

# Arteriosclerosis, Thrombosis, and Vascular Biology

## REVIEW

# Cardiovascular Manifestations and Immunobiology of Sarcoidosis

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**ABSTRACT:** Sarcoidosis is a chronic inflammatory disease of unknown cause that can affect the heart and blood vessels, causing cardiomyopathy, pulmonary hypertension, and vasculitis. The pathological hallmark of sarcoidosis is the formation of noncaseating granulomas consisting of monocytes and dendritic cells, macrophages, multinucleated giant cells, and T cells. Sarcoidosis has features of autoimmune disease, and many candidate self-epitopes have been identified, but experimental validation is lacking. There is a strong hereditary component associated with the human leukocyte antigen region on chromosome 6. Symptoms of the disease may be subtle and often go unrecognized by patients and practitioners. Catastrophic events, including sudden cardiac death caused by lethal arrhythmias, can be the initial manifestation of the disease. Diagnosis is challenging and limited by the lack of sensitive and specific diagnostic tools, which also hampers monitoring of disease activity. Here, we discuss the cardiovascular manifestations and underlying immunobiology of sarcoidosis. We also review current diagnostic and treatment approaches for cardiac sarcoidosis, as well as the challenges faced by patients and clinicians and opportunities for future research.

**GRAPHIC ABSTRACT:** A graphic abstract is available for this article.

**Key Words:** dendritic cells ■ hypertension, pulmonary ■ magnetic resonance imaging ■ monocytes ■ sarcoidosis

Sarcoidosis is a chronic inflammatory disease affecting many organs with variable presentation, ranging from a benign localized skin lesion to a life-threatening multiorgan disease.<sup>1</sup> Although sarcoidosis shares common features with autoimmune diseases, its etiological basis remains undefined, despite decades of research. Histologically, the immune response in sarcoidosis is characterized by the formation of noncaseating granulomas consisting of monocytes and dendritic cells (DC), macrophages, CD68<sup>+</sup> (cluster of differentiation) multinucleated giant cells, and T cells (Figure 1).<sup>1</sup>

Cardiac involvement is the second leading cause of death in patients with sarcoidosis.<sup>1</sup> The most common cardiac manifestations of sarcoidosis are cardiomyopathy, heart failure, and arrhythmias.<sup>2</sup> The most common reported vascular manifestation of sarcoidosis is pulmonary hypertension (PH), which is usually detected in sarcoidosis patients with advanced lung involvement.<sup>3</sup> Less commonly, sarcoidosis can involve coronary arteries

or other blood vessels, leading to vasculitis, myocardial infarction, vaso-occlusion, and aneurysms.

Cardiac sarcoidosis (CS) is responsive to corticosteroids and immunosuppressive drugs, resulting in reduced symptoms, arrhythmia burden, and ventricular dysfunction. Hence, it is crucial to diagnose CS, yet there are many challenges to diagnosing it, including a lack of awareness and expertise among providers and reliance on advanced cardiac imaging techniques that are often unavailable or inaccessible to patients. Moreover, the disease often relapses, requiring vigilant monitoring. Unfortunately, many patients with CS go undiagnosed, emphasizing the need for greater disease awareness and research to unravel the immunobiology of CS and to develop enhanced clinical screening tools and more pragmatic diagnostic tests.<sup>2</sup>

Here, we will discuss the cardiovascular manifestations of sarcoidosis and the underlying immunobiology. We will also briefly review epidemiology, clinical manifestations,

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## Nonstandard Abbreviations and Acronyms

<b>CMR</b>	cardiac magnetic resonance imaging
<b>CS</b>	cardiac sarcoidosis
<b>DC</b>	dendritic cell
<b>DMARD</b>	disease-modifying antirheumatic drug
<b>JAK</b>	Janus kinase
<b>LV</b>	left ventricle
<b>MHC</b>	major histocompatibility complex
<b>mTOR</b>	mammalian target of rapamycin
<b>PET-CT</b>	positron emission tomography–computed tomography
<b>PH</b>	pulmonary hypertension
<b>TNF</b>	tumor necrosis factor

and current diagnostic and treatment approaches for CS. Finally, we will consider the challenges faced by patients and clinicians dealing with CS, and the opportunity for future research to address these challenges.

