Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 80, NO. 4, 2022

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

COVID-19–Associated Fulminant Myocarditis

Pathophysiology-Related Phenotypic Variance*

Ajith Nair, MD,[a] Anita Deswal, MD, MPH[b]

Worldwide, there have been more than 6.2 million deaths resulting from SARS-CoV-2 infection to date. Although COVID-19 is associated with higher mortality in patients with pre-existing heart failure, it has also been associated with de novo myocardial dysfunction.[1] Acute myocarditis (AM) has been recognized as a rare complication of SARS-CoV-2 infection and of the COVID-19 mRNA vaccination.[2,3] In a retrospective international cohort of 56,963 hospitalized patients with COVID-19, the prevalence of AM varied from 2.4 to 4.1 per 1,000 patients if cases of only definite or probable AM cases were considered or if possible AM cases were also included.[4] Patients with AM were young (median age 38 years) and were more often male. The mortality was 6.6% at 120 days, and all deaths occurred in patients with concomitant pneumonia. Among patients with definite or probable AM, 39% had fulminant myocarditis requiring inotropic support or mechanical circulatory support.

Fulminant myocarditis is associated with cardiogenic shock, ventricular arrhythmias, multiorgan dysfunction, and a frequent need for mechanical circulatory support, including venoarterial extracorporeal membrane oxygenation (VA-ECMO).[5] There has been an evolving understanding of the pathogenesis of fulminant myocarditis in COVID-19. Direct myocardial injury and inflammatory-mediated myocardial dysfunction have been 2 suggested pathways for development of COVID-19-associated fulminant myocarditis. Immunologic dysregulation can lead to the multisystem inflammatory syndrome (MIS) in young adults,[6] as first described in children (MIS-C), with an onset occurring 2-6 weeks after acute infection.[7] The clinical profile includes fevers, elevated inflammatory markers, rash, conjunctivitis, gastrointestinal symptoms, and myocardial dysfunction. In a report from New York State, 53% of MIS-C patients had evidence of AM.[8] Seen at a later time point, results of SARS-CoV-2 polymerase chain reaction (PCR) testing were not always positive, yet serologic testing and history implicated COVID-19 as the culprit.

SEE PAGE 299

However, our knowledge of COVID-19-associated fulminant myocarditis remains limited. In this issue of the *Journal of the American College of Cardiology*, Barhoum et al[9] differentiate 2 phenotypes of this condition. One phenotype appeared to be associated with the adult MIS (MIS-A$^+$), whereas the second occurred in adults who failed to meet MIS criteria (MIS-A$^-$). This study was a single-center retrospective analysis from Paris, France of 38 patients without a history of COVID-19 vaccination who were admitted to the intensive care unit (ICU) (March 2020 to June 2021) for suspected fulminant COVID-19 myocarditis. Patients were confirmed to have SARS-CoV-2 infection by positive reverse transcription (RT)-PCR and/or by serologic testing. Myocarditis

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the author and do not necessarily represent the views of the *Journal of the American College of Cardiology* or the American College of Cardiology.

From the [a]Division of Cardiology, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA; and the [b]Department of Cardiology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA.

Christie Ballantyne, MD, served as Guest Editor-in-Chief for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2022.06.003

was defined as definite (76%) and probable (24%) by the criteria described by Bonaca et al[10] for cancer therapeutics-related myocarditis. As noted in other studies, patients were predominantly young men (median age 27.5 years). The patients had severe left ventricular dysfunction (median left ventricular ejection fraction [LVEF] 20%), 79% presented with cardiogenic shock, and 42% required VA-ECMO. Overall, the mortality was 13% during hospitalization. Most patients had normalized their LVEF by discharge, and LVEF remained preserved at a median follow-up of 235 days.

