Myocardial Involvement in Patients With Histologically Diagnosed Cardiac Sarcoidosis: A Systematic Review and Meta-Analysis of Gross Pathological Images From Autopsy or Cardiac Transplantation Cases

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Background—In patients with suspected cardiac sarcoidosis, late gadolinium enhancement on cardiovascular magnetic resonance imaging and/or 18F-fluorodeoxyglucose uptake on positron emission tomography are often used to reach a clinical diagnosis of cardiac sarcoidosis. On the basis of data from the imaging literature of clinical cardiac sarcoidosis, no specific features of myocardial involvement are regarded as pathognomonic for cardiac sarcoidosis. Thus, a diagnosis of cardiac sarcoidosis is challenging to make. There has been no systematic analysis of histologically diagnosed cardiac sarcoidosis for patterns of myocardial involvement. We hypothesized that certain patterns of myocardial involvement are more frequent in histologically diagnosed cardiac sarcoidosis.

Methods and Results—We performed a systematic review and meta-analysis of gross pathological images from the published literature of patients with histologically diagnosed cardiac sarcoidosis who underwent autopsy or cardiac transplantation. Thirty-three eligible articles provided images of 49 unique hearts. Analysis of these hearts revealed certain features of myocardial involvement in >90% of cases: left ventricular (LV) subepicardial, LV multifocal, septal, and right ventricular free wall involvement. In contrast, other patterns were seen in 0% to 6% of cases: absence of gross LV myocardial involvement, isolated LV midmyocardial involvement, isolated LV subendocardial involvement, isolated LV transmural involvement, absence of septal involvement, or isolated involvement of only one LV level.

Conclusions—In this systematic review and meta-analysis of histologically diagnosed cardiac sarcoidosis, we identified certain features of myocardial involvement that occurred frequently and others that occurred rarely or never. These patterns could aid the interpretation of cardiovascular magnetic resonance imaging and positron emission tomography imaging and improve the diagnosis and the prognostication of patients with suspected cardiac sarcoidosis. (J Am Heart Assoc. 2019;8:e011253. DOI: 10.1161/JAHA.118.011253.)

Key Words: autopsy • cardiac sarcoidosis • cardiac transplantation • late gadolinium enhancement • myocardial structure • phenotype • prognosis

Sarcoidosis is a multisystem granulomatous disorder of unclear cause. The heart is involved in up to 25% of patients with sarcoidosis, and cardiac sarcoidosis is often associated with a poor prognosis.1 Cardiovascular magnetic resonance imaging (CMR) is frequently used in the evaluation of patients with suspected cardiac sarcoidosis, and myocardial involvement identified as late gadolinium enhancement (LGE) is incorporated in the various diagnostic criteria used to make the diagnosis of cardiac sarcoidosis.2–6 Similarly, 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography is also often used in the evaluation and monitoring of patients with suspected cardiac sarcoidosis, with active myocardial involvement identified as 18F-FDG uptake.2–6 Patel et al first described diverse patterns of LGE in patients with extracardiac biopsy-proven sarcoidosis.7 Although 86% (18/21) of patients with LGE in the study had at least one region with LGE in a nonischemic pattern, subendocardial LGE typical for coronary artery disease was also noted as representing cardiac sarcoidosis in the absence of obstructive coronary artery disease. This study was the basis of statements

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Accompanying Figures S1 and S49 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011253

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in cardiac sarcoidosis has been suggested,9,10 there has been a pattern of LGE that is pathognomonic for cardiac sarcoidosis.

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We studied gross pathological images of hearts from either autopsy or cardiac transplantation cases.

Other patterns were seen in 0% to 6% of cases: absence of gross myocardial involvement, isolated LV midmyocardial involvement, isolated LV subendocardial involvement, isolated LV transmural involvement, absence of septal involvement, or isolated involvement of only one LV level.

Clinical Perspective

What Is New?

• We performed a systematic analysis and meta-analysis of histologically diagnosed cardiac sarcoidosis for patterns of myocardial involvement using gross pathological images from autopsy or cardiac transplantation cases.
• Certain features of myocardial involvement were seen in >90% of cases: left ventricular (LV) subepicardial, LV multifocal, septal, and right ventricular free wall involvement.
• Other patterns were seen in 0% to 6% of cases: absence of gross myocardial involvement, isolated LV midmyocardial involvement, isolated LV subendocardial involvement, isolated LV transmural involvement, absence of septal involvement, or isolated involvement of only one LV level.

