Hyperkalemic Renal Tubular Acidosis as Manifestation of Primary Adrenal Insufficiency: A Case Report and Review of the Pathophysiology

Mutiara Rizki Haryati[1,2,3*], Satriyo Dwi Suryantoro[1,2], Mochammad Thaha[1,2] Sonny Hadi Wijaya[2],

[1]*Nephrology Division, Department of Internal Medicine, Dr Soetomo General Academic Hospital, Surabaya, Indonesia*
[2]*Department of Internal Medicine, Universitas Airlangga Hospital, Surabaya, Indonesia*
[3]*Subspecialist Trainee Programme of Kidney and Hypertension Consultant, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, Indonesia*
*Corresponding author: drmutiara.rh@gmail.com

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ABSTRACT:
Hyperkalemic renal tubular acidosis (RTA), or type 4 RTA in adults, typically is an acquired condition characterized by non-anion gap metabolic acidosis that mostly suggests a dysfunction in the secretion of potassium, ammonium, and hydrogen ions of kidney tubules. It should be considered in hyperkalemic patients with moderately decreased glomerular filtration rate (GFR). This condition can be caused by hypoaldosteronism or impaired function of the cortical collecting duct. We present a case of a 45-year-old male who came to the emergency department with a chief complaint of nausea. A hyponatremia, hyperkalemia with normal anion gap metabolic acidosis, and mildly reduced glomerular filtration rate (GFR) were shown in his laboratory findings, suggesting a condition of hyperkalemic renal tubular acidosis caused by adrenal insufficiency. These findings have been confirmed by low serum cortisol, elevated adrenocorticotropic hormone (ACTH), low aldosterone levels, and an imaging result of adrenal mass. After receiving steroid replacement therapy, the patient steadily improved.

Introduction

Hyperkalemic renal tubular acidosis (RTA), or type 4 RTA in adults, is typically an acquired condition characterized by non-anion gap metabolic acidosis that mostly suggests a dysfunction in the secretion of potassium, ammonium, and hydrogen ions from kidney tubules. Clinical practice typically links it to true or functional hypoaldosteronism resulting from diseases or pharmacological toxicity, which leads to hyperkalemia [(1)].

Hypoaldosteronism should be thought about in anyone who has persistent hyperkalemia that doesn't seem to have a clear cause, like kidney failure, potassium supplementation, or taking diuretics that lower potassium levels [(2)]. The elevation of plasma potassium in this condition indicates the significant role of aldosterone in urinary potassium excretion. In addition to hyperkalemia, type 4 RTA, a mild metabolic acidosis with a normal anion gap, is typically associated with hypoaldosteronism [(3)].

It's hard to say how common or how often type 4 RTA happens because most of the time, it's not found until the patient has too much potassium in their diet, which is often caused by medical care. A new study found that type 4 RTA is common in people with severe hyperkalemia, which is often linked to diabetic nephropathy or tubulointerstitial nephritis. This type of RTA should always be thought about in people with severe hyperkalemia who only have a moderately decreased glomerular filtration rate (GFR) [(4)].

Low levels of aldosterone can happen when the body makes less of it or when it doesn't get enough of the signal it needs to release aldosterone. Primary adrenal insufficiency is a rare condition that can lead to hypoaldosteronism and has a low incidence rate. Its diagnosis is often difficult due to the nonspecific nature of the symptoms exhibited by patients. The prevalence of primary adrenal insufficiency ranges from 4.17 to 6.2 per million globally [5-7]. It is marked by decreased gland function, which leads to lower production of aldosterone and cortisol. It can cause general symptoms such as low blood pressure, changes in mental state, loss of appetite, vomiting, or an imbalance of electrolytes.

Cortisol and aldosterone replacement therapy are useful treatments for primary adrenal insufficiency that aim to stabilize hormone levels and alleviate symptoms (8). Well-treated patients can reduce the incidence of hospitalization due to electrolyte imbalance, especially the life-threatening hyperkalemia.

