A Novel BMPR2 Mutation Associated with Pulmonary Arterial Hypertension in an Octogenarian

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Abstract We describe the case of an 83-year-old man with a family history of pulmonary hypertension (PH) who presented with severe pulmonary arterial hypertension (PAH) and later tested positive for a novel bone morphogenetic protein receptor 2 (BMPR2) gene mutation. To our knowledge, this may be the oldest reported patient with PAH in whom a BMPR2 mutation was initially identified.

Keywords Heritable · Pulmonary arterial hypertension · BMPR2 mutation

Introduction

Pulmonary arterial hypertension (PAH) is a rare incapacitating disease with progressive functional limitation and deterioration to right heart failure and death. In addition to various disorders that can cause PAH, a genetic predisposition to this disease was identified with the discovery of mutations in the gene encoding the bone morphogenetic protein receptor type 2 (BMPR2), a member of the transforming growth factor-β (TGF-β) receptor, in both the familial and the sporadic cases of PAH [1–3]. Heritable PAH (HPAH) segregates as an autosomal-dominant disorder with variable age of onset, reduced penetrance, approximately a 2:1 female:male ratio, and genetic anticipation in some pedigrees [4–6]. Approximately 6% of the individuals diagnosed with PAH have a family history of this disorder. BMPR2 mutations are heterogeneous, with missense, nonsense, frameshift, splice site, and both small and large gene deletions and duplications found throughout the gene [7, 8]. Disease-causing mutations have been identified in approximately 70% of HPAH and 5–26% of idiopathic PAH (IPAH) patients [8–11].

We present a novel BMPR2 mutation-associated case of PAH first diagnosed at 83 years of age. To the best of our knowledge, our patient may be the oldest to be diagnosed with BMPR2-associated PAH.

Case Report

An 83-year-old World War II veteran presented for evaluation of fatigue and breathlessness with exertion at New York Heart Association III functional class with findings of elevated right-sided pressures on echocardiogram. He gave a history of progressive dyspnea with physical activity for
4 years and pedal edema for 6 months which was symmetrical and worse during the evenings.

His past medical history included mild hypertension, nocturnal hypoxemia requiring oxygen therapy, gout, and degenerative arthritis of his right knee from shrapnel injury during World War II. He had an episode of syncope approximately 1 year prior to evaluation that was attributed to dehydration and heat exhaustion. Echocardiogram done at that time had shown preserved left ventricular ejection fraction at 70%, enlarged right-sided chambers, and estimated right ventricular systolic pressures of 80 mmHg. He had no history of thromboembolic disease, chronic lung disease, or prior transfusions. He was on treatment with amlodipine for systemic hypertension, furosemide, and oxygen.

He had been a lifelong nonsmoker with no other dependence. He recalled his mother (nonsmoker) was diagnosed with pulmonary hypertension (PH) and emphysema and had died at age 65. His brother and a maternal first cousin had died with a diagnosis of PH at age 49 and 71, respectively. The patient remembered that PH was identified on echocardiograms in his affected relatives but did not recollect details of other diagnostic workup. One of his brothers died of cirrhosis while his youngest brother was alive and had a history of coronary artery disease. His sister was alive and healthy. The patient had never married and had no children.

On examination his blood pressure was 92/61 mmHg, heart rate was 105/min, respiratory rate was 18–20/min, oxygen saturation was 92% on room air, and body mass index was 26.6 kg/m². Abnormal findings on examination included accentuated pulmonic component of second heart sound, 3/6 pansystolic murmur at the left lower sternal border, and bilateral pitting pedal edema.

Abnormal laboratory parameters included a brain natriuretic peptide of 335 pg/ml, serum creatinine of 1.4 mg/dl, and hemoglobin of 18 g/dl. Chest X-ray showed cardiomegaly, prominent pulmonary vasculature, and normal lung fields. Pulmonary function tests revealed normal spirometry, lung volumes, and diffusion capacity. Polysomnogram confirmed sleep-disordered breathing with obstructive, mixed, and central apneas. He was started on nocturnal continuous positive airway pressure with oxygen therapy. Electrocardiogram showed right axis deviation, right ventricular hypertrophy, and inverted T waves in V1-V4. Echocardiogram was repeated and showed marked dilatation of right atrium and ventricle, impaired systolic right ventricular function, moderate to severe tricuspid regurgitation, and estimated peak pulmonary artery pressures of 100 mmHg with left ventricular ejection fraction of 55% without segmental wall motion abnormalities or pericardial effusion. Adenosine stress test did not show ischemia or infarction. A 6-min walk test was severely impaired with a total distance of 67.06 m or 30.9% of the predicted lower limit of normal calculated to be 216.8 m for his age and body mass index using the Enright and Sherrill formula [12]. He stopped after 3 min because of breathlessness. Ventilation perfusion scan did not reveal perfusion defects or ventilation perfusion mismatch. Collagen vascular workup and hepatitis screen were negative, and HIV testing was not done as he denied risk factors. Right heart catheterization confirmed pulmonary arterial hypertension with pulmonary artery pressures of 102/44 mmHg (mean = 63 mmHg), mean pulmonary artery occlusive pressure of 9 mmHg, mean right atrial pressure of 19 mmHg, mixed venous saturation of 61.5%, thermodilution cardiac output of 2.72 l/min, and cardiac index and pulmonary vascular resistance calculated at 1.48 l/min/m² and 1588 dyn s/cm⁵, respectively. Acute vasodilator study with inhaled nitric oxide did not show vasoreactivity.

