Primary Hyperaldosteronism Decoded: A Case of Curable Resistant Hypertension

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Patients with resistant hypertension have a higher incidence of secondary causes of hypertension compared with the general hypertensive population. It is important to screen such patients for secondary causes of hypertension because appropriate treatment can lead to improved blood pressure control or even cure these patients, and thus avoid the cardiovascular morbidity and mortality associated with uncontrolled hypertension. One common cause of secondary hypertension, often associated with hypokalemia, is primary hyperaldosteronism or Conn syndrome. Aldosterone is a mineralocorticoid hormone produced in the outer layer of the adrenal cortex (the zona glomerulosa); its primary action is to increase sodium and water reabsorption by the kidney. Once the diagnosis of primary aldosteronism is made, it is necessary to determine if aldosterone production is unilateral or bilateral. When production is unilateral (most often from a functional adenoma), surgery is potentially curative. The authors report a case and review the diagnostic workup of Conn syndrome in which resistant hypertension and hypokalemia were cured by unilateral adrenalectomy.

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KEY WORDS

Hyperaldosteronism • Conn syndrome • Resistant hypertension • Hypokalemia

Resistant hypertension is defined as blood pressure that remains above goal in patients treated simultaneously with three antihypertensive agents of different classes.[1] In average-risk patients, the goal blood pressure is 140/90 mm Hg. Medications must be given at the optimal dose, one of which should be a diuretic if tolerated. A recent population-based study examining 15,968 patients in the United States identified the prevalence of resistant hypertension in the hypertensive population to be 8.9%.[2] Patients with uncontrolled or resistant hypertension are at high risk for adverse cardiovascular events, including stroke, myocardial infarction, renal failure, and sudden cardiac death.

Patients with resistant hypertension are more likely to have secondary rather than essential

hypertension; therefore, it is important to screen for secondary causes. Common causes of secondary hypertension include obstructive sleep apnea, hyperaldosteronism, and renal parenchymal disease. Certain clinical clues can point to a specific etiology. Here we report on a case of a woman with a curable form of resistant hypertension.

Case Report

A 52-year-old white woman was referred to an outpatient cardiology clinic for the treatment of resistant hypertension. The patient was diagnosed and treated for hypertension by her primary care physician. She did not experience any symptoms related to elevated blood pressure. She had no additional past medical history and no prior surgeries. Family history was significant for her mother who died from complications relating to aortic dissection, and two out of five siblings with hypertension. She did not use tobacco, consumed alcohol several times per month, and did not use recreational drugs. Initially, home medications prescribed were nebivolol, 20 mg/d; amlodipine, 10 mg/d; valsartan/hydrochlorothiazide, 160/25 mg/d; cyclobenzaprine, 5 mg twice daily as needed; and potassium supplementation totaling 40 mEq daily. Spironolactone, 25 mg/d, was substituted for valsartan/hydrochlorothiazide once hyperaldosteronism was suspected.

Upon initial outpatient evaluation blood pressure was 163/94 mm Hg in her left arm, 164/109 mm Hg in her right arm (both sitting), and 155/100 mm Hg in her right arm while standing. Heart rate was 51 beats/min, respiratory rate was 16 breaths/min, and temperature was 98.0°. There was no evidence of retinopathy or papilledema on funduscopic examination. There were no carotid, abdominal, or femoral bruits. On chest auscultation the rate was regular, there were no murmurs or gallops, and the point of maximal impulse was not displaced. Peripheral pulses were strong and equal in the bilateral carotid, radial, femoral, dorsalis pedis, and posterior tibial arteries. The remaining examination results were unremarkable. Electrocardiogram showed a sinus rate of 56 beats/min, R wave axis of 75°, normal intervals, and no evidence of left ventricular hypertrophy. Echocardiogram revealed a structurally normal heart with no valvular abnormalities, no hypertrophy, normal chamber sizes, and no wall motion abnormalities.

