Zusammenfassung

Cardiale Sarkoidose ist eine Erkrankung, bei der sich entzündliche Zellen, sogenannte Granulome, im Herzmuskel ansammeln. Diese Entzündungen können das Herz beeinträchtigen und zu verschiedenen Herzproblemen führen, wie etwa Herzrhythmusstörungen (wenn das Herz unregelmäßig schlägt), Herzschwäche oder sogar zu einem vollständigen Block der elektrischen Signale, die den Herzschlag steuern. Manche Patienten bemerken Symptome wie Herzrasen, Kurzatmigkeit oder starke Müdigkeit, während andere keine offensichtlichen Anzeichen haben.

Die Erkrankung kann unterschiedlich verlaufen, je nachdem, welche Teile des Herzens betroffen sind. Wenn die Entzündungen zum Beispiel in einem speziellen Bereich des Herzmuskels auftreten, kann es zu einem Herzblock kommen, bei dem die elektrischen Signale nicht mehr richtig durch das Herz geleitet werden. In anderen Fällen kann die Entzündung den Herzmuskel schwächen, was zu Herzschwäche führt. Manche Patienten haben auch nur minimale Beschwerden, während bei anderen schwere Herzrhythmusstörungen auftreten können.

Diagnose: Die Diagnose einer cardialen Sarkoidose ist oft schwierig. Häufig wird eine Kombination aus verschiedenen Untersuchungen verwendet.

Die Diagnose einer kardialen Sarkoidose ist eine Herausforderung: Biopsien sind häufig falsch-negativ und auch Echo und EKG können blande sein. In diesen Fällen helfen spezielle Bildgebungsverfahren auf die Spur.

Bei systemischer Sarkoidose ist die Lunge in bis zu 90 % der Fälle beteiligt, das Herz dagegen nur bei etwa jedem fünften Betroffenen. Noch seltener ist eine kardiale Symptomatik mit etwa 5 %. Doch tückischerweise beginnt die Erkrankung oft am Herzen: Das Organ ist bei Diagnosestellung der kardialen Sarkoidose in etwa der Hälfte der Fälle das einzige klinisch erkennbar betroffene Organ. Ein isolierter kardialer Befall stellt allerdings eine Rarität dar, denn im Verlauf oder nach gründlicher Diagnostik offenbaren sich meist weitere Manifestationen der Sarkoidose, betonen Prof. Dr. Richard Cheng von der Universität Washington und sein Team.

Hinweise auf eine kardiale Sarkoidose sind Zeichen der Herzinsuffizienz und Rhythmusstörungen. Als besonders suspekt gelten höhergradige AV-Blöcke bei unter 60-Jährigen. Die Labordiagnostik erfolgt analog des Sarkoidoseverdachtes anderer Organe, spezifische Parameter für eine kardiale Sarkoidose gibt es nicht.

In der Echokardiografie stößt man häufig auf eine reduzierte linksventrikuläre Ejektionsfraktion. Weitere mögliche Befunde sind eine Ausdünnung des basalen Septums, Wandaneurysmen oder eine reduzierte Kontraktilität. Sowohl EKG als auch Echo können aber trotz des Vorliegens einer kardialen Sarkoidose mitunter blande sein. Bei gegebenem Verdacht ist eine weiterführende Bildgebung indiziert, z. B. mit einem Kontrastmittel-MRT (KM-MRT) oder einer FDG-PET*.

Eine Herz-MRT ohne Befund schließt die Erkrankung aus

Die KM-MRT mit Gadolinium hat eine hohe Sensitivität. Durch das gestörte Auswaschen des Kontrastmittels aus krankem Gewebe erkennt man pathologische Veränderungen, wobei diffuse, aber auch fokale oder multifokale Verteilungsmuster möglich sind. Der Manifestationsort der granulomatösen Entzündung in der KM-MRT korreliert oft mit EKG-Befunden und Symptomen. So führt eine basale septale Beteiligung typischerweise zu Schenkelblöcken. Sicher diagnostizieren lässt sich eine kardiale Sarkoidose allerdings mit der MRT nicht, da auch andere Erkrankungen wie eine Myokarditis sich mitunter ähnlich darstellen. Ist die MRT jedoch ohne Befund, gilt die Erkrankung als ausgeschlossen.

Die FDG-PET ersetzt die MRT bei Kontraindikationen. Teilweise fusioniert man auch beide Verfahren mit spezieller Software. Eine erweiterte FDG-PET bietet auch die Chance zu bewerten, ob eben doch andere Organe als das Herz betroffen sind. Vor der Bildgebung ist eine spezielle glukosearme, ketogene Diät erforderlich, da sonst unspezifische Signalanreicherungen im Myokard eine adäquate Auswertung verhindern.

Im Prinzip gibt es laut Prof. Cheng zwei Wege, eine kardiale Sarkoidose zu sichern: Der erste ist die myokardiale Biopsie. Deren Sensitivität gilt allerdings als gering. Durch die unregelmäßige Verteilung der Granulome gelingt selbst unter Bildgebung die histologische Sicherung der Diagnose in nur weniger als der Hälfte der Fälle. Häufiger wird die kardiale Sarkoidose durch ein stimmiges Ensemble von Klinik, Bildgebung und weiterem Befund, wie dem histologischen Nachweis einer Sarkoidose an einem anderen Organ (z.B. Lunge, Lymphknoten oder Tränendrüse) diagnostiziert. Insgesamt hat man bei der Diagnose einer kardialen Sarkoidose selten Sicherheit, betont das Expertenteam. Häufig bleibt es bei einem mehr oder weniger begründeten Verdacht.

Das trifft insbesondere auf die isolierte Form zu. Aufgrund des interventionellen Risikos der Herzbiopsie und der eingeschränkten Trefferquote ist dabei mitunter die Bildgebung das ausschlaggebende Werkzeug zur Diagnose. Sind die Befunde typisch, geht man von der Arbeitsdiagnose kardiale Sarkoidose aus, ansonsten bewertet man die Ergebnisse auf einem Kontinuum von „gesichert“ bis „unwahrscheinlich“. Vor allem bei isolierter kardialer Sarkoidose sind verschiedene Differentialdiagnosen zu bedenken: Mehrere Typen der Myokarditis, Kardiomyopathien, und Amyloidose. Man behandelt in der Regel Menschen mit gesicherter oder sehr wahrscheinlicher Sarkoidose. Ist die Erkrankung in der Kategorie „wahrscheinlich“ gilt es in besonderem Maße Nutzen und Risiken abzuwägen.

Weitere Übersetzung eines Studienteils:

Aktuelle diagnostische Algorithmen

Es gibt 2 allgemein anerkannte Wege zur Diagnose von CS (Tabelle 1 und Abbildung 2). Der erste Weg erfordert die direkte histologische Bestätigung von nicht-verkäsenden Granulomen (ohne Nachweis einer anderen Ursache) in Myokardgewebe, das aus einer Endomyokardbiopsie (EMB), einer apikalen LV-Kernbiopsie oder aus explantierten Herzen gewonnen wurde. Die EMB ist jedoch aufgrund der lückenhaften Myokardinfiltration nur begrenzt empfindlich, selbst wenn sie durch elektroanatomische und spannungsbezogene Kartierung gesteuert wird.47 Folglich kann die Diagnose von CS auch durch die Integration einer Reihe von klinischen, pathologischen und bildgebenden Kriterien gestellt werden, wobei zu beachten ist, dass die multimodale Bildgebung allein nicht ausreicht, um die Diagnose zu bestätigen.

Im Jahr 2014 veröffentlichten Experten der Heart Rhythm Society (HRS) in Zusammenarbeit mit mehreren anderen medizinischen Fachgesellschaften die erste internationale Konsenserklärung zur CS-Diagnose.48 Die einzigen bis 2014 veröffentlichten Diagnoserichtlinien waren die der World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG)18 und die Kriterien des japanischen Ministeriums für Gesundheit und Wohlfahrt.50 Die HRS-Diagnoserichtlinie lehnte sich eng an das WASOG-Dokument an,18,48 und die Japanese Circulation Society veröffentlichte 2019 neue Diagnoserichtlinien.50 Tabelle 1 enthält eine Zusammenfassung der Algorithmen.

Obwohl Ähnlichkeiten zwischen den HRS- und WASOG-Diagnoseleitlinien bestehen, ist die jüngste japanische Leitlinie einzigartig: Sie verlangt keinen Biopsie Nachweis für nicht-verkäsende Granulome und ist die einzige Leitlinie, die einen Algorithmus für die bildgebende Diagnostik bei isoliertem CS enthält. Es überrascht nicht, dass beim Vergleich der drei diagnostischen Leitlinien eine gute Übereinstimmung zwischen den WASOG- und den HRS-Kriterien und eine geringe Übereinstimmung zwischen den WASOG/HRS- und den japanischen Kriterien festgestellt wurde.51 Diese Diskrepanz unterstreicht eine wichtige und ungelöste Frage: Kann eine CS ohne histologische Bestätigung aus kardialem oder extrakardialem Gewebe genau diagnostiziert werden?

