Concurrent variant type 3 autoimmune polyglandular syndrome and pulmonary arterial hypertension in a Japanese woman

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Abstract. We describe a very rare case of concurrent variant type 3 autoimmune polyglandular syndrome (APS) and pulmonary arterial hypertension (PAH). A previously healthy 65-year-old Japanese woman was referred to our university hospital with a 2-month history of general fatigue and hyperglycemia. Laboratory tests revealed severe hyperglycemia (plasma glucose 543 mg/dL and HbA1c 10.7%) with ketonuria (3+). Glutamic acid decarboxylase (GAD) and IA-2 antibodies were positive, and the serum C peptide level was markedly decreased to 0.2 ng/mL. Accordingly, type 1 diabetes was diagnosed. Hashimoto’s thyroiditis was also diagnosed because she had a diffuse goiter and a mild hypothyroidism (TSH 8.20 μU/mL, and FT4 0.80 ng/mL) with positive autoantibodies for thyroid peroxidase and thyroglobulin. There was neither adrenal insufficiency nor hypocalcemia. In addition, chest X ray showed a suspicious PAH by a dilation of both pulmonary arteries, especially right descending artery, and right heart catheterization confirmed the presence of PAH. HLA Class II genotyping revealed DRB1-DQB1*0901-*0303, a common susceptibility haplotype in Japanese patients with type 3 APS or acute-onset type 1 diabetes. The combination of variant type 3 APS and PAH is extremely rare and to the best of knowledge, this is the first case reported in a Japanese patient.

Key words: Autoimmune polyglandular syndrome, Pulmonary hypertension, Type 1 diabetes, Hashimoto’s thyroiditis

AUTOIMMUNE POLYGLANDULAR SYNDROME (APS) is characterized by autoimmune disorders affecting multiple endocrine and non-endocrine organs [1-3] and it is classified into three major subtypes. Type 1 APS is a very rare autosomal recessive disorder that manifests in childhood with the triad of mucocutaneous candidiasis, hypoparathyroidism, and autoimmune Addison’s disease [1-3]. It is caused by mutation of the autoimmune regulator gene, which plays a role in maintaining immune tolerance. Type 2 APS presents in middle age with the combination of autoimmune Addison’s disease and autoimmune thyroid disease (AITD) and/or type 1 diabetes (T1D). Type 3 APS is defined as the combination of AITD with other autoimmune diseases, except for Addison’s disease and hypoparathyroidism. AITD combined with T1D is considered to be a variation of type 3 APS, which is known as variant type 3 APS [4].

Pulmonary arterial hypertension (PAH) is a rare disorder characterized by progressive remodeling of the distal pulmonary arteries that results in elevated pulmonary vascular resistance and eventually leads to right ventricular failure [5]. PAH is associated with a number of autoimmune diseases, such as AITD, systemic lupus erythematosus, scleroderma, and mixed connective tissue disease, suggesting that its pathogenesis may involve an autoimmune process [6]. However, there have been very few reports of APS coexisting with PAH in adults. We report a very rare case of concurrent variant type 3 APS and PAH in a 65-year-old Japanese woman. To our knowledge, this is the first Japanese patient with the simultaneous diagnosis of T1D and Hashimoto’s thyroiditis plus pulmonary artery hypertension.

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Case Report

A previously healthy 65-year-old woman was referred to our university hospital with a 2-month history of fatigue, thirst, and polyuria. Her body mass index was 19.86 kg/m², temperature was 37.1°C, blood pressure was 129/77 mmHg, and pulse rate was 103/min (regular). On examination, she had a small diffuse goiter. There was no family history of diabetes, thyroid disease, or PAH. Laboratory tests demonstrated severe hyperglycemia with a plasma glucose level of 543 mg/dL and HbA1c of 10.7%, as well as ketonuria (3+) (Table 1).

Blood gas analysis revealed a pH of 7.350, pO₂ of 64.7 mmHg, pCO₂ of 25.6 mmHg, HCO₃⁻ of 13.7 mmol/L, base excess of −9.9 mmol/L, and anion gap of 20.6 mmol/L. Glutamic acid decarboxylase (GAD) antibody measured by a radioimmunoassay (RIA; Cosmic Corporation Co., Tokyo, Japan) was slightly increased to 1.9 U/mL (reference range: <1.5 U/mL), and IA-2 antibody was markedly elevated to 24.6 U/mL (reference range: <1.0 U/mL). Fasting serum C peptide was markedly decreased to 0.2 ng/mL. Human leucocyte antigen (HLA) Class II genotyping revealed DRB1-DQB1*0901-*0303, DRB1-DQB1*1101-*0301. DRB1-DQB1*0901-*0303 is a common susceptibility haplotype in Japanese patients with acute-onset T1D. The HLA haplotype was examined by polymerase chain reaction-sequence specific primers (PCR-SSP; ONE LAMBDA, CA 91303, USA). She also had mild hypothyroidism with elevation of thyroid stimulating hormone (8.20 μU/mL) and a low free thyroxine level (0.8 ng/mL), and she was positive for antibodies to thyroglobulin and thyroid peroxidase (Table 1). She had no hypotension and hypokalemia. Laboratory findings showed a small number of eosinophil counts, ACTH of 24.4 pg/mL, and cortisol of 11.1 μg/dL. Taken together, we determined that she did not have clinically adrenal insufficiency, although it was not completely excluded. She did not have hypocalcemia (Corrected Ca 9.2 mg/dL).

