

Extrapulmonary Sarcoid

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October 7, 2026

Objectives

- Describe the systemic nature of sarcoid
- Review recommended screening for extra-pulmonary sarcoid
- Discuss common clinical scenarios and treatment strategies
- No disclosures



Extrapulmonary Manifestations

- Skin (erythema nodosum & lupus pernio)
- Ocular lesions
- Upper respiratory tract
- Myocardium
- Neurosarcoid
- Musculoskeletal system: joints, myopathy
- GI tract
- Liver and spleen
- Bone marrow: anemia, leukopenia
- Bones
- Thyroid and Parotid glands, endocrine organs
- Kidneys – GIN, nephrocalcinosis, hypercalciuria
- Reproductive organs



Guideline Directed Screening – Extrapulmonary Disease

- Baseline eye exam by ophthalmologist (conditional, very low quality)
- Baseline CBC, serum creatinine, alk phos (conditional, very low) $\pm$ AST/ALT
- Serum calcium (strong, very low quality)
- Serum 25OH Vit D and 1,25-OH Vit D before repletion (conditional, very low quality)
- ECG (conditional, very low quality)
- In absence of symptoms, no routine TTE or holter monitor

American Journal of Respiratory and Critical Care Medicine Volume 201 Number 8 | April 15 2020



Guideline Directed Screening – Suspected Cardiac Involvement/Pulmonary Hypertension

- Cardiac MRI over cardiac PET or TTE (conditional, very low-quality)
- If CMR not available, then cardiac PET, not TTE (conditional, very low-quality)
- Suspected PH: Screen with TTE (conditional, very low-quality)
- TTE suggesting PH: RHC (conditional, very low-quality)
- Suspicion of PH with reassuring echo: RHC case by case basis

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Real life – Case #1

- 46 yo black female with SLE, anemia, and fibromyalgia presents with mediastinal, paratracheal, hilar and extensive abdominal adenopathy
- Denies DOE
- PFT: mild restriction, no obstruction, normal DLCO (BMI 40.8)
- TBNA: multiple non-caseating epithelioid cell granulomas



Real life – Case #1

- Azathioprine 100 mg daily
- 25 OH Vit D = 18
- Vit D supplement prescribed by PCP
- Presents with nausea and vomiting
- Calcium 11.4
- Creatinine 1.85



Hypercalcemia of Sarcoid

- Over-production of 1,25-dihydroxyvitamin D3 (calcitriol) by activated macrophages and sarcoid granulomas
- Vit D $\xrightarrow{1-\alpha\text{-hydroxylase}}$ 25OH Vit D $\xrightarrow{\hspace{1cm}}$ 1,25-dihydroxyvitD
- 1,25-OH-Vit D increases the intestinal absorption of calcium
- Hypercalcemia
- Hypercalciuria
- PTH level is normal or suppressed



Hypercalcemia of Sarcoid

- Fluids → resolution of hypercalcemia
- Azathioprine dosed for renal function
- Hypercalcemia recurs: Prednisone burst and taper over one month
- August '09: probable renal stone, creatinine 2.95
- Sept '09: renal biopsy - GRANULOMATOUS INTERSTITIAL NEPHRITIS, ASSOCIATED WITH SARCOIDOSIS
- Changed to Prednisone and mycophenolate



Hypercalcemia of Sarcoid: Treatment

- Stop all calcium and Vit D supplements
- Limit sun exposure
- Fluids/Loop diuretic/calcitonin
- Bisphosphonates
- Prednisone: inhibits 1- α -hydroxylase in macrophages
- Ketoconazole: reduces synthesis of calcitriol
- Hydroxychloroquine: inhibits 1- α -hydroxylase



Vitamin D repletion in Sarcoid

- No published recommendations
- If bone mineral density or Vit D levels are low, check 24-hour urine for calcium and 1,25 OH-D level
- If elevated, then do not replete
- If normal, proceed cautiously with repletion but follow calcium levels closely and do not replete Vit D above the low normal range

