CASE REPORT

# Persistent severe hyperkalemia following surgical treatment of aldosterone-producing adenoma

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Primary aldosteronism is one of the most common causes of secondary hypertension. This condition is characterized by autonomous hypersecretion of aldosterone which produces sodium retention and potassium excretion, resulting in high blood pressure and potential hypokalemia. Transient postoperative hyporeninemic hypoaldosteronism with an increased risk of hyperkalemia may occur in some patients. We report the case of a 63-year-old patient with persistent hypokalemia, periodic paralysis, and refractory hypertension who was diagnosed with primary hyperaldosteronism due to elevated aldosterone, undetectable plasmatic renin concentration, and the presence of a left adrenal mass. One month after the surgery, the patient was admitted with signs of severe hyperkalemia (8 mmol/L) and worsened renal function, thus requiring hemodialysis. Fluid resuscitation, loop diuretic, and sodium bicarbonate treatment decreased his potassium. Zona glomerulosa insufficiency was confirmed by hormonal tests which exposed low aldosterone–renin axis. The fludrocortisone treatment was initiated and maintained, with consequent potassium and creatinine stabilization. Old age, long duration of hypertension, impaired renal function, severe hypokalemia before surgery, and large size of the aldosterone-producing adenoma are important risk factors for serious potassium imbalance after removal of the adenoma. We have to consider monitoring the patients after surgery for primary hyperaldosteronism in order to prevent severe hyperkalemia; therefore, postoperative immediate follow-up (arterial pressure, potassium, and renal function) is mandatory.

**Key words:** Aldosterone-producing adenoma, hyperkalemia, postoperative hyporeninemic hypoaldosteronism

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## INTRODUCTION

Primary aldosteronism (PA) is characterized by autonomous hypersecretion of aldosterone and is one of the common causes of secondary hypertension. About 5%–13% of all hypertensive patients and up to 20% of patients, with refractory hypertension, are affected by PA.[1] It is characterized by increased sodium retention and potassium excretion, resulting in high blood pressure (BP) and potential hypokalemia.[2] The negative impact of high aldosterone levels on the circulatory system, as well as deleterious renal and metabolic effects through BP-dependent and independent mechanisms, is well described.[3] The main causes of PA are bilateral idiopathic adrenal hyperplasia and aldosterone-producing adenoma (APA). The treatment of choice for these two pathologies is lifetime administration of mineralocorticoid receptor (MR) antagonists in idiopathic adrenal hyperplasia and unilateral adrenalectomy in APA, respectively; remission of hypertension is seen in 33%–72% of patients after adrenalectomy. A potential consequence of aldosterone excess is chronic suppression of renal renin release and decreased aldosterone secretion from the contralateral remaining adrenal gland after unilateral adrenalectomy. This situation may lead to a state of transient postoperative hyporeninemic hypoaldosteronism and to an increased risk of hyperkalemia in some patients.[2] We report the case of

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a patient with severe persistent hyperkalemia following APA surgical treatment.

## CASE REPORT

A 63-year-old male patient was examined for persistent hypokalemia with periodic paralysis due to low potassium associated with refractory hypertension that began developing 14 years before; B*P* values ranged from 150 to 210/80–100 mmHg and required four antihypertensive medications such as irbesartan 150 mg/day, calcium channel blocker amlodipine 10 mg/day, beta-blocker bisoprolol 5 mg/day, and spironolactone 50 mg/day. When he was admitted to our endocrinology department, he already had Electrocardiogram (EKG) abnormalities such as prolonged QT (751 ms), bradycardia, presence of U-wave, and QRS modifications suggestive for ventricular hypertrophy. Renal function showed abnormal urea: 76 mg/dl and creatinine: 2.79 mg/dl with a decreased estimated glomerular filtration rate (eGFR = 24.5 ml/min/1.73 $m^2$). The serum levels of aldosterone and renin without interruption of antihypertensive drugs and spironolactone (due to severe uncontrolled hypertension and hypokalemia in its absence) confirmed the clinical supposition of hyperaldosteronism: aldosterone: 261 ng/dL and Plasmatic renin concentration <0.5 mIU/L, K (mmol/L) with an aldosterone-to-renin ratio of 522 ng/dL (normal range <20). A suppressed renin under treatment with a mineralocorticoid blocker (spironolactone) and angiotensin receptor blockers (irbesartan) is highly suggestive for primary hyperaldosteronism. Abdominal computed tomography scan [Figure 1], performed with proper contrast nephropathy prophylaxis, revealed normal right adrenal gland and a left adrenal mass about 30/33/32 mm with washout and Hounsfield units suggestive for adenoma. The adrenal vein sampling with cosyntropin was not performed due to technical reasons, and further surgical removal was considered. Before surgery, the patient underwent oral potassium supplementation up to 2 g/day, and the treatment with spironolactone was stopped 3 days before. Left adrenalectomy was performed, and the histological examination confirmed the diagnosis of adrenal cortical adenoma [Figure 2].

