

# Genetic cause of pulmonary veno-occlusive disease

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## ABSTRACT

Pulmonary veno-occlusive disease (PVOD) is an important cause of pulmonary arterial hypertension (PAH) and is classified under idiopathic cause of PAH. Over a period of time, PVOD has been studied in detail in the western countries and various diagnostic criteria are formulated. Being a rapidly progressive disease, early diagnosis is of utmost importance which helps to initiate appropriate treatment. Recent studies suggest that PVOD has a genetic predisposition and has an autosomal recessive pattern of inheritance. Here, we discuss the case of siblings diagnosed with PVOD to have such genetic predisposition for this disease.

**KEY WORDS:** EIF2AK4 gene mutation, pulmonary arterial hypertension, pulmonary veno-occlusive disease

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## INTRODUCTION

Pulmonary arterial hypertension (PAH) is a condition when the mean pulmonary arterial pressure is  $\geq 25$  mmHg.<sup>[1]</sup> PAH is classified into five categories based on the pathophysiology, clinical features, and therapeutic approach as per the European Respiratory Society.<sup>[2]</sup> Pulmonary veno-occlusive disease (PVOD) is a rare cause of PAH which characteristically causes obliteration of small-sized pulmonary veins by causing fibrosis of the intimal layer of the vessel and causing patchy capillary proliferation.<sup>[3]</sup> PVOD is characterized by the typical triad of mean pulmonary arterial pressure (mPAP)  $\geq 25$  mmHg, normal pulmonary artery wedge pressure (PAWP)  $\leq 15$  mmHg, and elevated pulmonary vascular resistance. This term was coined in 1966;<sup>[4]</sup> prior to which terms like “obstructive disease of the pulmonary vein,” or the “venous form of primary pulmonary hypertension” were used to describe this syndrome.<sup>[5]</sup> The definitive diagnosis of PVOD is done by histopathological examination of

the lung tissue;<sup>[6]</sup> however, various radiological features are characteristic for this disorder. It was observed that there was genetic predisposition to this disorder in some individuals with autosomal recessive mode of transmission. Patients present with insidious onset of symptoms consistent with right heart failure which progresses to end-stage disease. PVOD does not respond appropriately to the medications used to decrease PAH. Rather, development of pulmonary edema post vasodilator therapy supports the diagnosis of PVOD. Here, we present two siblings who had findings consistent with PVOD having a genetic predisposition to this condition.

## CASE

### Case 1

Eleven-year-old male child (elder sibling) was brought to the hospital with complaints of abdominal pain, vomiting, chest pain, and intermittent cough for 15 days. The complaints had progressively increased and he had

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increasing dyspnea for 2 days before admission. On presentation, he had peripheral cyanosis, cold extremities, poor peripheral pulses, room air saturation of 75%, tender hepatomegaly, and blood pressure <5<sup>th</sup> percentile for age (all features suggestive of congestive right-sided heart failure). Two-dimensional (2D)-echocardiography showed severe PAH with right ventricular dysfunction along with some pericardial effusion. He was started on oxygen therapy by nonbreathing mask, intravenous antibiotics, and supportive management. To rule out thrombo-embolic state, computed tomography (CT) pulmonary angiogram was done which showed dilated central pulmonary artery and right cardiac chambers, suggestive of severe PAH along with bilateral pleural effusion. High-resolution CT of the chest showed diffuse ground-glass opacities of bilateral lungs with interlobar and intralobular septal thickening. Multiple ill-defined nodular opacities were observed peripherally in bilateral lungs suggesting the possibility of PVOD. Lung biopsy was done to look for any parenchymal pathology which showed patchy areas of vascular congestion with pulmonary arteriolar walls showing thickening by medial hyperplasia. There was a mild degree of interstitial fibrosis with no deposits or evidence of leiomyomatosis. The above histologic features were consistent with pulmonary vaso-occlusive disease. As pulmonary vasodilators are known to cause pulmonary edema in cases of PVOD, anti-PAH medications (Bosentan, Sildenafil) were started at a minimal dose. With the above given pulmonary vasodilator and diuretic therapy, he recovered and was discharged from the hospital with a plan to continue the same medications at home.

