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Case Report

Polyglandular Autoimmune Syndrome Type 2 Complicated by Multiple Organ Failure, Empty Sella Syndrome and Aplastic Anemia

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Polyglandular autoimmune syndrome (PAS) is a group of syndromes comprised of glandular and extra-glandular disorders characterized by autoimmunity. A 57-year-old woman presented with acute progressive dyspnea and generalized weakness for several months. The patient was assessed to have acute congestive heart failure with cardiomyopathy, chronic renal failure with hyporeninemic hypoaldosteronism, and pancytopenia in addition to primary hypothyroidism and adrenal insufficiency. With the diagnosis of PAS type 2 complicated by multiple organ failure (MOF), medium-dose prednisolone (30 mg/d) was introduced primarily to control the activity of autoimmunity, which triggered MOF over the adrenal insufficiency. Levothyroxine (25 μg/d) was followed for replacement of the thyroid hormone deficiency. However, the symptoms and signs fluctuated, depending on the dosage of prednisolone, and progressively worsened by empty sella syndrome and aplastic anemia. Here, we report on a case of PAS type 2 with MOF and atypical complications, and suggest that recognition, assessment, and control of PAS as a systemic autoimmune disease may be essential. **(J Rheum Dis 2015;22:111-117)**

Key Words. Polyglandular autoimmune syndrome, Cardiomyopathies, Nephropathy, Pancytopenia

INTRODUCTION

Polyglandular autoimmune syndrome (PAS) is an autoimmune disease involving multiple endocrine organs which leads to hormonal insufficiencies. According to the clinical manifestations and endocrine alterations, PAS is classified into type 1 to 4. It is simply accepted that hormonal replacement for the insufficiencies affected is the management for PAS; however, the endocrine deficiencies are only a result of disease. As the autoimmunity targeting glands can diversely affect extra-glandular tissues or organs in PAS, assessment and control of the disease activity would be critical for the successful treatments of PAS as well as the hormonal replacements.

CASE REPORT

A 57-year-old woman was admitted to our hospital due to aggravating dyspnea for 4 days. The symptoms and signs had developed suddenly and progressed to an inability to keep routine activities. On admission, the blood pressure was 100/70 mmHg in an irregular pulse rate, respiratory rate of 20 breathes per minute, and body temperature of 36.5°C. The patient complained of orthopnea and palpitation as well as shortness of breath, which had been associated with poor oral intake, nausea, vomiting, and general weakness ongoing even after conservative treatments. No specific past medical, family or social histories were disclosed. Except for the neck vein distension, brady-arrhythmia, and pitting edema in both lower legs, findings on physical examination and systemic review were unremarkable.

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Complete count for white blood cells (WBC) was 7,460 cells/ μL (neutrophil 85.8%, lymphocyte 9.5%, eosinophil 1.0%), hemoglobin (Hb) 9.9 cells/dL, and platelets 173,000 cells/ μL. A peripheral blood smear test revealed normochromic normocytic anemia, mild anisocytosis, and poikilocytosis with a few normoblasts. Erythocyte sedimentation rate and C-reactive protein were 54 mm/h and 9.662 mg/dL, respectively. Arterial blood gas analysis and electrolytes levels showed pH 7.256, pCO_2 16.2 mmHg, PO_2 136 mmHg, HCO_3 7 mmol/L, serum Na/K/Cl 139/2.9/114 mEq/L indicating metabolic acidosis with high anion gap. Serum levels of aspartate transaminase and alanine transaminase were increased as high as 544/122 U/L. Serum levels of blood urea nitrogen and creatinine were 23.06 mg/dL and 4.09 mg/dL respectively, which were associated with proteinuria 551 mg/24 h and microscopic hematuria ranged 3(+), red blood cells 20 to 30/high power field in an urinalysis. Chest posterial-anterial showed cardiomegaly with high cardiothoracic ratio and increased bronchovascular markings on the both lung fields. Initial electrocardiogram (ECG) revealed sinus bradycardia fluctuating down to 30 beats per minute (bpm) with normal axis, narrow QRS complexes (combination of three of the graphical deflections seen on a typical ECG), and prolonged QT interval (measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle) corrected for rate (QTc; 681 ms) (Figure 1A).

