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Heritable Pulmonary Arterial Hypertension Diagnosed during the Postpartum Period: A Case Report and Literature Review

Postpartum Dönemde Tanı Konulan Kalıtsal Pulmoner Arteriyel Hipertansiyon: Bir Olgu Sunumu ve Literatür Taraması

ABSTRACT

Approximately one-third of bone morphogenic protein receptor-2 (*BMPR2*) mutation carriers develop pulmonary arterial hypertension (PAH), which indicates that additional risk factors are needed for the manifestation of the disease. It is questionable whether pregnancy is a risk factor for PAH development in these patients. We represent a 30-year-old woman with a heterozygous *BMPR2* mutation who was diagnosed with PAH during the postpartum period and reviewed the literature in this report. We also discussed the possible underlying mechanisms that might have resulted in PAH development during pregnancy in *BMPR2* mutation carriers.

Keywords: BMPR2 mutation, heritable pulmonary arterial hypertension, pregnancy

ÖZET

Kemik morfogenetik protein reseptörü-2 (*BMPR2*) mutasyonu taşıyıcılarının yaklaşık üçte birinde pulmoner arteriyel hipertansiyon (PAH) gelişmektedir, Bu da hastalığın ortaya çıkması için ek risk faktörlerine ihtiyaç olduğunu göstermektedir. Bu hastalarda gebeliğin PAH gelişimi için bir risk faktörü olup olmadığı tartışmalıdır. Bu raporda, heterozigot *BMPR2* mutasyonu olan ve postpartum dönemde PAH tanısı konulan 30 yaşında bir kadın hasta sunulmuş ve literatür gözden geçirilmiştir. Ayrıca *BMPR2* mutasyonu taşıyıcılarında gebelik sırasında PAH gelişimine neden olabilecek olası altta yatan mekanizmalar da tartışılmıştır.

Anahtar Kelimeler: BMPR2 mutasyonu, kalıtsal pulmoner arteriyel hipertansiyon, gebelik

CASE REPORT
OLGU SUNUMU

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Heritable pulmonary arterial hypertension (HPAH) is frequently resulted from heterozygous mutations in the bone morphogenic protein receptor 2 (*BMPR2*), however, due to the incomplete penetrance, approximately 30% of mutation carriers develop pulmonary arterial hypertension (PAH).[1] Thus, it is proposed that additional risk factors, including environmental factors and modifier genes, are required to cause PAH. One of the suggested probable risk factors for the manifestation of PAH in *BMPR2* mutation carriers was inflammation-induced pulmonary vascular injury.[2] As the disease also affects women of reproductive age, PAH may initially be recognized during pregnancy or in the postpartum period in these subjects. It is questionable whether the pregnancy itself is a risk factor for PAH development in susceptible patients. Herein, we represent a 30-year-old woman with HPAH who was first diagnosed during the postpartum period.

Case Report

A 30-year-old primipara woman was presented to the outpatient cardiology clinic for dyspnea (World Health Organization functional class II), cough, and syncope. Her chest computed tomography revealed pericardial effusion and ectasia in the pulmonary artery (PA). As her father had PAH (Figure 1), she was referred to our institutional PAH clinic. Her father was diagnosed with PAH at the age of 37 years. She had one cardiology clinic visit at 15 years of age and had normal findings. She had a normal vaginal delivery without complication. She remained asymptomatic until the early postpartum period.

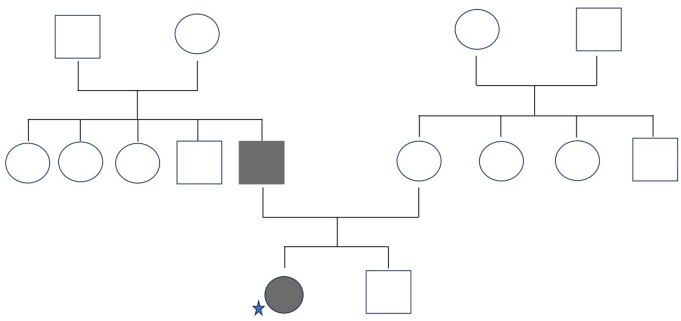

Figure 1. Pedigree of the patient (indicated with the star). Filled shapes point out documented pulmonary arterial hypertension.

