Clinical Consequences of an Untreated Cortisol-Producing Adrenal Adenoma: A 10-Year History

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INTRODUCTION

- Patients with newly discovered adrenal adenomas should be screened and monitored for hypercortisolism (Cushing syndrome)[1]
- Establishing a diagnosis of hypercortisolism caused by adrenal adenomas can be challenging
  - Many signs/symptoms overlap with other conditions (eg, impaired glucose tolerance/diabetes, obesity, osteoporosis, hypertension)[1,2]
  - Lack of consensus for biochemical diagnosis
    - Changes in recommended cut-off thresholds for cortisol post dexamethasone suppression test (DST) over time (normal lowered from <5 µg/dL to <1.8 µg/dL)[1,2]
    - Recommendation to interpret DST results on a continuum rather than use an exact cut-off[2]
- Here we describe a case of a patient with a long-standing history of type 1 diabetes mellitus (T1DM), with severe insulin resistance, cardiovascular disease, osteoporosis, and a history of an autonomous cortisol-producing adenoma. After 10+ years of observation and worsening metabolic profile, she was reevaluated for hypercortisolism and treated medically with mifepristone (Korlym®, Corcept Therapeutics).

CASE HISTORY (2007)

- A 56-year-old woman with a 30-year history of T1DM (severe insulin resistance, insulin lispro 43 units/24 hr basal and 25 units bolus per meal via insulin pump) and numerous comorbidities (**Table 1**) presented for treatment of endocrine-associated comorbidities (T1DM, hyperlipidemia, and osteoporosis)
- She noted a 100-lb weight gain in 8 years
- Physical examination revealed cushingoid features, including moon facies, dorsocervical fat pad, central obesity, and striae
- She had a 3-year history of a left adrenal adenoma (2.5 cm) (diagnosed by urologist, 2004)
- Initial biochemical evaluation: urinary free cortisol (UFC) 113 µg/24 hr (normal <50 µg/24 hr), cortisol post 1-mg DST 2.3 µg/dL (normal <5 µg/dL), and low ACTH (**Table 2**)
- Clinician at the time felt patient did not meet criteria for surgical or medical treatment and adrenal adenoma was radiologically monitored; comorbidities managed medically

CASE HISTORY (10+ YEARS LATER)

- Left adrenal adenoma remained radiographically stable (2.2 cm and 2.5 cm over 14 years)
- Patient's comorbidities worsened (**Table 1**)
- Based on history of multiple worsening comorbidities and biochemical evaluation, hypercortisolism was suspected

Table 1. Clinical Consequences During 10+ Years of Follow-Up (bold items note progressive comorbidities)

Cardiovascular	Gastrointestinal	Immune
• TIA 1999, **CVA 2018** • CAD, MI 1999 • Hypertension • Atherosclerotic heart disease • Paroxysmal AFib • **CHF**	• GERD **with esophageal stricture**	• **Osteomyelitis (2 amputations)** • **Recurrent staphylococcal/yeast infections** • **Recurrent UTIs**
Metabolic	**Musculoskeletal**	**Nephrologic**
• T1DM, **severe insulin resistance (insulin RU-500 125 units/24hr via insulin pump)** • Morbid obesity • Hyperlipidemia	• Osteoporosis, **ankle fracture repair** • Charcot foot • **Progressive muscle weakness, requiring wheelchair**	• **CKD stage III** • **Hyperparathyroidism, secondary to renal insufficiency** • **Anemia**
Neurologic	**Pulmonary**	**Ocular**
• Depression • Neuropathy • **Neurogenic bladder**	• Asthma • Sleep apnea **with CPAP**	• Retinopathy • **Retinal detachment**

AFib, atrial fibrillation; CAD, coronary artery disease; CHF, chronic heart failure, CKD, chronic kidney disease; CPAP, continuous positive airway pressure; CVA, cerebrovascular accident; GERD, gastroesophageal reflux disease; MI, myocardial infarction; T1DM, type 1 diabetes mellitus; TIA, transient ischemic attach; UTI, urinary tract infection.