As for the acute congestive heart failure with brady-arrhythmia, the levels of serum troponin I was 0.09 ng/mL,

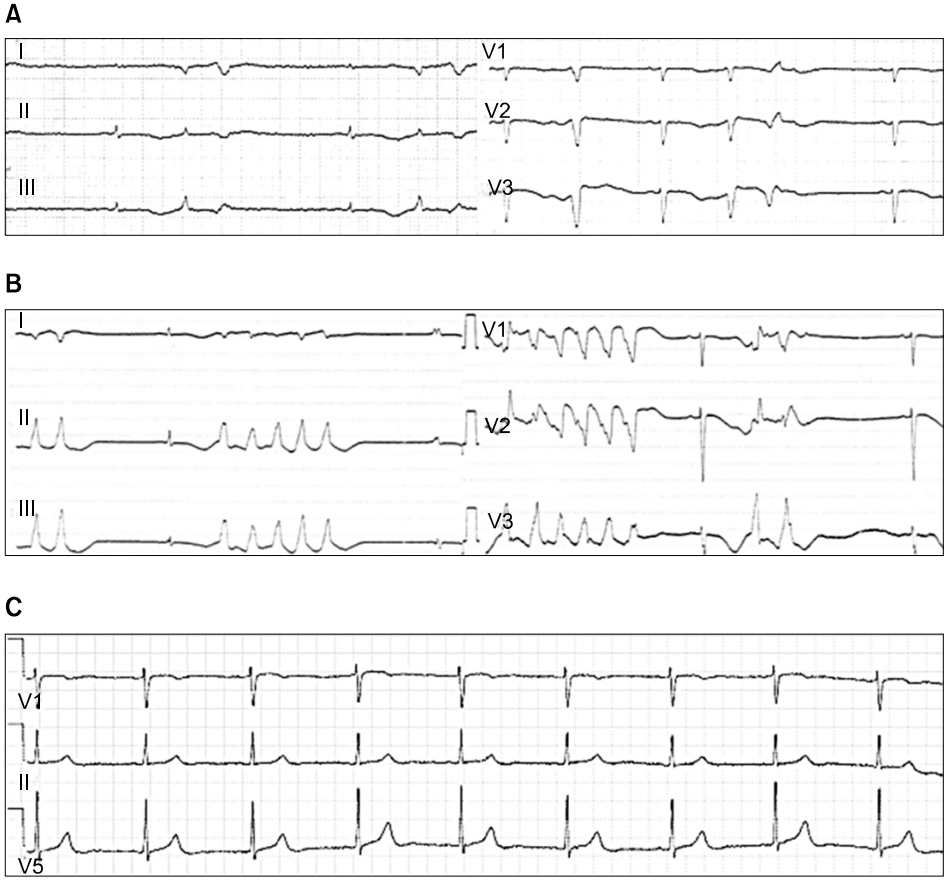

Figure 1. (A) An electrocardiogram at the admission to hospital revealed bradyarrhythmia rated as low as 30 beats per minute. The P waves appeared on the 12 leads were of normal morphology, axis and duration, but the PR intervals were variable beat to beat with some fusion beats and premature ventricular contractions (PVCs) of variable durations and reversed axes. The ST segments and T wave showed upward sloping which was also variable according to the preceding QRS complex. (B) During evaluation and treatment with levothyroxine, the bradyarrhythmia evolved into polymorphic VT showing consecutive PVCs of different morphologies that was intervened occasionally by normal P-QRS wave and became frequent. (C) Adding prednisolone 30 mg a day, the attack of polymorphic VT was to abate and ECG started to recover normal P, QRS and T waves in morphology, axis and duration to normal sinus rhythm and rate along with normalizing cardiac enzyme levels.

myoglobin 238 ng/mL, creatine kinase-MB 3.9 ng/mL, N-terminal fragment of the pro-hormone brain-type natriuretic peptide >25,000 pg/mL, free T4 5.83 pmol/L (10 to 25 pmol/L), T3 total <0.43 nmol/L (1.23 to 3.08 nmol/L), and thyroid stimulating hormone (TSH) 16.34 mU/L (0.3 to 4 mU/L). The left ventricular ejection fraction (LVEF) on 2-dimensional transthoracic echocardiography was decreased down to 17% with diffuse hypokinesia of the left (Figure 2A and 2C); however, the dimensions of the chambers were within normal ranges. The coronary angiography of this patient demonstrated the coronary arteries of no stenotic lesions or filling defects (Figure 3B).