What Are the Clinical Implications?

• These patterns of myocardial involvement in cardiac sarcoidosis could aid the interpretation of cardiovascular magnetic resonance imaging and 18F-fluorodeoxyglucose positron emission tomography imaging and improve the diagnosis and the prognostication of patients with suspected cardiac sarcoidosis.

in the 2014 Heart Rhythm Society Expert Consensus Statement on the Diagnosis and Management of Arrhythmias Associated With Cardiac Sarcoidosis that “there is no specific pattern of LGE that is pathognomonic for cardiac sarcoidosis” and “...even a pattern that is typical for prior myocardial infarction can also represent cardiac sarcoidosis.” The lack of a specific LGE pattern for cardiac sarcoidosis makes it challenging to make the diagnosis. This is an important issue as patient management is often guided by clinical diagnoses rather than histological diagnoses because an endomyocardial biopsy is deemed to have limited sensitivity to detect cardiac sarcoidosis. Although the presence of frequent LGE patterns in cardiac sarcoidosis has been suggested, there has been no systematic analysis of patterns of myocardial involvement in cardiac sarcoidosis, especially in histologically diagnosed cardiac sarcoidosis. We hypothesized that certain patterns of myocardial involvement are more frequent in histologically diagnosed cardiac sarcoidosis.

To determine patterns of myocardial involvement in cardiac sarcoidosis, we performed a systematic review and meta-analysis of published gross pathological images of the heart from patients with histologically diagnosed cardiac sarcoidosis.

Methods

All data supporting the findings are provided within the article. We studied gross pathological images of hearts from either patients who underwent a autopsy or those who had heart transplantation for cardiac sarcoidosis and had a definitive histological diagnosis of cardiac sarcoidosis. Patients who underwent a autopsy died from either sudden cardiac death attributed to cardiac sarcoidosis or other causes directly related to cardiac sarcoidosis (eg, multiorgan failure after recurrent ventricular arrhythmias attributed to cardiac sarcoidosis). We chose to specifically study these patients because they experienced the major adverse cardiac events that we aim to avoid in patients with suspected cardiac sarcoidosis.

Search Strategy

We searched the PubMed, Embase, and Cochrane databases in March 2018 to perform a systematic review of peer-reviewed publications that included gross pathological images of hearts taken from patients who either died from cardiac sarcoidosis or underwent heart transplantation for cardiac sarcoidosis. Search terms used were as follows: “cardiac sarcoidosis and pathology,” “cardiac sarcoidosis and autopsy,” “cardiac sarcoidosis and explant,” and “cardiac sarcoidosis and explant.”

Study Selection

Two investigators (O.O. and C.S.) independently scanned all titles and abstracts and obtained full-text reports of articles that indicated or suggested eligibility. The full-text articles were then assessed for eligible gross heart pathological images by the same investigators independently. We included images from patients who either died of causes related to cardiac sarcoidosis or underwent heart transplantation for cardiac sarcoidosis and had a histological diagnosis of cardiac sarcoidosis based on the presence of noncaseating granulomas. We excluded gross pathological images when the myocardium could not be assessed in at least 6 of 17 American Heart Association left ventricular (LV) segments because of either anatomical sections performed or poor image quality.

Data Collection

To identify features of myocardial involvement in patients with cardiac sarcoidosis, 2 investigators (O.O., F.K.) independently recorded the following 5 domains of myocardial damage features from the gross pathological images:

1. Location of involvement within the LV wall:
   • Subepicardial (involvement of the outer portion, including the right ventricular [RV] aspect of the interventricular septum);
   • Midmyocardial (involvement of the middle portion);
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- Subendocardial (involvement of the inner portion);
- Transmural (involvement of the entire thickness of the wall).

2. Focality within the LV:
- Unifocal (1 single lesion);
- Multifocal (>1 discrete lesion).

3. LV segments involved:
- Anterior segments;
- Septal segments;
- Inferior segments;
- Lateral segment.

4. LV levels involved:
- Basal LV;
- Mid LV;
- Apical LV.

5. Involvement of the RV free wall
- Yes;
- No.

Discordances were resolved after consensus with a third investigator (C.S.). Within each domain, the prevalence of various features of myocardial involvement was compared. Features that were either frequently (>90%) or rarely (<10%) present were identified.

### Statistical Analysis

Categorical variables were expressed as counts with percentages. $\chi^2$ Tests were used to compare discrete data between groups; in those cases in which the expected cell count was <5, the Fisher exact test was used. Statistical analyses were performed using R, version 3.3.3 (The R Foundation; https://www.r-project.org/). All statistical tests were 2 tailed, and $P<0.05$ was considered statistically significant.

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Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the flow of information through the different phases of the systematic review.
Table 1. Articles and Gross Pathological Images of Cardiac Sarcoidosis Included in the Study

| Figure | Article No. | Author and Year of Publication | Figure No. Within Article | Autopsy or Explant | Cause of Death | No. of LV Segments Seen |
|--------|-------------|--------------------------------|--------------------------|--------------------|---------------|------------------------|
| S1     | 1           | Fawcett and Goldberg, 1974 12  | 1                        | Autopsy            | Sudden cardiac death | 6                      |
| S2     | 2           | Fleming, 1974 13                | 4                        | Autopsy            | Sudden cardiac death | 6                      |
| S3     | 2           | Fleming, 1974 13                | 9                        | Autopsy            | Sudden cardiac death | 6                      |
| S4     | 3           | Roberts et al, 1977 14          | 5                        | Autopsy            | Sudden cardiac death | 6                      |
| S5     | 4           | James and Pounder, 1982 15      | 1                        | Autopsy            | Sudden cardiac death | 6                      |
| S6     | 5           | (Authors not listed), 1990 16   | 9                        | Autopsy            | Cardiogenic shock   | 6                      |
| S7     | 6           | Antecol and Roberts, 1990 17    | 5                        | Autopsy            | Sudden cardiac death | 12                     |
| S8     | 7           | Shirani and Roberts, 1993 18    | 4                        | Autopsy            | Sudden cardiac death | 17                     |
| S9     | 7           | Shirani and Roberts, 1993 18    | 5                        | Autopsy            | Sudden cardiac death | 6                      |
| S10    | 8           | Donsky et al, 2002 19           | 2                        | Explant            | ...             | 17                     |
| S11    | 9           | Wan Muhaiman et al, 2004 20     | 2                        | Autopsy            | Cardiogenic shock   | 16                     |
| S12    | 10          | Goyal and Aragam, 2006 21       | 1                        | Explant            | ...             | 6                      |
| S13    | 11          | Halushka et al, 2006 22         | 1                        | Explant            | ...             | 6                      |
| S14    | 12          | Hamilton et al, 2007 23         | 1                        | Autopsy            | Sudden cardiac death | 6                      |
| S15    | 13          | Morikawa et al, 2008 24         | 2                        | Autopsy            | Hemorrhagic shock   | 6                      |
| S16    | 14          | Luk et al, 2009 25              | 2                        | Explant            | ...             | 6                      |
| S17    | 15          | Riezzo et al, 2009 26           | 2                        | Autopsy            | Sudden cardiac death | 6                      |
| S18    | 16          | Roberts et al, 2009 27          | 2                        | Explant            | ...             | 17                     |
| S19    | 16          | Roberts et al, 2009 27          | 3                        | Explant            | ...             | 17                     |
| S20    | 16          | Roberts et al, 2009 27          | 4                        | Explant            | ...             | 12                     |
| S21    | 17          | Sharma et al, 2009 28           | 1, 2                     | Autopsy            | Sudden cardiac death | 17                     |
| S22    | 18          | Tavora et al, 2009 29           | 2                        | Autopsy            | Sudden cardiac death | 6                      |
| S23    | 18          | Tavora et al, 2009 29           | 2                        | Autopsy            | Sudden cardiac death | 6                      |
| S24    | 18          | Tavora et al, 2009 29           | 3                        | Autopsy            | Sudden cardiac death | 17                     |
| S25    | 18          | Tavora et al, 2009 29           | 7                        | Autopsy            | Sudden cardiac death | 6                      |
| S26    | 19          | Dubrey and Falk, 2010 30        | 2                        | Explant            | ...             | 6                      |
| S27    | 20          | Lagana et al, 2010 31           | 1                        | Explant            | ...             | 6                      |
| S28    | 21          | Bagwan et al, 2011 32           | 1                        | Autopsy            | Sudden cardiac death | 6                      |
| S29    | 22          | Strauss et al, 2011 33          | 2                        | Explant            | ...             | 6                      |
| S30    | 23          | Armstrong, 2013 34              | 2                        | Autopsy            | Sudden cardiac death | 6                      |
| S31    | 24          | Zacek et al, 2013 35            | 2                        | Autopsy            | Cardiogenic shock   | 6                      |
| S32    | 25          | Lynch et al, 2014 36            | 1                        | Autopsy            | Sudden cardiac death | 6                      |
| S33    | 26          | Roberts et al, 2014a 7          | 1                        | Explant            | ...             | 17                     |
| S34    | 26          | Roberts et al, 2014 47          | 2                        | Explant            | ...             | 17                     |
| S35    | 26          | Roberts et al, 2014 47          | 3                        | Explant            | ...             | 17                     |
| S36    | 26          | Roberts et al, 2014 47          | 4                        | Explant            | ...             | 17                     |
| S37    | 26          | Roberts et al, 2014 47          | 5                        | Explant            | ...             | 12                     |
| S38    | 27          | Roberts et al, 2014 38          | 27                       | Explant            | ...             | 17                     |
| S39    | 28          | Armstrong et al, 2015 39        | 1                        | Explant            | ...             | 17                     |
| S40    | 28          | Armstrong et al, 2015 39        | 3                        | Explant            | ...             | 17                     |