## Epidemiology

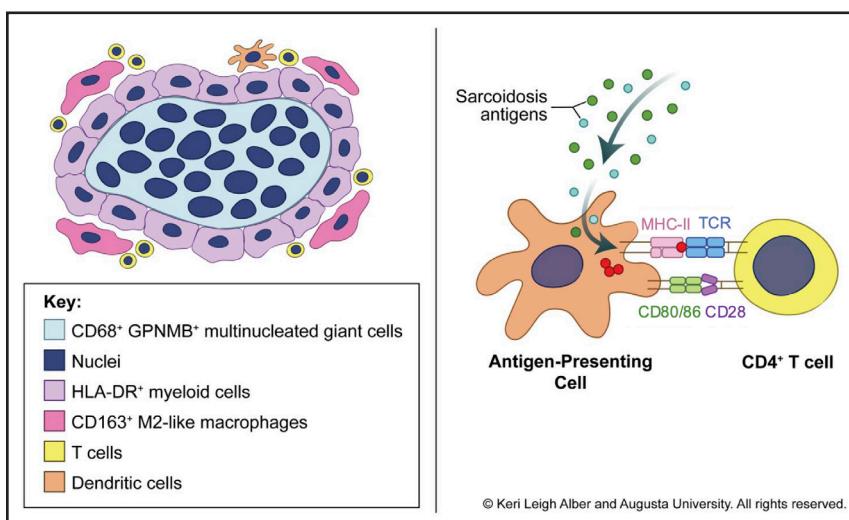
Sarcoidosis is most often diagnosed in young-to-middle-aged adults, with a slight female preponderance.<sup>1</sup> The disease appears to result from exposure to an environmental antigen that, in a genetically susceptible individual, leads to a dysregulated immune response.<sup>1</sup> Hereditary factors impact disease susceptibility; a strong association has been detected with the human leukocyte antigen–DRB1 region on chromosome 6.<sup>4</sup> For reasons that are not entirely clear, there is also a strong racial and ethnic predilection, with the rates of sarcoidosis being much higher in Black patients, and lower in Asian and Hispanic patients, compared with White patients.<sup>5</sup> Moreover, sarcoidosis-related mortality

## Highlights

- Sarcoidosis is a chronic inflammatory disease, most likely an autoimmune disorder.
- The hallmark pathological feature of sarcoidosis is the formation of granulomas consisting of clusters of inflammatory cells.
- Granuloma infiltration within the heart and blood vessels in sarcoidosis may be associated with devastating consequences, including sudden death.
- Diagnosis and treatment of sarcoidosis involving the cardiovascular system is complicated and best undertaken by an experienced team of specialists with complementary expertise and access to advanced imaging technology.
- Further research into the immunobiology of sarcoidosis is needed to confirm its autoimmune basis, develop effective screening approaches, and fine-tune immunotherapy.

was reported to be ≈12-fold higher in Black compared with White patients.<sup>6</sup>

The environmental antigens that trigger sarcoidosis have not been conclusively identified but likely include occupational agents, such as silica dust.<sup>1</sup> It may also begin with a systemic infection, potentially involving *Mycobacterium tuberculosis* or *Cutibacterium acnes*, remnants of which have been detected in sarcoidosis granulomas.<sup>7,8</sup> Strong evidence of immunoreactivity to mycobacterial antigens has also been reported in sarcoidosis patients.<sup>9</sup> The actual prevalence of sarcoidosis is unknown, however, because the disease is frequently mistaken for other conditions or undiagnosed altogether. The symptoms can be subtle, with spontaneous exacerbation and remission, further confounding efforts to establish the diagnosis. A major impediment to diagnosing sarcoidosis is the lack of sensitive and specific diagnostic tools. In



**Figure 1. Depiction of granuloma structure and key inflammatory cell interactions in sarcoidosis.**

Depiction of noncaseating granuloma (**left**) and antigen-presenting cell/T-cell interactions (**right**) in sarcoidosis. Color-coded key indicates the various types of inflammatory cells and their spatial distribution within the granuloma. CD indicates cluster of differentiation; DR, MHC (major histocompatibility complex) class II cell surface receptor; GPNMB, glycoprotein nonmetastatic melanoma protein B; HLA, human leukocyte antigen; and TCR, T cell receptor.

fact, sarcoidosis largely remains a diagnosis of exclusion, hinging on histological demonstration of noncaseating granulomas along with lack of clinical evidence of other diseases associated with granuloma formation.<sup>1</sup> Making the diagnosis often requires considerable clinical judgement and experience.

