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CASE REPORT

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A case of proteinase 3-antineutrophil cytoplasmic antibody-positive Sjögren's syndrome complicated with interstitial nephritis

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Abstract A 65-year-old woman who had fever was admitted. Laboratory data showed renal tubular dysfunction, elevated C-reactive protein, soluble interleukin-2 receptor (sIL-2R), and IgG. Her blood showed proteinase 3-antineutrophil cytoplasmic antibody (PR3-ANCA) as well as antinuclear antibody and anti-Ro/SS-A antibody. Salivary gland and renal biopsy showed inflammatory infiltration of lymphocytes. A diagnosis of Sjögren's syndrome (SS) and interstitial nephritis was made. β_2-microglobulin, sIL-2R, IgG, and PR3-ANCA were decreased in response to medium-dose oral prednisolone. Antineutrophil cytoplasmic antibody could be a new marker for extraglandular features of SS. It would be beneficial for SS patients who have positive ANCA to investigate extraglandular lesions such as interstitial nephritis.

Key words Extraglandular lesions · Interstitial nephritis · Proteinase 3-antineutrophil cytoplasmic antibody (PR3-ANCA) · Sjögren's syndrome

Introduction

In autoimmune disease, glomerulonephritis is more common than interstitial nephritis. Interstitial nephritis is common in Sjögren's syndrome (SS),[1,2] affecting approximately 10% of patients, but accurate prevalence of interstitial nephritis in SS is unknown. Diagnosis of interstitial nephritis is often difficult because interstitial nephritis usually develops insidiously. Early diagnosis is important, because interstitial nephritis is critical for prognosis, and there is a possibility of developing renal failure.[3]

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Sjögren's syndrome is a systemic autoimmune disease that mainly affects the exocrine glands and usually presents as persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands. In the absence of other collagen disease, such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, dermatomyositis, polymyositis, and mixed connected tissue disease, patients with this condition are classified as primary SS.[4] Patients with primary SS sometimes have autoantibodies considered characteristic of other systemic autoimmune disease, although the clinical significance of this immunological overlap is not well established.[4] Here, we report an SS case complicated with interstitial nephritis and positive proteinase 3-antineutrophil cytoplasmic antibody (PR3-ANCA), successfully treated by corticosteroid.

Case report

A 65-year-old woman developed general malaise, dry cough, and fever in May 2005. She was suspected to have viral myocarditis, and was admitted to our hospital for further investigation in August 2005. Her blood pressure was 138/86 mmHg. There were no cutaneous lesions and in particular no signs of vasculitis. There were no indications of hepatosplenomegaly or lymphadenopathy, central and peripheral neurological disturbances, muscle weakness, paralysis, and respiratory disturbances. The patient was not taking drugs such as nonsteroidal anti-inflammatory drugs, diuretics, phenytoin, allopurinol, or cimetidine.[4–6]

Laboratory data are shown in Table 1. The data showed leukocytosis (10 930/μl) and lymphocytopenia (1150/μl), elevated C-reactive protein (15.96 mg/dl), hypergammaglobulinemia (IgG 2600 mg/dl), positive antinuclear antibody (speckled ×5120), positive PR3-ANCA (65 IU/ml), elevated soluble interleukin-2 receptor (sIL-2R) (1210 U/ml), renal tubular dysfunction (urine *N*-acetyl-β-D-glucosaminidase (NAG) 5.4 U/day, urine β_2-microglobulin (β_2-MG) 20 988 μg/day), but no alkaline urine, hypokalemia, renal

