Hypokalemia Related to Distal Renal Tubular Acidosis as an Initial Presentation of Primary Sjogren's Syndrome

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ABSTRACT

Hypokalemia due to loss of potassium through the kidneys can be caused by distal Renal Tubular Acidosis (dRTA). The etiology of dRTA can be primary due to genetic defects or secondary to autoimmune diseases, especially Sjogren's syndrome (SS). The occurrence of dRTA in SS patients is low, at only 5% of cases. This case was interesting because dRTA was the initial clinical manifestation that led to the diagnosis of SS in the patient. A 48-year-old woman came with complaints of recurrent weakness. The patient was routinely hospitalized with severe hypokalemia and received potassium supplementation. The diagnosis of dRTA was based on repeated weakness, normal blood pressure, severe and recurrent hypokalemia, high urinary potassium, alkaline urine, low plasma bicarbonate, and normal anion gap metabolic acidosis. The diagnosis of SS in this patient was confirmed based on dry eyes, dry mouth, positive Schirmer's test, and positive autoantibodies to SS-A and Ro-52. There was a delay in the diagnosis of SS for two years in this patient because the complaints were initially subtle and non-specific. The hypokalemia in this patient was secondary to dRTA associated with primary SS. The possibility of an underlying autoimmune disorder should be considered in a patient presenting with recurrent severe hypokalemia. dRTA, as the etiology of hypokalemia, can be a gateway to the diagnosis of SS. In this patient, complaints related to dRTA appeared before the onset of sicca symptoms, and the diagnosis of SS was established.

Keywords: *Distal Renal Tubular Acidosis, Hypokalemia, Sjogren's Syndrome.*

INTRODUCTION

Distal renal tubular acidosis (dRTA) is a condition in which the kidneys cannot process urine acidification in the presence of systemic acidosis. The primary disturbance of dRTA lies in a defect in the basolateral $HCO3^-/Cl^-$ exchanger or H^+ ATPase subunit. The main features of dRTA are alkaline urine (pH >5.5) and hypokalemia (<3 mmol/L).[1] The etiology of dRTA is observed to be primary if a genetic defect is found, and secondary if it is caused by an autoimmune disease, drug, or other disorder. Secondary dRTA usually occurs in adults, the most common cause being an autoimmune disease, such as Sjogren's syndrome (SS).[2] If not appropriately treated, dRTA can develop into chronic kidney disease. Renal involvement in SS has been observed to be approximately

10%; notably, dRTA was found in 5% of patients with SS.[1,3] SS is a relatively rare autoimmune disease resulting from chronic inflammation of the exocrine glands, the salivary and lacrimal glands, with general symptoms of dry eyes and mouth.[4] Kidney disorders in SS can manifest into tubulointerstitial inflammation, such as dRTA, Fanconi syndrome, nephrogenic diabetes insipidus, hypokalemia, and glomerulopathy.[5] Here, we reported patients with dRTA who, after being investigated, were also accompanied by SS. This case was notable because dRTA was the initial clinical manifestation leading to the diagnosis of SS in the patient.

CASE ILLUSTRATION

A 48-year-old woman visited the internal medicine clinic of West Nusa Tenggara General Hospital on January 12, 2022, with the chief complaint of weakness throughout the body. The patient was treated with oral potassium supplementation at the District Hospital for incidental detection of hypokalemia of unknown etiology for the last two years. The patient was referred from East Lombok District Hospital for further investigation. Initially, in January 2020, the patient complained of weakness after strenuous exercise accompanied by cramping from the thigh to the leg. Subsequently, the patient felt weakness in both legs, so the patient could only lie down. The patient was treated for the first time at the East Lombok District Hospital for two days. The complaints improved after being administered an infusion and the patient was subsequently allowed to go home. The patient occasionally complained of dizziness and lightheadedness when their body felt weak. In July 2021, the patient complained of epigastric pain and a decreased appetite. The patient did not receive regular oral potassium supplementation because of dyspepsia syndrome. In addition, the patient complained of frequent urination, either day or night. Even at night, the patient reported passing urine of 3–4 times. The patient presumed that it was because she consumed a lot of water.

