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Use of Mifepristone in an Ectopic Cushing's Syndrome Patient Pending Tumor Localization

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ABSTRACT

Objectives: Ectopic adrenocorticotropic secretion accounts for 20% of the adrenocorticotropin hormone (ACTH)-dependent Cushing's syndrome (CS) cases. Yet, the biochemical and imaging modalities for localizing the tumor can be a complex and lengthy process. We detail the successful treatment with mifepristone (MIFE, Korlym®, Corcept Therapeutics), a competitive glucocorticoid receptor antagonist, for a patient with ectopic CS without tumor localization.

Case Presentation: A 64-year-old woman presented with uncontrolled HTN, associated with edema and hypokalemia. She experienced progressive CS symptoms: unexplained rapid weight gain (35 lbs in 6 months), abdominal obesity, fat pads, muscle weakness (using a walker), easy bruising, osteopenia, and acute hypokalemia with episodes of edema. Her history included diabetes mellitus (controlled w/Lantus 38 units/qhs), hyperlipidemia, hypothyroidism, sinus tachycardia, and a family history of lung cancer (father). Hormonal testing showed ACTH-dependent CS: Urinary free cortisol (UFC) 136.2 µg/24hr; unsuppressed ACTH (27 pg/mL) and serum cortisol (19.3 µg/dL) after a 2-day high-dose DST. MRI of the pituitary gland failed to demonstrate the presence of an adenoma; IPSS was consistent with ectopic CS. Abdominal CT revealed hyperplastic and nodular adrenals. Chest CT revealed the presence of a stable 6 mm lesion in the left upper lobe that did not change in size over time. Octreoscan failed to demonstrate a metabolically active lesion. Due to the patient's symptoms, MIFE was initiated at 300 mg/day and titrated to the current dose of 1200 mg/day a year later. Therapy was temporary held after the first month due to hypokalemia and edema. K supplementation was provided. During MIFE therapy, the patient was counseled to adjust her insulin to avoid potential hypoglycemic events due to improvements in her metabolic conditions. Her insulin was later stopped; A1C improved from 6.8% to 6.5% without insulin. Lisinopril was discontinued to prevent episodes of hypotension. She lost 47 lbs, her BMI was reduced from 39 to 28.6, and she reported improvements in her cushingoid features.

Further octreoscans are planned due to the potential change in somatostatin receptors after successful MIFE therapy.

Conclusion: The complexities and challenges of localizing the site of ectopic ACTH secretion are demonstrated with this case. In this patient, the addition of MIFE helped manage the manifestations of CS while further investigations were conducted. MIFE provided control and improvements in several manifestations of CS (A1C, weight, appearance) while eliminating the need for insulin and an antihypertensive, representing a viable option for patient whom tumor localization is difficult.

INTRODUCTION

- Ectopic adrenocorticotropin hormone syndrome (EAS) (non-pituitary) accounts for approximately 10%-20% of all adrenocorticotropin hormone (ACTH)-dependent Cushing's syndrome (CS)[1,2]
- EAS-associated tumors are localized primarily in the lungs, consisting mainly of bronchial carcinoids and small cell lung carcinoma, but are also associated with other tumor types (eg, medullary thyroid carcinomas, gastrointestinal neuroendocrine tumors, thymic carcinoids)[2-4]
- The primary treatment for EAS is surgical resection of the underlying tumor; however, in many patients with EAS (12% to 19%), the tumor source is not localized and these patients will require alternate therapies[3,4]
- Mifepristone (Korlym®, Corcept Therapeutics, Menlo Park, CA) is a glucocorticoid receptor antagonist that is approved for patients with all forms of CS who have diabetes or glucose intolerance and have failed or are not candidates for surgery
  - In addition to improvement in diabetes and/or hypertension, significant clinical improvement was noted in 87% of patients with CS treated with mifepristone in the 24-week, open-label, multicenter SEISMIC trial[5]
- We describe a patient with EAS without tumor localization who was treated with mifepristone therapy, resulting in several beneficial outcomes

CLINICAL PRESENTATION

History of present illness

- A 64-year-old woman presented with progressive symptoms of CS (**Figure 1**), including uncontrolled hypertension, episodes of acute hypokalemia and edema, rapid weight gain (35 lbs in 6 months), abdominal obesity, fat pads, muscle weakness (using a walker), easy bruising, and osteopenia
- Past medical history
  - Diabetes mellitus (controlled with insulin)
  - Hypertension
  - Hyperlipidemia
  - Hypothyroidism
  - Edema
  - Hypokalemia
  - Sinus tachycardia
- Family history of lung cancer (father)
- Concomitant medications are listed in **Table 1**

Figure 1. Patient images showing progression of CS-related comorbidities

Table 1. Concomitant medications before mifepristone initiation

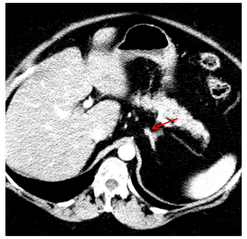
MEDICATIONS	DOSAGE
Antihypertensive medications	
Lisinopril	5 mg daily
Antidiabetes medications	
Insulin glargine (Lantus)	38 units at bedtime
Insulin lispro (Humalog)	As directed
Other medications	
KCl	10 mEq daily
Furosemide	40 mg daily
Pravastatin	40 mg at bedtime
Ropinirole	4 mg in the evening
Methocarbamol	750 mg as needed
Oxycodone/Acetaminophen	10/325 mg as needed

