The Heart of the Matter: Cardiac Imaging of Sarcoidosis

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Disclosures

• The authors have no financial relationships with the manufacturers of any commercial product and/or providers of commercial services in relation to this exhibit.
Cardiac Sarcoidosis

I. Background

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   - Gallium-67 scintigraphy
   - Myocardial perfusion imaging
   - 18F-FDG PET Scan
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   - Eosinophilic Granulomatosis with Polyangiitis
   - Endomyocardial Fibrosis (EMF)
   - Arrhythmogenic Right Ventricular Dysplasia (ARVD)

V. Management and Prognosis
I. Background

- Sarcoidosis is a multi-organ disease of unknown etiology most commonly affecting the lungs.
- Incidence is greatest between 20-39 years of age\(^1\):
  - 2:1 female to male preponderance
  - Annual incidence in African Americans 3x that of Caucasians
  - Prevalence greatest in northern European countries
- Cardiac involvement is reported in 2-7% of patients with systemic sarcoidosis\(^1, 3\)
- On autopsy, cardiac involvement is found to be higher, in 25-78% of individuals with sarcoidosis\(^1, 2\)
- Imaging is contributing to the increased detection of cardiac sarcoidosis\(^3\)
I. Background

- Cardiac sarcoidosis is associated with a poor prognosis, with multiple disease manifestations\textsuperscript{1, 3, 4}:
  - Clinically silent myocardial granulomas
  - Cardiomyopathy with arrhythmias (12-32%)
  - Heart failure (25-75%)
  - Sudden cardiac death (25-65%)

- 5 year mortality associated with cardiac sarcoidosis is reported to range from 25-66\% \textsuperscript{5}

- Cardiac imaging may allow for the early detection of cardiac sarcoidosis (CS) and/or the direction of endomyocardial biopsy
I. Background: Diagnostic Guidelines for Cardiac Sarcoidosis

Histologic Diagnosis

Endomyocardial biopsy showing noncaseating epithelioid cell granulomas in the setting of extra-cardiac sarcoidosis

Clinical Diagnosis

2 Major Criteria
OR
1 Major + 2 Minor

Major Criteria

• Gallium-67 scintigraphy: positive uptake
• Advanced atrioventricular block
• Basal thinning of interventricular septum
• Left ventricular ejection fraction <50%

Minor Criteria

• Gadolinium-enhanced MRI: delayed myocardial enhancement
• Myocardial perfusion imaging: perfusion defect
• Endomyocardial biopsy: interstitial fibrosis or monocyte infiltration
• Abnormal ECG (ventricular arrhythmias, bundle branch block, axis deviation, or abnormal Q wave)
• Abnormal echocardiography
II. Diagnostic Imaging Modalities

- Gallium-67 Scintigraphy
- 18F-FDG PET Scan
- Myocardial Perfusion Imaging (MPI)
- Cardiac Magnetic Resonance Imaging (CMR)
II. Diagnostic Imaging Modalities: Gallium Scan

- Abnormal accumulation of Gallium-67 corresponds to areas of active inflammation
  - For example, mildly **INCREASED UPTAKE IN THE HEART** is compatible with cardiac sarcoidosis
- **PANDA SIGN**: symmetric uptake in the nasopharynx, lacrimal and parotid glands
  - Present in 75% of patients with sarcoidosis
- **LAMBDA SIGN**: uptake in right paratracheal and bilateral hilar lymph nodes in pulmonary sarcoidosis

**Advantages**
- Highly specific
- Can assess treatment response
- Identification of extra-thoracic uptake

**Disadvantages**
- Low sensitivity (as low as 15%)
- Radiation exposure
II. Diagnostic Imaging Modalities: PET Scan

- Patient preparation:
  - Low carbohydrate diet for 8-24 hours; 4-18 hour fast to diminish physiologic uptake
- Myocardial uptake corresponds to macrophage-dense areas of active inflammation
- RV uptake a significant predictor of adverse cardiac events, controlling for LVEF and clinical factors\(^6\)
- RV uptake associated with 3x higher adverse event rate\(^6\)
- PET may be used to assess treatment response
II. Diagnostic Imaging Modalities: Myocardial Perfusion Imaging

- Radiopharmaceutical Agents:
  - Thallium-201
  - 99mTc-MIBI

- Mechanism:
  - Agents accumulate in normal myocardial cells
  - Regional distribution of myocardial blood perfusion is then estimated non-invasively

- Findings in cardiac sarcoidosis:
  - Resting images may show segmental areas of decreased perfusion in the ventricular myocardium
  - Decreased perfusion corresponds to areas of fibrogranulomatous replacement
  - REVERSE DISTRIBUTION: resting focal perfusion defects decrease or disappear during stress

