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Review

Extrapulmonary sarcoidosis with a focus on cardiac, nervous system, and ocular involvement

John A. Belperio[a,*], Faisal Shaikh[a], Fereidoun Abtin[b], Michael C. Fishbein[c], Rajan Saggar[a], Edmund Tsui[d], Joseph P. Lynch III[a,*]

[a] The Division of Pulmonary and Critical Care Medicine, Holt and Jo Hickman Endowed Chair of Advanced Lung Disease and Lung Transplantation, Clinical Immunology, and Allergy, David Geffen School of Medicine at UCLA, 10833 Le Conte Ave, Room 37-131 CHS, Los Angeles, CA 90095, United States
[b] Department of Radiology, Thoracic and Interventional Section, David Geffen School of Medicine at UCLA, United States
[c] Department of Pathology and Laboratory Medicine, David Geffen School of Medicine at UCLA, United States
[d] Department of Ophthalmology, David Geffen School of Medicine at UCLA, United States

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ABSTRACT

Sarcoidosis is a poorly understood granulomatous disease that involves the lungs and/or intrathoracic lymph nodes in more than 90% of cases. Although pulmonary sarcoidosis is the leading cause of mortality in this disease, this review focuses on three sites of extrapulmonary involvement (heart, nervous system, and eyes), since involvement of any of these sites can be catastrophic, leading to death, debilitation, or blindness.
Patients with cardiac, ocular and neurosarcoidosis necessitate a multidisciplinary approach with careful and long-term follow-up. Prompt diagnosis with imaging and/or biopsy and treatment is required to avoid irreversible damage. Corticosteroids are the mainstay of therapy and are often associated with rapid and durable remissions. Immunosuppressive or biologic agents are reserved for patients failing or experiencing side effects from steroids. Managing sarcoidosis requires vigilance, judgement, and awareness of the vagaries of this fascinating disease.

1. Introduction

Sarcoidosis is a poorly understood granulomatous disorder that involves the lungs and/or intrathoracic lymph nodes in more than 90% of cases. Although lung involvement is the leading cause of morbidity and mortality in sarcoidosis, virtually any organ can be affected. Sarcoidosis involving the heart, central nervous system (CNS), or eyes can be catastrophic and requires a multidisciplinary approach, with aggressive monitoring and therapy [1].

The course of sarcoidosis is usually benign, with stability or improvement at long-term follow-up (2−3 years), but sex, ethnicity, and geographic factors influence the sites of organ involvement, prognosis, and clinical course [2]. Mortality rates in North America and Europe are low (1−5%), and >80% of deaths are due to pulmonary complications. Conversely, in Japan, 77% of deaths in sarcoidosis resulted from cardiac involvement [3].

Some "phenotypes" have an excellent prognosis (eg, Löfgren's syndrome), whereas involvement of bone, chronic cutaneous sarcoid, or multiorgan involvement have been associated with a worse prognosis and lower rates of response to therapy [1]. Sarcoidosis involving the heart, CNS or eyes can be devastating, thus vigilance and expertise from multiple disciplines are required to minimize morbidity and mortality.

1.1. Search strategy and selection criteria

This Sarcoidosis Review Team performed PubMed and OVID searches for published, peer-reviewed articles using the keywords "Sarcoidosis", "granulomatous", "Cardiac Sarcoidosis", "Ocular Sarcoidosis" or "Neurosarcoidosis". Each author was assigned to sections and asked to review the literature. No specific inclusion/exclusion criteria were determined *a priori*. Members reviewed and edited all drafts and the final version of this review, and reached consensus for its accuracy and relevance.

1.2. Epidemiology and pathogenesis of sarcoidosis

Sarcoidosis is worldwide in distribution, but the incidence and prevalence varies according to racial and geographic factors. The incidence in Scandinavia is (1-64/100,000), British Isles (5.0-12.7/100,000) and the US (5-40/100,000). Sarcoidosis is rare (incidence <1-3/100,000) in Southern Europe, Central and South America, Israel,

* Corresponding authors.
E-mail addresses: jbelperio@mednet.ucla.edu (J.A. Belperio), jplynch@mednet.ucla.edu (J.P. Lynch).

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and East Asia as well as in children. Sarcoidosis is 4–8 times more common in blacks.

The cause of sarcoidosis is unknown, but environmental, microbes and occupational exposures have been implicated in some studies. A specific genetic defect has not been identified but aggregation within families and certain ethnicities is well established. The predominance of lung/mediastinal lymph node involvement suggests inhaled antigens may initiate the inflammatory-granulomatous process, but no inciting antigen(s) has been identified and may insinuate; in some, cases there is an autoimmune process. Many studies indicate an over-exuberant-inflammatory response with Th1 cytokines (eg, IFN-γ, TNF-α, inflammasomes-IL-1) are involved in the generation of sarcoid granulomas [4–8]. This seems to be true across multiple organs as the same pathways were found to be involved in the granuloma formation damaging both heart and lung tissues [4,9].

1.3. Histopathology of sarcoidosis

The histological hallmark of sarcoidosis is well-formed, discreet non-necrotizing granulomas (NNG) composed of epithelioid histiocytes and multinucleated giant cells surrounding by lymphocytes, plasma cells, and fibroblasts in the periphery. In some cases, extensive granulomas may destroy the normal tissue architecture.

1.4. Cardiac sarcoidosis (CaS)

Clinically evident sarcoidosis involves the heart in at least (2–7%) of patients with sarcoidosis [10], but occult involvement is much higher (>20%) [11]. Cardiac sarcoidosis (CaS) is often not recognized antemortem, as sudden death may be the presenting feature. Therefore, a high clinical suspicion is needed for CaS especially when there is an arrhythmia, atrioventricular block (AV) block, low ejection fraction (EF) or syncope with a negative coronary angiography (Fig. 1). The incidence of CaS is higher in Japanese patients and has been shown to account for approximately 77% of deaths [3]. By contrast, in the US, (13–50%) of sarcoid deaths have been attributed to CaS [11].

Granulomatous inflammation, the hallmark of sarcoidosis, may involve any part of the heart (i.e., myocardium, endocardium, or pericardium) [11] (Fig. 2, Panel I A–C). The myocardium is most frequently involved, while pericardial and endocardial involvement usually reflect direct extension of myocardial disease [11].

2. Clinical features

Conduction disturbances, atrial ventricular (AV) block, and ventricular arrhythmias (VA) are the most common cardiac manifestations and reflect granulomatous infiltration within the conduction system or ventricular walls [12]. Atrial involvement has been seen in (9–50%) of sarcoid cases [13]. Coronary arteries are typically normal, but extensive myocardial disease may lead to dilated cardiomyopathy [11]. These issues may result in syncope, heart block, tachyarrhythmias, sudden death, and congestive heart failure (CHF) [14]. Infiltration of the pericardium may lead to pericardial effusion and rarely, constrictive pericarditis. Significant valvular involvement, coronary arterial aneurysms, coronary artery spasm, acute coronary syndrome, coronary artery vasculitis, coronary artery occlusion, and ventricular aneurysms have been described, but are rare.