After the left laparoscopic adrenal intervention, serum potassium and BP values were normalized, without KCl supplementation or spironolactone administration. The patient was discharged 5 days following admission with the recommendation of BP self-monitoring at home. One month later, the patient's condition worsened and urgent hospitalization was required. Serum potassium was 8 mmol/L, with a lower eGFR than at the previous admission: 17 ml/min/1.73 $m^2$; renin values were still low at 2 uUI/L. Due to life-threatening refractory hyperpotassemia, the patient required hemodialysis. After fluid resuscitation and sodium bicarbonate treatment, potassium levels were corrected to 6 mmol/L and loop diuretic furosemide 20 mg/day proved further necessary to decrease serum potassium; however, serum creatinine remained high. The evolution of laboratory results is shown in Table 1.

Hormonal test confirmed zona glomerulosa (ZG) insufficiency with aldosterone–renin axis hypofunction (aldosterone: 1.83 ng/dl and direct renin concentration: 1.2 ng/dl), and fludrocortisone treatment 0.1 mg/day was initiated. At follow-up, biological tests revealed improved renal function and most important serum potassium up to normal values. After 1 month of fludrocortisone, a dose reduction was attempted, but at 0.05 mg/day, his potassium instantly increased to 5.4 mmol/L with following deterioration of renal function. Elevated potassium persisted, despite proper hydration, also mentioning that the patient was not under medication that could cause hyperkalemia. To manage this situation, fludrocortisone dose was again raised to 0.1 mg/day with consequent potassium normalization and serum creatinine improvement. After another month, fludrocortisone reduction was again undertaken, but clear

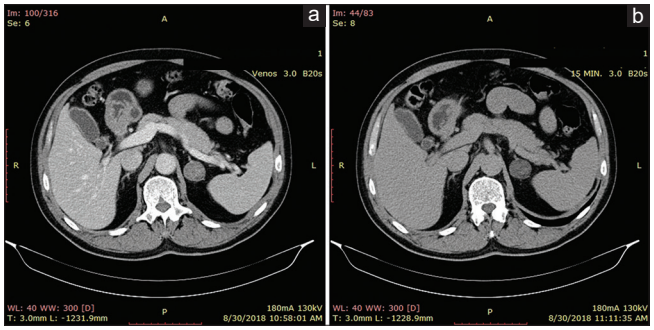


**Figure 1:** Abdominal computed tomography scan that reveals left adrenal mass. (a) Image of adrenal mass after administering the contrast. (b) Image after 15 min of contrast washout; to observe similitude among native and 15 min images

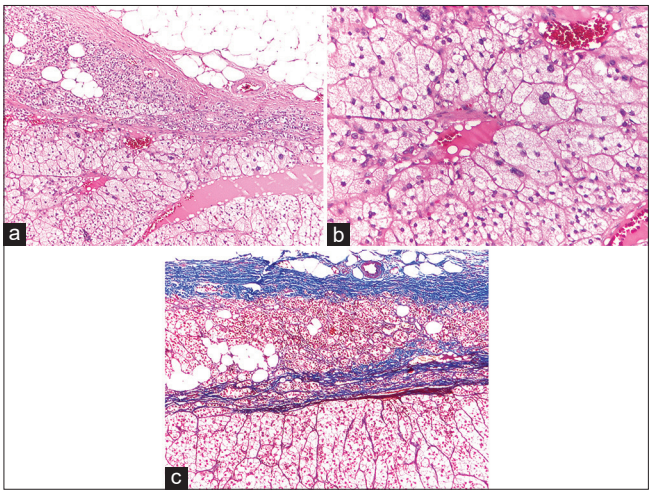


**Figure 2:** (a) Histological diagnosis of cortical adrenal adenoma. (a) Zona glomerulosa incorporated in adenoma – H and E, ×4. (b) Trabecular architecture of cortical adenoma – H and E, ×10. (c) Adenoma capsule – Masson ×4

biological signs of mineralocorticoid insufficiency were observed: mild hyponatremia 134 mmol/L, hyperkalemia 5.8 mmol/L, and elevated serum creatinine [Table 2]. Fludrocortisone treatment 0.1 mg × 2/day was, therefore, reinserted, and oral sodium bicarbonate was added for a better control of the patient's hyperkalemia and metabolic acidosis.

Seven months after surgery, the patient is still on fludrocortisone treatment, now having stable BP values up to maximum 140/90 mmHg and also stable renal function: eGFR 34 ml/min/1.73 $m^2$.

