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CASE STUDY

Fatal primary pulmonary hypertension in a 30-yr-old female with APECED syndrome

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Fatal primary pulmonary hypertension in a 30-yr-old female with APECED syndrome. L. Korniszewski, M. Kurzyna, B. Stolarski, A. Torbicki, A. Smerdel, R. Ploski. ©ERS Journals Ltd 2003.

ABSTRACT: Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is caused by mutations in the autoimmune regulator (AIRE) gene, which has a central function in maintaining immunological tolerance. A number of conditions with proven or likely autoimmune pathogenesis occur in APECED: hypoparathyroidism, adrenocortical insufficency, candidiasis, hypogonadism, type 1 diabetes, hypothyroidism, hypophysitis, hepatitis, malabsorption, nail dystrophy, enamel hypoplasia and keratopathy. It is not clear which factors are responsible for variation in clinical picture of APECED, but human leukocyte antigen (HLA) genotype may be important.

The authors report the first description of a case of primary pulmonary hypertension (PPH) in patient with APECED, caused by R257X mutation in AIRE. The HLA genotype of the patient (DRB1*01/DRB1*11, DQB1*0301/DQB1*0501) has been previously reported as a predisposing factor to PPH.

The findings from this study, provided that other similar cases are reported, suggest that immune deregulation plays a role in the pathogenesis of primary pulmonary hypertension.

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Autoimmune polyglandular syndrome type I, also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED; OMIM 240300), is an autosomal recessive disorder caused by mutations causing loss of function of the autoimmune regulator (AIRE) protein [1]. The AIRE protein is a transcriptional regulator expressed mainly in the thymus and plays a central role in the development and maintenance of immunological tolerance by promoting the ectopic expression of peripheral tissue-restricted antigens in medullary epithelial cells of the thymus [2]. The lack of AIRE results in a number of manifestations with proven or likely autoimmune pathogenesis, of which the most common are hypoparathyroidism, primary adrenocortical insufficency and candidiasis, whereas hypogonadism, insulin-dependent diabetes mellitus, hypothyroidism, hypophysitis, hepatitis, malabsorption, nail dystrophy, enamel hypoplasia and keratopathy, occur less frequently [3]. It is not clear which factors are responsible for the variation in the clinical picture of APECED. The human leukocyte antigen (HLA) genotype may be important, since it was observed that autoimmune conditions in the APECED cohort showed HLA associations that were similar to those found in non-APECED patients with respective autoimmune disorders [4].

Primary pulmonary hypertension (PPH) is a disorder characterised by lesions of pulmonary arterioles, which increase vascular resistance and lead to elevated pulmonary arterial pressure. The pathogenesis of PPH is not clear but recently it has been put in a novel perspective by the demonstration of mutations in BMPR-II (bone morphogenic protein receptor II) in a proportion of patients [5–7]. BMPR-II is a ubiquitously expressed receptor for a group of growth factors belonging to the transforming growth factor beta superfamily [7, 8]. Conversely, since the majority of mutations in BMPR-II were found in familial cases of PPH, it is not clear if defects in the BMPR-II signalling pathway are present in all cases of the disease or just in the subset showing familial aggregation [9].

However, there are observations suggesting that PPH may have an inflammatory component, which include the following: 1) in the lungs of patients an abnormal production of several cytokines, including RANTES, was demonstrated [10]; 2) PPH is known to associate with conditions that have significant immune deregulation, such as autoimmune diseases (systemic lupus erythematosus, scleroderma, rheumatoid arthritis, dermatomyositis, mixed connective tissue disease) or human immunodeficiency virus (HIV) infection; 3) in a significant percentage of PPH patients, including those without any associated diseases, antinuclear antibodies and/or the Raynauld phenomenon are found [11]; and 4) an increased frequency of HLA class II antigens DR3 [12] and DQ7 [11]

have been reported among PPH patients, further suggesting that immune deregulation plays a role in the pathogenesis of the disorder.

A recent study demonstrated an absence of mutations in BMPR-II in patients with PPH and connective tissue disease, thus suggesting that PPH associated with immune deregulation may have a different pathogenesis from the familial form [13].

The authors present a case of fatal PPH in a patient with APECED syndrome. The occurrence of PPH in the course of this rare disease with well documented dysfunction of immunological system [2] may suggest a possible role of immune deregulation in the pathogenesis of PPH.

Case report

The patient was a female of consanguineous parents (great-grand father and grandmother were first cousins). She had periodically recurring chronic candidiasis of oral mucosa from aged 2 yrs. At aged 4 yrs the patient presented with tetany secondary to hypocalcemia. Hypoparathyroidism was documented and patient was successfully treated with hydroxyvitamin D_3 and calcium gluconate. At aged 8 yrs she was hospitalised for hypotension, dehydration and hyponatremia. Primary adrenocortical insufficiency was diagnosed by hormone assays (low levels of cortisol and high levels of adrenocorticotropic hormone). Replacement treatment with hydrocortisone and fluorohydrocortisone was maintained. Diagnosis of APECED was established.

