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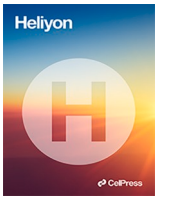

Common pathological findings in the heart in COVID-19-related sudden death cases: An autopsy case series

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ABSTRACT

Background: Cardiomyopathy is a leading cause of sudden out-of-hospital death after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus disease 2019 (COVID-19) vaccination. Such unexpected COVID-19-related cardiomyopathies are challenging to diagnose as specific pathological findings are not always identified.
Case summary: We reported the autopsy findings of two cases of sudden death due to COVID-19-related cardiomyopathies. In one case, death occurred after SARS-CoV-2 infection, while in the other, after COVID-19 vaccination. We found common pathological findings in both hearts: decreased staining intensity with special stains, loss of rhabdomeres, and multivacuolation in cardiomyocytes without inflammatory cell infiltration. The remaining organs showed no findings that could have contributed to the deaths.
Conclusion: In cases of sudden death after SARS-CoV-2 infection or COVID-19 vaccination, the decreased staining intensity with special stains may aid the diagnosis of sudden death due to COVID-19-related cardiomyopathy, even when H&E staining shows few findings.

1. Introduction

In the three years since the start of the coronavirus disease 2019 (COVID-19) outbreak, the reporting of sudden out-of-hospital deaths due to COVID-19 increased in various countries [1]. Diagnosing the etiology of some cases of sudden cardiac arrest has been challenging, as specific pathological findings, such as inflammation or myocardial necrosis, are not always observed, even on autopsy [2]. Cardiomyopathy, which is one of the leading causes of sudden cardiac arrest, can be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and vaccination against COVID-19, having been associated with poor outcomes and death [3, 4]. However, the pathophysiology of such COVID-19-related cardiomyopathies remains unclear.

Herein, we present the autopsy findings in two cases of patients with COVID-19-related sudden death without inflammation. These cases showed common histopathological findings in the myocardium, which may provide new evidence for the characteristics of the acute phase of cardiomyopathy.

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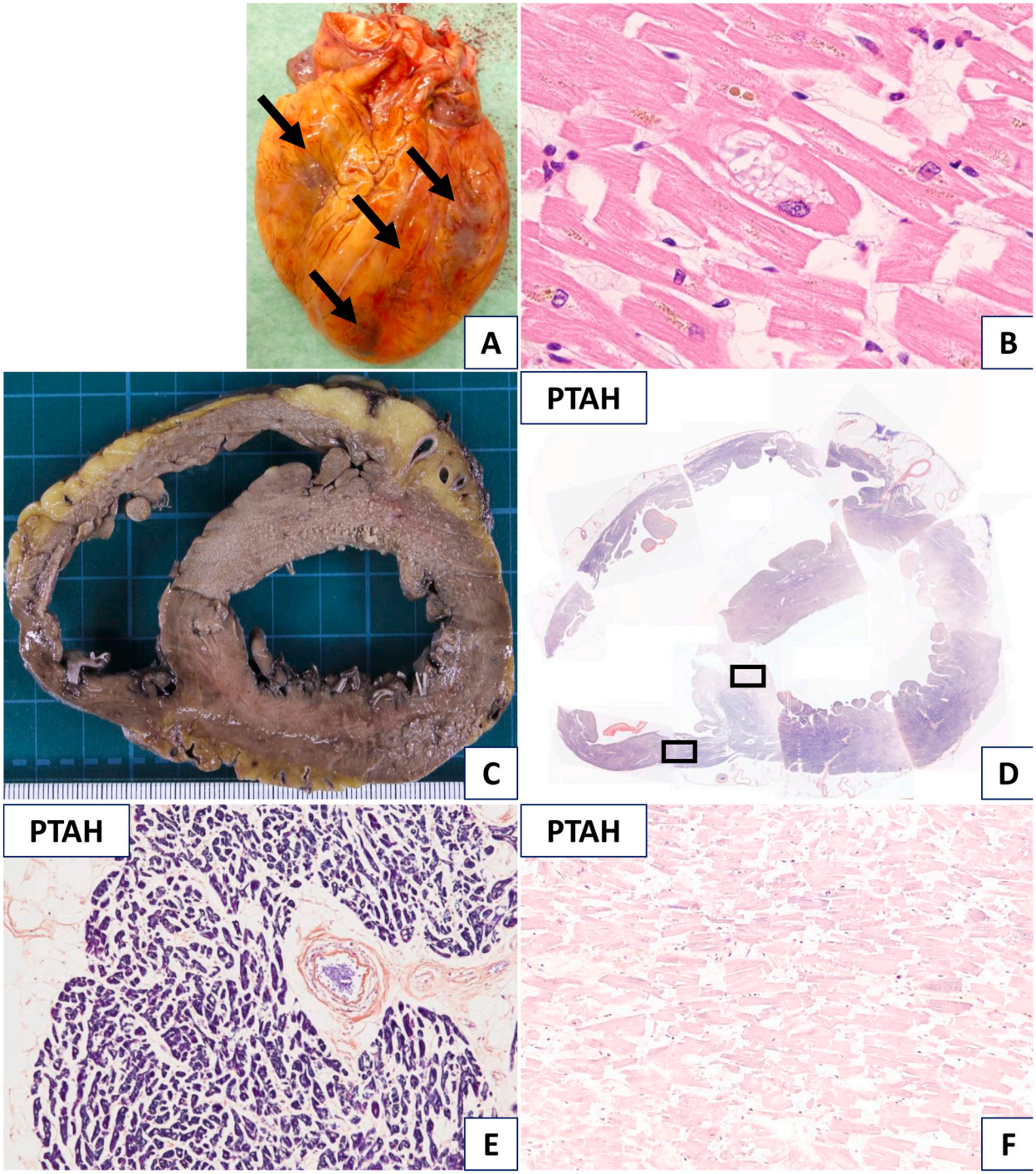