In vielen Einrichtungen wird bei Personen mit Verdacht auf Sarkoidose wegen des geringeren Verfahrensrisikos zuerst eine Lungen- oder Lymphknotenbiopsie durchgeführt. Darüber hinaus können die Ergebnisse der begleitenden Bronchoskopie auf der Grundlage der Analyse der bronchoalveolären Lavage und der Zellzahl und -kulturen die Diagnosesicherheit erhöhen. Bei Verdacht auf eine okuläre Sarkoidose sollte eine ophthalmologische Untersuchung durchgeführt werden, da eine Tränendrüsenbiopsie eine histologische Bestätigung liefern kann. In ausgewählten Fällen kann eine EMB erforderlich sein. Aufgrund

des fokalen und fleckigen Charakters der Erkrankung hat die ungesteuerte EMB jedoch eine geringe Sensitivität von ≈20 %, so dass eine negative Biopsie nicht unbedingt eine CS ausschließt.52 Sowohl die FDG-PET- oder CMR-Bildgebung22 als auch die spannungsgesteuerten Biopsieverfahren53,54 erhöhen die diagnostische Ausbeute auf 40 bis 50 %, aber selbst bei der gezielten EMB bleibt die diagnostische Ausbeute begrenzt.22,48,54-56

Abbildung 2 enthält einen vorgeschlagenen Diagnosealgorithmus für CS, der viele der Punkte dieser früheren Leitlinien und die Erfahrungen der Autorengruppe berücksichtigt. Es ist allgemein anerkannt, dass Patienten mit hoher Wahrscheinlichkeit eine CS haben, wenn sowohl PET als auch CMR typische Befunde einer CS zeigen und wenn diese Patienten auch eindeutige klinische Manifestationen einer CS haben. In Anbetracht der oben erwähnten Schwierigkeiten, eine endgültige histologische Bestätigung zu erhalten, und der bekannten Grenzen der klinischen Diagnosekriterien sind Kliniker häufig mit der Diagnose CS verunsichert. Anstatt die Diagnose von CS binär zu betrachten (d. h. positiv oder negativ), kann es hilfreicher sein, die Wahrscheinlichkeit von CS anhand der folgenden Kategorien zu beurteilen: definitiv, sehr wahrscheinlich, wahrscheinlich und möglich/geringe Wahrscheinlichkeit (Tabelle 2). Diese Kategorien basieren auf der von der WASOG entwickelten Terminologie zur Berücksichtigung der Wahrscheinlichkeit einer Krankheitsaktivität in anderen Organen, und mehrere Forscher haben dieses Konstrukt verwendet und vorgeschlagen, wie verschiedene Arten von Bildgebungsmustern zusammen mit klinischen Daten die Wahrscheinlichkeit einer kardialen Beteiligung bestimmen können.41,43,47,57

Diagnose von klinisch stillem CS bei Personen mit extrakardialer Sarkoidose

Personen mit systemischer Sarkoidose haben im Vergleich zur Allgemeinbevölkerung ein erhöhtes Risiko für negative kardiovaskuläre Ereignisse, einschließlich HF und Vorhofarrhythmie.58 Dieses erhöhte Risiko ist wahrscheinlich auf eine Kombination aus komorbiden kardiovaskulären Risikofaktoren und direkter kardialer Beteiligung der Sarkoidose zurückzuführen und ist sekundär auf pulmonale Hypertonie zurückzuführen, die durch pulmonale Fibrose, direkte Gefäßbeteiligung oder Entzündung verursacht wird. In den aktuellen Leitlinien besteht kein Konsens über das Screening auf CS. Der HRS-Konsens von 2014 schlägt beispielsweise vor, bei allen Patienten eine kardiologische Anamnese, ein EKG und ein Echokardiogramm durchzuführen, gefolgt von einer weiteren Untersuchung, wenn beim ersten Screening Anomalien festgestellt werden. Die klinische Praxisleitlinie der American Thoracic Society empfiehlt ein Basis-EKG, beschränkt aber die Verwendung von Echokardiographie und Herzrhythmusüberwachung auf Personen, die Symptome und Ereignisse wie Dyspnoe, Palpitationen oder Synkopen aufweisen.48,57 Viele Personen mit extrakardialer Sarkoidose haben möglicherweise eine subklinische CS ohne Symptome, weisen aber eine LGE im CMR auf.26,59,60 Die Auswirkungen der Behandlung bei subklinischer CS sind noch nicht vollständig geklärt. Daher kann eine routinemäßige kardiale Überwachung von asymptomatischen Personen mit extrakardialer Sarkoidose nicht empfohlen werden. Kliniker, die Personen mit extrakardialer Sarkoidose betreuen, sollten jedoch einen hohen Verdachtsindex aufrechterhalten. Jedes Symptom sollte eine kardiologische Untersuchung nach sich ziehen, insbesondere weil sich eine CS gelegentlich erst mehrere Jahre nach der ersten Sarkoidose-Diagnose manifestieren kann.17 Dieser Ansatz kann eine frühere Erkennung einer weniger schweren kardialen Beteiligung17 und eine rechtzeitige Einleitung von Therapien ermöglichen.

Differentialdiagnose

Die Sarkoidose wird aufgrund ihrer vielfältigen Erscheinungsformen oft als der große Maskenbildner bezeichnet und muss von anderen phänotypisch ähnlichen kardialen Syndromen wie akuter Myokarditis, chronisch entzündlichen Kardiomyopathien, einschließlich Autoimmunerkrankungen, vererbten und infiltrativen Kardiomyopathien, und anderen granulomatösen Erkrankungen abgegrenzt werden.61 Der klinische Kontext und die kardiale Bildgebung reichen oft nicht aus, um die Sarkoidose von anderen Formen kardialer Pathologien zu unterscheiden, die Myokarditis und vererbte arrhythmogene Kardiomyopathien verursachen. Personen mit arrhythmogener Kardiomyopathie sind zudem häufig relativ jung und können

klinische Merkmale aufweisen, die sich mit denen der CS überschneiden.62,63 Eine Untergruppe dieser Personen, insbesondere solche mit einer pathogenen Desmoplakin-Variante der Kardiomyopathie, kann auch ein Myokarditis-ähnliches Syndrom mit Brustschmerzen, erhöhten Serumtroponinwerten und ähnlichen Merkmalen wie die CS in der modernen kardialen Bildgebung aufweisen.64,65

Die richtige Diagnose zu stellen, kann in Fällen von klinisch isolierter CS besonders schwierig sein. In einer Studie wurde bei 5 von 16 Personen, bei denen aufgrund der kardialen Bildgebung eine klinisch isolierte CS vermutet wurde, nach einem Gentest eine genetische Kardiomyopathie festgestellt.23 Bei Personen, bei denen der Verdacht auf eine CS besteht, ist eine Familienanamnese von mindestens drei Generationen wichtig. Die Überweisung zu einer genetischen Beratung und zu Gentests kann nützlich sein, um pathogene Varianten bei entsprechend ausgewählten Personen zu identifizieren, die sich einer Untersuchung auf CS unterziehen, da dies Auswirkungen auf die Behandlung und das Kaskaden-Screening hat. Obwohl die Daten noch nicht vorliegen, führen wir in der Mehrzahl der Fälle von CS, die histologisch nicht bestätigt werden können, Gentests durch.

Die CS sollte auch von der Riesenzellmyokarditis unterschieden werden, einer tödlichen Form der Myokarditis, die durch einen fulminanten kardiogenen Schock, VA und Überleitungsstörungen gekennzeichnet ist. Die Riesenzellmyokarditis wird typischerweise durch das Vorhandensein eines diffusen myokardialen Entzündungsinfiltrats und vielkerniger Riesenzellen mit begleitender Myozytennekrose diagnostiziert, ohne dass ein viraler Ursprung auf der EMB erkennbar ist. Trotz immunsuppressiver Therapie kann es vorkommen, dass die Patienten eine mechanische Kreislaufunterstützung und eine Herztransplantation benötigen.65 Eine weitere infiltrative Kardiomyopathie, die kardiale Amyloidose, muss ebenfalls von der CS unterschieden werden. Bei kardialer Amyloidose kann gelegentlich eine abnorme FDG-Aufnahme im kardialen PET nachgewiesen werden.66 Allerdings können die Befunde einer LV-Hypertrophie und einer reduzierten globalen Längsdehnung mit einem apikalen Sparmuster helfen, kardiale Amyloidose von CS zu unterscheiden.

Das breite Spektrum klinischer Phänotypen bei CS und die Einschränkungen bei der Erlangung einer histopathologisch bestätigten Diagnose, insbesondere in Fällen von klinisch isolierter CS, sind zusätzliche Herausforderungen bei der Unterscheidung von CS von diesen alternativen Diagnosen. Ein multidisziplinäres Team aus Experten für systemische Sarkoidose, HF, Elektrophysiologie, moderne kardiale Bildgebung, kardiovaskuläre Genetik und kardiale Pathologie ist erforderlich, um diese Komplexität zu bewältigen.

BEHANDLUNG

Die Einleitung einer Behandlung sollte sich, ähnlich wie bei anderen Krankheiten, nach dem Nutzen-Risiko-Verhältnis richten. Im Allgemeinen sollte eine Behandlung bei definitiver und sehr wahrscheinlicher CS eingeleitet werden, wenn die Person symptomatisch ist. Bei der Gruppe mit wahrscheinlicher CS sollte eine sorgfältige Abwägung der Risiken und des Nutzens der Behandlung mit der betroffenen Person erfolgen. Bei der Gruppe mit möglicher/geringer Wahrscheinlichkeit würde eine Behandlung in den meisten Fällen nicht durchgeführt werden, da die Diagnose ungewiss ist, der Nutzen der Behandlung unklar ist und die Gefahr einer Schädigung besteht. Bei Personen mit unwahrscheinlicher CS gibt es in der Regel keine Indikation für eine Immunsuppression.

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Diagnosis and Management of Cardiac Sarcoidosis: A Scientific Statement From the American Heart Association

Richard K. Cheng, MD, MSc, Chair, Michelle M. Kittleson, MD, PhD, FAHA, Vice Chair, Craig J. Beavers, PharmD, FAHA, David H. Birnie, MD, Ron Blankstein, MD, Paco E. Bravo, MD, Nisha A. Gilotra, MD, Marc A. Judson, MD, Kristen K. Patton, MD, FAHA, and Leonie Rose-Bovino, PhD, APRN, FAHA on behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology, and Council on Cardiovascular and Stroke Nursing

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Abstract

Cardiac sarcoidosis is an infiltrative cardiomyopathy that results from granulomatous inflammation of the myocardium and may present with high-grade conduction disease, ventricular arrhythmias, and right or left ventricular dysfunction. Over the past several decades, the prevalence of cardiac sarcoidosis has increased. Definitive histological confirmation is often not possible, so clinicians frequently face uncertainty about the accuracy of diagnosis. Hence, the likelihood of cardiac sarcoidosis should be thought of as a continuum (definite, highly probable, probable, possible, low probability, unlikely) rather than in a binary fashion. Treatment should be initiated in individuals with clinical manifestations and active inflammation in a tiered approach, with corticosteroids as first-line treatment. The lack of randomized clinical trials in cardiac sarcoidosis has led to treatment decisions based on cohort studies and consensus opinions, with substantial variation observed across centers. This scientific statement is intended to guide clinical practice and to facilitate management conformity by providing a framework for the diagnosis and management of cardiac sarcoidosis.

Cardiac sarcoidosis (CS) is an infiltrative cardiomyopathy that results from granulomatous inflammation of the myocardium. Common presentations include high-grade conduction disease, ventricular arrhythmias (VAs), or left ventricular (LV) dysfunction. Accurate diagnosis is challenging because of the diverse and nonspecific presentations. The combination of multimodality imaging and multidisciplinary collaboration is needed to estimate the likelihood of an individual having CS.

