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CASE REPORT

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A case of Mikulicz's disease complicated with interstitial nephritis successfully treated by high-dose corticosteroid

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Abstract A 40-year-old woman who had bilateral swelling in the eyelids and submandibular region was admitted. Clinical findings suggested she had primary Sjögren's syndrome. Laboratory data showed glucosuria, positive CRP (0.50 mg/dl), liver dysfunction (AST 53 U/l, ALT 101 U/l, γ-GTP 241 U/l, ALP 914 U/l, LAP 496 U/l), hyperglycemia, hypergammaglobulinemia (IgG 3450 mg/dl, IgA 91 mg/dl, IgM 80 mg/dl), hypocomplementemia (C3 73 mg/dl, C4 2 mg/dl, CH50 < 19.0 U/ml), renal tubular dysfunction (urine *N*-acetyl-β-D-glucosaminidase 8.6 U/l, urine β_2-microglobulin 83 μg/l), and urinary concentration defect. Ammonium chloride loading test was normal. Gallium-67 scintigram indicated abnormal uptake in bilateral lacrimal glands, submandibular glands, and kidneys. A diagnosis of Mikulicz's disease and interstitial nephritis was made, since biopsy specimens of her lacrimal gland and minor salivary gland showed diffuse infiltration of lymphocytes. Renal biopsy specimens also showed severe interstitial infiltration of lymphocytes. Symptoms and laboratory data normalized in response to methylprednisolone pulse therapy and prednisolone 60 mg/day. This case of Mikulicz's disease complicated with interstitial nephritis was successfully treated by high-dose corticosteroid.

Key words Corticosteroid · Interstitial nephritis · Mikulicz's disease (MD) · Sjögren's syndrome (SS)

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Introduction

Mikulicz's disease (MD) is a unique condition in which enlargement of the lacrimal and salivary glands develops caused by lymphocytic infiltration,[1] as is also seen in Sjögren's syndrome (SS).[2] Mikulicz's disease has symmetrical swelling of more than two lacrimal and major salivary glands. Mikulicz's disease patients rarely show significant loss in saliva secretion, whereas SS patients show hyposalivation. Mikulicz's disease patients usually have no anti-SS-A or SS-B antibodies. Mikulicz's disease has recently been included within primary SS because both diseases were histologically similar.[3–5] Recently, it was revealed that elevated IgG_4 concentrations in the serum and prominent infiltration by plasmacytes expressing IgG_4 are seen in the lacrimal and salivary glands in MD, as is not seen in SS. For such reasons we consider that MD is a different disease entity from SS.[6]

In autoimmune disease, glomerulonephritis is more common than interstitial nephritis. Interstitial nephritis is common in SS,[7,8] affecting approximately 10% of the patients, but prevalence of interstitial nephritis in MD is unknown. Diagnosis of interstitial nephritis is 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.[9] Here, we report a case of MD complicated with early stage of interstitial nephritis and successfully treated by high-dose corticosteroid.

Case report

A 40-year-old woman developed bilateral swelling in the eyelids and submandibular region and dry mouth in August 2003. She was suspected to have primary SS, and was treated with cevimeline hydrochloride without significant improvement. She was admitted our hospital for further investigation in May 2004. Physical examinations showed

