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# Pulmonary arterial hypertension and lung transplantation: when one severe pathology is replaced by another

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**Abstract**

**English:**

*Pulmonary arterial hypertension (PAH) is a rare and severe disease characterised by the progressive narrowing of the small pulmonary arteries resulting in right-sided heart failure. Despite advances in treatment, some PAH patients require lung transplantation, which carries risks of long-term complications. We report the case of a male patient with no significant comorbidities, who developed progressive dyspnoea on exertion at the age of 38 years. After echocardiography and right heart catheterisation, he was confirmed with idiopathic PAH and was started treatment with bosentan, sildenafil and beraprost. After 3 years of stability, the PAH worsened. Treatment with continuous intravenous epoprostenol was introduced in a national premiere, unfortunately with little effect. The patient underwent lung transplantation at the age of 43 years. Afterwards, he developed several complications, including chronic lung allograft dysfunction, post-transplant lymphoproliferative disorder and pulmonary embolism. He died at the age of 52 years of invasive pulmonary aspergillosis. The case is noteworthy due to the above-average post-transplant survival despite multiple complications.*

**Keywords**

*pulmonary arterial hypertension • lung transplantation • invasive pulmonary aspergillosis • post-transplant lymphoproliferative disorder*

# Hipertensiunea arterială pulmonară și transplantul pulmonar: când o patologie severă este înlocuită de o alta

**Rezumat**

**Romanian:**

*Hipertensiunea arterială pulmonară (HAP) este o boală rară și gravă, caracterizată prin îngustarea progresivă a arterelor pulmonare mici, ceea ce duce la insuficiență cardiacă de partea dreaptă. În ciuda progreselor terapeutice, unii pacienți cu HAP necesită transplant pulmonar, ceea ce implică riscuri de complicații pe termen lung. Raportăm cazul unui pacient de sex masculin, fără comorbidități semnificative, care a dezvoltat dispnee progresivă la efort la vârsta de 38 de ani. După efectuarea unei ecocardiografii și a cateterizării inimii drepte, i s-a confirmat diagnosticul de HAP idiopatică și a început tratamentul cu bosentan, sildenafil și beraprost. După trei ani de stabilitate, HAP s-a înrăutățit. Tratamentul cu epoprostenol intravenos continuu a fost introdus în premieră națională, dar, din păcate, cu efecte reduse. El a suferit un transplant pulmonar la vârsta de 43 de ani. După intervenția chirurgicală, a dezvoltat mai multe complicații, inclusiv disfuncția cronică a grefei pulmonare, tulburarea limfoproliferativă post-transplant și embolia pulmonară. A decedat la vârsta de 52 de ani din cauza unei infecții invazive demonstrate a fi aspergiloza pulmonară. Cazul este remarcabil datorită supraviețuirii post-transplant peste medie, în ciuda mai multor complicații.*

**Cuvinte-cheie**

*hipertensiune arterială pulmonară • transplant pulmonar • aspergiloză pulmonară invazivă • sindrom limfoproliferativ post-transplant*

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## Introduction

Pulmonary arterial hypertension (PAH) is a rare disease in which the proliferation and remodelling of the small pulmonary arteries cause a progressive narrowing of the vascular lumen and increased pulmonary vascular resistance. In time, these changes lead to right-sided heart failure and death (1). The median survival after diagnosis in the absence of treatment is 2.8 years (2). The treatment of PAH relies on specific pulmonary vasodilators acting on three physiological pathways: the endothelin pathway, the nitric oxide pathway and the prostacyclin pathway (3). Epoprostenol is the first drug approved for PAH and the only drug to have improved PAH survival in a randomised trial (4). Due to its very low half-life, it needs to be administered in a continuous intravenous infusion. It is currently reserved for use in patients with severe PAH despite treatment with oral medication (1).

Recent advancements in the treatment of PAH have significantly improved survival; however, some patients progress to right heart failure despite optimal medical therapy. Lung transplantation is an important therapeutic option for these patients. Current PAH guidelines recommend early referral to transplantation centres for all eligible PAH patients who do not respond to initial oral medication. In addition, listing for lung transplantation is recommended in PAH patients who remain at high risk despite parenteral therapy, as their 1-year mortality rate exceeds that observed after transplantation (1). Some PAH patients require heart–lung transplantation, but most undergo bilateral lung transplantation. Median survival after lung transplantation is 6.7 years (5).

