131

Resistant Metabolic Abnormalities Prompting Cushing's Syndrome Work-up and Treatment With Mifepristone

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ABSTRACT

Objective: Hypertension (HTN) and metabolic abnormalities [diabetes (DM), obesity, and weight gain] are predominant in Cushing's syndrome (CS) patients, resulting in increased cardiovascular risk (eg, atherosclerosis, coronary artery disease, heart failure, and stroke). Yet, CS is not well recognized and often goes undiagnosed due to the pervasiveness of metabolic syndrome in the general population. Herein we detail a morbidly obese patient with uncontrolled HTN and DM, prompting a CS workup revealing bilateral adrenal adenomas secreting autonomous cortisol.

Case Presentation: A 61y/o male presented 14 years ago with multiple co-morbidities: uncontrolled HTN, DM, hyperlipidemia (Fredrickson Type IV), morbid obesity, degenerative joint disease requiring bilateral hip replacements, atherosclerosis, and peripheral arterial disease. Years of medical interventions and diets were unsuccessful in controlling weight and worsening co-morbidities. Indeed, the patient's weight increased 25lbs in the past year (peak weight 320lbs, BMI 45). Attempts to control hyperglycemia were unsuccessful even with Lantus (70U/d) and multiple anti-diabetes medications [HbA1c and fasting blood glucose (FBG) remained elevated at 9.1% and 197mg/dL, respectively]. He exhibited classic cushingoid features and failed to adequately suppress cortisol (5mcg/dL) on a 1mg dexamethasone suppression test. A CT scan revealed a right adrenal adenoma (18x13mm) and left adrenal hyperplasia with nodular formation (26x11mm). Unbeknownst to the clinician, a chest CT performed 6 years earlier had detected the adenoma but was never flagged by the radiologist for further work up. The size of the adenoma remained unchanged since the first scan. Refusing surgical treatment, he elected medical therapy with mifepristone (MIFE, Korlym®, Corcept Therapeutics), a selective glucocorticoid receptor antagonist. MIFE therapy was initiated and titrated to 600mg/d within 4 months, adjusting to QOD based on patient's tolerability. After 4 months, MIFE decreased HbA1c to 8.0% and FBG to 109 mg/dL. Weight decreased by 25lbs, resulting in improvements to the patient's cushingoid appearance (predominately facial).

Conclusion: CS can be difficult to diagnose in the presence of concomitant obesity, HTN, DM, and metabolic syndrome. CS should be suspected when HTN and DM are poorly controlled and rapid weight gain occurs. Interdisciplinary collaboration between primary care professionals, radiologists, and endocrinologists are necessary to identify patients with the potential for hypercortisolism to reduce the time to diagnosis of CS and appropriate care, which may include non-surgical alternatives.

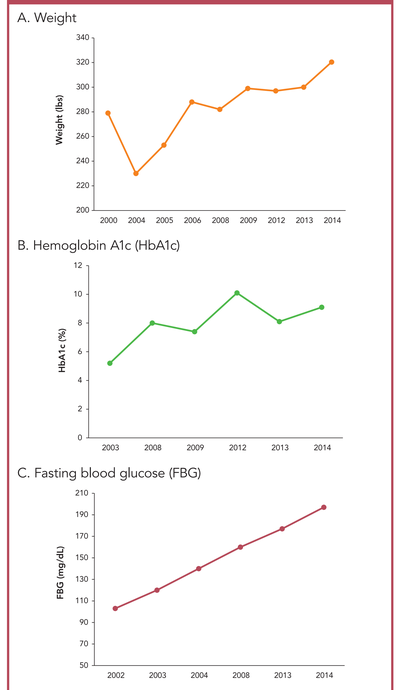
INTRODUCTION

- Endogenous Cushing's syndrome (CS) is a rare, complex disorder resulting from prolonged exposure to cortisol, either from excess adrenocorticotropin hormone secretion or direct production of cortisol from the adrenals[1]
- CS is associated with substantial morbidity and increased mortality[1-4]
- Many of the associated features of CS (eg, weight gain, hypertension [HTN], insulin resistance, diabetes mellitus [DM], and dyslipidemia) are also common in the general population, presenting a diagnostic challenge for clinicians[1,3]
- Guidelines recommend screening for CS in patients with multiple or progressive CS-associated features[1]
- **Surgical resection of the underlying tumor remains the definitive treatment for CS[3]**
  - **Medical treatment for CS is an option when surgery may not be feasible or when a patient declines surgery[3]**
  - Bilateral adrenalectomy leads to complete resolution of clinical features of CS; however, it requires the lifelong use of corticosteroid and mineralocorticoid replacement therapy and has been associated with the occurrence of adrenal crisis[3,5]
- The glucocorticoid receptor antagonist mifepristone (Korlym®, Corcept Therapeutics, Menlo Park, CA), is approved for patients with all forms of CS who have DM or glucose intolerance and have failed or are not candidates for surgery
  - In addition to improvement in glucose parameters and HTN, significant clinical improvement was noted in 87% of patients treated with mifepristone in the 24-week SEISMIC trial[6]
- We describe the case of a morbidly obese patient with a history of uncontrolled HTN and DM who underwent further examination, revealing bilateral adrenal nodules secreting autonomous cortisol, which we treated with mifepristone

CLINICAL PRESENTATION

- A 61-year-old man presented with a 14-year history of multiple comorbidities
  - HTN
  - DM (uncontrolled)
  - Hyperlipidemia — Fredrickson Type IV (triglycerides vary widely; range 2391 to 328 mg/dL during 2012-2014)
  - Morbid obesity
  - Degenerative joint disease (2003 hip replacement surgery x2)
  - Peripheral arterial disease (2010 vascular surgery)
  - Atherosclerosis
  - Depression
- Positive tobacco use (smokes ~1 pack/day)
- History of fluctuating metabolic derangements with worsening DM and increased weight in 2014 (**Figure 1**) despite several anti-diabetes treatments, including insulin therapy and lifestyle interventions
  - Additional concomitant medications included rosuvastatin, clopidogrel, and azilsartan/chlorthalidone.

