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Cardiovascular Pathology 53 (2021) 107336

Contents lists available at ScienceDirect

Cardiovascular Pathology

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

Editorial

A novel coronavirus meets the cardiovascular system: Society for Cardiovascular Pathology Symposium 2021

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ARTICLE INFO

Article history:
Received 6 April 2021
Accepted 8 April 2021

Keywords:
COVID-19
Pathology
Myocarditis
Endothelium

The year 2020 will go down in history as an *annus horribilis* due to the rampant pandemic of the novel human coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus (1-3). While COVID-19 begins as a respiratory illness, severe COVID-19 is a systemic disease with multifaceted manifestations of involvement of the cardiovascular system (4). Clinical evidence of cardiovascular involvement portents an adverse, and often fatal, outcome (1-3).

Cardiovascular pathologists, individually and through their organizations, the Society for Cardiovascular Pathology (SCVP) and the Association for European Cardiovascular Pathology (AECVP), have been committed to proactively studying and providing credible information about the pathological basis for the diverse manifestations of cardiovascular system involvement in COVID-19. Cardiovascular pathologists have advocated for autopsy-based investigation (5), participated in a multi-institutional autopsy interest group (6), published initial reports describing the pathological features of multi-organ involvement in COVID-19 (7,8), and lead investigative efforts to determine the multifaceted clinical manifestations of involvement of the cardiovascular system in COVID-19 (9-14).

Fittingly, the SCVP Symposium in 2021 was focused on COVID-19. The SCVP 2021 Symposium was organized by the SCVP program committee led by Dr. Dylan Miller and was held virtually on Saturday March 13 as part of the SCVP Companion Meeting accompanying the United States and Canadian Academy of Pathology (USCAP) Annual Meeting. The title was: "A Novel Coronavirus Meets the Cardiovascular System: What We Know and How We Know It." An important feature of the Symposium was the multidisciplinary approach to addressing the issues related to the topic. The speakers and titles of their presentations were as follows:

- Ornella Leone, MD (University of Bologna) – Cardiovascular Findings in COVID-19;
- Carolyn Glass, MD, PhD (Duke University) – COVID-19 Findings Outside the Heart and Development of Autopsy Research Tissue Models;
- Charles Lowenstein, MD (Johns Hopkins University) – Cardiovascular Manifestations of COVID-19; and
- Kate Hanneman, MD (University of Toronto) – Cardiovascular Imaging in COVID-19.

Early in the pandemic, clinicians noted that hospitalized COVID-19 patients frequently exhibited evidence of cardiovascular as well as respiratory involvement (1-3). Clinical features of cardiac involvement in COVID-19 included elevated serum troponin levels, arrhythmias and ST segment elevations, and/or depression on electrocardiograms pointing to some form of myocardial injury, often in the absence of obstructive coronary artery disease. Another manifestation of cardiac involvement was Takotsubo stress cardiomyopathy or, as it is commonly known, the "broken heart

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[1] Given his role as Editor in Chief, Dr. Buja had no involvement in the peer-review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Dr. Giulia Ottaviani.

https://doi.org/10.1016/j.carpath.2021.107336
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syndrome."(15) The troponin elevations, especially when accompanied by elevations of brain natriuretic peptide (BNP), carried an increased risk for adverse outcomes. Clinicians initially gravitated to myocarditis as a common underlying basis for the clinical findings, and these suspicions were reinforced by certain magnetic resonance imaging (MRI) findings in many of these patients. However, when autopsy findings began to be collected, initial autopsy findings were largely negative for classical myocarditis, which is characterized by lymphocytic infiltrates with associated myocyte damage (4).

In order to address these discrepancies, a COVID-19 Working Group was established through the leadership of the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology. Dr. Leone presented the initial findings of this COVID-19 Working Group which featured a comprehensive approach to the evaluation of hearts of patients dying with severe COVID-19 (9). In this international multicenter study, cardiac tissue from the autopsies of 21 consecutive COVID-19 patients was assessed by cardiovascular pathologists. The presence of myocarditis, as defined by the presence of multiple foci of inflammation with associated myocyte injury, was determined, and the inflammatory cell composition analyzed by immunohistochemistry. Other forms of acute myocyte injury and inflammation were also described, as well as coronary arterial, endocardial, and pericardial involvement. Lymphocytic myocarditis was present in 3 (14%) of the cases. In two of these cases, the T lymphocytes were CD4 predominant, and in one case the T lymphocytes were CD8 predominant. Increased interstitial macrophage infiltration was present in 18 (86%) of the cases. A mild pericarditis was present in four cases. Acute myocyte injury in the right ventricle, most probably due to strain/overload, was also present in four cases. There was a non-significant trend toward higher serum troponin levels in the patients with myocarditis compared with those without myocarditis. Disrupted coronary artery plaques, coronary artery aneurysms, and large pulmonary emboli were not identified. Conclusions of the study were as follows: 1) In SARS-CoV-2 there are increased interstitial macrophages in a majority of the cases and multifocal lymphocytic myocarditis in a small fraction of the cases; 2) other forms of myocardial injury are also present in these patients; and 3) the macrophage infiltration may reflect underlying diseases rather than COVID-19, but the macrophage infiltrates were often more intense than typically caused by underlying conditions.