The biochemical tests showed an increase of CK, accompanied by elevated levels of AST, ALT and LDH (Table 1). Subsequently, in parallel with an improvement of CK, all of these enzymes were decreased.

She also had thrombocytopenia, low plasma fibrinogen level, and mild elevated level of D dimer. However, she did not show prolonged PT time or APTT time. No hemorrhagic events were found in this case. Thus, it was unlikely that disseminated intravascular coagulation (DIC) occurred in this case.

Intravenous fluid supplementation was initiated for rehydration, followed by insulin infusion. The blood glucose level was normalized after 24 hours of treatment, and she was switched to subcutaneous basal/bolus insulin therapy.

The chest X-ray film obtained on admission raised suspicion of PAH due to dilation of both pulmonary arteries, especially the right descending artery (Fig. 1A), although she had none of the relevant symptoms. The electrocardiogram showed right axis deviation and peaked P waves. Echocardiography identified tricuspid regurgitation and showed that the right ventricular systolic pressure was markedly increased to 90 mmHg, which was identical to the pulmonary artery systolic pressure. Left ventricular diastolic and systolic function were normal, with a left ventricular ejection fraction of 55%. Right heart catheterization confirmed the diagnosis of PAH, since the mean pulmonary arterial pressure was 36 mmHg and the mean pulmonary capillary wedge pressure was 10 mmHg on room air (Fig. 1B). Lung perfusion scintigraphy showed no evidence of pulmonary embolism. To exclude the possibility of secondary PAH, autoantibodies for collagen vascular diseases were examined, as well as portal hypertension and her HIV status. These investigations found no abnormalities. She was treated with warfarin for anticoagulation and home oxygen therapy for hypoxia, followed by addition of a prostaglandin I₂ analogue.

Discussion

We reported a 65-year-old Japanese woman who presented with the simultaneous diagnosis of variant type 3 APS and PAH. APS is a relatively rare disorder and PAH is also rare, so coexistence of both disorders is even more unusual. To the best of our knowledge, only 7 cases of concurrent APS and PAH have been reported so far. The clinical characteristics of all 8 reported patients with this combination, including our case, are summarized in Table 2 [7-12]. To date, only 4 cases of concurrent type 3 APS and PAH have been reported. Thus, our patient is the fifth case of type 3 APS combined with PAH and the third case of variant type 3 APS with PAH worldwide.

To the best of our knowledge, she is also the first Japanese patient to have variant type 3 APS coexisting with PAH, and at the age of 65, she is the oldest patient reported with both of these diseases (Table 2). A previous Japanese report demonstrated that the age at onset of T1DM was older in patients with variant type 3 APS (33.5
± 16.9 years) than in those with T1DM alone (23.6 ± 17.5 years) [13]. Considering this, in our case, the age at onset of T1DM was remarkably older as acute-onset T1DM. The components of APS in our patient were T1D and Hashimoto’s thyroiditis. Type 3 APS is also known as incomplete type 2 APS, because it is known to be associated with progression to full type 2 APS over time [14]. Two of the previously reported patients had auto-antibodies targeting the adrenal cortex without adrenal insufficiency (Table 2), but it is possible that these patients will develop type 2 APS in the future.

Our patient presented with the simultaneous diagnosis of both variant type 3 APS and PAH. The diagnostic criteria for PAH by right heart catheterization are a mean pulmonary arterial pressure >25 mm Hg and a pulmonary capillary wedge pressure <15 mmHg [15], and our patient fulfilled these criteria. In patients with the combination of type 2 or 3 APS and PAH, the timing of onset of PAH varies from the early 20s to the late 60s. APS sometimes develops before PAH, while PAH precedes APS in other cases. This is only the second patient with simultaneous diagnosis of type 3 APS and PAH. The other patient with concurrent type 3 APS and PAH had Hashimoto’s thyroiditis and pernicious anemia as auto-

| Chemistry       | Hematology      | Diabetology     |
|-----------------|-----------------|-----------------|
| AST 52 U/L      | WBC 10,500 × 10^9/L | Glucose 543 mg/dL |
| ALT 46 U/L      | NEUTRO 86.3%    | HbA1c 10.7%     |
| LDH 475 U/L     | EOSINO 0.0%     | GAD Ab 1.9 U/mL <1.5 U/mL |
| GGT 20 U/L      | BASO 0.2%       | IA-2 Ab 24.6 U/mL <0.4 U/mL |
| T-Bil 0.8 mg/dL | Mono 4.0%       | ICA: negative |
| TP 5.0 g/dL     | LYMPHO 9.5%     | Fasting serum C peptide 0.2 ng/mL |
| Alb 2.5 g/dL    | RBC 5.17 × 10^{12}/L | Urinary C peptide 15.0 μg/day |
| UN 43 mg/dL     | Hb 16.2 g/dL    | Urinary albumin 65.0 mg/gCr |
| CRE 0.95 mg/dL  | Ht 48.9%       | HLA Class II haplotype |
| eGFR 45 mL/min/1.73 m² | MCH 94.6 | DRB1*0901-DQB1*0303 |
| Na 146 mEq/L    | MCV 31.7       | DRB1*1101*DQB1*0301 |
| K 5.5 mEq/L     | PLT 7.0 × 10^{5}/μL |
| Cl 110 mEq/L    | PT 11.9 sec    | Endocrinology   |
| Ca 7.7 mg/dL    | PT-NC 12.2 sec |
| Corrected Ca 9.2 mg/dL | APTT 29.9 sec |
| P 2.0 mg/dL     | APTT-NC 30.4 sec |
| UA 8.8 mg/dL    | Fibrinogen 118 mg/dL |
| CK 1,161 U/L    | D-dimer 3.6 μg/mL |
| myoglobin 1,101 ng/mL | Anti-thrombin III 63% |
| CRP 0.1 mg/dL   | TPOAb 1,020.0 U/mL |
| NT-proBNP 196 pg/mL | ACTH 24.2 pg/mL |
| Total-chol 181 mg/dL | Cortisol 11.1 μg/dL |
| LDL-chol 93 mg/dL | TgAb 132.0 U/mL |
| HDL-chol 60 mg/dL | TSH 8.2 U/mL |
| Blood gas analysis |               |
| pH 7.350        | pO₂ 64.7 mmHg   |
| Specific gravity 1.046 | pCO₂ 25.6 mmHg |
| PH 5.5          | HCO₃⁻ 13.7 mmol/L |
| Protein 30 mg/dL| BE –9.9 mmol/L  |
| Glucose >2,000 mg/dL | Anion gap 20.6 mmol/L |
| Ketone bodies 3+|                |
| Blood 2+        |                |

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immune disorders [10], unlike our patient who had Hashimoto’s thyroiditis and T1D (variant type 3 APS).

Our patient had the HLA Class II haplotype DRB1-DQB1*0901-DQB1*0303. HLA class II molecules present antigenic peptides to CD4+ T cells and HLA class II overexpression is found in the target tissues of most human autoimmune diseases, together with infiltration of activated T lymphocytes. In the Japanese population, DRB1*0405-DQB1*0401 (but not DRB1*0901-DQB1*0303) is a common susceptibility haplotype in patients with variant type 3 APS or T1D [13], while DRB1*0901-DQB1*0303 is more frequent in patients with acute-onset T1D alone [16]. Thus, the HLA genotype of our patient was not typical of variant type 3 APS in the Japanese population. A family linkage study has shown that HLA-DR3 is the major HLA allele contributing to susceptibility for AITD and T1D in Caucasians [17]. In addition, several population studies have suggested that both HLA DR3-DQB1*0201 and DR4-DQB1*0302 contribute to variant type 3 APS with the combination of AITD and T1D in Caucasians [16]. These reports indicate that there may be racial differences of the HLA Class II haplotypes related to APS susceptibility. In Caucasians, PAH is associated with a high frequency of HLA Class II DQ7 (DQB1*0301) [18], suggesting that its

