Primary hyperaldosteronism with type V Bartter syndrome

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Abstract

Primary hyperaldosteronism (PHA) is one of the main causes of endocrine hypertension (HTN). Excessive aldosterone is associated with hypokalemia, metabolic alkalosis and predominantly nocturnal polyuria. Very few cases reported around the world are related to primary hyperaldosteronism without hypertension.

Type V Bartter syndrome is a rare autosomal dominant disorder characterized by increased calcium-sensitive receptor function, which causes metabolic alkalosis, hypokalemia, and elevated natriuresis with stable blood pressure levels.

We present the case of a 61-year-old woman with primary hyperaldosteronism and type V Bartter syndrome confirmed by biochemical, imaging and anatomy and pathology results. **(Acta Med Colomb 2024; 49. DOI: https://doi.org/10.36104/amc.2024.2957).**

Keywords: *hyperaldosteronism, hypokalemia, alkalosis, hypertension, polyuria, Bartter syndrome*.

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Introduction

Primary hyperaldosteronism (PHA) is defined as inappropriate aldosterone production in the context of a low plasma renin concentration (1). It was first described by the endocrinologist Jerome W. Conn in a young woman with a syndrome associated with seven years of muscle spasms, asthenia and paralysis; Conn found a relationship between hypertension (HTN), alkalosis and hypokalemia (2).

The prevalence of PHA has been increasing: in the 90s, it was suspected in 1-2%; however, using the aldosterone-renin ratio (ARR) as a screening test for hypertensive patients, the diagnosis has increased 5-14 times (3). Some prospective studies indicate a greater than 5% prevalence in hypertensive patients, and only 9 to 37% have hypokalemia (4). However, the presence of PHA associated with hypokalemia without HTN is rare, with only 38 cases reported to date (5). The importance of PHA lies in overstimulation of the cardiovascular system by aldosterone, which has been associated with hypokalemia, HTN, and myocardial hypertrophy and fibrosis, causing left ventricular dysfunction, with mineralocorticoid antagonist treatment being the mainstay of treatment (6).

For a diagnostic approach, PHA can be divided into two main groups: unilateral PHA, generally caused by an aldosterone-producing adenoma (APA), and bilateral PHA secondary to bilateral adrenal hyperplasia (BAH). This simplified classification leaves out rare cases like adrenocortical carcinoma, familial hyperaldosteronism, bilateral macronodular hyperplasia and unilateral hyperplasia (7).

On the other hand, type V Bartter syndrome occurs at a rate of approximately one case per 1,000,000 people. This syndrome is attributed to activation of the basolateral calcium-sensing receptor in the ascending limb of the loop of Henle, characterized by a clinical picture including hyperrenin-hyperaldosteronism, hypercalciuria, hypokalemia, hypocalcemia, hypomagnesemia and metabolic alkalosis (8, 9). At the time of this writing, no case reports of primary hyperaldosteronism with type V Bartter syndrome had been found.

Below, we present the case of a patient with primary hyperaldosteronism and Bartter syndrome who was cured after undergoing laparoscopic adrenalectomy and taking potassium-sparing diuretics.

Case report

We present the case of a 61-year-old woman from the rural area of the department of Caldas, Colombia. She had no significant medical history. She consulted in the emergency room with a complaint of 15 days of asthenia, up to 15 episodes of nocturnal polyuria, and gradually increasing fatigue.

On admission, her vital signs were within normal range, and she had no relevant physical exam findings. Laboratory tests were drawn and are summarized in Tables 1-3, showing evidence of hypokalemia and metabolic alkalosis.

In view of 15% hypokalemia, intravenous replacement was ordered, noting an average variability between daytime and nighttime urinary output on follow-up of 0.8 mL/kg/hr and 2.4 mL/kg/hr, respectively. Regarding the finding of

metabolic alkalosis (Table 2) with increased kaliuresis, 24-hour urine chloride was ordered, with a report of 276 mEq/L (more than 40 meq/L), which was elevated.

