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MINI-REVIEW

Pathophysiological Gaps, Diagnostic Challenges, and Uncertainties in Cardiac Sarcoidosis

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ABSTRACT: Cardiac sarcoidosis can mimic any cardiomyopathy in different stages. Noncaseating granulomatous inflammation can be missed, because of the nonhomogeneous distribution in the heart. The current diagnostic criteria show discrepancies and are partly nonspecific and insensitive. Besides the diagnostic pitfalls, there are controversies in the understanding of the causes, genetic and environmental background, and the natural evolution of the disease. Here, we review the current pathophysiological aspects and gaps that are relevant for future cardiac sarcoidosis diagnostics and research.

Key Words: cardiac inflammatory disease ■ cardiac sarcoidosis ■ myocarditis ■ sarcoidosis diagnostic criteria

Cardiac sarcoidosis (CS) is a granulomatous inflammatory disease of the heart that is characterized by a patchy distribution almost invariably involving the septum.[1] Inflammation, fibrosis, and deterioration of the cardiac function are important features of CS. The course and the severity of the disease are variable, and the clinical presentation can resemble almost any cardiomyopathy.[2] Therefore, the key to diagnosis is the awareness and the careful interpretation of symptoms, laboratory and imaging findings that may be indicative of CS. Although confirmation of the diagnosis requires histological evidence of noncaseating granulomas, the sensitivity of endomyocardial biopsy is relatively low because of the patchy and midmyocardial distribution of the noncaseating (ie, nonnecrotizing) inflammation.[3] Recognizing the low sensitivity of the current criterion standard test for CS, different working groups proposed combinations of histological and clinical criteria to determine the probability of CS and to guide the immunosuppressive therapy.[4]

The recognition of CS as an important cause of heart failure and arrhythmias fostered extensive experimental and clinical research during the past years. The main cell types, chemokines, and signal pathways that participate in the inflammation and fibrosis have been identified.[5] However, the triggers that start or curb the inflammation, and the mechanisms of healing or transition to a fibrotic stage still are not well understood.[5] Also, the role of environment and how it interacts with the genetic background are a matter of ongoing research. Because of the rising number of scientific publications and the increasing attention to CS, we decided to contemplate a short review that focuses on the current knowledge gaps in CS research (Figure 1).

IS THERE A DEFINITIVE DIAGNOSTIC ALGORITHM FOR CS?

What Is Known

Several diagnostic algorithms for CS make use of electrocardiographic criteria, different imaging modalities, and the response to immunosuppressive therapy to

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Nonstandard Abbreviations and Acronyms

CS	cardiac sarcoidosis
PET-CT	positron-emission tomography–computed tomography

secure the diagnosis and at the same time recognize the low diagnostic yield of the endomyocardial biopsy[6–9] (Table 1). These multiple diagnostic tools partly allow diagnosis and treatment of CS in the absence of a positive endomyocardial biopsy. As pointed out in recent publications, the same person may fulfill the criteria to diagnose CS in 1 score but may fail to do so in another.[4,10] Classifying patients as having CS can be especially difficult in borderline cases where some criteria are met in 1 score but not fulfilled or nonexistent in another.

There are no specific diagnostic findings for CS, but some occur frequently:

1. ECG: signs of conduction disturbance (higher-degree atrioventricular block), premature ventricular contractions, or ventricular tachycardia.[10,11]
2. Echocardiography: reduced regional strain values, segmental postsystolic contraction, hypertrophy, septal thinning, and delayed time to peak strain.[12]
3. Cardiovascular magnetic resonance imaging: multifocal late-gadolinium enhancement with involvement of the interventricular septum, left lateral free wall, and right ventricle.[1,13]
4. Positron-emission tomography (F18-fluorodeoxyglucose-PET-computed tomography [CT]): focal or focal on diffuse F18-fluorodeoxyglucose uptake, if possible in combination with myocardial perfusion imaging.[13,14]

All these findings reflect the severity and the recurring nature of the inflammation in CS, which explain the fluctuations (clinically active or silent disease) and the plethora of symptoms and imaging findings in the same patient over the course of disease (Figure 2). In addition, the limitations and suggestions for improvement of the aforementioned diagnostics need to be taken into account (eg, influence of different fast protocols from prior F18-fluorodeoxyglucose-PET-CT studies that lead to different myocardial background uptake suppression[15] and

