Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

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Objectives

• To discuss the prevalence and epidemiology of CTEPH
• To present the pathogenesis of CTEPH including current knowledge and gaps
• To discuss treatment options in CTEPH
• To show how imaging plays an integral part in evaluation and management of CTEPH

Prevalence and Epidemiology of CTEPH

• ~ 2500 new cases of CTEPH occur in the US/year (~ 600,000 episodes of acute PE/year)
• ~ 3 cases of CTEPH/100 cases acute PE w/cumulative incidence of 3.8%
• CTEPH – long term complication of symptomatic acute PE w/incidence of 1-5% within 2 years of the acute PE

CTEPH – Associated Factors

• Splenectomy
• Ventriculocostal shunt for treatment of hydrocephalus
• Inflammatory bowel disease
• Low-grade malignancy
• Thyroid replacement therapy

CTEPH - Overview

• Number of controversies regarding pathophysiology, natural hx, dx, and treatment
• Regarded by many to be simply a complication of acute PE arising subsequent to VTE – embolic hypothesis
• Studies suggest PE rarely the sole cause of CTEPH
• 1º arteriopathy w/2º in situ thrombosis relevant in pathogenesis and progression
• Distal small-vessel arteriopathy major contributor to progression of PH as CTEPH develops over time

Pathogenesis of CTEPH: Current Knowledge and Gaps

• Key question: where do the initiating thrombotic events occur which would explain the PH associated w/CTEPH?
• Is the etiology and pathogenesis embolic or thrombotic?
Pathogenesis of CTEPH: Current Knowledge and Gaps

- What are the contributions of small vessel vs large vessel disease in CTEPH?
- Are CTEPH and idiopathic pulmonary arterial hypertension (IPAH) separate diseases or are they on a continuum?

Pathogenesis: Embolic vs Thrombotic

- Embolic Hypothesis - classical or accepted scheme
- CTEPH develops after a single or recurrent pulmonary emboli arise from sites of venous thrombosis

Pathogenesis: Embolic vs Thrombotic

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Pathogenesis: Embolic vs Thrombotic

- Thrombotic Hypothesis
  - primary arteriopathy and endothelial dysfunction lead to in situ thrombosis which contributes to failure of thrombotic resolution
  - pulmonary arteriography could be initial pathology and thromboembolic events may occur as clinical sequelae rather than as the initiating factor

CTEPH Pathogenesis: Gaps in Knowledge

- IPAH = idiopathic pulmonary arterial hypertension; PH = pulmonary hypertension.

Pathogenesis: Embolic vs Thrombotic

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Pathogenesis: Embolic vs Thrombotic

- gained traction because > 50% cases of CTEPH lack documented h/o prior DVT or PE, calling the embolic hypothesis into question
- elevated endothelial plasminogen activator-inhibitor and Factor VIII expression have been shown in areas of fresh thrombus and endothelial cells and smooth muscle cells in organized thromboembolic material in CTEPH suggesting that in situ thrombosis indeed may play a role in CTEPH pathogenesis
Contribution of Small Vessel vs Large Vessel Disease in CETPH

- Precise mechanism & natural history of microvascular disease in CETPH - speculative


Contribution of Small Vessel vs Large Vessel Disease in CETPH

- However, seems that substantial component of persistent post-op PH is related to distal pulmonary vasculo-pathy in small pre-capillary vessels in both occluded & non-occluded pulmonary vascular bed


Contribution of Small Vessel vs Large Vessel Disease in CETPH

- Small vessel arteriopathy is believed to appear and worsen later in course of disease and contribute to progression of hemodynamic and symptomatic decline


Contribution of Small Vessel vs Large Vessel Disease in CETPH

- This can explain progressive PH and RV dysfunction without recurrent PE


Postoperative Pulmonary Classification of CTEPH

<table>
<thead>
<tr>
<th>Type</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Central organized clot (main/lobar pulmonary arteries)</td>
</tr>
<tr>
<td>II</td>
<td>Intimal thickening and fibrosis proximal to the segmental arteries</td>
</tr>
<tr>
<td>III</td>
<td>Disease within distal segmental and subsegmental arteries only</td>
</tr>
<tr>
<td>IV</td>
<td>PAH w/hypertensive distal vasculopathy w/o visible thromboembolic disease</td>
</tr>
</tbody>
</table>

Radiologic Manifestations CXR

- Pattern of PAH
  - asymmetry in size of central pulmonary arteries
  - relative areas of hypoperfusion and hyperperfusion
  - parenchymal or pleural scars
  - enlargement of RV
Contribution of Imaging to Workup and Management in CTEPH

- Pts with CTEPH Types I, II who show significant and accessible organized thromboemboli in proximal pulmonary vessels are likely to benefit from PEA.

- Selected pts with Type III CTEPH (disease in distal segmental or subsegmental arteries) can undergo successful PEA.

- No indication for PEA in Type IV (isolated distal vasculopathy) disease.

Radiologic Manifestations CT

- Thrombus eccentric and contiguous with the vessel wall
- Arterial stenosis or web
- Recanalization within an area of arterial hypoattenuation
- Reduction of more than 50% of the overall arterial diameter
- Complete occlusion of pulmonary arteries
Recanalized thrombus perpendicular to arterial wall creates a web or band and thickens the arterial wall if recanalization is parallel to wall.