He stayed well for 3 months after which he was again brought to the hospital with complaints of cough and vomiting for 5 days. There was progressively increasing swelling in bilateral lower limbs and scrotal area observed over 3 days. 2D echocardiography showed significant right ventricular dysfunction secondary to severe pulmonary arterial dysfunction. With a diagnosis of progressive congestive cardiac failure secondary to an underlying progressive chronic lung disease, genetic studies were done which showed biallelic mutation in EIF2AK4 gene. He was started on anti-failure medications with pulmonary vasodilator medications. He continued to require high oxygen support and hence was put on mechanical ventilation and inotropic support for poor cardiac function. As the disease pathology progressed, he had an episode of cardiac arrest and could not be resuscitated back.

### Case 2

Seventeen-year-old male child (younger sibling) presented to the hospital 7 years after the demise of the elder brother with complaints of fever, abdominal pain, and progressive respiratory distress for 7 days. He was tested positive for COVID 19 virus and had received initial treatment in some outside hospital. As the symptoms persisted, he was referred to our center for further management. On presentation, he was hypotensive, with poor peripheral pulses and cold extremities.

2D echocardiography showed isolated right ventricular dysfunction with severe pulmonary arteriolar hypertension. X-ray of the chest showed bilateral pleural effusion. High-resolution CT scan of the chest showed multiple tiny centrilobular ground-glass density nodules diffusely distributed in both lungs with diffuse distribution of smooth interlobular septal thickening in both lungs [Figure 1]. Dilated main pulmonary artery and its branches up to peripheral aspect of both lungs were suggestive of PAH. With these characteristic findings on high-resolution CT (HRCT) and a positive history of death of elder brother with a similar pulmonary pathology, the diagnosis of PVOD was considered.

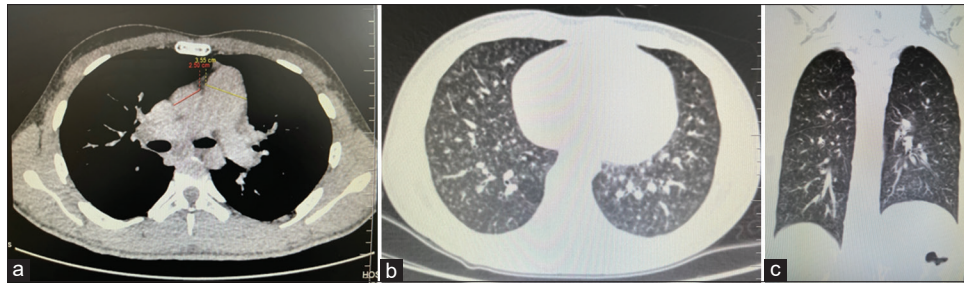
He was started on oxygen by high-flow nasal cannula in view of his increasing respiratory distress. Low-dose sildenafil along with other anti-failure medications was also initiated. He responded to the given line of management but required minimal oxygen support and hence was discharged with home oxygen therapy. On his follow-up visit, 2D echocardiography was done which showed persistent of moderate-to-high PAH. He was referred to the lung transplant team and was enrolled for lung transplantation.

## DISCUSSION

PVOD is a rare cause of PAH which is due to preferential involvement of pulmonary venous system. The characteristic feature in PVOD includes diffuse involvement of pulmonary veins and venules causing luminal narrowing secondary to intimal fibrosis. Such intimal remodeling may range from loose fibrous tissue to dense, sclerotic lesions. Vessel wall calcification and giant cells may be observed on histopathological examination.

PVOD is considered in class 1 of the recent classification of PAH (i.e., idiopathic PAH) as it shares similar clinical presentation and clinical examination. Patients present most commonly with progressive exertional dyspnea which is the earliest marker of failing right heart. Often, this subtle sign is neglected, which delays the diagnosis.<sup>[6]</sup> Frank signs of right heart failure may be observed in end-stage disease when the right ventricle is unable to tolerate the pressure overload from the pulmonary circulation. Clubbing and Raynaud's phenomenon has been observed in these patients.<sup>[3]</sup>

PVOD is characterized by the typical triad of mean pulmonary arterial pressure (mPAP)  $\geq$ 25 mmHg, normal pulmonary artery wedge pressure (PAWP)  $\leq$ 15 mmHg, and elevated pulmonary vascular resistance. PAWP in cases of PVOD is normal even though the obstruction is in the postcapillary venules. During the measurement of PAWP, the balloon catheter occludes the branch of pulmonary artery, producing a static column of blood. Therefore, PAWP measures the pressure in a relatively larger diameter pulmonary vein, which is actually not