Evaluations as to the primary hypothyroidism revealed that two small cysts less than 4 mm were present in the right lobe on thyroid ultrasonography (Figure 3A); anti-thyroglobulin antibody and anti-thyroid peroxidase antibody were negative. As for the renal failure with hematuria and tubular proteinuria, a computed tomography scan showed decreased both kidneys in size, the serum

A

RVDmid/L:	/ mm	IVSd (8~11):	6 mm	LV mass:	107 g	LVOT (18~22):	mm
FAC:	mm	IVSs:	6.5 mm	LV m index:	80 g/m^2	Ao_{ROOT} (22~23):	27 mm
LVEDD (42~54):	52 mm	PWd (8~11):	6.5 mm	SP index		LA (A-P) (27~44):	36 mm
LVESD (24~36):	48 mm	PWs:	8.8 mm	Min: D/S:	46 / 44	(M-L) (27~44):	40 mm
LVEF (55~76)	32 mm	RVW:	mm	Mj: D/S:	65 / 62	(S-I) (27~44):	50 mm
Mmode/vol:	17 / 15 %			Ratio: D/S:	0.7 / 0.7	LA volume:	38 mm
TV annular:	32 mm	MV annular 4C:	29/2C		mm	LA vol index:	28 ml/m^2

B

RVDmid/L:	/ mm	IVSd (8~11):	7.1 mm	LV mass:	150 g	LVOT (18~22):	mm
FAC:	mm	IVSs:	7.7 mm	LV m index:	110 g/m^2	Ao_{ROOT} (22~23):	25 mm
LVEDD (42~54):	55 mm	PWd (8~11):	8.2 mm	SP index		LA (A-P) (27~44):	39 mm
LVESD (24~36):	43 mm	PWs:	10 mm	Min: D/S:	/	(M-L) (27~44):	43 mm
LVEF (55~76)		RVW:	mm	Mj: D/S:	/	(S-I) (27~44):	57 mm
Mmode/vol:	39 / 41 %			Ratio: D/S:	/	LA volume:	50 mm
TV annular:	28 mm	MV annular 4C:	30/2C		mm	LA vol index:	38 ml/m^2

