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SUCCESSFUL MEDICAL MANAGEMENT WITH MIFEPRISTONE IN A PATIENT WITH OCCULT ECTOPIC CUSHING SYNDROME

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ABSTRACT

Background: Tumor localization is a challenging and lengthy process when a tumor producing Cushing syndrome (CS) is occult. Managing CS manifestations in the interim is necessary. We present a complex case of suspected ectopic CS successfully treated with a glucocorticoid receptor antagonist, mifepristone (Korlym®, Corcept Therapeutics).

Case: 63-year-old woman presented via the emergency department (ED) with severe weakness and recent mental status changes. She complained of polyuria, polydipsia, and weight gain (~40 pounds in 3 months) without a history of diabetes mellitus. She was emotionally labile, irritable, and depressed.

Physical examination: blood pressure (BP) 160/81 mmHg, 185 pounds (body mass index, 31.6 kg/m^2), cushingoid features (moon facies, facial plethora, hirsutism), edema of the lower extremities, thin skin.

Laboratory values: K+ 2.9 mEq/L, glucose 512 mg/dL, A1C 10.6%, AM cortisol 74.60 µg/dL, PM cortisol 62.9 µg/dL, urinary free cortisol 1201 µg/d, dexamethasone suppression test 33.39 µg/dL, ACTH 132 pg/dL.

Imaging: negative pituitary MRI, right adrenal adenoma (3.1 X 2.9 cm) on CT scan, negative octreoscan.

Medications: Lasix 40 mg twice daily (BID), metoprolol 50 mg BID, nifedipine 90 mg QD, ramipril 15 mg QD.

Treatment at ED: patient received 20 U insulin STAT and was started on insulin therapy (84 U total daily dose [TDD]) and labetalol 200 mg 3 times a day (TID); and she was continued on nifedipine and ramipril, hydralazine 10 mg TID, KCl, and heparin (for deep vein thrombosis risk). She was discharged to a rehabilitation center.

Within 1 week, patient was re-admitted to the ICU with a suspected infection. She was increasingly depressed and confused. Insulin TDD was increased (84 U to 146 U) to maintain glucose in the mid 200-mg/dL range.

Mifepristone 300 mg was initiated for hypercortisolemia, with spironolactone 100 mg BID for persistent hypokalemia. Within 24 hours, BP decreased (160/90 to 100/70 mmHg), and insulin TDD was reduced (48 U). She became alert and awake, and remained hemodynamically stable. She returned to the rehabilitation facility with a plan for inferior petrosal sinus sampling (IPSS) to localize the ACTH-producing tumor.

Six weeks after ED visit: mifepristone was titrated to 600 mg with control of BP; A1C improved to 5.5%.

At 2 months: patient was re-admitted with hypotension and altered mental status related to urosepsis. During this hospitalization, she required intubation and mechanical ventilation. Mifepristone was interrupted and IV dexamethasone given. Two weeks later, mifepristone was restarted at 300 mg/d and within 6 weeks, she looked and reported feeling better.

At 6 months: 57-pound weight loss, normotensive with only spironolactone, and euglycemic without insulin. She regained activities of daily living, ambulating independently, with improvements in depression and hirsutism while taking mifepristone 300 mg/d and spironolactone 100 mg BID. Repeat octreoscan remained negative.

Conclusion: Mifepristone therapy led to significant improvements in CS manifestations (appearance, muscle weakness, glycemic control, BP, and weight), with elimination of all antidiabetic medications and reductions in antihypertensive medications, making mifepristone a viable option when an ACTH-secreting tumor cannot be localized.

INTRODUCTION

Cushing Syndrome (CS) is a complex, multisystem condition resulting from exposure to excessive cortisol activity. CS is associated with significant comorbidities, including diabetes mellitus, hypertension, dyslipidemia, obesity, coagulopathies, psychiatric disturbances, infections, and reproductive abnormalities. Despite advances in imaging techniques, tumor localization can be a challenging and lengthy process when evidence of hypercortisolism is present and no tumor is evident. In a series of patients with ectopic adrenocorticotropic syndrome (EAS), no source of the EAS was found in 5 of 40 patients (12.5%) despite bilateral inferior petrosal sinus sampling (IPSS).[1] Therefore, managing CS manifestations in the interim is necessary to reduce morbidity and mortality.

We report a case of successful treatment of a patient with occult ectopic CS using mifepristone (Korlym®, Corcept Therapeutics), a glucocorticoid receptor antagonist approved for patients with endogenous CS who have hyperglycemia related to hypercortisolemia and have failed or are not eligible for surgery.

CLINICAL PRESENTATION

A 63-year-old woman presented to the emergency department (ED) with severe weakness of her lower extremities; recent change in mental status; and complaints of polyuria, polydipsia, and a 40-pound weight gain in the past 3 months. The patient's daughter accompanied her and reported a marked change in her mother's behavior and health status, including her appearance, over the last 3 months.

