Case presentation

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History

- 3 years and 7 months male child presented with history of recurrent syncopal attacks mainly during sleep started at the age of 1.5 years.
- He was diagnosed to have epilepsy maintained on sodium valproate (depakin) and levetiracetam (teratam) without improvement.

History. Continue..

- Family history of similar attacks in his sister who died at the age of 4 years.
- Positive consanguinity with 3 times first trimester abortions

General examination

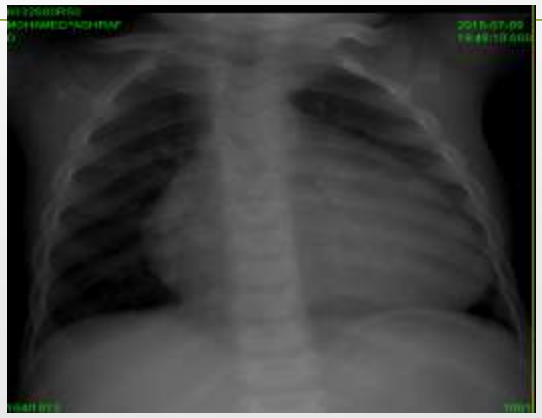
- Normal complexion (SPo2 97 %)
- Centiles are within normal
- HR 85 b/m
- RR 32 b/m
- Temp 37.2
- Blood pressure 90/60
- Bilateral LL pitting edema

- **Cardiac examination:**
- Accentuated P2
- Pan-systolic murmur grade III over LLSB
- **Chest, abdominal and neurological examinations:**
- Normal

