A Case of Primary Biliary Cirrhosis Associated with Hashimoto's Thyroiditis, Scleroderma and Sjögren's Syndrome

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A 53-year-old woman was admitted because of Raynaud's phenomenon, polyarthralgia and polymyalgia. Biopsy specimens of the liver and thyroid gland revealed characteristic findings of primary biliary cirrhosis (PBC) (stage I by Scheuer's classification) and chronic thyroiditis. Her clinical features were also complicated by scleroderma (type I by Barnett's classification) and Sjögren's syndrome (Sjs) with keratoconjunctivitis sicca. Thyroid hormone replacement therapy led to improvement in thyroid function, normalization of the biliary tract enzymes and alleviation of subjective symptoms.

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Key words: autoimmune disease, thyroid hormone replacement therapy, antimitochondrial antibody, anticentromere antibody

Introduction

Primary biliary cirrhosis (PBC) is an autoimmune disease with a poor prognosis that occurs most frequently in middle-aged women. It is characterized serologically by a positive antimitochondrial antibody test and histologically by chronic non-suppurative destructive cholangitis (CNSDC). Furthermore, PBC is known to be associated with other autoimmune diseases (1). We observed a patient diagnosed as having asymptomatic PBC complicated by Hashimoto's thyroiditis, scleroderma and Sjögren's syndrome (Sjs). To the best of our knowledge, there has been only one other report of a similar case in Japan (2). It is noteworthy that thyroid hormone replacement therapy led to improvement in thyroid function, normalization of biliary tract enzymes and alleviation of subjective symptoms.

Case Report

A 53-year-old woman suffered from Raynaud's phenomenon for the past twenty years. In 1987, she was diagnosed by a local physician as having Hashimoto's thyroiditis. Systemic arthralgia with dorsal and hypochondrial myalgia appeared in May of 1988, and she was admitted to our hospital on November 29 of that year. Two months prior to her admission, she experienced

a sensation of dryness of the mouth. Her elder sister has Grave's disease. Her younger sister died of renal failure that developed as the result of an unknown type of collagen disease.

On admission, the patient's height was 156 cm and her body weight was 55 kg. Her temperature was 36°C, pulse rate was 78/min and blood pressure was 136/88 mmHg. Physical examination failed to demonstrate jaundice of the tunica conjunctiva bulbi. Cervical palpation revealed a diffuse, elastic goiter. Respiratory sounds were clear and heart sounds were normal. The liver and spleen were not palpable. Her extremities showed Raynaud's phenomenon and sclerodactylia in the fingers (Fig. 1), but there were no abnormal neurological findings.

Laboratory findings (Tables 1, 2) were as follows. Blood cell counts were normal. With respect to blood chemistry, elevations in γ -globulin (27.5%), GOT (58 IU/l), LDH (454 IU/l) and biliary tract enzymes (ALP: 335 IU/l, LAP: 110 IU/l, γ -GTP: 62 IU/l) were found. However, the aldolase level was within normal limits. Serological examination revealed the presence of antinuclear antibodies ($\times 640$), antithyroglobulin antibody ($\times 1,600$), antimicrosomal antibody ($\times 1,600$), antimitochondrial antibody ($\times 160$), anti-smooth muscle antibody ($\times 320$) and anticentromere antibody ($\times 640$). In addition, immune complexes were detected (4.5 mg/dl) and IgG was elevated (2,300 mg/dl), but IgM was normal

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Fig. 1. Sclerodactylia with Raynaud's phenomenon

Table 1. Laboratory Findings on Admission (1)

Urine		Blood chemistry	
glucose	(-)	TP	7.9 g/dl
protein	(-)	Alb	58.8%
bilirubin	(-)	γ -gl	27.5%
urobilinogen	($\pm$)	TBil	0.6 mg/dl
		TTT	28 KU
Peripheral blood		GOT	58 IU/l
RBC	$404 \times 10^4/\text{mm}^3$	GPT	30 IU/l
Hb	12.1 g/dl	ChE	7.0×10^3 IU/l
Ht	36.4%	ALP	335 IU/l
Plat	$13.2 \times 10^4/\text{mm}^3$	LAP	110 IU/l
WBC	$4,940/\text{mm}^3$	γ -GTP	62 IU/l
EOSI	5.8%	CPK	69 IU/l
BASO	0.5%	Aldolase	2.2 MU/ml
NEUT	46.6%	LDH	454 IU/l
LYMP	40.0%	TC	191 mg/dl
MONO	6.3%	AMY	110 U/l
		BUN	13 mg/dl
ESR	21 mm/h	Cr	0.8 mg/dl
		UA	6.2 mg/dl
		Na	142 mEq/l
		K	4.2 mEq/l
		Cl	105 mEq/l

