



Case report

Pulmonary hypertension secondary to pulmonary veno-occlusive disease complicated by right heart failure, hypotension and acute kidney injury



Nima Golzy^{a,*}, Stuti Fernandes^{b,c}, Justin Sharim^a, Rikin Tank^{b,c}, Henry D. Tazelaar^d, Howard E. Epstein^e, Victor Tapson^{b,c}, Antoine Hage^{b,c}

^a Department of Internal Medicine, David Geffen School of Medicine at UCLA, 757 Westwood Plaza, Suite 7501, Los Angeles, CA 90095, USA

^b Pulmonary Hypertension Program, Department of Pulmonology, Cedars-Sinai Medical Center, 127 South San Vicente Blvd, Suite A3600, Los Angeles, CA 90048, USA

^c Department of Solid Organ Transplant Cardiology, Cedars-Sinai Medical Center, 127 South San Vicente Blvd, Suite A3600, Los Angeles, CA 90048, USA

^d Department of Pathology, Mayo Clinic, 13400 East Shea Blvd, Scottsdale, AZ 85259, USA

^e Department of Pathology, Hoag Hospital, 1 Hoag Dr, Newport Beach, CA 92663, USA

ARTICLE INFO

Article history:

Received 31 January 2016

Received in revised form

23 September 2016

Accepted 25 September 2016

Keywords:

Pulmonary veno-occlusive disease

Pulmonary hypertension

Lung biopsy

Epoprostenol

ABSTRACT

Pulmonary veno-occlusive disease (PVOD) is rare condition which can lead to severe pulmonary hypertension, right ventricular dysfunction, and cardiopulmonary failure. The diagnosis of PVOD can be challenging due to its nonspecific symptoms and its similarity to idiopathic pulmonary arterial hypertension and interstitial lung disease in terms of diagnostic findings. This case describes a 57 year old female patient who presented with a 5-month history of progressive dyspnea on exertion and nonproductive cough. Workup at another hospital was nonspecific and the patient underwent surgical lung biopsy due to concern for interstitial lung disease. She subsequently became hemodynamically unstable and was transferred to our hospital where she presented with severe hypoxemia, hypotension, and suprasystemic pulmonary artery pressures. Preliminary lung biopsy results suggested idiopathic pulmonary arterial hypertension and the patient was started on vasodilating agents, including continuous epoprostenol infusion. Pulmonary artery pressures decreased but remained suprasystemic and the patient did not improve. Final review of the biopsy by a specialized laboratory revealed a diagnosis of PVOD after which vasodilating therapy was immediately weaned off. Evaluation for dual heart-lung transplantation was begun. The patient's hospital course was complicated by hypotension requiring vasopressors, worsening right ventricular dysfunction, and acute kidney injury. During the transplantation evaluation, the patient decided that she did not want to undergo continued attempts at stabilization of her progressive multi-organ dysfunction and she was transitioned to comfort care. She expired hours after removing inotropic support.

© 2017 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Background

Pulmonary veno-occlusive disease (PVOD) is a rare cause of pulmonary arterial hypertension (PAH) in which the pulmonary venules and small veins undergo intimal fibrosis, leading to pulmonary hypertension, interstitial and pleural edema, and right ventricular failure [1]. PVOD has been associated with connective tissue diseases, HIV infection, bone marrow transplantation, and

chemical exposures but is idiopathic in the majority of cases [2]. Definitive diagnosis requires lung biopsy for histology but acquiring such a tissue specimen is usually contraindicated in patients with respiratory and hemodynamic instability [3]. Although there are alternative diagnostic tests that are less invasive than biopsy, without histology it can be difficult to differentiate PVOD from idiopathic PAH and interstitial lung disease (ILD) [4]. Treatments for PVOD reported in the literature have included PAH-specific therapies, which are associated with an increased risk of pulmonary edema, but which may act as a bridge to lung or combined lung-heart transplantation [5].

* Corresponding author.

E-mail address: ngolzy@mednet.ucla.edu (N. Golzy).

2. Case description

A 57-year-old female presented with a 5-month history of progressively worsening dyspnea and non-productive cough. Her symptoms were initially associated only with moderate exertion, but progressed to dyspnea at rest. Her medical history was significant for hypertension for which she had been taking a combination angiotensin receptor blocker-thiazide diuretic for 20 years; she was a lifetime non-smoker and had no other significant history of cardio-pulmonary disease. Her past surgical, family, and social history were otherwise non-contributory. On presentation, she was severely hypoxemic and hypotensive. Cardiac exam revealed a loud second heart sound, ventricular gallop (S3), parasternal heave, and tachycardia. Pulmonary exam was significant for increased work of breathing and bilateral rhonchi. Her extremities showed significant bilateral pitting edema up to her thighs. The remainder of her exam was unremarkable.

