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Case Report

# An interesting case of progressive dyspnoea and diffuse mediastinal adenopathy in a 25-year-old man

A 25-year old man was admitted to hospital with a 12-month history of progressive dyspnoea and fatigue, with an acute deterioration over the preceding 2 weeks. He denied any significant past medical history, was a lifelong non-smoker and had moved to Ireland from Brazil with his family 1 year prior. On presentation, he was hypoxic, with peripheral oxygen saturations of 79% on room air and tachycardic at 110 beats·min$^{-1}$. Examination revealed a loud pulmonary component of the second heart sound, but was otherwise unremarkable, as he was clinically euvolaemic, with clear lung fields and there were no audible cardiac murmurs. Chest radiograph demonstrated prominent hilar vasculature (figure 1).

An electrocardiogram (ECG) revealed diffuse T wave inversion, suggestive of right ventricular strain and therefore a computed tomography pulmonary angiogram (CTPA) was ordered to assess for a pulmonary embolism and an echocardiogram to exclude intrinsic cardiac disease. The CTPA demonstrated good opacification of the pulmonary arterial tree, with no evidence of a pulmonary embolism, but some abnormalities were noted (figure 2a and b).

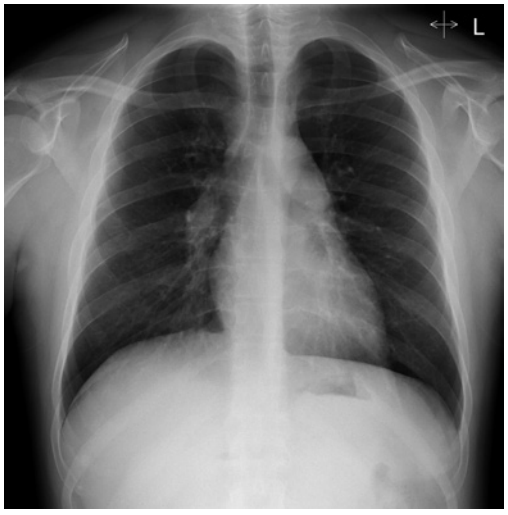


**Figure 1** *Chest radiograph of a 25-year-old man with dyspnoea and hypoxia, demonstrates normal pulmonary parenchyma and clear lung fields, with prominent hilar vasculature.*

**Task 1**
Described the abnormalities shown in the CTPA (figure 2).

**Cite as**: Cullivan S, Morris J, McCormack C, *et al*. An interesting case of progressive dyspnoea and diffuse mediastinal adenopathy in a 25-year-old man. *Breathe* 2021; 17: 200289.

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**Mediastinal adenopathy, septal line thickening, centrilobular ground glass opacities on CT and a markedly reduced $T_{LCO}$ in a young patient with pulmonary hypertension, should alert the clinician to this potential diagnosis** https://bit.ly/3cfe9pX

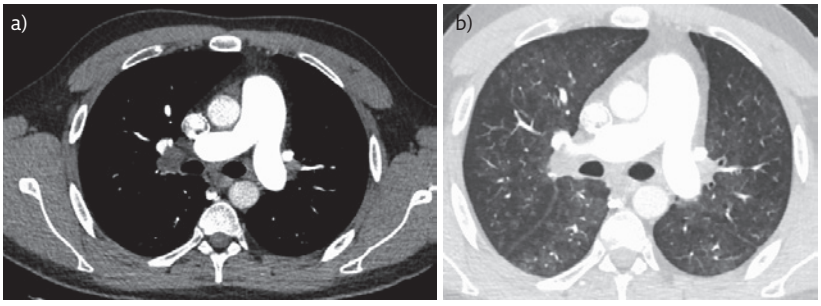


**Figure 2** *Computed tomography pulmonary angiogram.*

**Table 1** *Right heart catheterisation with a fraction of inspired oxygen ($F_{iO_2}$) of 0.32*

| Right heart catheterisation | |
|---|---|
| **mPAP** | 66 mmHg |
| **mRAP** | 6 mmHg |
| **mPAWP** | 9 mmHg |
| **PVR** | 15 Wood Units |
| **Cardiac index** | 1.8 L·min·m$^{-2}$ |
| **Pulmonary artery saturations** | 63% |
| **Radial artery saturations (high/mid/low)** | 63/63/63% |

mPAP: mean pulmonary artery pressure; mRAP: mean right atrial pressure; mPAWP: mean pulmonary artery wedge pressure; PVR: pulmonary vascular resistance.