The diagnosis of the clinical picture of hypokalemia with sodium chloride-resistant metabolic alkalosis was approached considering Bartter syndrome, Gitelman syndrome and primary hyperaldosteronism as the first options, despite normal blood pressure figures. Likewise, treatment was begun with spironolactone, titrating the dose up to 400 mg per day.

Elevated plasma aldosterone and normal renin levels were found, and abdominal imaging with contrast was ordered, detecting a nodule suggestive of an adrenal adenoma (Figure 1). However, it was striking that the blood pressure remained stable, with elevated calciuria.

She underwent surgery with a subsequent pathology report indicating an adrenocortical adenoma (Figures 2 and 3). Follow-up showed normalization of the plasma potassium levels, with an average of 4 mEq/L and cortisol levels of 13 mcg/dL, along with stable blood pressure, and the urinary output variability resolved.

Discussion

When faced with a patient with hypokalemia, the possible pathophysiological mechanisms should be sought. These could be secondary to low intake, redistribution phenomena and sweat, gastrointestinal or renal losses (10). In this case, redistribution phenomena and urinary losses were plausible, the first due to metabolic alkalosis and the second due to excessive mineralocorticoids and primary tubulopathies (10).

In metabolic alkalosis, for every 0.1 unit increase in plasma pH there is an expected 0.6 mEq/L reduction in potassium (11); therefore, for a pH of 7.5, potassium was expected to have decreased to 3 mEq/L, which was higher than what was found in the patient. There was an elevated 24-hour potassium excretion of 132 mEq/L (greater than 30 mEq/L). Since her blood pressure was within normal range, the probable etiological causes were diuretics (loop, thiazide), Bartter syndrome and Gitelman syndrome (11).

The finding of high plasma aldosterone levels with normal renin led to the analysis of other differential diagnoses such as glucocorticoid-remediable aldosteronism (11), and aldosteronism secondary to a chimeric aldosterone synthase/11β-hydroxylase gene, in which both aldosterone and cortisol are produced in the fascicular zone of the adrenal cortex. However, this consideration should only be applied if the patient is under 20 years old and has had a cerebrovascular accident (CVA) before the age of 40 or has family history of hyperaldosteronism (4, 12), which was not the case here.

To confirm the diagnosis in cases of spontaneous hypokalemia with hyperaldosteronism, plasma renin activity (PRA) should be measured (usually > 20 ng/dL), or a factor of 8.21 applied when plasma renin concentration is measured. Our patient had a PRA of 1.19 ng/mL/hr with a serum aldosterone of 557 ng/dL, obtaining an aldosterone/renin activity ratio (ARR) > 100, specifically an ARR of 468.

Due to the persistent hypokalemia, a confirmatory PHA test with a saline solution, captopril or fludrocortisone infusion was not performed (4). Regarding the aldosterone

Table 1. *Blood biochemistry tests.*

	Admission	Follow up	Postoperative
K mEq/L	2.0	2.8	4.0
24-hour urine K mEq/L	132		
Na mEq/L	144		
24-hour urine Na mEq/L	339		
24-hour urine Cl mEq/L RV 110-250	276		
Mg mEq/L	2.1		
24-hour urine Mg (mg in 24 hours) RV 50-150			68.7
Ionized Ca mmol/L	1.16		
24-hour urine Ca (mg/24 hours) RV 60-200			342
BUN mg/dL	14	22	
Cr mg/dL	1.08	1,3	
Cortisol mcg/dL RV 5-25	15.9		13.1
ACTH pg/mL. RV 0-60			8.4
Aldosterone ng/dL RV 2.94 – 16.15		557	
Plasma renin concentration. RV 8-35 mU/L		9.8	
Serum phosphorus mg/dL	3.3	3.1	
Urine adrenaline mcg/24 hr. RV 0-20	6.9		
Urine noradrenaline mcg/24 hr. RV 0-90	20.1		
TSH mU/L	1.59		
FT4 ng/dL	1.12		
NT pro-BNP pg/mL VR <125			126

K: potassium; Na: sodium; Cl: chloride; Mg: magnesium; Ca: calcium; BUN: blood urea nitrogen; Cr: creatinine.

