2015 SCVP Young Investigator Award Presentations

Md Shahrier Amin: Amyloidosis in Atrial Appendages Removed During the Cox-Maze Procedure: A Study of 349 Consecutive Cases (2010-2014) with Clinical Implications.

Thomas C. Wright: Myocardial Metal Levels in the Setting of Total Joint Arthroplasty: A Study of 94 Cases with Establishment of Normative Range.

Mahboubeh Rahmani: CD123 (IL3-Receptor) Identifies Antigen Presenting Cells in Cardiac Sarcoidosis and Eosinophilic Myocarditis but not in Idiopathic Giant Cell Myocarditis.


George Eng: Optimization of serum free light chain analysis for rapid and reliable subclassification of cardiac amyloidosis.
Amyloidosis in Atrial Appendages Resected During Cardiac Surgeries: A Study of 346 Consecutive Cases (2010-2014) with Clinical Implications

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¹Department of Laboratory Medicine and Pathology
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MAYO CLINIC, ROCHESTER, MN.
Background

- Atrial appendages are commonly encountered in surgical pathology practice.

- Atrial amyloidosis (including different amyloid types) has been recognized in the pathology literature, though its significance is not known.

- Whether or not further diagnostic evaluation is required for incidental amyloidosis in atrial appendages, has not been studied.

Objectives

- Study morphologic characteristics and distribution of amyloid in atrial appendages.

- Evaluate the types and epidemiologic parameters of amyloid in atrial appendages.

- Investigate association between atrial amyloid deposition with pre-existing and persistent clinical correlates.
Amyloid deposits are present in 47% of resected atrial appendages

‘Euamyloid’

‘Heteroamyloid’
161 (47%) patients with atrial amyloid

- ‘Euamyloid’
  - 5 patients (3%)
- ‘Heteroamyloid’
  - 149 patients (92%)
- Mixed
  - 7 patients (4%)

Mass spectrometry based typing

- ‘Euamyloid’ = ATTR
- ‘Heteroamyloid’ = AANF
Conclusions

- Atrial amyloid is more common than expected.

- Two morphologies of amyloid can be seen in atrial appendages, that appear to be type-specific:
  - ‘Euamyloid’ = ATTR
  - ‘Heteroamyloid’ = AANF

- Most atrial amyloid is of the ‘heteroamyloid’ variety (AANF):
  - This does not appear to be associated with post-op recurrence of atrial fibrillation.
  - Does not appear to have significant clinical implications at this point.
Myocardial Metal Levels in the Setting of Total Joint Arthroplasty: A Study of 94 Cases with Establishment of Normative Range

T. Carson Wright, BS

CC Wyles BS, MS Amin MBBS PhD, SM Jenkins MS, PL Day MT, DL Murray MD PhD, RT Trousdale MD, WD Edwards MD, JJ Maleszewski MD

Mayo Clinic
Rochester, MN
Background

• Implants used in total joint arthroplasty (TJA) contain cobalt (Co) and chromium (Cr)
• Co/Cr undergoes wear-related release

Methods

• Tissue Registry Archive (1990-11)
• 80 age- and sex-matched controls
• Autopsy/medical record searched
• Tissue acid digestion
• Mass spectroscopy: Cobalt, Chromium, Vanadium
Results

- Demographics: 94 TJA cases, 77.4 years, 46.8% women

- Myocardial Vanadium and Chromium: No significant difference between TJA and controls

- Myocardial Cobalt: Total Joint Arthroplasty > Controls
  - Median Co: 0.105 vs 0.077 µg/g ($p$-value 0.003)

- Cardiomegaly: Total Joint Arthroplasty > Controls
  - Incidence: 43.6% vs. 21.3% ($p$-value 0.002)

- Interstitial Fibrosis: Total Joint Arthroplasty > Controls
  - Incidence: 27.7% vs. 13.8% ($p$-value 0.025)
Discussion

Cobalt levels in two cases of clinical cobalt cardiotoxicity associated with metal-on-metal prosthetics:

- ⭐ 8.32 µg/g (Allen et al. 2014)
- ❌ 3.76 µg/g (unpublished)

Myocardial Co (µg/g) in 2 cases of clinical Co cardiotoxicity and in TJA cohort
CD123 (IL3-Receptor) Identifies Antigen Presenting Cells in Cardiac Sarcoidosis and Eosinophilic Myocarditis but not in Idiopathic Giant Cell Myocarditis

