Respiratory Medicine Case Reports 20 (2017) 82–86

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Pulmonary veno-occlusive disease: Two children with gradual disease progression☆

Ronald W. Day [a, *], Parker W. Clement [b], Aimee O. Hersh [a], Susan M. Connors [c], Kelli L. Sumner [d], D. Hunter Best [d], Mouied Alashari [b]

[a] University of Utah Department of Pediatrics, 81 North Mario Capecchi Drive, Salt Lake City, UT 84113, USA
[b] University of Utah Department of Pathology, 15 North Medical Drive, Suite 1100, Salt Lake City, UT 84132, USA
[c] Vascular Biology Program of Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA
[d] ARUP Institute for Clinical and Experimental Pathology, 500 Chipeta Way, Salt Lake City, UT 84108, USA

ARTICLE INFO

Article history:
Received 28 November 2016
Received in revised form
27 December 2016
Accepted 27 December 2016

Keywords:
Pulmonary arterial hypertension
Pulmonary capillary hemangiomatosis
Pulmonary veno-occlusive disease

ABSTRACT

Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis are rare forms of pulmonary vascular disease. We report two cases of affected children who had evidence of pulmonary hypertension 3–5 years before developing radiographic findings of pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis. Both patients experienced a moderate decrease in pulmonary arterial pressure during acute vasodilator testing. Both patients experienced an improvement in six-minute walk performance without an increase in pulmonary edema when treated with targeted therapy for pulmonary hypertension. In some patients, pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis may progress slowly over a period of months to years. A favorable acute vasodilator response may identify patients who will tolerate, and demonstrate transient clinical improvement with, medical therapy.

1. Introduction

Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are rare forms of pulmonary vascular disease [1]. In adults, these disorders have distinct histological findings, yet are sometimes observed together in the same patient [2,3]. Affected patients often present with advanced disease and frequently respond poorly to medical therapy. Several clinical, functional, radiographic, and hemodynamic characteristics of PVOD have been described in adults and children [4–6]. However, little is known concerning the progression of PVOD and PCH because most patients are usually not identified before they develop an advanced stage of disease.

Montani and associates reported a mean interval of 11.8 months from diagnosis to death or lung transplantation in a series of predominantly adult patients with PVOD [4]. The interval between the diagnosis of pulmonary hypertension and PVOD was not reported. Woerner and associates reported a mean interval of 21 months (range of 0–47 months) from diagnosis to death or lung transplantation in a series of children with PVOD [5]. The mean interval between the diagnosis of pulmonary hypertension and the diagnosis of PVOD was less than one year [5]. We provided care for two individuals who had evidence of pulmonary hypertension 3–5 years before developing radiographic findings of pulmonary edema, septal thickening, ground glass opacification, or centrilobular nodules. This allowed us to retrospectively review echocardiographic findings, hemodynamic measurements, sub-maximal exercise tests, levels of B-type natriuretic peptide, and the response to medical therapy for pulmonary hypertension before their deaths. The patients were included in a retrospective study that was approved by the Institutional Review Board of the University of Utah. The medical records of each patient were reviewed. Pertinent clinical findings are reported descriptively without a statistical analysis.

Abbreviations: PCH, Pulmonary Capillary Hemangiomatosis; PVOD, pulmonary veno-occlusive disease.

☆ Institution where work was performed: Primary Children's Hospital, 100 North Mario Capecchi Drive, Salt Lake City, UT 84113, USA.

* Corresponding author.
E-mail addresses: ronald.day@hsc.utah.edu (R.W. Day), parker.clement@hsc.utah.edu (P.W. Clement), aimee.hersh@hsc.utah.edu (A.O. Hersh), susan.connors@childrens.harvard.edu (S.M. Connors), kelli.sumner@aruplab.com (K.L. Sumner), hunter.best@aruplab.com (D.H. Best), mouied.alashari@imail2.org (M. Alashari).

http://dx.doi.org/10.1016/j.rmcr.2016.12.007

2. Case reports

2.1. Case 1

A 6-year old girl presented in critical condition with acute respiratory failure, pulmonary edema and severe pulmonary hypertension. She had symptoms of dyspnea, exercise intolerance and syncope for a period of approximately two months. Her pulmonary edema rapidly progressed and she died after six days while being treated with milrinone, epoprostenol, epinephrine and inhaled nitric oxide. She had histological evidence of PVOD and PCH. A 9-year old sister (Case 1) was identified with evidence of pulmonary hypertension by using echocardiography to screen family members. She was referred to our program 3 years after her initial evaluation. Her functional class, the results of pertinent diagnostic studies and the medications that were used over time are presented in Table 1.

