

A Case of Sjögren's Syndrome Complicated with Interstitial Nephritis and Delayed Onset Autoimmune Hepatitis

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A 61-year-old woman was admitted to our hospital because of muscle paralysis and was found to have severe hypokalemia. A gallium-67 scintigram revealed a positive accumulation in the bilateral salivary glands, and a labial minor salivary gland biopsy demonstrated a massive lymphocyte infiltrate around the salivary ducts. She was diagnosed with Sjögren's syndrome (SS) associated with renal tubular acidosis. Renal biopsy revealed tubulointerstitial nephritis with a mild focal infiltration of lymphocytes and plasma cells. These pathological features were compatible with SS with renal involvement. Acidosis and hypokalemia were corrected with sodium bicarbonate and potassium chloride, which relieved the patient's symptoms. Although steroid therapy has been reported to be effective in SS-associated tubulointerstitial nephritis, the patient's serum potassium level could be controlled without administering steroids during the first admission. Five years later, she was admitted again because of severe liver dysfunction attributed to autoimmune hepatitis. Oral administration of prednisolone resulted in the normalization of her transaminase levels, and the control of her serum potassium level became easier. It has been reported that patients with SS with salivary gland involvement tend to have hepatic complications, and those with hepatic complications tend to have renal involvement. Physicians should be aware of hepatic involvement, even if there is no liver dysfunction at the initial diagnosis of SS with salivary gland and renal involvement. It remains uncertain whether the administration of a low dose of steroids before the onset of autoimmune hepatitis might have prevented the development of liver dysfunction in our patient. (J Nippon Med Sch 2018; 85: 117–123)

Key words: Sjögren's syndrome, renal tubular acidosis, hypokalemia, autoimmune hepatitis

Introduction

Sjögren's syndrome (SS) may be associated with extraglandular involvement in several different organs^{1,2}. Tubulointerstitial disease in the kidneys is common in SS, with the major presenting feature being distal renal tubular acidosis (RTA)^{3–6}. Steroids have been reported to be effective for interstitial nephritis complicating SS^{7–9}. Anti-neutrophil cytoplasmic antibodies (ANCA) are known to stain positive in some cases of SS^{10,11}, and vasculitis is included in extraglandular manifestations of SS¹². Therefore, patients with SS may have ANCA-associated vascu-

litis (AAV)^{12,13}. Hepatic complications, including autoimmune hepatitis, are also some of the extraglandular manifestations of SS¹. The prevalence of autoimmune hepatitis in patients with primary SS is approximately 1 to 4%^{14–17}. We have recently encountered a case of SS complicated with interstitial nephritis and the presence of positive proteinase 3 (PR3)-ANCA, followed by delayed onset autoimmune hepatitis.

Case Presentation

A 61-year-old woman was admitted to our hospital com-

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Table 1 Laboratory findings in the first admission

Urinary analysis		Blood chemistry		Serological tests	
pH	7.0	TP	8.4 g/dL	ANA (speckled)	×640
urine specific gravity	1.006	Alb	4.2 g/dL	anti-SSA-antibody (index)	×104.8
protein	(-)	AST	44 IU/L	anti-SSB-antibody (index)	×190.9
glucose	(-)	ALT	33 IU/L	PR3-ANCA	53.0 U/mL
occult blood	(-)	LDH	220 IU/L	Arterial blood gas	
urobilinogen	(+/-)	ALP	180 IU/L	pH	7.28
sediment		T.Bil	0.6 mg/dL	PaO ₂	98.5 Torr
RBC	1-4 /HPF	NH ₃	136 µg/dL	PaCO ₂	32.6 Torr
WBC	20-29 /HPF	BUN	15.1 mg/dL	HCO ₃	14.6 mEq/L
hyaline cast	(-)	Cr	0.9 mg/dL	BE	-10.9 mEq/L
granular cast	(-)	Na	145 mEq/L	saturation	96.8 %
Complete blood count		K	1.5 mEq/L	Urinary chemistry	
WBC	7,060 /µL	Cl	119 mEq/L	U-Na	41 mEq/L
RBC	411×10 ⁴ /µL	Ca	8.8 mg/dL	U-K	10.9 mEq/L
Hb	12.8 g/dL	P	5.0 mg/dL	U-Cl	37 mEq/L
Hct	35.8 %	T.chol	152 mg/dL	U-Cr	8.77 mg/dL
MCV	87.1 fL	TG	79 mg/dL	U-Osm	212 mOsm/L
MCH	31.1 pg	UA	1.2 mg/dL	U-NAG	4.8 U/L
MCHC	35.8 %	glucose	112 mg/dL	U-β 2MG	10,230 µg/L
PLT	23.6×10 ⁴ /µL	CRP	0.33 mg/dL	Anion gap	11.4 mEq/L
		Serum Osm	326 mOsm/L	FENa	2.90 %
				Urinary anion gap	14.9 mEq/L
				TTKG	11.2

