Carcinoid Heart Disease and other Neuroendocrine Tumor Cardiac Complications

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September, 2018
Background

• Neuroendocrine tumors (NETs) are increasing in incidence.
• Metastatic NETs of the distal small intestine (midgut) produce serotonin and are typically associated with the carcinoid syndrome (flushing, diarrhea, wheezing).
• Carcinoid heart disease is a late manifestation of carcinoid syndrome.

1. Dasari et al. JAMA Oncol. 2017 Oct 1;3(10):1335-1342
Incidence

- Older literature: Carcinoid heart disease occurs in 20-50% of patients with the carcinoid syndrome\(^1\)

- Recent literature: Carcinoid heart disease develops in 10% of patients with metastatic midgut NETs\(^2\)

Pathophysiology

- Degree of damage correlates with extent and duration of serotonin exposure (median 5HIAA >200mg/24h)
- Right sided valves (tricuspid, pulmonary) predominantly affected
- Left sided valves involved <10%, likely due to inactivation of serotonin in the pulmonary circulation

• Plaque-like deposits of fibrous tissue on the endocardium of valvular cusps, leaflets, papillary muscles, cords, and cardiac chambers

• Plaques composed of myofibroblasts, smooth muscle cells and extracellular components

• Serotonin is likely the causative factor; 5HT receptors abundant on heart valves

• Similar pathology seen with anorectic drugs fenfluramine and phentermine (fen-phen), also thought to be serotenergic

• Affected valves have white appearance
  – thickened leaflets
  – shortened chordae
  – thickened papillary muscles

• Plaque usually involves ventricular aspect of tricuspid valve and arterial aspect of pulmonic valve
Signs/Symptoms

• Fatigue
• Dyspnea on exertion
• Edema
• Cardiac cachexia
• JVD (with prominent v wave)
• Murmur (accented by inspiration)


Davar et al J Am Coll Cardiol 2017 Mar 14;69(10):1288-1304
Screening

• **NCCN¹**: For patients with carcinoid syndrome, echo every 2-3 years or as clinically indicated

• **NANETS²**:  
  – Annual echo in all patients with significant elevations of urine 5-HIAA (>5 x ULN)  
  – Monitor patients with known early CHD more closely  
  – No consensus on screening asymptomatic patients with mild elevations of urine 5-HIAA

• **Uptodate³**:  
  – For patients with carcinoid syndrome, measure NT-proBNP levels.  
  – Echo in anyone with signs/symptoms or NTproBNP >260ng/ml (or 31 pml/L)

3. Connolly Uptodate 2018
NT-proBNP and echo findings

• NP-proBNP>260pg/ml
  – Sensitivity 69-82%
  – Specificity 80-91%

• Echo (trans-thoracic)
  – Thickening and retraction of tricuspid valve leaflets with associated tricuspid regurgitation
  – Tricuspid valve stenosis
  – Immobility of pulmonary valve cusps (may be difficult to visualize)
  – Right ventricular volume overload and diastolic pressure elevation (late finding)

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Echo findings

Tricuspid valve
- Thickening of the valve leaflets and subvalvular apparatus
- Diminished normal concave curvature of the leaflets
- Altered dynamic motion of the leaflets during diastole
- Fused and shortened chordae
- Retraction and reduced excursion of the valve leaflets
- Tricuspid regurgitation, ranging from mild to severe

Pulmonary valve
- Diffusely thickened valve cusps
- Straightening of cusps
- Fixed, retracted, and thickened cusps
- Pulmonary regurgitation and/or (annular) stenosis

Right atrium
- Dilated
- Inferior vena cava

Right ventricle
- Dilated
- Reduced function
Prevention

• Strategies to reduce circulating serotonin likely reduce development/progression of CHD.
  – Somatostatin analogs
  – Telotristat ethyl (oral serotonin inhibitor)
  – Hepatic transarterial embolization
  – Surgical debulking
  – Peptide receptor radiotherapy ($^{177}$Lu-dotatate)

• No evidence of reversal of CHD with medical treatments

Cardiologic management

- Diuretics may improve symptoms, but may also result in decreased cardiac output
Valve Replacement

• Consider in symptomatic patients with reasonably controlled metastatic disease
  – Symptomatic valve dysfunction
  – Decline in right ventricular function

• Typically replacement of tricuspid and pulmonary valves (unless clear uninvolvment of pulmonary valve)

• Need octreotide prophylaxis (iv 50-100mcg/h)

Davar et al  J Am Coll Cardiol 2017 Mar 14;69(10):1288-1304
Bioprosthetic vs. Mechanical Valve

• Bioprosthetic: risk of degeneration caused by carcinoid heart disease
• Mechanical: increased risk of thrombosis (up to 4% a year). Also need for permanent anticoagulation (vs. 3-6 months with bioprosthetic)

Raja et al. Future Cardiol. 2010 Sep;6(5):647-55
Prognosis

• Non-operative cases with severe carcinoid heart disease (NYHA class III or IV), median survival <1 year
• Operative mortality of about 5%
• With surgery, median OS improved from from 1.5 years in the 1980s, to 4.4 years in the late 1990s.

NET Cardiac Metastases

- Rare occurrence (<5% of metastases)
- Reported as myocardial nodules or pedunculated masses
- Can be a/w pericardial effusions
- Resections and XRT have been reported

MRI images courtesy of Dr. Daniel Jeong

Strosberg et al. J Med Case Rep. 2007 Sep 19;1:95