シェーグレン症候群における肝病変

—臨床病理学的検討—

土肥 和 紘・梅村 康 義・藤本 隆・石川 兵 衛
辻 井 正*・杉岡 五 郎**・中沼 安 二****Jpn. J. Clin. Immun., 15 (4) : 370~377, 1992.*Survey of hepatobiliary diseases in Sjögren's syndrome
—A clinicopathological study—Kazuhiro Dohi, Yasuyoshi Umemura, Takashi Fujimoto, Hyoe Ishikawa,
Tadasu Tsujii*, Goro Sugioka** and Yasuni Nakanuma****First Department of Internal Medicine,***Third Department of Internal Medicine, Nara Medical University****Department of Internal Medicine, National Kanazawa Hospital*****Second Department of Pathology, School of Medicine, Kanazawa University*

【Summary】

Sjögren's syndrome (SS) is occasionally reported in patients with hepatobiliary diseases such as chronic hepatitis and primary biliary cirrhosis. However, the incidence and type of hepatobiliary diseases in patients with SS has not fully been evaluated. We surveyed hepatobiliary diseases in 162 patients with SS and found that 15 patients with SS disclosed hepatic dysfunction without any hepatitis B virus markers or history of excessive alcohol intake and blood transfusion. The pathological study of liver biopsies from 14 patients revealed 4 with chronic persistent hepatitis, 5 with chronic active hepatitis and 5 with primary biliary cirrhosis. Abnormal salivary gland lesions were found in 11 of 13 patients with SS and hepatic dysfunction, whereas they were found in 50 of 103 patients with SS without hepatic injury ($p < 0.025$). Anti-hepatitis C virus associated antibody (HCV - Ab) was positive in 5 of 6 patients with chronic persistent hepatitis or active hepatitis, and negative in all 3 patients with primary biliary cirrhosis examined. The optical density values of HCV - Ab in 4 of the 5 HCV - Ab positive patients were more than 3.0. These findings suggest that the greater part of chronic hepatitis associated with SS might be caused by infection of hepatitis C virus in Japan, and that primary biliary cirrhosis might be the most likely complication of SS.

奈良県立医科大学第1内科 *同 第3内科

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【概 要】

目 的：Sjögren 症候群 (SS) に合併する肝病変としては慢性持続性肝炎 (CPH)、慢性活動性肝炎 (CAH) や原発性胆汁性肝硬変 (PBC) などが知られている。しかしながら SS に合併する肝病変について少数の報告をみるにすぎず、現在でも全容について明らかにされているとはいえないようである。そこで、われわれは SS に合併する肝病変の実態を明確にする目的で自験例について検討した。

方 法：厚生省特定疾患「シェーグレン病」調査研究班の診断基準を満足する SS 確実例 162 例中、臨床検査でトランスアミナーゼ上昇などの肝機能障害を示すが、輸血歴、アルコール多飲歴がなく、B 型肝炎ウイルスマーカー陰性の 15 例を対象に唾液腺生検や肝生検などを実施した。

結 果：SS 162 例中、肝機能障害が認められた 15 例のうち 14 例に肝生検を施行したが、CPH が 4 例、CAH が 5 例、PBC が 5 例に認められた。厚生省特定疾患「シェーグレン病」調査研究班診断基準の唾液腺組織に特徴的な所見を示す症例の頻度は、肝機能障害を伴わない SS では 103 例中 50 例 (49%) であったのに対し、肝機能障害を伴う SS では 13 例中 11 例 (85%) であった。抗 C 型肝炎ウイルス関連抗体は、CPH および CAH の 6 例中 5 例に陽性であったのに対し、PBC の 3 例全例が陰性であった。

考 察：厚生省特定疾患「シェーグレン病」調査研究班診断基準の唾液腺組織に特徴的な所見を示す症例の頻度は、肝病変非合併例に比して合併例で有意に高かったといえる。SS に合併する慢性肝炎は C 型肝炎ウイルス感染によるものが多く、SS に特異的な肝合併症は PBC だけといえるかもしれない。

I. Introduction

Sjögren's syndrome (SS) is a chronic inflammatory disorder of exocrine glands such as the lacrimal and salivary glands¹⁾. SS is now thought to be an autoimmune disorder because it might be associated with collagen-vascular diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), and disorders of extraglandular manifestations including the lung and kidney^{2~7)}, and also reveal serological abnormalities suggestive of autoimmune diseases. SS has been occasionally reported in hepatobiliary diseases such as chronic hepatitis or primary biliary cirrhosis (PBC). However, the exact incidence and type of hepatobiliary diseases in SS have not been surveyed using a considerable number of patients with SS to the best of our knowledge.