Given the morbidity and mortality associated with cardiac involvement of sarcoidosis, timely and accurate diagnosis to enable prompt tailored management is essential. However, as a result of the lack of randomized clinical trials in CS, diagnostic and treatment strategies are based on cohort studies and consensus opinions. A recent survey of participants who treat CS found substantial variation in approach, particularly with regard to treatment,1 underscoring the need for a scientific statement to guide clinicians. Although unanimous consensus on all elements was not possible, we aimed to deliver the highest level of agreement possible. This scientific statement provides a practical resource for clinicians on the diagnosis and management of individuals with CS.

PATHOPHYSIOLOGY AND EPIDEMIOLOGY

The exact cause and pathophysiology of sarcoidosis remain incompletely understood. The most common hypothesis involves environmental exposure (including mold, insecticides, or silica dust) to an unknown antigen in the context of genetic predisposition.1–3 Genome-wide studies have demonstrated a genetic susceptibility related to the HLA class II alleles, with increased risk of developing sarcoidosis in individuals with a family history of sarcoidosis.3

There is a dysregulated T-cell immunological response2,3 with activation of type 1 T-helper cells and upregulation of cytokines and chemokines, including interferon-γ, tumor necrosis factor-α, transforming growth factor-β, interleukin-2, interleukin-12, and others.4,5 The regulatory T-cell response is impaired, resulting in persistent local effector T-cell response to tissue antigens.3 The immune system dysregulation ultimately leads to activation of macrophages and formation of nonnecrotic inflammatory (so-called noncaseating) granulomas that may be

observed in almost any organ system, including the heart. There is an active inflammatory phase that can progress to a fibrotic phase, both of which may contribute to cardiac dysfunction. Studies have shown an association between HLA class II alleles and the risk of developing sarcoidosis6,7 and the severity of disease.8

The incidence and prevalence of sarcoidosis vary by region, sex, and race. In the United States, systemic sarcoidosis has a prevalence of 35.2 cases per 100 000 population with clustering on the East Coast near urban areas9 and with higher incidence and prevalence in Black Americans.10 The prevalence of systemic sarcoidosis is higher in women compared with men.11 Likely related to growing awareness and diagnostic advances, the prevalence of CS, in both patients with known systemic sarcoidosis and those with new sarcoidosis diagnoses, has increased over the past several decades. For example, there was a 20-fold increase in the annual detection rate of CS in Finland between 1988 and 2012,12 and an estimated prevalence of clinically manifest CS of 14 cases per 100 000 population in 2021.12a There appears to be racial variation in cardiac involvement; CS is particularly prevalent in the Japanese population.13 Furthermore, the clinical phenotype of CS appears to vary by race and sex, with symptomatic heart failure (HF) more common in Black individuals compared with White individuals and in women compared with men, whereas VAs have been reported to be more frequent in men than in women.14

CLINICAL PRESENTATION

Classic Manifestations

In individuals with systemic sarcoidosis, the lung is the most frequently involved organ, affected in up to 90% of cases. Although ≈20% of patients with systemic sarcoidosis referred for imaging have cardiac involvement, clinically manifest disease is encountered in only ≈5%.15 Certain clinical scenarios raise “red flags” that should prompt evaluation for CS. These include unexplained high-grade atrioventricular block in an individual <60 years of age, unexplained VA, or echocardiographic findings, including reduced LV ejection fraction (LVEF), regional wall aneurysm, or basal septal thinning in the absence of coronary artery disease or another explanation. Laboratory data can be helpful because sarcoidosis may present with hypercalcemia due to increased production of 1,25-dihydroxyvitamin D by activated macrophages.

The clinical presentation of CS depends on the location, extent, and activity of the myocardial granulomatous infiltration. For example, individuals with involvement of the basal interventricular septum are more likely to present with heart block, whereas subjects with extensive replacement myocardial fibrosis are more likely to develop ventricular systolic dysfunction and HF. Similarly, the presence and extent of myocardial granulomatous scar are strongly associated with the occurrence of VA, with right ventricular (RV) involvement being associated with increased VA risk.16 A substantial proportion of patients diagnosed with CS will present with cardiac manifestations as their presenting organ of involvement, with ≈49% to 65% initially presenting without clinically evident extracardiac involvement.12,17

On comprehensive evaluation, the majority of individuals with CS will demonstrate systemic involvement, underscoring the need to perform a thorough organ assessment.18 In a small number of cases, truly isolated CS can occur in the context of subclinical or later diagnosed extracardiac disease19; however, reported rates of clinically isolated CS are unreliable because of variation in diagnostic strategies and confirmation.12,20–22 It is important to note that in cases of clinically isolated CS, other causes for the cardiac presentation must be excluded, notably inherited cardiomyopathy, as discussed later.23,24

DIAGNOSIS

Diagnostic Modalities

Electrocardiography and Echocardiography

Given the wide differential diagnosis, confirmation of CS can be challenging. ECG and echocardiography have limited sensitivity but can provide clues to the presence of CS. On ECG, nonspecific findings may include conduction delay, AVB, fragmented QRS complexes, and right or left bundle-branch block. Ambulatory

electrocardiographic monitoring may increase suspicion for CS if frequent premature ventricular contractions, high-grade conduction abnormalities, or VAs are present.

Echocardiography may demonstrate reduced LVEF, regional wall aneurysm, basal septal thinning, and abnormal global longitudinal strain.25,26 Despite limited sensitivity and specificity, echocardiography can be useful for screening for CS and serial monitoring because of its wide accessibility and low cost. However, individuals with CS may have both normal ECG and normal echocardiography; thus, cardiac magnetic resonance (CMR) imaging and fluorine-18 fluorodeoxyglucose (FDG)–positron emission tomography (PET) are the fundamental imaging modalities for accurately diagnosing CS (Figure 1). Furthermore, fusion of cardiac FDG-PET and CMR images may be helpful when both the software and clinical expertise are available.

Figure 1. CMR and corresponding PET findings by progression of disease. Phenotypes and typical clinical presentation(s) based on cardiac magnetic resonance (CMR) and positron emission tomography (PET) imaging findings in patients with suspected cardiac sarcoidosis. Red and black arrows highlight the location of late gadolinium enhancement (LGE) and fluorodeoxyglucose (FDG), respectively. PET–magnetic resonance (MR) images were fused offline with commercial software (MIMvista Corp, Cleveland, OH). LV indicates left ventricular.

Cardiac Magnetic Resonance Imaging

CMR is a high-spatial-resolution technique used to localize and quantify areas of late gadolinium enhancement (LGE) as a marker of myocardial involvement from sarcoidosis.

Gadolinium is an extracellular contrast agent with rapid washout from normal myocardium but slow washout from areas of fibrosis and inflammation, resulting in LGE within the expanded extracellular space.27

With clinical criteria used as the reference and nonischemic LGE patterns used as the definition of a positive case, CMR had a high sensitivity (95%) and specificity (85%) for the diagnosis of CS in a meta-analysis of 17 studies and 1031 individuals.28 It is important to note that myocardial LGE also carries significant prognostic value as the strongest predictor for all-cause mortality and sustained VA among individuals with known or suspected CS.16

Myocardial LGE can occur because of sarcoidosis-related inflammation or fibrosis/scar. In a systematic review and meta-analysis of gross pathological heart images of individuals with histologically diagnosed CS, certain common locations of CS involvement were identified (Figure 1): LV subepicardial, septal, LV multifocal, or RV free wall involvement was observed in >90% of cases (pathology-frequent features); other features such as the absence of gross myocardial involvement, isolated LV midmyocardial involvement, isolated LV subendocardial involvement, and the absence of septal involvement were rare or absent (pathology-rare features).29

When the CMR correlates of these gross pathological findings were subsequently validated in 504 individuals with biopsy-proven extracardiac sarcoidosis,30 the prevalence of pathology-frequent LGE was 20.4% and of pathology-rare LGE was 11.5%. The remaining individuals had no evidence of myocardial LGE, including a subset with reduced LVEF (10.5%). It is remarkable that pathology-frequent LGE was associated with a high risk of arrhythmic events independently of LVEF and extent of LGE. On the other hand, the absence of pathology-frequent LGE was associated with a low risk of arrhythmic events, even in the presence of LGE or abnormal LVEF.30

These data reinforce the concept that the pattern of LGE can be used to better understand the likelihood of having CS and that certain patterns are more likely to be associated with adverse prognosis. However, there are no patterns of LGE that are sufficient for the diagnosis CS; thus, even when patients have pathology-frequent LGE, cardiac or extracardiac tissue confirmation may still be helpful because other processes (eg, giant-cell myocarditis) may have CMR findings indistinguishable from CS.31 Furthermore, CMR interpretation may be subject to interreader interpretation due to nonspecific findings for CS.32 Last, the absence of LGE does not fully exclude CS because early cardiac involvement may exist before the presence of LGE on imaging.

A practical advantage of CMR compared with cardiac FDG-PET is that patient preparation before the test (discussed later) is not needed. CMR also offers a high negative predictive value (both to rule out disease and to identify patients who have a low event rate) and can be useful in evaluating for competing causes (eg,

arrhythmogenic RV cardiomyopathy, myocarditis, prior myocardial infarction). Although CMR and FDG-PET modalities are considered complementary, there are center-specific variations in practice, but in general, CMR is frequently the initial test for evaluating individuals with low clinical suspicion for CS, whereas both CMR and FDG-PET may be pursued simultaneously when the pretest probability for CS is higher.33

Cardiac PET

FDG-PET is an integral tool in the evaluation and management of CS. FDG-PET is generally performed in conjunction with CMR to assess disease activity and monitor treatment response. FDG-PET should also be performed if a high pretest probability remains despite negative, nondiagnostic, or equivocal CMR results or in situations when CMR is contraindicated.