With regard to the 2 phenotypes, 66% of patients met MIS-A$^+$ criteria, whereas the other 34% were classified as having MIS-A$^-$. The 2 groups had significant differences in presentation, immunologic profiles, and outcomes, likely driven by pathophysiologic differences. In general, the MIS-A$^-$ patients were sicker and had worse outcomes. Specifically, compared with the MISA-A$^+$ patients, the MIS-A$^-$ group had a shorter time between the onset of COVID-19 symptoms and the development of AM, a shorter time to ICU admission, and more severe presentations as assessed by lower LVEF and sequential organ failure assessment (SOFA) scores. Further, the MIS-A$^-$ patients had higher lactate levels, were more likely to undergo VA-ECMO (92% vs 16%), had higher ICU mortality (31% vs 4%; $P = 0.04$), and a had lower 3-month cumulative probability of survival (68% $\pm$ 13%) compared with MIS-A$^+$ patients (96% $\pm$ 4%). The immunologic profiles also differed. The MIS-A$^+$ patients demonstrated markers of severe systemic inflammation (higher white blood cell count, C-reactive protein, procalcitonin, and tumor necrosis factor-α) and elevated levels of interleukin (IL)-17 and IL-22 consistent with the mucocutaneous manifestations, as compared with MIS-A$^-$ patients, who had higher interferon (IFN)-α_2 and IL-8 levels. The MIS-A$^-$ phenotype may thus represent an exaggerated innate immune response to the COVID-19 infection, whereas the MIS-A$^+$ phenotype may represent a maladaptive acquired immune response. Interestingly, more than one-half of MIS-A$^-$ patients had RNA-polymerase III antibodies. Although the true significance of this finding is uncertain, an association with pre-existing RNA-polymerase III autoantibodies in patients without systemic sclerosis who developed viral myocarditis has been previously reported.[11] Investigators have postulated that this finding may represent an altered viral defense or immune response. Genetic susceptibility to myocarditis has been described, suggesting that some patients may have vulnerable myocardium prone to inflammatory-mediated injury.[12]

Barhoum et al[9] should be commended on their work in furthering our understanding of fulminant myocarditis related to COVID-19 infection. However, a few limitations should be acknowledged. Although this study presents the largest case series of COVID-19 related fulminant myocarditis to date, it consists of a modest number of 38 patients from a single center. This study is not able to estimate the incidence of fulminant myocarditis at the center given that the number of all COVID-19 hospitalizations during that time is not available. Most patients were treated with immunosuppressive medications, although in this observational study, it is unclear whether therapies altered the clinical course. Immunosuppressive therapy is generally not well supported for most acute viral myocarditis, but it does have a role in myocarditis of noninfectious origin (eg, immune checkpoint inhibitors, giant cell myocarditis, necrotizing eosinophilic myocarditis).[13] Corticosteroids are recommended, however, for treatment of MIS-C, as well as for COVID-19 myocarditis and mRNA vaccine-associated myocarditis.[3] Additionally, only 3 patients underwent endomyocardial biopsies, and only 2 of these biopsy specimens were diagnostic of myocarditis and were absent of viral inclusions. Other reports have rarely demonstrated the presence of viral inclusions by electron microscopy.[14] In addition to an immune-mediated mechanism, viral injury in AM has been hypothesized to occur through myocardial tropism and direct cellular invasion. SARS-CoV-2 targets angiotensin-converting enzyme 2 receptors, which are expressed by a variety of cardiac cells. In a study by Bailey et al,[15] SARS-CoV-2 was shown to infect cardiomyocytes directly through an angiotensin-converting enzyme 2- and endosomal cysteine protease-dependent pathway and cause myocardial dysfunction by sarcomere breakdown and cardiomyocyte cell death. Engineered human tissue demonstrated evidence of cardiomyocyte infection, cell death, and macrophage infiltration. The inflammatory finding was similar in autopsy and endomyocardial specimens, where viral RNA staining was positive within cardiomyocytes. These findings are relevant to the current study, where MIS-A$^-$ patients had evidence of early infection, including positive PCR results without a positive serologic response.

