Case Report: Cardiac Sarcoidosis

A silent killer behind Dilated Cardiomyopathy

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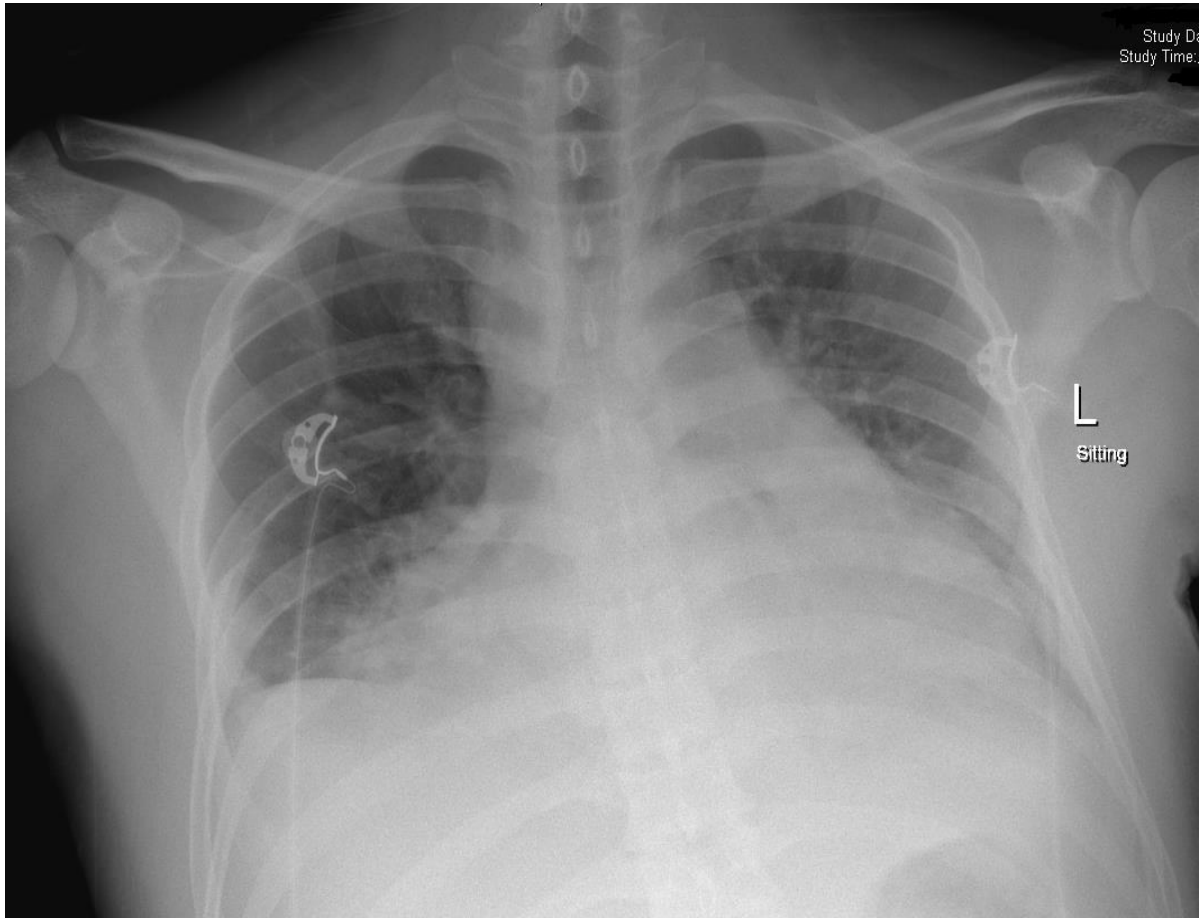
Declaration for conflicts of interest

