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CASE REPORT

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Hypokalemic paralysis and osteomalacia secondary to renal tubular acidosis in a case with primary Sjögren's syndrome

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Abstract A 39-year-old Japanese woman was admitted to our hospital for severe weakness owing to potassium deficiency caused by type 1 renal tubular acidosis (RTA1). Sicca complex, serological tests, and lip biopsy revealed that she had Sjögren's syndrome (SS). Acidosis was corrected by alkali supplement treatment. She also had an impaired renal function with proteinuria, and high absorbance on Ga scintigram was recognized in both kidneys. She was taking warfarin potassium after aortic valve substitution due to aortic regurgitation, therefore renal biopsy was not performed. Prednisone (20 mg/day) was administered for renal inflammation. One month later, she suffered severe chest wall pains with some local tender points over the costae of both sides, which was presumed to be due to pseudofractures based on osteomalacia. Hypokalemic paralysis and osteomalacia should be taken into consideration in the diagnosis of SS with RTA1.

Key words Hypokalemic paralysis · Osteomalacia · Renal tubular acidosis type 1 (RTA1) · Sjögren's syndrome (SS) · Tubular interstitial nephritis

Introduction

Clinically significant renal disease is uncommon in Sjögren's syndrome (SS); however, type 1 renal tubular acidosis (RTA1) is occasionally accompanied with tubulointerstitial nephropathy based on SS.[1] Hypokalemic paralysis is a well known but rare complication of severe RTA1.[2] Osteomalacia is also one of the clinical manifestations of RTA1.[3] We report a patient with primary SS who presented with RTA1, hypokalemic muscle paralysis, and severe chest wall pains over the costae, probably due to pseudofractures based on osteomalacia, a manner of combination that has rarely been described.

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Case report

A 39-year-old woman was admitted to our hospital in January 1993 because she had difficulty in standing up owing to severe muscle weakness of sudden onset. She had an episode of parotid stone 13 years before admission and had dryness of the eyes for several years. Fourteen years previously she underwent aortic valve substitution because of aortic regurgitation, and since then she had been taking 2.5 mg/day of warfarin potassium. She had no family history of rheumatic disease.

On examination, she appeared ill but had no abnormalities in the respiratory system or in the abdomen. There was no palpable lymphadenopathy and her thyroid was not swollen. The oral cavity was dry. Schirmer's test was abnormal (less than 10 mm wetting in 5 min) and an ophthalmological assessment revealed the presence of keratoconjunctivitis sicca.

Laboratory tests on admission were as follows: white blood cell count (WBC) 3570/mm^3, with 48% neutrophils, 39% lymphocytes, 8% monocytes and 5% eosinophils; hemoglobin 9.9 g/dl; platelet count 28.9×10^4/μl; erythrocyte sedimentation rate 75 mm/h; serum protein 7.79 g/dl; albumin 3.37 g/dl; γ-globulin 32.4% (normal 9.0–18.2); aspartate aminotransferase 13 IU/l; alanine aminotransferase 10 IU/l; alkaline phosphatase 106 IU/l (normal 42–172); lactate dehydrogenase 277 IU/l (normal 203–442); blood urea nitrogen 11.7 mg/dl; creatinine 1.25 mg/dl (normal 0.59–1.24); sodium 137 mmol/l; potassium 2.6 mmol/l; chloride 114 mmol/l; calcium 7.9 mg/dl (normal 8.0–10.0); phosphorus 1.8 mg/dl (normal 2.4–4.7); C-reactive protein 0.1 mg/dl;

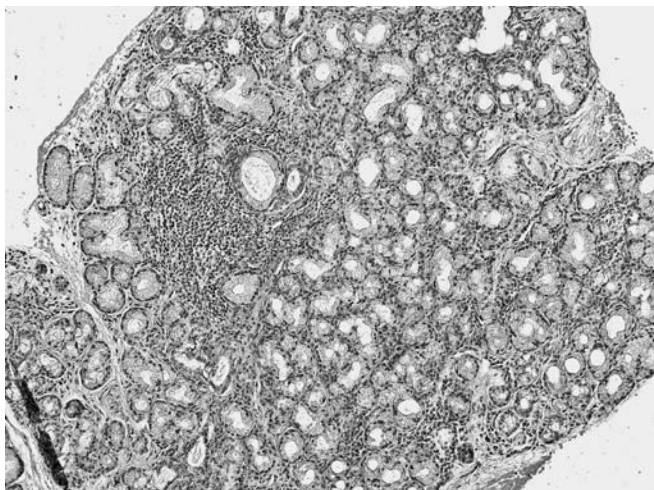

Fig. 1. Atrophy of minor salivary glands with focal aggregates of lymphocytes and plasma cells is shown by a light microscopic examination. Hematoxyline-eosin staining, ×100

