Journal of the American Heart Association

EDITORIAL

Cardiac Sarcoidosis and Giant Cell Myocarditis: Actually, 2 Ends of the Same Disease?

David H. Birnie, MB ChB; Vidhya Nair, MD; John P. Veinot, MD, FRCPC

For some decades, "giant cell myocarditis (GCM)" and "granulomatous myocarditis" were considered the same disease.[1] However, since the late 1960s, most authors have recognized the well-organized granulomatous lesions of cardiac sarcoidosis (CS) as distinct from the diffuse nongranulomatous inflammatory infiltrates of GCM, and most experts consider that CS and GCM are different diseases.[2,3] However, a few publications in the past 20 years have revisited this question.[1,4,5] In this issue of the *Journal of the American Heart Association* (*JAHA*), Nordenswan and coworkers report findings from the MIDFIN (Myocardial Inflammatory Diseases in Finland) Study.[6] They identified 311 patients with CS, who were followed up for a median of 6.3 years, and 25 patients with GCM, who were followed for 3.6 years. The study has many strengths; the patients were identified mostly prospectively, at multiple centers, follow-up was complete, and they present imaging and biomarkers on some patients. Also, there was some important selection bias, which can be considered a strength rather than a weakness. Specifically, they only included patients at the severe end of the CS spectrum (ie, those with clinically manifest CS [patients presenting with ≥1 of atrioventricular block, ventricular tachycardia, and/or heart failure]).[6] Approximately 5% of patients with sarcoidosis have clinically manifest cardiac involvement. Another 20% to 25% of patients have asymptomatic (ie, clinically silent) cardiac involvement.[7] This is based largely on late gadolinium-enhanced cardiac magnetic resonance imaging of patients with pulmonary sarcoidosis[8] and findings from autopsy studies.[9]

See Article by Nordenswan et al.

Perhaps the greatest strength of the current study is the quantity and quality of the histopathological assessment.[6] All patients had histological confirmation, with the diagnosis of CS directly from cardiac tissue in 224 cases, 150 from endomyocardial biopsy, 10 posttransplant, 64 autopsies, and the others from lymph nodes (n=102) or extracardiac organs (n=25). In addition, there was central overreading by 2 cardiac pathologists of histological features in all patients with GCM (but not patients with CS). These data have been published separately and showed that, after overreading of all available histological material, 45 of the 73 cases of GCM (62%) were reclassified as CS.[10] The reclassification was based on identifying typical sarcoid granulomas that had either been misread or overlooked or were found in subsequent specimens. The quality of the histopathological assessment is clearly key here as the findings of GCM and CS intersect to some extent and there is no agreed consensus among cardiac pathologists as to the respective diagnostic criteria. The criteria used in the current study and one similar study are shown in the Table. As the authors importantly state, "our comparative data are specific to the criteria used to distinguish GCM from CS on myocardial microscopy." The only significant weakness is that the patients were 100% White patients.[6]

Key Words: Editorials ■ cardiac sarcoidosis ■ giant cell myocarditis

Correspondence to: David H. Birnie, MB ChB, Division of Cardiology, University of Ottawa Heart Institute, 40 Ruskin St, Ottawa, ON, Canada K1Y 4W7. E-mail: dbirnie@ottawaheart.ca

For Disclosures, see page 3.

JAHA is available at: www.ahajournals.org/journal/jaha

Table. Summary of Criteria Used for Diagnosis of CS and GCM (Key Difference Is That in Article by Nordenswan et al,[6] Presence of Myocardial Granulomas Excluded the Diagnosis of GCM)

