Case Report: Cardiac Sarcoidosis

A silent killer behind Dilated Cardiomyopathy

Speaker: Dr. Tou Chang
Declaration for conflicts of interest

• I do not have any conflict of interest
Case

- 29 y/Male, Filipino, Non-Smoker, Social drinker
- Past Medical History: Nil
- Family History: Unremarkable
- C/C: Exertional SOB 4 months w/ lower limbs edema and fever 4 days
- ABG: PH 7.2, metabolic acidosis
- NTproBNP >9000 pg/ml
- AKI + Congestive liver
Chest X-Ray

Cardiomegaly
Bilateral pleural effusion
ECG

Baseline ECG
Sinus rhythm with first degree AVB

Monomorphous VT
LBBB and inferior Axis
Originated from the RVOT
Case

• IMP: Acute decompensate HF with Ventricular tachycardia
  Acute renal failure with metabolic acidosis, MODS
  S/P intubation +mechanical ventilation + CRRT

• QT prolongation w/ TdP-VT after Amiodarone

• Succeed extubation after 4d MV supported
Case

• Sustained spiking fever with normal inflammatory indexes
• R/O: Malignance? Infection? Auto-immune? etc
  • TB: Interferon-gamma test Neg-
  • HIV screening Neg-
  • Syphilis: RPR/VDRL Neg-
  • Lymphoma
  • Anto-immune parameters: Neg-
• Thoracentesis: Transudate
Chest CT

Mediastinal and hilar lymphadenopathy
Lymphoma VS Sarcoidosis?
Dilated LA and LV w/ systolic function global compromised, basal and mid septum Septum AK and global HK, EF=22%, Severe concentric MR/TR
• Possible Diagnosis:
  DDx: Lymphoma? Cardiac Sarcoidosis?

• Multidisciplinary Consultation
  -EBUS: Lymph nodes needle biopsy --Favoring Granulomatous inflammation
Lymph node Biopsy from EBUS

Histopathologic results of mediastinal lymph node biopsy show non-caseating granulomata
• Highly suspected Silent Cardiac Sarcoidosis
• Refuse ICD (financial problem)
• Tx: ACEI, β -B, MRA, Ivabradine etc..
  Prednisolone 40mg po daily

• ECHO before discharge: EF~40%
What is Sarcoidosis?

- Multisystem, granulomatous disease of unknown etiology.
- Triggered by unidentified antigen, in genetically susceptible persons
- Occurs in age 25-60, rare in <15 or >70, Female>Male
- Prevalence: 10-40/100,000, 3.8-fold higher in African
- Mortality rate 1-5%
  - Cardiac sarcoidosis is the leading cause of death among pts w/ sarcoidosis which mortality rate of 50-85%
Pathophysiology of Sarcoidosis

Hypothesized immunopathogenesis

Hallmark: Non-caseating epithelioid cell granuloma

Examples of agents suggested to be involved in the etiology of sarcoidosis

<table>
<thead>
<tr>
<th>Type of Agent</th>
<th>Infectious</th>
<th>Inorganic</th>
<th>Organic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viruses</td>
<td>Arboviruses, HSV, EBV, retrovirus</td>
<td>Aluminum</td>
<td>Pine tree pollen</td>
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<tr>
<td>Coxsackie B3</td>
<td></td>
<td>Zincium</td>
<td>Clay</td>
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<tr>
<td>B. burgdorferi</td>
<td></td>
<td>Talc</td>
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<tr>
<td>Propionibacterium acnes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycobacterium tuberculosis and other mycobacteria</td>
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<tr>
<td>Mycoplasma</td>
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*Beryllium, which causes berylliosis and not sarcoidosis, is not included.

Am J Respir Crit Care Med 1999;160(2):736-55

Extrapulmonary Sarcoidosis

- Cutaneous: 25-35%
- Ophthalmologic: 25-80%
- **Cardiac: 5-25%**
  - Clinically manifest cardiac involvement: ~ 5%
  - Asymptomatic cardiac involvement: ~ 25%
- Liver & Spleen: 20-30%
- Neurologic: 5%
- Joints & Musculoskeletal: 10-20%
Clinical features of CS depend on the location, extent, and activity of the disease,
Asymptomatic (2/3 of Pts)
- Conduction abnormalities
- Ventricular arrhythmia including SCD
- Heart failure

Nonspecific signs and symptoms!
A spontaneous remission is often observed in extracardiac cases such as skin sarcoidosis. However, when cardiac involvement exists, the prognosis is not favorable.

