Lung transplantation as a viable option of treatment for pulmonary veno-occlusive disease

The authors declare no financial disclosure

Abstract

Pulmonary veno-occlusive disease (PVOD) is a rare form of pulmonary hypertension caused by alteration of pulmonary veins. Many clinical and hemodynamic similarities to idiopathic pulmonary arterial hypertension (IPAH) may cause diagnostic and therapeutic difficulties. This case report is about a patient with PVOD, whose first symptoms of the disease occurred after infectious mononucleosis. The patient was administered prostacycline (PGI2) mimetic (Treprostinil), which made qualification process and lung transplantation possible. Despite more and more knowledge about the causes, ethiopathogenesis and changes in pulmonary veins on molecular level, lung transplantation is the only successful therapeutic option for patients suffering from PVOD.

Key words: pulmonary veno-occlusive disease, lung transplantation, idiopathic pulmonary arterial hypertension

Introduction

Pulmonary veno-occlusive disease (PVOD) is a rare form of pulmonary hypertension (PH) with estimated occurrence of 0.1–0.2 cases per million people [1]. PVOD etiology involves progressive occlusion of small lung veins, which causes increased pulmonary resistance and right ventricle dysfunction [2]. The term PVOD was coined by Heath et al. [3], who recognized that the disease was a distinct entity from so-called “primary pulmonary hypertension” [2]. According to the classification system from the Fifth World Symposium on PH (Nice, 2013) and the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS), which is presented in Table 1, PVOD is a subgroup of pulmonary artery hypertension (PAH), but its prognosis is worse and more serious. Pulmonary edema can occur when PAH-specific advanced therapy is administered [4, 5]. Most of the cases are identified at an early age. The cause of pulmonary veno-occlusive disease is unknown, nevertheless, several risk factors including infection, chemotherapy and medications toxicity, radiation, autoimmunity and genetic predisposition are thought to be involved [6].

Case presentation

In 2012, 19-year-old male patient was admitted to the Infectious Diseases Ward, where doctors diagnosed him with infectious mononucleosis and interstitial pneumonia. Chest X-ray revealed a mark of fluid in the pleural cavity. After treatment was initiated, was dis-
Table 1. Classification of pulmonary hypertension according to European Society of Cardiology/European Respiratory Society Guidelines 2015

1. Pulmonary arterial hypertension
   1.1. Idiopathic
   1.2. Heritable
      1.2.1. BMPR2 mutation
      1.2.2. Other mutations
   1.3. Drugs and toxins induced
   1.4. Associated with:
      1.4.1. Connective tissue disease
      1.4.2. HIV infection
      1.4.3. Portal hypertension
      1.4.4. Congenital heart disease
      1.4.5. Schistosomiasis

2. Pulmonary hypertension due to left heart disease
   2.1. Left ventricular systolic dysfunction
   2.2. Left ventricular diastolic dysfunction
   2.3. Valvular disease
   2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
   2.5. Congenital/acquired pulmonary vein stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia
   3.1. Chronic obstructive pulmonary disease
   3.2. Interstitial lung disease
   3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4. Sleep disordered breathing
   3.5. Alveolar hypoventilation disorders
   3.6. Chronic exposure to high altitude
   3.7. Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
   4.1. Chronic thromboembolic pulmonary hypertension
   4.2. Other pulmonary artery obstructions
      4.2.1. Angiosarcoma
      4.2.2. Other intravascular tumours
      4.2.3. Arteritis
      4.2.4. Congenital pulmonary arteries stenoses
      4.2.5. Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
   5.1. Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
   5.2. Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis
   5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4. Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

charged in a good general condition. Since then, the patient was feeling progressive dyspnea.

In 2015, following findings were observed in echocardiography: enlarged right ventricle and a small diastolic flattening of the intraventricular septum (EF: 64%, RV: 28mm, IVS: 9, TAPSE: 23, AcT: 85ms). This image suggested elevated pressure in pulmonary arteries.