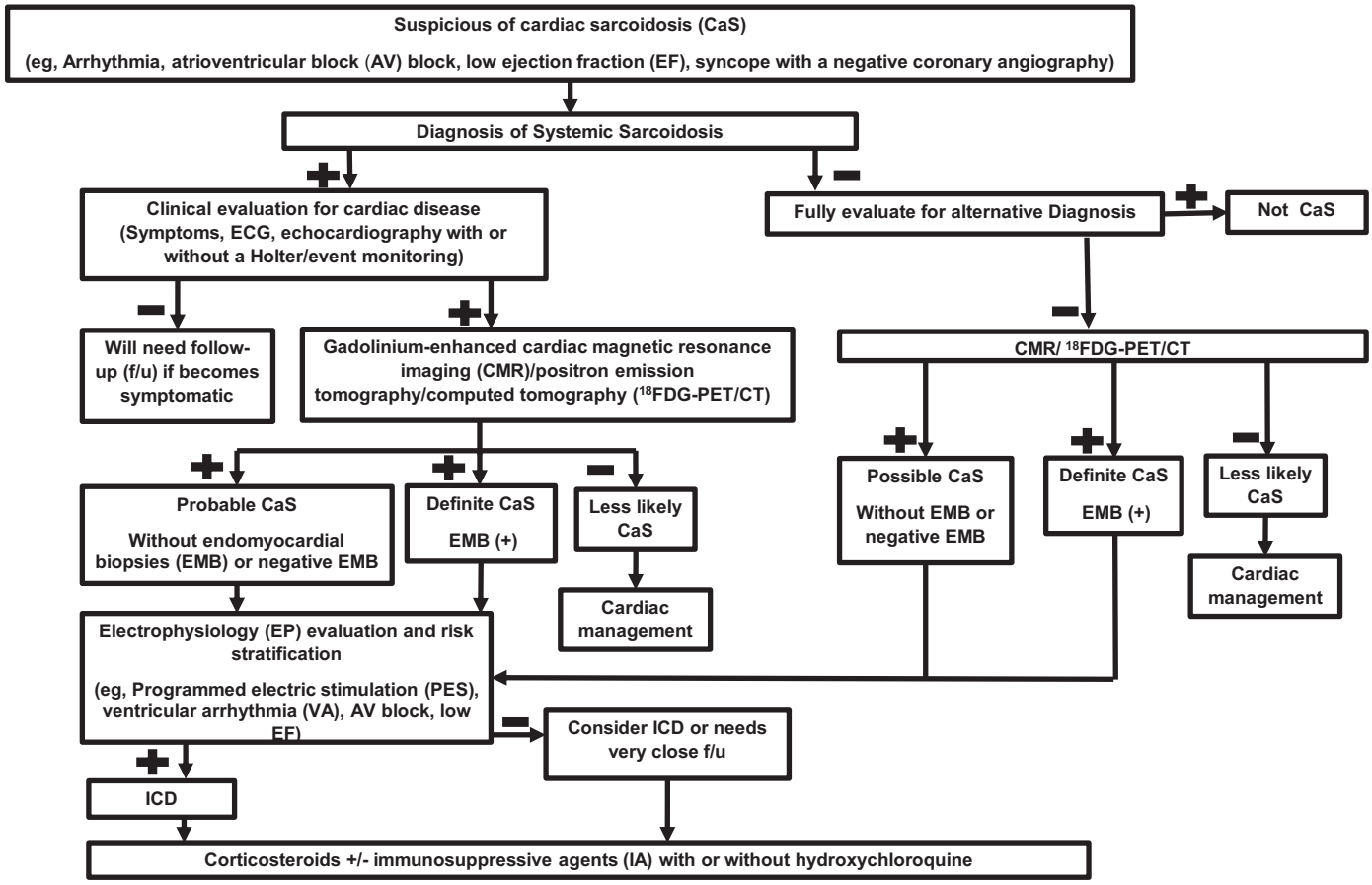

Fig. 1. Proposed flow diagram for the diagnosis and management of cardiac sarcoidosis. A basic approach when there is a suspicion of cardiac sarcoidosis.

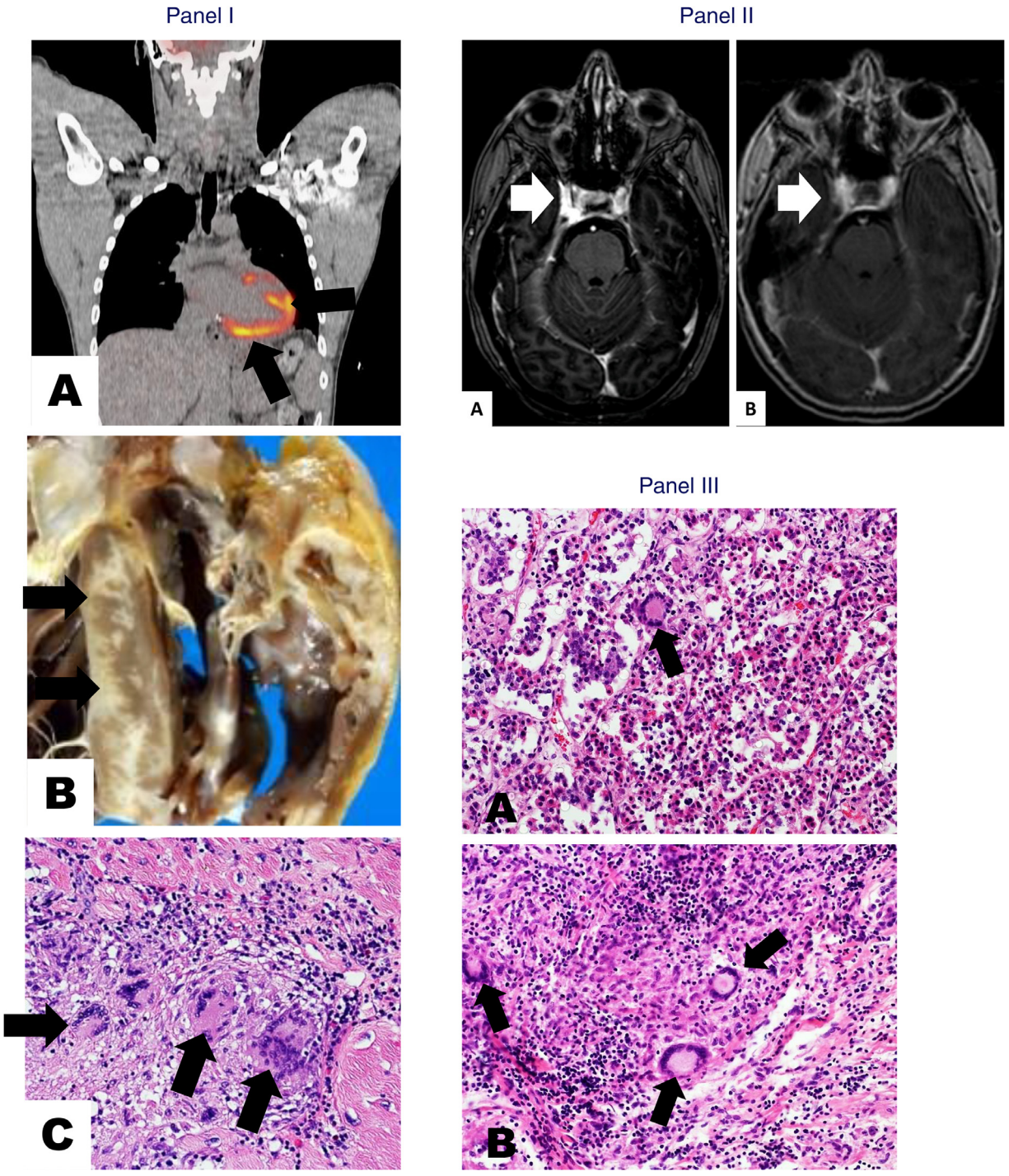

Fig. 2. Cardiac and Neurosarcoidosis Cases. Panel I 37 year old black man with clinical diagnosis of dilated cardiomyopathy: (A) positive 18FDG-PET CT scan, arrows demonstrating cardiac 18FDG uptake; (B) heart showed normal coronary arteries and scars in unusual locations (arrows), and (C) non-necrotizing granuloma with giant cells (arrows) in myocardium (H&E stain, x200). Panel II 50-year-old white female developed sinus congestion, headaches then facial pain, headaches and diplopia. (A) MRI scan on 7/22/13 showed an enhancing lesion in right Meckel's cave extending into the cerebellopontine angle. A surgical biopsy of the mass lesion in Meckel's cave showed granulomatous inflammation with epithelioid cells and multinucleated giant cells. Special stains for AFB and fungi were negative. No pathological evidence of vasculitis and her ANCA was negative. She was treated with pulse solumedrol 1 g a day for 3 days then prednisone 40 mg qd and appropriately tapered. Infliximab 5 mg/kg every 8 weeks was added on one month after the biopsy. (B) Follow-up MRI demonstrates dramatic reduction in the right cavernous sinus lesion (arrow). Panel III 27 year old white woman who presented with pituitary failure and a CXR consistent with stage 3 sarcoidosis. She died of endstage cardio-pulmonary disease: Pituitary gland at autopsy demonstrated (A) isolated giant-cell (arrow), and (B) non-necrotizing granulomas and multinucleated giant cells (arrows) (H&E stain, x200).

3. Involvement of other organs

Extra-cardiac involvement is usually present in patients with CaS [13,15]. Some series of CaS demonstrated that (44–60%) of the cases had extra-cardiac involvement [16]. A US study involving 84 sarcoidosis patients noted that those with CaS had a high frequency of extra-cardiac involvement: lungs (90%); liver (40%); lymph nodes (38%); spleen (32%); kidney (7%) [17]. Australian investigators found that of 32 patients with positron emission tomography/computed tomography (PET/CT) scans with 18-flurodeoxyglucose (^{18}FDG)

contrast (^{18}FDG-PET/CT) positivity for CaS only 3 (9%) had isolated CaS [15]. Overall extrapulmonary involvement is common in patients with CaS and the variability between studies is likely due to differences in detection of extracardiac disease (eg, autopsy, organ biopsy, or ^{18}FDG-PET/CT).

3.1. Diagnosis of CaS

Guidelines from the American Thoracic Society (ATS) and World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) published in 1989 recommend a resting electrocardiogram (ECG) to screen for CaS in all patients with sarcoidosis [18]. However, resting ECGs are insensitive for detecting cardiac involvement; further, the clinical significance of nonspecific ECG abnormalities is unclear. Any abnormality on ECG or Holter monitor should be further evaluated by transthoracic echocardiography (TTE) or other imaging studies (discussed below).