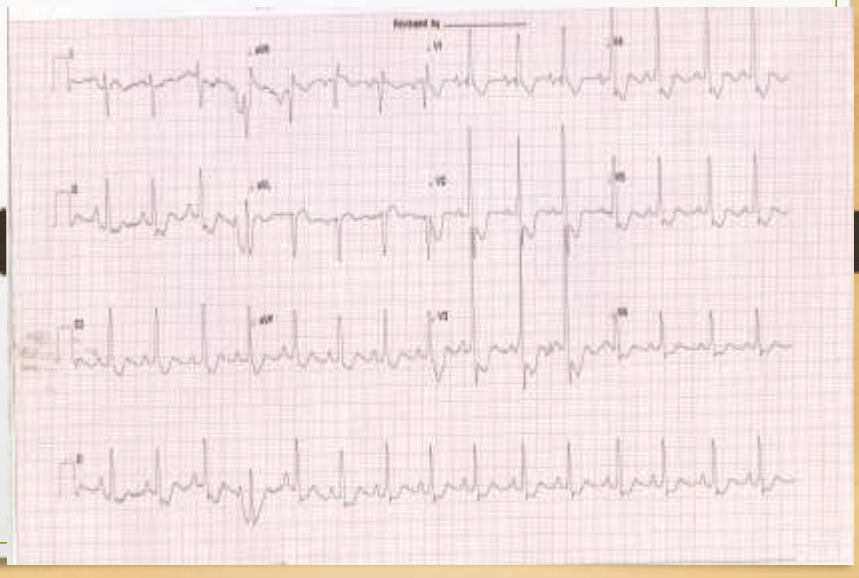
Laboratory investigations

- **ABG**
  - PH 7.39
  - PCO2 44
  - PO2 61
  - HCO3 26

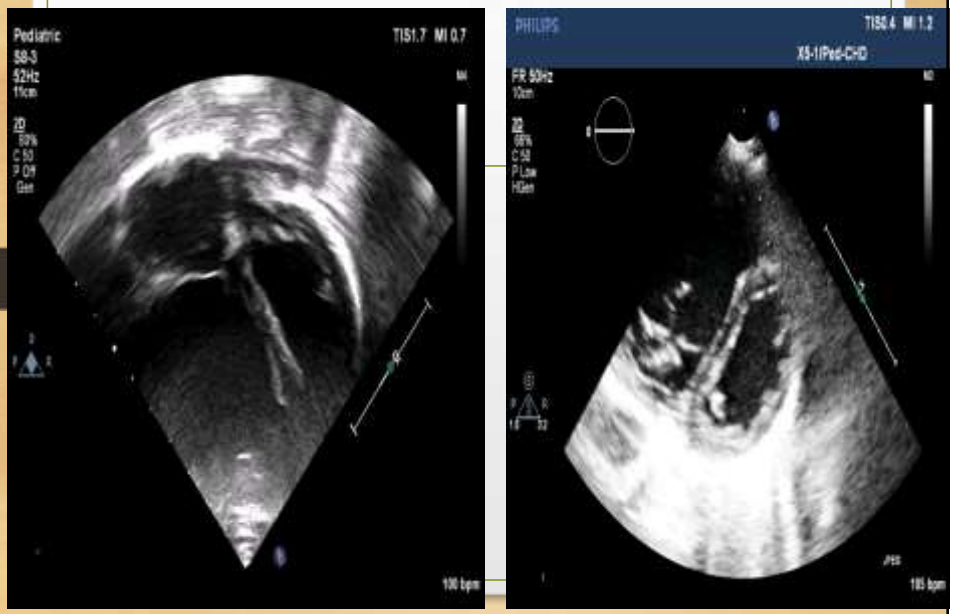
Chest x ray

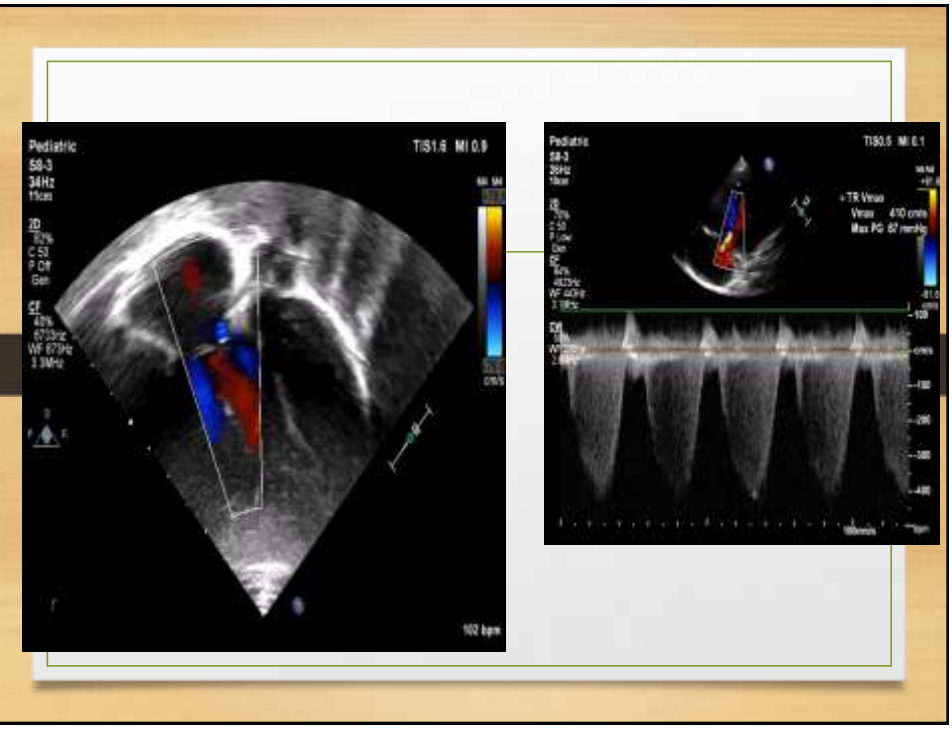


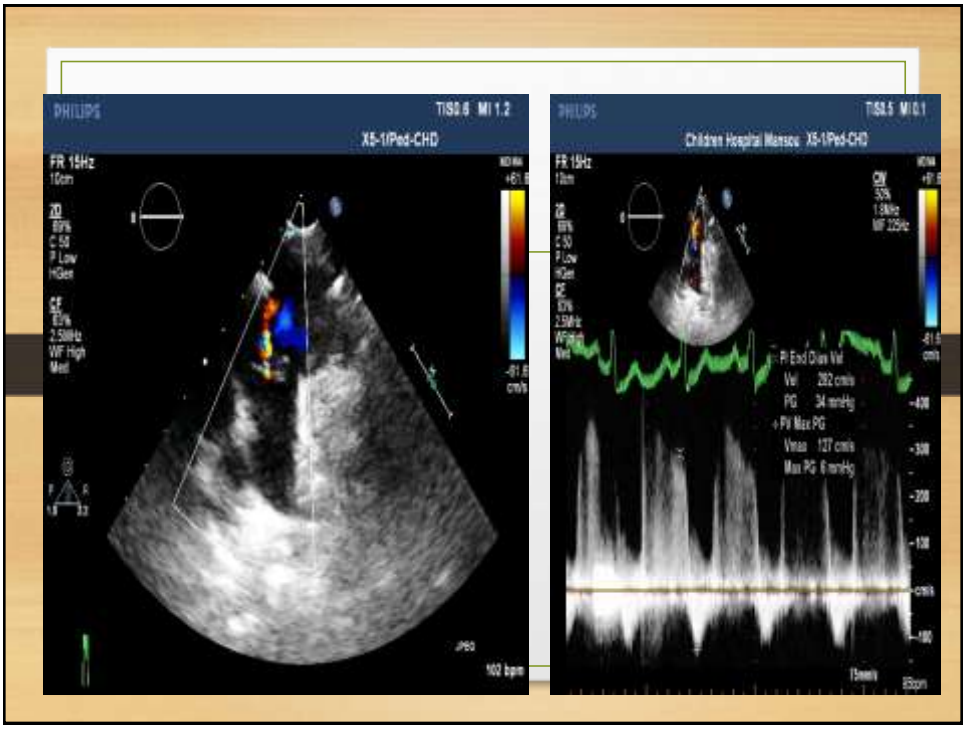
ECG

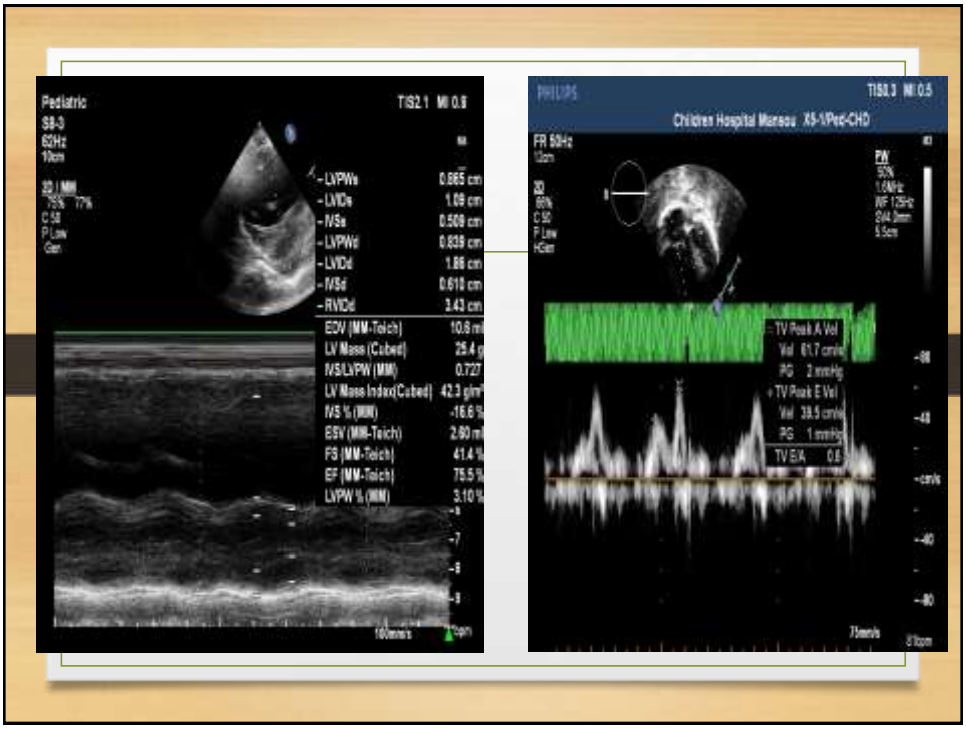


Echocardiography

