"I have a NET… Why Focus upon the Heart? And What’s a Cardiologist Doing on My Team, Anyway!"

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Today’s Tour
• Epidemiology - incidence
• Etiology - cause
• Pathoanatomy - functional and anatomic manifestations of Carcinoid Heart Disease
• Treatment of Carcinoid Heart Disease
• Perioperative management – protecting the Carcinoid patient
• Timing of Procedures - to operate heart or tumor first?
• Other Concerns – pertaining to the Carcinoid patient
• Brief Case Presentation – Final Exam
• What it all means to the Patient

Epidemiology
• Incidence of carcinoid cancer ranges from 3-4 per 100,000 / year in USA
• Berge and Linell et al. showed an incidence of 8.4 per 100,000 / year in Sweden

Etiology of Carcinoid Heart Disease
Was described by Maria Spatz in 1964 based on research experience with guinea pigs
Experimental carcinoid heart lesions required 3 abnormalities or derangements:
1) Hepatic injury
2) Elevated serotonin level
3) Relative tryptophan deficiency (which results from the excessive production of serotonin)

Treatment pearl: Tryptophan deficiency is treated with Niacin.
Pathoanatomy

- Serotonin...receptors...fibroblast proliferation (scarring)
- Severe fibrotic endocardial *pearly plaques* occur due to high serotonin levels
- Structural changes occur in valve leaflet architecture
- Mainly involving right-sided valves
- Left-sided involvement in the presence of a shunt, bronchial carcinoid tumor, or a very high serotonin level.

Clinical Pearl: We monitor tumor markers: urinary 5-HIAA, and blood Serotonin, Chromogranin-A, Pancreastatin and Neuron-specific enolase levels. (Goal: add bradykinin assay...more on this later)

In the Test Tube

- Fibroblasts + Serotonin $\rightarrow$ Fibroblast proliferation
- Addition of Omega III fish oil $\rightarrow$ Inhibits this effect

Clinical Pearl: Our Carcinoid patients are treated with Pro-Omega (purified/processed Omega III fish oil).
CARCINOID TUMORS

- "Functional" – Secretors → Carcinoid Syndrome
- "Nonfunctional" – Nonsecretors → No Syndrome

CARCINOID SYNDROME – Functional tumor

Occurs in 50% of patients with Carcinoid Syndrome.
95% do not have tumor in heart; 5% have cardiac mets.
Functional CARCINOroid CANCER releases vasoactive substances (including serotonin) which stimulates serotonin receptors resulting in fibroblast proliferation (scar formation) on the inner lining of the heart.

Somatostatin

An inhibitory peptide hormone
6 somatostatin genes in vertebrates; only 1 in humans

Somatostatin Receptors (Facilitate inhibition)
5 SSTR’s: SSTR2

Somatostatin Analogues
Octreotide, Lanreotide, Pasireotide

Serotonin
Secreted by Carcinoid tumors
Major contributor to carcinoid syndrome
Stimulates Serotonin Receptors in the heart

Clinical Pearl: Somatostatin analogues have affinity to SSTR2, suppressing NET growth by suppressing tumor growth factors and inhibiting tumor release of vasoactive substances, including serotonin and bradykinin.

CARCINOID CRISIS

Flushing
Diarrhea
Wheezing
Carcinoid Heart Disease

Clinical Pearl: Octreotide and Solucortef are mainstays of Crisis treatment.
Pathoanatomy
CARCINOID HEART DISEASE
Caused by high concentration of serotonin secreted by large burden of metastases in the liver (or by tumor in the ovaries)
RIGHT HEART (More common)
- Tricuspid Valve
- Pulmonic Valve
LEFT HEART (Less common)
- Mitral Valve
- Aortic Valve
Reason: SEROTONIN IS INACTIVATED IN LUNGS

Pathoanatomy
CARCINOID HEART DISEASE (Continued)
IF THERE IS LEFT HEART INVOLVEMENT, search for 3 possible causes:
• Hole in the heart
  - atrial septal defect
  - patent foramen ovale
• Carcinoid Tumor in Chest or Lungs
  - serotonin
  - mitral and aortic valves
• Extremely High Concentration of Serotonin

Pathoanatomy
CARCINOID HEART DISEASE (Continued)
CONSEQUENCES OF RIGHT HEART FAILURE:
- EDEMA, ASCITES, EFFUSIONS
- EDEMA OF LEGS
- ASCITES WITHIN ABDOMEN
- Bowel Edema/Malabsorption
- Malnutrition (cardiac cachexia)
CONGESTION OF LIVER
- Congestion - high risk of bleeding dictates the therapeutic sequence
  - (Fix the heart first)
PLEURAL EFFUSIONS AROUND LUNGS
- Causes shortness of breath (due to pulmonary edema and restriction of lung expansion).