- 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

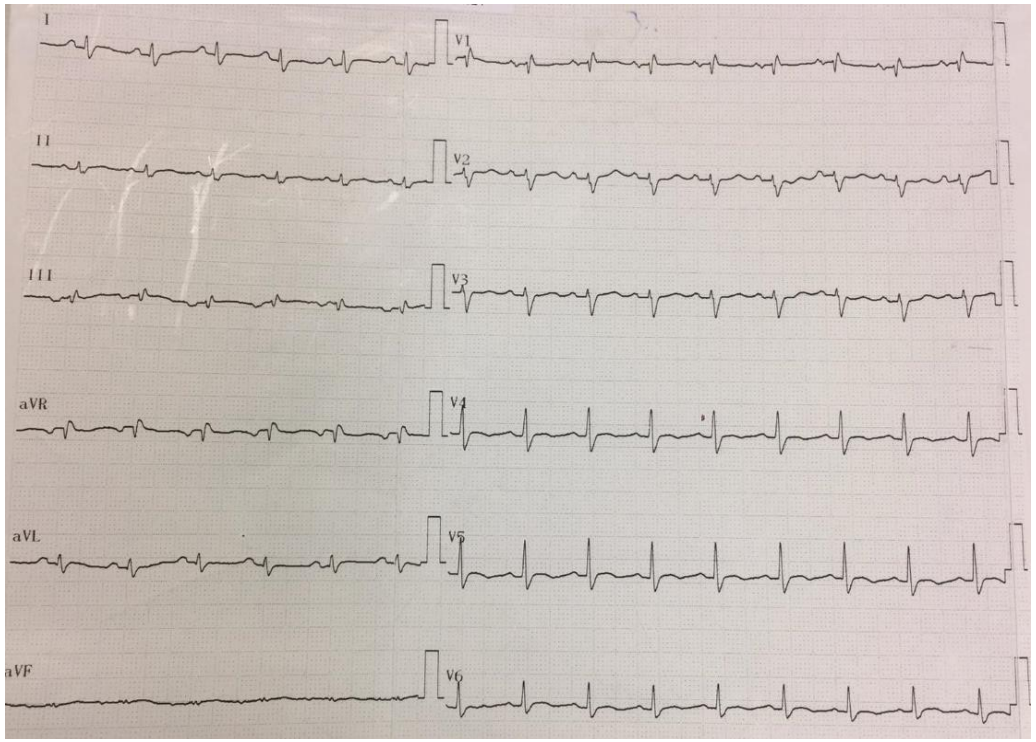
Chest X-Ray



Cardiomegaly
Bilateral pleural effusion

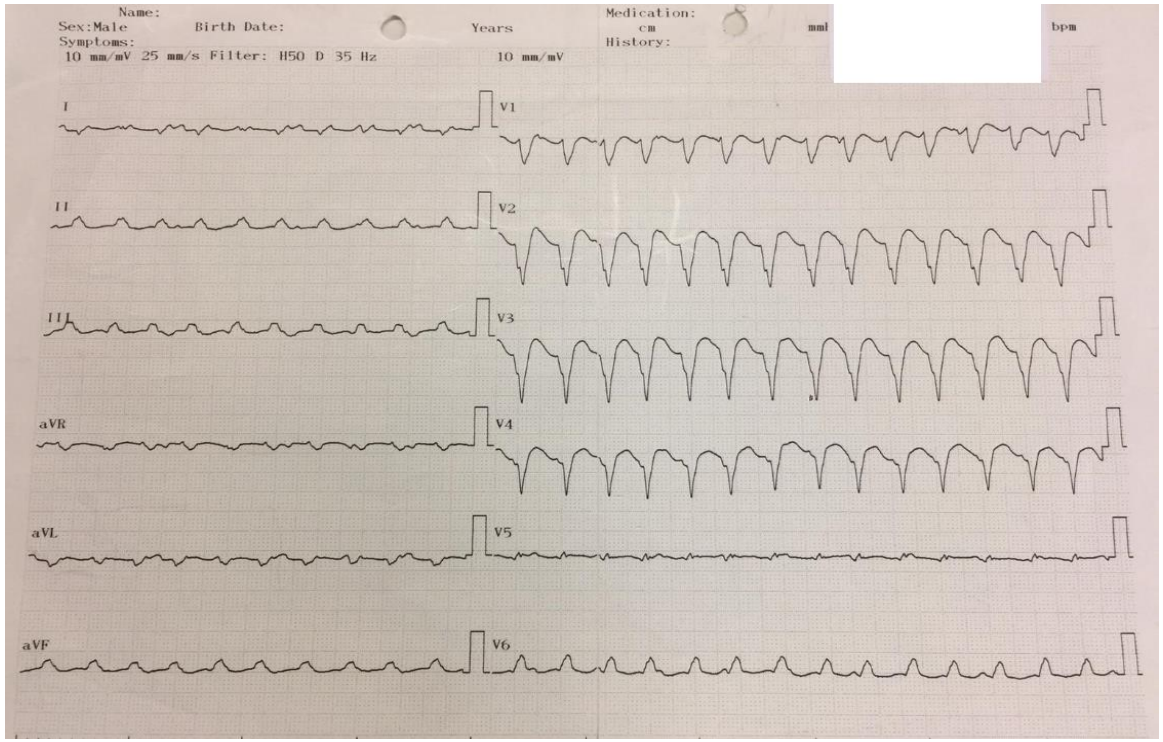
ECG

Baseline ECG



Sinus rhythm with first degree AVB

Monomorphic 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

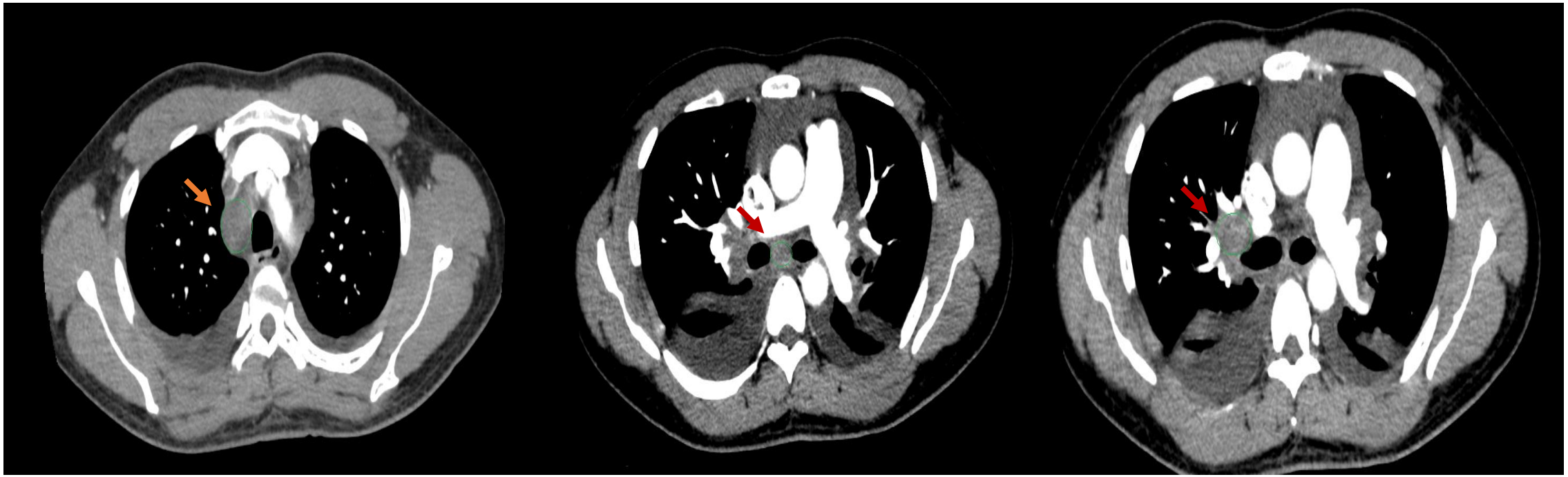
- QT prolongation w/ TdP-VT after Amiodarone

- Succeed extubation after 4d MV supported

Case

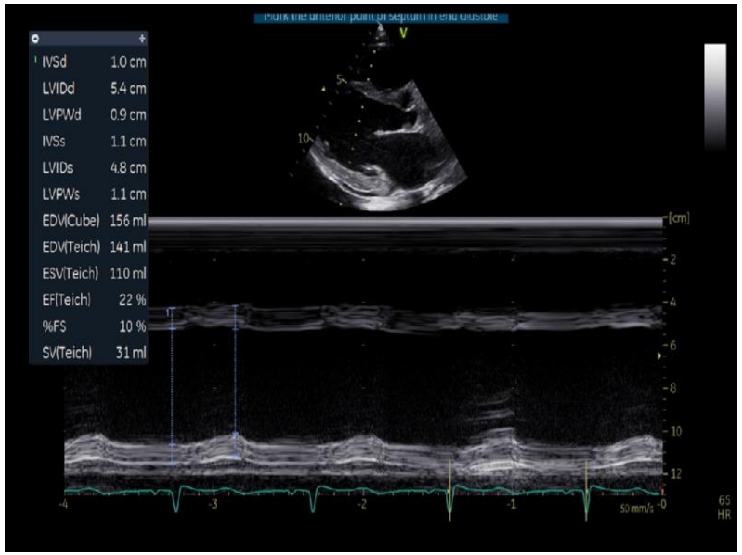
- Sustained spiking fever with normal inflammatory indexes
- R/O: Malignance ? Infection? Auto-immune? etc
  - TB :Interferon-gamma test Neg-
  - HIV screening Neg-
  - Syphilis:RPR/VDRL Neg-
  - Lymphoma
  - Anto-immune parameters: Neg-
- Thoracentesis: Transudate

