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 58 (2022) 107416

Contents lists available at ScienceDirect

Cardiovascular Pathology

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

Editorial

Diffuse mononuclear inflammatory response to COVID-19: friendly fire or smoldering enemy?

A recent paper by Goldman et al. [1] described a series of six patients who presented to the University of Rochester Medical Center over a 2 years period with acute onset of cardiogenic shock. All six patients underwent endomyocardial biopsy for pathologic diagnosis and every biopsy demonstrated interstitial myocardial inflammation that consisted of predominantly large, mononuclear cells. Five of the six cases (5/6) showed microvascular luminal narrowing associated with reactive mononuclear cells, changes similar to antibody mediated rejection in cardiac allografts. The biopsies were subsequently stained for cluster of differentiation (CD[68]) and CD31 which showed CD68 positive cells adjacent to and sometimes within myocardial microvasculature. The authors proposed a new term, distinct from currently used classification systems, to characterize the findings.

According to the World Health Organization and/or International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies, inflammatory cardiomyopathy is defined as myocarditis in association with cardiac dysfunction. The term myocarditis is defined as "an inflammatory disease of the myocardium" that is diagnosed by established histological, immunological, and immunohistochemical criteria [2]. In the position statement of the European Society of Cardiology, they cite the World Health Organization as stating that an endomyocardial biopsy could be diagnosed as myocarditis after immunohistochemical detection of focal or diffuse mononuclear infiltrates with >14 leukocytes per 1 mm^2 ($CD3^+$ T lymphocytes and/or $CD68^+$ macrophages). The consortium further refined the definition to include ≥14 leucocytes/mm^2, including up to 4 monocytes/mm^2, with the presence of CD3-positive T-lymphocytes at ≥7 cells/mm^2 [3]. The Dallas Criteria, generally considered the gold standard for endomyocardial diagnosis of myocarditis, simply state that the diagnosis requires the presence of an inflammatory infiltrate and definitive myocyte damage [4]. Some reports have shown large numbers of macrophages infiltrating the myocardium but these cases are usually discussed in the context of chronic myocarditis which is associated with significant fibrosis. By these currently accepted criteria, the Goldman cases would not qualify as acute myocarditis because they require the presence of both CD3+ T lymphocytes independent from the presence of macrophages and the macrophages present do not cluster at >14 leukocytes per 1 mm^2. In their analysis, Goldman noted that two cases occurred in patients with no significant prior medical history while two others developed in the background of known systemic lupus erythematosus (SLE); one of which was associated with macrophage activation syndrome . They concluded that all six cases represented a form of histiocytic inflammatory myocardial disease distinct from chronic inflammatory cardiomyopathies and coined the term "histiocytic myocardial inflammatory disease" to explain the findings of acute inflammation with associated cardiac dysfunction. They further hypothesized that histiocytic myocardial inflammatory disease may be primary or secondary and that myocyte necrosis could be seen in both forms.

We recently published a paper in this Journal also describing the diffuse interstitial monocyte and/or macrophage myocardial infiltrate present in autopsied patients who died of severe COVID-19 [5]. In our study, we noted that SARS-CoV-2 infected hearts did not show a significant lymphocytic infiltrate characteristic of acute viral myocarditis which was commonly assumed to be underlying cardiac complications in early reports from China. We, as well as others, [6] noticed that some small capillaries contained platelet/fibrin clots associated with varying degrees of acute myocyte necrosis in nearby myocytes. We originally hypothesized [7] that SARS-CoV-2 was infecting the endothelium causing damage and the reported swelling and clot formation. After recognizing the increased monocyte and/or macrophage population, we proposed that this pattern of inflammation may be a unique consequence of COVID-19 infection. Given the cases reported by Golden et al., we agree that acute macrophage-predominant inflammatory infiltrates may represent a distinct form of inflammatory heart disease that occurs in a variety of clinical contexts and may be important in understanding the growing concern regarding long COVID-related cardiac effects.

Increased numbers of macrophages in COVID hearts were reported early by Basso et al. [8]. The European consortium found that 86% of the 21 COVID hearts they examined contained increased numbers of interstitial macrophages. They concluded that the increased macrophages likely reflected the underlying vascular damage consequent to the co-morbid vascular conditions of the patient population. Since hypertension, diabetes, and diabetes are known to cause endothelial dysfunction, it was important to control for these underlying conditions. Our study showed that COVID-19 hearts contained increased numbers of CD68+ cells compared to control, non-COVID autopsied hearts from patients with these important underlying risk factors [5].