Thus, the primary finding of this study was that MIS-A$^+$ fulminant myocarditis likely represents a postinfectious complication of SARS-CoV-2 infection, characterized by a greater delay from initial symptoms to cardiac manifestations, positive serologic results, and negative RT-PCR results. In contrast, MIS-A$^-$ fulminant myocarditis occurred earlier after viral infection and was marked by negative serologic

results, positive RT-PCR results, and an overwhelming immune response, including profound cardiogenic shock, and higher mortality. COVID-19 has increased the focus on the mechanisms of myocarditis and viral-associated myocardial dysfunction. Myocardial complications are caused by a direct viral insult, a systemic inflammatory response, or microvascular and macrovascular thrombosis. Fulminant myocarditis is rare and may result from either of 2 mechanisms: viral tropism or an immune-mediated mechanism. It remains to be seen whether using antiviral therapy vs immunomodulatory therapy on the basis of clinical and cytokine profiles will yield benefits. Fulminant myocarditis invariably requires hemodynamic support and carries a high mortality risk if it is recognized late. However, the long-term prognosis in patients who survive the critical period is favorable, with recovery of myocardial function. This study highlights the ever-shifting understanding of the pathophysiology and therapeutic approaches to fulminant myocarditis.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Ajith Nair, Division of Cardiology, Department of Medicine, Baylor College of Medicine, 7200 Cambridge Street, Suite 6C, Houston, Texas 77030, USA. E-mail: ajith.nair@bcm.edu. Twitter: @ajith1230.

REFERENCES

1. Bhatt AS, Adler ED, Albert NM, et al. Coronavirus disease-2019 and heart failure: a scientific statement from the Heart Failure Society of America. *J Card Fail*. 2022;28:93–112.

2. Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA vaccines. *Circulation*. 2021;144:471–484.

3. Writing C, Gluckman TJ, Bhave NM, et al. 2022 ACC expert consensus decision pathway on cardiovascular sequelae of COVID-19 in adults: myocarditis and other myocardial involvement, post-acute sequelae of SARS-CoV-2 infection, and return to play: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2022;79:1717–1756.

4. Ammirati E, Lupi L, Palazzini M, et al. Prevalence, characteristics, and outcomes of COVID-19-associated acute myocarditis. *Circulation*. 2022;145:1123–1139.

5. Kociol RD, Cooper LT, Fang JC, et al. Recognition and initial management of fulminant myocarditis: a scientific statement From the American Heart Association. *Circulation*. 2020;141:e69–e92.

6. Morris SB, Schwartz NG, Patel P, et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection - United Kingdom and United States, March-August 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1450–1456.

7. Feldstein LR, Tenforde MW, Friedman KG, et al. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. *JAMA*. 2021;325:1074–1087.

8. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children in New York State. *N Engl J Med*. 2020;383:347–358.

9. Barhoum P, Pineton de Chambrun M, Dorgham K, et al. Phenotypic heterogeneity of fulminant COVID-19-related myocarditis in adults. *J Am Coll Cardiol*. 2022;80:299–312.

10. Bonaca MP, Olenchock BA, Salem JE, et al. Myocarditis in the setting of cancer therapeutics: proposed case definitions for emerging clinical syndromes in cardio-oncology. *Circulation*. 2019;140:80–91.

11. Pineton de Chambrun M, Charuel JL, Hekimian G, et al. Severe viral myopericarditis with autoantibodies directed against RNA polymerase III. *Ann Intern Med*. 2020;172:502–504.

12. Kontorovich AR, Patel N, Moscati A, et al. Myopathic cardiac genotypes increase risk for myocarditis. *J Am Coll Cardiol Basic Trans Science*. 2021;6:584–592.

13. Rajpal S, Kahwash R, Tong MS, et al. Fulminant myocarditis following SARS-CoV-2 infection: JACC patient care pathways. *J Am Coll Cardiol*. 2022;79:2144–2152.

14. Albert CL, Carmona-Rubio AE, Weiss AJ, Procop GG, Starling RC, Rodriguez ER. The enemy within: sudden-onset reversible cardiogenic shock with biopsy-proven cardiac myocyte infection by severe acute respiratory syndrome coronavirus 2. *Circulation*. 2020;142:1865–1870.

15. Bailey AL, Dmytrenko O, Greenberg L, et al. SARS-CoV-2 infects human engineered heart tissues and models COVID-19 myocarditis. *J Am Coll Cardiol Basic Trans Science*. 2021;6:331–345.

KEY WORDS cardiomyopathy, COVID-19, myocarditis, SARS-CoV-2