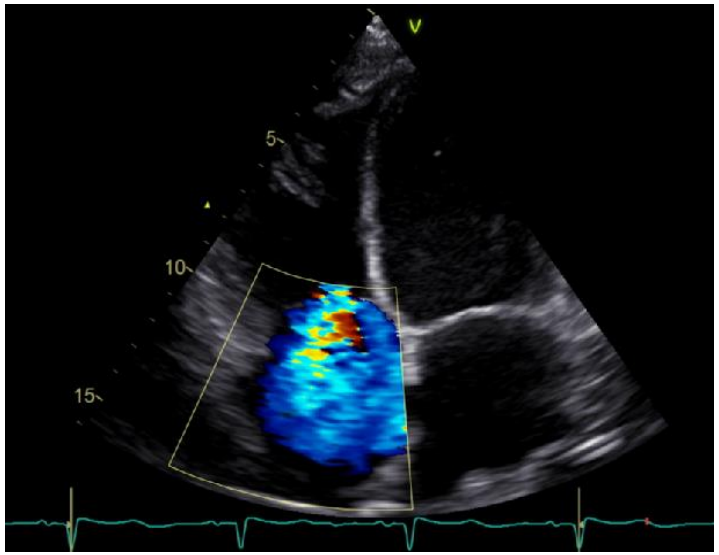
Chest CT

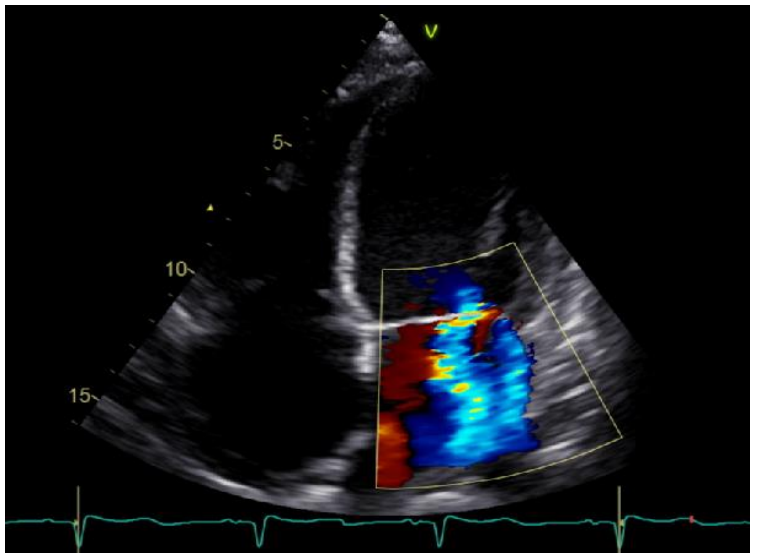


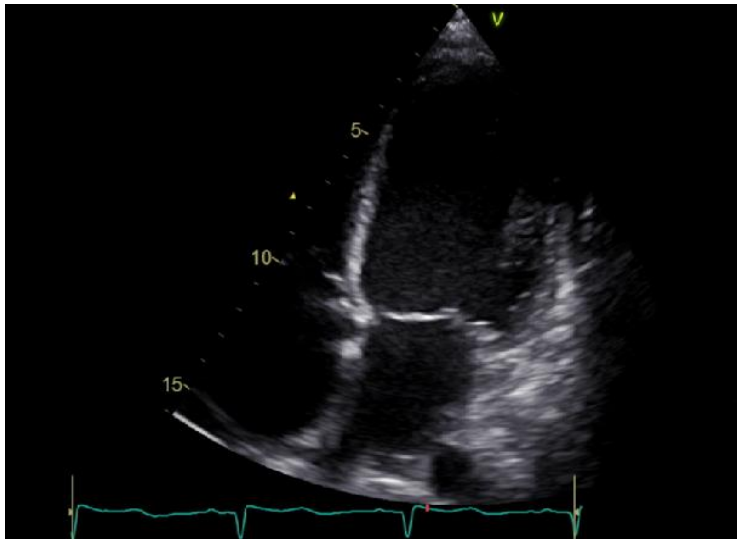
Mediastinal and hilar lymphadenopathy
Lymphoma VS Sarcoidosis ?

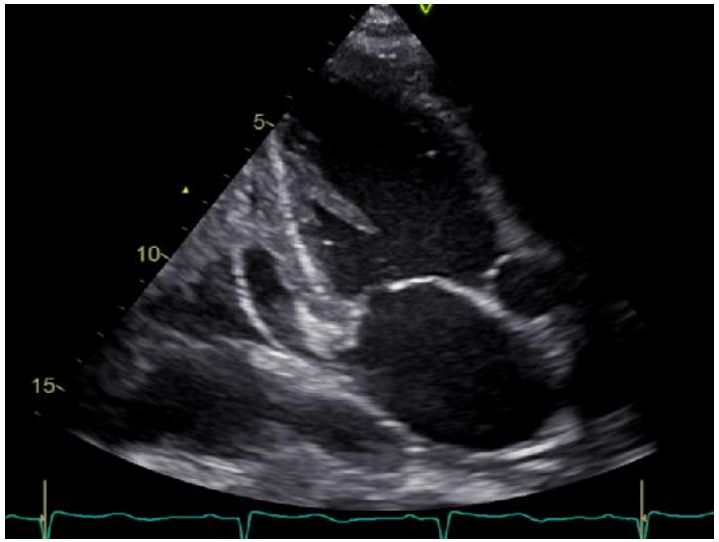
ECHO

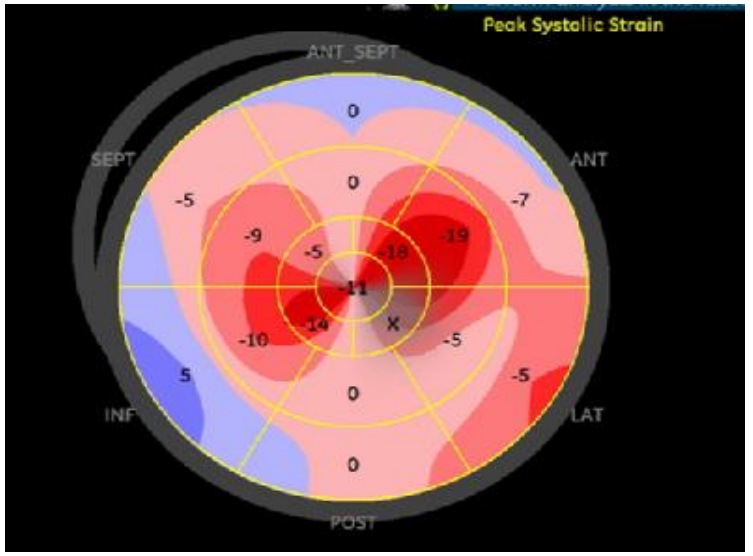












Dialted LA and LV w/ systolic function global compromised, basal and mid septum Septum AK and global HK, EF=22%, Severe concentric MR/TR