Case report

In 2023, the emergency department admitted a 45-year-old male who complained of nausea and vomiting. The patient complained of frequent nausea and vomiting accompanied by feelings of weakness in the lower extremities. He had frequent hospitalizations due to hyperkalemia for the last 3 years, which was often said to be due to kidney problems and eating too much fruit. He denied having hypertension, diabetes mellitus, a history of kidney stones, or taking any medicine or supplements regularly. His urine output was 2000 cc/24 hours on average. His blood pressure was 100/80 mmHg, with normal temperature and respiratory rate. An electrocardiographic examination was performed, which resulted in a sinus rhythm with a heart rate of 94 beats per minute with a tall T wave. A chest X-ray revealed no lung or heart abnormalities, and the ultrasound examination revealed normal kidneys. His high plasma potassium level (7.0 mmol/L) and increased plasma creatinine level (1.73 mg/dl) prompted a referral to a nephrologist. As shown in Table 1, electrolytes and hematologic tests showed low sodium levels, high potassium levels, a lower estimated GFR (stage IIIa), and normal anion gap metabolic acidosis. The lab tests also showed that the hemoglobin level (15.1 g/dL), white blood cell density (6.33 x 10^3/mm^3), and platelet density (393,000/mm^3) were all normal. The HbA1C level (5.0%) and random blood glucose level (109 mg/dL) were also normal, as were liver function tests. His urinalysis showed pH 5.0, specific gravity 1.020, nitrite, leukocytes, erythrocytes, ketones, glucose, and protein+1. These findings were suggesting the patient had type 4 renal tubular acidosis.

The patient was asked to abstain from foods high in potassium and was given a series of lowering potassium therapies with furosemide, calcium gluconate, and dextrose with insulin. Despite interventions with a combination of potassium shifting and elimination, his lowest potassium level was 5.5 mmol/L at best.

More tests showed that he had low levels of plasma cortisol, high levels of adrenocorticotropic hormone (ACTH), and low levels of aldosterone (**Table 1**). This suggested that he had primary adrenal insufficiency. We later prescribed oral hydrocortisone, 10 mg in the morning and 5 mg in the early afternoon. The next step involved performing an abdominal computed tomography (CT), which revealed an enhancing solid mass size of +/- 1.42 x 1.83 x 1.04 cm in the left adrenal gland. After

glucocorticoid replacement, the electrolyte imbalances and his symptoms had improved greatly.

Table 1. Laboratory result

Biochemical test, units	**Laboratory Reference range**	**Results**
Sodium, mmol/L	135–147	125
Potassium, mmol/L	3.5–5	7.0
Chloride, mmol/L	98–108	100
Creatinine, mg/dl	0.60–1.10	1.73
eGFR, mL/min	> 60	49
Bicarbonate, mmol/L	22–26	12.7
Aldosterone, ng/dL	2.52–39.2	1.74
ACTH, nmol/L	9–52	127.2
Cortisol, µg/dL	3.7–19.4	< 1.0
Anion gap, mmol/L	8–16	12.3

ACTH, adrenocorticotropic hormone; eGFR, estimated glomerular filtration rate.

Discussion

Hyperkalemia is a potentially fatal condition characterized by serum potassium levels exceeding 5.5 mmol/l. It could happen because the kidneys aren't getting rid of enough potassium, the body is taking in too much potassium, or potassium is leaving cells [(9)].

Urine eliminates most potassium, but perspiration and digestive tract secretions also excrete some of it. In the kidney, the management of potassium within the nephron relies on both passive and active processes. The glomerulus freely filters potassium, with most of it reabsorbed in the proximal tubule (60-75%) and the loop of Henle (15-20%). The cortical collecting duct is where most of the excretion takes place because of activity in the epithelial sodium channel (ENaC), which takes sodium back from the tubular fluid. Consequently, potassium leaks out of the tubule cells to preserve electroneutrality. Elevated sodium delivery to the distal nephron enhances sodium reabsorption and exacerbates potassium loss. Most of the potassium that is secreted in the distal nephron is helped by ROMK channels, which are found on the outside of the kidney.

An imbalance in potassium intake compared to excretion or a maldistribution of potassium between intra- and extracellular space can lead to hyperkalemia. People with chronic kidney disease (CKD) are more likely to have high potassium levels. The kidneys can make up for lost nephrons by improving the removal of different substances by a single nephron. This is especially important for controlling potassium levels. When kidney function drops to a very low level (GFR or creatinine clearance ≤ 15 mL/min), hyperkalemia only happens. It doesn't happen very often when compensation is still good. Occasionally, tubular adaptation is compromised, resulting in hyperkalemia manifesting earlier in the progression of CKD.