Figure 1. Metabolic parameters from 2000 to Feb 2014

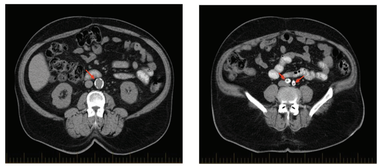


Assessments

- Feb 2014
  - Weight 320 lbs (↑25 lbs in past year); body mass index (BMI) 45
- May 2014
  - Abdominal CT scan revealed major occlusive arterial disease (80% stenosis in left external iliac and 80% stenosis right external iliac) and bilateral adrenal nodules (**Figure 2**)
- June 2014
  - Hemoglobin A1c (HbA1c) 9.1%, fasting plasma glucose (FBG) 197 mg/dL, total cholesterol 149 mg/dL
- July 2014
  - Cushingoid features present, including central obesity, moon facies, buffalo hump, and striae (**Figure 3**)
  - Failure to suppress cortisol with 1 mg dexamethasone suppression test (5 mcg/dL) and a high index of suspicion of CS prompted initiation of mifepristone
  - A re-examination of the patient's chart found a radiologist note for bilateral adrenal nodules in 2008, which was not flagged for additional work-up
  - Patient repeatedly declined surgery

Figure 2. Abdominal CT images of aorta and adrenals (May 2014)

A. Aortic and iliac stenoses



B. Right adrenal adenoma (18 x 13 mm) and left hyperplasia with nodular appearance (26 x 11 mm) on the anterior limb

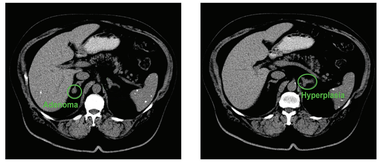


Figure 3. Patient before (July 2014) and after 4 and 7 months of mifepristone therapy

Pre-mifepristone | Month 4 | Month 7

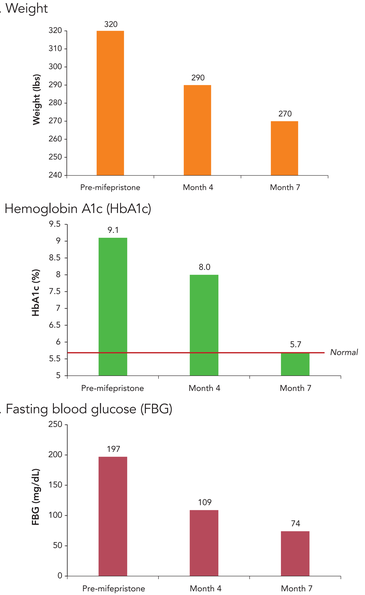
TREATMENT WITH MIFEPRISTONE

- Mifepristone was titrated over 4 months to 600 mg, adjusting the frequency based on the patient's tolerability (nausea, unmasking pain, and constipation reported)

Clinical outcomes

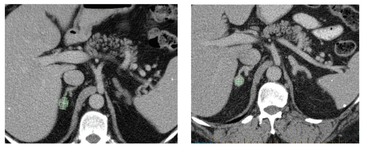
- Cushingoid appearance improved (**Figure 3**)
- After starting mifepristone treatment, several metabolic parameters improved (**Figure 4**)
- Insulin therapy was discontinued once HbA1c goal was reached
- BP fluctuated (118/80 mm/Hg, 137/93 mm/Hg) as several adjustments to antihypertensive therapy were made
- High-sensitivity C-reactive protein (hs-CRP) decreased from 2.4 to 0.7 mg/L
  - hs-CRP reflects inflammation in the vascular system and is considered a biomarker for elevated risk of cardiovascular disease
- Total cholesterol remained stable (121 mg/dL)

Figure 4. Metabolic parameters before and after 4 and 7 months of mifepristone therapy



- Depression improved
- Patient has reported fatigue, nausea, and arthralgia during mifepristone treatment, but has remained on therapy
- April 2015 CT scan showed reduction in intra-abdominal fat; right adrenal adenoma appears stable in size compared with 2014 image (**Figure 5**)

Figure 5. Abdominal CT images of intra-abdominal fat and adrenals before (2014) and after (2015) mifepristone therapy



2014 | 2015

SUMMARY AND CONCLUSIONS

- **Mifepristone is a useful treatment option for many patients with CS who refuse or are poor candidates for surgery**
- This case report details a patient with a history of obesity and DM who was followed by the same internist for 15 years. During this time the patient remained refractory to aggressive treatment (eg, insulin, advanced insulin sensitization therapy, intensive lipid therapy) until he was diagnosed with CS and started on mifepristone.
- Screening for CS is warranted when several clinical features (eg, HTN, DM, and obesity) are present, particularly when poorly controlled or rapidly progressive in nature
- Collaboration between primary care professionals, radiologists, and endocrinologists is necessary in order to identify patients with features suggestive of CS and prevent lengthy delays in diagnosis and treatment
- Treatment with mifepristone resulted in several beneficial outcomes, including reductions in weight/BMI, HbA1c, and hs-CRP (<1 mg/L), as well as subsequent elimination of insulin

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