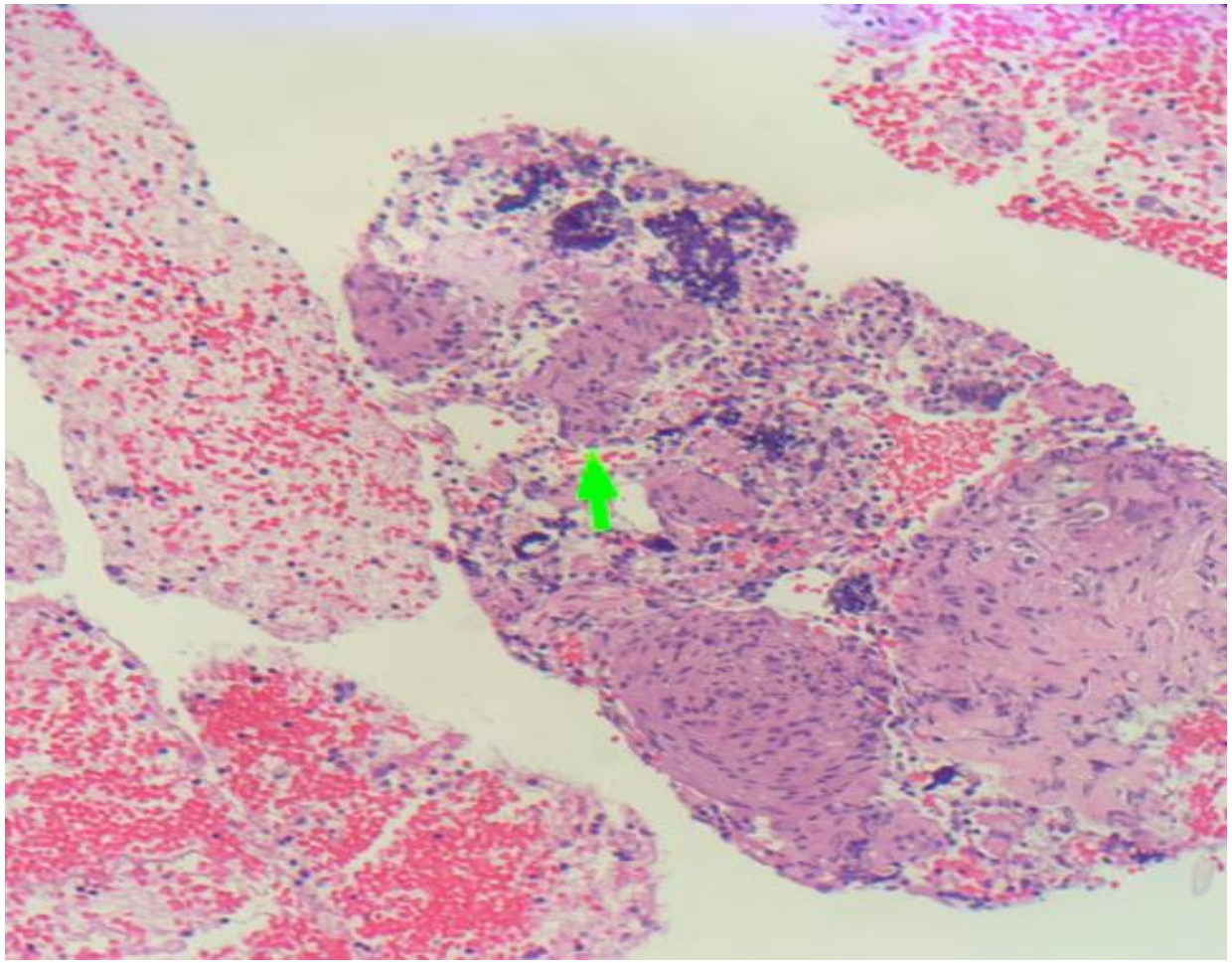
- Possible Diagnosis:

  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

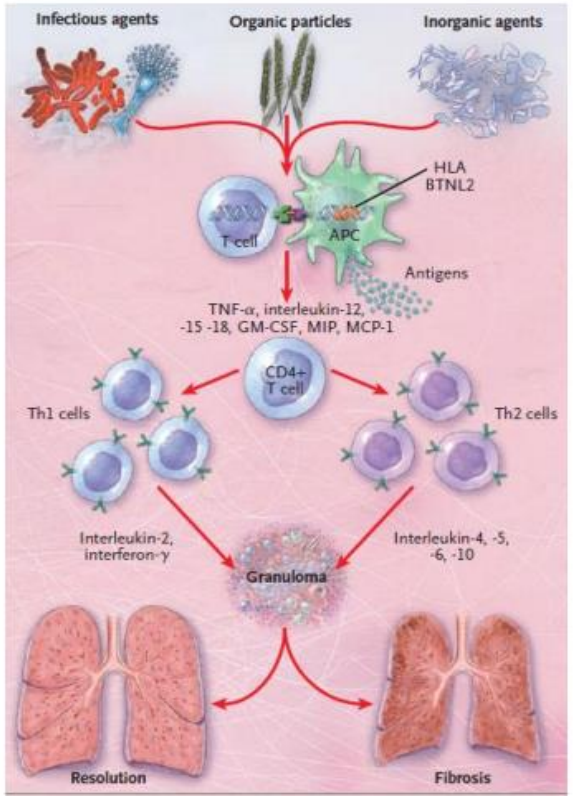
Hypothesized immunopathogenesis

EXAMPLES OF AGENTS SUGGESTED TO BE INVOLVED IN THE ETIOLOGY OF SARCOIDOSIS

Type of Agent		
Infectious	Inorganic*	Organic
Viruses (herpes, Epstein–Barr, retrovirus, coxsackie B virus, cytomegalovirus)	Aluminum	Pine tree pollen
Borrelia burgdorferi	Zirconium	Clay
Propionibacterium acnes	Talc	
Mycobacterium tuberculosis and other mycobacteria		
Mycoplasma		

*Beryllium, which causes berylliosis and not sarcoidosis, is not included.