In March 2016, he was admitted to the Department of Cardiology for diagnostics of progressive respiratory failure. Medical imaging showed linear interstitial diffused lesions in both lungs, best defined in costophrenic areas (X-ray) (Fig. 1). The most extensive changes localized in the subpleural regions bilaterally (SPECT). His Six-minute walking test (6MWT) result was 510 meters. During this test, the patient presented significant desaturation of SpO\textsubscript{2} level (from 96% to 83%). Arterial blood gases (ABG) test revealed respiratory alkalosis (pH — 7.468, pCO\textsubscript{2} — 31.5 mm Hg, pO\textsubscript{2} — 72 mm Hg). Echocardiography revealed a small flattening of the intraventricular septum, a trace of mitral valve incompetence, small tricuspid valve incompetence (EF — 77%, RV — 26 (LAX), IVS — 9 (LAX), AcT — 92 ms, TAPSE — 20 mm, TVPG — 52 mm Hg, TVI — 361, Vmax of tricuspid regurgitation — 361 cm/s). A suspicion of pulmonary hypertension was created. During his hospital stay, antinuclear antibodies (ANA) level was tested — titre was 1:160, but systemic
sclerosis was excluded due to video capillaroscopy of fingers II–IV results in May. There was no microangiopathy typical of diseases in the systemic sclerosis group.

In April 2016, body plethysmography, spirometry, heart catheterization, angio-CT of the lung arteries and NT-proBNP level were performed. The results are presented in Table 2.

On the base of radiological image (shown in Fig. 2), PVOD as the cause of PH suspicion was identified. Diltiazem was administered, however because of drug intolerance (bradycardia — 35 beats/min), treatment was changed to amlodipine (5 mg twice a day) with dosage escalation to 10 mg twice a day. An improvement of mood was noticed, but the therapeutic effect was unsatisfactory.

After a week of treatment, fluid levels in both pleural cavities were noticed.

In June 2016, treprostinil was added to the treatment plan — subcutaneously (amp. 1 mg/ml) 0.032 ml/h with dosage escalation to 0.034 ml/h (9.8 ng/kg/min for 58 kg of body weight). Also, furosemide was added to the therapy. A month later, the next hospitalization proved that the treatment resulted in regression of interlobular septa thickening and of pleural fluid accumulation (Fig. 3). A reduction of density and opacities in imaging were also noted. Body plethysmography, spirometry and ABG results remained comparable to ones in April except DLCO, which lowered to 34.4%. The administered treatment was sustained.

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Table 2. Results of test — April 2016

<table>
<thead>
<tr>
<th>Test</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirometry</td>
<td>FEV₁ — 87%, FVC — 77%, Tiffeneau index 95.83%</td>
</tr>
<tr>
<td>Body plethysmography and DLCO</td>
<td>TLC — 90.7%, RV — 126%, RV/TLC 138% DLCO — 60%</td>
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<tr>
<td>6 MWT</td>
<td>Distance — 531 m, Borg’s scale — 2, desaturation from 98% to 82%</td>
</tr>
<tr>
<td>Right heart catheterization</td>
<td>Precapillary pulmonary hypertension, vasoreactivity test was positive</td>
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<tr>
<td>Angio-CT</td>
<td>Signs of pulmonary hypertension, widened pulmonary trunk (35 mm), pulmonary arteries and right ventricle. Ground glass areas in perihilar region in both lungs, confluent and thickened interlobular septa matching pulmonary oedema — image similar to hypersensitivity pneumonitis (allergic alveolitis). Both lungs showed nodules (ø4 mm) — probably after pneumonitis; cyst of pericardium in costocardiac angle was revealed. There were also enlarged lymph nodes (subcarinal, para-aortic, and right hilar)</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>144 pg/ml</td>
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However, the disease was progressing, which was noticeable in test results. Decrease in pulmonary function tests (spirometry and bodyplethysmography), persisting severe decrease of DLCO, and reduced 6MWT distance (444 m) with desaturation to 83% were noted. Echocardiography showed features of serious overload of the right ventricle. NT-proBNP level was 444.4 pg/ml.