TTE is nonspecific, but is invaluable to assess cardiac chamber(s) size/function in patients with suspected or confirmed CaS. Salient abnormalities may include: ventricular wall thinning; global or focal hypokinesis or dyskinesia; wall motion abnormalities; chamber enlargement; ventricular dilatation or hypertrophy; depressed left ventricular ejection fraction (LVEF); valvular regurgitation; papillary muscle dysfunction; pericardial effusions [11]. TTE is not sensitive to detect early myocardial sarcoid lesions, but is noninvasive and an inexpensive way to assess and follow cardiac size and function.

A definitive diagnosis of isolated CaS is difficult. Transvenous ventricular endomyocardial biopsies (EMB) have been used to diagnose CaS but sensitivity is low (19−35%). Higher yields may be achieved by electroanatomic mapping-guided EBM. However, given the potential for complications associated with EMB, most clinicians rely on non-invasive imaging to diagnose CaS. A consensus statement by the American Heart Association, American College of Cardiology and European Society of Cardiology emphasized that the role of EMB is controversial and data are not robust [19]. We do not recommend EMB to diagnose CaS.

High resolution computed tomographic (HRCT) scans may reveal enlarged mediastinal lymph nodes (MLN) in cases subsequently confirmed to have CaS. The best imaging tests to assess CaS are gadolinium-enhanced cardiac magnetic resonance imaging (CMR) [20] and ^{18}FDG-PET/CT [15,21]. Expert consensus guidelines published in 2014 by the Heart Rhythm Society recommended whole body ^{18}FDG-PET/CT as an important diagnostic study for CaS [12].

3.2. ^{18}FDG-PET/CT and CaS

^{18}FDG-PET/CT has been used to diagnose CaS and “stage” activity of sarcoidosis in thoracic and extrathoracic sites. Increased avidity of ^{18}FDG in myocardium suggests active granulomatous inflammation. Additionally, among patients lacking a histological diagnosis, increased uptake of ^{18}FDG at extracardiac sites (particularly lung or MLN) may target extra-cardiac sites to biopsy. It should be emphasized, however, that increased cardiac ^{18}FDG uptake is not specific for CaS and may be observed with arrythmogenic cardiomyopathy and other dilated cardiomyopathies [22]. A meta-analysis of 164 patients with systemic sarcoidosis found that ^{18}FDG-PET/CT had a sensitivity of 89% and a specificity of 78% [23]. A small follow-up study demonstrated similar findings [21]. A more recent single center retrospective study involving 205 patient with endstage heart failure that underwent heart transplantation found that a high probability ^{18}FDG-PET/CT scan (multiple, noncontiguous perfusion defects with associated FDG uptake or multiple areas of focal FDG uptake with extracardiac FDG uptake present) for CaS had a sensitivity of 83% and a specificity of 100% [22]. A probable ^{18}FDG-PET/CT scan (single perfusion defect with associated focal or focal on diffuse FDG uptake or no perfusion defects, but focal or focal on diffuse FDG uptake) had a sensitivity of 100% and specificity of 33% [22]. Serial ^{18}FDG-PET/CT scans may be useful to assess response to therapy but ^{18}FDG-PET/CT scans are expensive, and costs are often not reimbursed by insurance carriers. Although ^{18}FDG-PET/CT is invaluable to assess inflammation and possible response to therapy, its precise role to diagnose and follow CaS needs to be clarified.

3.3. Gadolinium-enhanced cardiac MRI (CMR) and CaS

Gadolinium-enhanced cardiac MRI (CMR) may identify regional differences in tissue characteristics and enhancement between diseased and normal myocardial tissue. CaS lesions appear as patchy or focal hyper-enhancement patterns in the left ventricular (LV) free wall, papillary muscles, or interventricular septum (IVS). Late gadolinium enhancement (LGE) is common in CaS, and is an indicator of severity of disease [24] and prognosis [20]. In a recent meta-analysis, the diagnostic accuracy of CMR was evaluated for CaS. The search was from 1980 to 2018, involved 8 studies with 649 patents. CMR had an overall pooled sensitivity of 91% and pooled specificity of 80% for CaS [25].

With regard to prognosis, Dutch investigators performed CMR in 37 cases of steroid naïve CaS, 26 of whom had LGE [24]. Compared to cases without LGE, there was a trend to a higher rate of VA (29% vs 0%, $p = 0.12$) and higher rate of the composite clinical endpoint (VA, heart failure hospitalization, or cardiovascular death) (41% vs 0%, $p < 0.05$) [24]. A meta-analysis reviewed 7 studies comprising 694 subjects with sarcoidosis found that those with LGE on CMR had a higher annualized mortality, VA and the combined endpoint (VA or death) [26]. Similar results were seen in smaller studies and another meta-analysis [20,27,28]. These various studies cited above support the CMR as a way to document the extent of myocardial disease and may be able to predict the course of CaS, and monitor response to therapy. However, given the high expense, CMR are often not covered by insurance in the US, and their role to diagnose and follow-up of CaS needs to be refined.

3.4. Is there a role for routine screening for CaS?

Mehta et al. screened 62 ambulatory patients with sarcoidosis for possible cardiac involvement by ECG, Holter monitoring, TTE, and cardiac symptoms (i.e., palpitations, syncope, or pre-syncope) [29]. Those with cardiac symptoms or positive screening tests underwent CMR and ^{18}FDG-PET/CT scans. Overall, 39% had CaS. Cardiac symptoms were more common in those with CaS (46% vs 5%, $p < 0.001$). Patients with symptoms were more likely to have abnormal Holter and TEE [29]. Subsequently, these authors evaluated 76 patients with biopsy-proven systemic sarcoidosis without cardiac symptoms, but with evidence of CaS by ^{18}FDG-PET/CT or CMR [30]. Programmed electric stimulation (PES) of the ventricle was performed in all cases. Sustained VA was induced in 11% and all received an ICD. Initial LVEF by TTE was lower in subjects with inducible VA and 75% of the cases with inducible VA had further episodes of VA or died, compared with only 2% in the non-inducible group [30]. Since sudden death can occur even in asymptomatic patients with CaS, we recommend an ICD in any patient with CaS and a history of serious VA or inducible VT. The course for patients with CaS and negative PES (non-inducible) is not clear.

3.5. Prognosis of CaS

Cardiac involvement can occur at any time with sarcoidosis and may occur in the absence of pulmonary or systemic involvement [10]. Fatalities in subjects with CaS may be due to arrhythmias, conduction defects, or progressive heart failure [14]. An early Japanese study involving 95 treated patients with CaS, overall survival rates were 85%, 60% and 44% at 1-, 5- and 10-years; respectively [14]. By multivariate analysis predictors of mortality included New York

Heart Association (NYHA) functional class, LV end-diastolic diameter and sustained VT [14]. More contemporary studies with aggressive treatments from Finland, France and the US have demonstrated 1-, 5-, and 10-year survivals of (97%), (90–96%), and (90–93%); respectively [10]. Predictors of poor outcomes in these studies were presenting with CHF, high degree AV block, LGE on CMR, older age and lack of a defibrillator. Differences between studies likely has to do with ethnic, geographic and treatment differences.

3.6. Treatment of CaS

Mortality rates of untreated CaS are high. While randomized clinical trials (RCT) have not been done, there is evidence that morbidity and mortality rates are lower in patients treated with corticosteroids (CS) [alone or combined with immunosuppressive agents (IA)] [10,31–37]. More specifically, there are multiple studies involving the treatment of CaS with CS with or without IA and ICD's with follow-up ranging between 4- and 10-years demonstrating an impact on outcomes [32,34–36]. Continuous treatment leads to a reduction in mortality from (15–42%) to (0–12%) [32,34], improvements in LVEF (especially in those with a LVEF between (35% and 54%) [34,36], improvements in AV block from (0%) to (47–57%) [32,35], reduction in VT from (41–62%) to (6–14%) [32,36] and fewer admissions for CHF [33]. Even when CaS is considered cured, relapses can occur [31]. Factors associated with cardiac relapse included renal disease, high degree AV block and LGE on CMR [31]. These data support ICD's and long-term (possibly indefinite) CS therapy with or without IA for patients with CaS, provided there are no serious adverse effects associated with CS. Additionally, early initiation of treatment may prevent or reverse myocardial remodeling/inflammation whereas delayed treatment may be less effective.