- Lower attenuation values in acute PE – mean 33HU ± 15 and higher in chronic PE – mean 87HU ± 30
- Calcification with thrombus
- Hypertrophied bronchial arteries

Acute PE with acute angle with vessel wall

Chronic PE with obtuse margin with vessel wall

Radiologic Manifestations CT

Wittram et al. Radiology 2005; 235:1050-1054

Wittram et al AJR 2007; 188:1255-1261
**Signs of Pulmonary Hypertension**

- Right ventricular enlargement
- Enlargement of central pulmonary arteries and rapid tapering of vessels distally
- Distal vessels may be large, normal or reduced in caliber but disparity in size between central and distal vessels

**Signs of Pulmonary Hypertension**

- Right descending pulmonary artery at midpoint: 16-17mm
- Mean pulmonary artery diameter - 3cm from bifurcation - should be < 29mm - PPV of 0.97 for predicting PAH
- PAH likely when diameter of main PA > adjacent ascending aorta - PPV 93%

**Parenchymal Signs of Pulmonary Hypertension**

- Mosaic attenuation
- Parenchymal scarring – subpleural opacities – do not enhance
- Moderate lymph node enlargement
Comparison of CTEPH and IPAH

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>CTEPH</th>
<th>IPAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross pathology</td>
<td>Organized, central thrombus</td>
<td>Some thrombotic pathology</td>
</tr>
<tr>
<td>Histopathology</td>
<td>Plexogenic arteriopathy</td>
<td>Plexogenic arteriopathy</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Shortness of breath</td>
<td>Shortness of breath</td>
</tr>
<tr>
<td>Signs</td>
<td>PH and right heart failure</td>
<td>PH and right heart failure</td>
</tr>
<tr>
<td>Contributory</td>
<td>DVT/DVT (single or recurrent PE)</td>
<td>Endothelial/smooth muscle dysfunction</td>
</tr>
<tr>
<td>mechanisms</td>
<td>In situ thrombosis?</td>
<td>In situ thrombosis?</td>
</tr>
<tr>
<td></td>
<td>Endothelial dysfunction</td>
<td>Endothelial dysfunction, smooth muscle dysfunc</td>
</tr>
<tr>
<td></td>
<td>Prothrombotic factors (factor VIII)</td>
<td>Endothelial/smooth muscle dysfunction</td>
</tr>
<tr>
<td></td>
<td>Anti-O blood groups, plasma</td>
<td>Anti-phospholipid antibodies</td>
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<tr>
<td></td>
<td>Antiphospholipid antibodies</td>
<td>Prothrombotic factors?</td>
</tr>
<tr>
<td>Treatment responses</td>
<td>PEA/lung transplantation</td>
<td>Lung transplantation</td>
</tr>
<tr>
<td></td>
<td>Anticoagulants</td>
<td>Vasodilator therapy</td>
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<tr>
<td></td>
<td>Advanced Therapies</td>
<td>Anticoagulants</td>
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<tr>
<td></td>
<td>Reduced vasodilator response</td>
<td>Advanced therapies</td>
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Idiopathic Pulmonary Artery Hypertension

- No clinically discernible cause
- Normal pulmonary arterial wedge pressure
- Extensive obliteration of pulmonary vascular bed

Radiologic Manifestation of IPAH

- Mosaic attenuation less prevalent
- Small low attenuation centriflobular nodules, similar to those in hyper-sensitivity pneumonitis, sometimes seen; nodules may be cholesterol granulomas due to macrophage ingestion of red blood cells following repeated hemorrhage

Radiologic Manifestation of IPAH

- Dilatation of proximal and segmental pulmonary arteries
- Small pericardial effusion
Treatment of CTEPH

- Pulmonary Endarterectomy (PEA)
  - potentially curative but 10% mortality rate
  - fails to significantly reduce PVR in 10-15% of patients
  - the degree of postoperative residual in PVR is the factor which most strongly correlated with mortality
  - removal of scar tissue rather than removal of chronic thrombus is focus of surgical procedure
Mechanisms For Distal Inoperable Microvascular Disease in CTEPH

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Vascular Pathology</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Predominant obstructions of “small” subsegmental elastic pulmonary arteries</td>
<td>Occlusions of “small” subsegmental elastic arteries w/stenosis, webs, and bands. Similarity/overlap w/IPAH.</td>
</tr>
<tr>
<td>2</td>
<td>Classical pulmonary arteriopathy of small muscular arteries and arterioles distal to nonobstructed elastic pulmonary arteries</td>
<td>Intimal proliferation and/or increased media thickness, plexiform lesions. Endothelial dysfunction possibly related to low pressure and flow.</td>
</tr>
<tr>
<td>3</td>
<td>Pulmonary arteriopathy of small muscular arteries and arterioles distal to partially or totally obstructed elastic pulmonary arteries</td>
<td>Endothelial dysfunction probably related to poor perfusion and/or bronchial-to-pulmonary vascular anastomoses.</td>
</tr>
</tbody>
</table>

Treatment of CTEPH

- Medical Management
  - oral dual endothelin receptor antagonist: bosentan
- Lung Transplantation

Correlation of CT Scan Findings with Outcome of PEA in CTEPH

- Heinrich study of 60 pts who underwent PEA for CTEPH
  - neither PA diameter nor ratio of PA:aorta showed significant correlation w/post-operative PVR
  - PVR sig lower in pts with visible central PE
  - mean post-op PVR significantly lower in pts w/dilated bronchial arteries


Conclusion

- CTEPH is a complex disease entity with many controversial issues, particularly relating to its pathophysiology and natural history
- Meticulous interpretation of images including presence or absence of thrombus, location of thrombus as well as other ancillary findings is important for critical evaluation and management of these patients