Hospitalization in the Silesian Center for Heart Diseases was scheduled to be in January 2017. Until then, treprostinil’s subcutaneous dosage was increased to 0.048 ml/h (13.25 ng/kg/min for 58 kg). Since October, the patient was paying for his bosentan treatment (dosage 125 mg twice a day).

During the consult in The Department of Cardiac, Vascular and Endovascular Surgery and Transplantology, the decision of preliminary qualification for lung transplantation was made.

In February, genetic tests confirmed the diagnosis of PVOD. Genetic testing showed mutation of EIF2AK4 gene, which is responsible for the disease. Family history seemed to be noncontributory. Later that month, the patient was admitted to the Department of Cardiology in a very severe general condition, with dyspnea during the minimal physical effort, hepatomegaly and peripheral edema. He fainted several times; hypotension and hypoperfusion was noticed. Since the admission day, progressive increasing of NT-proBNP level was observed (up to > 6000 pg/ml).

During hospitalization, the patient was treated with intensive oxygen supplementary therapy, furosemide, dopamine and steroids. Treprostinil dosage was increased gradually until 26.3 ng/kg/min was reached. The patient was discharged in improved condition, with a recommendation of Treprostinil dosage increase and constant oxygen therapy.

Next deterioration happened in April. The patient was admitted to the hospital with severe stomachache, persistent cough and tachycardia. He also had an exacerbation of right heart failure, present peritoneal signs and signs of multiple organ disfunction. There was a need for mechanical circulatory support and forced diuresis with intravenous supply of norepinephrine and furosemide. Empirical antibiotics, morphine and sildenafil treatment were also used. The dosage of Treprostinil was increased simultaneously (74.4 ng/kg/min), which let the discontinuation of norepinephrine administration and allow to change the way of application of furosemide (from intravenous to oral administration). A decrease of NT-proBNP serum level was noticeable (from 9135 to 5798 pg/ml).

The patient was discharged in May in an optimal clinical condition with recommendation of constant Treprostinil infusion (74.4 ng/kg/min) and consistent oxygen supplementary therapy (3 l/min).

One hundred days after qualification to LT, the man was admitted to the Silesian Center for Heart Diseases with end-stage circulatory and respiratory failure for lung transplantation due to the availability of a compatible donor. Uncomplicated, orthotopic lung transplantation with a use of Extracorporeal Membrane Oxygenation (ECMO) was performed. Immunosuppressive maintenance therapy including cyclosporine and rapamycin was administered. Despite preventive measures, the patient showed signs of CMV infection, which had to be treated with high doses of antiviral drugs. Additionally, the bronchial tree was colonised with Burkholderia spp. The man was treated with antifungal drugs administered by inhalation and oral antiviral medicines. He was discharged after 6 weeks in good general condition without the need for supplementary oxygen therapy.

Two months after LT, during a follow-up appointment in Silesian Center for Heart Diseases, the patient’s state was improving. During 6MWT he achieved the distance of 525.5m (Borg’s scale — 2, without desaturation). Echocardiography showed heart measurements within normal limits, good systolic and diastolic function of the left and right ventricle and efficiently working valves (EF 66%, TAPSE 23 mm, RVSP 30 mmHg, AcT 96 ms). There were also no signs of pulmonary hypertension. Currently, the patient is alive and well 11 months after lung transplantation (Fig. 4).

**Discussion**

The described case pertains to a young man who suffered from progressive physical exercise...
intolerance that lasted for a couple of years. The beginning of his symptoms was associated with mononucleosis infection.