Reverse ischemia pattern: Lateral and anterolateral wall defects are seen, with rest defect (middle column) greater than stress defect (leftmost column).
II. Diagnostic Imaging Modalities: Combined MPI/PET

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Perfusion at Rest</th>
<th>FDG Metabolism</th>
<th>Pathology</th>
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<tbody>
<tr>
<td>Normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
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<tr>
<td>Early Sarcoid</td>
<td>normal</td>
<td>HIGH</td>
<td>Active inflammation</td>
</tr>
<tr>
<td>Advanced Sarcoid</td>
<td>LOW</td>
<td>HIGH</td>
<td>Severe inflammation+/- scar</td>
</tr>
<tr>
<td>End Stage Sarcoid</td>
<td>LOW</td>
<td>normal</td>
<td>Myocardial scar</td>
</tr>
</tbody>
</table>

- Patient with no defect on MPI

- Patient with + on PET
## II. Diagnostic Imaging Modalities: Nuclear Imaging versus CMR

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Radiation</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MPI</strong></td>
<td>35-46% [^8,9] (Th-201)</td>
<td>--</td>
<td>-18mSv (Th-201)</td>
<td>-pattern distinct from that of ischemia</td>
<td>-reverse distribution not specific to CS</td>
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<tr>
<td></td>
<td>65% [^7] (Tc-99m)</td>
<td>--</td>
<td>-12mSv (Tc-99m)</td>
<td></td>
<td></td>
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<tr>
<td><strong>67Gallium scintigraphy</strong></td>
<td>0-36% [^10,11]</td>
<td>80-100% [^10,11]</td>
<td>9mSv</td>
<td>-whole body imaging -may assess Rx response</td>
<td>-low spatial resolution -low sensitivity</td>
</tr>
<tr>
<td></td>
<td>Finding: Segmental perfusion defect at rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>18F-FDG PET</strong></td>
<td>89-100% [^11-14]</td>
<td>38-97% [^11-14]</td>
<td>7mSv</td>
<td>-whole body imaging -may assess Rx response</td>
<td>-cumbersome patient preparation</td>
</tr>
<tr>
<td></td>
<td>Finding: increased myocardial uptake</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>CMR</strong></td>
<td>100% [^14,15]</td>
<td>78% [^14,15]</td>
<td>None</td>
<td>-high spatial resolution -high sensitivity</td>
<td>-renal function -metallic devices</td>
</tr>
<tr>
<td></td>
<td>Finding: High intensity lesions; ventricular thinning</td>
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</table>
III. MR Imaging of CS

A. Sites of cardiac involvement
B. LGE pattern
C. T2 signal features
D. T1 mapping
E. Cine imaging
III. MR Imaging of CS: Sites of Cardiac Involvement

- Noncaseating myocardial granulomas are most commonly found in the interventricular septum and left ventricular free wall.\(^1,16\)
- Common clinical manifestations include heart block (septal involvement), mitral regurgitation (LV free wall involvement), and ventricular aneurysm.\(^7\)
III. MR Imaging of CS: LGE Pattern

- Abnormal myocardium with fibrogranulomatous infiltration/scar will demonstrate LGE
  - *Typically* subEPIcardial or mid-myocardial, may be subendocardial or transmural
  - RV septal fibrosis $\rightarrow$ characteristic AV block due to Purkinje fiber involvement
- LGE is associated with 9x greater adverse cardiac event rate, and 11.5x higher rate of sudden death$^{17}$
- An increased number of cardiac segments demonstrate LGE with increasing duration of extra-cardiac sarcoidosis$^{18}$

**Distinguishing Features of Cardiac Sarcoidosis:**
- Enhancement at RV aspect of septum very specific
- Corollary imaging findings on nuclear medicine studies
- History of extracardiac sarcoidosis
III. MR Imaging of CS: T2 Signal Features

- Focal high T2 signal represents myocardial edema associated with granulomatous inflammation
- May have corresponding delayed enhancement or wall motion abnormality
- Increased T2 signal is not specific to CS, and may be seen in the setting of myocarditis, infiltrative and ischemic cardiomyopathy

- T2W image (left) shows increased signal in the mid-inferior wall.
- Accompanying LGE image (right) shows subepicardial and midmyocardial enhancement of the same region. Granulomas are also noted in the spleen.