Goldman also described coagulative myocyte necrosis in two of the six cases based on Masson trichrome staining. Interestingly, the same two hearts showed cytoplasmic positivity with C4d and/or C9 and the authors concluded that these areas represented coagu-

https://doi.org/10.1016/j.carpath.2022.107416

lation necrosis with complement activation. It was not clear to the authors whether the coagulative necrosis was secondary to direct histiocytic injury (complement mediated cell death) or to ischemia and/or reperfusion secondary to microvascular injury and resulting hypoperfusion. Pellegrini et al. [6] performed a systematic pathological analysis of 40 hearts from hospitalized patients dying of COVID-19 in Italy. Of the 40 hearts examined, 35% (14) contained myocyte necrosis, predominantly in the left ventricle. Importantly, the incidence of severe coronary artery disease (defined as >75% cross-sectional narrowing) was not different between hearts with or without myocyte necrosis. Cardiac thrombi were present in 11 of the 14 hearts with necrosis (78.6%) and the microthrombi contained significantly more fibrin and terminal complement (C5b-9) immunostaining than thromboemboli from COVID-19 negative patients. The authors concluded that microthrombi was the most common cause of myocyte necrosis in COVID patients.

In our cohort, we observed focal myocyte positivity with C5b-9 in individual myocyte necrosis consistent with the data from Goldman. However, in the larger areas of coagulative necrosis, the dead myocytes were negative for C4d and C5b-9 staining. Similar to other reports, the majority of necrotic myocytes were present in the left ventricle but were also identified in the right ventricle which may be consistent with acute right heart strain commonly seen in severely ill COVID-19 patients. However, because many of the necrotic myocytes showed evidence of contraction band necrosis, we believe that the majority injury is due to microvascular and/or endothelial injury and consequent ischemia and/or reperfusion injury. Interestingly, a recent report by Dutt et al. demonstrates that enhanced circulating endothelial cells (CD452CD31+ CD34+ CD146+), circulating endothelial progenitors (CD452CD31+ CD34+/2CD1462), and neutrophils (CD11b+ CD66b+) correlated with the severity of COVID-19 disease suggesting that SARS-CoV-2 infection causes damage and increased turnover of endothelial cells [9]. In our recent review article, we pointed out a possible important role of monocyte-derived macrophages in the pathogenesis of severe COVID-19 induced myocardial damage either by causing a cytokine-mediated endothelial damage and/or by causing localized endothelial damage and/or apoptosis [10].

Diffuse myocardial infiltration with mononuclear inflammatory cells has been typically discussed in relation to chronic myocarditis and/or inflammatory dilated cardiomyopathy [11]. Interestingly, diffuse interstitial mononuclear infiltrates have been shown in other systemic viral infections (e.g., Hentavirus, Ebola) and was even described in the SARS-Co-V epidemic of 2009 [12]. There is now convincing evidence that monocyte/macrophages can be infected by SARS-CoV-2 which suggests that the virus can reach the heart during transient viremia and/or through actual infiltration of the myocardium [13, 14]. It is important to note that changes described in most COVID-19 autopsy hearts may not exactly coincide with currently accepted definition of inflammatory cardiomyopathy. Although there have been reports of cardiac and renal dysfunction associated with SARS-CoV-2 infection (excluding rare reports of acute viral myocarditis) [15, 16], respiratory damage and/or failure is responsible for the vast majority of COVID-19 mortality. Furthermore, to date no documented reports of long-term cardiac dysfunction and/or ventricular remodeling in patients who survive COVID-19.

Given the multiple reports of diffuse monocyte and/or macrophage infiltration of COVID-19 hearts, it is interesting to speculate whether this pattern of inflammation is “friendly fire,” given that the non-traditional monocyte and/or macrophage subsets are considered to be anti-inflammatory in nature and therefore protective of the heart, or “enemy fire” in that persistent presence of significant numbers of inflammatory cells could result in chronic, low grade inflammation and potentially in fibrosis and/or remodeling of the affected ventricle. At this point, there is not enough basic knowledge (i.e., immunology/microbiology) or clinical follow up to answer these questions. It is clear that more investigation is needed to understand the effects of COVID-19 on the heart especially given the increasing concern about cardiac symptoms in COVID survivors (“long haulers”). These studies should include both basic and clinical studies but should include the systematic collection of endomyocardial biopsies and autopsied hearts to generate histology and tissue biobanks to better characterize the pathology of SARS-CoV-2 infection in the heart.