As the cause of PVOD remains unknown, the assumption of multiple risk factors was made. Such disease is idiopathic in most of the cases. However, there were instances of familial occurrence and many other factors that may cause the outbreak of the disease. One of the hypothesis of PVOD pathogenesis is the existence of biallelic mutation of EIF2AK4 gene. Giererd et al. [7] emphasized the role of this mutation in their work. Twelve different families (19 people with PVOD) had genetic factor of EIF2AK4 mutation. Whereas in the study group consisting of 81 patients, biallelic mutation was confirmed in 7 (9%) [7]. Genetic tests of the described patient detected 2 mutations, both of them caused gene inactivation, which is consistent with PVOD diagnosis. Biallelic character was not confirmed, but it must be validated in family testing. The presented patient is a carrier of recessive mutation in EIF2AK4, which is also characteristic of diagnosis of PVOD. Eyries et al. [8] detected the aforementioned mutation among individuals with familial and sporadic PVOD. The next risk factor described as a prelude to PVOD is infection. In many studies there were reports of infections caused by flu-like viruses, Toxoplasma gondii, measles and Epstein-Barr virus [9–12]. It was reported that our patient had a history of mononucleosis, which is caused by one of the aforementioned viruses. However, to this day, this hypothesis was not supported by evidence. Montani et al. [13] proved that PVOD patients report an occupational history of significant exposure to chemicals such as organic solvents (e.g. trichloroethylene). Moreover, the absence of exposure to them was associated with a younger age of disease and a high prevalence of harbouring bi-allelic EIF2AK4 mutations. These findings are consistent with our patient's characteristics.

Clinical symptoms do not allow to distinguish PVOD from PAH. The results of bodyplethysmography, spirometry, DLCO, or severe hypoxemia and decrease in hemoglobin saturation suggest rather PVOD than other forms of IPAH. Medical imaging using HRCT showed some features that may lead to PVOD consideration — ground glass opacities, thickened interlobular septa and enlargement of mediastinal lymph nodes. However, these abnormalities in radiological imaging may not occur in all of the cases of PVOD and may be difficult to see at an early stage of the disease [1]. Histopathological examination allows (with the highest probability) to confirm the gold standard in diagnostic process of the disease. Lung biopsy is the diagnostic gold standard. However, it is not required due to high risk of complications [2].

The only effective method of PVOD treatment is lung transplantation. PAH-specific therapy should be used with great caution in PVOD due to a high risk of pulmonary edema. However, Montani et al. assessed that cautious use of continuous intravenous epoprostenol improved clinical and hemodynamic parameters in PVOD patients at 3–4 months without commonly causing pulmonary edema, and may be a useful bridge to urgent lung transplantation [14]. So was the case when it comes to our patient. Such therapy was extended only as a bridge to lung transplantation.

Without the procedure, a mean time of survival from diagnosis and from first noticeable symptoms are 1 year and 2 years, respectively [1, 15]. Administering medications that are intended for PAH therapy is controversial. Prostacyclin I2 (PGI2) and its mimetics, such as iloprost and treprostinil have a dilating effect on both pulmonary veins and arteries. The study by Benyahia et al. [16] suggested that iloprost and treprostinil cause similar decrease in human pulmonary arteries’ and veins’ resistance, thus they should be the most effective clinically available agonists to decrease pulmonary vascular resistance and to prevent edema formation. Treprostinil in comparison to iloprost has more responsive impact on pulmonary veins and arteries. Potential vasodilating effect of using PGI2 mimetics in both types of pulmonary vessels can be a strong indicator of applying them for PVOD treatment [16]. Treprostinil administered to
our patient slowed the progression of the disease and let him live until the lung transplantation was possible. Before the aforementioned drugs, the patient was treated with calcium blockers. At the beginning, he received diltiazem, but it was not well tolerated. Indeed, it was previously observed that this drug could lead to worsening among patients with PVOD [17]. Treatment was changed to amiodipine with dosage escalation to 10 mg twice a day. Even though, this therapy did not provide satisfactory results either, there was a case report about a patient with PVOD confirmed by biopsy, who presented clinical and hemodynamic response to therapy with nifedipine with a significant reduction in pulmonary arterial hypertension, as misdiagnosing them as PAH could worsen the patients’ condition [18]. The use of medications dedicated for PAH treatment should be carefully considered, and the decision must be well thought while taking care of patients with PVOD.

In conclusion, patients with PVOD require thorough diagnostic process in order to properly distinguish this disease from pulmonary arterial hypertension, as misdiagnosing them as PAH could worsen the patients’ condition. Moreover, any pharmacotherapy proves to be finally unsatisfactory in case of PVOD. Lung transplantation remains the only therapeutic option for such patients.

Conflict of interest

The authors declare no conflict of interest.

References:


