Acta Med. Okayama, 2019
Vol. 73, No. 4, pp. 367–372

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Case Report

A Patient with Type 3 Autoimmune Polyglandular Syndrome who Developed Systemic Lupus Erythematosus 8 years after the Diagnosis of Autoimmune Hepatitis

Tomoyo Mifune-Morioka[a], Haruhito A. Uchida[a,b]*, Kazuhiko Fukushima[a], Mayu Watanabe[a], Chihiro Ouchi[a], Koki Mise[a], Chieko Kawakita[a], Yuzuki Kano[a], Akifumi Onishi[a,c], Kishio Toma[a], Jun Eguchi[a], Nozomu Wada[d], Fusao Ikeda[d], Erika Sasaki[e], Yu Suganami[e], Masayuki Kishida[e], Hitoshi Sugiyama[a,c], Hiroyuki Okada[d], and Jun Wada[a]

Departments of [a]Nephrology, Rheumatology, Endocrinology and Metabolism, [b]Chronic Kidney Disease and Cardiovascular Disease, [c]Human Resource Development of Dialysis Therapy for Kidney Disease, [d]Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan, [e]Department of General Internal Medicine and Endocrinology, Okayama City Hospital, Okayama 700-8557, Japan

Eight years prior to her present admission, a 61-year-old Japanese woman was diagnosed with autoimmune hepatitis, slowly progressive insulin-dependent diabetes mellitus, and chronic thyroiditis; she had been treated with oral prednisolone (PSL). After she suddenly discontinued PSL, she newly developed systemic lupus erythematosus. A combination therapy of oral PSL and intravenous cyclophosphamide resulted in remission. She was finally diagnosed with autoimmune polyglandular syndrome (APS) type 3 (3A, 3B, 3D), complicated with four different autoimmune diseases. Since patients with type 3 APS may present many manifestations over a long period of time, they should be carefully monitored.

Key words: autoimmune polyglandular syndrome type 3, systemic lupus erythematosus, autoimmune hepatitis, slowly progressive insulin-dependent diabetes mellitus, chronic thyroiditis

Autoimmune polyglandular syndrome (APS) is defined as multiple endocrine gland disorders [1]. APS is categorized as types 1 to 4. Among them, only type 3 APS is not accompanied by Addison's disease, but type 3 APS includes several autoimmune diseases such as type 1 diabetes, autoimmune thyroid disease, and collagen disease [1-3]. Here we describe the case of a 61-year-old woman who newly developed systemic lupus erythematosus (SLE) 8 years after the first diagnosis of autoimmune hepatitis (AIH), slowly progressive insulin-dependent diabetes mellitus (SPIDDM), and chronic thyroiditis.

Case Presentation

A 53-year-old Japanese woman was referred to our hospital because of her high serum concentrations of AST (327 U/L) and ALT (541 U/L). A detailed examination had revealed antinuclear antibody positivity (×160 with homogenous pattern and ×1,260 with nucleolar pattern), elevated IgG (3,007 mg/dL), and negative viral serology: HBsAg (–), HBsAb (–) and HCV (–). Her liver biopsy demonstrated interface hep-

Received October 12, 2018; accepted March 22, 2019.
*Corresponding author. Phone: +81-86-235-7235; Fax: +81-86-222-5214
E-mail: hauchida@okayama-u.ac.jp (HA. Uchida)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

atitis with a lymphoplasmacytic infiltration of portal tracts and focal necrosis (Fig. 1A-C). At this point, anti-Sm antibody was negative (< 5.0 index) and complement levels were in normal ranges (C3 113.7 mg/dL, C4 14.9 mg/dL, CH50 41 U/mL). Antinuclear antibody, anti-dsDNA antibody, and anti-cardiolipin antibody were not measured.

Based on these findings, we diagnosed AIH and initiated oral prednisolone (PSL) 20 mg/day. After the initiation of PSL therapy, she presented postprandial hyperglycemia; her blood glucose level was > 300 mg/dL, without ketosis or ketoacidosis. We administered an additional examination which revealed that the patient's fasting glucose level was 85 mg/dL, HbA1c was 5.6%, and insulin secretion was maintained (urine C-peptide 141.0 μg/day), while glutamic acid decarboxylase autoantibody (GADAb) was positive (20.6 U/mL). The evaluation of hormonal values showed a thyroid-stimulating hormone (TSH) elevation with low free T4 and free T3 levels, and positivity to antibodies against thyroid peroxidase (TPOAb), thyroglobulin (TgAb), and TSH receptor (TRAb).

