PVOD/Pulmonary Capillary Hemangiomatosis - Clinical Presentation, Pathology, and Treatment

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Disclosures

This talk will include discussion of off-label therapies for pediatric PAH and PVOD

Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH)

• Unusual disorders which present as pulmonary arterial hypertension
• Since earliest description, debated as to whether two distinct diseases or single entity
• Characteristics and pathophysiology remain poorly understood

PVOD: Historical Background

• 1934 – First documented case
  – Dr. Julius Horas, Munich
  – 48 year old baker, died after illness complicated by edema, shortness of breath and cyanosis
• 1966 - British pathologist Donald Heath coined term PVOD as distinct entity
• 1976 – Dutch pathologist CA Wagenvoort
  – PVOD as acquired syndrome of devastating venous thrombosis due to endothelial injury
Pulmonary Capillary Hemangiomatosis (PCH)

- Reported less frequently in literature than PVOD
- 1978 – First recognized by Wagenvoort
  - 71 year old woman with shortness of breath, hemoptysis and hemorrhagic pleural effusions
  - Distinct “atypical proliferation of capillary-like channels” as well as “angiomatic growth” in lung tissue

(Wagenvoort et al, Histopathology 1978)

Microscopic Anatomy
Normal lung (level of secondary pulmonary lobule and interlobular septum)

Centrilobular pulmonary artery
Interlobular septal veins
Capillary network
Lymphatic network

Frazier et al, Radiographics 2007

Pulmonary veno-occlusive disease

Occluded interlobular septal veins
Engorged lymphatics
Edematous interlobular septum
Dilated capillary network

Frazier et al Radiographics, 2007

Pulmonary Capillary Hemangiomatosis

Discrete areas of capillary proliferation
No primary changes in pulmonary veins or interlobular septum

Frazier et al, Radiographics, 2007
### Nomenclature

- **Pulmonary vaso-occlusive disease**
  - Involvement of arterial component of pulmonary circulation as well as veins
  - Intimal fibrosis and smooth muscle hypertrophy in both arterioles and venules (Harsh et al., 2009)

- **Overlap of PVOD and PCH**
  - PCH is present in 75% of those with PVOD
  - 80% with primary dx of PCH have foci of PVOD in biopsy specimens (Lanteujel et al., 2006)

### Mechanism of Disease

- Cause of PVOD remains unknown
- Multiple factors provoke pattern of vascular endothelial cell injury and repair leading to:
  - Venous obstruction
  - Thrombosis

### Clinical Classification has evolved over time

- **Evian WHO Classification**
  - PVOD and PCH in two separate groups
  - PVOD in pulmonary venous hypertension
  - PCH in miscellaneous diseases affecting pulmonary vasculature

- **Dana Point Classification**
  - PVOD/PCH shares features with PAH
  - Similar changes in pulmonary parenchyma
  - Similar pathologic alterations in small PAs
  - Overlapping causes and associated conditions

### Updated Clinical Classification PH

- **Dana Point, 2008**

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- 1 Pulmonary arterial hypertension (PAH)
  - 1.1 Idiopathic PAH
  - 1.2 Heritable
    - 1.2.1 BMPR2
    - 1.2.2 ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
  - 1.2.3 Unknown
  - 1.3 Drug- and toxin-induced
  - 1.4 Associated with
    - 1.4.1 Connective tissue diseases
    - 1.4.2 HIV infection
    - 1.4.3 Portal hypertension
    - 1.4.4 Congenital heart diseases
    - 1.4.5 Schistosomiasis
  - 1.6 Chronic hemolytic anemia
  - 1.5 Persistent pulmonary hypertension of the newborn
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- **1 Pulmonary vaso-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)**
PVRI Panama Pediatric Classification
(Pulm Circ 2011)

5. Isolated PPHVD or PAH
   5.1 Idiopathic
   5.2 Inherited
   5.3 Drugs and Toxins
   5.4 PVOD and PCH
      5.4.1 Idiopathic
      5.4.2 Inherited

Epidemiology

- PVOD
  - 5 – 10% of idiopathic PAH
  - Using French National Registry (Humbert, 2006)
    - Annual incidence rate 0.1-0.2 cases/million/year
  - Wide age range, primarily in children and young adults
  - 30-50% < age 20 yrs
  - In adults M/F ratio 2:1
  - Median survival from diagnosis 2 years
- PCH
  - Wide age range, mean age 30 yrs
  - M/F 1:1 for all ages
  - Median survival from diagnosis 3 years
- TOPP Registry- PVOD/PCH in 2% (Berger et al, Lancet 2012)