Table 2. *Arterial gases*

Arterial gases					
pH	PCO_2	PO_2	FiO_2	PaO_2/FiO_2	HCO_3
7521	45.2	60	0.21	285	37

Table 3. *Urinalysis*

Urine test											
Color	Asp	pH	Dens	Leu cel/uL	Prot	Glu	Bil	Ket	Uro	Nit	Sed
Amber	Cloudy	5	1,015	30	Neg	Neg	Neg	Neg	Neg	Neg	Bac ++

Asp: aspect; Dens: density; Leu: leukocytes; Prot: protein; Glu: glucose; Bil: bilirubin; Uro: urobilinogen; Nit: Nitrites; Sed: sediment; Bac: bacteria.

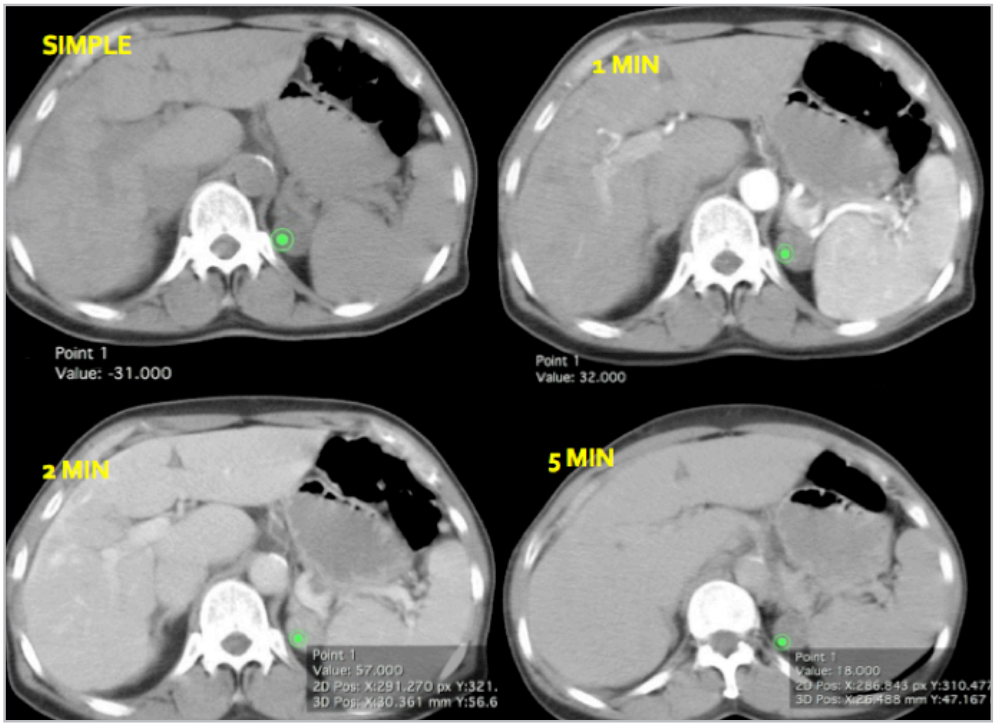

Figure 1. *An abdominal CT with contrast. An adrenal adenoma with rapid contrast clearance in less than five minutes.*

sample from the adrenal vein, recent studies such as the one by the SPARTACUS group (13), have shown that this type of measurement is not necessary, since it only increases costs and does not provide a better diagnostic approach compared to tomography studies, and therefore it was not considered. Instead, an abdominal computed tomography with contrast was performed which showed a 22 x 25 adrenal mass compatible with an adrenocortical adenoma, according to the histopathological study. Following surgical resection, the polyuria resolved and potassium levels normalized. A test at a tertiary care center showed hypercalciuria characteristic of type V Bartter syndrome (14).