She had exertional dyspnea after delivery but she consulted a doctor when her symptoms were aggravated. At admission, her blood pressure was 102/80 mmHg, pulse rate 102 bpm, and pulse oximetry 98% at room air. Physical examination revealed no signs of heart failure and grade 2 pansystolic murmur at the left sternal border. Electrocardiography indicated normal rhythm with right ventricular hypertrophy. Anti-nuclear antibodies were negative and laboratory examination was in the normal range except for brain natriuretic peptide of 305 pg/mL. Transthoracic echocardiography revealed a D-shape with marked right atrial and ventricular dilatation and systolic PA pressure of 99 mmHg. The presence of congenital heart defects was ruled out with transesophageal echocardiography. Pulmonary function tests were normal and pulmonary embolism was excluded with both invasive pulmonary angiography and ventilation-perfusion lung scan. Invasive hemodynamics demonstrated precapillary PAH with a mean pulmonary artery pressure (mPAP) of 40 mmHg and pulmonary vascular resistance (PVR) of 14.6 Woods (Table 1). DNA analysis showed a heterozygous *BMPR2* gene mutation c.1015_1016 del (p.Val339ProfsTer5) which is probable to be pathogenic.

Table 1. Right Heart Catheterization Data

Systolic pulmonary artery pressure	103 mmHg
Mean pulmonary artery pressure	40 mmHg
Diastolic pulmonary artery pressure	66 mmHg
Pulmonary capillary wedge pressure	-
Right ventricular pressure	79/0/5 mmHg
Left ventricular pressure	115/0/6 mmHg
Right atrial pressure	1 mmHg
Pulmonary vascular resistance	14.6 WU
Systemic vascular resistance	21.3 WU
Cardiac output	4.04 L/min
Cardiac index	2.84 L/min/m^2
Mixed venous oxygen pressure	74%

ABBREVIATIONS

BMPR2	Bone morphogenic protein receptor-2
HPAH	Hereditary pulmonary arterial hypertension
mPAP	Mean pulmonary artery pressure
PA	Pulmonary artery
PAH	Pulmonary arterial hypertension
PVR	Pulmonary vascular resistance
5-LO	5-lipoxygenase

Discussion

The main pathology in PAH is progressive vasculopathy resulting from multifactorial mechanisms including genetic predisposition, inflammation, impaired angiogenesis, and the effect of sex and sex hormones.[3] Aberrations in the signaling pathways of *BMPR2* and transforming growth factor beta exhibit a critical role in PAH development. *BMPR2* gene mutations resulted in HPAH in about 30% of mutation carriers.[1] These mutations are uncommon and have incomplete penetrance, which suggests that contributor risk factors are required to cause PAH. Our case report supports that pregnancy might be one of the potential risk factors for PAH development in *BMPR2* mutation carriers.

Maternal blood volume expands to maintain the perfusion of vital organs during pregnancy. Normal pre-pregnancy pressures are maintained through a decline in both systemic vascular resistance and PVR. Under normal conditions, PVR decreases and mPAP remains unchanged in pregnant women.[4] However, preexisting data demonstrated that pregnancy might also facilitate PAH in women.

There are two case reports in the literature that demonstrates the initiation of PAH during pregnancy in *BMPR2* mutation carriers (Table 2). Limoges et al.[5] were the first authors that described a de-novo diagnosis of PAH during pregnancy in 33-year-old woman with BMPR2 mutation. Their patient had one uncomplicated pregnancy, however, in the second trimester of her second pregnancy, she was diagnosed with PAH. Jaliawala et al.[6] published a second case report. Their patient was 30 years of age and diagnosed with PAH in the third trimester of her first pregnancy. She had a heterozygous *BMPR2* mutation and chronic amphetamine usage. They discussed whether chronic amphetamine usage added to the physiological stress of pregnancy in *BMPR2* mutation carriers contributes to the development of PAH in their patient. Our patient differs from other cases in that her symptoms started just after delivery and she was diagnosed with PAH in the postpartum period.