Table 2 Clinical characteristics of reported patients with concurrence of autoimmune polyglandular syndrome (APS) and pulmonary artery hypertension (PAH)

| Case | Sex | Age (y) | Race    | APS type | Adrenal insufficiency | AITD | T1D | Onset                                           | Genetic testing                                                                 |
|------|-----|---------|---------|----------|-----------------------|------|-----|------------------------------------------------|--------------------------------------------------------------------------------|
| 1 [7]| M   | 14      | AA +    | 1        | No                    | No   | Yes | Type 1 diabetes at 11 years old PAH at 14 years old | AIRE mutation at c1203T (p. P401p)                                           |
| 2 [8]| F   | 30      | Polish  | 1        | No                    | Yes  | No  | Candidiasis at 2 years old Hypoparathyroidism at 4 years old Adrenal insufficiency at 8 years old PAH at 30 years old | AIRE homozygous mutation at R257X HLA genotype: DRB1*01-DRB1*11, DQB1*0301-DQB1*0501 |
| 3 [9]| F   | 50s     | French  | 2        | Yes                   | Yes  | No  | Adrenal insufficiency and hypothyroidism at mid-20s PAH at early 50s |                                                                              |
| 4 [10]| F | 50 | Spanish | 3v (2)   | No (positive for Ab to adrenal gland) | Yes  | Yes | PAH → Hashimoto’s thyroiditis → Type 1 diabetes |                                                                              |
| 5 [10]| F   | 31      | Spanish | 3 (2)    | No (positive for Ab to adrenal gland) | Yes  | No  | Simultaneous onset: Hashimoto’s thyroiditis, Pernicious anemia, PAH |                                                                              |
| 6 [11]| F   | 26      | Jewish  | 2        | Yes                   | Yes  | No  | Hashimoto’s thyroiditis → Adrenal failure and PAH |                                                                              |
| 7 [12]| M   | 21      | Caucasian | 3v | No                    | Yes  | Yes | PAH at 12 years old Graves disease and type 1 diabetes at 18 years | HLA Class II genotype: DRB1-DQB1*0901-*0303                               |
| 8    | Ours | F | 65      | Japanese | 3v | No | Yes | Simultaneous onset: Type 1 diabetes, Hashimoto’s thyroiditis, PAH |                                                                              |

AITD, autoimmune thyroid disease; T1D, type 1 diabetes; AA, African-American; AIRE, autoimmune regulator gene; ab, antibodies; v, variant.
pathogenesis may involve an autoimmune mechanism. Unfortunately, there have been no reports about the association of HLA Class II haplotypes and PAH in Asian populations. Further studies are required to investigate the relationship between HLA Class II antigens and PAH in Japan.

We found a markedly increased levels of CK in this case. This high CK level seemed not to be due to mild hypothyroidism as shown in Table 1. Her lipid profiles showed Total-cholesterol 180 mg/dL, LDL-cholesterol 93 mg/dL, and HDL-cholesterol 60 mg/dL, suggesting that these cholesterol levels were not compatible with hypothyroid state. Since electrocardiogram did not show any ST-T changes, it is unlikely for the presence of ischemic heart disease in this case. We also found that serum myoglobin, another muscle-related marker, was increased to 1,101 ng/mL. We speculated that high CK level was associated with rhabdomyolysis caused by diabetic ketoacidosis (DKA). In DKA, serum CK levels are increased by a variety of factors; 1) a reduction in intracellular potassium concentration induced by acidosis; 2) a disruption of myocyte membranes due to hyperosmolality; 3) peripheral circulation failure due to volume depletion; 4) impaired production of ATP in muscle cells due to glucose utilization disorder [19]. Since her plasma osmolality was markedly elevated at 348.6 mOsm/L, she had concomitant hyperglycemic hyperosmolar state (HHS) with DKA. On the basis of these findings, we speculate that marked dehydration may contribute largely to high level of CK on admission in this case.

Her complete blood count showed a low platelet count (thrombocytopenia) on admission. The reasons responsible for thrombocytopenia in this case remained unclear. She had no chronic liver diseases, because abdominal echocardiography show no evidences of chronic liver diseases or splenomegaly. Moreover, no HBs antigen or HCV was found. Thus, her thrombocytopenia may be not attributed to chronic liver disease. Simultaneously, low plasma fibrinogen level and mild elevation of D dimer were found. However, neither PT time nor APTT time was prolonged. No hemorrhagic events were found in this case. We made a decision that the diagnosis of disseminated intravascular coagulation (DIC) was clinically denied in this case. Similarly to our case, there was a previous case report showing the combination of rhabdomyolysis and thrombocytopenia in DKA. Although the mechanism responsible for thrombocytopenia in DKA remains to be determined, platelets count returned spontaneously to normal, accompanied by a decrease in CK levels in this case [20].

Our patient did not display any symptoms of PAH on admission, but we made the diagnosis from the typical findings on chest radiography and echocardiography. Early diagnosis of PAH led to its early treatment. Approximately half of all patients with PAH have concomitant AITD, which was Hashimoto’s thyroiditis in our patient [21]. Although it cannot be denied that coexistence of APS type 3 and PAH is simply by chance in our patient, it is possible that APS and PAH may be linked by common immunogenetic susceptibility. Investigation of PAH may be warranted to detect coexisting asymptomatic disease in patients with APS.

Disclosure

None of the authors have any potential conflicts of interest associated with this manuscript.

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