**Answer 1**
The CTPA shows a dilated pulmonary artery trunk and mediastinal adenopathy (figure 2a), and diffuse centrilobular ground glass opacities (figure 2b).

The echocardiogram revealed an enlarged right atrium and ventricle, and a normal left heart. A small patent foramen ovale (PFO) was suggested by a positive bubble study. He was transferred to our unit for a right heart catheterisation (RHC) and further investigations for suspected pulmonary hypertension (table 1). The RHC was performed on supplemental oxygen with a fraction of inspired oxygen ($F_{iO_2}$) of 0.32.

**Task 2**
Select the correct answer. This right heart catheterisation:

1 Confirms postcapillary pulmonary hypertension
2 Shows a clinically significant shunt due to a suspected PFO.
3 Confirms precapillary pulmonary arterial hypertension (PAH)
4 Cannot be interpreted as the patient was on supplemental oxygen

**Answer 2**
The RHC confirmed precapillary PAH, with a mean pulmonary artery pressure (mPAP) ≥20 mmHg, pulmonary vascular resistance (PVR) ≥3 Wood Units and a normal pulmonary artery wedge pressure ≤15 mmHg [1]. There was no evidence of a significant left-to-right shunt, as saturations were stable in the upper, middle and lower right atrium. Nitric oxide testing was not performed.

In light of these results, the patient was commenced on initial double combination therapy with an endothelin receptor antagonist (ERA) and a phosphodiesterase type 5 (PD5) inhibitor. On further questioning, he denied toxin exposure, drug use including diet pills, features suggestive of a connective tissue disease or any occupational exposures. His family history was significant for cardiopulmonary disease, as his sister died at 23 years old, following a cardiorespiratory arrest of uncertain aetiology. Serological investigations revealed a normal B-type natriuretic peptide (BNP) at 31 ng·L$^{-1}$, positive antinuclear antibodies (homogenous pattern), negative connective tissue disease panel, vasculitis screen and HIV test. Baseline renal, liver and bone profiles were normal. Pulmonary function tests revealed normal spirometry and a markedly reduced transfer factor for carbon monoxide ($T_{LCO}$) of 24%. His 6 min walk distance was 300 m, which required 10 L of supplemental oxygen to maintain saturations at 90%.

Despite PAH targeted medication he remained unwell, oxygen dependent and intermediate risk, with NYHA functional class III symptoms.

**Task 3**
What is the most likely diagnosis in this case given the above information:

1 Idiopathic pulmonary arterial hypertension (IPAH)
2 Systemic vasculitis complicated by pulmonary hypertension
3 Pulmonary veno-occlusive disease (PVOD)
4 Pulmonary hypertension due to chronic lung disease
5 Pulmonary artery obstruction due to hydatidosis

**Task 4**
Why might acute vasoreactivity testing be avoided in this condition?

**Answer 3**
A diagnosis of PVOD was suspected based on the combination of persistent high oxygen requirements, poor response to PAH-targeted medications, diffuse centrilobular ground glass opacities with mediastinal adenopathy and a markedly reduced $T_{LCO}$. Sarcoidosis was also within the differential diagnosis, though considered less likely.

