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CASE BASED REVIEWS

Hypokalemic paralysis due to renal tubular acidosis: uncommon initial manifestation of primary Sjögren's syndrome

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ABSTRACT

Primary Sjögren's Syndrome is an immune-mediated disease characterized by exocrine glands dysfunction due to lymphoplasmacytic infiltration with sicca symptoms being one of its main features. The disease may, however, present as distal renal tubular acidosis due to renal involvement, which can range from asymptomatic to life-threatening. We describe the case of a 33-year-old woman with hypokalemic paralysis and metabolic acidosis secondary to distal renal tubular acidosis, leading to the diagnosis of primary Sjögren's Syndrome. Although rare, recognizing primary Sjögren's Syndrome as a possible cause of distal renal tubular acidosis may elicit an earlier diagnosis and treatment, improving the patient's prognosis.

Keywords: Renal; Immunosuppressants; Sjögren's syndrome.

INTRODUCTION

Primary Sjögren's Syndrome (pSS) is an immune-mediated disease characterized by the dysfunction of the exocrine glands due to the presence of a lymphoplasmacytic infiltrate. It has an estimated prevalence of 0.1% and specially affects middle-aged women, with sicca symptoms as the hallmark of the disease [1–3].

Renal involvement in pSS has a variable prevalence, ranging from 1-50%[1,3,4]. Tubulointerstitial nephritis (TIN) is the most frequent manifestation and results from the infiltration of inflammatory cells[1]. Inflammation and autoantibodies may damage distal tubular cells and lead to renal tubular acidosis (dRTA) [1–3]. This entity is characterized by an inability to acidify the urine, with an urine pH above 5,5. TIN and dRTA are often asymptomatic and so under-diagnosed, but severe forms of hypokalemia and metabolic acidosis may also be found and lead to life-threatening manifestations such as hypokalemic paralysis and respiratory arrest[2,5].

We report the case of a patient admitted to the hospital with a hypokalemic paralysis secondary to dRTA that led to the diagnosis of pSS.

CASE REPORT

A 33-year-old woman with no relevant medical history presented to the emergency room (ER) with a 2-day history of severe lack of muscle strength and asthenia. Nine days before she developed headaches and nasal obstruction, tested positive for COVID19 infection and used non-steroidal anti-inflammatory drugs (NSAID). Because of persistent symptoms and productive cough, she was medicated with amoxicillin and clavulanic acid 2 days prior to her visit to the ER. At admission, she was apyretic, with an arterial blood pressure of 115/65 mmHg and a peripheric oxygen saturation of 97%. Severe muscle weakness with tetraparesia was reported. The remaining physical examination was unremarkable. The initial laboratory workup identified normal cell blood count, an acute kidney disease (creatinine 1.27 mg/dL), moderate hypokalemia (2.5 mmol/L), elevated C-reactive protein (10.24 mg/dL) and increased d-dimer (4698,8 ng/mL). A contrasted thoracic computed tomography (CT) was performed and excluded signs of thromboembolism, pleural or pericardial effusion, and parenchymal disease. At this point, the patient started potassium levels correction.

One day after admission in the ER, she became dyspneic with desaturation and need of invasive ventilatory support. Severe hypokalemia (K^+ 1.1 mmol/L) and severe metabolic acidosis [blood pH 7.02; serum bicarbonate (HCO^{3-}) 7 mmol/L] were showed by arterial blood gas analysis. The electrocardiogram (EKG) revealed a bradycardia of 45 bpm and the presence of U waves. She was admitted to the Intensive Care Unit for

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intravenous potassium and bicarbonate replacement. Correction of hypokalemia and metabolic acidosis allowed a progressive improvement in her clinical condition and withdrawal of mechanic ventilation after 3 days.

Further laboratory work up (Table I) showed elevated erythrocyte sedimentation rate, high serum osmolarity, positive immunofluorescent anti-nuclear antibody, positive anti-SSA (Ro52 and Ro60) and anti-SSB in high titer, positive rheumatoid factor and polyclonal hypergammaglobulinemia. Urine analysis revealed a urinary pH of 7.5, a positive urinary anion gap, a low urinary osmolarity, leukoerythrocyturia and a protein/creatinine ratio of 1.76 mg/mg. Renal CT showed normal-sized kidneys with preserved differentiation and without lithiasis or calcinosis.

