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CASE REPORT

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BMPR2 mutation and clinical response to imatinib in a case of heritable pulmonary arterial hypertension

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Abstract

Bone morphogenetic protein receptor 2 (BMPR2) mutation is the most common gene mutation implicated in the pathogenesis of pulmonary arterial hypertension (PAH). We describe, for the first time, an excellent clinical response to tyrosine kinase inhibitor imatinib in a patient with heritable PAH from BMPR2 mutation.

KEYWORDS

Bmpr2 mutation, hereditary, imatinib, pulmonary hypertension

CASE REPORT

The proband is currently a 42-year-old male with severe heritable pulmonary arterial hypertension (HPAH) resulting from a bone morphogenetic protein receptor 2 (BMPR2 mutation). The mother and elder sister had deceased from severe progressive idiopathic PAH (IPAH) before genetic study was available (Figure 1, panel c). The father and all the second-degree family members were unaffected. The mutation is a heterozygous missense mutation c.346T>C (thymine replaced by cytosine) in the exon 3 of the BMPR2 gene which encodes for the ligand binding domain (Figure 1, panel a). This mutation leads to the replacement of amino acid cysteine at position 116 by arginine (p.(Cys116Arg)). The pathologic significance of the mutation was confirmed by detailed analysis (Figure 1, panel b) along with the presence of highly conserved cysteine at position 116 across multiple species including humans. The cysteine residues in BMPR2 proteins are responsible for the five disulphide bridges which are essential for maintaining the integrity of the protein structure.[1] The changes in the secondary structural elements of the mutant were decrease in the β sheets (β-3, β-4, and β-6) and the loop conformation of β-4 sheet when compared to wild type (Figure 1, panel d). In addition, the molecular electrostatic potential surface mapping showed a change in charge distribution from negative (cysteine) to positive (arginine) on the mutated structure (Figure 1, panel e). The genetic analysis was done by Sanger sequencing method.

The patient was initially diagnosed with severe HPAH at 24 years of age in 2005. The secondary causes of PAH were ruled out (Table 1); the patient however did not consent to cardiac catheterization. He was in WHO functional class (WHO FC) II and was initially started on sildenafil 25 mg three times a day and anticoagulant acenocoumarol. With progression of disease, he was appropriately transitioned to dual therapy with tadalafil 40 mg and ambrisentan 10 mg once a day and remained in FC II. In 2014 while on dual therapy, he worsened to WHO FC IV with right heart failure and severe right