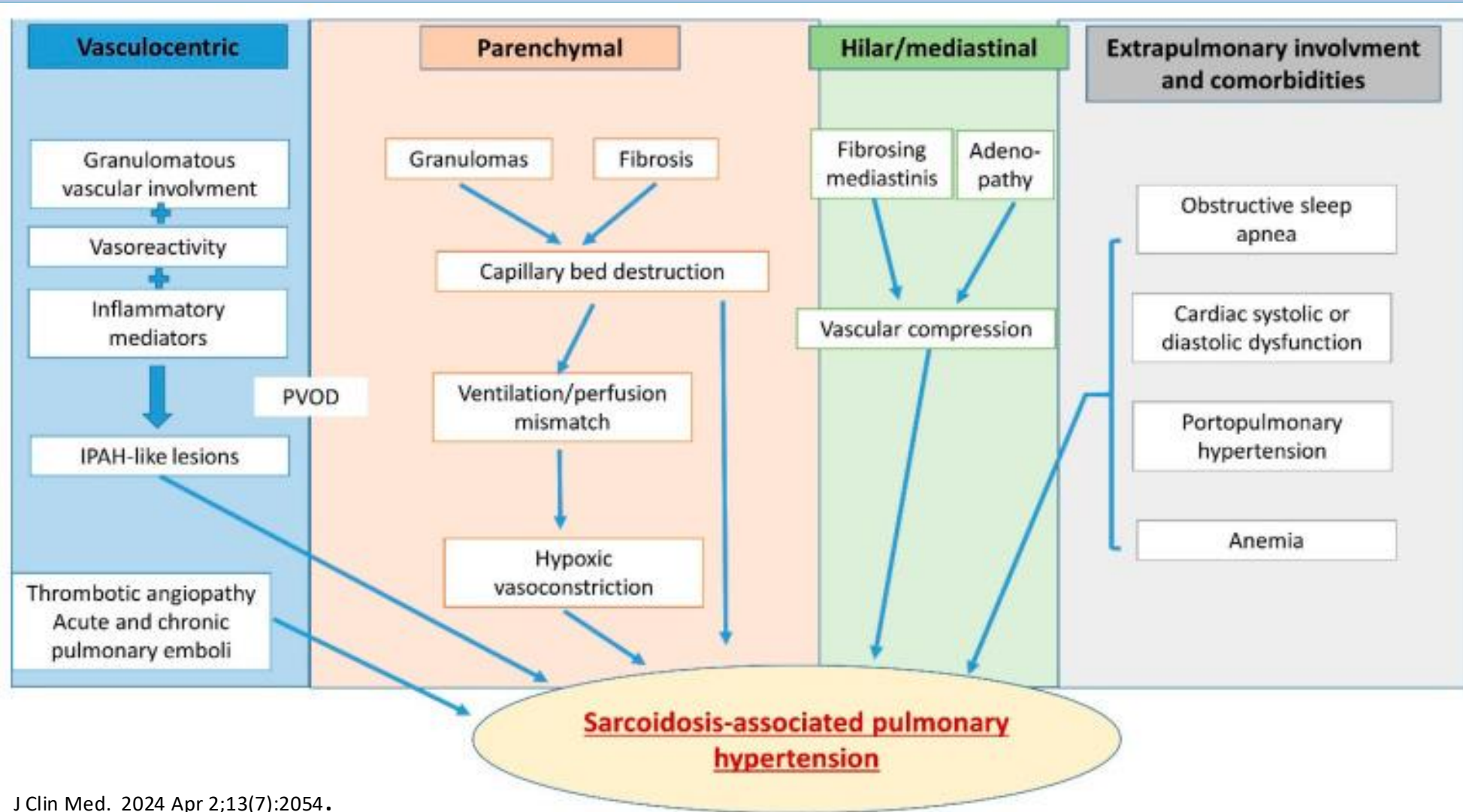


Real Life Scenario

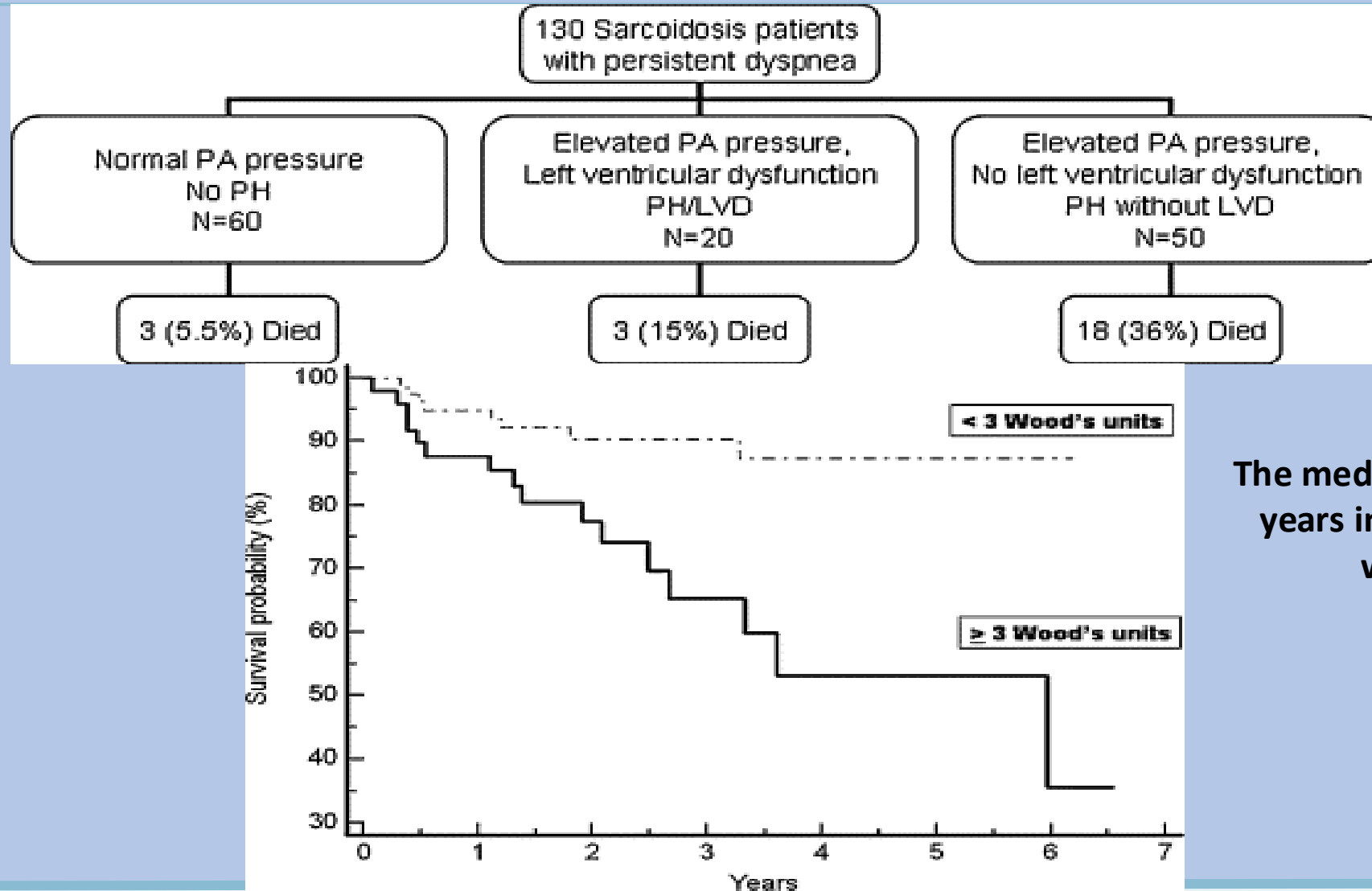
- Your patient is on appropriate therapy for pulmonary sarcoid and is showing a positive response, but complains of persistent dyspnea
- What should you do?



SAPH (WHO Group 5)



Persistent Dyspnea: SAPH



The median survival was 4.2 years in patients with PH without LVD

Real life – Case #2

- 53 yo black male with history of provoked PE presents with SOB and LE edema, diagnosed with bilateral DVT
- EKG with 2:1 block and RBBB



Case #2 continued.....

- TTE showed slightly depressed LV systolic function
- CT showed hilar and mediastinal LAD
- EBUS-TBNA – small non-necrotizing granulomas
- Prednisone plus Methotrexate



Real life – Case #3

- 43 yo white male with reduced ability to run
- Chest CT showed bulky paratracheal, mediastinal, and hilar adenopathy with conglomerate masses in lungs
- LN biopsy with non-necrotizing granulomas



Real life – Case #3 – Cardiac MR

- Free wall of RV and RVOT as well as inferoseptal LV wall thickened and hyperintense on T2 weighted images
- Hypokinesis of IS wall, focal thinning and WMA basal inferolateral wall
- Patchy areas of delayed gadolinium enhancement basal inferoseptal wall



