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Idiopathic giant cell myocarditis and cardiac sarcoidosis

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Abstract Idiopathic giant cell myocarditis (GCM) and cardiac sarcoidosis (CS) are rare disorders that cause cardiomyopathy, often with ventricular arrhythmias or heart block. Infection, autoimmune processes, and genetics have all been implicated in the pathogenesis of these diseases, but the etiology for both diseases is likely a complex multifactorial process. Both GCM and CS are generally progressive despite treatment with standard heart failure and arrhythmia therapies. Making the diagnosis of GCM or CS on initial clinical presentation is possible in only a small percentage of patients, so myocardial tissue diagnosis is required. The use of multiple noninvasive imaging modalities may aid in diagnosis and assessment of response to treatment. Establishing the diagnosis of GCM or CS early is crucial, as tailored immunosuppressive treatment may significantly alter the clinical course of these patients. The prognosis of patients with GCM is poor, while the prognosis for patients with CS varies according to degree of left ventricular dysfunction.

Keywords Myocarditis · Sarcoidosis · Dilated cardiomyopathy · Endomyocardial biopsy · Heart failure

Introduction

Idiopathic giant cell myocarditis (GCM) and cardiac sarcoidosis (CS) are rare disorders that mimic common causes of heart failure and arrhythmias but have distinct prognosis and treatment. Both disorders cause cardiomyopathy, often with ventricular arrhythmias or heart block. Both typically progress despite guideline-based treatment of heart failure and arrhythmias. GCM is usually an acute disease with rapid deterioration over weeks, while CS progresses over months to years. Since our last review of this subject in 2005, [1] advances in noninvasive imaging and endomyocardial biopsy have affected the management of these disorders. Advances in our understanding of the immunopathology of myocarditis suggest potentially more effective immunosuppressive strategies in these specific disorders. The present report minimizes overlap with our prior paper by focusing on these recent and provocative data.

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Nomenclature

In 1905, Saltykow [2] described a case of fatal myocarditis characterized by giant cells associated with widespread inflammation and myocyte necrosis. This was the first published case report of *idiopathic giant cell myocarditis* (GCM). In 1929, Bernstein et al. [3] described a different histologic type of myocarditis in which giant cells were present, but as opposed to GCM, the giant cells were located within noncaseating granulomas and associated with fibrosis rather with lymphocytic infiltrates. This type of myocarditis is now called *cardiac sarcoidosis* (CS) or *idiopathic granulomatous myocarditis*. Until the late 1950s, the terms "giant cell myocarditis" and "granulomatous myocarditis" were used interchangeably by authors to describe myocardial disease in which multinucleated giant cells were present as well as either granulomas (CS) or diffuse inflammatory myocardial infiltrates (GCM) [4]. Since the late 1960s, however, most publications distinguish the well-

organized granulomatous lesions of CS from the diffuse nongranulomatous inflammatory infiltrates of GCM [5].

Epidemiology

GCM

GCM and CS are rare diseases. Autopsy studies conducted a number of years ago in England and Japan reported the incidence of GCM as 23.4 per 100,000 [6] and 6.6 per 100,000, [7], respectively. Since autopsies are not routinely performed on an unselected population, the true incidence is likely lower than these estimates.

CS

The incidence of CS in a clinical population can be estimated from population-based studies of sarcoidosis. Scandinavians have the highest reported incidence rates of sarcoidosis at 50–60 cases per 100,000 [8]. The incidence of sarcoidosis in the Untied States has been estimated at 10.9 per 100,000 in whites and 35.5 per 100,000 in African Americans [9, 10]. The lifetime risk for sarcoidosis in the United States is estimated at 0.85 % in whites and 2.4 % in African Americans [10]. Extrathoracic CS involvement is more common in African Americans than white Americans [11]. Of the 763 patients with symptomatic sarcoidosis enrolled in A Case Control Etiologic Study of Sarcoidosis (ACCESS), only 2.5 % had cardiac involvement, indicating that the risk for individuals developing overt CS is low. However, the rate of CS in an autopsy series of patients who had systemic sarcoidosis is much higher at 25 % [12]. Therefore, most CS probably remains asymptomatic.

A study of 115 cases of GCM and CS in the United States and Japan revealed a slight male predominance (52 and 60 %, respectively), [13] while several other studies from these same countries indicate a female predominance of 60–80 % in CS [14–17]. The average age at presentation is 43 years for GCM patients and 38–51 years for CS patients [18–20].

Etiology and pathophysiology

GCM

GCM likely has multiple causes. Viral infection is the most common cause for lymphocytic myocarditis (LM) in Western Europe and North America and may occasionally trigger GCM as well. Single case reports have suggested that infection with human herpes virus, [21], coxsackie B2 virus [22], and parvovirus B-19 [23] may each play a role in GCM. Alternatively, GCM may be caused by various autoimmune responses triggered by a number of different factors with a common final pathway. Up to 20 % of GCM cases occur in patients with autoimmune disorders, including inflammatory bowel disease. The autoimmune reaction is specific to the myocardium, profound, and sustained. Antibodies that bind cardiac myosin and cross-react with the beta adrenergic receptor may form by molecular mimicry or epitope spreading [24].