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

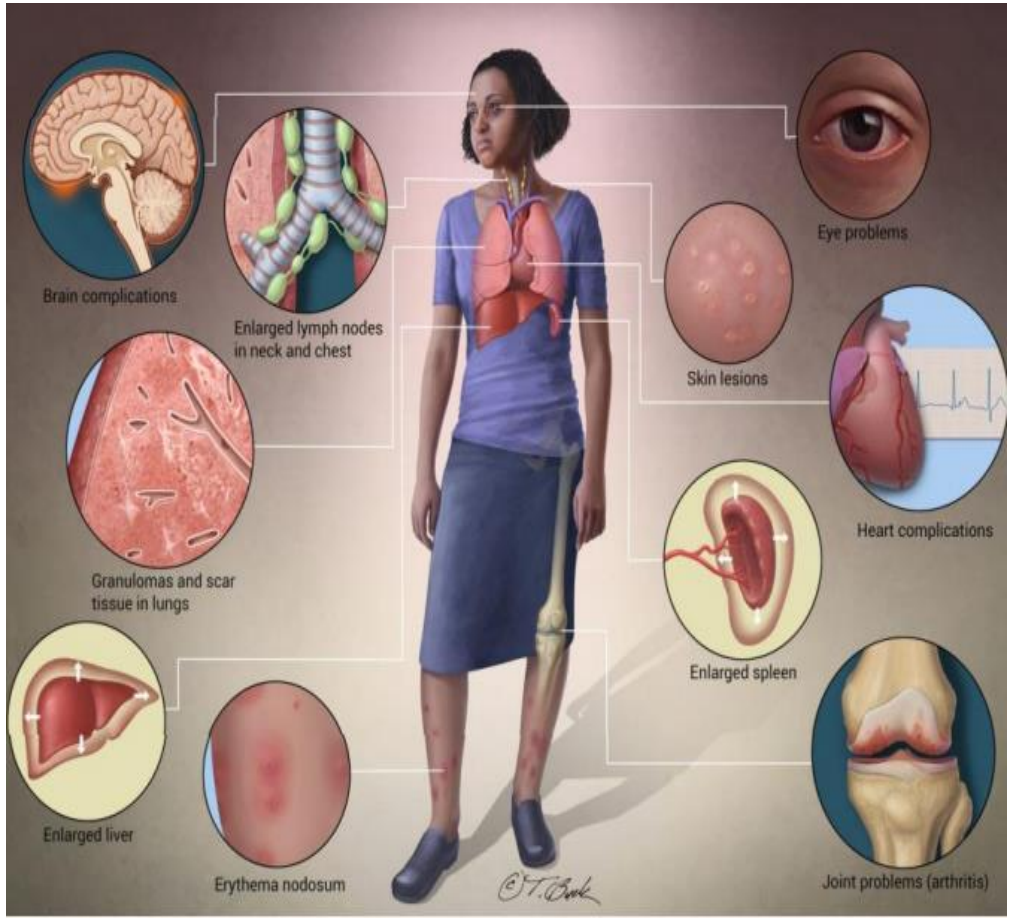


Hallmark: Non-caseating epithelioid cell granuloma

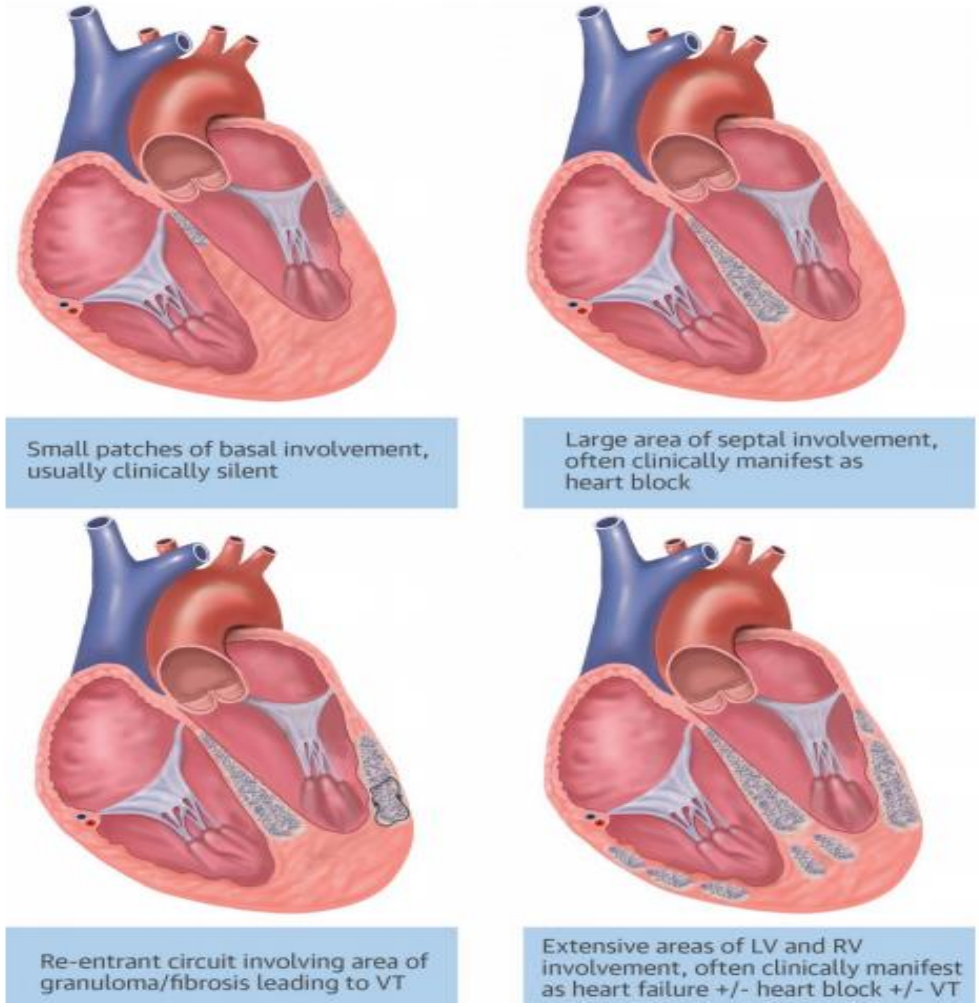
N Engl J Med 2007;357:2153-65. Harrison’ s Priciples of Internal Medicine,18e

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%



Signs and Symptoms



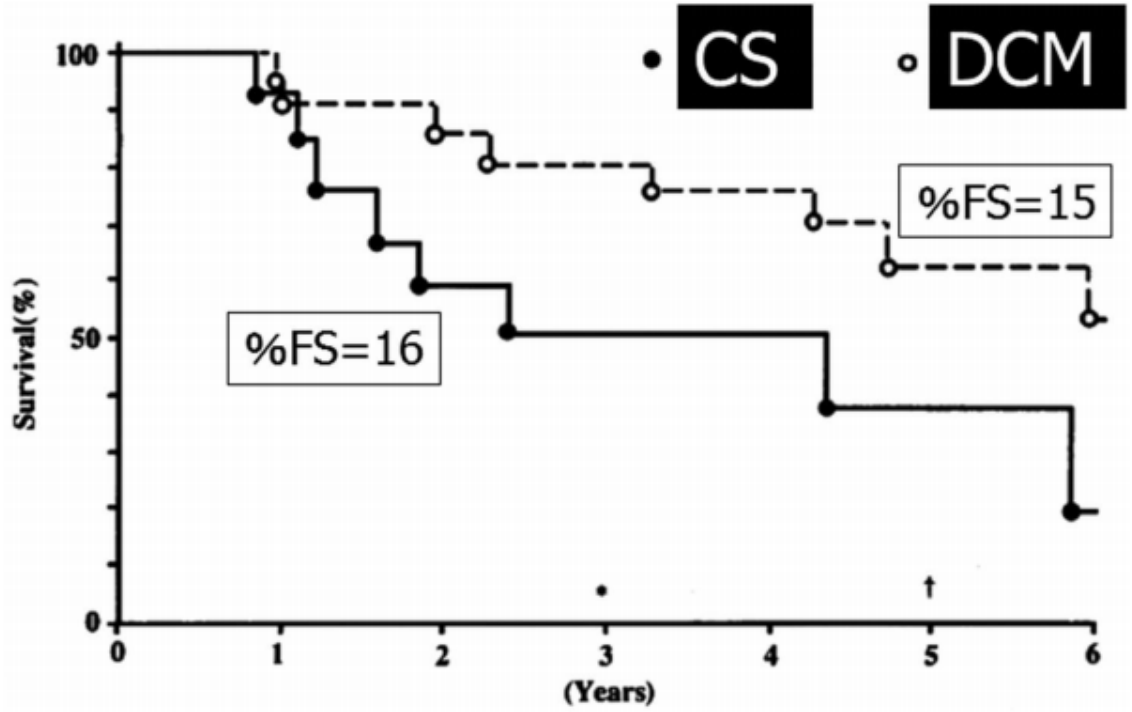
Clinical features of CS depend on the location, extent, and activity of the disease,
Asymptomatic (2/3 of Pts)

- Conduction abnormalities
- Ventricular arrhythmia including SCD
- Heart failure

Nonspecific signs and symptoms !