Table 1. Laboratory data

URINALYSIS:	
pH 6.0	6.0
specific gravity	1.02
proteinuria	2+
hematuria	3+
gluc	(–)
WBC	1–4/HPF
RBC	30–49/HPF
24h URINALYSIS:	
24h	1560ml
Cr	65.5mg/dl
CCr	83.24ml/min
Prot	0.6g/day
Glu	0.12g/day
Na	106mEq/day
K	49.9mEq/day
Alb	211.2mg/day
β_2MG	20988μg/day
NAG	5.4U/day
BLOOD COUNT:	
RBC	339×10^4/μl
Hb	10.4g/dl
Ht	31.5%
WBC	10930/μl
Neu	80.2%
Lymph	12.3%
Eos	0.4%
Plts	24.4×10^4/μl
COAGULATION:	
PT	67.8%
PT(INR)	1.15
APTT	33.7s
Fbg	842mg/dl
D-Dimer	2.66μg/ml
BLOOD CHEMISTRY:	
Na	135mEq/l
K	4.6mEq/l
Cl	101mEq/l
Ca	8.8mg/dl
P	2.6mg/dl
Mg	2.1mg/dl
BUN	21mg/dl
Cr	1.0mg/dl
TP	7.7g/dl
Alb	3.3g/dl
T-bil	0.5mg/dl
LDH	263U/l
AST	50U/l
ALT	23U/l
γ-GTP	21U/l
ALP	185U/l
CK	165U/l
Amy	79U/l
T-cho	132mg/dl
TG	104mg/dl
Glu	119mg/dl
HbA1C	5.2%
SEROLOGY:	
ESR	127mm/h
CRP	16mg/dl
IgG	2600mg/dl
IgA	258mg/dl
IgM	109mg/dl
C3	117mg/dl
C4	25mg/dl
CH50	>66.8U/ml
ferritin	828ng/dl
C1q-IC	1.5μg/ml
sIL-2R	1210U/ml
KL-6	1255U/ml
SP-D	99ng/ml
IgG SUBCLASS:	
IgG_1	58.5%
	1790mg/dl
IgG_2	31.7%
	970mg/dl
IgG_3	1.25%
	38.2mg/dl
IgG_4	8.59%
	263mg/dl
AUTOIMMUNITY:	
RF	15IU/ml
ANA	(+)
Speckled	×5120
Anti-DNA Ab	7IU/ml
Anti-Sm Ab	(–)
Anti-RNP Ab	(–)
Anti-SS-A Ab	102
Anti-SS-B Ab	(–)
Anti Jo-1 Ab	(–)
Anti Scl-70	(–)
PR3-ANCA	65IU/ml
MPO-ANCA	<10IU/ml
Thyroid test	(–)
Microsome test	(–)
ENDOCRINOLOGY:	
fT3	1.97pg/ml
fT4	1.04ng/dl
TSH	3.7IU/ml
ANP	76pg/ml
BNP	83pg/ml
ABG (Room air):	
pH	7.45
$PaCO_2$	28.7torr
PaO_2	64.6torr
BE	–3.4mmol/l
HCO_3^-	19.4mmol/l
$A\text{-}aDO_2$	51.5torr

dysfunction, or proteinuria was found (blood urea nitrogen: BUN 21mg/dl, creatinine 1.03mg/dl, creatinine clearance 83.4ml/min). There was no hypocomplementemia (C3 117mg/dl, C4 25mg/dl, CH50 > 68.8U/ml, and IgG_4 elevation), and C1q-immune complex was negative. Arterial blood gas was as follows: pH 7.445, PCO_2 28.7torr, PO_2 64.6torr, base excess –3.4mEq/l, HCO_3^- 19.4mEq/l, A-a DO2 51.0torr. The Saxon test was 0.69g/2min. Ophthalmologic examinations were as follows: Fluorescein test rt 2, lt 1, rose bengal test rt 2, lt 2, Schirmer rt 13mm, lt 25mm, and typical keratoconjunctivitis sicca was not diagnosed. Her chest radiograph and computed tomography (CT) showed cardiomegaly and pericardial effusion (Fig. 1A). Abdominal CT showed swelling of kidneys (Fig. 1A). Gallium-67 scintigram indicated abnormal uptake in pericardial membrane (Fig. 2A), and in bilateral parotid gland (Fig. 2B), but no uptake in kidneys. Salivary gland scintigram showed severe hyposalivation. Magnetic resonance (MR) sialography showed cysts of 1–3mm in diameter in bilateral parotid, and salivary gland biopsy showed infiltration of mononuclear cells (Fig. 3A, focus score 2.6/4mm^2). A diagnosis of SS was made, based on of hyposalivation, positive MR sialography, positive anti Ro/SS-A antibody, and sialadenitis. Renal biopsy (Fig. 3B) also showed diffuse inflammatory infiltrates in the tubulointerstitium, mainly consisting of small lymphocytes. No glomerulonephritis was found, and a diagnosis of interstitial nephritis was made.

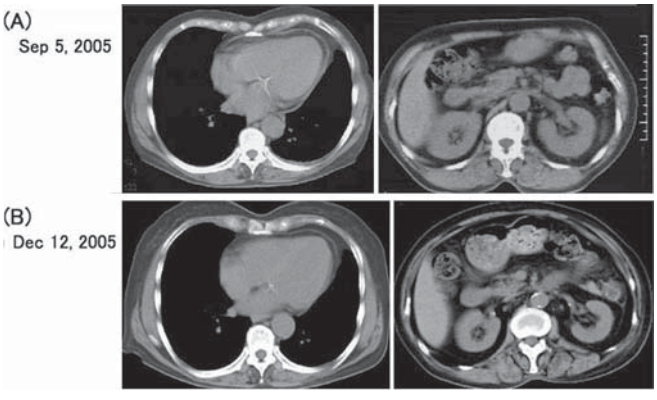

Fig. 1A,B. Chest and abdominal computed tomography (CT). **A** Chest CT showed cardiomegaly and pericardial effusion. Abdominal CT showed bilateral swelling of kidney. **B** One month later, chest CT returned to normal without particular treatment. Swelling of kidney was normalized in response to corticosteroid therapy for 3 months

Medium-dose oral prednisolone (40 mg/day) was started for her interstitial nephritis. Renal tubular dysfunction, β_2-MG, sIL-2R, and IgG were normalized, and PR3-ANCA was decreased in response to the therapy (Fig. 4).