Sex differences may play a role in GCM. Preliminary work by Fairweather et al. [141] suggests that testosterone promotes myocarditis, including GCM, through the soluble ST2 pathway. Soluble ST2 levels are higher in male versus female patients with GCM. Increased sST2 levels in male mice correlate with poorer heart function, and male mice develop more severe myocarditis and progress to chronic DCM more often than female mice. If confirmed, these data suggest that the immunopathogenesis of severe myocarditis in males may differ from females. Further investigation is needed to determine whether differences in pathogenesis will impact prognosis or treatment.

CS

The etiology of sarcoidosis remains under investigation but, similar to GCM, is likely a complex multifactorial process. It has been suggested that granulomas are an immunologic response to a specific antigen or antigens associated with infectious, environmental, and occupational clustering [25]. There is considerable variability in incidence and severity of disease based on race and ethnic background, while genetic analysis has also revealed substantial variation.

Similar to GCM, infection has been implicated in CS. Mycobacterial and propionibacterial DNA and RNA have been recovered from sarcoid tissue, [26], and serum samples from patients with sarcoidosis often contain antibodies to mycobacterial antigens [27–29]. Hepatitis C infection has occasionally been associated with sarcoidosis. Most commonly, sarcoidosis is induced due to treatment with interferon-alpha, [30–32] which is known to induce autoimmune responses, but two studies have also reported sarcoidosis in treatment naïve hepatitis C patients [33, 34].

Genetics

GCM

Genetic factors influence susceptibility to giant cell myocarditis in model systems. Shioji et al. [35] reported the incidence, histopathology, and histocompatibility characteristics of 5 inbred strains of rats in which myocarditis was

induced with porcine cardiac myosin. Immune-mediated GCM was induced in Lewis, Dahl (DIR/Eis) (RT-1), and Fisher rats but not in brown Norway rats or a second strain of Dahl rats (DIS/Eis) (RT-1). The disease was most severe in the Lewis rats and seemed to correlate with major histocompatibility complex class II region differences between the strains. Kittleson et al. [36] examined left ventricular samples from two GCM patients harvested during ventricular assist device (VAD) placement and six unused donor hearts using Affymetrix U133A microarrays and found 115 differentially expressed genes between GCM and nonfailing hearts. The majority of upregulated genes were involved in the immune response, primarily the Th1 pathway.

A recent study suggests that altered desmosomal proteins may also play a role in the pathogenesis of GCM associated with ventricular arrhythmias, similar to arrhythmogenic right ventricular cardiomyopathy (ARVC) [37]. Immunohistochemistry was used to analyze junctional proteins in myocardial samples obtained at autopsy or biopsy from patients with GCM, CS, ARVC, and LM. This revealed that plakoglobin expression was diminished at myocardial intercalated disks in GCM, CS, and ARVC, but not in LM (Fig. 1). Neonatal rat myocytes were incubated with various concentrations of cytokines. Cytokines IL-9, IL-12, IL-4, and INFγ, which have been implicated in nongranulomatous inflammation, had no apparent effect on plakoglobin distribution. In contrast, IL-17 and TNFa, both of which are thought to mediate granulomatous myocarditis, caused a marked redistribution of plakoglobin signal from myocardial cell–cell junctional to intracellular sites. These findings suggest potentially important new links between GCM, CS, and ARVC. Further studies are warranted to elucidate disease mechanisms and potentially identify new therapeutic targets.

CS

Multiple genes may have a role in the genetic predisposition for sarcoidosis [25, 38]. In the past decade, human leukocyte antigen (HLA) class II antigens, encoded by HLA-DRB1 and DQB1 alleles, have been associated with distinct sarcoidosis phenotypes with varying results [39–41]. A recent study of 642 sarcoidosis patients and 740 controls from the United Kingdom, the Netherlands, and Japan, however, revealed that distinct sarcoidosis phenotypes have similar genotypes across ethnic groups [42]. No clear HLA associations were found for patients with cardiac involvement in the study. Polymorphisms in multiple cytokines, [43–45] as well as a number of immunoglobulin receptor genes such as butytrophilinlike-2 (BTNL2) [46–48] and toll-like receptors [49] have all been associated with sarcoidosis.

As susceptibility to sarcoidosis seems to depend on a complex interplay of genetic, environmental, and occupational exposures, identifying interactions between specific sarcoidosis-susceptibility genetic loci and environmental and occupational triggers should be a high research priority. To date, the only interaction identified is an association between the HLA-DQB1 sarcoidosis-susceptibility locus and exposure to water damage or high humidity in the workplace [50].

Clinical presentation

Patients with GCM generally present with heart failure symptoms that inexorably progress to death or transplantation despite optimal heart failure treatment (Table 1) [13]. Palpitations, syncope, and even sudden death may be the presenting symptoms, likely due to ventricular arrhythmias or high grade atrioventricular heart block (AVB) (Table 1) [13, 51–53]. In less than 10 % of cases, GCM patients present with heart failure symptoms that progress more slowly or may even be self-limited [13, 54, 55].

Like patients with GCM, patients with CS commonly present with heart failure symptoms (Table 1) [13, 56]. The clinical course of CS, however, is generally more indolent than that of GCM, with symptoms developing over months to years [13]. Patients with CS are more likely to present with syncope and sudden death than patients with GCM (Table 1) [13, 18–20, 56, 57]. Although dilated cardiomyopathy is most frequent, CS occasionally presents as hypertrophic cardiomyopathy [58]. Ventricular aneurysms that do not follow coronary artery distribution sometimes develop and may spontaneously rupture [59, 60]. Pericardial effusion may be present and occasionally results in cardiac tamponade [61].

