Amyloidosis

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Love-Making Reveals a Broken Heart:
A 46-Year-Old Man with Recurrent Hemoptysis During Sexual Intercourse

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Case presentation

• 46-year-old man w/history of type 2 diabetes

• Chief complaint:
  » Recurrent hemoptysis during sexual intercourse
  » Chest pain
  » Shortness of breath

• Physical exam: normal

• ECG in office:
  » Normal sinus rhythm, normal voltage
  » Left anterior fascicular block

• CXR: normal
Pulmonary work-up: negative

- Pulmonary function testing
- Chest CT
- Bronchoscopy with BAL
- Transbronchial biopsy
• Findings at rest:
  » Normal LV size
  » Normal LVEF and wall motion
  » Moderate concentric LVH
  » No significant valvular disease
  » Grade 3 diastolic dysfunction
Stress echocardiography

- Stress test:
  » Bruce protocol
  » Chest pain at 6 minutes
  » Total exercise time = 8 minutes (9.4 METs)
Stress echocardiography
Cardiac catheterization

- Angiographically normal coronary arteries
- Normal hemodynamics
Adenosine Perfusion

Rest

Stress
Adenosine Perfusion

Rest

Stress
Summary of MRI findings

- Normal LV size and systolic function
- Moderate concentric LVH
- No focal hyper-enhancement
- Mild mitral regurgitation
- Diffuse reversible subendocardial hypoperfusion with adenosine (in the absence of significant CAD → microvascular dysfunction)
Unifying diagnosis?

- Microvascular ischemia:
  - Cardiac syndrome X?
  - May explain exertional dyspnea, chest pain
- What about exertional hemoptysis?
- Is this Hickam’s Dictum or can we push forward and satisfy Occam’s Razor?
Unifying diagnosis?

• Occam’s Razor:
  » “pluritas non est ponenda sine necessitas”
  » “plurality should not be posited without necessity”

• Hickam’s Dictum:
  » “Patients can have as many diseases as they damn well please”
DDx of hemoptysis during intercourse

- **Cardiogenic**
  - Heart failure
  - Mitral stenosis
  - Coronary artery disease
  - Systemic hypertension

- **Vascular**
  - Pulmonary vascular problem
    - Pulmonary embolism
    - Vasculitis

Another look at the echo...

Apical 4-chamber view

Tissue Doppler

s' = 5 cm/s

e' = 4 cm/s
Global longitudinal strain (GLS)
Global longitudinal strain (GLS)

“Cherry on top”
Another look at the cardiac MRI
Mechanisms of contrast enhancement in myocardial infarction.

Adapted from: Mahrholdt H et al. Eur Heart J 2005;26:1461-1474

Intact Cell Membrane

Ruptured Cell Membrane

Collagen matrix
Extracellular Volume Fraction (Ve) in our patient on CMR T1 mapping:

<table>
<thead>
<tr>
<th>Ve% of Whole Myo</th>
<th></th>
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<tbody>
<tr>
<td>4CH</td>
<td>43.8%</td>
</tr>
<tr>
<td>SA Base</td>
<td>40.4%</td>
</tr>
<tr>
<td>SA Mid</td>
<td>37.8%</td>
</tr>
<tr>
<td>Normal</td>
<td>&lt; 25%</td>
</tr>
</tbody>
</table>
Repeat right heart cath w/exercise

- **REST 1-MIN. OF EXERCISE**
  - PA 38/15 (24)
  - PA 78/40 (54)
Repeat right heart cath w/exercise

PCWP 15

REST

100

PCWP 37

1-MIN. OF EXERCISE
Case summary

- 46-year-old diabetic man with hemoptysis during intercourse, angina, dyspnea
- Pulmonary work-up negative
- Normal LVEF but severely reduced longitudinal systolic and diastolic function
- Increased, diffuse protein infiltration in the myocardium + subendocardial ischemia
- Marked exercise-induced pulmonary venous hypertension due to severe diastolic dysfunction
What’s the diagnosis?

