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 52 (2021) 107333

Contents lists available at ScienceDirect

Cardiovascular Pathology

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

Letters to the Editor

Histopathological findings in the hearts of COVID-19 autopsies: a letter to Cardiovascular pathology journal editor in response to Halushka et al. 2020 ☆

Dear Editor,

With great interest we read the study by Dr. Halushka and Dr. Vander Heide on the cardiovascular findings in the hearts of patients who died of COVID-19 [1]. Their extensive literature review and meta-analysis of histopathologic changes in 277 autopsied hearts over 22 separate publications yielded a low rate of myocarditis (1.4%-7.2%), but reported other significant findings: non-myocarditis inflammation in 35 cases (12.6%), single cell ischemia in 38 cases (13.7%), small vessel thrombi in 30 cases (10.8%), pericarditis in 19 cases (6.9%) and amyloidosis in 11 cases (4%).

The authors of this study warn that the histopathological findings in the hearts of COVID-19 patients may be subtle, and therefore easily missed. They provide a checklist to help assess, record and report the relevant clinical information, gross findings, and microscopic findings in the hearts of COVID-19 decedents. A standard vocabulary and index of findings would facilitate comparison across autopsy reports for changes related to COVID-19 disease and thereby allow the scientific community a better window into the pathophysiology of the disease, at least as it relates to the heart.

Since the COVID-19 pandemic started, the pathologists at the MetroHealth Medical System (Cleveland, OH), had the opportunity to perform autopsies on six patients who had tested positive for COVID-19 at the time they were admitted to the hospital. We retrospectively examined sections from the hearts of these patients with the checklist provided by Dr. Halushka and Dr. Vander Heide (Table 1). We examined the sections that were prepared per standard autopsy protocol at our hospital (right ventricle, left ventricle and septum), and recorded findings for each section. Because the findings described by Dr. Halushka and Dr. Vander Heide are indeed subtle, we were curious to know whether they were specific to COVID-19 disease, or were seen in patients who died of other causes, as well. We chose 6 age- and sex- matched controls for whom bronchopneumonia was a primary or contributory cause of death, and examined the standard sections taken from the hearts of these patients at autopsy. In addition to the criteria on the checklist provided by Dr. Halushka and Dr. Vander Heide, we also recorded the presence/absence and the extent of interstitial edema and the presence, absence and extent of myocytolysis.

The hearts from the COVID-19 decedents were remarkable for single cell ischemia in 4 cases (66%), transmural and extensive interstitial edema in all 6 cases (100%), fibrosis in 5 cases (83%), near-transmural myocytolysis in 5 cases (83%), non-myocarditis-myocardial inflammation in 4 cases (66%), and epi/pericarditis in 2 cases (33%). We did not identify myocarditis, microvascular megakaryocytes, microvascular thrombi or small vessel vasculitis in any of the cases. The control hearts showed mild edema in all 6 cases (100%), focal myocytolysis in all 6 cases (100%), fibrosis in 3 cases (50%), non-myocarditis-myocardial inflammation in 2 cases (33%), microvascular thrombi in 2 cases (33%), single cell ischemia in 1 case (16.6%) and epicarditis in 1 case (16.6%). None of the other findings on the checklist for the histopathologic examination of COVID-19 hearts were present in the sections from the "control" hearts.

Myocytolysis and interstitial edema are common findings at autopsy in agonal hearts, and it is difficult to quantify these in such a way that they could distinguish between Covid- and non-Covid related injury. However, the fact that both findings were much more prominent in our small series of COVID-19 patients than in the control hearts should not be dismissed simply because it is a common finding. Moreover, these findings correlate with the premortem cardiologic impression of edematous hearts [2]. In our series, fibrosis correlated with degree of coronary artery atherosclerosis and hypertension, but single-cell necrosis, the most specific finding in this series, did not. Worthy of note also is that, consistent with the original observation that the morphologic changes are subtle, single-cell necrosis was a rare and subtle finding. In only one case it was multifocal and easy to identify. Importantly, the findings in our series support Dr. Halushka and Dr. Vander Heide's impression that the incidence of COVID-19 "myocarditis" appears to be over reported in the literature, as not even the case in our series in which there was a very high clinical suspicion for myocarditis had any evidence of lymphocytic myocardial injury (Autopsy 1 in Table 1).