Fig. 1. Macroscopic and histopathological findings in the heart in Case 1
(A) Ventral side of the heart. Arrows indicate soft and tension-free muscles. (B) Vacuolated cardiomyocytes. H&E staining; magnification × 400. (C and D) Macroscopic image (C) and phosphotungstic acid hematoxylin (PTAH) staining (D) of the myocardial cross-section. The staining intensity decreases in the ventricular septum. Squares indicate locations (E) and (F). (E and F) PTAH staining of the ventricular septum; (E) normal staining intensity, magnification × 100; (F) and decreased staining intensity, magnification × 200.

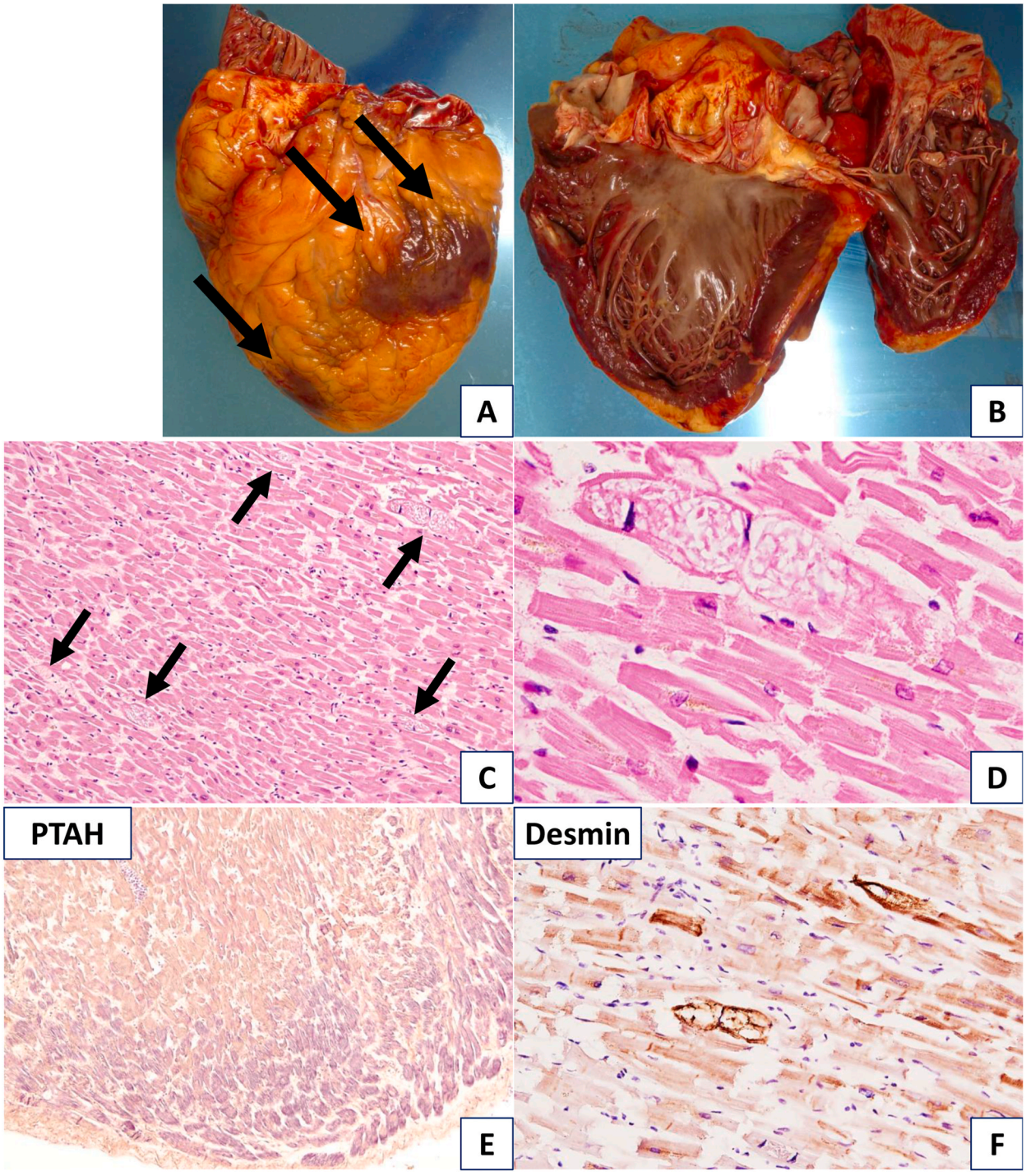

Fig. 2. Macroscopic and histopathological findings in the heart in Case 2
(A) Ventral side of the heart. Arrows indicate soft and tension-free muscles. (B) Left ventricular myocardium with hypotonia. (C) Cardiomyocytes with multiple vacuolations (arrows). H&E staining; magnification × 40. (D) Vacuolated cardiomyocytes. H&E staining; magnification × 400. (E and F) Decreased staining intensity of cardiomyocytes stained with phosphotungstic acid hematoxylin (E) and desmin (F); magnification × 40 (E) and × 200 (F).

2. Case Series presentation

2.1. Case 1