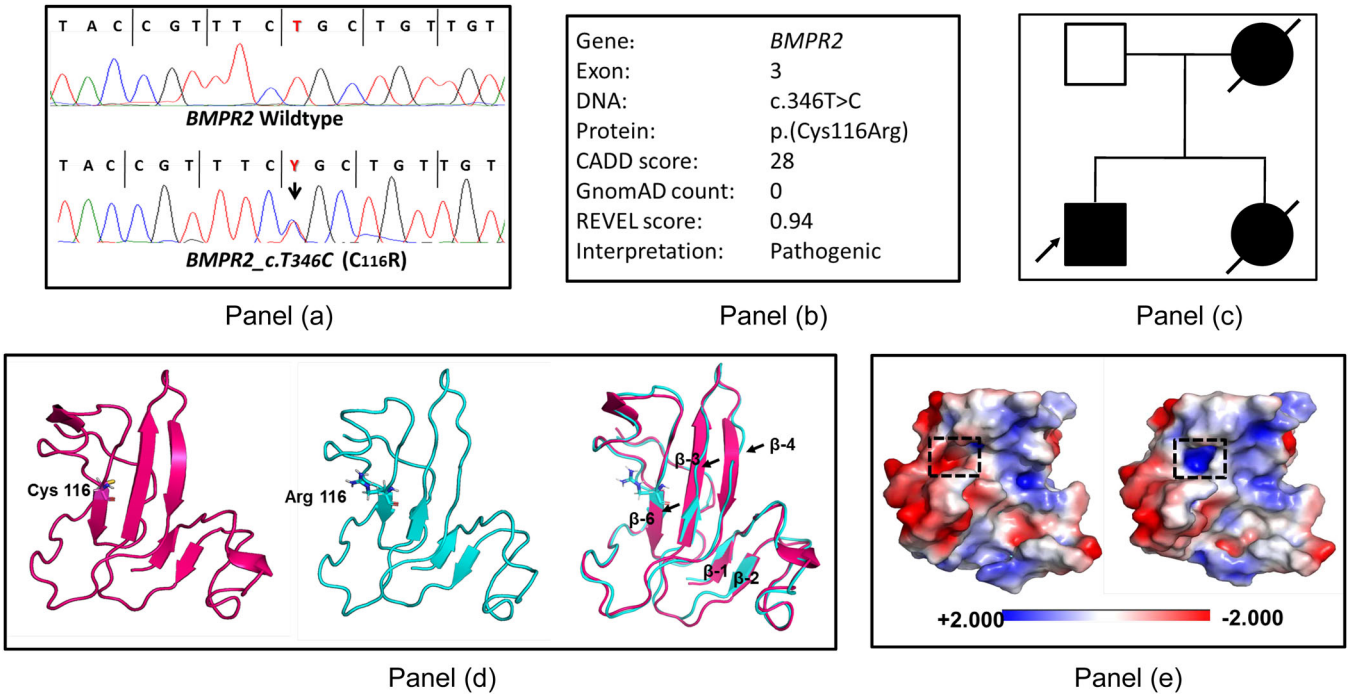

FIGURE 1 Molecular details of BMPR2 mutation and pedigree chart. Panel (a) Electropherogram of the normal wild type (above) and the c.346T>C mutation in the BMPR2 gene (below) resulting in the substitution of cysteine by arginine at the position 116. Panel (b) Details of the pathogenic BMPR2 variant (*rs1574464160*) identified in the patient. Panel (c) Pedigree chart of the family. Panel (d) Structure of the extracellular domain of the BMPR2 wild type (PDB ID: 2HLQ; pink cartoon); mutated (cyan cartoon); and the superimposed image of wild type and mutated gene in order from left to right. Changes in the secondary structural elements are indicated by black arrows. Panel (e) MEP surface map of mutated BMPR2 gene (left) and wild type gene (right) showing change in electrostatic potential from negative to positive, marked by black boxes. Arg, arginine; BMPR2, bone morphogenetic protein receptor 2; CADD score, combined annotation dependent depletion score; Cys, cysteine; GnomAD, genome aggregation consortium used ensemble transcript and reference sequence for the BMPR2 gene: ENST00000374580.8, NM_001204; MEP, molecular electrostatic potential; REVEL, rare exome variant ensemble learner.

ventricular dysfunction (Table 1). The genetic evaluation available then identified the BMPR2 gene mutation. In view of nonavailability of other pulmonary vasodilators including prostacyclins, imatinib a tyrosine kinase inhibitor (TKI) was started as an add on off label therapy at an initial dose of 100 mg once a day, stepping up to 200 mg once a day and the anticoagulant acenocoumarol was stopped to avoid the known complication of subdural hematoma.[2] The patient had excellent clinical response to imatinib therapy with complete resolution of symptoms. After 9 years of follow-up on triple therapy, not requiring further dose escalations, he is currently in FC II with normal RV function (Table 1) and without any drug related adverse events although severe PAH has persisted.

DISCUSSION

BMPR2 gene is in chromosome number 2 and has 13 exons that code for various proteins. Pathogenic variations in this gene are responsible for 70%–80% of patients with HPAH (autosomal dominant) and 10%–20% of patients with IPAH.[3] The BMPR2 normally activate the type 1 receptors after binding with the BMP ligand which sequentially phosphorylates the SMAD 1, 5, and 8. This activate the downstream signaling pathway that control the pulmonary arterial smooth muscle cells (PASMC) generation by regulating the cell cycle. BMPR2 signaling also exerts the antiproliferative effects through two other downstream effectors—transcription factor PPARγ and its putative target apoE, independent of SMAD 1, 5, and 8.[4] The latter prevents platelet derived growth factor (PDGF)-BB-induced proliferation and migration of PASMCs by binding to the LDL receptor related protein and internalizing PGDFR-β. Conversely PDGF-BB induced miR-376b upregulation mediates the down-regulation of BMPR2, in turn promoting proliferation of PASMC in multiomics analysis.[5] These cross talks between PDGF signaling and BMPR2 expression has further highlighted the therapeutic potential of TKI in these subsets.