ADDITIONAL DETAILS

- Cushingoid features
  - Moon facies, facial plethora, hirsutism
  - Edema and redness of the lower extremities
  - Thin skin
  - Emotionally labile, irritable, fatigued, and depressed
  - Muscle weakness
  - Central obesity: weight 185 pounds and body mass index 31.6 kg/m^2
- History of hypertension previously controlled on medications until 3 months ago
  - Blood pressure (BP) 160/81 mmHg
- Laboratory findings were as shown in **Table 1**

Table 1. Laboratory Results at Initial Emergency Department Visit

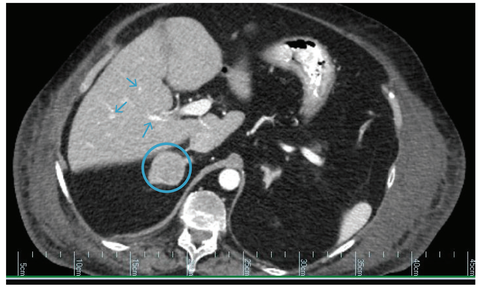
Laboratory test	Value	Normal range
Fasting glucose (mg/dL)	512	65-99
A1C (%)	10.6	<5.7
K+ (mEq/L)	2.9	3.3-4.9
Na+ (mEq/L)	154	134-142
BUN (mg/dL)	24	8-26
Creatinine (mg/dL)	1.2	0.6-1.2
Osmolality (mOsm)	335	275-300
AM cortisol (µg/dL)	74.60	7.0-25
PM cortisol (µg/dL)	62.9	2-14
DST (µg/dL)	33.39	<1.8
UFC (µg/d)	1201	4-50
ACTH (pg/mL)	132	6-50

A1C, glycated hemoglobin; ACTH, adrenocorticotropic hormone; BUN, blood urea nitrogen; DST, dexamethasone suppression test; UFC, urinary free cortisol.

DIAGNOSIS

Biochemical evidence of hypercortisolism was present, and ectopic ACTH-dependent CS was suspected but not confirmed due to rapidly evolving symptoms with hypokalemia, edema, and high levels of ACTH and cortisol, with a negative magnetic resonance imaging (MRI) scan of the pituitary gland and octreoscan that did not visualize the tumor. The patient had a negative computed tomography (CT) of the chest. While an adrenal CT showed a benign-appearing right adrenal adenoma (3.1 X 2.9 cm; see **Figure 1**), this was unlikely as the source of the patient's presenting signs and symptoms of hypercortisolism due to the patient's significantly elevated ACTH levels. A complete tumor localization workup was delayed due to the patient's severity of illness.

Figure 1. Adrenal CT, which shows right adrenal adenoma measuring 3.1 X 2.9 cm (shown in circle; arrows show fatty deposits in the liver)



MEDICATION

- For a listing of the initiation, doses given, and discontinuation of the patient's medications at various timepoints, see **Table 2** directly below

Table 2. Initiation, Doses Given, and Discontinuation of Medications

Medications	Initial ED visit	Pre MIFE 1 week later	On MIFE 300 mg Day 3	On MIFE 300 mg Week 4	On MIFE 600 mg Week 8	On MIFE 300 mg Week 12	On MIFE 300 mg Month 6	On MIFE 300 mg Month 15
Lantus (U)	20-54 U	56 U	26 U	15 U	Discontinued	Discontinued	Discontinued	Discontinued
NovoLog (U)	10-30 U	90 U	12 U	Sliding scale coverage	Sliding scale coverage	Sliding scale coverage	Discontinued	Discontinued
Repaglinide (mg)						0.5 x 3 (TDD)	Discontinued	Discontinued
Spironolactone (mg)		200 mg	200 mg	200 mg	200 mg	150 mg	150 mg	100 mg
Lasix (mg)	80	Discontinued	Discontinued	Discontinued	Discontinued	Discontinued	Discontinued	Discontinued
KCl (mEq/L)	80	80	80	120	40	20	Discontinued	Discontinued
Metoprolol (mg)	100 mg	Discontinued	Discontinued	Discontinued	Discontinued	Discontinued	Discontinued	Discontinued
Nifedipine (mg)	90 mg	90 mg	90 mg	Discontinued	Discontinued	Discontinued	Discontinued	Discontinued
Ramipril (mg)	15 mg	15 mg	15 mg	Discontinued	Discontinued	Discontinued	Discontinued	Discontinued
Labetalol (mg)		600 mg	600 mg	600 mg	600 mg	600 mg	Discontinued	Discontinued
Hydralazine (mg)		30 mg	30 mg	30 mg	30 mg	30 mg	Discontinued	Discontinued
Losartan (mg)				100 mg	100 mg	100 mg	Discontinued	Discontinued
Clonidine (mg)				0.1 mg	0.1 mg	Discontinued	Discontinued	Discontinued
Norvasc (mg)				5 mg	Discontinued	Discontinued	Discontinued	Discontinued
Lovenox (mg)	80 mg	80 mg	80 mg	80 mg, then discontinued due to bleeding risk	140 mg *PE	Switch to Coumadin	Coumadin 2 mg	Coumadin 2 mg

KCl, potassium chloride; MIFE, mifepristone; PE, pulmonary emboli; TDD, total daily dose.