Studies have shown that this kind of hyperkalemia is common in people with mild to moderate chronic kidney disease (stages 2-4). Multiple pathophysiological mechanisms implicate RTA 4 as one important condition [(4, 11)]. Our patient's history of recurrent hyperkalemia necessitated frequent visits to the emergency department, leading to his discharge shortly after his potassium levels stabilized. Renal impairment and high-potassium diets had always been considered the culprits. He agreed to further investigate

the disease only after consulting with a nephrologist, and we found that his problem is not only about eating too many fruits.

The effective renal potassium excretion depends on aldosterone and adequate distal delivery of water and sodium within the nephron. When renal failure presents, hypoperfusion (e.g., volume depletion, congestive heart failure) or hypoaldosteronism impairs one of these mechanisms, possibly resulting in hyperkalemia. Patients without advanced renal failure or hypoperfusion may have hyperkalemia due to hypoaldosteronism [(2)].

Conditions characterized by normal anion gap metabolic acidosis caused by renal tubular dysfunction in the presence of relatively normal glomerular filtration rate are seen in this patient known as renal tubular acidosis (RTA), as the result of tubular defects in acid excretion of bicarbonate ion reabsorption that prevent the kidneys from maintaining normal acid-base homeostasis.

Four subtypes of RTA have been discovered: i) Type 1 or distal RTA (dRTA), results from inadequate acidification of the urine by the distal tubule. It is primarily a disorder of alpha-intercalated cells of the distal convoluted tubule and the cortical collecting duct. Typically present with hypokalemia; ii) Type 2, or proximal RTA (pRTA), is caused by inadequate reclamation of filtered bicarbonate by the proximal tubule and often presents with hypokalemia; iii) Type 3, or combined proximal and distal RTA (cRTA), is due to dysfunction of carbonic anhydrases; iv) Type 4 RTA, also known as hyperkalemic renal tubular acidosis, is a particular type of RTA marked by hyperkalemia due to hypoaldosteronism or a cortical collecting duct abnormality [(12)].

Some of the things that can cause type 4 RTA are conditions that lower the amount of aldosterone in the blood or conditions that make the cortical collecting duct (CCD) work less well. A defect in distal H^+ secretion arises in both scenarios.

Aldosterone has several effects on the renal acid-base balance. Aldosterone works on the distal convoluted tubule/collecting duct principal cells by activating luminal sodium channels. This increases the reabsorption of Na^+ ions and the flow of H^+ and K^+ ions into the tubules and urine (**Figure 1**) [(13)]. It is also known that aldosterone directly stimulates intercalated cells, which makes them release more H^+ [(14)]. Patients with hyperkalemic RTA have a primary defect in aldosterone production or aldosterone receptor sensitivity. In Type 4 RTA, hyperkalemia is not proportional to the reduction in GFR due to concomitant dysfunction of potassium and acid secretion.

If the main cell can't reabsorb Na^+ as well as it should, it can lower the CCD's luminal electronegativity. This can stop H^+ from entering the tubular lumen, which stops distal acidification. Lowered luminal electronegativity in CCD also makes it harder for the kidneys to get rid of K^+, which leads to hyperkalemia. The decrease in ammonia that serves as a urine buffer due to hyperkalemia exacerbates the distal acidification defect [(3)].

Several studies show that hyperkalemia, which affects the metabolism of ammonia, is the main way that metabolic acidosis happens in type 4 RTA [(8)]. In order to neutralize acid, the kidneys generate and eliminate ammonia. In a healthy kidney response to metabolic acidosis, more ammonia (NH_3) is made to neutralize acid (H^+) and make ammonium (NH_4^+). This is an essential process for neutralizing acid, and without this buffering, the

elimination of the daily acid load would lead to a urine pH level below 3. The kidneys normally get rid of 30 to 40 meq of ammonium every day, but when there is metabolic acidosis, they can increase this amount to 200 to 300 meq every day to help them get rid of more acid. The breakdown of glutamine within the proximal tubule generates ammonia. The process of recycling ammonia raises the amount of ammonia in the medullary interstitial spaces, which makes it easier for it to move into the tubular lumen. Released protons in this compartment maintain ammonia as NH_4^+. The main problem in type 4 RTA is the impairment of ammoniagenesis [3]. Because potassium moves into cells and proton moves out of cells, intracellular alkalosis happens in the renal tubules. This lowers the production of ammonia. The proximal renal tubular cells respond by decreasing ammonia production. The ability to acidify the urine, e.g., to release protons, is unimpaired. Because H^+ATPase pumps normally get rid of acids and urine has less buffer, the process of urine becoming more acidic in response to acidosis is not changed. This means that urine has a pH of less than 5.5.

