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CASE REPORT

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A case of Sjögren's syndrome complicated by nephrogenic diabetes insipidus and renal tubular acidosis

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Abstract We describe the case of a 46-year-old woman with Sjögren's syndrome (SS) presenting with a 6-year history of polyuria and polydipsia. Laboratory data revealed hyperchloremic metabolic acidosis, a normal anion gap, and an inability to acidify urine following an acid loading test and to concentrate the urine in response to water deprivation and antidiuretic hormone administration. Lymphocyte infiltration in the interstitium was found on renal biopsy. These findings allowed us to diagnose distal renal tubular acidosis (RTA) and nephrogenic diabetes insipidus (NDI). Steroid pulse therapy resulted in normalization of the blood pH, but failed to remit the inability to concentrate the urine. These observations suggest therapeutic applications for RTA in SS, and that further investigation is required to design a therapeutic strategy for NDI in SS.

Key words Sjögren's syndrome · Nephrogenic diabetes insipidus · Renal tubular acidosis · Steroid therapy

Introduction

Sjögren's syndrome (SS) is an immunological disorder characterized by progressive destruction of the exocrine gland leading to mucosal and conjuctival dryness associated with autoimmune disease affecting various organs. Renal involvement is clinically manifest by renal tubular acidosis (RTA) and pathologically by tubulointerstitial nephritis.[1,2] Although nephrogenic diabetes insipidus (NDI) has been listed in the textbooks as one renal manifestation secondary to SS, only a few cases of SS complicated by NDI have been documented since the 1960s.[3–8] Its pathogenesis is not clear. In this report, we describe a patient showing this association and RTA in whom RTA remitted but NDI did not improve following intravenous steroid pulse therapy, and discuss its implications. Pertinent literature relating to SS complicated by NDI is also discussed.

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Case report

A 46-year-old woman presenting with a 6-year history of polyuria and polydipsia and a 13-year history of intermittent purpura, which was symmetric and began at the feet and extended to the abdomen, was admitted to the Urawa City Hopital on October 12, 1996. Three months before admission she consulted her family physician and was found to have abnormal renal function tests. However, the etiology of polyuria, polydipsia, purpura, and renal dysfunction was not evaluated. She noted dryness of the mouth and eye irritation and burning, and being frequently awakened by urinary urgency during the night. She denied arthralgia, alopecia, photosensitivity, and a history of Raynaund's phenomenon.

On admission she was found to have conjunctivitis, dry oral mucosa, and left parotid gland swelling. Neither generalized lymphadenopathy nor hepatosplenomegaly were noted. Palpable purpura on the lower extremities was noted.

Erythrocyte sedimentation rate on admission was 51 mm/h, and C-reactive protein was 0.14 mg/dl. Hemoglobin was 11.5 g/dl and white blood cell count was 2600/μl with a normal differential, and platelet count was 17.6×10^4/μl. Plain films of the chest and abdomen were normal. Serum bilirubin, alkine phosphokinase, and glutamic oxaloacetic acid were within normal limits. Serum creatinine was 1.80 mg/dl and blood urea nitrogen was 17.3 mg/dl. Creatinine clearance was 33.3 ml/min. Sodium content was 143 mEq/l, potassium 3.5 mEq/l, chloride 118 mEq/l, phosphate 3.3 mg/dl, and calcium 7.7 mg/dl. Urinalysis showed a specific gravity of 1.007, with a pH of 7.5 and trace protein.