When specifically asked, she reported xerostomia and mild xerophthalmia for about 6 months. She denied inflammatory arthralgias, mucocutaneous lesions or respiratory complaints. She was submitted to an ophthalmological examination and presented a Schirmer Test of 3-4mm bilaterally and a Tear Break Up Time (BUT) of 7 seconds. The ultrasound of the parotid gland revealed an heterogenous parenchyma with some hypoechoic dots and the parotid biopsy showed the presence of lymphoid aggregates with germinal center.

Taken together, these findings suggest the diagnosis of pSS as the cause of the dRTA. Therapy with prednisolone 40 mg/day was started in a weaning regimen and supplementation with oral potassium (6000 mg of potassium chloride per day) and sodium bicarbonate (1 teaspoon of bicarbonate powder per day) was maintained. The patient fully recovered from the motor deficits and was discharged 4 weeks later.

Four months after starting prednisolone, at a dose of 2.5 mg per day, and under 4200mg per day of oral potassium supplementation, she experienced a resurgence of fatigue, worsening hypokalemia (3.2 mmol/L) and lymphopenia ($1x10^3$/uL). By then, the team decided to start mycophenolate mofetil (MMF) in a dose of up to 2 g per day to better control the disease and spare glucocorticoids (GC). Concurrently, an increase in prednisolone to the previous clinical beneficial dose (to 5 mg per day), oral potassium (to 6000 mg per day) and sodium bicarbonate (to 2 teaspoon of bicarbonate powder per day) was done. After 1 month of therapy, she reports an improvement of her general well-being and her serum potassium is now 3.6 mmol/L.

DISCUSSION

Our patient presented with severe hypokalemia and metabolic acidosis causing muscular weakness with involvement of the respiratory muscles and changes

Table I. Results of the subsequent laboratory investigation.

Laboratory investigation	Results
Urinalysis	pH 7.5, leucocytes 11/HPF, erythrocytes 26/HPF, epithelial cells 3/HPF
Urinary anion gap	14
Urinary osmolarity	193 mOsm/L
Serum osmolarity	317 mOsm/L
Erythrocyte sedimentation rate	81 mm/h
Angiotensin converting enzyme (ACE)	39 UI/L
Rheumatoid factor	191,3 UI/mL
ANA	1:320, large speckled anti-cell pattern
Anti-SSA (Ro52 and Ro60) and Anti-SSB	Positive
Anti-double stranded DNA	Negative
Complement	C3 117 mg/dL; C4 36.2 mg/dL
Plasma protein electrophoresis	Polyclonal hypergammaglobulinemia
Thyroid panel	TSH 0.33 UI/mL; free T4 0.95 ng/dL
Muscular enzymes	CK 54 UI/L; myoglobin 325 mg/mL
Virus serologies	Anti-HIV1 and Anti-HIV2 negative, Anti-HCV negative, Anti-HBc negative
Urine culture	Negative
Blood culture	Negative

HPF - high power field; ANA - antinuclear antibodies; HIV - human immunodeficiency virus; HCV - hepatitis C virus; HBc - hepatitis B core antigen; TSH - thyroid stimulating hormone; T4 - thyroxine; CK - creatine kinase

on the EKG. Exclusion of other causes and an alkaline urine, raised the suspicion of dRTA.

Causes of dRTA were then investigated thoroughly. No new drugs or herb supplements had been started and the patient was not in contact with toxins. She had COVID19 1 week previously with exposure to NSAID and antibiotics for a short period of time. The laboratory values revealed negative HIV, HBV and HCV serologies, normal ACE and excluded an urinary tract infection. On the other hand, positive ANA, anti-SSA and anti-SSB, elevated inflammatory markers, hypergammaglobulinemia and positive rheumatoid factor were found. Although subtle, the patient reported sicca symptoms and had an altered Schirmer Test and tear BUT. Applying the 2016 American College of Rheumatology (ACR) /European League Against Rheumatism (EULAR) classification criteria for pSS, our patient obtained 4 points: 3 points for anti-SSA/Ro-positive and 1 point for Schirmer Test ≤ 5 mm/5 min in at least one eye[6]. We recognize that infection, NSAID and antibiotics are possible causes of TIN, but at this point, we assumed that the patient had pSS and a probable secondary dRTA, which might be triggered by COVID19.