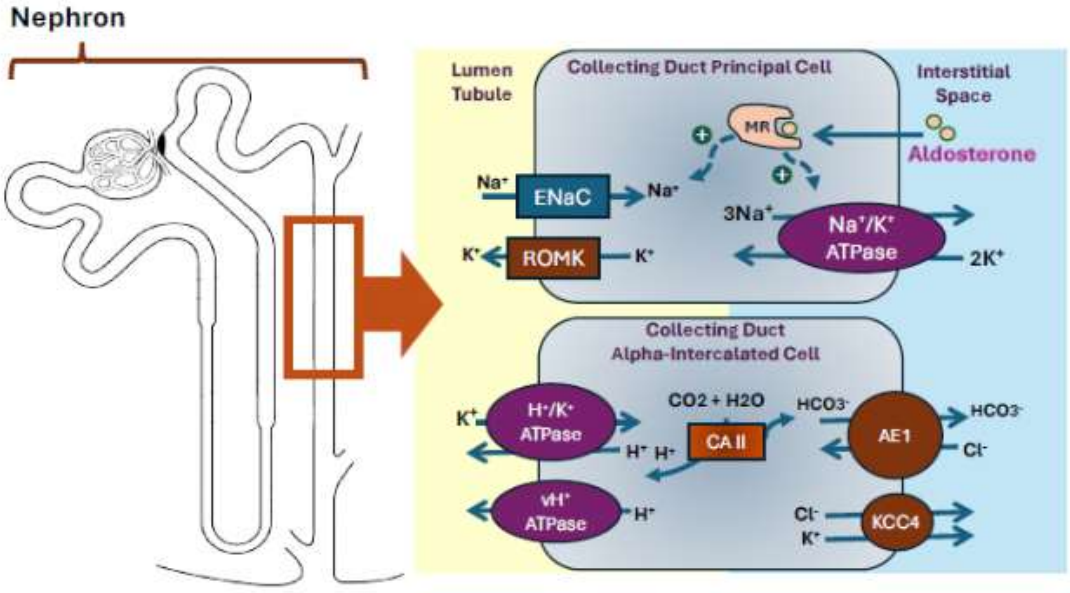

Figure 1. The effect of aldosterone is observed in the distal renal tubules. Aldosterone lowers the amount of Na^+ inside cells by making the main cell's basolateral Na^+/K^+-ATPase work better. This lets Na^+ enter through the apical channel. By increasing the number of Na^+ channels in the principal cell, aldosterone also affects the transepithelial voltage. It raises the amount of H^+-ATPase in the cortical collecting duct (CCD) by moving H^+-ATPase from the vacuole to the apical membrane. This is another direct effect of aldosterone on the intercalated cell. These genes are called AE1 (anion exchanger 1), CA II (carbonic anhydrase II), ENaC (epithelial sodium channel), KCC4 (K+Cl-cotransporter-4), MR (minerolocorticoid receptor) and ROMK (renal outer medullary small-conductance K).

Different types of RTA type 4 can be broken down into those that are caused by cortical collecting duct defects or those that are linked to hypoaldosteronism. If the pH of your urine is less than 5.5, it means that there is a problem with aldosterone activity and the availability of NH_3. This problem is worse than H^+ secretion problems. On the other hand, when structural damage to the cortical collecting duct causes the primary defect, the urine pH becomes more alkaline [8]. Selective aldosterone deficiency can be confirmed after

other causes of hyperkalemia are ruled out, including transcellular shifts in K^+ or the use of KCl, K^+-sparing diuretics, or renin-angiotensin-aldosterone-system (RAAS) inhibitors. After correction for serum K^+, persistently low aldosterone levels suggest aldosterone deficiency. Urinary K^+ excretion below 40 mmol/L or fractional K^+ excretion below 20% is a sign of a problem with renal K^+ secretion in people with hyperkalemia. We found that our patient had RTA 4 and that hypoaldosteronism was the cause. This was after ruling out many other conditions that could have caused hyperkalemia (**Figure 2**).