When there is clinical suspicion for extracardiac sarcoidosis or no recent study evaluating for extracardiac sarcoidosis has been completed, a limited whole-body PET study should be performed with the same FDG injection to assess for extracardiac uptake. Evaluating for extracardiac involvement may identify potential biopsy sites or guide the use of systemic immunosuppression.34

FDG-PET imaging identifies metabolically active, inflammatory lesions. FDG, a glucose analog, is sequestered in activated inflammatory cells such as macrophages and lymphocytes through insulin-independent glucose transport proteins (GLUT1 and GLUT3) and thus accumulates in areas of upregulated glucose metabolism such as hypermetabolic sites of myocardial sarcoidosis infiltration. It is important to note that glucose is also a common energy source of healthy myocardial cells, but unlike inflammatory cells, myocytes take up glucose through an insulin-dependent mechanism (GLUT4) regulated by fasting and dietary composition. Consequently, inducing a "metabolic switch" in the heart, defined as a shift from utilization of glucose to fatty acids and fatty acid–derived ketones,35 can lead to suppression of normal FDG uptake in the heart (through GLUT4 translocation inhibition) and identification of FDG-avid inflammatory cells. In theory, this metabolic switch can be induced by strategies that increase fatty acid or ketones levels and, at the same time, reduce insulin release, including prolonged fasting and dietary switch to a lipid-rich/carbohydrate-deprived (or ketogenic) diet for a minimum of 24 hours before the examination.36 Myocardial FDG suppression is achieved in ≈80% of subjects following the ketogenic diet for at least 24 hours,37,38 and up to 95% of subjects will demonstrate myocardial FDG suppression within 72 hours of ketosis.39,40

The hallmark of CS on FDG-PET imaging is the presence of multifocal FDG uptake, particularly when associated with resting perfusion defects (eg, perfusion-metabolism mismatch) or in association with extracardiac inflammation (Figure 1B). When PET (or CMR) findings are inconclusive, having abnormal findings in CMR and PET are complementary and may increase the likelihood of diagnosing CS.41 Occasionally, focal FDG uptake within the septum (with or without corresponding LGE) can be the only imaging evidence of CS infiltration, particularly in patients presenting with heart block (Figure 1A).42 However, CS can also be present in the absence of myocardial FDG uptake in cases of "burned out" CS, in which metabolically active granulomas are replaced by metabolically inactive fibrotic tissue (Figure 1C).

The pattern of FDG uptake can significantly change the test characteristics.43 For example, when histological confirmation from explanted hearts is used as the reference, the sensitivity and specificity of any FDG uptake pattern were 100% and 33%, respectively. In contrast, more specific patterns for CS (eg, multiple noncontiguous perfusion defects with associated FDG uptake or multifocal FDG uptake in combination with extracardiac FDG uptake) showed a sensitivity and specificity of 83% and 100%, respectively.43

These observations emphasize the importance of evaluating imaging findings beyond just a binary outcome and considering the pattern of involvement. Further examples of different patterns of CS on FDG-PET are shown in Figure 1. False-positive results (Figure 1D) may occur as a result of incomplete physiological suppression44 or glucose upregulation in other disease states such as ischemic (hibernating) myocardium45; other forms of dilated, inflammatory, or genetic cardiomyopathy46; or recent myocardial infarction. In addition, recent cardiac procedures such as ablation for VAs may result in acute inflammation and lead to a false-positive study.

Current Diagnostic Algorithms

There are 2 widely accepted pathways to diagnose CS (Table 1 and Figure 2). The first pathway requires direct histological confirmation of noncaseating granulomas (with no alternative cause identified) in myocardial tissue obtained from endomyocardial biopsy (EMB), LV apical core biopsy, or explanted hearts. However, EMB has limited sensitivity because of the patchy nature of myocardial infiltration, even when guided by electroanatomic and voltage mapping.47 Consequently, the diagnosis of CS may also be made by integrating a series of clinical, pathological, and imaging criteria, keeping in mind that multimodality imaging by itself is insufficient for confirming the diagnosis.

Table 1. Summary of Diagnostic Criteria for CS

HRS criteria	2014	Definite CS: histological diagnosis from myocardial tissue CS is diagnosed in the presence of noncaseating granuloma on histological examination of myocardial tissue with no alternative cause identified Probable CS: clinical diagnosis from invasive and noninvasive studies There is a histological diagnosis of extracardiac sarcoidosis, and 1 of the following is present: Immunosuppressant-responsive cardiomyopathy or heart block Unexplained reduced LVEF <40% Unexplained sustained VT or high-degree AVB Patchy FDG uptake on a dedicated cardiac PET in a pattern consistent with CS LGE on CMR in a pattern consistent with CS Positive ^{67}Ga uptake in a pattern consistent with CS And other causes have been reasonably excluded.
JCS criteria (with systemic involvement)	2016	Histologic diagnosis group EMB or surgical specimens demonstrate noncaseating granulomas Clinical diagnosis group Those with negative myocardial biopsy or not undergoing myocardial biopsy. The patient is clinically diagnosed as having CS when: 2 or more of the 5 major criteria are satisfied OR 1 in 5 major and ≥2 minor criteria are satisfied: Major criteria: High-degree AVB or fatal VT/VF Basal thinning of the ventricular septum or abnormal ventricular wall anatomy LV contractile dysfunction ^{67}Ga or FDG-PET reveals abnormally high tracer uptake in the heart CMR reveals LGE of the myocardium Minor criteria: Abnormal ECG findings (nonsustained VT, premature ventricular complexes, bundle-branch block, axis deviation, abnormal Q waves) Perfusion defects on SPECT Monocyte infiltration and moderate fibrosis on EMB AND Granulomas are found in organs other than the heart OR the individuals show clinical findings strongly suggestive of pulmonary or ophthalmic sarcoidosis AND at least 2 of 5 characteristic findings of sarcoidosis are present: Bilateral hilar lymphadenopathy Elevated angiotensin-converting enzyme or serum lysozyme levels Elevated serum soluble interleukin-2 receptor levels Significant tracer accumulation in ^{67}Ga citrate scintigraphy or FDG-PET

		A high percentage of lymphocytes in bronchoalveolar lavage fluid with a CD4/CD8 ratio>3.5
JCS criteria (isolated cardiac sarcoidosis)	2016	Histological diagnosis group EMB or surgical specimens demonstrate noncaseating granulomas Clinical diagnosis group Those with negative myocardial biopsy or not undergoing myocardial biopsy; isolated CS is diagnosed clinically when there is significant tracer accumulation in ^{67}Ga citrate scintigraphy or FDG-PET and at least 3 of the other major criteria are satisfied: Major criteria: High-degree AVB or fatal VT/VF Basal thinning of the ventricular septum or abnormal ventricular wall anatomy LV contractile dysfunction CMR reveals LGE of the myocardium AND the following prerequisites are met: No clinical findings of sarcoidosis in any organs other than the heart ^{67}Ga citrate scintigraphy or FDG-PET reveals no abnormal tracer uptake in organs other than the heart Chest CT shows no findings consistent with pulmonary sarcoidosis (shadow along lymphatic tracts in the lungs or hilar/mediastinal lymphadenopathy >10 mm) Coronary artery disease and other inflammatory myocardial diseases are ruled out
WASOG criteria	2014	Granulomatous inflammation has been demonstrated in another organ and 1 of the following: Treatment-responsive cardiomyopathy and AVB Reduced LVEF in the absence of other risk factors Spontaneous or inducible sustained VT with no risk factors High-degree AVB Patchy uptake on a dedicated cardiac PET LGE on CMR Positive ^{67}Ga uptake Defect on perfusion scintigraphy or SPECT scan T2 prolongation on CMR And alternative causes have been reasonably excluded

AVB indicates atrioventricular block; CMR, cardiac magnetic resonance; CS, cardiac sarcoidosis; CT, computed tomography; EMB, endomyocardial biopsy; FDG, fluorodeoxyglucose; HRS, Heart Rhythm Society; JCS, Japanese Circulation Society; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; PET, positron emission tomography; SPECT, single-photon emission cardiac tomography; VF, ventricular fibrillation; VT, ventricular tachycardia; and WASOG, World Association of Sarcoidosis and Other Granulomatous Disorders.

Modified from Judson et al,[18] Aitken et al,[28] and Divakaran et al.[43]