The patient denied other complaints, such as a history of palpitations, excessive sweating, hearing loss, intolerance to heat, weight loss, tremor, fever, vomiting, coughing, shortness of breath, or fainting. Complaints of hair loss, joint pain and swelling, bone pain, rash, and bruising on the skin, and mouth ulcers were also ruled out by the patient. The patient had no history of hypertension, diabetes mellitus, asthma, heart disease, autoimmune disease, kidney disease, and liver disease. The patient had no drug allergies. None of the patient's families had the same illness. The patient denied a family history of hypertension, diabetes mellitus, asthma, heart disease, kidney disease, or liver disease. The patient was a teacher who was married with two children.

On physical examination, the following were observed: blood pressure of 110/70 mmHg, pulse rate of 86 bpm, respiration rate of 18 breaths/minute, temperature of 36.5 °C, body weight of 52 kg, height of 150 cm, and body mass index of 23.2 kg/m^2. Examination of the head, neck, chest, and abdomen revealed normal findings. Examination of the extremities revealed that both lower extremities were warm, there was no visible edema, and there was decreased muscle strength (4/5) in both legs; however, there was no other significant neurological deficit.

Laboratory investigation revealed a white blood cell counts of 7570 /µL, hemoglobin value of 13.1 g/dL, thrombocyte count of 212000 / µL, urea level of 25 mg/dL, creatinine level of 1.0 mg/dL, estimated glomerular filtration rate value of 66.6 ml/minute/1.73 m^2, glucose level of 107 mg/dL, aspartate aminotransferase value of 61 U/l, alanine aminotransferase value of 47 U/l, albumin value of 3.3 mg/dL, sodium value of 138 mmol/L, potassium value of 1.9 mmol/L, and chloride value of 111 mmol/L. The thyroid function test showed a TSH value of 2.42 uIU/mL and free T4 value of 15.12 Pmol/L. Urinalysis revealed a specific gravity of 1.020, a urine pH of 7.0, negative proteinuria, and urine sediment within normal limits. Blood gas analysis showed a pH of 7.32, pCO_2 of 22.0 mmHg, pO_2 of 119 mmHg, base excess of -12.2 mmol/L, HCO_3 value of 11.8 mmol/L, and SO_2 value of 97%. Chest radiography revealed no abnormal findings. Electrocardiographic examination showed a sinus rhythm of 86 beats/minute and a normal axis. Abdominal ultrasonography showed

no nephrolithiasis, nephrocalcinosis, or other abnormalities.

The patient was diagnosed with severe hypokalemia due to dRTA and dyspepsia. The patient's 24-h urine collection was subsequently sent for potassium examination. In addition to potassium correction, lansoprazole was administered intravenously. After being treated in the hospital for two days, the patient was discharged with a final electrolyte level of 141 mmol/L of sodium, 3.1 mmol/L of potassium, and 118 mmol/L of chloride. The patient was administered oral potassium, KSR 600 mg twice daily and lansoprazole 30 mg twice daily. Oral sodium bicarbonate was not available when the patient was discharged from the hospital.

The patient was observed to feel better at the first outpatient visit after hospitalization on January 17, 2022. An electrolyte examination revealed a sodium level of 137 mmol/L, potassium level of 3.8 mmol/L, and chloride level of 120 mmol/L. Examination of 24-h urine potassium showed an increase of 48 mmol/24 hours, fasting glucose of 83 mg/dL, and glycated hemoglobin level of 5.1 percent. Oral sodium bicarbonate (500 mg three times daily) was administered. On further questioning at the second visit on January 29, 2022, the patient complained of dry eyes and mouth for several months. This may have caused the patient to feel thirst, drink, and urinate frequently. The patient denied any inflammation of the eye or use of artificial tears. Because SS was suspected, an antinuclear antibody (ANA) profile test and consultation with the ophthalmology department were performed.

