Sjögren's Syndrome Associated with Renal Tubular Acidosis, Medullary Sponge Kidney and Multiple Immunological Abnormalities

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A 20-year-old Japanese female was admitted to hospital with quadriplegia and arthralgia. Three years previous to admission proteinuria and polyarthralgia were evidenced and the following year erythematous eruptions on both cheeks and upper extremities, quadriplegia, high fever and stomatitis developed. A hypopotassemia was also present. Since that time she had recurrent attacks of painful swelling of both parotid glands, myalgia, alopecia and nodular erythema. She had also passed urinary stones without concomitant pain or fever. A metabolic acidosis with hypopotassemia was demonstrated in the arterial blood. The urine was alkaline and urine concentrating ability was impaired. Inadequate urinary acidification was evident after administration of ammonium chloride. Such findings supported the diagnosis of renal tubular acidosis (RTA) of the distal type. An intravenous pyelogram (IVP) suggested medullary sponge kidney (MSK). Hypergammaglobulinemia was accompanied by multiple immunological abnormalities such as positive anti-thyroid antibodies and the evidence for anti-nuclear and anti-DNA antibodies. Biopsy specimens of the kidney, salivary and thyroid glands showed small, round cell infiltration in the interstitial tissues. Although sicca syndrome was not prominent, salivary secretion was decreased and a sialectasis was demonstrated by a sialogram. A diagnosis of Sjögren's syndrome was made and following treatment with potassium salt the patient recovered and was discharged. A 3 year follow-up revealed that the patient was well and living a normal life. Discussion was made regarding the etiological relationship between Sjögren's syndrome, MSK and RTA.

Key Words: Renal tubular acidosis (RTA), Sjögren's syndrome, Medullary sponge kidney (MSK), Sialectasis, Anti-DNA antibodies

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In 1936, Butler et al reported a case of acidosis accompanied by nephrocalcinosis¹⁾ and since that time many cases of renal tubular acidosis (RTA) have reported in the literature. The fact that RTA is occasionally associated with hypergammaglobulinemia has been given increasing attention by clinicians. In 1962 Tsuda et al²⁾ published the first case of RTA in Japan and some forty such cases can now be found in the Japanese literature. In 1963, Yawata and Kitamura³⁾ reported a case of Sjögren's syndrome accompanied by RTA and hypergammaglobulinemia and the present authors recently encountered a 20 year old female with this syndrome plus RTA, medullary sponge kidney and multiple immunological abnormalities.

CASE REPORT

A 20-year-old woman was referred to Kyoto University Hospital because of quadriplegia and arthralgia. Dental caries had increased during puberty and all teeth had decayed. Three years previous to admission she had a proteinuria and pain in the knee and ankle joints. The next year she entered Saiseikai Noe Hospital with complaints of fever, stomatitis, thirst, dry skin, vomiting and paralysis of the lower extremities, and laboratory examination revealed a hypopotassemia. The paralysis improved by oral administration of potassium salt. Subsequently, erythematous eruptions on both cheeks and arms developed. Recurrent attacks of painful swelling of both parotid glands appeared that year. One year before admission, myalgia of the lower extremities, alopecia and passage of urinary stones without pain or fever occurred. The same year, high fever and arthralgia developed and were followed by nodular erythema on the face, chest, back and extensor side of the extremities. A photosensitivity was noted but Raynaud's phenomenon was not present. Body temperature remained elevated despite antibiotic administration, however, antipyretics of the pyrazolon derivatives and steroid hormones were effective. Physical examination on admission revealed a female

of average build who was fairly well nourished. General observations included: BP 116/70, pulse 100 per min., dry skin with small papules, erythema and nodules were noted but jaundice not present. Teeth of all her own had decayed, the thyroid gland was slightly enlarged, swelling of parotid glands not present, lymph nodes not palpable, chest and abdomen appeared normal, deformity and swelling of the joints was nil and in addition there was no evidence of muscular atrophy or neurological abnormalities.

Laboratory data are outlined in Table 1. The urine was positive for protein but repeated cultures all proved negative. Potassium clearance after loading 10% sodium thiosulfate increased suggesting an increased urinary excretion of potassium. With ammonium chloride, 6.2l was the lowest pH in the urine samples despite a marked decrease in the plasma bicarbonate level. Such findings suggested marked impairment of renal acidification.