Given these findings, we diagnosed SPIDDM and chronic thyroiditis. The PSL was gradually tapered to 2.5 mg/day over 5 years. Strict diet and exercise therapy managed her HbA1c level at < 6.0%. Low-dose PSL (2.5 mg/day) was continued for 3 years. However, the patient suddenly discontinued her medication by her own decision, and 1 month later, she presented with a rash on her face, edema of her legs and face, stomatitis, and fever. She was thus admitted to our hospital in 2017.

On physical examination, she was ill-appearing and febrile at 38.5°C. Her blood pressure was 115/87 mmHg, and her pulse rate was 107/min, with O_2 saturation of 98% on room air. She had small rushes on her face and edema of her legs and face. Struma was not palpable. She had no history of vitiligo or alopecia. The results of a cardiovascular examination were normal; the lungs were clear to auscultation, and an abdominal examination was unremarkable.

The patient's laboratory data are summarized in Table 1. Liver enzymes were elevated without hepatitis viral infection or IgG elevation. Serum levels of FT3 and FT4 were low. The serum levels of adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), growth hormone (GH) and prolactin (PRL) were all within the normal ranges. TPOAb, TgAb, and TRAb were seropositive. HbA1c was 8.1%, GADAb was elevated to 1,586.5 U/mL, and insulin secretion was severely depleted (urine C-peptide 3.8 μg/day), suggesting an insulin-dependent status. Other laboratory investigations showed leukopenia, anemia, and kidney injury. A urine analysis showed protein (2+), 751.1 mg/day, but occult blood was negative. Antinuclear antibody, anti-dsDNA antibody, anti-Sm antibody and anti-cardiolipin antibody were seropositive, and she had hypocomplemen-

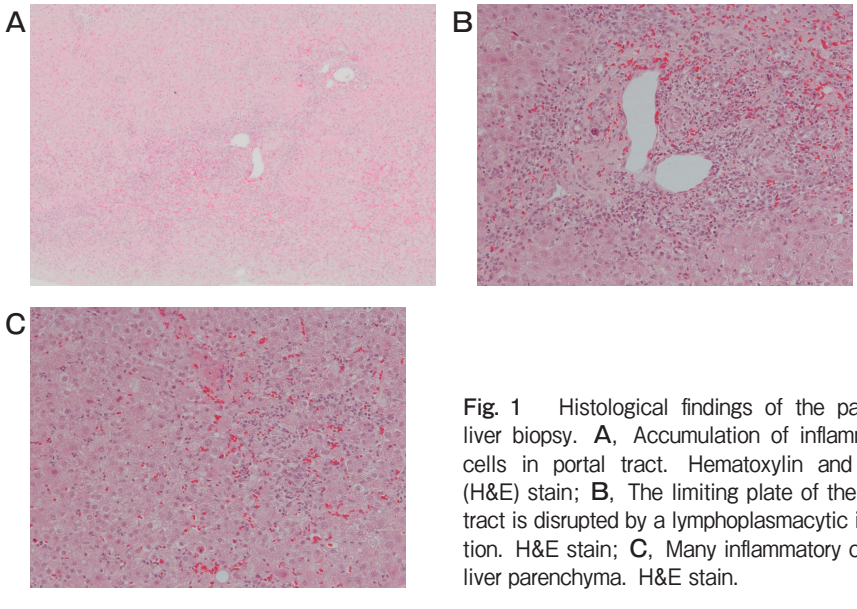

Fig. 1 Histological findings of the patient's liver biopsy. **A**, Accumulation of inflammatory cells in portal tract. Hematoxylin and eosin (H&E) stain; **B**, The limiting plate of the portal tract is disrupted by a lymphoplasmacytic infiltration. H&E stain; **C**, Many inflammatory cells in liver parenchyma. H&E stain.