Treatment - Valve Surgery
CARCINOID HEART DISEASE (CONTINUED)
SURGERY for Carcinoid Valve Disease:
- Tricuspid and Pulmonic Valve Replacement
- Prosthetic Valve Choice:
  - Mechanical (Metal)-durable but need Coumadin
  - Biologic (Tissue)-less durable but do not need Coumadin
SEROTONIN LEVEL - critical factor
- 46% recurrence of fibrosis with bioprosthetic valves
  - Telotristat could change this (more on this later).

Treatment - Prosthetic valves
Bioprosthesis
Mechanical

Treatment - Other Cardiac Surgery
Close Interatrial Defects
- atrial septal defect
- patent foramen ovale
Carcinoid Tumor in the Heart
- chemotherapy trial preferable
- monitor with serial MRI or CT studies
- rarely requires surgical excision
Treatment – Other Cardiac Surgical

- **Balloon Valvuloplasty** - occasionally, for isolated stenosis (but disease usually involves combined stenosis and insufficiency of more than one valve)

- **Transcatheter Valve replacement**
  - Pulmonic valve; IVC valve; SVC valve
  - Bioprosthetic valves (therefore, susceptible to recurrent Carcinoid Valvulopathy)

(Karl Stangl – Charite, Univ of Berlin)

Treatment - Other Surgery

**CARCINOID HEART DISEASE** (Continued)

**Other Cardiopulmonary Procedures:**

- Pacemakers for Electrical Heart Blocks
  - Prevent slow rhythm / fainting
- Decortication of lung for Scarring / Entrapment of Lung
  - Alleviate shortness of breath

Treatment - Medical

**CARCINOID HEART DISEASE** (Continued)

**MEDICAL THERAPY**

- Somatostatin analogues – inhibit tumor, reduce serotonin
- Diuretics - remove fluid
- Beta Blockers - slow the heart rate
- ACE Inhibitors – vasodilators / lower blood pressure
- Digoxin - strengthen contractility / control rhythm
- Ketanserin - vasodilator; reduce pulmonary hypertension

**Experimental** – Telotristat – Most hopeful – 70-80% reduction of serotonin (greater reduction of serotonin than somatostatin analogues)

Perioperative management can be life-saving!

Written instructions prior to cardiac cath, surgery, procedures

1. For prevention of a carcinoid crisis during and after surgery:
   a. Start an octreotide IV drip at 100 mcg/hour at least 2 hours pre-cath or pre-operatively and continue the drip throughout cath or surgery and in the ICU for 24-48 hours post-cath or post-operatively or until stable.
   b. For signs or symptoms of a carcinoid crisis (flushing, diarrhea, wheezing and/or extreme increase or decrease of blood pressure) give an extra 100mcg bolus of octreotide IV and increase the drip to 200mcg/hr.
   c. For persistence or recurrence of a crisis, give a repeat bolus of octreotide 100mg IV and increase the drip to 300mcg/hr; repeat IV boluses and increase the drip by 100mcg/hr increments as often as necessary (We have used doses as high as 500mcg/hr without significant adverse effects; others have used even higher doses).

2. To inhibit tumor release of bradykinin, give 100mg Solucortef IV on call to the cath lab or the OR.

3. I remain available by telephone during the time of surgery and postoperatively 24/7.

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Timing of Procedures

- Timing of procedures is critical
- In the absence of right heart failure, abdominal tumor-reductive procedures can proceed
- In the presence of right heart failure, **FIX THE HEART FIRST**, then reduce tumor burden and serotonin levels
- Often, right heart failure is advanced when the patient is first seen by a cardiologist
Other Concerns
Other effects of Cancer and Therapy upon the Heart

ANTITUMOR DRUGS
ADRIMYCYIN - heart failure
Monitor with Serial Echocardiograms
MONOCLONAL ANTIBODIES
Can adversely affect cardiac function