The role of PDGF signaling is well known in pathogenesis of PAH. PDGF is a potent mitogen inducing

TABLE 1 Clinical and investigation parameters.

Parameters	At diagnosis (2005)	At addition of imatinib (2014)	At last follow-up (2022)
Clinical			
WHO FC	II	IV	II
SpO_2 (%)	96	95	98
6 MWT (m)	330	Bed rest	400
Risk stratification[a]	Intermediate low	High	Low
Investigations			
Nt-proBNP (pg/mL)	-	336	106
ANA screen	Negative		
Thyroid function test	Normal		
PFT/DLCO	Normal		
CT pulmonary angiogram	Normal		
Echocardiography			
RVSP[b] (mmHg)	110	50	77
TAPSE (mm)	17	8.9	22.1
RVTDI S' (cm/s)	-	-	13.4
LVEI	-	-	2.3
LVEF (%)	58	55	57
Pericardial effusion	Mild	Mild	Nil

Abbreviations: DLCO, diffusion capacity of lung for carbon monoxide; LVEF, left ventricular ejection fraction; LVEI, left ventricular eccentricity index; PFT, pulmonary function test; RVSP, right ventricular systolic pressure; RVTDI, right ventricular tissue doppler imaging; SpO2, pulse oximetry saturation; TAPSE, tricuspid annular plane systolic excursion; WHO, world health organization; 6MWT, 6-minute walk test.

[a]Simplified four strata risk assessment tool from Humbert M, Kovacs G, Hoeper MM, et al. ESC/ERS Scientific Document Group. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43(38):3628–3731.

[b]RVSP was calculated from tricuspid regurgitation jet velocity and adding approximate mean right atrial pressures (obtained from inferior venacava collapsibility).

proliferation and migration of PASMC resulting in medial hypertrophy and vascular remodeling.[6] The upregulation of PDGF pathway is well described in PAH in animal models and humans with IPAH.[7,8] Imatinib, a potent PDGF/ABL/c-KIT kinase inhibitor reversed pulmonary vascular remodeling there by reducing right ventricular hypertrophy and improving cardiac output and survival in monocrotaline induced rat PAH models.[9] Imatinib reduced the expression and inhibited phosphorylation of PDGFβ along with suppression of antiapoptotic effects of PDGF axis. In addition, imatinib also inhibited ERK phosphorylation, a strong stimulant for downstream PDGFR activation. Recently imatinib and an inhaled form of another TKI seralutinib in two different rat models with PAH demonstrated comparable improvement in cardiopulmonary hemodynamics (mean pulmonary artery pressure, right ventricular systolic pressure, and pulmonary vascular resistance), reduction in Nt-proBNP levels and normalization of small pulmonary artery muscularization.[10] Seralutinib also restored BMPR2 levels to normal, however was not evident with imatinib. The major clinical trial with imatinib (IMPRES trial) though included patients with HPAH, did not analyze the subset outcomes.[2]

Our patient was empirically initiated on imatinib in a life-threatening situation. The recent discoveries in animal models have revealed plausible mechanisms for the response in our patient. We hypothesize that the mutation induced structural changes resulted in down-regulation of BMPR2 gene and imatinib would have ameliorated the disease process by various mechanisms thus improving RV function and symptomatic status.

We report for the first time the long-term clinical response to TKI imatinib in a BMPR2 gene mutation in human. We duly acknowledge the limitation of lack of invasive hemodynamic data in supporting the clinical response and the pending in vitro studies to determine the precise impact of this mutation on protein function. Our case strongly recommends the need for large scale studies for the potential utility of TKI in this unique subset of PAH population.

AUTHOR CONTRIBUTIONS

Shine Kumar collected the data and wrote the preliminary manuscript. Lalitha Biswas and Anju Choorakottayil Pushkaran did the molecular and genetic analysis and revised the manuscript. Raman Krishna Kumar supervised and critically revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Informed consent was obtained from patient for publication.

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