The aim of our study is 1) to survey the incidence and type of hepatic complications in SS, and 2) to

examine the relationship between hepatic complications and laboratory findings in a considerable number of patients with SS.

II. Patients and Methods

1. Patients

SS was defined by the presence of at least one of the following criteria, 1) objective evidence of keratoconjunctivitis sicca, as documented by rose bengal dye staining and Schirmer's test, 2) salivary gland biopsy having at least a focus of lymphocyte infiltration, 3) sialography having globular, cavitory or destructive pattern. Several laboratory data such as glutamate oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT), γ -glutamyl transpeptidase (γ -GTP) and alkaline phosphatase (Al-p), suggesting hepatic dysfunction, were surveyed in 162 patients with SS. All of these patients were examined at the Department of Internal Medicine, National Kanazawa

Hospital between 1977 and 1980 and the First Department of Internal Medicine, Nara Medical University between 1980 and 1988. Anti-hepatitis C virus associated antibody (HCV-Ab) was surveyed by the "Ortho-HCV" enzyme-linked immunosorbent assay (Ortho Diagnostics, Raritan, New Jersey, USA). The assay uses a recombinant HCV polypeptide encoded by the NS 3/4 region of the HCV genome (C100-3)⁹. The sample was considered positive for HCV-Ab if the optical density value of HCV-Ab was above the cutoff value (mean 0.450).

2. Rose bengal dye staining and Schirmer's test

Schirmer's test was evaluated from the wetting length of a filter paper placed in the eye. Rose bengal dye staining was estimated from the stained area of the corneal epithelial surface. Its scale ranged from class (-) to (3+). Class (-) was defined as no staining, class (+) in the palpebral fissure, class (2+) in the palpebral fissure and the lower part of bulbar conjunctiva, and class (3+) in the palpebral fissure, and the upper and lower part of bulbar conjunctiva. Keratoconjunctivitis sicca was diagnosed if there was less than 10 mm moistening of the filter paper strips in both eyes for 5 minutes and a more than class (+) rose bengal dye staining.

3. Sialogram

Sialogram was classified into four stages: punctate, early stage; globular, moderately advanced stage; cavitary, advanced stage; destructive, end stage⁹.

4. Salivary gland biopsy

Salivary gland biopsies were performed on biopsy samples obtained from the minor and submandibular salivary gland. The specimens were divided into four grades based on their histopathologic features: grade 1, salivary gland with a few lymphocytes; grade 2, one or two lymphocyte foci defined as a cluster of 50 to 100 lymphocytes around

ducts in a lobule; grade 3, focal or diffuse infiltration of lymphocytes, whereby the area was less than half of that of a lobule; and grade 4, infiltration of lymphocyte whereby the area was more than half of that of a lobule.

5. Liver biopsy

Needle biopsy was done under laparoscopic control. Wedge biopsy was performed at laparotomy in case 11. Biopsy specimens were stained with hematoxylin and eosin, Mallory's azan, and silver impregnation. Chronic hepatitis was classified into three types: chronic lobular hepatitis (CLB), chronic persistent hepatitis (CPH) and chronic active hepatitis (CAH)¹⁰. PBC was classified into four stages according to Scheuer: stage 1, florid bile duct lesions; stage 2, ductular proliferation; stage 3, scarring (septal fibrosis and bridging); stage 4, cirrhosis¹¹.

