—Case Reports—

A Case of Juvenile Sjögren's Syndrome with Interstitial Nephritis

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Abstract

Primary Sjögren's syndrome (SS) is a rare autoimmune disease, especially in children. Juvenile primary SS with interstitial nephritis is rare in Japan. We report on a 12-year-old girl in whom salivary gland swelling had recurred from the age of 5 years, SS was diagnosed at the age of 10 years, and interstitial nephritis developed at the age of 12 years. The patient presented with a chief complaint of swelling of both parotid glands. The patient had a history of recurrent parotitis from 5 years of age, with episodes recurring 5 to 6 times a year and resolving within 3 days each time. However, at the age of 11 years, the patient had continuous mild swelling of the parotid glands. Examination on admission showed bilateral nontender parotid gland swelling; mild swelling of the lower extremities, xerostomia, and xerophthalmia but no exanthem. Laboratory findings were as follows: serum protein, 10.1 g/dL; immunoglobulin (Ig) G, 3,828 mg/dL; antinuclear antibodies, 1,280-fold; anti-Ro/SS-A antibody, 512-fold; anti-Ro/SS-B antibody, 4-fold; creatinine, 0.45 mg/dL; blood β2-microglobulin, 2.2 mg/L (slightly elevated); and cystatin C, 0.86 mg/L. Urinalysis showed proteinuria and a β2-microglobulin concentration of 11,265 mg/L. Thus, this patient had low molecular weight proteinuria. Schirmer's test showed decreased tear secretion (5 mm), and fluorescein staining showed marked bilateral superficial punctate keratitis. A lip biopsy showed infiltration by small round cells (mild to moderate), interstitial fibrosis, loss of salivary gland parenchyma, and atrophy, with no obvious epimyoepithelial islands, leading to a diagnosis of SS. Light microscopic examination of the renal biopsy specimens showed expansion of mononuclear cell infiltration in the renal interstitium, inflammatory cell infiltration of interstitial areas with edema and mild fibrosis, and tubulitis and mononuclear cell infiltration that included many lymphocytes and plasma cells. There were no pathological findings of glomerulonephritis. Small arteries showed no obvious abnormalities. Immunofluorescent staining showed slight, nonspecific deposition of IgM, but no deposition of IgG, complement 1q, 3, or 4. On the basis of the renal biopsy showing nonspecific chronic interstitial nephritis, renal tubular atrophy, and interstitial enlargement, tubulointerstitial nephritis associated with SS was diagnosed.
(J Nippon Med Sch 2012; 79: 286–290)

Key words: Sjögren's syndrome, interstitial nephritis, pediatric

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Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disorder characterized by xerostomia, keratoconjunctivitis sicca, and the presence of various autoantibodies. SS is common in adults, especially in middle-aged women, but is rare in children[1–3]. Involvement of the brain and glandular organs other than the salivary and lacrimal glands is common in adults[4]. The latter complications suggest that SS, at least in adults, is a systemic inflammation of ducts or exocrine glands[5,6].

We report on a patient in whom salivary gland swelling had recurred from the age of 5 years, SS was diagnosed at the age 10 years, and interstitial nephritis developed at age 12 years.

Case Report

Chief complaint: Swelling of bilateral parotid glands

Medical history: Allergic rhinitis

Family history: Grandmother with rheumatoid arthritis

Clinical course: Parotitis had recurred 5 to 6 times per year from the age 5 years. Each time the condition resolved within 3 days. Since March 2009 there had been continuous mild swelling of the parotid glands.

Status on admission: Blood pressure was 102/60 mm Hg, heart rate was 110 beats/minutes, respiratory rate 22 breaths/minute, and temperature was 36.6℃. There was no pallor of the palpebral conjunctiva or jaundice of the bulbar conjunctiva. There were no obvious abnormal findings, such as stomatitis, oral redness, or swelling. The patient had bilateral nontender parotid gland swelling. On chest auscultation, the respiratory sounds were clear bilaterally, with no crackles, cardiac murmurs, or other abnormal sounds. On abdominal examination, the bowel sounds were normal, and the abdomen was soft with no tenderness. There was mild swelling of the lower extremities and no exanthem, but the patient had xerostomia and xerophthalmia.