Abdominal X-rays revealed multiple, small calcifications which resembled bunches of grapes and such were evident in both kidneys. The IVP revealed these calcifications to be in the pyramid areas (Fig. 1) and such findings were characteristic of medullary sponge kidney (MSK).

Mild anemia and leukopenia were evident. Arterial blood gas analysis was pH 7.24, P_{CO_2} 21 mmHg, bicarbonate 9.1 mEq/L. There was a hypopotassemia and the sedimentation rate was 41 mm/hr. The gammaglobulin level was 3.2g/dl and rheumatoid, antinuclear factors and anti-thyroid and anti-DNA antibodies were positive. Thyroid function tests were normal. Although renal tubular reabsorption of phosphate, phosphate clearance and phosphate excretion index were all within normal limits, calcium loading tests revealed a slight hyperparathyroidism.

Salivary secretion was decreased and sialogram of the parotid gland showed a sialectasis (Fig. 2). The Schirmer's test was negative and keratoconjunctivitis sicca was not demonstrated.

Table 1. Laboratory findings.

Urine		Anti-microsomal antibody	10×2^9
volume	1100–2400 ml/day	Anti-thyroglobulin antibody	(–)
s.g.	1.008–1.014	ANF	(+)
pH	6.5–7.5	Anti-n DNA antibody	(+)
protein	ca. 1g/day	Wasserman's reaction	(–)
sugar	(–)	Mantoux reaction	(+)
amino acids	(–)	LE cell phenomenon	(–)
sediment: RBC	5–10/HPF	Serum complement (CH_{50})	42.1
WBC	0–2/HPF		
casts	(–)	Renal function	
culture	negative	BUN	21mg/dl
Serum electrolytes		Serum creatinine	0.78mg/dl
Na	130mEq/L	Fishberg's concentration test	
K	1.8 mEq/L	and injection of Pitressin tannate	
Cl	106mEq/L	max. urine s.g.	1.014
Ca	9.6 mg/dl	PSP excretion rate	15min 13%
P	4.6 mg/dl		120min 65%
Immunological examinations		RPF	390ml/min
Total serum proteins	9.5g/dl	GFR	50ml/min
Albumin	51.6%	FF	0.128
α_1 -globulin	1.6%	K clearance (10% sodium thiosulfate, 80ml)	
α_2 -globulin	5.2%	before	10.0 ml/min
β -globulin	7.4%	after	33.4 ml/min
γ -globulin	34.2%	Ammonium chloride loading test	
IgG	3160mg/dl	min. plasma bicarbonate	10.3mEq/L
IgA	296mg/dl	min. urinary pH	6.21
IgM	324mg/dl	Thyroid function	
RA-factor	(+)	BMR	+9.5%
Coombs' test	(–)	Triosorb	23.0%
Cold agglutinin	(–)	Tetrasorb	8.5 μ g/dl
Blood		Parathyroid function	
Ht	11.8g/dl	%TRP	89.9%
RBC	380×10^4 /mm ³	P clearance	9.0ml/min
WBC	3000/mm ³	Phosphate excretion index	–0.08
Platelets	23.6×10^4 /mm ³	Ca loading test	
Arterial blood gas analysis		Parathyroid index	1.21
pH	7.26	Urinary P fluctuation ratio	–11.4%
Pco ₂	21mmHg		
Po ₂	106.7mmHg		
[HCO ₃ [–]]	9.1mEq/L		
ESR (1°)	41mm		
CRP	(–)		

Bony absorption of alveolar bone was advanced for her age, but other bones demonstrated no sign of osteoporosis.

A renal biopsy showed an infiltration of inflammatory cells, chiefly lymphocytes in the renal interstitial tissues. Thickening of the basement membranes of the glomeruli and Bowman's capsules and increased mesangial cells were demonstrated. A wire-loop lesion-like change was noted (Fig. 3). Biopsy of the submandibular salivary gland

revealed infiltration of the mononuclear cells of which some areas were dense and other scanty. Several ductules were atrophic and destruction of some of the acini was evident. The thyroid gland showed a focal thyroiditis consisting of mild cellular infiltration and fibrosis.