## Case presentation

A 38-year-old male patient developed progressive dyspnoea on exertion. He had smoked 7 pack-years, but he was otherwise healthy, with no significant medical history and no known allergies. He denied any history of wheezing, syncope, haemoptysis or paroxysmal dyspnoea. Initial workup included lung function tests, which were normal, and echocardiography, which revealed a high probability of pulmonary hypertension with dilated right-sided heart chambers. The patient was subsequently referred to a PAH expert centre where a right heart catheterisation was performed and pre-capillary pulmonary hypertension was confirmed (see Table 1). Additional tests were negative for connective tissue disease, liver disease, human immunodeficiency virus infection or chronic thromboembolic pulmonary hypertension. The patient was therefore diagnosed with idiopathic PAH.

Treatment was started with sildenafil, an inhibitor of phosphodiesterase 5 (IPDE-5). Bosentan, an endothelin receptor antagonist (ERA), was added a few months later due to insufficient improvement on sildenafil alone. The patient was treated with bosentan and sildenafil for 1 year. Signs of PAH severity persisted, however, other medications were unavailable in Romania at that time. After 1 year, his pulmonary artery pressure and pulmonary vascular resistance were unchanged (see Table 1). He was then included in a clinical trial through which he received beraprost, an oral prostacyclin analogue. With triple therapy, his condition improved significantly.

**Table 1.** Evolution of right heart catheterisation parameters

| Time (years since diagnosis): | Diagnosis (no treatment) | 1 year (bosentan, sildenafil) | 4 years (bosentan, sildenafil, beraprost) |
|---|---|---|---|
| PAPm (mmHg) | 81 | 86 | 101 |
| PCWP (mmHg) | 8 | 8 | 32 |
| CO (l/min) | 4.5 | 4.6 | 3.4 |
| CI (l/min/m$^2$) | 2.4 | 2.4 | 1.7 |
| PVR (WU) | 16.2 | 16.9 | 20.35 |

CI, cardiac index; CO, cardiac output; PAPm, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; WU, Wood units.

After 3 years of stability, his dyspnoea worsened and he developed signs of right heart failure. Right heart catheterisation was repeated and an increase in pulmonary arterial pressure, pulmonary vascular resistance and a decreased cardiac output were found (see Table 1). In addition, the beraprost clinical trial ended and treatment had to be stopped. At this time, the patient was referred and listed for lung transplantation at the Allgemeine Krankenhaus (AKH) hospital in Vienna, through the Eurotransplant network. At the same time, treatment with continuous intravenous epoprostenol was introduced through a tunnelled central venous catheter, a national premiere in Romania. The patient's condition remained severe despite epoprostenol treatment. He was transported to AKH Vienna by a medical aeroplane 3 weeks later and underwent bilateral lung transplantation, at 43 years of age. He required several days of extracorporeal membrane oxygenation (ECMO) and prolonged mechanical ventilation but was eventually discharged after 34 days of hospitalisation.

After 2 years, the first post-transplant complications appeared. The patient became increasingly short of breath, pale and jaundiced. A blood count showed a haemoglobin concentration of 6 g/dL. He was hospitalised in the haematology department and was diagnosed with warm autoimmune haemolytic anaemia. He was started on IV immunoglobulins and corticosteroid pulse therapy and received packed red blood

cells. Additionally, he developed severe hypoxemia, with a $SpO_2$ of 75% in ambient air. A contrast-enhanced chest computed tomography (CT) revealed a pulmonary embolism. Anticoagulation was started with fondaparinux. The anaemia did not improve with treatment, so the patient was transferred to AKH hospital in Vienna. There he received four cycles of rituximab, which allowed for the normalisation of the haemoglobin concentration. Anticoagulation for pulmonary embolism was continued after discharge for a total duration of 3 months.

One year later, dyspnoea on exertion reappeared. Lung function tests showed a severe obstructive syndrome with FEV1 of 40% predicted, compared with 80% 2 years before. Chronic lung allograft dysfunction was suspected and transbronchial biopsy was performed. The histopathological aspect was that of bronchiolitis obliterans, consistent with lung graft dysfunction. Corticosteroid pulse therapy improved the patient's dyspnoea, but the functional obstructive syndrome persisted.