Examination on Admission

Laboratory findings were as follows: serum protein, 10.1 g/dL; immunoglobulin (Ig) G 3,828, mg/dL, antinuclear antibodies, 1,280-fold; anti-Ro/SS-A antibody, 512-fold; and anti-Ro/SS-B antibody, 4-fold. Complete blood count demonstrated hypochromic anemia with a hemoglobin concentration of 11.0 g/dL. The erythrocyte sedimentation rate was 66 mm/hour. The blood chemistry profile was normal except for an elevated value of total protein. Serum protein electrophoresis disclosed an increase in the gamma globulin fraction. Venous blood gas analysis on room air showed PO_2, 48.2 mm Hg; PCO_2, 44.7 mm Hg; HCO_3, 25.1 mmol/L; base excess, 0.2 mmol/L; and pH, 7.37. For renal function, creatinine was 0.45 mg/dL, blood β2-microglobulin was 2.2 mg/L (slightly elevated), and cystatin C was 0.86 mg/L. Urinalysis showed proteinuria and a urinary β2-microglobulin concentration of 11,265 mg/L (**Table 1**). Thus, low molecular weight proteinuria was seen.

Schirmer's test showed decreased tear secretion of 5 mm. Fluorescein staining showed marked bilateral superficial punctate keratitis.

Biopsy of the lip showed infiltration by small round cells (mild to moderate), interstitial fibrosis, loss of salivary gland parenchyma, and atrophy. No obvious epimyoepithelial islands were seen. This patient was given a diagnosis of SS on the basis of the revised Japanese criteria for Sjögren's syndrome (1999)[7] and the classification criteria for Sjögren's syndrome proposed by the American-European Consensus Group (2002)[8].

The light microscopic examination of renal biopsy specimen, which included renal cortex and medulla, showed expansion of mononuclear cell infiltration in the renal interstitium (**Fig. 1**). Interstitial areas with inflammatory cell infiltration showed edema and mild fibrosis. Tubulitis was also noted with infiltration of mononuclear cells, which included large numbers of lymphocytes and plasma cells. The specimens included 52 to 57 glomeruli that showed minor glomerular abnormalities without any pathological evidence of glomerulonephritis. Small arteries showed no obvious abnormalities. Immunofluorescent findings indicated slight, nonspecific deposition of IgM but no deposition of

Table 1

Urine		Protein fraction	
Protein	(1+)	Albumin	48.4 %
Glucose	(−)	α1-globulin	2.0 %
Occult blood	(−)	α2-globulin	7.8 %
Sediment		β-globulin	8.4 %
RBC	<1 /HPF	γ-globulin	33.4 %
WBC	1–4 /HPF		
Transitional cells	<1 /HPF	Immunological tests	
Tubular epithelial cells	1/1–5 HPF	CRP	0.46 mg/dL
Urinary protein	38 mg/dL	C3	164 mg/dL
Urinary Cr (CRE)	203.1 mg/dL	C4	24 mg/dL
		Complement activity (CH50)	58.8 U/mL
Blood count		Immune complex-C1q	≤1.5 μg/mL
WBC	50×10^2 /μL	IgG	3,828 mg/dL
Neutro	76.1 %	IgA	431 mg/dL
Lympho	18.1 %	IgM	265 mg/dL
Mono	4.2 %	IgG4	32 mg/dL
Eosino	1.4 %	ASO	270 IU/mL
Baso	0.2 %	ANA	×1,280
RBC	409×10^4 /μL	Anti-DNA antibody (RIA)	2.3 IU/mL
Hb	11.0 g/dL	Anti-ssDNA antibody-IgG	12 AU/mL
Ht	33.0 %	Anti-dsDNA antibody-IgG	2 IU/mL
Plts	29.5×10^4 /μL	Anti-SS-A antibody	×512
Erythrocyte sedimentation rate (ESR)	66 mm (1h)	Anti-SS-B antibody	×4
		Anti-RNP antibody	≤7 U/mL
Blood biochemistry		Anti-Sm antibody	≤7 U/mL
T.P.	10.1 g/dL		
Alb	4.2 g/dL	Kidney function	
Cr (CRE)	0.45 mg/dL	Cystatin C	0.86 mg/L
BUN	13.1 mg/dL	Ccr	159 ml/min
GOT	18 IU/L	Serum β2-MG	2.2 mg/L
GPT	17 IU/L	Urinary β2-MG	11,265 μg/L
LDH	157 IU/L	NAG	12.9 U/L
ALP	789 IU/L	NAG index	6.4 U/g·Cr
AMY	61 IU/L		
Na	138 mEq/L	Vein Blood gas analysis	
K	3.7 mEq/L	pH	7.37
Cl	106 mEq/L	PCO_2	44.7 mmHg
Ca	9.5 mg/dL	PO_2	48.2 mmHg
P	4.5 mg/dL	HCO_3	25.1 mmol/L
		BE	0.2 mmol/L