III. Results

1. Clinicopathological features

Fifteen of 162 patients with SS were found to reveal hepatic dysfunction. The main clinical features of these 15 patients are shown in Table 1. They were of one male and 14 females, with a mean age of 56 years (range 42 to 78). All of these patients reportedly had no history of excessive alcoholic abuse and blood transfusion, and were negative for hepatitis B surface antigen and/or antibody in their serum. The initial symptoms were general malaise in 4, fever of unknown origin in 3, Raynaud's phenomenon in 3, and proteinuria, malar rash, arthralgia, itching and dry eye in the other patients. Association of extrahepatic autoimmune diseases was found in 5 (33%) patients of these 15 patients, of whom 2 (13%) had RA and 3 (20%) had chronic thyroiditis. On the one hand, 52 (32.1%) of 162 patients with SS had autoimmune diseases, including RA (9.9%), SLE (10.5%), chronic thyroiditis (4.9%), polymyositis (PM) (3.7%), dermatomyositis (DM) (0.6%), progressive systemic sclerosis (PSS) (1.9%) and mixed connective tissue disease (MCTD) (1.9%). On the

Table 1 Clinical features in 15 patients with SS and hepatic complications

Case No.	Age	Sex	Initial symptom	Age at onset of initial symptom	Age at onset of hepatic injury	Liver biopsy	Other complication
1	42	M	fever of unknown origin	42	42	CPH	—
2	45	F	fever of unknown origin	41	42	CPH	chronic thyroiditis
3	65	F	proteinuria	45	65	CPH	—
4	67	F	Raynaud's phenomenon	64	66	CPH	RA
5	44	F	general malaise	43	43	CAH	—
6	48	F	malar rash	48	48	CAH	—
7	54	F	fever of unknown origin	44	44	CAH	—
8	66	F	arthralgia	51	61	CAH	RA
9	66	F	general malaise	61	61	CAH	chronic thyroiditis
10	44	F	Raynaud's phenomenon	20	42	PBC 2	—
11	47	F	Raynaud's phenomenon	42	47	PBC 3	—
12	51	F	general malaise	46	46	PBC 2	—
13	64	F	general malaise	64	64	PBC 1	—
14	78	F	itch	75	78	PBC 2	chronic thyroiditis
15	57	F	dry eye	56	57	not done	—

Table 2 Hepatic function tests in 15 patients with SS and hepatic complications

Case No.	GOT (IU/l)	GPT (IU/l)	Al-p (KAU)	γ -GTP (IU/l)	ICG (%)
1	73	50	7.1	128	12
2	65	91	4.7	13	71
3	47	39	13.8	108	13
4	16	11	17.4	29	8
5	44	38	5.6	17	5
6	69	73	7.6	53	30
7	81	86	11.0	14	16
8	41	55	7.7	54	9
9	39	34	8.0	38	21
10	129	69	32.3	346	13
11	31	24	10.3	87	6
12	67	50	35.4	440	12
13	75	157	11.4	246	not done
14	48	31	21.0	113	6
15	62	58	8.6	9	6

other hand, 31 (30.0%) of 103 patients with SS without hepatic injury, in whom salivary gland biopsy was performed, had autoimmune diseases, including RA (15.5%), SLE (15.5%), chronic thyroiditis (3.9%), PM (2.9%), DM (1.0%) and PSS (1.9%). As to the hepatic complications in these 15 patients, the age of onset of hepatic injury ranged from 42 to 78 years. Of the 15 patients, 10 (66%) had elevated GOT level, 12 (80%) had ele-

vated GPT level, 7 (50%) had elevated γ -GTP level and 5 (23%) had elevated Al-p level. eight (57%) of 14 patients showed abnormality in the ICG retention test. In one of them (case 2) a marked ICG retention was revealed and diagnosed as a constitutional ICG excretory defect because of the absence of elevation of bilirubin (Table 2).

Liver biopsy was performed in 14 of these 15 patients with SS; 4 patients were of CPH, 5 of CAH and 5 of PBC. As to the patients with PBC, one case was of stage 1, 3 of stage 2 and the remaining of stage 3 (Table 1).

