

# clinicopathological conference



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## Poorly Controlled Hypertension in a 64-Year-Old Male

### Introduction

This is the first published case in the monthly Clinicopathological Conference conducted by the Internal Medicine residency program at the University of Illinois at Urbana-Champaign. A clinical faculty member is presented a case of which he/she has no prior knowledge and then proceeds to describe the clinical reasoning involved in reaching a final diagnosis. This case was discussed in December 2006.

### Discussants

Endocrinology: Robert Kirby, MD  
Radiology: Juan Jimenez, MD  
Pathology: Ikechukwu Uzoaru, MD

### Case Presentation: A 64-year-old male with poorly controlled hypertension

*The patient presents to the clinic with no acute or specific complaints. He was diagnosed with hypertension 20 years ago and has had poor blood pressure control during the past five years. The patient denies any chest pain, shortness of breath, rash or significant weight change. Additionally, he reports no experience of abdominal pain, palpitations, flushing or visual changes.*

*Past medical history includes hypertension, hyperlipidemia and benign prostatic hypertrophy. The patient has no known drug allergies. Medications include benazepril 20 mg daily, amlodipine 10 mg daily, amiloride 10 mg twice daily, terazosin 5 mg at night, aspirin 8 mg daily, atorvastatin 20 mg daily, potassium chloride 20 mEq twice daily, and a nicotine patch. Family history is non-contributory. The patient is an occasional smoker currently trying to quit.*

*Upon examination, the patient was afebrile, resting pulse was 72/min, and resting blood pressure of 160/100 mm of Hg. Pupils were equal and reactive to light with no hypertensive changes on funduscopic examination. Carotid upstrokes were strong and symmetric, and no bruits were audible.*

*Heart, lungs and abdominal examinations were unremarkable. No pedal edema or rash was observed. Peripheral pulses were easily palpated.*

### Discussion

Poorly controlled hypertension is an important medical problem frequently faced by primary care physicians. The most common causes include suboptimal therapy, lack of patient adherence to prescribed therapy, volume overload, obesity, alcohol abuse and, finally, a group of conditions described as identifiable causes of hypertension in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.<sup>1</sup> The identifiable causes are summarized in Table 1.

### Table 1. Identifiable Causes of Hypertension as Outlined in the JNC 7 Report

- Chronic kidney disease
- Obstructive uropathy
- Renovascular hypertension
- Cushing's syndrome and other glucocorticoid excess states including chronic glucocorticoid therapy
- Pheochromocytoma/paraganglioma
- Primary aldosteronism and other mineralocorticoid excess states
- Thyroid or parathyroid disease
- Coarctation of the aorta
- Drug-induced or drug-related
- Sleep apnea

A question that often arises in clinical practice is who to screen for these secondary causes of hypertension. The following clinical clues alert the clinician to the existence of these less common causes of hypertension:

1. Age of onset before puberty or above the age of 50–55 years

2. Severe or refractory hypertension
3. Sudden elevation in a patient with previously stable blood pressure
4. History, examination or laboratories indicate the presence of one of these disorders

This patient is not on potassium-wasting diuretics yet requires potassium supplements. This helps us focus our differential diagnosis on one class of disorders—those associated with hypertension and hypokalemia. (Table 2)

**Table 2. Conditions Associated with Hypertension and Hypokalemia**

- Primary hyperaldosteronism
- Renovascular disease
- Surreptitious diuretic use
- Cushing’s syndrome
- Licorice ingestion
- Renin secreting tumors
- Deoxycorticosterone secreting tumors
- Certain types of Congenital Adrenal Hyperplasia

**Differential Diagnoses**

Pathophysiologically, these disorders can be broadly classified as primary hyperaldosteronism, secondary hyperaldosteronism, and apparent aldosterone excess mediated syndromes. Excess production of aldosterone by the zona glomerulosa independent of normal renin-angiotensin stimulation characterizes primary hyperaldosteronism. Adrenal adenomas (30–60% of cases), bilateral adrenal hyperplasia (idiopathic hyperaldosteronism, IHA) and, rarely, adrenal carcinomas cause primary hyperaldosteronism.

Secondary hyperaldosteronism may be due to primary hyperreninism (renin secreting tumors) or secondary hyperreninism (disorders such as renal vascular disease where renal hypoperfusion causes hypersecretion of renin). Cortisol has almost equal affinity for the mineralocorticoid receptor as aldosterone, but it is converted to inactive cortisone by the enzyme 11 beta-hydroxysteroid dehydrogenase type 2 (11-beta-HSD2). This enzyme is inhibited by glycyrrhetic acid contained in imported licorice, leading to a syndrome mimicking mineralocorticoid excess. Cushing’s syndrome, especially due to ectopic adrenocorticotrophic hormone (ACTH) production, may cause very high levels of cortisol that overwhelm the metabolic capacity of 11-beta-HSD2 and directly activate mineralocorticoid receptors. Consequently, there is no demonstrable mineralocorticoid excess and

plasma renin activity is usually normal or suppressed. Other mechanisms proposed include direct inhibition of 11-beta-HSD2 by ACTH and production of other nonaldosterone mineralocorticoids such as deoxycorticosterone and corticosterone. Renin and deoxycorticosterone secreting tumors are rare.