Mahboubeh Rahmani, Robert N. Salomon and Monika Pilichowska
Introduction

Giant Cell Myocarditis

Cardiac Sarcoid
### Materials

<table>
<thead>
<tr>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Giant Cell Myocarditis (IGCM)</td>
<td>7</td>
</tr>
<tr>
<td>Cardiac Sarcoid (CS)</td>
<td>9</td>
</tr>
<tr>
<td>Eosinophilic Myocarditis (EM)</td>
<td>3</td>
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<tr>
<td>Lymphocytic Myocarditis (LM)</td>
<td>3</td>
</tr>
<tr>
<td>Myocarditis, NOS</td>
<td>1</td>
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Table 1.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Marker of</th>
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<tbody>
<tr>
<td>CD123 (IL3 receptor)</td>
<td>Plasmacytoid dendritic cells</td>
</tr>
<tr>
<td>CD1c (BDCA-1)</td>
<td>Myeloid dendritic cells</td>
</tr>
<tr>
<td>CD68</td>
<td>Macrophages</td>
</tr>
<tr>
<td>CD3</td>
<td>T-cells</td>
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<tr>
<td>CD4</td>
<td>Helper T-cells</td>
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<td>CD8</td>
<td>Cytotoxic T-cells</td>
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<td>Ki67</td>
<td>Proliferation factor</td>
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<tr>
<td>CD117</td>
<td>Hematopoietic stem cell marker</td>
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<tr>
<td>CD34</td>
<td>Hematopoietic stem cell marker</td>
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Table 2.
## Results

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<th>Dx</th>
<th>Antibody</th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
<th>Score 4</th>
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<tbody>
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<td>CD123</td>
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<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>CD1c</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Cardiac Sarcoid (9)</td>
<td>CD123</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>CD1c</td>
<td>2</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Eosinophilic Myocarditis (3)</td>
<td>CD123</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>CD1c</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Lymphocytic Myocarditis (3)</td>
<td>CD123</td>
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<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>CD1c</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myocarditis, NOS (1)</td>
<td>CD123</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>CD1c</td>
<td>1</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

All control cases of nodal, pulmonary, cutaneous sarcoidosis and granulomas in tuberculosis were positive for CD123 with score 4.
Summary and Conclusions

- PDCs and mDC are not significant in IGCM and macrophages in IGCM do not express CD123 (IL3R)
- In CS, CD123(IL3R) is expressed in granulomas

- IL3R ligand likely plays a role in granuloma formation
- CD123 staining is helpful in identifying granulomas
Molecular Assessment of Antibody-Mediated Rejection (AMR) in Formalin-fixed, Paraffin-embedded (FFPE) Human Cardiac Allograft Biopsies

Bahman Afzali1,2, Erin Chapman1, Benjamin Adam1, Fernando Gil2, Daniel Kim3, Luis Hidalgo1, Patricia Campbell1, Banu Sis1, Michael Mengel1
1. Dept. of Laboratory Medicine & Pathology, University of Alberta, 2. Dept. of Pathology, University Duisburg-Essen, 3. Div. of Cardiology, University of Alberta
BACKGROUND

• Antibody-mediated Rejection (AMR) is emerging as a major clinical challenge and leading cause for cardiac allograft failure
• ISHLT consensus for diagnosing AMR is based on histo- and immunopathology correlates of antibody-mediated tissue injury, i.e. microcirculation inflammation (H+), complement deposition (I+)
• Current diagnostic criteria are frequently equivocal and thus have limited clinical utility
• The unmet need is for more precise diagnostic tools to assess the disease stage and activity of antibody-mediated tissue injury, which can be applied in routine diagnostics to support clinical decision-making
MATERIAL AND METHODS

107 FFPE cardiac Bx

22 pAMR2

37 pAMR1 H+

11 pAMR1 I+

22 ACR

15 Normal

clinical / serologic data

Treatment, Ejection Fraction, DSA, CAV, Graft Status, Survival

HE-slide review: identification of myocardium

endothelial swelling measurement (TEM)

RNA isolation & multiplex gene expression quantification

34-gene set: 18 endothelial, 6 NK-cell, 10 inflammatory
RESULTS AND CONCLUSIONS

• nCounter® is suitable for routine molecular diagnostics on FFPE cardiac allograft samples
• Gene set is associated with histopathological and ultrastructural phenotype of microcirculation injury and inflammation
• Higher diagnostic accuracy than DSA and C4d
• Increase of gene set expression is associated with inferior prognosis

CONCLUSIONS
Optimization of Serum Immunoglobulin Free Light Chain Analysis for Subclassification of Cardiac Amyloidosis

George Eng MD, PhD., Marc K. Halushka MD, PhD., A. Bernard Collins, Daniel P. Judge MD., Marc J. Semigran MD., James R. Stone MD, PhD.