No significant events occurred in the following 4 years. Then the patient developed a laterocervical adenopathy accompanied by progressive fatigue. Biopsy revealed a B-type cell post-transplant lymphoproliferative disorder. A PET-CT was performed to evaluate extension and revealed metabolically active supra- and sub-diaphragmatic adenopathies. High-dose corticosteroids and rituximab were introduced. The evolution was favourable, with a reduction in the size of all adenopathies and an improvement in fatigue.

After another year, in September 2021, he was once again hospitalised for dyspnoea and a non-productive cough. Acute non-hypercapnic respiratory failure was present on admission. Chest CT revealed a new pulmonary embolism. Anticoagulation was reintroduced with low-molecular-weight heparin, given the history of lymphoproliferative disorder. The symptoms improved partially, but the respiratory failure persisted and the patient needed to start long-term oxygen therapy after discharge.

He was readmitted 2 months later, in November 2021, for dyspnoea and productive cough with purulent sputum. A new chest CT scan revealed several large cavitary lesions in both lungs, some with air-fluid levels, some containing rounded masses consistent with aspergilloma (see Figure 1). Bronchoalveolar lavage found numerous fungal colony-forming units, but fungal identification was not technically possible in our institution at the time. Based on the clinical context, radiological appearance and presence of fungi in respiratory secretions, a diagnosis of invasive pulmonary aspergillosis was established. Treatment with voriconazole was initiated and the patient was discharged with a slight improvement in symptoms.

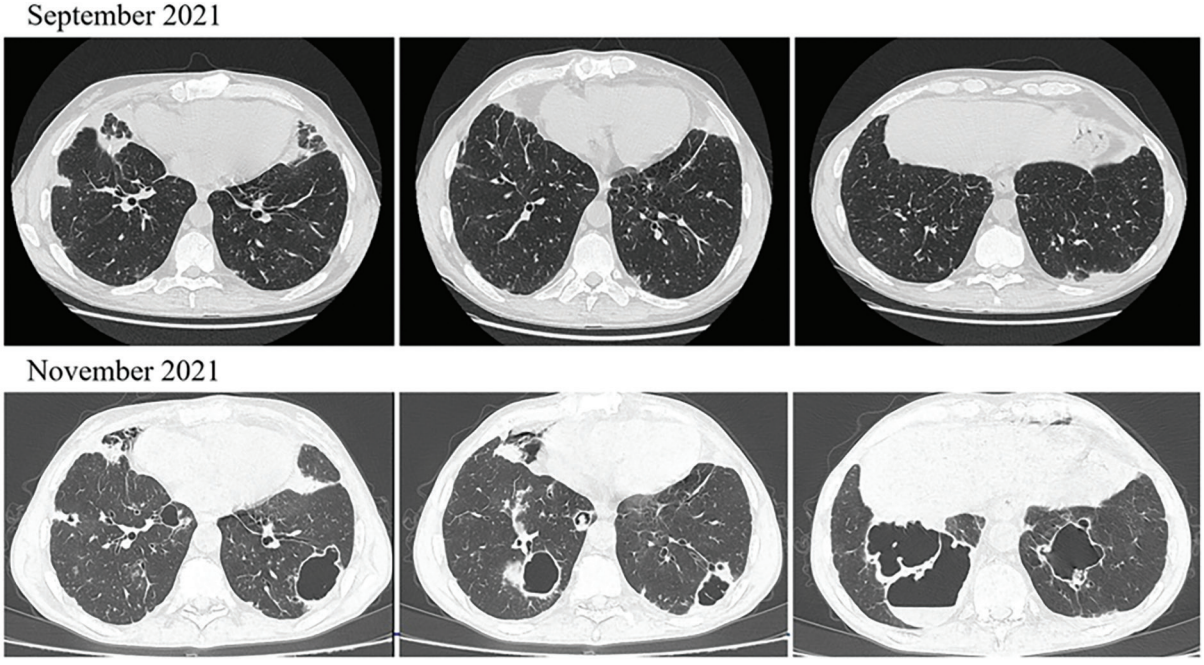



**Figure 1.** Chest computed tomograpthy (CT) san from November 2021 (bottom row) in comparison with September 2021 (top row). Large bilateral cavitary lesions with air-fluid levels and intracavitary masses can be seen on the November CT scan, which were absent two months prior.

