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Case Report

Biomedical Science and Clinical Research

Case of Myocarditis, Pericarditis, and Fatal Aortic Dissection Following COVID-19 mRNA Vaccination

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Abstract

We present a case study of a 34-year-old male who was in good health prior to his COVID-19 mRNA vaccination. Sixteen days after his first dose, he experienced acute inflammation, sudden thoracic aortic dissection, and pericardial tamponade, rapidly leading to his death. Studies suggest that young males, in particular, appear to be at increased risk of adverse cardiac events following COVID-19 mRNA vaccination. Although the incidence of such complications are believed to be low, we propose that information gaps exist in the criteria and findings that inform both public health agencies and the public on incidence rates of even severe myocarditis and cardiac adverse events following COVID-19 vaccination. This view is shared within many COVID-19 vaccine myocarditis studies and is evident within the findings of this case of Myocarditis, Pericarditis, and Fatal Aortic Dissection presented here.

Keywords: Aortic Dissection, Myocarditis, Pericarditis, mRNA, Covid-19 Vaccine, Cardiology, Spike Protein, Public Health, Cardiac Damage, Aortitis, Hypersensitivity Reaction and LNP

1. Introduction

Several adverse events and cardiac complications have been linked to COVID-19 vaccination and are found in case reports, which help to inform the medical community, the public, and public health officials of these findings [1-6]. Studies suggest that young males, in particular, appear to be at increased risk of adverse cardiac events following the COVID-19 mRNA vaccination.

Individual case studies and larger cohort studies show mRNA COVID-19 vaccine-related pathogenic and histologic links to myocarditis and pericarditis in some who receive these vaccines [4,7-10]. The CDC also recognizes this risk for young males and advises: “People, especially males ages 12–39 years, should be made aware of the rare risk of myocarditis and pericarditis following receipt of these vaccines…” Pericarditis, Myocarditis, Myocardial Infarction, Takotsubo Cardiomyopathy, and Aortic Dissections are also cardiac pathologies associated with COVID-19 vaccines [4,8,9,11].

2. Case Presentation

Herein, we present a case study of a 34-year-old male who was in apparent good health prior to his COVID-19 mRNA vaccination. Sixteen days after his first dose, he experienced acute inflammation, sudden thoracic aortic dissection, and pericardial tamponade, rapidly leading to his death.

His premorbid cardiac echocardiograms had demonstrated no evidence of aortic root dilation or of aortic aneurysm, although a bicuspid aortic valve was present. No previous reports of aortic dissection in other family members were reported. His autopsy also showed no evidence of aortic aneurysm, and his aortic valves were also noted to be flexible. The intimal tear found at autopsy extended through the aortic media into the adventitial layer of the aorta (Figure 1). This injury formed a pocket that dissected across the aortic arch into the descending aorta. As it grew, it entered the pericardial space, filling it with blood. The subsequent hemopericardium could be expected to have led to cardiac tamponade and then cardiac arrest. Of note, a toxicology drug screen was also performed and failed to find any illicit drugs that could have contributed to such a catastrophic event.

From a clinical perspective, he was at low risk for such a devastating complication given his age, normal blood pressure, and his history as a nonsmoker with unremarkable glucose and lipid levels. He was also found to lack any evidence of genetically linked connective tissue disorders confirmed by postmortem genetic testing.

In his case, his hospital records show that he was asymptomatic

until a few hours before he was rushed to the ER. The family reports that on the night of his passing, he complained of epigastric pain within four hours before his smartwatch displayed a heart rate of 190 bpm, and then he had numbness in his jaw and chest pain, which prompted him to call for emergency services around 1:30 a.m. He was actively walking and talking to paramedics until he collapsed. He presented to the hospital with CPR in progress and died within the hour.

Although he was tested for troponin, his levels were not raised. It should be noted that troponin levels are sometimes not detectable or negative early in the process of cardiac injury and are often tested two or more times before testing positive in diagnosing heart damage, such as heart attack or myocarditis. In this case, the patient passed away shortly after cardiac injury, and his troponin levels likely had not yet risen to detectable levels.

