

# Progression of pulmonary veno-occlusive disease without pulmonary hypertension

Sarah Beshay<sup>1</sup> | Marc Humbert<sup>2,3,4</sup> | Roberto Barrios<sup>5</sup> | Sandeep Sahay<sup>1</sup> 

<sup>1</sup>Department of Internal Medicine, Division of Pulmonary, Critical Care & Sleep Medicine, Houston Methodist Lung Center, Houston, Texas, USA

<sup>2</sup>School of Medicine, Université Paris-Saclay, Le Kremlin-Bicêtre, France

<sup>3</sup>Assistance Publique-Hôpitaux de Paris (AP-HP), Service de Pneumologie et Soins Intensifs Respiratoires, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

<sup>4</sup>INSERM UMR\_S 999, Hôpital Marie Lannelongue, Le Plessis-Robinson, France

<sup>5</sup>Department of Pathology and Genomics, Houston Methodist Hospital, Houston, Texas, USA

## Correspondence

Sandeep Sahay, Weill Cornell Medicine,  
Department of Internal Medicine,  
Houston Methodist Hospital, Houston,  
TX 77030, USA.  
Email: [ssahay@houstonmethodist.org](mailto:ssahay@houstonmethodist.org)

## Funding information

None

## Abstract

Pulmonary veno-occlusive disease (PVOD) is a progressively fatal disease with no definitive treatment options. PVOD can be a result of genetic mutation but can also be due secondary to exposure to solvents or chemotherapeutic agents. Generally, at the time of diagnosis PVOD is associated with hemodynamically confirmed pulmonary hypertension (PH). In this study, we describe a patient who was diagnosed with PVOD early in the disease without hemodynamically confirmed PH. She had histologically confirmed PVOD. Her clinical presentation posed management challenges and prednisone therapy was used to stabilize her disease. This case and some recently published reports highlight possible immune dysregulation in PVOD and role for immuno-suppressive therapy in these patients.

## KEYWORDS

drug toxicity, pulmonary hypertension, pulmonary veno-occlusive disease

## INTRODUCTION

Pulmonary veno-occlusive disease (PVOD) is an orphan disease with no treatment options. It is categorized as a rare subtype of pulmonary arterial hypertension (PAH) with features of venous/capillary involvement.<sup>1</sup> Clinically and hemodynamically, it has similarities with group 1 PAH.<sup>2,3</sup> The biallelic mutation in the gene eukaryotic translation initiation factor 2 alpha kinase 4 (*EIF2AK4*) is pathogenic and leads to the development of heritable PVOD.<sup>3</sup>

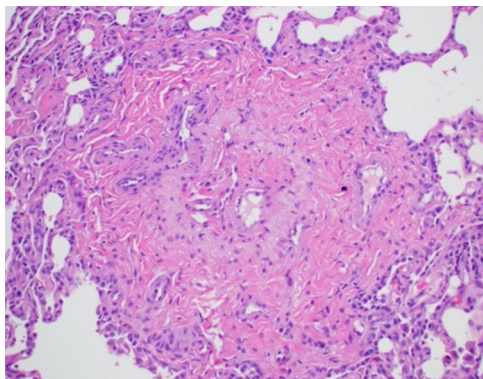
PVOD can also occur due to exposure to solvents or chemotherapeutic agents.<sup>4,5</sup> There is no approved therapy for treatment of PVOD. PAH-specific therapy may precipitate life-threatening pulmonary edema.<sup>6</sup> Recently, Bergaum et al.<sup>7</sup> published a series of patients with idiopathic and hereditary PVOD with treatment response to steroids and mycophenolate. In this study, we are presenting a case of a young woman who was diagnosed with drug-induced PVOD without pulmonary hypertension (PH) who was managed with prednisone therapy.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

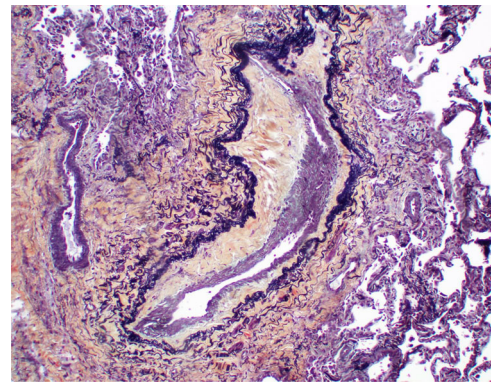
© 2022 The Authors. *Pulmonary Circulation* published by John Wiley & Sons Ltd on behalf of Pulmonary Vascular Research Institute.

