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PHENOTYPIC AND METABOLIC IMPROVEMENTS IN A PATIENT WITH EQUIVOCAL FINDINGS OF HYPERCORTISOLISM TREATED WITH MIFEPRISTONE: PHOTOGRAPHIC AND RADIOGRAPHIC EVIDENCE

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INTRODUCTION

- Increasing evidence suggests that Cushing syndrome has a negative impact on subsequent health (quality of life, diabetes, hypertension, depression/anxiety, brain atrophy), even after a surgical cure and long-term remission[1-3]
- Cushing syndrome usually is diagnosed when evidence of hypercortisolism and hypothalamic-pituitary-adrenal (HPA) axis dysregulation is coupled with radiological evidence of a source[4]
- However, many patients endure years of damaging metabolic, cardiovascular, and cognitive impairment effects related to hypercortisolism before receiving a definitive diagnosis and appropriate treatment[5,6]
- A common challenge faced by clinicians is posed by the discrepancies among multiple biochemical test results, despite clinical suspicion based on patient presentation
- This case describes a patient with equivocal biochemical testing for mild cortisol excess and negative imaging who benefited from medical therapy with mifepristone (Korlym®, Corcept Therapeutics), a competitive glucocorticoid receptor antagonist

CASE PRESENTATION

CLINICAL PRESENTATION AT BASELINE

- A 60-year-old woman with a history of hypertension (controlled with metoprolol) and with sub-centimeter thyroid nodules with normal thyroid function tests/biopsy presented with:
  - Increased fatigue
  - Increasing cushingoid appearance over a 4-year period
    - Increased supraclavicular fullness
    - Increased size of dorsocervical fat pad
    - Increased moon facies
    - Increased truncal obesity
  - Weight gain over a more than 4-year period
    - 63.5 kg to 68.6 kg
    - Body mass index (BMI): 24 to 26.8 (normal 18.5-24.9; overweight 25-29.9)
  - Worsening insulin resistance over a 2-year period
    - Fasting Blood Glucose (FBG): 104 mg/dL to 106 mg/dL (normal <100 mg/dL)
    - Fasting Blood Insulin: 5.7 µIU/mL to 12.7 µIU/mL (normal <8 µIU/mL)
    - Homeostatic Model Assessment for Insulin Resistance (HOMA-IR): 1.5 to 3.3 (normal <1.9)
    - HbA1c: 5.7% (normal <5.7%)

SUSPICION

- Possible hypercortisolism/Cushing syndrome

ENDOCRINE WORKUP

- Equivocal biochemical results (**Table 1**) that often did not correlate with physical manifestations
- Only 1 out of 14 serial late night salivary tests in 2016 and 2017 was positive for hypercortisolism

Table 1. Biochemical Diagnostic Tests

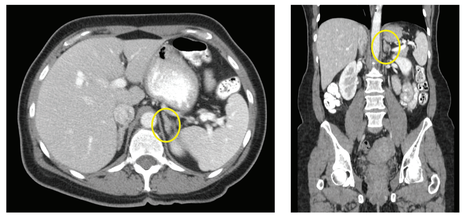
Date	Cortisol (µg/dL) (normal <20)	ACTH (pg/mL) (normal 10-50)	UFC (µg/24h) (normal ≤45)	DST (µg/dL) (normal <1.8)
2014	31.3*	NA	50*	NA
2015	38.9*	71.5*	66*	0.7
2016	NA	NA	NA	0.8

* Positive for cortisol excess
ACTH = adrenocorticotropic hormone; DST= overnight dexamethasone suppression test; NA = not available; UFC = urinary free cortisol.