ANA: anti-nuclear antibody, PR3-ANCA: proteinase 3-anti-neutrophil cytoplasmic antibody, NAG: N-acetyl-β-D-glucosaminidase, β2M: β2-microglobulin, FENa: fractional excretion of sodium, TTKG: transtubular K gradient.

plaining of the sudden onset of muscle paralysis. Laboratory findings on admission showed metabolic acidosis (HCO₃⁻: 14.6 mEq/L) with a normal anion gap (11.4 mEq/L) and severe hypokalemia (1.5 mEq/L). The urine anion gap was positive at 14.9 mEq/L, and the transtubular K gradient (TTKG) was elevated at 11.2. The serum uric acid level was low (1.2 mg/dL). The level of N-acetyl-β-D-glucosaminidase (NAG) in the urine was normal (4.8 U/L), while that of urinary β2-microglobulin (MG) was elevated (10,230 µg/L). The serum creatinine level was nearly normal (0.90 mg/dL). PR3-ANCA was positive at 53.0 U/mL (**Table 1**). We diagnosed the acid-base disorder as type I RTA. In addition, Shirmer test results were positive, the rose bengal staining score was 7, and anti-Ro/SS-A and La/SS-B antibodies also stained positive. Computed tomography revealed bilateral calcification of the kidneys. A gallium-67 scintigram showed a positive accumulation of the tracer in the bilateral salivary glands, and a labial minor salivary gland biopsy demonstrated a massive infiltration of lymphocytes around the salivary ducts (**Fig. 1**). We diagnosed the patient with SS associated with type I RTA, based on revised Japanese criteria for SS¹⁸. To evaluate the renal tubulointerstitial lesion, we performed a renal biopsy on

the 11th hospital day. Specimens from the renal biopsy showed mild infiltration of lymphocytes and plasma cells in the tubulointerstitium. There was very little inflammation in the glomerular region (**Fig. 2**). We attributed the findings to tubulointerstitial nephritis due to SS, because interstitial inflammatory cells were mainly CD3⁺ T cells and CD138⁺ plasma cells, with only a few CD20⁺ B cells, indicative of plasma cell-rich interstitial nephritis (**Fig. 2**). Treatment with sodium bicarbonate and potassium chloride was initiated, which gradually relieved the patient's symptoms. She was discharged on the 29th hospital day.

After the first discharge, treatment with sodium bicarbonate and potassium chloride was continued at the same dose on an outpatient basis. The levels of both urinary β2-MG and serum PR3-ANCA decreased without steroid therapy (urinary β2-MG: 2,990 µg/L, serum PR3-ANCA: 1.5 U/mL). The levels of serum creatinine and potassium remained nearly unchanged. However, five years later, the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were noted to be elevated (AST: 984 U/L, ALT: 858 U/L). Serum levels of anti-nuclear antibody (ANA) and immunoglobulin G (IgG) were also elevated. Surface antigens of hepatitis B, anti-hepatitis C virus antibodies, and anti-hepatitis A-

