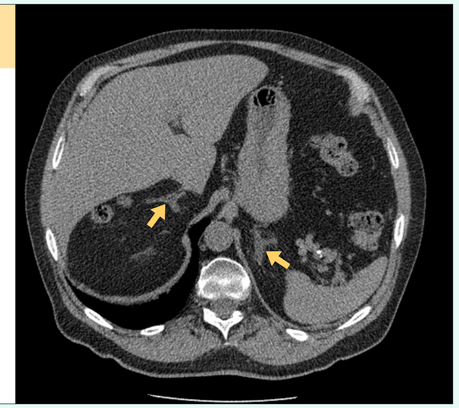
4 Confirmation of Diagnosis: Hypercortisolism of Adrenal Etiology

- The favorable clinical and biochemical response to mifepristone treatment provided post-hoc evidence that hypercortisolism was the driver of the patient's metabolic disease.

Search for cortisol source

- Baseline adrenal CT scan was presented to an expert in adrenal disease

⇨ Upon expert review, the prior normal adrenal findings were reinterpreted as indicative of bilateral adrenal hyperplasia



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Disclosures

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