## DISCUSSION

Hyperkalemia following surgery of an APA is a well-known entity with unclear incidence and prevalence due to rather low number of case reports and case series recorded in the literature.

Our case report highlights the particular complications of the postsurgical evolution of an APA such as severe persistent hyperkalemia and renal function deterioration. Our patient meets all the risk factors for postadrenalectomy hyperkalemia such as old age, long duration of hypertension, impaired renal function, and severe hypokalemia before surgery. The unusual size of APA (3 cm) is another risk factor contributing to the postoperative severe hyperkalemia in our case.[4]

Similar to Tahir *et al*. case series, our patient required permanent fludrocortisone substitution: the successive failures in minimizing the doze proved mineralocorticoid treatment to be the only efficient preserver of normal serum potassium. The struggle to titrate fludrocortisone therapy is similar to one of the reported cases, pointing up the severe complication of long-lasting hyperaldosteronism.[5]

The postoperative evolution of our patient can be explained by the classical mechanism of low renin/low aldosterone encountered after surgery for primary hyperaldosteronism. ZG in the adrenal cortex is mainly regulated by the renin–angiotensin system, but adrenocorticotropin hormone (ACTH) and potassium also stimulate its secretion. Aldosterone induces urinary potassium excretion through its action on the principal cells of the collecting renal tubule. Unilateral aldosterone excess produces the suppression of contralateral ZG by inhibiting serum renin production.[1]

The renin–angiotensin–aldosterone system usually recovers rapidly after unilateral adrenalectomy for APA, without any mineralocorticoid replacement, due to ACTH that maintains

**Table 1: Evolution of laboratory tests after left adrenalectomy and changes in serum potassium, creatinine, and blood pressure with needed treatment**

| mmol/L | Creatinine (mg/dl) | eGFR (ml/min/1.73 $m^2$) | BP | Treatment |
|---|---|---|---|---|
| 8 | 3.8 | 17 | - | Hydration: Sodium chloride 0.9%<br>GS 5% - 4 IU insulin<br>Hemodialysis |
| 6 | 3.36 | 19.7 | 140/80 | Sodium bicarbonate, hydration (GS 5% + 4 IU insulin) |
| 5.51 | 3.34 | 19.9 | 140/90 | Fludrocortisone (0.1 mg/day) |
| 5.34 | 2.93 | 23.1 | 140/80 | None |
| 5.9 | 3.11 | 21.6 | 140/70 | Fludrocortisone (0.1 mg/day)<br>Sodium bicarbonate |
| 5 | 3.07 | 20.4 | 140/80 | Fludrocortisone (0.1 mg/day) |
| 4.7 | 2.77 | 24.7 | 170/90 | Fludrocortisone (0.1 mg/day)<br>Furosemide (20 mg) |
| 4.3 | 2.87 | 23.7 | 140/90 | Fludrocortisone (0.1 mg/day) |

eGFR=Estimated glomerular filtration rate; GS=Glucose solution; BP=Blood pressure

**Table 2: Follow-up biological results and required treatment**

| Follow-up | Dose | K (mmol/L) | Creatinine (mg/dl) | BP |
|---|---|---|---|---|
| 7 days | Fludrocortisone (0.1 mg/day) | 4.4 | 2.79 | 140/80 |
| 2 weeks | Fludrocortisone (0.1 mg/day) | 5 | 3.04 | - |
| 3 weeks* | Fludrocortisone (0.05 mg/day) | 5.4 | 3.19 | 140/80 |
| 4 weeks | Fludrocortisone (0.1 mg/day) | 5 | - | - |
| 2 months* | Fludrocortisone (0.05 mg/day) | 5.8 | 3.03 | 140/90 |
| | Fludrocortisone (0.2 mg/day) | 4.8 | - | - |
| 3 months | Fludrocortisone (0.2 mg/day) | 4. 4 | - | 130/80 |
| 4 months* | Fludrocortisone (0.1 mg/day | 5.92 | - | 140/90 |
| | Fludrocortisone (0.2 mg/day) | 4.76 | - | 130/80 |
| 6 months | Fludrocortisone (0.2 mg/day) | 4.4 | - | 130/80 |

*Intention to reduce the dose. BP=Blood pressure

some degree of ZG activity in the contralateral adrenal gland. In case of an APA, surrounding ZG tissue is generally not atrophic and can even be hyperplasic; however, severe hyperkalemia after surgical treatment of aldosterone excess can occur. In these cases, immunohistochemical analyses show completely suppressed mineralocorticoid production both in the adjacent adrenal tissue and in the contralateral adrenal gland. The other two adrenal regions are fully functioning, thus explaining that only ZG is affected in these particular cases and the hypothalamic–pituitary–adrenal axis is not impaired.[1]

The mechanism of the delayed recovery of the aldosterone–renin system after surgical removal of APA is multifactorial. Hypotheses involve the hyporeninemic state due to the renal impairment by the aldosterone excess, the long duration of severe hypertension that irreversibly harms the renal target tissues, and also hypoaldosteronism due to delayed recovery of the ZG cell function.[1,6] In our case, all three mechanisms are potentially involved in the pathogenesis of persistent postsurgical hyperkalemia: long duration of hypertension (14 years), presurgery severe hyperaldosteronism, and also the possible nephron impairment masked by the relative renal hyperfiltration until the adenoma removal. As such, the low renin levels may have two possible causes: hyperaldosteronism but also renal deterioration before APA.

