Case Report

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Peripheral pulmonary stenosis with Noonan syndrome treated by balloon pulmonary angioplasty

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Abstract

Noonan syndrome is known to have various cardiovascular defects, which include pulmonary artery stenosis. Pulmonary artery stenosis is characterized by obstruction of pulmonary artery blood flow that can cause elevated pulmonary artery pressure and ventilation-perfusion inequality, which can cause dyspnea on exertion and eventually, heart failure. Although the etiology of pulmonary artery stenosis related to congenital diseases is still unknown, balloon pulmonary angioplasty has being reported to be effective to selected patients with Alagille and Williams syndromes, but not from Noonan syndrome despite of modest prevalence of pulmonary artery stenosis. Here, we report the first Noonan syndrome patient with pulmonary artery stenosis who underwent successful balloon pulmonary angioplasty. The strategy used in balloon pulmonary angioplasty was planned with careful morphologic evaluation by computed tomographic angiography, and performed with scoring balloons in a graded approach with multiple sessions. After balloon pulmonary angioplasty, we confirmed maintained dilation of lesions and symptom alleviation, suggesting that balloon pulmonary angioplasty can be performed safely on pulmonary artery stenosis in a Noonan syndrome patient.

Keywords

pulmonary hypertension, ventilation perfusion ratio inequality, catheter intervention

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Introduction

Peripheral pulmonary artery stenosis (PPS) is a rare cardiovascular defect characterized by obstruction of pulmonary artery blood flow that can cause elevated pulmonary artery pressure and ventilation-perfusion inequality, which can cause dyspnea on exertion and eventually, heart failure. PPS is frequently reported in congenital rubella syndrome and genetic syndromes, mostly Alagille and Williams syndromes[1]. As for Noonan syndrome (NS), while it frequently coexists with pulmonary valvular stenosis (PVS), the frequency of PPS varies from 3.0% to 12.1%.[2,3] PPS etiology in patients with each genetic disease is mostly unknown; however, recent reports have demonstrated improved management of PPS with symptomatic genetic congenital heart disease by catheter intervention or surgical treatment.[1,4] However, there is no previous literature reporting successful balloon pulmonary angioplasty (BPA) to PPS in NS patients.

Case description

A 21-year-old man with a history of atrial septal defect repaired during his infancy was presented to our hospital for investigation of exertional dyspnea. He had short

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stature, chest deformity, and severe lordoscoliosis, which became apparent during his adolescence. His face showed a prominent forehead, depressed nasal bridge, and hypertelorism. Percutaneous oxygen saturation was 98% in room air, and his dyspnea was classified as New York Heart Association (NYHA) class III. Although there was no extra heart sound, ejection murmur was auscultated in lung area. His brain natriuretic peptide was 28.7 pg/ml. Electrocardiogram showed right ventricular hypertrophy, and echocardiography revealed a bicuspid aortic valve with mild regurgitation without other remarkable findings. Spirometry revealed combined ventilatory impairment. Computed tomographic angiography (CTA) showed multiple strictures without webs, bands, or thickened arterial walls in the pulmonary arteries (Fig. 1a and b), and lung perfusion scintigraphy showed ventilation perfusion ratio inequality (Fig. 1c). Catheter examination revealed mean pulmonary artery pressure (mPA) of 27 mmHg and pulmonary vascular resistance (PVR) of 183 dyne·sec·cm^{-5}. Angiography showed stenosis in almost all left pulmonary artery branches and mild to moderate stenosis in middle and lower lobe branches of the right pulmonary artery (Fig. 1d and e). These findings showed a diagnosis of peripheral pulmonary artery stenosis (PPS) classified as type III of Gay's classification.[5] After considering the patient's outlook and cardiovascular defect, the patient underwent genetic testing, which revealed a *PTPN11* mutation-p.Thr42Ala, indicating a diagnosis of NS.[2]

At first, his dyspnea was explained by severe combined ventilatory impairment, which was resistant to bronchodilator and steroid inhalation. As his lordoscoliosis was thought to have caused most part of his dyspnea, operation to his lordoscoliosis was considered. However, the surgical risks associated with lordoscoliosis were considered to be high, taking the severity of scoliosis, combined ventilatory impairment with the presence of ventilation perfusion ratio inequality into consideration. Therefore, we decided to focus on the treatment of PPS. Over seven months, we performed four sessions of BPA (Fig. 1f–h), and the mPA was eventually lowered from 27 to 17 mmHg, and PVR dropped from 183 to 159 dyne·sec·cm^{-5} with symptom alleviation from NYHA class III to II. Eventually, the patient could undergo surgery for lordoscoliosis. A follow-up catheter examination was performed 18 months after treatment and showed mPA was 20 mmHg and PVR was 94 dyne·sec·cm^{-5} with maintained dilatation of the lesions (Figure 1).