With a family history of relatives carrying a diagnosis of PH, genetic testing was offered to assess for the presence of HPAH. Using previously described techniques, BMPR2 DNA and RNA mutation screening was performed upon peripheral lymphocytes and identified mutation c.241insT in exon 2 of the BMPR2 gene (Fig. 1) [8]. This disease-causing mutation in codon 81 replaced lysine with a stop codon.

Amlodipine was stopped and he was started on digoxin, warfarin, and bosentan, which was titrated to a target dose of 125 mg two times a day. At the time of his last office
visit and after a year of bosentan therapy, he reported better tolerance for physical activity with improvement in functional class to NYHA II. His 6-min walk distance had improved to 146.3 m (67.5% of predicted lower limit of normal [12]) and was mainly limited by knee pain. Follow-up right heart catheterization showed a right atrial mean pressure of 3 mmHg, pulmonary artery pressure of 95/20 mmHg (mean = 45 mmHg), pulmonary capillary wedge pressure of 6 mmHg, cardiac output of 2.9 l/min, and calculated cardiac index and pulmonary vascular resistance of 1.6 l/min/m² and 1075 dyn s/cm⁵, respectively. His extended family had undergone genetic counseling but declined genetic testing.

**Discussion**

We describe the case of an 83-year-old man presenting with pulmonary arterial hypertension due to a previously unreported BMPR2 mutation c.241insT. This DNA single base insertion at codon 81 results in a frameshift with a stop codon at this site causing premature truncation of the BMPR2 protein. This mutation creates messenger ribonucleic acid (mRNA) that would be identified and subjected to nonsense-mediated decay (NMD) [13]. Interestingly, a low level of aberrant mRNA was detected in the lymphocytes from this patient (Fig. 1).

This case is interesting in that this patient presented at the age of 83. Recently, Sztrymf et al. [14] reported that PAH carriers of BMPR2 mutations presented 10 years earlier than IPAH patients (36.5 ± 14.5 vs. 46.0 ± 16.1). Carriers of BMPR2-truncating mutations (NMD positive) have a later age of diagnosis and death than carriers of a BMPR2 missense mutation (NMD negative) [15]. This recent study of NMD-associated BMPR2 mutations provides additional evidence of the protective function of NMD in heterozygote carriers of dominant disorders [16]. Since only 10–20% of individuals with a BMPR2 mutation develop PAH, it is suggested that both environmental factors and modifier genes explain the reduced penetrance of HPAH [17–21]. Single nucleotide polymorphisms in the TGFβ1 gene and variations in genes associated with proliferation, GTP signaling, stress response, and estrogen metabolism have been proposed to modulate the age of diagnosis and penetrance in these families [18, 19]. Recently, expression of wild-type allele BMPR2 transcripts has been reported as being important in determining penetrance of HPAH [20]. Thus, the late age of onset in our patient can be likely explained by a NMD-positive BMPR2 mutation and the presence of modifier genes and/or unknown environmental factors which conveyed protection from PAH at an earlier age. It is interesting that the mutant BMPR2 mRNA was detected at a low level in the lymphocytes of the patient and apparently escaped complete NMD in this tissue. The status of the mutant BMPR2 mRNA in the lung of the patient is unknown. However, if the mutant BMPR2 mRNA also escaped complete degradation by NMD in the lung tissue of our patient, it is then presumed that the severely truncated mutant protein was unable to interfere effectively with the function of the wild-type BMPR2 protein in a dominant-negative manner. Thus, one would predict that this patient probably developed PAH through haploinsufficiency of the BMPR2 protein [17].

**Conclusion**

Clinical testing for BMPR2 mutations is appropriate care for the management of patients with a family history of PAH regardless of the age at presentation as detection of family-specific mutations can be used to counsel family members at risk for developing PAH. Identification and analysis of different mutations will help understand the disease at a genetic level and explore treatment options that can be offered to patients and their families with HPAH. The future holds promise for targeting therapies at a molecular level.

Prior to proceeding with presymptomatic genetic testing, counseling to discuss the complexity of this disease and the reduced risk for developing the disease in the presence of the mutation is required.

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