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Pulmonary hypertension of complex aetiology: contemporary treatment options

Nadciśnienie płucne o złożonej etiologii — możliwości współczesnego leczenia

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Abstract

We present the case of an 80 year-old female patient with pulmonary arterial hypertension of complex aetiology, including late-diagnosed congenital heart disease. We describe the diagnostic procedures and staged treatment (percutaneous closure of an ostium secundum atrial septal defect and drug treatment with riociguat) which resulted in a significant clinical improvement.

Key words: pulmonary hypertension, atrial septal defect, chronic thromboembolic pulmonary hypertension, riociguat

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Introduction

Pulmonary hypertension leads to a significant impairment of exercise tolerance and is associated with adverse long-term outcomes [1]. The aetiology of pulmonary hypertension is not always clear and may be multifactorial, as exemplified by the case reported below. In addition, increasing rates of a complex aetiology of this condition may be expected with an ageing population.

Case report

An 80 year-old woman was admitted on an elective basis to our Department of Cardiology in May 2017 due to worsening exercise tolerance that had progressed gradually over several years (in the weeks prior to the admission, dyspnoea developed after walking 50 metres). Past medical history included permanent atrial fibrillation, chronic hepatitis C (without evidence of cirrhosis or portal hypertension in imaging studies), and cholecystectomy in 2008. Pulmonary computed tomographic angiography (angio-CT) performed on an outpatient basis showed no evidence of pulmonary embolism. Chronic medications included acenocoumarol, metoprolol succinate 50 mg/day, spironolactone 25 mg/day, and valsartan 80 mg/day.

On admission, the patient was in general good condition, with irregular heart rate of 112 bpm, blood pressure of 120/70 mm Hg, and mild calf oedema with evidence of post-thrombotic syndrome. Deep venous thrombosis was excluded based on Doppler ultrasonography of the lower limb veins. Echocardiography showed an increased right atrial area (RAA) of 40 cm^2 and an enlarged right ventricle (RV), with right ventricular diameter (RVID) in the 4-chamber view of 5.4 cm compared to 4.9 cm for the left ventricle, impaired RV systolic function with the tricuspid annular plane systolic excursion (TAPSE) of 14 mm, increased RV systolic pressure (RVSP; 67 mm Hg), and a dilated vena cava inferior (29 mm) with reduced respiratory variation. Left ventricular function was normal. Laboratory tests showed elevated levels of total bilirubin (1.76 mg/dL) and B-type natriuretic peptide (BNP: 324 pg/mL). The 6-minute walking test result was 190 metres, without a reduction in oxygen saturation. Right heart

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Table 1. Clinical characteristics of the patient at follow-up visits

	May 2017 Before initiation of sildenafil	November 2017 Sildenafil treatment	June 2018 After ASD II closure	September 2018 Riociguat treatment	March 2019 Riociguat treatment
WHO/NYHA class	III/IV	III	III	III	**II/III**
6-minute walking test [m]	190		162*	250	**270**
Laboratory tests:					
• haemoglobin [g/dL]	13.0	12.6	12.2	12.8	**13.2**
• creatinine [mg/dL]	0.73	0.81	0.9	0.82	**0.9**
• total bilirubin [mg/dL]	1.76		1.81	1.17	**1.04**
• BNP [pg/mL]	324	270	290	136	**146**
Echocardiography:					
• RV:LV [mm]	54:49			50:53	**41:52**
• RAA [cm^2]	40			36	**31.3**
• LAA [cm^2]	44			38.1	**39**
• TI Vmax [m/s]	3.9			3.4	**2.6**
• RVSP [mm Hg]	67			55	**32**
• VCI [mm]	29/20			21/10	**15/9**
• TAPSE [mm]	14			18	**18**
Cardiac catheterisation:					
• mRAP [mm Hg]					
• mPAP [mm Hg]	9	20	6		
• PCWP [mm Hg]	32	44	32		
• CI [$L/min/m^2$]	14	12	10		
• PVR [Wood units]	2.91	2.27	2.29		
	3.2	4.06	5.51		

*Distance limited by knee pain; ASD II — secundum-type atrial septal defect; WHO — World Health Organization; HYHA — New York Heart Association; BNP — B-type natriuretic peptide; RV:LV — right ventricular to left ventricular diameter ratio in the apical 4-chamber view; RAA — right atrial area; LAA — left atrial area; TI V_{max} — peak tricuspid regurgitant jet velocity; RVSP — right ventricular systolic pressure; VCI — vena cava inferior diameter/respiratory variability; TAPSE — tricuspid annular plane systolic excursion; mRAP — mean right atrial pressure; mPAP — mean pulmonary artery pressure; PCWP — pulmonary capillary wedge pressure; CI — cardiac index; PVR — pulmonary vascular resistance

catheterisation showed precapillary pulmonary hypertension with increased mean pulmonary artery pressure (mPAP) of 32 mm Hg and pulmonary vascular resistance (PVR) of 3.2 Wood units, with normal pulmonary capillary wedge pressure (PCWP) of 14 mm Hg. The mean right atrial pressure (RAP) was 9 mm Hg, cardiac index (CI) was 2.91 $L/min/m^2$, and RV oxygen saturation was 84%. No significant changes in these parameters were seen following iloprost administration (inhaled). Routine diagnostic evaluation of pulmonary hypertension included transoesophageal echocardiography which showed an ostium secundum-type atrial septal defect (ASD II) with the dimensions of 16 × 12 mm with a left-to--right shunt. Lung scintigraphy revealed high probability of pulmonary embolism, and invasive arteriography showed thrombi in distal branches of pulmonary arteries, mainly in the lower lobes of both lungs.