Table 1 Laboratory data on admission

【Urinalysis】			AST	64	U/L	LAC	1.0	mL/min/1.73m^2
pH	6.0		ALT	35	U/L	anti-CL. β2GPI Ab	2.1	U/mL
Pro	(2+)		ALP	158	U/L	anti-M2 Ab	−	
Glu	(−)		γ-GTP	35	U/L			
Bld	(−)		LDH	370	U/L	【Endocrinology】		
Ket	(−)		Na	129	mEq/L	freeT3	1.52	pg/mL
Bil	(−)		K	4.1	mEq/L	freeT4	0.64	ng/dL
NAG	4.7	U/L	Cl	101	mEq/L	TSH	0.35	μU/mL
β2MG	1.660	μg/mL	Ca	7.3	mg/dL	TGAb	30.1	IU/mL
u-TP	0.75	g/day	IP	2.2	mg/dL	TPOAb	72.9	IU/mL
			UN	22.2	mg/dL	TRAb	3.40	IU/L
【Complete blood count】			Cr	1.02	mg/dL	ACTH	10.0	pg/mL
WBC	3,220	/μL	UA	7.4	mg/dL	FSH	76.5	mIU/mL
Sg	52.0	%	CRP	0.12	mg/dL	LH	24.6	mIU/mL
St	13.0	%	Ferritin	1,779.0	ng/mL	GH	1.59	ng/mL
Lymph	24.0	%	Hpt	149	mg/dL	PRL	15.1	ng/mL
Mono	10.0	%				AVP	1.7	pg/mL
Eosi	0.0	%	【Serological data】			Cor	12.3	μg/dL
Baso	0.0	%	C3	21.1	mg/dL			
RBC	354×10^4	/μL	C4	2.1	mg/dL	【Diabetology】		
Hb	10.8	g/dL	CH50	<14	U/mL	HbA1c (NGSP)	8.1	%
Ht	31.0	%	IgG	1,397.9	mg/dL	glucose	120	mg/dL
Plt	18.5×10^4	/μL	IgA	500.3	mg/dL	C-peptide	1.95	ng/mL
			IgM	38.2	mg/dL	IRI	6.2	μU/mL
【Coagulation test】			PR3-ANCA	<0.50	IU/mL	GAD Ab	1,586.5	U/mL
PT	11.7	sec	MPO-ANCA	<0.50	IU/mL	ZnT8 Ab	<10.0	U/mL
PT-INR	1.10		anti-GBM Ab	1.78	IU/mL	u-CPR	3.8	μg/day
APTT	34.1	sec	RF	<5.0	IU/mL			
D-D	17.6	μg/mL	anti-nuclear Ab	×640	(HOMOGE)	【Infections】		
			anti-SM Ab	16.5	U/mL	HBsAb	−	
【Biochemistry】			anti-dsDNA Ab	211.00	IU/mL	HbsAg	−	
TP	5.7	g/dL	anti-SS-A Ab	31.90	U/mL	HCVAb	−	
Alb	2.6	g/dL	anti-SS-B Ab	0.82	U/mL			
T-Bil	0.49	mg/dL	anti-cardiolipin Ab	22.90	U/mL			

NAG, N-acetyl-β-D-glucosaminidase; β2MG, β2microglibulin; u-TP, urinary-total protein; WBC, white blood cell; Sg, segmented cell; St, stab cell; Lymph, lymphocyte; Mono, monocyte; Eosi, eosinophil; Baso, basophil; RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit; Plt, platelet; PT, prothrombin time; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time; D-D, D-dimer; TP, total protein; Alb, albumin; T-Bil, total-bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; Na, sodium; K, potassium; Cl, chloride ; Ca, calcium; IP, inorganic phosphate; UN, urea nitrogen; Cr, creatinine; UA, uric acid; CRP, cross-reactive protein; Hpt, haptoglobin; C3, complement C3; C4, complement C4; CH50, hemolytic complement; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; PR3-ANCA, proteinase 3-anti-neutrophil cytoplasmic antibody; MPO-ANCA, myeloperoxidase anti-neutrophil cytoplasmic antibody; anti-GBM Ab, anti-glomerular basement membrane antibody; RF, rheumatoid factor; anti-nuclear Ab, anti-nuclear antibody; anti-SM Ab, anti-smith antibody; anti-dsDNA Ab, anti-double stranded DNA antibody; LAC, lupus anticoagulant; anti-CL. β2GPI Ab, anti-cardiolipin. β2-glycoproteinI Ab; anti-M2, antibody anti-mitochondrial M2 Ab; freeT3, free triiodothyronine; freeT4, free thyroxine; TSH, thyroid stimulating hormone; TGAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; TRAb, TSH receptor autoantibody; ACTH, adrenocorticotropic hormone; FSH. follicle stimulating hormone; LH, luteinizing hormone; GH, growth hormone; PRL, prolactin; AVP, arginine vasopressin; Cor, cortisol; HbA1c, Hemoglobin A1c; IRI, immunoreactive insulin; GAD Ab, glutamic acid decarboxylase antibody; ZnT8 Ab, zinc transporter 8 antibody; u-CPR, urinary-C-peptide immunoreactivity; HBsAb, Hepatitis B surface antibody; HbsAg, Hepatitis B surface antigen; HCVAb, Hepatitis C virus antibody