WORKUP FOR SUSPECTED HYPERCORTISOLISM

- Initial and repeat biochemical evaluation 10+ years later are shown in **Table 2**
- Results of biochemical evaluation supported diagnosis of hypercortisolism

Table 2. Baseline Biochemical, Radiological, and Clinical Examination

	Initial Testing (2007)	Pre-mifepristone (2018)
Cortisol, µg/mL post 1-mg DST	2.3[a]	5.1[b]
UFC, µg/24 hr (normal: 0-50)	113	—
DHEA, ng/dL (normal 31-701)	106	—
ACTH, pg/mL (normal 7.2-63.3)	5	<5
HbA1c, %	8.0	6.3
K+, mEq/L	4.6	4.2
Left adrenal adenoma, cm	2.2[c]	2.5
BP, mmHg	167/86	118/70
Weight, lbs	286	281
BMI, kg/m^2	47.6	46.8

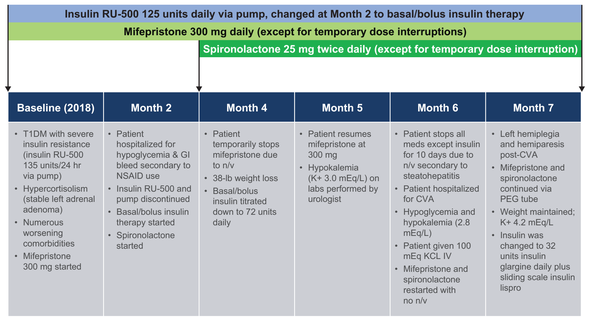
[a]Normal: <5 µg/dL. [b]Normal: <1.8 µg/dL. [c]Initial imaging performed 2004.

ACTH, adrenocorticotropic hormone; BMI, body mass index; BP, blood pressure; DHEA, dehydroepandrosterone; DST, dexamethasone suppression test; UFC, urinary free cortisol.

MEDICAL THERAPY

- Patient not considered a surgical candidate because of poor overall health and medical treatment with mifepristone was initiated (**Figure 1**)

Figure 1. Timeline of Treatment and Patient Response

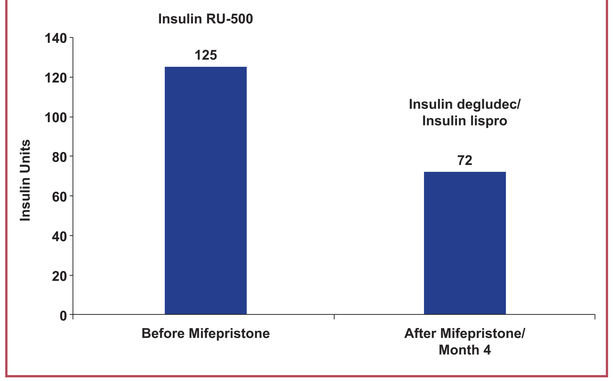


CVA, cerebrovascular accident; GI, gastrointestinal; IV, intravenous; KCL, potassium chloride; NSAID, nonsteroidal anti-inflammatory drug; n/v, nausea/vomiting; PEG, percutaneous endoscopic gastrostomy.

RESULTS WITH MIFEPRISTONE

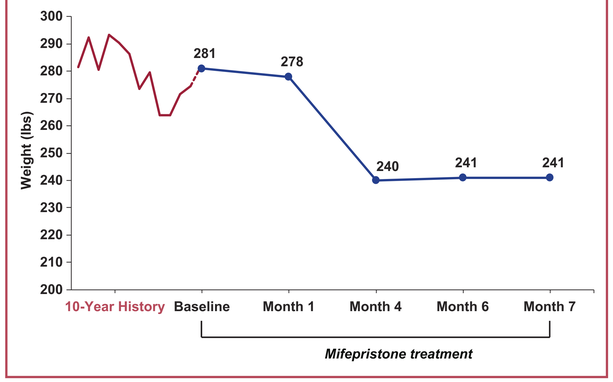
- At Month 1 of treatment, her BP was 148/74 mmHg and K+ was 3.7 mEq/L
  - Spironolactone 25 mg twice daily added 1 month later
- At Month 2 of treatment, patient was hospitalized for hypoglycemia and gastrointestinal bleed secondary to NSAID usage
- Insulin pump discontinued and concentrated insulin RU-500 switched to basal/bolus therapy with insulin degludec/insulin lispro (**Figure 2**)
- Within 4 months her insulin usage decreased by 42% (72 units daily), achieving a weight-based insulin dose
  - Her HbA1c remained stable at 6.4%, compared with 6.3% at baseline