Table 1. Laboratory data

Urinalysis		**Serology**		**Urinalysis (24 h)**	
pH	5.0	IgG	3450 mg/dl	Vol	700 ml
Specific gravity	1.01	IgG_4	42.35%	Amy	165 mg/dl
Protein	(–)		2400 mg/dl	Osm	528 Osm
Occult blood	(–)	IgA	91 mg/dl	Cr	110 mg/dl
Gluc	3+	IgM	80 mg/dl	Prot	0.06 g/day
WBC	5/HPF	IgD	3.7 mg/dl	Glu	0.57 g/day
RBC	0/HPF	IgE	272 IU/ml	Na	45.2 mEq/day
Blood Count		C3	73 mg/dl	K	21.9 mEq/day
RBC	450×10^4/μl	C4	2 mg/dl	NAG	8.6 U/l
Hb	13.2 g/dl	CH50	<19.0 U/ml	Alb	7.2 mg/day
Ht	40.3%	Ferritin	126 ng/dl	β_2-MG	83 μg/l
Retic	15.0‰	C1q-IC	4.5 μg/ml	**Other Tests**	
WBC	7730/μl	Lipase	26 IU/l/37°C	**Urinary concentration test**	
Neu	83.0%	Trypsin	150 ng/ml	Hypofunction	
Lymph	10.0%	Phospholipase	159 ng/dl		Specific gravity
Mono	5.0%	Elastase-1	200 ng/dl	0 h	1.012
Eos	2.0%	sIL-2R	3250 U/ml	1 h	1.013
Baso	0%	**Infection**		2 h	1.010
Plts	22.5×10^4/μl	HBs-Ag	(–)	**Ammonium chloride loading test**	
Inflammation		HBs-Ab	(–)	Normal	
ESR	68 mm/h	HCV-Ab	(–)		Urine pH
CRP	0.5 mg/dl	Lues	(–)	1 h	5.5
Blood Chemistry		**Autoimmunity**		2 h	5.5
Na	134 mEq/l	RF	62	3 h	5.5
K	3.9 mEq/l	RAPA	×80	4 h	5.0
Cl	99 mEq/l	ANA	(–)	5 h	5.0
Ca	9.2 mg/dl	Anti-DNA Ab	(–)	6 h	5.0
P	2.8 mg/dl	Anti-Sm Ab	(–)	**ABG (Room air)**	
Mg	1.7 mg/dl	Anti-RNP Ab	(–)	pH	7.410 torr
BUN	14 mg/dl	Anti-SS-A Ab	(–)	$PaCO_2$	41.2 torr
Cr	0.74 mg/dl	Anti-SS-B Ab	(–)	PaO_2	86.1 torr
TP	8.8 g/dl	Anti-mitochondria Ab	(–)	BE	0.8 mmol/l
Alb	3.6 g/dl	Anti-mitochondria 2 Ab	(–)	HCO^{3-}	25.5%
T-bil	0.6 mg/dl	Anti-LKM-1 Ab	(–)	SaO_2	96.6 torr
LDH	147 U/l	Anti-SMA Ab	×40	A-aDO_2	13.3 torr
AST	53 U/l	**Coagulation**		**Ophthalmology**	
ALT	101 U/l	TT	63.6%	Keratoconjunctivitis sicca	(–)
γ-GTP	241 U/l	HPT	76.9%	Fluorescein	rt 0-1-1/9, lt 1-1-0/9
ALP	914 U/l	PT	84.7%	Rose Bengal	rt 0-1-1, lt 1-1-0
CK	28 U/l	PT (INR)	1.09	Schirmer	rt 13 mm, lt 25 mm
Amy	64 U/l	APTT	23 s	**Salivary Function Test**	
T-chol	147 mg/dl	Fbg	847 mg/dl	Saxon test	1.78 g/2 min
TG	111 mg/dl	FDP	3.8 μg/ml	Salivary scintigraphy	hypofunction
Glu	317 mg/dl	D-Dimer	0.7 μg/ml		
		ATIII	143%		

enlargement of the lacrimal gland and submandibular region (Fig. 1). 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, cardiovascular, or respiratory disturbances.

Laboratory data are shown in Table 1. The data showed glucosuria (1000 mg/dl), lymphocytopenia (154 /μl), positive C-reactive protein (0.50 mg/dl), liver dysfunction (AST 53 U/l, ALT 101 U/l, γ-GTP 241 U/l, ALP 914 U/l, ALP 496 U/l), hyperglycemia (glucose 317 mg/dl), hypocomplementemia (C3 73 mg/dl, C4 2 mg/dl, CH50 < 19.0 U/ml), elevated C1q-immune complex (4.5 IU/ml), elevated sIL-2R (3250 U/ml), rheumatoid factor 62 U/ml, but negative for antinuclear antibody (ANA), anti-SS-A antibody, and anti-SS-B antibody. Renal tubular dysfunction was noted (urine *N*-acetyl-β-D-glucosaminidase [NAG] 8.6 U/l, urine β_2-microglobulin [β_2-MG] 83 μg/l), and urinary concentration test was abnormal, but no renal dysfunction or proteinuria was found (blood urea nitrogen 14 mg/dl, creatinine 0.74 mg/dl). The data showed hypergammaglobulinemia (IgG 3450 mg/dl, IgA 91 mg/dl, IgM 80 mg/dl, IgE 272 IU/ml), and IgG_4 was significantly increased (42.35% of total IgG, 2400 mg/dl), but there was no monoclonal gammopathy or cryoglobulinemia. Arterial blood gas (ABG) showed no acidemia, and ammonium chloride loading test was normal. The Saxon test was 1.78 g/2 min. Ophthalmologic examinations were as follows: fluorescein test rt 1, lt 1, Rose Bengal test rt 2, lt 2, Schirmer test rt 13 mm, lt 25 mm, and keratoconjunctivitis sicca (KCS) was not diagnosed. Her chest radiograph was normal. Computed tomography (CT) scans and magnetic resonance imaging (MRI) (Fig. 2) showed diffuse enlargement with wedge-shaped contour in bilateral parotid glands, submandibular glands,