**Answer 4**
Acute vasoreactivity testing during RHC has been associated with pulmonary oedema in cases of PVOD, due to preferential vasodilatation of precapillary arterioles, with subsequent flooding of capillaries, as blood is unable to proceed through narrowed postcapillary venules and veins. Furthermore, an acute response during vasoreactivity testing in PVOD is uncommon, unlikely to reflect long-term responsiveness, and treatment with calcium channel blockers may result in pulmonary oedema. Therefore vasoreactivity testing is typically avoided when PVOD is suspected as it is unlikely to change patient management and may be associated with harmful effects.

Genetic testing was subsequently requested to assess for potential associated gene mutations, which could provide additional diagnostic and prognostic information and may have implications for family planning and screening.

**Task 5**
Which gene is most commonly implicated in the pathogenesis of this condition?

1 Bone morphogenetic protein receptor type 2 (*BMPR2*)
2 Endoglin (*ENG*)
3 Eukaryotic translation initiation factor 2 alpha kinase 4 (*EIF2AK4*)
4 Activin A receptor type II-like kinase 1 (*ACVRL1*)

**Answer 5**
Mutations in *EIF2AK4* are associated with heritable and some sporadic cases of PVOD. In this case, biallelic gene variants in the *EIF2AK4* gene were identified, confirming the diagnosis of PVOD. Mutations in *BMPR2* are typically associated with heritable PAH (HPAP) and mutations in *ENG* and *ACVRL1* genes are potential causes of PAH in hereditary haemorrhagic telangiectasia.

Bilallelic gene variants c.3766C>T; p.Arg1256* (classified as pathogenic) and c.2609C>T; p.Ala870Val (likely pathogenic) were isolated in this case. PAH targeted medications and supportive measures including supplemental oxygen were optimised, and he was referred for lung transplant assessment given the poor prognosis of this condition.

This is an interesting case of PVOD due to biallelic *EIF2AK4* gene mutations, that highlights important clinical features that should alert the physician to this potential diagnosis, and emphasises the clinical utility of genetic testing in these complex and rare cases.

## Discussion

PVOD was first described by Julius Hora in the 1930s and later distinguished from IPAH in 1966 by Heath *et al*. [2, 3]. Due to its rarity and the lack of effective treatment options, PVOD is classified as an orphan lung disease, with an estimated prevalence of 1–2 cases per million inhabitants [3]. While PVOD can be heritable in nature, it is also associated with connective tissue diseases, such as systemic sclerosis and specific drugs, chemotherapeutic agents and toxins [3–5]. Heritable PVOD typically presents at a younger age, with an average age of disease onset of 26 years, and has an equal sex distribution due to its recessive nature. This differs from sporadic disease which presents later, typically in the 6th decade and exhibits a male predominance, which is potentially linked to specific occupational exposures [3–5].

Once considered separate clinical entities, PVOD and pulmonary capillary haemangiomatosis (PCH) are now classified together as "Group 1.6: PAH with overt features of venous/capillaries (PVOD/PCH) involvement" [1]. This updated classification following the 6th World Symposium on Pulmonary Hypertension reflects an appreciation for shared characteristics between PVOD/PCH and PAH, as venous pathology may also be observed in PAH and separation of these conditions into different subgroups may be an oversimplification of a spectrum of pulmonary vascular disease [4, 6, 7]. The patient in this case was classified as group 1.6 heritable PVOD due to biallelic *EIF2AK4* mutations,

with the reported gene variants previously described in association with PVOD [8–10]. The importance of this gene in the pathogenesis of PVOD was first reported by the French Pulmonary Hypertension Network in 2014, when they performed whole-exome sequencing in 13 families with heritable PVOD [11]. Recessive mutations in *EIF2AK4* were identified in all of these families and in additional sporadic cases of PVOD, which was a major breakthrough in our understanding of this rare condition [11]. The *EIF2AK4* gene encodes a kinase that controls phosphorylation of the alpha subunit of the eukaryotic initiation factor 2 (EIF2$\alpha$), which can induce changes in gene expression and protein synthesis. These gene mutations can be homozygous or compound heterozygous such as in this case. Further work is required to fully elucidate the exact genotype–phenotype relationship and link with specific pulmonary vascular changes [3, 8, 9, 11, 12].