The prevalence of CS is likewise unknown; although it is recognized in only 5% of patients with systemic sarcoidosis, autopsy studies indicate that it is detectable in  $\approx$ 20% of cases.<sup>10</sup> Thus, many sarcoidosis patients have silent cardiac involvement. In other cases, the heart may be the only organ clinically affected by sarcoidosis, a condition known as isolated CS. In a retrospective study in Finland, isolated CS accounted for about 2-thirds of all cases of CS.<sup>11</sup> However, in that study, imaging tests frequently detected evidence of asymptomatic disease in mediastinal lymph nodes, and less often outside the heart and mediastinum, suggesting that the true prevalence of isolated CS may have been overestimated. Interestingly, CS may be more prevalent in the Japanese population and is the leading cause of sarcoidosis-related death in Japan.<sup>12</sup>

Diagnosing CS is based on probability, as categorized per the World Association of Sarcoidosis and Other Granulomatous Disorders as definite, highly probable, probable, possible, low probability, and unlikely.<sup>13,14</sup> Cardiac biopsy to obtain tissue for histology is seldom performed to diagnose CS, as it carries risk, and sensitivity is low, with a reported yield of 25% to 50%, depending on whether advanced cardiac imaging techniques or voltage-guided biopsy procedures are applied.<sup>15</sup> Sensitivity of cardiac biopsy is low due to patchy, focal myocardial lesion distribution with epicardial or midmyocardial predominance rather than endocardial involvement.<sup>15</sup> Consequently, CS is most often diagnosed based on major and minor clinical criteria, including results of advanced cardiac imaging (discussed later) and responsiveness to immunosuppressive therapy.<sup>16</sup>

## IMMUNOBIOLOGY

Sarcoidosis is not recognized as an established autoimmune disease, but clearly has autoimmune features. Autoimmunity is defined as an ongoing immune response to self, and CD4<sup>+</sup> T cells are central to this process. Some CD4<sup>+</sup> T cells become follicular helper cells that are required for antibody isotype switching and affinity maturation in the germinal centers, while others interact with antigen-presenting cells. Some antigen-presenting cells can cross-present antigenic peptides to CD8<sup>+</sup> T cells. Products like interferon- $\gamma$ , made by both CD4<sup>+</sup> and CD8<sup>+</sup> T cells, activate macrophages and exacerbate inflammation.

Self-epitopes are peptides derived from host proteins that have elicited a T-cell response. Candidate self-epitopes can be discovered by elution from MHC (major histocompatibility complex) molecules, followed by mass

spectrometry, but must be validated by systematic restimulation assays. *In vivo*, T cells responsive to relevant self-epitopes show clonal expansion, which can persist for years given their longevity. Candidate sarcoidosis epitopes have been identified in a study involving human bronchial lavage fluid cells.<sup>17</sup> They are human leukocyte antigen-DR1:03:01 restricted and are shown in Table S1.<sup>17</sup>

MHC restriction means that T-cell responses are restricted to epitopes presented on MHC molecules. MHC-I presents  $\approx$ 9-mer peptides to CD8<sup>+</sup> T cells, and MHC-II presents longer peptides to CD4<sup>+</sup> T cells. Both MHC-I and II are highly polymorphic, and each person expresses multiple MHC-I and II molecules. The evidence for a role of CD4<sup>+</sup> T cells in sarcoidosis is well established. Seventy-eight self-epitopes restricted by DRB1\*03:01 have been reported,<sup>17</sup> but only one has been experimentally validated.<sup>18</sup> Many of these peptides can also bind other MHC-II molecules, and no detailed mapping of sarcoidosis epitopes is available.

Antigen-presenting cells *in vivo* are DCs and monocytes that can initiate an immune response by triggering naive T cells. DCs are rare ( $<0.1\%$  of white blood cells). In humans, DC are subdivided into conventional, plasmacytoid, and monocyte-derived, the latter of which seem in chronic inflammatory diseases like sarcoidosis. Once an immune response ensues, many other cells can boost the response, including monocytes and macrophages.<sup>19</sup> More than 80% of human monocytes are classical monocytes, whereas about 5% to 10% each are intermediate and non-classical monocytes, respectively. All antigen-presenting cells express costimulatory molecules like CD80 and CD86 that can drive T-cell clonal expansion (Figure 1, right) and secrete cytokines that determine the polarization of the resulting T cells. Figure 1, left, illustrates the spatial arrangement of these cells in a sarcoid granuloma.