She did not consistently use supplemental oxygen. However, she tolerated oxygen and medication changes without an acute change in the severity of pulmonary edema. Her parents also treated her with fish oil, vitamins and colloidal silver. She gradually developed progressive pulmonary hypertension and right heart failure while being treated with supplemental oxygen, digoxin and aspirin. We treated her cautiously with medications for pulmonary hypertension due to concerns that she would develop severe pulmonary edema. Sildenafil was started 1 month before her 6-min walk performance of 200 m. Her 6-min walk performance improved to 288 m 19 months after starting sildenafil and 8 months after starting simvastatin. She was treated with sildenafil for 29 months, simvastatin for 18 months and iloprost for 1 month before her death at 14 years of age. She and her family declined the option for lung transplantation from the onset of care. She died nearly 6 years after her initial evaluation. Pulmonary hypertension and right heart failure appeared to have a greater role in her demise than pulmonary edema and hypoxemia. Histological findings consistent with PVOD and PCH in her lung following death are shown in Fig. 1. There was also evidence of pulmonary arterial muscular hypertrophy in other histological sections. Of note, the vascular changes of PVOD and PCH were less severe in the upper lobes of her lung. Sanger sequencing of the *EIF2AK4* gene on DNA extracted from frozen lung tissue did not reveal causative mutations. Urinary basic fibroblast growth factor (4911 pg/l) and vascular endothelial growth factor (69 pg/ml) levels were only mildly elevated or normal. Urinary matrix metalloproteinases (MMP) were present and quantified by scoring the band intensity which correlates to the level of each type of MMP examined on a zymogram using a scale of zero to six, with zero indicating the absence of MMP species and six indicating strong MMP activity. While being treated with sildenafil and simvastatin, her urine contained three species of MMPs: MMP-9 (intensity score of four), MMP-9/NGAL (Neutrophil Gelatinase-Associated Lipocalin; Lipocalin 2) complex (intensity score of three) and MMP-2 (intensity score of one). An individual assigned these scores before the patient's death with no knowledge of the patient's hemodynamic measurements or radiographic findings. There was no evidence of stenosis in large pulmonary veins by echocardiography, angiography or histology. She had no history of

Table 1
Progression of disease and therapy for Case 1.

Age, years	9	10	11	12	13	14
Functional class	I	II	III	III	III	IV
Six-minute walk distance, m			335	200	288	
Pulmonary function tests						
Diffusion	Normal			Normal		
Obstructive ventilatory defect	Mild			Mild		
Restrictive ventilatory defect	None			Mild		
Response to albuterol[a]	Yes			Yes		
Electrocardiogram						
RAD, RVH	No	No	Yes	Yes	Yes	Yes
Echocardiogram						
TVR Gradient, mm Hg	40	40	52	119	131	162
LVSF/LVEF, %	41/61	40/-	50/77	64/-	59/-	56/77
Thin-section, high resolution CT scan of the lung						
Evidence of PVOD[b]	No	No		Yes		
Hemodynamic measurements						
Mean PAP, mm Hg	49			66		
Mean PCWP, mm Hg	11			8		
CI, L/min-m^2	3.1			3.2		
Mean PAP, mmHg with AVT[c]	28			45		
B-type Natriuretic Peptide, pg/ml				258	255	1519
Medical therapy						
Fluticasone/beta-agonists	Yes	Yes		Yes		
Montelukast	Yes	Yes				
Oxygen			Yes	Yes	Yes	Yes
Digoxin				Yes	Yes	Yes
Diuretics						Yes
Aspirin				Yes	Yes	Yes
Sildenafil				Yes	Yes	Yes
Simvastatin					Yes	Yes
Arginine chloride					Yes	Yes
Doxycycline						Yes
Inhaled Iloprost						Yes

AVT: acute vasodilator testing, CI: cardiac index, CT: computerized tomography, LVEF: left ventricular ejection fraction, LVSF: left ventricular shortening fraction, PAP: pulmonary arterial pressure, PCWP: pulmonary capillary wedge pressure, PVOD: pulmonary veno-occlusive disease, RAD: right axis deviation, RVH: right ventricular hypertrophy or enlargement, TVR: Tricuspid valve regurgitation.