Four months prior to admission, the patient had a transthoracic echocardiogram suggestive of mild-moderate pulmonary hypertension with pulmonary arterial (PA) systolic pressure of approximately 40 mmHg as well as evidence of septal flattening. Subsequent left and right-heart catheterization revealed a PA pressure of 50/19 (mean 31) and non-obstructive coronary artery disease. Despite aggressive diuresis with furosemide and vasodilator therapy with sildenafil, the patient continued to have worsening dyspnea with associated palpitations.

Prior to admission to our hospital, she underwent an extensive pulmonary hypertension workup that revealed worsening PA systolic pressure of approximately 80 mmHg, increased septal flattening with D-shaped left ventricle, and moderate right ventricular

dilatation. After diuresis, computed tomographic angiography (CTA) of the chest showed nonspecific mild reticular interstitial changes concerning for ILD with no evidence of pulmonary embolism. Pulmonary function tests were significant for a diffusing capacity of the lungs for carbon monoxide at 41% of the predicted value. Laboratory testing including thyroid function, HIV, and ANA was unremarkable.

At this point, given the concern for ILD as suggested by the patient's severe hypoxemia, CTA, and pulmonary function tests, a decision was made at the outside hospital to perform a bronchoscopy and video-assisted thoracoscopic lung biopsy, a course of action which we would not have recommended. The procedure was complicated by pulseless electrical activity arrest immediately after anesthesia induction. The patient underwent cardiopulmonary resuscitation for less than 5 minutes at which point return of spontaneous circulation was attained and the procedure was completed. Subsequently, the patient became hypotensive and required inotropic support with dopamine and milrinone. Preliminary lung biopsy results were consistent with idiopathic PAH (IPAH); biopsy slides were sent to a specialized outside laboratory (Fig. 1). The patient was then transferred to a nearby hospital for consultation and therapy. She had a Swan-Ganz catheter placed showing suprasystemic PA pressure of 104/46 (mean 67) mm/Hg; pulmonary capillary wedge pressure was 10 mmHg with an augmented cardiac output of 4.98 L/min. The patient was started on treatment for IPAH including vasodilation with inhaled nitric oxide, sildenafil, and epoprostenol. The patient had mild improvement in her PA pressure but remained hypoxemic and symptomatically dyspneic.

