Contents lists available at ScienceDirect

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Case report

BMPR2 gene mutation in pulmonary arteriovenous malformation and pulmonary hypertension: A case report

Tomohiro Handa[a,*], *Yoshiaki Okano*[b], *Norifumi Nakanishi*[c], *Takayuki Morisaki*[d], *Hiroko Morisaki*[d], *Michiaki Mishima*[a]

[a]*Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan*
[b]*Department of Internal Medicine, Hanwa Daini Senboku Hospital, Sakai, Japan*
[c]*Division of Pulmonary Circulation, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan*
[d]*Department of Bioscience and Genetics, National Cerebral and Cardiovascular Center Research Institute, Suita, Japan*

ARTICLE INFO

Article history:
Received 13 December 2012
Received in revised form
14 July 2013
Accepted 2 August 2013

Keywords:
Ambrisentan
Bone morphogenetic protein receptor type 2
Pulmonary arterial hypertension
Pulmonary arteriovenous malformation
Sildenafil

ABSTRACT

The transforming growth factor-β superfamily signaling pathway is thought to be involved in the pathogenesis of pulmonary arteriovenous malformation (PAVM). However, the association between *bone morphogenetic protein receptor type 2* (*BMPR2*) gene mutations and PAVM remains unclear. We present a case of concurrent PAVM and pulmonary arterial hypertension (PAH), with a deletion mutation in exon 6 and exon 7 of the *BMPR2* gene. Drug treatment for PAH improved the patient's hemodynamics and exercise capacity, but worsened oxygenation. This case suggests that *BMPR2* gene mutation may be associated with the complex presentation of PAVM combined with PAH.

Abbreviations: ACVRL1, *activin A receptor type 2-like 1*; BMP, bone morphogenetic protein; *BMPR2*, *bone morphogenetic protein receptor type 2*; CI, cardiac index; CO, cardiac output; *MADH4*, *decapentaplegic homologue 4*; ENG, endoglin; HHT, hereditary hemorrhagic telangiectasia; HRCT, high resolution computed tomography; *MADH4*, *decapentaplegic homologue 4*; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PAVM, pulmonary arteriovenous malformation; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RHC, right heart catheterization; TGF-β, transforming growth factor-β

*Correspondence to: Department of Rehabilitation Medicine/Respiratory Medicine, Kyoto University Hospital, 54 Shogoin Kawahara-cho, Sakyo, Kyoto 606-8507, Japan. Tel.: +81 75 751 3830; fax: +81 75 751 4643.
E-mail addresses: hanta@kuhp.kyoto-u.ac.jp (T. Handa), yokano2@kuhp.kyoto-u.ac.jp (Y. Okano), nnakanis@hsp.ncvc.go.jp (N. Nakanishi), morisaki@ri.ncvc.go.jp (T. Morisaki), hirokom@ri.ncvc.go.jp (H. Morisaki), mishima@kuhp.kyoto-u.ac.jp (M. Mishima).

2212-5345/$ - see front matter © 2013 The Japanese Respiratory Society. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.resinv.2013.08.003

1. Introduction

Hereditary pulmonary arterial hypertension (PAH) and hereditary hemorrhagic telangiectasia (HHT) are associated with mutations in the transforming growth factor-β (TGF-β) and bone morphogenetic protein (BMP) pathways and have a major impact on lung vasculature [1,2]. Pulmonary arteriovenous malformation (PAVM) is a complication of HHT, occurring in 20–40% of patients. Conversely, approximately 80–95% of PAVM cases are associated with HHT [3]. The most frequent cause of hereditary PAH is *bone morphogenetic protein receptor type 2* (*BMPR2*) gene mutation. However, its association with HHT or PAVM remains unclear. We present a case of concurrent PAVM and PAH, with a novel deletion mutation in exon 6 and exon 7 of the *BMPR2* gene.