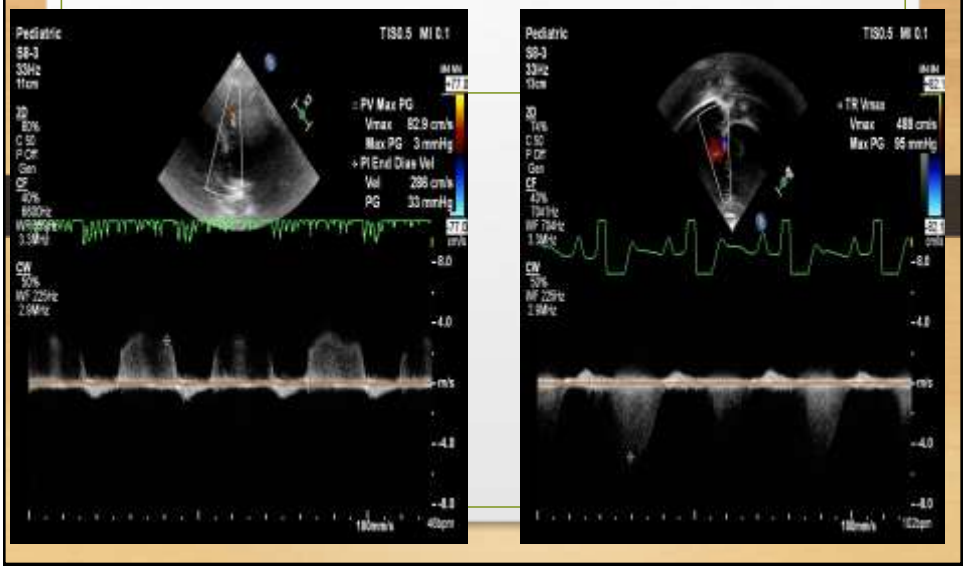





PHILIPS
X5-1/Ped-CHD
Children Hospital Mansou X5-1/Ped-CHD
FR 15Hz
PI End Diast Vel
Vel 282 cm/s
PG 34 mmHg
+ PV Max PG
Vmax 127 cm/s
Max PG 6 mmHg

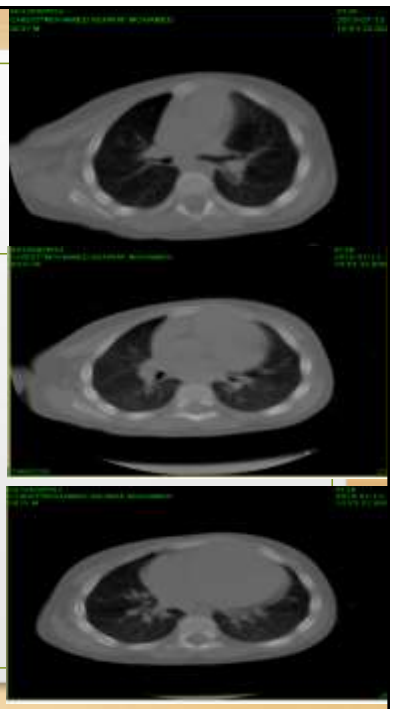

Pediatric
S8-3
LVPWs 0.865 cm
LVIDs 1.09 cm
IVSs 0.508 cm
LVPWd 0.839 cm
LVIDd 1.86 cm
IVSd 0.618 cm
RVIDd 3.43 cm
EDV (MM-Teich) 10.8 ml
LV Mass (Cubed) 25.4 g
IVS/LVPW (MM) 0.727
LV Mass Index(Cubed) 42.3 g/m²
IVS % (MM) -16.6 %
ESV (MM-Teich) 2.60 ml
FS (MM-Teich) 41.4 %
EF (MM-Teich) 75.5 %
LVPW % (MM) 3.10 %
Children Hospital Mansou X5-1/Ped-CHD
FR 60Hz
TV Peak A Vel
Vel 61.7 cm/s
PG 2 mmHg
+ TV Peak E Vel
Vel 39.5 cm/s
PG 1 mmHg
TV E/A 0.6