Screening for Cardiac Sarcoid

Expert Consensus Recommendations on Screening for Cardiac Involvement in Patients With Biopsy-Proven Extracardiac Sarcoidosis

- Class I
1. It **is recommended** that patients with biopsy-proven extracardiac sarcoidosis **should be** asked about unexplained syncope/presyncope/significant palpitations*
 2. It **is recommended** that patients with biopsy-proven extracardiac sarcoidosis **should be** screened for cardiac involvement with a 12-lead electrocardiogram (ECG).
- Class IIa
1. Screening for cardiac involvement with an echocardiogram **can be useful** in patients with biopsy-proven extracardiac sarcoidosis.
 2. Advanced cardiac imaging, CMR or FDG-PET, at a center with experience in CS imaging protocols **can be useful** in patients with one or more abnormalities detected on initial screening by symptoms/ECG/echocardiogram.
- Class III
1. Advanced cardiac imaging, CMR or FDG-PET, **is not recommended** for patients without abnormalities on initial screening by symptoms/ECG/echocardiogram.

*Palpitations were defined as "a prominent patient complaint lasting > 2 weeks."²⁵



Screening for Cardiac Sarcoid

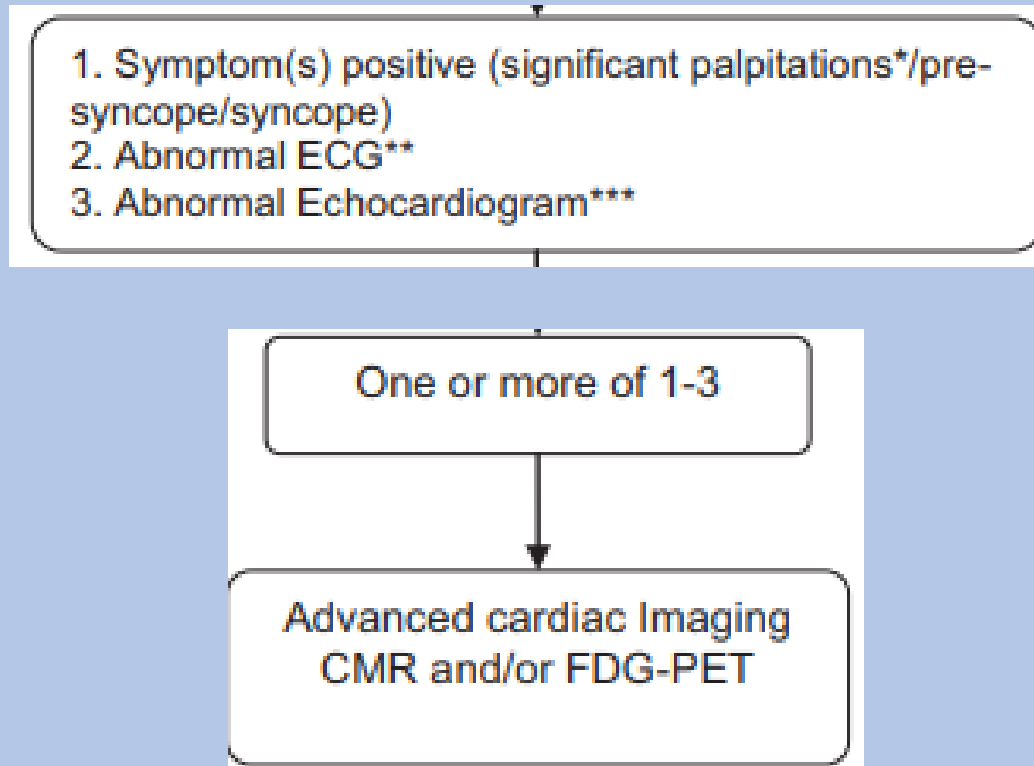


Table 1. JMHW and HRS diagnostic criteria for CS^{29,30}

JMHW	HRS
Histologic diagnosis group	Histologic diagnosis from myocardial tissue