Conduction abnormalities appear more frequently in CS than in GCM (Table 2) [12, 13, 18–20, 57, 62]. Complete heart block is the most common presenting conduction abnormality, but left or right bundle branch block, all degrees of atrioventricular block and even sinus arrest may occur. Conduction abnormalities may be apparent even though there is no significant evidence of cardiomyopathy.

Ventricular arrhythmias are common in both GCM and CS. The prevalence of ventricular tachycardia or ventricular fibrillation is as high as 42 % in some cohorts (Table 2). Ventricular tachycardia may remain refractory to medical treatment in CS patients [63, 64]. Sudden cardiac due to either ventricular arrhythmias or complete heart block is a feared complication of GCM and CS and, importantly, is the presenting symptom in up to 17 % of CS patients [65]. A recent study from Finland revealed that GCM and CS explain ≥25 % of initially unexplained AVB in patients 18–55 years old who are referred for pacemaker placement [52].

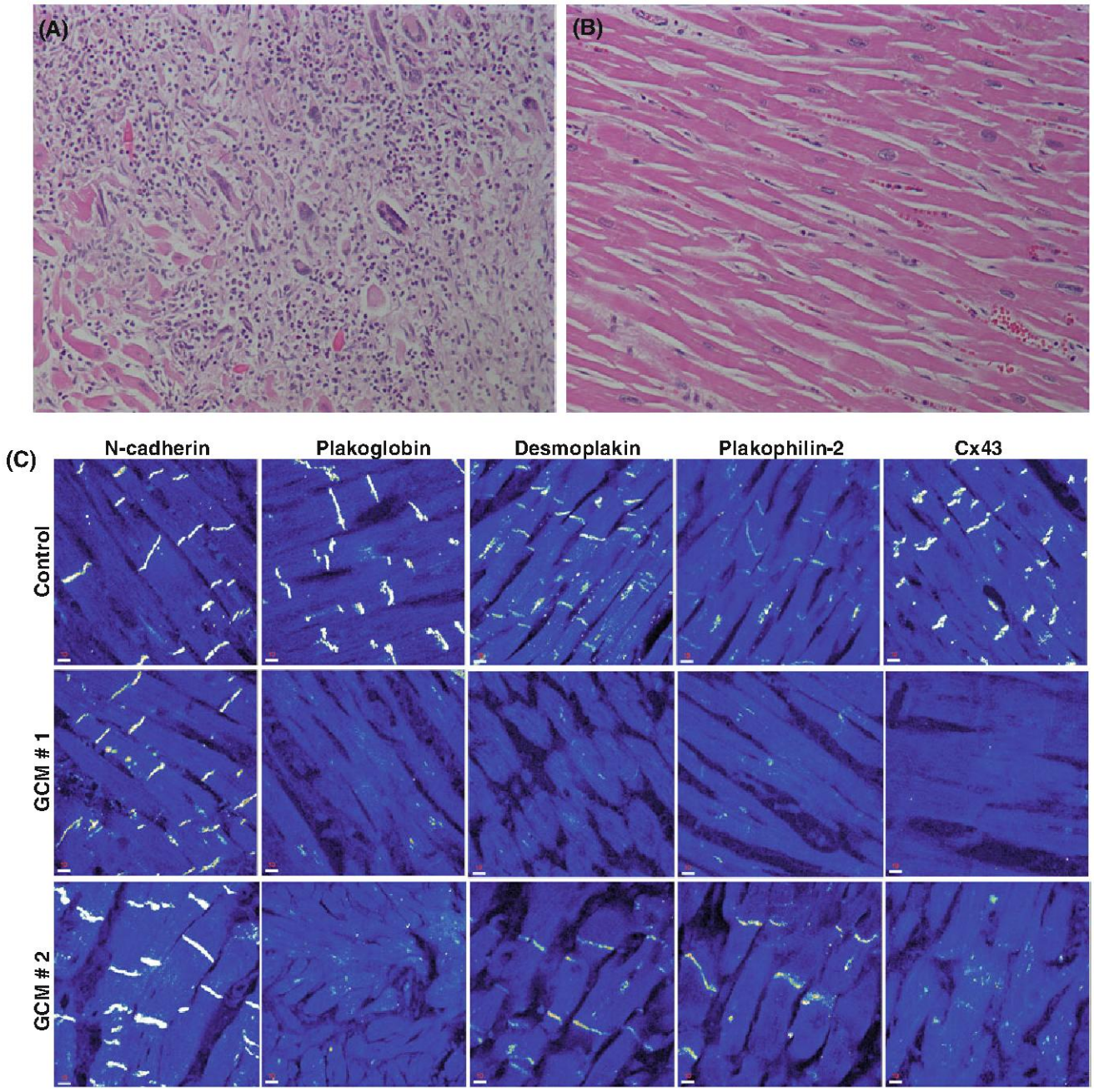

Fig. 1 **a** Microscopic appearance of the myocardium from a patient with cardiac sarcoidosis, showing fibrosis and multinucleated giant cells within granulomatous lesions (Masson trichrome, magnification ×20). **b** Normal-appearing myocardium from the same patient, showing no apparent inflammatory or degenerative changes (Masson trichrome, magnification ×20). **c** Representative confocal immuno fluorescence images of control myocardium and myocardium from a patient with cardiac sarcoidosis clinically masquerading as ARVC and from another patient with pathologically documented cardiac sarcoidosis. Specific immunoreactive signal for plakoglobin was significantly depressed in both cases compared with controls, as was signal for the major gap junction protein Cx43. Expression of other desmosomal proteins, including desmoplakin and plakophilin-2, varied, but signal for the nondesmosomal adhesion protein N-cadherin was always present and indistinguishable from controls. ARVC indicates arrhythmogenic right ventricular cardiomyopathy; Cx43, connexin43. From Asimaki et al. [37] used with permission

Up to 20 % of patients who have suspected CS have ECG changes such as right bundle branch block or ventricular ectopy. Asymptomatic ECG changes are probably the most common CS manifestation, but these should not prompt a search for a rare disease such as CS unless associated with a suggestive clinical presentation.