C

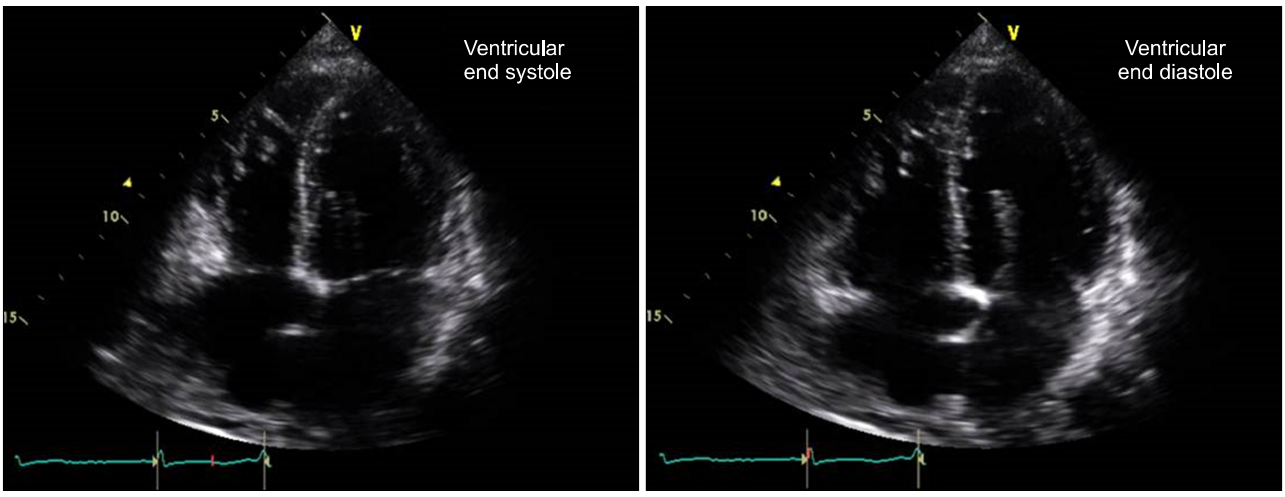

Figure 2. (A, C) A transthoracic echocardiography (TTE) at admission showed an enlarged LA with reduced LV systolic function (EF=15% by Simpson). Severe RV hypokinesia was observed with slightly dilated IVC (21 mm) and decreased collapsibility. Increased RVP (30 mmHg) with moderate TR, mild MR, but no visible thrombus were noted within the range of examination. Unfortunately, frequent arrhythmia (R/O PVC) put limitation on the study. (B) With some improvements and less PVCs on ECG after treatment of prednisolone and levothyroxine, a follow-up TEE was carried out to compare parameters with those of prior one. Even though LA and LV showed being enlarged and reduced in systolic function, the results indicated the heart had got some degree of recovery showing improved LVEF, RWMA, RV function as compared with previous TTE (EF=41% from 15% by Simpson) even with mild pulmonary hypertension (RVSP=37 mmHg), moderate TR, tethering of chordae and mild to moderate MR.

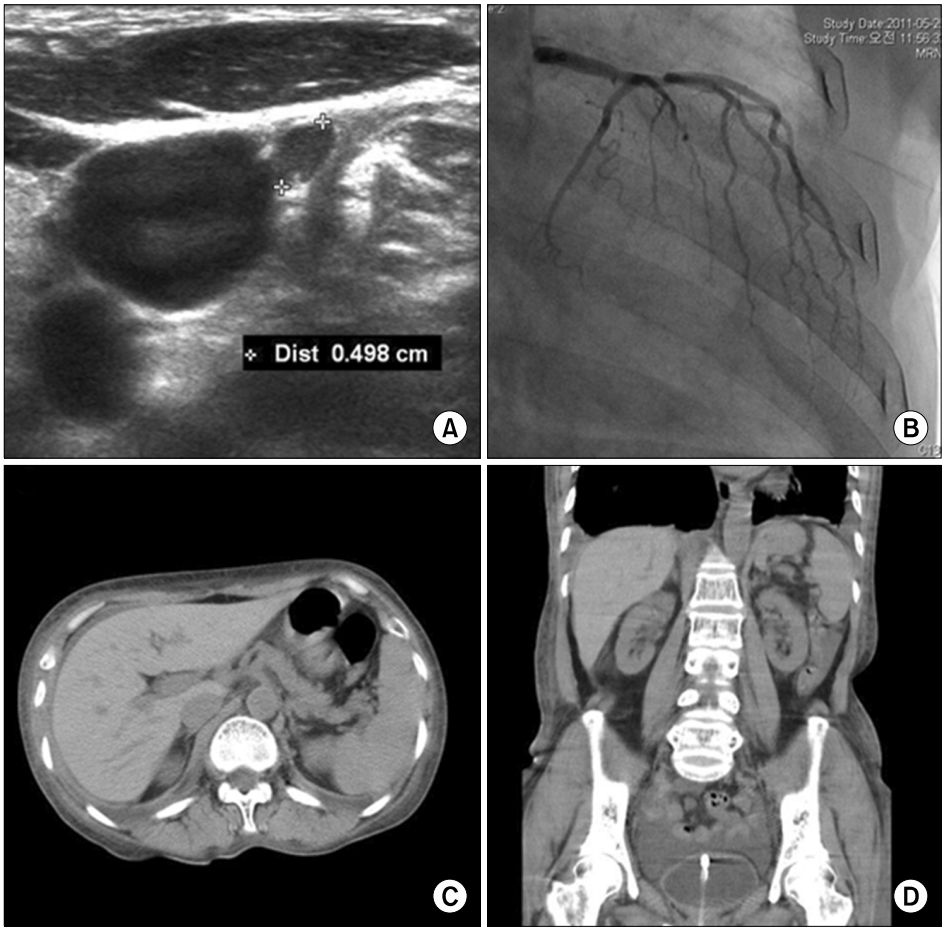

Figure 3. (A) On a thyroid ultrasonography for primary hypothyroidism, diffuse enlargement and a small cystic lesion were observed with no other abnormalities. (B) A coronary angiography for frequent polymorphic VT along with serum cardiac enzymes increasing as high as several folds of normal ranges showed no abnormalities of LCA, LCX, RCA and their branches. as for the renal failure and hyporeninemic hypoaldosteronism, a computed tomography scan revealed that the adrenal glands were normal in size with no mass (C) and the both kidneys were shrunk with no mass or lesion, indicating that it may be a chronic nephropathy (D).