CS confirmed by EMB, and histologic or clinical diagnosis of extraCS	Noncaseating granuloma on EMB with no alternative cause identified
Clinical diagnosis group	Clinical diagnosis
Histologic or clinical diagnosis of extraCS and	Probable diagnosis of CS exists if
Two or more major criteria or	There is histologic diagnosis of extraCS* and
One major criterion and two or more minor criteria	One or more of the following is present:
Major criteria	Cardiomyopathy or atrioventricular block responsive to immunosuppressive treatment*
Advanced atrioventricular block	Unexplained reduced LVEF (<40%)
Basal thinning of intraventricular septum	Unexplained ventricular tachycardia
⁶⁷ Ga uptake in heart	Mobitz II second- or third-degree heart block
Depressed LVEF (<50%)	Patchy ¹⁸ F-FDG uptake on cardiac PET consistent with CS*
Minor criteria	Late gadolinium enhancement on cardiac MRI consistent with CS
Electrocardiography: ventricular tachycardia, PVCs, RBBB, abnormal axis, abnormal Q wave	Cardiac ⁶⁷ Ga uptake and
Echocardiography: structural or wall motion abnormality	Exclusion of other causes of cardiac manifestations
Nuclear medicine: perfusion defect, ²⁰¹ Tl, ^{99m} Tc*	
Cardiac MRI: late gadolinium enhancement	
EMB: moderate fibrosis or monocyte infiltration	

PVC premature ventricular contractions, RBBB right bundle branch block

* Significant difference between JMHW and HRS criteria

Areas of Involvement: Autopsy

