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Exceptional Case

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Masking by hypokalemia—primary aldosteronism with undetectable aldosterone

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ABSTRACT

Primary aldosteronism is the most common cause of secondary hypertension; however, the dynamic regulation of aldosterone by potassium is less well studied and current diagnostic recommendations are imprecise. We describe a young man who presented with resistant hypertension and severe hypokalemia. The workup initially revealed undetectable aldosterone despite acute potassium repletion. Chronic potassium supplementation eventually uncovered hyperaldosteronism. *In situ* genetic studies revealed a gain-of-function *KCNJ5* mutation within an aldosterone-producing adenoma that was clinically responsive to changes in extracellular potassium. We highlight a unique presentation of Conn's syndrome and discuss the implications for the molecular mechanisms of potassium regulation of aldosterone.

Keywords: aldosterone, hypertension, hypokalemia, potassium channel, somatic mutation

Primary aldosteronism is the most common cause of secondary hypertension. The physiological stimuli for aldosterone secretion through the renin–angiotensin–aldosterone system are well described. However, the dynamic regulation of aldosterone secretion by potassium balance is less well studied and guidelines for diagnostic tests are imprecise.

CASE REPORT

A 33-year-old Korean male presented to the Emergency Department with progressively worsening generalized weakness and undetectable serum potassium (<2 mmol/L). His past medical history was notable for resistant hypertension. He was prescribed four antihypertensive medications: lisinopril, hydrochlorothiazide, amlodipine and atenolol. Metabolic alkalosis was present with a serum carbon dioxide of 35 mmol/L. Serum electrolytes, thyroid function tests and cortisol were within normal limits. A spot urine potassium:creatinine ratio of 27.3 mEq/g was indicative of renal potassium wasting. After discontinuation of hydrochlorothiazide and aggressive repletion, serum potassium levels improved to 3.1 mmol/L the following morning, accompanied by a reported undetectable serum aldosterone (<4 ng/dL) and plasma renin activity (<0.6 ng/mL/h). By Day 2 he was discharged with a serum potassium of 4.0 mmol/L. On a

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regimen of lisinopril 20 mg, amlodipine 10 mg, atenolol 50 mg daily and potassium chloride 40 mEq thrice daily for 3 weeks, the patient's symptoms of weakness fully resolved and follow-up laboratory tests showed a serum potassium of 4.3 mmol/L, serum aldosterone 22 ng/dL and plasma renin activity <0.6 ng/mL/h. Renal Doppler ultrasonography was negative for renal artery abnormalities. Two hours after administration of 25 mg oral captopril, the serum aldosterone level was 20 ng/dL (positive test, aldosterone >12 ng/dL), confirming biochemical evidence for primary aldosteronism [1]. A computed tomography scan of the abdomen revealed a 1.5 cm × 1.1 cm left adrenal nodule. Adrenal vein sampling showed lateralization of aldosterone secretion to the left adrenal gland with contralateral suppression (Table 1). The patient underwent laparoscopic left adrenalectomy. Pathologic examination revealed a 1.5 cm benign adrenocortical adenoma with high expression of cytochrome P450 family 11 subfamily B member 2, aldosterone synthase(CYP11B2) compared with adjacent normal tissue. Sanger sequencing of the adenoma revealed a glycine-to-arginine substitution at residue 151 (c.451G>A, p.G151R) of the *KCNJ5* gene (Figure 1). Three months after adrenalectomy he was weaned off all antihypertensive medications and had average home blood pressures of ~115/85 mmHg.

Table 1. Adrenal venous sampling results on a post-cosyntropin stimulation protocol

Measurement	Left adrenal	Right adrenal	Inferior vena cava (below adrenals)
Cortisol (μg/dL)	400.0	516.0	17.0
Aldosterone (ng/dL)	5460.0	85.0	66.0
Cortisol-corrected aldosterone	13.7	0.2	3.9
Selectivity index	23.5	30.4	
Lateralization index	82.9		

DISCUSSION

The patient initially presented with undetectable serum aldosterone levels, suppressed in the setting of severe, and presumedly chronic, hypokalemia. Hypokalemia can inhibit aldosterone production; however, we are unaware of prior reports that have demonstrated a syndrome defined by hormone excess to initially present with hormone deficiency. Due to the severity of the hypokalemia, we were unable to repeat this measurement. We confirmed that his specimen yielded a chromatogram consistent with a low aldosterone level (3.5 ng/dL) rather than a systematic laboratory error. His initial low aldosterone level could not be attributed to heparinoid products or licorice, as he had not received these agents before or during the index admission. Only after chronic potassium repletion did he manifest a classic presentation of an aldosterone-producing adenoma (APA; Conn's syndrome). Endocrine Society guidelines state that patients should 'ideally' be potassium replete prior to screening for hyperaldosteronism [1]. However, the duration of normokalemia is not emphasized and the strength of this recommendation is not graded. Appropriate interpretation of screening studies is relevant given the increasing awareness of milder forms of hyperaldosteronism [3]. There are no currently validated formulas to mathematically adjust serum aldosterone levels to normative values in the setting of altered potassium balance. Thus further studies may be warranted to outline the optimal duration and level of serum potassium.