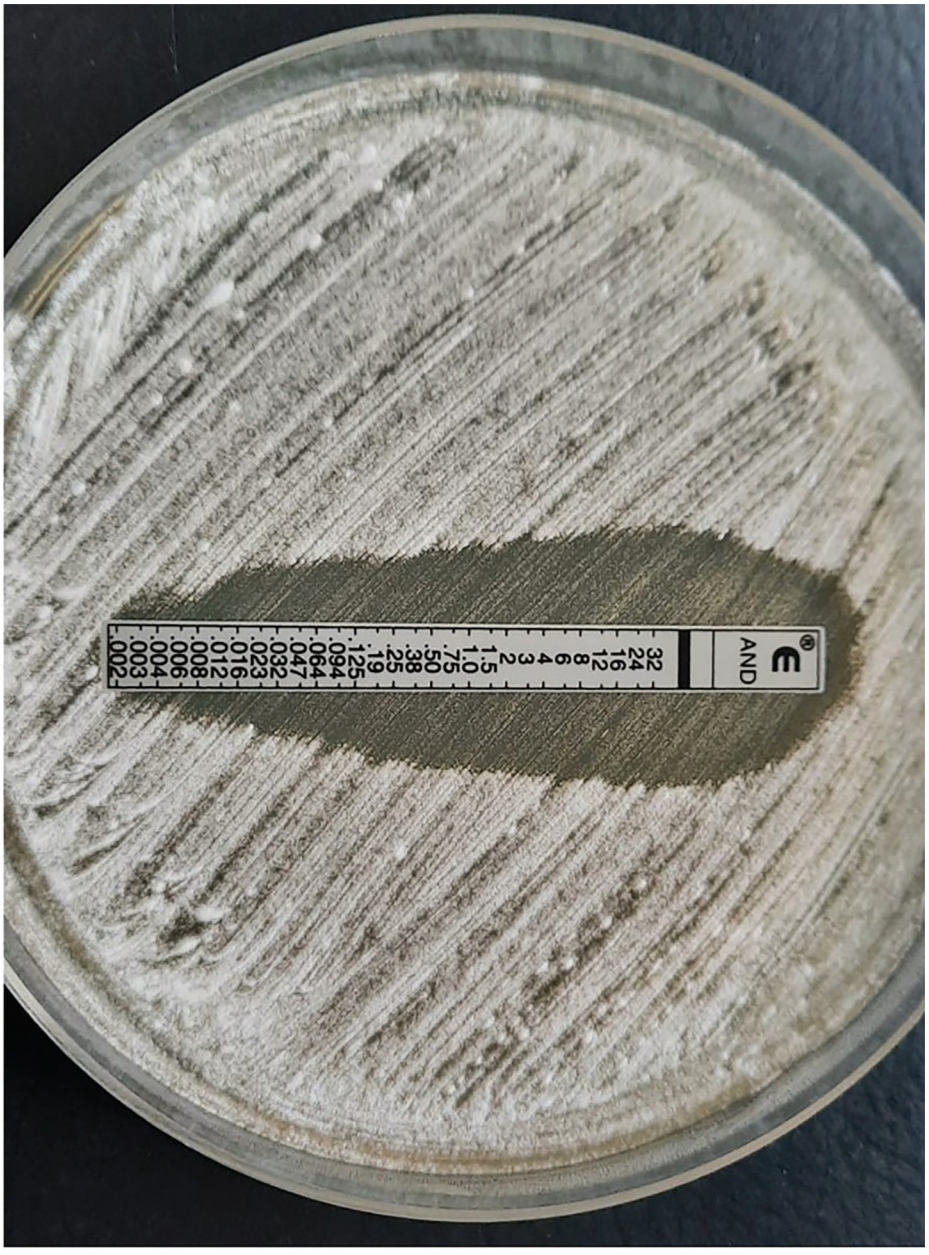



**Figure 2.** Anidulafungin E-test. Dual behavior, with one fungal population inhibited by anidulafungin in a concentration dependent manner and another with no inhibition. (Image courtesy of Biol. Dr. Olguța Corneli).

The cough and dyspnoea progressed once again and the patient needed to be re-hospitalised in December 2021. Chest CT showed a stable appearance of the cavitary lesions. Sputum samples were sent for fungal identification in another institution and were positive for *Aspergillus terreus* and *Aspergillus flavus*, as well as *Klebsiella oxytoca* and *Enterobacter kobei*. A short course of antibiotic therapy was administered, but the clinical state continued to worsen. A repeat CT scan 2 weeks later showed progression of cavitary lesions despite treatment with voriconazole. Anidulafungin was added to voriconazole as rescue therapy for invasive aspergillosis. Complete antifungal susceptibility testing could not be performed, however, an E-test for anidulafungin was performed at the 'Cantacuzino' Institute of Medico-Military Research and Development and showed a dual behaviour of the isolated fungi, with one population inhibited by anidulafungin and another population which was not inhibited (Figure 2).