Reference	Criteria for GCM	Criteria for CS	Details of Core Laboratory Overreading
6	Myocyte injury with or without necrosis associated with an inflammatory infiltrate variably composed of lymphocytes, histiocytes, eosinophils, and multinuclear giant cells.	Presence of nonnecrotic epithelioid cell granulomas together with multinuclear giant cells, sharply demarcated areas of inflammation and fibrosis, and absence of considerable myocardial necrosis or abundant tissue eosinophilia.	73 Patients diagnosed with GCM, and 45 reclassified as CS.
5	Presence of a widespread inflammatory infiltrate with multinucleated giant cells in association with myocyte damage. The presence of a nonnecrotizing granuloma alone in this background was insufficient to classify a case as CS if the degree of necrosis was judged to be out of proportion of the degree of granulomatous inflammation.	Presence of at least 1 nonnecrotizing granuloma, with or without foci of lymphocytic myocarditis, necrosis, or the presence of isolated giant cells.	Two pathologists overread specimens from 10 patients and scored various features on a 4-point scale. They agreed completely or disagreed by 1 point for multinucleated giant cells (100%), granulomas (88%), necrosis (100%), lymphocytes (100%), eosinophils (88%), fibrosis (100%), and foci of lymphocytic myocarditis (100%).

CS indicates cardiac sarcoidosis; and GCM, giant cell myocarditis.

In our opinion, much of the data presented in the current article suggest different clinical entities.[6] For example, they found that GCM had a much more acute onset (mean time from symptom onset to diagnosis was 0.3 months compared with 7 months for CS), and heart failure was the presenting manifestation for GCM in 50% versus 15%. Also, at presentation, cardiac troponin was almost always elevated in cases of GCM but in less than a quarter of cases of CS. Finally, they found that the prognosis was much worse for GCM than CS, with a 5-year event-free survival of 27% compared with 77%. Of 18 surviving patients with GCM, 11 (61%) underwent transplant compared with 25 of 272 (9.1%) of patients with CS. After adjustment for presentation and baseline left ventricular function, patients with GCM had a 5-fold higher risk of the primary end point.[6] These outcomes are clearly different between the 2 groups and are consistent with a previous similar article from the Multicenter Idiopathic GCM Registry, with 42 patients with CS and 73 patients with GCM.[5] Patients with CS had a 5-year transplant-free survival of 69.8% versus 21.9% for GCM, and that study also found a much more acute onset of GCM, with a mean of 1.2 months from symptom onset to presentation compared with 5.5 months for CS.[5]

It should be noted that there are some important similarities between the conditions, including both often present with high-grade atrioventricular block (21% versus 43% of GCM and CS, respectively); these rates of atrioventricular block are both much higher than in all other forms of myocarditis.[3] Age at disease presentation and female preponderance were also similar.[6] Also, T lymphocyte–mediated inflammatory injury appears important in both conditions.[1] Finally, there have been several reports of patients possibly having both conditions, with biopsy evidence of extracardiac sarcoidosis and cardiac biopsies suggesting GCM.[11,12] However, it is also possible that the cardiac histopathological features in these cases were misread as GCM.

We will clearly need more data to resolve this debate. Further histological studies may help answer this question, specifically by a systematic assessment of regional lymph nodes of autopsy specimens in patients with CS and GCM. Our (J.V. and V.N.) unpublished experience is that we invariably find reactive changes and congestion in regional lymph nodes in patients with GCM and granulomas in patients with CS. This brings up the related controversial issue of "isolated CS," and the authors also suggest that GCM may be a subtype of isolated CS.[6] Sarcoidosis is, by definition[13] and biological features, a systemic disease, so really the debate is whether there is "a sarcoidosis-like disease" that only involves the heart. The reported prevalence of isolated CS varies widely, from 3.2% to 54%,[14–16] and there is one primary reason for this variability: the lack of an agreed definition of isolated CS. It is clear that there are many patients, with manifest CS, who have no other clinically apparent disease (ie, "*clinically isolated CS*").[14] When these patents are imaged with whole body ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), almost all of them have evidence of subclinical disease in other organs.[14,16] However "*imaging and clinically isolated CS*" clearly occasionally does occur,[14] but it is unclear whether this represents truly isolated CS. Sarcoidosis is a dynamic disease, and we also know that FDG-PET imaging has limitations, including spatial resolution, but the data would suggest that that there is a small subset of patients who at the moment of FDG-PET imaging have "PET detectable inflammation" *only* in their heart.[14,16] Findings from Petek et al[17] are relevant; they investigated 12 patients with presentations and cardiac

imaging consistent with CS, with no history of extracardiac sarcoidosis and with normal computed tomography of the thorax. Also, 8 of the patients had FDG-PET scans, and only 1 subject had extracardiac FDG uptake. Of the 12 patients, 10 had biopsies (transbronchial in 9 and endobronchial in 1), and in 4 of 10, there were clear granulomas. Currently, there are no data to support the concept of "truly isolated CS," and it is possible that some patients with "imaging and clinically isolated CS" have GCM.

