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Case Report

Pulmonary artery hypertension and type 1 diabetes mellitus with suspected autoimmune polyendocrine syndrome in a pediatric patient

Ildiko H. Koves[1]* and Delphine Yung[2]

[1]Division of Endocrinology and Diabetes, Seattle Children's Hospital, Seattle WA 98040, USA.
*Corresponding author. E-mail: ildiko.koves@seattlechildrens.org. Tel: + 1 206 987 5037. Fax: +1 206 987 2720.
[2]Division of Cardiology, Seattle Children's Hospital, 4800 Sand Point Way NE, USA.

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The objective of this study was to describe a constellation of rare pediatric disorders, pulmonary arterial hypertension (PAH) and autoimmune polyendocrine syndromes (APS). This study present a brief report of a child diagnosed with autoimmune type 1 diabetes mellitus (T1DM) at age 11 and with PAH three years later, when he was re-presented with symptoms of chest pain, lethargy, syncope and vomiting. Following a saline bolus, he became severely hypoxic. Echocardiogram and cardiac catheterization confirmed PAH. Following a literature search of these two concomitant rare conditions, suspicion was raised of a uniform diagnosis of APS; autoimmune regulator (AIRE) gene analysis revealed a heterozygous c1203T>C (p.P401P) mutation on chromosome 21q22. Screening for other autoimmune involvement was negative thus far. Pulmonary AH should be included within the rare components of APS as the independent occurrence of these two rare disorders is highly unlikely in particular in the context of an identified mutation within the AIRE gene.

Key words: Autoimmune polyglandular syndrome, pulmonary arterial hypertension, type 1 diabetes mellitus, autoimmune regulator gene, polyglandular endocrinopathy.

INTRODUCTION

Autoimmune polyendocrine syndromes are rare. There have been approximately 500 patients worldwide. The highest prevalence was found among the Iranian Jewish community (1:9,000), in Sardinia (1:14,400) and in Finland (1:25,000) (Weiler et al., 2012). It is characterized by multiple autoimmune illnesses, most typically Addison disease, hypoparathyroidism, and/or chronic mucocutaneous candidiasis. Type 1 diabetes mellitus (DM) is infrequent, present in 18% of cases (Eisenbarth and Gottlieb, 2004). Type 1 APS (OMIM#240300) is caused by homozygous, compound heterozygous, or heterozygous mutation in the autoimmune regulator gene (AIRE; 607358) on chromosome 21q22, which encodes a transcription factor.

Pulmonary arterial hypertension is a rare disorder associated with autoimmune illnesses and should be

considered as an autoimmune association. This case report broadens the currently recognized autoimmune components of APS.

CASE REPORT

An 11 year old male, presented with symptoms consistent with type 1 diabetes mellitus (T1DM) of vomiting, weight loss, lethargy and hyperglycemia. He lived at an altitude of 1600 m in Arvada, Colorado, and three years later he represented chest pain and syncope during vomiting. Echocardiogram suggested pulmonary hypertension. Cardiac catheterization confirmed PAH with mean pulmonary arterial pressure of 77 mmHg in room air, which decreased to 32 mmHg on acute vasodilator testing with oxygen and inhaled nitric oxygen. Due to the severity of his presentation, he was initially managed on intravenous epoprostenol and oral sildenafil. Due to the side effects, he was weaned off intravenous epoprostenol, and started on diltiazem as repeat catheterization showed acute pulmonary vasoreactivity. Nineteen months later, he relocated to Seattle to live at lower altitude.

He is of mixed ancestry; mother of mixed German, Irish and father of African-American background. There was no consanguinity, separated parents. The family history was significant for aunts on both parental side with systemic lupus erythematosus and both maternal grandparents with autoimmune thyroid disease. A half brother on the paternal side was diagnosed with PAH at 9 years and passed away at 14 years of age.

He was born at term with no other significant illnesses. Following T1DM, PAH was diagnosed as possibly associated with hereditary component, living at high altitude and/or autoimmune disease. At presentation to Seattle, height was 172.8 cm (46th), weight 59 kg (46th), body mass index (BMI) 20 (42nd), blood pressure 123/66 mmHg, pulse 66 min^{-1}, respiratory rate 18 min^{-1}, pulse oximetry in room air 100%. Salient physical examination finding: loud P2, otherwise negative examination.

The initial diagnostic evaluation is summarized as shown in Table 1. He had poor metabolic control of diabetes (HbA1C: 12.1%) due to poor adherence with insulin therapy. Laboratory screening for other autoimmune involvement (thyroid, parathyroid) were negative. Clinically, he had no suggestion of Addison's disease or other mucocutaneous involvement. He continued on basal bolus subcutaneous insulin therapy for T1DM. Fifteen months after relocation to sea level, cardiac catheterization demonstrated almost normal mean pulmonary pressure (23 mmHg) and further decrease with oxygen and inhaled nitric oxide to 19 mmHg. To improve adherence, he is now on tadalafil therapy, 20 mg daily and amlodipine 5 mg twice a day.

He receives regular follow up and clinical screening for other potential associated autoimmune illnesses and complications of diabetes. Pulmonary pressure and cardiac function remain stable on the aforementioned therapy.

