Scholars Journal of Medical Case Reports
Abbreviated Key Title: Sch J Med Case Rep
ISSN 2347-9507 (Print) | ISSN 2347-6559 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Cardiology

Pulmonary Veno-Occlusive Disease: A Rare Cause of Pulmonary Hypertension – A Case Report and Comprehensive Review of the Literature

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DOI: https://doi.org/10.36347/sjmcr.2026.v14i01.001 | **Received:** 21.10.2025 | **Accepted:** 27.12.2025 | **Published:** 02.01.2026

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Abstract | **Case Report**

Pulmonary veno-occlusive disease (PVOD) is a rare and severe form of precapillary pulmonary hypertension, classified in group 1′ of the 2022 ESC/ERS guidelines [1]. It is characterized by progressive fibrotic occlusion of post-capillary pulmonary venules, frequently associated with abnormal capillary proliferation, forming a pathological spectrum with pulmonary capillary hemangiomatosis (PCH) [2,7]. The incidence is estimated at fewer than one case per million inhabitants per year, with a particularly poor prognosis (median survival less than two years without transplantation) [4]. We report the case of a 34-year-old man admitted for acute right heart failure with progressive dyspnea, productive cough, and a 10-kg weight loss. Investigations revealed severe hypoxemia, a marked and isolated reduction in diffusing capacity for carbon monoxide (DLCO, 60% of predicted values), echocardiographic signs of severe pulmonary hypertension, and the classical radiological triad on high-resolution chest computed tomography (centrilobular ground-glass opacities, septal thickening, and mediastinal lymphadenopathy) [11,12]. Dual vasodilator therapy (macitentan 10 mg/day and tadalafil 20 mg/day) was cautiously initiated, allowing clinical stabilization at six months [8]. This case illustrates the diagnostic and therapeutic challenges of PVOD, the importance of early suspicion to avoid iatrogenic worsening with vasodilators, and the need for rapid evaluation for bilateral lung transplantation, the only curative option [9].

Keywords: Pulmonary veno-occlusive disease; pulmonary hypertension; EIF2AK4; high-resolution chest computed tomography; lung transplantation.

INTRODUCTION

Pulmonary veno-occlusive disease is a rare entity, initially described by Höra in 1934, accounting for approximately 5–10% of precapillary pulmonary hypertension cases initially considered idiopathic [2,7]. In the updated 2022 classifications, it is included in group 1′ ("pulmonary arterial hypertension with manifest venous/capillary involvement"), highlighting its distinct nature from classical arteriolar forms due to preferential involvement of post-capillary venules [1].

The pathology combines obliterative intimal fibrosis of septal and pre-septal pulmonary venules with anarchic intra-alveolar capillary proliferation, often forming a continuum with pulmonary capillary hemangiomatosis [10,11]. Etiologies are multifactorial and include sporadic and hereditary forms (biallelic mutations of the EIF2AK4 gene identified in 100% of familial cases and 20–25% of sporadic cases) [3], toxic exposures (alkylating chemotherapy such as cyclophosphamide or mitomycin C, organic solvents), connective tissue diseases (systemic sclerosis), infections (HIV), and thoracic radiotherapy [4,6].

Clinical presentation is insidious and nonspecific, mimicking idiopathic pulmonary arterial hypertension: progressive exertional dyspnea, fatigue, cough, syncope, and signs of right heart failure at advanced stages [2]. The main differential diagnosis remains idiopathic pulmonary arterial hypertension; however, PVOD is distinguished by a major risk of acute pulmonary edema upon initiation of specific vasodilator therapies and by a poorer prognosis (median survival 1–2 years after diagnosis) [5,8]. Through a clinical case observed in our center, this review details the updated epidemiological, pathophysiological, diagnostic, and therapeutic aspects.

CLINICAL OBSERVATION

A 34-year-old man, a former moderate smoker who quit two years earlier, with no significant medical history, was admitted to the emergency department for acute right heart failure secondary to progressive exertional dyspnea (NYHA class III–IV), productive cough, and a 10-kg weight loss over four months.

Clinical examination revealed sinus tachycardia at 110 bpm, moderate hypotension (100/60 mmHg), oxygen saturation of 87% on room air (corrected to 100% with 1 L/min oxygen), jugular venous distension, dependent edema, and tender hepatomegaly.

Laboratory findings showed hemoglobin of 17.8 g/dL (secondary polycythemia), elevated BNP (>2000 pg/mL), with normal inflammatory markers and normal hepatic and renal function.

Arterial blood gas analysis demonstrated partially compensated chronic respiratory alkalosis (pH 7.43; $PaCO_2$ 26 mmHg; PaO_2 89 mmHg on oxygen; HCO_3^- 17 mEq/L).

Pulmonary function tests showed normal spirometry (FVC 92%, FEV_1 93%, TLC 116% of predicted), with a severe isolated reduction in DLCO to 60%, a highly suggestive sign of impairment of the alveolo-capillary barrier [2,11].