A 71-year-old man with a history of rheumatoid arthritis drowned at home in his bathtub. Cardiopulmonary resuscitation efforts were not successful, and he died. After his death, the patient was diagnosed with COVID-19, of presumed BA.5 variant based on timing [5]. The patient had received the fourth messenger ribonucleic acid (mRNA) vaccine for COVID-19 two months before his death. An autopsy was performed with permission from his family.

The autopsy findings were as follows: the heart weighed 375 g without unusual findings on initial inspection. The anterior wall of the left ventricle and posterior wall of the right ventricle were poorly tensed and soft, suggesting degeneration (Fig. 1A). Hematoxylin-eosin (H&E) staining revealed multiple vacuolations in the cardiac myocytes (Fig. 1B), and phosphotungstic acid hematoxylin (PTAH) staining, which is employed to visualize striated muscle fibers and, especially, the rhabdomeres within the muscle fibers, revealed a loss of rhabdomeres and a sporadic decrease in staining intensity in the myocytes near the ventricular septum (Fig. 1C–F). The areas of decreased staining intensity on PTAH staining did not alter the findings of the H&E staining.

The lungs had increased weight (left: 790 g, right: 770 g) and hardness, with poor overall air content. The trachea and bronchi were filled with frothy mucus, and extensive submucosal hemorrhage was observed. Histological examination revealed pulmonary congestive edema, possibly associated with left heart failure. No significant inflammation was observed in the lungs or heart.