Other Concerns
OTHER EFFECTS OF CANCER UPON THE HEART
NUTRITIONAL RISK – diminished appetite

Heart Failure → ascites / bowel edema
→ Malnutrition (Cardiac Cachexia)

Other Concerns
CAUSES OF HEART FAILURE
HYPERTENSION (Stage I Heart Failure)
NONCARCINOID VALVULAR HEART DISEASE

Caution: Hypertension + valvular disease = increased risk of heart failure

Other Concerns
OTHER CAUSES OF HEART FAILURE
CORONARY HEART DISEASE
- Myocardial Infarction - scar
- Global ischemia (severe diffuse coronary disease)

CONGENITAL HEART DISEASE
- Hypertrophy - thickened cardiac walls
- Infiltrative Diseases
- Endocardial Diseases
  (Loss of compliance / decreased contraction)
- Anatomic and valvular anomalies

Other Concerns
HEART FAILURE SYMPTOMS

LEFT HEART FAILURE SYMPTOMS
- SHORTNESS OF BREATH
- CHEST TIGHTNESS
- PALPITATIONS

RIGHT HEART FAILURE SYMPTOMS / SIGNS
- EXERTIONAL FATIGUE
- LIVER PAIN / ASCITES
- LOWER EXTREMITY EDEMA

Other Concerns
PREVENT / TREAT HEART FAILURE

Control Blood Pressure
- Vasodilators – preferred
- Beta Blockers -- preferred
- Diuretics -- often needed

Repair or Replace Diseased Left Heart Valves
Repair or Replace Diseased Right Heart Valves
Prevent progressive endocardial scarring
- Somatostatin analogues
- Telotristat – more promising!
Other Concerns
PREVENT / TREAT HEART FAILURE – cont’d
TREAT RIGHT HEART FAILURE
Treat Left Heart Failure
Treat Reversible Pulmonary Disease
Treat chronic pulmonary embolism / Pulmonary hypertension / vasoconstriction
R/O deep vein thrombosis (blood clots)
Anticoagulation
Vasodilator therapy
Inferior Vena Cava filter

Brief Case Presentation – Final Exam
Typical referral – phone call from Dick Warner
• 62 yo male
• 6 yr History of diarrhea – Rx’d as Irritable Bowel Syndrome
• 2 yr Hx of flushing and occasional mid-abdominal pain
• Abdominal CT recently revealed 5 liver nodules, a mesenteric mass with spiculated calcified pattern, ascites and bilateral pleural effusions
• Physical examination: JVD with prominent V-waves, systolic murmurs, a firm pulsatile liver edge with HJR, and edema up to the lower ribs.
• EGD and Colonoscopy failed to reveal a primary tumor
• Very high urinary 5-HIAA, and blood markers (Serotonin, Chromogranin A and Pancreastatin levels).
• What we know before we’ve met the patient: (explain)
Clinical pearl: resection of the primary tumor results in prolonged survival.

WHAT IT ALL MEANS TO THE PATIENT
KNOWLEDGE of
HOW CANCER AFFECTS ONES HEART and HOW ONES HEART AFFECTS ONES CANCER
EMPOWERS US TO DO SOMETHING
Team Approach to the cancer patient
No one person can cover all the bases!
The patient is the most important team member.
The patient is involved in all decisions.
Collaboration among team is critical.
Focus on the PATIENT
Main Ingredients = Courage / Persistence

WHAT IT ALL MEANS TO THE PATIENT II
REWARDS of Repairing the Heart
Eliminates Heart Failure thereby enabling Safe abdominal Tumor-reducing Surgery
Eliminates edema, ascites and pleural effusions – improves mobility, cures malnutrition, eliminates shortness of breath.

WHAT IT ALL MEANS TO THE PATIENT V
REWARDS of CV RISK REDUCTION
Repairing Body / Fighting Cancer with greater Margin of Safety.
Reasonable and Prudent to Tune the Heart while Targeting Cancer.