How antigen presentation occurs in sarcoidosis is unknown. Based on other diseases, the initial antigen presentation likely happens in secondary lymphoid organs. The immunobiology of CS has not been studied in detail; it is thus unclear how sarcoidosis spreads to the heart. DCs take up unknown self-antigens and present them to naive T cells through MHC molecules. These interactions trigger T-cell activation and release cytokines, such as interferon- $\gamma$  and TNF (tumor necrosis factor), which further recruit and activate macrophages, leading them to form organized clusters. Activated macrophages then fuse to create multinucleated giant cells and release more inflammatory mediators, which maintain the granuloma structure and promote tissue injury. Persistent antigen presentation and continued T-cell stimulation prevent the normal resolution of inflammation. In the heart, this process results in chronic granulomatous inflammation that disrupts myocardial tissue, leading to arrhythmias and heart failure.

Spatial transcriptomic analysis of CS granulomas identified abundant monocyte/DC, CD68<sup>+</sup> giant cells,

and proliferating human leukocyte antigen-DR+ macrophages that possessed elevated mTOR (mammalian target of rapamycin) signaling within the cardiac granulomas.<sup>20</sup> Such findings further implicate monocytes/DCs and macrophages in mediating granuloma formation. Moreover, myeloid cells, including macrophages with M2-like activation, seem elevated in sarcoidosis and are associated with distinct functional profiles. Bulk RNA sequencing and array studies reported increased TNF and type 1 interferon responses in monocyte/DC in sarcoidosis.<sup>21</sup> These studies collectively indicate that sarcoidosis involves dysregulated monocyte and DC activity, underscoring their roles as key drivers of disease progression. Recent advances in single-cell RNA sequencing technology have enabled detailed characterization of immune cell populations in sarcoidosis.<sup>22,23</sup> For example, Garman et al reported expanded monocyte and T-cell subsets with strong interferon and TNF signaling, suggesting an amplified inflammatory circuit within granulomas.<sup>22</sup> Liao et al<sup>23</sup> further revealed transcriptional heterogeneity among macrophages, including populations expressing both M1- and M2-like genes, which may explain the coexistence of inflammation and fibrosis in sarcoid tissues. Building on these advances, physically interacting immune cells contributing to granuloma formation can now be detected by analyzing biological doublets using single-cell RNA sequencing.<sup>24</sup> The combination of single-cell RNA sequencing with paired single-cell T-cell receptor sequencing provides a direct link between activated T-cell transcriptomes and their paired TCR $\alpha$  and TCR $\beta$  chain sequences. If these TCR sequences have been reported before, databases like the Immune Epitope Database can be used to find antigen specificity.<sup>25</sup> These techniques provide insights that conventional methods cannot, such as identifying which T-cell clones dominate within granulomas,<sup>19</sup> whether specific clonotypes are shared between lung and cardiac lesions, and how macrophage-T-cell signaling networks sustain chronic inflammation. They may also reveal how persistent antigen presentation shapes T-cell polarization, cytokine production, and cytotoxic activity within granulomas. Together, these approaches can help define whether sarcoidosis is driven by autoreactive or persistent antigen-specific immune responses. In the future, applying these single-cell technologies to CS may clarify how immune cell interactions evolve during granuloma progression and identify new therapeutic targets that interrupt T-cell-macrophage crosstalk.

## CLINICAL MANIFESTATIONS

The cardiovascular manifestations of CS are highly variable, ranging from asymptomatic cardiac involvement detected pathologically or by imaging studies to sudden death. Most symptoms of CS fall into 2 categories: those

related to arrhythmias and those related to cardiomyopathy/heart failure. Fundamentally, both types of symptoms are attributed to granulomas contained in cardiac tissues.

A portion of the cardiac conduction system is located in the interventricular septum, a common site of granuloma formation, where the associated inflammation and fibrosis can lead to the development of advanced heart block.<sup>10</sup> When an advanced heart block is unexpectedly encountered in younger patients, CS must be considered. Likewise, CS is a relatively common cause of ventricular tachycardia. In a study of 435 patients with nonischemic cardiomyopathy referred for ventricular tachycardia ablation, CS was identified in 5% of the patients.<sup>26</sup> The inflammation and fibrosis associated with cardiac granulomas may cause ventricular arrhythmias via several mechanisms, including establishing reentrant circuits in regions of scarring. Atrial tachyarrhythmias, including atrial fibrillation, may also be seen in patients with CS.<sup>2</sup> All these types of arrhythmias may be seen in association with various other types of heart disease occurring independent of or concurrent with sarcoidosis, which may confound attempts to diagnose and manage CS.