Descending order of frequency:

- 1) left ventricular free wall
- 2) interventricular septum (IVS)
- 3) papillary muscles
- 4) right ventricle (RV)
- 5) atria



Screening with CMR: Advantages & Disadvantages

- Higher spatial resolution of CMR compared with PET → visualization of subcentimeter lesions, delineates between subepicardium, mid-myocardium, and subendocardium involvement
- Less exposure for the patient to radiation
- Less non-diagnostic studies
- No dietary preparation
- **Presence of LGE is the strongest predictor for mortality and sustained ventricular arrhythmias, SCD, all cause death**
- Very high negative predictive value for adverse outcomes in general and ventricular arrhythmic events in particular

Interpretation CMR

- DGE - gado washes out of normal myocardium but where there is edema (inflammation)/scar enhancement persists
- T2 weighted images tell about inflammation (edema)
- Location and pattern:
 - In ischemic distribution – could be old infarct
 - Non-ischemic distribution: could be sarcoid
 - Linear and mid wall, subepicardial – could be myocarditis
 - Mass like, basal wall or septum – could be sarcoid
- The **degree of scar is most predictive of VT**, not the degree of inflammation



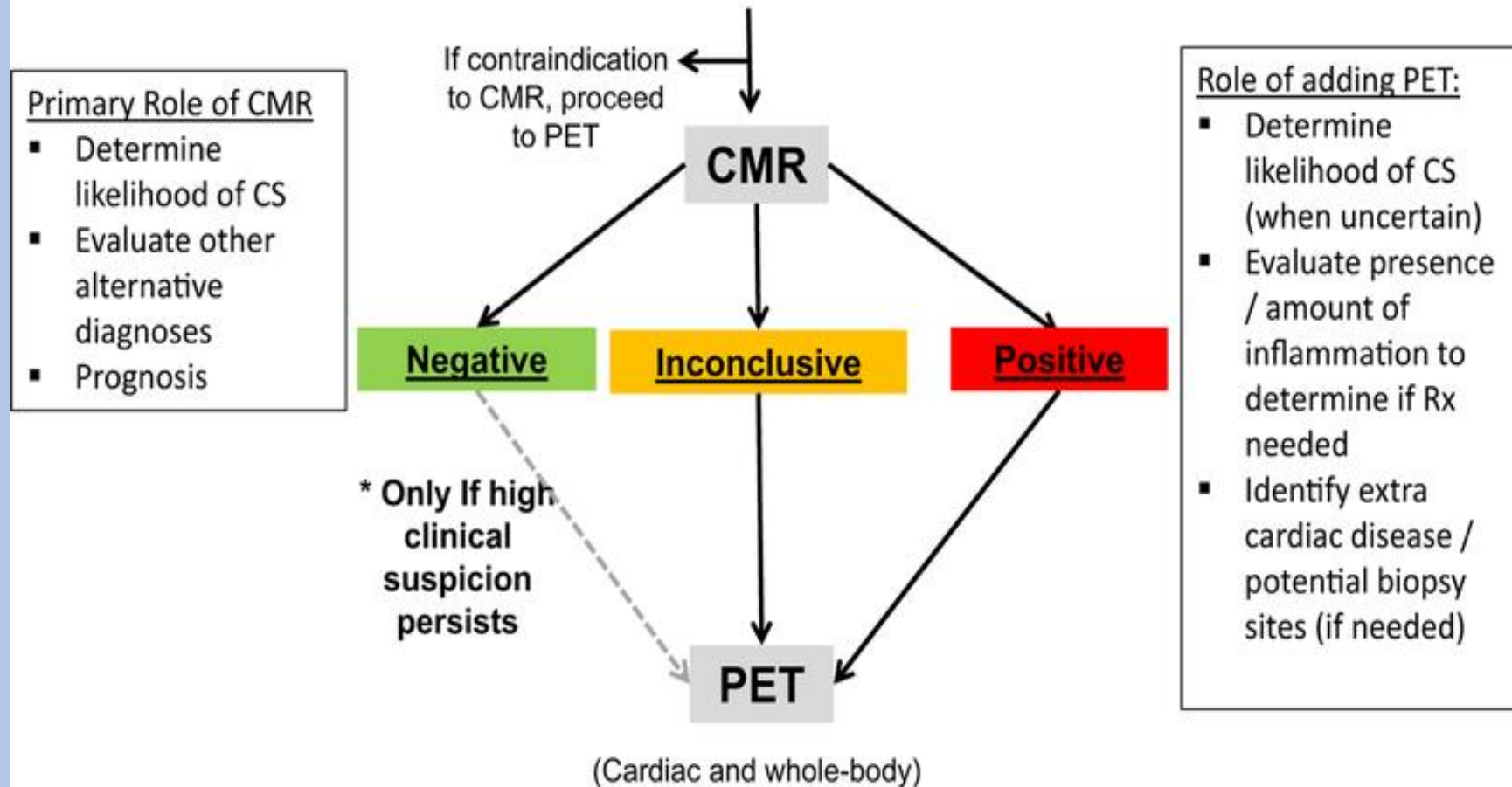
Scar does not mean no granulomas, just means no hypermetabolism, so still may treat