With discontinuation of potassium salt and sodium bicarbonate on admission, a progression in metabolic acidosis occurred and the serum potassium levels dropped to

Fig. 1. Intravenous pyelogram. Note multiple calcifications in the renal pyramids appearing as bunches of grapes.

Fig. 2. Sialogram. Typical sialectasis is demonstrated.

1.8 mEq/L. Quadriplegia and myalgia soon followed. Treatment with potassium salt resulted in a rapid recovery.

DISCUSSION

There are two forms of RTA, the distal form (type 1) and a proximal form (type 2),

Fig. 3. Renal biopsy specimen. A glomerulus shows thickening of glomerular basement membrane and Bowman's capsule. Lymphocytic infiltration in the interstitial tissue is seen. (PAS stain)

Fig. 4. Biopsy specimen of the submandibular gland. Considerable lymphocytic infiltration around a ductule is present. (Hematoxylin and eosin stain)

either of which may be primary or secondary manifestations⁴⁻⁶. In distal RTA, the pH gradient between blood and tubular fluid is inadequate. Proximal RTA is caused by a defect in the tubular reabsorption of bicarbonate and has a low renal threshold for bicarbonate excretion. The proximal form is characterized by the ability to adequately acidify urine when the plasma bicarbonate is below the renal threshold. The present case was considered to be a distal RTA as acidification of urine was markedly disturbed when plasma bicarbonate was lower than the renal threshold (Fig. 5).

RTA may be associated with a number of hypergammaglobulinemic syndromes, including SLE⁷, Sjögren's syndrome^{8,9}, cryo-

Fig. 5. Relationship of urinary pH to concentration of plasma bicarbonate. The broken curve represents the mean response in healthy adults.

globulinemia¹⁰⁾, multiple myeloma¹¹⁾, hypergammaglobulinemic purpura¹²⁾, idiopathic hyperglobulinemia¹³⁾ and lupoid hepatitis¹⁴⁾.

In this case, multiple immunological abnormalities such as hypergammaglobulinemia and positive tests for antinuclear, rheumatoid factors, anti-DNA and anti-thyroid antibodies were present. Wire-loop lesion-like change of the glomeruli was seen and leukopenia was present. In addition, facial erythema, polyarthritis, alopecia and photosensitivity were noted. These laboratory and clinical findings were met with diagnostic criteria for SLE^{15,16)}. Although sicca syndrome was not prominent, recurrent swelling of the parotid glands, decreased salivary secretion, histological findings of the salivary gland and the picture of the sialogram suggested Sjögren's syndrome.

The association of SLE and malfunctioning exocrine glands is not frequently encountered while disturbances in salivary and lacrimal glands are principal features of Sjögren's syndrome. The underlying disorder in Sjögren's syndrome may be as in the case of SLE, a defect in the antibody producing system and clinical manifestations would include organic and functional abnormalities of the exocrine glands including the renal tubules. Should such a postulation be valid, then our patient demonstrated Sjögren's syndrome.

Antibodies to DNA are positive exclusively in SLE patients and such is also the case sometimes in Sjögren's syndrome, although the titer is rather low in the latter.

Another important feature of this case is

association of MSK¹⁸⁾. MSK is a congenital, non-hereditary anomaly of cystic dilatation of the collecting tubules frequently accompanied by mild renal function disturbances. Several cases of MSK associated with RTA have been reported. Deck¹⁸⁾ proposed three possible ways of explaining the combination of the two conditions. He thought it most probable that RTA is the result of pyelonephritis, a well known complication of MSK. Ekström et al¹⁹⁾ stated that all the kidneys they examined revealed inflammatory changes histologically. In our case, there was no increase of white blood cells in urinary sediment and repeated urine cultures were negative. Intravenous pyelography also showed no sign suggesting pyelonephritis.

It is difficult to explain the combination of MSK, RTA and Sjögren's syndrome. Popa²⁰⁾ reported a child presenting RTA, hypergammaglobulinemic purpura and roentgenographic signs suggesting MSK. It appears unlikely that these combination is merely an accident. If examinations of the exocrine glands such as salivary and lacrimal glands are performed in addition to pyelography in patients with RTA and hypergammaglobulinemia, similar cases as described in this report might be increased in incidences.

It remains unknown that congenital anomalies of tissues or organs such as MSK play any role in the pathogenesis of autoimmune diseases. This case may offer a clue to the problem.

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