The sediment was negative. The urine volume ranged from 3.5 to 4.01 daily. The concentration of urinary β2 microglobulin was 47000 μg/l (normal is less than 200). Urinary calcium excretion was 177 mg/day. Rheumatoid factor was positive at a level of 135 IU/ml. Antinuclear antibody was positive at a titer of 40× in a speckled pattern. Anti-SS-A/Ro antibody was positive at a titer of 32×, but anti-SS-B/La antibody was negative. Cryoglobulin in the serum was negative. A thyroid microsome test was positive at a titer of 1:1600. Platelet-associated surface IgG was positive (47.9 ng/10^7 cells). Antibody to DNA was negative. Serum immunoglobulins showed IgG of 1860 mg/dl, IgA of 548 mg/dl, and IgM of 548 mg/dl. Complement components (CH_{50}, C3, and C4) in the serum were within normal limits. Circulating immune complex was less than 2.0 μg/ml. Analysis of blood gas showed the following levels: pH 7.242, PO_2 105.7 mmHg, PCO_2 32.8 mmHg, HCO_3 13.8 mMol/l, and base excess −12.3 mMol/l. Thus the anion gap was calculated as 11.2 mMol/l. Thyroid function tests revealed mild hypothyroidism (free triiodothyronone 2.5 pg/ml, free thyroxine 0.92 ng/dl, TSH 6.4 μU/ml). The serum concentration of antidiuretic hormone (ADH) ranged from 2.5 to 4.0 pg/ml. HBs antigen and antibodies to hepatitis C virus (HCV) and human immunodeficiency virus (HIV) were negative. Nephrocalcinosis was not demonstrated with a computed tomography (CT) scan of the abdomen.

The response to Schirmer's test for tears was remarkably low (3 mm in both eyes) and keratoconjunctivitis sicca was demonstrated on Rose Bengal staining (+4 by the van Bijsterveld score). Both salivary gland and skin biopsies were carried out on the 3rd day of hospitalization. Pathological examinations of the minor salivary glands and the skin showed chronic inflammation of lymphocytic infiltration and acinal atrophy (Fig. 1a) and leukocytoclastic vasculitis (Fig. 1b). These clinical and laboratory findings, including hyperchloremic metabolic acidosis, a normal anion gap (11.2 mMol/l), and alkaline urine (pH 7.5), led us to make a diagnosis of SS with RTA. Despite the systemic acidosis, the pH of the urine was never lower than 7.0. The hourly observed responses of urinary pH to ammonium chloride, 0.1 g/kg body weight, administered orally after a 2-h control period, are shown in Fig. 2. The acid loading test failed to lower urine pH to less than 7.0, indicating the presence of a distal acidification defect. Furthermore, the urine and plasma osmolalities were compared after 12 h water deprivation that resulted in a loss of >3% of body weight and after the administration of 5 units of vasopressin. Throughout these examinations, the urine osmolality never exceeded the plasma osmolality (Table 1). The impairment in the ability to concentrate urine observed in this patient indicated the presence of NDI. Renal biopsy revealed a mild lymphocytic interstitial infiltration, tubular atrophy, and dilatation compatible with interstitial nephritis (Fig. 1c).

The patient was started on 9 g sodium and potassium citrate, which is equivalent to 1.45 mEq/kg [HCO_3^-], and which resulted in increased blood pH and HCO_3 up to 7.327 and 18.8 mMol/l. After steroid pulse therapy with 500 mg/day methylprednisolone for 3 days, she was subsequently treated with 30 mg/day prednisolone to treat the interstitial nephritis. Two weeks after starting steroids, her blood pH had increased to 7.425, but the clinical and laboratory manifestations of NDI, such as polyuria and hyposthenuria, had not improved. The dose of prednisolone was tapered off