Kusano KF, et al. Heart 2015;0:1-7
Electrocardiogram

• ECG: 3.2-8.6% abnormal in silent CS

Table 1. Electrophysiologic manifestations of cardiac sarcoidosis, and their prevalence during the course of disease [1–5,6**]

<table>
<thead>
<tr>
<th>Electrophysiologic manifestations</th>
<th>Prevalence in study series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrioventricular block</td>
<td>26–67%</td>
</tr>
<tr>
<td>Bundle branch block</td>
<td>12–61%</td>
</tr>
<tr>
<td>Atrial arrhythmias</td>
<td>23–25%</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>11–73%</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>12–65%</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>10–30%</td>
</tr>
</tbody>
</table>

Curr Opin Pulm Med 2013, 19:485 – 492
Sarcoidosis: Cardiac Involvement

Common sites:

- Myocardium
  - LV free wall and papillary muscles
  - Basal septum;
- Pericardium
- Endocardium

Pattern of focal cardiac sarcoidosis. Late gadolinium enhancement cardiac magnetic resonance (left) and cardiac $^{18}$F-fluorodeoxyglucose positron emission tomography (right) images from a patient with only a small focal area of cardiac sarcoidosis. The arrows point to areas with myocardial involvement by sarcoidosis.
Echocardiogram in the diagnosis of CS

Predilection for the base of the interventricular septum?

Nonspecific findings are more common!
How to Diagnosis

• The challenge: No single reference standard to diagnose cardiac sarcoidosis

• Endomyocardial biopsy (EMB) has an excellent specificity, but its sensitivity in patients with suspected cardiac sarcoidosis is approximately 20% to 30%
Diagnosis Criteria

- Three clinical criteria:
  - The Heart Rhythm Society (HRS)
  - The Japanese Ministry of Health and Welfare (JMHW)
  - The World Association for Sarcoidosis and Other Granulomatous Disorders Criteria

- No gold standard diagnostic criteria exists

- Because CMR was unavailable to us, we reached the diagnosis of cardiac sarcoidosis on the basis of the clinical
Heart Rhythm Society (HRS) consensus statement for diagnosis of cardiac sarcoidosis

**Histological diagnosis of cardiac sarcoidosis**
Endomyocardial biopsy specimens with non-caseating epithelioid granulomas and no alternative cause identified

**Clinical diagnosis of probable cardiac sarcoidosis**
Histologic diagnosis of extracardiac sarcoidosis and one or more of the following is present while reasonable alternative cardiac causes other than CS have been excluded:
- Corticosteroid or immunosuppressive therapy responsive cardiomyopathy or heart block
- Unexplained reduced LVEF (<40%)
- Mobitz type two second degree heart block or third degree heart block
- Depressed left ventricular ejection fraction <50%
- Patchy uptake on cardiac FDG-PET in a pattern consistent with CS
- Late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging in a pattern consistent with CS

Table 1. The WASOG criteria for the diagnosis of cardiac sarcoidosis

<table>
<thead>
<tr>
<th>Highly Probable</th>
<th>At Least Probable</th>
<th>Possible</th>
<th>No consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy with granulomatous inflammation of no alternate cause</td>
<td>Treatment-responsive cardiomyopathy or AV block</td>
<td>Reduced LVEF in the presence of other clinical risk factors (e.g., HTN and DM)</td>
<td>Frequent ectopy (&gt;5% QRS)</td>
</tr>
<tr>
<td></td>
<td>Reduced LVEF in the absence of other clinical risk factors</td>
<td>Abnormal QRS or dysrhythmias</td>
<td>Bundle branch block</td>
</tr>
<tr>
<td></td>
<td>Spontaneous or induced sustained VT with no other risk factors</td>
<td></td>
<td>Impaired RV function with a normal PVR</td>
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<tr>
<td></td>
<td>Mobitz type II or third-degree AV block</td>
<td></td>
<td>Fragmented QRS or pathologic Q waves in two or more anatomically contiguous leads</td>
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<tr>
<td></td>
<td>Patchy uptake on dedicated cardiac PET</td>
<td></td>
<td>At least one abnormal SAECG domain</td>
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<td>Delayed enhancement on CMR</td>
<td></td>
<td>Intestinal fibrosis or monocye infiltration</td>
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<td></td>
<td>Positive gallium uptake</td>
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<tr>
<td></td>
<td>Defect on perfusion scintigraphy or SPECT scan</td>
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<td></td>
<td>72 prolongation on CMR</td>
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Definition of abbreviations: AV = atrioventricular; CMR = cardiac magnetic resonance imaging; DM = diabetes mellitus; HTN = hypertension; LVEF = left ventricular ejection fraction; PET = positron emission tomography; PVR = pulmonary vascular resistance; RV = right ventricle; SAECG = signal-averaged electrocardiogram; SPECT = single-photon emission computed tomography; VT = ventricular tachycardia; WASOG = World Association for Sarcoidosis and Other Granulomatous Disorders.