*Recent laboratory results:*

Sodium	141 mmol/L	(135–145)
Potassium	2.8 mmol/L	(3.6–5.0)
Chloride	101 mmol/L	(101–111)
Bicarbonate	32.4 mmol/L	(21–31)
BUN	11 mg/dL	(6–20)
Creatinine	1.2 mg/dL	(0.5–1.2)

*Review of previous laboratories revealed intermittent hypokalemia for the past five years. Complete blood count, TSH, calcium and liver function tests were unremarkable.*

Hypokalemia with metabolic alkalosis in this patient with hypertension points to a primary mineralocorticoid excess state. Normokalemia does not rule out a diagnosis of primary hyperaldosteronism as demonstrated by a retrospective study in which less than 50% of patients had a low potassium level at presentation.<sup>2</sup> A rare disorder worth mentioning is glucocorticoid-remediable aldosteronism where aldosterone is synthesized in the ACTH sensitive zona fasciculata (instead of the zona glomerulosa) and in which normokalemia is usually present. Steroids are the mainstay of therapy.

*The patient’s hypokalemia was corrected with potassium supplements and 8 AM simultaneous measurements of plasma aldosterone and renin activity were obtained. Benazepril was held for a week prior to testing.*

*Plasma Aldosterone*

*Concentration (PAC) 68 ng/dL (3–16)*

*Plasma Renin*

*Activity (PRA) 0.2 ng/mL/hr (0.65–5 ng/mL/hr)*

*PAC/PRA ratio 340*

The PAC/PRA ratio is the initial screening test of choice.<sup>3</sup> Hypokalemia is treated prior to testing as it can suppress aldosterone levels and lead to false negative results. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are usually discontinued as they may elevate plasma renin activity and decrease the sensitivity of the ratio. A ratio >30 with simultaneous PAC >20 ng/dL is suggestive of primary hyperaldosteronism. An increased PAC and PRA and a PAC/PRA ratio <10 suggests secondary

hyperaldosteronism. Conditions that cause apparent mineralocorticoid excess result in suppressed PAC and PRA levels.

The screening test in this patient is definitely suggestive of primary hyperaldosteronism. The next step is to confirm the diagnosis by demonstrating lack of aldosterone suppression with salt loading. There are two commonly used and validated methods:

1. **Saline suppression test** (intravenous sodium chloride infusion and measurement of plasma aldosterone concentration)
2. **Oral salt loading over three days and 24 hour urine collection for aldosterone, sodium and creatinine** (creatinine allows for confirmation of adequacy of the 24 hour collection, >200 mEq/24 hours of sodium documents adequate sodium loading and an aldosterone level >14  $\mu\text{g}/24$  hours confirms hyperaldosteronism)

*A saline suppression test was performed after ensuring normokalemia with potassium supplements. Two liters of normal saline was infused over four hours and PAC was measured. Failure to suppress aldosterone is indicative of hyperaldosteronism.*

<6 ng/dL	normal aldosterone suppression
6–10 ng/dL	equivocal
>10 ng/dL	failure to suppress and hyperaldosteronism

*An initial test yielded a PAC of 7 ng/dL. A PAC of 12 ng/dL was obtained on repeat testing and felt to confirm the diagnosis of primary hyperaldosteronism.*

Once the diagnosis is confirmed, the next step is to image the adrenal glands. Computed tomography (CT) and magnetic resonance imaging (MRI) are both appropriate choices. The presence of a typical unilateral macroadenoma in a patient under 40 years-of-age is diagnostic of a functional adrenal adenoma. A large (>4 cm) unilateral mass raises concern for adrenocortical carcinoma, though this is a rare cause of aldosterone excess.