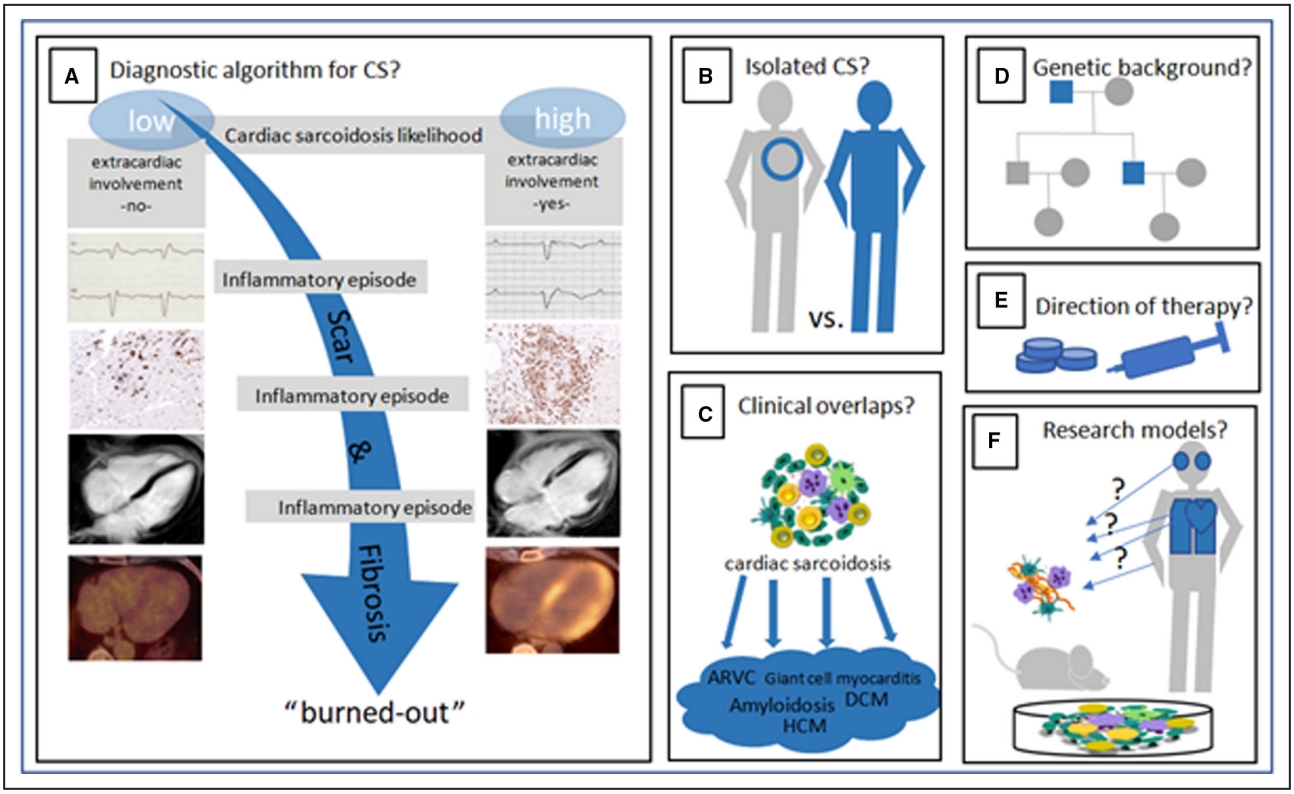

Figure 1. Current knowledge gaps in cardiac sarcoidosis.
A, Is there a definite diagnostic algorithm for CS? (**B**) Is there an isolated CS phenotype? (**C**) Is the cardiac noncaseating granulomatous inflammation a unique feature of cardiac sarcoidosis? (**D**) Is there a genetic background that predisposes to CS? (**E**) How can the treatment of CS be directed? (**F**) Which models are useful to study CS? ARVC indicates arrhythmogenic right ventricular cardiomyopathy; CS, cardiac sarcoidosis; DCM, dilated cardiomyopathy; and HCM, hypertrophic cardiomyopathy.