Two days after initiation of vasodilating agents, final review of

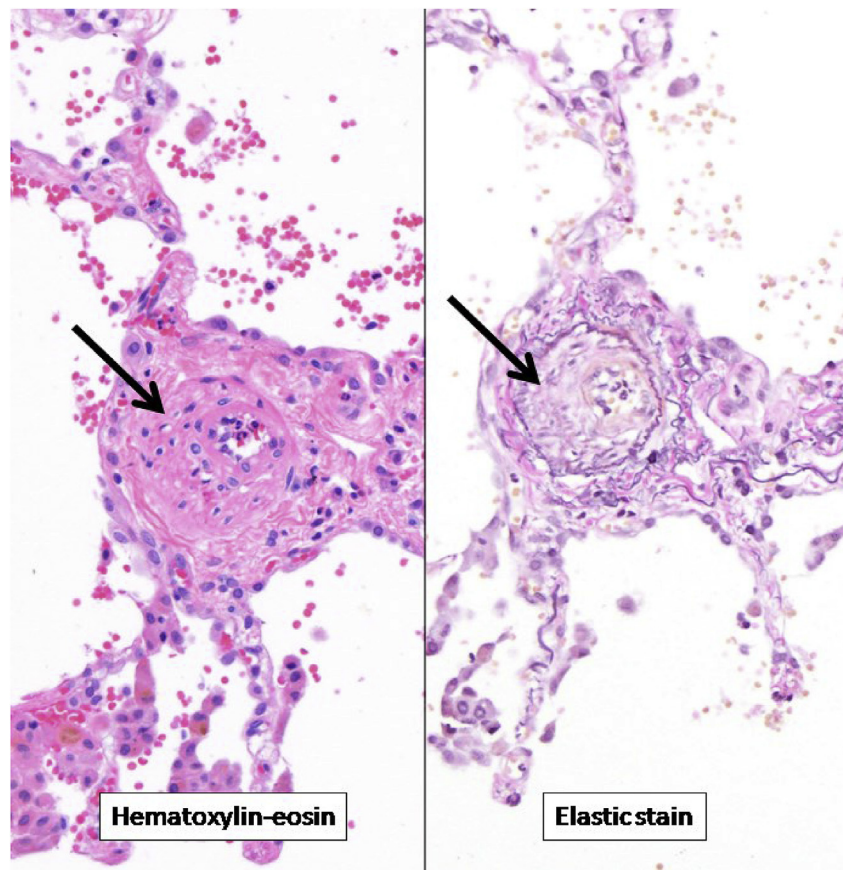


Fig. 1. Lung biopsy pathology slides. Subpleural vein in intralobular septum with luminal compromise by proliferating fibrous tissue (arrows).

the biopsy revealed PVOD rather than IPAH. Epoprostenol was weaned off given the risk of iatrogenic pulmonary edema with PA vasodilation in the setting of PVOD. The patient then underwent evaluation for a dual heart-lung transplant given her persistent symptoms and severe hypoxemia with suprasystemic PA pressures. During the course of this evaluation, the patient decided that she did not want to undergo the continued attempts at stabilization of her progressive multi-organ dysfunction as it was not within her maximal tolerable burden of therapy. The patient was transitioned to comfort care and expired a few hours after removing her inotropic support.

3. Discussion

PVOD is a rare cause of pulmonary hypertension that is usually diagnosed late in the disease course and has a very poor prognosis. The annual incidence of PVOD is estimated at 0.1 to 0.2 cases per million persons with many cases misdiagnosed as other etiologies of IPAH [6]. Most cases of PVOD are idiopathic but the disease has also been reported in association with connective tissue diseases, HIV infection, bone marrow transplant, and exposure to anorexigens and some chemotherapeutic agents [2]. Histologically, the predominant lesion is intimal fibrosis occurring most commonly in small veins. This fibrosis causes obstruction of pulmonary veins, resulting in pulmonary capillary congestion, interstitial and pleural edema, lymphadenopathy, and alveolar hemosiderosis [1]. Pulmonary arterial occlusion also occurs in as many as half of patients with PVOD [7]. Chronically, patients develop PAH, right ventricular dysfunction, and in spite of medical therapy, progress to cardiopulmonary failure.

PVOD can be difficult to diagnose and patients usually progress to a New York Heart Association functional class III or IV before histological confirmation [2]. The difficulty in diagnosing PVOD is due to its nonspecific symptoms and clinical findings which are also compatible with IPAH, which occurs more commonly than PVOD.

Definitive diagnosis requires histological examination of lung tissue but a biopsy is usually contraindicated in patients with advanced disease and tenuous hemodynamic status. If a biopsy is to be performed, the anesthesiologist should be aware of the diagnosis of pulmonary hypertension since the risk of right-sided heart failure is markedly increased. Additionally, optimal pulmonary blood flow should be maintained throughout the procedure [8]. The patient described in this report had PEA arrest during bronchoscopy at the outside hospital. Moreover, the patient was initially diagnosed with IPAH before a second reading of her lung biopsy slides revealed a diagnosis of PVOD. This case thus highlights the importance of confirming preliminary pathology reports and underscores the risks of invasive procedures in the context of significant cardiopulmonary disease.

Clinical suspicion must be high in order to diagnose PVOD. Approximately 10% of patients thought to have IPAH actually have PVOD [6]. A case series showed that 12 of 14 patients with clinically diagnosed PAH who failed to respond to medical therapy actually had PVOD on examination of lung tissue [9]. Guidelines for the diagnosis and treatment of pulmonary hypertension recommend noninvasive tests when evaluating a patient for PVOD [3]. With the exception of a reduced DLCO, pulmonary function tests are usually within normal limits in patients with PVOD. In patients with presumed PAH, a DLCO <55% has a sensitivity of 64.3% and specificity of 89.5% for a diagnosis of PVOD [10]. High resolution CT often shows centrilobular ground-glass opacities, thickened septal lines, and mediastinal lymph node enlargement. Bronchoalveolar lavage, although not required in all patients being evaluated for PAH, may be performed to detect an increased alveolar cell count with an elevated percentage of hemosiderin-laden macrophages, a finding that favors PVOD over other causes of PAH [2].