Continued
Results

The systematic review yielded 33 articles\(^{12-44}\) published in the peer-reviewed literature between 1974 and March 2018 (Figure 1). The 33 articles provided gross pathological images of 49 unique hearts with cardiac sarcoidosis: 25 were from autopsy examinations, and 24 were explanted for heart transplantation (Table 1). All heart transplantations occurred for cardiac sarcoidosis, and of the 25 hearts from autopsy examinations, 18 (72%) had sudden death and 7 (28%) died of immediate causes other than sudden death but cardiac sarcoidosis directly contributed to the death. Five representative examples\(^ {17,24,29,39,44}\) with details of features of myocardial involvement are reproduced in Figure 2. All 49 gross pathological images are reproduced with permission in Figures S1 through S49.

Prevalence of Features of Myocardial Involvement

Location of involvement within the LV wall

Within the LV wall, the involvement was subepicardial in 98% of cases, with significantly lower midmyocardial (65.3%), subendocardial (53.1%), or transmural (63.3%) involvement (\(P<0.05\) for all) (Tables 2 and 3).

Focality within the LV

Multifocal LV involvement was significantly more common than unifocal involvement (93.9% versus 6.1%; \(P<0.05\)).

LV segments involved

The septal segments were involved in 98% of cases, with significantly lower involvement of the anterior (75.0%), lateral (71.4%), and inferior (82.5%) segments (\(P<0.05\) for all).

LV levels involved

The basal and mid LV were almost always involved (97.5% and 100%, respectively), and the apical LV was less often involved when compared with either basal or mid LV (80.8%; \(P<0.05\) for both comparisons). However, the difference was not significant when comparisons were made only using the 26 patients who had pathological images of all LV levels.

Involvement of the RV free wall

The RV free wall was involved in 90.7% of cases.

Rare Features of Myocardial Involvement

On the basis of the above, we identified a list of rare features (Table 4). These features had a prevalence of <6%, and many were never present. There were no patients without gross LV myocardial involvement. LV midmyocardial or subendocardial involvement without subepicardial involvement was never present. LV transmural involvement without separate subepicardial involvement was present in only 1 patient (2.0%). Unifocal involvement was present in only 6.1% of patients. Absence of septal involvement was noted in only 1 patient (2.0%). In terms of the levels of involvement, isolated involvement of only one LV level was seen in only 1 patient (2.0%) for the basal level and 0 patients for the mid and apical levels.