Advance cardiac imaging will play a key role in informing the debate about CS and GCM. For example, our group recently published what we believe is the first description of serial FDG-PET in a patient with GCM. The appearances were similar to what has been observed in imaging isolated CS (ie, no FDG uptake on the whole body images).[18] Another research avenue to explore is transcriptomics, and there are some preliminary data. Lassner et al analyzed the myocardial expression in GCM and CS patients; five genes showed importantly different profiles.[4]

To conclude, we would like to congratulate the authors on their excellent work.[6] However, our assessment of their data in the context of the published literature and our own experience would suggest separate disease entities with different clinical courses; clearly, more data are required. For now, the clinician needs to be aware of 2 key messages. First, and perhaps most important, is to always consider both these diagnoses in younger patients with specific cardiac presentations (eg, they have shown to be the underlying cause in 25%–34% of White patients aged <55–60 years, presenting with idiopathic high-degree atrioventricular block).[19,20] Second, the value of trying to distinguish GCM from CS should be considered, as they likely need different urgency and intensity of immunosuppression.[3]

ARTICLE INFORMATION

Affiliations

From the Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada (D.H.B.); and Department of Pathology and Laboratory Medicine, The Ottawa Hospital and University of Ottawa, Ottawa, Ontario, Canada (V.N., J.P.V.).

Disclosures

None.

