JACC: CASE REPORTS VOL. 2, NO. 10, 2020

EDITORIAL COMMENT

Giant Cell Myocarditis

Still the Deadly Giant*

Nowell M. Fine, MD, SM

Giant cell myocarditis (GCM) remains a feared diagnosis among health care providers. This disease has remained somewhat of an enigma over the years, partly because of its low incidence, often fulminant clinical presentation with similarities to other forms of myocarditis (both clinically and histopathologically), variable treatment approaches, frequently rapid clinical progression, and overall poor prognosis. GCM presents significant challenges at all stages of its disease course, from its initial presentation through to its long-term management for those patients who survive the acute stage. As a result, there has been much written about GCM; however, our knowledge about the disease has actually advanced relatively slowly, and much remains uncertain and still to be determined. As an example, the pathophysiology of GCM is not well understood beyond its recognition as an autoimmune disorder attributable to T-lymphocyte–mediated myocardial inflammation (1). There is a known association with other autoimmune disorders such as inflammatory bowel disease, fibromyalgia, and Hashimoto thyroiditis (2). However, the true nature of this relationship, including which patients may be most at risk for GCM, remains unclear.

The clinical presentation is typically marked by rapidly progressive myocarditis deteriorating to a fulminant state accompanied by cardiogenic shock. However, other clinical presentations may occur, including those characterized predominantly by arrhythmia such as atrioventricular block or ventricular arrhythmias (3). Such features are shared with other causes of myocarditis, such as lymphocytic or cardiac sarcoidosis, and clinical features, in addition to laboratory and imaging findings, are typically unhelpful for differentiating among them. Furthermore, in some series, more indolent presentations of GCM have been described (1,4,5). Therefore, diagnostic confirmation requires demonstration of characteristic features by endomyocardial biopsy (EMB). These features include diffuse myocardial inflammatory infiltrate and the presence of multinucleated giant cells with associated myocyte necrosis in the absence of a viral origin. However, pathologic characteristics may resemble those of other forms of myocarditis, in particular cardiac sarcoidosis, whose primary distinguishing feature is the predominance of noncaseating granulomas, as well as more extensive fibrosis (6). In addition, EMB may also be subject to sampling error, leading to a possible false negative result, and therefore the need for repeat EMB in the setting of high clinical suspicion in a patient with a negative or equivocal pathologic result has been advocated (1,4,7). Some reports have also recommended targeted biopsy of involved myocardial regions on the basis of cardiovascular magnetic resonance findings (7). Early diagnosis and differentiation from other forms myocarditis are critical to facilitate prompt initiation of immunosuppression therapy because GCM remains one of the few causes of fulminant myocarditis where immunosuppression has been proven to improve outcomes when therapy is administered in the acute stage (1). However,

*Editorials published in *JACC: Case Reports* reflect the views of the authors and do not necessarily represent the views of *JACC: Case Reports* or the American College of Cardiology.

From the Division of Cardiology, Department of Cardiac Sciences and Community Health Sciences, Libin Cardiovascular Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada. Dr. Fine has reported that he has no relationships relevant to the contents of this paper to disclose.

The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2020.07.001

reliance on EMB may present a barrier to early diagnosis depending on availability, awareness, and clinical course, given that physicians may be less likely to pursue EMB for patients with less severe presentations or a high burden of comorbid illness. The spread of the coronavirus disease-2019 (COVID-19) pandemic and the risk of associated cardiomyopathy may contribute to such barriers (8) because clinicians may wish to exclude a diagnosis of COVID-19 before considering an invasive work-up. A high index of clinical suspicion remains vital for appropriate diagnostic work-up and early recognition.

Once the diagnosis is confirmed, early institution of combined (multiple-agent) immunosuppression is considered the standard of care because treatment with corticosteroids alone is generally recognized as inadequate to achieve disease stabilization and remission. The importance of this approach is now well established, and some series have demonstrated improved outcomes with immunosuppression regimens that combine both corticosteroid and non-corticosteroid agents (1,2). Despite this improvement, multiple regimens may be used at different centers, usually on the basis of experience, and no consensus approach exists, nor have clinical trials been conducted to guide decision making. Perhaps even more challenging are decisions about long-term therapy, including approach to weaning immunosuppression and total duration of therapy, because clinicians rely on a constellation of clinical, imaging, and serum markers to determine the optimal approach for each patient. The role of serial EMB to guide treatment decisions beyond the acute phase remains an area of uncertainty. Again, the low incidence translates into limited experience for many clinicians, thus adding further to the degree of difficulty. Long-term immunosuppression is often required given the known risk of recurrence, even after heart transplantation (1,2,4,5,9).

The proliferation of mechanical circulatory support (MCS) devices has expanded the armamentarium of treatment options available to patients presenting with fulminant myocarditis. MCS therapies may allow for stabilization of patients to facilitate further investigations such as EMB, and they may also bridge patients toward recovery as immunosuppression is instituted. Patients remaining on long-term MCS support even after cessation of immunosuppression have also been described (10). Although MCS provides opportunities to improve survival, its use in patients with GCM also presents unique challenges. Important among these is the heightened risk of infection in patients receiving concurrent immunosuppression therapy.