Table 1. Continued

| Figure | Article No. | Author and Year of Publication | Figure No. Within Article | Autopsy or Explant | Cause of Death | No. of LV Segments Seen |
|--------|-------------|--------------------------------|--------------------------|-------------------|----------------|------------------------|
| S41    | 29          | Jeudy et al, 2015\(^ {30}\)    | 2                        | Autopsy           | Sudden cardiac death | 6                      |
| S42    | 29          | Jeudy et al, 2015\(^ {30}\)    | 3                        | Explant           | ...             | 6                      |
| S43    | 29          | Jeudy et al, 2015\(^ {30}\)    | 4                        | Explant           | ...             | 6                      |
| S44    | 30          | Kajimoto et al, 2015\(^ {41}\) | 2                        | Autopsy           | Hemorrhagic shock | 17                     |
| S45    | 31          | Vasaturo et al, 2015\(^ {42}\) | 1                        | Autopsy           | Toxic shock syndrome | 16                    |
| S46    | 32          | Di Gesaro et al, 2016\(^ {43}\) | 2                        | Explant           | ...             | 17                     |
| S47    | 33          | Roberts et al, 2016\(^ {44}\)  | 2                        | Explant           | ...             | 6                      |
| S48    | 33          | Roberts et al, 2016\(^ {44}\)  | 2                        | Explant           | ...             | 6                      |
| S49    | 33          | Roberts et al, 2016\(^ {44}\)  | 2                        | Explant           | ...             | 6                      |

LV indicates left ventricular.
subepicardial, LV multifocal, septal, and RV free wall involvement were frequent (present in >90% of patients) features. On the other hand, lack of gross LV myocardial, isolated LV midmyocardial, or isolated LV subendocardial involvement was never present. Similarly, isolated LV transmural involvement, absence of septal involvement, and isolated involvement of only one LV level were rare (present in 2% of patients) features.

One of the key strengths of our data is that they are derived only from patients with histologically diagnosed cardiac sarcoidosis. The contemporary understanding of myocardial involvement in cardiac sarcoidosis, in which no...
Table 2. Features of Myocardial Involvement in Cardiac Sarcoidosis on Gross Pathological Images