Laboratory testing revealed serum potassium of 2.7 mmol/L despite oral supplementation. Sodium was 140 mmol/L, carbon dioxide was 36 mmol/L, chloride was 99 mmol/L, creatinine was 0.7 mg/dL, and blood urea nitrogen was 14 mg/dL. Complete blood count, serum glucose, liver function tests, urinalysis, coagulation studies, thyroid function studies, and uric acid were all within normal parameters. Spironolactone was held for 4 weeks and potassium supplementation was increased to attain a serum potassium level of 3.6 mmol/L in order to obtain a plasma aldosterone concentration (PAC)/renin activity (RA) ratio. Plasma aldosterone was 29 ng/dL and plasma renin activity was < 0.1 ng/mL/hour. Renin concentration was too low to measure; therefore, we were unable to calculate the exact PAC:RA ratio. In order to exclude Cushing disease and confirm nonsuppressible aldosterone secretion, 24-hour urine collection was performed after oral sodium loading. Collection revealed sodium of 224 mmol/d, potassium of 71 mmol/d, creatinine 1.1 g/d, aldosterone 14.32 μg/d, and cortisol 8 μg/day. Computed tomography (CT) angiogram of the renal arteries (performed prior to measurement of PAC and RA) showed a 2-cm mass in the left adrenal gland and no renal artery stenosis (Figure 1).

The patient was referred to interventional radiology for adrenal vein sampling. Sequential samples were taken from the inferior vena cava (IVC), right adrenal vein, and left adrenal vein. Aldosterone level was 66.0, 699.0, and 2932.0 ng/dL, respectively. Serum cortisol was 24.7, 472.5, and 256.4 μg/dL, respectively. Calculated cortisol-corrected ratios were 1.48 on the right and 11.44 on the left. The ratio on the left was 7.7 times that of the right.

The patient underwent laparoscopic removal of the left adrenal gland. Gross pathologic review showed a $2.1 \times 2 \times 1.8$ cm soft tan-orange round subcapsular mass that abuts normal adrenal parenchyma (Figure 2). Cut section showed

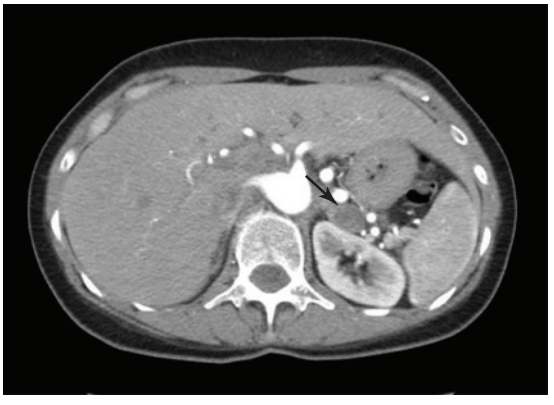

Figure 1. Abdominal computed tomography scan demonstrating 2-cm adrenal mass (*arrow*).

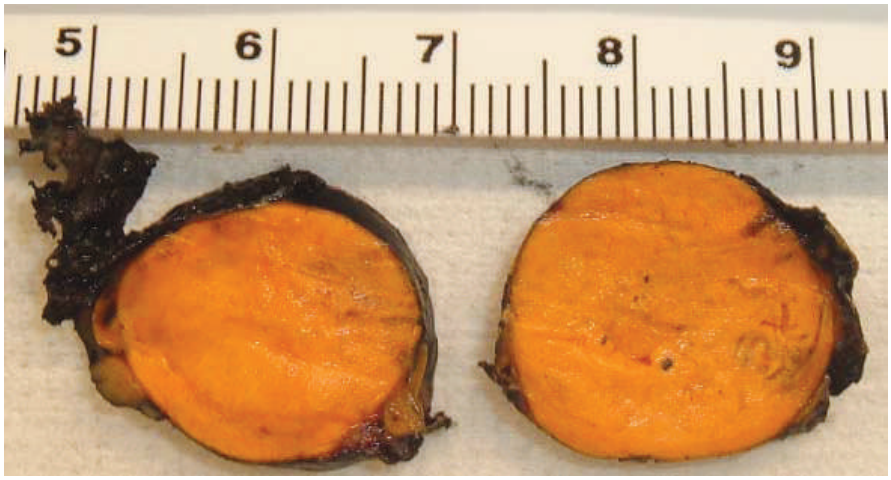

Figure 2. Gross pathology specimen showing a round, tan-orange, adrenal subcapsular mass (units on ruler are cm).