Transthoracic echocardiography demonstrated estimated severe pulmonary hypertension (tricuspid regurgitation velocity >4 m/s) with severe tricuspid regurgitation and significant dilation of the main pulmonary artery (>35 mm), associated with moderate right ventricular dysfunction [1].

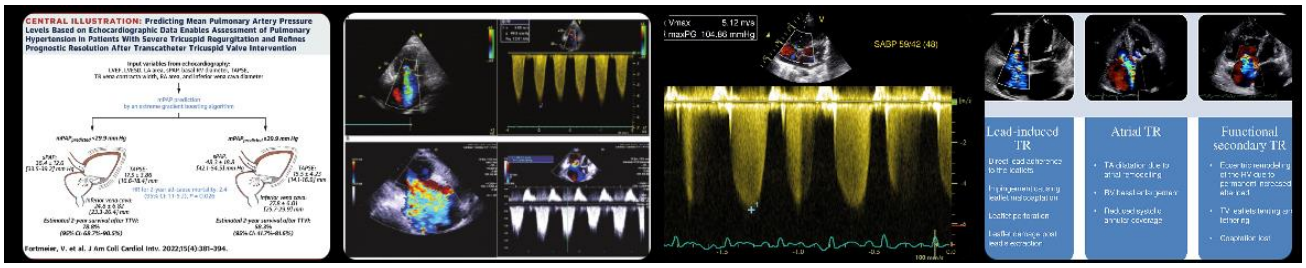

Figure 1: Transthoracic echocardiography showing severe tricuspid regurgitation with a large regurgitant jet, an indirect sign of severe pulmonary hypertension

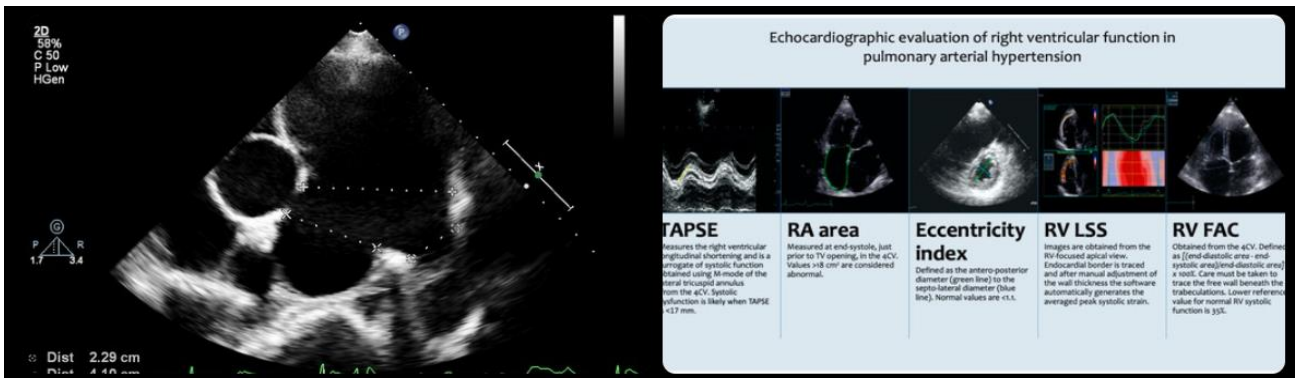

Figure 2: Parasternal short-axis view demonstrating dilation of the main pulmonary artery, typical of chronic pulmonary hypertension

High-resolution chest computed tomography revealed the classical triad: diffuse centrilobular ground-glass opacities, smooth interlobular septal thickening, and mediastinal lymphadenopathy, with no abnormalities suggestive of alternative etiologies [11,12].

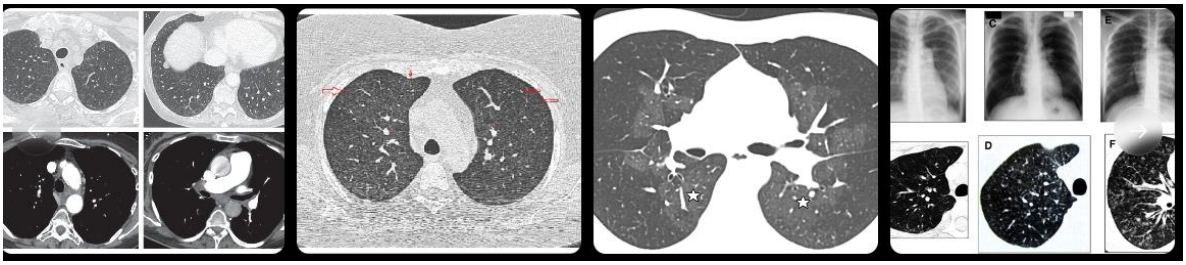

Figure 3: Axial high-resolution chest CT images showing centrilobular ground-glass opacities, septal thickening, and mediastinal lymphadenopathy—a radiological triad highly suggestive of PVOD

Initial treatment consisted of oxygen therapy, diuretics, followed by cautious initiation of dual therapy (macitentan 10 mg/day + tadalafil 20 mg/day) under inpatient monitoring [8].