AMYLOID PROTEIN

APPLE-GREEN BIREFRINGENCE
Case summary

- Patient treated with:
  - Bortezomib (Velcade)
  - Warfarin
  - Spironolactone
  - Bumetanide (low dose)
- Marked improvement in functional status
- Underwent autologous stem cell transplantation with uneventful course
- No sign of recurrence of amyloid
Systemic amyloidoses

- Group of disorders characterized by extracellular deposition of fibrillar protein
- Deposits composed of amyloid fibrils → progressive end-organ dysfunction
- > 20 proteins form amyloid fibrils in vivo
- 2 predominant types involve the heart:
  - AL: typically assoc. w/plasma cell dyscrasia
  - Transthyretin (TTR)-associated:
    - Hereditary (mutation) and senile (wild-type)
Cardiac amyloid: rare disease?

- Annual incidence of systemic amyloid:
  » 6-10 cases per million in United States
- But...
  » Amyloidosis likely under-recognized
  » Transthyretin (TTR) amyloid may be common
    – 3-4% of African Americans carry V122I mutation in TTR gene
    – Wild-type (senile) TTR amyloidosis increasing in prevalence
Cardiac amyloid: rare disease?

In older patients with HF and preserved EF, amyloid deposition is common.

Circulation. 2010; 122: A17926
Cardiac amyloidosis

- **Primary (AL) amyloid (light chains)**
  - Order serum immunofixation, not SPEP

- **Familial (TTR) amyloid**
  - Due to TTR gene mutation (3-4% of AAs have V122I)
  - Neuropathy, cardiomyopathy

- **Secondary (AA) amyloid**
  - Cardiac involvement is rare

- **Senile cardiac amyloid**
  - Due to wild-type TTR accumulation
Clinical clues for the diagnosis

- Bilateral carpal tunnel syndrome
- Macroglossia
- Easy bruising, decreased Factor X levels
- Heart failure with...
  - Kussmaul’s sign
  - Peripheral neuropathy
  - Autonomic dysfunction / orthostatic hypotension
  - Continuous low-level troponin release
- Low BP, low volts, and thick heart
Typical echo findings

Loss of longitudinal cardiac function
Typical echo findings

Severely reduced longitudinal tissue velocities

“5-5-5 sign”
Typical cardiac MRI findings

Diffuse subendocardial delayed enhancement
Typical cardiac MRI findings

*Diffuse subendocardial delayed enhancement*
Speckle-tracking: “cherry on the top”

“Cherry on top”
Speckle-tracking: “cherry on the top”

Speckle-tracking: “cherry on the top”

A1, A2, A3, A4: CARDIAC AMYLOID

B1, B2, C1, C2: HYPERTROPHIC CM, AORTIC STENOSIS
Cardiac amyloidosis: key echo findings

- Severely reduced longitudinal function
  - TDI e’, a’, and s’ typically < 5 cm/s
  - Absolute global longitudinal strain < 15% (often < 10%)
- Preserved radial and apical function
Cardiac amyloid: echo pearls

• “Sparkling texture” on echo:
  » Still helpful in era of harmonic imaging
  » Look at renal function: if no severe CKD or ESRD, sparkling appearance (especially with severely decreased longitudinal function), think infiltrative (most commonly amyloid)

• Remember to look at tissue Doppler s’, e’, and a’ velocities:
  » They will be severely reduced (< 5 cm/s) in most cases of cardiac amyloid
Cardiac amyloid can be treated!

- **Cardiac amyloid:** *not a death sentence*
  - Primary (AL) amyloidosis:
    - Stem cell transplantation *or*
    - Cardiac transplant followed by stem cell tx
  - Familial or wild-type TTR amyloidosis:
    - Several novel drugs in pipeline (TTR stabilizers, RNA interference, RNA anti-sense molecules)
    - Phase 3 clinical trials in TTR cardiac amyloid: ATTR-ACT and ENDEAVOUR
    - Heart-liver transplant
Primary (AL) cardiac amyloid: improved survival with stem-cell tx

Northwestern all patients (N=26)
- Chemo only (N=7)
- Chemo + stem cell tx (N=19)

Historical controls (N=24)
- Dubrey et al. Heart 1997

Friedman J....Shah SJ. ACC 2014
Take home points

- Amyloidosis is not 1 disease
- Prognosis of amyloidosis varies by organ involvement and type of amyloid
- **Echo clues:**
  - Sparkling, granular texture of myocardium
  - Thick LV out of proportion to ECG voltage
  - Severely reduced longitudinal systolic/diastolic function
  - “Cherry on the top” on speckle-tracking
- *Cardiac amyloid: not a death sentence*
thank you!