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#### Unique Diagnostic Challenges of Cushings From Large Bilateral Adrenal Adenoma and Mifepristone Utilization for Hypercortisolism Prior to Surgery

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# Unique Diagnostic Challenges of Cushings From Large Bilateral Adrenal Adenoma and Mifepristone Utilization for Hypercortisolism Prior to Surgery Vasudev Magaji MD, Sarah Park DO, Maura Bucciarelli DO, Katie Mastoris DO, and Scott Beman MD

### ABSTRACT

A 47 year old female was found to have a 1.8 x 4.9 cm right adrenal nodule and 2.8 x 4.3 cm left adrenal nodule with calcification on CT during abdominal pain evaluation. Extensive workup was done that was negative for pheochromocytoma and Conn syndrome. Her work up showed hypercortisolism with laboratory studies revealing high urine free cortisol, unsuppressed cortisol on 1mg & 8mg overnight dexamethasone suppression testing (ODST), high 11pm salivary cortisol X2 along with elevated random cortisol and undetectable ACTH. She had normal DHEA-S, plasma metanephrine, and rosteindione, renin and aldosterone levels.

Since her adenomas were > 4 cms bilaterally, adrenal surgery was indicated due to increased risk of adrenal carcinoma<sup>1</sup>. Adrenal venous sampling (AVS) done with dexamethasone 2 mg PO Q6hours X 1 day, for nodule functional assessment, showed elevated right and left adrenal cortisol and epinephrine levels compared to Inferior vena cava levels. Adrenal vein epinephrine levels stepup >100pg/mL indicated successful catheterization. Bilateral adrenal vein to venocaval cortisol ratio >4 was consistent with autonomous cortisol secretion, and left to right adrenal cortisol ratio < 2 suggested bilateral Cushing's based on literature from Mayo Clinic<sup>2</sup>.

Initial step was right adrenalectomy but was deferred for her carotid artery surgery. She also had multiple comorbidities including uncontrolled hypertension, poor functional status requiring walker and cane, chronic cellulitis, glucose intolerance, and hypokalemia. Medical management of hypercortisolism prior to surgery was needed. Mifepristone was initiated after her carotid surgery. She had > 50lbs weight loss, improved blood pressure, complete healing of chronic lower extremity cellulitis, and she could ambulate independently by 4 months of Mifepristone initiation. Her potassium, blood pressure and liver functions tests were closely monitored. Her right adrenal adenoma resection on pathology had multiple adrenocortical nodules without adrenal carcinoma and measured 6.5 x 5.0 x 1.7cm.

Learning objectives: Mifepristone, FDA approved for inoperable Cushing, facilitated pre-surgery optimization by mitigating hypercortisolism. Mifepristone could potentially be utilized as a bridge when surgery needs to be deferred.

47 year old female with past medical history significant for hypertension, hyperlipidemia, glucose intolerance, carotid artery disease, peripheral vascular disease, coronary artery bypass grafting, and chronic leg cellulitis presented with abdominal pain. Initial work up included CT scan of the abdomen which showed right adrenal nodule 1.8 x 4.9 cm and left adrenal nodule 2.8 x 4.3 cm. She had workup for pheochromocytoma and Conn syndrome which were negative but was positive for Cushing syndrome. See Table 1.

Surgery team evaluated the patient and recommended right adrenalectomy, which was the larger of the two adenomas. However to assess if one of the adrenal nodule was producing excessive cortisol adrenal venous sampling was performed using Dexamethasone 2mg oral every 6 hrs for 24 hrs preceding the procedure. See Table 2.

Difference in adrenal gland epinephrine levels compared to peripheral levels was > 100 pg/ml suggesting successful localization of the catheter. Adrenal vein to peripheral vein cortisol ratio > 4 was consistent with bilateral cortisol secretion. Ratio of left to right adrenal cortisol levels < 2 again was consistent with bilateral cortisol hypersecretion. It was determined patient should undergo right adrenalectomy as it was larger in size compared to the left adrenal adenoma. See Figure 1.

