Sarcoidosis:
Diagnostic challenges and
difficult clinical decisions

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Introduction to Sarcoidosis

• First described as a skin disorder in 1869
• Further descriptions of lymph-node disease lead to the proposed name “sarkoid” i.e. sarcoma-like
• Multi-system granulomatous disease of unknown aetiology.
• Lifetime prevalence 5-40/100 000 in Caucasians
  ➢ 3X higher in African Americans
• Typically presents <40 years
• ?Immune reaction to unknown antigen in genetically predisposed individual
Introduction to Sarcoidosis

• Activation of Th1 T-cells and production of IFNγ, TNFα, TGFβ, IL-2 and IL-12

• The immune response ultimately leads to the formation of granulomas that consist of a central core of mononuclear cells surrounded by CD4+ T-cells and a small number of CD8+ T-cells and B-cells

• *Non-caseating, non-necrotic granulomas are the histological hallmark*

• The disease can affect any organ symptoms but most frequently the LN and lungs. The majority of sarcoidosis with organ involvement are not life-threatening.
Introduction to Sarcoidosis
Cardiac Sarcoidosis
Cardiac Sarcoidosis

- Clinically evident in 2-7% of sarcoid patients but autopsy studies suggest cardiac sarcoid occurs in up to 25% of patients with sarcoidosis. More than 50% of these are subclinical.

- Most commonly affects:
  - Myocardium especially basal ventricular septum
  - LV free wall
  - Papillary muscles
  - RV

- Cardiac sarcoid accounts for 10-25% of all deaths from sarcoidosis
  - Need for recognition and intervention

Figure 1 | A well-formed non-necrotizing granuloma in the heart.
Cardiac Sarcoidosis: Epidemiology and Aetiology

- Prevalence unclear due to lack of standardised criteria
- M>F 3.4% vs. 1.7%
- Genetic association:
  - HLADRB1*1101 plus insecticide exposure
  - HLADQB1*0601, HLADRB1*1502, HLADQA1*0103 and HLADRB1*0803 in Japanese
  - Other studies have found HLA types that are protective
  - These studies have compared Cardiac sarcoid to healthy volunteers (not sarcoid patients with no cardiac involvement)
Cardiac Sarcoidosis: Presentation

- Asymptomatic
- Pre-syncope or syncope
- Atrial arrhythmias are increasingly recognised as early manifestation
- Ventricular dysfunction that is directly related to granulomatous infiltration
- 25% present with sudden cardiac death
- 65% of all cardiac sarcoid occurs without evidence of extra-cardiac sarcoidosis
Cardiac Sarcoidosis: Screening

- Current American Thoracic Society/European Respiratory Guidelines recommend screening for asymptomatic cardiac sarcoidosis in patients diagnosed with sarcoid in other organs:
  - Medical history and cardiac examination
  - 12-lead ECG (abnormal in <50% of pts with cardiac sarcoidosis) looking for fragmentation of QRS complex, LBBB and RBBB
  - Echocardiography (Sens 25%; Spec 95%)
    - Cannot detect infiltration; May see reduced LV function, wall motion abnormalities, increased LV wall thickness or thinning and aneurysm formation
- At present there is no biomarker used in the screening of cardiac sarcoidosis
  - ACE, lysozyme, urinary calcium levels, hstroponin and BNP are often elevated in patients with cardiac sarcoid but have low sensitivity.
Cardiac Sarcoidosis: Screening

Biopsy proven extra-cardiac sarcoidosis

Cardiac history, ECG, Echocardiogram

1. Symptom(s) positive (significant palpitations*/pre-syncope/syncope)
2. Abnormal ECG**
3. Abnormal Echocardiogram***

One or more of 1-3

Advanced cardiac Imaging
CMR and/or FDG-PET

None of 1-3

Negative – Low probability of cardiac sarcoidosis
Cardiac Sarcoidosis: Diagnostic Imaging

- Cardiac MRI with gadolinium (sens 76-100%; spec 78-92%)
  - Looking for the presence of delayed enhancement

Figure 3 | Cardiac MRI with evidence of delayed enhancement. The presence of delayed enhancement (arrows) is suggestive of cardiac sarcoidosis and scar tissue formation.
Cardiac Sarcoidosis: Diagnostic Imaging