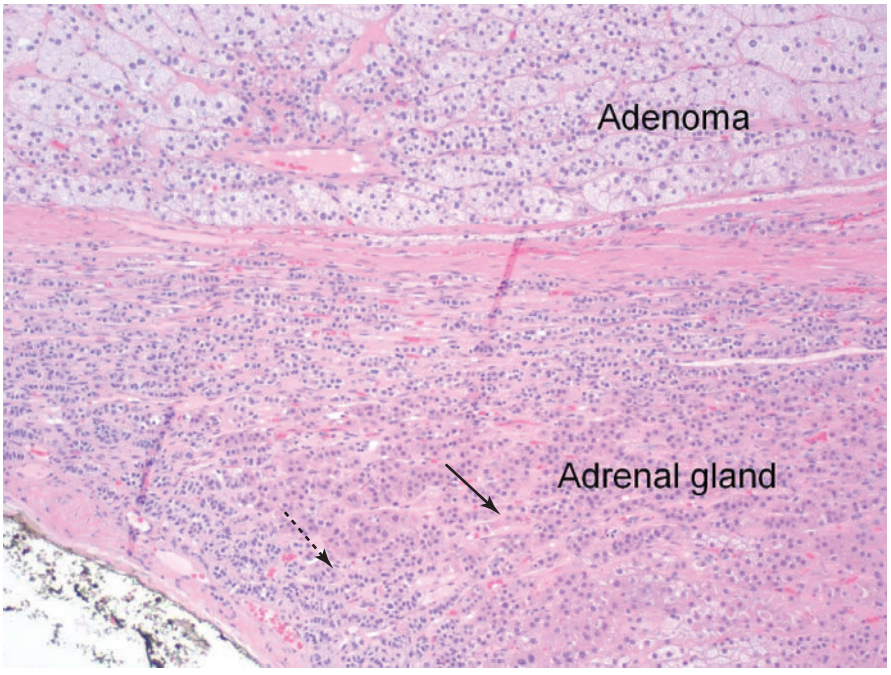

Figure 3. Routine hematoxylin and eosin stain, 100 × magnification, adenoma with adjacent adrenal gland showing atrophy of zona glomerulosa (*dashed arrow*). *Solid arrow,* zona fasciculata.

a whorled pattern. Microscopic examination revealed a circumscribed adrenal cortical neoplasm consistent with adenoma; there were no areas of necrosis or hemorrhage (Figure 3). There was atrophy of adjacent adrenal gland, particularly in the zona glomerulosa. One month after surgery her blood pressure was 124/76 mm Hg off antihypertensive medications and serum potassium was 4.4 mmol/L without supplementation.

Discussion

Aldosterone is a steroid hormone (in the mineralocorticoid family) produced within the zona glomerulosa or outer layer of the adrenal cortex. Under normal conditions production is stimulated by angiotensin II (via the diacylglycerol-inositol trisphosphate, and protein kinase C pathway), hyperkalemia, corticotrophin, acetylcholine, endothelin, norepinephrine, prolactin, prostaglandins, vasopressin, and several other substances.[3] Aldosterone acts on the distal nephron to increase reabsorption of sodium and excretion of potassium and hydrogen ions. Sodium retention results in expansion of the extracellular fluid compartment. Aldosterone also acts on arterial smooth muscle resulting in vasoconstriction.[4] The combined effect is elevation of systemic blood pressure. Ultimately, under normal physiologic conditions aldosterone acts to maintain circulatory integrity and sodium and potassium balance.