IgG or complement 1q, 3, or 4. The diagnosis based on the renal biopsy findings was tubulointerstitial nephritis associated with SS.

Discussion

In SS, exocrine gland inflammation (dacryoadenitis, sialadenitis) occurs, and xerostomia and xerophthalmia appear. SS is classified as primary SS or secondary SS, such as a complication of rheumatoid arthritis or systemic lupus erythematosus. Primary SS is a chronic systemic disease, characterized by lymphatic infiltration around epithelial ducts of exocrine glands and B-cell hyperactivity resulting in the production of autoantibodies and immune complexes[9]. Primary SS can be classified as glandular, in which the lacrimal and salivary glands are impaired, or extraglandular, in which nonglandular tissue lesions are also present. Extraglandular SS invades many organs, including

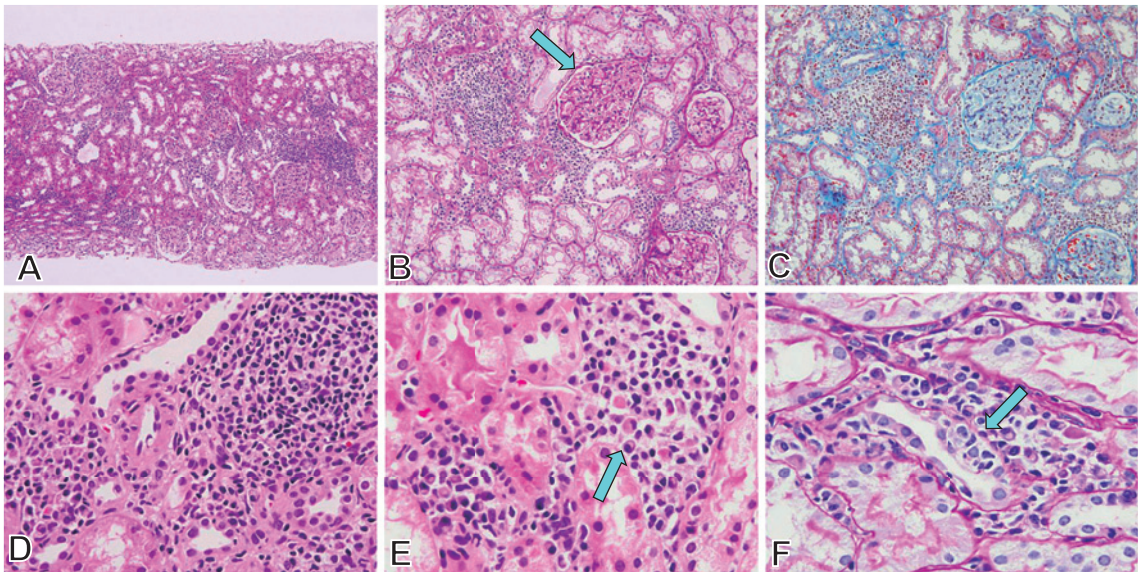

Fig. 1 Light microscopic findings.
A: Expanded mononuclear cell infiltration is noted in the renal cortex, indicating interstitial nephritis (hematoxylin and eosin [HE] stain, ×100). **B**: Patchy mononuclear cells infiltrate the interstitium. Glomeruli show minor glomerular abnormalities with no pathological findings of glomerulonephritis **(arrow)** (periodic acid-Schiff stain [PAS], ×200). **C**: Interstitium with mononuclear cell infiltration shows interstitial edema with only mild interstitial fibrosis (Masson stain, ×200). **D**: Within the inflammatory cell infiltration, many lymphocytes and plasma cells are noted (HE stain, ×600). **E**: Focal plasma cell aggregation is also observed **(arrow)** in the interstitium (HE stain, ×800). **F**: Mononuclear cells have infiltrated into the tubules and formed tubulitis **(arrow)** in the renal tubules (PAS stain, ×600).

the skin, kidneys, lungs, liver, and thyroid[10]. SS also occurs in children. In a national survey conducted in Japan in 1994, 61 cases were recorded (9 in boys and 52 in girls). The cases were primary SS in 70% (42 cases) and secondary SS in 30% (19 cases). Of the 42 patients with primary SS, 3 had interstitial nephritis[11].

Recurrent salivary gland swelling is a typical presenting symptom, and salivary gland swelling is seen in nearly all cases of pediatric SS[12], whereas severe extraglandular symptoms are rare[13]. In adults, extraglandular symptoms are more frequent, as are symptoms of dryness[14]. Thus, in the early stages, extraglandular symptoms, such as fever and arthralgia, are common in adults, whereas glandular symptoms, such as salivary gland swelling, are the main symptoms in children. Therefore, the onset pattern of SS might differ in children and adults. In children, subclinical SS with few symptoms of dryness is common. Cases of juvenile SS complicated by interstitial nephritis, such as the present case, are rare.

