Pulmonary arterial hypertension unveils itself: a cancer-like progression — a case report

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Background
Pulmonary arterial hypertension (PAH) is a rare disorder with a poor prognosis, characterized by progressive remodelling of the small pulmonary arteries that precede the clinical and haemodynamic manifestations of the disease. Thus, a prompt diagnosis and early intervention are crucial.

Case summary
A 39-year-old pregnant women presented with persistent severe hypoxaemia after the diagnosis of influenza B and an elective caesarean delivery at 33 weeks. Ten months after, an extensive and inconclusive investigation that included a lung biopsy, despite of a spontaneous improvement in oxygen saturation, clinical deterioration led to further testing, namely genetic screening. It revealed a fast-progressing case of hereditary PAH caused by BMRP2 mutation.

Discussion
This case highlights the challenges of a timely diagnosis of PAH and the importance of close clinical monitoring of patients at high risk of PAH. In addition, it emphasizes the fast development of severe haemodynamic changes associated with a BMPR2 mutation. The availability of a lung biopsy without signs of pulmonary vascular disease (PVD) and a right heart catheterization with mild pulmonary hypertension at the baseline assessment demonstrates that PVD can progress in a neoplastic-like manner in a matter of months.

Keywords
Hypoxaemia • Pulmonary arterial hypertension • Pulmonary hypertension • Interstitial lung disease • BMPR2 • Case report

Learning points
• Pulmonary vascular disease can progress in a matter of months from mild to severe haemodynamics.
• Cardiopulmonary exercise testing is an invaluable tool to assess dyspnoea symptoms.
Introduction

Pulmonary arterial hypertension (PAH) is a rare disorder characterized by progressive remodelling of the small pulmonary arteries that precede the clinical and haemodynamic manifestations of the disease.1 A prompt diagnosis and early intervention are crucial in improving survival, given the poor prognosis.2,3 Here, we report a fast-progressing case of hereditary pulmonary arterial hypertension (HPAH).

Timeline

| Day 0 (February 2018) | 30-week pregnant patient develops dyspnoea, cough, and fever; diagnosed with influenza B infection and treated as an outpatient with oseltamivir. |
| Day 2 | Clinical deterioration with severe hypoxaemia, admitted to the Infectious Diseases Department and treated with oseltamivir and amoxicillin-clavulanate. |
| Day 9 | Transferred to the Prenatal Ward after clinical improvement; but severe hypoxaemia persisted. |
| Day 14 | Worsening fatigue and persistent hypoxaemia; ventilation/perfusion lung scan negative for pulmonary embolism. |
| Day 20 | Worsening fatigue and persistent hypoxaemia; computed tomography pulmonary angiogram negative for pulmonary embolism. |
| Day 21 (March 2018) | Elective caesarean delivery at 33 weeks. |
| Day 24 | Persistent severe hypoxaemia after caesarean; transferred to the Pneumology Department for further explorations. |
| Day 52 | After an extensive and inconclusive investigation, including a right heart catheterization (RHC) and a lung biopsy, the patient was discharged under continuous supplementary oxygen therapy (SaO2 92% with FiO2 21%). |
| June and August 2018 | Re-evaluation as an outpatient; hypoxaemia requiring supplementary oxygen therapy with relatively stable levels of fatigue (SaO2 94% with FiO2 21%). |
| December 2018 | Worsening fatigue with spontaneous resolution of hypoxaemia (SaO2 98% with FiO2 21%); cardiopulmonary exercise test suggestive of significant tissue hypoxia and transthoracic echocardiogram showed de novo mild dilatation of the right ventricle and a tricuspid regurgitation velocity of 3.5 m/s. |
| January 2019 | A diagnosis of heritable pulmonary arterial hypertension was made based on the RHC that revealed severe haemodynamics, with markers of high risk, and identification of a pathogenic heterozygous variant in BMRP2 gene. Upfront double combination pulmonary vasodilator therapy with sildenafil 20 mg t.i.d. and bosentan 125 mg b.i.d. was initiated. |
| April 2019 | Marked clinical improvement, as well as improvement of the 6-min walking test and normalization of the cardiac biomarkers. |
| October 2020 | Despite clinical stability [New York Heart Association (NYHA) functional class II] and normal cardiac biomarkers, a low cardiac index (1.95 L/min/m²) led to the addition of selexipag 200 mg b.i.d. |
| February 2021 | Clinical improvement (NYHA functional class I) and normal cardiac biomarkers. Selexipag was slowly titrated to 1000 mg b.i.d. based on clinical tolerance. |