Despite the lack of RCTs, clinical experience strongly supports aggressive treatment with CS (alone or combined with IA) for clinically-evident CaS [10]. CS therapy is warranted for every patient with CaS unless specific contraindications exist. IA should be used in cases refractory to or as a CS-sparing agent. Additionally, an ICD is mandatory for patients with severe VA, heart block, or cardiomyopathy (Fig. 1). For patients with proven/suspected CaS, we initiate treatment with CS. Symptomatic patients or those with severe VA typically receive a 3-day pulse of intravenous (IV) methylprednisolone (500–1000 mg daily), followed by prednisone 40 mg/day for 4-weeks (Fig. 1). Prednisone is then tapered to a maintenance dose of 10 mg by 6-months depending on clinical status. We add an IA [typically methotrexate (MTX) or azathioprine (AZA)] at 6-weeks, but other agents may be considered. At 12-weeks, we sometimes add hydroxychloroquine (HCQ) 200 mg once or twice daily (Fig. 1). The duration of therapy depends upon the individual case, but we typically maintain low dose prednisone (5–10 mg daily) with low dose IA for a minimum of (2–3) years since relapses can be life-threatening and may cause permanent damage. Clinical relapses of CaS require re-treatment with high dose CS (usually IV pulse methylprednisolone) with or without IA. A multicenter randomized trial to assess efficacy and toxicity associated with standard dose prednisone therapy versus low dose prednisone plus MTX is in progress [38].

Favorable responses to tumor necrosis factor antagonists (TNFA) have been cited in patients with CaS recalcitrant to CS or IA [39]. In a prospective study, 38 patients with CaS were treated with TNFA (30 infliximab; 8 adalimumab). The use of TNFA was associated with reduced CS dose at 6- and 12-months as well as a reduced maximum FDG uptake, however there was no change in LVEF [40]. Favorable responses have been cited with rituximab, but data are limited to a few cases.

4. Adjunctive therapy (catheter ablation, anti-arrhythmics, ICDs and ablation)

The predictive value of PES-induced VA and guided anti-arrhythmic medical therapy in CaS is limited. However, serious VT can develop even in cases in whom VT could not be induced. The efficacy of antiarrhythmic agents to treat CaS is variable and breakthroughs can occur. Given the potential for sudden death, all sarcoid patients with severe VA, heart block, or cardiomyopathy should receive an ICD in addition to medical therapy. The diagnosis of CaS is a class IIa indication for ICD implantation according to expert consensus in the ACC/AHA/HRS guidelines for prevention of sudden cardiac death [41]. Mehta and associates evaluated electrophysiological testing for risk stratification in patients with asymptomatic CaS and found that the majority of patients with inducible VT had a reduced LVEF [30]. There is some suggestion for patients with a LVEF>35% the use of CMR/^{18}FDG-PET/CT with electrophysiological testing may be incremental in risk stratifying for arrhythmias, however large prospective studies are needed [42].

Cardiac ablation may be efficacious in patients with persistent VT despite medical therapy. However, relapses and fatalities may occur. Importantly, medical therapy for CHF is necessary for patients with cardiomyopathy.

5. Cardiac transplantation

Cardiac transplantation should be considered for sarcoidosis patients with severe intractable heart failure refractory to medical therapy. Sarcoidosis accounts for ~0.5% of cardiac transplants performed in the US. In the US, 65 patients received heart transplants for CaS from 1987 to 2005; 1- and 5-year survival rates were 88% and 81% [43]. Recurrent sarcoidosis has been described in cardiac allografts, but is rarely severe and may respond to intensification of CS.

5.1. Neurosarcoidosis (NS)

Clinically significant nervous system involvement (neurosarcoidosis (NS)) occurs in (5–10%) of patients with sarcoidosis [44]. Most patients (70–90%) with NS have extraneural involvement either at the onset or during the course of the disease [44]. In patients with NS, neurological signs are the presenting feature of sarcoidosis in >30% [44]. Neurosarcoidosis accounts for ~15% of deaths due to sarcoidosis in the US [44]. Any part of the nervous system may be affected, but most common sites include: cranial nerves, meninges, hypothalamus-pituitary axis, brain parenchyma, spinal cord, and peripheral nerves [44,45]. The facial nerve [7th cranial nerve (CN7)] is affected in (15–39%) of cases of NS [44,45] followed by optic nerves (4–25%) [45] and trigeminal nerves (8–19%) [44,45]. Optic neuropathy may reflect elevated intracranial pressure or direct involvement of the optic nerve or chiasm [44]. Involvement of the optic chiasm can cause visual field defects, blurred vision, and visual loss [44,45]. Involvement of the auditory nerve (CN8) may cause hearing loss, vertigo, or trigeminal neuralgia [44]. Involvement of the pituitary/hypothalamic axis may cause hormonal deficiencies [eg, syndrome of inappropriate antidiuretic hormone (SIADH), hypothyroidism, hypoadrenalism] [46,47]. Sarcoidosis involving the brain may cause acute or chronic cognitive dysfunction, headaches, seizures, gait disturbances, cerebrovascular accidents (CVA), and hydrocephalus [44]. Meninges are involved in (12–40%) of cases with NS [44,45]. Mass lesions in the brain parenchyma occur in (20–45%) of cases with NS [44,45]. Any part of the spinal cord can be involved and may result in paresis, motor or sensory deficits, bladder/bowel incontinence, and sexual dysfunction [48]. Peripheral nerve involvement occurs in (4–17%) of subjects, usually due to granulomatous perineuritis or vasculitis [44]. Cognitive decline and/or fatigue are common in patients with sarcoidosis (with or without NS). Causes may be difficult to determine, since a variety of non-neurological factors may be causative [eg, depression, anxiety, effects of treatment, impaired ability to exercise due to pulmonary or neurological factors].

5.2. Diagnosis of NS

Biopsies of mass lesions (eg, in brain, orbit, or spinal cord) have been done in NS cases presenting with neurological signs or symptoms, principally because of high suspicion for malignancy and can reveal NNG (Fig. 2, Panel II *A&B* and Panel III *A&B*). Given the risk of biopsies of lesions in brain or spinal cord, the diagnosis of NS is usually made by biopsies of extraneural sites. Site of biopsy depends upon the clinical features, but lung(s), MLN, or skin may substantiate the diagnosis provided enlarged lymph nodes or other lesions are present on imaging or physical examination. HRCT scans or whole body PET-CT scans may suggest appropriate biopsy sites. In a cohort of 69 patients with NS, HRCT scans revealed abnormalities suggesting intrathoracic sarcoidosis in 71%, even though pulmonary function tests were normal in most patients. When the clinical syndrome is consistent with NS (eg, Bell's palsy, involvement of pituitary/hypothalamus, or optic chiasm), biopsy of MLN or lung may establish a diagnosis of probable NS.

Gadolinium-enhanced MRI is the imaging modality of choice for brain or spinal cord lesions. The most common pattern for intracranial sarcoidosis are parenchymal lesions, dural thickening or mass, leptomeningeal enhancement, CN enhancement, and mass lesions [44]. Isolated involvement of cranial nerves (8–12) and pituitary involvement are difficult to visualize by MRI [44]. Overall, the MRI is considered to be one of the best modalities to be used to evaluate sarcoidosis CNS involvement as it has a high sensitivity (82–97%), however it lacks in specificity [49,50].

Lumbar puncture has limited value to diagnose NS; cerebrospinal fluid (CSF) pleocytosis, lymphocytosis, elevated protein, low glucose and elevated IgG have been noted in >50% of cases [44,51], but these findings are nonspecific. Serum or CSF biomarkers [eg, angiotensin converting enzyme (ACE)] are rarely of value to diagnose NS [44].

5.3. Treatment of NS

Symptomatic NS requires early/aggressive treatment, to prevent permanent sequela or death. A multidisciplinary approach involving neurologists, neurosurgeons, pulmonologists or rheumatologists, and/or ophthalmologists is required. Optimal therapy for NS has not been elucidated, as RCTs are lacking. CS have been the cornerstone of therapy for years, with improvement in (27–49%) [47]; unfortunately, complete remissions (CR) are achieved in fewer than 1/3 of patients with CS alone [47]. Even with treatment, permanent neurological sequelae occur in up to (35–92%) of patients with NS [48,52]. Combining CS with IA or TNFA is often done, with improved response rates [48,52]. In a retrospective multicenter trial, 40 cases of NS were treated with CS plus either MTX (n = 32) or mycophenolate moftetil (MMF) (n = 14) [53]. Relapse rates were 47% in the MTX group compared to 79% in the MMF group. Median time to relapse was shorter in the MMF group (11-months) compared to MTX (28-months) [53]. We do not recommend MMF to treat NS. French investigators found that among 160 NS cases followed >60 months, the following factors were associated with increased mortality: older age [HR per 10 years (1.6); peripheral nervous system involvement (HR 6.8); higher baseline expanded disability scale score (EDSS) (HR per point 1.21)] [54]. Estimated 10-year relapse-free survival rates were 28% for neurological relapses. Ten-year relapse-free survival rates were significantly improved with IV cytoxan (HR 0.26, $p < 0.001$), MTX (HR 0.47, $p < 0.02$), and infliximab (HR 0.16, $p < 0.08$) [54].