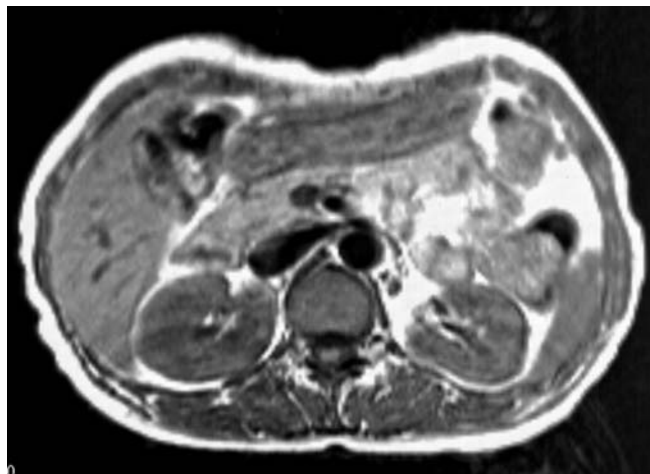

Fig. 2. Slight atrophy of left kidney and ill-defined borders between cortex and medulla of bilateral kidneys are shown by magnetic resonance imaging

parathyroid hormone 580 pg/ml (normal 230–560); thyroid-stimulating hormone 3.65 mU/ml (normal 0.33–4.05); free T3 1.88 pg/ml (normal 2.7–5.5); free T4 0.73 ng/dl (normal 0.78–1.8); serum immunoglobulin (Ig) G 3095.0 mg/dl; IgA 295.7 mg/dl; IgM 168.2 mg/dl; rheumatoid factor 169.2 IU/ml (normal < 18); CH_{50} 38.3 U/ml; C3 56.0 mg/dl; C4 23.8 mg/dl. A test for antinuclear antibodies was positive in a titer of 1:1280 with a speckled pattern and a titer of 1:40 with a nucleolar pattern; antibodies to SS-A and SS-B were positive in a titer of 1:256 and 1:8, respectively, and anti-RNP, Sm, and DNA antibodies were all negative. The arterial blood pH was 7.277; pCO_2 35.9 mmHg; pO_2 103.1 mmHg; HCO_3^- 16.3 mmol/l; base excess −9.3 mmol/l. The creatinine clearance was 36.6 ml/min. The urinary protein was 1160 mg/24 h; urinary *N*-acetyl-β-D-glucosaminidase (NAG) 21.6 U/l (normal 1.1–20.3); urinary pH 8.0; sediment contained 5 red cells and 20 white cells per high-power field. The prothrombin time was 13.0 s (normal 13.5–15.0); activated partial thromboplastin time 44.5 s (normal 30.0–39.0); thrombotest 22% (normal >70).

A labial salivary gland biopsy showed an atrophy of minor salivary glands with focal aggregates of lymphocytes and plasma cells (Fig. 1), and the focus score was 1. Magnetic resonance imaging (MRI) showed a slight atrophy of left kidney and ill-defined borders between cortex and medulla of bilateral kidneys (Fig. 2), and ^{67}Ga citrate whole-body scintigram (Ga-scintigram) revealed a strong uptake in both kidneys (Fig. 3).

An acid load test to evaluate the capacity to acidify the urine was not necessary to make a diagnosis of RTA1 because her urine constantly showed alkalinity in spite of the metabolic acidosis with hypokalemia. A diagnosis of SS was made according to the criteria for the classification of this disease proposed by European Study Group,[4] and this patient fulfilled the revised version of the European criteria proposed by the American–European Consensus Group.[5] She was immediately treated with sodium bicarbonate (up to 5 g/day) and potassium chloride (1.2 g/day) orally.