A common complication of PAH is right ventricular dysfunction. On presentation, our patient required vasoactive support which could not be weaned off. Before PVOD was diagnosed, PAH-specific therapies (inhaled nitric oxide, sildenafil, and epoprostenol) were

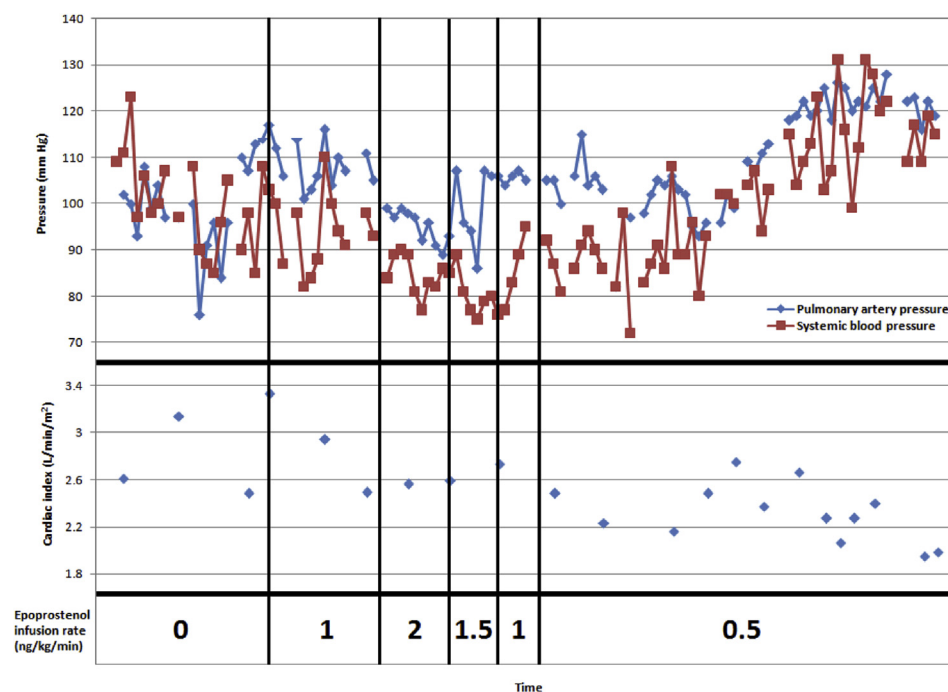


Fig. 2. Pulmonary artery systolic pressure, systemic systolic blood pressure, and cardiac index in response to epoprostenol infusion. During epoprostenol infusion, pulmonary artery pressures remained suprasystemic. Weaning off epoprostenol resulted in increases in both pressures but did not improve the patient's cardiac index, which continued to decline.

started in sequential manner. After epoprostenol was started, the patient's pulmonary and systemic pressures both decreased, but she remained severely hypoxemic and pulmonary pressures remained suprasystemic. When a second pathology reading confirmed PVOD as the diagnosis, epoprostenol was weaned off due to the concern for pulmonary edema in PVOD patients being treated with vasodilators [2,5]. Discontinuation of epoprostenol resulted in subsequent increases in systemic and pulmonary pressures. During this time, progressively increasing pulmonary artery pressures were associated with a decline in cardiac index (Fig. 2), likely due to increased right ventricular dysfunction. The patient's complaint of shortness of breath remained constant during hospitalization and she continued to have an extremely high oxygen requirement.

Our patient also developed acute kidney injury, most likely of cardiorenal etiology. Clinically, serum creatinine doubled, blood urea nitrogen (BUN) progressively increased, lower extremity edema worsened, and the patient became oliguric. Diuresis with maximum doses of intravenous bumetanide and oral metolazone resulted in increases in urine output but did not normalize the creatinine or BUN. Numerous discussions were had between consultants on diuresis goals given the tenuous balance between maintaining perfusion in the context of a preload-dependent state and the risk of persistent vascular congestion leading to pulmonary edema. This case highlights the difficulty in managing fluid status in patients diagnosed with PVOD.