In this issue of *JACC: Case Reports*, we are again reminded of the numerous management challenges this diagnosis presents. Ma et al. (11) describe a case of 1 of the older patients (76 years of age) reported to have this disease, which typically manifests in the fourth or fifth decade of life. Previous reports have also highlighted the importance of maintaining a high index of clinical suspicion among patients presenting with fulminant myocarditis at both extremes of the age spectrum because GCM has been reported in patients as young as the second decade of life and as old as the eighth decade (4,12,13). Older patients are naturally at higher risk of poor outcomes, in part because of their more limited eligibility for heart transplantation, regarded as the definitive therapy for patients with GGM who do not achieve remission with immunosuppression. In this case, percutaneous microaxial biventricular assist devices were used to stabilize the patient and facilitate initiation of immunosuppression therapy, thereby allowing for a degree of recovery and eventual discontinuation of MCS. The use of multiple types of MCS devices has been described to manage GCM, including percutaneous MCS, extracorporeal membrane oxygenation, paracorporeal ventricular assist devices, and durable (ambulatory) ventricular assist devices (14). This case further illustrates how MCS device selection depends on several patient- and facility-related factors, including availability and experience. Despite this patient's survival beyond the acute stage and eventual discharge from the hospital, this case also illustrates how susceptible patients with GCM are to complications of both the disease and its therapy. This patient ultimately died only 3 months after diagnosis as a result of sepsis related to a catheter infection, after he became dependent on hemodialysis during the index hospitalization with GCM.

More recent series have demonstrated that patient survival and outcomes are better than the abysmal mortality rates described in earlier reports. Much has been learned about GCM, in particular the spectrum of clinical presentations and the disease course. Our understanding of its management has also evolved, with regard to both immunosuppression and the value of MCS in the acute phase and in the longer term for some patients. However, advances and

dissemination of knowledge can move slowly for rare diseases, and there remains much to learn. Important areas of ongoing research include disease-specific markers of prognosis and response to therapy toward developing consensus criteria to guide clinical decision making. In addition, the need for more multicenter data remains high. Despite the important advances that have improved our understanding and management of GCM, it still remains a very deadly giant among cardiovascular diseases.

ADDRESS FOR CORRESPONDENCE: Dr. Nowell M. Fine, University of Calgary, Libin Cardiovascular Institute, South Health Campus, 4448 Front Street Southeast, Calgary, Alberta T3M 1M4, Canada. E-mail: nmfine@ucalgary.ca.

REFERENCES

1. Kandolin R, Lehtonen J, Salmenkivi K, Raisanen-Sokolowski A, Lommi J, Kupari M. Diagnosis, treatment, and outcome of giant-cell myocarditis in the era of combined immunosuppression. Circ Heart Fail 2013;6:15–22.

2. Cooper LT Jr., Berry GJ, Shabetai R. Idiopathic giant-cell myocarditis–natural history and treatment. Multicenter Giant Cell Myocarditis Study Group Investigators. N Engl J Med 1997;336:1860–6.

3. Ekstrom K, Lehtonen J, Kandolin R, Raisanen-Sokolowski A, Salmenkivi K, Kupari M. Incidence, risk factors, and outcome of life-threatening ventricular arrhythmias in giant cell myocarditis. Circ Arrhythm Electrophysiol 2016;9:e004559.

4. Maleszewski JJ, Orellana VM, Hodge DO, Kuhl U, Schultheiss HP, Cooper LT. Long-term risk of recurrence, morbidity and mortality in giant cell myocarditis. Am J Cardiol 2015;115:1733–8.

5. Ekstrom K, Lehtonen J, Kandolin R, Raisanen-Sokolowski A, Salmenkivi K, Kupari M. Long-term outcome and its predictors in giant cell myocarditis. Eur J Heart Fail 2016;18:1452–8.

6. Blauwet LA, Cooper LT. Idiopathic giant cell myocarditis and cardiac sarcoidosis. Heart Fail Rev 2013;18:733–46.

7. Kalra A, Kneeland R, Samara MA, Cooper LT Jr. The changing role for endomyocardial biopsy in the diagnosis of giant-cell myocarditis. Cardiol Ther 2014;3:53–9.

8. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. Eur Heart J 2020 Mar 16 [E-pub ahead of print].

9. Toscano G, Tartaro P, Fedrigo M, Angelini A, Marcolongo R. Rituximab in recurrent idiopathic giant cell myocarditis after heart transplantation: a potential therapeutic approach. Transpl Int 2014;27:e38–42.

10. Bireta C, Tirilomis T, Grossmann M, et al. Long term biventricular support with Berlin Heart Excor in a septuagenarian with giant-cell myocarditis. J Cardiothorac Surg 2015;10:14.

11. Ma J, Ammirati E, Brambatti M, Adler E. Biventricular intravascular microaxial blood pumps and immunosuppression as bridge to recovery in giant cell myocarditis. J Am Coll Cardiol Case Rep 2020;2:1484–8.

12. 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;4:303–9.

13. Kasouridis I, Majo J, MacGowan G, Clark AL. Giant cell myocarditis presenting with acute heart failure. BMJ Case Rep 2017;2017:bcr2017219574.

14. Nakajima-Doi S, Mochizuki H, Iwasaki K, et al. Mechanical circulatory support combined with immunosuppression for the treatment of giant cell myocarditis- a single-center experience in Japan. Circ J 2020;84:815–9.

KEY WORDS cardiogenic shock, immunosuppression, mechanical circulatory support, myocarditis