[a] Favorable response to albuterol: greater than 20% increase in Forced Expiratory Flow 25–75%.

[b] CT scan of the lung with evidence of PVOD: extensive, patchy centrilobular ground-glass opacities; ill-defined nodular densities; and interlobular septal thickening.

[c] Lowest MPAP: response to 100% oxygen or 100% oxygen with 20 parts per million inhaled nitric oxide.

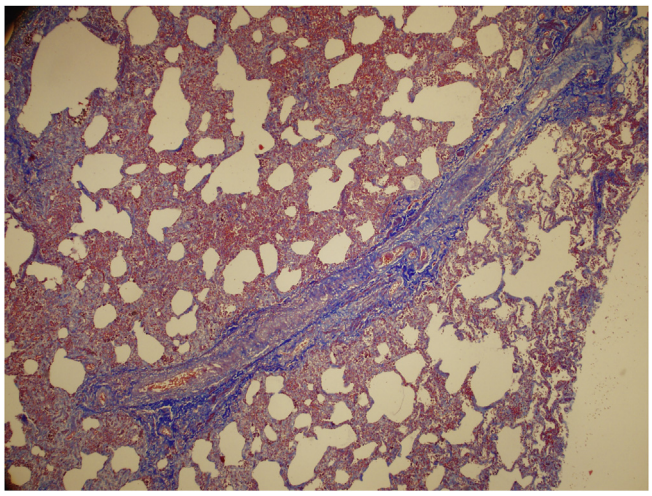

Fig. 1. Histological findings of pulmonary veno-occlusive disease in Case 1. Trichrome stain demonstrating findings consistent with pulmonary veno-occlusive disease. There is collagenous (blue) obliteration of a prominent interlobular septal vein as well as scattered background fibrotic vessels and pulmonary capillary hemangiomatosis.

malignancy, treatment with radiation or treatment with chemotherapy. Anti-nuclear antibody was not detected. Antibodies for the human immunodeficiency virus were not evaluated. Variants in Factor V Leiden (p.Arg506Gln) and Prothrombin c.*97G > A were not detected. No lupus anticoagulant was detected, including antibodies for cardiolipin. Variants in methylenetetrahydroflolate reductase c.665C > T and c.1286A > C were not evaluated. She was not evaluated for Toxoplasmosis. She was not exposed to tobacco smoke in the home. She was never treated with anorexigens.

2.2. Case 2

An 8-year old girl with a history of oligoarticular juvenile idiopathic arthritis presented with a large pericardial effusion and a small right pleural effusion. She underwent placement of a pericardial drainage catheter. At that time, an electrocardiogram showed evidence of right axis deviation and right ventricular hypertrophy or enlargement. Echocardiograms were focused on the size of her pericardial effusion without reported evidence of increased pulmonary arterial pressure. She subsequently developed a progressive overlap connective tissue disease with features of systemic lupus erythematosus and juvenile idiopathic arthritis. Anti-nuclear antibody was detected with a titer of 1:320. Five years after her initial electrocardiogram, an evaluation of right lower quadrant pain with an abdominal CT angiogram showed incidental evidence of a pericardial effusion. On the same day, an echocardiogram also showed evidence of pulmonary hypertension and decreased right ventricular function. Thin-section CT angiography of the lung was performed to evaluate for a pulmonary embolus. The images revealed changes consistent with PVOD with no evidence of pulmonary thromboembolic disease. Her functional class, the results of pertinent diagnostic studies and the medications that were used for treatment are presented in Table 2. Her functional class was not evaluated before a diagnosis of pulmonary hypertension was established by heart catheterization. Reliable pulmonary function tests could not be performed due to severe temporal-mandibular joint arthritis resulting in severely limited jaw excursion.

She consistently used supplemental oxygen and all of her medications. She tolerated each medication without an acute change in the severity of pulmonary edema and her pulmonary

Table 2
Progression of disease and therapy for Case 2.