Table 1 Symptoms in Patients with GCM versus CS at Presentation

Symptom	GCM (%)	CS (%)
Heart failure, nonspecified	75	24–68
Left-sided heart failure	64	40
Right-sided heart failure	3	5
Both-sided heart failure	29	7
Syncope	5	31
Palpitations	11	17–32
Chest pain	19	14
Sudden death	3	5–17

Data from references 13, 18, 19 and 56

Table 2 Conduction abnormalities and arrhythmias in patients with GCM and SC

Conduction abnormality	GCM (%)	CS (%)
Bundle branch block	–	12–61
AVB	15	26–60
1st degree AVB	7	21
2nd degree AVB, Type I	0	0–10
2nd degree AVB, Type II	0	2
Complete heart block	5–8	5–48
Arrhythmias		
Supraventricular arrhythmia	–	5–28
Ventricular tachycardia	14–29	2–42
Ventricular fibrillation	3	5

Data from references [13, 18–20, 56, 57]

Diagnosis

Endomyocardial biopsy

Making the diagnosis of GCM or CS on initial clinical presentation is possible in only a small percentage of patients [66], so myocardial tissue diagnosis is required. Because of the possibly life-threatening complications associated with GCM and the potential for benefit from treatment, early percutaneous or surgical myocardial biopsy is recommended.

GCM and CS are pathologic diagnoses (Fig. 2). The diagnosis of GCM requires a diffuse or multifocal inflammatory infiltrate of lymphocytes and multinucleated giant cells in the absence of granuloma formation [67]. The giant cells are frequently located at the edges of the inflammation and are associated with myocyte destruction and active inflammation [13]. CS is characterized by noncaseating granulomas with limited lymphocyte infiltrate and patchy fibrosis. Giant cells, if present, are usually in the center of follicular granulomas and sometimes extensive [13]. Eosinophils are significantly more common in GCM, while fibrosis is significantly more common in CS.

Extracardiac involvement may or may not be present with either disease. The author (LTC) has seen 5–10 % of GCM cases associated with extracardiac granulomatous inflammation in lymph nodes or the liver, while in one case series, about half the CS cases occurred without clinical evidence of extracardiac involvement [13, 52, 68].

Endomyocardial biopsy (EMB) has proven to be useful for histologic verification of the presence of granulomas in cardiac tissues, as well as for excluding other causes for cardiac disease. The histological differential diagnosis for GCM includes hypersensitivity myocarditis and myocarditis associated with systemic lupus erythematosus or Takayasu's aortitis. The histologic differential diagnosis of CS includes infectious and noninfectious granulomatous diseases such as tuberculous myocarditis, fungal myocarditis, Whipple disease, acute rheumatic heart disease, Wegener's granulomatosis, and foreign body reactions.

GCM

The specificity of right ventricular EMB for both GCM and CS is quite high [69]. The sensitivity of EMB in patients with GCM who present early in the course of fulminant disease is 80–85 %, likely due to the diffuse pattern of endocardial inflammation [70]. In a series of 20 GCM patients with complete clinical data and serial heart tissue specimens (biopsy, explanted heart, or autopsy), the strongest predictor of a negative explanted heart or autopsy specimen was time from symptom onset ($P = .006$) [70]. Thus, early EMB in cases of suspected GCM is warranted.

The role of EMB in the evaluation of cardiovascular disease was addressed in a scientific statement by the American Heart Association in concert with the American College of Cardiology and the European Society of Cardiology [71]. Only two scenarios, one of which described the most common presentation of GCM, received a class I recommendation.

CS

In contrast to GSM, the sensitivity for CS using standard histological criteria is only 20–30 %, likely due to sampling error secondary to the focal nature of myocardial involvement [16]. EMB is a prognostic indicator in patients with CS. A study of 28 patients with initially unexplained cardiomyopathy who underwent EMB revealed that a positive CS result for sarcoid is associated with decreased median survival [69]. The most likely explanation for this finding is that patients with positive biopsies probably have more extensive granulomatous inflammation of the myocardium. In patients where CS is strongly suspected but cardiac biopsy is negative, treatment with immunosuppression may be considered.

