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.

Cardiovascular Pathology 61 (2022) 107450

Contents lists available at ScienceDirect

Cardiovascular Pathology

journal homepage: www.elsevier.com/locate/carpath

Commentary

Commentary on an inflammatory discussion: Society for Cardiovascular Pathology journal club☆,☆☆

Melanie C. Bois*

Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

ARTICLE INFO

Article history:
Received 3 July 2022
Accepted 3 July 2022

Keywords:
Myocarditis
Inflammation
Dallas criteria

ABSTRACT

The histologic criteria for myocarditis are a focal point of scientific debate in the wake of the SARS-CoV-2 pandemic. Variable methodologies have evolved in an evaluation already plagued by high intraobserver variability and low sensitivity. In this commentary, two topical manuscripts are reviewed in the context of this unfolding discussion.

1. Introduction

The histologic diagnosis of myocarditis has been, and remains, controversial. Provocative questions gained traction in the setting of the recent SARS-CoV-2 global pandemic; however, the tenets of this diagnostic conundrum date back decades. In 1986, a consensus panel met in Texas (USA) to address this very problem. The resultant criteria, aptly known as the Dallas criteria, governed the histologic diagnosis of myocarditis through the end of the 20th century [1,2]. However, in the early 2000s, concern regarding the poor sensitivity and specificity of the Dallas criteria began to emerge [3]. Highlighted among the chief limitations were high interobserver variability and variable treatment outcomes among Dallas-positive and Dallas-negative patients. A call for multidisciplinary, integrated diagnoses performed in conjunction with ancillary studies to increase diagnostic yield (such as polymerase chain reaction [PCR] for viral nucleic acid and immunohistochemical [IHC] staining) was popularized. In response, the European Society of Cardiology embraced such recommendations and submitted a position statement on myocardial diseases in 2013 [4]. In this, specific recommendations for the use of histology, IHC, and viral PCR were outlined for the histologic diagnosis of myocarditis by endomyocardial biopsy. Since that time, divergent practices for the histologic diagnosis of myocarditis have emerged in a region-dependent fashion.

The emergence of SARS-CoV-2 and controversial presence of myocardial inflammation related to coronavirus disease 2019 (COVID-19) heart disease brought the shortcomings of current practices to light. While criteria for a diagnosis of myocarditis by endomyocardial biopsy exist, consensus statements on the histologic features of myocarditis in explantation and autopsy specimens are not readily available. The possibility of histiocyte-predominant inflammatory infiltrates added additional complexity to an already convoluted practice of the histologic diagnosis of myocarditis [5]. Moreover, identification of patients with COVID-19-associated myocardial inflammation became further opacified as imaging studies reported a high prevalence of myocarditis which were largely not substantiated in autopsy-based studies [6,7].

Several articles have addressed the concerns outlined above. In this commentary, two such manuscripts will be highlighted [8,9].

1.1. Factual summary of articles

Article 1:
Endomyocardial biopsy-confirmed myocarditis and inflammatory cardiomyopathy: clinical profile and prognosis

In the first article [8], 99 patients with a high clinical suspicion for acute myocarditis or inflammatory cardiomyopathy underwent endomyocardial biopsy (1997-2019) with the goal of evaluating the sensitivity of the Dallas criteria versus the IHC-based criteria. The authors report that the use of immunohistochemical methodologies significantly increased overall sensitivity among patients with high clinical suspicion and meeting American Heart Association criteria for endomyocardial biopsy, both in the acute

Abbreviations: PCR, Polymerase chain reaction; IHC, Immunohistochemistry; COVID-19, Coronavirus disease 2019; MRI, Magnetic resonance imaging; HMID, Histiocytic myocardial inflammatory disease.

☆ Note: He Wang, MD, PhD, Department of Pathology, Yale University, is the coordinator of the SCVP Journal Club, a forum for discussion of contemporary topics and publications relevant to the science and practice of cardiovascular pathology.

☆☆ The author has no conflict of interest to disclose.

* Corresponding Author: Melanie C. Bois, MD, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.

E-mail address: bois.melanie@mayo.edu

https://doi.org/10.1016/j.carpath.2022.107450
1054-8807/

setting (P= .04) and in those with subacute, inflammatory cardiomyopathy presentations (P< .001). Moreover, while prognosis and clinical outcome were strongly dependent on clinical stage and hemodynamic parameters, the finding of inflammation on endomyocardial biopsy portended a worse prognosis for stage- and cardiac function-matched peers. Conversely, the use of immunosuppression among a subset of individuals with endomyocardial biopsy-proven myocarditis was not associated with a reduction in adverse outcomes (P= .6). The authors also observed a poor correlation with cardiac magnetic resonance imaging (MRI) as evaluated by the classic Lake Louise criteria.