Puberty occurred in the patient at aged 15 yrs and menstruation occurred regularly. At aged 22 yrs the patient had acute episode of abdominal pain in right lower quadrant. Surgical exploration revealed a large cyst on the right ovary, which was removed. She had no signs of hypogonadism, thyroid disease, malabsorption, hepatitis or gastritis. Luteinizing hormone, follicle-stimulating hormone, oestradiol, thyrotropin and thyroid hormone levels were all normal. At aged 30 yrs the patient developed progressive dyspnoea at exertion (New York Heart Association (NYHA) II). Echocardiography suggested severe pulmonary hypertension. Right heart catheterisation revealed markedly elevated pulmonary artery pressures, decreased cardiac index (1.4 $L \cdot min \cdot m^{-2}$) and high pulmonary vascular resistance (25 Wood Units). Transthoracic and transoesphageal echocardiography, lung scintigraphy, lung function tests, high resolution and contrast enhanced spiral computed tomography, failed to disclose cardiopulmonary causes. Connective tissue disease, HIV infection, portal hypertension and fenfluramine use was excluded and ultimately, PPH was diagnosed [14]. Family history of pulmonary hypertension was negative.

The patient received treatment with anticoagulants, diuretics and digoxin. Because of a 35% reduction of pulmonary vascular resistance induced with inhaled nitric oxide (NO) and an improvement related to calcium channel blockers, nifedipine treatment was resumed and the patient was in stable condition. Two months later she was readmitted because of rapidly progressing right heart failure and systemic hypotension. Despite intensive therapy with diuretics, inotropic agents and prostacycline (Beraprost), the oedema, pericardial and pleural effusion persisted and the patient remained in NYHA class IV. Ballon atrial septostomy [15] resulted in a drop of oxygen saturation, cardiac index increased from 1.2 to 1.5 $l \cdot min \cdot m^{-2}$ and clinical condition mildly improved; but severe hypoxemia remained a significant problem. The patient developed cardiac arrest 14 days after septostomy. She was successfully resuscitated but remained haemodynamically unstable and despite continuous inhaled NO treatment and support with dopamine and dobutamine, died 10 days later with symptoms of low cardiac output and finally, intractable shock.

Autopsy was not performed. *Post mortem* sequencing of the AIRE gene was performed as described by SCOTT *et al.* [16] and revealed homozygous substitution of cytosine by thymine in nucleotide position 8473.

HLA typing was performed using SSP kit (Dynal, Oslo, Norway), which allows the main groups of antigens to be determined at the deoxyribonucleic acid (DNA) level. Two loci were analysed: HLA-DRB1 and HLA-DQB1, which encode the beta chain of the HLA-DR and -DQ molecules, respectively. The results showed the DRB1*01/DRB1*11, DQB1*0301/DQB1*0501 genotype, which encodes DR1 and DR5, as well as DQ1 and DQ7 molecules [17].

Discussion

The authors present the case of fatal PPH in a 30-yr-old female with APECED syndrome caused by homozygous R257X mutation in AIRE gene.

PPH is not a condition listed as a manifestation of APECED. To the extent of the authors' knowledge, this is the first report of the coexistence of the two diseases. The important question is whether the observed association has a biological basis or is caused by chance. Since both PPH and APECED are rare, the authors favour the former hypothesis (the incidence of PPH was estimated to be 1–2 per million [18] whereas the prevalence of APECED was reported as 1 in 80 000 [19]). Also, it should be noted that the patient did not have conditions known to increase the chance of pulmonary hypertension, such as connective tissue disease, HIV infection, portal hypertension or exposure to appetite-suppressing drugs.

The occurrence of genetically determined PPH in the patient cannot be fully excluded, but the lack of history of pulmonary hypertension in patient's family argues against it. However, the fact that the patient's parents were related could be taken to suggest that the likelihood of genetically determined disease in the patient was increased. However, it should be borne in mind that genetically determined PPH is a dominant trait and thus should not preferentially occur in consanguineous families. It should also be noted that the patients parents were related only distantly (great-grand father and grandmother were first cousins).

Provided that the co-occurrence of PPH and AIRE is not a stochastic event, there should be a pathogenic link between the two disorders. Given the function of AIRE protein [2], it could be speculated that occurrence of PPH in the patient was secondary to the AIRE-related immune deregulation. The presence in the patient of the HLA-DQB1*0301 allele encoding the HLA-DQ7 molecule, which has been previously associated with pulmonary hypertension, is also consistent with the possible role of autoimmune reactions in the pathogenesis of PPH in this case [11].

The present report is also the first description of APECED in the Polish population with the diagnosis verified by DNA sequencing. The authors found the homozygous substitution of cytosine by thymine in nucleotide position 8473 of AIRE gene in the patient. This substitution results in the change of arginine into a stop codon at aminoacid position 257 (R257X), which results in a significantly truncated and thus nonfunctional AIRE protein. The R257X mutation is common in White patients with APECED [20].

In conclusion, the authors report the first description of a case of primary pulmonary hypertension in a patient with a diagnosis of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. These findings, provided that other

similar cases are reported, support the role of immune deregulation in the pathogenesis of primary pulmonary hypertension.

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