Table 1. Comparison of Present Criteria in Expert Consensus Statements and Guidelines

	JCS[9]	HRS[7]	WASOG[8]
Histological diagnosis of CS			
EMB with noncaseating granulomas	x	x	X
Clinical diagnosis of CS			
Histological diagnosis of extracardiac sarcoidosis mandatory for clinical diagnosis		X	x
Mobitz type II 2nd-degree heart block or 3rd-degree heart block	x	X	x
Unexplained sustained (spontaneous or induced) VT	x	X	x
Patchy uptake on dedicated cardiac PET (pattern consistent with CS)	x	X	x
Late gadolinium enhancement on CMR (pattern consistent with CS)	x	X	x
Positive gallium uptake (pattern consistent with CS)	x	X	x
Steroid ± immunosuppressant-responsive cardiomyopathy or heart block		X	x
Unexplained reduced LVEF <40%		X	x
Defect on perfusion scintigraphy or SPECT scan	x		x
T2 prolongation on CMR			x
Reduced LVEF in the presence of other risk factors			x
Basal thinning of the ventricular septum or abnormal ventricular wall anatomy (ventricular aneurysm, thinning of the middle or upper ventricular septum, regional ventricular wall thickening)	x		
Abnormal ECG findings (ventricular arrhythmias [nonsustained VT, multifocal or frequent PVCs], bundle branch block, axis deviation, abnormal Q wave)	x		
Atrial dysrhythmias			x
EMB with monocyte infiltration, moderate or severe myocardial interstitial fibrosis	x		

CMR indicates cardiovascular magnetic resonance; CS, cardiac sarcoidosis; EMB, endomyocardial biopsy; HRS, Heart Rhythm Society; JCS, Japanese Circulation Society; LVEF, left ventricular ejection fraction; PET, positron-emission tomography; PVCs, premature ventricular contractions; SPECT, single-photon emission computed tomography; VT, ventricular tachycardia; and WASOG, World Association of Sarcoidosis and Other Granulomatous Diseases.

electroanatomical mapping-guided biopsy to enhance diagnostic yield).[16]

Awareness of CS is especially important in patients presenting with sudden cardiac death. Current data point to a 10.3% incidence of fatal or aborted sudden cardiac death and 24.6% with sudden cardiac death or sustained ventricular tachycardia as the first event in a cohort of patients with definite or probable CS in 5 years.[17]

What Is Unknown

Since the endomyocardial biopsy remains frequently negative, the diagnosis relies on clinical criteria only in a significant number of cases. Data about outcome of patients meeting only the clinical diagnostic criteria, usually labeled as "suspected CS," in comparison to histologically confirmed diagnosis, are scarce,[1] and whether both groups have a comparable natural evolution without immunosuppressive therapy is currently unknown.[18,19]

DOES ISOLATED CS EXIST?

What Is Known

Myocardial granulomatous inflammation without an extracardiac involvement, the so-called "isolated CS" phenotype, has been a subject of discussion for over 50 years,[20,21] contradicting the observations of sarcoidosis as a systemic inflammatory condition and suggesting a high rate of unrecognized or subclinical extracardiac foci. Possible explanations for a clinically isolated cardiac manifestation have been discussed by Birnie and colleagues,[21,22] who assumed the following:

1. Extracardiac lesions are, although present, not detected by CT or PET-CT.[23]
2. Extracardiac lesions form at a later stage of disease.[24]
3. Disease progress leads to fibrosis without detectable inflammation.[25]
4. The diagnosis of CS is wrong.[26]

Although Kupari and colleagues argue that invisible extracardiac granulomas are clinically irrelevant,[27] it is important from a pathophysiological point of view to understand whether or not a truly isolated cardiac phenotype exists. If we assume the existence of isolated CS, we should stipulate the presence of a tissue-specific myocardial predisposition as well as the nature of CS as a "second hit" disease in analogy to other acquired cardiomyopathies, such as alcoholic-induced dilated cardiomyopathy[28] or acquired long QT syndrome[29] showing classical mutations in genes encoding different myocardial proteins. On the other hand,