Screening with PET: Advantages & Disadvantages

- Cardiac FDG PET imaging is aimed at identifying metabolically active sarcoid
- FDG provides a unique role for assessing the response to anti-inflammatory therapy
- FDG has limitations, as healthy myocardial cells can utilize glucose
- **10%–15%** of FDG PET remain nondiagnostic due to incomplete FDG suppression
- More exposure to radiation with serial imaging
- There is growing evidence supporting the combined use of CMR and FDG PET imaging for enhancing both the diagnostic and prognostic performance of evaluating patients with suspected CS

Suspected Cardiac Sarcoidosis



Advanced cardiovascular imaging for the evaluation of cardiac sarcoidosis J Nucl Cardiol. 2019 February ; 26(1): 188–199

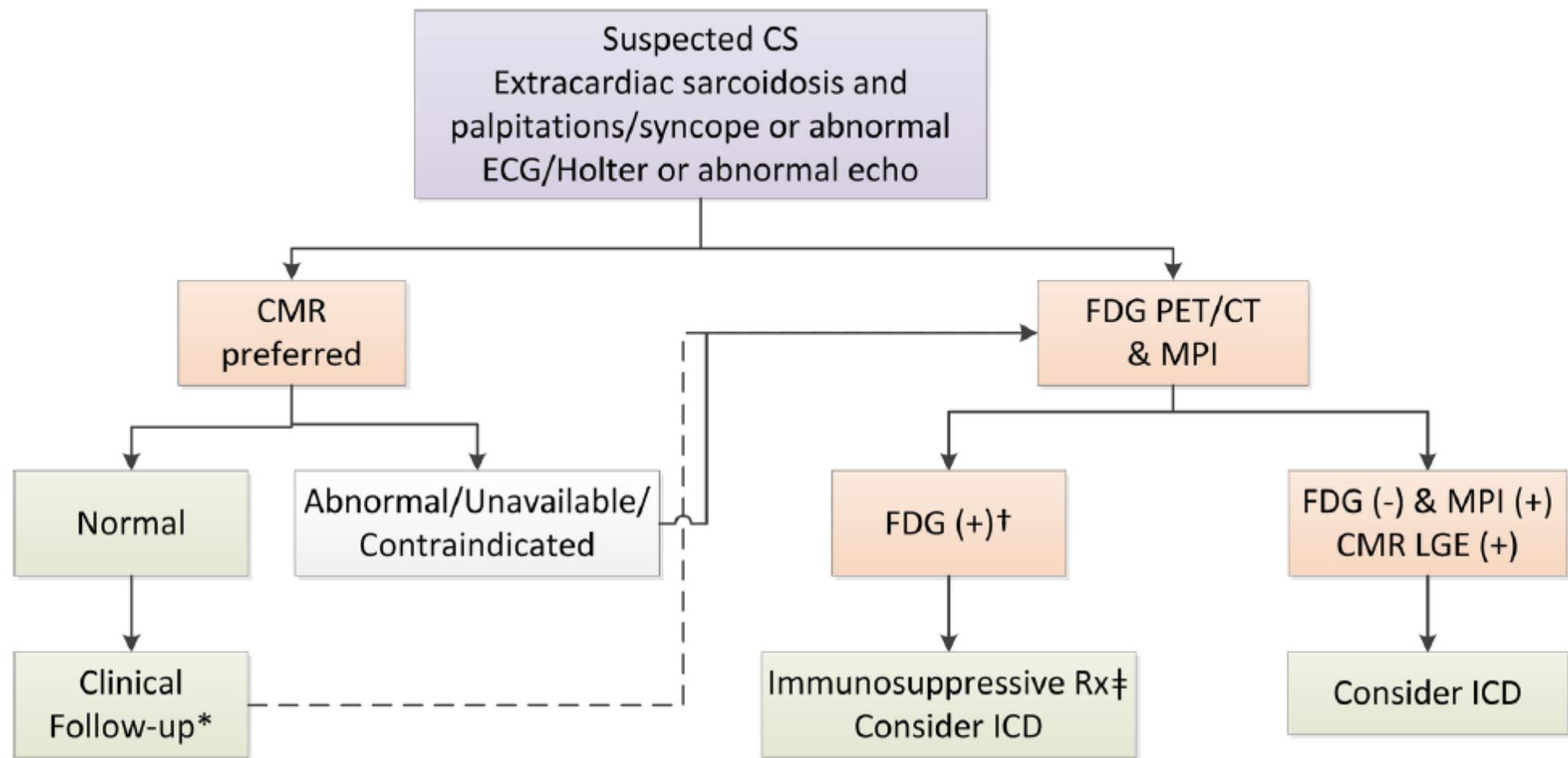


Figure 5. Non-invasive imaging approach to initial evaluation of patients with suspected cardiac sarcoidosis. *CS*, cardiac sarcoidosis, *CMR*, cardiovascular magnetic resonance imaging, *ECG*, electrocardiogram, *Echo*, echocardiogram, *FDG*, ^{18}F -fluorodeoxyglucose, *ICD*, implantable cardioverter defibrillator, *LGE*, late gadolinium enhancement, *MPI*, myocardial perfusion imaging, *Rx*, therapy. [†]Identify coexistent inflammation; FDG-PET/CT may be preferred first test in individuals with known systemic sarcoidosis where systemic sarcoidosis activity needs to be assessed. ^{*}If clinical suspicion is high or symptoms persist, FDG-PET/CT and MPI may be considered in patients with normal CMR. [‡]Immunosuppressive Rx may be considered taking into account the amount of inflammation. Patients with ICD are excluded for CMR.

Table 1. 2017 American Heart Association/American College of Cardiology/Heart Rhythm Society Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death
Recommendations for ICD Implantation in Cardiac Sarcoidosis

Class I	Class IIa
Sustained VT or cardiac arrest	LVEF >35% with syncope
LVEF ≤35%	LVEF >35% with scar by CMR or PET
	LVEF >35% with an indication for permanent pacing
	LVEF >35% with inducible ventricular arrhythmia
Recommendations apply to patients who are ICD candidates as determined by functional status, life expectancy of >1 y, and patient preference. CMR indicates cardiovascular magnetic resonance; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; PET, positron emission tomography; and VT, ventricular tachycardia.	