CLINICAL COURSE AND INITIATION OF MIFEPRISTONE THERAPY

- The patient was discharged to a subacute rehabilitation center for treatment and stabilization until it was possible to perform further testing to complete tumor localization, including IPSS
- Within a week of the initial ED visit, the patient worsened clinically, requiring re-hospitalization to the ICU with suspected infection of her lower extremities
  - The patient was more depressed, confused, and unable to ambulate on her own
  - Insulin requirements had increased to a total daily dose (TDD) from 84 U to 146 U to maintain blood glucose in the mid 200-mg/dL range (**Table 2**)

INITIATION OF MIFEPRISTONE THERAPY

- Mifepristone 300 mg daily was initiated for treatment of hypercortisolemia
  - Spironolactone 100 mg BID was added to manage persistent hypokalemia
  - Bactrim was instituted for prophylaxis of *Pneumocystis carinii* pneumonia

MIFEPRISTONE: CLINICAL COURSE

- The patient experienced rapid clinical improvement over the next 24 hours
  - BP decreased from 160/90 to 100/70
  - TDD insulin decreased to 40-48 U
  - Patient became alert and awake
  - She was hemodynamically stable and returned to the rehabilitation facility with plan to perform IPSS as an outpatient to determine source of the ACTH-producing tumor
- At 6 weeks from ED visit, mifepristone was titrated to 600 mg daily; BP was under control and hemoglobin A1C was 5.5%
- The patient would experience further hospitalizations over the next 2 months
  - One admission for pulmonary emboli and poor wound healing of her lower extremities, requiring wound debridement
  - Two months from the ED visit, she presented with altered mental status and hypotension related to urosepsis
    - Patient required mechanical ventilation
    - Mifepristone therapy was interrupted and IV dexamethasone was administered
    - The patient was extubated and stabilized within 24 to 48 hours
  - Mifepristone 300 mg daily was re-initiated 2 weeks later
    - On 6-week follow-up the patient remained wheelchair bound but looked and reported feeling better

SUMMARY OF CHANGE OF CONDITION WITH MIFEPRISTONE THERAPY

- 6 months from diagnosis, the patient had demonstrated significant clinical improvement on mifepristone 300 mg QD and spironolactone 100 mg BID (**Table 2**)
  - Weight loss of 57 pounds
  - Euglycemic without insulin therapy or oral antidiabetic medication
  - Normotensive (BP 120/80) on only spironolactone 150 mg daily
  - Independent ambulation and return to all normal activities of daily living, including caring for her elderly mother
  - Depression, hirsutism, and cushingoid appearance improved
- 15 months from diagnosis, the patient maintained continued improvement
  - Weight loss and other improvements in metabolic parameters vs baseline are shown in **Table 3**
  - Current medications: mifepristone 300 mg daily, spironolactone 100 mg daily
- A repeat octreoscan was negative for a potential source of ACTH, but a positive axillary lymph node was detected and a biopsy is planned

Table 3. Metabolic Parameters Before and After Mifepristone

Parameter	Baseline	On MIFE Month 15
Weight (pounds)	185	133.8
Blood pressure (mmHg)	160/81	140/85
A1C (%)	10.6	5.7
Fasting glucose (mg/dL)	512	88
K+ (mEq/L)	2.9	4.3

A1C, glycated hemoglobin; MIFE, mifepristone.

SUMMARY/CONCLUSIONS

When no source of ACTH production is identified on initial imaging, repeated imaging is warranted. Medical therapy is needed in these case, to control the manifestations of hypercortisolemia until the tumor can be localized. In some cases, when hypercortisolism cannot be managed effectively with medication and the tumor remains occult, bilateral adrenalectomy is performed, leaving the patient with permanent adrenal insufficiency. It has been shown that hypercortisolemia can cause downregulation of somatostatin subtype 2 (SST2) receptors; with lowering of cortisol activity, there may be an upregulation of the receptors, leading to tumor localization on octreoscan to identify a surgical target.[2] This case demonstrates rapid onset of action leading to significant clinical improvement using medical therapy with mifepristone in a critically ill patient presenting with sudden onset of manifestations of Cushing syndrome. Clinical improvement of glycemic control, BP, weight, ambulation, and psychiatric symptoms was demonstrated, with elimination of antidiabetic and antihypertensive medications (except spironolactone).

Mifepristone proved to be a viable treatment option when an ACTH-secreting tumor cannot be localized.

REFERENCES

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DISCLOSURES

SF: None.

ML: Employee, Corcept Therapeutics.

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