The use of PAH-specific therapies in treating PVOD requires close clinical surveillance because of the risk of pulmonary edema that comes with preferential dilation of pulmonary arteries. The literature includes a case of PVOD where a patient expired after she developed acute pulmonary edema and respiratory failure following initiation of low-dose prostacyclin infusion [11]. More recently, cautious administration of epoprostenol has been shown to temporarily improve clinical and hemodynamic parameters in some patients with PVOD, acting as a bridge to lung transplantation [5]. Although all classes of PAH-specific vasodilators are associated with pulmonary edema in PVOD patients, another report describes a case with a patient who experienced worsening hypoxemia after starting low-dose epoprostenol but improved with other vasodilating agents [12]. Similarly, our patient did not tolerate low-dose epoprostenol as she was hypotensive despite inotropic support. Had she continued to receive epoprostenol, she might have decompensated even further. For most of her hospitalization, however, she was maintained on inhaled nitric oxide and oral sildenafil. Although there is evidence that epoprostenol infusion can be helpful in some PVOD patients, our case and other cases previously reported suggest that not all patients with PVOD will gain

benefit from prostacyclin therapy.

In conclusion, PVOD is a rare cause of PAH and is usually diagnosed late in the course of disease. There is no clearly demonstrated effective nonsurgical therapy and it is unclear which patients will benefit from prostacyclin infusion as a bridge to lung transplantation, which is the only effective treatment for PVOD. The patient in this case experienced hypotension secondary to severe right ventricular dysfunction and epoprostenol infusion which resulted in acute kidney injury. When treating patients with PAH, it is important to make an accurate diagnosis quickly while weighing the risks and benefits of various diagnostic tests and therapeutic options. Vasodilator therapy in PVOD, if started, must be done so cautiously. Finally, management of fluids in patients with cardiogenic shock and acute kidney injury is difficult and should be done in consultation with a cardiologist and nephrologist.

References

- [1] A.P. Fishman, Pulmonary veno-occlusive disease, in: A.P. Fishman (Ed.), Pulmonary Circulation: Normal and Abnormal: Mechanisms, Management, and the National Registry, University of Pennsylvania Press, Philadelphia, PA, 1990.
- [2] D. Montani, L.C. Price, P. Dorfmueller, et al., Pulmonary veno-occlusive disease, *Eur. Respir. J.* 33 (1) (2009) 189–200.
- [3] N. Galie, M. Humbert, J.L. Vachiery, et al., 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European society of cardiology (ESC) and the European respiratory society (ERS) endorsed by: association for European paediatric and congenital cardiology (AEPC), International society for heart and lung transplantation (ISHLT), *Eur. Heart J.* 37 (1) (2016) 67–119.
- [4] M. Palazzini, A. Manes, Pulmonary veno-occlusive disease misdiagnosed as idiopathic pulmonary arterial hypertension, *Eur. Respir. Rev.* 18 (113) (2009) 177–180.
- [5] D. Montani, X. Jais, L.C. Price, et al., Cautious epoprostenol therapy is a safe bridge to lung transplantation in pulmonary veno-occlusive disease, *Eur. Respir. J.* 34 (6) (2009) 1348–1356.
- [6] J. Mandel, E.J. Mark, C.A. Hales, Pulmonary veno-occlusive disease, *Am. J. Respir. Crit. Care Med.* 162 (2000) 1964–1973.
- [7] C.A. Wagenvoort, N. Wagenvoort, T. Takahashi, Pulmonary veno-occlusive disease: involvement of the pulmonary arteries and review of the literature, *Hum. Pathol.* 16 (1985) 1033–1041.
- [8] G. Blaise, D. Langleben, B. Hubert, Pulmonary arterial hypertension: pathophysiology and anesthetic approach, *Anesthesiology* 99 (2003) 1415–1432.
- [9] S. Harch, H. Whitford, C. McLean, Failure of medical therapy in pulmonary arterial hypertension: is there an alternative diagnosis? *Chest* 135 (6) (2009) 1462–1469.
- [10] D. Montani, L. Achouh, P. Dorfmueller, et al., Pulmonary veno-occlusive disease: clinical, functional, radiologic, and hemodynamic characteristics and outcome of 24 cases confirmed by histology, *Medicine* 87 (4) (2008) 220–233.
- [11] S.M. Palmer, L.J. Robinson, A. Wang, J.R. Gossage, T. Bashore, V.F. Tapson, Massive pulmonary edema and death after prostacyclin infusion in a patient with pulmonary veno-occlusive disease, *Chest* 113 (1) (1998) 237–240.
- [12] E. Sourla, A. Paspala, A. Boutou, P. Kontou, I. Stanopoulos, G. Pitsiou, A case of pulmonary veno-occlusive disease: diagnostic dilemmas and therapeutic challenges, *Ther. Adv. Respir. Dis.* 7 (2) (2013) 119–123.