At the third visit on January 31, 2022, the patient showed a positive ANA profile test for autoantibodies against SS-A, Ro-52, and AMA-M2. The serological tests for rheumatoid factor, hepatitis B, and hepatitis C were negative. The ophthalmologist's consultation confirmed sicca symptoms using an objective test (Schirmer's test, 0 mm/5 minutes in each eye). The patient was administered artificial eye drops six times daily. The patient was unwilling to undergo salivary gland biopsy, and salivary gland scintigraphy was unavailable. A diagnosis of SS was established, and the patient was started on methylprednisolone 8 mg twice daily.

On follow-up after 6 months, the patient has had no significant complaints and has never been hospitalized again. The last therapy was KSR 600 mg twice daily, lansoprazole 30 mg once daily, sodium bicarbonate 500 mg three times daily, and methylprednisolone 8 mg once daily.

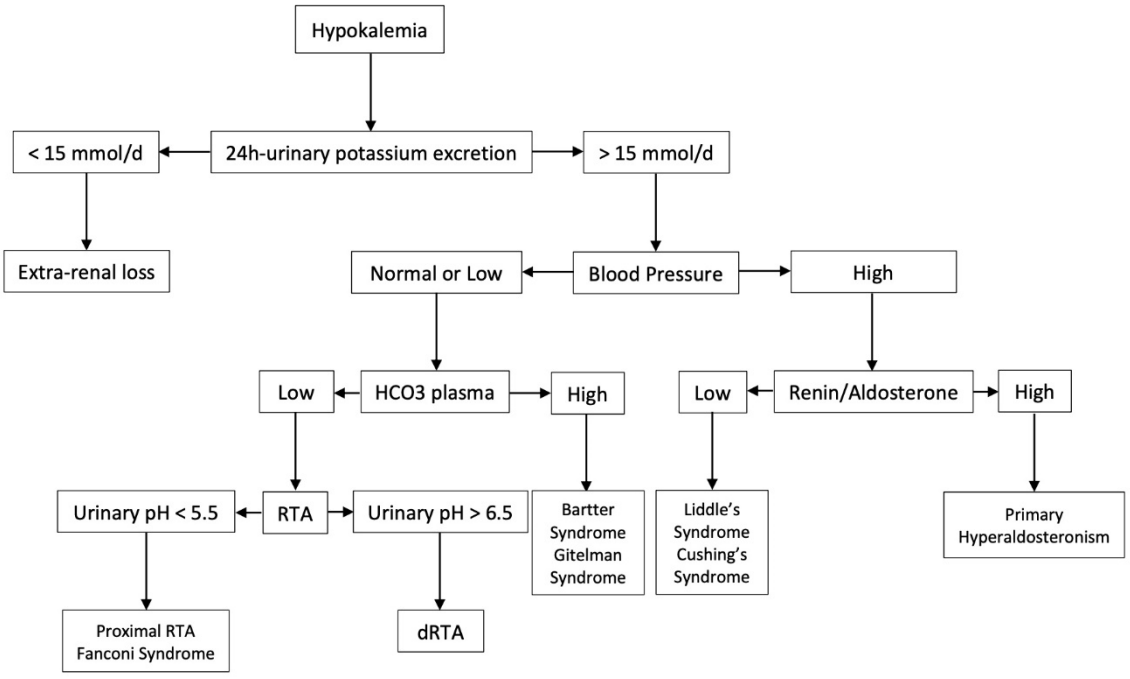

Figure 1. Simplified approach to diagnose patients with hypokalemia (Adapted from [2] and [6]).

Subsequently, the patient requested to be referred back to the East Lombok District Hospital because the hospital was closer to her family so that she could adhere more to the treatment.

The authors obtained all appropriate consent forms from the patients to publish this case report.

DISCUSSION

In general, the causes of hypokalemia are divided into three categories: low potassium intake, excess potassium loss, and changes in the distribution of intra- and extra-cellular potassium.[6] Endocrine diseases with renal potassium loss can be caused by primary hyperaldosteronism, Liddle syndrome, renal tubular acidosis (RTA), and Bartter syndrome. Renal tubular acidosis is a collection of disorders due to the inability of various segments of the renal tubules to reabsorb bicarbonate and secrete acid, causing acid-base disorders. There are four types of RTA based on their pathophysiology and location. Type 1 RTA, also known as dRTA, is the inability of the distal nephron to excrete protons maximally under conditions of metabolic acidosis. dRTA is the most common type.[7] RTA type 2 is a disorder due to the inability of the proximal tubule to reabsorb bicarbonate. Type 3 RTA is a mixture of type 1 and type 2 RTA. Type 4 RTA is caused by either aldosterone deficiency or renal tubular resistance to aldosterone.[2] The diagnosis of dRTA in this patient was based on recurrent weakness, normal blood pressure, severe hypokalemia, high urinary potassium, alkaline urine, low plasma bicarbonate, and normal anion gap metabolic acidosis (Figure 1).