JACC 2016;68:411-21

Poor of prognosis of CS



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••]

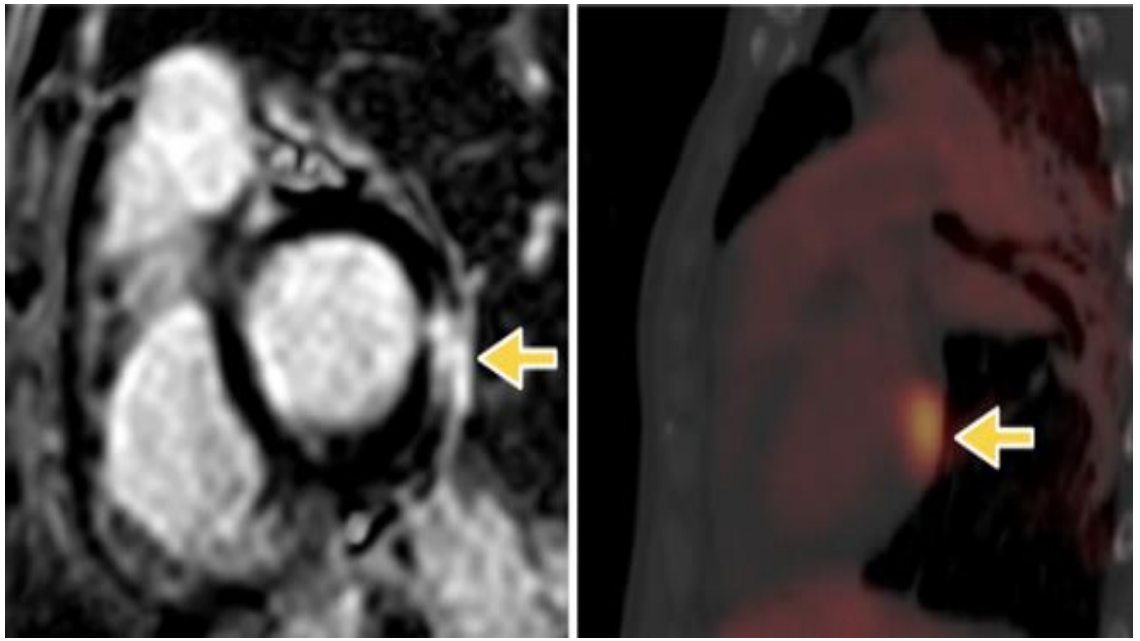
Electrophysiologic manifestations	Prevalence in study series
Atrioventricular block	26–67%
Bundle branch block	12–61%
Atrial arrhythmias	23–25%
Ventricular arrhythmias	11–73%
Sudden cardiac death	12–65%
Congestive heart failure	10–30%

Curr Opin Pulm Med 2013, 19:485 – 492

Sarcoidosis :Cardiac Involvement

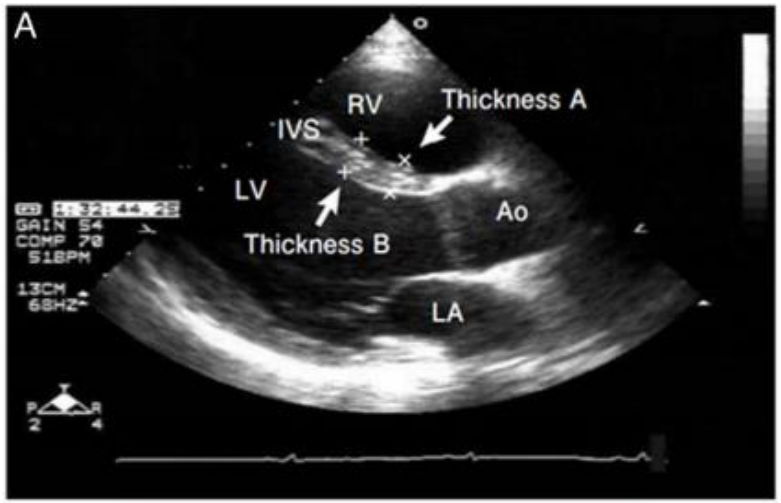
Common sites:

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



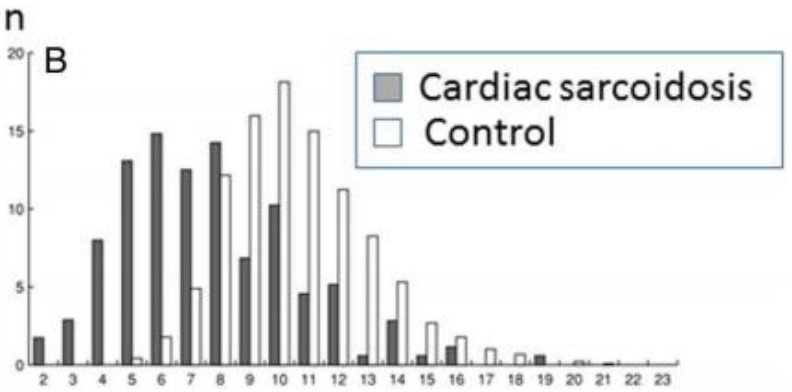
Pattern of focal cardiac sarcoidosis. Late gadolinium enhancement cardiac magnetic resonance (left) and cardiac ^{18}F-fluorodeoxyglucose positron emission tomography (right) images from a patient with only a small focal area of cardiac sarcoidosis. The arrows point to areas with myocardial involvement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