temia. A human leukocyte antigen (HLA) analysis showed positive A24, A26, B54, B59, DRB1 04:05:01, and DQB1 04:01:01.

Computed tomography (CT) revealed ground glass opacity in the superior lobe of the right lung, bilateral pleural effusion, pericardial effusion, and ascites. The results of an ultrasound examination of thyroid were consistent with chronic thyroiditis. A kidney biopsy revealed diffuse lupus nephritis class IV-G(A) with wire loop lesion, hyaline thrombus, and endo-capillary proliferation (Fig. 2A-C). Additional staining for anti-GAD antibody, anti-IA-2 antibody, and anti-Thyroglobulin antibody was performed. All antibodies showed positive staining (Fig. 2D).

In light of these data, we concluded that the patient was suffering from SLE in association with AIH, SPIDDM, and chronic thyroiditis. We thus diagnosed type 3 (3A, 3B, 3D) APS. We immediately administered PSL at 40 mg/day (1.0 mg/kg/day) and intravenous cyclophosphamide (500 mg/month). After the initiation of this therapy, the patient's physical status and laboratory data improved notably (Fig. 3). On the 47th hospital day, she was discharged. At present, she is taking PSL 10 mg/day and levothyroxine sodium 25 μg/day, with insulin therapy.

Discussion

This was a rare case of type 3 APS, complicated with four different autoimmune diseases, *i.e.*, AIH, SPIDDM, chronic thyroiditis, and SLE. APS is characterized by the coexistence of at least 2 autoimmune

