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.