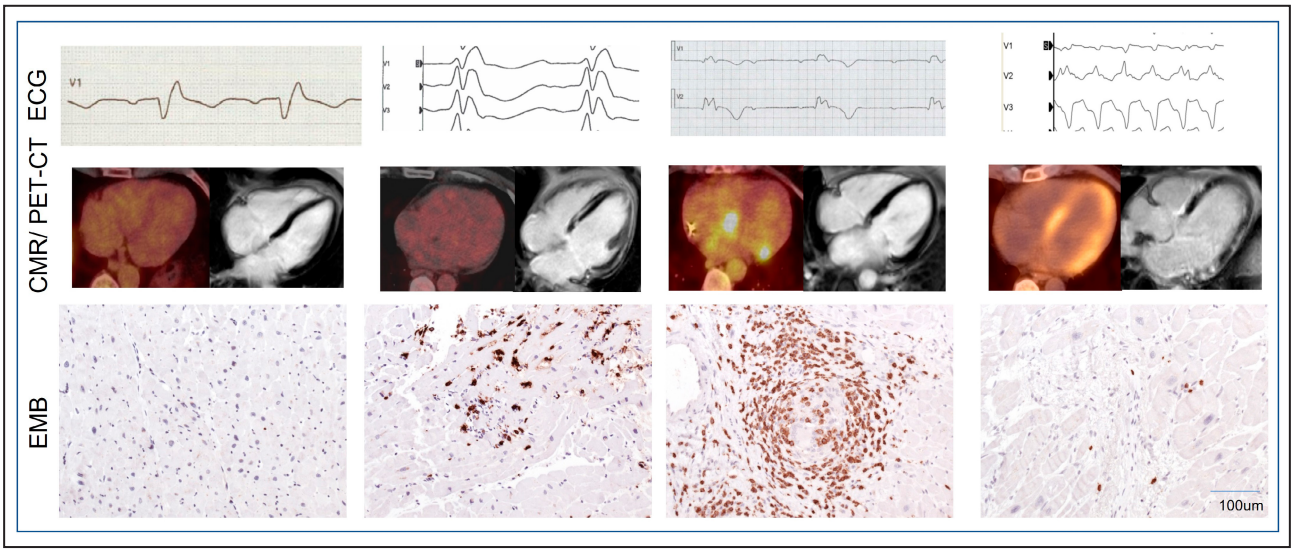

Figure 2. Examples of diagnostic findings in patients with CS.
Fulfillment of current diagnostic criteria may vary because of different points in time of presentation (subclinical, active, quiescent, or burned-out disease). All of the following findings are associated with patients with cardiac sarcoidosis and positive endomyocardial biopsy. Upper row (left to right): incomplete right bundle branch block, right bundle branch block, atrioventricular block III, and ventricular tachycardia. Middle row (left to right): no FDG uptake in PET-CT and no late gadolinium enhancement in CMR, no FDG uptake in PET-CT and late gadolinium enhancement in CMR, FDG uptake in PET-CT and no late gadolinium enhancement in CMR, and FDG uptake in PET-CT and late gadolinium enhancement in CMR. Bottom row (left to right): normal finding (sampling error), CD3+ T lymphocytes in lymphocytic myocarditis, CD3+ lymphocytes in noncaseating granuloma, and isolated CD3+ T lymphocytes and fibrosis; all images ×200. CMR indicates cardiovascular magnetic resonance; CS, cardiac sarcoidosis; EMB, endomyocardial biopsy; FDG, F18-fluorodeoxyglucose; and PET-CT, positron-emission tomography-computed tomography.

there are observations supporting the theory of misclassification, such as the report by Wiltshire and colleagues that showed recurrent isolated CS in a transplanted heart,[30] an unlikely finding in an isolated cardiac condition.

What Is Unknown

The number of reports about isolated CS is growing, despite the progress in multimodality imaging.[2,31,32] Moreover, there are multiple reports about isolated extracardiac sarcoidosis (eg, the spleen[33] or isolated hepatic sarcoidosis).[34] Whether all these represent misclassified cases with clinically nondetectable systemic disease is not clear to date. Findings of noncaseating granulomas in autopsies of people who died of other cardiac conditions question the role of unrecognized systemic inflammation in the cardiac pathophysiology.[35]

IS THE CARDIAC NONCASEATING GRANULOMATOUS INFLAMMATION A UNIQUE FEATURE OF CARDIAC SARCOIDOSIS?