(181 mg/dl). Immunological investigation of peripheral blood revealed a decrease in B lymphocytes, but the OKT4/OKT8 ratio remained normal (1.27) and lymphocyte blastic transformation by each type of mitogen was within the normal range. A tuberculin test produced a negative result. A thyroid function test revealed a normal lower limit of free T4 (0.93 pg/ml) and a slightly elevated TSH value (7.9 μ U/ml). A TRH loading test exhibited a delayed response. Scintigraphy of the thyroid gland using $^{99m}\text{TcO}_4^-$ showed normal uptake (1.6% in 30 minutes). An oral glucose tolerance test (OGTT) exhibited impaired glucose tolerance (IGT). A gum test for salivary secretion and sialography gave negative results. However, Schirmer's test was positive (<10 mm) and a rose bengal staining test was strongly positive.

Table 2. Laboratory Findings on Admission (2)

Immunology		HLA	
CRP	(-)	A24, A31, BW54, BW60	
RA	(-)	CW1, CW3, DR4, DR8	
LE test	(-)	DRw52, DRw53, DQw1,	
Antinuclear antibody	(+)	DQw4	
	×640	Thyroid function	
	centromere pattern	free T3	3.46 pg/ml
AntiENA antibody	(-)	free T4	0.93 pg/ml
AntiScl-70 antibody	(-)	TSH	7.90 μU/ml
AntiRNP antibody	(-)	TRH test	
AntiSS-A antibody	(-)	Time (min)	TSH (μU/l)
AntiSS-B antibody	(-)	0	8.3
AntiDNA antibody	(-)	15	47.1
Antithyroglobulin antibody	(+)	30	62.0
	×1,600	60	55.6
Antimicrosomal antibody	(+)		
	×1,600	75 g OGTT	
Antimitochondrial antibody	(+)	Time	PG
	×160	(min)	(mg/dl)
Anti-smooth muscle antibody	(+)	0	98
	×320	30	152
Anticentromere antibody	(+)	60	179
	×640	120	157
			40
Immune complex	4.5 mg/dl	Liver function	
CH50	32.9 U/l	ICG (15)	7.5%
IgG	2,300 mg/dl		
IgA	160 mg/dl	Gum test	10'
IgM	181 mg/dl	Shirmer's test	rt.
			4 ml
			lt.
			1.5 ml
Tcell	89%		
Bcell	2%		
OKT4	38.8%		
OKT8	30.5%		
OKT4/OKT8	1.27		
Lymphoblastogenesis	(S.I.*)		
PHA	321		
Con A	221		
PWM	50		

* Stimulation Index

The patient had elevated biliary tract enzymes and tested positive for antimitochondrial antibodies, suggesting the existence of PBC. Consequently, we conducted a liver biopsy using a laparoscope. Laparoscopic findings showed smooth irregularities on the liver surface, but no tumescence. Histological findings (Fig. 2) revealed infiltration of lymphocytes and plasma cells to Glisson's capsule, extensive reduction of the bile duct, chromatic agglutination in the epithelium of the residual bile duct and partial disappearance of the epithelium. These findings were compatible with those of stage I CNSDC using Scheuer's classification. As the presence of diffuse goiter with reduced thyroid function and the serological tests suggested Hashimoto's thyroiditis, we performed an open biopsy. As shown in Fig. 3, the pathological findings were chronic inflammatory cell infiltration accompanying the lymphoid follicles, indicating classic chronic thyroiditis. A skin biopsy from the finger showed

Fig. 2. Liver biopsy specimen showing lymphocyte and plasma cell infiltration to Glisson's capsule, and degeneration and partial disappearance of the epithelial cells of the bile duct (arrow). (HE stain $\times 200$).

Fig. 3. Histology of the thyroid gland. Mononuclear cell infiltration with lymphoid follicles (HE stain $\times 100$).

Fig. 4. Clinical course. Administration of levothyroxine ($50 \mu\text{g/day}$) improved subjective symptoms as well as GOT and biliary tract enzymes in association with normalization of thyroid function.

an increase in collagen fiber, but there were no atrophic findings of the appendages.

Subjective symptoms, particularly myalgia, continued after admission despite the administration of antiinflammatory drugs. Beginning on February 8, levothyroxine was given at a dosage of $50 \mu\text{g/day}$. The clinical course of the patient is shown in Fig. 4. With the amelioration of thyroid function, GOT and biliary tract enzymes were also normalized, and the subjective symptoms improved. However, no change was found in the antimitochondrial antibody titer.