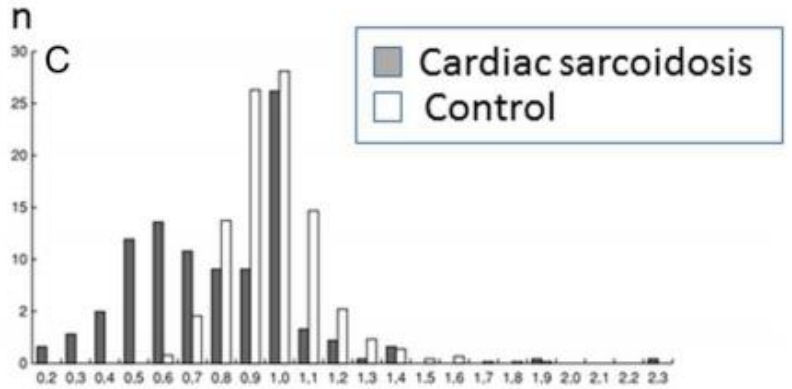
Echocardiogram in the diagnosis of CS



A<4mm: specificity 100%
sensitivity 12.6%

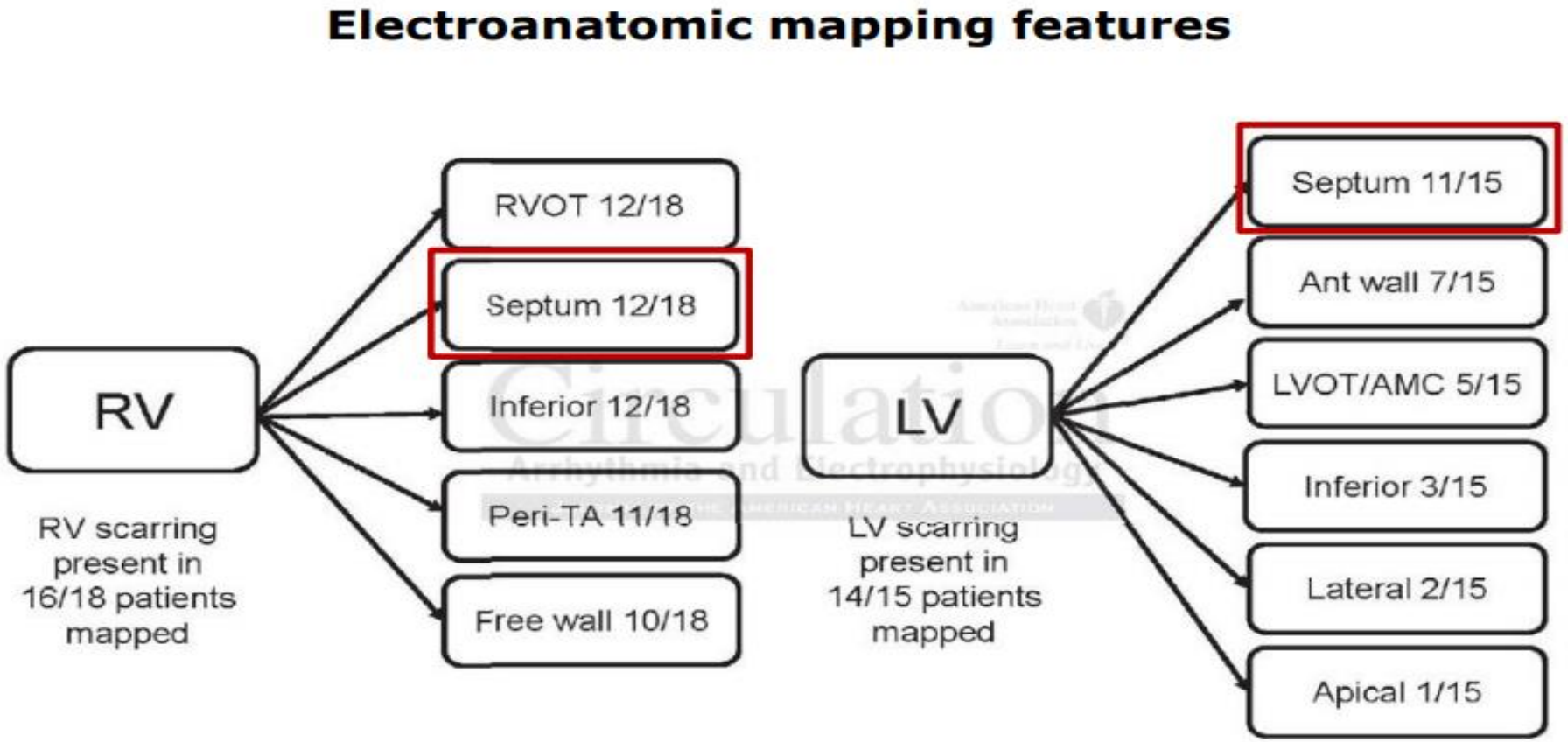
A/B<0.6: specificity 99%
sensitivity 38.9%





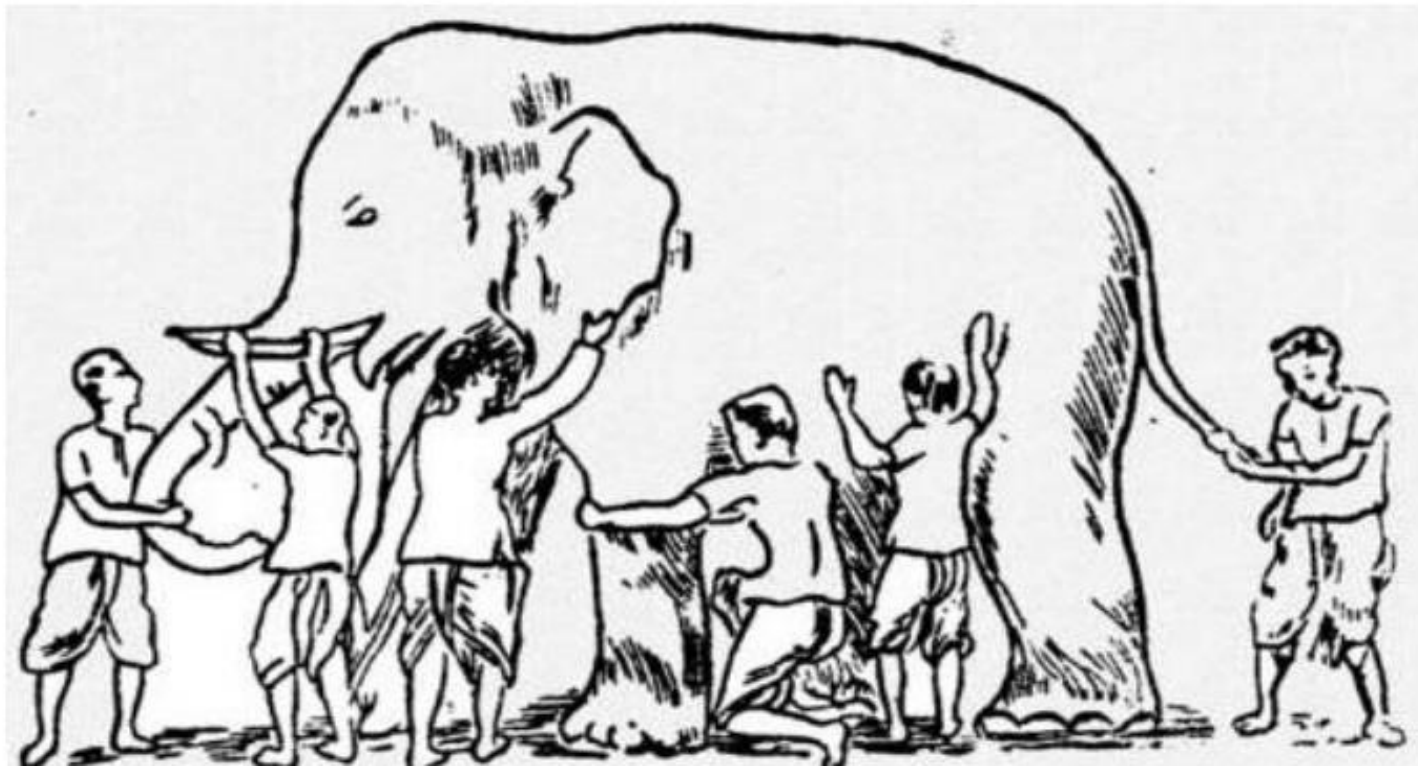
Kato Y, et al. Jpn J Sarcoidosis Granulomatous Disord 2008; 28:15~24

Predilection for the base of the interventricular septum?



Kumar S, et al. Circ Arrhythm Electrophysiol 2015; 8:87-93 .