Japanese Ministry of Health and Welfare Criteria for Diagnosis of Cardiac Sarcoidosis (Revised 2000)

**Histological diagnosis group**
Cardiac sarcoidosis is confirmed when endomyocardial biopsy specimens demonstrate non-caseating epithelioid granulomas with histological or clinical diagnosis of extra-cardiac sarcoidosis

**Clinical diagnosis group**
Although endomyocardial biopsy specimens do not demonstrate non-caseating epithelioid granulomas, extra-cardiac sarcoidosis is diagnosed histologically or clinically and satisfies the following conditions and more than one is
Diagnosis of Cardiac Sarcoidosis

• Screening for cardiac sarcoidosis
  • 1) 1 or cardiac symptoms (significant palpitations, syncope, or pre-syncope)
  • 2) An abnormal cardiac test

Nature Reviews | Cardiology

Nat Rev Cardiol 2015;12(5):278-88
Pharmacological treatment

- Treatment:
  - Corticosteroid: Traditionally high dose steroid is initiated, such as 40-60mg prednisolone daily then tapered and continued at a lower dose for at least 6-12 months.
  - Alternative drugs therapy: Methotrexate, infliximab, azathioprine, cyclosporine, antimalarials, etc.
  - Other immune modulating agents: Infliximab and adalimumab, rituximab have been reported to have efficacy in case series and small cohorts but are not considered standard therapy currently.
# PPM & ICD

**Summary of device and surgical therapies for cardiac sarcoidosis based upon recommendations of the American College of Cardiology, American Heart Association, and the Heart Rhythm Society.**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mechanism</th>
<th>Potential benefit</th>
<th>Potential harm</th>
</tr>
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<tbody>
<tr>
<td>Device therapy</td>
<td>Defibrillation of potential recurrent VT/VF</td>
<td>Class I recommendation to reduced mortality in patients with structural heart disease and syncope, VT/VF, or sustained VT/VF inducible by EP study. Class III if life-expectancy &lt;1 year (2)</td>
<td>Pain, infection, cost, lead fracture, need for re-implantation, inappropriate shock</td>
</tr>
<tr>
<td>ICD, secondary prevention</td>
<td>Defibrillation of potential recurrent VT/VF</td>
<td>Class I recommendation to reduce mortality in patients with structural heart disease and EF &lt;30–35% despite medical therapy. Class Ila for those needing pacemaker, unexplained syncope, or sustained VT/VF inducible by EP study. LGE on CMR may be used to consider EP study. Class Iib for LV EF 36–49% or RV EF &lt;40% despite medical therapy. Class III if life-expectancy &lt;1 year (2)</td>
<td>Pain, infection, cost, lead fracture, need for re-implantation, inappropriate shock</td>
</tr>
<tr>
<td>Pacemaker (level of evidence C)</td>
<td>Prevention of immediately fatal arrhythmia</td>
<td>Class I recommendation to reduce mortality and symptoms from complete heart block and bradyarrhythmias (2,21)</td>
<td>Pain, infection, cost, lead fracture, need for re-implantation, device removal complex if heart block resolves</td>
</tr>
<tr>
<td>Surgical</td>
<td>Surgical replace organs affected by sarcoidosis with donor organs when end-stage organ dysfunction that may include refractory cardiogenic shock, IV inotrope dependence, peak VO&lt;sub&gt;2&lt;/sub&gt; &lt;10 mL·kg&lt;sup&gt;-1&lt;/sup&gt;·min&lt;sup&gt;-1&lt;/sup&gt; with achievement of anaerobic metabolism, refractory VT/VF (20)</td>
<td></td>
<td>Infection, need for chronic immunosuppression, risk of surgery, acute and chronic rejection, chance of recurrence (17)</td>
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<tr>
<td>Heart and lung transplantation (level of evidence C)</td>
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ICD, implantable cardiac defibrillator; VT, ventricular tachycardia; VF, ventricular fibrillation; EP, electrophyslogic; EF, ejection fraction; LGE, late gadolinium enhancement; CMR, cardiac magnetic resonance.
Take Home Messages

- Clinical Diagnosis for CS: Exclusion Diagnosis
  - Medical History, Physical examination (lung, eye, liver, heart..)
  - Biopsy — Noncaseating granulomas
  - ECG: Conduction disorder/VT etc
- Cardiac Images study:
  - CXR/CT/Echocardiogram/CMR/PET etc
  - Echo: basal septal thinning
  - CMR: absence LGE → Negative predictive value for exclude CS
  - $^{18}$F-FDG PET → CMR contra-indication pts & activity of CS
Take Home Messages

• Corticosteroid Tx:
  • No randomized trial exists to establish a definitive role
  • Experts still debate the benefits versus harm as well as the optimal dosing and duration for therapy

• Risk of SCD: ICD implantation for primary and secondary prevention
Thank You!