**Figure 1:** (a) Computed tomography of the chest mediastinal window showing dilated main pulmonary artery suggestive of severe pulmonary arterial hypertension, (b and c) high-resolution computed tomography chest axial and coronal view showing multiple tiny centrilobular ground-glass density nodules diffusely distributed in both lungs with diffuse distribution of smooth interlobular septal thickening in both lungs

affected by the disease. Hence, PAWP in cases of PVOD is not the true reflection of the pulmonary capillary pressure, which ideally should be elevated due to obstruction to the downstream flow in pulmonary venules.

Acute vasodilator challenge helps to identify cases of PVOD who will respond well to calcium channel blocker therapy.<sup>[7]</sup> According to the European Respiratory Society (ERS) guidelines, positive vasodilator challenge is defined by  $>10$  mmHg fall in mPAP to an absolute level of  $<40$  mmHg without altering cardiac output. Pulmonary edema on vasodilator challenge is observed in PVOD cases.<sup>[6]</sup> However, studies done in the past have shown that this pulmonary edema could be prevented if inhaled nitric oxide (iNO) was used for vasodilator challenge test in concentration of 10 ppm.<sup>[8]</sup>

HRCT stays the best imaging modality to diagnose PVOD. The classic triad includes mediastinal lymph node enlargement, centrilobular ground-glass opacities, and smooth thickening of the interlobular septa.<sup>[9,10]</sup> Other noninvasive modalities used to support the diagnosis of PVOD are ventilation/perfusion lung scan, pulmonary function test, gas exchange capacity, and exercise testing. Bronchoalveolar lavage may be sent for examination in cases of suspected alveolar hemorrhage. Histopathological examination stays the gold standard for definitive diagnosis of PVOD but is not recommended in all cases because of various adverse events postprocedure. Finally, genetic analysis forms a very essential investigation to evaluate hereditary cause of PVOD. As in our case, presence of biallelic mutation in EIF2AK4 (eukaryotic translation initiation factor 2 alpha kinase 4) has been proved to be a rare cause of hereditary PVOD. Not many pediatric cases have been evaluated in the past having such hereditary causes of PVOD.

EIF2AK4 encodes a protein named as “General control nonderepressible 2” (GCN2) protein which has been identified to cause PVOD.<sup>[11]</sup> GCN2 is a serine–threonine kinase which acts by phosphorylation of  $\alpha$  subunit of eukaryotic translation initiation factor.<sup>[12]</sup> GCN2 also inhibits the inflammatory response and systemic autoimmunity triggered by increased cell apoptosis.<sup>[13]</sup> This inflammation and autoimmunity plays an integral

role in the pathogenesis of PAH, and thus, loss of GCN2 is considered as the main pathobiology of PVOD.

Various therapeutic options in PVOD have been discussed in studies done in the western countries. Supportive therapy in the form of oxygen administration in hypoxic patients is of utmost importance. ERS guidelines have concluded that the use of oral anticoagulant should be confined to cases with idiopathic PAH, heritable PAH, and PAH due to anorexigens. There are no such recommendations for patients with PVOD.<sup>[1]</sup> Targeted PAH therapy involves drugs which specifically target one of the three pathways responsible for PAH pathogenesis: prostacyclin, endothelin-1, and nitric oxide pathway.<sup>[7]</sup> All these drugs mainly cause vasodilation and have variable antiproliferative effects on the pulmonary vasculature.<sup>[14]</sup> Immunosuppressive drugs such as glucocorticoids, cyclophosphamide, and azathioprine have been proved to be beneficial in a few cases of PVOD.<sup>[15]</sup> Finally, lung or heart–lung transplant remains the only definitive therapy in cases of PVOD. However as this disorder is rapidly progressive in nature, early referral to the transplant unit is essential.

## CONCLUSION

PVOD is a rare cause of PAH which has characteristic clinical, radiological, histopathological findings. Genetic testing is of importance in cases with PVOD as these hereditary causes of PVOD could be diagnosed earlier and appropriate management could be initiated promptly.

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## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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