What Is Known

Diagnosis of CS in histopathology is currently defined by "myocarditis with non-necrotizing granulomas with macrophages and multinucleated giant cells, surrounded by fibrosis and a lymphocytic infiltrate."[36] Although not completely understood, the initiation of the inflammatory process appears to be a combination of genetic predisposition and environmental triggers. The current understanding of pathophysiologic pathway of cardiac granuloma formation is depicted in Figure 3 (according to Drent et al[5] and Kato et al[37]).

The clinical presentation of CS can mimic various cardiomyopathies such as amyloidosis,[38] hypertrophic cardiomyopathy,[2] or arrhythmogenic right ventricular cardiomyopathy.[39,40] However, the histological alterations in sarcoidosis show similarities to giant cell myocarditis.[41] The presence of cardiac noncaseating granulomas has been described as incidental findings and in patients with evidence for other cardiomyopathies (Table 2).[42,43] Thus, it is likely that the noncaseating granulomatous inflammation is the main pathophysiological pathway initiated in patients with sarcoidosis but is not unique for sarcoidosis.

What Is Unknown

To date, the histopathological definition of CS is usually based on histology, immunohistology, and molecular viral analysis with numerous protocols for immunostaining and classification of immune cell subtypes similarly to other types of myocarditis.[44] The interaction of many different subtypes of immune cells that interact over time to form the granuloma poses difficulties for

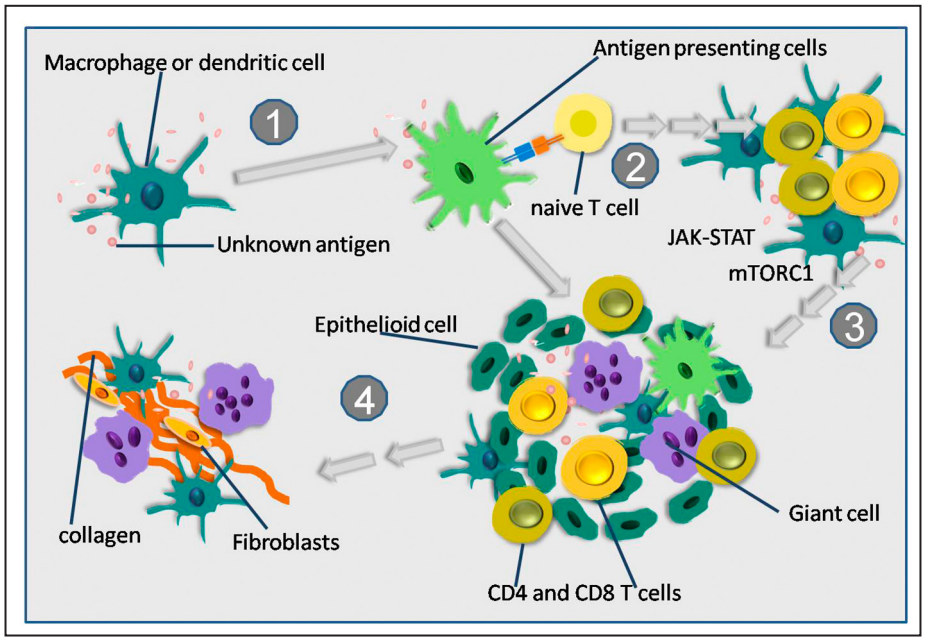

Figure 3. General proposed concept of granuloma formation in sarcoidosis.
(1) Presentation of an unknown antigen by dendritic cells and macrophages to lymphocytes. (2) Recruitment of naive T cells and conversion to T helper 1 cells is followed by lymphocytic infiltration, accumulation of dendritic cells and macrophages caused by cytokines (ie, interleukin (IL-2) and interferon-γ. (3) M1 macrophages turn into epithelioid cells, epithelioid cells fuse to form multinucleated giant cells, granuloma formation including activated M1 macrophages, multinucleated giant cells, CD4+ helper T cells, and CD8+ cytotoxic T cells. (4) Transition from Th1 to Th2 predominance, induction of M2 macrophages, M2 macrophages potentially produce cytokine signals that stimulate fibrosis.

understanding the pathogenesis of a noncaseating granulomatous inflammation. In the future, the application of microRNA profiling,[45] transcriptome-based biomarker analysis, single-cell-sequencing, and analysis of anti-heart and anti-intercalated disc autoantibodies[46] may be helpful to define subtypes of noncaseating granulomatous diseases.