The AHA/ACC/ESC Writing Group addressed the role of EMB for evaluation of possible CS. On the basis of expert

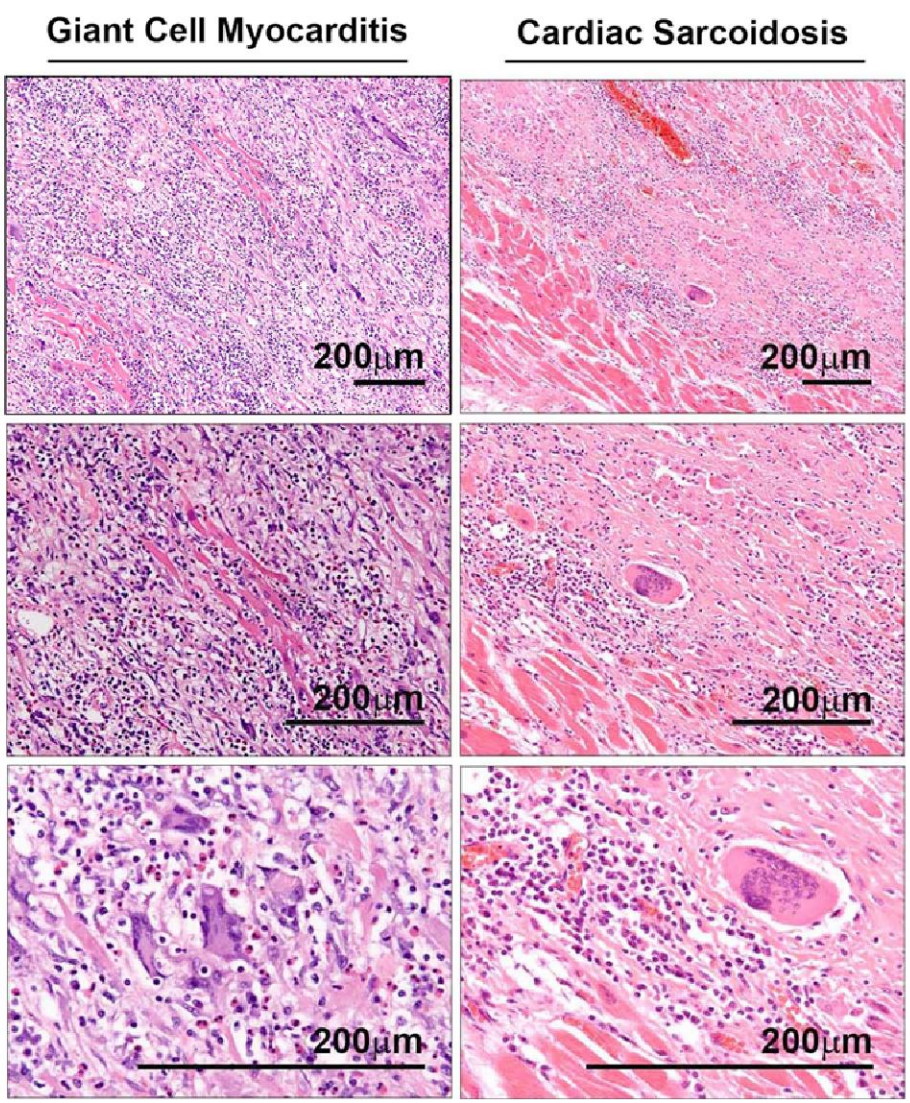

Fig. 2 Endomyocardial biopsy specimens from a patient with giant cell myocarditis (*left panel*) showing giant cells, lymphocytes, histiocytes, cosinophils, and widespread necrosis of myocytes (hematoxylin and cosin) and from a different patient with cardiac sarcoidosis (*right panel*) showing nonnecrotizing granulomas composed of epithelioid histiocytes and giant cells embedded in callagenous stroma surrounded by mononuclear inflammatory cells and fibroblasts (hematoxylin and cosin)

opinion at the time, the role of EMB in this scenario only received a IIa recommendation due to low diagnostic yield relative to potential benefits [71]. Recently, however, a study of 72 young adult patients in Finland with initially unexplained atrioventricular block revealed that CS or GCM was found in 14 (19 %) and 4 (6 %) of patients, respectively [52]. Of these 18 patients, 7 (39 %) experienced cardiac death, cardiac transplantation, or ventricular fibrillation or were treated for sustained ventricular tachycardia over an average follow-up of 48 months. The positive EMB rate in this study was 25 %, suggesting that EMB should probably be recommended in populations at similar risk.

Although EMB can be quite beneficial in establishing the diagnosis of GCM and CS, the risk and costs must be weighed against the potential benefit of initiating treatment in a timely fashion. EMB is an invasive procedure with a 1:1000 risk of death and 1:2450 risk of perforation in adult patients when the relatively stiff Stanford-Caves bioptome is used [72]. Additional potential complications include bradycardia, tachyarrhythmias, tricuspid regurgitation, vasovagal reactions, bleeding, and cardiac tamponade. Risks when using newer, more flexible bioptomes with smaller jaws are likely lower when performed by experienced operators [73].

If EMB seems indicated based on clinical presentation, it should be performed by an experienced operator in a medical center with a low procedural complication rate, surgical back-up, and timely expert cardiac pathology consultation available.

Echocardiography

GCM

Echocardiographic findings in patients with acute GCM vary and may include wall thickening, normal left ventricular size, and poor left ventricular systolic function. As the disease progresses, the left ventricle usually dilates and left

ventricular systolic function deteriorates even further, sometimes over a matter of days. Right ventricular function often deteriorates after left ventricular function worsens.