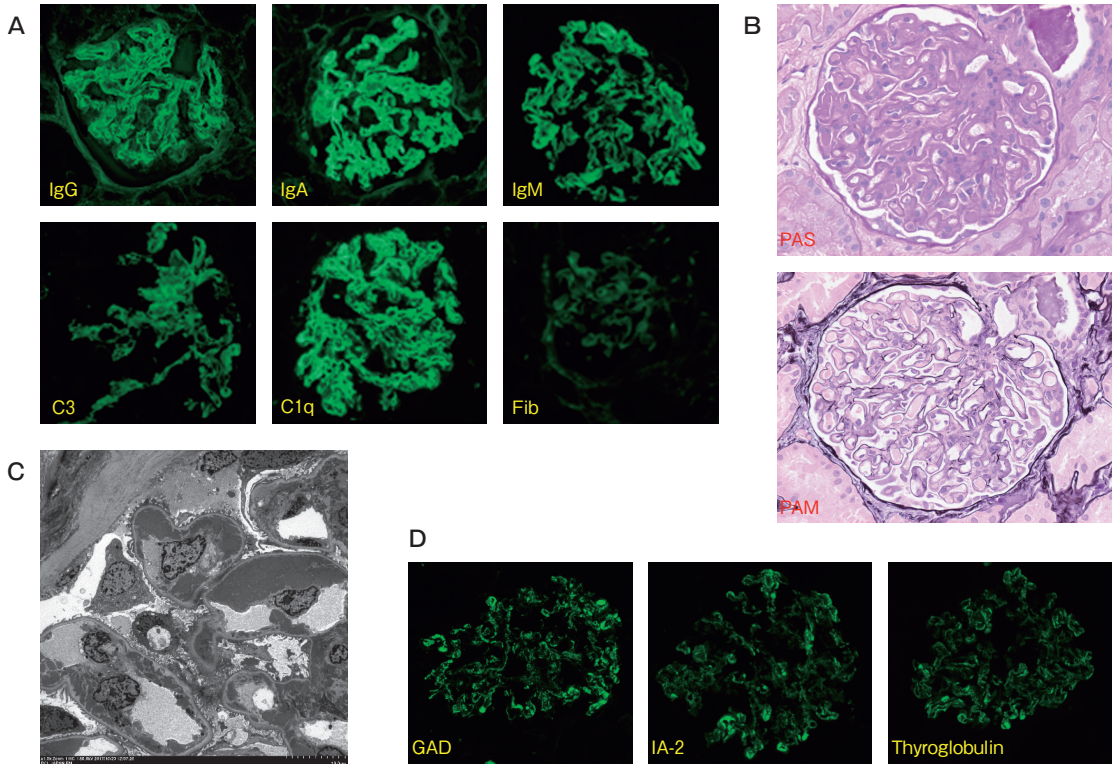

Fig. 2 Kidney biopsy. **A**, Immunofluorescence staining. The full-house pattern with intense or diffuse staining in the glomerular mesangial lesion and capillary loops of all three immunoglobulins and complements (C3 and C1q) and fibrinogen are observed; **B**, Light microscopy findings. Diffuse proliferative global glomerulonephritis with the following findings are observed; glomerular sub-endothelial deposits with wire loops lesion, endo-capillary proliferation, hyaline thrombus in almost all glomeruli, and double counter of base membrane in some glomeruli. No crescent formation is observed. Interstitial inflammation is mild; **C**, Electron microscopy findings. Diffuse and massive sub-endothelial dense deposits, mild endo-capillary proliferation, and frequent mesangial interposition are seen. No sub-epithelial and intramembranous deposits are observed. Effacement of foot processes is observed in part; **D**, Immunofluorescence staining for anti-GAD antibody, anti-IA-2 antibody, and anti-thyroglobulin antibody. All antibodies showed positive staining granularly and focally in glomerular capillary and mesangial lesions.

endocrine gland insufficiencies, and non-endocrine autoimmune diseases may occur. APS is categorized into four types based on the patient's age at presentation, the combination of diseases, and genetics. Type 1 APS usually occurs in childhood. It is defined by chronic mucocutaneous candidiasis, acquired hypoparathyroidism, and adrenal failure (Addison's disease). It is caused by mutations in the *AIRE* gene on chromosome 21 and is inherited in an autosomal recessive manner. Mutations in the *AIRE* gene disturb the body's immunological tolerance.

Types 2, 3, and 4 APS occur in adulthood. Only type 3 APS does not involve adrenal failure. Type 1 diabetes, Graves' disease, Hashimoto thyroiditis, vitiligo, alopecia, hypogonadism, pernicious anemia, and collagen diseases are frequent complications of these types of APS, and the manifestations of these phenotypes usually do not occur simultaneously. Unlike type 1 APS, types 2-4 are associated with many factors such as HLA, polygenic polymorphism, and environmental factors. HLA DR3, DR4, DQA1 0301 and 0501, and DR3-DQB1 0201 are correlated with APS type 2 [4,5], and DR3-DQ2, DRB1 0401-DQ8, and DRB1 0405, 0802 are correlated with APS type 3 [6]. *PTPN22* (protein tyrosine phosphatase non-receptor type 22), *MICA* (MHC class I polypeptide-related sequence A), *CTLA-4* (cytotoxic T lymphocyte-associated antigen 4), and *FOXP3* (forkhead boxP3) genes are known to be susceptibility gene variants that may lead to the loss of immunological tolerance [7,8]. Our patient had HLA DRB1 04:05, which is related to type 3 APS.

In addition to such a genetic background in our patient, her sudden cessation of PSL might have caused a failure of immunological tolerance, followed by re-activation of the inflammatory status and the excessive production of various autoantibodies.

Regarding the onset of various manifestations of APS, there appears to be no fixed pattern [9-12]: some patients first present type 1 diabetes and/or autoimmune thyroid disease, then suffer from SLE at 1 year or