PVOD Risk Factors

- Variety of risk factors described
- Primarily small case series

Genetics

- PVOD may occur in siblings (Voordes et al 1977, Rosenthal et al 1973)
- Hereditary PVOD (Runo et al 2003)
- BMPR2 mutations reported in PVOD
**BMPR2 mutation in PVOD**

Frameshift mutation producing truncated non-functioning protein

Ruo et al, Am J Respir Crit Care Med, 2003

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**BMPR2 Mutations - Implications**

- Possible role for BMPR2 pathway in development of PVOD
- Suggests relationship between PVOD and other forms of PAH
- Support screening for history of PAH in family members of patients with PVOD
- Genetic counseling in PVOD as indicated

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**Autoimmune disease and PVOD**

- PVOD described in patients with sclerderma and sarcoid associated PH (Johnson et al, 2006)
- Dorfmuller and colleagues (2007)
  - Lung samples from connective tissue disease patients with associated PH
    - Scleroderma (4), SLE (2), mixed connective tissue disease (1), rheumatoid arthritis (1)
  - 75% biopsies with fibrous venous obstruction

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**Infection**

- Long considered possible cause
- No convincing data linking to particular infectious etiology
- Serologic evidence of prior infection with Toxoplasma or measles
- Influenza-like illness precedes PVOD in many cases
- Reports of PVOD associated with HIV (Ruchelli et al, 1994)
Toxins and PVOD

- Case reports of PVOD with fenfluramine exposure
  - Suggests association with anorexigen exposure as with PAH
- Chemical exposures
  - Case Reports
  - Post Chemotherapy
    - Bleomycin, mitomycin, cyclophosphomide

PVOD is associated with Bone Marrow or Stem Cell Transplant

- Underlying etiology not known
  - Chemotherapy
  - Whole body irradiation
  - Underlying disease
  - Graft vs. host
  - Secondary to pulmonary toxicity

Tobacco Use and PVOD

- Higher tobacco exposure and increased proportion of smokers in PVOD vs PAH
  (Montani et al, Medicine, 2008)
- Link between PVOD and pulmonary Langerhans cell granulomatosis – disease occurring predominantly in pts with h/o smoking
  -(Montani et al , Eur Resp J 2009)
- Mechanism of association not known

Clinical Presentation

- Symptoms
  - Progressive dyspnea on exertion
  - Cough
  - Hypoxemia
  - clubbing
- Exam
  - Auscultory crackles
- Hemoptysis – in both PCH and PVOD
3 Pediatric Cases

Case 1

- 16 year old female with h/o tobacco use
  - 6 month h/o cough, SOB, weight loss
  - Insidious deterioration of exercise capacity
  - Sats 70% on presentation

- CXR

Case 1 Evaluation

- Echocardiogram
  - Suprasystemic RV pressure, Severely depressed RV function, intact atrial septum
- BNP 1800
- Rheumatologic work up negative
- PFTs normal, severely depressed DLCO
- Contrast CT negative for PE
Case 2

- 12 yr old male presented along with other classmates with presumed viral illness
  - Abdominal pain
  - No fevers
  - Progressive cough, dyspnea
  - Chest radiograph: reticulonodular pattern

Case 2: CXR

Reticulonodular opacities
Enlarged PAs

Kothari et al, Circulation, 2009

Case 2 - Evaluation

- Echocardiogram: tricuspid regurgitation, systemic RV pressures, dilated RV with moderate dysfunction, right ventricular hypertrophy
- Infectious Disease w/u negative
- PFTs: mild obstructive defect with severely decreased diffusing capacity
- V/Q scan –no areas of mismatch
- Chest CT
Case 2 CT

Case 3

- 8 year old boy with acute myeloid leukemia
- Induction chemotherapy daunorubicin and cytosine arabinoside and re-induction chemotherapy failed to induce remission
- Allogeneic stem cell transplant with unrelated HLA-matched donor
- Conditioning regimen: fludarabine, melphalan, anti-thymocyte globulin and 4 Gy TBI
- Bone Marrow Transplant
- Day 90 post transplant, presented to clinic with marked shortness of breath, sats 82% RA

Case 3

- Patient admitted to ICU with continued respiratory deterioration
- Infectious work up unrevealing
- Echocardiogram - suprasystemic RV pressure, moderately depressed RV function
- Hemoptysis, Intubation, Hypotension requiring vasopressors
- Chest CT
Diagnostic Strategies in PVOD/PCH

- Biopsy is most definite but carries risk in critically ill patients with severe RV dysfunction
- Non-invasive evaluation
  - CXR
  - HRCT of Chest
  - Pulmonary Function Tests
  - Arterial blood gas measurements
  - BAL