IMAGING WORKUP

- Pituitary magnetic resonance imaging (MRI) (2015, 2016, and 2018, not shown) – normal
- Octreoscan (2015, not shown) - normal
- Adrenal computed tomography (CT) scan (2014, shown in **Figure 1**) – mild adrenal nodularity; (2015, not shown) – stable

Figure 1. Adrenal CT Scan 2014



POSTULATED DIAGNOSIS

- Intermittent/cyclical ACTH-dependent Cushing syndrome

PLAN OF ACTION

- With equivocal cortisol testing, a negative pituitary MRI, and a negative octreoscan, but with an adrenal CT scan showing adrenal gland nodularity, a therapeutic trial of mifepristone was offered
  - Initiated mifepristone 300 mg every day (QD)
  - Increased to 600 mg QD after 2 weeks
  - Increased to 900 mg QD after 2 months

RESULTS OF TREATMENT WITH MIFEPRISTONE

- Treatment with mifepristone reversed a pattern of increasing insulin resistance (**Table 2**), with decreases in the following:
  - HOMA-IR from 3.3 to 0.9
  - Fasting insulin from 12.7 µIU/mL to 3.7 µIU/mL
  - FBG from 106 mg/dL to 97 mg/dL
  - HbA1c from 5.7% to 5.3%
- With metabolic control, weight similarly improved from 68.6 kg to 59.7 kg, resulting in a significant improvement in cushingoid appearance (**Figures 2** and **3**)

Table 2. Effect of Mifepristone on Insulin Resistance and Glycemic Control

Date (mo/yr)	FBG (mg/dL) (normal <100)	Fasting Insulin (µIU/mL) (normal <5)	HOMA-IR (normal ≤1)	HbA1c (%) (normal ≤5.6)
12/2015	104	5.7	1.5	5.6
10/2016	102	8.4	2.1	5.7
03/2017	106	12.7	3.3	5.7
05/2017	Initiation of Mifepristone Therapy			
10/2017	102	3.7	0.9	5.3
02/2018	97			5.3

FBG = Fasting Blood Glucose; HbA1c = glycated hemoglobin;
HOMA-IR = Homeostatic Model Assessment for Insulin Resistance.

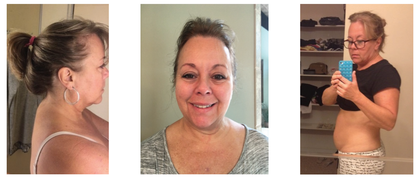
ADVERSE EVENTS EXPERIENCED ON MIFEPRISTONE

- Mild elevation in liver transaminases that normalized
- Mild hypertension required the addition of spironolactone (300 mg/day) and verapamil (240 mg twice daily [BID]), and the continued use of valsartan (160 mg QD)
- Mild hypokalemia treated with the addition of spironolactone and potassium chloride (20 mEq)
- Mild hypothyroidism developed after the initiation of mifepristone. The patient was treated with levothyroxine (100 µg QD) to normalize thyroid-stimulating hormone
- Endometrial thickening with some vaginal bleeding (patient was 7 years post-menopausal); endometrial biopsy was benign

Figure 2. Effect of Mifepristone on Phenotypic Appearance

Appearance Before CS (2011)

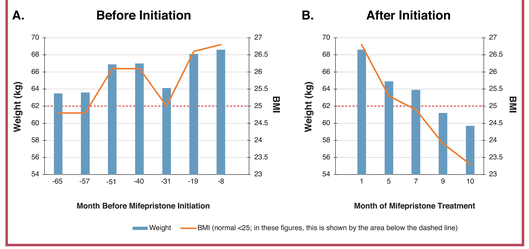
Appearance With CS (2016)



Appearance After MIFE (2018)

CS = Cushing syndrome; MIFE = mifepristone.

Figure 3. Effect of Mifepristone on Body Weight and BMI



BMI = body mass index.

SUMMARY

- These metabolic and phenotypic improvements are consistent with those observed in patients with more biochemically and radiographically obvious hypercortisolism and suggest that early intervention can have a beneficial effect on the trajectory of disease in cases of cortisol excess, as well as on a patient's overall health and wellbeing

CONCLUSIONS

- Patients often seek a causal diagnosis and treatment due to phenotypic and symptomatic changes; these changes should not be dismissed
- The diagnosis of hypercortisolism can be challenging when equivocal results do not align with a patient's clinical presentation and the physician's suspicion; such situations delay patients from receiving a potentially beneficial intervention
- A therapeutic trial of mifepristone can be useful in diagnosing and treating patients where testing for cortisol excess is equivocal and surgery is not warranted

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DISCLOSURES

MJT: Consultant, Corcept Therapeutics.
JJS: Employee, Corcept Therapeutics.

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