Renal involvement in pSS is variable but has been reported in about 1-50%[1,3,4]. This is a heterogeneous form of extraglandular involvement in pSS which may cause acute and chronic TIN, electrolytic disturbances such as dRTA, diabetes insipidus and Fanconi, Gitelman or Bartter-like syndromes, nephrolithiasis and nephrocalcinosis, as a consequence of prolonged dRTA, as well as glomerulopathies, the most frequent of which is membranoproliferative glomerulonephritis in the setting of cryoglobulinemia[1].

Distal RTA results from a tubular function defect characterized by the inability to acidify the urine which results from a decrease in H^+ excretion by α-intercalated cells located in the collecting duct[1,4]. This may occur in 5 to 24% of pSS patients and be complete or incomplete[3,4,7]. Complete dRTA is defined by the presence of metabolic acidosis with normal anion gap, hypokalemia and an inappropriately alkaline urine (pH>5.5)[3]. In the incomplete form, serum bicarbonate is normal but the urinary pH fails to fall to < 5.3 after ammonium chloride loading[1]. The mechanism explaining dRTA is unclear, but data suggest that there is a downregulation of H^+-ATPase pumps in the collecting duct and a production of auto-antibodies against the carbonic anhydrase II[3,4].

The main consequence of this tubular defect is the increased excretion of potassium, causing hypokalemia, the most common ion disturbance[2,4,7]. Other manifestations of dRTA are hypercalciuria, hyperphosphaturia and hypocitraturia with increased risk of nephrocalcinosis and osteomalacia. This happens as a consequence of acidosis, where the calcium phosphate is reabsorbed from the bone to work as a buffer of H+ in the kidney. As a consequence of this process, there is a high secretion in the urine of calcium and phosphate, which associated to an alkaline urine, allows its precipitation leading to the formation of calcinosis[3,4,7].

In the majority of the patients, hypokalemia is asymptomatic and consequently underdiagnosed. When clinically significant, it may present with muscle cramps and more rarely with paralysis[2,3,7]. This is a possible life-threatening presentation as it can lead to a cardiorespiratory arrest. These extraglandular manifestations such as renal involvement must be kept in mind as possible initial presentations of pSS in order to make an early diagnosis, as it is fundamental to the patient's prognosis. Therefore, screening for renal involvement in pSS must be part of the routine including determination of serum creatinine, serum potassium, bicarbonate and chloride, urinary pH and osmolarity, and protein/creatinine ratio in punctual urine[1].

According to the 2020 EULAR Recommendations for the management of Sjögren's Syndrome, treatment of renal involvement depends on the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI). Patients with mild disease activity (ESSDAI 1-4) receive symptomatic treatment and hydro-electrolytic corrections. Moderate disease activity (ESSDAI 5-13) should receive GC 0.5 mg/kg/day as first line; MMF, azathioprine or cyclosporine A as second line, and rituximab (RTX) or intravenous cyclophosphamide (CyC) as third line treatment. High disease activity (ESSDAI ≥14) should get GC 0.5-1 mg/Kg/day; RTX and CyC are second line options[8].

Our patient presented an ESSDAI of 13 (10 points for the renal involvement and 3 points for the biological involvement) thereby considered moderate[9], so we initiated GC, oral potassium and bicarbonate supplementation. The patient had a remarkable improvement in her clinical state and presented a sustained normalization of ionic disturbances only with symptomatic treatment and GC. However, when the GC was being tapered, hypokalemia intensified, so we opted to initiate MMF to restore remission and to continue tapering CG. This case raises the hypothesis that, in cases of severe presentation, even if the patient does not classify as having a highly active disease, an association of GC and immunosuppressants as the first line therapy may be considered.

Renal involvement in pSS has a good prognosis, but progression to end stage chronic kidney disease may occur in 10-20% of the patients[1,3]. Complement

consumption, hypergammaglobulinemia, positive rheumatoid factor and cryoglobulinemia were identified as risk factors for poor prognosis in pSS, with the presence of two or more of these factors indicating a higher prevalence of visceral organ complications and need for a more aggressive treatment[10]. Fortunately, in our case, the renal function remained normal.

In conclusion, it is important to consider pSS as a differential diagnosis of dRTA, because it may be a life threatening manifestation and require early treatment.

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