Clinically PVOD can be difficult to distinguish from IPAH, as both present with progressive dyspnoea, fatigue and right heart failure if left untreated. Clinical findings that should alert the clinician to the potential diagnosis of PVOD include high supplemental oxygen requirements, pulmonary oedema during vasoreactivity testing and a poor response to PAH targeted therapies. Relevant investigations that may also suggest the diagnosis include severe reductions in $T_{LCO}$, <50% of predicted values, mediastinal adenopathy with associated septal line thickening and centrilobular ground glass opacities on computed tomography, and occult haemorrhage on bronchoalveolar lavage [2, 3, 10]. Interestingly RHC is not helpful to differentiate PVOD from other causes of Group 1 PAH, as it typically demonstrates a precapillary pattern, even though the principle anatomical abnormality is located on the postcapillary side. This is related to the technique used to obtain a PAWP during RHC. In order to obtain a PAWP, a small balloon is wedged into a medium-sized pulmonary artery; this creates a static column of blood downstream, to similarly sized pulmonary veins and the resultant pressure is the reported PAWP. In PVOD, these larger veins are typically spared, as the anatomical abnormalities are more proximal, in the post capillary venules and small veins [10]. Therefore if the condition is suspected, gene testing for *EIF2AK4* mutations is recommended, as RHC is not specific for the condition and histological confirmation with lung biopsy is not practical or safe [6]. The histopathology of PVOD has been clearly described in *post mortem* and post-transplant lung specimens. It is characterised by diffuse intimal thickening and fibrosis of venules and small veins, with associated vessel narrowing and obliteration. Luminal thrombosis, recanalised thrombotic lesions termed "colander-like lesions", haemosiderin deposition, occult haemorrhage and secondary angioproliferation of alveolar capillaries are frequently seen. Lymphatic abnormalities are also described, but importantly plexiform lesions are not observed, which is a key differentiator from IPAH [3].

PVOD is frequently associated with a poor response to targeted PAH medications. In this case, our patient tolerated double oral combination therapy with an ERA and PD5 inhibitor with no adverse events, but he remained intermediate risk, oxygen dependent and functional class III. Additional parenteral prostacyclin could also be considered with cautious titration given the associated risk of pulmonary oedema. Supportive measures, such as supplemental oxygen, vaccinations, diuretics and treatment of comorbidities are important to consider, but double lung transplant remains the only curative option for these patients. Interestingly, our patient has a small PFO, which technically could offload the right ventricle by shunting blood from right to left if the right atrial pressure exceed that of the left, acting like a balloon atrial septostomy (BAS). Evidence for BAS in PVOD is lacking, as theoretically profound hypoxaemia in PVOD precludes BAS, though anecdotal evidence suggests that BAS could be combined with veno–venous ECMO as a bridge to transplant in highly selected cases [13, 14].

Unfortunately the prognosis of this condition is poor, with a mean time from diagnosis to death or lung transplantation of 11.8 months [3]. Genetic counselling and testing should be offered to siblings of affected individuals for this recessive condition, as evidence suggests that early diagnosis of PAH and prompt intervention may translate into better long-term clinical outcomes [9].

## Affiliations

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## Author contributions

All authors contributed equally to the manuscript preparation and subsequent review.

## Conflict of interest

S. Cullivan is the Janssen Pharmaceutical Newman Fellow in Pulmonary Hypertension and Translational Medicine, this has no implications for the submitted work. J. Morris has nothing to disclose. C. McCormack has received funding from Janssen Pharmaceuticals for PhD in pulmonary hypertension and exercise training, this has no implications for the submitted work. A. Alameeri has nothing to disclose. S.P. Gaine has received honoraria and speaker's fees from Actelion and Janssen Pharmaceuticals, and is an advisory board member for United Therapeutics, outside the submitted work. B. McCullagh has nothing to disclose.

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