Richard S. Vander Heide*
Service Line Medical Director of Pathology and Laboratory Medicine, Marshfield Clinic Health System, Marshfield, Wisconsin, United States

*Corresponding author: Richard S. Vander Heide, Marshfield Clinic Health System, Pathology, 1000 N. Oak Avenue, Marshfield, Wisconsin 54449, United States.
E-mail address: vanderheide.richard@marshfieldclinic.org
Revised 1 February 2022

References

[1] Goldman BI, Choung HY, Sainvil M, Miller CW. The spectrum of macrophage-predominant inflammatory myocardial disease presenting as fulminant heart failure. Cardiovasc Pathol 2021 Oct 23;57:107393 Epub ahead of print. PMID: 34699976. doi:10.1016/j.carpath.2021.107393.
[2] Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, Olsen E, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies. Circulation 1996 Mar 1;93(5):841–2 PMID: 8598070. doi:10.1161/01.cir.93.5.841.
[3] Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, 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 Sep 2648a-2648dEpub 2013 Jul 3. PMID: 23824828. doi:10.1093/eurheartj/eht210.
[4] Leone O, Veinot JP, Angelini A, Baandrup UT, Basso C, Berry G, Bruneval P, et al. 2011 consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. Cardiovasc Pathol 2012;21(4):245–74 Jul-Aug Epub 2011 Dec 3. PMID: 22137237. doi:10.1016/j.carpath.2011.10.001.
[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 Epub 2021 Jun 24. PMID: 34174415; PMCID: PMC8223028. doi:10.1016/j.carpath.2021.107361.
[6] Pellegrini D, Kawakami R, Guagliumi G, Sakamoto A, Kawai K, Gianatti A, Nasr A, et al. Microthrombi as a major cause of cardiac injury in COVID-19: a pathologic study. Circulation 2021 Mar 9;143(10):1031–42 Epub 2021 Jan 22. PMID: 33480806. doi:10.1161/CIRCULATIONAHA.120.051828.
[7] Fox SE, Li G, Akmatbekov A, Harbert JL, Lameira FS, Brown JQ, Vander Heide RS. Unexpected features of cardiac pathology in COVID-19 infection. Circulation 2020 Sep 15;142(11):1123–5 Epub 2020 Jul 21. PMID: 32689809. doi:10.1161/CIRCULATIONAHA.120.049465.
[8] Basso C, Leone O, Rizzo S, De Gaspari M, van der Wal AC, MC Aubry, Bois MC, et al. Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study. Eur Heart J 2020 Oct 14;41(39):3827–35 PMID: 32968776; PMCID: PMC7543528. doi:10.1093/eurheartj/ehaa664.
[9] Dutt TS, LaVergne SM, Webb TL, Baxter BA, Stromberg S, McFann K, Berry K, et al. Comprehensive immune profiling reveals CD56+ monocytes and CD31+ endothelial cells are increased in severe COVID-19 disease. J Immunol 2022 Feb 1;208(3):685–96 Epub 2022 Jan 5. PMID: 34987111. doi:10.4049/jimmunol.2100830.
[10] Fox SE, Heide RSV. COVID-19: the heart of the matter-pathological changes and a proposed mechanism. J Cardiovasc Pharmacol Ther 2021;26(3):217–24 May Epub 2021 Mar 11. PMID: 33703938. doi:10.1177/1074248421995356.
[11] Nakayama T, Sugano Y, Yokokawa T, Nagai T, Matsuyama TA, Ohta-Ogo K, Ikeda Y, et al. Clinical impact of the presence of macrophages in endomyocardial biopsies of patients with dilated cardiomyopathy. Eur J Heart Fail 2017;19(4):490–8 Apr Epub 2017 Feb 20. PMID: 28217949. doi:10.1002/ejhf.767.
[12] Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, Butany J. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest 2009;39(7):618–25 Jul Epub 2009 May 6. PMID: 19453650; PMCID: PMC7163766. doi:10.1111/j.1365-2362.2009.02153.x.
[13] Zhang D, Guo R, Lei L, Yawen Wang, Yili Wang, Qian H, Dai T, et al. COVID-19 infection induces readily detectable morphological and inflammation-related

phenotypic changes in peripheral blood monocytes, the severity of which correlate with patient outcome. bioRxiv 2020. doi:10.1101/2020.03.24.20042655.
[14] Boumaza A, Gay L, Mezouar S, Bestion E, Diallo AB, Michel M, Desnues B, et al. Monocytes and macrophages, targets of severe acute respiratory syndrome coronavirus 2: the clue for coronavirus disease 2019. Immunoparalysis. J Infect Dis. 2021 Aug 2;224(3):395–406 PMID: 33493287; PMCID: PMC7928817. doi:10.1093/infdis/jiab044.
[15] Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, Cani DS, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:819–24.
[16] Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, Hazzan AD, et al. Northwell nephrology COVID-19 research consortium. 2020. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020;98:209–18.