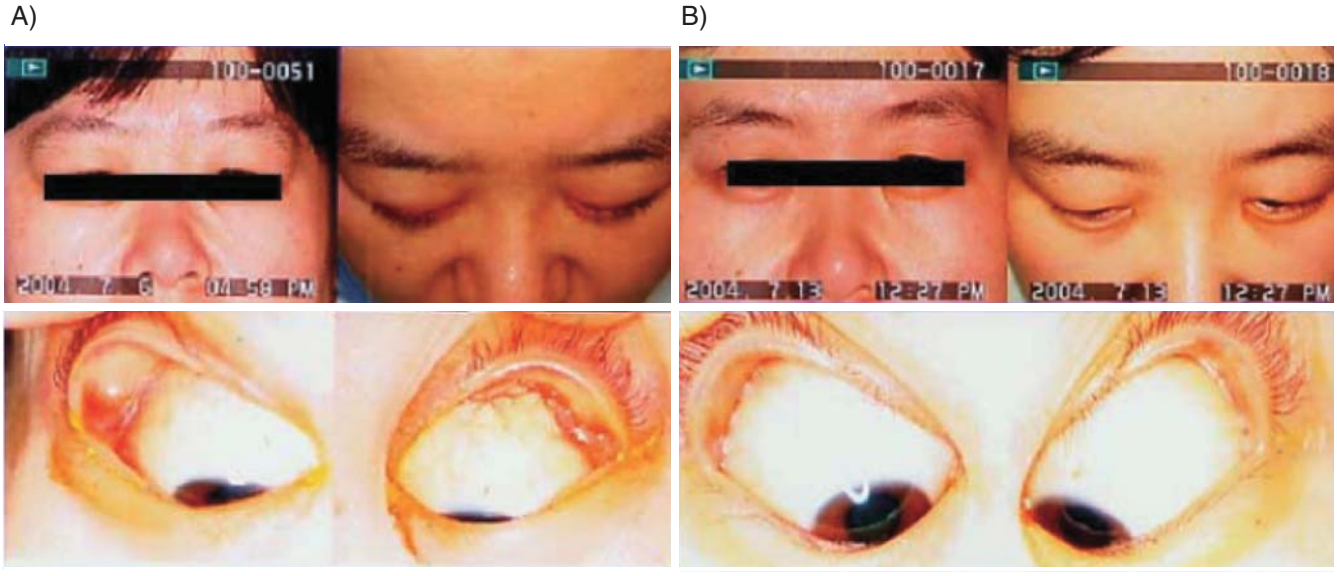


Fig. 1A,B. Appearance of lacrimal gland before and after corticosteroid treatment. Enlargement of the lacrimal gland and submandibular region (**A**) disappeared in response to corticosteroid therapy for 3 months (**B**)