| Figure | Subepicardial LV Involvement | Midmyocardial LV Involvement | Subendocardial LV Involvement | Transmural LV Involvement | Multifocal LV Involvement | Septal LV Involvement | Lateral LV Involvement | Anterior LV Involvement | Inferior LV Involvement | Basal LV Involvement | Mid-LV Involvement | Apical LV Involvement | RV Free Wall |
|--------|-----------------------------|-----------------------------|------------------------------|---------------------------|--------------------------|----------------------|----------------------|------------------------|----------------------|---------------------|---------------------|---------------------|--------------|
| S1     | Yes                         | Yes                         | Yes                          | No                        | Yes                      | Yes                  | Yes                  | Yes                    | No                    | Yes                 | Yes                 | Yes                 | Yes          |
| S2     | Yes                         | No                          | Yes                          | Yes                       | Yes                      | Yes                  | No                   | Yes                    | No                    | Yes                 | Yes                 | Yes                 | Yes          |
| S3     | Yes                         | Yes                         | Yes                          | Yes                       | No                       | Yes                  | Yes                  | Yes                    | No                    | Yes                 | Yes                 | Yes                 | Yes          |
| S4     | Yes                         | No                          | Yes                          | Yes                       | Yes                      | Yes                  | Yes                  | Yes                    | No                    | Yes                 | No                  | Yes                 | Yes          |
| S5     | Yes                         | No                          | Yes                          | Yes                       | Yes                      | Yes                  | Yes                  | Yes                    | Yes                   | Yes                 | No                  | Yes                 | Yes          |
| S6     | Yes                         | Yes                         | No                            | Yes                       | Yes                      | Yes                  | Yes                  | Yes                    | No                    | Yes                 | Yes                 | Yes                 | Yes          |
| S7     | Yes                         | Yes                         | No                            | Yes                       | Yes                      | Yes                  | Yes                  | Yes                    | No                    | Yes                 | Yes                 | No                   | Yes          |
| S8     | Yes                         | No                          | Yes                          | Yes                       | Yes                      | Yes                  | Yes                  | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | Yes          |
| S9     | Yes                         | No                          | Yes                          | Yes                       | Yes                      | Yes                  | Yes                  | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | Yes          |
| S10    | Yes                         | No                          | Yes                          | Yes                       | Yes                      | Yes                  | Yes                  | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | Yes          |
| S11    | Yes                         | No                          | Yes                          | Yes                       | Yes                      | Yes                  | Yes                  | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | Yes          |
| S12    | Yes                         | Yes                         | Yes                          | Yes                       | Yes                      | Yes                  | Yes                  | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | Yes          |
| S13    | Yes                         | No                          | No                            | Yes                       | Yes                      | No                   | No                   | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | Yes          |
| S14    | Yes                         | Yes                         | Yes                          | Yes                       | Yes                      | Yes                  | Yes                  | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | Yes          |
| S15    | Yes                         | Yes                         | Yes                          | Yes                       | Yes                      | Yes                  | Yes                  | Yes                    | Yes                   | Yes                 | Yes                 | No                   | Yes          |
| S16    | Yes                         | Yes                         | No                            | Yes                       | Yes                      | Yes                  | Yes                  | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | Yes          |
| S17    | Yes                         | No                          | Yes                          | Yes                       | Yes                      | Yes                  | Yes                  | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | Yes          |
| S18    | Yes                         | Yes                         | No                            | Yes                       | Yes                      | Yes                  | No                   | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | Yes          |
| S19    | Yes                         | Yes                         | No                            | Yes                       | Yes                      | Yes                  | Yes                  | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | Yes          |
| S20    | Yes                         | Yes                         | No                            | Yes                       | Yes                      | Yes                  | No                   | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | Yes          |
| S21    | Yes                         | Yes                         | Yes                          | Yes                       | Yes                      | Yes                  | Yes                  | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | Yes          |
| S22    | No                          | No                          | No                            | Yes                       | Yes                      | Yes                  | Yes                  | Yes                    | Yes                   | Yes                 | No                  | Yes                 | Yes          |
| S23    | Yes                         | Yes                         | No                            | Yes                       | Yes                      | Yes                  | Yes                  | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | Yes          |
| S24    | Yes                         | No                          | No                            | Yes                       | Yes                      | Yes                  | Yes                  | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | Yes          |
| S25    | Yes                         | Yes                         | No                            | No                        | Yes                      | No                   | No                   | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | No           |
| S26    | Yes                         | No                          | No                            | Yes                       | Yes                      | Yes                  | Yes                  | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | Yes          |
| S27    | Yes                         | Yes                         | Yes                          | Yes                       | Yes                      | No                   | Yes                   | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | Yes          |
| S28    | Yes                         | Yes                         | No                            | Yes                       | Yes                      | No                   | Yes                   | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | No           |
| S29    | Yes                         | No                          | Yes                            | Yes                       | Yes                      | Yes                  | No                   | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | Yes          |
| S30    | Yes                         | No                          | No                            | Yes                       | Yes                      | Yes                  | No                   | Yes                    | Yes                   | Yes                 | Yes                 | Yes                 | Yes          |