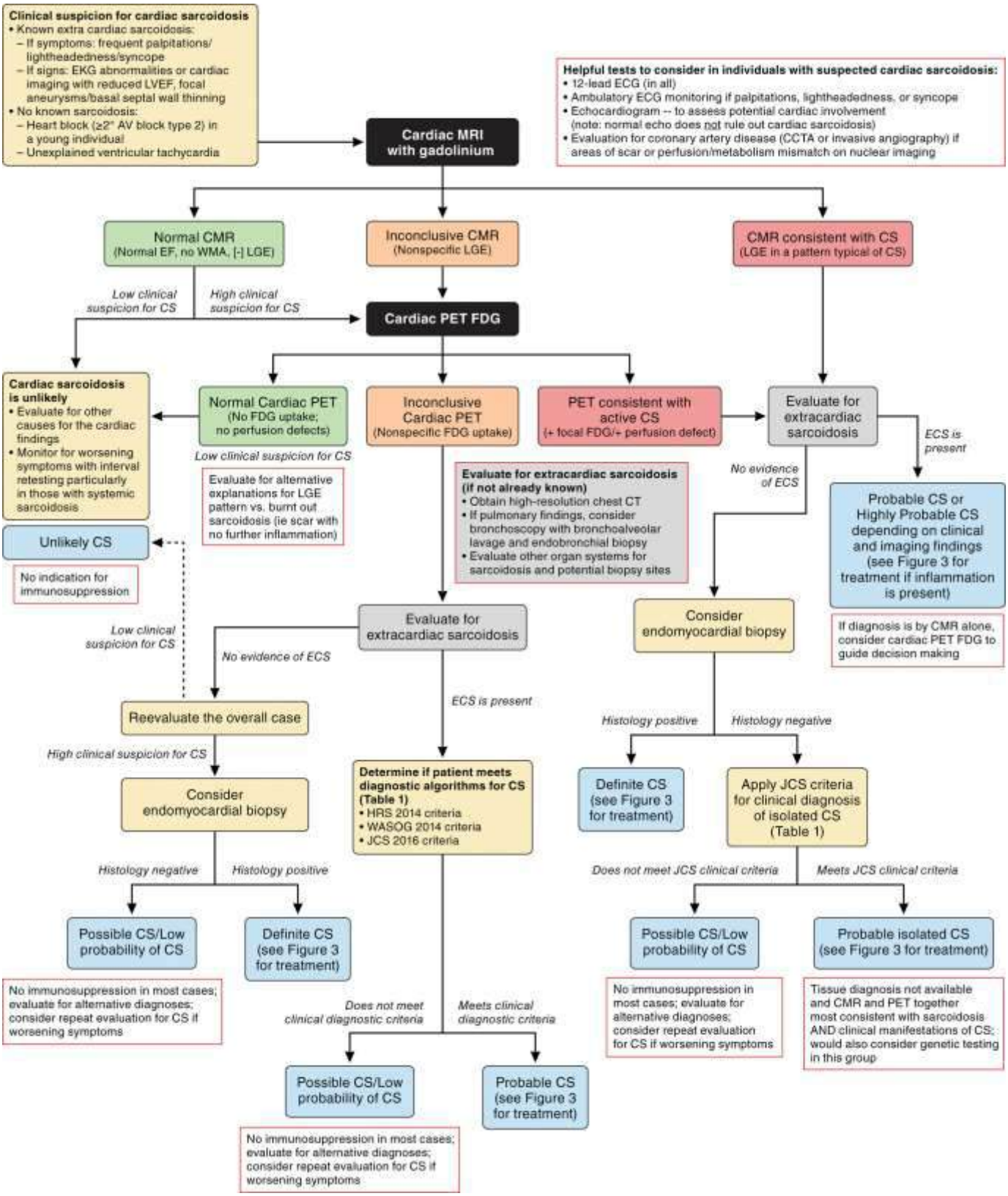

Figure 2. Proposed algorithm for the diagnosis and evaluation of CS. Although not all scenarios can be fully accounted for, we attempted to include the most frequently encountered scenarios in this algorithm. In cases in which diagnosis is made with cardiac magnetic resonance imaging (MRI), a cardiac positron emission tomography (PET)–fluorodeoxyglucose (FDG) study should be considered to guide decision-making for treatment. In general, treatment is initiated in those with definite, highly probable, and probable cardiac sarcoidosis (CS). For possible/low probability of CS, treatment is not initiated in most cases although individualized evaluation should be considered. Although unanimous consensus on all elements was not possible, this algorithm represents the highest level of agreement possible. AV indicates atrioventricular; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance imaging; CT, computed tomography; ECS, extracardiac sarcoidosis; EF, ejection fraction; EKG, electrocardiogram; HRS, Heart Rhythm Society; JCS, Japanese Circulation Society; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; WASOG, World Association of Sarcoidosis and Other Granulomatous Disorders; and WMA, wall motion abnormality.

In 2014, in collaboration with several other medical societies, experts from the Heart Rhythm Society (HRS) published the first international CS diagnosis consensus statement.48 The only published diagnostic guidelines until 2014 were those by the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG)18 and the Japanese Ministry of Health and Welfare's criteria.50 The HRS diagnostic guideline aligned closely with the WASOG document,18,48 and the Japanese Circulation Society published new diagnostic guidelines in 2019.50 Table 1 provides a summary of algorithms.

Although similarities exist between the HRS and WASOG diagnostic guidelines, the most recent Japanese guideline is unique: It does not require biopsy evidence of noncaseating granulomas, and it is the only guideline to include an imaging diagnostic algorithm for isolated CS. Not surprisingly, when the 3 diagnostic guidelines were compared, there was good concordance between the WASOG and HRS criteria and poor concordance between the WASOG/HRS and Japanese criteria.51 This discrepancy underscores an important and unresolved question: Can CS be accurately diagnosed without histological confirmation from cardiac or extracardiac tissue?

At many institutions, lung or lymph node biopsy is pursued first in individuals with suspected sarcoidosis because of lower procedural risk. In addition, accompanying bronchoscopy results can add diagnostic certainty based on bronchoalveolar lavage fluid analysis and cell counts and cultures. Ophthalmology examination should be performed when there is suspected ocular sarcoidosis because lacrimal gland biopsy may provide histological confirmation. EMB can be necessary in selected cases. However, because of the focal and patchy nature of the disease, unguided EMB has a low sensitivity of ≈20%, so a negative biopsy does not necessarily rule out CS.52 Both FDG-PET or CMR imaging22 and voltage map–guided biopsy procedures53,54 increase the diagnostic yield to 40% to 50%, but the diagnostic yield remains limited even with targeted EMB.22,48,54–56

Figure 2 includes a suggested diagnostic algorithm for CS, incorporating many of the points of these prior guidelines and the experience of the writing group. It is generally accepted that patients have highly probable CS if both PET and CMR show typical findings of CS and when such patients also have clear clinical manifestations of CS. Given the aforementioned challenges in obtaining definitive histological confirmation and the known limitations of clinical diagnostic criteria, clinicians often face uncertainty about the diagnosis of CS. Thus, rather than thinking of the diagnosis of CS in a binary fashion (ie, positive or negative), it may be more helpful to think of the likelihood of CS according to the following categories: definite, highly probable, probable, and possible/low probability (Table 2). These categories are based on terminology developed by the WASOG for incorporating the likelihood of disease activity in other organs, and several investigators have used this construct and suggested how different types of imaging patterns, together with clinical data, may inform the likelihood of cardiac involvement.41,43,47,57

Table 2. Likelihood of CS Based on Clinical, Pathological, and Imaging Criteria

Diagnostic category of cardiac sarcoidosis	**Criteria**
Definite CS	Detection of a noncaseating granuloma on histological examination of myocardial tissue (EMB or other myocardial specimens) with no alternative cause identified
Uncertain diagnosis	
Highly probable CS	Requires all 4 of the following criteria: Confirmed diagnosis of extracardiac sarcoidosis Clinical findings consistent with CS* Imaging finding by CMR or FDG-PET consistent with CS Other potential causes for the clinical and imaging findings have been excluded
Probable CS	With histological diagnosis of extracardiac sarcoidosis; requires both of the following criteria:

Diagnostic category of cardiac sarcoidosis	Criteria
	One of the following types of cardiac findings: Clinical findings consistent with CS* Imaging finding by CMR or FDG-PET consistent with CS Other potential causes for the clinical and imaging findings have been excluded
	Without histological or clinical diagnosis of extracardiac sarcoidosis; requires all 3 of the following criteria: Imaging findings by both CMR and FDG-PET consistent with CS 1 or more clinical findings consistent with CS* Other potential causes for the clinical and imaging findings have been excluded
Possible or low probability of CS	Includes patients with or without a histological or clinical diagnosis of extracardiac sarcoidosis not meeting criteria for definite, highly probable, or probable CS

CMR indicates cardiac magnetic resonance; CS, cardiac sarcoidosis; EMB, endomyocardial biopsy; FDG, fluorodeoxyglucose; and PET, positron emission tomography.

Clinical findings consistent with CS may include unexplained left or right ventricular dysfunction, ventricular arrhythmias, or high-grade heart block.

Modified from Ozutemiz et al,[40] Orii et al,[42] Crouser et al,[57] and Yafasova et al.[58]

Diagnosis of Clinically Silent CS in Individuals With Extracardiac Sarcoidosis

Individuals with systemic sarcoidosis are at increased risk of adverse cardiovascular events, including HF and atrial arrhythmia, compared with the general population.58 This increased risk is likely due to a combination of comorbid cardiovascular risk factors and direct cardiac involvement of sarcoidosis and is secondary to pulmonary hypertension driven by pulmonary fibrosis, direct vascular involvement, or inflammation. Current guidelines lack consensus on screening for CS. For example, the 2014 HRS consensus suggests performing baseline cardiac history, ECG, and echocardiogram in all patients, followed by further evaluation if abnormalities are detected on initial screening. The American Thoracic Society clinical practice guideline recommends baseline ECG but limiting the use of echocardiogram and cardiac rhythm monitoring to individuals according to symptoms and events such as dyspnea, palpitations, or syncope.48,57 Many individuals with extracardiac sarcoidosis may have subclinical CS without symptoms but have evidence of LGE on CMR.26,59,60 The impact of treatment in subclinical CS is incompletely understood. Thus, routine cardiac surveillance of asymptomatic individuals with extracardiac sarcoidosis cannot be recommended. However, clinicians caring for individuals with extracardiac sarcoidosis should maintain a high index of suspicion. Any symptom should prompt cardiac assessment, especially because CS may occasionally manifest several years after the initial sarcoidosis diagnosis.17 This approach may allow earlier identification of less severe cardiac involvement17 and more timely initiation of therapies.

Differential Diagnosis

Sarcoidosis is often referred to as the great masquerader because of its diverse manifestations and must be differentiated from other phenotypically similar cardiac syndromes such as acute myocarditis; chronic inflammatory cardiomyopathies, including autoimmune disease-related, inherited, and infiltrative cardiomyopathies; and other granulomatous diseases.61 Clinical context and cardiac imaging often are insufficient to differentiate sarcoidosis from other forms of cardiac pathology causing myocarditis and inherited arrhythmogenic cardiomyopathies. Individuals with arrhythmogenic cardiomyopathy are also often relatively young and can have overlapping clinical features with CS.62,63 A subset of these individuals, particularly those with a desmoplakin pathogenic variant cardiomyopathy, can also present with a myocarditis-like syndrome, with chest pain, elevated cardiac serum troponin level, and features similar to CS on advanced cardiac imaging.64,65

Arriving at the correct diagnosis can be particularly challenging in cases of clinically isolated CS. In 1 study, 5 of 16 individuals with presumed clinically isolated CS based on cardiac imaging were reclassified as having genetic cardiomyopathy after genetic testing.23 A 3-generational family history at minimum is important in individuals suspected of having CS. Referral to genetic counseling and testing can be useful to identify pathogenic variants in appropriately selected individuals undergoing evaluation for CS, given implications for treatment and cascade screening. Although data are still emerging, we pursue genetic testing in the majority of cases of CS that lack histological confirmation.

CS should also be distinguished from giant-cell myocarditis, a lethal form of myocarditis characterized by fulminant cardiogenic shock, VA, and conduction disease. Giant-cell myocarditis is typically diagnosed by the presence of a diffuse myocardial inflammatory infiltrate and multinucleated giant cells with associated myocyte necrosis in the absence of a viral origin on EMB. Despite immunosuppressive therapy, patients may require mechanical circulatory support and heart transplantation.65 Another infiltrative cardiomyopathy, cardiac amyloidosis, also requires distinction from CS. Cardiac amyloidosis can occasionally demonstrate abnormal FDG uptake on cardiac PET.66 However, findings of LV hypertrophy and reduced global longitudinal strain with an apical sparing pattern can help differentiate cardiac amyloidosis from CS.67

The broad spectrum of clinical phenotypes in CS and the limitations to obtaining a histopathologically confirmed diagnosis, particularly in cases of clinically isolated CS, are added challenges in distinguishing CS from these alternate diagnoses. A multidisciplinary team comprising experts in systemic sarcoidosis, HF, electrophysiology, advanced cardiac imaging, cardiovascular genetics, and cardiac pathology is necessary to address this complexity.