Genetic assessment

Genetic testing was pursued following literature review and another case identification (Alghamdi et al., 2010). A novel heterozygous mutation was identified in the AIRE gene (21q22.3) at c1203T>C (p.P401P) using genomic DNA sequence analysis with PCR amplification of exons1-14 with automated fluorescence dideoxy sequencing method (DNA Diagnostic Laboratory, Baylor College of Medicine, Huston).

DISCUSSION

Several recent novel mutations were identified from Scandinavian (Wolff et al., 2007), Arabic (Faiyaz-Ul-Haque et al., 2009), Polish (Stolarski et al., 2006), Slovenian (Podkrajsek et al., 2005) and Indian (Zaidi et al., 2009) populations with racial differences affecting the AIRE gene (gene locus MIM#607358). This patient had a mixed racial northern European and African-American background and his mutation may relate to the latter ancestry. Some APSs have milder phenotypes and both the clinical features and AIRE mutations may be more diverse than previously thought (www.omim.org) . Defects in this gene cause the rare autosomal-recessive systemic autoimmune disease known as type 1 APS syndrome previously also termed as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED).

To our knowledge this is the youngest patient described with the two rare disorders and an identifiable AIRE gene mutation. There are a few young adult case reports (Alghamdi et al., 2010; Barrou et al., 1989; Garcia-Hernandez et al., 2006) with the constellation of PAH, T1DM and APS. The timing of autoimmune component of their presentation varied with recognized morbidities from the early 20s to later diagnosis of PAH in their 50s. Patients with type 1 APS with any two of spe-cific autoimmune conditions: mucocutaneous candidiasis, Addison's disease, T1DM or hypoparathyroidism, almost always have AIRE mutations. Recognized AIRE gene mutations cause different autoimmune illnesses including hypothyroidism, pernicious anemia, alopecia, vitiligo, hepatitis, ovarian atrophy, keratitis, Graves disease, myasthenia gravis (McAlpine and Thomson, 1988), enterochromaffin cells hormone secretion leading to malabsorption (Hogenauer et al., 2001).

Our patient without Addison's disease, hypoparathyroi-dism, enteropathy, evidence of hypogonadism, pernicious anemia, atrophic gastritis and/or mucocutaneous candidiasis did not fit the typical type 1 APS, yet an AIRE

Table 1. Diagnostic evaluation.

T1DM and APS 1 (Reference)	PAH
HBA1C: 10-14% (<6%)	Echocardiogram: Severe septal wall flattening; Estimated RV systolic pressure: 115 mmHg
C-peptide < 0.1 ng/ml (0.8-3.1)	Cardiac catheterization: PA pressure; Mean: 77 mmHg
GAD: 93 (<25)	Presentation O_2 sats: 80s
Insulin antibody: 0.143 (<0.013)	Spirometry: FVC: 3.34 L (76% predicted); FEV1: 2.8 (75%); FEV1: FVC 83.8%; TLC: 4.01 L
ICA512A: 0 (<7)	Lung ventilation perfusion scan: normal
TSH: 2.81 mIU/ml (0.5-4.5)	-
Free T4:1.3 ng/dl (0.8-2)	-
Antithyroglobulin Ab: neg	-
Anti TPO: neg	-
TSH receptor Ab: <1 IU/L (<1.75)	-
PTH related peptide: 0.5 pmol/ml (<2)	-
Total Ca: 9.4 mg/dl (8.7-10.7)	-
ACTH: 13 pg/ml (10-60)	-

HBA1C: Hemoglobin A1C; GAD: Glutamic acid decarboxylase antibody; ICA512: Islet cell antibody 512a; TSH: thyroid stimulating hormone; Free t4: Free thyroxine4; PTH: parathyroid hormone; Ab: antibody; AntiTPO: anti thyroid peroxidase antibody; ACTH: Adrenocorticotropic hormone; RV BP: Right ventricle blood pressure; PA: pulmonary artery pressure; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; TLC: total lung capacity.

AIRE gene mutation was found. A similar scenario has been described by Bhansali et al. (2003) whereby an adolescent with the specific association of PAH and type 1 APS had no clinical evidence of mucocutaneous candidiasis and an adult with fatal PAH had previously recognized type 1 APS (Korniszewski et al., 2003). This case fatality underscores the need to consider PAH in all children with APS.

Pulmonary arterial hypertension is characterized by obliteration of the small vasculature of pulmonary arteries. It is a rare, inhomogeneous disorder and a subset of patients have associated autoimmune morbidity such as Hashimoto thyroiditis, systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, scleroderma and T1DM (Morse et al., 1992; Badesch et al., 2010).

Type 2 APS and PAH have also been described in an adolescent who developed Hashimoto thyroiditis and T1DM following PAH diagnosis (Alghamdi et al., 2010) and in adults (Garcia-Hernandez et al., 2006) and no AIRE gene mutation was found. This further broadens the clinical and genetic variations and perhaps autoimmune polyendocrinopathy should be considered as a spectrum disorder with phenotypic and genotypic overlap.

Conclusion

To our knowledge, this is the youngest reported patient with the constellation of these two rare disorders with a novel mutation in the AIRE gene region on chromosome 21q22.3.

In the authors opinion, PAH should be included within the rare components of APS as the independent occurrence of these two rare disorders is highly unlikely in particular in the context of an identified mutation within the AIRE gene region. More cases are needed to indicate that the concurrence is a true association.

Conflict of interest

The authors have no relevant conflict of interest to enclose.

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