- T2 black blood image demonstrates hyperintensity at the basal anteroseptum and RV free wall.
- Delayed post contrast sequence (right) shows multiple areas of mid-myocardial, subepicardial and transmural LGE in the LV and RV. Subendocardial enhancement is seen at the basal septum.
III. MR Imaging of CS: LGE and T2

- TOP ROW: Delayed post-contrast imaging shows multiple areas of intramyocardial scar in the basal anterolateral, basal anterior, basal anteroseptal, basal inferior, mid anteroseptal, mid inferoseptal and mid inferolateral segments in this patient with pulmonary sarcoidosis.
- BOTTOM ROW: T2 weighted imaging shows increased signal intensity compatible with myocardial edema in multiple corresponding segments.
- Findings consistent with active myocardial sarcoidosis.
III. MR Imaging of CS: T1 Mapping

- Emerging CMR technique to differentiate non-involved from diseased myocardium
- **Method:** Quantification of intrinsic T1 relaxation time of tissue by measuring myocardial extracellular volume fraction
  - T1 mapping sequences include look locker (LL), modified LL inversion recovery (MOLLI), and shortened MOLLI (shMOLLI)
- **Findings:**
  - SHORTENED POST-CONTRAST myocardial T1 time correlates with diffuse fibrosis, edema and amyloid\(^{19}\) (increased extracellular volume fraction) → found in heart failure,\(^{20}\) hypertrophic cardiomyopathy,\(^{21}\) infarct,\(^{22}\) and muscular dystrophy\(^{23}\)
  - SHORTENED PRE-CONTRAST myocardial T1 time correlates with lipid (Fabry disease)\(^{24},^{25}\) and iron deposition\(^{24}\)
- **Improved diagnostic value:**
  - Potentially more sensitive than LGE in diffuse disease processes
  - Detects significantly more areas of myocardial involvement in myocarditis as compared to T2 and LGE sequences\(^{26}\)
  - Prognostic implications have been reported in patients with heart failure, amyloidosis
III. MR Imaging of CS: Cine Imaging

- Cine imaging provides a functional assessment of the left and right ventricles.
- Focal areas of wall thinning/motion abnormality most often found in the basal anteroseptum or left lateral wall.
- Wall motion may remain normal until a significant portion of the myocardium is involved, rendering CMR of superior sensitivity in comparison to echocardiography.

Bright blood images in diastole and systole show thinning, hypokinesis, and absence of thickening in the mid inferolateral segment (top row). There is no myocardial edema on T2 weighted sequence (bottom left). On delayed imaging, there is near transmural enhancement of the mid inferolateral segment (bottom right).
IV: LGE Differential Diagnosis

- Myocarditis
- Fabry disease
- Amyloidosis
- Endomyocardial fibrosis
- Eosinophilic granulomatosis with polyangiitis
- Arrhythmogenic right ventricular dysplasia (ARVD)
IV. LGE Differential Diagnosis: Myocarditis

- **Etiology:** Most commonly viral; also autoimmune, toxic/ischemic, drug, post-transplant etiologies
- **Lake Louise consensus criteria**—presence of 2/3 findings compatible with myocarditis:
  1. T2 myocardial to skeletal muscle signal ratio >1.9
  2. T1 global relative enhancement >4
  3. SubEPICardial or transmural LGE
- **Cine-CMR:** Global LV systolic dysfunction
- **LGE:**
  - Typically subEPICardial or midmyocardial
  - Preference for lateral free wall

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**Differentiating features from CS:**

- Clinical history
- Lake Louise consensus criteria
- Signs including pericarditis, pulmonary edema

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- Circumferential subepicardial enhancement throughout the LV. The patient reported preceding GI illness.
- Small pericardial effusion also seen.
IV. LGE Differential Diagnosis: Fabry Disease

- **Etiology:** X-linked lysosomal storage disease due to α-galactosidase A deficiency → intracellular accumulation of glycosphingolipid
- **Cine-CMR:**
  - Left ventricular hypertrophy (LVH)
- **LGE (may precede LVH):**
  - Midmyocardial or subepicardial
  - Focal at basal inferolateral wall
  - Positive association between LV mass and LGE

**Differentiating features from CS:**
- LGE characteristically at basal inferolateral wall
- Left ventricular hypertrophy
- Extra-cardiac disease—kidneys, nervous system
- Positive family history

Focal mid-myocardial and subepicardial enhancement at the basal inferolateral segment.