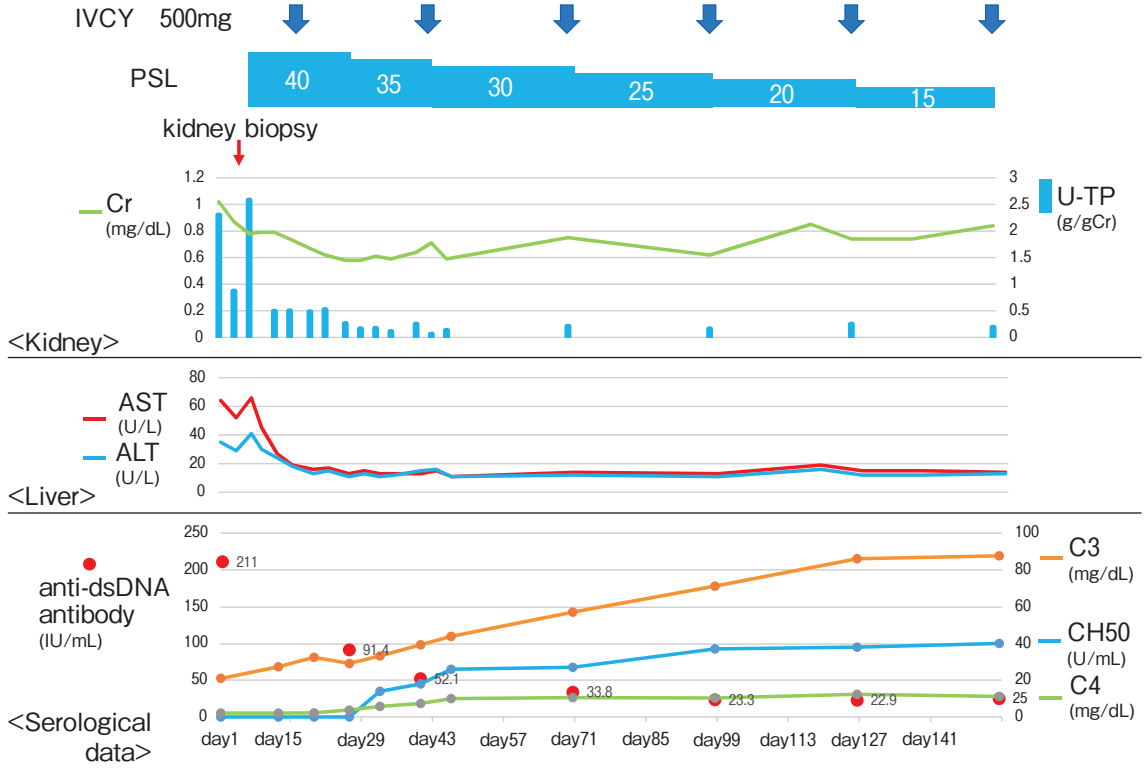

Fig. 3 Clinical course. After diagnosis based on the kidney biopsy results, the patient was administered PSL 40 mg/day (1.0 mg/kg/day). She was also given monthly intravenous cyclophosphamide for 6 months, followed by maintenance therapy with PSL alone. The proteinuria disappeared, the level of liver enzymes and complements improved within normal ranges, and anti-dsDNA antibody was gradually decreased. IVCY: intravenous cyclophosphamide.

a few years later, whereas others present type 1 diabetes or autoimmune thyroid disease with SLE simultaneously. These reports support the possibility that the manifestation of SLE in patients with type 3 APS occurs due not only to the patients' genetic background but also environmental factors. Our patient developed SLE at 8 years after she had been diagnosed with 3 autoimmune diseases. In her case, the sudden cessation of PSL might have been the trigger for the development of SLE as an environmental factor.

In our patient, the immunohistochemistry analyses showed the deposition of immune complex of various autoantibodies in the patient's kidney tissue, suggesting that these autoantibodies themselves or immune complexes, at least including these autoantibodies, are associated with the development of lupus nephritis. This might be one of the reasons why temporal and spatial diversity occurs in various manifestations of type 3 APS.

Regarding the treatment of patients with type 3 APS, each of their diseases should be managed properly. In our patient's case, SLE with diffuse lupus nephritis class IV-G(A) was diagnosed. Lupus nephritis class IV-G is currently the most prevalent form in Japan and is associated with a more severe clinical renal presentation [13]. The clinical outcome of lupus nephritis class IV-G for end-stage renal disease is very poor [14], thus necessitating intensive treatment including methylprednisolone pulse therapy. In our patient's case, the combination therapy of oral PSL and IVCY successfully resulted in remission as well as normal levels of liver enzymes. Since our patient is relatively old, careful and continuous monitoring will be needed to avoid infection by immunosuppressive treatment. Her diabetic status was well-controlled by insulin therapy with a proper diet regimen. Her thyroid function was controlled within the normal range by the proper dosage of levothyroxine sodium, although the pathophysiological meaning of TRAb seropositive is obscure. No other specific treatment is required.