Results and Follow-Up

A probable diagnosis of PVOD (with suspected associated PCH component) was retained according to the 2022 ESC/ERS criteria: severe precapillary pulmonary hypertension, DLCO <60%, complete radiological triad, and disproportionate hypoxemia [1,11]. No biopsy or initial right heart catheterization was performed due to the associated risks. Genetic testing for EIF2AK4 mutations was recommended but not performed urgently [3].

At six months, the patient showed clinical stabilization (NYHA class II), improvement in oxygen saturation, and absence of iatrogenic pulmonary edema. Referral for lung transplantation listing was initiated [9].

DISCUSSION

PVOD results from venous and capillary vascular remodeling with occlusive fibro-myofibroblastic intimal proliferation and anarchic capillary angiogenesis (intense CD34-positive staining) [10]. EIF2AK4 mutations impair cellular stress response mechanisms, promoting endothelial apoptosis and fibrosis under hypoxic conditions [3].

High-resolution CT is pivotal, with sensitivity exceeding 80% for the diagnostic triad (centrilobular ground-glass opacities 90–100%, septal thickening 85%, lymphadenopathy 75–80%). A DLCO <60% strongly favors PVOD over idiopathic pulmonary arterial hypertension [11,12].

Histologically, fibrotic occlusion of pulmonary venules and dense capillary proliferation are observed in cases with associated PCH [10].

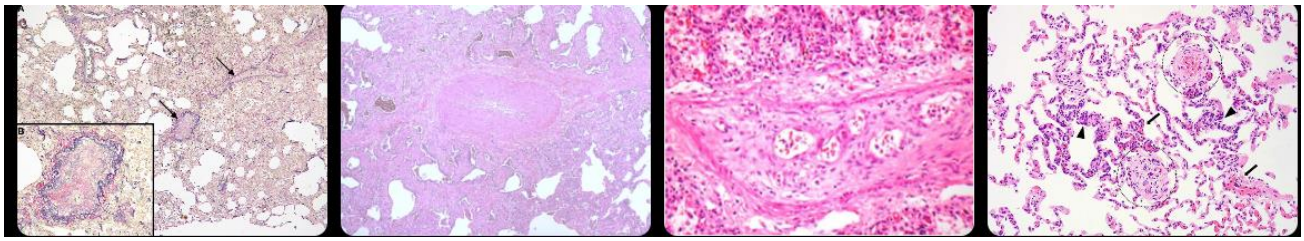

Figure 4: Histopathological features of PVOD showing eccentric or concentric fibrotic occlusion of pulmonary venules. *

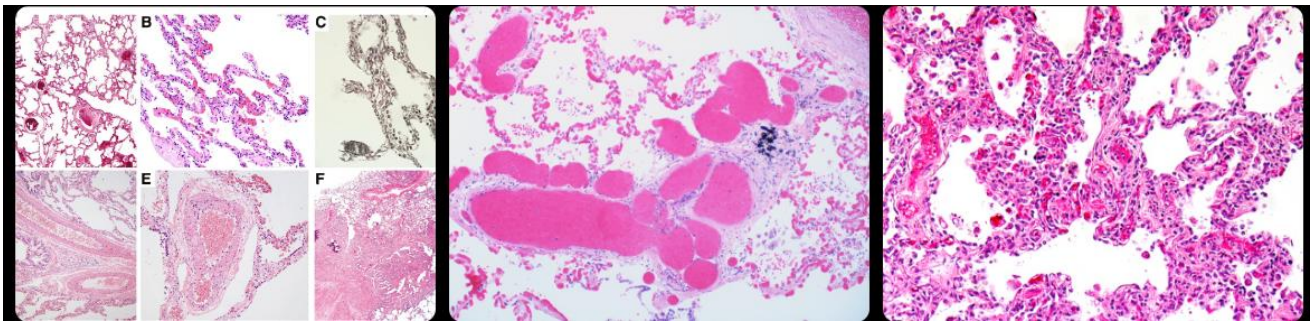

Figure 5: Histology of pulmonary capillary hemangiomatosis showing dense capillary proliferation infiltrating alveolar septa and air spaces

PAH-specific vasodilators carry a high risk of acute pulmonary edema (increased capillary flow without adequate venous drainage); however, cautious initiation may benefit selected stable patients [8]. Bilateral lung transplantation remains the only curative treatment, with a 5-year survival rate of approximately 75% [9].

CONCLUSION

PVOD should be systematically considered in cases of pulmonary hypertension associated with reduced DLCO and the characteristic radiological triad on CT [1,11]. Early suspicion allows noninvasive diagnosis, therapeutic caution, and timely referral for transplantation. Despite advances in genetics and imaging, this orphan disease remains associated with high mortality and requires management in specialized multidisciplinary expert centers [4,12].

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