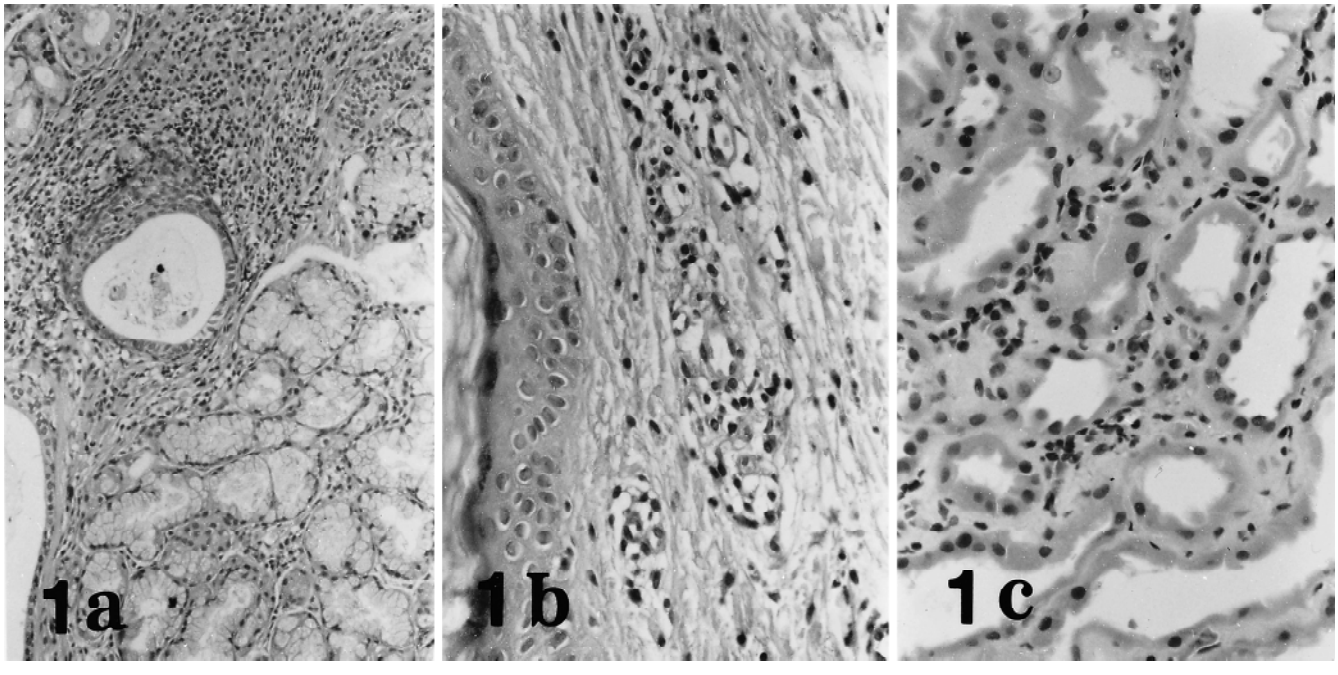

Fig. 1. **a** Section of a labial biopsy showing a marked lymphocytic infiltration and focal acinar destruction, ×100. **b** Section of a skin biopsy showing the involvement of capillary venules with leukocyte infiltration and leukocytoclasis, ×200. **c** Section of a renal biopsy showing a mild lymphocytic infiltrate in the the interstitium, and tubular dilatation and atrophy, ×200

Table 1. Response of urine and plasma osmolality to water deprivation and vasopressin administration

	Before water deprivation	After water deprivation	With 5 units of vasopressin	
			After 1 h	After 2 h
P[a] osm (mOsm/l)	285	307	311	290
U[b] osm (mOsm/l)	177	255	275	210
U osm/P osm	<1	<1	<1	<1