This clinical case is interesting not only due to the convergence of clinical signs that led to the diagnosis of primary hyperaldosteronism along with type V Bartter syndrome, but also due to the unique aspect of presenting as non-hypertensive hyperaldosteronism. The persistent hypokalemia, along with the detection of an adrenal mass on computed tomography and the confirmation of hypercalcuria, constituted the diagnostic mainstays. In addition, the fact that the patient did not have hypertension presented a less common clinical scenario, which forced us to closely consider rarer causes of the disease. This atypical presentation resonates with the current medical literature in which only 38 cases of non-hypertensive and hypokalemic hyperaldosteronism have been reported to date, predominantly in women. However, while the HyperPATH nested cohort study reported a greater prevalence of non-hypertensive hyperaldosteronism, the mean serum potassium in these cases was greater than 3.5 mEq/L, which is different from our case (15).

The proposed pathophysiological hypotheses for normotensive and hypokalemic hyperaldosteronism include low estrogen levels and severe hypokalemia or hypokalemia secondary to natriuretic peptides (ANP). The first hypothesis is ruled out since many of the cases occur at postmenopausal ages. The second hypothesis is rejected since hypokalemia occurs after hyperaldosteronism and usually progresses over a long period of time (5). The natriuretic peptide theory seems interesting; this would explain why the patient had such a high natriuresis, mainly with normal saline infusion. Kawabe et al. observed that patients with aldosteronism who received saline solution infusions had a statistically significant increase in natriuresis and ANP levels (16).

In our case, the blood pressure figures continued to be within the normal range despite stopping the saline solution and having normal ANP levels. Therefore, 24-hour urine calcium was measured, which showed hypercalciuria. Consequently, type V Bartter syndrome plus primary hyperaldosteronism was diagnosed; this explained the natriuresis, stable blood pressure, hypokalemia, metabolic alkalosis and hypercalciuria. While it is possible to have hypercalciuria with primary hyperaldosteronism, it is secondary to hyperparathyroidism, which produces hypercalcemia, with both conditions leading to increased blood pressure (14).

This is the first reported clinical case illustrating the coexistence of primary hyperaldosteronism and type V Bartter syndrome. The uniqueness of the diagnosis lies in the confluence of two clinical conditions which rarely occur together, posing significant diagnostic and therapeutic challenges. The identification of this case broadens the borders of