Follow up echo



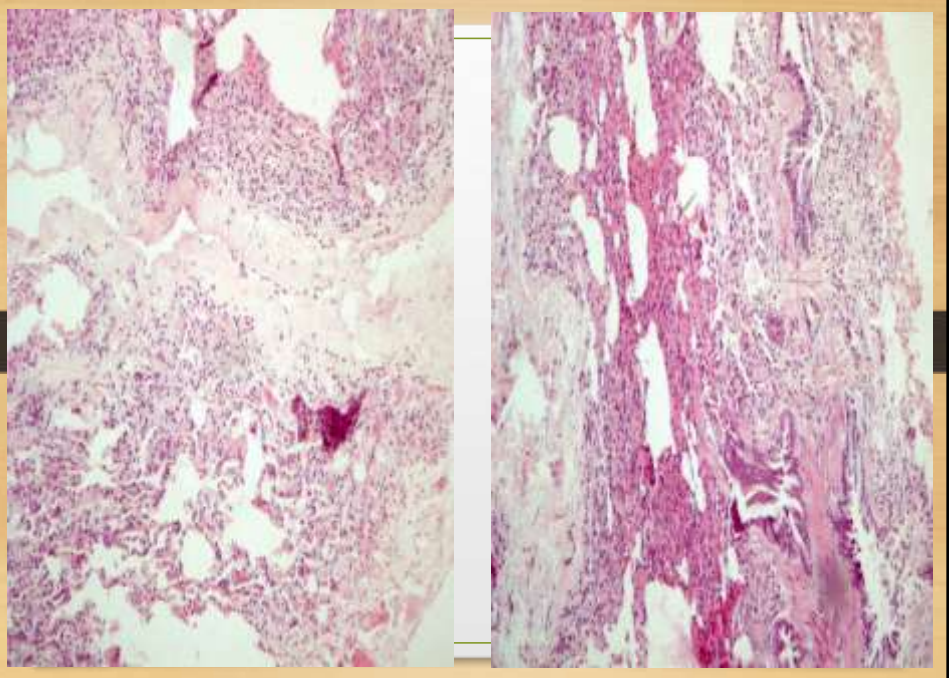
CT chest

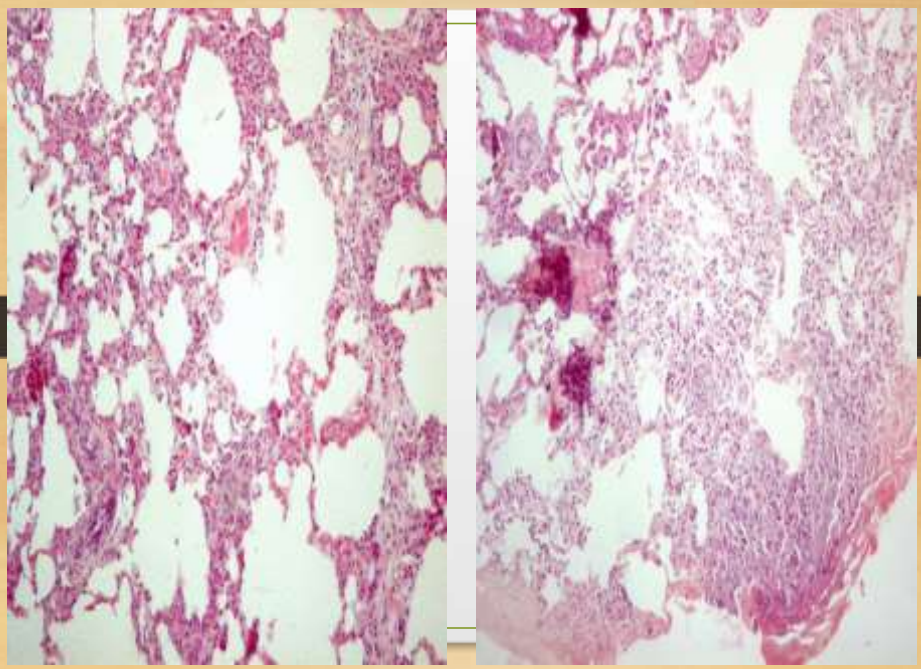
- Dilated main pulmonary artery
- Right ventricular dilatation and hypertrophy.
- Normal parenchyma on both lungs.