Cardiomyopathy is a common manifestation of CS. Usually, the cardiomyopathy is dilated in phenotype, though it has rarely been reported to resemble hypertrophic cardiomyopathy due to granuloma formation in the interventricular septum.<sup>27</sup> Both the left and the right ventricle may be involved, and depending on the extent of granulomatous infiltration, patients may present with manifestations ranging from asymptomatic ventricular dysfunction to full-blown systolic heart failure. Involvement of valve leaflets or papillary muscles may lead to valvular regurgitation. In a study of 1230 patients undergoing cardiac biopsy to investigate the cause of idiopathic dilated cardiomyopathy, 1.1% were determined to have CS.<sup>28</sup> At that time, advanced cardiac imaging and voltage mapping were not available to guide the biopsy procedures, and a definitive diagnosis was established in only half of the patients. Because the sensitivity of unguided cardiac biopsy to detect sarcoidosis is reported to be in the range of 19% to 25%,<sup>2</sup> the true prevalence of CS in that study could have been higher than reported.

The coronary vasculature can also be impacted by sarcoidosis. Notably, granulomatous involvement of the epicardial coronary arteries has been reported to lead to acute coronary syndromes.<sup>29</sup> Cases of coronary artery aneurysms and coronary artery dissection due to sarcoidosis have also been described.<sup>30,31</sup> In addition, evidence of impaired hyperemic myocardial blood flow and myocardial flow reserve has been detected in conjunction with cardiac inflammation in sarcoidosis patients, suggesting coronary microcirculatory dysfunction.<sup>32</sup> Sarcoidosis is associated with oxidative stress and dyslipidemia, likely caused by chronic inflammation plus the effects of corticosteroid therapy.<sup>33</sup> Oxidative stress and dyslipidemia

are key pathological features of atherosclerosis, suggesting that sarcoidosis may accelerate the process of coronary artery disease.<sup>33</sup> In a population-based cohort study, patients with sarcoidosis were found to have a 20% increased risk of myocardial infarction compared with matched controls.<sup>34</sup> Cardiac events were more commonly observed in newly diagnosed patients initiating immunosuppression therapy, suggesting that the systemic inflammation associated with symptomatic sarcoidosis might perturb coronary atherosclerotic lesions.

Many other vascular abnormalities have been reported in patients with sarcoidosis. In patients with neurosarcoidosis, granulomas commonly infiltrate intracranial vessels and may cause lacunar infarctions and microhemorrhages.<sup>35</sup> The spleen is also a frequent site of granuloma formation in sarcoidosis, which may be associated with splenic artery aneurysms that can rupture and lead to sudden death.<sup>30</sup> Sarcoidosis may also cause a systemic vasculitis syndrome that can mimic other forms of vasculitis, such as polyarteritis nodosa, Takayasu arteritis, and IgG4-related disease.<sup>36,37</sup> Finally, compared with healthy controls, patients with sarcoidosis were reported to exhibit vascular stiffness and endothelial dysfunction, which correlated with inflammatory status.<sup>38</sup> These findings further suggest that systemic inflammation in sarcoidosis may perturb vascular function.

PH can complicate both pulmonary and CS and may occur in the absence of significant cardio-pulmonary disease, as a primary vasculopathy. It portends a worse prognosis with patients having greater functional limitations, and early diagnosis of PH in the sarcoidosis patient thus becomes critically important because treatment can help preserve functional status. The prevalence of sarcoidosis-associated PH was reported to range from ≈3% to 20% but is much more common in patients with advanced pulmonary sarcoidosis.<sup>3</sup>

Multiple mechanisms have been reported to contribute to PH in sarcoidosis patients.<sup>3</sup> Precapillary PH is associated with progressive parenchymal disease, pulmonary fibrosis, and hypoxic vasoconstriction. In addition, granulomatous infiltration or compression of pulmonary arteries by adenopathy can contribute to precapillary PH in sarcoidosis. Postcapillary PH is commonly associated with cardiac dysfunction in sarcoidosis patients due to increased LV filling pressures and retrograde pressure transmission through the pulmonary vasculature. This, in turn, leads to chronic pulmonary vasoconstriction, elevated pulmonary vascular resistance, and precapillary PH. Also, granulomas infiltrating small venules, lymphatic vessels, and vasa vasorum can lead to replacement fibrosis, thus contributing to postcapillary PH.<sup>39</sup>

Sarcoidosis is associated with a 2- to 3-fold increased risk of venous thromboembolism. This may be propelled by an inflammation-driven systemic hypercoagulable state or glucocorticoid therapy and can produce large, central pulmonary emboli as well as smaller segmental

and subsegmental emboli that can cause or exacerbate PH.<sup>40</sup> Obstructive sleep apnea and obesity hypoventilation syndrome occur commonly in sarcoidosis patients, particularly because of corticosteroid therapy, and likewise can cause or exacerbate PH.<sup>41</sup> Finally, granulomatous infiltration of the liver can cause chronic hepatic disease and porto-PH, a rare disease associated with liver failure.

