

CLINICAL CASE OF THE MONTH

Persistent Hypertension in a Young Woman: A Classic Presentation of Conn's Syndrome

Gretchen Yandle, MD; Derek J. Vonderhaar, MD; Theepa Thayalakulasingam, MD; Arthur Zieske, MD; David Smith, MD; Lee S. Engel, MD, PhD; Robert Richards, MD; Fred A Lopez, MD

INTRODUCTION

Primary aldosteronism (PA) is a secondary cause of hypertension that is often missed due to inadequate clinical evaluation and the lack of classically described laboratory abnormalities. Based on guidelines from the Endocrine Society, primary aldosteronism should be suspected in young patients with moderate to severe hypertension, patients with hypertension and coexisting hypokalemia, any patient with hypertension and an incidental adrenal adenoma, and hypertension in the setting of a significant family history of early onset hypertension or cerebral vascular accident in a first degree relative less than 40 years of age.¹ In previous years, primary aldosteronism was attributed to less than one percent of all causes of secondary hypertension. However, recent research and increased utilization of aldosterone/plasma renin ratio (ARR) as a method for screening has led to the understanding that majority of patients with PA are not hypokalemic, and the current literature now places the incidence

of PA between 5-13 percent.² Additionally, a growing body of evidence has demonstrated inflammatory, fibrotic, and remodeling effects on the cardiovascular and renal tissue that appear to be independent of PA-induced hypertension.^{2,3} Therefore a high suspicion for PA must be incorporated into evaluation of hypertensive patients, as diagnosis and subsequent treatment not only improves blood pressure control, but also acts to diminish cardiovascular morbidity and mortality.^{4,5} Here we present a case of a young woman with a seven-year history of hypertension prior to receiving a diagnosis of Conn's Syndrome.

CASE PRESENTATION

A 24 year-old woman presented to the Emergency Department from the Endocrine clinic with "low potassium." The patient had been sent to the Endocrine Clinic for evaluation of persistent hypertension. Her blood pressure at presentation was 159/99 mmHg and her potassium level was 1.5 mmol/L [normal value

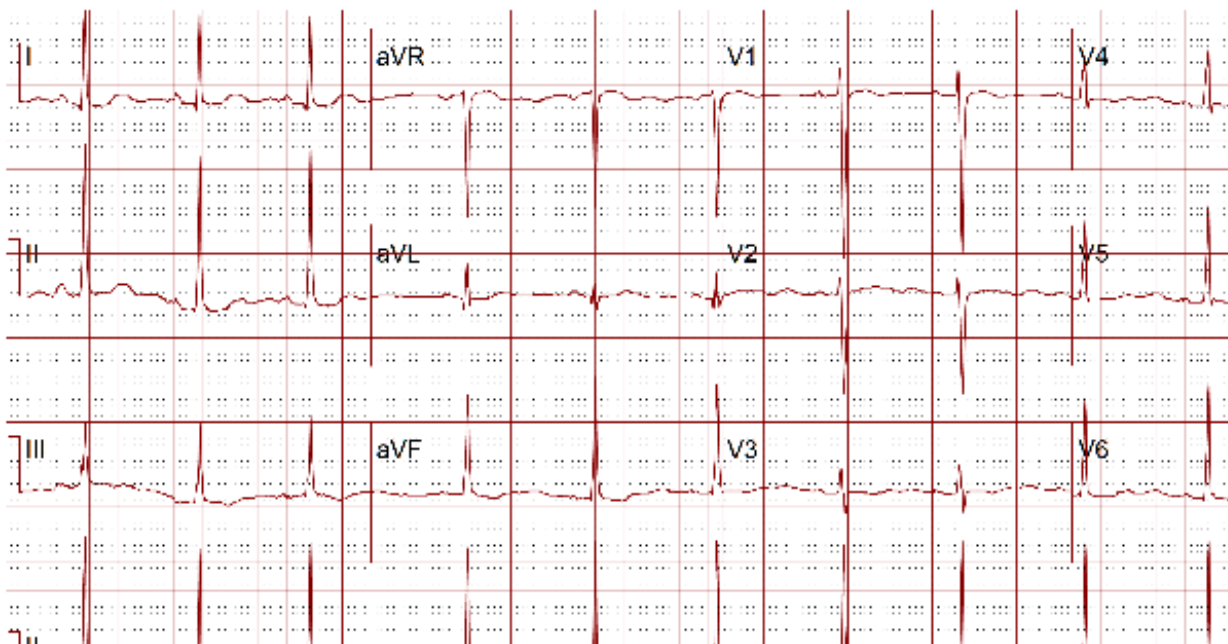


FIGURE 1. Admission EKG demonstrating triad of ST segment depression, low amplitude T waves, and prominent U waves consistent with profound hypokalemia.