Continued
**Table 2. Continued**

| Figure | Subepicardial LV Involvement | Midmyocardial LV Involvement | Subendocardial LV Involvement | Transmural LV Involvement | Multifocal LV Involvement | Septal LV Involvement | Lateral LV Involvement | Anterior LV Involvement | Inferior LV Involvement | Basal LV Involvement | Mid-LV Involvement | Apical LV Involvement | RV Free Wall |
|--------|-----------------------------|------------------------------|-------------------------------|--------------------------|--------------------------|----------------------|-----------------------|-----------------------|-----------------------|---------------------|-------------------|----------------------|-------------|
| S31    | Yes                         | Yes                          | No                            | No                       | Yes                      | No                   | Yes                   | Yes                   | Yes                   | ...                 | ...               | Yes                  |             |
| S32    | Yes                         | Yes                          | No                            | No                       | Yes                      | Yes                  | No                    | Yes                   | Yes                   | Yes                 | Yes               | No                   |             |
| S33    | Yes                         | Yes                          | Yes                           | No                       | No                      | Yes                  | Yes                   | Yes                   | Yes                   | Yes                 | Yes               | Yes                   |             |
| S34    | Yes                         | Yes                          | Yes                           | Yes                      | Yes                     | Yes                  | Yes                   | Yes                   | Yes                   | Yes                 | Yes               | Yes                   |             |
| S35    | Yes                         | Yes                          | No                            | Yes                      | Yes                     | Yes                  | Yes                   | Yes                   | Yes                   | Yes                 | Yes               | Yes                   |             |
| S36    | Yes                         | Yes                          | Yes                           | No                       | Yes                     | Yes                  | Yes                   | Yes                   | Yes                   | Yes                 | Yes               | Yes                   |             |
| S37    | Yes                         | Yes                          | Yes                           | Yes                      | Yes                     | Yes                  | Yes                   | Yes                   | Yes                   | Yes                 | Yes               | Yes                   |             |
| S38    | Yes                         | Yes                          | Yes                           | No                       | Yes                     | Yes                  | Yes                   | Yes                   | Yes                   | Yes                 | Yes               | Yes                   |             |
| S39    | Yes                         | Yes                          | Yes                           | Yes                      | Yes                     | Yes                  | Yes                   | Yes                   | Yes                   | Yes                 | Yes               | Yes                   |             |
| S40    | Yes                         | Yes                          | Yes                           | Yes                      | Yes                     | Yes                  | Yes                   | Yes                   | Yes                   | Yes                 | Yes               | Yes                   |             |
| S41    | Yes                         | Yes                          | Yes                           | Yes                      | Yes                     | Yes                  | Yes                   | Yes                   | Yes                   | Yes                 | Yes               | Yes                   |             |
| S42    | Yes                         | Yes                          | Yes                           | Yes                      | Yes                     | Yes                  | No                    | Yes                   | Yes                   | ...                 | Yes               | Yes                   |             |
| S43    | No                          | No                            | No                            | No                       | Yes                     | No                   | Yes                   | No                    | Yes                   | Yes                 | Yes               | Yes                   |             |
| S44    | Yes                         | No                            | No                            | Yes                      | Yes                     | Yes                  | Yes                   | Yes                   | Yes                   | Yes                 | Yes               | Yes                   |             |
| S45    | Yes                         | No                            | Yes                           | Yes                      | Yes                     | No                   | No                    | No                    | No                    | Yes                 | Yes               | Yes                   |             |
| S46    | Yes                         | No                            | Yes                           | Yes                      | Yes                     | Yes                  | Yes                   | Yes                   | Yes                   | No                  | Yes               | Yes                   |             |
| S47    | Yes                         | No                            | No                            | Yes                      | Yes                     | Yes                  | No                    | Yes                   | Yes                   | Yes                 | Yes               | Yes                   |             |
| S48    | Yes                         | Yes                          | Yes                           | Yes                      | Yes                     | Yes                  | Yes                   | Yes                   | Yes                   | Yes                 | Yes               | Yes                   |             |
| S49    | Yes                         | Yes                          | Yes                           | No                       | Yes                     | Yes                  | Yes                   | Yes                   | Yes                   | Yes                 | Yes               | Yes                   |             |

LV indicates left ventricular; RV, right ventricular.
specific patterns are believed to be pathognomonic for cardiac sarcoidosis, is largely based on LGE CMR data, which include patients with clinical but not histologically diagnosed cardiac sarcoidosis. In these studies, a clinical diagnosis of cardiac sarcoidosis is reached after excluding other explanations for the LGE, which may not always be accurate. For instance, coronary artery disease as the cause for subendocardial LGE in patients with suspected cardiac sarcoidosis is typically excluded by the absence of obstructive coronary artery disease on coronary angiography. However, this does not exclude the possibility of myocardial infarction with nonobstructive coronary arteries.