CS

Echocardiographic abnormalities, including left ventricular systolic or diastolic dysfunction, regional wall motion abnormalities, ventricular aneurysms, and abnormal septal wall thickness (either thinning or thickening) have been reported in 14–56 % of patients with sarcoidosis [74–79]. These findings, however, are not specific for CS. Wall motion abnormalities, ventricular aneurysms, or septal thinning that is not in a coronary artery distribution suggests CS. One study of 19 patients with CS found that wall motion abnormalities, mitral regurgitation, left ventricular dimensions, and left ventricular systolic and diastolic function correlated with the degree of myocardial involvement detected by MRI [19].

Cardiac magnetic resonance imaging

GCM

Cardiac MRI may be useful in diagnosing GCM, but data are limited because few GCM patients are stable enough to undergo cardiac MRI in the acute setting.

CS

In contrast, cardiac MRI has been studied in CS patients and results indicate that it may assist in establishing the diagnosis. MRI images typically show segmental wall motion abnormalities in a noncoronary distribution or regions of focal myocardial thinning or thickening. Increased signal intensity of T2-weighted and early gadolinium-DTPA (Gd)-enhanced images may demonstrate areas of edema. Sarcoid granulomas may appear as nodules on these image sequences as well. Late Gd-enhanced images may show focal areas of increased signal intensity, usually in the mid-myocardium and most commonly affecting the basal segments of the septum and lateral walls (Fig. 3) [80–83]. These areas of enhancement likely represent a combination of inflammation and fibrogranulomatous replacement.

Cardiac MRI may also be useful to assess the response to treatment in CS patients. Two studies have shown a correlation between the extent of late Gd-enhancement and the clinical severity of cardiac disease [84, 85].

Computed tomography

CS

Case reports have described the manifestations of cardiac sarcoidosis demonstrated by ECG-gated multidetector CT, with a pattern of subepicardial enhancement in the basal and lateral subepicardial myocardium at delayed imaging performed 10 min after the injection of iodinated contrast material. These CT images have been shown to be similar to MRI in terms of both localization and extent of myocardial involvement [86, 87].

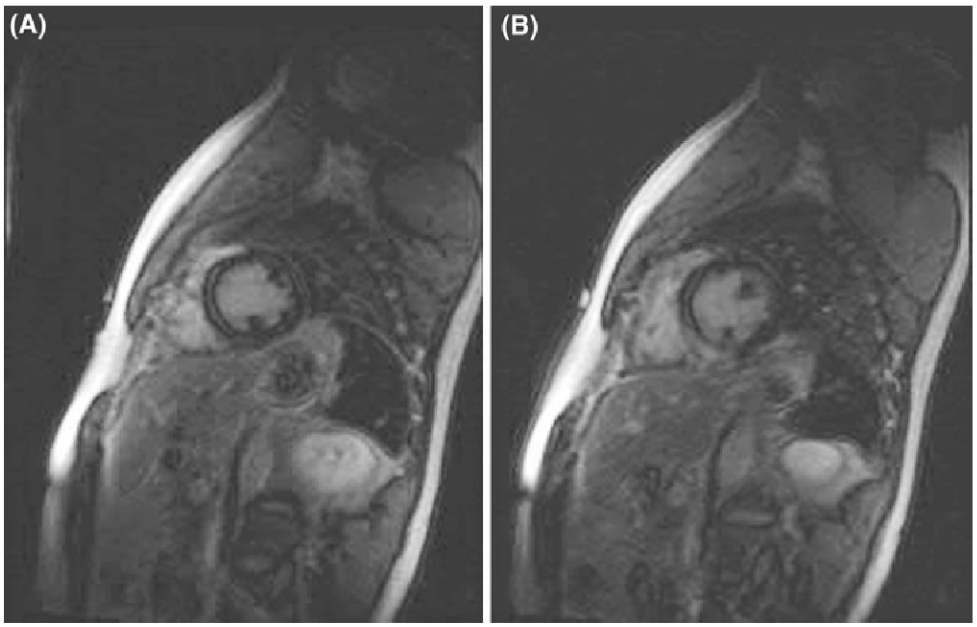

Fig. 3 Cardiac MRI delayed enhancement images of a patient with suspected cardiac sarcoidosis. **a** Image demonstrates a mid myocardial stripe enhancement pattern with enhancement in the middle of the septum, sparing the outer walls. **b** The delayed enhancement pattern extends to a more transmural focus in the inferoseptal region

Thallium 201 and technetium 99 m scintigraphy

CS

Both thallium 201 and technetium 99 m scintigraphy have been used to detect cardiac sarcoidosis. Resting perfusion scans may show areas of decreased uptake in CS patients. These resting defects often improve after exercise or vasodilator therapy [88, 89]. This reverse distribution pattern is characteristic for CS and may indicate potential responsiveness to treatment [90].

Positron emission tomography

CS

Positron emission tomography (PET) has not been studied in GCM patients, but it has become increasingly useful for the diagnosis of patients with suspected CS. Several studies have shown that ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake is increased in the myocardium in patients with suspected CS [91–94]. In addition to measuring ^{18}F-FDG uptake, PET is also able to provide perfusion analysis, which may indicate the extent of fibrogranulomatous replacement of the myocardium. Yamagishi et al. [91] studied this hypothesis in a small number of patients and reported ^{18}F-FDG abnormalities significantly improved in patients treated with corticosteroids, but there was no significant improvement in perfusion defects. Several case reports have also shown ^{18}F-FDG uptake improves after corticosteroid treatment [95–98]. Isiguzo et al. [99] showed that the association of metabolism-perfusion mismatch demonstrated by rubidium-FDG PET with clinically active disease in CS patients was highly significant. More recently, Pandya et al. [95] reported that the recurrence of symptomatic ventricular tachycardia was predicted by increased ^{18}F-FDG uptake during steroid tapering. These reports suggest the practical role of ^{18}F-FDG PET in monitoring the disease activity of CS during and after steroid therapy.