Case presentation

A Caucasian 39-year-old 30-week pregnant woman presented with dyspnoea, cough, and fever. She was severely hypoxaemic, and a diagnosis of influenza B infection by real-time polymerase chain reaction was made. After a course of oseltamivir and amoxicillin-clavulanate, no improvement was found in the pattern of hypoxaemia and hypocapnia. A pulmonary embolism workup, including a computed tomography (CT) pulmonary angiogram and a ventilation/perfusion lung scan, was carried out and was negative. Following an elective caesarean delivery at 33 weeks, hypoxaemia requiring supplemental oxygen persisted.

Her past medical history was significant for arterial hypertension and hypothyroidism during the current pregnancy. Her family history was remarkable by the death of a sister at a young age.

On admission, she denied chest pain, syncope, haemoptysis, and prior smoking. On physical examination, she was slightly dyspnoeic and hypoxaemic with fraction of inspired oxygen (FiO2 21%) of 99%. There were bibasilar lung crackles but no peripheral oedema, and no skin, finger, or nail changes.

The initial investigation showed severe hypoxaemia [PaO2 59 mmHg with fraction of inspired oxygen (FiO2) 21%] with hypocapnia, but with good response to oxygen therapy (Table 1). The biochemical and autoimmunity studies were unremarkable (Table 1). The chest radiography did not reveal pleural or pulmonary changes (Figure 1). Pulmonary function testing revealed normal spirometry volumes, but a low diffusing capacity for carbon monoxide (DLCO) —56.9%. High-resolution CT excluded lung parenchymal involvement (Figure 1).

A transthoracic echocardiogram (TTE) demonstrated a non-dilated right ventricle (RV) and a tricuspid regurgitation velocity gradient of 3.0 m/s (Figure 2A, Video 1). A bubble study excluded an
intracardiac or intrapulmonary shunt. Finally, a right heart catheterization (RHC) was performed and revealed severe resting hypoxemia. 

Additionally, as the breathing reserve was not exhausted, pulmonary limitation to exertion was not an issue. TTE repetition showed a peak oxygen consumption (VO2 16.4 mL/min/kg; predicted value >25 mL/min/kg), a VE/VCO2 slope of 32.9 (predicted value 22–28), and a marked increase of arterial lactate level upon exertion.

Taking into consideration the relative disproportion between the severity of the hypoxia and the mild PH, a surgical lung biopsy was performed. The main finding was a non-specific pattern of chronic lung disease, leading to the performance of a lung biopsy, a valuable diagnostic tool in suspected PH. Sildenafil 20 mg t.i.d. and bosentan 125 mg b.i.d. was initiated, leading to a marked clinical and functional improvement. Eighteen months later, despite clinical stability and normal cardiac biomarkers, the follow-up RHC revealed a low cardiac index (Table 2), and selexipag 200 mg b.i.d. was promptly added to the initial therapy.

**Discussion**

PH is a clinical syndrome, and the guidelines recommend a comprehensive set of investigations after an echocardiogram with a moderate-to-high probability of PH, in order to establish an etiology. However, the interpretation of such investigations is challenging, as our case showed. Initially, the first set of inconclusive exams led to the performance of a lung biopsy, which actually is no longer recommended in PAH patients due to a substantial risk of morbimortality. However, the combination of mild PH in the context of severe, unexplained hypoxaemia after a viral pneumonia and a non-suggestive lung biopsy shifted away the suspicion of PVD. Additionally, the degree of hypoxaemia in PAH is generally mild to moderate, with a mean PaO2 of 70 ± 13 mmHg in males and 72 ± 16 mmHg in females. More severe hypoxaemia should prompt the consideration of alternative causes of PH, namely pulmonary veno-occlusive disease (excluded by the chest CT and biopsy), thromboembolic disease (excluded by a pulmonary ventilation/perfusion lung scan), and intracardiac or intrapulmonary shunts. Besides PVD, an isolated decrease in the DLCO with normal spirometry raises the suspicion for early interstitial lung disease (ILD), anaemia, hepatopulmonary syndrome, and carboxyhaemoglobinemia due to cigarette smoking. These last three causes were promptly excluded. Finally, ILD was the strongest diagnostic hypothesis after the initial investigation. The presumed low risk of complications led to the performance of a lung biopsy, a valuable diagnostic tool in ILD; however, its findings were unspecific.