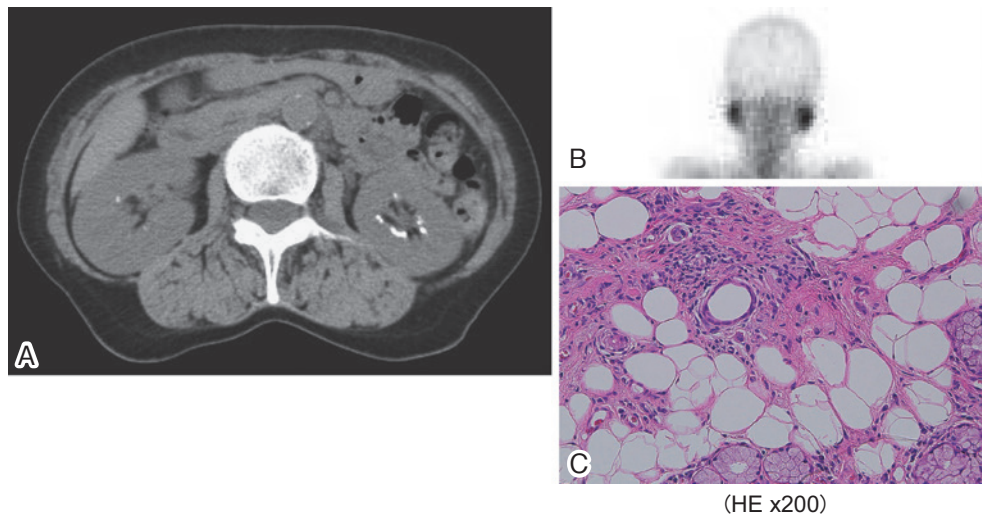


Fig. 1 (A, B) Abdominal computed tomography and Gallium-67 scintigraphy in the patient. The kidneys have calcification bilaterally (A), and there is a positive gallium accumulation in the bilateral salivary glands (B). (C) Labial minor salivary gland biopsy. Massive lymphocyte infiltration (>50/one salivary duct) is seen around a salivary duct (HE stain, ×200).

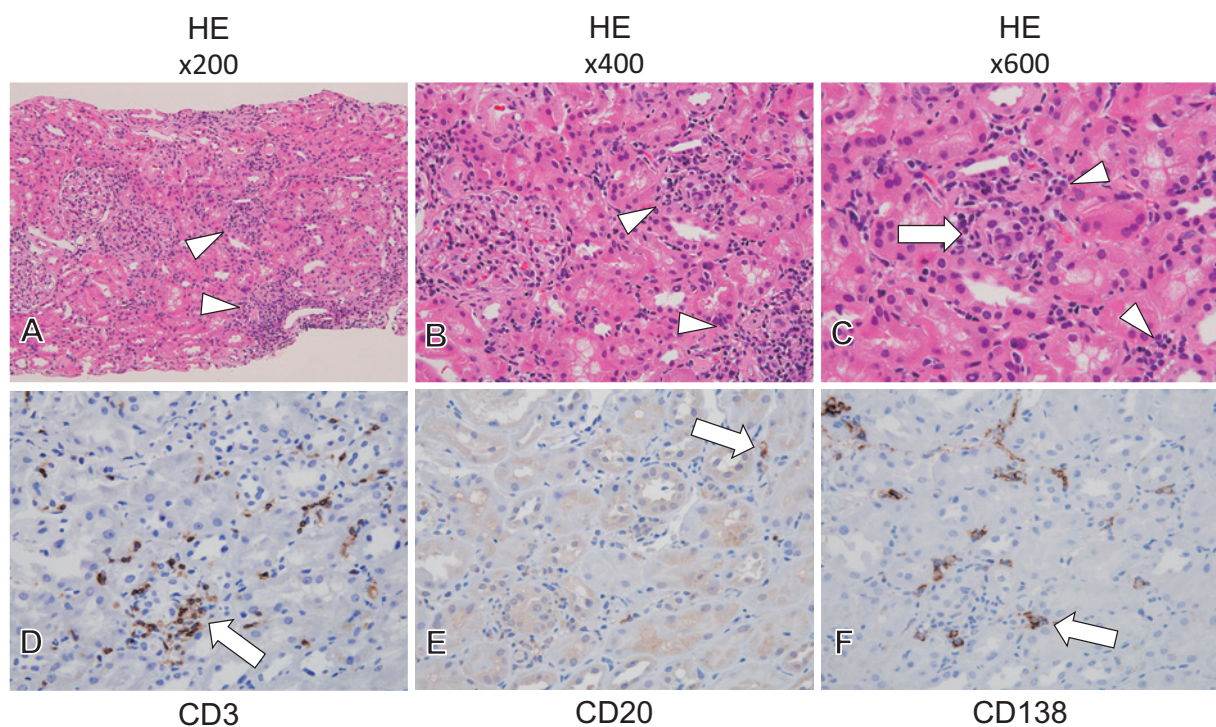


Fig. 2 Light microscopic findings of a renal biopsy specimen. In the renal cortex, a mild focal inflammatory infiltrate (**arrowhead** in A and B) is seen in the interstitium (A, B: HE stain, A: ×200, B: ×400). The renal biopsy tissue included 18 glomeruli that showed only minor abnormalities. There are inflammatory infiltrates indicating focal tubulitis (**arrow** in C) and peritubular capillaritis (**arrowhead** in C) (C: HE stain, ×600). The interstitial infiltrate includes many CD3⁺ T cells (**arrow** in D) and CD138⁺ plasma cells (**arrow** in F), and only a few CD20⁺ B cells (**arrow** in E) (D, E, F: ×600), indicating plasma cell-rich interstitial nephritis.