In the present patient, serum protein was 10.1 g/dL, IgG was 3,828 mg/dL, antinuclear antibodies were 1,280-fold, anti-Ro/SS-A antibody was 512-fold, and anti-Ro/SS-B antibody was 4-fold. These values were high and characteristic of SS. Precipitating antibodies to the Ro/SSA antigen occur in the sera of 40% to 70% of patients with primary SS[15]. In addition, urinary β2-microglobulin was elevated to 11,265 μg/L, and interstitial nephritis was suspected. The pathological findings in the kidney included infiltrating plasmacytes and lymphocytes. The infiltration of inflammatory cells, such as lymphocytes (predominately CD4-positive T cells), plasmacytes, and mononuclear cells, plays a critical role in interstitial nephritis. No significant lesions are seen in typical cases. The present patient showed a picture of nonspecific chronic interstitial nephritis with renal tubular atrophy and interstitial enlargement[16], and, so, interstitial nephritis, was diagnosed.

Anti-Ro/SS-A antibody was elevated 512-fold. Lymphocyte extracts contain 2 Ro/SSA antigens with protein moieties of 60 kDa and 52 kDa[15]. Previously, we examined the quantitative and

qualitative changes of the Ro/SSA protein induced by stress, such as with heat shock and UV irradiation, and found that only Ro52 could be expressed on the cell surface of human peripheral lymphocytes by either heat shock or UV irradiation. Moreover, flow cytometric analysis revealed that heat shock-treated and UV-treated lymphocytes could be stained with patient sera, and with a technique that combined immunoprecipitation and Western immunoblotting, it has been confirmed that Ro52 expressed on the cell surface can be recognized by anti-Ro/SSA antibodies in native form, whereas cytoplasmic Ro52 cannot be recognized. These findings suggest that Ro52 can be antigenic in vivo when expressed on the cell surface and may explain the mechanism of direct tissue damage by anti-Ro/SSA antibodies[17]. Generally, the main treatment for SS is symptomatic treatment for dryness, with steroids or other drugs administered only when extraglandular symptoms, such as fever and arthralgia, appear[10]. In cases, such as the present one with concurrent interstitial nephritis, steroid therapy is given.

In this paper, a case of juvenile SS with interstitial nephritis has been described. The prognosis of this patient is good, but latent nephritis can still occur.

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(Received, September 11, 2011)
(Accepted, November 11, 2011)