There may also be significant variation in mechanisms of potassium-stimulated aldosterone secretion. Sanger sequencing of the adenoma unexpectedly revealed a G151R mutation in the selectivity filter of the inward rectifying potassium channel Kir3.4, encoded by *KCNJ5*. This allows sodium entry, resulting in constitutive depolarization, aldosterone synthesis and cellular proliferation [4]. The rates of somatic *KCNJ5* mutations in APAs range from 34% in European to 70% in Asian cohorts [5]. This patient continued to demonstrate potassium-sensitive aldosterone production despite the loss of the selectivity filter. However, the underlying mechanism remains unclear. One

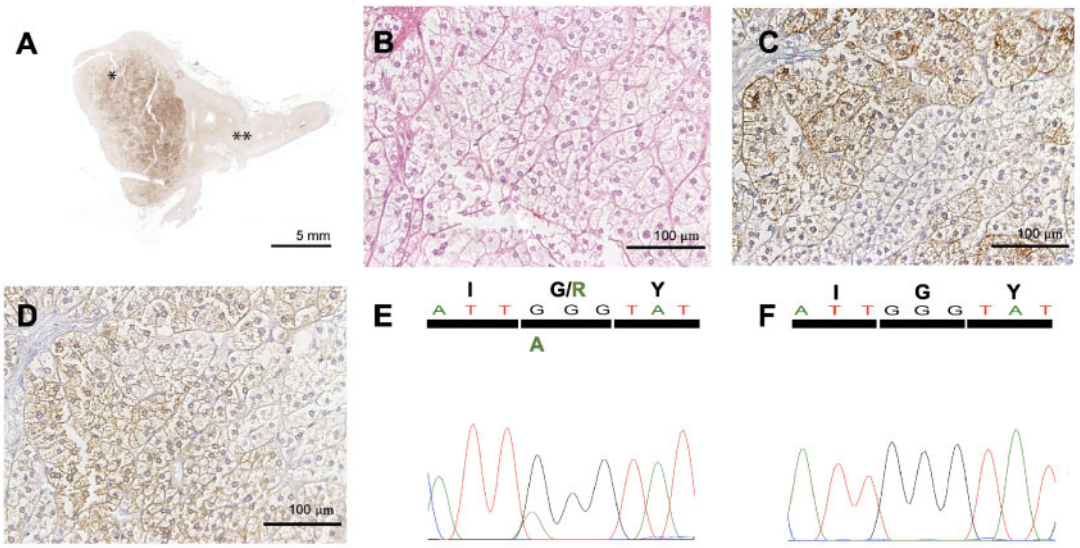

FIGURE 1: Adrenal adenoma histology and *in situ* sequencing. (**A**) Low-power magnification of CYP11B2 immunohistochemistry. Asterisks indicate location of high-resolution scans (*adenoma, **normal adrenal tissue). (**B**) Hematoxylin and eosin stain of adrenal adenoma (×20). (**C**) CYP11B2 immunohistochemistry of adrenal adenoma (×20). (**D**) CYP17A1 immunohistochemistry (×20). (**E**) Sanger sequencing of adenoma DNA indicating a c.451G>A, p.G151R *KCNJ5* mutation. (**F**) Chromatogram from Sanger sequencing of adjacent normal adrenal tissue with wild-type *KCNJ5*. Staining and sequencing performed as previously described in Nanba *et al.* [2].

possible explanation derives from the published observation that larger inward, nonselective sodium conductance (via mutant *KCNJ5*) can reduce cell survival [4]. The ensuing death of constitutively active APA cells may curtail aldosterone production until potassium repletion of sufficient duration to permit growth of mutant *KCNJ5*-expressing cells.

Our case demonstrates the critical need to interpret diagnostic studies for primary aldosteronism in the context of potassium balance and the complexity of genotype–phenotype correlations in Conn's syndrome.

PATIENT CONSENT

We obtained informed verbal consent from this patient for anonymized reporting.

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AUTHORS' CONTRIBUTIONS

R.B. and V.B. conceived the experiments. J.E.B. and V.C. performed the experiments. R.B., J.E.B., W.E.R. and V.B. analysed the data. R.B. and V.B. drafted the manuscript. W.E.R. and V.B. edited the manuscript. All authors approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Funder JW, Carey RM, Mantero F *et al*. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2016; 101: 1889–1916
2. Nanba K, Omata K, Tomlins SA *et al*. Double adrenocortical adenomas harboring independent KCNJ5 and PRKACA somatic mutations. *Eur J Endocrinol* 2016; 175: K1–K6
3. Brown JM, Siddiqui M, Calhoun DA *et al*. The unrecognized prevalence of primary aldosteronism. *Ann Intern Med* 2020; 173: 10–20
4. Scholl UI, Lifton RP. New insights into aldosterone-producing adenomas and hereditary aldosteronism: mutations in the K+ channel KCNJ5. *Curr Opin Nephrol Hypertens* 2013; 22: 141–147
5. Seccia TM, Caroccia B, Gomez-Sanchez EP *et al*. The biology of normal zona glomerulosa and aldosterone-producing adenoma: pathological implications. *Endocr Rev* 2018; 39: 1029–1056