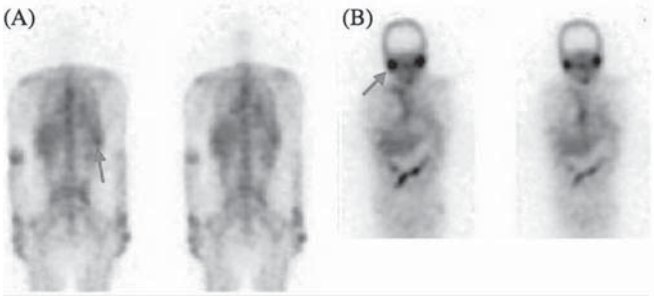

Fig. 2A,B. Gallium-67 scintigram. Gallium-67 scintigram indicated abnormal uptake in pericardial membrane (**A**, *arrow*), and bilateral parotid gland (**B**, *arrow*), but no uptake in kidneys

Discussion

We report a case of PR3-ANCA-positive SS complicated with interstitial nephritis. Minor salivary gland and renal biopsy showed infiltration of mononuclear cells. The patient had severe inflammatory infiltrates in the tubulointerstitium, hypergammaglobulinemia, positive PR3-ANCA, elevated sIL-2R, renal tubular dysfunction, but no renal dysfunction or proteinuria was found, and she also had no hypocomplementemia, C1q-immune complex, and IgG_4 elevation. Symptoms and laboratory data were normalized in response to medium-dose corticosteroid. Pericarditis was suspected to be caused by viral infection because pericardial effusion returned to normal without particular treatment. Moreover, she had prior cold-like symptoms such as general malaise, cough, and fever.

The presence of ANCA dose not always mean the diagnosis of vasculitis.[7] Ramos-Casals et al. reported atypical autoantibodies in patients with primary SS.[7] In their report, 13 (6%) of 201 patients had positive ANCA: 12 had

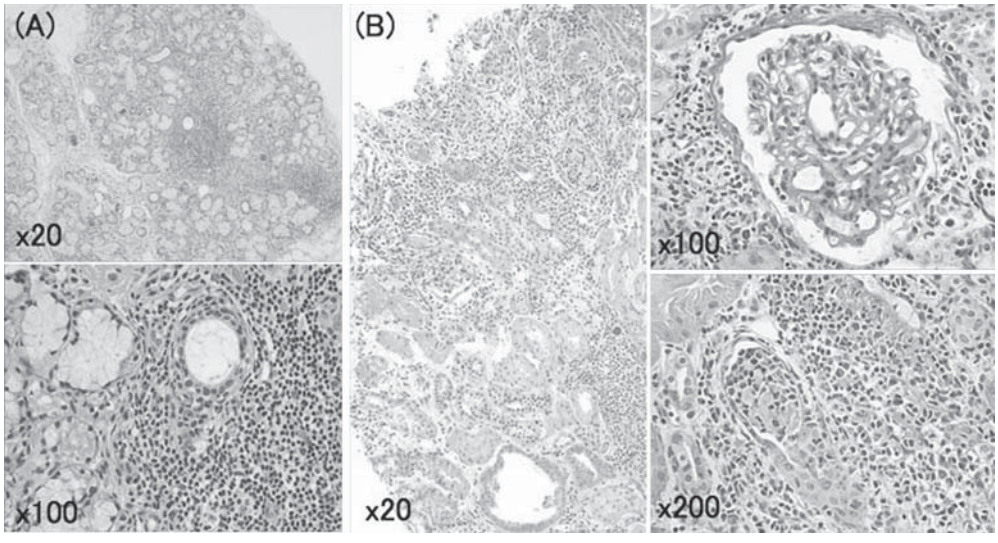

Fig. 3A,B. Salivary gland biopsy and renal biopsy. **A** Salivary gland biopsy showed infiltration of mononuclear cells (Focus score 2.6/4 mm^2). **B** Renal biopsy showed diffuse inflammatory infiltrates in the tubulointerstitium, mainly consisting of small lymphocytes