Summary
The management of patients with Carcinoid Heart Disease is focused upon
• Accurately defining the pathoanatomy
• Aggressively managing heart failure
• Enlisting the active participation of patient and family
• Creating the proper medical / surgical / family team
• Protecting the patient from Carcinoid Crisis
• Prioritizing procedures
• Treating the whole patient
• Preventing recurrent valvulopathy
• Transitioning the patient to their next phase of anti-tumor treatment.
Thank you...and I wish to thank my colleagues at Mount Sinai’s Center for Carcinoid and Neuroendocrine Tumors who, as do I, feel so strongly that a team approach is the formula for success.
3 - **Decision re TPN** – Could delay surgery

- Estimated Dry Weight / Serum albumin
- Decision re home vs hospital TPN.

4 - **Referral for surgical consultations (CT and Onc)**

- Prioritize procedures – which procedure is performed first depends upon IVC pressure (in our case - fix the heart first)

5 - **Review all data with team members**

- NET Expert, Surgical Oncologist, Cardiac Surgeon

6 - **Arrange Admission for Cardiac Cath/Surgery**

- Selection of prosthetic valve – Tissue vs Mechanical

   *(Heidi Connally’s experience with this issue is invaluable)*

   *Telotristat on the horizon – this could change our choice of valves*

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7 – **The Protocol for Protection through**

- Cardiac Cath and Surgery includes:
  - Solucortef – inhibits release of bradykinin
  - Octreotide Drip -

   *(Rodney Pommier et al published article – 2013 - entitled “Octreotide LAR and Solox Octreotide Are Ineffective for Preventing Intraoperative Complications in Carcinoid Patients”)*

   *And we await a follow-up from his group when he reports more on this topic.*

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8 - **Instructions/warning for Surgeon, Anesthesiologist, Intensivist and Cath team** –

- Continuous Octreotide Drip throughout
- Octreotide bolus and increase drip pm signs/symptoms of carcinoid crisis / I Define crisis for the team
- Avoid adrenergic pressors – treat hypotension with fluids, Solucortef and octreotide
- Avoid anesthetics which stimulate an adrenergic response
- Avoid analgesics which stimulate an adrenergic response

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**Twenty years later, Drs Bhattacharyya, Davar, Dreyfus and Caplin admonished in the Journal, Circulation:**

**“Avoiding or minimizing the use of drugs known to precipitate mediator release such as opioids, the neuromuscular relaxant atracurium, and catecholamine producers like dopamine and epinephrine may reduce the risk of carcinoid crisis.”**

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**And Drs Powell, Mukhtar and Mills commented upon the alternative to adrenergic pressors for hypotension:**

**“Reliable large bore access in case of rapid volume loss and the availability of fluid warmers and the use of a rapid infusion system are sensible standards.”**

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**In a 1987 Case report**

- Larry Kvols and colleagues demonstrated the reversal of carcinoid crisis (with shock, and severe vasoconstriction following adrenergic pressors) within 40 seconds of two 50mcg IV doses of a somatostatin analag

   *(which was considered experimental at that time).*

**Carcinoid Crisis during Anesthesia: Successful Treatment With a Somatostatin Analogue**


*Anesthesiology: January 1987 - Volume 66 - Issue 1 - pp 89-91*
Postoperative management

9 - Treatment of Carcinoid Crisis after surgery—Same
   Treat hypotension with fluids and octreotide boluses! Sometimes
   Solucortef is given in the post-op period.

10 - When BP stable: Return patient to dry weight
   I write orders:
   Daily Am weights – Often I’m the only one interested in this!
   Diurese to dry weight
   Monitor BP sitting and standing once/8-hour shift

11 - Postoperative echocardiogram — within 1 week of surgery
   4 chamber status
   Immediate postoperative valvular status

12 - Pre-dismissal instructions to patient and family:
   Check weight and BP sitting and standing each AM
   Phone data to me daily.
   Physiotherapy is arranged at patient’s home – very important

Post-dismissal management

13 - Follow-up every two weeks in office
   Blood tests (weekly, at home or in our office)
   Nutritional assessment
   Decision re multitasking tumor-reductive procedure
   at 6-12 weeks post-op (avoid recurrence of carcinoid
   valvulopathy on prosthetic tissue valves)

14 - Repeat echocardiogram and biomarkers at 4 weeks post-op
   Recurrence of carcinoid valvulopathy as early as
   3-4 months post-op (Drs Caplin, Davar et al)

15 – Finally - Prepare patient for multitasking tumor-
   reductive surgery or other tumor-directed procedure
   or therapy
   If serotonin elevated, we urge entry into one of the
   two Telotristat trials