Assessments

- Hormonal testing (May 2013) suggested ACTH-dependent CS
  - Urinary free cortisol (UFC) 136.2 µg/24 hour, ACTH 26 pg/mL, serum cortisol 42.3 µg/dL
  - Nonsuppressed ACTH (40 pg/mL) and cortisol (26.1 µg/dL) following a 2-day low-dose dexamethasone suppression test (DST) and 2-day high-dose DST (27 pg/mL and 19.3 µg/dL, respectively)
- Imaging
  - Abdominal CT (May 2013) showed hyperplastic and nodular adrenals (**Figure 2**)
  - MRI of sella (June 2013) did not show presence of a pituitary adenoma
  - Octreoscan (August 2013) did not show a metabolically active lesion (**Figure 3**)
  - Chest CT revealed a 6 mm pulmonary lesion in the left upper lobe (**Figure 2**) with no change following repeat CT in 2014
  - Hepatic steatosis incidentally observed
- Inferior petrosal sinus sampling (July 2013) consistent with ectopic CS

Figure 2. A) Abdominal CT image and B) chest CT image

A. Abdominal CT image revealing hyperplastic and nodular adrenal



B. Chest CT image revealing 6 mm pulmonary lesion

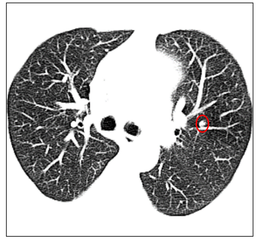
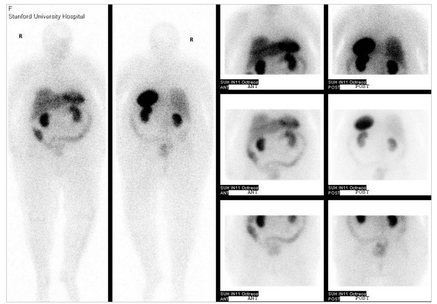


Figure 3. Octreoscan images



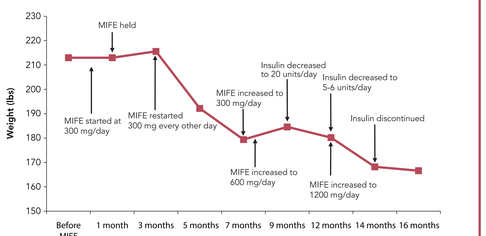
TREATMENT COURSE

- Mifepristone was initiated at a dose of 300 mg/day and titrated over the course of a year to 1200 mg/day
- Mifepristone was temporarily held the first month of therapy due to a severe episode of hypokalemia and edema
  - Potassium supplementation was provided during the episode of hypokalemia
- Improvement in metabolic parameters, including reduction in hemoglobin A1C (A1C) and body mass index (BMI), were noted during treatment with mifepristone (**Table 2**)
  - Insulin therapy was titrated downward during mifepristone therapy to avoid hypoglycemia and was discontinued after 14 months (**Figure 4**)
  - Low-dose nebivolol (2.5 mg) was added for sinus tachycardia; lisinopril was later discontinued to prevent hypotension
  - Patient lost a total of 47 lbs during mifepristone treatment (**Figure 4**)

Table 2. Cardiometabolic parameters before and after mifepristone therapy

	Before mifepristone	After mifepristone (16 months)
BMI, mg/kg/m^2	39	28.6
A1C, %	6.8	6.5
Blood pressure, mmHg	120/82	118/74

Figure 4. Weight loss and changes in insulin therapy during mifepristone treatment



- Improvement in cushingoid features was noted; bilateral edema was reduced
- Further evaluation for tumor localization using octreoscan is planned because of the potential change in somatostatin receptors after mifepristone treatment

SUMMARY AND CONCLUSIONS

- Tumor localization in patients with EAS can be difficult and may require multiple imaging procedures over time
- This report describes a patient with EAS and negative tumor localization who was treated with mifepristone, resulting in substantial improvements in A1C, BMI/weight, and cushingoid appearance, as well as elimination of antidiabetic therapy (insulin) and reduction in antihypertensive therapy
- Treatment with mifepristone resulted in beneficial effects in this patient with ectopic CS in whom tumor localization was not initially obtained
- Treatment with mifepristone must be titrated based on the patient's clinical improvement and tolerability; hypokalemia should be corrected prior to starting treatment with mifepristone and monitored during treatment
- Mifepristone treatment influences somatostatin receptor expression in EAS-associated tumors, and has been associated with positive tumor localization using octreoscan
- Additional analysis is needed to evaluate the effects of mifepristone treatment on repeat tumor visualization using octreoscan in patients with EAS

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DISCLOSURES

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