His sister

- She was diagnosed to have pulmonary hypertension
- Lung biopsy was done





His sister

- Lung biopsy revealed possibility of veno-occlusive disease

- This child was investigated for pulmonary hypertension at the age of 1 year based on the data of his sister and was normal

Pulmonary veno-occlusive disease

PVOD

- Rare disorder contributing to severe pulmonary hypertension and right heart failure.

Condensed clinical classification of PH(Simonneau et al. 2013)

1. Pulmonary arterial hypertension (PAH)
- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2 mutation
  - 1.2.2 Other mutations
- 1.3 Drugs and toxins induced
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease (Table 6)
  - 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease
- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
- 2.5 Other

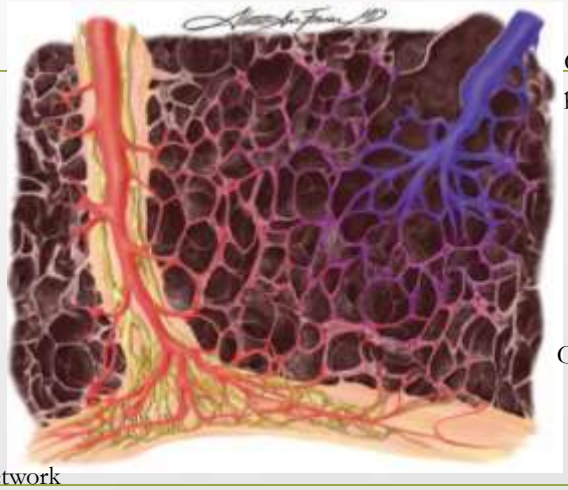
3. Pulmonary hypertension due to lung diseases and/or hypoxia
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
- 4.1 Chronic thromboembolic pulmonary hypertension
- 4.2 Other pulmonary artery obstructions

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders
- 5.2 Systemic disorders
- 5.3 Metabolic disorders
- 5.4 Others

Pathology

Normal lung



Interlobular septal veins

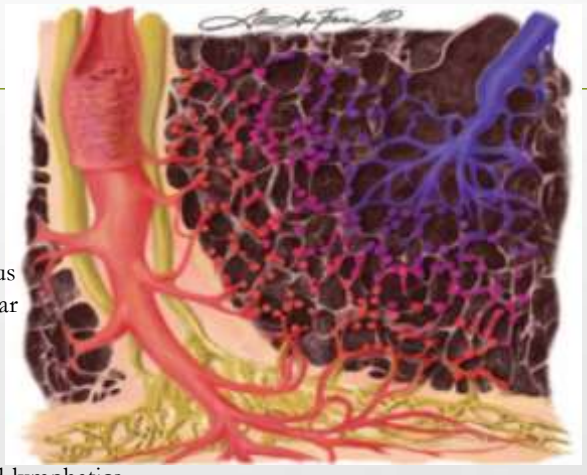
Centrilobular pulmonary artery

Capillary network

Lymphatic network

Frazier et al, Radiographics 2007

Pulmonary veno-occlusive disease



Occluded interlobular septal veins

Edematous interlobular septum

Dilated capillary network

Engorged lymphatics

Frazier et al Radiographics, 2007

Nomenclature (PVOD) is it adequate?

