PROGRESSIVE DYSPNEA
A CASE OF IDENTIFYING THE KEY ELEMENT

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Case: Background

60 y/o Caucasian male with complicated PMHx transferred to us from OSH for **progressive dyspnea on exertion**.

HPI (February 2014 to December 2014)
- **Multiple admissions** (4) over the past several months for cellulitis, worsening renal function, progressive shortness of breath. Was admitted in 2/2014 for IgA vasculitis of skin/kidney.
- **New 2L O2 requirement**
- Mild cough, non-productive
- Dyspnea with minimal exertion

ROS
- No chest pain, nausea, vomiting, fevers, chills, no rashes.
- Knees ache
- Long term steroids started in 2/2014: resulted in worsening DM, anxiety, tremor
Past Medical History

- Diastolic Heart failure with preserved EF
- Paroxysmal atrial fibrillation
- Obstructive sleep apnea
- Moderate Pulmonary Hypertension
- CAD (stent 2008, med mgmt)
- Type II DM
- CKD Stage III
- IgA Vasculitis (skin, ? kidney)
- Anxiety
Medications

• Amiodarone 200 mg daily
• Amlodipine 10 mg daily
• Atorvastatin 40 mg nightly
• Duloxetine 60 mg daily
• Furosemide 40 mg daily
• Insulin Glargine 30 units BID
• Losartan 20 mg daily
• Nebivolol 20 mg daily
• Prednisone 10 mg daily
• Warfarin 5 mg
Family History: No history of early cardiac death.

Social History:
- Lives with his wife in North Conway.
- Previously independent with ADLs.
- He works as a marketing consultant.
- No smoking, EtOH, or other drugs.
- 4 cats.
- No recent travel.
Admission Physical Exam

**VS:** BP 160/63 HR 64 Temp 36.8 RR 16 Sp02 97% on 2L BMI 39

**Gen:** Pleasant, appears older than stated age, AOx3

**HEENT:** PERRL, EOMI, conjunctiva pink, anicteric, MMM

**Lungs:** comfortable breathing, diminished breath sounds

**CV:** reg rate, no M/R/G, no JVD appreciated

**Abd:** obese, soft, benign

**Ext:** no clubbing, 2+ edema b/l

**Skin:** chronic venous stasis changes in LE, ecchymoses

**Neuro:** CN2-12 intact, strength 5/5 symmetric
Preliminary Evaluation
Portable Chest X-Ray

1 year prior to this admission
## Labs

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
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<tbody>
<tr>
<td>Na</td>
<td>139</td>
</tr>
<tr>
<td>K</td>
<td>3.6</td>
</tr>
<tr>
<td>Cl</td>
<td>104</td>
</tr>
<tr>
<td>CO2</td>
<td>27</td>
</tr>
<tr>
<td>BUN</td>
<td>35</td>
</tr>
<tr>
<td>Cr</td>
<td>1.26 (at baseline)</td>
</tr>
<tr>
<td>Glu</td>
<td>159</td>
</tr>
<tr>
<td>WBC</td>
<td>13.0</td>
</tr>
<tr>
<td>Hgb</td>
<td>10.2</td>
</tr>
<tr>
<td>Plt</td>
<td>307</td>
</tr>
<tr>
<td>MCV</td>
<td>87</td>
</tr>
<tr>
<td>INR</td>
<td>6.7</td>
</tr>
<tr>
<td>Protein</td>
<td>6.4</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.0</td>
</tr>
<tr>
<td>Bili</td>
<td>0.5</td>
</tr>
<tr>
<td>Alk phos</td>
<td>66</td>
</tr>
<tr>
<td>AST</td>
<td>28</td>
</tr>
<tr>
<td>ALT</td>
<td>30</td>
</tr>
<tr>
<td>Ca</td>
<td>8.9</td>
</tr>
</tbody>
</table>
Additional history?
Hospital Course:

• **Preliminary Diagnosis:** Acute decompensated diastolic heart failure
• Aggressive diuresis is attempted
• 5 days later patient 12 pounds lighter
• Dyspnea persists
• O2 requirement persists
• Patient develops atrial fibrillation with RVR (rates 110-140s) refractory to metoprolol 75 mg q 6.
• **What other data do we need?**
CT Chest
Transthoracic Echocardiogram

Vel 440 cm/s
PG 77 mmHg
Pulmonary Function Testing

FVC 51%
FEV1 47%
FEV1/FEV 70%
DLCO 28%

Interpretation:
There is a moderate obstructive defect. An additional restrictive defect cannot be excluded by spirometry alone. There is a severe decrease in diffusing capacity.
Recap:

Over the course of 10 months:
- New hypoxia with progressive dyspnea on exertion
- Atrial fibrillation with rapid and refractory rate
- Preserved LVEF, moderate diastolic dysfunction
- Worsening, now severe pulmonary hypertension
- PFTs showing severely reduced DLCO
- No evidence of cardiac ischemia
- Vasculitis appears quiescent: CRP/ESR wnl
- CKD is stable

Occam’s razor versus Hickam’s dictum?
Thyroid Function Tests

12/8/2014
TSH < 0.02 uIU/mL (0.27 – 4.20)
FT4 2.21 → 4.0 ng/dL (0.9-1.7)
TT3 224.1 → 244.2 → 436.9 ng/dL (80 – 200)

2/20/2014 (prior)
TSH 10.12 uIU/mL (0.27 – 4.20)
FT4 1.39 ng/dL (0.9 – 1.7)
TT3 72 ng/dL (80 – 200)
Diagnosis

• Amiodarone toxicity with simultaneous involvement of the lung and thyroid gland.
Amiodarone

- Heavily iodinated molecule
- Progenitor molecule, khellin, from plant extract of Khella or Ammi visnaga, a common plant in north Africa
- Cured anginal symptoms
- Approved only for refractory ventricular arrhythmias
Amiodarone Pharmacodynamics

• Prolongs myocardial repolarization via potassium channel blockade (class III effect)

• Also class I, II, and IV antiarrhythmic effects:
  • Decreases conduction velocity by blocking sodium channels (I)
  • Beta-blockade (II)
  • Reduces inward L-type (slow) calcium channel activity (IV)
Adverse Effects

- Hypothyroidism (6%)
- Hyperthyroidism (0.9-2%)
- Pulmonary toxicity (1-17%)
Amiodarone Pharmacokinetics

- Variable oral bioavailability (avg 50%).
- Highly lipophilic
- Long elimination half life
- Cytochrome p450 system

Iodine Content

- 37% iodine by weight
- 200 mg tablet has 75 mg of organic iodide
- Up to 17% of that is available as free iodide (12.75 mg)
- Total daily requirement of iodide about 75 mcg
- Therefore, amiodarone 200 mg BID dose equivalent to 340x (or 34,000%) daily iodine requirement
Amiodarone Induced Thyrotoxicosis (AIT)

- **Prevalence 3-5% in US**
- **Intrinsic Drug Effects**
  - Inhibits thyroxine (T4) deiodination to triiodothyronine (T3).
  - Blocks T3 binding to nuclear receptors and decreases expression of thyroid hormone related genes.
  - Direct toxic effect to thyroid follicular cells (Type II AIT).
Amiodarone Induced Thyrotoxicosis (AIT)

• **Effects Due to Iodine**
  - **Normal thyroid**: Wolff-Chaikoff effect
  - **Underlying thyroid disease**:
    - *Autoimmune thyroid disease*: “Fail to escape” Wolff Chaikoff effect resulting in goiter, hypothyroidism
    - *Nodular disease, latent Grave’s*: No autoregulation of iodine, excessive TH synthesis and thyrotoxicosis (Jod-Basedow effect) (Type I AIT).
AIT: Two Types

Type I AIT

• Increased synthesis of thyroxine (T4) and triiodothyronine (T3).
• Pre-existing multinodular goiter or latent Graves’ disease.
• Excess iodine provides increased substrate = enhanced thyroid hormone production.