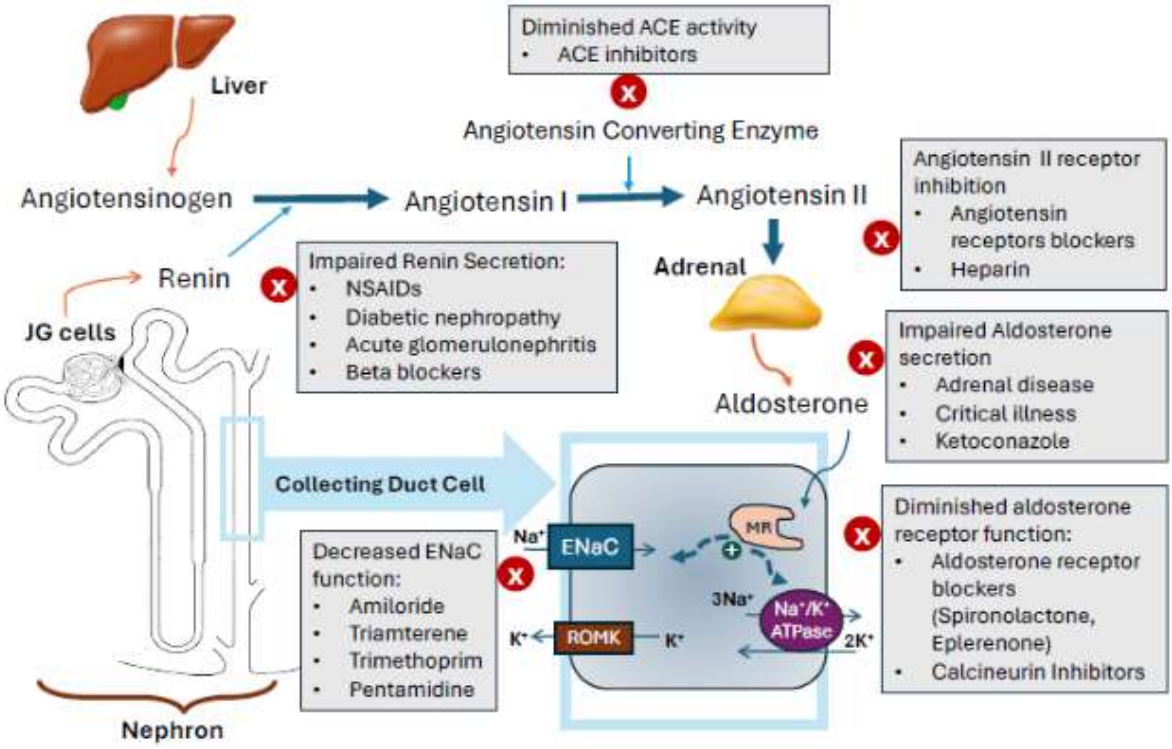

Figure 2. Many conditions can lead to hyperkalemia by interfering with the renal angiotensin-aldosterone system (RAAS). ACE, angiotensin-converting enzyme; ENaC, epithelial sodium channel; JG cells, juxtaglomerular cells; K^+, kalium/potassium; MR, mineralocorticoid receptor; Na^+, natrium/sodium; NSAIDs, non-steroidal anti-inflammatory drugs; ROMK, renal outer medullary small conductance kalium

Hypoaldosteronism, as a causative factor of hyperkalemic RTA, may be either hereditary or acquired. Low aldosterone production is passed down through genes, as seen in congenital isolated hypoaldosteronism or pseudohypoaldosteronism type 2 (Gordon syndrome). This may also result from aldosterone resistance, as observed in type 1 pseudohypoaldosteronism [(12)]. Hyporeninism can lead to acquired hypoaldosteronism. This is common in people with mild to moderate chronic kidney disease caused by diabetic nephropathy or chronic interstitial nephritis. Different things can cause hypoaldosteronism in people whose renin levels are normal. These include damage to the adrenal glands, infectious adrenalitis (like tuberculosis or human immunodeficiency viruses), autoimmune adrenalitis, Addison's disease, critical illness, RAAS inhibitor therapy, or heparin-induced suppression of aldosterone synthesis [(8,12)]. Upon investigating the etiology of his diminished aldosterone level, we identified primary adrenal insufficiency as the underlying cause of our patient's problems.

