Journal of Investigative Medicine High Impact Case Reports
Volume 9: 1–6

DOI: 10.1177/23247096211034337
journals.sagepub.com/home/hic
SAGE

A Real Saline Challenge: Diagnosing Primary Aldosteronism in the Setting of Chronic Kidney Disease

Sasan Mirfakhraee, MD[1], Maria Rodriguez, BS[1], Niloofar Ganji, BS[2], Richard J. Auchus, MD, PhD[3], and Oksana Hamidi, DO[1]

Abstract

Primary aldosteronism (PA) is the most common cause of secondary hypertension but remains largely undiagnosed. Chronic kidney disease (CKD) complicates the diagnosis of PA by affecting the biochemical screening evaluation and confirmatory testing, and by increasing the complication rate of adrenal venous sampling (AVS). To raise clinician awareness of the challenges of PA diagnosis in CKD, we present an illustrative case with subsequent review of the literature and discuss some recent developments in PA diagnostic strategies particularly applicable to the CKD population. A 67-year-old man with stage IIIb CKD was suspected of having PA due to treatment with 6 antihypertensive agents and the presence of intermittent hypokalemia. He had a positive biochemical screen for PA, and AVS demonstrated unilateral aldosterone excess. Subsequently, unilateral adrenalectomy resolved his PA, eliminating the patient's hypokalemia and improving his blood pressure. A MEDLINE literature search revealed 10 studies totaling 11 cases (including our own) of PA diagnosed in the setting of CKD. For each case, the clinical presentation, biochemical data, results of cross-sectional imaging, AVS details, and clinical response to surgery or medical therapy were characterized. The optimal strategy for the diagnosis and management of PA patients with CKD is not known. Although CKD patients often receive screening and subtype testing for PA similar to non-CKD patients, there are challenges in the interpretation of these tests. Novel strategies may include less invasive subtype testing or empiric treatment with mineralocorticoid receptor antagonists but additional studies are necessary.

Keywords

primary aldosteronism, hypertension, chronic kidney disease

Introduction

Primary aldosteronism (PA) is the most common cause of secondary hypertension and has a prevalence as high as 20% among adults with resistant hypertension.[1] Despite this high prevalence, PA remains largely undiagnosed in the United States, and as few as 1.6% of patients with treatment-resistant hypertension undergo evaluation for PA.[2] The consequences of untreated PA are significant, as PA increases the risk of adverse cardiovascular[3,4] and renal[5,6] outcomes compared with primary hypertension. Increased case detection testing is therefore an important step in reducing these end-organ complications, which necessitates increased clinician recognition and understanding of PA.

While the screening criteria for PA are well established,[7] the diagnosis of PA in patients with chronic kidney disease (CKD) presents several challenges. Aldosterone levels are higher in dialysis subjects compared with healthy volunteers,[8] and even in CKD subjects without PA, there is a progressive increase in aldosterone levels as creatinine clearance declines.[9,10] Furthermore, plasma renin activity (PRA) increases in advanced CKD[11] and with increased duration of dialysis.[12] As the biochemical screening for PA begins with the assessment of plasma aldosterone concentration (PAC) and PRA, the effect of CKD on circulating aldosterone and renin therefore confounds the biochemical screening of PA regardless of whether the plasma aldosterone/renin ratio (ARR)[7] or absolute values of PAC and PRA[13] are utilized as the case detection test. Furthermore, confirmatory testing of

[1]University of Texas Southwestern Medical Center, Dallas, TX, USA
[2]University of Toronto, Toronto, Ontario, Canada
[3]University of Michigan, Ann Arbor, MI, USA

Received May 26, 2021. Revised July 1, 2021. Accepted July 4, 2021.

Corresponding Author:
Sasan Mirfakhraee, MD, Department of Internal Medicine, Division of Endocrinology, University of Texas Southwestern Medical Center, WCB3 8th Floor, 2001 Inwood Road, Dallas, TX 75390, USA.
Email: Sasan.Mirfakhraee@UTSouthwestern.edu

PA is challenging in patients with advanced CKD, as reduced urine output underestimates urine aldosterone levels during 24-hour collection and raises the risk of volume overload during sodium-loading protocols. Furthermore, while the utility of adrenal venous sampling (AVS) is well established for PA patients with normal renal function, concern for contrast-induced acute kidney injury (AKI) limits the use of this procedure in the presence of CKD.

In order to raise clinician awareness of the challenges of PA diagnosis in advanced CKD, we present an illustrative case and a subsequent review of the literature. For each case from the literature, we reveal the clinical features that led to the diagnosis of PA, as well as the outcomes following treatment. Finally, we discuss some recent developments in PA diagnostic strategies that might be particularly applicable to the CKD population.