## CASE REPORT

A 45-year-old woman was recently diagnosed with nodular lymphocyte predominant Hodgkin lymphoma and was treated with rituximab-cyclophosphamide, doxorubicin, vincristine, prednisone (RCHOP). A month later, she presented with worsening dyspnea. A high-resolution computed tomography (CT) chest showed interlobular septal thickening and ground-glass opacities. Dyspnea was associated with hypoxemia (PaO<sub>2</sub> 58.7 mmHg on arterial blood gas analysis). Transthoracic echocardiogram, spirometry, lung volumes were unremarkable, but the diffusion capacity of the lung for carbon monoxide (DLCO) was severely reduced to 55% predicted. Other causes of hypoxemia like pulmonary embolism were excluded. Patient was being treated at an outside cancer hospital and the treating team decided to proceed with an open lung biopsy to ascertain the cause of CT chest abnormality and hypoxemia. Biopsy findings were significant for capillary proliferation, marked intimal and medial thickening of the pulmonary arterioles, sclerosis of pulmonary veins with focal occlusion associated with dilated lymphatics (Figure 1). Special stain with movat pentachrome showed intra-alveolar hemosiderin and septal thickening with collagen deposition associated with veno-occlusive changes in pulmonary veins with sclerosis and fibrosis, together with capillary proliferation and arterial changes (Figure 2). These changes were diffusely present in pulmonary arterioles with associated changes suggesting pulmonary capillary hemangiomatosis (PCH). A diagnosis of PVOD was suspected and patient was transferred to our pulmonary vascular diseases center for further evaluation and management. Ventilation-perfusion lung scan was abnormal with multiple perfusion defects raising suspicion for chronic thromboembolic pulmonary disease (CTEPH) but pulmonary artery (PA) angiogram excluded CTEPH. Right heart catheterization (RHC) showed mean right atrial pressure of 4 mmHg,



**FIGURE 1** High magnification of an interlobular septum showing occlusion of a vein. H&E stain with 200x magnification



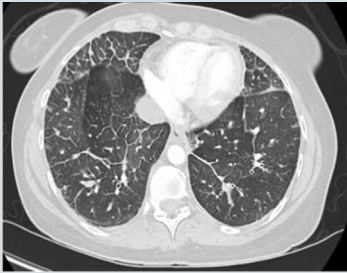


**FIGURE 2** Movat stain section showing an interlobular septum with a pulmonary vein showing thickening of the wall with marked fibrous proliferation

mean pulmonary artery pressure of 19 mmHg, mean pulmonary artery wedge pressure of 7 mmHg, preserved cardiac output (4.8 L/min), and PVR of 2.5 Wood Units (WU). A 6-min walk test showed walk distance of 388 m with oxygen desaturation to 75%. There was no evidence of left heart disease. A cardiac coronary computed tomography was done which showed normal coronaries. Left ventricular function and size was normal. In light of above evaluation and the pathology findings, a diagnosis of PVOD induced by chemotherapeutic alkylating agent (cyclophosphamide) was made. In this case, open lung biopsy helped us to establish the diagnosis, but, open lung biopsy is of high morbidity/mortality in PVOD, and risk/benefit needs to be weighed very carefully in all such patients. Faced with the management challenge in this case, with patient's permission, we discussed her case with our international colleagues with expertise in this disease. Corticosteroids were suggested, with slow taper and close monitoring. She was started on prednisone 60 mg daily with marked improvement in her symptoms. Her steroid dose was slowly tapered over a year with closely monitoring her DLCO, arterial blood gases, and echocardiograms. Table 1 shows her progression over the first 2-years following her diagnosis. Her most recent RHC (October 2020) showed hemodynamically confirmed PH and a careful trial with sildenafil and macitentan on two separate occasions required immediate discontinuation after single dose due to worsening of hypoxemia. In the last 1 year, she has been tapered off prednisone, while remaining on supplemental oxygen and is clinically stable.

## DISCUSSION

Biopsy-proven diagnosis of PVOD without PH as in our case raised difficult management question. PH is defined hemodynamically with elevation of mPAP > 20 mmHg as

**TABLE 1** Evolution of patient's clinical characteristics over 3 years of follow-up

	Diagnosis	12 months from diagnosis	24 months from diagnosis
6MWD (m)	411	513	497
RHC			
RAP (mmHg)	4	1	8
PAP (mmHg)	29/14/19	28/13/19	42/23/29
PAWP (mmHg)	7	6	14
PVR (WU)	2.5	2.8	2.7
TDCO (L/min)	4.8	4.6	5.6
TDCI (L/min/m <sup>2</sup> )	2.4	2.3	3.1
PA O <sub>2</sub> sat (%)	72		73
Chest CT			
			
DLCO (% predicted)	58	46	52

Abbreviations: 6MWD, 6-minute walk distance; Bpm, beats per minute; DLCO, diffusion lung capacity for carbon monoxide; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; RVP, right ventricular pressure; TDCI, thermodilution cardiac index; TDCO, thermodilution cardiac output; WU, Wood units.