Biventricular dilatation noted on 4-chamber view.
IV. LGE Differential Diagnosis: Amyloidosis

- **Etiology:** Extracellular amyloid deposition
- **Cine-CMR:**
  - Biventricular myocardial hypertrophy
- **LGE:**
  - Diffuse; may also demonstrate *atrial* LGE
  - Circumferential
  - Typically subENDOCardial; severe may be transmural
  - Altered gadolinium kinetics: increased blood pool clearance + inability to adequately suppress myocardial signal → small difference in T1 relaxation between blood and myocardium

**Differentiating features from CS:**
- Diffuse cardiac involvement may include both atria and ventricles
- Altered gadolinium kinetics with similar LGE signal in myocardium and blood pool
- Circumferential, subendocardial LGE pattern

- Diffuse subendocardial ventricular and atrial enhancement (arrows) on four-chamber post-contrast view (top right).
- A “zebra” pattern of enhancement on MDE, with dark blood pool, bright subendocardium, and dark mid-mycocardium in another patient (bottom right).
- Short axis SSFP images show LVH.
IV. LGE Differential Diagnosis: Eosinophilic Granulomatosis with Polyangiitis

- Formerly Churg-Strauss Syndrome
- Etiology: Vasculitis of small and medium size arteries
- LGE:
  - Predominately subendocardial
  - Often not confined to one coronary territory\(^2\)
- Additional findings: pericardial effusion common; valvular insufficiency; heart failure

**Differentiating features from CS:**
- Subendocardial pattern of LGE
- Additional diagnostic criteria\(^3\) (≥4): asthma; eosinophilia >10%; mono/polyneuritis; transient pulmonary opacities; paranasal sinus abnormality; extravascular eosinophils

- Diffuse subendocardial enhancement/fibrosis on 4 chamber and 2 chamber views (top row).
- Small pericardial effusion (*).
- Bilateral upper lobe opacities and pleural effusion on axial black blood image, and again on coronal localizer (bottom).
IV. LGE Differential Diagnosis: Endomyocardial Fibrosis (EMF)

- **Synonyms:** Davies disease, Loffler endocarditis, restrictive obliterative cardiomyopathy
- **LGE & Distribution:**
  - 45% biventricular; 40% right ventricle; 5% left ventricle
  - Endomyocardial fibrosis with destruction of the ventricular apex +/- thrombus
- **Clinical manifestation:** severe (right) heart failure with normal/small ventricles and accompanying atrial enlargement

**Differentiating features from CS:**
- Subendocardial pattern of LGE
- Most cases biventricular or right ventricular
- Atrial enlargement in the setting of an often-normal heart size

**Vertical and horizontal long axis delayed post-contrast images show biventricular endomyocardial enhancement, prominent apically, with a shrunken RV and enlarged RA (top left and right). Also seen is a small pericardial effusion.**

**Companion case shows delayed subendocardial LV enhancement on short axis view (bottom left).**
IV. LGE Differential Diagnosis: Arrhythmogenic Right Ventricular Dysplasia

- Etiology: Cardiomyopathy secondary to desmosomal protein gene mutations → fibrofatty myocardial replacement
- Diagnostic criteria: clinical, pathologic, electrophysiological and imaging
  - Imaging—global/regional dysfunction and structural alterations (dilatation, aneurysms, ↓ RVEF)—may only satisfy one criterion
- Distribution: predominantly right ventricular free wall and RV outflow tract (both often dilated)
- Associated with arrhythmias, sudden cardiac death

Differentiating features from CS:
- Predominantly RV free wall involvement
- Presence of multiple diagnostic criteria such as family history, arrhythmias, conduction abnormalities, and pathology

- Bright blood four chamber cine shows scalloping along the anterior right ventricular free wall compatible with numerous microaneurysms (top).
- There is near transmural LGE in the RV wall, and predominantly subepicardial LGE in the LV, in another patient (bottom).
IV: LGE Differential Diagnosis: Summary

Ischemic

- Subendocardial
- Transmural

Non-Ischemic

- Subendocardial: Eosinophilic granulomatosis with polyangiitis, Endomyocardial Fibrosis
- Mid-myocardial: Sarcoidosis, Myocarditis, Fabry disease, Chagas disease, Dilated cardiomyopathy
- Subepicardial: Sarcoidosis, Myocarditis, Fabry disease, Chagas disease
- Circumferential: Amyloidosis, Systemic Sclerosis, Cardiac Transplant

Differential considerations reviewed in this exhibit.
V. Management and Prognosis

- Cardiac sarcoidosis is an indication for treatment given increased risk of sudden death\(^3\)
- Cardiac sarcoidosis demonstrates characteristic findings on Gallium scintigraphy, MPI, PET and CMR—setting it apart from numerous LGE mimics
- Imaging provides an essential opportunity for diagnosis, and multiple possible interventions:
  - Corticosteroids
  - Immunosuppressive agents: methotrexate, azathioprine, cyclophosphamide
  - Pacemaker/implantable defibrillator
  - Cardiac transplant: for end-stage disease refractory to medical therapy
- Early intervention may mitigate morbidity and mortality
References

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