Case Presentation

A 67-year-old man with history of coronary artery disease, stage IIIb CKD (estimated glomerular filtration rate [GFR] 33 mL/min) with urine protein to creatinine ratio of 887 mg/g, and hypothyroidism presented to our endocrine clinic with a 15-year history of hypertension and hypokalemia. Despite his reported adherence to a 6-drug antihypertensive drug regimen of lisinopril 20 mg daily, furosemide 40 mg daily, methyldopa 500 mg twice daily, metoprolol extended release 100 mg daily, nifedipine 30 mg twice daily, and eplerenone 50 mg twice daily, he had uncontrolled stage 2 hypertension, with blood pressure readings of 143/90 to 156/103 mm Hg during clinic visits. He also took potassium chloride 40 mEq daily to maintain appropriate serum potassium levels. During an evaluation for secondary hypertension, the morning PAC was 92 ng/dL with PRA of 11 ng/mL/h and serum potassium of 3.8 mmol/L. Six weeks after eplerenone was discontinued, PAC remained elevated (56 ng/dL), while PRA fell to 1.1 ng/mL/h.

Due to the patient's markedly elevated PAC, near-suppressed PRA, and intermittent hypokalemia despite potassium supplementation, PA was diagnosed, and localization was pursued. Computed tomography (CT) of the abdomen revealed a 1.2 cm right adrenal mass with washout features consistent with a cortical adenoma (Figure 1). AVS revealed marked right adrenal lateralization of aldosterone with a lateralization index ([dominant PAC/cortisol]/[nondominant PAC/cortisol]) of 133 as well as contralateral suppression of the left adrenal gland ([nondominant PAC/cortisol]/[IVC PAC/cortisol]) of 0.1 (Table 1).

The patient subsequently underwent laparoscopic resection of the right adrenal gland; surgical histopathology identified a 1.5 cm adrenal cortical adenoma. His postoperative PAC was 5.6 ng/dL. The patient's potassium supplementation was stopped perioperatively, and his serum potassium remained within the reference range during weekly postoperative assessments. At his 1-month follow-up, the patient remained normotensive while taking furosemide 40 mg daily, nifedipine 30 mg daily, and metoprolol extended release 50 mg daily—3 fewer medications than his preoperative regimen. His defined daily dose (DDD) of antihypertensive medications based on the 2021 Anatomical Therapeutic Chemical Classification/DDD Index improved from 7.67 prior to adrenalectomy to 2.33 postoperatively. The patient's creatinine clearance diminished slightly following adrenalectomy, and 2 months after surgery, his estimated GFR was 28 mL/min. On assessment 5 months following adrenalectomy, the patient remained normotensive and normokalemic on his 3-drug antihypertensive regimen, and his estimated GFR improved to his preoperative baseline of 33 mL/min with urine protein to creatinine ratio of 956 mg/g.

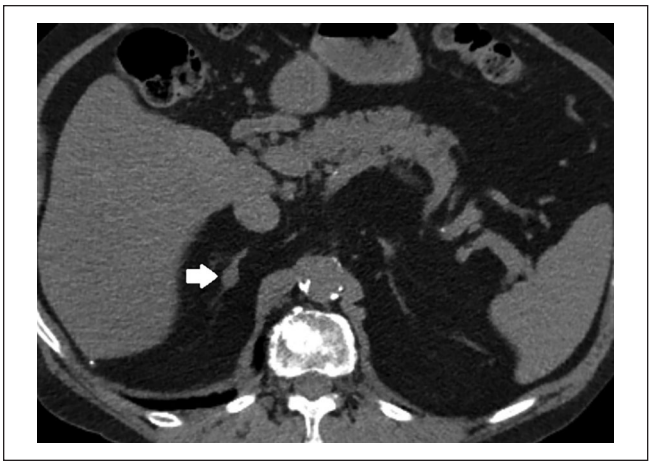

Figure 1. Computed tomography abdomen revealed a 1.2 cm right adrenal mass (white arrow) with pre-contrast attenuation of 12 Hounsfield units, absolute washout 60%, and relative washout 53%, consistent with a benign cortical adenoma.

Literature Search

In our case, pretest suspicion for PA was heightened by the patient's use of 6 antihypertensive agents and the presence of intermittent hypokalemia. We performed a literature search to describe how other cases of PA in patients with CKD were suspected, diagnosed, and ultimately treated. A MEDLINE literature search was conducted, and studies that met the following criteria were included: (1) CKD present at time of laboratory evaluation of PA, (2) history of hypertension with positive biochemical screening for PA (PAC >10 ng/dL with PAC/PRA ratio ≥ 20), and (3) published up to January 1, 2021, in English. Case series were included provided that pertinent demographic and clinical details of individual subjects were described. The following data were extracted: clinical presentation, CKD stage, PAC and PRA values, results of cross-sectional imaging (if performed), results of AVS (if performed), and clinical response to surgery or medical therapy. The details are summarized in Table 2.