The combination of resistant hypertension (blood pressure $>$ 140/70 mm Hg despite simultaneous use of three antihypertensive medications) and refractory hypokalemia along with alkalosis suggested the presence of mineralocorticoid excess, most likely primary hyperaldosteronism. The initial screening test for primary hyperaldosteronism is measurement of plasma aldosterone concentration and renin activity and calculation of the aldosterone/RA ratio. A ratio $>$ 25 is suggestive of hyperaldosteronism as long as the plasma aldosterone concentration is $>$ 15 ng/dL. In normal subjects with essential hypertension the ratio is typically between 4 and 10.[5] In our patient we were not able to calculate the PAC:RA due to renin activity measuring $<$ 0.1 ng/mL/h; however, if we substitute the value 0.5 in the denominator the ratio becomes 58 with an aldosterone concentration of 29 ng/dL. Weinberger and Fineberg[6] determined that a PAC above 20 ng/dL with a PAC:RA ratio above 30 had a sensitivity and specificity of 90% for aldosterone-producing adenoma. In the past it was believed that hypokalemia was required to make the diagnosis of primary hyperaldosteronism. In an analysis including data from five international centers, Mulatero and colleagues[7] determined, that,

with the use of the PAC:RA ratio to screen hypertensive patients, hypokalemia is present in only up to 37% of patients with primary hyperaldosteronism. When a functional adenoma is responsible for primary aldosteronism, the proportion of patients with hypokalemia is much higher. Additionally, increased sodium intake promotes the development of hypokalemia in the setting of hyperaldosteronism. The 2008 Endocrine Society Guidelines recommend screening for hyperaldosteronism in the following patients: stage 2 or 3 hypertension (pressure > 160/100 mm Hg) or resistant hypertension, hypokalemia, presence of an adrenal incidentaloma, or family history of early-onset hypertension.

Once an elevated PAC:RA ratio is identified, further testing is indicated to confirm nonsuppressible aldosterone production and thus primary hyperaldosteronism. Douma and associates[8] screened 1616 patients with resistant hypertension and found 20.9% had a positive PAC:RA ratio; however, only approximately half (53.8%) were confirmed to have hyperaldosteronism. The high rate of false-positives is because this ratio is denominator sensitive and laboratory assays are not able to accurately quantify very low levels of renin activity. According to the 2008 Endocrine Society Guidelines, possible confirmatory tests include oral sodium loading, saline infusion, fludrocortisone suppression, or captopril challenge.[9]

We elected to perform oral sodium loading for confirmation of nonsuppressible aldosterone secretion. Spironolactone was held for 4 weeks and the patient was placed on a high sodium diet (5000 mg/d) for 3 days. Urine sodium excretion of at least 200 mmol/d indicates adequate sodium loading (hers was 224 mmol/d). Urine aldosterone excretion > 12 μg/d is consistent with hyperaldosteronism (hers was 14.62 μg/d). Additionally, our patient did exhibit evidence of renal potassium wasting consistent with hyperaldosteronism with a 24-hour urine potassium > 30 mmol/d (hers was 71 mmol/d) in the setting of hypokalemia. Twenty-four hour urinary cortisol excretion of 8 μg excluded Cushing disease.

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Once primary hyperaldosteronism is confirmed, it is necessary to determine if there is a unilateral aldosterone-producing adenoma (or rarely carcinoma or unilateral hyperplasia) versus bilateral adrenal hyperplasia. Montori and colleagues[10] determined adenomas account for approximately 35% of cases of primary hyperaldosteronism. The 2008 Endocrine Society Guidelines recommend CT scan as first-line imaging to identify solitary adenomas and masses with malignant features (carcinomas). A CT scan in our patient demonstrated a 2-cm mass in the left adrenal gland. Given the high prevalence of nonfunctioning adrenal adenomas, renal vein sampling is necessary to demonstrate lateralization of aldosterone production. A meta-analysis including 950 patients found that CT/magnetic resonance imaging did not correlate with adrenal vein sampling in 37.8% of cases of primary hyperaldosteronism, which could lead to unnecessary surgery or missed opportunity for surgical correction.[11] The Endocrine Society recommends adrenal vein sampling in all patients considering undergoing surgery for potential cure.