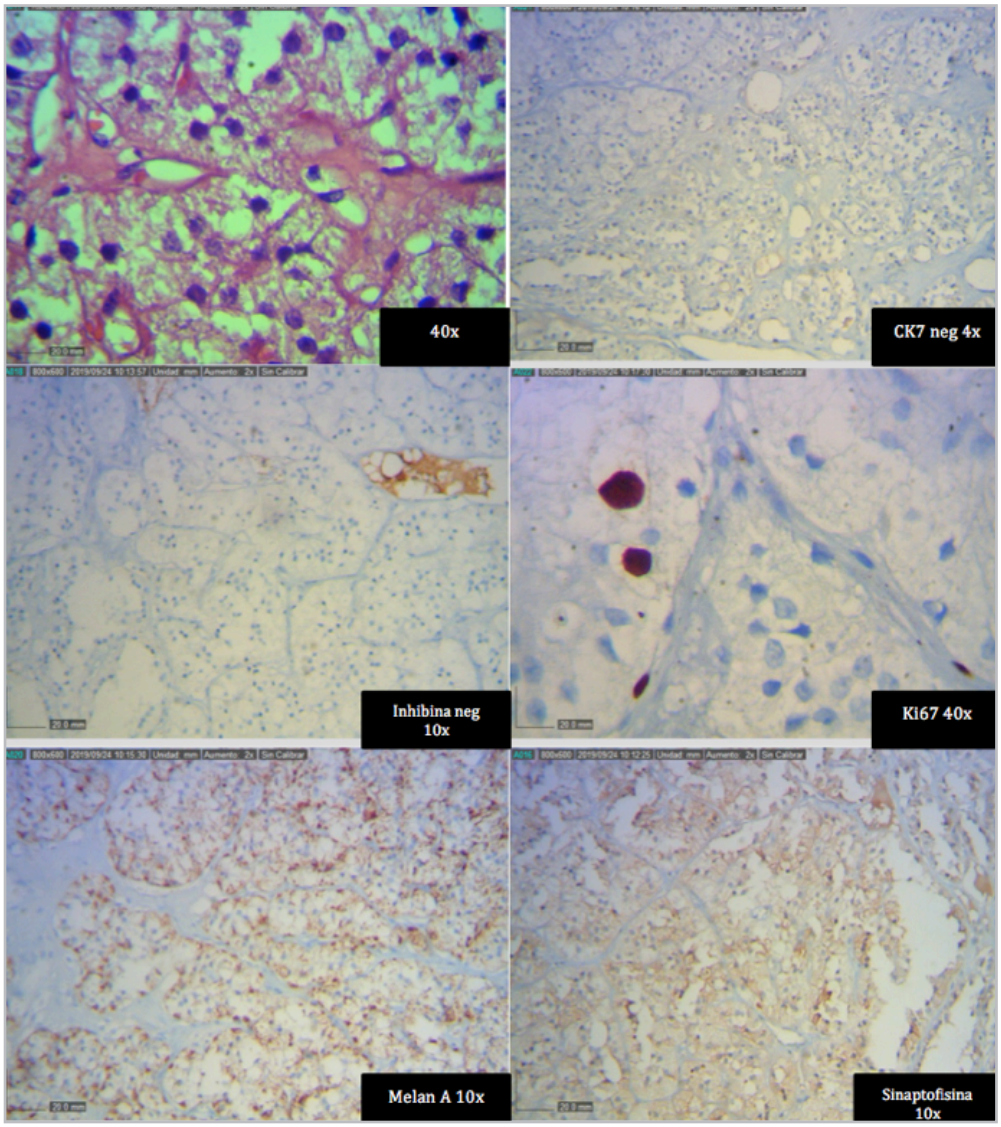

Figure 2. *Adrenal adenoma histology; the first image shows Giemsa-stained cytology with no abnormalities, and negative inhibin, Melan A, synaptophysin, k1G6 and CK7 staining, ruling out a neuroendocrine origin and adenocarcinoma.*

our clinical knowledge and highlights the need to consider atypical potential diagnoses when faced with hypokalemia with sodium chloride-resistant metabolic alkalosis.

The limitations of this case include, in particular, the lack of specific confirmatory tests for primary hyperaldosteronism, due to the patient's clinical condition. Another limitation was the unavailability of genetic studies, mainly an analysis of potential gain-of-function mutations of the extracellular calcium-sensing receptor (CASR) gene reported in type V Bartter syndrome (17).

Conclusion

In summary, this case presents an unusual convergence of primary hyperaldosteronism and type V Bartter syndrome. Despite diagnostic limitations, including the lack of specific confirmatory tests and genetic analyses, the clinical findings and response to treatment provided a significant understanding of the patient's condition. This case highlights the importance of a meticulous clinical assessment and diagnostic adaptability when faced with atypical presentations, emphasizing the prevailing need for more research to improve our understanding and management of these rare clinical conditions.

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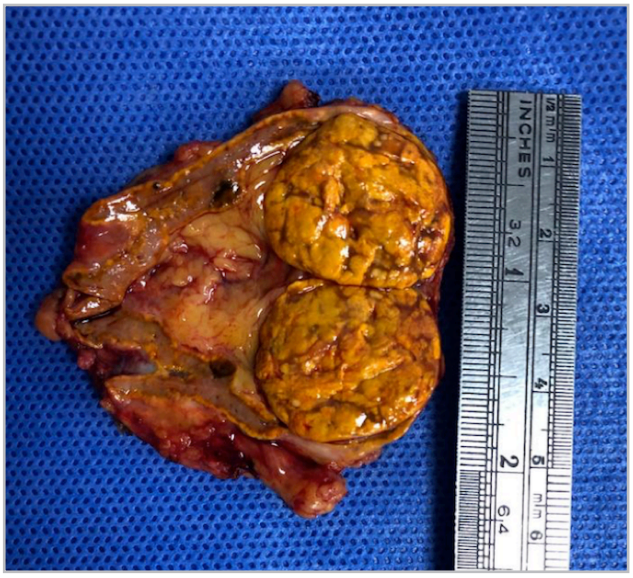

Figure 3. *Macroscopic adrenal adenoma findings.*

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