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CASE REPORT
Other

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 • BMRP2 • 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.

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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 (SaO_2 92% with FiO2 21%).
June and August 2018	Re-evaluation as an outpatient: hypoxaemia requiring supplementary oxygen therapy with relatively stable levels of fatigue (SaO_2 94% with FiO2 21%).
December 2018	Worsening fatigue with spontaneous resolution of hypoxaemia (SaO_2 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/m^2) 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 [oxygen saturation (SaO_2) with supplemental oxygen at 4 L/min 99%]. There were bibasilar lung crackles but no peripheral oedema, and no skin, finger, or nail changes.

The initial investigation showed severe hypoxaemia [PaO_2 59 mmHg with fraction of inspired oxygen (FiO_2) 21%] with hypocapnia, but with a 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

Table 1 Basic laboratory studies: comprehensive metabolic panel

	Value	Reference range
Arterial blood gas		
PaO_2 (FiO_2 21%)	59	80–100 mmHg
$PaCO_2$ (FiO_2 21%)	21	35–45 mmHg
PaO_2 (FiO_1 40%)	132	80–100 mmHg
$PaCO_2$ (FiO_2 40%)	24	35–45 mmHg
Biochemical profile		
Sodium	139	136–146 $mmol \cdot L^{-1}$
Potassium	3.8	3.5–5.1 $mmol \cdot L^{-1}$
Chloride	105	101–109 $mmol \cdot L^{-1}$
Blood urea nitrogen	17.4	7.94–20.9 $mg \cdot dL^{-1}$
Creatinine	0.62	0.55–1.02 $mg \cdot dL^{-1}$
Estimated glomerular filtration rate	114	>59 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$
Calcium	8.6	8.8–10.6 $mg \cdot dL^{-1}$
AST	26	<31 $U \cdot L^{-1}$
ALT	53	<34 $U \cdot L^{-1}$
Alkaline phosphatase	126	30–120 $U \cdot L^{-1}$
Total bilirubin	0.3	0.2–1.2 $mg \cdot dL^{-1}$
Albumin	3.0	3.5–5.2 $g \cdot dL^{-1}$
LDL	106	<130 $mg \cdot dL^{-1}$
Complete blood count		
Haemoglobin	11.1	12.0–16.0 $g \cdot dL^{-1}$
Platelets	271	150–400 $\times 10^9 \cdot L^{-1}$
White blood cells	10.9	4.0–10.0 $\times 10^9 \cdot L^{-1}$
Mean corpuscular value	78.2	
Cardiac enzymes		
Troponin I	23	<27 $ng \cdot L^{-1}$
BNP	<10	<100 $pg \cdot mL^{-1}$
Inflammatory markers		
C-reactive protein	0.57	0–0.5 $mg \cdot dL^{-1}$
Iron studies		
Ferritin	13	4.6–204 $ng \cdot mL^{-1}$
Iron	31	60–180 $\mu g \cdot dL^{-1}$
Total iron binding capacity	378	250–400 $\mu g \cdot dL^{-1}$
Percent saturation	8	20–40%

ALT, alanine aminotransferase; AST, aspartate transaminase; BNP, brain natriuretic peptide; FiO_2, fraction of inspired oxygen; LDL, low-density lipoprotein.

intracardiac or intrapulmonary shunt. Finally, a right heart catheterization (RHC) was performed and revealed severe resting hypoxaemia (SaO_2 86%) and mild, pre-capillary pulmonary hypertension (PH), partially reversible with 100% O_2 (*Table 2*).

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 bronchiolitis (*Figure 3*). As the findings did not support the diagnosis of pulmonary vascular disease (PVD), the patient was discharged under oxygen therapy without specific medication.