Treatment Cardiac Sarcoid

Table 2. Indications for Immunosuppressive Therapy in CS Patients(2, 6, 7)

ERS guideline indications	Functional cardiac abnormalities	<u>Heart blocks and conduction abnormalities</u> Complete Heart Block High-grade AVB <u>Arrhythmias</u> Sustained VT <u>Cardiomyopathy/LV Dysfunction</u> Moderate LV dysfunction (LVEF 35% to 50%) Severe LV dysfunction (LVEF < 35%)
Other possible Indications	Evidence of cardiac inflammation Symptom burden Abnormal serum biomarkers	Abnormal ¹⁸ F FDG-PET scan Extensive myocardial LGE NYHA functional class III or IV symptoms Elevated Troponin Elevated BNP

Key: AVB = atrioventricular block, VT = Ventricular tachycardia, LV = left ventricular, LVEF = left ventricular ejection fraction, cMRI = cardiac magnetic resonance imaging, ¹⁸F FDG-PET - [(18)F] fluorodeoxyglucose (FDG) – Positron Emission Tomography scan, BNP = brain natriuretic peptide



Medical Management CS

- Open-label trial of prednisone alone versus MTX + initial prednisone, addition of MTX was associated with long term improvement of ejection fraction and BNP after five years of therapy
- The Japanese Circulation Society (JCS): grade C1 recommendation (despite no strong supporting evidence) for the use of methotrexate as monotherapy or in combination with corticosteroids in CS patients who:
 - do not respond well to corticosteroids
 - cannot use them or cannot increase their dose due to adverse drug effects

SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2022; 39 (2); e2022015



Real life – Case #4

- 60 yo NP presented with history of bone pain 2014
- Sclerotic lesion right femur
- MRI right knee noted T2 hyperintense, T1 hypointense lesion right femur suspicious for malignancy
- Biopsy x 2 non-diagnostic



Case #4 continued.....

- Developed chest pain and a dry cough 2019
- CT revealing adenopathy and scattered perilymphatic nodules
- EBUS guided LN biopsy revealed non-necrotizing granulomas



Osseous Sarcoid

- Often found incidentally, usually asymptomatic in 1-15% patients
- All races, but bone cysts of hands and feet more common in black people



Imaging Patterns Osseous Sarcoid

- Moth eaten appearance of phalanges with soft tissue swelling
- Lytic lesions (also called bone cysts) in phalanges
- Sclerotic lesions in spine similar to mets
- Skull, nasal bones, maxilla, sternum, ribs, vertebra, pelvis, tibia, femur



Treatment of Osseous Sarcoid

- If asymptomatic, no treatment indicated
- Severe disease, treated with prednisone, methotrexate (no studies)
- Hydroxychloroquine for acute arthritis
- Anti-TNF alpha agents



Sarcoid Chronic Myopathy

- Sarcoid myopathy affects up to 75% of all individuals with sarcoidosis, usually reported in females ages 50-60; associated with chronic disease
- Muscle involvement is often asymptomatic
- Insidious onset of symmetrical proximal muscle weakness, can also involve trunk and neck muscles
- Symmetric limb involvement
- May be painful and lead to contractures
- Acute myopathy least common, usually early in course of disease in those < 40 yo



Sarcoid Myopathy

- CPK and aldolase may be normal but EMG may be abnormal
- Muscle biopsy reveals non-caseating granulomas
- Imaging: MRI, CT, or PET



Sarcoid Myopathy

- Star shaped lesions in muscles on MRI
- Muscle atrophy or fatty degeneration
- Nodular sarcoid – single or multiple nodules in the muscles which are round, ovoid or fusiform and extend along muscle fibers



Sarcoid Related Fatigue

- Fatigue is a difficult problem in the management of sarcoidosis patients
- No consistent definition, but reported in up to 85% of symptomatic sarcoidosis patients in multi-national studies
- Fatigue is multidimensional, with physical and mental manifestations of weariness and decreased energy
- Disruption of sleep architecture is not essential
- Fatigue is frequently associated with an impaired QOL
- Despite treatment, a substantial number of sarcoidosis patients suffer from persistent fatigue



Sarcoid Related Fatigue

- No correlation with pulmonary function, metabolic measures, laboratory parameters of inflammation, or T cell activation and granuloma formation
- Positive association with acute phase response, 6MWD, dyspnea, pain, and extrapulmonary involvement



Sarcoid Related Fatigue: Treatment

- As inflammatory factors play a role, consider low dose prednisone 10 mg daily
- Neurostimulants
 - Two double-blind, randomized, placebo-controlled, crossover trials looking at **dexmethylphenidate hydrochloride** and **armodafinil**
 - improvement in fatigue associated with sarcoid as measured by the Fatigue Assessment Scale (FAS) and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)