- • **pulmonary vaso-occlusive disease**
- – Involvement of arterial component of pulmonary circulation as well as veins

(Harsh et al , 2009)

Epidemiology

- – 5 – 10% of idiopathic PAH
- – Wide age range
  - – 30-50% < age 20 yrs
- – In adults M/F ratio 2:1
- – Median survival from diagnosis 2 years

(Humbert, 2006)
(Berger et al, Lancet 2012)

Risk Factors

- Genetics
- Autoimmune Disease
- Infection
- Toxins
- Tobacco Use

Genetics

- BMPR2 mutations reported in approximately 75% of familial cases of PVOD and in almost 20% of apparently sporadic cases of PVOD
  - autosomal-dominant trait with incomplete penetrance

(Rosenthal et al 1973, Voordes et al 1977)
(Runo et el 2003)

- presence of at least two affected siblings and unaffected parents.

- EIF2AK4 mutation that affect BMP signaling is also a major new cause of heritable PVOD

Eyries M et al, 2014

Autoimmune disease

- • PVOD described in patients with associated PH
  - Scleroderma,
  - sarcoidosis,
  - SLE,
  - mixed connective tissue disease,
  - rheumatoid arthritis

- – 75% biopsies with fibrous venous obstruction

(Johnson et al, 2006, Dorfmuller and colleagues (2007)

Infection

- • Suspected infection
  - Toxoplasma
  - Measles
  - HIV

Toxins

- • Chemical exposures
  - fenfluramine exposure
  - anorexigen exposure
- – 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

Clinical Presentation

- • **Symptoms**
- – Progressive dyspnea on exertion
- – Cough
- – Hemoptysis
- **• Examination**
- – Cardiac auscultation shows a prominent P2 and a systolic murmur of TR
- – Clubbing
- – Signs of right heart failure occur in the late phase

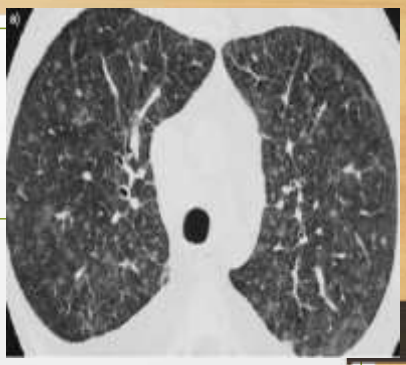
Diagnostic Workup

- Biopsy is most definite but carries risk in critically ill patients with severe RV dysfunction

- – CXR
- – HRCT of Chest
- – Pulmonary Function Tests
- – Arterial blood gas measurements
- – BAL

CXR and HRCT

- **– CXR**
- Cardiomegaly
- Kerley B lines
- Pleural Effusion



- **– 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)

Pulmonary Function Testing

- •Normal mean values of FEV1, FEV1/forced vital capacity ratio and total lung volume.
- • Low diffusing capacity of lung for carbon monoxide.

(Montani et al 2004

ABG

- Exaggerated hypoxemia

BAL

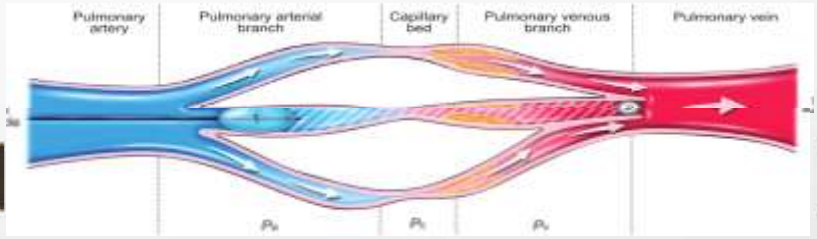
- • Bronchoscopy not routine procedure in PAH
- –elevated percentage of haemosiderin- laden macrophages

• Rabiller and colleagues (2006)

Transthoracic echocardiography

- Transthoracic echocardiography to assess the presence of elevated right-sided pressures and exclude underlying cardiac causes.