An attempt was made to replace the antifungal therapy with posaconazole and caspofungin, however, the patient continued to worsen. He became increasingly hypoxemic and eventually developed severe hypercapnia. He was admitted to the intensive care unit (ICU), where he required orotracheal intubation and mechanical ventilation. He eventually developed multi-organ dysfunction syndrome and died on the 7th day in the ICU, at 52 years of age, 8.5 years after lung transplantation and 13 years after PAH diagnosis.

## Discussion

The initial presentation of our case was that of progressive dyspnoea on exertion in a young patient with no known pathologies. Such a symptom frequently translates into chronic lung or heart disease, which most often require lung function tests and echocardiography for diagnosis. Echocardiography raised the suspicion of pulmonary hypertension in our patient, as is frequently the case. However, echocardiography is not sufficient for a firm diagnosis given its low sensitivity and specificity for pulmonary hypertension. Right heart catheterisation is considered the gold standard for PH diagnosis (1).

PAH is a rare disease with an estimated prevalence of 55 per million adults and an annual incidence of 6 per million adults. It was previously considered a disease that predominantly affects young patients, especially women; however, recent registry data have shown that the distribution between sexes is more balanced (1). Studies on older cohorts of untreated patients report a severe prognosis with a median survival of 2.8 years after diagnosis (2). However, recent decades have seen remarkable progress in terms of treatment options for these patients (6). Our patient, despite a very severe form of pulmonary hypertension and limited access to the more potent parenteral medications, managed to survive for 5 years before transplantation due to medical treatment.

Lung transplantation is a last-resort therapeutic option for eligible PAH patients who remain unresponsive to medical treatment. Given the significant number of young patients affected by PAH, early referral to lung transplantation centres is of great importance and recommended in international guidelines (1). Our patient was referred for transplantation when his state worsened and became high-risk despite oral treatment, before the introduction of parenteral epoprostenol. This decision proved correct, as his condition remained severe despite epoprostenol and he required urgent transfer for transplantation. Ultimately, lung transplantation prolonged his survival to 13 years after diagnosis of PAH.

Mortality after lung transplantation is generally highest in the first post-transplant year, and this is particularly true of patients transplanted for PAH (1). Those who survive the first year are faced with the long-term complications of lung transplantation, which include chronic allograft dysfunction (7), haemolytic anaemia (8), venous thromboembolic disease, post-transplant lymphoproliferative disorders and pulmonary infections (9). Our patient experienced a diverse array of complications, and despite all of them, he managed to survive beyond the median survival after lung transplantation, which is currently estimated at 6.7 years (5).

***Case particularity***

Our case is remarkable in several regards. First, PAH remains a very rare disease that only affects about 5 out of every 100.000 adults. Second, even though treatment for PAH has been available in Romania for several years, our patient was the only one in which intravenous epoprostenol treatment was successfully implemented, although for a short time and with little benefit. Third, our patient experienced various post-transplant complications which required collaboration between several medical specialities. Finally, despite all these complications, his 13-year survival after the initial diagnosis highlights the immense progress that has been achieved in the treatment of PAH patients.

## Conclusions

PAH is a rare disease which has seen many advances in treatment over the past 20 years which have allowed for significant improvement in survival. Lung transplantation remains a vital option for those patients who do not respond to medical therapy. Transplant recipients are at risk for many complications, requiring collaboration between various medical specialities for appropriate management, but with proper pre-transplant selection and post-transplant follow-up, they stand to gain an important increase in life expectancy.

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None.

## Author's contributions

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3. Coordinating author: Tudor Constantinescu

T.C. conceived and designed the analysis. A.N. performed the analysis and wrote the manuscript. All authors contributed data or analysis tools.

## Conflict of interest

The authors declare no conflict of interest.

## Institutional review board statement

Not Applicable.

## Informed consent statement

Informed consent was obtained from all subjects involved in the study. No informed consent was necessary.

## Data availability statement

Data used to support the findings of this study are available from the corresponding author upon request.

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