IgM antibodies were all negative. Anti-mitochondrial M2 antibodies were also negative. It became difficult to control the serum potassium level, and her hypokalemia recurred (**Table 2**). She was admitted again to clarify the

cause of liver dysfunction. A liver needle biopsy was performed and revealed that the cause of her liver dysfunction was interface hepatitis characterized by infiltration of lymphocytes and plasma cells around the hepatic por-

Table 2 Laboratory findings in the second admission

Urinary analysis		Blood chemistry		Blood coagulation tests	
pH	6.5	TP	8.9 g/dL	PT-INR	1.36
urine specific gravity	1.010	Alb	3.4 g/dL	fibrinogen	144 mg/dL
protein	(-)	AST	984 IU/L	FDP	8.0 µg/mL
glucose	(-)	ALT	858 IU/L	D-dimer	3.4 µg/mL
occult blood	(-)	LDH	325 IU/L	antithrombin III	43 %
urobilinogen	(+/-)	ALP	741 IU/L		
sediment		T.Bil	7.8 mg/dL	Serological test	
RBC	<1 /HPF	NH3	124 µg/dL	ANA (speckled)	×1,280
WBC	1-4 /HPF	BUN	16.6 mg/dL	anti-SSA/Ro-antibody	>240 U/mL
hyaline cast	(-)	Cr	1.39 mg/dL	anti-SSB/La-antibody	>320 U/mL
granular cast	(-)	Na	144 mEq/L	HBs-Ag	(-)
Complete blood count		K	2.2 mEq/L	HCV-Ab	(-)
WBC	6,530 /µL	Cl	114 mEq/L	IgM-HA-Ab	(-)
RBC	390×10 ⁴ /µL	Ca	10.1 mg/dL	anti-mitochondrial M2-Ab	(-)
Hb	12.1 g/dL	P	3.2 mg/dL	IgG	4,183 mg/dL
Hct	33.8 %	T.chol	126 mg/dL	IgA	306 mg/dL
MCV	86.7 fL	TG	114 mg/dL	IgM	215 mg/dL
MCH	31.0 pg	UA	4.5 mg/dL	IgG4	72 mg/dL
MCHC	35.8 %	glucose	117 mg/dL		
PLT	22.1×10 ⁴ /µL	CRP	0.65 mg/dL		

ANA: anti-nuclear antibody, IgM-HA-Ab: anti-hepatitis A-IgM antibody.

tal canal (Fig. 3); this was followed by the diagnosis of autoimmune hepatitis, based on revised criteria of the International Autoimmune Hepatitis Group¹⁹. Treatment with oral prednisolone (40 mg/day) was initiated, and AST and ALT levels gradually returned to normal level (Fig. 4). She was discharged on the 35th hospital day with continued outpatient follow-up.

Discussion

The spectrum of SS extends from autoimmune exocrinopathy to systemic involvement, including renal involvement^{1,2}, with interstitial nephritis being a common manifestation³⁻⁶. In this report, we presented a case of PR3-ANCA-positive SS associated with interstitial nephritis and delayed onset autoimmune hepatitis. Vasculitis is also one of the extraglandular manifestations of SS^{1,2}, and ANCAs have been reported to be in association with SS^{10,11}. AAV is sometimes associated with interstitial nephritis^{12,13}. Therefore, it was unclear whether our patient's interstitial nephritis was due to AAV or was an extraglandular manifestation of SS.

Interstitial infiltration of leukocytes may occur in both SS and AAV. A characteristic histological feature of interstitial nephritis in AAV is extensive infiltration of neutrophils²⁰, whereas the findings in SS are focal and diffuse infiltration of lymphocytes and plasma cells³.

However, while those are reported as typical histologi-

cal features in AAV and SS, there may be an overlap, with plasma cells²⁰ as well as lymphocytes¹³ observed in some cases of AAV. Therefore, we could not distinguish whether interstitial nephritis in the present case was due to SS or AAV, although her renal biopsy demonstrated plasma cell-rich interstitial nephritis (Fig. 2), which is typical in SS as noted above.

RTA is common in SS, with the major presenting feature being distal RTA³⁻⁶. Because of the hypokalemia and the positive urine anion gap demonstrated on the first admission, we diagnosed the patient with distal RTA. Moreover, the serum level of uric acid was low, and the urinary level of β2-MG was elevated. Thus, we speculate that a disorder of proximal tubular reabsorption of uric acid was also associated with interstitial nephritis in our patient.

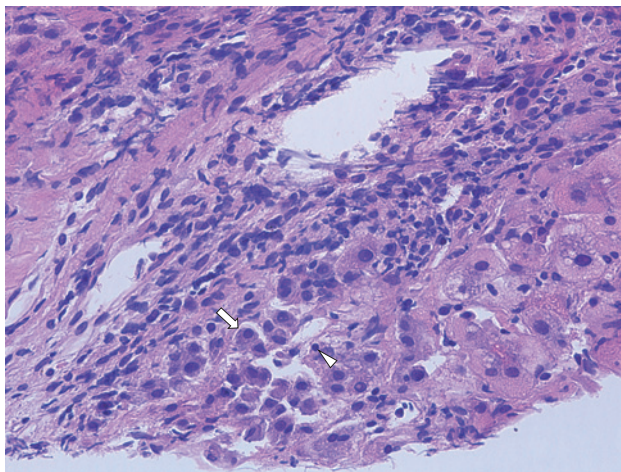
Treatment for interstitial nephritis in patients with SS depends on the severity of the disease. The administration of steroids can be considered in those with severe RTA which is resistant to replacement therapy¹. Komatsu et al.⁷ reported two cases of interstitial nephritis with SS successfully treated with steroid therapy. Kawamoto et al.⁸ reported a case of SS-associated interstitial nephritis and interstitial pneumonia that was successfully treated with steroids.

Although steroids are reported to be effective in SS-associated interstitial nephritis, we initially treated our

patient with sodium bicarbonate and potassium chloride without using steroids. One reason is that the inflammatory infiltrate in the tubulointerstitium was mild and the serum creatinine level was only slightly elevated. Shimoyama et al.⁹ reported a case of PR3-ANCA-positive interstitial nephritis with SS successfully treated with steroids, while the tubulointerstitial lesion was severe in their case. Another reason is that the patient refused

prednisolone because she was concerned about the side effects of long-term administration. Thus, administration of sodium bicarbonate and potassium chloride without prednisolone had been continued until the levels of AST and ALT suddenly became elevated. It was possible to control metabolic acidosis and hypokalemia by the oral administration of sodium bicarbonate and potassium chloride before the onset of autoimmune hepatitis.

Patients with SS sometimes have hepatic complications, including autoimmune hepatitis and primary biliary cholangitis^{14,15,21,22}. The prevalence of autoimmune hepatitis varies from 1 to 4%¹⁴⁻¹⁷. Our patient had no manifestations of hepatic complications during her first admission. It was five years later that she suddenly presented with elevated transaminase levels and recurrence of hypokalemia (**Table 2**). After the diagnosis of autoimmune hepatitis, oral prednisolone was started, along with continued use of sodium bicarbonate and potassium chloride. The onset of autoimmune hepatitis encouraged us to initiate oral prednisolone treatment, resulting in the normalization of her serum potassium level (**Fig. 4**). This raised the question of whether we should have started oral prednisolone when SS-associated RTA was diagnosed during the first admission. The serum levels of AST, ALT, and potassium, however, remained within normal limits until five months before the second admission, whereas those levels slightly worsened approximately 40



HE x400

Fig. 3 Light microscopic findings of the liver biopsy specimen. Massive lymphocyte (arrowhead) and plasma cell (arrow) infiltrates are present around the portal hepatic canal (HE stain, ×400).

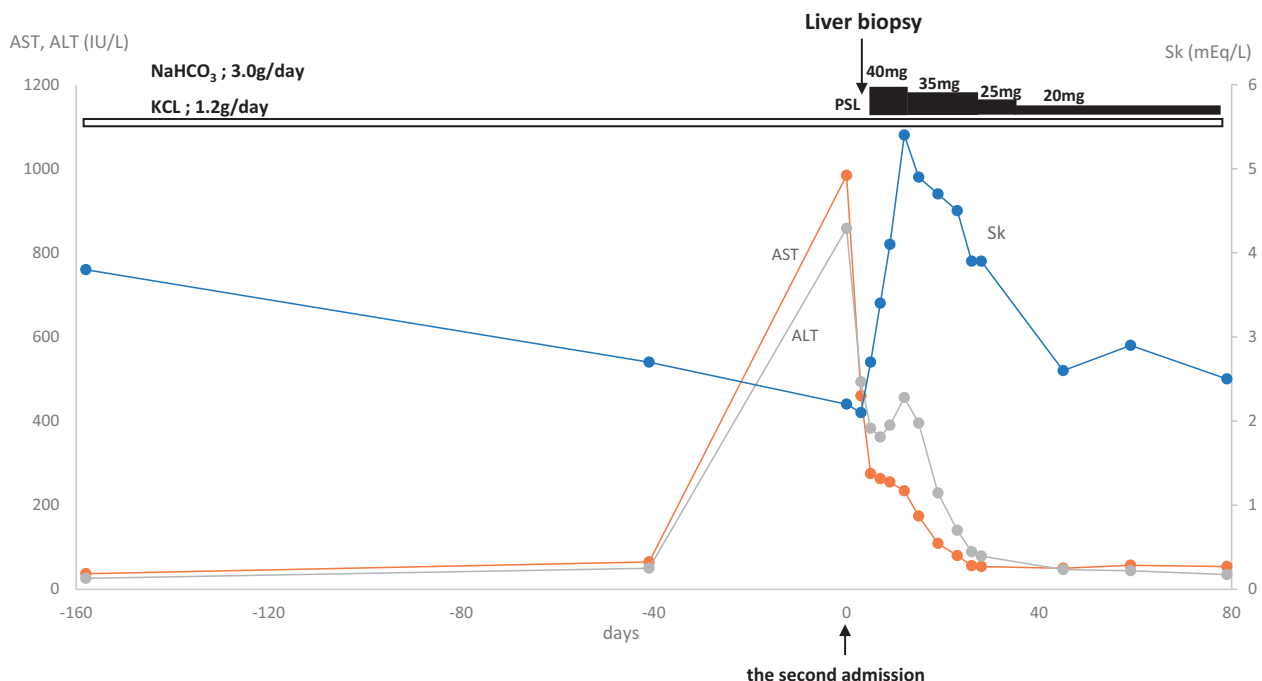


Fig. 4 Clinical course of the patient in the second admission, with the administration of prednisolone resulting in normalization of serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and potassium. Sk: serum potassium level.

days before the development of autoimmune hepatitis (Fig. 4). During the second admission, oral prednisolone plus sodium bicarbonate and potassium chloride resolved the patient's hypokalemia. Therefore, we conclude that the administration of prednisolone is effective in maintaining a normal serum potassium level in hypokalemia associated with interstitial nephritis, along with treatment with sodium bicarbonate and potassium chloride. It is uncertain whether treatment with low-dose prednisolone before the onset of liver dysfunction could have prevented the development of autoimmune hepatitis.

Umemura et al.²¹ examined 14 cases of SS complicated with hepatic injury diagnosed by laboratory testing. Abnormal salivary glands were found in 11 of 12 patients with SS who had hepatic dysfunction, whereas the salivary glands were affected in only 50 of 103 patients with SS without hepatic disease. These findings suggest that the development of hepatic complications in SS is associated with abnormal salivary glands²¹. Of those with hepatic complications, 50% had liver abnormalities at the same time when SS was diagnosed, whereas the remaining 50% did not have hepatic involvement at the initial diagnosis of SS. The time lag between the diagnosis of SS and the onset of hepatic complications varies from 1 year to 20 years²¹.

In addition, Kaplan et al.²² reported that patients with liver involvement were more likely to have renal manifestations, when compared to those without liver involvement.

Our patient had salivary gland involvement when SS was diagnosed, as demonstrated by the positive Gallium-67 scan and the labial minor salivary gland biopsy (Fig. 1 B and Fig. 1C), and interstitial nephritis as demonstrated by the renal biopsy (Fig. 2), but her liver was normal at that time. Based on the findings of Umemura et al.²¹ and Kaplan et al.²², our patient was at risk for eventual hepatic involvement and therefore required monitoring of her liver function.

In summary, we encountered a patient with SS associated with distal RTA and delayed onset autoimmune hepatitis. Steroid therapy induced the remission of autoimmune hepatitis and hypokalemia. In a case such as ours, there is no way to judge the hypothesis that low-dose steroid administration would prevent the development of extraglandular involvement in SS. Physicians should be aware of hepatic involvement, even if there is no liver dysfunction at the time when SS with salivary gland and renal involvement is diagnosed.

Conflict of Interest: The authors declare no conflict of interest.

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