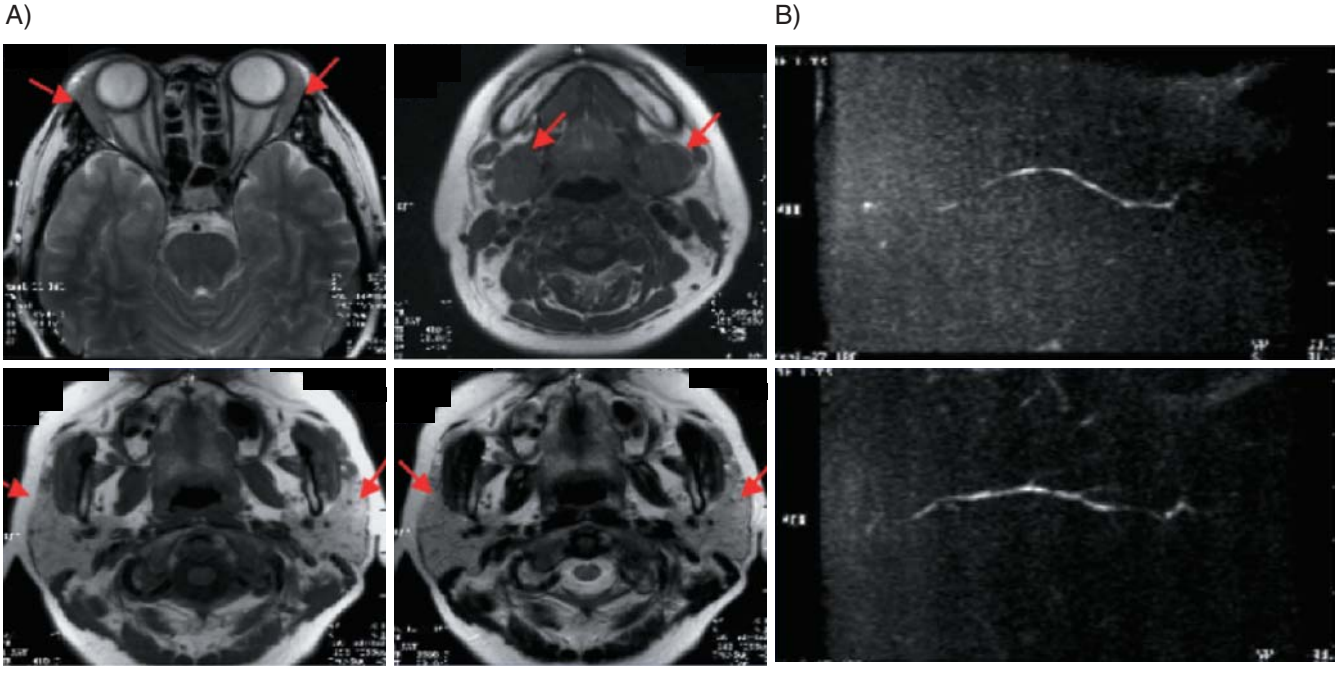


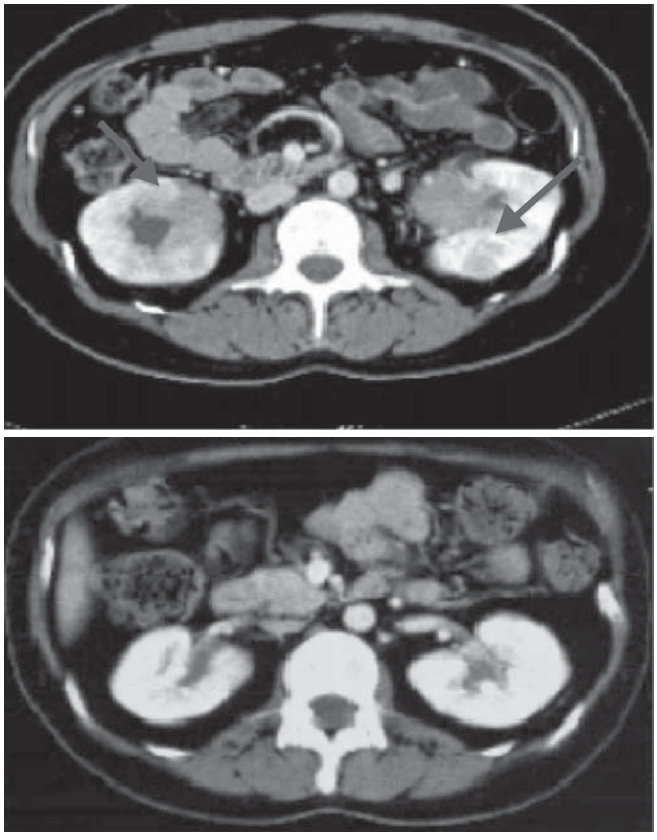
Fig. 2A,B. Salivary gland magnetic resonance imaging (MRI) and MR sialography. Salivary gland MRI (**A**) showed diffuse enlargement with wedge-shaped contour in bilateral parotid glands, submandibular glands, and lacrimal glands (*arrows*). MR sialography (**B**) was normal

and lacrimal glands. Abdominal CT showed bilateral calicectasis and enhanced heterogeneity (Fig. 3). Gallium-67 scintigram (Fig. 4) indicated abnormal uptake in bilateral lacrimal glands, submandibular glands, and kidneys.

Salivary gland (Fig. 5) and lacrimal gland (Fig. 6) biopsy showed diffuse infiltration of mononuclear cells and plasmacytes expressing IgG_4. A diagnosis of MD was made based on: (1) enlargement of lacrimal and salivary glands, (2) slight hyposalivation, (3) negative anti-SS-A or SS-B antibodies, (4) IgG_4 elevation, (5) minor salivary gland and lacrimal gland with severe mononuclear infiltration,[10] and (6) plasmacytes expressing IgG_4. At the same time, a diagnosis of SS was made based on hyposalivation and mononuclear cell infiltration in salivary gland and lacrimal gland biopsy. Renal biopsy (Fig. 7) also showed diffuse inflammatory infiltrates in the tubulointerstitium, mainly consisting of plasma cells and small lymphocytes. No glomerulonephritis was found, and a diagnosis of interstitial nephritis was made.