CXR and HRCT Essential

- **CXR**
  - Kerley B lines
  - Pleural Effusions

- **HRCT**
  - Centrilobular ground glass opacities
  - Septal Lines
  - Mediastinal Lymph node abnormalities
  - Presence of 2 or 3 have sensitivity of 75% and specificity of 84.6% for detection of PVOD
  (Montani et al, Medicine 2008)

HRCT of Chest in PVOD

Mediastinal Lymphadenopathy

Montani et al, Eur Resp J 2009
CT Image through Lung Bases in PVOD

- Pulmonary veins normal sized
- Ground glass opacities
- Septal thickening
- Enlarged arteries


Pulmonary Function Testing

- Normal mean values of FEV₁, FEV₁/FVC ratio and total lung volume in pts with PVOD (Montani et al 2004)
- Low diffusing capacity of lung for carbon monoxide \(D_{LCO}\) noted in PVOD
- Exaggerated hypoxemia noted

Pulmonary Function Testing in VOD

- DLCO and PaO₂ both significantly lower at rest in patients with PVOD


BAL in Diagnosis of PVOD

- Bronchoscopy not routine procedure in PAH and carries risk
- Patients with PVOD and associated parenchmal lung disease may undergo BAL as part of routine evaluations
- Rabiller and colleagues (2006)
  - BAL from PVOD (8) and idiopathic PAH (11)
  - Used Golde score to assess alveolar hemorrhage, measuring hemosiderin laden macrophage
Distinct hemodynamics in PVOD and PCH

- Elevated PA pressure
- Normal or Low PCWp

Case 1

- Cardiac Catheterization
  - Desaturated baseline requiring 35% FM
    - RA 8, RV 95/11, PAp 95/51, mean 69, Ao 77/8
    - Qp/Qs = 1
    - LPCW = LVEDp = 8
    - CI 2.3, PVR 26 WU
  - 100% FiO2 + 80 PPM NO
    - Mean Pap 46
    - CI 2.6
    - PVR 13

Golde Score Markedly elevated in PVOD

PCWp reflects pressure in larger pulmonary veins distal to PA catheter
Case 2

• Cardiac catheterization
  – RV and PA pressures 80% systemic on baseline 2 Liters oxygen
  – PCWp 12
  – PVR indexed 24
  – No change with 100% O2 + 80 PPM Nitric Oxide

PVOD- Pathology

• Extensive and diffuse occlusion of pulmonary veins by fibrous tissue
• Venules and small veins in lobular septa with eccentric intimal thickening
• Media of veins may become arterialized
• Intimal fibrous tissue may be loose and edematous or dense

Small Pulmonary Vein in PVOD

![Small Pulmonary Vein in PVOD](Mandel et al, Am J Resp Crit Care Med 2000)

Lobular septa widened by interstitial edema and fibrosis in PVOD

![Lobular septa widened by interstitial edema and fibrosis in PVOD](Mandel et al, Am J Resp Crit Care Med 2000)
Alveolar capillary dilation in lung parenchyma upstream from occluded veins

- Intraalveolar hemosiderin laden macrophages, vascular fibers coated with iron

PCH- Pathology

- Proliferation of capillary channels within alveolar walls
- Proliferating capillaries compress pulmonary venules and veins causing secondary veno-occlusion

PCH – multiple small nodules of proliferating capillaries

Frazier et al, Radiographics, 2007

Case 1

Pulmonary arteries with hypertensive changes
Case 1 PVOD

Pulmonary vein occluded with fibrinous material

Case 1 Sclerotic Vein

Case 2 Leopard Lung in PCH

Case 2 PCH
Case 2 Abnormal Vessel in PCH

Fibrin exudates, hemorrhage and occluded veins

Case 3 - PVOD

Occluded vein with surrounding hemorrhage

Case 3 PVOD

Pulmonary vein occluded by fibrin
Treatment Strategies in PVOD/PCH

- Only curative therapy lung transplantation
- Standard medical treatments
  - Diuretics, oxygen, anticoagulation
- Immunosuppressive therapies
  - Glucocorticoids

Pulmonary Vasodilator therapy in PVOD/PCH

- Vasodilators
  - Established role in PAH
  - Concern in PVOD
    - Dilation of pulmonary arterioles with fixed resistance of pulmonary veins → pulmonary edema
  - Clinical data conflicting
    - Early reports of massive pulmonary edema and death with vasodilator challenge during hemodynamic catheterization