level of intact parathyroid hormone increased as high as 443.1 pg/mL (Figure 3C and 3D). These findings indicate that the renal disease is of chronic renal failure (CRF). Despite levothyroxine 25 μg/d up to 50 μg/d and supportive treatment for congestive heart failure and brady-arrhythmia, the symptoms aggravated with fluctuating consciousness and profound weakness. Additional dynamic studies for the hormonal alterations and renal function were carried out, including rapid adrenocorticotropic hormone (ACTH) stimulation test, serum renin-aldosterone levels for the adrenal gland function and response to CRF. Rapid ACTH stimulation test revealed primary adrenal insufficiency showing blunted responses of serum cortisol 10.54 ng/dL at 30 minutes and 12.53 μg/dL at 60 minutes to ACTH stimulation compared with the basal cortisol 8.35 μg/dL and ACTH 9.90 pg/mL. Serum renin level was 0.08 ng/mL/h; serum aldosterone <10 pg/mL even after correcting electrolytes to normal ranges, which is compatible with hyporeninemic hypoaldosteronism. Fasting serum glucose and capillary glucose levels were all less than 120 mg/dL, and the level of hemoglobin-A1c (HbA1c) was 5.2%. Serum calcium level was 6.1 mg/dL, inorganic phosphate 3.7 mg/dL, and magnesium 1.3 mg/dL with normal serum osmolarity 294 mOsm/kg. The results may indicate chronic kidney disease (CKD) as a result of tubule-interstitial nephropathy.

Along with frequent polymorphic ventricular tachycardia (VT) (Figure 1B), the follow-up tests showed remarkable pancytopenia of WBC 3,000 cells/μL (neutrophil 71.6%, lymphocyte 13.6%), Hb 7.2 cells/dL, and platelet 87,000 cells/μL. Prothrombin time (PT) and activated partial thromboplastin time were within normal ranges, and follow-up peripheral blood smear tests showed only pancytopneia without any morphological changes for microangiopathic hemolytic anemia or immune hemolytic anemia. Although bone marrow aspiration smear revealed an adequate number of megakaryocytes, proliferated erythroid series, and suppressed myeloid with increased plasma cells as a finding for peripheral bicytopenia with agranulocytosis, bone marrow biopsy showed marked hypocellularity less than 5%.

The results of antinuclear antibody, anti-double strand

(ds-) DNA antibody, myeloperoxidase anti-neutrophil cytoplasmic antibody, proteinase 3 anti-neutrophil cytoplasmic antibody, rheumatoid factor, anti-platelet antibody, anti-cytomegalovirus immunoglobulin M, heterophil antibody, anti-human immunodeficiency virus antibody, and blood cultures were all negative demonstrating that they were unremarkable for systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and primary systemic vasculitides, as well as infectious diseases.

Prednisolone 30 mg/d was added to control disease activity under the diagnosis of PAS type 2 with primary hypothyroidism, primary adrenal insufficiency presenting as multiple organ failure (MOF) with cardiomyopathy, CRF of tubulo-interstitial nephritis, and immune pancytopenia indicating autoimmune pathogenesis.

With the medium dose prednisolone in addition to levothyroxine and treatments for congestive heart failure and polymorphic VT, the symptoms and signs faded out gradually. Pancytopenia reversed to WBC 6,490 cells/ μL, Hb 10.9 cells/dL, and platelet 188,000 cells/ μL, and a follow-up echocardiogram and ECG showed improvement of several parameters: LVEF 39%, improved biventricular hypokinesia, and recovery to normal sinus rhythm with normal QT/QTc (446/452 ms) with regular heart rate $>$60 bpm (Figures 1C and 2B).