Methylprednisolone (mPSL) pulse therapy and subsequent high-dose oral prednisolone (PSL 60 mg/day) were

A)



B)

Fig. 3A,B. Abdominal computed tomography. **A** Abdominal CT showed bilateral calicectasis and enhanced heterogeneity (*arrows*). **B** These findings normalized in response to corticosteroid therapy for 3 months

started for her interstitial nephritis. Administration of corticosteroids caused rapid diminution in the size of lacrimal glands and salivary glands (Fig. 1). Salivation was recovered (4.80 g/2 min), and hypergammaglobulinemia and hypocomplementemia returned to normal after the treatment. A second renal biopsy performed 3 months after the beginning of the treatment showed remarkable improvement of the interstitial cell infiltration (Fig. 7).

Discussion

We report a case of MD complicated with interstitial nephritis. The characteristics of this case were atypical onset, the negative anti SS-A and SS-B antibodies, and reversibility of dryness by corticosteroid treatment. These findings suggest that the pathogenesis of this case may be different from typical SS. The patient had hypergammaglobulinemia and IgG_4 was markedly increased. Minor salivary gland, lacrimal gland, and renal biopsy showed diffuse infiltration of mononuclear cells and plasmacytes expressing IgG_4.[6] She also had renal tubular dysfunction and urinary concentration defect, but no renal dysfunction was noted. Symptoms and laboratory data normalized in response to high-dose corticosteroid.

Mikulicz's disease was first described in 1937 as a benign, asymptomatic, symmetrical enlargement of the lacrimal and salivary glands.[3,10,11] In 1953 and 1954, Morgan and Castleman described the relation between MD and SS, emphasizing the identical morphologic appearance of the salivary and lacrimal glands of the two diseases.[10,11] Yamamoto et al. recently raised the possibility that MD and

A)

B)

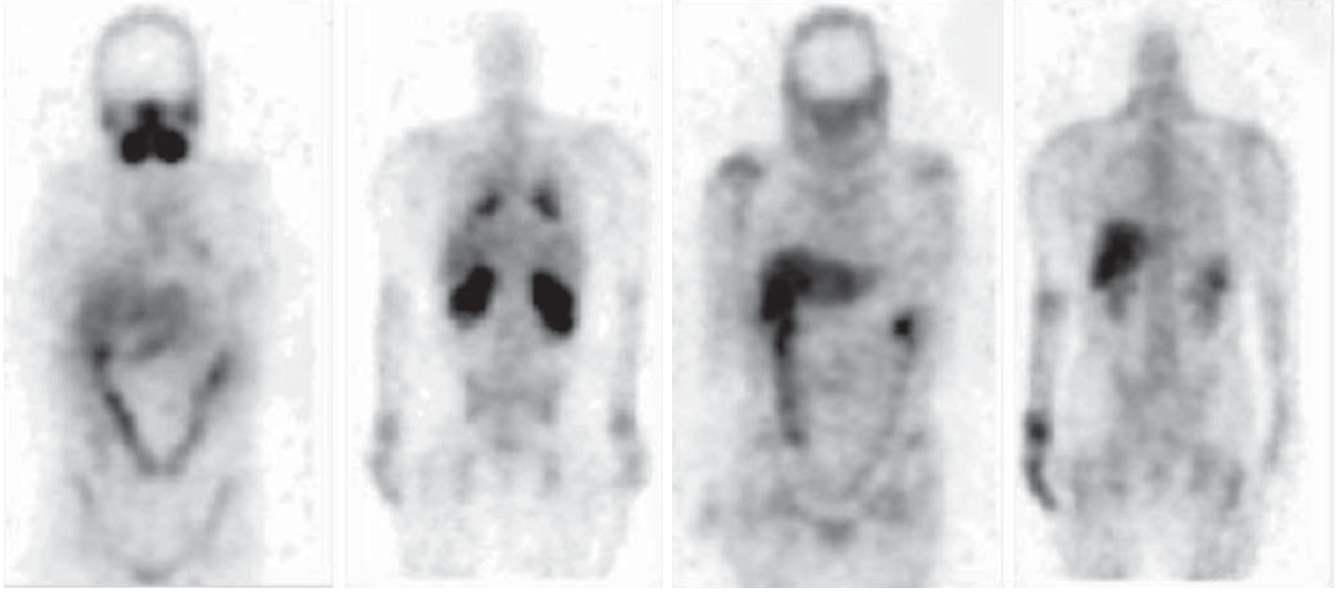


Fig. 4A,B. Gallium-67 scintigram. **A** Gallium-67 scintigram indicated abnormal uptake in bilateral lacrimal glands, submandibular glands, and kidneys. **B** Abnormal uptake returned to normal in response to corticosteroid therapy for 3 months