The finding of Leone and colleagues of a measurable but relatively low frequency of myocarditis has been confirmed by other cardiovascular pathologists based on their own case series and two literature reviews of nearly 300 patients (10-14). The pathology studies also have documented that other histopathologic findings occur including focal cardiomyocyte necrosis, macro- or microvascular thrombi, inflammation, and intraluminal megakaryocytes (9-14), and collectively these non-myocarditis changes are more frequent than is myocarditis. Various mechanisms for myocardial involvement have been advanced. The presence of virus-like particles have been reported in endothelial and perivascular cells by electron microscopy, raising the possibility of endothelialitis (16-18). However, evidence has now been presented that normal vesicular organelles can be misidentified as coronavirus particles (19,20). Also, virus is detected only rarely in cardiac endothelial cells and cardiomyocytes using probes for viral RNA and protein (in situ hybridization and indirect immunofluorescence) (14,21,22). A recent study has shown that the degree of both myocardial macrophage and lymphocyte infiltration correlates with the presence of SARS-CoV-2 infected cells in the interstitium and the duration of disease, but not with underlying medical conditions (22). Another study has found evidence of viral replication in cardiomyocytes in human engineered heart tissues (23). Further work is needed to resolve key issues relating to viral involvement of the myocardium, including the identification of the most commonly infected cell type (22,23). A synthesis of published work to date indicates that myocardial involvement accounting for elevated troponin is multifaceted and may include myocarditis, relatively infrequently, and other types of pathology, collectively more frequently. Importantly, right heart strain secondary to the pulmonary disease and hypoxemia also can trigger troponin release (9,24).

Dr. Hanneman reviewed the diagnostic imaging findings in COVID-19, including computed tomography (CT) for the diagnosis and subsequent serial imaging of COVID-19 pulmonary disease and magnetic resonance (MR) imaging for the diagnosis of myocarditis (25). Consensus criteria (Lake Louise criteria) are used for the MR diagnosis of myocarditis. These criteria are based on presence and pattern of imaging findings consistent with myocardial edema determined by T1 and T2 protocols and late gadolinium enhancement indicative of myocardial injury (26-31). Dr. Hanneman made the important but often overlooked point that these criteria were validated for confirmation of myocarditis in cases with clinical features of myocarditis but were not intended for non-discriminate screening of patients. While as a group, patients who recover from COVID-19 have been reported by some centers to have more abnormalities on MR imaging than control groups, only a small percentage of patients who recover from COVID-19 meet full imaging criteria for myocarditis.

Dr. Glass reviewed the vascular findings in COVID-19 patients with an emphasis on the occurrence of pulmonary thromboemboli and microthrombi not only in the lungs but also in the myocardium and other vascular beds. These pathology studies have been the basis for the determination that a major feature of COVID-19 is the development of a pro-thrombotic state, and that severe COVID-19 has features of a systemic vascular disease (32,33). Dr. Glass also presented work in progress on the cellular and molecular biology of COVID-19 being conducted by a large multidisciplinary group at Duke. Implementation of the contemporary research autopsy is an essential element in carrying out such work (34).

Dr. Lowenstein discussed COVID-19 from his perspective of a cardiologist with an interest in endothelial biology. Clinically, severe COVID-19 is characterized by a hypercoagulable state, with venous thrombosis and arterial thrombosis, along with elevated markers such as VWF and D-dimer (35-37). Patients with severe COVID-19 also show clinical signs of systemic inflammation and have elevated inflammatory markers including IL-6 and CRP (36,37) They may also show elevations in VWF and P-selectin, which are stored in resting endothelial cells and released from endothelial cells during vascular injury. The combination of high VWF levels, elevated P-selectin levels, vascular thrombosis, and vascular inflammation all suggest that vascular injury may be a common trigger for both the inflammatory and thrombotic complications of COVID-19 (38).

Thus, clinical, laboratory, and autopsy evidence indicate that endothelial activation plays an important role in the pathogenesis of severe COVID-19 (39). Several important questions remain to be answered. First, what is the nature of the injury that activates endothelial cells during COVID-19, direct viral infection of endothelial cells or an indirect host inflammatory response to infection? Endothelialitis due to viral infection of endothelial cells initially was advanced as the mechanism of endothelial dysfunction (40,41). However, infection of endothelial cells outside the lungs appears to be rare, raising the likelihood of indirect mechanisms for endothelial activation and injury (42-44). Second, what are the pathways of endothelial injury that are activated during severe COVID-19? Third, are the mediators released by injured endothelial cells merely linked to severe COVID-19 or do they play a role in the pathogenesis of COVID-19, and are these mediators therapeutic targets?

This last year has seen an impressive and rapid accumulation of knowledge concerning the pulmonary and extrapulmonary pathology of COVID-19. However, given the many unanswered questions regarding the nature of the virus-host interactions in COVID-19, additional well-designed and well-controlled studies will be needed. This will be particularly important as more attention turns towards elucidating the pulmonary and extrapulmonary pathologies in patients suffering from post-acute sequelae of SARS-CoV-2 infection (PASC) or long COVID (45). For autopsy pathologists, it is important to remember that observations made at autopsy on patients who died from acute or subacute SARS-CoV-2 infection may not be readily applicable to those patients who recover from their illness.

While mysteries related to the COVID19 pandemic will require ongoing studies for years to come, the spectacular achievement of vaccine development against the SARS-Cov-2 virus has given much needed optimism that the pandemic can be brought under control (46). There is hope that 2021 will be an *annus mirabilis*.

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