## ROLE OF ADVANCED IMAGING IN DETECTING AND MONITORING CS

Cardiac imaging plays a dominant role in the diagnostic and prognostic evaluation of CS, although it is insufficient in itself to make the diagnosis. Cardiac involvement in sarcoidosis typically results in inflammation followed by fibrosis. The sensitivity and specificity of different imaging studies vary depending on the stage of the disease. The role of imaging to diagnose CS is summarized below:

1. Transthoracic echocardiogram: transthoracic echocardiogram is typically utilized as an initial screening tool to assess LV ejection fraction and wall motion abnormalities. Wall motion abnormalities in CS are typically observed in a noncoronary distribution. Areas of hypokinesis/akinesis/aneurysm often involve the basal segment (especially the septum) of the LV.<sup>10,15</sup> The wall thickness may be increased initially, but subsequent fibrosis/scarring results in the thinning of LV segments and a variable degree of LV systolic dysfunction.
2. Cardiac magnetic resonance imaging (CMR): CMR accurately assesses LV function and wall motion using steady-state free precession sequences and is superior to the transthoracic echocardiogram owing to better endocardial definition. T2-weighted cardiac magnetic resonance images reveal high signal intensity in areas of myocardial inflammation and edema. Gadolinium-based contrast is used to demonstrate delayed myocardial enhancement, a marker of myocardial fibrosis, typically involving basal segments in a noncoronary distribution. Greater extent of the myocardial enhancement is associated with a worse prognosis, including increased risk of ventricular tachycardia and death. In addition, an expansion of extracellular volume is common in CS. T1 and T2 mapping are increasingly being utilized to diagnose early stages of CS and to monitor responses to therapy.<sup>2</sup> The right ventricle may also be involved in sarcoidosis, resulting in late gadolinium enhancement in the free wall. In a pooled analysis of 649 patients with a histologically confirmed extra-CS, CMR exhibited a sensitivity of 93% and specificity of 85% to detect CS.<sup>42</sup> Notably, CMR may be limited by artifacts in the presence of cardiac implantable electronic devices.

3. Positron emission tomography-computed tomography (PET-CT) scanning: special preparation is required with extended fasting and consumption of low low-carbohydrate, high-fat/protein diet to suppress physiological cardiac uptake of the fluorodeoxyglucose.<sup>2</sup> Maximum intensity projection images are obtained to visualize fluorodeoxyglucose uptake in the left and right ventricles. PET-CT scanning has excellent sensitivity for assessment of active inflammation and can be performed in the presence of cardiac implantable electronic devices. In a meta-analysis, its sensitivity and specificity to detect CS were reported to be 84% and 83%, respectively.<sup>43</sup> It offers an additional advantage of being able to concurrently image the whole body, thus detecting and monitoring foci of inflammation in extracardiac organs and tissues. It is also used to monitor responses to therapy. Limitations include radiation exposure, specialized preparation, and long acquisition times. Given the unique advantages and disadvantages of CMR and PET-CT, a hybrid approach with integration of both imaging modalities is increasingly being adopted for evaluation of CS (Figure 2).
4. Computed tomography: delayed phase contrast-enhanced CT may be utilized in a similar manner to CMR to detect fibrosis in CS, but it is not widely used or well validated. However, with more research, it may become a valuable single diagnostic tool to assess coronary anatomy, wall thickness, LV function, and fibrosis in patients with suspected CS.