IS THERE A GENETIC BACKGROUND THAT PREDISPOSES TO CS?

What Is Known

The hypothesis for a genetic susceptibility to sarcoidosis is supported by studies on homozygotic twins, higher prevalence in certain ethnic groups, and familial clustering.[47,48] In a large national cohort, the risk of developing the disease was up to 4-fold higher in first-degree relatives of patients with sarcoidosis.[49] Like many multifactorial diseases, predisposition to CS most probably has a complex genetic architecture. Associations with loci of the human leukocyte antigen gene, with annexin A11, NOTCH4, and the X-linked inhibitor of apoptosis-associated factor 1 gene have been described for sarcoidosis.[50] A homozygous point mutation in exon 5 of the butyrophilin-like 2 gene has been found in a patient with isolated CS,[51] and a small cohort study identified the association of the −857C/T and the −308G/A tumor necrosis factor-α polymorphisms with cardiac involvement of patients with sarcoidosis.[52] These gene loci are implicated in pathways of apoptosis and T-cell activation. Of note, the aforementioned studies showed some interesting associations but no causal relationship.

What Is Unknown

Although several genetic variations have been associated with CS in the past, it is unlikely that a single gene defect can cause predisposition to cardiac granulomatous inflammation. Nevertheless, there are data demonstrating significant inflammatory response in certain monogenic cardiomyopathies. Recently, Smith and colleagues observed an abnormal F18-fluorodeoxyglucose -PET activity in patients with an arrhythmogenic right ventricular cardiomyopathy phenotype caused by a pathogenic desmoplakin mutation, suggesting some overlap between the monogenic cardiomyopathies and myocarditis.[26] Unfortunately, in many cases of primary cardiomyopathy, the diagnosis relies on a combination of clinical traits and a positive family history, without making use of the possibilities of

Table 2. There Are Several Cardiac Diseases With Reported Noncaseating Granulomas. The Distinct Histopathological Features Are Depicted Along With References

Disease or clinical status	Histopathologic features	Refs.
ARVC	Cardiac fibrofatty infiltration and concomitant cardiac or extracardiac noncaseating granulomata	35
AL amyloidosis	Cardiac deposition of Ig lambda II light chain and noncaseating granulomas	42
Giant cell myocarditis	Mixed inflammatory infiltrate with histiocytes, histiocyte giant cells, and lymphocytes, but in second biopsy well-formed, circumscribed, nonnecrotizing granulomas	41
Dilated cardiomyopathy, possible "end-stage" cardiac sarcoidosis	Dilated LV cavity, former presence of noncaseating granulomas, no granulomas at explant of native heart but extensive scarring	25
Incidental finding	Nonnecrotizing granulomatous inflammation in excised valve tissue, no systemic disease identified	43

AL amyloidosis indicates amyloid light chain or primary amyloidosis; ARVC, arrhythmogenic right ventricular cardiomyopathy; and LV, left ventricular.

genetic testing. The same applies for patients with CS in whom systematic testing for allelic variants in genes encoding the proteins of sarcomere, Z-disc, cell-to-cell adhesion, or calcium handling are missing.[53] This poses the question of how some of these known allelic variants can influence the prognosis of the disease and whether they can predispose to a specific phenotypic expression of CS.

HOW CAN THE TREATMENT OF CS BE DIRECTED?

What Is Known

The current therapeutic options for CS include immunosuppressive agents, heart failure medication, cardiac electronic implantable devices, and ablation.[54,55] Not only is the treatment goal to stop active inflammation but also to prevent recurrence of inflammatory episodes and to reduce myocardial damage and prevent complications.