There are some risk factors for developing hypoaldosteronism after the APA surgery. It was observed that patients over 50 years old had more chances in developing postsurgical hyperkalemia than younger patients.[7] It is reported that patients with a duration of hypertension above 9.5 years have a 10-fold higher risk of developing postsurgical hypoaldosteronism with consequent hyperkalemia compared to those with hypertension duration under 9.5 years.[8] Studies demonstrate that patients with chronic kidney disease Stages III–IV were 30% more likely to develop postoperative hyperkalemia after APA excision.[9] Aldosterone excess itself may lead to renal hyperfiltration, thus masking nephron impairment until the adrenal surgery, which reverses the effects of aldosterone.

Urinary albumin excretion is greater in aldosterone adenomas than in essential hypertensive patients; therefore, adrenalectomy is followed by decreased urinary albumin excretion and GFR improvement.[5] These data suggest that aldosterone excess is associated with a relative hyperfiltration, overturned after blockade of MRs or APA removal.[1] Low potassium may itself impair the kidney, favoring cyst formation, tubular vacuolization, or interstitial inflammation until failure of renal function.[1,10]

Spironolactone is the treatment of choice in many cases of aldosterone excess in order to control hypokalemia. Long-term treatment with spironolactone may influence the epigenetic modulation of CYP11B2; long-term therapy may lead to the formation of body cell inclusions, thus worsening the postsurgical hypoaldosteronism.[11] On the other hand, spironolactone metabolites have a very long half-life and may also contribute to the postoperative hyperkalemia. Nevertheless, general opinions regarding the preoperative renin disinhibition with spironolactone and the immediate presurgery (3–7 days or more) stop of spironolactone are contradictory.[1] In general, preoperative treatment with MR antagonists did not influence the incidence of hypoaldosteronism and hyperkalemia. More so, it is not yet confirmed whether the presurgical use of spironolactone is involved in hyperkalemia progression after adrenal surgery.[5,8]

Postsurgical hyperkalemia studies from German Conn's registry revealed that 14 patients out of 18 developed hyperkalemia with undetectable aldosterone values. ZG insufficiency was defined as aldosterone <97 pmol/L in the presence of increased potassium >5 mmol/L.[1] It is plausible that aldosterone synthesis of adjacent and contralateral adrenal glands is severely impaired in some cases of primary aldosterone excess, in a manner similar to Cushing's syndrome, where glucocorticoid synthesis is impaired due to ACTH suppression.[12]

For the correct management of these particular situations of severe hyperkalemia after APA surgery, the measurement of postoperative serum potassium in order to detect and properly treat the life-threatening hyperkalemia is mandatory. Severe hyperkalemia is a state of emergency requiring prompt treatment, as in the case of our patient who needed hemodialysis. It is necessary to exclude medication as nonsteroidal anti-inflammatory drugs and renin–angiotensin–aldosterone system inhibitors or other causes that may increase potassium such as hypovolemia or urinary tract obstruction. The treatment of hyperkalemia includes increased renal potassium excretion and/or potassium binders. When postsurgical hypoaldosteronism is confirmed, fludrocortisone is the treatment of choice; however, one should consider the possible associated risks such as hypertension, edema, and heart failure deterioration. In case of hypervolemia or fludrocortisone overdose, loop diuretics to increase renal potassium excretion or sodium bicarbonate administration should be considered. Therefore, an alternative solution to replacing mineralocorticoid is to increase distal nephron flow and sodium delivery through increased sodium intake (ideally with NaHCO3), increased water intake, and/or loop diuretics.[13]

In these particular cases of hypoaldosteronism following the surgical treatment of aldosterone-producing adenomas, we have to consider monitoring our patients to prevent the

occurrence of serious potassium imbalance, such as severe hyperkalemia. Therefore, the screening patient's risk factors are recommended: older age, hypertension evolution, presurgical impaired renal function, size of the adenoma, and higher presurgical aldosterone. Postoperative close follow-up (arterial pressure, potassium, and renal function) is mandatory, and aggressive treatment to prevent further cardiovascular and renal complications may be necessary.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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