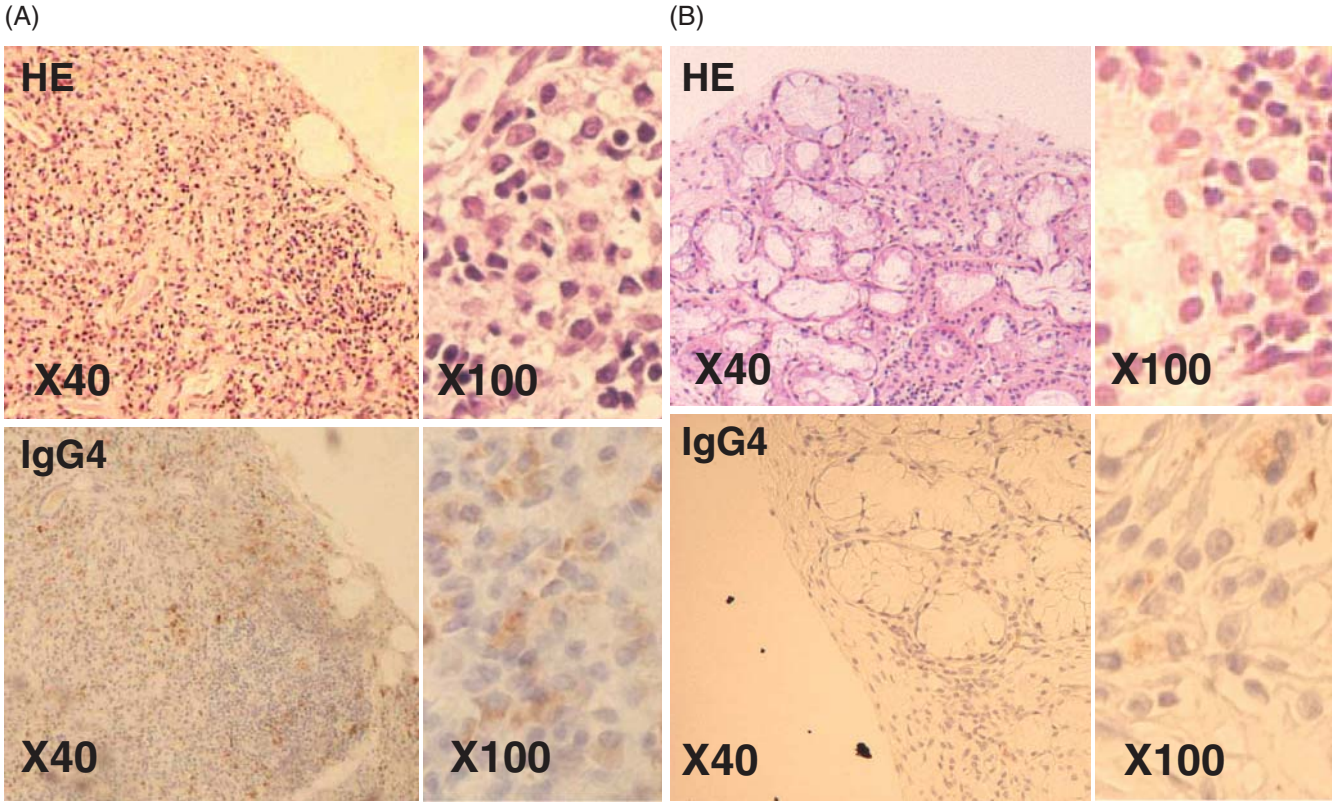


Fig. 5A,B. Minor salivary gland biopsy. **A** Biopsy specimens of minor salivary gland showed diffuse infiltration of lymphocytes (Focus score 12) and plasmacytes expressing IgG_4. **B** Lymphocytic infiltration markedly decreased after corticosteroid therapy for 3 months (Focus score 0.8)