Age, years	8	9	10	11	12	13	14
Functional class						III	III
Six-minute walk distance, m						244	300
Electrocardiogram							
RAD, RVH	Yes					Yes	Yes
Echocardiogram							
TVR Gradient, mm Hg						100	60
LVSF/LVEF, %	44/74					61/-	-/79
Thin-section CT angiogram of the lung							
Evidence of PVOD[a]						Yes	
Hemodynamic measurements							
Mean PAP, mm Hg						60	
Mean PCWP, mm Hg						13	
CI, L/min-m^2						2.2	
Mean PAP, mmHg with AVT[b]						43	
B-type Natriuretic Peptide, pg/ml						2916	58
Medical therapy							
Fluticasone/Beta-agonists	Yes	Yes				Yes	
Cetirizine	Yes	Yes	Yes				
Montelukast	Yes				Yes	Yes	
Prednisone	Yes	Yes		Yes	Yes	Yes	
Cyclosporin		Yes	Yes	Yes			
Hydroxychloroquine	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Meloxicam					Yes	Yes	
Rituximab					Yes		
Methotrexate/Folic acid						Yes	Yes
Narcotics	Yes					Yes	
Lansoprazole	Yes						
Acyclovir				Yes			
Valaciclovir					Yes	Yes	
IVIG					Yes		
Oxygen						Yes	Yes
Digoxin						Yes	Yes
Diuretics						Yes	Yes
Amlodipine	Yes						
Tadalafil						Yes	Yes
Ambrisentan						Yes	Yes
Inhaled Treprostinil						Yes	Yes

AVT: acute vasodilator testing, CI: cardiac index, CT: computerized tomography, LVEF: left ventricular ejection fraction, LVSF: left ventricular shortening fraction, PAP: pulmonary arterial pressure, PCWP: pulmonary capillary wedge pressure, PVOD: pulmonary veno-occlusive disease, RAD: right axis deviation, RVH: right ventricular hypertrophy or enlargement, TVR: Tricuspid valve regurgitation.

[a] CT scan of the lung with evidence of PVOD: extensive, patchy centrilobular ground-glass opacities; ill-defined nodular densities; and interlobular septal thickening.

[b] Lowest MPAP: response to 51% oxygen with 0.08 mg/kg intravenous sildenafil.

hypertension appeared to be improving. Unfortunately, she died unexpectedly from pneumococcal bacteremia at 14 years of age. The histological findings of PCH in her lung following death are shown in Fig. 2. There was also evidence of PVOD and evidence of muscular hypertrophy, intimal proliferation and sparse occlusive changes in the pulmonary arteries of other histological sections. Of note, the vascular changes of PVOD and PCH were less severe in the upper lobes of her lung. Due to a lack of available tissue, molecular testing for mutations in the *EIF2AK4* gene was not performed. Soon after the onset of treatment with sildenafil, before other medications were approved by her insurance, urinary basic fibroblast growth factor (2388 pg/l) and vascular endothelial growth factor (66 pg/ml) levels were normal. Her urine contained three species of MMPs: a dimer of MMP-9 (intensity score of four), MMP-9/NGAL complex (intensity score of four) and MMP-2 (intensity score of five). An individual assigned these scores before the patient's death with no knowledge of the patient's hemodynamic measurements or radiographic findings. There was no evidence of stenosis in large pulmonary veins by echocardiography, angiography or histology. She had no history of malignancy, treatment with radiation or treatment with chemotherapy. Antibodies for the human

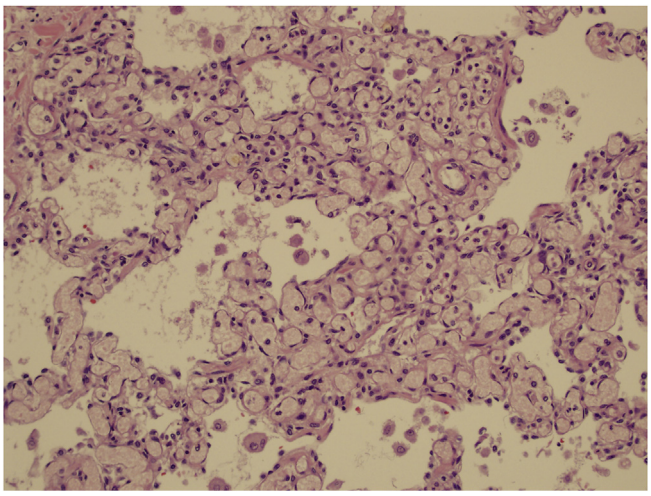

Fig. 2. Histological findings of pulmonary capillary hemangiomatosis in Case 2. Hematoxylin and Eosin stain showing alveolar septa with numerous capillary-size blood vessels consistent with pulmonary capillary hemangiomatosis.

immunodeficiency virus were not detected. Variants in Factor V Leiden (p.Arg506Gln) and Prothrombin c.*97G > A were not detected. No lupus anticoagulant was detected, including antibodies for cardiolipin and β2glycoprotin. She was compound heterozygous for variants in methylenetetrahydroflolate reductase c.665C > T and c.1286A > C. She was not evaluated for Toxoplasmosis. She was not exposed to tobacco smoke in the home. She was never treated with anorexigens.