*CT of the abdomen utilizing an adrenal protocol was performed and revealed a 2 cm left adrenal mass. The mass had an attenuation of 32 Hounsfield units (HU) on the noncontrast scan and 90 HU on a delayed enhancement scan.*

**Figure 1.** CT scan without contrast showing a 2 cm left adrenal mass



There are certain features on imaging that suggest an adrenal mass is benign. An attenuation coefficient of less than 10 HU on an unenhanced scan and a delayed enhancement measurement of less than 30 HU on a scan with intravenous contrast are suggestive of an adrenal adenoma. In this case, these features were not useful in clinical decision-making. There are also several problems with relying on imaging alone to distinguish between adrenal adenomas and adrenal hyperplasia:

1. Bilateral adrenal hyperplasia may present with normal appearing glands on imaging.
2. Absence of a mass does not rule out an adenoma since lesions less than 1 cm can be missed on CT imaging.
3. Bilateral lesions are not diagnostic of hyperplasia as one of them could be an aldosteronoma and the other a non-functioning tumor.
4. Approximately 5% of the population, especially individuals over age 40 years, has adrenal “incidentalomas” discovered during imaging for other reasons. The vast majority (approximately 95%) are nonfunctional. Adrenal hyperplasia or a small (<1 cm) aldosteronoma on the contralateral side can be missed if an incidentaloma is considered the source of aldosterone production.
5. Aldosteronomas are treated by surgical excision while the management of adrenal hyperplasia is aldosterone antagonist therapy. Failure to lateralize aldosterone hypersecretion to the side of the nodule may subject a patient over age 40 years to unnecessary and ineffective surgery.<sup>4</sup>

*Selective adrenal sampling was performed through a transfemoral approach.<sup>5</sup> Continuous infusion of ACTH was maintained throughout the procedure. Blood was drawn from the right and left adrenal veins and the*

inferior vena cava for measurement of plasma aldosterone concentration and cortisol (to ensure proper catheter placement). Results are summarized in Table 3.

**Table 3. Results of Selective Adrenal Vein Sampling**

	Aldosterone (ng/dL)	Cortisol (mg/dL)
R adrenal vein	973	> 120
L adrenal vein	37,814	> 120
IVC	1109	26.9

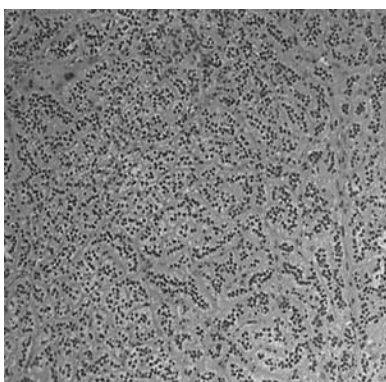
The significant (greater than four-fold) increase of aldosterone in the left adrenal vein samples confirms the diagnosis of an aldosterone producing adenoma. Definitive therapy is surgical resection of the adenoma.

Laparoscopic left adrenalectomy was performed and the adrenal gland was submitted for pathological examination. The gross specimen revealed a 1.5 cm encapsulated yellowish-colored mass with no visible areas of necrosis or hemorrhage. Microscopic examination was consistent with an adrenal cortical adenoma.

Figure 2. Macroscopic appearance



Figure 3. Microscopic section of adrenocortical adenoma



The patient had an uneventful postoperative course. His potassium returned to normal in a week and he is now off potassium supplements. The effect of surgery on blood pressure remains to be fully observed.

**Patient Diagnosis: Primary hyperaldosteronism due to a left adrenal adenoma (Conn's syndrome)**

**Summary**

This case represents a fairly classic presentation of Conn's syndrome, named after Jerome W. Conn who first described it in 1955. Primary hyperaldosteronism historically has been reported to account for only 0.05–2% of all cases of hypertension, but recent studies indicate a much higher prevalence (5–15%).<sup>2</sup> This may reflect more widespread screening than an actual increased frequency of occurrence. Conn's syndrome represents a surgically treatable etiology of hypertension. Approximately two thirds of patients are normotensive off medication (19%) or on reduced doses of medication (47%); 95% are normokalemic within the first postoperative year.<sup>5</sup>

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### **CME Questions 5a-d**

Please select the best answer for the following:

- 5a. Which of the following statements regarding primary hyperaldosteronism is true?
- Edema is always present
  - Occurrence of hypokalemia is variable
  - Renin levels are elevated
  - Metabolic acidosis is present
- 5b. Elevation of plasma aldosterone concentration and renin activity in a hypertensive patient with hypokalemia would be consistent with the following diagnosis:
- Bilateral adrenal hyperplasia
  - Secondary hyperaldosteronism due to congestive heart failure
  - Licorice ingestion
  - Renovascular disease
- 5c. Therapy of choice in patients diagnosed with primary hyperaldosteronism due to bilateral adrenal hyperplasia is
- Mineralocorticoid receptor antagonist (eg, spironolactone)
  - Dietary sodium restriction
  - a and b
  - Adrenalectomy
- 5d. The rationale for performing selective adrenal vein sampling in patients with primary hyperaldosteronism includes all of the following **except**:
- Bilateral adrenal hyperplasia carries a poor prognosis
  - Hypertension of bilateral adrenal hyperplasia responds poorly to surgery
  - Computed tomography may miss small (<1 cm) unilateral adenomas
  - A radiographically detectable adenoma may be non-functional in a patient over 40 years of age ("incidentaloma")