Article 2:
The spectrum of macrophage-predominant inflammatory myocardial disease presenting as fulminant heart failure

The second article [9] investigated the spectrum of macrophage-predominant inflammatory myocardial diseases among a subset of patients with acute heart failure. This article is particularly relevant in today's era, given the increased discussions surrounding histiocytic myocardial inflammatory disease (HMID) as proposed in the setting of SARS-CoV-2 infection and COVID-19-related myocardial disease. The authors highlight that current histologic classifications of myocarditis do not include a macrophage-predominant subtype and make a case for such on the basis of a small, anecdotal series. They present six cases with significant hemodynamic failure and histiocytic myocardial inflammation, in which four had histologically evident myocyte necrosis and one had distinct zones of myocyte loss. Due to overlap with features seen in pathologic antibody-mediated rejection in cardiac allotransplantation patients, C4d staining was pursued in these individuals. The authors postulate an antibody-mediated pathogenesis underpinning the macrophage-predominant type of myocarditis. While they observed two individuals with this presentation in the setting of systemic lupus erythematosus, they recognize a variable patient presentation and possible confounding features such as ischemia and the (potential) role of chronic disease in this presentation. Viral testing was not performed on these specimens.

2. Discussion

The articles presented generated excellent commentary and discussion from Journal Club attendees. Article 1 [8] was timely and discussed a highly relevant assessment of myocarditis by light microscopy versus immunohistochemistry. The authors found that the use of immunohistochemistry improved sensitivity and correlated with patient outcome. The data are exceptionally useful as the current criteria for the diagnosis of myocarditis by endomyocardial biopsy are reviewed and updated. Correlation with additional like-minded studies will be of utility, with particular attention to separating acute myocarditis (and the clinical presentation/outcomes) from subacute/chronic forms. Expert discussion during the Journal Club found variable practices and preferences among the Society for Cardiovascular Pathology members, with both those in favor of the use of immunohistochemistry and others who cautioned about the possibility of overcalling myocarditis with these ancillary studies. All agreed that any newly penned definitional paradigms must be rooted in patient outcome to avoid the use of arbitrary quantification of leukocytes on tissue samples.

Article 2 [9] generated a robust discussion about the concept of histiocytic myocardial inflammation. Varying opinions regarding the overall significance of the finding (secondary to ischemic injury versus a primary infiltrate that mediates myocardial damage) was debated. The article provided case-based scenarios; however, the lack of a control group makes it challenging to assign meaning to anecdotal patient presentations. Nevertheless, the article brings to light the current challenges we face in decoding histocytic inflammatory infiltrates and the differences of opinions regarding its underlying etiology. Members of the Journal Club cited the propensity of C4d to highlight ischemic and damaged myocardium without specificity to antibody-mediated mechanisms, thus cautioning against the use of C4d immunohistochemistry to draw strong conclusions about the pathogenesis of this process.

3. Commentary

Herein, we discussed two articles in which the authors raise questions as to the meaning of inflammation in the heart and how we can best interpret such changes. This inquiry is aptly placed chronologically with current trends in the literature as well as with relevant global health concerns.

After reading these articles, physicians and researchers are well-positioned for additional inquiry. The need for investigations into the characteristic inflammatory milieu in both acute pathologies and chronic cardiomyopathies is highlighted as a natural subsequent step to this interpretation. Resultant proposed diagnostic systems and investigations must be anchored in clinical outcome. In this author's opinion, further investigations into the role of endomyocardial biopsy and cardiac MRI (or a synergism therein) may provide meaningful insights into a multidisciplinary approach to this challenging question.

Overall, authors of the reviewed manuscripts and Journal Club members provided provocative questions and observations with critical appraisal of data provided. Through venues such as this, we can continue to work toward a more reliable diagnostic system with improved patient outcomes.

References

[1] Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ Jr, et al. Myocarditis: a histopathologic definition and classification. Am J Cardiovasc Pathol 1987;1:3–14.
[2] Aretz HT. Myocarditis: the Dallas criteria. Hum Pathol 1987;18(6):619–24.
[3] Baughman KL. Diagnosis of myocarditis: death of Dallas criteria. Circulation 2006;113:593–5.
[4] Caforio AL, Pankuweit S, Arbustini E, et al. European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013;34(33):2636–48 2648a-2648d.
[5] Fox SE, Falgout L, Vander Heide RS. COVID-19 myocarditis: quantitative analysis of the inflammatory infiltrate and a proposed mechanism. Cardiovasc Pathol 2021;54:107361 Sep-Oct.
[6] Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). [published correction appears in JAMA Cardiol. 2020 Nov 1;5(11):1308].. JAMA Cardiol 2020;5(11):1265–73. doi:10.1001/jamacardio.2020.3557.
[7] Halushka MK, Vander Heide RS. Myocarditis is rare in COVID-19 autopsies: cardiovascular findings across 277 postmortem examinations. Cardiovasc Pathol 2021;50:107300.
[8] Domínguez F, Cobas Paz R, Salas Antón C, et al. Endomyocardial biopsy-confirmed myocarditis and inflammatory cardiomyopathy: clinical profile and prognosis. *Rev Esp Cardiol* (Engl Ed) 2022 S1885-5857(22)00060-3.
[9] Goldman BI, Choung HY, Sainvil M, Miller CW. The spectrum of macrophage-predominant inflammatory myocardial disease presenting as fulminant heart failure. Cardiovasc Pathol 2022;57:107393.