PVOD Therapy: Epoprostenol

- 50% of PVOD patients died after receiving epoprostenol therapy (Montani et al, 2008)
- Recent reports of cautious use of intravenous prostanoids in PVOD

Montani et al Medicine 2008
Epoprostenol for PVOD


Impact of Epoprostenol on Hemodynamics in Patients with PVOD


Impact of Epoprostenol on NYHA Functional Class in Patients with PVOD

Proposed innovative therapies for PVOD

- **Defibritide**
  - Single stranded DNA derivative with anticoagulant and anti-inflammatory properties
  - Prophylaxis decreases risk of hepatic veno-occlusive disease in pediatric hematopoietic stem cell transplantation (Corbacioglu, Lancet 2012)

- Case report in treatment transplant associated PVOD

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**HRCT myeloproliferative disorder associated PVOD**

- Septal thickening
- Mosaic type ground glass opacities

**HRCT post tx IV defibrotide**

- Resolution of septal thickening, ground glass opacities and pleural effusion

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**Epoptrostenol for PVOD**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis of PVOD</th>
<th>Time between isolation and LTx days</th>
<th>Type of LTx</th>
<th>Alive at day 30 after LTx</th>
<th>Evolution on December 1, 2008</th>
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<tbody>
<tr>
<td>1</td>
<td>Pulmonary edema with OCB</td>
<td>209</td>
<td>Heart-LTx</td>
<td>Yes</td>
<td>Death 50 days after LTx</td>
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<tr>
<td>3</td>
<td>Explanted lungs</td>
<td>203</td>
<td>Heart-LTx</td>
<td>Yes</td>
<td>Death 145 days after isolation</td>
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<tr>
<td>4</td>
<td>Explanted lungs</td>
<td>45</td>
<td>Double lung</td>
<td>Yes</td>
<td>Alive at 390 days</td>
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<tr>
<td>6</td>
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<td>173</td>
<td>Double lung</td>
<td>Yes</td>
<td>Alive at 30 days</td>
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<tr>
<td>5</td>
<td>Explanted lungs</td>
<td>307</td>
<td>Heart-LTx</td>
<td>Yes</td>
<td>Alive at 670 days</td>
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<tr>
<td>7</td>
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<td>18</td>
<td>Heart-LTx</td>
<td>Yes</td>
<td>Alive at 820 days</td>
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<tr>
<td>8</td>
<td>Multiple approach weighing</td>
<td>Bill waiting for lung transplant at day 87</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Explanted lungs</td>
<td>40</td>
<td>Double lung</td>
<td>Yes</td>
<td>Alive at 270 days</td>
</tr>
<tr>
<td>10</td>
<td>Explanted lungs</td>
<td>227</td>
<td>Double lung</td>
<td>Yes</td>
<td>Alive at 80 days</td>
</tr>
<tr>
<td>11</td>
<td>Explanted lungs</td>
<td>42</td>
<td>Heart-LTx</td>
<td>Yes</td>
<td>Alive at 220 days</td>
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<tr>
<td>12</td>
<td>Explanted lungs</td>
<td>1</td>
<td>Heart-LTx</td>
<td>Yes</td>
<td>Death 74 days after LTx</td>
</tr>
</tbody>
</table>

TABLE 4: Lung transplantation of pulmonary veno-occlusive disease (PVOD) patients with bringing therapy by epoprostenol.

Treatment Algorithm for PVOD

Montani et al, Medicine 2008

Treatment for PCH

- Standard therapies
  - Supplemental oxygen, diuretics, anticoagulation
- Alpha-interferon 2a
  - Inhibit endothelial proliferation and migration
  - Suppress endothelial growth factors
- Doxycycline
  - Modulate increased matrix metalloproteinase activity (MMP) associated with dysregulated angiogenesis

Summary 1

- PVOD/PCH - rare disorders that present with dramatic clinical signs
- Risk factors may suggest underlying etiologies
- Non-invasive tests useful in diagnosis
  - HRCT
  - PFTS
    - Decreased DLCO
    - Low PaO₂
Summary 2

- Hemodynamics characterized by elevated PAp, normal PCWp
- Lung Transplant definitive therapy
- Standard therapies and cautious use of low dose vasodilators may help bridge to transplant

Future Directions

- Improved understanding of disease mechanisms may assist in development of targeted therapies
- Better diagnostic strategies and clinically algorithms for PVOD/PCH important to decrease mortality
- Patients with PVOD/PCH may be ideal candidates for mechanical support while awaiting lung transplant
- Multicenter studies of therapeutic approaches and novel agents are needed to improve survival

Acknowledgements

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