3. Discussion

PVOD and PCH are life-threatening forms of pulmonary vascular disease that typically respond poorly to medical therapy. The presence of a common genetic association suggests that these pathological findings are different manifestations of a similar disease process [7,8]. Our cases provided a unique opportunity to observe the progression of disease over time. They had evidence of pulmonary hypertension years before they had CT scans with evidence of PVOD or PCH: including pulmonary edema, septal thickening, ground glass opacification, or centrilobular nodules [9]. One patient had two previous CT scans without these findings when her pulmonary hypertension was moderately severe.

Our patients had histological findings of less extensive PVOD or PCH in the upper lung segments. They experienced a moderate decrease in mean pulmonary arterial pressure during acute pulmonary vasodilator testing. They also showed improvement in six-minute walk distance while being treated with a phosphodiesterase V inhibitor, statin, endothelin receptor antagonist or prostacyclin analog. Montani and associates have claimed that an acute response to nitric oxide does not imply that a patient will have a favorable early result from pulmonary vasodilators [4]. This claim was based upon the outcome of a single patient who developed pulmonary edema while being treated with a calcium channel blocker, but tolerated treatment with bosentan for a period of 8 months. In addition, pulmonary edema occurred in only 7 of the 16 patients with PVOD that they treated with a calcium channel blocker, bosentan, iloprost or epoprostenol. Our findings, and the findings of others, suggest that acute vasodilatory testing may help to identify a subset of children or adults with PVOD or PCH who could benefit from therapy while waiting for lung transplantation [6,10]. Montani and associates used the Sitbon criteria to identify a single responder to acute vasodilator testing. The accuracy of the Sitbon criteria was 79% in patients with pulmonary arterial hypertension [11]. It is not clear whether the accuracy is similar in predicting the long-term response to medications in PVOD or PCH. Our patients experienced a decrease in mean pulmonary arterial pressure greater than 20% but did not achieve a mean pressure less than 40 mm Hg. Perhaps, their response to oral phosphodiesterase V inhibitors, oral endothelin receptor antagonists or inhaled prostacyclin analogs was sufficient to improve functional capacity without causing a clinical increase in pulmonary edema.

Our patients were treated with various medications before they developed clinical findings of PVOD and PCH with right heart failure. Inhaled fluticasone, inhaled beta agonists, montelukast, cetirizine, prednisone, cyclosporine, hydroxychloroquine and fish oil were used by at least one patient for more than one year. It is unknown whether these medications or other agents potentially delayed, or contributed to, the progression of disease.

Urinary MMPs may signal abnormal angiogenesis or tumor growth and have been evaluated in PCH [12,13]. MMP-9 and MMP2 species were increased in the urine of our patients. We did not have serial measurements to evaluate the influence of therapy. Additional studies are needed to determine whether urinary MMP values correspond with the severity of disease or the response to therapy in patients with PVOD or PCH.

Our patients had evidence of pulmonary hypertension before they developed symptoms and radiographic evidence of PVOD and PCH. While pulmonary hypertension may occur with subclinical efferent pulmonary vascular changes, it is possible that the pathology of PVOD and PCH evolved after the onset of pulmonary hypertension in our patients.

Our patient with familial PVOD and PCH did not test positive for an *EIF2AK4* mutation. However, individuals with *EIF2AK4* mutations, or mutations in yet to be determined genes, may be a subset of susceptible patients that could be screened and identified before developing a life-threatening stage of disease. Additional experience is needed to clarify whether genetic testing will allow care providers to identify factors that initiate or prevent the progression of disease in relatives of affected patients. If so, acute vasodilator testing should not be abandoned. It may help to determine whether some individuals with a tendency to develop PVOD or PCH may benefit from medical therapy early in the course of their disease.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

The Vascular Biology Program of Boston Children's Hospital graciously determined the amount of urinary basic fibroblast growth factor, vascular endothelial growth factor and matrix metalloproteinases in our patients.

References

[1] J. Mandel, E.J. Mark, C.A. Hales, Pulmonary veno-occlusive disease, Am. J. Respir. Crit. Care Med. 162 (2000) 1964–1973, http://dx.doi.org/10.1164/ajrccm.162.5.9912045.