Figure 2. Change in Insulin Requirement Before and After Mifepristone



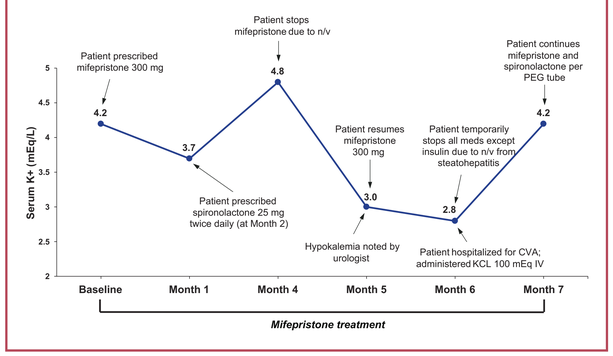
- By Month 4, the patient lost 38 lbs (14.6% reduction from baseline) (**Figure 3**)
- Patient temporarily stopped taking mifepristone due to nausea/vomiting

Figure 3. Change in Weight During Mifepristone Treatment



- At Month 5, the patient restarted mifepristone (300 mg); her urologist noted hypokalemia during routine labs (3.0 mEq/L) (**Figure 4**)

Figure 4. Potassium Levels During Mifepristone Treatment



CVA, cerebrovascular accident; KCL, potassium chloride; n/v, nausea/vomiting; PEG, percutaneous endoscopic gastrostomy.

- At Month 6, the patient experienced nausea/vomiting due to steatohepatitis and she stopped all meds except insulin for 10 days
- Two weeks later, she was hospitalized for a CVA
  - Patient reported hypoglycemia
  - Random cortisol level was 33 µg/dL
  - K+ was 2.8 mEq/L, likely due to the underlying hypercortisolism during the patient's drug holiday; 100 mEq KCL was administered by IV
  - Patient was restarted on mifepristone and spironolactone in hospital with no nausea/vomiting
- The patient was diagnosed with left hemiplegia and hemiparesis post-CVA and continued on mifepristone 300 mg and spironolactone 25 mg twice daily per PEG tube
- At Month 7, the patient's weight was maintained (241 lbs) and her blood pressure (115/60 mmHg) and K+ (4.7 mEq/L) were normal

SUMMARY/CONCLUSIONS

- This report details a patient with long-standing history of T1DM, severe insulin resistance, numerous comorbidities, and a cortisol-producing adrenal adenoma, who after 10+ years of observational follow-up was diagnosed with hypercortisolism. She was not a surgical candidate due to her poor overall health and was treated with mifepristone.
- At the time of initial workup (2007), the patient's post-DST result did not meet the recommended treatment threshold and the clinician decided to monitor the patient's adrenal adenoma and manage comorbidities medically
- Her metabolic profile continued to deteriorate and repeat biochemical testing performed 10+ years later resulted in a diagnosis of hypercortisolism
- These findings suggest:
  - Long-term observation may be insufficient and earlier intervention with appropriate treatment may decrease chance of disease progression and worsening of comorbidities
  - Greater awareness of current recommendations for screening and treating hypercortisolism due to adrenal adenomas[2] is needed, especially in complex patient cases that involve multidisciplinary care teams
- In this patient, mifepristone treatment was associated with clinical improvements in weight and a dramatic decrease in insulin requirements
- Patients initiated on mifepristone therapy should be monitored for potential readjustment of antidiabetic therapy, as demonstrated in this patient with T1DM and severe insulin resistance, in order to prevent hypoglycemia. Patients should also be monitored and treated for hypokalemia during treatment with mifepristone.

REFERENCES

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2. Fassnacht M, et al. *Eur J Endocrinol.* 2016;175(2):G1-G34.

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RR: Employee, Corcept Therapeutics.

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