Experts advocate starting immunosuppressive therapy if signs of cardiac involvement are present.[6,54] These include arrhythmias, conduction disturbances, and heart failure symptoms, although precise criteria are lacking. Current retrospective studies and case series recommend steroid-sparing regimens with the use of methotrexate, azathioprine, mycophenolate mofetil, leflunomide, cyclophosphamide, infliximab, and adalimumab.[54,56] Initiation of immunosuppressive treatment calls for predefined criteria for therapeutic response. Currently, no biomarker, single imaging technique, or clinical parameter has been validated to direct the long-term treatment strategy. However, if initially abnormal, the following PET-CT-based follow-up regimen has been suggested by Birnie and colleagues[57]:

1. PET-CT baseline and after 3 months of treatment
2. If no abnormal uptake: PET-CT 3 months after stopping treatment
3. If no relapse: evaluation at 6, 12, 24, 36 months (clinical, ECG, and echocardiogram)
4. If relapse occurs: intensification of treatment/more frequently PET-CT

What Is Unknown

Although the use of immunosuppressive drugs is reasonable in the context of the inflammatory character of CS, one of the most important downsides is the lack of prospective, placebo-controlled data showing better outcomes after treatment with immunosuppressives.[6,54,56] Severe cardiac manifestations may represent an end-stage fibrotic remodeling that is not reversible with immunosuppressive drugs. In addition, the overall clinical benefit of immunosuppressive therapy in patients without life-threatening symptoms (eg, premature ventricular contractions) is even more arguable.[5] Current recommendations on the induction corticosteroid dose and the use of steroid-sparing agents are not uniform, although high-dose corticosteroids are generally not recommended.[6,54,56] It is also unknown which tool is the most appropriate one for assessment of the therapeutic response. Different strategies based on the clinical evolution and advanced imaging techniques have been proposed. Finally, the duration of immunosuppressive therapy and whether it should be discontinued after achieving a remission or be continued indefinitely is also a matter of future research.[56]

WHICH MODELS ARE USEFUL TO STUDY CS?

Animal and in-vitro models can be useful to fill the knowledge gaps in the complex pathophysiology of CS and to identify possible targets for new treatments or diagnostic biomarkers. However, development of animal models in sarcoidosis is in an early stage and the in-vivo models do not replicate all components of the histological features.

What Is Known

In animals, spontaneous sarcoidosis-like granuloma formation has been described in horses,[58] dogs,[59] and brown Norwegian rats.[60] Artificial animal models have been created using bacteria or bacteria-related agents, microparticles, or gene-knockout models but without sufficient validation against human noncaseating granulomas.[61]

As discussed by Locke and colleagues, the problem with unstimulated peripheral blood mononuclear cell–based models of patients with sarcoidosis is that unstimulated immune cells do not entirely replicate granuloma formation.[61] On the other hand, diseased tissue does not allow understanding of the early disease mechanisms but reflects the later stages of the disease.[61]

The Kveim-Siltzbach test, formerly labeled as "enigmatic",[62] has been used for several decades in the diagnosis of sarcoidosis, but was abandoned because of lack of standardization and, more importantly, lack of pathophysiologic understanding. Initially described by Kveim in 1941, the test was performed using a sarcoid spleen- or lymph node–derived reagent that was inoculated into the skin of patients with suspected sarcoidosis, leading to granulomatous cutaneous response in ≈4 weeks. The sensitivity of the test was described as high as 80%. Despite extensive research, the culprit antigen, cell subtype, or cytokine responsible for Kveim reaction has not been identified and the test was abandoned when the *Lancet* published the Moratorium on the Kveim test because of fear of Creutzfeld-Jacob disease or sarcoidosis transmission.[63] Although the Kveim test no longer plays a role as a diagnostic test, its effectiveness to induce sarcoid granulomas in humans makes it suitable as a research tool.[64,65]

What Is Unknown

Because current pathophysiological models do not entirely reproduce the clinical human disease, it might be the right moment to step back and re-evaluate some pitfalls of the previous research. Although the general principles of granuloma formation were studied in the past, the specific mechanisms of granuloma formation in different organs are not clear. In addition, most of the prior models focused on noncaseating granulomas in the lungs. Systematic studies comparing cell composition of granulomas in different organs of the same patient are lacking to date. Of note, the role of resident and recruited macrophages in the heart in homeostasis and under disease conditions, and immune cell heterogeneity in general, are still the subject of ongoing research.[66]

In summary, most likely only a complex approach taking into account the genetic background, environmental factors, tissue-specific immune responses exhibiting different intensity, and recruitment of different cell types will be successful to model this complex disease. Prospective registry data with deep phenotyping of patients will be important to complement the mechanistic studies.

ARTICLE INFORMATION

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