[a] Plasma osmolality
[b] Urine osmolality

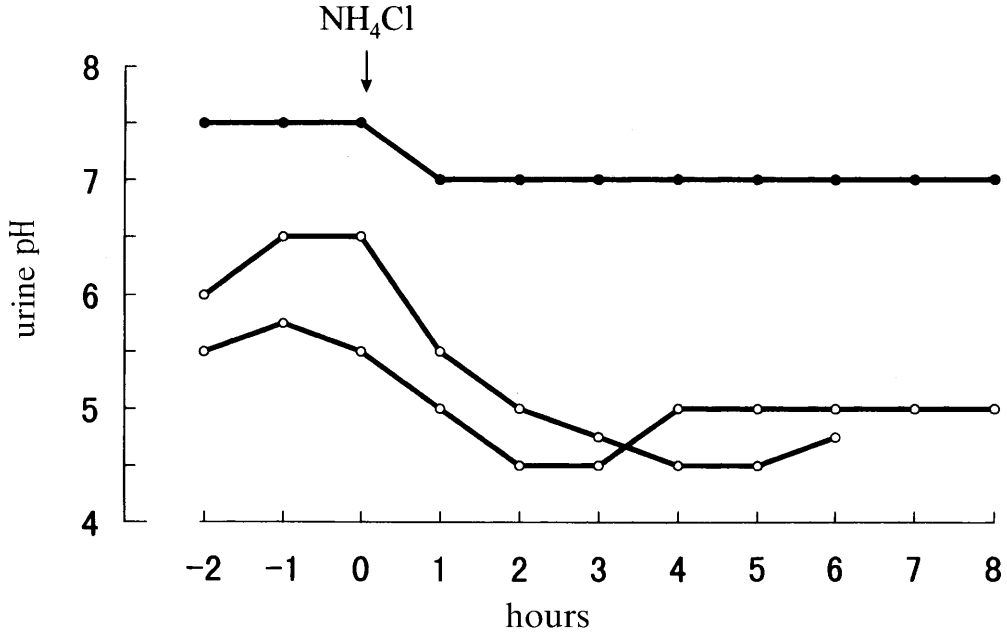

Fig. 2. Urinary pH response to oral administration of 0.1 g/kg ammonium chloride to the patient (*closed circles*) and to two healthy volunteers (*open circles*)

and administration of sodium and potassium citrate was stopped. She was discharged home with medication of 15 mg/day prednisolone and 50 mg/day hydrochlorothiazide, which decreased the daily urine volume to around 2 l. During the 12 months after discharge, her blood pH has been maintained around at 7.4 without sodium or potassium citrate.

Discussion

NDI is a disorder of the renal tubular cells characterized by insensitivity to both endogenous and exogenous antidiuretic hormones. The disease may be inherited as a sex-linked disorder, or may be aquired in certain electrolyte abnormalities (hypercalcemia, hypokalemia) as a complication of drug therapy (lithium), or in various systemic diseases including SS and amyloidosis. Clinically, NDI is characterized by polyuria and polydipsia and a marked impairmant in the ability to concentrate urine.[9]

Nephrocalcinosis and nephrolithiasis in SS have been known to result from hypercalciuria induced by metabolic acidosis.[6] Moutsopoulos et al.[6] reported that one case out of five of SS with nephrocalcinosis and RTA presented with a severe inability to concentrate the urine, together with NDI. A similar case of SS complicated by nephrocalcinosis has also been described by Nagayama et al.[7] Since nephrocalcinosis is characterized microscopically by calcium deposition at/around the distal and collecting nephrons[10] where ADH exerts its action, they[7] speculated that such calcium deposition might play a pivotal role in the occurrence of urinary concentrating defect and also NDI. However, unlike their cases, neither nephrocalcinosis nor hypercalciuria were present in our case, or in cases described by Shearn and Tu[4] and Koura et al.[8] This suggests that nephrocalcinosis seems unlikely to be a necessary condition for the occurrence of NDI, and may occur only as a result of persistent metabolic acidosis in SS, and depend on the degree and duration of hypercalciuria.

It is well documented that renal tubular impairment in SS may be immunologically mediated.[1,6] That is, the interstitial infiltrations of lymphocytes and plasma cells in the kidney, which can also be seen in our case, may interfere with the capacity for water reabsorption in the collecting tubules, as well as with the ability to secrete acid in the distal nephrons, resulting in the urinary concentrating defect/NDI. One would assume that if tubular dysfunction in SS results from renal changes secondary to an immunological process, steroid and/or immunosuppressant therapy would

be effective. To observe whether renal tubule cells can recover their sensitivity to endogenous vasopressin and concentrate the urine, the patient was started on the methylprednisolone intravenous pulse therapy. Although the high-dose steroid therapy increased the blood pH from 7.327 to 7.425, it unexpectedly failed to improve the clinical manifestations of NDI. It is of interest that there have been two reports in which successful treatment of RTA secondary to SS are documented. In one report, long-term low-dose glucocorticoid regimens induced remission of overt RTA in SS.[11] In the other, treatment with intravenous pulse methylprednisolone resulted in rapid and sustained normalization of kidney function.[12]