There are two primary components in the urine acidification process in the kidneys. HCO_3^- reabsorption occurs mainly in the proximal tubule and in the thick ascending limb of loop of Henle. This complete absorption process causes urine pH to decrease to approximately 6. Second, proton secretion occurs in the distal collecting tubules of the nephron. In healthy adults, this process can cause a decrease in the pH of urine to 4.5–5.5. If the urine acidification process fails to fall below 5.5 in the state of acidosis, it will lead to the diagnosis of a distal acidification disorder.[8] Nephrocalcinosis or urolithiasis occurs in approximately 65% of patients with dRTA. The primary inhibitor of urinary calcium precipitation is citrate. In acidosis, excess protons are buffered by bone apatite, resulting in the release of calcium in the blood and causes hypercalciuria. In addition, the proximal convoluted tubule increases citrate reabsorption, leading to hypocitraturia. The combination of hypercalciuria and hypocitraturia in dRTA increases calcium precipitation.[8]

According to the European Rare Kidney Disease Reference Network and inherited kidney diseases of the European Society for Pediatric Nephrology guidelines, dRTA is a treatable disease. The etiology of dRTA is divided into two categories: primary, which occurs in children, and secondary, which occurs in adults. Secondary dRTA is most commonly associated with autoimmune diseases, such as SS, systemic lupus erythematosus, primary biliary cirrhosis, autoimmune hepatitis, and autoimmune thyroiditis.[8] Other differential diagnoses that need to be considered in secondary dRTA include drugs (ifosfamide, amphotericin B, lithium carbonate, and ibuprofen), hypercalciuric conditions (hyperparathyroidism, vitamin D intoxication, and sarcoidosis), and inherited disorders (medullary sponge kidney and Wilson's disease).[4]

SS is an autoimmune exocrinopathy with systemic involvement caused by monolymphocytic infiltration.[7,9] SS often affects middle-aged women aged 30–50 years with an incidence of 2.2–10.3 per 10,000 population.[4,10] The systemic disorders of SS may include QT prolongation, pulmonary disease, neurologic involvement, and renal tubulointerstitial disease (tubulointerstitial nephritis, RTA, Fanconi syndrome, and glomerulonephritis). However, the mechanism of action of dRTA in SS remains unknown. It is thought to be due to damage to the ATPase hydrogen pump in type A intercalated cells mediated by the immune system and the presence of autoantibodies to the carbonic anhydrase II enzyme.[5,9] The anatomic pathologies of SS in the kidneys are tubulointerstitial nephritis and glomerulonephritis.[4] Tubulointerstitial nephritis that occurs in SS has a pathological picture of predominantly lymphocytic infiltration of CD4

T cells, few CD8 T cells, and only 10% B cells, similar to that of salivary glands.[11]

The biochemical characteristic of dRTA is metabolic acidosis without an anion gap. The normal urine pH ranges from 6.7 to 7.4, and the serum bicarbonate level is approximately 5–20 mmol/L with an equivalent increase in chloride, such that the anion gap remains normal. Upon laboratory examination, it is possible to find auto-antibodies against type-A intercalated cell antigens.[8] The characteristic symptoms of SS are xerosis (dry eyes) and xerostomia (dry mouth). Approximately 70–80% of patients with SS complain of dry mouth. Other organ disorders include skin, lung, gastrointestinal, and kidney disorders.[4,7] The extra-glandular symptoms of SS include arthralgia, arthritis, Raynaud's phenomenon, myalgia, pulmonary disease, gastrointestinal disease, leukopenia, anemia, lymphadenopathy, neuropathy, vasculitis, and lymphoma.[1] The diagnosis of SS is often delayed, with a delay of approximately four years since disease onset was reported in one study.[3] The symptoms and signs associated with dRTA, even in a patient without sicca symptoms, can be indicative of SS cases.[4,12]