The procedure was deferred as patient needed carotid artery surgery. Patient needed medical management for hypercortisolism during the interim. She also had several co-morbidities including uncontrolled hypertension on Metoprolol and Lisinopril, hypokalemia on Potassium supplements, chronic leg cellulitis on antiobiotics for 10 months, glucose intolerance, and poor functional status requiring walker and cane. Ketoconazole was contraindicated for interactions with plavix and atorvastatin which could not discontinued due to her vascular disease. Mifepristone was initiated at 300mg PO every other day and titrated up to once daily. She had 65lb(240lbs to 175lb) weight loss, hypertension improved, had complete healing of cellulitis, and could ambulate independently by 4 months of starting Mifepristone. Her potassium, liver function tests and BP were monitored closely. Patient stopped taking Mifepristone 1 week prior to the right adrenalectomy. Perioperatively she was placed on hydrocortisone and eventually tapered off. Post surgery, she did not require hydrocortisone or Mifepristone. Symptomatically she had increased energy levels, nausea had resolved and denied any weakness.

Pathology showed a right adrenal mass measuring 6.5X5.0X1.7cm larger than on the CT scan dimension containing multiple and renocoritcal nodules without any evidence of mitosis, necrosis or vascular invasion and the immunostaining was negative for adrenal carcinoma. She continues to be followed in the outpatient endocrinology clinic her work up shows suppressed ACTH with high normal cortisol, suggestive of persistent Cushing's despite unilateral surgical adrenal resection. See Table 3.

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# **CASE & CLINICAL COURSE**

24 hr urine free 1mg ODST Cort 8mg ODST cort 11pm salivary Random cortiso Random ACTH **CRH** stimulatio

Left adrenal g Right adrenal g Inferior vena ca

> Figure 1. CT scan abdomen showing right and left adrenal adenomas, respectively.



7am Cortisol (4-ACTH (6-50 pg/ 7am Cortisol (4-ACTH (6-50 pg/

TABLE 1.	
e cortisol (4-50ug/24hrs)	89.2
tisol (<1.8 ug/dL)	15.7
tisol (<1.8ug/dL)	20.0
cortisol x2 (<100ng/dL)	156 & 151
ol (3-22 ug/dL)	17.3
(6-50pg/ml)	Undetectable
n test	No cortisol or ACTH response

TABLE 2.		
e	Cortisol (3-22ug/dL)	Epinephrine (<84pg/ml)
and	84.9	433
land	56.5	1911
ava	11.7	28



ТΛ	DI		0
IA	DL	- 5	3

22ug/dL)	17.5 (post op day #21)
ml)	Undetectable (post op day #41)
22ug/dL)	17.5 (post op day #41)
ml)	Undetectable (post op day #41)

This case had unique diagnostic and management dilemmas. Aldosterone in AVS, reportedly used in case reports, might have helped in diagnosis, given the subtly low right adrenal cortisol and low left adrenal epinephrine levels (likely from phrenic vein dilution) but based on size, bilateral adrenal resection was indicated. Simultaneous aldosterone assessment has been used in case reports during adrenal venous sampling and this would have provided additional information but was not used in our case<sup>3</sup>. The patient needed medical management for hypercortisolism during the interim before adrenalectomy. Mifepristone is a glucocorticoid receptor antagonist that affinity 18 times greater than that of endogenous cortisol and has been FDA approved for inoperable Cushing's<sup>4</sup>. The evaluation of response is based on clinical evaluation and not laboratory measurements. Side effects include hypokalemia, worsening blood pressure and increase risk for adrenal insufficiency<sup>4</sup>.

Persistent hypercortisolism increases the risk of perioperative morbidity by increasing infectious complications and delayed tissue healing<sup>5</sup>. The options of outpatient management of hypercortisolism include ketoconazole, metyrapone and mifepristone. Ketoconazole could not be used due to drug interactions with atorvastatin, and metyrapone is not readily available. Mifepristone has been FDA approved and studied in the SEISMIC trial with positive clinical reports in managing specific signs and symptoms of Cushing's<sup>6</sup>. The drug was utilized in this case to antagonize the hypercortisolism, which facilitated healing of her chronic cellulitis, optimized her functional status, improved her blood pressure and reduced her weight by greater than 50lbs. Following her right adrenal resection, her work up showed suppressed ACTH and suggestive of persistant cushing. She will be evaluated for continued Cushing's symptoms and will obtain a repeat 11pm salivary cortisol level x 2. She has the left adrenal adenoma intact, measuring >4cm which will need resection in the future. Mifepristone could potentially be used as bridge therapy when surgery needs to be deferred.

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## DISCUSSION

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