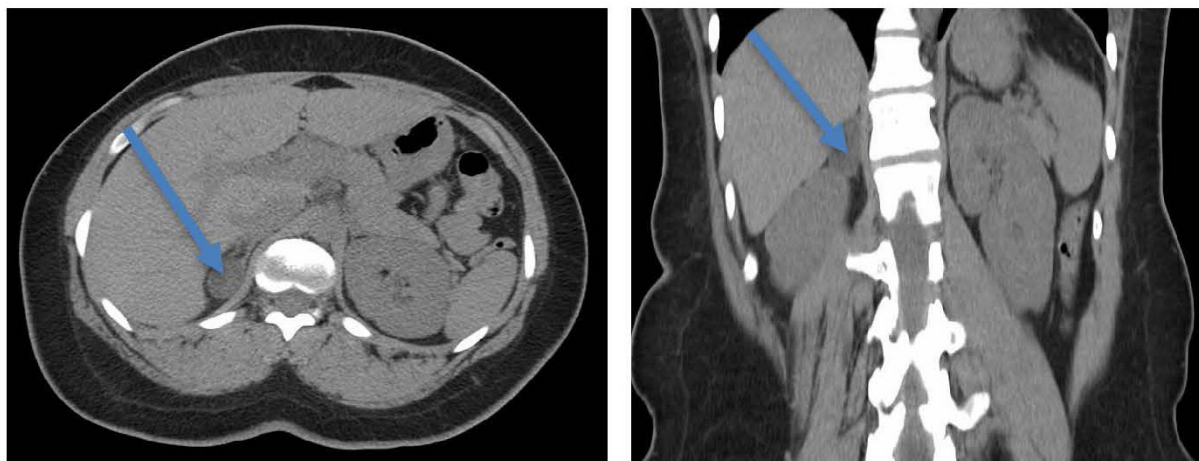


FIGURE 2. Axial and coronal non-contrast images of the abdomen demonstrate a right suprarenal hypoattenuating nodule (arrows) arising from the adrenal gland. The lesion measured 17 HU.

3.6-5.2 mmol/L]. She was asymptomatic, though she did report intermittent mild shortness of breath at night. She denied nausea, vomiting, muscle cramps, chest pain, diaphoresis, headache, visual disturbances abdominal pain or dizziness. Her physical exam revealed no abnormalities. Past medical history was significant for hypertension since adolescence, mild intermittent asthma and premature birth. She did not smoke, drink alcohol, or use illicit drugs. Family history was significant for hypertension and type II diabetes on the maternal side. Her medications included amlodipine, lisinopril, and a multivitamin. She has no allergies to medications. Laboratory data revealed a normal complete blood count and differential, normal basic metabolic profile with the exception of the potassium 2.0 mmol/L post oral replacements. The serum aldosterone level was 85.7 ng/dL [normal range 1.0 to 16.0 ng/dL], serum renin 0.28 ng/mL/hr [normal range 1.31 to 3.95 ng/mL/hr], and the ratio of renin to aldosterone was 306.1 ng/dL per ng/mL/hr [normal range 0.0 to 30.0 ng/dL per ng/mL/hr] indicative of a primary aldosteronism. An electrocardiogram demonstrated a sinus arrhythmia with U waves (Figure 1). Cardiac echo showed good left ventricular function and an ejection fraction of 55 percent. Computed tomography scan of the abdomen reported a right adrenal mass measuring approximately 1 x 1.5 cm (Figure 2). Endocrine and Surgery services discussed the findings, and were in agreement that she likely had an aldosterone secreting adrenaloma. During her admission, she received potassium supplementations both oral and intravenously; spironolactone was added and lisinopril was increased to 80 mg per day. She received a right adrenalectomy two weeks later with an uncomplicated post-operative course. Pathology examined the surgical specimen and confirmed the diagnosis of an adrenal cortical adenoma (Figure 3). She was followed by both endocrinology and internal medicine clinics post discharge. One month post-adrenalectomy, the hypokalemia resolved, repeat ratio of renin to aldosterone normalized at 6.6 ng/dL per ng/mL/hr, and her blood pressure was well controlled with amlodipine 10 mg per day. She is now discharged from endocrinology clinic and continues to do well.