- Cardiac FDG-PET (Sens 79-100%; Spec 38-100%
  - Pattern of focal uptake or focal on diffuse uptake are most consistent with cardiac sarcoidosis
  - Beware false negatives with BSL > 7.5 mmol/L

Figure 4 | Pattern of uptake on an ¹⁸F-fluorodeoxyglucose PET scan. a | No uptake. b | Patchy uptake. c | Diffuse uptake. d | Patchy on diffuse uptake.
Cardiac Sarcoidosis: Diagnostic Imaging

- Cardiac FDG-PET appears to have the highest sensitivity compared with other imaging modalities

<table>
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<th>First author, year</th>
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<th>Protocol</th>
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- In a study of 21 pts who underwent both FDG-PET and CMRI
  - FDG-PET had Sens 87.5% Spec 38.5%
  - CMRI Sens 75% and Spec 76.9% using JWMH as gold std

Aggarwal et al Eur Heart J Card Imag 2015
Cardiac Sarcoidosis: Emerging role of combined FDG-PET and MRI

Cardiac MRI and PET likely image different pathophysiology of cardiac sarcoid. The strengths of each modality may be combined.

Aggarwal et al Eur Heart J Card Imag 2015
Cardiac Sarcoidosis: Diagnosis

- There is no standardised diagnostic criteria and none have supporting RCT evidence or prospective evaluation.
- Endomyocardial biopsies are low yield (sensitivity 25%) due to the patchy nature of disease and are associated with significant complications.

**Expert Consensus Recommendations on Criteria for the Diagnosis of CS**

There are 2 pathways to a diagnosis of Cardiac Sarcoidosis:

1. **Histological Diagnosis from Myocardial Tissue**
   - CS is diagnosed in the presence of non-caseating granuloma on histological examination of myocardial tissue with no alternative cause identified (including negative organismal stains if applicable).

2. **Clinical Diagnosis from Invasive and Non-Invasive Studies:**
   - It is probable\* that there is CS if:
     a) There is a histological diagnosis of extra-cardiac sarcoidosis and
     b) One or more of the following is present
        - Steroid +/- immunosuppressant responsive cardiomyopathy or heart block
        - Unexplained reduced LVEF (< 40%)
        - Unexplained sustained (spontaneous or induced) VT
        - Mobitz type II 2nd degree heart block or 3rd degree heart block
        - Patchy uptake on dedicated cardiac PET (in a pattern consistent with CS)
        - Late Gadolinium Enhancement on CMR (in a pattern consistent with CS)
        - Positive gallium uptake (in a pattern consistent with CS)
     and
     c) Other causes for the cardiac manifestation(s) have been reasonably excluded.

\*In general, "probable involvement" is considered adequate to establish a clinical diagnosis of CS.\(^{33}\)
Cardiac Sarcoidosis: Treatment

• Paucity if evidence based data; largely based on expert opinion

• Immunosuppressive therapy
  - Corticosteroids most common first line agent
  - Methotrexate second most common
    • One study found no difference LVEF or LVEDD between corticosteroids vs. corticosteroids and MTX over 5 years
  - Azathioprine and Mycophenolate have also been used
  - TNFα blockade has been reported in case studies but should only be used with caution if LVEF<35% as may worsen LV function
Cardiac Sarcoidosis: Treatment

• Cardiac specific therapy to manage heart failure and arrhythmias

• Implantable defibrillator therapy
  ➢ General cardiac guidelines are inadequate
  ➢ Class I indication for AICD for patients with cardiac sarcoidosis AND ventricular arrhythmias AND LVEF<35%
  ➢ Unnecessary shock occur in 10-30% of patients

• Antiarrhythmic therapy

• VT ablation

• Management of heart failure
  ➢ B-blockers
  ➢ ACEi

• Consideration for Heart transplant (1.5% of all transplants)
Cardiac Sarcoidosis: Prognosis

- Prognosis is closely related to LV function and patients with preserved LV function appear to have better prognosis with immunosuppression.

- One study showed that in patients with normal (>55%) or reduced (<30%) LV function this did not improve with immunosuppression while patients with moderate (30-54% LVEF) showed improved LV function with immunosuppression.