TREATMENT

The initiation of treatment should be based on the risk-benefit ratio, similar to other disease states. In general, if the individual is symptomatic, treatment should be initiated in those with definite and highly probable CS. For the probable group, there should be careful discussion with the individual about the risks versus benefits of treatment. For those in the possible/low-probability group, treatment would not be pursued in the majority of cases given the uncertainty of diagnosis, unclear benefit of treatment, and potential for harm. For individuals with unlikely CS, there is typically no indication for immunosuppression.

Immunomodulating Agents

There are no randomized controlled trials to guide therapy with immunomodulating agents in CS (available therapies summarized in Table 3 and Figure 3). Treatment is typically initiated in individuals with clinical manifestations, including VA, advanced atrioventricular block, or HF in the presence of active inflammation. Whether asymptomatic individuals with cardiac FDG-PET scans consistent with active inflammation require treatment is unclear. In these cases of subclinical disease, the decision to initiate immunomodulation therapy should be individualized.

Drug	Mechanism of action	Suggested dosing	Toxicities	Considerations
Prednisone	Has multiple mechanisms of action, including suppression of TNF-α and downregulation of multiple components of the immune system involved in granuloma	30–40 mg orally with tapering guided by response	Depression, insomnia, psychosis, sodium and fluid retention, worsening HF, impaired wound healing, hyperglycemia, hypertension, osteoporosis, myopathy, adrenal insufficiency, gastritis,	Before treatment, assess cardiovascular risk and optimize when possible, exclude latent tuberculosis and update vaccines, determine fracture risk, screen for psychiatric illness, and conduct a baseline eye examination. While on treatment, monitor for hypertension, hyperglycemia, hyperlipidemia,

Drug	Mechanism of action	Suggested dosing	Toxicities	Considerations
	formation		and ulceration	fluid retention, bone density, fracture risk, glaucoma, and cataract formation. Consider the following for prophylaxis: histamine-2 blockers or proton pump inhibitors for gastric protection, pneumocystis prophylaxis for doses ≥20mg daily, and therapy for fracture risk as indicated. Pregnancy category: C
High-dose intravenous methylprednisolone (for use in individuals with life-threatening manifestations or rapidly progressive disease)	Has multiple mechanisms of action, including suppression of TNF-α and downregulation of multiple components of the immune system involved in granuloma formation	Fixed dose: 500–1000 mg/d IV for 3–5 d followed by oral prednisone	Insomnia, psychosis, sodium and fluid retention, worsening HF, impaired wound healing, hyperglycemia, hypertension, myopathy, adrenal insufficiency, gastritis, and ulceration	While on treatment, monitor for hypertension, hyperglycemia, hyperlipidemia, fluid retention, bone density, fracture risk, glaucoma, and cataract formation. Pregnancy category: C
Methotrexate	Inhibits the metabolism of folic acid in purine and pyrimidine synthesis	Initiate 5–15 mg weekly orally or subcutaneously; titrate increments every 4 wk to target a dose of 10–20 mg weekly	Hepatotoxicity, myelosuppression, gastrointestinal intolerance, mucositis, pneumonitis, and teratogenic (contraindicated in men and women 3 mo before a planned pregnancy, during pregnancy, and breastfeeding)	Before treatment, exclude tuberculosis; screen for hepatitis B and C and HIV; perform baseline chest radiograph, CBC, and LFTs; monitor serum creatinine; and ensure vaccines are up to date. While on treatment, monitor CBC, LFTs, and serum creatinine every 2–4 wk for the first 3 mo of treatment, every 8–12 wk for 3–6 mo of therapy, and every 12 wk beyond 6 mo. During treatment, provide folic acid 1–5 mg/d on 5–7 d/wk to minimize myelosuppression and gastrointestinal intolerance; consider leucovorin rescue therapy in toxicity unresponsive to increase folic acid. Pregnancy category: X
Azathioprine	As a purine analog, inhibits purine synthesis necessary for T- and B-cell proliferation	50–200 mg/d orally	Leukopenia, hepatotoxicity, risk of infection, and skin cancer	Before initiation, consider thiopurine level. While on treatment, monitor CBC and LFTs every 2–4 wk for the first 3 mo of treatment, every 8–12 wk for 3–6 mo of therapy, and every 12 wk beyond 6 mo. Pregnancy category: D

Drug	Mechanism of action	Suggested dosing	Toxicities	Considerations
Leflunomide	Inhibits cyclooxygenase-2 enzyme; dihydroorotate dehydrogenase inhibition affecting pyrimidine synthesis	10–20 mg/d orally	Leukopenia, hepatotoxicity, risk of infection, skin rash, fatigue, pneumonitis, and peripheral neuropathy	While on treatment, monitor CBC and LFTs every 2–4 wk. If needed, may require cholestyramine to remove the drug and its metabolites in the setting of toxicity. Pregnancy category: X
Mycophenolate	Inhibits de novo guanosine nucleotide synthesis and has a cytostatic effect on T- and B-cell proliferation	1500–3000 mg/d orally	Leukopenia, risk of infection, lymphoproliferative disorders, and skin cancer	Limited data from case reports for support in sarcoidosis Pregnancy category: First trimester: X Second/third trimester: C
Infliximab	TNF-α antagonist	3–5 mg/kg IV initially and at 2 and 6 wk, then every 4–6 wk	Worsening of preexisting HF, allergic reactions, risk of infection, increased risk of malignancy	Before treatment, exclude latent tuberculosis; screen for hepatitis B, C, and HIV; perform baseline chest radiograph, CBC, and LFTs; assess serum creatinine and LVEF; and ensure vaccines are up to date. During treatment, monitor CBCs and LFTs every 1–3 mo, monitor ejection fraction and signs/symptoms of HF, and monitor for malignancy. Consider low-dose methotrexate±corticosteroid to limit the development of anti–TNF-α antibodies. Consider avoiding in decompensated HF or severe LV dysfunction. If an active infection develops, consider a temporary hold. Pregnancy category: C
Adalimumab	TNF-α antagonist	80–160 mg SC at wk 0, 40–80 mg on wk 1, and 40 mg on wk 2; then 40 mg weekly thereafter	Worsening of preexisting HF, allergic reactions, risk of infection, and increased risk of malignancy	Before treatment, exclude latent tuberculosis; screen for hepatitis B, C, and HIV; perform baseline chest radiograph, CBC, LFTs; assess serum creatinine and LVEF; and ensure vaccines are up to date. During treatment, monitor CBCs and LFTs every 1–3 mo, monitor ejection fraction and signs/symptoms of HF, and monitor for malignancy. Consider low-dose methotrexate±corticosteroid to limit the development of anti-TNF-α antibodies.

Drug	Mechanism of action	Suggested dosing	Toxicities	Considerations
				Consider avoiding in decompensated HF or severe LV dysfunction. If an active infection develops, consider a temporary hold. Pregnancy category: B
Rituximab	Monoclonal antibody against CD20 surface antigen of B lymphocytes	500–1000 mg every 1–6 mo	Transfusion reaction, pancytopenia, opportunistic infection, fatigue, headache, neuropathy	Before treatment, exclude latent tuberculosis; screen for hepatitis B, C, and HIV; perform baseline chest radiograph, CBC, and LFTs; monitor serum creatinine and LVEF; and ensure vaccines are up to date. During treatment, monitor CBC before each dose and weekly to monthly intervals after. Follow protocols to minimize infusion-related reaction. Pregnancy category: X

CBC indicates complete blood count; HF, heart failure; LFT, liver function test; LV, left ventricular; LVEF, left ventricular ejection fraction; and TNF-α, tumor necrosis factor-α.