The possible underlying mechanisms that might have resulted in PAH development during pregnancy in *BMPR2* mutation carriers might be described as follows. First, estrogen and its metabolites have been shown to be related to both the penetrance and the development of HPAH.[7,8] However, there is an "estrogen paradox" in the literature to describe the discrepancy between female predominance in PAH and the protective influences of estrogens in some animal experiments.[9] It is presumed that estrogen has a protective effect on the healthy endothelium, however, in injured endothelium, estrogen stimulates angioproliferation and increases the risk and the progression of PAH.[9] As pregnancy is associated with elevated levels of estrogens and vascular shear stress in response to increased vascular volume, this might explain the appearance of PAH during the peripartum period in our patient. In addition, in familial PAH, hormone replacement therapy with estrogen and progesterone was also described as a risk factor for PAH, which further supports this hypothesis.[10] Second, it has been shown that asymptomatic patients with

Table 2. Summary of All Available Case Reports in the Literature

No.	Authors	Year	Age	Pregnancy period	Susceptibility	Gestational age, anesthesia and mode of delivery	Maternal and neonatal status	Echocardiographic data	RHC data	Treatment during pregnancy	Treatment after pregnancy
1	Limoges et al.	2015	33	2. trimester	*BMPR2* gene mutation c.741C>A (p.Tyr247X)	34 weeks, 4 days Combined spinal-epidural Cesarean	Alive	TAPSE: 23 mm sPAP: 111 mmHg	sPAP: 64 mmHg mPAP: 42 mmHg dPAP: 31 mmHg CO: 5.8 L/min	IV treprostinil and IV norepinephrine	Sildenafil, ambrisentan and treprostinil,
2	Jaliawala et al.	2022	30	3. trimester	*BMPR2* gene mutation and chronic exposure to amphetamine	32 weeks Spinal Cesarian	Alive	sPAP: 68 mmHg	RAP: 1 mmHg sPAP:45 mmHg mPAP: 28 mmHg dPAP: 18 mmHg PVR: 3.8 WU CO: 5.8 L/min CI: 3.1 l/min/m^2	IV epoprostenol	Tadalafil and macitentan
3	Colak, et al.	2023	30	Postpartum	*BMPR2* gene mutation c.1015_1016 del (p.Val339ProfsTer5)	38 weeks No anesthesia Normal delivery	Alive	sPAP: 99 mmHg	RAP: 1 mmHg sPAP:103 mmHg mPAP: 40 mmHg dPAP: 66 mmHg PVR: 14.6 WU CO: 4.04 L/min CI: 2.84 l/min/m^2	None	Macitentan, riociguat and selexipag

BMPR2, Bone morphogenic protein receptor-2; CI, Cardiac index; CO, Cardiac output; dPAP, Diastolic pulmonary artery pressure; IV, Intravenous; mPAP, Mean pulmonary artery pressure; PVR, Pulmonary vascular resistance; RAP, Right atrial pressure; RHC, Right heart catheterization; sPAP, Sysytolic pulmonary artery pressure; TAPSE, Tricuspid annular plane systolic excursion

BMPR2 mutations had an increased risk for hypertensive PA pressure response to exercise and hypoxia.[11] Pregnancy causes higher stress on the circulatory system with increased plasma volume, which may be resulted in a *de novo* diagnosis of PAH during the peripartum period.[5] Finally, it has been demonstrated that the maternal immune system undergoes different phases during pregnancy. The first and third trimesters are predominantly pro-inflammatory, whereas the second trimester is an anti-inflammatory environment, which is regulated by increased 5-lipoxygenase (5-LO) mRNA expression in decidua in the third trimester.[12] Interestingly, phenotypically normal *BMPR2* mutant rats who were exposed to 5-LO expressing adenovirus developed severe PAH with occlusive lesions.[2] Increased levels of decidual 5-LO mRNA expressions in the course of pregnancy might have resulted in lung inflammation and PAH in pregnant women with *BMPR2* mutations.

Conclusion

Our patient is one of the first cases that showed that pregnancy might be a possible trigger for PAH development in *BMPR2* mutation carriers. These patients raise the question of whether pregnancy should be avoided in female subjects with a history of familial PAH and who have a *BMPR2* mutation.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report.

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