As prednisolone tapered down to 7.5 mg/d, which is sufficient to maintain adrenal insufficiency, the patient had recurred pancytopenia which was reversed by increasing the prednisolone dosage up to 20 mg/d. Follow up hormonal tests showed free T4 24.34 pmol/L (10 to 25 pmol/L), total T3 0.43 nmol/L (1.23 to 3.08 nmol/L), TSH 0.20 mU/L (0.3 to 4 mU/L), basal cortisol 24.08 μg/dL and ACTH 1.80 pg/mL. On a sella magnetic resonance imaging, empty sella turcica with no other abnor-

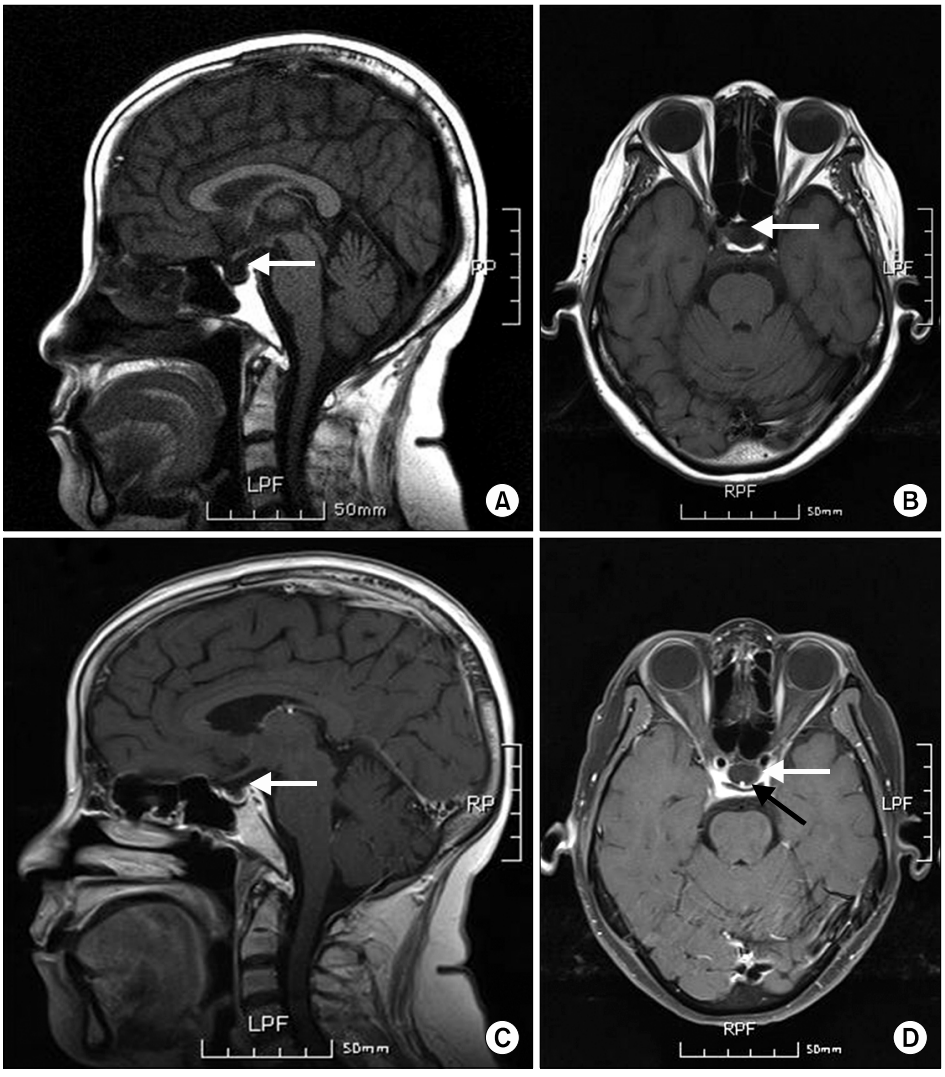

Figure 4. A T1 weighted magnetic resonance imaging revealed low signal changes of the sella turcica on the sagittal (A: without contrast, C: with contrast; white arrows) and transverse sections (B: without contrast, D: with contrast; white arrows) with the pituitary stalk demonstrating a high signal changes (black arrow), which is consistent with the empty sella. No other abnormal signal change of the brain was noted on this study.

mal signal change at brain was noted (Figure 4), which may indicate additive primary hypo-pituitary pathology as to hypophysitis and empty sella syndrome.

We are managing the patient with levothyroxine 100 μg /d and prednisolone 10 mg/d as PAS type 2 with unusual manifestations of MOF showing cardiomyopathy, CKD of tubule-interstitial nephropathy, and pancytopenia that was steroid-dependent.