- Subclassification dictates management
- Most common ventricular types: AL and ATTR amyloidosis
- Direct subtyping can have slow turn-around times and can be costly
- Serum free light chains quantifies amount of κ and λ light chains in serum
### Design

**85 total cases**

- Endomyocardial biopsies: n = 72
- Explanted hearts: n = 9
- Autopsy: n = 2
- Interventricular septal myectomy: n = 1
- Left ventricular apical core: n = 1

85 cases of proven ventricular amyloid were directly subtyped by mass spectrometry or immunofluorescence

### Patient Characteristics and SFLC Values by Type of Amyloid

<table>
<thead>
<tr>
<th></th>
<th>AL-κ</th>
<th>AL-λ</th>
<th>ATTR</th>
<th>AA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>12</td>
<td>30</td>
<td>42</td>
<td>1</td>
</tr>
<tr>
<td><strong>Age (mean ± SD)</strong></td>
<td>60 ± 7</td>
<td>62 ± 9</td>
<td>75 ± 9</td>
<td>68</td>
</tr>
<tr>
<td><strong>Gender (M/F)</strong></td>
<td>7/5</td>
<td>18/12</td>
<td>33/9</td>
<td>0/1</td>
</tr>
<tr>
<td><strong>κ range (mg/L)</strong></td>
<td>80 to 6700</td>
<td>1.0 to 97.4</td>
<td>6.1 to 154</td>
<td>22</td>
</tr>
<tr>
<td><strong>λ range (mg/L)</strong></td>
<td>0.53 to 47</td>
<td>41 to 6800</td>
<td>8.0 to 82</td>
<td>42</td>
</tr>
<tr>
<td><strong>κ/λ range</strong></td>
<td>6.7 to 967</td>
<td>0.01 to 0.41</td>
<td>0.63 to 2.7</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>κ-λ range (mg/L)</strong></td>
<td>68 to 6700</td>
<td>-32 to -6700</td>
<td>-22 to 72</td>
<td>-20</td>
</tr>
</tbody>
</table>
# Test Characteristics for using SFLC Values to Subtype Ventricular Cardiac Amyloidosis as AL Amyloid.

<table>
<thead>
<tr>
<th>Cutoff Method</th>
<th>Cutoff Values</th>
<th>True</th>
<th>False</th>
<th>False</th>
<th>True</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absolute Value of κ and λ (mg/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>κ &gt; 19.4 or λ &gt; 26.3</td>
<td>42</td>
<td>0</td>
<td>36</td>
<td>7</td>
<td>100% (90-100%)</td>
<td>16% (7-31%)</td>
</tr>
<tr>
<td>Optimized</td>
<td>κ &gt; 70 or λ &gt; 40</td>
<td>42</td>
<td>0</td>
<td>8</td>
<td>35</td>
<td>100% (90-100%)</td>
<td>81% (66-91%)</td>
</tr>
<tr>
<td><strong>κ - λ Difference (mg/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimized</td>
<td>&lt; -25 or &gt; 60</td>
<td>42</td>
<td>0</td>
<td>1</td>
<td>42</td>
<td>100% (90-100%)</td>
<td>98% (86-100%)</td>
</tr>
<tr>
<td><strong>κ / λ Ratio</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>&lt; 0.26 or &gt; 1.65</td>
<td>41</td>
<td>1</td>
<td>5</td>
<td>38</td>
<td>98% (86-100%)</td>
<td>88% (74-96%)</td>
</tr>
<tr>
<td>Standard with Renal Adjusted</td>
<td>Cr ≤ 1.3: &lt; 0.26 or &gt; 1.65</td>
<td>41</td>
<td>1</td>
<td>2</td>
<td>41</td>
<td>98% (86-100%)</td>
<td>95% (83-99%)</td>
</tr>
<tr>
<td></td>
<td>Cr &gt; 1.3: &lt; 0.37 or &gt; 3.1</td>
<td>41</td>
<td>1</td>
<td>2</td>
<td>41</td>
<td>98% (86-100%)</td>
<td>95% (83-99%)</td>
</tr>
<tr>
<td>Optimized</td>
<td>&lt; 0.5 or &gt; 5.0</td>
<td>42</td>
<td>0</td>
<td>0</td>
<td>43</td>
<td>100% (90-100%)</td>
<td>100% (90-100%)</td>
</tr>
</tbody>
</table>
Use is indicated with tissue diagnosis of ventricular amyloidosis

Patient must not have received prior therapy for plasma cell dyscrasia

Recommend direct subtyping in “grey zone”, or other forms of amyloidosis