DISCUSSION

Hypertension, defined as systolic blood pressure greater than or equal to 140 mmHg and diastolic blood pressure greater than or equal to 90mmHg, is one of the most prevalent diseases in the United States. Accepted nomenclature in the medical community classifies hypertension as primary or secondary. Primary hypertension is the more prevalent type, accounting for 90 to 95 percent of all hypertensive patients. While primary hypertension is without an identifiable etiology, secondary hypertension is attributable to an identifiable cause, accounting for five to ten percent of hypertensive patients.^{6,7}

The National Health and Nutrition Examination Survey (NHANES) quoted an estimate of the prevalence of primary hypertension in United States of America to be 28.6 percent in 1999-2002. Prevalence of hypertension worldwide ranged from 20 to 50 percent. Overall, 972 million persons or 26.4 percent of the adult world population suffer from this chronic condition.⁷ It has been estimated that by 2025, 1.56 billion individuals will have hypertension, an increase of 60 percent from 2000.⁷

Secondary causes of hypertension should be considered in patients who develop hypertension when they are young in the absence of risk factors such as obesity or family history and when the hypertension is severe or refractory to treatment.⁷ Our patient had a triad of hypertension, hypokalemia, and metabolic alkalosis that prompted a suspicion of primary aldosteronism. Yet, the manifestations of PA are not uniform and a metabolic alkalosis and hypokalemia need not be present in the setting of PA.^{2-3,7} The incidence of primary aldosteronism is noted to 5 to 13 percent in the literature, and is the most curable form of secondary hypertension.^{4,8} Thus, it is crucial to identify PA as treatment differs from individuals with primary hypertension. Response to therapy directly correlates with the duration of hypertension and age of diagnosis.

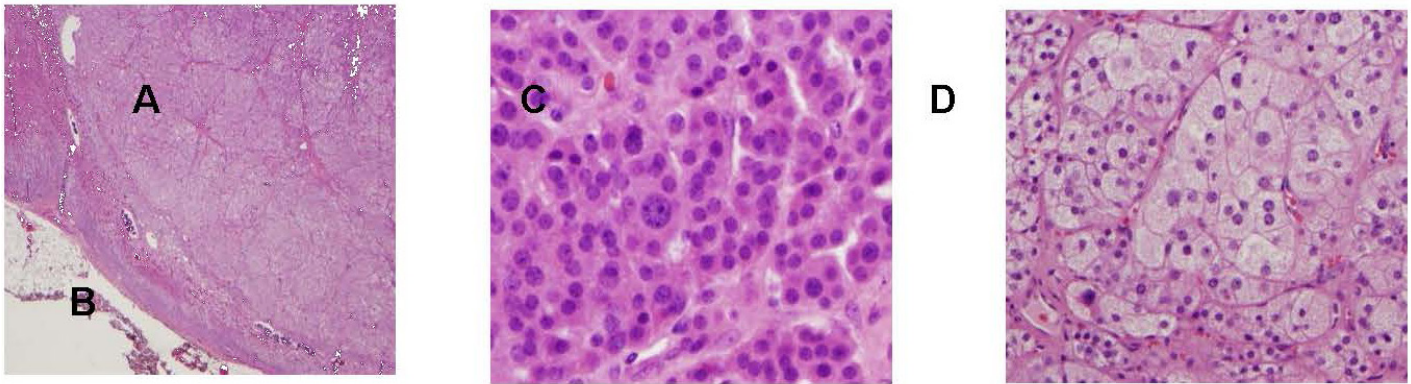


FIGURE 3. H&E stained sections of adrenal gland showing the relationship of the adenoma (A) to non-tumoral adrenal (B). Regions resembling the zona fasciculata (C) and zona reticularis (D) were present.

The differential diagnosis for secondary hypertension is broad, and will limit the focus of this report to the diagnosis and management of PA. In any patient with suspected PA, the initial approach to diagnosis should start with evaluation of an aldosterone/plasma renin ratio (ratio greater than 30 ng/dL per ng/mL/hr is usually indicative of PA). The screening should include hypokalemic and normokalemic patients (although the exact data is difficult to quantify given the lack of high-powered randomized controlled trials, current research is finding greater prevalence of PA without hypokalemia), as it is widely noted in the literature that hypokalemia has a low sensitivity and positive predictive value for PA.^{1-2,5} Although the ARR is widely recognized as the most reliable screening test, it is not without limitations, and results are variably affected by a variety of factors (time of day, posture, potassium levels, diet, and method of blood collection) and medications (diuretics, aldosterone receptor antagonist, beta blockers, angiotensin receptor blockers, angiotensin converting enzyme inhibitors, and dihydropyridine calcium channel blockers).^{2,8} The ARR is a screening test and not diagnostic of PA. All patients with a positive ARR should be followed up with a confirmatory test prior to establishing a diagnosis. The optimal confirmatory test is still debatable, but options include fludrocortisone suppression test, oral or intravenous salt loading, and captopril challenge testing.^{2,8} Once the patient is diagnosed with PA, the initial step in differentiating PA subtypes should start with a high-resolution contrast CT scan to evaluate for adrenocortical carcinoma or solitary adrenal nodule. If the CT scan is non-diagnostic, adrenal vein sampling should be undertaken to differentiate bilateral adrenal hyperplasia (BAH) from an adrenal primary adenoma (APA).^{1-2,9} Differentiation of the PA subtypes is paramount as it has implications regarding appropriate therapy and management. BAH is the most common etiology of PA accounting for 65 to 70 percent of all cases. Medical management includes treatment with a mineralocorticoid receptor antagonist such as spironolactone. APA accounts for the second highest etiology, representing the underlying causative factor in 30 to 35 percent of patients with PA (158). In contrast to the management of BAH, treatment for APA is generally operative. Resolution of hypertension is seen in 50 percent