DISCUSSION

PAS is characterized by the presence of a combination of multiple autoimmune disorders, and, in some cases, immunodeficiency as a group of syndromes comprising a combination of endocrine and non-endocrine autoimmune diseases [1]. The failure of several endocrine glands as well as non-endocrine organs results from an immune-mediated destruction of the tissues. In 1980, Neufeld and Blizzard [2] published a classification of PAS on clinical grounds indicating the existence of four main distinct types [3]. Type 1 PAS is classified by at least two chronic conditions, including candidiasis, chronic hypoparathyroidism, and Addison's disease and usually manifests in infancy or childhood at age 3 to 5 or in early adolescence. Type 3 PAS is defined as thyroid autoimmune diseases associated with other autoimmune diseases, except for those referred to as type 2 and the combination of organ-specific autoimmune diseases that are not included in the previous groups is classified as type 4. As for type 2, also known as Schmidt syndrome, primary adrenal insufficiency is the principal manifestation in conjunction with thyroid autoimmune diseases and/or type 1A diabetes mellitus. It is much more common than type I, affecting about 1.4 to 4.5 per 100,000 inhabitants, and is three times more frequent in females than males [4-6]. Approximately one half of the cases are familiar; however, age of onset is from childhood to late adulthood. Genetically, type 1 PAS shows polygenic association with HLA-DR3, -DR4, and non-HLA genes, such as MICA5.1, PTPN22, CTLA4, and VNTR. Predisposed individuals develop autoantibodies to the steroid 21-hydroxylase enzyme, gradually lose the ability to produce cortisol, and eventually manifest with symptoms of adrenal insufficiency [1,3,7]. Autoimmune adrenalitis accounts for more than 70% of all cases of primary adrenal insufficiency. 50% of patients with this form of Addison's disease have an association with autoimmune disease, thyroid disease being the most common [8]. Autoantibodies are useful markers for the prediction of the development of PAS. In case of absence of these antibodies does not exclude PAS, because not all patients demonstrate positive antibodies [9].

The usual autoimmune endocrine diseases associated with type 2 PAS are thyroid disease, type 1 diabetes, Addison's disease, hypoparathyroidism, and hypopituitarism. However, non-endocrine diseases are rare in type 2 PAS compared with type 1, with which immune gastritis, pernicious anemia, celiac disease, immune hepatitis, vitiligo, alopecia areata, Sjögren's syndrome, SLE, RA, and myasthenia gravis have been reported to be associated. Hormonal replacement is the mainstay for the treatment of PAS, so that replacement therapy with hydrocortisone or cortisone acetate and replacement of levothyroxine with simultaneous adrenal steroid replacement in a hypothyroid patient in type 2 PAS should be considered as to not precipitate an adrenal crisis [7].

In this case, the patient presented with MOF with non-ischemic cardiomyopathy, tubulo-interstitial nephropathy (TIN), and immune cytopenia and was treated with prednisolone 30 mg/d so as to suppress systemic autoimmunity under the diagnosis of complicated PAS type 2. Among the complications, congestive heart failure by cardiomyopathy presenting polymorphic VT, complete AV block, and long QT and peripheral pancytopenia have been improved with medium-dose prednisolone and levothyroxine. The effects achieved by medium-dose prednisolone have been regarded to be associated with immune modulation and suppression of autoimmunity in addition to the effects of hormonal replacement. Only a few cases of cardiomyopathy [10,11] and TIN [12] but not MOF and pancytopenia have been reported to be associated with PAS type 2 in the English literature.

SUMMARY

Here we report a case of PAS type 2 presenting as MOF complicated by unusual manifestations of CHF by polymorphic VT, complete AV block and long QT, CKD by tubule-interstitial nephropathy with hypo-reninemic hypo-aldosteronism, and peripheral autoimmune pancytopenia. Even though PAS can be perceived only as a combined endocrinopathy and managed simply with hormonal replacements, the presenting symptoms and signs of PAS can be as severe as MOF and potentially life-threatening as in this case. Therefore, early recognition of PAS as a systemic autoimmune disease is critical for the man-

agement and recovery from illness with immunosuppression such as glucocorticoids in fulminant cases.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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