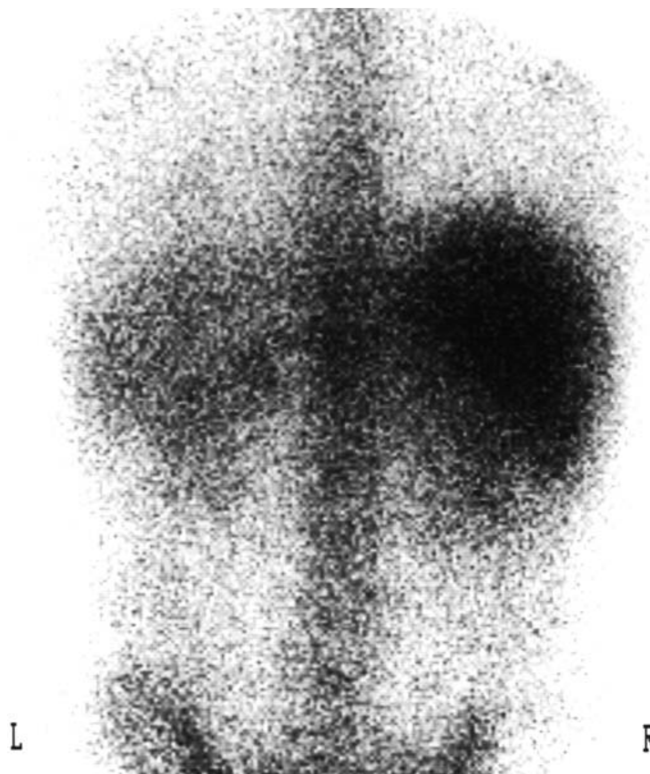

Fig. 3. Strong inflammation in both kidneys is shown by ^{67}Ga citrate whole-body scintigram

A diagnosis of active interstitial nephritis was made because of the findings of MRI or Ga scintigram, impaired renal function, urinary NAG level, and the pattern of urinary sediment. Renal biopsy was not done because she was taking warfarin potassium. Lupus nephritis could not be completely excluded because of her positive antinuclear antibodies test, decreased WBC and lymphocyte count, and proteinuria, all of which could be observed in SS. There

were no disease-specific laboratory data of lupus such as anti-DNA or Sm antibody, or decreased levels of serum complement, so we attributed her renal disease to SS. For the treatment of interstitial nephritis, 10 mg/day of prednisone was initiated on February 11 and increased to 20 mg/day on February 23. She experienced some localized and chest wall pains and tenderness over the costae of both sides without any bruises on March 5. They became exacerbated in a couple of days, and she could not breathe deeply owing to the severe pain. She was clinically presumed to have osteomalacia based on RTA1, even though Looser's zones were not clearly seen on the radiograph. Alfacalcidol (0.5 μg/day) was administered for the treatment of osteomalacia and prednisone was gradually decreased. Within 2 months there was satisfactory symptomatic improvement of muscle weakness and chest wall pain, and the abnormal laboratory parameters such as arterial blood pH and HCO_3^-, serum calcium, and serum phosphorus returned to normal levels. The creatinine clearance also improved (45.7 ml/min) and the urinary protein decreased (540 mg/24 h).

Two years later she decided on her own to stop taking drugs. She developed severe fatigue, muscle weakness, and back pain after an episode of vomiting and diarrhea, and she was admitted to our hospital again in January 1995. The laboratory data on the second admission were as follows: serum potassium 2.6 mmol/l; calcium 6.8 mg/dl; phosphorus 1.1 mg/dl; IgG 3986.6 mg/dl; arterial blood pH 7.262; HCO_3^- 13.8 mmol/l; base excess −11.9 mmol/l. She was treated successfully again by an administration of drugs (sodium bicarbonate, potassium chloride, alfacalcidol, precipitated calcium carbonate, and elcatonin), and the improvement was maintained during the follow-up period.

Discussion

The widespread manifestation of SS is considered to be due to lymphocytic infiltration in different organs and tissues. A similar mechanism might be involved in the renal disorder of SS. Renal involvement is reported to occur in up to 67% of patients with primary SS;[6] however, clinically significant renal disease is uncommon. The typical pathology is interstitial nephritis, while thickening of basement membrane or glomerulonephritis has been infrequently reported.[7]

RTA1, frequently asymptomatic or minimally symptomatic, is a condition characterized by an impaired distal nephron function to acidify the urine, resulting in hyperchloremic metabolic acidosis and excessive renal loss of potassium. The pathogenesis of RTA1 in SS has not yet been clarified; however, it is suggested that autoimmune tubulointerstitial nephropathy might be responsible.[6] Although renal biopsy was not performed because our patient was taking warfarin, the histologic lesion in the kidney of patients with SS and RTA1 was reported to be characterized by a prominent interstitial infiltrate composed of lymphocytes and plasma cells.[8] A secretory defect of the distal tubules was shown in SS secondary to immunological mechanisms, and an immunohistochemical examination revealed that there was absence of intact H^+-ATPase in intercalated cells in kidney of SS patients with RTA1.[9] In addition, hypergammaglobulinemia might also make some contribution to distal renal tubular dysfunction and therefore to the tubular pathology in SS;[10] indeed, our patient showed a marked hypergammopathy.

