CLINICAL VIGNETTE

A Patient with Multi-Treatment Resistant Hypertension

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Case Presentation

A 62-year-old African American female presented to endocrinology with long-standing hypertension that was initially diagnosed 15 years prior. She reports being started on treatment at the time of the diagnosis, but her blood pressure (BP) did not improve. Over the next few years, she had tried various blood pressure medications, the names of which she does not recall, without any improvement in her BP. The patient was later referred to a cardiologist who, over the last three years, developed the current medical regimen. Despite the changes in her medications, the patient's BP remained elevated, which prompted an endocrine consultation. She reported adherence to her medications. She denied any recurrent headaches, palpitations, or sweats. The patient was physically inactive and followed a low salt diet with estimated daily intake around 1500 milligrams (mg) per day.

Her past medical history was significant for hyperlipidemia and impaired fasting glucose. She denied any surgeries. In discussing her family, patient stated both her parents had hypertension with her father dying from heart failure complications. Her sister also has hypertension while her brother has type 1 diabetes. She denied any alcohol, tobacco, or illicit drug use. A review systems yielded only progressive weight gain and fatigue.

At the time of her visit, she was taking losartan-hydrochlorothiazide 100mg-25mg, verapamil (extended release) 240mg, carvedilol 25mg twice a day, clonidine patch .1mg weekly, simvastatin 20mg, and metformin (extended release) 500mg. The clonidine patch was added two months prior to her visit with some improvement in her BP; however, her fatigue had worsened since starting this medication. Her primary care physician was suspecting pheochromocytoma and had asked that this be considered when evaluating the patient.

On exam her BP was 153/70 with heart rate of 57 and BMI of 34.6. She did not appear Cushingoid, and the rest of her physical exam was normal. Initial labs included sodium of 138, potassium 4.2, chloride 105, carbon dioxide 25, blood urea nitrogen 39, creatinine 1.41, and glucose (non-fasting) 123. Outside of her hypertension, the patient did not have any symptoms to suggest pheochromocytoma. However, given the resistant hypertension, a 24-hour urine for catecholamines and metanephrines was ordered. The results yielded levels on the lower end of the reference range. The concurrent hyperglycemia also prompted the same 24-hour urine specimen to be tested for free cortisol, which was on the lower range of normal at 15.4 micrograms. The suspicion for hyperaldosteronism was also present, so her blood was also processed for aldosterone and renin levels. The patient had a serum aldosterone of 20 nanograms/deciliter with a plasma renin activity of 0.12 nanograms/milliliter/hour. The aldosterone/renin ratio was 167.

A diagnosis of primary hyperaldosteronism was made, and the patient was started on spironolactone at a dose of 50 mg daily. Also she was advised to stop using the clonidine patch. An adrenal MRI without contrast was normal and did not reveal an adenoma. Upon returning in a month, the patient's BP was 112/60. Her fatigue had improved, but she now was complaining of dizziness and lightheadedness. In response, her verapamil was stopped and her dizziness resolved. Her BP was 114/68 at that time. Next, the patient was asked to stop her carvedilol, and her BP was maintained. Her losartan-hydrochlorothiazide dose was tapered and eventually stopped. At her last visit, the patient's BP on spironolactone alone was 114/80 with a pulse of 72. In between these visits, her serum potassium levels were monitored and remained normal. Of note, her creatinine (and GFR) started to improve once she was taken off losartan-hydrochlorothiazide. The patient's primary physician preferred to manage her hyperglycemia and was reminded to consider a low dose ACE-inhibitor or ARB for renal protection if her sugars progressed to a diabetic range.

Discussion

The major clinical findings of hypertension with hypokalemia seen in primary aldosteronism (PA) are mostly mediated by aldosterone, which acts on the kidneys (at the cortical collecting tubule) to open sodium channels–thereby increasing sodium reabsorption into the blood. The increase in vascular

sodium results in hypervolemia from the subsequent fluid retention. This hypervolemia causes suppressed renin levels, which is another hallmark of PA. One would expect significant edema with such fluid retention; however, patients with PA do not commonly present with edema. The lack of this finding is speculated to be related to 'aldosterone escape' – a phenomenon of natural diuresis. The increase in fluid excretion is attributed to a number of factors, some of which being secretion of atrial natriuretic peptide (ANP) stimulated by the hypervolemia and increased renal sodium excretion due to high renal perfusion pressure.