During the next 10 months, a progressive and spontaneous improvement in SaO_2 was seen, leading to oxygen supplementation withdrawal. Conversely, fatigue worsened, prompting the performance of a cardiopulmonary exercise test. Although no desaturation at rest or peak exertion was noted, it revealed a decreased peak oxygen consumption (VO_2 16.4 mL/min/kg; predicted value >25 mL/min/kg), a VE/VCO_2 slope of 32.9 (predicted value 22–28), and a marked increase of arterial lactate level upon exertion. Additionally, as the breathing reserve was not exhausted, pulmonary limitation to exertion was not an issue. TTE repetition showed *de novo* mild dilatation of the RV and an increasing tricuspid regurgitation velocity of 3.5 m/s (*Figure 2B*, *Video 2*). These findings led to a new RHC that confirmed PAH (*Table 2*). Later on, the patient recalled that the death of her 17-year-old sister, 20 years ago, was due to an unspecified pulmonary disease, leading to the performance of genetic testing of PVD-related genes and the identification of a pathogenic heterozygous variant in *BMRP2* gene [c.647dup p.(Val217Serfs*3)]. A diagnosis of HPAH was then made, based on haemodynamic and genetic grounds. 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 aetiology.[1] However, the interpretation of such investigations is challenging, as our case showed. Initially, the first set of inconclusive exams lead to the performance of a lung biopsy, which actually is no longer recommended in PAH patients due to a substantial risk of morbimortality.[1] 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 (FiO_2 21%) of 70 ± 13 mmHg in males and 72 ± 16 mmHg in females.[4,5] 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.[6] 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.[7] 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[8]; however, its findings were unspecific.

Ten months later, after significant clinical deterioration despite the SaO_2 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,[1] 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

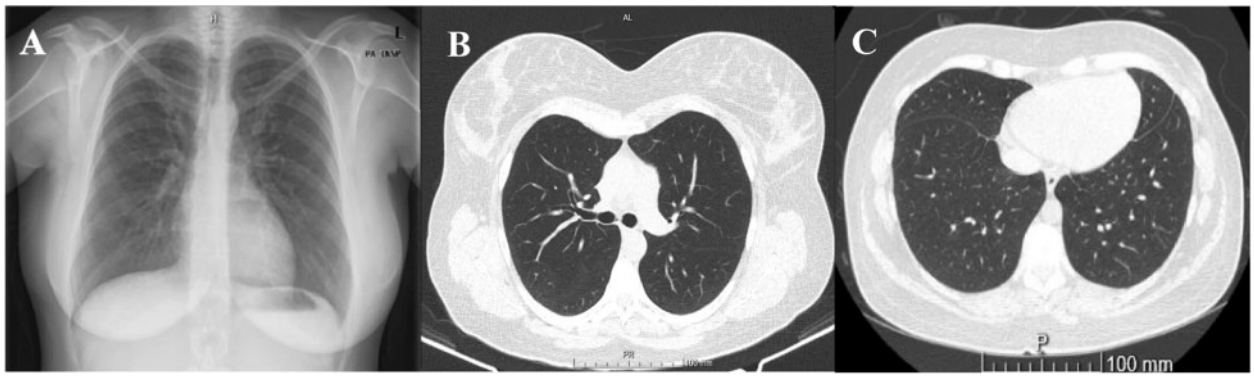


Figure 1 Chest imaging. (*A*) Normal chest radiograph. (*B* and *C*) Normal high-resolution computed tomography.