per the proceedings of the 6th World Symposium on PH.<sup>1</sup> In PVOD, the vascular remodeling predominates in the pulmonary venules leading to rise in pressure at the post-capillary side with resultant elevated pressures at the pre-capillary side with disease progression.<sup>8,9</sup> The biallelic mutations of the *EIF2AK4* gene, are responsible for heritable form of PVOD.<sup>3</sup> In our patient genetic testing revealed heterozygous *EIF2AK4* mutation c.744-11 T > G which is a benign variant of unclear clinical significance. Our patient was treated with chemotherapy, but it is not known if her heterozygous *EIF2AK4* mutation status predisposed her to develop PVOD upon exposure to chemotherapeutic agent. Lung biopsy in our patient showed characteristic features to suggest PVOD with diffuse involvement of venules and septal veins with intimal fibrosis causing luminal narrowing and obliteration with engorgement and proliferation of the pulmonary capillaries, these findings are similar to previously reported in PVOD.<sup>2,10</sup> Our patient was recently treated with cyclophosphamide and was likely culprit factor in her case. PVOD induced by alkylating agents, bone marrow transplantation, and occupational exposure to organic solvents is very well reported.<sup>4,5,11,12</sup> This case raised management questions, as she neither had hemodynamically confirmed PH nor was eligible for lung

transplantation due to recent diagnosis of lymphoma. We possibly, diagnosed her early in the disease course due to early referral to a PH center and availability of lung biopsy findings. Use of prednisone in her management was novel. Recently, Bergaum et al.<sup>7</sup> reported the first series of use of steroids and mycophenolate in idiopathic and heritable PVOD. However, use of immunosuppressive agents in connective tissue disease-associated PVOD is very well reported.<sup>13,14</sup> There is early clinical evidence of use of tyrosine kinase inhibitor, imatinib in PVOD.<sup>15</sup> Prednisone use possibly delayed her disease progression and stabilized her symptoms. Our patient is now 3 years from diagnosis and clinically stable. Her most recent routine RHC showed mPAP of 29 mmHg and PVR 2.7 WU which is abnormal but the PVR cutoff to define PAH as per the current hemodynamic definition is  $\geq 3$  WU.<sup>1</sup> This hemodynamics clearly shows progression of disease over the last three years. Dubrock et al.<sup>16</sup> reported three cases of unexplained dyspnea where cardiopulmonary exercise testing suggested pulmonary vascular disease. Subsequent lung biopsy confirmed PCH. Two of these three patients showed no PH at the time of diagnosis like in our patient.

Our case is unique to show progression from no PH to hemodynamically confirmed PH over a period of 3 years

in patient with PVOD. It also highlights a potential role of prednisone/immunosuppressive therapy in stabilizing the disease.

In conclusion, in the absence of any proven therapy, prognosis remains poor in PVOD. The clinical improvement/stabilization upon prednisone use in our case favors immune dysregulation as an underlying mechanism playing role in its development. Further exploration of role of immunosuppressive therapy in treatment of PVOD is needed. A high index of clinical suspicion is warranted for early diagnosis and referral to an expert center.

### ACKNOWLEDGMENT

Drs. Saadia Faiz and Lara Bashoura, MD Anderson Cancer Center, Houston, Texas, USA.

### CONFLICT OF INTERESTS

Dr. Marc Humbert reports personal fees from Acceleron, grants and personal fees from Bayer, grants and personal fees from Janssen, grants and personal fees from GSK, grants and personal fees from Merck, outside the submitted work. Sandeep Sahay: Speaker and consultant for Actelion, Bayer, and United Therapeutics. Advisor for Boehringer Ingelheim, Liquidia Technologies, Gossamer Bio and Altavant Sciences. Clinical trial endpoint adjudication committee member for a GSK sponsored RCT, Research grant from ACCP CHEST Foundation. Sarah Beshay and Roberto Barrios: Nothing to disclose.

### ETHICS STATEMENT

This work was published after obtaining informed consent from the patient.

### AUTHOR CONTRIBUTIONS

Sarah Beshay: Initial draft of the manuscript and revisions. Marc Humbert: Provided guidance in patient management and writing the manuscript and critical revisions. Roberto Barrios: Pathology review and support. Sandeep Sahay: Guarantor and clinician managing this patient. Involved in patient management, revisions of the manuscript.

