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MEDICAL MANAGEMENT OF MILD HYPERCORTISOLISM AND PRIMARY ALDOSTERONISM IN A PATIENT WITH ACTH-INDEPENDENT MACRONODULAR HYPERPLASIA PRESENTING WITH RESISTANT HYPERTENSION

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OBJECTIVE: Co-secretion of cortisol and aldosterone from adrenal nodules has been reported (Spath, 2001; Hayashi 1998) and is typically managed surgically. We present a case of hypercortisolism and primary aldosteronism (PA) managed medically with glucocorticoid and mineralocorticoid receptor antagonists.

CASE: A 71 y/o man with resistant hypertension was referred for suspected PA. Prior to presentation his blood pressure (BP) ranged from 170/90 to 230/100 mmHg on 5 anti-hypertensive agents. His screening aldosterone to renin ratio was elevated at 53 ng/dL:ng/mL/hr with serum potassium 3.8 mmol/L (3.5-5.3). Plasma metanephrines performed prior to referral were normal, as was 24-hr urine free cortisol 34.5 µg/d (4-50).

RESULTS: Physical examination was notable only for obesity with BMI 33.2 kg/m^2. Oral salt load test confirmed PA with a 24-hr urine aldosterone of 17.9 µg/d. The patient declined adrenal vein sampling and surgery. Spironolactone was initiated at 100 mg/d. Abdominal CT performed to exclude adrenal cortical carcinoma demonstrated four bilateral adrenal adenomas ranging from 1.9 to 3.5 cm. Random ACTH was undetectable, suggesting ACTH-independent macronodular adrenal hyperplasia (AIMAH). 1 mg DST was 2.6 µg/dL. Late-night salivary cortisol was normal x 2. BP control improved on spironolactone. However, he developed worsening anxiety, weight gain of 10 lbs, and pre-diabetes over the next year. Repeat 1 mg DST was 3.4 µg/dL. Surgery was again declined, and mifepristone 300 mg/d was initiated. After 3 months of therapy, he reported weight loss, improved energy, and less anxiety. ACTH 2 months following mifepristone initiation rose to 29 pg/mL.

DISCUSSION: Hypercortisolism secondary to AIMAH is a rare cause of Cushing syndrome. Concurrent PA has been described in adrenal nodular disease (Spath, 2001) as well as AIMAH (Hayashi 1998). Surgery is typically the preferred approach in managing PA due to an adenoma as well as hypercortisolism due to AIMAH. We present a case in which medical management of (i) hypercortisolism with mifepristone, a glucocorticoid receptor antagonist, and (ii) PA with spironolactone, a mineralocorticoid receptor antagonist, was successful.

CONCLUSION: In this patient with bilateral adrenal nodular disease not desiring surgical management, medical management of aldosterone excess with spironolactone and glucocorticoid excess with mifepristone resulted in improvement in symptoms and hemodynamic parameters.

INTRODUCTION

- Co-secretion of aldosterone and cortisol has been described in aldosterone producing adenomas (APAs) and in ACTH-independent macronodular adrenal hyperplasia (AIMAH)
- While recent clinical practice guidelines for the management of patients with suspected primary aldosteronism (PA) have been developed, a subtype of PA where patients present with co-secreting cortisol and APAs may be under-reported
- A prospective study by Lau and colleagues, reported the incidence of adrenal adenomas co-secreting aldosterone and cortisol as 14%.[1] The majority of these patients present with treatment-resistant hypertension and electrolyte disturbances and additional clinical features that will impact their management.
- Surgical management has been the typical approach in PA, making the pre-operative diagnosis of co-existing cortisol hypersecretion imperative to avoid post-operative adrenal crisis
- Bilateral adrenal nodules pose a challenge when it comes to treatment options since bilateral adrenalectomy leads to permanent adrenal insufficiency

CASE PRESENTATION

- The patient is a 71-year-old man who initially presented to a primary care physician to establish care with the complaint of daily debilitating headaches. He had not seen a physician for 5 years.
- He presented with a long standing history of hypertension on pharmacologic therapy in the past, but had discontinued treatment without medical advice several years prior to this consultation
- He was noted to have severe hypertension (230/100 mmHg)
  - Despite initiation of 5 anti-hypertensive agents his blood pressure was still 170/90 mmHg
- Plasma metanephrines performed prior to referral were normal as was a 24-hr urinary free cortisol 34.5 µg/d (4-50) and renal artery Doppler examination
- Further evaluation was notable for elevated aldosterone:renin ratio at 53 ng/dL:ng/mL/hr, suggesting PA, and he was referred for endocrinology evaluation
- He denied history of hypokalemia or family history of adrenal disease or sudden cardiac death
- Physical Examination:
  - Anxious-appearing obese gentleman
  - **Weight 238 lbs, pulse 96 bpm, BP 170/90 mmHg, BMI 33.2 kg/m^2**
  - Thyroid was normal in size with no nodules
  - Cardiac exam was normal with no murmurs or edema
  - Abdomen was obese
  - Motor strength was normal with no evidence of wasting
  - Skin was without bruising or striae
- Anti-hypertensive medications at presentation:
  - Clonidine 0.2 mg three times daily
  - Valsartan 320 mg three times daily
  - Hydralazine 100 mg three times daily
  - Hydrochlorothiazide-triamterene 25/37.5 mg daily

DIAGNOSIS (TABLE 1)

Primary aldosteronism: resistant hypertension and elevated aldosterone renin ratio (ARR). PA confirmed with abnormal oral salt loading test.