Hypokalemic periodic paralysis (HPP) is an uncommon complication of RTA1, and HPP during the course of SS has been reported in only a few patients.[11] Severe hypokalemia may rarely lead to sudden life-threatening hypokalemic muscle paralysis, and therefore is the most serious pathogenic consequence of the metabolic acidosis. Hypokalemia and metabolic acidosis were successfully treated in these reports by potassium replacement and alkali supplement with bicarbonate.

Systemic steroids or immunosuppressive drugs can be used for severe extraglandular disease, although the impact of these agents on the natural course of SS is not well established. Besides this, there are a few reports on the successful treatment of SS-associated RTA1 with corticosteroids.[10,12] These authors mentioned that steroid therapy should be considered in SS-associated RTA1 cases with renal infiltrates of interstitial plasma cells and lymphocytes or with HPP. Our patient showed both RTA1 and HPP in addition to signs of active interstitial nephritis and impaired renal function. Therefore she was administered corticosteroids.

Osteomalacia has been rarely reported in SS patients with RTA1.[3] The mechanism of osteomalacia due to RTA1 is not clear; however, all reported cases showed that osteomalacia seen in SS patients was always accompanied by RTA1.[3] The metabolic acidosis, hypocalcemia, and hypophosphatemia might combine to cause osteomalacia. We overlooked the signs of osteomalacia in our patient and gave her corticosteroids for the treatment of renal disease. Severe chest wall pains occurred 1 month after the initiation of steroid therapy, probably due to pseudofractures of costae, although it was not clear if there were any direct effects of steroids on chest wall pains.

We reported a case of SS accompanied by RTA1 and renal insufficiency probably due to interstitial nephritis, HPP, and likely osteomalacia. The combination of all these conditions in a case is quite rare; however, RTA1 is not an uncommon manifestation of SS and we should be aware of the possibility of those patients' developing HPP or osteomalacia in their disease course.

References

1. Aasarod K, Haga HJ, Berg KJ, Hammerstrom J, Jorstad S. Renal involvement in primary Sjögren's syndrome. Q J Med 2000;93:297–304.
2. Soy M, Pamuk ON, Gerenli M, Celik Y. A primary Sjögren's syndrome patient with distal renal tubular acidosis, who presented with symptoms of hypokalemic periodic paralysis Report of a case study and review of the literature. Rheumatol Int 2005;26:86–9.
3. Fulop M, Mackay M. Renal tubular acidosis, Sjögren syndrome, and bone disease. Arch Intern Med 2004;164:905–9.

4. Vitali C, Bombardieri S, Moutsopoulos HM, Balestrieri G, Bencivelli W, Bernstein RM, et al. Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. Arthritis Rheum 1993;36:340–7.
5. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554–8.
6. Eriksson P, Denneberg T, Larsson L, Lindstrom F. Biochemical markers of renal disease in primary Sjögren's syndrome. Scand J Urol Nephrol 1995;29:383–92.
7. Skopouli FN, Dafni U, Ioannidis JP, Moutsopoulos HM. Clinical evolution, and morbidity and mortality of primary Sjögren's syndrome. Semin Arthritis Rheum 2000;29:296–304.
8. Shioji R, Furuyama T, Onodera S, Saito H, Ito H, Sasaki Y. Sjögren's syndrome and renal tubular acidosis. Am J Med 1970;48:456–63.
9. DeFranco PE, Haragsim L, Schmitz PG, Bastani B. Absence of vacuolar H(+)-ATPase pump in the collecting duct of a patient with hypokalemic distal renal tubular acidosis and Sjögren's syndrome. J Am Soc Nephrol 1995;6:295–301.
10. Siamopoulos KC, Mavridis AK, Elisaf M, Drosos AA, Moutsopoulos HM. Kidney involvement in primary Sjögren's syndrome. Scand J Rheumatol Suppl 1986;61:156–60.
11. Soy M, Pamuk ON, Gerenli M, Celik Y. A primary Sjögren's syndrome patient with distal renal tubular acidosis, who presented with symptoms of hypokalemic periodic paralysis. Report of a case study and review of the literature. Rheumatol Int 2005;26:86–9.
12. el-Mallakh RS, Bryan RK, Masi AT, Kelly CE, Rakowski KJ. Long-term low-dose glucocorticoid therapy associated with remission of overt renal tubular acidosis in Sjögren's syndrome. Am J Med 1985;79:509–14.