Adrenal vein sampling is the gold standard for differentiating between unilateral (functional adenoma) and bilateral (hyperplasia) aldosterone production. This procedure is technically difficult and therefore should be referred to a high-volume center. The test is best preformed using continuous cosyntropin stimulation (as an infusion of 50 μg/h, started 30 min prior to the procedure).[12] Aldosterone and cortisol measurements are made from sequential blood samples taken from the right and left adrenal veins and the inferior vena cava. In order to confirm that specimens are taken from within the adrenal veins, the measured cortisol levels in each adrenal vein is compared with the IVC. When using cosyntropin stimulation the ratio of adrenal vein to IVC cortisol should be at least 5:1, typically it will be > 10:1.[12] Our patient had ratios of 19 on the right and 10 on the left, confirming successful catheterization.

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Once successful catheterization is confirmed, the cortisol-corrected ratio must be calculated. This corrects for dilution that may take place if samples are not taken the same distance away from the respective adrenal gland. The cortisol-corrected ratio is calculated by dividing the measured aldosterone level by the cortisol level for each gland. Our patient had ratios of 1.48

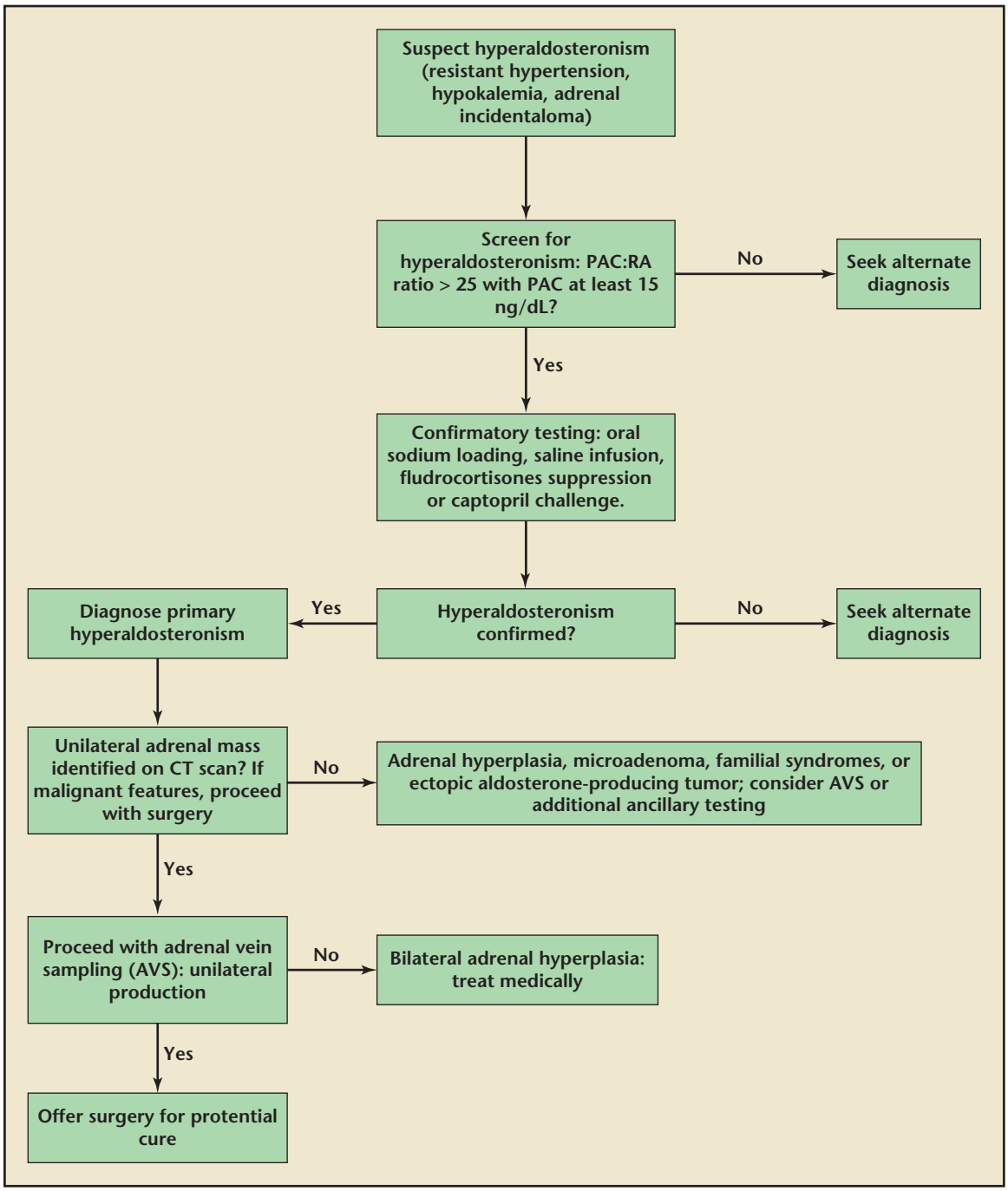

Figure 4. Diagnostic algorithm for primary hyperaldosteronism. AVS, adrenal vein sampling; CT, computed tomography; PAC, plasma aldosterone concentration; RA, renin activity.

on the right and 11.44 on the left. The ratio of the ratios (left to right) was 7.7. A lateralizing ratio $>$ 4 is consistent with unilateral aldosterone production, 3 to 4 is indeterminate, and $<$ 3 is consistent with bilateral production. When performed with cosyntropin stimulation, adrenal vein sampling is 95% sensitive and 100% specific for detecting unilateral aldosterone production.

Once unilateral aldosterone production is identified, if the patient is otherwise an appropriate surgical candidate, the treatment of choice is laparoscopic adrenalectomy. The removal of an aldosterone-producing adenoma cures hypertension in 30% to 69% of patients and invariably improves hypokalemia.[13] If aldosterone production is bilateral, the treatment is medical management with mineralocorticoid receptor-blocking agents. The diagnostic approach for primary hyperaldosteronism is summarized in Figure 4.