Primary adrenal insufficiency happens when there is a problem with the adrenal gland itself. It is marked by lower production of aldosterone and cortisol and higher production

of ACTH. Primary adrenal insufficiency frequently manifests with electrolyte imbalances, with hyponatremia and hyperkalemia being the most observed conditions, and they were found in our patient. Increased release of antidiuretic hormone (ADH) mediates hyponatremia, leading to water retention and a decrease in plasma sodium concentration [15]. Both cortisol and aldosterone deficiency contribute to this problem.

Cortisol deficiency may cause hypotension and decreases in cardiac output, which may contribute to the hypersecretion of ADH. Deficit in glucocorticoids also lowers renal free water clearance. Animal models have linked glucocorticoid deficiency to increased distal tubular water permeability and decreased urinary diluting capacity. Glucocorticoid deficiency causes the vasopressin-sensitive water channel aquaporin 2 (AQP2) in the collecting duct to express and become phosphorylated more frequently at the molecular level [16, 17]. Lack of aldosterone also leads to too much ADH being released, which is caused by the kidneys losing salt and water. In hypovolemia, ADH levels go up because the osmotic threshold to release ADH from the hypothalamus goes down, and the amount of ADH goes up in response to changes in plasma osmolality [18].

Bilateral adrenal destruction due to tuberculosis earlier was the predominant cause of adrenal insufficiency [19]. Tuberculosis now represents only 7–20% of cases, while autoimmune diseases account for 70–90%, except in countries where tuberculosis remains endemic [20]. The remaining cases are attributed to other infectious diseases, metastatic neoplastic diseases, pharmaceuticals, or various other causes.

Most patients with primary adrenal insufficiency need to have their glucocorticoid and mineralocorticoid levels replenished. **Table 2** shows some widely known steroids with their glucocorticoid and mineralocorticoid potencies [21]. In most cases, oral prednisone or hydrocortisone is used as glucocorticoid replacement. You can administer hydrocortisone in two or three daily doses, whereas you only need to take one dose of prednisone. Fludrocortisone is given once a day in the morning instead of mineralocorticoids to mimic changes in the body's aldosterone production throughout the day. It is given in a dose that keeps plasma renin levels within the upper limit of the normal range.

Table 2. The glucocorticoid and mineralocorticoid potencies of some widely used synthetic steroids

	Glucocorticoid	**Mineralocorticoid**
Hydrocortisone	1	1
Prednisone	4	0.8
Methylprednisolone	5	0.5
Dexamethasone	30	Negligible
Betamethasone	30	Negligible
Fludrocortisone	10	125

The administration of loop diuretics aids in managing hyperkalemia by enhancing sodium supply to the collecting duct. Instruction on the avoidance of potassium-rich foods is indeed a component of the treatment plan, along with the exclusion of drugs that may induce hyperkalemia. The dosage of alkaline treatment for metabolic acidosis resulting from renal tubular acidosis often approximates 30 mEq/day, given that this patient exhibits only moderate acidity. An alternative method that has proven effective is the utilization of potassium binders, such as patiromer or sodium zirconium cyclosilicate, for the management of refractory hyperkalemia [4, 22].

Conclusion

We have presented a case of a 45-year-old male who came to the emergency department with a chief complaint of nausea. His laboratory findings of hyponatremia, hyperkalemia with normal anion gap metabolic acidosis and mildly reduced GFR are suggestive of hyperkalemic RTA. This condition for our patient was caused by primary adrenal insufficiency, confirmed by low serum cortisol, elevated ACTH, low aldosterone level and an imaging of adrenal mass. It is often difficult to diagnose primary adrenal insufficiency due to the nonspecific nature of the symptoms exhibited by the patients, which results from decreased production of cortisol and aldosterone. Hypoaldosteronism must be considered in any patient presenting persistent hyperkalemia without an apparent etiology, such as renal failure, potassium supplementation, or administration of potassium-sparing diuretics. In mild to moderate CKD (stages 2-4), hyperkalemia is prevalent in clinical practice. Although multiple pathophysiological mechanisms could play parts, type 4 RTA is an important diagnosis that should be kept in mind, since it suggests a tubular defect affecting the secretion of potassium and acid, which may occur at any GFR and is frequently linked to a reduction in the action of aldosterone in the distal renal tubules. After receiving replacement steroid therapy, the patient's complaints have decreased, and his electrolyte levels were stabilized within normal ranges, preventing him from frequent hospitalization due to hyperkalemia.

Disclosure

The authors report no conflicts of interest in this work.

Ethics and Consents

Informed consent was obtained from the patient to publish the case for educational purposes.

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