2. Clinical evaluation of sicca complications

Keratoconjunctivitis sicca diagnosed by Schirmer's test and rose bengal dye staining was found in 8 (53%) of the 15 patients with hepatic dysfunction. Xerostomia diagnosed by sialography was present in 3 (23%) of the 13 patients examined. The pathological findings of salivary gland biopsies from 3 patients with CPH revealed grade 2 in all 3, that from 5 with CAH revealed grade 1 in 2, grade 2 in 1 and grade 3 in 2 and that from 4 patients with PBC revealed grade 2 in 3 and grade 3 in 1. Some of the patients with CAH or PBC showed grade 3 or 4 in salivary gland biopsies, however patients with CPH did not show more than grade 3 (Table 3). On the

Table 3 Clinical evaluation of sicca complications in 15 patients with SS and hepatic complications

Case No.	Schirmer's test (mm)		Rose bengal test		Sialography	Salivary gland biopsy (grade)
	rt.	lt.	rt.	lt.		
1	6	5	(2+)	(2+)	normal	not done
2	11	12	(-)	(-)	punctate	2
3	4	6	(-)	(-)	punctate	2
4	2	2	(2+)	(2+)	punctate	2
5	3	3	(-)	(-)	not done	2
6	6	9	(-)	(-)	normal	3
7	3	3	(-)	(-)	cavitary	3
8	8	6	(2+)	(2+)	normal	1
9	1	4	(2+)	(2+)	punctate	1
10	10	5	(2+)	(2+)	normal	4
11	5	6	(-)	(-)	normal	2
12	3	0	(-)	(-)	not done	2
13	2	5	(2+)	(2+)	globular	2
14	2	6	(2+)	(3+)	globular	not done
15	10	6	(2+)	(2+)	punctate	2

Table 4 Serological tests in 15 patients with SS and hepatic complications

Case No.	HCV-Ab O.D. value	LE cell	RA	ANF	AMA	SS-A	SS-B
1	not done	(-)	(+)	(-)	not done	not done	not done
2	(+)	>3.0	(-)	(-)	(-)	(-)	(-)
3	not done	(-)	(-)	(-)	(-)	(-)	(-)
4	not done	(-)	(+)	10(diffuse)	(-)	(-)	(-)
5	not done	(-)	(-)	(-)	not done	not done	not done
6	(-)	(-)	(-)	(-)	(-)	(-)	(-)
7	(+)	>3.0	(-)	(-)	(-)	(-)	(-)
8	(+)	1.6	(+)	(-)	(-)	(-)	(-)
9	(+)	>3.0	(-)	(-)	(-)	(-)	(-)
10	(-)	(-)	(-)	(-)	(+)	(-)	(-)
11	(-)	not done	(-)	320(speckled)	(+)	(-)	(-)
12	not done	(-)	(+)	(-)	(+)	not done	not done
13	not done	(-)	(+)	(-)	(-)	(+)	(-)
14	(-)	(-)	(-)	(-)	(+)	(-)	(-)
15	(+)	>3.0	(-)	(-)	(-)	(-)	(-)

other hand, the pathological findings of salivary gland biopsies from 103 patients of SS without hepatic injury were normal in 12, of grade 1 in 41, grade 2 in 28, grade 3 in 18 and grade 4 in 4 patients. Abnormal salivary gland lesions were found more often in patients with hepatic complications (11 of 13) than in those without hepatic complications (50 of 103) ($p < 0.025$).

3. Serological tests in 15 patients with hepatic dysfunction (Table 4)

HCV-Ab was positive in 5 of the 6 patients with CPH or CAH, and negative in all 3 patients with PBC examined. The optical density values of HCV-Ab in 4 of 5 HCV-Ab positive patients were more than 3.0. LE cell test was negative in 14 patients. Amongst these 15 patients, RA test was positive in 2 patients with CPH, a patient with CAH and 2

patients with PBC. Of 15 patients anti-nuclear factor (ANF) was positive in a patient with CPH and a patient with PBC. Anti-mitochondrial antibody (AMA) was positive in 4 of the 5 patients with PBC. Anti-SS-A antibody (SS-A) was positive in a patient with PBC. On the other hand anti-SS-B antibody (SS-B) was negative in all patients examined.