REFERENCES

1. Blauwet LA, Cooper LT. Idiopathic giant cell myocarditis and cardiac sarcoidosis. *Heart Fail Rev*. 2013;18:733–746. DOI: 10.1007/s10741-012-9358-3.
2. Trachtenberg BH, Hare JM. Inflammatory cardiomyopathic syndromes. *Circ Res*. 2017;121:803–818. DOI: 10.1161/CIRCRESAHA.117.310221.
3. Ammirati E, Frigerio M, Adler ED, Basso C, Birnie DH, Brambatti M, Friedrich MG, Klingel K, Lehtonen J, Moslehi JJ, et al. Management of acute myocarditis and chronic inflammatory cardiomyopathy: an expert consensus document. *Circ Heart Fail*. 2020;13:e007405. DOI: 10.1161/CIRCHEARTFAILURE.120.007405.
4. Lassner D, Kuhl U, Siegismund CS, Rohde M, Elezkurtaj S, Escher F, Tschope C, Gross UM, Poller W, Schultheiss HP. Improved diagnosis of idiopathic giant cell myocarditis and cardiac sarcoidosis by myocardial gene expression profiling. *Eur Heart J*. 2014;35:2186–2195. DOI: 10.1093/eurheartj/ehu101.
5. Okura Y, Dec GW, Hare JM, Kodama M, Berry GJ, Tazelaar HD, Bailey KR, Cooper LT. A clinical and histopathologic comparison of cardiac sarcoidosis and idiopathic giant cell myocarditis. *J Am Coll Cardiol*. 2003;41:322–329. DOI: 10.1016/S0735-1097(02)02715-8.
6. Nordenswan HK, Lehtonen J, Ekström K, Räisänen Sokolowski A, Mäyränpää MI, Vihinen T, Miettinen H, Kaikkonen K, Haataja P, Kerola T, et al. Manifestations and outcome of cardiac sarcoidosis and idiopathic giant cell myocarditis by 25-year nationwide cohorts. *J Am Heart Assoc*. 2021;10:e019415. DOI: 10.1161/JAHA.120.019415.
7. Birnie DH, Nery PB, Ha AC, Beanlands RS. Cardiac sarcoidosis. *J Am Coll Cardiol*. 2016;68:411–421. DOI: 10.1016/j.jacc.2016.03.605.
8. Patel MR, Cawley PJ, Heitner JF, Klem I, Parker MA, Jaroudi WA, Meine TJ, White JB, Elliott MD, Kim HW, et al. Detection of myocardial damage in patients with sarcoidosis. *Circulation*. 2009;120:1969–1977. DOI: 10.1161/CIRCULATIONAHA.109.851352.
9. Iwai K, Tachibana T, Takemura T, Matsui Y, Kitaichi M, Kawabata Y. Pathological studies on sarcoidosis autopsy, I: epidemiological features of 320 cases in Japan. *Acta Pathol Jpn*. 1993;43:372–376.
10. Ekstrom K, Raisanen-Sokolowski A, Lehtonen J, Nordenswan HK, Mayranpaa MI, Kupari M. Idiopathic giant cell myocarditis or cardiac sarcoidosis? A retrospective audit of a nationwide case series. *ESC Heart Fail*. 2020;7:1362–1370. DOI: 10.1002/ehf2.12725.
11. Nakasuka K, Ito S, Miyata K, Inomata M, Yoshida T, Tamai N, Suzuki S, Murakami Y, Sato K, Suzuki S, et al. A case of idiopathic giant cell myocarditis with a past history of sarcoidosis. *J Cardiol Cases*. 2014;9:35–39. DOI: 10.1016/j.jccase.2013.09.004.
12. Ziegler JP, Batalis NI, Fulcher JW, Ward ME. Giant cell myocarditis causing sudden death in a patient with sarcoidosis. *Autops Case Rep*. 2020;10:e2020238. DOI: 10.4322/acr.2020.238.
13. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. *Am J Respir Crit Care Med*. 1999;160:736–755.
14. Juneau D, Nery P, Russo J, de Kemp RA, Leung E, Beanlands RSB, Birnie DH. How common is isolated cardiac sarcoidosis? Extra-cardiac and cardiac findings on clinical examination and whole-body (18) F-fluorodeoxyglucose positron emission tomography. *Int J Cardiol*. 2018;253:189–193. DOI: 10.1016/j.ijcard.2017.09.204.
15. Okada DR, Bravo PE, Vita T, Agarwal V, Osborne MT, Taqueti VR, Skali H, Chareonthaitawee P, Dorbala S, Stewart G, et al. Isolated cardiac sarcoidosis: a focused review of an under-recognized entity. *J Nucl Cardiol*. 2018;25:1136–1146. DOI: 10.1007/s12350-016-0658-1.
16. Giudicatti L, Marangou J, Nolan D, Dembo L, Baumwol J, Dwivedi G. The utility of whole body (18)F-FDG PET-CT in diagnosing isolated cardiac sarcoidosis: the Western Australian Cardiac Sarcoid Study. *Heart Lung Circ*. 2020;29:e1–e6. DOI: 10.1016/j.hlc.2019.07.007.
17. Petek BJ, Rosenthal DG, Patton KK, Behnia S, Keller JM, Collins BF, Cheng RK, Ho LA, Bravo PE, Mikacenic C, et al. Cardiac sarcoidosis: diagnosis confirmation by bronchoalveolar lavage and lung biopsy. *Respir Med*. 2018;144S:S13–S19. DOI: 10.1016/j.rmed.2018.09.008.
18. Lamacie MM, Almufleh A, Nair V, Stadnick E, Birnie D, Beanlands RSB, Chih S. Serial (18)F-fluorodeoxyglucose positron emission tomography imaging in a patient with giant cell myocarditis. *Circ Cardiovasc Imaging*. 2020;13:e009940.
19. Nery PB, Beanlands RS, Nair GM, Green M, Yang J, Mcardle BA, Davis D, Ohira H, Gollob MH, Leung E, et al. Atrioventricular block as the initial manifestation of cardiac sarcoidosis in middle-aged adults. *J Cardiovasc Electrophysiol*. 2014;25:875–881. DOI: 10.1111/jce.12401.
20. Kandolin R, Lehtonen J, Kupari M. Cardiac sarcoidosis and giant cell myocarditis as causes of atrioventricular block in young and middle-aged adults. *Circ Arrhythm Electrophysiol*. 2011;4:303–309. DOI: 10.1161/CIRCEP.110.959254.