Since patients with type 3 APS may present many manifestations over a long period of time, these complications should be taken into consideration even when the patients received treatment.

Final diagnosis. Autoimmune polyglandular syndrome type 3 associated with systemic lupus erythematosus.

Acknowledgments. We thank Ms. Nana Ugawa for performing the immunofluorescence staining of renal biopsy specimens.

References

1. Neufeld M, Maclaren N and Blizzard R: Autoimmune polyglandular syndromes. Pediatr Ann (1980) 9: 154–162.
2. Hansen MP, Matheis N and Kahaly GJ: Type 1 diabetes and polyglandular autoimmune syndrome: A review. World J Diabetes (2015) 6: 67–79.
3. Oki K, Yamane K, Koide J, Mandai K, Nakanishi S, Fujikawa R and Kohno N: A case of polyglandular autoimmune syndrome type III complicated with autoimmune hepatitis. Endocr J (2006) 53: 705–709.
4. Kahaly GJ: Polyglandular autoimmune syndromes. Eur J Endocrinol (2009) 161: 11–20.
5. *Dittmar M and* Kahaly GJ: Polyglandular autoimmune syndromes: immunogenetics and long-term follow-up. J Clin Endocrinol Metab (2003) 88: 2983–2992.
6. Flesch BK, Matheis N, Alt T, Weinstock C, Bux J and Kahaly GJ: HLA class II haplotypes differentiate between the adult autoimmune polyglandular syndrome types II and III. J Clin Endocrinol Metab (2014) 99: E177–182.
7. Horie I, Kawasaki E, Ando T, Kuwahara H, Abiru N, Usa T, Yamasaki H, Ejima E and Kawakami A: Clinical and genetic characteristics of autoimmune polyglandular syndrome type 3 variant in the Japanese population. J Clin Endocrinol Metab (2012) 97: E1043–1050.
8. Dittmar M and Kahaly GJ: Genetics of the autoimmune polyglandular syndrome type 3 variant. Thyroid (2010) 20: 737–743.
9. Yanagida I, Kamiya A, Sugimoto K, Noda T, Nagasako H, Noma E, Haraoka S, Maruoka H, Sugimura T, Kodera T, Abe I, Kubo T and Kobayashi K: A Case of Autoimmune Polyglandular Syndrome Type 3 Which Developed Chronic Thyroiditis, autoimmune Hepatitis, Slowly Progressive Type 1 Diabetes Mellitus and Systemic Lupus Erythematosus Through 16-Year Duration. J. Japan Diab Soc (2016) 59: 163–173 (in Japanese).
10. Horita M, Shiga N, Okeda T, Ono J, Takaki R and Komura K: Coexistence of Autoimmune Thyroid Disease, Systemic Lupus Erythematosus and Sjogren's Syndrome in a Patient with Insulin-Dependent Diabetes Mellitus. J Japan Diab Soc (1990) 33: 817–821 (in Japanese).
11. Al-Mutairy M and Malaviya AN: Systemic lupus erythematosus with polyglandular autoimmune syndrome type II: report of an unusual case. Lupus (2001) 10: 445–447.
12. Melcescu E, Kemp EH, Majithia V, Vijayakumar V, Uwaifo GI and Koch CA: Graves' disease, hypoparathyroidism, systemic lupus erythematosus, alopecia, and angioedema: autoimmune polyglandular syndrome variant or coincidence? Int J Immunopathol Pharmacol (2013) 26: 217–222.
13. Hiromura K, Ikeuchi H, Kayakabe K, Sugiyama H, Nagata M, Sato H, Yokoyama H and Nojima Y: Clinical and histological features of lupus nephritis in Japan: A cross-sectional analysis of the Japan Renal Biopsy Registry (J-RBR). Nephrology (Carlton) (2017) 22: 885–891.
14. Yokoyama H, Wada T, Hara A, Yamahana J, Nakaya I, Kobayashi M, Kitagawa K, Kokubo S, Iwata Y, Yoshimoto K, Shimizu K, Sakai N and Furuichi K: Kanazawa Study Group for Renal Diseases and Hypertension. The outcome and a new ISN/RPS 2003 classification of lupus nephritis in Japanese. Kidney Int (2004) 66: 2382-2388.