For severe NS, we favor immediate therapy with high dose CS (eg, IV pulse methylprednisolone 500–1000 mg daily for 3 days, followed by prednisone taper). If improvement does not occur rapidly, or if CS side effects develop, we add an IA or infliximab. Long-term treatment (often >2–3 years) is warranted, given the propensity for relapses and serious sequelae.

5.4. Small fiber neuropathy

Small fiber neuropathy due to loss of unmyelinated or thinly myelinated small nerve fibers occurs in (>10%) of patients with sarcoidosis [44,55]. The pathogenesis is unknown. Unfortunately, CS or IA are usually ineffective [55]. Anecdotal responses have been cited with intravenous immunoglobulin (IVIG) [55], TNFA [55], and ARA-290 (cibinetide), but optimal therapy remains unclear.

5.5. Ocular involvement in sarcoidosis

Ocular sarcoidosis (OS) is a common extrapulmonary manifestation. The incidence of ocular involvement is high (12–89%) among sarcoidosis patients [56–58]. If left untreated, OS can lead to irreversible damage, including partial or complete loss of vision [59]. Symptoms of OS are the presenting complaints in (20–40%) of sarcoidosis patients [59]. The incidence and presentation vary across age, gender, ethnicity and geographic location [56,58,59]. The highest incidence rates are in women, blacks, and Japanese [56–58]. The US-based ACCESS study cited ocular involvement in 12% of 736 cases of sarcoidosis, while ocular involvement was documented in (51–68%) of sarcoidosis cases in Japan [56,57]. Certain polymorphisms in HLA and non-HLA gene-loci increase susceptibility to OS and may be markers for different phenotypes of sarcoidosis.

Ocular manifestations of sarcoidosis are protean, and almost all structures can be affected including: uvea, vitreous, retina, orbit, optic nerves, lacrimal gland, conjunctiva, eyelids, and extraocular muscles [58]. Involvement of an experienced ophthalmologist is essential to diagnose/follow OS. Fundoscopic exam should be done regularly by an ophthalmologist at clinic visits. Visual field tests are important when the hypothalamus, pituitary gland, or optic chiasm are suspected sites [46,47]. Decisions regarding appropriate diagnostic tests and therapy must be made in conjunction with ophthalmologists and a physician (pulmonologist or rheumatologist) with expertise in sarcoidosis.

Uveitis is the most common manifestation of OS, present in up to 70% of cases [58,59]. Amongst all patients with uveitis, sarcoidosis is identified as the causative etiology among (2–15%) of cases, making it a common cause of chronic, non-infectious uveitis [60]. There is a distinct female predominance [58,61,62]. Two peaks of incidence have been noted: the first in those (20–30) and the second (50–60)-years of age [58]. Whites present with uveitis at a later age than non-whites and have a more chronic form [58,61].

Sarcoid uveitis can be categorized as either anterior, intermediate, posterior, or pan-uveitis [58]. The anatomic frequency of uveitis is dependent on race; anterior uveitis accounts for (70–75%) of cases in blacks and posterior uveitis accounts for (65–83%) in whites [59]. Depending on acuity and location, presenting symptoms vary. Sarcoidosis involving the anterior chamber can present as acute iritis or iridocyclitis, usually affecting both eyes [58,61]. Slit lamp examination may also reveal mutton-fat keratic precipitates or iris nodules (Fig. 3A). Ocular pain, redness, and decreased visual acuity may be present, but up a third of sarcoid uveitis may be asymptomatic [59]. This "silent sarcoid uveitis" is worrisome, as chronic untreated inflammation can lead to irreversible damage including band keratopathy, glaucoma, cataract formation and severe loss of vision (including blindness) [58,59].

Intermediate uveitis refers to inflammation primarily localized to the vitreous body [58]. Vitreous opacities may cause "floaters" or blurry vision. Fundoscopic exam by an ophthalmologist may reveal "snowballs" or "string of pearls" that are highly suggestive of a granulomatous process [58,63]. Cystoid macular edema is the leading cause of decreased vision in patients with intermediate uveitis, but optic neuritis and glaucoma may contribute to visual loss [58,64].

Posterior segment involvement occurs at varying frequency in OS (20–28%) with much higher frequencies in elderly white women

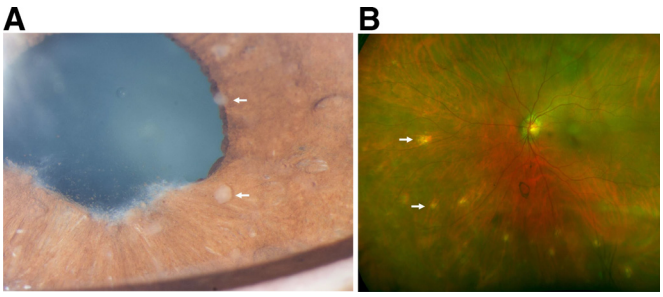

Fig. 3. Ocular Sarcoidosis. (A) Slit lamp photograph of iris nodules (arrows) at the pupillary margin and iris surface. (B) Fundus photograph of multiple peripheral chorioretinal lesions (arrows) in a patient with sarcoidosis.

[59]. In cases of posterior uveitis, 70% demonstrate classic findings of perivenous infiltrates and segmental cuffing termed "taches de bougies" or "candle wax drippings" [58]. These lesions may be subclinical and only visible on fluorescein angiography [58]. Inflammation in the posterior segment may reveal fundoscopic findings of capillary interruption and ischemia, neovascularization and vitreous hemorrhage, retinal vascular occlusion, macular edema, and multiple peripheral chorioretinal lesions (Fig. 3B) [58,63]. Unfortunately, profound irreversible visual loss may occur if this inflammatory process is not recognized and aggressively treated. This underscores the need to have experienced ophthalmologists perform appropriate dilated fundoscopic examinations. Ancillary testing such as optical coherence tomography, fundus autofluorescence, and fluorescein angiograms can be obtained at the discretion of the ophthalmologist to monitor posterior segment inflammation in patients with OS. Newer non-invasive imaging modalities such as optical coherence tomography angiography may also be utilized to evaluate abnormalities of the retinal microvasculature [65]. Additionally, posterior uveitis is associated with optic nerve and neurologic involvement in (25–35%) of cases [59].

Panuveitis occurs in (9–48%) of cases of OS [58,61,66]. Permanent visual loss may occur if chronic uveitis is not recognized and treated in the early phases. In a series of 121 cases of sarcoidosis, uveitis was diagnosed in 29 (24%), 10 of whom had no ocular symptoms at the time of initial ophthalmological screening.

The incidence of extraocular ophthalmic sarcoidosis (eg, lacrimal glands, eyelids, orbit, extraocular muscles) among cases of OS varies from (8–40%) [66], but will not be further discussed herein [67–69].

5.6. Diagnosis and treatment of OS

The diagnosis of OS may be difficult. Biopsies of superficial sites, such as conjunctiva, are positive in only 33% although higher yields (66%) have been cited when biopsies target conjunctival nodules [58]. Studies evaluated biopsies of salivary glands for the histological diagnosis of sarcoidosis in uveitis patients; yields were low (3–5%), and we do not recommend this procedure [70]. In one study of 60 cases with suspected OS with no enlarged intrathoracic lymph nodes or pulmonary infiltrates on chest X-rays, transbronchial biopsies (TBBs) revealed NNG in 38 (62%) [71]. Higher yields would be expected in the presence of enlarged MLN or pulmonary infiltrates on HRCT. HRCT and ^{18}FDG-PET/CT scans may identify target sites (particularly MLN or lung) to confirm the diagnosis of sarcoidosis [72]. In a series of 44 cases of OS in China, abnormalities on HRCT scan were detected in 42 (95%). In another study of 67 cases of uveitis with normal HRCT scans, ^{18}FDG-PET/CT scans demonstrated hypermetabolic foci in MLN in 19 (28%) [72]. A histological diagnosis of sarcoidosis was established in 10 cases. Endobronchial ultrasound (EBUS)-guided fine needle aspiration (FNA) has a high diagnostic yield (~60%) when enlarged MLN are present; higher yields (> 83%) were cited when TBBs were added [73]. Hence, HRCT and/or ^{18}FDG-PET/CT [72] scans in cases with uveitis of unknown cause may identify potential target sites to biopsy (for suspected sarcoidosis) [72].

5.7. Treatment of OS

The International Workshop on OS (IWOS) has provided expert recommendations on the management of anterior, intermediate and posterior uveitis in OS [74]. A total of 98 participants from 29 countries completed a survey and participated in a consensus workshop to establish recommendations for the management of OS [74].