IV. Discussion

SS is occasionally associated with various autoimmune diseases such as RA, SLE, PSS and chronic thyroiditis^{12,13}. Takeda and coworkers have demonstrated that 18.2% (9 of 49) of autopsy subjects with SS had autoimmune diseases, including RA (4.1%), SLE (6.1%), PSS (4.1%), chronic thyroiditis (2.0%) and DM (2.0%)³. In our study, association of extrahepatic autoimmune diseases was found in about 30% of SS patients with or without hepatobiliary diseases. As to the hepatobiliary diseases and SS patients, Golding and coworkers described that 13 (72%) of 18 patients with PBC and 10 (42%) of 24 patients with CAH had xerostomia and/or keratoconjunctivitis¹⁴. Similar observations were reported by McFarlane and coworkers, who described the presence of sicca feature in 20 (77%) of 26 patients with PBC and 10 (45%) of 22 patients with CAH¹⁵. By contrast, postmortem survey in 49 patients with SS revealed 2 with liver cirrhosis, 1 with PBC and 2 with chronic hepatitis³. Thus, about 10% of SS patients are associated with hepatobiliary diseases such as PBC, CAH and CPH. In the present study, the liver biopsies were available in 14 of the 15 patients with hepatic injury, which were obtained from consecutive 162 patients. Amongst these 14 patients, 4 were of CPH, 5 of CAH and 5 of PBC.

Abnormal salivary gland lesions were found in 11 (83%) of 13 patients with SS and hepatic complication and in 50 (49%) of 103 patients with SS without hepatic complication. Some of the patients with CAH or PBC revealed extensive lymphocyte infiltration of more than grade 3 in salivary gland biopsies, although none of patients with CPH did.

The grade of salivary gland biopsies is related to the progression of liver injury, as McFarlane and coworkers have reported that sicca features were found more frequently in patients who had progressed to cirrhosis¹⁵.

As to the relation between chronic hepatitis and SS, immunological assaults have been considered to date. The present study disclosed that HCV-Ab was positive in 5 of 6 patients with CPH or CAH, while negative in all 3 patients with PBC examined. The optical density values of HCV-Ab in 4 of 5 HCV-Ab positive patients were more than 3.0. Onji and coworkers described that the optical density values of HCV-Ab positive sera from autoimmune hepatitis patients were less than 1.0 in 6 of the 8 patients (75%), whereas those of HCV-Ab positive sera from non-A, non-B hepatitis patients were more than 2.0 in 60 of the 72 patients (83%)¹⁶. The greater part of chronic hepatitis in our patients with SS might be due to hepatitis C viral infection. In CAH, the primary lesion is usually regarded as being confined to the hepatocytes. However, it is recognized that there is an immunological and histological overlap between this condition and PBC. Whether the condition called CAH-PBC mixed-type is an "overlapping syndrome" or a true entity it has not been resolved^{17,18}. As CAH or PBC may be complicated with SS, such a condition is interesting in the study of etiology of hepatic injury complicated with SS. McFarlane and coworkers described the high frequency of SS in CAH and PBC, and the possible occurrence of immunological cross-reactions between antigens in salivary glands and those in the liver as a basis for the development of SS¹⁵. Epstein and coworkers proposed that PBC is part of a dry gland syndrome characterized by dry eye, dry mouth, and biliary and pancreatic hyposecretion, and that ductulitis is a common pathological process¹⁹.

Bernstein and coworkers described that neither SS-A nor SS-B was found in 32 patients with PBC and SS and that SS-A alone was found in 5 (6.4%) of 78 patients with PBC without SS²⁰. Although there was no complete agreement between

Bernstein's and our study, the incidence of SS-A and SS-B in patients with PBC and SS may be low. Doniach and coworkers reported that 40 (98%) of 41 patients with PBC and 12 (28%) of 43 patients with CAH had AMA²¹⁾. On the other hand, Whaley and coworkers reported that one (1.5%) of 41 patients with SS and RA, and 3 (6%) of 50 patients with SS without RA possessed AMA⁹⁾.

Finally, although it has been thought that SS is accompanied by various hepatic diseases, the present study disclosed that the greater part of chronic hepatitis accompanied by SS might not be caused by SS but by infection of hepatitis viruses, especially hepatitis type C virus, in Japan. PBC alone might be a complication specific to SS.

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