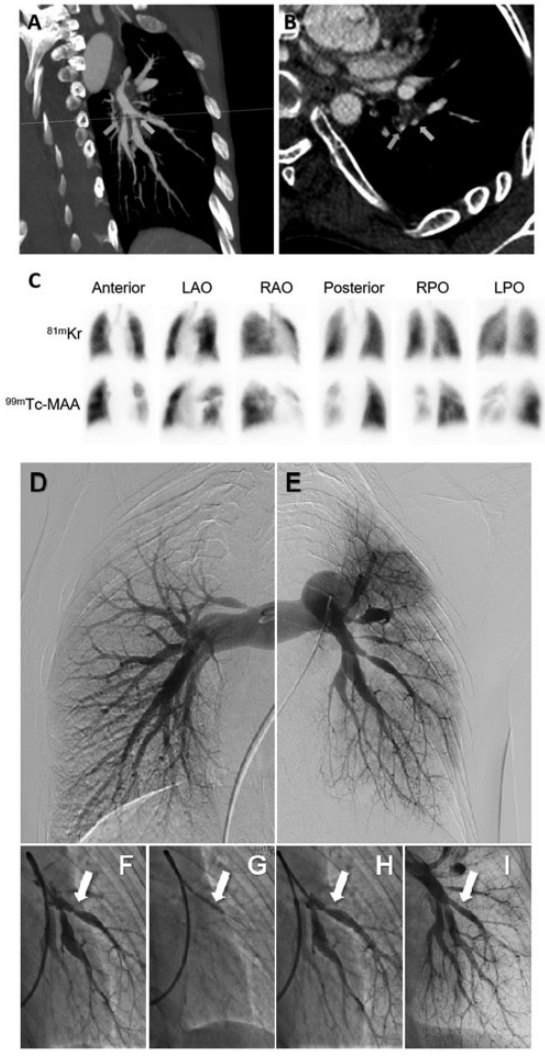

Fig. 1. (a) Oblique coronal, (b) oblique axial Image of maximal intensity projection computed tomography angiography (CTA) focusing on the strictures (arrows) in the left pulmonary artery branches. (c) Images of ^{81m}Kr ventilation scintigraphy are shown in upper row. Images of ^{99m}Tc-macro aggregated albumin (MAA) lung perfusion scintigraphy is shown in the lower row. There is significant decrease of ^{99m}Tc-MAA uptake. LAO: left anterior oblique. RAO: right anterior oblique. RPO: right posterior oblique. LPO: left posterior oblique. (d)–(i) Pulmonary artery angiographs (PAGs) of the patient. (d) PAG of right and (e) left pulmonary arteries before balloon pulmonary angioplasty (BPA). (f) Selective PAG of the left lower branches and target lesion of BPA (arrow). (g) Balloon (arrow) dilating the lesion. (h) Improved blood flow distal to the lesion (arrow) right after BPA. (i) PAG at 18 months follow-up showing improved dilation (arrow).

Discussion

As for the patient we reported, CTA implied the lesions had less capacity of dilatation by BPA than that of chronic thromboembolic pulmonary hypertension. Moreover, PPS due to undefined genetic disease is reported to be associated with frequent restenosis after BPA, which is reported to be 35% in a mean follow-up period of 21 months.[4] Taking the patient's condition, which is at very high risk of surgical treatment, we put more weight on safety, minimizing the risk of complication as well as recurrent stenosis. As the lesions of the PPS were expected to be coarctations of external elastic membrane of each vessel which would explain its limited capacity of dilatation[6], we avoided using stents or cutting balloons. Instead, we used scoring balloons in a graded approach in order to avoid vessel injuries caused by excessive dilation. Consequently, BPA was performed

safely, and it was effective not only in lowering mPA and correcting the mismatch of ventilation and perfusion but also for maintaining or even improving dilatation of the lesion. Our report implies that less invasive BPA may be considered in a NS patient who suffer from dyspnea on exertion with PPS, even if the mPA is not very high. In a setting of a patient having multiple or unidentifiable causes of dyspnea, the efficacy of symptom alleviation by correcting pulmonary hemodynamic status alone is usually unpredictable. Less invasive BPA may be considered in such situation.

Concerning the genetic issue, there is only one literature discussed about genotype-phenotype correlation between *PTPN11* mutation and PPS separately from PVS,[2] which revealed statistically insignificant. However, taking the fact that the patient who did not have PVS, which is highly associated with *PTPN11* mutation,[2] its phenotype expression is highly variable among patients with the same mutation. Different patterns of PPS may be due to different etiologies, and genetic background or epigenetic factors may contribute to the variance. Further investigation on patterns of PPS may contribute to uncover its etiology, which may be of reference to planning treatment strategy.

All in all, we demonstrated that BPA can be performed safely on PPS in a NS patient. However, there is still a need for elucidating the etiology, practices on evaluation of lesions, directed therapy and optimization of treatment strategy.

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Author contributions

The manuscript was drawn by S. K. and J. K. The images were prepared by S. K., J. K., Y. Y. and T. Kawakami. The patient information was collected by S. K., J. K., Y. K., T. Kawakami and K. K. A critical revision of the manuscript for the key intellectual content and supervision was provided by Y.K., Y.S., T. Kawakami, S. Y., T. Kohno, Y. Y., K. K. and K. F. All of the authors have approved all aspects of our work, read, and approved the manuscript.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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