In general, oral hydration and the administration of diuretic agents such as hydrochlorothiazide are the only adequate treatments for primary NDI. On the other hand, in spite of speculation by several authors[6–8] that lymphocyte infiltration into the interstitium in the kidney may play a dominant role in the pathophysiology of NDI secondary to SS, no specific treatment for NDI with SS has yet been established. There has been only one documented case concerning overt NDI with SS in which an aggressive therapy combined with prednisolone and cyclophosphamide was prescribed. In that case, no clinical improvement of NDI was observed.[8]

The question remains of why the inability to concentrate the urine was not improved in spite of normalization of the blood pH in response to steroids. One possibility is that the impaired function of the collecting tubules which are responsible for water reabsorption was already irreversible at the time of initiating the treatment. If further investigations, such as pathological and physiological examinations of the kidney, were performed immediately after treatment, that data might help to clarify the issue.

In conclusion, we believe that clinical investigations, including the accumulation of reports on similar cases, the characterization of renal involvement secondary to SS, and clarification of the pathophysiology of NDI with SS, can be expected to provide important insights into therapeutic strategies for the disease.

References

1. Talal N, Zisman E, Shur PH. Renal tubular acidosis, glomerulonephritis, and immunologic factors in Sjögren's syndrome. Arthritis Rheum 1968;11:774–86.
2. 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.
3. Kahn M, Merritt AD, Wohl MJ, Orloff J. Renal concentrating defect in Sjögren's syndrome. Ann Intern Med 1962;56:883–95.
4. Shearn MA, Tu WH. Nephrogenic diabetes insipidus and other defects of renal tubular function in Sjögren's syndrome. Am J Med 1965;39:312–8.
5. Shearn MA, Tu WH. Latent renal tubular acidosis in Sjögren's syndrome. Ann Rheum Dis 1968;27:27–32.
6. Moutsopoulos HM, Cledes J, Skopouli FN, Elisaf M, Youinoa P. Nephrocalcinosis in Sjögren's syndrome: a late squela of renal tubular acidosis. J Intern Med 1991;230:187–91.
7. Nagayama Y, Shigeno M, Nakagawa Y, Suganuma A, Takeshita A, Fujiyama K, et al. Acquired nephrogenic diabetes insipidus secondary to distal renal tubular acidosis and nephrocalcinosis associated with Sjögren's syndrome. J Endocrinol Invest 1994;17: 659–63.
8. Koura T, Nishinarita S, Matsukawa T, Kobayashi T, Shimada H, Takei M, et al. A case of Sjögren's syndrome complicated with cryoglobulinemia, nephrogenic diabetes insipidus and renal tubular acidosis (in Japanese). Jpn J Clin Immunol 1995;18:221–7.
9. Moses AM, Streeten DHP. Deficiency of vasopressin: diabetes insipidus. In: Isselbacher KJ, Braunwald E, Wilson JD, et al., editors. Harrison's principles of internal medicine. 13th ed. New York: McGraw-Hill; 1994. p. 1923–8.
10. Hill GS. Calcium and the kidney: hydronephrosis. In: Jennette JC, Olson JL, Schwartz MM, et al., editors. Heptinstall's pathology of the kidney. 5th ed. Philadelphia/New York: Lippincott–Raven; 1998. p. 891–936.
11. 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.
12. Rosenberg AM, Dyck R, George DH. Intravenous pulse methylprednisolone for the treatment of a child with Sjögren's nephropathy. J Rheumatol 1990;17:391–4.