[2] G.G. Pietra, F. Capron, S. Stewart, O. Leone, M. Humbert, I.M. Robbins, L.M. Reid, R.M. Tuder, Pathologic assessment of vasculopathies in pulmonary hypertension, J. Am. Coll. Cardiol. 43 (2004) 25S–32S, http://dx.doi.org/10.1016/j.jacc.2004.02.033.

[3] S. Lantuéjoul, M.N. Sheppard, B. Corrin, M.M. Burke, A.G. Nicholson, Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis: a clinicopathologic study of 35 cases, Am. J. Surg. Pathol. 30 (2006) 850–857, http://dx.doi.org/10.1097/01.pas.0000209834.69972.e5.

[4] D. Montani, L. Achouh, P. Dorfmüller, J. Le Pavec, B. Stzrymf, C. Tchérakian, A. Rabiller, R. Haque, O. Sitbon, X. Jaïs, P. Dartevelle, S. Maître, F. Capron,

D. Musset, G. Simonneau, M. Humbert, Pulmonary veno-occlusive disease: clinical, functional, radiologic, and hemodynamic characteristics and outcome of 24 cases confirmed by histology, Medicine 87 (2008) 220–233, http://dx.doi.org/10.1097/MD.0b013e31818193bb.

[5] C. Woerner, E. Cutz, S.J. Yoo, H. Grasemann, T. Humpl, Pulmonary veno-occlusive disease in children, Chest 146 (2014) 167–174, http://dx.doi.org/10.1378/chest.13-0172.

[6] B.W. Holcomb, J.E. Loyd, E.W. Ely, J. Johnson, I.M. Robbins, Pulmonary veno-occlusive disease: a case series and new observations, Chest 118 (2000) 1671–1679 not available.

[7] M. Eyries, D. Montani, B. Girerd, C. Perret, A. Leroy, C. Lonjou, N. Chelghoum, F. Coulet, D. Bonnet, P. Dorfmüller, E. Fadel, O. Sitbon, G. Simonneau, D.A. Tregouët, M. Humbert, F. Soubrier, EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension, Nat. Genet. 46 (2014) 65–69, http://dx.doi.org/10.1038/ng.2844.

[8] D.H. Best, K.L. Sumner, E.D. Austin, W.K. Chung, L.M. Brown, A.C. Borczuk, E.B. Rosenzweig, P. Bayrak-Toydemir, R. Mao, B.C. Cahill, H.D. Tazelaar, K.O. Leslie, A.R. Hemnes, I.M. Robbins, C.G. Elliott, EIF2AK4 mutations in pulmonary capillary hemangiomatosis, Chest 145 (2014) 231–236, http://dx.doi.org/10.1378/chest.13-2366.

[9] B. Dufour, S. Maître, M. Humbert, F. Capron, G. Simonneau, D. Musset, High-resolution CT of the chest in four patients with pulmonary capillary hemangiomatosis or pulmonary veno-occlusive disease, Am. J. Roentgenol. 171 (1998) 1321–1324, http://dx.doi.org/10.2214/ajr.171.5.9798872.

[10] H.I. Palevsky, G.G. Pietra, A.P. Fishman, Pulmonary veno-occlusive disease and its response to vasodilator agents, Am. Rev. Respir. Dis. 142 (1990) 426–429, http://dx.doi.org/10.1164/ajrccm/142.2.426.

[11] O. Sitbon, M. Humbert, X. Jaïs, V. Ioos, A.M. Hamid, S. Provencher, G. Garcia, F. Parent, Hervé, G. Simonneau, Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension, Circulation 111 (2005) 3105–3111, http://dx.doi.org/10.1161/CIRCULATIONAHA.104.488486.

[12] J.J. Marler, S.J. Fishman, S.M. Kilroy, J. Fang, J. Upton, J.B. Mulliken, P.E. Burrows, D. Zurakowski, J. Folkman, M.A. Moses, Increased expression of urinary matrix metalloproteinases parallels the extent and activity of vascular anomalies, Pediatr 116 (2005) 38–45, http://dx.doi.org/10.1542/peds.2004-1518.

[13] L.C. Ginns, D.H. Roberts, E.J. Mark, J.L. Brusch, J.J. Marler, Pulmonary capillary hemangiomatosis with atypical lymphangiomatosis: successful anti-angiogenic therapy with doxycycline, Chest 124 (2003) 2017–2022.