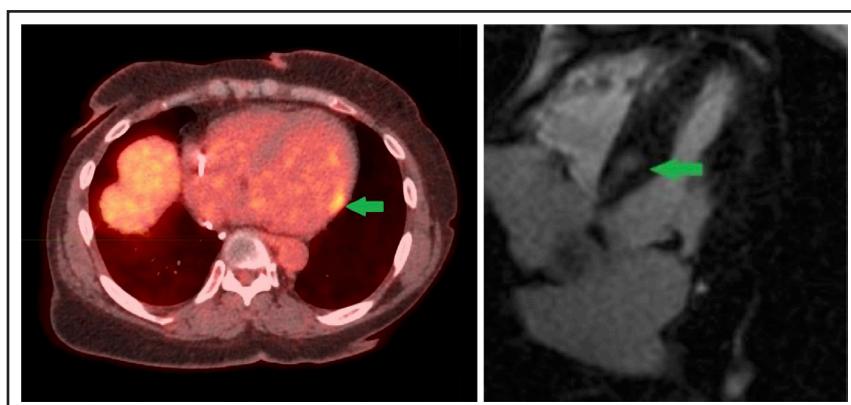
## TREATMENT OF CS

The decision to initiate immunosuppressive therapy for CS is not standardized and must weigh the confidence in the diagnosis of CS with patient symptoms, their impact on quality of life, and the risk of progressive cardiac dysfunction or death.<sup>1,15</sup> Treatment initiation recommendations are typically stratified based on the likelihood of CS, using categories from the World Association of Sarcoidosis and Other Granulomatous

Disorders.<sup>13,14</sup> Whether asymptomatic individuals with cardiac PET-CT findings suggestive of active inflammation require treatment is uncertain, and the decision to start immunosuppressive treatment in such cases must be individualized.<sup>13</sup> Immunosuppressive medications for CS include: systemic glucocorticoids (prednisone, prednisolone), conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs; azathioprine, leflunomide, methotrexate, mycophenolate mofetil), biologic DMARDs (tumor necrosis factor inhibitors and rituximab), targeted synthetic disease-modifying antirheumatic drugs (JAK [Janus kinase] inhibitors), and mTOR inhibitors (sirolimus, everolimus).

Once the decision to initiate treatment is made, the therapeutic goal is to balance suppression of inflammation-induced cardiac dysfunction with avoidance of the toxic effects of immunosuppressant medications.<sup>1</sup> Systemic glucocorticoids are recommended as initial therapy for CS at a dose of 0.5 mg/kg per day or prednisone equivalents (maximum 30–40 mg/d) in most cases.<sup>13</sup> The utility of glucocorticoids in CS is limited by cumulative dose-related toxicity (including hyperglycemia, hypertension, weight gain, osteoporosis, infection, and neuropsychiatric disturbance, among many others) and by the high risk of disease relapse during tapering. Therefore, combination glucocorticoid and steroid-sparing DMARD therapy should be considered first-line, supported by evidence of noninferiority of methotrexate monotherapy to glucocorticoids in pulmonary (albeit excluding cardiac) sarcoidosis and the lower relapse rate of combination therapy to glucocorticoid monotherapy (17% versus 50%) in CS.<sup>44,45</sup>

The complexity of CS management is exacerbated by a lack of randomized controlled trials and limited high-quality evidence.<sup>44</sup> Choice of agent must be individualized, weighing potential toxicities and patient-specific comorbidities, ideally in collaboration with a multidisciplinary team including a rheumatologist. Methotrexate is the most commonly utilized DMARD for CS.<sup>44</sup> Support for the use of azathioprine, leflunomide, and mycophenolate mofetil in CS is likewise from small, retrospective studies.<sup>44</sup>



**Figure 2. The utility of advanced imaging techniques in cardiac sarcoidosis.**

Representative positron emission tomography-computed tomography scan (**left**) showing fluorodeoxyglucose avidity in the inferolateral wall of the left ventricle, and contrast-enhanced cardiac magnetic resonance imaging (**right**) showing late gadolinium enhancement in the basal inferoseptum (arrows), in cardiac sarcoidosis.

Biologic therapies are typically reserved for patients with progressive disease on, contraindication to, or intolerance of multiple or combination conventional synthetic disease-modifying antirheumatic drugs, extrapolating from the consensus recommendations for treatment of pulmonary sarcoidosis.<sup>1,13</sup>

Infliximab, the most studied and widely used biologic DMARD in sarcoidosis, has the strongest evidence base for use in CS.<sup>44</sup> Adalimumab is an alternative TNF inhibitor that can be used for CS, with the benefit of subcutaneous self-administration, but data in support is more limited than infliximab.<sup>44</sup> The B-cell depleting agent rituximab is often used in TNF inhibitor–refractory CS or patients with CS presenting with heart failure.<sup>44</sup>