Effective treatment for OS is pivotal as delay in treatment is strongly associated with lack of improvement or deterioration in visual acuity [59]. Frequent topical CS along with mydriatic agents is the first-line treatment for anterior uveitis and is sufficient for most cases [74]. Second line therapy for anterior uveitis can include local CS injection or if needed systemic CS [74]. For intermediate uveitis, first-line therapy consists of local CS injection and systemic CS. For posterior uveitis, first-line therapy consists of systemic CS alone or with CS-sparing non-biologic systemic IA [74].

Intraocular injections of CS can be done in severe cases, but carries the risks of retinal detachment, endophthalmitis and vitreous hemorrhage, and visual loss [59]. Notably, with the long-term use of topical CS or local injections, the clinician should be aware of the risk of development of cataract and steroid-induced glaucoma [75]. In this context, initiation of steroid-sparing IA needs to be considered to avoid further complications associated with CS use. CS-refractory cases may also require the initiation of IA. In up to 15% of cases of uveitis associated with sarcoidosis, steroid sparing IA may be required to achieve quiescence. MTX has been most often used; additional non-biologic IA for treatment of uveitis include MMF, AZA and cyclosporine. If uveitis remains refractory to non-biologic IA, then biologics, such as TNFA have also been used with anecdotal successes. When TNFA are used, consensus recommendations from the IWOS most frequently report using adalimumab [74].

5.8. Prognosis of OS

OS is usually associated with a favorable outcome, with most patients experiencing mild or no permanent visual impairment [58]. One series of 83 patients reported that 60% of cases achieved complete recovery of vision and none developed blindness (<20/400 visual acuity). However, severe visual impairment (defined as best-corrected visual acuity < 20/200 in at least one eye) occurs in (2–10%) of sarcoid patients with uveitis [58,62,76,77]. Factors associated with a worse visual prognosis include: advanced age; black race; female gender; posterior segment uveitis; cystoid macular edema, multifocal choroiditis; persistent ocular inflammation; glaucoma [58]. Unfortunately, OS is generally chronic, with approximately 90% of patients demonstrating chronic uveitis [78]. Close follow-up and compliance with medication regimen is needed to achieve treatment success as a small case series of OS demonstrated the mean duration of the patients' active disease was 6-years [79].

5.9. Important questions for future research in extrapulmonary sarcoidosis

Small studies involving imaging to assess CaS include CMR and ^{18}FDG-PET/CT suggest they may help with diagnose and treatment efficacy. Unfortunately, patients insurance rarely cover these expensive imaging modalities. Thus, appropriately designed and powered clinical trials are needed to determine their impact on diagnose, prognosis and responsiveness to treatment. Additionally, the most effective treatment of NS has not been established. Therefore, multicenter RCTs involving NS at centers of excellence are needed to evaluate the most effective therapies in management. Furthermore, the definitive diagnosis of cardiac, ocular and neurosarcoidosis is difficult

due to the patchy nature of the granulomas and/or its involvement is in areas were a biopsy cannot be safely performed. Consequently, the use of large scale peripheral blood "omics" is needed for optimization to make these diagnosis and spare patients from biopsy compilations.

5.10. Outstanding questions

Sarcoidosis is a relatively uncommon granulomatous disease whose manifestations may be similar to tuberculosis and a variety of infectious and autoimmune disorders. Before considering treatment for sarcoidosis, these "competing" disorders must be vigorously excluded. Once a diagnosis of sarcoidosis is substantiated, careful and long-term follow-up is required to ascertain if and when treatment is warranted as well as the recognition of an unpredictable course that may require CS with or without an IA or biologic. For some complications (especially cardiac, neurological, ocular), a multidisciplinary approach is essential. Managing sarcoidosis requires vigilance, judgement, and awareness of the vagaries of this fascinating disease.

Declaration of Competing Interest

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Author contribution

Joseph P. Lynch, III, M.D.: conceptualisation, writing, visualization, reviewing, and editing

Faisal Shaikh, M.D.: writing, literature search, reviewing, and editing

Fereidoun Abtin, M.D.: validation, literature search, visualization, and writing

Michael C. Fishbein, M.D.: writing, literature search, and visualization

Rajan Saggar, M.D.: validation, literature search, writing, reviewing, and editing

Edmund Tsui, M.D.: writing, visualization, and literature search

John A. Belperio, M.D1: conceptuallisation, literature search, writing, reviewing, editing, supervision, and visualization

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References

[1] Lynch J, Baughman R, Sharma O. Extrapulmonary sarcoidosis. Semin Respir Infect 1998;13:229–54.
[2] Judson MA, Baughman RP, Thompson BW, et al. Two year prognosis of sarcoidosis: the ACCESS experience. Sarcoidosis Vasc Diffuse Lung Dis 2003;20(3):204–11 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14620163.
[3] Iwai K, Tachibana T, Takemura T, Matsui Y, Kitaichi M, Kawabata Y. Pathological studies on sarcoidosis autopsy. I. Epidemiological features of 320 cases in Japan. Acta Pathol Jpn 1993;43(7−8):372–6. doi: 10.1111/j.1440-1827.1993.tb01148.x.
[4] Huppertz C, Jager B, Wieczorek G, et al. The NLRP3 inflammasome pathway is activated in sarcoidosis and involved in granuloma formation. Eur Respir J 2020;55(3). doi: 10.1183/13993003.00119-2019.
[5] Kron J, Sauer W, Schuller J, et al. Efficacy and safety of implantable cardiac defibrillators for treatment of ventricular arrhythmias in patients with cardiac sarcoidosis. Europace 2013;15(3):347–54 (Multicenter Study) (In eng). DOI:. doi: 10.1093/europace/eus316.
[6] Weigt SS, Palchevskiy V, Belperio JA. Inflammasomes and IL-1 biology in the pathogenesis of allograft dysfunction. J Clin Invest 2017;127(6):2022–9. doi: 10.1172/JCI93537.
[7] Busuttil A, Weigt SS, Keane MP, et al. CXCR3 ligands are augmented during the pathogenesis of pulmonary sarcoidosis. Eur Respir J 2009;34(3):676–86. doi: 10.1183/09031936.00157508.
[8] Palchevskiy V, Hashemi N, Weigt SS, et al. Immune response CC chemokines CCL2 and CCL5 are associated with pulmonary sarcoidosis. Fibrogenesis Tissue Repair 2011;4:10. doi: 10.1186/1755-1536-4-10.
[9] Kron J, Mauro AG, Bonaventura A, et al. Inflammasome formation in granulomas in cardiac sarcoidosis. Circ Arrhythm Electrophysiol 2019;12(9):e007582. doi: 10.1161/CIRCEP.119.007582.
[10] Kandolin R, Lehtonen J, Airaksinen J, et al. Cardiac sarcoidosis: epidemiology, characteristics, and outcome over 25 years in a nationwide study. Circulation 2015;131(7):624–32. doi: 10.1161/CIRCULATIONAHA.114.011522.
[11] Birnie DH. Cardiac Sarcoidosis. Semin Respir Crit Care Med 2020;41(5):626–40. doi: 10.1055/s-0040-1712535.
[12] Birnie DH, Sauer WH, Bogun F, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart Rhythm 2014;11(7):1305–23. doi: 10.1016/j.hrthm.2014.03.043.
[13] Juneau D, Nery P, Russo J, et al. How common is isolated cardiac sarcoidosis? Extra-cardiac and cardiac findings on clinical examination and whole-body (18)F-fluorodeoxyglucose positron emission tomography. Int J Cardiol 2018;253:189–93. doi: 10.1016/j.ijcard.2017.09.204.
[14] Yazaki Y, Isobe M, Hiroe M, et al. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. Am J Cardiol 2001;88(9):1006–10 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11703997.
[15] Giudicatti L, Marangou J, Nolan D, Dembo L, Baumwol J, Dwivedi G. The utility of whole body (18)F-FDG PET-CT in diagnosing isolated cardiac sarcoidosis: the western Australian cardiac sarcoid study. Heart Lung Circ 2020;29(1):e1–6. doi: 10.1016/j.hlc.2019.07.007.
[16] Kandolin R, Lehtonen J, Graner M, et al. Diagnosing isolated cardiac sarcoidosis. J Intern Med 2011;270(5):461–8 (In eng). doi: 10.1111/j.1365-2796.2011.02396.x.
[17] Webb M, Conway KS, Ishikawa M, Diaz F. Cardiac involvement in sarcoidosis deaths in Wayne County, Michigan: a 20-year retrospective study. Acad Forensic Pathol 2018;8(3):718–28. doi: 10.1177/1925362118797744.
[18] Statement on sarcoidosis. Joint statement of the American thoracic society (ATS), the European respiratory society (ERS) and the world association of sarcoidosis and other granulomatous disorders (wasog) adopted by the ats Board of Directors and by the ERS executive committee, february 1999. Am J Respir Crit Care Med 1999;160(2):736–55 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10430755.
[19] Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American heart association, the American college of cardiology, and the European society of cardiology. Circulation 2007;116(19):2216–33. doi: 10.1161/CIRCULATIONAHA.107.186093.
[20] Coleman GC, Shaw PW, Balfour PC, et al. Prognostic value of myocardial scarring on CMR in patients with cardiac sarcoidosis. JACC Cardiovasc Imaging 2017;10(4):411–20. doi: 10.1016/j.jcmg.2016.05.009.
[21] Ohira H, Birnie DH, Pena E, et al. Comparison of (18)F-fluorodeoxyglucose positron emission tomography (FDG PET) and cardiac magnetic resonance (CMR) in corticosteroid-naive patients with conduction system disease due to cardiac sarcoidosis. Eur J Nucl Med Mol Imaging 2016;43(2):259–69. doi: 10.1007/s00259-015-3181-8.
[22] Divakaran S, Stewart GC, Lakdawala NK, et al. Diagnostic accuracy of advanced imaging in cardiac sarcoidosis. Circ Cardiovasc Imaging 2019;12(6):e008975. doi: 10.1161/CIRCIMAGING.118.008975.
[23] Youssef G, Leung E, Mylonas I, et al. The use of 18F-FDG PET in the diagnosis of cardiac sarcoidosis: a systematic review and metaanalysis including the Ontario experience. J Nucl Med 2012;53(2):241–8 (Meta-Analysis Research Support, Non-U.S. Gov't Review) (In eng). DOI:. doi: 10.2967/jnumed.111.090662.
[24] Shafee MA, Fukuda K, Wakayama Y, et al. Delayed enhancement on cardiac magnetic resonance imaging is a poor prognostic factor in patients with cardiac sarcoidosis. J Cardiol 2012;60(6):448–53 (In eng). DOI:. doi: 10.1016/j.jjcc.2012.08.002.
[25] Zhang J, Li Y, Xu Q, Xu B, Wang H. Cardiac magnetic resonance imaging for diagnosis of cardiac sarcoidosis: a meta-analysis. Can Respir J 2018;2018:7457369. doi: 10.1155/2018/7457369.
[26] Hulten E, Agarwal V, Cahill M, et al. Presence of late gadolinium enhancement by cardiac magnetic resonance among patients with suspected cardiac sarcoidosis is associated with adverse cardiovascular prognosis: a systematic review and meta-analysis. Circ Cardiovasc Imaging 2016;9(9):e005001. doi: 10.1161/CIRCIMAGING.116.005001.
[27] Gowani Z, Habibi M, Okada DR, et al. Utility of cardiac magnetic resonance imaging versus cardiac positron emission tomography for risk stratification for ventricular arrhythmias in patients with cardiac sarcoidosis. Am J Cardiol 2020. doi: 10.1016/j.amjcard.2020.08.007.
[28] Kennel PJ, Raza F, Kim J, et al. A case series on inflammatory cardiomyopathy and suspected cardiac sarcoidosis: role of cardiac PET in management. Eur Heart J Case Rep 2020;4(4):1–9. doi: 10.1093/ehjcr/ytaa146.
[29] Mehta D, Lubitz SA, Frankel Z, et al. Cardiac involvement in patients with sarcoidosis: diagnostic and prognostic value of outpatient testing. Chest 2008;133(6):1426–35 (In eng). doi: 10.1378/chest.07-2784.
[30] Mehta D, Mori N, Goldbarg SH, Lubitz S, Wisnivesky JP, Teirstein A. Primary prevention of sudden cardiac death in silent cardiac sarcoidosis: role of programmed ventricular stimulation. Circ Arrhythm Electrophysiol 2011;4(1):43–8 (In eng). doi: 10.1161/CIRCEP.110.958322.
[31] Cacoub P, Chapelon-Abric C, Resche-Rigon M, Saadoun D, Desbois AC, Biard L. Cardiac sarcoidosis: a long term follow up study. PLoS ONE 2020;15(9):e0238391. doi: 10.1371/journal.pone.0238391.