Our data demonstrate that there are characteristic features of myocardial involvement in cardiac sarcoidosis. These features could be used to identify patients with cardiac sarcoidosis using LGE CMR and 18F-FDG positron emission tomography, particularly those in whom cardiac sarcoidosis was not suspected before the imaging study. More important, these data imply that patients with LGE or 18F-FDG uptake in patterns that were never or rarely present in this systematic review could have an alternate explanation for the imaging findings. For instance, isolated subendocardial LGE may represent a myocardial infarction, and in the absence of coronary artery disease, it may still represent myocardial infarction with nonobstructive coronary arteries, rather than cardiac sarcoidosis. Similarly, 18F-FDG uptake isolated to the lateral wall may represent inadequate suppression of physiological uptake rather than true cardiac sarcoidosis.

Limitations
Our systematic review and meta-analysis is based on the published pathological literature, which introduces bias. Only a third of cases had 16 or 17 segments included in the gross pathological images, which raises the possibility that some of the features of myocardial involvement could have been missed. Cases included in the publications represent the most impressive cases and may not be representative of the entire spectrum of pathologically identified myocardial involvement in cardiac sarcoidosis. Similarly, our systematic review focuses on end-stage cardiac sarcoidosis (ie, those who either died of cardiac sarcoidosis or underwent heart transplantation because of it). Thus, it could be argued that our data do not include features of early myocardial involvement in cardiac sarcoidosis. However, our cases represent the adverse outcomes that we aim to avoid in patients with suspected cardiac sarcoidosis (ie, cardiac death and heart transplantation). Therefore, our data may carry prognostic implications. Studies are ongoing using these patterns of myocardial involvement on LGE CMR or 18F-FDG to risk stratify patients with suspected cardiac sarcoidosis.

Conclusions
Myocardial involvement in end-stage cardiac sarcoidosis involves frequent (LV subepicardial, LV multifocal, septal, and RV free wall involvement) and rare (lack of gross LV myocardial involvement, isolated LV midmyocardial involvement, isolated

Table 3. Prevalence of Features of Myocardial Involvement in Cardiac Sarcoidosis

| Feature of Myocardial Involvement | Prevalence, No./Total (%) |
|----------------------------------|--------------------------|
| LV subepicardial involvement (any) | 48/49 (98.0) |
| LV midmyocardial involvement (any) | 32/49 (65.3) |
| LV subendocardial involvement (any) | 26/49 (53.1) |
| LV transmural involvement (any) | 31/49 (63.3) |
| LV multifocal involvement | 46/49 (93.9) |
| Septal segment involvement (any) | 48/49 (98.0) |
| LV lateral segment involvement (any) | 35/49 (71.4) |
| LV anterior segment involvement (any) | 30/40 (75.0) |
| LV inferior segment involvement (any) | 33/40 (82.5) |
| Basal LV involvement (any) | 39/40 (97.5) |
| Mid-LV involvement (any) | 38/38 (100.0) |
| Apical LV involvement (any) | 21/26 (80.8) |
| RV free wall involvement (any) | 39/43 (90.7) |

LV indicates left ventricular; RV, right ventricular.

Table 4. Rare Features of Myocardial Involvement in Cardiac Sarcoidosis

| Feature of Myocardial Involvement | Prevalence, No./Total (%) |
|----------------------------------|--------------------------|
| No gross LV involvement | 0/49 (0.0) |
| No LV subepicardial involvement | 1/49 (2.0) |
| LV midmyocardial involvement without subepicardial involvement | 0/49 (0.0) |
| LV subendocardial involvement without subepicardial involvement | 0/49 (0.0) |
| LV transmural involvement without separate subepicardial involvement | 1/49 (2.0) |
| LV unifocal involvement | 3/49 (6.1) |
| No septal wall involvement | 1/49 (2.0) |
| LV lateral wall involvement without septal wall involvement | 1/49 (2.0) |
| No LV basal involvement | 1/26 (3.8)* |
| No LV mid involvement | 0/26 (0.0)* |
| Apical LV involvement without basal or mid LV involvement | 0/26 (0.0)* |

LV indicates left ventricular.
*A total of 26 patients had images of the basal, mid, and apical LV.
LV subendocardial involvement, isolated LV transmural involvement, absence of septal involvement, or isolated involvement of only one LV level) features. These patterns could be used to improve diagnosis and prognostication of suspected cardiac sarcoidosis with noninvasive imaging modalities, such as LGE CMR and 18F-FDG positron emission tomography.

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