2. Case report

A 33-year-old woman was referred to a clinic due to cough, where she was found to have a chest CT abnormality. At presentation in our hospital, she had no chest symptoms. Physical examination revealed a body temperature of 36.5 °C, blood pressure of 116/78 mmHg, and pulse rate of 80 beats/min with a regular rhythm. Heart and lung auscultation revealed no abnormalities, and there was no pretibial edema. There was no sign of mucocutaneous telangiectases on the fingers, lips, or oral cavity. Additionally, there was no previous history of drug abuse. Moreover, there was no family history of HHT, recurrent nasal hemorrhage, or abnormal chest shadow. Laboratory tests showed mild polycythemia, and autoantibody screening for collagen vascular diseases was negative. Electrocardiography and arterial blood gas at rest revealed no abnormalities. Pulmonary function tests showed decreased diffusing capacity (supplementary Table S1). Chest HRCT revealed meandering vasculature in bilateral lung fields (Fig. 1A). A 3-dimensional reconstruction image showed a saccular aneurysm with an afferent artery and efferent vein, suggesting the presence of PAVM (Fig. 1B). Tc MAA scintigraphy and the 100% oxygen inhalation method showed a mild increase in the arteriovenous shunt ratio (8.4% and 5.1%, respectively), and contrast echocardiography revealed microbubble flow from the pulmonary vein to the left atrium, such that LA enhancement was delayed from RA enhancement by more than 3 cardiac cycles. Based on these findings, the patient was diagnosed with multiple PAVMs. Abdominal CT and brain MRI showed no AVM in other organs, and portal hypertension was ruled out by abdominal echocardiogram. According to the International Clinical Diagnostic Criteria for HHT, a diagnosis of HHT was unlikely [4].

Right heart catheterization (RHC) revealed concurrent pulmonary arterial hypertension as follows: pulmonary artery pressure (PAP) 55/29 (41) mmHg, pulmonary capillary wedge pressure (PCWP) 14 mmHg, cardiac output (CO) 3.81 L/min, cardiac index (CI) 2.75 L/min/m^2, pulmonary vascular resistance (PVR) 7.1 Wood. A series of examinations showed no evidence of left-sided heart failure, pulmonary embolism, obstructive or restrictive pulmonary disease, portal hypertension, or connective tissue disease. Mutation analysis of entire coding exons and adjacent introns of the *BMPR2*, *endoglin* (*ENG*), *activin A receptor type 2-like 1* (*ACVRL1*), and *decapentaplegic homologue 4* (*MADH4*)

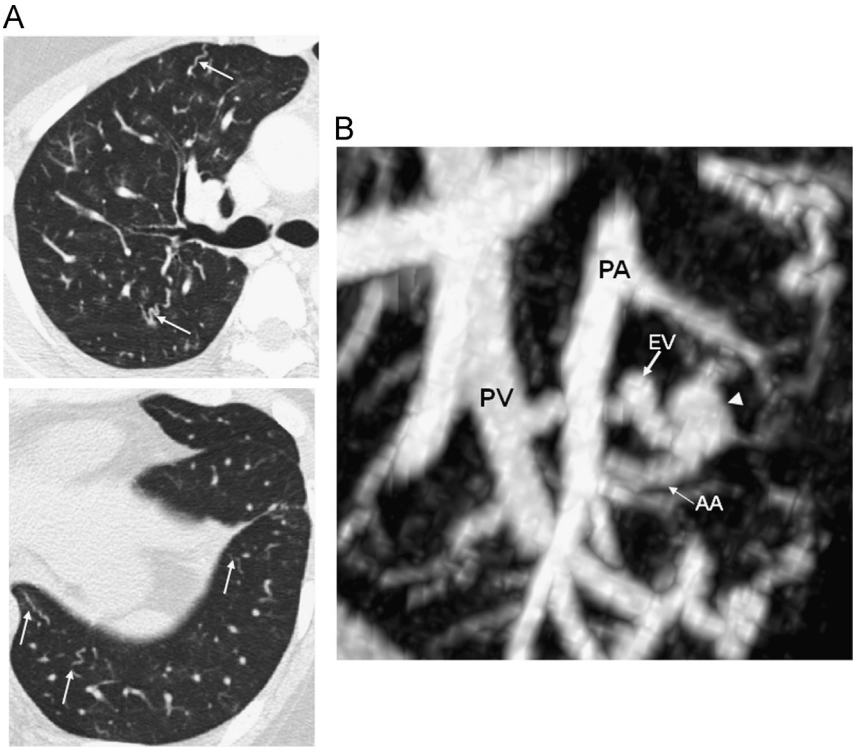

Fig. 1 – (A) Chest HRCT on admission. Multiple meandering feeding vessels (arrows) are found in bilateral lung fields. (B) 3-dimentional reconstruction image of chest CT. A saccular aneurysm (5.8 mm in diameter, arrowhead) with an afferent artery (2.6 mm in diameter) and efferent vein (2.7 mm in diameter) is shown (arrows). PA, pulmonary artery; PV, pulmonary vein; AA, afferent artery; EV, efferent vein.

Please cite this article as: Handa T, et al. *BMPR2* gene mutation in pulmonary arteriovenous malformation and pulmonary hypertension: A case report. Respiratory Investigation (2013), http://dx.doi.org/10.1016/j.resinv.2013.08.003