of patients postoperatively, and significantly improved blood pressure control is anticipated in the remainder of patients.⁴ In conclusion, although our patient had laboratory findings seen in PA, review of the literature demonstrates that her presentation is not as common as initially thought. After careful review of her prior medical history, the hypokalemia and metabolic alkalosis were relatively new findings despite her seven-year history of hypertension. Based on increased and ongoing research, it appears that hypertension likely precedes metabolic abnormalities seen in PA.³ Thus, even in the absence of hypokalemia and alkalosis, clinicians should become more diligent in evaluating patients for PA, as delay in obtaining an accurate diagnosis increases cardiovascular and renal morbidity, and lowers the likelihood of successful surgical or pharmacological interventions. Screenings for PA in the subgroup of hypertensive patients with high prevalence will not only decrease significant morbidity and mortality, but should add clarity to the exact prevalence of PA in our hypertensive population.

REFERENCES

1. Funder JW et al. Case Detection, Diagnosis, and Treatment of Patients with Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism*. 2008;93:3266-3281.
2. Stowasser M, Taylor PJ, Pimenta E, Al-Asaly Ahmed A, and Gordon RD. Laboratory Investigation of Primary Aldosteronism. *Clin Biochem Rev*. 2010;31:39-56.
3. John W. Funder. *Minireview: Aldosterone and Mineralocorticoid Receptors: Past, Present and Future*. November 2010, 154(11)
4. Ra Mi Kim, Jandee Lee, and Euy-Young Soh. Predictors of Resolution of Hypertension after Adrenalectomy in Patients with Aldosterone-producing Adenoma. *Journal Korean Med Sci* 2010;25: 1041-1044.
5. Amar et al. Aldosterone producing adenoma and other surgically correctable forms of primary aldosteronism. *Orphanet Journal of Rare Diseases* 2010; 5(9):1-12.
6. Leonardo A. Sechi. Cardiovascular and Renal Damage in Primary Aldosteronism: Outcomes After Treatment. *American Journal of Hypertension*. June 2010; 1-8.
7. Hajjar I, Kotchen JM, Kotchen TA. Hypertension: Trends in Prevalence, Incidence, and Control. *Annu Rev Public Health*. 2006;27:465-490.
8. Reincke M et al. Progress in Primary Aldosteronism. *Horm Metab Res* 2010; 42: 371 - 373.

9. Lynnette K. Nieman. Approach to the Patient with an Adrenal Incidentaloma. *The Journal of Clinical Endocrinology and Metabolism*. September 2010; 95(9):4106–4113.
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Dr. Yandle is a first year fellow in the Pulmonary/Critical Care Medicine Program in the Department of Medicine at Louisiana State University Health Sciences Center in New Orleans. **Dr. Vonderhaar** is a fourth year resident in Emergency Medicine/Internal Medicine in the Department of Medicine at Louisiana State University Health Sciences Center in New Orleans. **Dr. Thayalakulasingam** is a first year fellow in the Pulmonary/Critical Care Medicine Program in the Department of Medicine at Louisiana State University Health Sciences Center in New Orleans. **Dr. Zieske** is a Co-Director, Hematopathology in the Department of Pathology and Genomic Medicine at the Methodist Hospital Physician Organization in Houston, TX. **Dr. Smith** is an Assistant Professor in the Department of Radiology at Louisiana State University Health Sciences Center in New Orleans. **Dr. Engel** is an Assistant Professor in Clinical Medicine and Assistant Program Director of the Internal Medicine Residency Program in the Department of Medicine at Louisiana State University Health Sciences Center in New Orleans. **Dr. Roberts** is an Associate Professor in Endocrinology and the Director of Endocrinology, Diabetes and Metabolism Fellowship Program in the Department of Medicine at Louisiana State University Health Sciences Center in New Orleans. **Dr. Lopez** is the Richard Vial Professor and Vice Chair for Education in the Department of Medicine at Louisiana State University Health Sciences Center in New Orleans.