- Overall survival of patient with cardiac sarcoidosis:
  - 98% 1 year; 90% 5 years; 84% 10 years

- But survival rates if LV<30% are
  - 91% at 1 year; 57% at 5 years; 19% at 10 years
Neurosarcoidosis
Neurosarcoidosis: Introduction

• Emerging evidence of CNS involvement of sarcoidosis documented from 1948

• Rare disorder affecting 5-15% of patients with sarcoidosis
  - Incidence much higher in autopsy studies where 50% of cases were not detected ante mortem.
  - The majority (99%) have concomitant extra neural disease

• Is a differential for a number of neurological conditions:
  - Atypical meningitis
  - Cranial neuropathies
  - Myelopathy
  - Cerebral mass lesion
  - Headache
Neurosarcoidosis: Introduction

- No conclusive predisposing factors, triggers or demographics associated with the development of neurosarcoidosis.
- Difficult to diagnose and to treat
Neurosarcoidosis: Histopathology Findings

- Meningo-encephalitomyelitic infiltration resulting in focal or disseminated nodules or plaques with a tendency to affect basal meninges.

  ➢ Note: Multinucleated cells may be sparse in neurosarcoid and if present smaller than in sarcoid at other locations.

![Images of histopathological findings](Schwendimann et al Am J Ther 2013)
Neurosarcoidosis: Clinical Presentation

• Cranial Nerves
  - Facial Nerve (CNVII) most frequently affected and bilateral in 30% of cases
  - Optic neuritis also common
  - Anosmia and sensorineural hearing loss reported

• Intracranial Lesions
  - Parenchymal sarcoid lesions at any location
  - Common in hypothalamus/pituitary axis
  - Brainstem infiltration resulting in intractable hiccups, binocular diplopia, sudden death from autonomic dysfunction
Neurosarcoidosis: Clinical Presentation

• Spinal Cord Lesions
  - Myelopathy from intramedullary sarcoid lesions
  - Most prevalent in cervical spine
  - Average size 3.9 segments; Tends to affect older patients with more established disease

• Cerebrovascular events
  - May occur in the absence of atherosclerotic risk factors or embolic source
  - Granulomatous invasion of the cerebral vessel wall is not uncommon
Neurosarcoidosis: Diagnosis

- Challenging due to inaccessibility of tissue for biopsy
- Clinicians frequently default to extra-neural site for biopsy

Probable neurosarcoidosis is justified by:

1. Signs of neuroinflammation on imaging
   - Gadolinium enhancing MRI
     - May mimic MS
   - FDG PET
     - Superior to gallium-67
     - May help identify biopsy sites

2. Positive histology from extra neural site

3. And positive for 2 of:
   - Gallium scan
   - HRCT
   - BAL with elevated CD4:CD8 ratio >3.5 or >5 in CSF
Other biomarkers:
- CSF often shows T-cell pleocytosis and raised protein
- Emerging role for CSF soluble IL-2R
Neurosarcoidosis: Treatment

- Informed by case series only
- Corticosteroids is mainstay of treatment at 1mg/kg/day or 3-5 days of pulse methyl prednisone
- Systemic immunosuppression
  - Azathioprine
  - Methotrexate
  - Hydroxychloroquine
  - Cyclosporin A
  - Mycophenolate Moefetil
Neurosarcoidosis: Treatment

• In disease refractory to above measures:
  ➢ Anti-TNFα agents e.g. infliximab and adalimumab as an adjunctive treatment
    • TNFα plays a role in granulomata formation
  ➢ Case reports report successful use of Rituximab ?reduction in B-cell priming
  ➢ Trial of ustekinumab (anti-IL-17/22)
Neurosarcoidosis: Prognosis

- Overall prognosis for patients with neurosarcoidosis is less favourable than those without
  - 40% of patients with sarcoid optic neuritis had significant recovery following treatment
  - 73% of patients with spinal cord disease deteriorated over 18 months
- Patient with acute or subacute presentation appear to have better outcome than those with a insidious onset
- Better prognosis group appears to include patients with cranial neuropathy or aseptic meningitis.