Table 1. Laboratory Data From the Adrenal Venous Sampling Procedure.

	Right adrenal vein	Left adrenal vein	IVC
Plasma aldosterone concentration (ng/dL)	38 000	87	60
Serum cortisol (μg/dL)	365	111	8.4
Aldosterone: cortisol (A/C) ratio (ng/μg)	>100	<1	7

Abbreviation: IVC, inferior vena cava.

A total of 10 studies totaling 11 cases (including our case) were found. The most common presenting symptoms that led to case-detection assessment for PA were difficult to control hypertension (27% of cases), hypertension and hypokalemia (55% of cases), and hypertension with an incidentally discovered adrenal tumor (18% of cases). The PAC was highly variable, ranging from 12 to 3200 ng/dL, with a median of 56 ng/dL. PRA was generally low and was suppressed (defined by PRA <1 ng/mL/h) in 55% of cases. An adrenal mass was noted on CT imaging in 90% of cases. Cross-sectional imaging was not performed in one case, and in another, thickening was noted in the left adrenal gland without a discrete mass. AVS was performed in only 27% of the published cases but demonstrated unilateral aldosterone excess in all subjects. Adrenalectomy was performed in 55% of cases—for 2 patients based on cross-sectional imaging results alone—while 45% of patients were treated with spironolactone. Hypertension resolved or improved in all but one case, and hypokalemia that was evident prior to treatment resolved in all cases.

Discussion

The prevalence of PA in the CKD population is unknown, as individuals with PA diagnosed in the context of CKD are predominantly characterized in case reports. A single cross-sectional study of PA screening in hypertensive renal transplant recipients found a PA prevalence of 15.7% using criteria of PAC >15 ng/dL and ARR ≥20.[14] Numerous quandaries and disincentives discourage screening for PA among patients with CKD despite the high prevalence and documented benefits. These problems for CKD patients include alterations in aldosterone clearance and renin dynamics, risk of volume overload during sodium loading for confirmatory testing, potential for intravenous contrast-induced AKI, and concern for hyperkalemia and GFR reduction following treatment of PA with surgery or mineralocorticoid-receptor antagonists (MRAs). The presence of CKD complicates the screening evaluation for PA in part by raising PRA and thus lowering the ARR and potentially resulting in false-negative screen results.[15] While higher values of ARR have been shown to increase the likelihood of aldosterone-producing adenoma (APA) in subjects with normal renal function,[16] this association has not been validated in patients with CKD. Even if the biochemical evaluation is unequivocal for PA, the localization of aldosterone excess in CKD patients is not straightforward. Strategies endocrine providers have employed for CKD patients include deferring diagnostic testing until after renal transplant for transplant-eligible patients,[17] using the same tests and criteria (ie, AVS) as non-CKD patients despite limited performance data, or the cautious use of MRAs without workup for PA.

Given a heightened risk of bleeding and contrast-induced AKI during AVS in CKD patients, there is a need for alternative means of subtype classification in this group. Recently, the use of alternative means of PA diagnosis in non-CKD patients—peripheral hybrid steroid assessment and the use of novel radiopharmaceuticals—might permit less invasive subtype testing compared with AVS in patients with CKD. Measurement of peripheral 18-oxocortisol, a "hybrid steroid," has been used to differentiate unilateral adenoma from bilateral hyperaldosteronism and could reduce the need for AVS for subtype classification[18]; however, cutoff values would need to be defined and validated for CKD stages. Additionally, novel imaging agents might also help visualize the source of aldosterone excess and limit the use of AVS. High expression of CXC chemokine receptor type 4 (CXCR4) has been observed in aldosterone-producing tissue. The radiolabeled specific CXCR4 ligand 68Ga-pentixafor has been shown to differentiate APA from bilateral hyperaldosteronism using positron emission tomography imaging.[19] Additionally, radio-iodinated I-6-B-iodomethyl-19-norcholesterol (NP-59) single-photon emission CT has been used to lateralize the source of aldosterone excess in a CKD patient,[20] but this agent is not sensitive enough to detect most small tumors.

While the classic effect of aldosterone in binding to the MR and controlling sodium reabsorption and potassium secretion is well described, MR activation in nonclassic tissues, including the endothelium, smooth muscle cells, inflammatory cells, podocytes, and fibroblasts, may adversely affect renal structure and function.[21] In addition, PA increases sympathetic nerve activity, which raises blood pressure independent of renal sodium handling and declines to normal following surgical cure.[22] A recent meta-analysis revealed that MRA addition to renin-angiotensin system inhibition in trials of CKD subjects reduced protein/albumin excretion by nearly 40% but could not analyze cardiovascular or renal end points due to insufficient events.[23] Subsequently, finerenone, a selective MRA, was found to lower risk of CKD progression and cardiovascular events compared with placebo in CKD patients with type 2 diabetes.[24] Two large, ongoing

Table 2. Clinical, Biochemical, and Radiographic Features of Published Cases of PA Diagnosed in the Context of CKD.