Discussion

The present patient showed an elevation of biliary tract enzymes, a high titer of antimitochondrial antibodies and the histological characteristics of CNSDC on liver biopsy, although jaundice and dermal pruritis did not occur. Hence, she was diagnosed as having asymptomatic PBC. In addition, a diffuse, elastic hard goiter that was diagnosed as Hashimoto's thyroiditis because of its histology was detected through palpation. The patient also suffered from Raynaud's phenomenon and sclerodactylia, leading to the diagnosis of type I scleroderma according to Barnett's classification. Furthermore, the results of both the rose bengal staining and Schirmer's tests were positive, and keratoconjunctivitis of unknown etiology was present in this patient, thus meeting the criteria for Sjs, although no characteristic findings were observed on sialography.

Sasaki et al (1) investigated 180 cases of PBC and reported that complications of PBC were most frequent in those with Sjs (55 cases), less frequent in those with Hashimoto's thyroiditis (9 cases) and far less frequent in those with scleroderma (2 cases). However, the association of these four diseases is considered to be very rare (2).

It is noteworthy that the present patient showed positive results for several autoantibody tests, including antimitochondrial antibodies which are characteristic of PBC, and anticentromere antibody which is characteristic of the CREST syndrome. Recent reports have demonstrated the presence of antimitochondrial antibodies in progressive systemic sclerosis (PSS) and anticentromere antibody in PBC (3–5), suggesting a relationship between the two disorders. The CREST syndrome is currently thought to be a limited form of PSS and the presence of anticentromere antibody appears to be a marker for a favorable prognosis in patients with PSS (6). The association between PBC and typical PSS is uncommon (7), but there have been a number of reported cases of PBC associated with mild PSS and sclerodactylia, as in our patient (8, 9). The liver is closely related to the thyroid gland, since it metabolizes and stores thyroid hormone. Chronic liver disease has long been implicated as a complication of Hashimoto's thyroiditis, and Fukase

and Ito (10) proposed the term "liver-thyroiditis syndrome" to describe the condition. It is conceivable that the coexistence of PBC and Hashimoto's thyroiditis in our patient is compatible with this concept. The high incidence of PBC with Sjs was partly explained by the presence of a common antigen in the epithelium of the bile and salivary gland ducts (11).

Tanaka et al (2) reported a case of PBC associated with PSS, Hashimoto's thyroiditis, and Sjs. Compared with their case, the present patient showed a high titer of autoantibodies but had less severe clinical symptoms. The reason for this is not clear, but it has been reported that the titer and variation of antimitochondrial antibodies are not related to the severity of PBC. The coexistence in both patients of four different autoimmune diseases may not have occurred by chance, but may be attributed to the autoimmune reaction elicited by the recognition of common antigens in each organ. Common antigenicities may exist in the epithelium of the bile duct and the thyroid gland follicle or salivary gland. The expression of class II MHC antigens on epithelial cell surfaces of the bile duct that normally do not express them can be induced by certain agents (eg. cytokines). Recognizing these molecules, CD4 T lymphocytes induce cytotoxic T lymphocytes and produce lymphokines, which damage cells with common antigens. There have been reports of abnormal cellular immunity such as elevation of the OKT4/OKT8 ratio and reduction in each mitogen-stimulated lymphocyte blastic transformation in biliary cirrhosis (12, 13). In the present patient, all of these indices were normal.

It is interesting that the administration of thyroid drugs resulted in not only an improvement in thyroid function, but also normalization of GOT and biliary tract enzymes and further amelioration of subjective symptoms. Miki et al (14) reported that replacement therapy for reduced thyroid function in Hashimoto's thyroiditis with PBC led to an improvement in abnormal findings related to PBC in addition to improvement in thyroid function. Although the mechanisms responsible for this improvement are unclear, a recent experimental study revealed that thyroid function may influence bile flow. Layden and Boyer (15) reported that the administration of L-thyroxine to hypothyroid animals restored bile acid-independent canalicular secretion that was associated with an increase in the activity of liver plasma membrane enzymes such as Na^+ , K^+ -ATPase. Keeffe et al (16) also reported that bile acid-independent flow was increased by thyroid hormone in rats. Improvement in bile flow may result in an improvement in liver cell dysfunction due to bile stagnancy. These experimental findings may hold true for the present patient. However, the possibility that subsequent thyroid hormone-induced improvement in systemic metabolism exerted a favorable effect on the immune system that is linked to liver function cannot be excluded. PBC has been recognized

as a progressive disease with a poor prognosis, but the recent advances in diagnostic technology make it possible to diagnose patients at an asymptomatic stage. Patients with PBC follow one of two clinical courses; one form rapidly progresses through symptomatic PBC to liver cirrhosis, and the other remains asymptomatic for many years. The mechanisms underlying the differences between the clinical courses are not known. However, the findings in the present patient and the case reported by Miki et al (14) indicate the possible inhibitory effect of thyroid drugs on the progression of PBC.

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