Distinct hemodynamics in PVOD



- PAp severely elevated
- PCWp is normal or low

Montani, et al. Eur Resp J 2009;33:189

- The triad of severe PH and radiographic pulmonary edema in the presence of a normal pulmonary artery wedge pressure is highly suggestive of PVOD

Can we treat PVOD as other types of PH?

Pulmonary Vasodilator therapy

- – Established role in PAH but doubt in PVOD
- •Dilation of pulmonary arterioles with fixed resistance of pulmonary veins leads to pulmonary edema
  - More with endothelin 1 receptor blocker
- However, clinical improvement or at least stabilization
  - intravenous prostacyclin,
  - oral sildenafil monotherapy.

- Standard medical treatments
  - Diuretics, oxygen, anticoagulation
  - Digoxin
- Immunosuppressive therapies
  - Glucocorticoids, cyclophosphamide and azathioprine

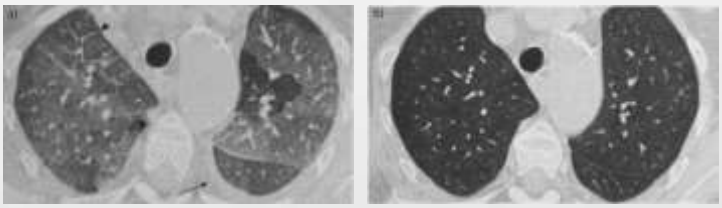
- **Lung transplantation is the only curative therapy**

Defibritide

- Single stranded DNA derivative with anticoagulant and anti-inflammatory properties
- Stem cell transplantation PVOD

HRCT pre and post IV defibritide

- Case report in treatment transplant associated PVOD

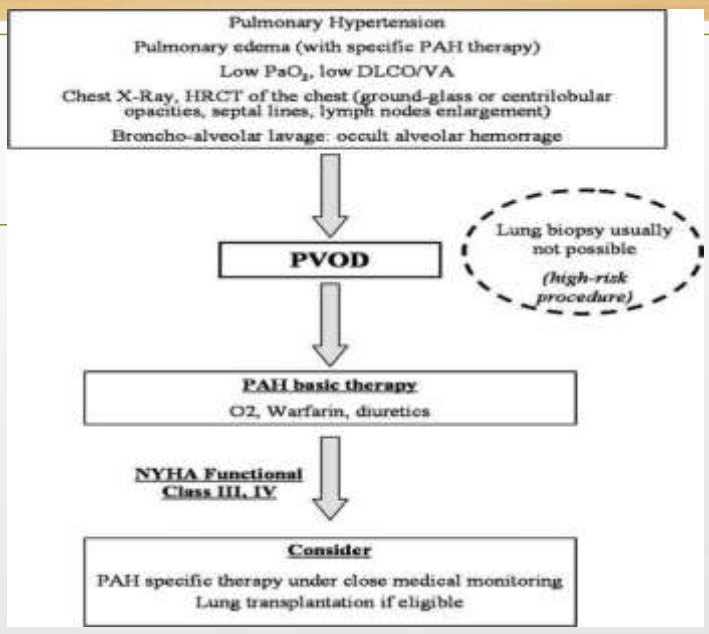


Williams et al, Eur Resp J, 2009

Mechanical Support

- Lung assist with Novalung has been used as a bridge to transplant
- Type of ECMO
- 15 year old patient with PVOD underwent successful bilateral lung transplant after 30 days of Novalung support

(Taylor et al, Anesth Analg 2009)



Montani et al, Medicine 2008

Conclousion

- • PVOD - rare disorder that present with dramatic clinical signs
- • Risk factors may suggest underlying etiologies
- • Non-invasive tests useful in diagnosis
  - HRCT
  - PFTS
  - Decreased DLCO
  - Low PaO2

- • 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