The sensitivity for detection of CS by PET in small studies has been reported to be 82–100 % [92, 100], which is significantly higher than that of 99 m Technetium-MIBI single-photon emission CT (63.6 %) or 67-Ga scintigraphy (36.3 %) [101]. The specificity for detection of CS by PET is less clear, with several small studies reporting the specificity to be 39–91 % [92, 94, 100]. Possible explanations for this include nonspecific myocardial uptake of ^{18}F-FDG in the normal heart [102, 103] and the ability of PET to detect subclinical CS [104].

Multimodality imaging

CS

Two studies have compared the diagnostic capability of ^{18}F-FDG PET and MRI in CS. In both studies, ^{18}F-FDG PET had greater sensitivity that MRI in detecting CS (86 vs 36 % and 87.5 vs 75 %) [100, 105]. In the study by Ohira et al. [100], however, the specificity of ^{18}F-FDG PET (38.5 %) was much lower than that of MRI (76.9 %). These results suggest a complimentary role of ^{18}F-FDG PET and MRI in the assessment of CS in that ^{18}F-FDG PET is better at detecting active lesions and assessing response to treatment, while MRI might more clearly show fibrotic regions [106].

Although scintigraphy has a long history of being used to diagnose and perhaps monitor response to treatment in patients with CS, emerging modalities such as ^{18}F-FDG PET, ^{18}F-FDG PET/CT, and MRI are likely to replace scintigraphy due to the increased spatial resolution and decreased radiation exposure of these newer techniques. In addition, it seems likely that using multiple imaging modalities will enable clinicians to more easily diagnose and better manage patients with CS.

GCM and CS in children

GCM

There have been only 23 cases of GCM in children reported in the literature [107–111]. Of these, 22 have died or required heart transplantation. The rate of GCM is relatively equal among males and females, but only females have had associated immune-related disorders [112]. Similar to adults with GCM, children with GCM primarily present with acute heart failure symptoms and/or arrhythmias and their clinical status rapidly deteriorates over several days to weeks. Few children have been treated with immunosuppression prior to heart transplantation, so the efficacy and safety of corticosteroid or other immunosuppressive treatment is not known. GCM recurrence post-transplant may be more aggressive in children than it is in adults [112].

CS

CS is extremely rare in children. Only one case of CS in a child has been reported in the literature to date [113], making it difficult to comment on this disease in children.

Management

Similar to treatment of heart failure from other causes, treatment for GCM and CS with standard heart failure medications including nonselective beta blockers, ACE-Inhibitors or Angiotensin Receptor II blockers, aldosterone inhibitors and diuretics is indicated. Digoxin should be

avoided due to the risk for heart block and arrhythmias in the setting of acute inflammation. As patients with acute GCM can deteriorate rapidly over hours to days, initial management in an intensive care unit is recommended.

In contrast to patients with GCM, patients with CS generally present with chronic heart failure symptoms and do not require treatment in an acute care setting in the absence of life-threatening arrhythmias.

Antiarrhythmic therapy

Acute inflammation and fibrogranulomatous lesions are substrates for ventricular tachyarrhythmias in both GCM and CS. Amiodarone may be useful in GCM patients, but chronic therapy is often avoided in CS patients due to potential pulmonary toxicity. Beta-blockers should be used with caution in CS patients due to propensity for high grade AVB. Catheter radiofrequency ablation may be useful in some CS patients with ventricular tachycardia resistant to antiarrhythmic drug therapy, but results have been mixed [114, 115].

Device therapy

CS

There is a high rate of recurrence of ventricular tachycardia or sudden death with antiarrhythmic drug therapy in CS patients, even when guided by electrophysiologic testing [63, 142]. For this reason, an implantable cardiac defibrillator (ICD) is usually implanted in CS patients with sustained ventricular tachycardia or ventricular fibrillation [116]. It is not clear whether ICD implantation is indicated in CS patients with normal cardiac function and no spontaneous life-threatening ventricular arrhythmias [117]. The 2008 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines state that "ICD implantation is reasonable for patients with cardiac sarcoidosis," giving it a class IIa indication rating with level of evidence C [116]. Pacemaker implantation is frequently indicated in CS patients due to high grade AVB. It seems reasonable to implant either a single chamber or dual chamber ICD, rather than a pacemaker system, in these patients.

Mechanical circulatory support

GCM

Mechanical circulatory support with intra-aortic balloon pumps, extracorporeal membrane oxygenation, and ventricular assist devices (VADs) have all been used in GCM patients as bridge to transplantation [118, 119] or occasionally, recovery [120].

Nine patients from the Giant Cell Myocarditis Registry received VADs [121]. Seven of the nine (78 %) patients were successfully bridged to transplant, which is similar to the rate reported for other VAD recipients. Post-transplantation survival was worse, however, than for patients who did not receive VADs before transplantation. The risk of device infection needs to be weighed against the possible benefit of bridge to recovery when considering immunosuppression after VAD placement for GCM.