Table 3. Common Immunosuppressive Agents in the Management of CS

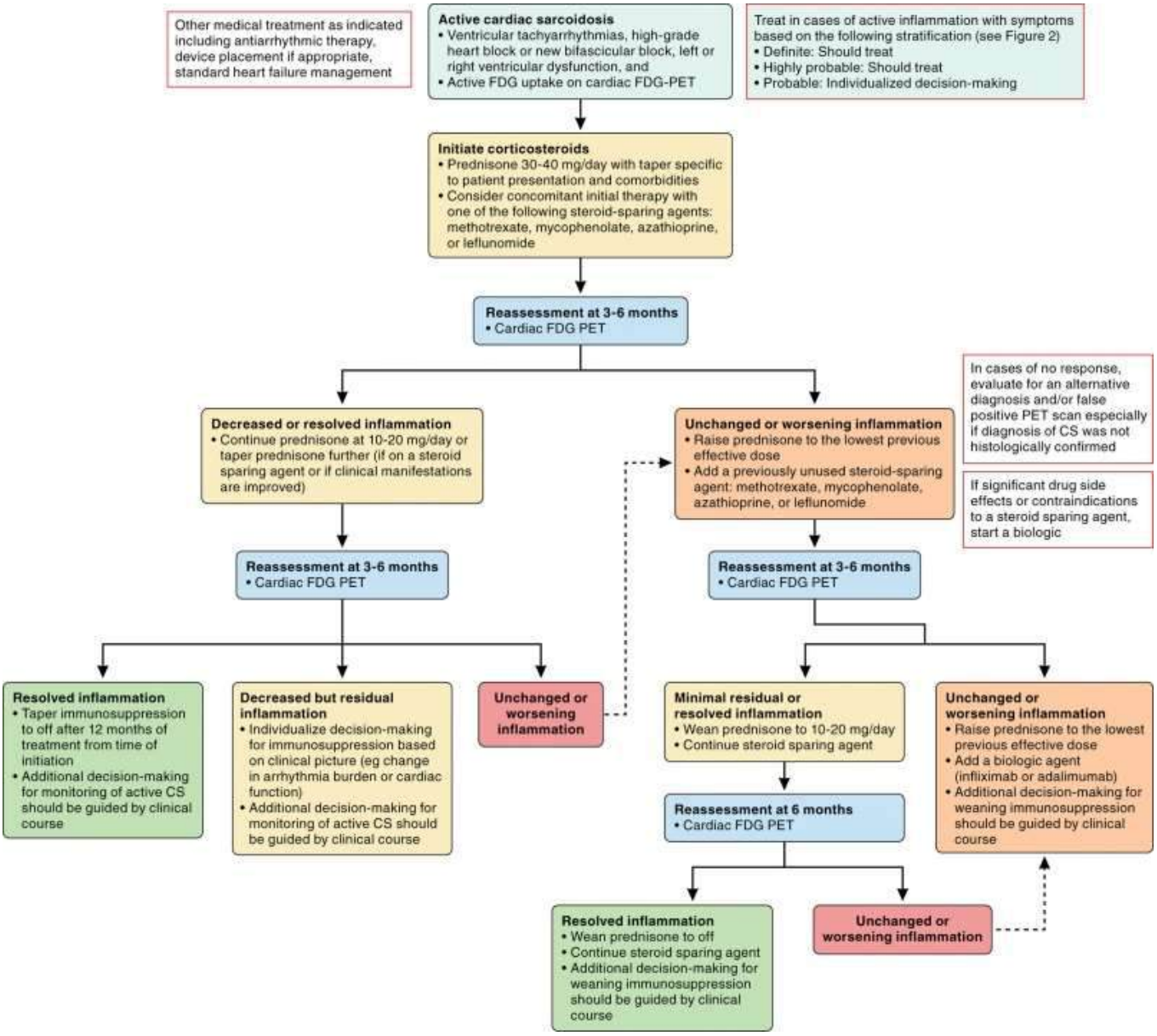

Figure 3. Proposed tiered approach to medical treatment of CS. Although not all treatment scenarios can be fully accounted for, we attempted to include the most frequently encountered scenarios in this algorithm. Unanimous consensus on all elements was not possible; however, this algorithm represents the highest level of agreement possible. CS indicates cardiac sarcoidosis; FDG, fluorodeoxyglucose; and PET, positron emission tomography.

Corticosteroids are currently considered the first-line treatment for individuals with CS.1 Corticosteroids can improve conduction in cases of AVB, but their benefit specific to other arrhythmias, LV dysfunction, and mortality remains unclear.12,68–70 Corticosteroids are initiated at doses of 30 to 40 mg/d of prednisone equivalent because there is no demonstrated benefit with higher starting doses.71–73 For those with life-threatening manifestations such as cardiogenic shock, higher initial corticosteroid doses, including intravenous doses of methylprednisolone of up to 1000 mg/d, can be prescribed until other causes of acute myocarditis (such as giant-cell myocarditis) are excluded.

Symptomatic cardiac sarcoidosis can relapse when corticosteroids are tapered in as high as 75% of individuals.74 Several immunosuppressive agents can reduce the lowest effective corticosteroid dose, including methotrexate, mycophenolate, azathioprine, infliximab, adalimumab, and rituximab.75–78 Initial combination therapy of corticosteroids with a steroid-sparing agent can be considered in severe clinical presentations or in individuals intolerant of moderate to high doses of corticosteroids. Although there is emerging interest in the routine upfront use of combination corticosteroids with steroid-sparing agents, data are lacking, and a recent survey of CS experts found no consensus on the combination approach.1

In a tiered approach to treatment (Figure 3), individuals with relapse or ongoing inflammation after corticosteroids would receive a second-line agent (methotrexate, mycophenolate, azathioprine, or leflunomide) in combination with corticosteroids. If there is evidence of ongoing inflammation on follow-up FDG-PET, then tumor necrosis factor-α–targeted therapy with infliximab or adalimumab can be considered as a third-line agent. Tumor necrosis factor-α–targeted therapy should be used cautiously in individuals with HF with reduced ejection fraction and New York Heart Association class III to IV symptoms because prior trials investigating these agents in HF suggested potential harm in patients with HF (keeping in mind that these studies were not specific to individuals with CS-related cardiomyopathy).79 For this reason, individuals with CS and cardiomyopathy on these agents should undergo echocardiographic monitoring and volume assessment at regular intervals after initiation.

The response to treatment is measured in 2 ways: (1) improvement or resolution of the clinical presentation of arrhythmias, heart block, or HF and (2) reduction in the degree of active granulomatous inflammation in the myocardium. Although there is no perfect method to assess the degree of inflammation, cardiac FDG uptake correlates well with clinical evidence of active CS.80,81 Although the optimal timing and frequency of surveillance FDG-PET scans during active treatment while immunosuppression therapy is being adjusted are not well established, 3- to 6-month intervals are typically used.1 If there is clinical resolution but persistence of inflammation on FDG-PET imaging, the decision to continue treatment is individualized on the basis of multiple factors, including the severity of previous manifestations of CS, the risk of a poor outcome should an adverse event occur, the risk of ongoing or increased use of immunomodulatory agents, and the extent of the FDG-PET scan abnormalities. Once patients are well controlled on minimally tolerated immunosuppression dosing, various approaches to surveillance for disease recurrence can be pursued, including cardiac rhythm monitoring, echocardiography, and FDG-PET.

Management of Cardiomyopathy

Management of sarcoidosis-related cardiomyopathy requires a tailored approach based on the specific HF pathophysiological phenotype. These include LV systolic dysfunction, predominant RV systolic dysfunction, or HF with preserved LVEF, which can result in restrictive physiology in advanced cases of reduced ventricular compliance.

Although HF guideline-directed medical therapy has not been prospectively studied in individuals with CS cardiomyopathy, the benefits of these medications are extrapolated from existing studies in individuals with HF.82 These agents include β-blockers, renin-angiotensin blockade including angiotensin receptor neprilysin inhibition, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 inhibitors for managing LV dysfunction. For individuals with HF with preserved LVEF, sodium-glucose cotransporter-2 inhibitors can be used. Diuretics should be used for symptomatic management of volume overload.

When there is concern for acute inflammation, as in myocarditis, exercise restrictions are recommended by some according to established consensus recommendations.83

Advanced HF Therapies

Despite immunosuppression and HF guideline-directed medical therapy, some individuals will develop progressive HF from CS.17,84 Advanced HF therapies such as durable mechanical circulatory support or heart transplantation may be considered.85,86 There are several sarcoidosis-specific considerations when individuals with CS are evaluated for advanced HF therapies.87 First, individuals should be evaluated for the degree of extracardiac sarcoidosis organ involvement that may affect posttransplantation survival, quality of life, and rehabilitation efforts. Second, individuals may have preexisting immunosuppression-related end-organ complications such as diabetes, risk for perioperative adrenal insufficiency, and poor wound healing.

For those in whom an LV assist device (LVAD) is considered, the degree of RV involvement, arrhythmic risk, and infection risk of immunosuppression should be evaluated. For example, predominant RV failure, restrictive cardiomyopathy, or high VA burden may be less amenable to durable LVAD therapy and warrant specific bridge-to-transplantation strategies that include biventricular mechanical support.88

Compared with other cardiomyopathies, individuals undergoing heart transplantation for CS have similar or better outcomes according to United Network for Organ Sharing registry analyses.86,89 Limited data exist on the long-term outcomes of mechanical circulatory support in individuals with CS.86,90 It should be noted that despite increasing awareness and diagnosis of CS, the diagnosis of sarcoidosis frequently is unrecognized until examination of native heart tissue at the time of LVAD or transplantation,91,92 with clinical misclassification in up to 66% of individuals (most often as dilated cardiomyopathy).93

Posttransplantation or post-LVAD management includes ongoing immunosuppression therapy and monitoring for systemic sarcoidosis. Limited survey experience indicates that most programs maintain heart transplant recipients with explantation-confirmed sarcoid cardiomyopathy on prednisone to mitigate the risk of CS recurrence in the allograft.94,95 Continued collaboration between the multispecialty sarcoidosis team and the advanced HF team is necessary for individuals with CS who undergo heart transplantation or LVAD support.

Arrhythmia Considerations

Arrhythmic manifestations of CS are caused by granuloma formation that results in conduction system abnormalities, atrial arrhythmias, or VA, depending on the anatomic localization, the extent of involvement, and the inflammatory stage.96,97

Conduction System Abnormalities

Conduction system abnormalities are common in CS. At diagnosis, 26% to 43% of individuals have a right bundle-branch block on ECG, and a high proportion of patients with clinically isolated CS present with symptomatic high-grade or complete heart block.12 An autopsy study of individuals who died suddenly of CS showed sarcoidosis lesions in the intraventricular septum in 32%, supporting the underlying pathophysiology often evident on MRI or FDG-PET imaging.99 A study of individuals 18 to 60 years of age presenting with complete heart block showed that 34% had undiagnosed CS, indicating that unexplained heart block in young individuals should prompt evaluation for CS.100 It is important to note that individuals with heart block caused by CS have an unusually high risk of VA, heart transplantation, or cardiac death.100 This increased risk of VA and sudden death underlies the Class IIa expert consensus recommendation for implantable cardioverter defibrillator (ICD) implantation in individuals with an indication for pacing therapy.48

Recovery of conduction is variable and observed in 24% to 100% of individuals with CS, likely related to whether heart block is due to inflammation or fibrosis.101 Because reversibility is unreliable, cardiovascular implantable electronic device implantation is recommended for individuals with guideline-based pacing indications,102 even if heart block resolves.48

Atrial Arrhythmias

Atrial fibrillation had a reported prevalence of 32% in 1 single-center study of individuals with CS.103,104 Atrial fibrillation is more common in individuals with CS who have atrial tracer uptake on FDG-PET scan105 or myocardial LGE on CMR (although none of these atrial findings are specific to sarcoidosis). Limited data suggest that immunosuppression may reduce the burden of atrial arrhythmias.104 Anticoagulation and arrhythmia management are the same for individuals without CS, and atrial fibrillation ablation appears to be of similar efficacy in individuals with and those without CS.106

Ventricular Arrhythmia

Ventricular tachycardia and fibrillation are among the most feared complications of CS and may be the primary presentation.107 The underlying mechanism of VA in CS can be autonomic, triggered, or reentry, depending on the inflammatory to fibrotic phase of granulomatous infiltration, and the variability in mechanisms mandates a comprehensive approach to therapy comprising immunosuppression, antiarrhythmic medications, and ablation.48 Antiarrhythmic medications are commonly used in conjunction with immunosuppression or alone when evidence of inflammation is absent.108

In individuals with CS and ventricular tachycardia (VT), ablation studies demonstrate the complex myocardial substrate, even without active inflammation, which can involve the Purkinje system, both ventricles, and intramural or epicardial locations.108,109 In a multicenter study of VT ablation in CS, complete procedural success was achieved in 54% and elimination of VT storm in 82%.109 ICD shocks were reduced from a median of 2 to 0 shocks 30 days after ablation, and antiarrhythmic drug requirements were significantly reduced. However, 46% experienced VT recurrence in 1 to 5 years of follow-up, indicating the challenging arrhythmia substrate and progressive nature of the disease. In select patients, cardiac sympathetic denervation can be considered for refractory VAs.110 If refractory VAs persist after all interventions are exhausted, heart transplantation should be considered.