Type II AIT

• Destructive thyroiditis that results in excess release of T4 and T3.
• No underlying thyroid disease.
• Hyperthyroid then hypothyroid phase.
• Toxic effect may take 2-3 years to become evident.
Treatment of AIT

• Type I AIT:
  • Amiodarone should NOT be discontinued until hyperthyroid symptoms are well controlled with thionamides (increased T3 levels if amiodarone is d/c’ed)
  • Thionamides (methimazole)
  • Radioiodine (not usually an option due to low radioiodine uptake)
  • Surgery

• Type II AIT (most common):
  • Glucocorticoids
  • Treatment of hypothyroidism

• If unknown (most common of all):
  • Thionamides and glucocorticoids
  • 99mTc-sestaMIBI thyroid uptake and scintigraphy may help to distinguish between Type I/II
Amiodarone Induced Pulmonary Toxicity

- Occurs most frequently as **ILD (31.4%), pulmonary fibrosis (25.6%) and pleural effusion (24.8%).**
- Cough, new chest infiltrates, reduced lung diffusing capacity… (68 patterns on pneumotox)
- Proposed mechanisms of action:
  1. direct toxic effect;
  2. immune mediated mechanisms;
  3. the angiotensin enzyme system activation.
- Treatment is discontinuation of drug and corticosteroids.
- Mortality 9-50%
Clinical Course

- Amiodarone stopped for likely pulmonary toxicity
- Thyrotoxicosis refractory to escalating doses of methimazole, steroids, beta-blockers
- Thyroidectomy
- Diuresis
- Improved Pulmonary HTN
- Decreased DLCO
- Feels “fantastic” since he’s had his thyroid removed
Follow up

Most recent echocardiogram
Thyroid Pathology

Saad et al, 2004
<table>
<thead>
<tr>
<th>System</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Possible Adverse Effect</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>ECG</td>
<td>Yearly</td>
<td>QT prolongation; torsades; symptomatic SA node/conduction system impairment</td>
<td>Reduce/Discontinue</td>
</tr>
<tr>
<td>Endo</td>
<td>TFT</td>
<td>q 6 mos</td>
<td>Hyperthyroidism; hypothyroidism</td>
<td>Discontinue; refer to endocrinology; treat if hypothyroid</td>
</tr>
<tr>
<td>Hepatic</td>
<td>AST/ALT</td>
<td>q 6 mos</td>
<td>AST/ALT elevation 2x upper limit nml</td>
<td>Reduce/Discontinue</td>
</tr>
<tr>
<td>Pulm</td>
<td>PFT; CXR</td>
<td>Yearly CXR; PFT PRN symptoms</td>
<td>Pulmonary toxicity (cough, fever, dyspnea)</td>
<td>Discontinue; consider corticosteroid treatment</td>
</tr>
<tr>
<td>Neuro</td>
<td>PE</td>
<td>PRN</td>
<td>Ataxia, dizziness, fatigue</td>
<td>Reduce or discontinue</td>
</tr>
<tr>
<td>Optho</td>
<td>Eye exam</td>
<td>PRN</td>
<td>Corneal microdeposits; optic neuropathy</td>
<td>Continue treatment; discontinue treatment</td>
</tr>
<tr>
<td>Derm</td>
<td>PE</td>
<td>PRN</td>
<td>Photosensitivity; blue-grey skin discoloration</td>
<td>Avoid sunlight; reduce/discontinue dose</td>
</tr>
</tbody>
</table>

Screening Guidelines

Learning Points

• A careful history is key to diagnosis.
• Amiodarone is a complex and fascinating drug.
• Two types of AIT.
• Routine multi-organ system screening is essential for patients starting (and continuing) amiodarone therapy.
References

- Ross, D. “Amiodarone and Thyroid Dysfunction.” In: UpToDate, Cooper, D (Ed). UpToDate Waltham, MA. (Accessed online on Sept 10 2015)
Thank You

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