[32] Kato Y, Morimoto S, Uemura A, Hiramitsu S, Ito T, Hishida H. Efficacy of corticosteroids in sarcoidosis presenting with atrioventricular block. Sarcoidosis Vasc Diffuse Lung Dis 2003;20(2):133–7 (Clinical Trial Comparative Study Controlled Clinical Trial) (In eng) http://www.ncbi.nlm.nih.gov/pubmed/12870723.
[33] Nagai T, Nagano N, Sugano Y, et al. Effect of corticosteroid therapy on long-term clinical outcome and left ventricular function in patients with cardiac sarcoidosis. Circ J 2015;79(7):1593–600. doi: 10.1253/circj.CJ-14-1275.
[34] Nagai T, Nagano N, Sugano Y, et al. Effect of discontinuation of prednisolone therapy on risk of cardiac mortality associated with worsening left ventricular dysfunction in cardiac sarcoidosis. Am J Cardiol 2016;117(6):966–71. doi: 10.1016/j.amjcard.2015.12.033.
[35] Sadek MM, Yung D, Birnie DH, Beanlands RS, Nery PB. Corticosteroid therapy for cardiac sarcoidosis: a systematic review. Can J Cardiol 2013;29(9):1034–41 (In eng). DOI:. doi: 10.1016/j.cjca.2013.02.004.
[36] Yodogawa K, Seino Y, Ohara T, Takayama H, Katoh T, Mizuno K. Effect of corticosteroid therapy on ventricular arrhythmias in patients with cardiac sarcoidosis. Ann Noninvasive Electrocardiol 2011;16(2):140–7 (In eng). DOI:. doi: 10.1111/j.1542-474X.2011.00418.x.
[37] Yodogawa K, Seino Y, Shiomura R, et al. Recovery of atrioventricular block following steroid therapy in patients with cardiac sarcoidosis. J Cardiol 2013 (In Eng). doi: 10.1016/j.jjcc.2013.07.007.
[38] Birnie D, Beanlands RSB, Nery P, et al. Cardiac Sarcoidosis multi-center randomized controlled trial (CHASM CS- RCT). Am Heart J 2020;220:246–52. doi: 10.1016/j.ahj.2019.10.003.
[39] Krishnan M, Cupps TR, Sheikh FH. Tumor necrosis factor-alpha inhibitor use for treatment of refractory cardiac sarcoidosis in a patient with left ventricular assist device: adalimumab use in refractory sarcoidosis in a patient with left ventricular assist device. J Heart Lung Transpl 2020. doi: 10.1016/j.healun.2020.08.001.
[40] Gilotra NA, Wand AL, Pillarisetty A, et al. Clinical and imaging response to tumor necrosis factor alpha inhibitors in treatment of cardiac sarcoidosis: a multicenter experience. J Card Fail 2020. doi: 10.1016/j.cardfail.2020.08.013.
[41] Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American college of cardiology/American heart association task force on practice guidelines (writing committee to revise the ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices) developed in collaboration with the American association for thoracic surgery and society of thoracic surgeons. J Am Coll Cardiol 2008;51(21):e1–62 (Practice Guideline) (In eng). DOI:. doi: 10.1016/j.jacc.2008.02.032.
[42] Crawford T, Mueller G, Sarsam S, et al. Magnetic resonance imaging for identifying patients with cardiac sarcoidosis and preserved or mildly reduced left ventricular function at risk of ventricular arrhythmias. Circ Arrhythm Electrophysiol 2014;7(6):1109–15. doi: 10.1161/CIRCEP.113.000156.
[43] Zaidi AR, Zaidi A, Vaitkus PT. Outcome of heart transplantation in patients with sarcoid cardiomyopathy. J Heart Lung Transpl 2007;26(7):714–7 (In eng). DOI:. doi: 10.1016/j.healun.2007.05.006.
[44] Culver DA, Ribeiro Neto ML, Moss BP, Willis MA. Neurosarcoidosis. Semin Respir Crit Care Med 2017;38(4):499–513. doi: 10.1055/s-0037-1604165.
[45] Carlson ML, White JR, Espahbodi M, et al. Cranial base manifestations of neurosarcoidosis: a review of 305 patients. Otol Neurotol 2015;36(1):156–66. doi: 10.1097/MAO.0000000000000501.
[46] Langrand C, Bihan H, Raverot G, et al. Hypothalamo-pituitary sarcoidosis: a multicenter study of 24 patients. QJM 2012;105(10):981–95 (Multicenter Study) (In eng). doi: 10.1093/qjmed/hcs121.
[47] Leonhard SE, Fritz D, Eftimov F, van der Kooi AJ, van de Beek D, Brouwer MC. Neurosarcoidosis in a tertiary referral center: a cross-sectional cohort study. Medicine 2016;95(14):e3277. (Baltimore). doi: 10.1097/MD.0000000000003277.
[48] Cohen Aubart F, Bouvry D, Galanaud D, et al. Long-term outcomes of refractory neurosarcoidosis treated with infliximab. J Neurol 2017;264(5):891–7. doi: 10.1007/s00415-017-8444-9.
[49] Gullapalli D, Phillips LH. Neurologic manifestations of sarcoidosis. Neurol Clin 2002;20(1):59–83 vi.. doi: 10.1016/s0733-8619(03)00054-9.
[50] Stern BJ, Royal W, Gelfand JM, et al. Definition and consensus diagnostic criteria for neurosarcoidosis: from the neurosarcoidosis consortium consensus group. JAMA Neurol 2018;75(12):1546–53. doi: 10.1001/jamaneurol.2018.2295.
[51] Cohen-Aubart F, Galanaud D, Grabli D, et al. Spinal cord sarcoidosis: clinical and laboratory profile and outcome of 31 patients in a case-control study. Medicine 2010;89(2):133–40 (Baltimore). doi: 10.1097/MD.0b013e3181d5c6b4.
[52] Durel CA, Marignier R, Maucort-Boulch D, et al. Clinical features and prognostic factors of spinal cord sarcoidosis: a multicenter observational study of 20 BIOPSY-PROVEN patients. J Neurol 2016;263(5):981–90. doi: 10.1007/s00415-016-8092-5.
[53] Bitoun S, Bouvry D, Borie R, et al. Treatment of neurosarcoidosis: a comparative study of methotrexate and mycophenolate mofetil. Neurology 2016;87(24):2517–21. doi: 10.1212/WNL.0000000000003431.
[54] Joubert B, Chapelon-Abric C, Biard L, et al. Association of prognostic factors and immunosuppressive treatment with long-term outcomes in neurosarcoidosis. JAMA Neurol 2017;74(11):1336–44. doi: 10.1001/jamaneurol.2017.2492.