Other histological findings revealed myoglobin nephropathy. We speculated that arrhythmia caused by cardiomyopathy led to the loss of consciousness, which resulted in the patient drowning. Therefore, arrhythmia was diagnosed as the cause of death in this patient.

2.2. Case 2

A 68-year-old woman with a history of depression and spondylolisthesis, who had been vaccinated against COVID-19 with an mRNA vaccine nine days before, experienced sudden tightness in the chest. That had been her fourth vaccination against SARS-CoV-2, all doses being mRNA vaccines and without related adverse effects. An ambulance was called; however, upon its arrival, the patient was found unconscious. Electrocardiography showed ventricular fibrillation, and the patient died despite cardiopulmonary resuscitation with electrical cardioversion being performed. A polymerase chain reaction test for SARS-CoV-2 was performed and confirmed negative. An autopsy was performed with permission from the patient's family.

The autopsy findings were similar to those described in Case 1. The heart weighed 355 g without unusual findings on inspection. The anterior wall of the left ventricle and the posterior wall of the right ventricle were soft and poorly tensed, suggesting degeneration (Fig. 2A and B). H&E staining revealed the presence of multiple vacuolations in cardiac myocytes. Additionally, PTAH and desmin staining showed a loss of rhabdomeres and sporadic decrease of the staining intensity in the myocytes (Fig. 2C–F). The areas of decreased staining intensity with the special stains did not alter the H&E staining findings.

The lungs had increased weight (left:700 g, right:850 g) and hardness, with poor overall air content. The trachea and bronchi were filled with frothy mucus, and extensive submucosal hemorrhage was observed. Histological examination revealed pulmonary congestive edema, which may have been associated with left heart failure. No significant inflammation was observed in the lungs or heart.

Other histological findings included the presence of fatty liver disease and myoglobin nephropathy. Therefore, arrhythmia due to myocardial damage was diagnosed as the cause of death.

3. Discussion

In this study, we reported the autopsy findings of two cases of sudden death, one after SARS-CoV-2 infection and the other after COVID-19 vaccination. Both cases presented a sporadic decrease in PTAH and desmin staining intensities, decrease in the myocardial tonus, loss of rhabdomeres, presence of multiple vacuolations, and no inflammatory cell infiltration in the myocytes; such findings indicated cardiomyopathy development. Interestingly, decreased staining intensity with the special stains clearly demonstrated the area of myofibril degeneration that was unchanged upon H&E staining. The initial loss of desmin was experimentally shown to be critical for subsequent myofibril destruction [6]. However, its decreased staining intensity in immunohistochemistry has not been extensively employed in pathological diagnosis. Thus, this result is useful for identifying cause of death and extent of myocardial degeneration.

Cardiomyopathy is a heart muscle disease that hinders blood pumping by the heart to the rest of the body. Cardiomyopathy has many causes, including genetic mutations, coronary artery disease, autoimmune disease, alcohol abuse, comorbidities including hypertension and diabetes, and infections [7]. Viral infection-related cardiomyopathy includes myocarditis, a non-inflammatory dilated cardiomyopathy, and congestive heart failure [8]. The most common etiologic agents are enteroviruses, adenoviruses, and erythroviruses [8]. Myocardial infection by SARS-CoV-2 presents various clinical features that are common to the aforementioned pathologies. SARS-CoV-2 can cause direct or indirect cardiac complications, including acute myocardial injury, myocarditis, heart failure, Takotsubo cardiomyopathy, coagulation abnormalities, arrhythmia, acute myocardial infarction, cardiogenic shock, and cardiac arrest [9]. In patients with COVID-19, the incidence of acute myocardial injury, heart failure, arrhythmia, and cardiac arrest has been found to be 21%, 14%, 16%, and 3.46%, respectively; whereas in deceased patients with COVID-19, acute myocardial injury and arrhythmia incidence rates were 56% and 47.5%, respectively, as shown in an umbrella meta-analysis study, which included

articles published from December 2019 to April 2021 [10]. Cruz Rodriguez et al. reported that acute myocardial injury was associated with worse prognosis and high mortality (50−60%) in hospitalized patients with COVID-19 [3]. The proposed mechanisms underlying COVID-19-related cardiomyopathy are diverse, including systemic inflammation, interferon-mediated immune response, exaggerated cytokine response by type 1 and 2 helper T cells, coronary plaque destabilization, stress, and hypoxia [11,12]. Furthermore, SARS-CoV-2 enters cells through the angiotensin-converting enzyme-2 receptor present on the surface of cardiomyocytes [12], and COVID-19 infection downregulates such receptors, which can lead to cardiomyopathy, cardiac dysfunction, and heart failure [11].