Conclusions

Aldosterone-secreting adenoma is an important cause of secondary hypertension. Originally described by Jerome Conn in 1955,[14] Conn syndrome represents one of the few clinical scenarios in which hypertension can potentially be cured. Evaluation of a patient suspected of having a mineralocorticoid excess is complicated as it involves multiple steps, measurement of very dilute substances, and specialized procedures. Once a functional adenoma is identified, successful removal can prevent the cardiovascular morbidity and mortality associated with both uncontrolled hypertension and high plasma concentrations of aldosterone. Given the favorable outcomes with treatment, it is important to be aggressive in both the diagnosis and treatment of this syndrome. In the world of cardiology, in which many conditions are chronic and require life-long management, the opportunity for cure is rare and should not be missed. ■

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MAIN POINTS

- Resistant hypertension is defined as blood pressure that remains above goal in patients treated simultaneously with three antihypertensive agents of different classes. Patients with resistant hypertension are more likely to have secondary rather than essential hypertension; common causes of secondary hypertension include obstructive sleep apnea, hyperaldosteronism, and renal parenchymal disease.
- Aldosterone is a steroid hormone (in the mineralocorticoid family) produced within the zona glomerulosa or outer layer of the adrenal cortex. It acts on the distal nephron to increase reabsorption of sodium and excretion of potassium and hydrogen ions.
- The combination of resistant hypertension and refractory hypokalemia along with alkalosis in this patient suggested the presence of mineralocorticoid excess, most likely primary hyperaldosteronism.
- Aldosterone-secreting adenoma is an important cause of secondary hypertension. Conn syndrome represents one of the few clinical scenarios in which hypertension can potentially be cured.
- Hypokalemia is present in only around 37% of patients with primary hyperaldosteronism.