[55] Tavee JO, Karwa K, Ahmed Z, Thompson N, Parambil J, Culver DA. Sarcoidosis-associated small fiber neuropathy in a large cohort: clinical aspects and response to IVIG and anti-TNF alpha treatment. Respir Med 2017;126:135–8. doi: 10.1016/j.rmed.2017.03.011.
[56] Hattori T, Konno S, Shijubo N, et al. Nationwide survey on the organ-specific prevalence and its interaction with sarcoidosis in Japan. Sci Rep 2018;8(1):9440. doi: 10.1038/s41598-018-27554-3.
[57] Sawahata M, Sugiyama Y, Nakamura Y, et al. Age-related and historical changes in the clinical characteristics of sarcoidosis in Japan. Respir Med 2015;109(2):272–8. doi: 10.1016/j.rmed.2014.12.012.
[58] Seve P, Jamilloux Y, Tilikete C, Gerfaud-Valentin M, Kodjikian L, El Jammal T. Ocular sarcoidosis. Semin Respir Crit Care Med 2020;41(5):673–88. doi: 10.1055/s-0040-1710536.
[59] Groen F, Rothova A. Ocular involvement in sarcoidosis. Semin Respir Crit Care Med 2017;38(4):514–22. doi: 10.1055/s-0037-1602382.
[60] Hsu YR, Huang JC, Tao Y, et al. Noninfectious uveitis in the Asia-Pacific region. Eye 2019;33(1):66–77 (Lond). doi: 10.1038/s41433-018-0223-z.
[61] Coulon C, Kodjikian L, Rochepeau C, et al. Ethnicity and association with ocular, systemic manifestations and prognosis in 194 patients with sarcoid uveitis. Graefes Arch Clin Exp Ophthalmol 2019;257(11):2495–503. doi: 10.1007/s00417-019-04415-x.
[62] Ma SP, Rogers SL, Hall AJ, et al. Sarcoidosis-related uveitis: clinical presentation, disease course, and rates of systemic disease progression after uveitis diagnosis. Am J Ophthalmol 2019;198:30–6. doi: 10.1016/j.ajo.2018.09.013.
[63] Acharya NR, Browne EN, Rao N, Mochizuki M. International ocular sarcoidosis working g. distinguishing features of ocular sarcoidosis in an international cohort of uveitis patients. Ophthalmology 2018;125(1):119–26. doi: 10.1016/j.ophtha.2017.07.006.
[64] Ness T, Boehringer D, Heinzelmann S. Intermediate uveitis: pattern of etiology, complications, treatment and outcome in a tertiary academic center. Orphanet J Rare Dis 2017;12(1):81. doi: 10.1186/s13023-017-0638-9.
[65] Cerquaglia A, Iaccheri B, Fiore T, et al. New insights on ocular sarcoidosis: an optical coherence tomography angiography study. Ocul Immunol Inflamm 2019;27(7):1057–66. doi: 10.1080/09273948.2018.1497665.
[66] Rothova A. Ocular involvement in sarcoidosis. Br J Ophthalmol 2000;84(1):110–6. doi: 10.1136/bjo.84.1.110.
[67] Demirci H, Christianson MD. Orbital and adnexal involvement in sarcoidosis: analysis of clinical features and systemic disease in 30 cases. Am J Ophthalmol 2011;151(6):1074–1080e1. doi: 10.1016/j.ajo.2010.12.011.
[68] Kidd DP, Burton BJ, Graham EM, Plant GT. Optic neuropathy associated with systemic sarcoidosis. Neurol Neuroimmunol Neuroinflamm 2016;3(5):e270. doi: 10.1212/NXI.0000000000000270.
[69] Mavrikakis I, Rootman J. Diverse clinical presentations of orbital sarcoid. Am J Ophthalmol 2007;144(5):769–75. doi: 10.1016/j.ajo.2007.07.019.
[70] Blaise P, Fardeau C, Chapelon C, Bodaghi B, Le Hoang P. Minor salivary gland biopsy in diagnosing ocular sarcoidosis. Br J Ophthalmol 2011;95(12):1731–4. doi: 10.1136/bjophthalmol-2011-300129.
[71] Ohara K, Okubo A, Kamata K, Sasaki H, Kobayashi J, Kitamura S. Transbronchial lung biopsy in the diagnosis of suspected ocular sarcoidosis. Arch Ophthalmol 1993;111(5):642–4. doi: 10.1001/archopht.1993.01090050076033.
[72] Chauvelot P, Skanjeti A, Jamilloux Y, et al. (18)F-fluorodeoxyglucose positron emission tomography is useful for the diagnosis of intraocular sarcoidosis in patients with a normal CT scan. Br J Ophthalmol 2019;103(11):1650–5. doi: 10.1136/bjophthalmol-2018-313133.
[73] Agarwal R, Aggarwal AN, Gupta D. Efficacy and safety of conventional transbronchial needle aspiration in sarcoidosis: a systematic review and meta-analysis. Respir Care 2013;58(4):683–93. doi: 10.4187/respcare.02101.
[74] Takase H, Acharya NR, Babu K, et al. Recommendations for the management of ocular sarcoidosis from the international workshop on ocular sarcoidosis. Br J Ophthalmol 2020. doi: 10.1136/bjophthalmol-2020-317354.
[75] Thorne JE, Sugar EA, Holbrook JT, et al. Periocular triamcinolone vs. intravitreal triamcinolone vs. intravitreal dexamethasone implant for the treatment of uveitic macular edema: the periocular vs. intravitreal corticosteroids for uveitic macular edema (POINT) trial. Ophthalmology 2019;126(2):283–95. doi: 10.1016/j.ophtha.2018.08.021.
[76] Birnbaum AD, French DD, Mirsaeidi M, Wehrli S. Sarcoidosis in the national veteran population: association of ocular inflammation and mortality. Ophthalmology 2015;122(5):934–8. doi: 10.1016/j.ophtha.2015.01.003.
[77] Paovic J, Paovic P, Sredovic V, Jovanovic S. Clinical manifestations, complications and treatment of ocular sarcoidosis: correlation between visual efficiency and macular edema as seen on optical coherence tomography. Semin Ophthalmol 2016:1–8. doi: 10.1080/08820538.2016.1206576.
[78] Dana MR, Merayo-Lloves J, Schaumberg DA, Foster CS. Prognosticators for visual outcome in sarcoid uveitis. Ophthalmology 1996;103(11):1846–53. doi: 10.1016/s0161-6420(96)30417-x.
[79] Gungor SG, Akkoyun I, Reyhan NH, Yesilirmak N, Yilmaz G. Choroidal thickness in ocular sarcoidosis during quiescent phase using enhanced depth imaging optical coherence tomography. Ocul Immunol Inflamm 2014;22(4):287–93. doi: 10.3109/09273948.2014.920034.