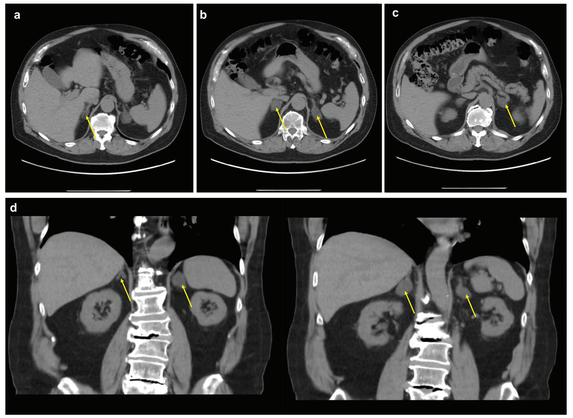
Hypercortisolism: abnormal 1 mg dexamethasone suppression test (DST) with undetectable ACTH and bilateral adrenal nodules suggesting AIMAH

Table 1. Initial Laboratory Evaluation

Lab Test	Value	Normal Range
Aldosterone to renin ratio	53 ng/dL: ng/mL/hr	elevated
K+	3.8 mEq/L	3.5-5.3 mEq/L
Plasma metanephrines	normal	
24-hr urine aldosterone	17.9 µg/d	A positive oral salt load is >12 µg/d with concomitant existing 24-hr urine sodium of >200 mg/day[2]
Adrenal vein sampling	Patient declined	
24-hr UFC	34.5 µg/d	4-50 µg/d
ACTH	undetectable	6-9 pg/mL
1 mg DST	2.6 µg/dL	<1.8 µg/dL
Late night salivary cortisol X 2	1.7 nmol/L 3.4 nmol/L	0.3-4.3 nmol/L

ACTH, adrenocorticotropic hormone; DST, dexamethasone suppression test; UFC, urine free cortisol.

Figure 1. CT images demonstrating bilateral adrenal nodules: a) Axial view of normal right adrenal and left adrenal nodule; b) Axial view of right adrenal nodule and second left adrenal nodule; c) Axial view of third left adrenal nodule; d) Coronal images of bilateral adrenal nodules



CLINICAL COURSE

Treatment of Primary Aldosteronism

- Following confirmatory testing for PA, the patient declined adrenal vein sampling (AVS) and surgery in favor of medical management
- He was initiated on spironolactone 25 mg daily and titrated to 100 mg over the next 3 months with a subsequent reduction in concomitant medications to valsartan-HCTZ (320-25 mg) with BP 140/80 mmHg

Hypercortisolism Diagnosis

- Abdominal CT performed to exclude adrenal cortical carcinoma demonstrated 4 adrenal adenomas ranging from 1.9 to 3.5 cm warranting further evaluation for hypercortisolism (**Figure 1**)
- Following the diagnosis of hypercortisolism, he declined surgery and further medications at that time due to the presence of mastodynia associated with spironolactone use
  - A trial of eplerenone was used but blood pressure control again worsened and he transitioned back to spironolactone
- Over the next year, the patient developed worsening anxiety, insomnia requiring pharmacologic treatment, weight gain of 10 pounds, and pre-diabetes with hemoglobin A1c 6.1%
  - Unsuppressed 1 mg DST (3.4 µg/dL)
  - Multiple normal results for late night salivary cortisol (0.03 µg/dL [0.83 nmol/L]; normal range <0.09 µg/dL [2.48 nmol/L])

Hypercortisolism Treatment with Mifepristone

- Mifepristone 300 mg (Korlym®, Corcept Therapeutics) was initiated to treat manifestations of hypercortisolism (**Table 2**)
- Changes in ACTH suggested restoration of hypothalamic-pituitary axis

Table 2. Patient-reported Symptoms Before and After Mifepristone Treatment

Hypercortisolism symptoms before MIFE	Hypercortisolism symptoms after 3 months MIFE treatment
Worsening anxiety	Improved anxiety
Insomnia requiring pharmacologic treatment	Improved sleep
10 lb weight gain	5 lb weight loss
HbA1c = 6.1%	HbA1c = 5.8%
ACTH = undetectable	ACTH = 29 pg/mL
	Improved energy

ACTH, adrenocorticotropic hormone.

DISCUSSION

- Hypercortisolism secondary to AIMAH is a rare cause of Cushing syndrome. AIMAH has been reported with concurrent PA.[3]
- Spath and colleagues report a series of patients with aldosterone- and cortisol-producing adenomas (A/CPA) in which 29 patients (85.3%) had a single adenoma and 5 patients (14.3%) had multiple lesions.[4] Of those five, 3 had bilateral disease.
- Adrenal venous sampling is effective in detecting lateralization of aldosterone secretion. Determination of cortisol co-secretion with AVS can lead to false negative results.
- In studies of the characteristics of A/CPA lesions, the size has been described as an average diameter of 26.2 mm in comparison to an APA size of 15 mm. This difference in size may attribute to why the cortisol co-secretion becomes clinically significant.
- Surgical intervention has been the typical approach in the management of an APA and for autonomous cortisol secretion due to AIMAH.
- Surgery may not be feasible or ideal in a patient with bilateral disease since the patient will experience permanent adrenal insufficiency.
- In this case, the patient refused surgery. Initial medical management with a mineralocorticoid receptor antagonist, spironolactone was effective in managing the signs and symptoms of PA.
- As clinical manifestations of hypercortisolism became apparent and worsened over time, further treatment with mifepristone, a glucocorticoid receptor antagonist, was added for successful treatment.

SUMMARY/CONCLUSIONS

- In this patient with bilateral adrenal nodular disease declining surgical management, medical treatment of aldosterone excess with spironolactone and glucocorticoid excess with mifepristone resulted in significant clinical improvement of symptoms and hemodynamic parameters

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DISCLOSURES

SG: Speaker, Corcept Therapeutics.
ML: Employee, Corcept Therapeutics.

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