### ORCID

Sandeep Sahay  <http://orcid.org/0000-0002-0672-1680>

### REFERENCES

- Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53:1801913.
- Humbert M, Guignabert C, Bonnet S, Dorfmüller P, Klinger JR, Nicolls MR, Olschewski AJ, Pullamsetti SS, Schermuly RT, Stenmark KR, Rabinovitch M. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *Eur Respir J*. 2019;53:1801887.
- Eyries M, Montani D, Girerd B, Perret C, Leroy A, Lonjou C, Chelghoum N, Coulet F, Bonnet D, Dorfmüller P, Fadel E, Sitbon O, Simonneau G, Tregouët DA, Humbert M, Soubrier F. EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension. *Nat Genet*. 2014;46:65–9.
- Ranchoux B, Günther S, Quarck R, Chaumais MC, Dorfmüller P, Antigny F, Dumas SJ, Raymond N, Lau E, Savale L, Jaïs X, Sitbon O, Simonneau G, Stenmark K, Cohen-Kaminsky S, Humbert M, Montani D, Perros F. Chemotherapy-induced pulmonary hypertension: role of alkylating agents. *Am J Pathol*. 2015;185:356–71.
- Montani D, Lau EM, Descatha A, Jaïs X, Savale L, Andujar P, Bensefa-Colas L, Girerd B, Zindah I, Le Pavec J, Seferian A, Perros F, Dorfmüller P, Fadel E, Soubrier F, Sitbon O, Simonneau G, Humbert M. Occupational exposure: a risk factor for pulmonary veno-occlusive disease. *Eur Respir J*. 2015;46:1721–31.
- Palmer SM, Robinson LJ, Wang A, Gossage JR, Bashore T, Tapson VF. Massive pulmonary edema and death after prostacyclin infusion in a patient with pulmonary veno-occlusive disease. *Chest*. 1998;113:237–40.
- Bergbaum C, Samaranayake CB, Pitcher A, Weingart E, Semple T, Kokosi M, Wells AU, Montani D, Dimopoulos K, McCabe C, Kempny A, Harries C, Orchard E, Wort SJ, Price LC. The use of steroids and mycophenolate mofetil in idiopathic and heritable pulmonary veno-occlusive disease: a case series: is there a role for immunosuppression? *Eur Respir J*. 2021;57:2004354.
- Montani D, Dorfmüller P, Girerd B, Le Pavec J, Fadel E, Simonneau G, Sitbon O, Humbert M. Natural history over 8 years of pulmonary vascular disease in a patient carrying bi-allelic EIF2AK4 mutations. *Am J Respir Crit Care Med*. 2018;198:537–41.
- Montani D, Lau EM, Dorfmüller P, Girerd B, Jaïs X, Savale L, Perros F, Nossent E, Garcia G, Parent F, Fadel E, Soubrier F, Sitbon O, Simonneau G, Humbert M. Pulmonary veno-occlusive disease. *Eur Respir J*. 2016;47:1518–34.
- Pietra GG, Capron F, Stewart S, Leone O, Humbert M, Robbins IM, Reid LM, Tuder RM. Pathologic assessment of vasculopathies in pulmonary hypertension. *J Am Coll Cardiol*. 2004;43(Suppl):25S–32S.
- Certain MC, Chaumais MC, Jaïs X, Savale L, Seferian A, Parent F, Georges M, Favrolt N, Bourdin A, Boissin C, Cottin V, Traclet J, Renard S, Noel V, Picard F, Girerd B, Ghigna MR, Perros F, Sitbon O, Bonniaud P, Humbert M, Montani D. Characteristics and long-term outcomes of pulmonary veno-occlusive disease induced by Mitomycin-C. *Chest*. 2021;159:1197–207.
- Hagenburg J, Savale L, Lechartier B, Ghigna MR, Chaumais MC, Jaïs X, Sitbon O, Humbert M, Montani D. Pulmonary hypertension associated with busulfan. *Pulm Circ*. 2021;11:20458940211030170. <https://doi.org/10.1177/20458940211030170>
- Naniwa T, Takeda Y. Long-term remission of pulmonary veno-occlusive disease associated with primary Sjögren's

- syndrome following immunosuppressive therapy. *Mod Rheumatol*. 2011;21:637–40.
14. Sanderson JE, Spiro SG, Hendry AT, Turner-Warwick M. A case of pulmonary veno-occlusive disease responding to treatment with azathioprine. *Thorax*. 1977;32:140–8.
  15. Ogawa A, Miyaji K, Matsubara H. Efficacy and safety of long-term imatinib therapy for patients with pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis. *Respir Med*. 2017;131:215–9.
  16. DuBrock HM, Kradin RL, Rodriguez-Lopez JM, Channick RN. Pulmonary capillary hemangiomatosis: the role of invasive cardiopulmonary exercise testing. *Pulm Circ*. 2015;5:580–6.

**How to cite this article:** Beshay S, Humbert M, Barrios R, Sahay S. Progression of pulmonary veno-occlusive disease without pulmonary hypertension. *Pulm Circ*. 2022;12:e12046. <https://doi.org/10.1002/pul2.12046>