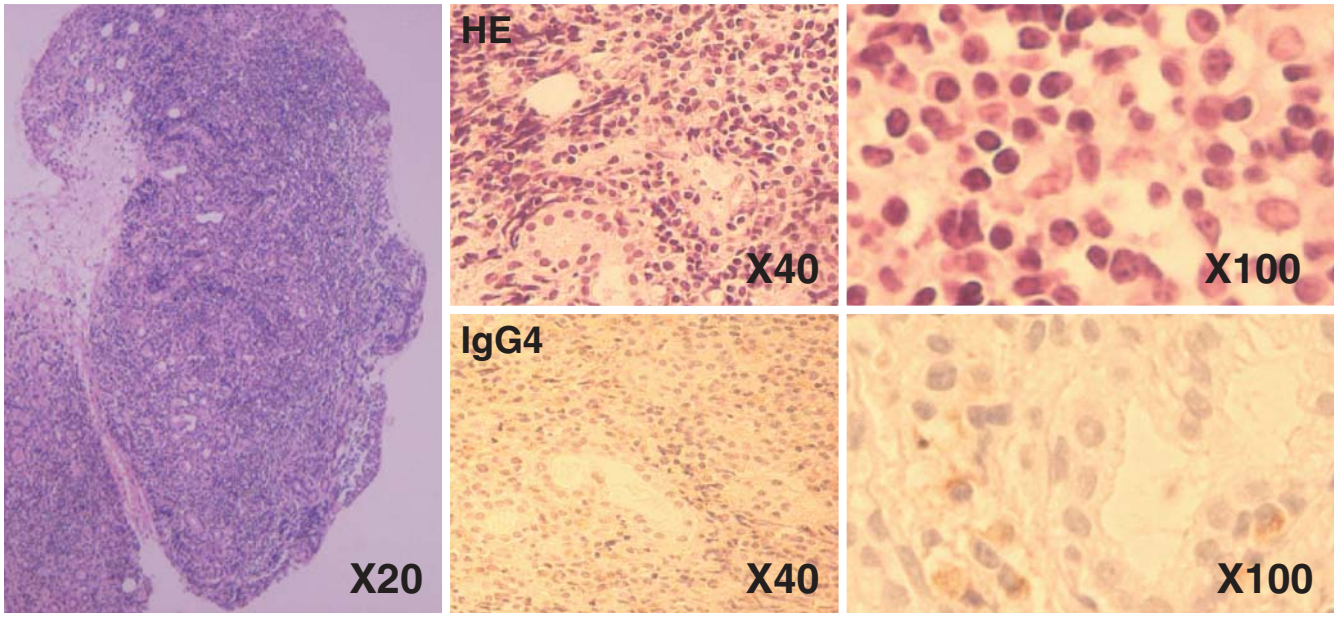


Fig. 6. Lacrimal gland biopsy. Lacrimal gland biopsy showed diffuse infiltration of mononuclear cells and plasmacytes expressing IgG_4