To conclude, the most remarkable histopathological findings in this small series of COVID-19 autopsies were single cell necrosis and prominent edema. Single cell necrosis was seen only in one of the age- and sex-matched patients for whom bronchopneumonia was a primary or contributory cause of death, and interstitial edema was not nearly as extensive as in patients who died of or with COVID-19 disease. A limitation of our study is that we only reviewed 3 slides for each heart. Because some findings are subtle and focal, they might have been missed. We believe that utilization of the tool provided by Dr. Halushka and Dr. Vander Heide to uniformly identify, categorize and report the cardiac findings in patients who died of or with COVID-19 is feasible and effective at identifying changes that are consistently seen in this disease. Increased reporting of these findings could provide more nuanced understanding of the pathophysiologic effects of COVID-19 disease on the heart.

☆ Conflicts of Interest and Source of Funding: The authors have no conflicts of interest.

https://doi.org/10.1016/j.carpath.2021.107333

	Autopsy 1	Autopsy 2	Autopsy 3	Autopsy 4	Autopsy 5	Autopsy 6
Age/sex/BMI	59 / Female / 38.4	60 / Male / 37	53 / Female / 32.7	73 / Male / 30.28	70 / Male / 34.2	57 / Female / 25.2
Maximum Serum Troponin I	Increased (15.2 ng/mL)	Increased (0.191 ng/mL)	Normal (0.04 ng/mL)	N/A	Normal (0.029 ng/mL)	Normal (0.029 ng/mL)
Serum BNP/Ferritin/D-dimer levels	Normal/ Increased/ Increased	Increased/ Increased/ Increased	Normal/ Increased/ Increased	Increased/ Increased / N/A	N/A / Increased / Increased	Increased/ Increased/ Increased
Cardiovascular past medical history	HTN, HLD, T2DM	HF, atrial fibrillation, Long QT syndrome	HTN, HLD, T2DM, HF	HTN, HLD, T2DM, HF, atrial fibrillation	HTN, HLD, T2DM, Atrial fibrillation	DVT
Heart Weight	440 g	640g	380g	550g	420g/	300g/
/RV:LV chamber diameters	N/A	N/A	N/A	N/A	2.5cm:1.5cm	3.3cm:2.5cm
Degree of atherosclerosis in coronary arteries	LAD: 10% LCX: 10% RCA: 20%	LAD: 60% LCX: 10% RCA: 70%	LAD: 75% RCA: 40%	LAD: 40-50% LCX: 30-40% RCA: 30-40%	LAD: 40% LCX: Patent RCA: Patent	LAD: 10% LCX: Patent RCA: 80%
Cardiac large vessel or mural thrombosis	No	No	No	No	No	No
Non-cardiac large vessel thrombosis	Pulmonary embolism	No	No	No	Brachiocepha-lic vein	Lung (left upper lobe), Superior mesenteric vein, Brachiocepha-lic vein
Non-myocarditis, myocardial inflammation	Yes	No	Yes	No	Yes	Yes
Myocarditis	No	No	No	No	No	No
Epi/pericarditis	Yes	No	No	No	No	Yes
Single cell ischemia	Yes	Yes	Yes	No	No	Yes
Microvascular thrombi	No	No	No	No	No	No
Microvascular megakaryocytes	No	No	No	No	No	No
Small vessel vasculitis	No	No	No	No	No	No
Fibrosis/Scarring	Yes	Yes	Yes	Yes	No	Yes
Edema:						
- Transmural & extensive:	Yes	Yes	Yes	Yes	Yes	Yes
- Mild:	No	No	No	No	No	No
Myocytolysis	No	Yes	Yes	Yes	Yes	Yes

HTN, Hypertension; HLD, Hyperlipidemia; T2DM, Type 2 Diabetes Mellites; HF, heart failure; DVT, deep vein thrombosis; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; RV, right ventricle; LV, left ventricle.

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Revised 8 March 2021