The criteria for the diagnosis of SS follow the American-European Consensus Group guidelines.[10] Patients must meet at least four of the six criteria (Table 1). The diagnostic test for SS finds a homogeneous or speckled pattern of ANA with positive anti-Ro/SSA and anti-La/SSB.[1] The prevalence of positive SSA-52 positive is approximately 63.2% in SS. The presence of positive anti-Ro/SSA indicates that the patient with SS is at an early stage accompanied by extraglandular involvement.[9] The diagnosis of SS in this patient was based on complaints of dry eyes, dry mouth, positive Schirmer's test, and positive autoantibodies to SS-A and Ro-52. Histopathological examination of the salivary glands and salivary scintigraphy were not performed due to limited diagnostic facilities. The patient had complaints related to dRTA since two years ago and complaints related to SS, which had also been around for a long time, but were only realized six months ago. Severe undiagnosed hypokalemia may cause muscle weakness that may precede sicca symptoms for months or even years before the diagnosis of primary SS, as in this case. There was a delay in the diagnosis of SS because the complaints were subtle and non-specific. Hypokalemia in this patient was secondary to dRTA associated with primary SS.

European guidelines recommend alkaline supplementation for dRTA therapy.[8] The mechanism of hypokalemia is due to excessive

Table 1. Revised International classification criteria for Sjogren's Syndrome[10]

I	Ocular symptoms: a positive response to at least one of the following questions:
	1 Have you had daily, persistent, troublesome dry eyes for more than 3 months?
	2 Do you have a recurrent sensation of sand or gravel in the eyes?
	3 Do you use tear substitutes more than 3 times a day?
II	Oral symptoms: a positive response to at least one of the following questions:
	1 Have you had a daily feeling of dry mouth for more than 3 months?
	2 Have you had recurrently or persistently swollen salivary glands as an adult?
	3 Do you frequently drink liquids to aid in swallowing dry food?
III	Ocular signs—that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:
	1 Schirmer's I test, performed without anaesthesia (≤5 mm in 5 minutes)
	2 Rose bengal score or other ocular dye score (≥4 according to van Bijsterveld's scoring system)
IV	Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue
V	Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
	1 Unstimulated whole salivary flow (≤1.5 ml in 15 minutes)
	2 Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts
	3 Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer
VI	Autoantibodies: presence in the serum of the following autoantibodies:
	1 Antibodies to Ro(SSA) or La(SSB) antigens, or both

sodium reabsorption in the collecting duct; therefore, excess potassium is secreted as a substitute for sodium. Sodium base salt supplementation is expected to increase the blood potassium levels. However, oral potassium formulations often cause dyspepsia. Moreover, it must be consumed 3–4 times per day. The liquid form of potassium aspartate is tolerable because it contains additional bases. Patients on a vegetarian diet may need lesser alkaline supplementation than those on a high animal protein diet.[8] SS with or without renal involvement adequately responds to steroid treatment.[1,9,13,14] Patients with early-stage SS with renal involvement usually have a poor prognosis.[3] This patient was given a moderate dose of corticosteroids and responded well. Potassium supplementation was continued while monitoring the serum potassium levels. The patient's prognosis was good as she has never been hospitalized again and was able to return to her daily activities as a teacher and housewife.

CONCLUSION

Patients with recurrent hypokalemia should be investigated for the cause, one of which is dRTA. The symptoms and signs of SS are often nonspecific and underdiagnosed. The dRTA can serve as a gateway for the diagnosis of SS. In this patient, complaints related to dRTA appeared before the onset of the sicca symptoms, and a diagnosis of SS was established. Both diseases can be managed simultaneously, even though the patient has to take medication for a long time. Education regarding treatment compliance is a crucial aspect of management.

COMPETING INTERESTS

The authors have no conflicts of interest to declare.

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None.

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