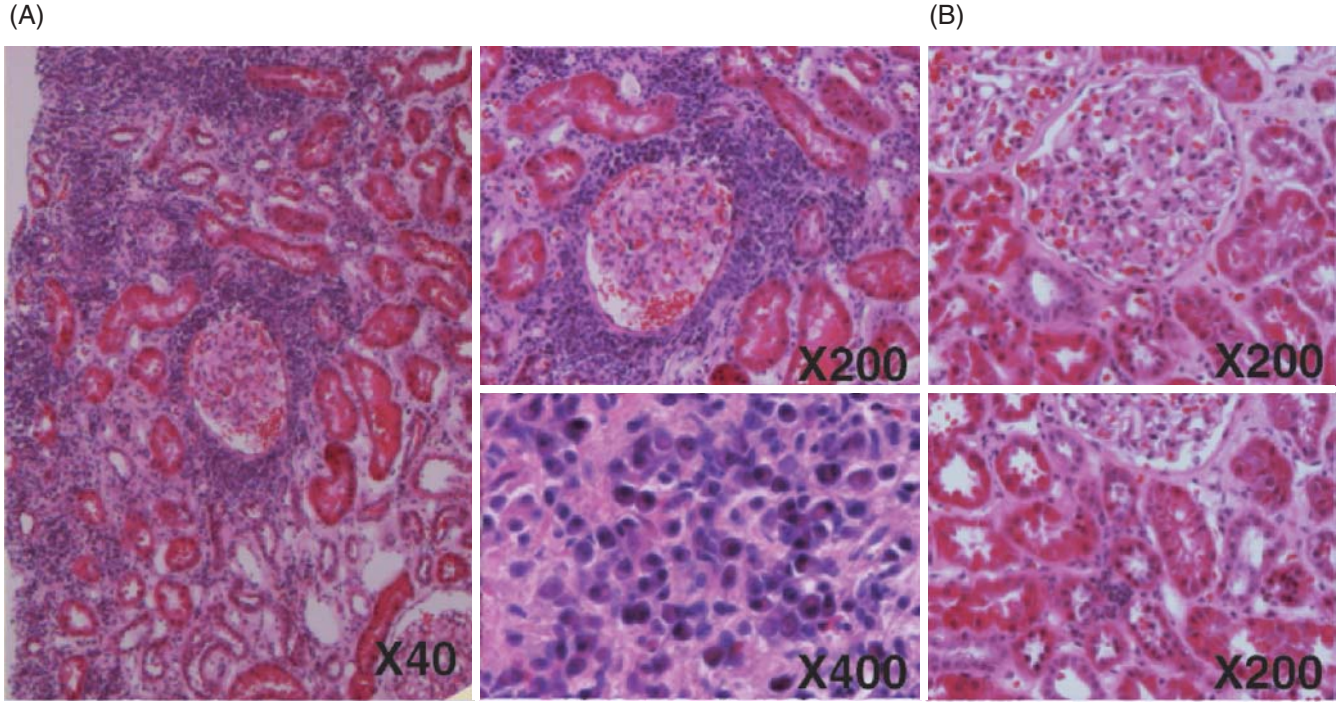


Fig. 7A,B. Renal biopsy. **A** Renal biopsy showed diffuse inflammatory infiltrates in the tubulointerstitium, mainly consisting of plasma cells and small lymphocytes. No glomerulonephritis was found. **B** Renal lesions showed improvement in response to corticosteroid therapy

SS are separate diseases.[3,4] Clinical manifestation of MD is as follows. (1) MD mainly affects middle-aged or elderly females. (2) The swelling of lacrimal and salivary glands is persistent in MD. (3) Half of the patients with MD do not have KCS and salivary hypofunction, and it is improved by steroid treatment. (4) MD has no anti-SS-A or SS-B antibodies. (5) The serological characteristics of MD are hypergammaglobulinemia, especially IgG_4 elevation. (6) Specimens of the minor salivary glands from MD patients show severe mononuclear infiltration[10] and plasmacytes expressing IgG_4. Our case is consistent with these characteristics.

Diagnosis of interstitial nephritis is often difficult because clinical and laboratory abnormalities are generally mild. Clinical manifestations of interstitial nephritis are as follows.[9] (1) Laboratory data are almost normal in general. (2) Alkaline urine and excretion of the tubular protein of low molecular weight exist. (3) Urinary β_2-MG is elevated and NAG is normal or slightly elevated. β_2-MG is a freely filterable protein which, under normal circumstances, is almost totally reabsorbed in the proximal tubule. Damage to this section of the nephron leads to increased β_2-MG in the urine. Urinary NAG is a marker of proximal tubular damage. This enzyme shows a negative correlation to creatinine clearance. (4) When the symptoms, such as limbs paralysis, polyuria, and appetite loss are present, it is necessary to consider renal tubular acidosis and tubular concentration defect.[1] (5) Therapy usually consists of steroids. It is necessary that interstitial nephritis be considered, even if laboratory abnormalities such as elevation in plasma creatinine concentration, leukocyturia, and proteinuria, are mild. When the renal tubular dysfunction is noted even if other laboratory abnormalities are slight, abdominal CT and Gallium-67 scintigram should be taken and it is necessary to consult a specialist. Early diagnosis of interstitial nephritis is important, because interstitial nephritis is critical for prognosis, and there is a possibility of developing renal failure,[9] while the extent of urinary concentration defect correlates with that of nephritis. Pertovaara et al. reported that high levels of serum total gammaglobulin, serum protein, and serum β_2-MG were the best predictors of the development of distal renal tubular acidosis (dRTA) in primary SS patients.[12] Matsumura et al. and Komatsu et al. reported that there are severe lymphoproliferative lesions in part of SS with interstitial nephritis.[13,14] It is reported serum sIL-2R level is a possible marker of lymphoproliferative lesions.[14] It is possible that sIL-2R could be the index of the activity of interstitial nephritis. The standard therapy for interstitial nephritis is unknown. In previous reports, mPSL pulse therapy and/or moderate to high-dose corticosteroid therapy were used.[12–17] in SS complicated with interstitial nephritis. This case had severe inflammatory infiltrates in the tubulointerstitium, hypocomplementemia, positive immune complex, and elevation of sIL-2R. In addition, immunosuppressive agents should be avoided as much as possible in SS because SS has risk of lymphoma development. For such reasons, mPSL pulse therapy and subsequent high-dose oral prednisolone (60 mg/day) was chosen for our case.

In conclusion, complication of interstitial nephritis should be considered in MD patients, with or without significant renal dysfunction. Early treatment with corticosteroids is recommended for patients with MD complicated by interstitial nephritis.

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