Conversely, cardiomyopathy after COVID-19 vaccination is rare, with an incidence of 5.98 cases per million doses administered, as reported in an observational study conducted in the USA from December 2020 to August 2021 [13]. However, it has been associated with severe adverse events, such as permanent left ventricular dysfunction and sudden death [4]. Additionally, COVID-19 vaccination has been associated with cardiac arrhythmias, with an incidence ranging between 1 and 76 per 10,000 people, with higher ranges for mRNA than for vector-based vaccines [14]. The mechanisms by which COVID-19 vaccination causes cardiomyopathy and myocarditis are not fully elucidated.

A hypothesis of a common mechanism for cardiomyopathy following SARS-CoV-2 infection and COVID-19 vaccination has been proposed by Cadegiani, who suggested that a hyper-catecholaminergic state due to the components of SARS-CoV-2 is a critical myocarditis trigger, based on the fact that mRNA and spike proteins act on the production of catecholamines in the adrenal gland [15]. Moreover, Takotsubo cardiomyopathy, often associated with catecholamine excess, has been reported after SARS-CoV-2 infection [16] and COVID-19 vaccination [17]. The clinical features of pheochromocytoma-related cardiomyopathy include cardiac arrhythmia and arrest. Miura et al. reported that the biopsied myocardium of a patient with catecholamine-induced cardiomyopathy showed vacuolar myocyte degeneration, mild contraction band formation of myocytes, a small number of necrotic myocytes, focal fine interstitial fibrosis, and cellular infiltration 2−3 days after the initiation of myocardial injury [18]. Our histopathological findings were partly compatible with these findings and may be explained by the acute phase of myofibril degeneration with cardiomyopathy associated with SARS-CoV-2 infection and COVID-19 vaccination. Furthermore, decreased staining with PTAH and desmin is a useful finding indicating the early phase of cardiomyocyte degeneration. The histological findings of the heart in the two present cases resemble the histological findings of another catecholamine cardiomyopathy in our hospital (Supplemental Fig. 1) and differ from the histology of the normal heart (Supplemental Fig. 2), supporting the hypothesis that the pathogenesis of COVID-19-related cardiomyopathy is similar to that of catecholamine cardiomyopathy.

The mechanism underlying myofibril degeneration in the current cases could not be elucidated by histological examination alone, which is a limitation of the present study. Another limitation is that no direct evidence that COVID-19 and the vaccine caused the cardiomyopathy in both cases exists. However, as no other cause of sudden cardiomyopathy was suggested, including those related to comorbidities and circumstances, both cases were considered as COVID-19-related cardiomyopathy. Further research is necessary to clarify the mechanism of COVID-19-related cardiomyopathies.

4. Conclusion

Both SARS-CoV-2 infection and COVID-19 vaccination can cause cardiomyopathy, leading to sudden cardiac arrest. The autopsy findings in the current COVID-19-related cardiomyopathies included a sporadic decrease in PTAH and desmin staining intensity, prominent loss of tone, loss of rhabdomeres, and multiple vacuolations in the myocytes. In particular, the decreased staining intensity with special stains can aid in the diagnosis of sudden death after SARS-CoV-2 infection or COVID-19 vaccination, even when H&E staining presents few findings. The pathophysiology of COVID-19-related cardiomyopathy remains unclear, and accumulating findings from pathological autopsies is crucial to broaden the knowledge base and contribute to future research in this area.

Ethics statement

This study was reviewed and approved by the Sapporo Medical University Ethics Committee, with the approval number: 3-1-27.
All patients' families provided informed consent to participate in the study.
All patients' families provided informed consent for the publication of their anonymised case details and images.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20564.

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