Cardiac Implantable Electronic Device Therapy for Sudden Cardiac Death

It is important to note that risk stratification for sudden cardiac death is nuanced, and risk may evolve in unpredictable patterns. Potential risk factors include syncope, heart block, myocardial scarring on PET or cardiac MRI, and inducible sustained VA at electrophysiology study.111 Although patients with LVEF ≤35% should be considered for ICD implantation, patients with mildly or moderately reduced and even normal LVEF can be at increased risk.60,112 LGE on MRI is a risk factor for VT and death and is an independent predictor separate from LVEF. In a large study of 205 patients, the rate of VT or death per year was 20-fold higher in patients with LGE compared with those without LGE (4.9% versus 0.2%).60 An evaluation of the performance of guideline recommendations for ICD implantation showed a high annualized event rate for heart block (19.4%) and >5.7% LGE (12%).113 Although abnormal PET findings are associated with an increased risk of VA and death, offering prognostic information beyond LVEF, the optimal index for use is still undetermined.81 A systematic review of electrophysiology study in CS revealed a pooled sensitivity of 0.70 and specificity of 0.93 for predicting adverse clinical outcomes, including subgroup analysis of patients with LVEF >35%.115

In 2014, the HRS proposed recommendations for risk stratification and ICD implantation in patients with CS, which have been widely used48 (Figure 4). In the “2017 AHA [American Heart Association]/ACC [American College of Cardiology]/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death,” ICD implantation in CS has a standard Class I recommendation for secondary prevention (individuals who have sustained VT or cardiac arrest) and a Class I recommendation for primary prevention of sudden cardiac death in individuals who have LVEF ≤35%.111 Additional Class IIa recommendations include individuals with CS and LVEF >35% who have syncope or myocardial scar on MRI60 or FDG-PET,81 indication for permanent pacing,113 or inducible sustained VT at electrophysiology study.111,115

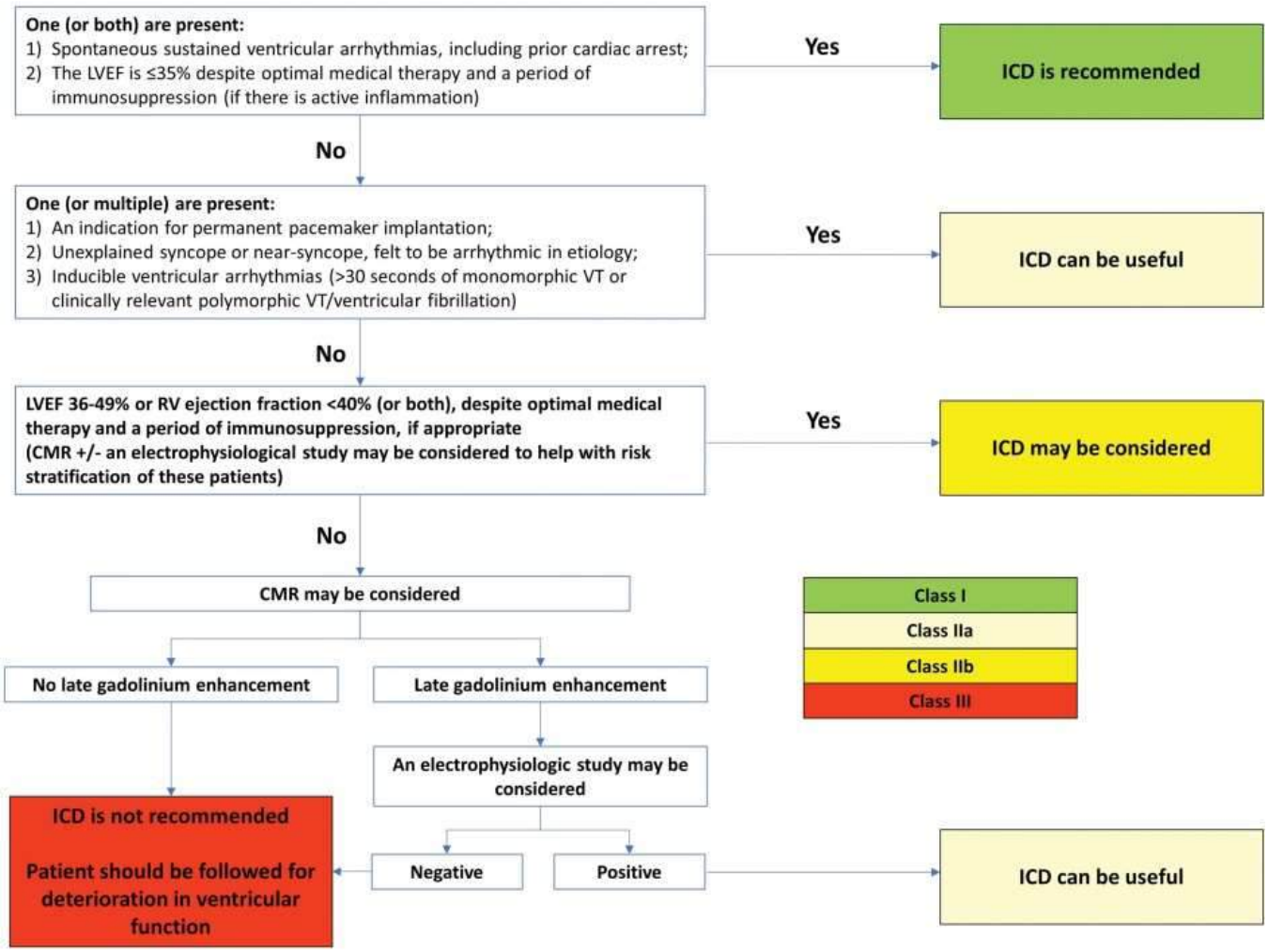

Figure 4. Risk stratification and recommendations for ICD implantation in individuals with cardiac sarcoidosis.* RV indicates right ventricle; and VT, ventricular tachycardia. *Note that the "2017 AHA/ACC/HRS [American Heart Association/American College of Cardiology/Heart Rhythm Society] Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death"111 used a slightly different algorithm. Specifically, in individuals with left ventricular ejection fraction (LVEF) >35% who have syncope or evidence of myocardial scar by cardiac magnetic resonance (CMR) imaging or fluorodeoxyglucose–positron emission tomography or have an indication for permanent pacing, implantation of an implantable cardioverter defibrillator (ICD) is a Class IIa recommendation. In addition, an electrophysiological study in individuals with LVEF >35% is reasonable for additional risk stratification (Class IIa). Adapted with permission from Birnie et al.48 Copyright © 2023 Elsevier.

Multidisciplinary Care of the Patient With CS

The multisystem involvement of sarcoidosis warrants a multidisciplinary team approach for accurate diagnosis, treatment, and comprehensive care.116–118 Chronic, refractory, severe, and life-threatening cases of CS, particularly in individuals with cardiac, pulmonary, and neurological manifestations, carry high morbidity and mortality. These individuals should be referred to a subspecialist or subspecialty center for comprehensive management.119 Indications for specialty referral include (1) diagnostic uncertainty, (2) the need for second- or third-line immunosuppression agents for refractory disease, and (3) severe cardiac manifestations such as recurrent VT or end-stage HF.

The multidisciplinary team may comprise an advanced HF cardiologist, electrophysiologist, advanced cardiac imager, pulmonologist, rheumatologist, and other extracardiac organ–specific specialists such as a neurologist or ophthalmologist, as well as advanced practice professionals, including nurse practitioners, and pharmacists.119,120 Pulmonologists are integral because lung involvement is observed in >90% of individuals with sarcoidosis.121 Rheumatologists and other extrapulmonary organ–specific medical specialists provide expertise in diagnosis and therapies.87,121 Pharmacists help mitigate polypharmacy and manage drug interactions and side effects.121 Nurse practitioners may assist in managing chronic disease manifestations.87,118 Social workers can assist with managing caregiver burden attributable to the chronic nature of CS. In cases of refractory CS requiring advanced HF therapies, input from cardiac surgery experts is important.

FUTURE DIRECTIONS

There are significant unmet needs in the optimal diagnostic and management strategies in sarcoidosis. Although several diagnostic algorithms exist, accurate noninvasive diagnosis is not yet established. Whether emerging multimodality imaging and radiomic techniques combined with clinical and laboratory testing will improve specificity for distinguishing CS from other conditions and measuring CS activity remains to be seen. There is also a dearth of high-quality evidence supporting immunomodulation strategies in CS. Unanswered questions include timing, choice, and duration of therapy; the role of first-line monotherapy compared with combination therapy; and the optimal sequencing of immunosuppression for cases of persistent inflammation. We need higher-quality evidence to guide the use of these therapies, which may be expensive and have potential for harmful side effects. Furthermore, it remains unclear whether we should treat cases of asymptomatic cardiac involvement manifest with myocardial inflammation but no clinically relevant cardiac dysfunction or arrhythmias. Future advancements in CS treatment should include targeted, biologically plausible therapies. Multi-institutional collaborations are needed to address these gaps in knowledge.

CONCLUSIONS

The increasing recognition of CS provides the opportunity to initiate effective therapies and perform systematic case ascertainment. A high index of clinical suspicion is paramount to identify a unifying diagnosis rather than only addressing clinical manifestations of HF or arrhythmias. From a clinician's perspective, ongoing educational efforts are essential to increase awareness. Multidisciplinary collaboration is necessary to ensure accurate diagnosis and provide the best care possible for individuals with CS. Because of the many gaps in knowledge that persist with CS, randomized clinical trials should be pursued to address whom and when we should treat and which treatment strategy is preferred and to better understand the optimal duration of treatment.

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