Based on the overall clinical presentation and imaging findings, pulmonary hypertension of mixed aetiology was diagnosed: chronic thromboembolic pulmonary hypertension (CTEPH) combined with a congenital heart disease (ASD II). At the meeting of a CTEPH heart team that included a cardiac surgeon and an invasive cardiologist experienced in pulmonary artery balloon angioplasty, the patient was not deemed a candidate for invasive treatment of CTEPH due to distal changes in pulmonary arteries. Drug treatment with torasemide 10 mg/day and sildenafil 25 mg TID was started, initially with a subjective improvement in the patient's wellbeing.

After six months, the patient was readmitted in November 2017 for a follow-up cardiac catheterisation which showed an increase in mPAP to 44 mm Hg, with PVR of 4.06 Wood units and PCWP of 12 mm Hg (Table 1). These

findings were interpreted as resulting from an increased shunt through ASD (sildenafil reduced PVR, which led to an increase in the left-to-right shunt). Due to severe exertional dyspnoea, a follow-up 6-minute walking test was not performed. BNP level was 270 pg/mL. Pulmonary angio-CT showed no evidence of pulmonary embolism. Sildenafil was withdrawn, and the patient was referred for ASD closure.

That procedure was performed in January 2018 with local anaesthesia via the right femoral vein access, using the Figulla Flex II ASD 24 mm device with good immediate procedural outcomes. In addition to acenocoumarol, acetylsalicylic acid was prescribed for six months.

In June 2018, follow-up right heart catheterisation showed mPAP of 32 mm Hg, PVR of 5.51 Wood units, PCWP of 10 mm Hg, RAP of 6 mm Hg, and CI of 2.29 L/min/m^2. The 6-minute walking test result was only 162 metres, but this was related to pain in the right knee felt by the patient. Total bilirubin level was 1.81 mg/dL, and BNP level was 290 pg/mL. The patient was put on riociguat treatment under the National Health Fund programme for CTEPH.

Riociguat is a soluble guanylate cyclase stimulator which increases cyclic guanosine monophosphate (cGMP) production and sensitises guanylate cyclase to endogenous nitric oxide [2]. As a result, the arteries and pulmonary arterioles dilate, and this mechanism is responsible for the reduction of pulmonary artery pressure and improvement of exercise tolerance. Drug efficacy has been supported by the results of several clinical trials [3, 4].

In our patient, riociguat treatment was started in July 2018, and the dose was gradually increased to the target dose of 2.5 mg TID. Diuretic treatment was continued (torasemide 20 mg, spironolactone 50 mg) but due to bradycardia on 48-hour ECG Holter monitoring and low systemic blood pressure values, beta-blocker dose was reduced and valsartan was withdrawn.

Follow-up echocardiography in September 2018 showed persistent right heart chamber enlargement (RAA 36 cm^2, RVID 50 mm). RVSP was 55 mm Hg but RV systolic function was normal, with TAPSE of 18 mm and the systolic velocity of RV free wall in spectral tissue Doppler of 13 cm/s. The vena cava inferior was not widened, with preserved respiratory variability, and no shunt was seen at the atrial septal occluder. Following riociguat treatment, a significant subjective improvement was accompanied by an increase in the 6-minute walking distance to 270 metres, and laboratory tests showed reductions of total bilirubin level to 1.04 mg/dL and BNP level to 146 pg/mL Echocardiography in April 2019 showed a significant decrease in RVSP (40 mm Hg), reductions of right atrial and RV diameter (31 cm^2 and 47 mm, respectively), and normal RV systolic function.

Conclusions

Our case highlights the importance of multifactorial aetiology of pulmonary hypertension. Staged therapeutic strategy targeted at various aetiological mechanisms of pulmonary hypertension led to a gradual improvement of the clinical condition along with cardiac catheterisation, echocardiographic, and laboratory parameters. It is worth noting that the initial deterioration of the patient's condition was related to sildenafil treatment which resulted in worsening of the left-to-right shunt. It was only after ASD II closure that effective treatment with riociguat, a drug with a similar mechanism of action to sildenafil, was possible. The procedural success of ASD closure changed the pathophysiology of the condition, allowing drug-related haemodynamic improvement.

Conflict(s) of interest

The authors declare no conflict of interest.

Streszczenie

W pracy zaprezentowano przypadek 80-letniej pacjentki z tętniczym nadciśnieniem płucnym o złożonej etiologii, w tym z powodu późno rozpoznanej wrodzonej wady serca. Opisano diagnostykę oraz etapowe leczenie (przezskórne zamknięcie ubytku przegrody międzyprzedsionkowej typu II oraz farmakoterapia riociguatem), które przyniosły istotną poprawę kliniczną.

Słowa kluczowe: nadciśnienie płucne, ubytek przegrody międzyprzedsionkowej, zakrzepowo-zatorowe nadciśnienie płucne, riociguat

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