Cardiac transplantation

GCM

The Multicenter Giant Cell Myocarditis Study Group recorded 63 patients in whom the rate of death ($n = 22$) or cardiac transplantation ($n = 34$) was 89 % [51]. Only 15 % of the 34 who underwent heart transplant (median 6 months after symptom onset) died within 3 years of transplant despite the occurrence of GCM in the graft of 9 of these 34 patients, whereas median survival time was only 12.3 months after symptom onset among the 22 patient treated with immunosuppression without heart transplant. Despite post-transplantation immunosuppression, there is a 20–25 % GCM recurrence rate in the transplanted heart [51]. When GCM recurs in the transplanted heart, it is generally asymptomatic and temporary augmentation of immunosuppression usually resolves the histological recurrence [122].

CS

Cardiac transplantation for CS is rare but has been used for patients with refractory arrhythmias or end-stage cardiomyopathy. Review of the United Network for Organ Sharing database between 1987 and 2005 revealed that 65 patients with cardiac sarcoidosis underwent cardiac transplantation [123]. The short- and intermediate-term post-transplant survival was significantly better for sarcoid patients compared with contemporaneous patients receiving transplantation for all other diagnoses (87.7 vs 84.5 %). Survival benefit persisted out to 5 years. Recurrence of CS has rarely been reported in transplanted hearts [124–126] in patients on no or low dose steroid treatment.

Immunologic therapy

GCM

Treatment with a combination of immunosuppressive agents that include cyclosporin prolongs transplant-free survival in

GCM patients [51, 127–129]. Patients in the Giant Cell Myocarditis Registry who were treated with cyclosporine and corticosteroids, occasionally with the addition of muromonab-CD3, had a median transplant-free survival of 12.6 months compared with only 3 months for those not treated with immunosuppressive agents [51]. In patients who develop renal failure, refractory hypertension, or neurological symptoms on cyclosporine, an author (LTC) has substituted sirolimus (with a 23 h trough level of 4–8 ng/dl) with acceptable efficacy. If muromonab-CD3 is unavailable, alemtuzumab has been substituted and resulted in rapid clinical improvement in a few cases of acute or recurrent GCM.

CS

Corticosteroids are the principle treatment for CS, although there is no prospective data or expert consensus to guide timing, intensity, and duration of treatment. A retrospective study of 20 patients with AVB and normal cardiac function which compared steroid-treated ($n = 7$) and nonsteroid-treated ($n = 13$) patients showed that there was a marked decline in left ventricular ejection fraction (LVEF) in the untreated group compared with the treated group (LVEF 37.6 vs 62.1 %) [130]. Ventricular tachycardia occurred in only 1 of 7 (14.3 %) treated patients during the follow-up period but was present in 8 of 13 (61.5 %) of the untreated patients. There were no deaths in the treated group, while two patients in the untreated group died [130]. In a retrospective study by Chapelon-Abric et al. [18], 39 patients received steroid therapy (initial dose, 1 mg/kg/day), 13 with additional immunosuppressive treatment. Thirty-four (87 %) showed improvement and 21 showed complete resolution of clinical and/or laboratory findings in long-term follow-up. In another retrospective study by Yazaki et al. [20], 95 patients treated with steroids had a 5-year survival rate of 75 % and a 10-year survival rate of 61 %. There was no significant difference in survival curves of patients treated with an initial prednisone dose >30 mg daily versus ≤30 mg daily.

Currently, there is a lack of consensus on steroid dosing, duration of therapy, and use of additional immunosuppressive agents in CS patients [131]. Initiation of corticosteroid therapy in CS patients with significant symptoms is common practice, but there is no consensus on initiation of steroid therapy in minimally or asymptomatic CS patients. Current opinion and practice differ on optimal corticosteroid dosing, but there is agreement that initial dosing should be relatively high and then slowly tapered. Some experts advocate 6–12 months of therapy, while others recommend consideration of life-long treatment due to anecdotal reports of relapse or sudden death [18, 132]. Certainly, it is recommended that clinical response to corticosteroid therapy be assessed on a regular basis with clinical assessment as well as serial imaging.

Other immunosuppressive therapies such as infliximab, methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, pentoxifylline, and thalidomide have been used with some success in treating systemic sarcoidosis, [133–139], but data regarding their use in CS are limited. These agents may be considered for CS patients who are intolerant to corticosteroids or who do not respond to corticosteroid treatment and may also be used in combination with corticosteroids in order to reduce the risk of steroid-associated adverse effects.

Prognosis

GCM

The median transplant-free survival in GCM managed without immunosuppression is approximately 12 weeks from symptom onset [51]. The likelihood of death or transplantation at 1 year from symptom onset in GCM patients diagnosed by biopsy is approximately 86 % [13, 140].

CS

The prognosis of CS is better than GCM and likely varies with the degree of left ventricular dysfunction [13].

Summary

GCM and CS, although rare, should be considered in all cases of unexplained dilated cardiomyopathy, particularly in young adults. A negative EMB should not preclude the diagnosis of either of these diseases, especially CS. Non-invasive testing, including PET and MRI for suspected CS, may support the diagnosis or guide the decision to proceed to EMB. Establishing the diagnosis of GCM or CS early is key, as tailored immunosuppressive treatment may significantly alter the clinical course of these patients.

Due to the rarity of these diseases, randomized, controlled treatment trials are unlikely in the future. Multicenter registries will be the main tool to gain clinical and immunopathologic insights to better outcomes for patients with these unusual forms of cardiomyopathy.

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