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 b

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 pa

Positive gallium uptake in a pattern consistent with CS

Adapted from (7). "Probable Cardiac Sarcoidosis" defined as >50% likelihood. LVEF, le
fraction; FDG PET, fluorodeoxyglucose positron emission tomography; CS, cardiac sarc

Japanese Ministry of Health and Welfare Criteria for Diagnosis of Cardiac Sarcoidosis (Revised 2006)

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 condition and more than one in

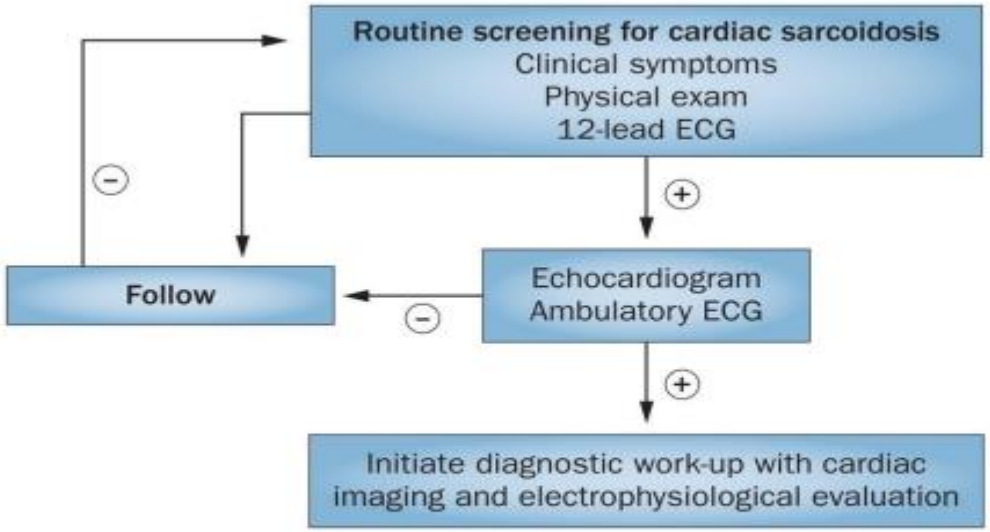
Table 1. The WASOG criteria for the diagnosis of cardiac sarcoidosis

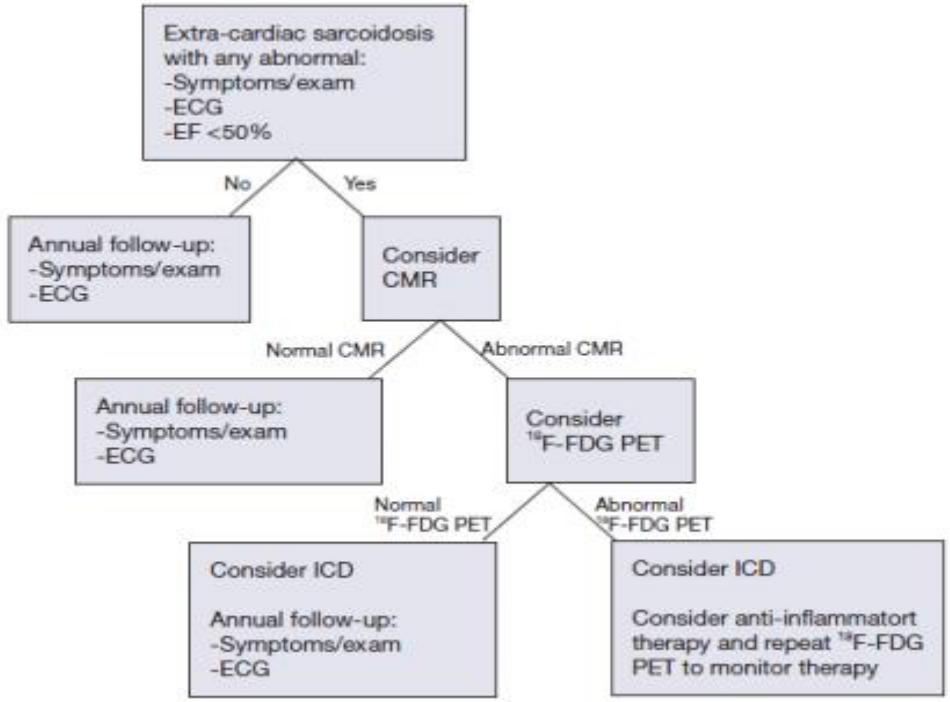
Highly Probable	At Least Probable	Possible	No consensus
Biopsy with granulomatous inflammation of no alternate cause	Treatment-responsive cardiomyopathy or AV block Reduced LVEF in the absence of other clinical risk factor Spontaneous or induced sustained VT with no other risk factors Mobitz type II or third-degree AV block Patchy uptake on dedicated cardiac PET Delayed enhancement on CMR Positive gallium uptake Defect on perfusion scintigraphy or SPECT scan T2 prolongation on CMR	Reduced LVEF in the presence of other clinical risk factor (e.g., HTN and DM) Atrial dysrhythmias	Frequent ectopy (>5% QRS) Bundle branch block Impaired RV function with a normal PVR Fragmented QRS or pathologic Q waves in two or more anatomically contiguous leads At least one abnormal SAECG domain Interstitial fibrosis or monocyte inflammation

Definition of abbreviations: AV = atrioventricular; CMR = cardiac magnetic resonance imaging; DM = diabetes mellitus; HTN = hypertension; LVEF = left ventricle ejection fraction; PET = positron emission tomography; PVR = pulmonary vascular resistance; RV = right ventricle; SAECG = signal-averaged electrocardiogram; SPECT = single-photon emission computerized tomography; VT = ventricular tachycardia; WASOG = World Association for Sarcoidosis and Other Granulomatous Disorders.

Diagnosis of Cardiac Sarcoidosis

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





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, azathiaoprine, 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

	Intervention	Mechanism	Potential benefit	Potential harm
Device therapy	ICD, secondary prevention (level of evidence C) (7)	Defibrillation of potential recurrent VT/VF	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 <1 year (7)	Pain, infection, cost, lead fracture, need for re-implantation, inappropriate shock
	ICD, primary prevention (level of evidence C) (7)	Defibrillation of potential VT/VF	Class I recommendation to reduce mortality in patients with structural heart disease and EF <30–35% despite medical therapy. Class IIa 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 LVEF 36–49% or RVEF <40% despite medical therapy. Class III if life-expectancy <1 year (7)	Pain, infection, cost, lead fracture, need for re-implantation, inappropriate shock
	Pacemaker (level of evidence C) (7)	Prevention of immediately fatal arrhythmia	Class I recommendation to reduce mortality and symptoms from complete heart block and bradyarrhythmia (7,21)	Pain, infection, cost, lead fracture, re-implantation, device removal complex if heart block resolves
Surgical	Heart and lung transplantation (level of evidence C)	Surgical transplant	Surgically replace organs affected by sarcoidosis with donor organs when end-stage organ dysfunction that may include refractory cardiogenic shock, IV inotrope dependence, peak VO_2 <10 mL/kg per min with achievement of anaerobic metabolism, refractory VT/VF (20)	Infection, need for chronic immunosuppression, risk of surgery, acute and chronic rejection, chance of recurrence (17)

ICD, implantable cardiac defibrillator; VT, ventricular tachycardia; VF, ventricular fibrillation; EP, electrophysiologic; 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!