Ten months later, after significant clinical deterioration despite the SaO2 normalization, genetic testing confirmed the HPAH diagnosis. Although BMPR2 genetic testing should be offered to patients with idiopathic PAH (IPAH), drug-induced PAH, or with a family history of PAH, the timing of the screening is not clear. We acknowledge that if it was performed sooner, it could have obviated the need for a lung biopsy; however, neither the clinical presentation nor the diagnostic
testing strongly supported PAH at first. Nonetheless, there was a game-changing clue that was initially missed and might have prevented an earlier diagnosis, the family history of the death of her adolescent sister due to lung disease, which was only recalled by the patient later on. Heterozygous BMPR2 mutations account for approximately 75% of HPAH and up to 25% of sporadic PAH cases and may be associated with PAH development at younger ages and a more severe clinical and haemodynamic phenotype. Importantly, the availability of a lung biopsy without signs of PVD and an RHC with mild PH on baseline demonstrates that PVD can progress in a neoplastic-like manner in a matter of months, in the presence of a BMPR2 mutation.

The mechanism of the hypoxaemia that persisted for months after influenza B infection and spontaneously ameliorated is debatable, particularly in the setting of a PAH-causing mutation. Pregnant women are a high-risk group for influenza complications, and it is known that the physiological changes seem to be poorly tolerated by PAH patients.

The treatment strategy for PAH includes general, supportive, and PAH-specific therapy. Regarding PAH-specific therapy, the first step is to identify who is suitable for high-dose calcium channel blockers...
among patients with IPAH, HPAH, or drug-induced PAH. Our patient did not undergo pulmonary vasoreactivity testing during the second RHC due to symptomatic hypotension secondary to a vagal response. The patient was treated with upfront combination therapy, as it has proven to be superior to monotherapy. Lastly, when treatment goals are not met, sequential combination therapy is recommended. 

**Conclusions**

We present a case of HPAH caused by a BMPR2 mutation in a patient with symptom onset during pregnancy, progressing in a...

| Baselin RHC | Follow-up RHC (10 months later) | Follow-up RHC (18 months after PAH therapy) |
|------------|---------------------------------|--------------------------------------------|
| Baselin RHC | Baselin RHC | Follow-up RHC (10 months later) | Follow-up RHC (18 months after PAH therapy) |
| Right atrial pressure -mmHg | 7 | 7 | 4 | 8 |
| Mean pulmonary artery pressure -mmHg | 29 | 26 | 48 | 28 |
| Pulmonary capillary wedge pressure -mmHg | 8 | 13 | 4 | 15 |
| Transpulmonary pressure gradient -mmHg | 21 | 13 | 44 | 13 |
| Pulmonary vascular resistance –Wood units | 7.7 | 3.9 | 16 | 3.7 |
| Cardiac index –L/min/m² | 2.2 | 2.0 | 1.6 | 1.95 |
| Mixed venous oxygen saturation -% | 57 | 69 | 53 | - |
| Aortic oxygen saturation -% | 86 | 100 | 98 | - |

FiO2: fraction of inspired oxygen; PAH: pulmonary artery hypertension; RHC: right heart catheterization.

**Figure 3** Lung biopsy. (A and B) Peri-arteriolar and peri-bronchiolar lymphocytes and macrophages with epithelioid granuloma immune response running with arteriolar wall hyperplasia and constrictive bronchiolitis (H&E × 100/CD68 × 100). (C and D) Revision of the biopsy highlighted previous non-characterized capillary vessel walls changes overdue to lymphocytes infiltration and epithelioid granulomas exuberance. The presence of singular millimetric fibrovascular remodelling, mostly found in BMPR2-related pulmonary arterial hypertension, was underestimated and prevented pulmonary arterial hypertension diagnosis (Elastin–van Gieson × 100/Actin × 100).

**Video 2** Second transthoracic echocardiogram: de novo mild dilatation of the right ventricle with preserved function.
neoplastic-like manner, from an unremarkable biopsy to overt disease in a matter of months. Close monitoring is paramount in patients at high risk.

**Lead author biography**

Cátia Santos-Ferreira graduated from Faculty of Medicine, University of Coimbra in 2015. She is following a residency in Cardiology at Centro Hospitalar e Universitário de Coimbra. Moreover, she is completing a PhD degree on Health Sciences at University of Coimbra. Her academic interests include pulmonary hypertension and heart failure.

**Supplementary material**

Supplementary material is available at European Heart Journal - Case Reports online.

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**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

**Consent:** The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidelines.

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