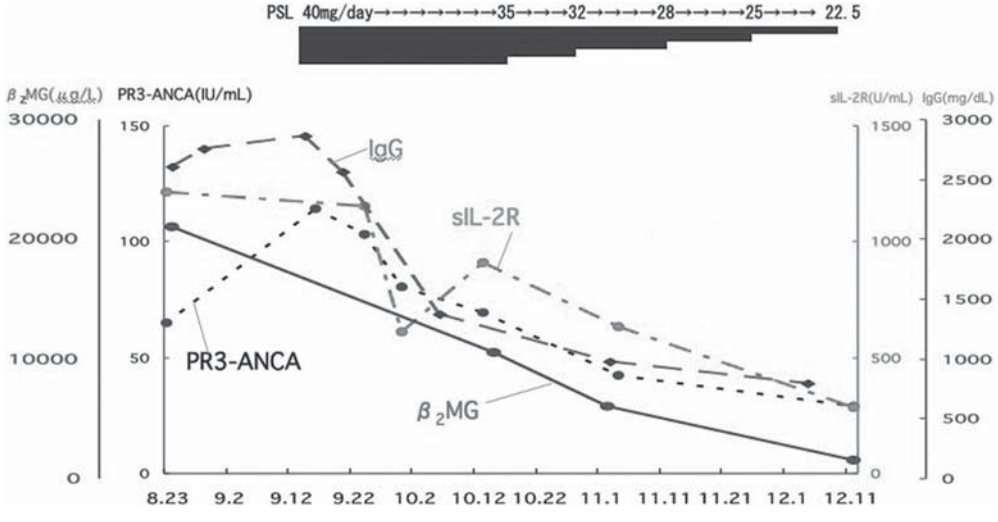

Fig. 4. Clinical course. Medium-dose oral prednisolone (40 mg/day) was started for interstitial nephritis. Renal tubular dysfunction, β_2-MG, sIL-2R, and IgG were normalized, and PR3-ANCA was decreased in response to the therapy. β_2-*MG*, β_2-microglobulin; *sIL-2R*, soluble interleukin-2 receptor; *IgG*, immunoglobulin G; *PR3-ANCA*, proteinase 3-antineutrophil cytoplasmic antibody; *PSL*, prednisolone

perinuclear antineutrophil cytoplasmic antibody (P-ANCA) and 1 had cytoplasmic antineutrophil cytoplasmic antibody. Antigen specificity determined by ELISA showed that 5 patients had myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA). No patient had PR3-ANCA.[8–10] Nine (69%) of 12 patients had extraglandular features, including Raynaud's phenomenon (n = 8), pulmonary involvement (n = 7), articular involvement (n = 7), peripheral neuropathy (n = 4), cutaneous vasculitis (n = 3), and renal involvement (n = 1). Their report indicated the clinical feature of SS patients with ANCA is high prevalence of extraglandular manifestations.[7–10] Antineutrophil cytoplasmic antibody could be a new marker for extraglandular features of SS.

Our patient was diagnosed as having interstitial nephritis with severe inflammatory infiltrates in the tubulointerstitium, although clinical and laboratory abnormalities were mild. Overt or latent renal tubular acidosis (RTA) with interstitial nephritis develops in 33% of patients with SS.[11] However, our patient did not have RTA. Early diagnosis of interstitial nephritis is important, because interstitial nephritis is critical for prognosis, and there is a possibility of developing RTA and/or renal failure.[3] Diagnosis of interstitial nephritis is often difficult because clinical and laboratory abnormalities are generally mild.[12–18] It is necessary that interstitial nephritis be considered when there exist alkaline urine and excretion of the tubular protein of low molecular weight, serum and urinary β_2-MG, and/or urinary NAG elevation, and symptoms such as limb paralysis, polyuria, and appetite loss,[13] even if laboratory abnormalities such as elevation in plasma creatinine concentration, leukocyturia, and proteinuria are mild. It is possible that serum total gamma-globulin, serum protein, serum β_2-MG,[12] serum sIL-2R level,[19] and severe lymphoproliferative lesions in kidney[12,15,19] could be the index of the activity of interstitial nephritis.

The standard therapy for interstitial nephritis is not established.[12–18] Our patient had severe inflammatory infiltrates in the tubulointerstitium, renal tubular dysfunction (urine NAG 5.4 U/day, urine β_2-MG 20 988 μg/day), elevation of sIL-2R, positive PR3-ANCA, but without hypocomplementemia and elevated immunocomplex, and showed no clinically significant vasculitis. For such reasons, medium-dose corticosteroid therapy (PSL 40 mg/day) was chosen for our patient. In our case, the titer of ANCA was used as one of the disease markers for interstitial nephritis.

We report a case of PR3-ANCA positive SS complicated with interstitial nephritis. Antineutrophil cytoplasmic antibody is one of the atypical antibodies which is occasionally seen in SS patients, and clinical features of SS patients with ANCA were high prevalence of extraglandular manifestations.[7–9] Antineutrophil cytoplasmic antibody could be a new marker for extraglandular features of SS. It might be beneficial for SS patients who have positive ANCA to investigate extraglandular lesions such as interstitial nephritis. Further study is needed to clarify the significance of ANCA in SS.

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