Case	Reason for presentation	CKD stage	PAC (ng/dL)	PRA (ng/mL/h)	ARR	Adrenal lesion	AVS?	Management	Reference
1	HTN, hypokalemia	4	56	1.1	51	Yes (1.5 cm)	Yes	Surgery, Nl [K], ↓BP	Current case
2	HTN, hypokalemia	5 (dialysis)	146	14.2 (direct renin)	103	Yes (2.2 cm)	Yes	Surgery, Nl [K], and BP	Fava et al[25]
3	HTN, adrenal mass	5 (dialysis)	32	<0.1	∞	Yes (2 cm)	Yes	Surgery, ↓BP	Watanabe et al[26]
4	HTN, hypokalemia	N/A, creatinine 2.2 mg/dL	43	0.64	67	Thickening without mass	No, I-131 NP-59 SPECT/CT	Surgery, Nl [K], ↓BP	Chen et al[20]
5	HTN	5 (dialysis)	12	<0.2	∞	N/A	No	Spironolactone 50 mg daily, ↓BP	Kazory and Weiner[27]
6	HTN, hypokalemia	5	99	0.18	550	Yes (4.4 cm)	No	Spironolactone 100 mg daily, Nl [K] and BP	Na et al[28]
7	HTN, adrenal mass	5 (dialysis)	3200	1.2	2667	Yes (6 cm)	No	Surgery, Nl [K], ↓BP	Koshiyama et al[29]
8	HTN	4	37-47	1.9-2.3	20	Yes (3 cm)	No	Surgery, ↓BP	Nakada and Kimura[30]
9	HTN, hypokalemia	3B	125	0.14	1043	Yes (1 cm)	No	Spironolactone 50 mg daily, Nl [K], ↓BP	Hoorn et al[31]
10	HTN, hypokalemia	5	91	1.4	65	Yes (2.5 cm)	No	Spironolactone 75 mg daily, Nl [K]	Matsuda et al[32]
11	HTN	5	28.9	0.15	193.5	Yes (size not given)	No	Spironolactone, ↓BP	Hajji et al[33]

Abbreviations: ARR, aldosterone/renin ratio; AVS, adrenal venous sampling; BP, blood pressure; CKD, chronic kidney disease; CT, computed tomography; HTN, hypertension; K, potassium; N/A, not applicable; Nl, normalized; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; SPECT, single-photon emission CT.

international clinical trials of dialysis patients—ALdosterone antagonist Chronic HEModialysis Interventional Survival Trial (ALCHEMIST, NCT01848639) and Aldosterone bloCkade for Health Improvement EValuation in End-stage Renal Disease trial (ACHIEVE NCT03020303)—are clinical trials with major-outcome endpoints using spironolactone at a dose of up to 25 mg per day. These trials might underscore the importance of treating PA among advanced CKD patients if the safety and efficacy of empiric MR antagonism is demonstrated in this population.

In conclusion, we highlight a case of PA due to right APA diagnosed in the setting of hypertension and hypokalemia in a patient with advanced stage CKD. Subsequent adrenalectomy resulted in resolution of hypokalemia, marked improvement of his blood pressure control, and significant reduction of antihypertensive medications. We then present similar cases from the literature to show the reason for presentation, laboratory, imaging, AVS details, and the management response to medical versus surgical therapy. While PA is presumably underdiagnosed in CKD patients, to date, there are no epidemiologic studies assessing the prevalence of PA in the CKD population. As such, the optimal strategy for the diagnosis and management of such patients is not known. Although patients often receive screening and subtype testing similar to non-CKD patients, there are challenges in the interpretation of these tests. Ultimately, novel strategies such as peripheral hybrid steroid assessment and the use of novel radiopharmaceuticals, versus the empiric treatment of advanced CKD patients with MRAs, may be utilized, but additional studies are necessary.

Declaration of Conflicting Interests

The author declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: OH reports research collaboration with Mayo Clinic and advisory board participation with Corcept Therapeutics, Pfizer, Novo Nordisk, and Strongbridge Pharma outside the submitted work. RJA has contracted research support from Novartis Pharmaceuticals, Neurocrine Biosciences, Spruce Biosciences, and Corcept Therapeutics as well as consulting fees from Quest Diagnostics, Corcept Therapeutics, Janssen Pharmaceuticals, Novartis Pharmaceuticals, Strongbridge Biopharma, Crinetics Pharmaceuticals, Adrenas Therapeutics, PhaseBio Pharmaceuticals, OMass Therapeutics, and Recordati Rare Diseases. All other authors have stated explicitly that there are no conflicts of interest in connection with this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.

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