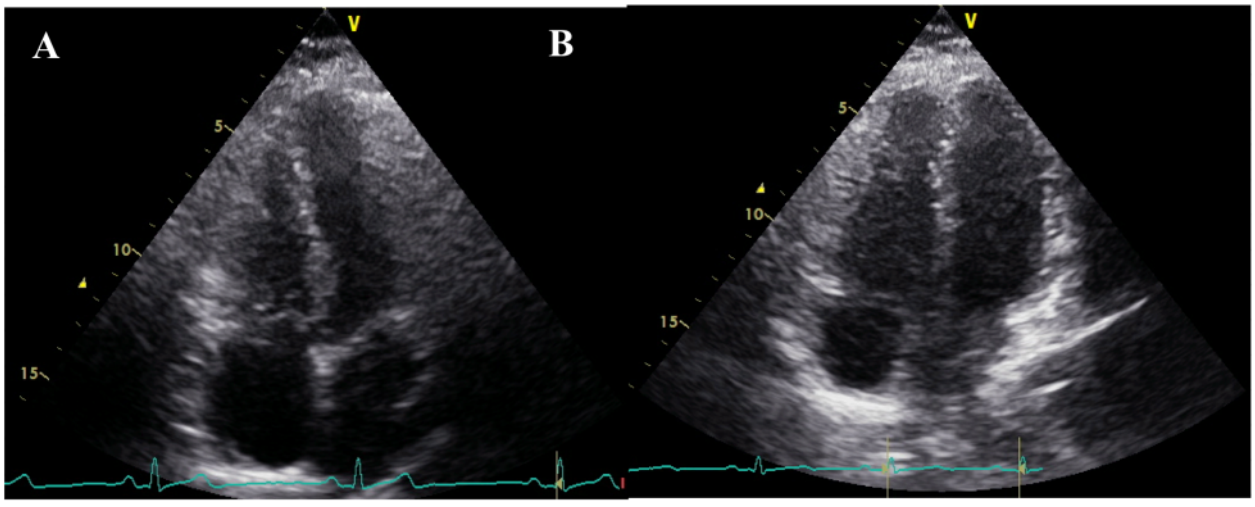
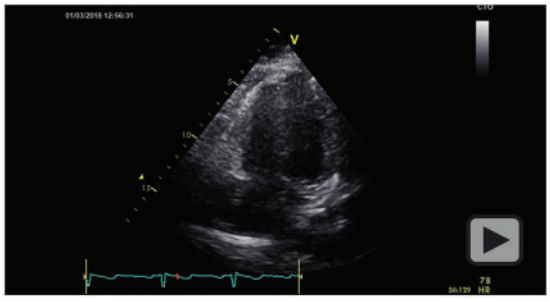


Figure 2 Serial transthoracic echocardiogram. (*A*) Normal-sized chambers. (*B*) Mildly dilated right ventricle.



Video 1 First transthoracic echocardiogram: normal-sized chambers with preserved biventricular function.

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[1] and may be associated with PAH development at younger ages and a more severe clinical and haemodynamic phenotype.[9] 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,[10] and it is known that the physiological changes seem to be poorly tolerated by PAH patients.[11]

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

Table 2 Hemodynamic parameters measured using RHC

Baselin	Baselin RHC		Follow-up RHC (10 months later)	Follow-up RHC (18 months after PAH therapy)
	FiO_2 21%	After FiO_2 100%	FiO_2 21%	FiO_2 21%
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/m^2	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.

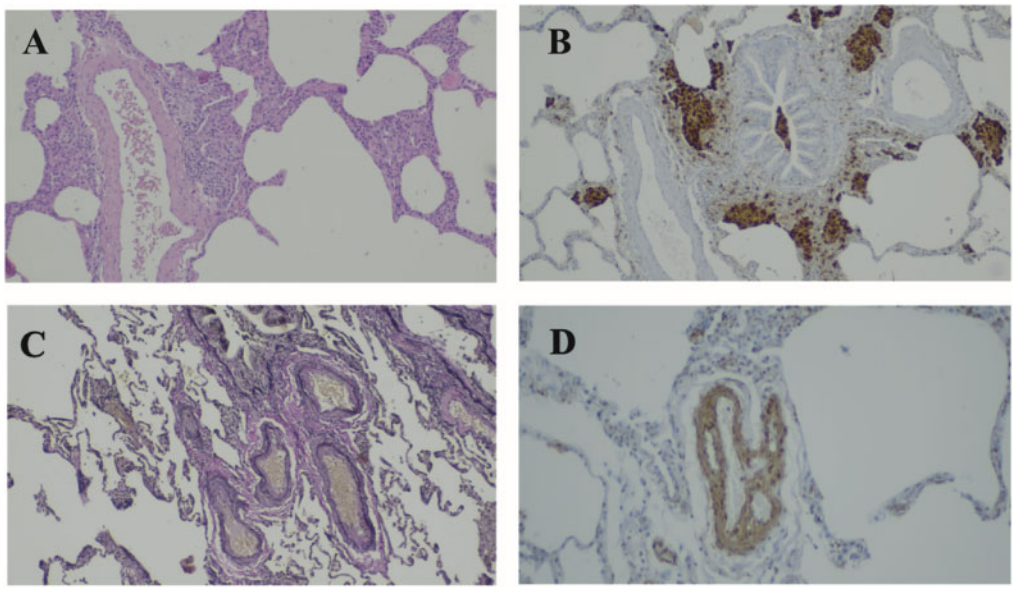
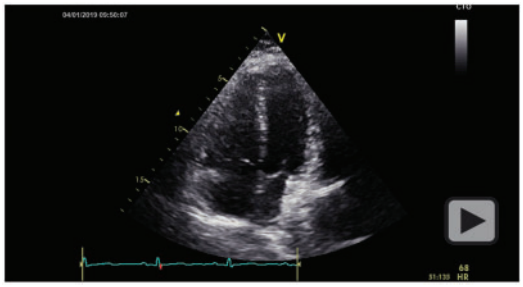