The shift of sodium from the urine also creates an electrical gradient in the renal collecting tubules resulting in potassium passing into the urine – thus, explaining why patients with PA may develop hypokalemia. A case presented in the September 2014 UCLA Proceedings by Dr. Rumi Cader, et al., described a patient with PA who had hypokalemia. Our patient had normal potassium levels, which is not surprising given that hypokalemia is not always found in the setting of PA. In fact, a review of patients with PA from data collected from five different international medical centers, showed only 10 to 40% of patients had low potassium levels.[1]

In 2008, the Endocrine Society published guidelines regarding primary aldosteronism (PA). They recommend testing for PA in patients who have BP readings greater than 160/100, drug resistant hypertension (with failure to achieve BP goals with three drugs), hypertension and diuretic-induced hypokalemia, hypertension with an adrenal adenoma (found incidentally), or hypertension with a family history of hypertension or cerebral vascular accident occurring in a family member younger than 40, as well as any first-degree relatives of patients with PA.[2]

The initial tests should be plasma levels of both aldosterone and renin activity. The aldosterone to renin ratio (ARR) is what is being measured when assessing for PA. An ARR over 20 is considered diagnostic for PA.[2] Keep in mind that, in PA, renin levels tend to be low (due to hypervolemia) with values usually less than 1 nanogram/milliliter/hour. With renin levels less than 1, even normal aldosterone levels can result in high ARR. Thus, a patient with PA may have an aldosterone level well within the reference range. Certain anti-hypertensive medications can interfere with ARR measurements. ACE-inhibitors and ARBs can raise renin levels. As such, patients on these medications who have a low ARR cannot be excluded from having PA. Of note, patients with low renin levels despite being on ACE-inhibitors or ARBs tend to have high chances of having PA. Referring back to our patient, she was on losartan (an ARB), had low renin levels, had normal aldosterone levels, and had an ARR of 167.

The Endocrine Society recommends that patients with ARR levels greater than 20 should undergo one of four confirmatory tests: oral sodium load, saline infusion, fludrocortisone suppression, or a captopril challenge.[2] The details of these tests can be reviewed in Endocrine Society's 2008 published guidelines and are beyond the scope of this presentation. A confirmatory test was not sent in our patient primarily because she did not wish to do so.

Once the diagnosis has been confirmed, the source of PA will need to be determined. The most common causes are unilateral adrenal adenomas or bilateral idiopathic hyperplasia of the adrenals. Of more concern, patients with adrenocortical carcinomas and para-neoplastic tumors may present with PA. Thus, patients with diagnosed PA should undergo imaging. The preferred modality is CT; however, our patient underwent MRI (rather than a non-contrast CT) due to concerns of contrast-induced nephropathy given her impaired kidney function. Her MRI was normal, but the absence of adrenal abnormalities does not exclude the diagnosis of PA. Patients with bilateral adrenal hyperplasia can have normal imaging.[3] Likewise patients may have unilateral nonfunctional adrenal adenomas–commonly found incidentally. Therefore, a unilateral adrenal nodule does not confirm the diagnosis of PA, but it does potentially provide a patient with a surgical treatment option as patients respond well to resection of solitary functional adenomas.

Because of the chance of benign nonfunctional adrenal growths, it is recommended that, after imaging, patients undergo adrenal vein sampling to determine between a functional unilateral adenoma and bilateral adrenal hyperplasia – even in cases where imaging is negative. This is a highly specialized procedure and should only performed in experienced centers. Our patient did not accept the risks of this test and, furthermore, stated that she would not pursue surgery in the case of positive findings.

Patients, such as ours, who refuse surgery (in the setting of unilateral disease) or have suspected bilateral adrenal hyperplasia, will benefit from spironolactone or eplerenone (Inspra)–both of which act as aldosterone antagonists. Eplerenone has the benefit of having less endocrine side effects such as breast tenderness in women and gynecomastia in men (both conditions are more prominent in users of spironolactone). The purpose of treating with these agents is not only to reduce blood pressure but to also reduce aldosterone-induced cardiovascular mortality. Patients with PA have significantly higher risks of stroke and myocardial infarction after being matched for age, gender, and blood pressure.[4] The risks were reduced to that of their peers when treated aldosterone antagonists.

Our patient had a dramatic response to spironolactone with a seemingly immediate improvement in her BP once she started treatment. Moreover, she was able stop all of her other anti-hypertensive medications and still maintain her BP. Curiously, she was hypertensive at a much later follow up visit. She admitted that she had stopped her spironolactone. Upon returning to the medication, her BP dropped to normal.

This case demonstrates that patients do not present necessarily with ‘classic’ symptoms and can have unusual outcomes for any given condition.

REFERENCES

1. **Mulatero P, Stowasser M, Loh KC, Fardella CE, Gordon RD, Mosso L, Gomez-Sanchez CE, Veglio F, Young WF Jr**. Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. *J Clin Endocrinol Metab*. 2004 Mar;89(3):1045-50. PubMed PMID:15001583.
2. **Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, Young WF Jr, Montori VM; Endocrine Society.** Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2008 Sep;93(9):3266-81. doi:10.1210/jc.2008-0104. Epub 2008 Jun 13. PubMed PMID: 18552288.
3. **Harper R, Ferrett CG, McKnight JA, McIlrath EM, Russell CF, Sheridan B, Atkinson AB**. Accuracy of CT scanning and adrenal vein sampling in the pre-operative localization of aldosterone-secreting adrenal adenomas. *QJM*. 1999 Nov;92(11):643-50. PubMed PMID: 10542304.
4. **Milliez P, Girerd X, Plouin PF, Blacher J, Safar ME, Mourad JJ**. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. *J Am Coll Cardiol*. 2005 Apr 19;45(8):1243-8. PubMed PMID:15837256.

Submitted on October 13, 2014