Consistent with the immunobiology of CS outlined above, emerging immunosuppressive therapies such as mTOR inhibitors modulate granuloma inflammation by suppressing mTOR signaling and target the type 1 interferon pathway through JAK inhibition, with encouraging results.<sup>44</sup> mTOR inhibitors demonstrate efficacy in 50% of CS patients in one case series, and sirolimus has further evidence of efficacy in cutaneous sarcoidosis in a single-center, crossover study.<sup>46</sup> Evidence for Janus kinase inhibition in sarcoidosis includes case reports, small retrospective series, and 2 open-label trials of tofacitinib for cutaneous and pulmonary disease, one of which reported myocardial fluorodeoxyglucose-PET resolution after 6 months.<sup>46</sup> An ongoing Phase 2 Open-label trial of baricitinib (URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT06868381) may further define the role of JAK inhibition in CS.

Treatment response is assessed both by clinical improvement (such as reduction in arrhythmia burden, stabilization or improvement of ejection fraction) and by decreased active myocardial granulomatous inflammation on PET-CT scan, often repeated every 3 to 6 months while therapy is being adjusted. Once CS is deemed controlled on a minimum tolerated immunosuppression regimen, ongoing surveillance is tailored to detect recurrence. Optimal management of CS requires coordinated immunosuppressive and cardiac-directed therapy by clinicians with specific expertise in sarcoidosis. Cardiac implantable electronic devices have an essential role in CS management for the prevention of sudden cardiac death, with indications extending beyond standard criteria to include patients with LV ejection fraction >35% and syncope or myocardial scar, pacing needs, or inducible sustained ventricular tachycardia.<sup>13</sup>

## CURRENT CHALLENGES AND FUTURE OPPORTUNITIES

Sarcoidosis is an enigmatic disease that poses challenges to patients, clinicians, and researchers alike. For

researchers, the most perplexing question remains what causes sarcoidosis? Although available data strongly point towards autoimmunity, the causative antigens have yet to be identified. Monocyte/DC and macrophages play a key role in disease pathogenesis, and in particular granuloma formation, but how they interact with T cells to drive the immune response is not known. Answering these questions may provide insight into a question that has baffled clinicians for decades: is sarcoidosis a single disease with protean manifestations, or is it a spectrum of different diseases? Because sarcoidosis is an uncommon disease, researchers at individual institutions rarely have access to enough patients needed to address these questions. By collaborating regionally and participating in robust patient registries, researchers can pool their expertise and resources to advance our understanding of sarcoidosis.

From the clinical perspective, sarcoidosis can present in many ways, and subtle findings are often overlooked or mistaken for other ailments by patients and practitioners. Like other rare diseases, public awareness of sarcoidosis is low. Sadly, unrecognized cardiovascular involvement can lead to heart failure or sudden death. In patients diagnosed with extra-CS, screening for cardiac involvement is recommended,<sup>16</sup> but the efficacy of screening protocols is unclear. Developing effective, pragmatic approaches to screen for CS is needed to identify at-risk patients. Finally, accumulating data indicate that treating inflammation improves outcomes and leads to reduced arrhythmias and enhanced cardiac function. However, the immunosuppressive regimens were largely empirically derived and lack precision, especially considering factors such as race, which impacts disease prevalence, severity, and outcomes.<sup>5</sup>

Patients with sarcoidosis not only have to live with symptoms that can be burdensome or debilitating, but they also face the possibility of death from a variety of mechanisms, often involving the cardiovascular system. Although immunosuppressive therapy is increasingly effective at controlling the inflammation and its consequences, the therapies themselves are associated with toxicities and side effects. If sarcoidosis is indeed an autoimmune disorder, it may be possible to develop a tolerogenic vaccine that could effectively treat or even prevent the disease. Advanced cardiac imaging techniques are proving useful in detecting CS and guiding immunosuppressive therapy, but these techniques are not available in most community medical centers. Identification of soluble biomarkers that faithfully reflect cardiac inflammatory activity is sorely needed to facilitate detection and management of CS.

Finally, the level of expertise and costs required to provide state-of-the-art care for sarcoidosis patients are immense and often insurmountable for patients who lack insurance or live in rural regions devoid of dedicated sarcoidosis clinical programs. Developing regional centers

with expertise in sarcoidosis, and coordinating care among specialists, can potentially break down barriers to care and help to promote equity.

## ARTICLE INFORMATION

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### Disclosures

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### Supplemental Material

Table S1

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