Figure 3 Lung biopsy. (*A* and *B*) Peri-arteriolar and peri-bronchiolar lymphocytes and macrophages with epithelioid granuloma immune response running with arteriolar wall hyperplasia and constrictive bronchiolitis (H&E ×100/CD68 ×100). (*C* and *D*) Revision of the biopsy highlighted previous non-characterized 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.

among patients with IPAH, HPAH, or drug-induced PAH.[1] 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.[12] Lastly, when treatment goals are not met, sequential combination therapy is recommended.[1]

Conclusions

We present a case of HPAH caused by a BMRP2 mutation in a patient with symptom onset during pregnancy, progressing in a

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.

Conflict of interest: None declared.

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References

1. Galié N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A *et al.* 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2016;**37**:67–119.
2. Brown LM, Chen H, Halpern S, Taichman D, McGoon MD, Farber HW *et al.* Delay in recognition of pulmonary arterial hypertension: factors identified from the REVEAL Registry. *Chest* 2011;**140**:19–26.
3. Swinnen K, Quarck R, Godinas L, Belge C, Delcroix M. Learning from registries in pulmonary arterial hypertension: pitfalls and recommendations. *Eur Respir Rev* 2019;**28**:190050.
4. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM *et al.* Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987;**107**:216–223.
5. Khirfan G, Naal T, Abuhalimeh B, Newman J, Heresi GA, Dweik RA *et al.* Hypoxemia in patients with idiopathic or heritable pulmonary arterial hypertension. *PLoS One* 2018;**13**:e0191869.
6. Porteous MK, Fritz JS. Hypoxemia in a patient with pulmonary arterial hypertension: getting to the heart of the matter. *Ann Am Thorac Soc* 2014;**11**:836–840.
7. McCormack M. Diffusing capacity for carbon monoxide. Up-to-date. https://www.uptodate.com/contents/diffusing-capacity-for-carbon-monoxide?search=Diffusing%20capacity%20for%20carbon%20monoxide.&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1 (6 May 2020).
8. Raj R, Raparia K, Lynch DA, Brown KK. Surgical lung biopsy for interstitial lung diseases. *Chest* 2017;**151**:1131–1140.
9. Soubrier F, Chung WK, Machado R, Grünig E, Aldred M, Geraci M *et al.* Genetics and genomics of pulmonary arterial hypertension. *J Am Coll Cardiol* 2013;**62** (25 Suppl):D13–D21.
10. Louie JK, Acosta M, Jamieson DJ, Honein MA. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. *N Engl J Med* 2010;**362**:27–35.
11. Warnes CA. Pregnancy and pulmonary hypertension. *Int J Cardiol* 2004;**97**:11–13.
12. Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin Vv *et al.* Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015;**373**:834–844.