Myocarditis and pericarditis were not investigated by the hospital, and the medical examiner diagnosed "acute aortic dissection." Without the findings gathered in his further immunohisto-pathology, myo and pericarditis, in this case, would not have been documented, and his complete diagnosis would not have been learned.

The patient's further pathology, including histology of the heart and pericardial sac, showed lymphocytic infiltrates (Figure 2 and Figure 3), indicative of pericarditis and myocarditis, as is seen in other peri and myocarditis cases following COVID-19 mRNA vaccine. Significant eosinophilic infiltrates were also present in his arterial tissues (Figure 4), consistent with a hypersensitivity reaction [12-18]. His immunohisto-pathology noted the presence of spike protein in aorta (Figure 5) as well as vascular tissues but an absence of staining for nucleocapsid antigens, indicating that the spike protein was vaccine-derived rather than of viral origin [19]. Given these findings and a lack of underlying genetic disease, this inflammatory response is suspected to have initiated the deadly vascular and cardiac inflammatory cascade that ultimately took his life. The Pfizer Covid-19 mRNA vaccine is the suspected catalyst for this chain of events.

The postmortem pathology report documented: "Arterial vessels show enlarged intima, lipid deposit areas, and a small perivascular inflammatory infiltration from macrophages and lymphocytes in the area of the vasa vasorum which reaches into the intima media. Circumscribed evidence of SARS- Covid-2 Spike subunit 1 in individual endothelia and macrophages.

No evidence of SARS-Cov-2 nucleocapsid." The lack of nucleocapsid antigens found on immunohistopathologic analysis excludes a natural Covid-19 infection or viral etiology for his myocarditis, pericarditis, or the aortitis, and vascular inflammation found at autopsy and in postmortem histology [19].

2.1 Supporting Evidence

2.1.1 Supporting Evidence also Includes Extensive Cytokine Analysis, in which we See

Acute inflammatory response consistent with elevations of interleukins IL-1, IL-1RA, IL-18, and IL-6 [20-21].

Coagulopathy as demonstrated with elevations of plasminogen activator inhibitor-1 (PAI-1) and D-dimer levels, typically seen in aortic dissection cases [22-24].

Evidence of myocardial injury with significant elevations of myoglobin and fatty acid binding protein 3 (FABP3) indicative of inflammatory infiltration of the myocardium [25].

Each of these abnormalities is a recognized complication of myocarditis or the myocardial effects of COVID-19 mRNA vaccine.

2.2 Figures and Tables

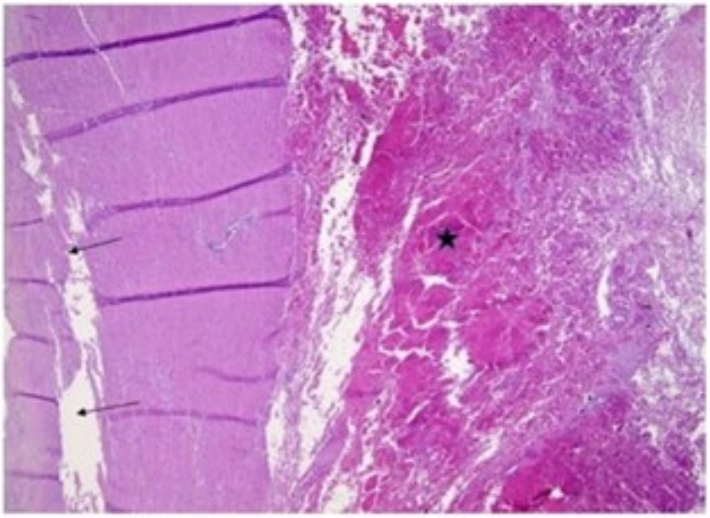

Figure 1: Overview of Rupture of the Aorta with Wide Under Bleeding of Adventitia (star) and Dissection of Intima and Media (Arrows). Magnification 20x, H&E. (300 x 300 DPI)

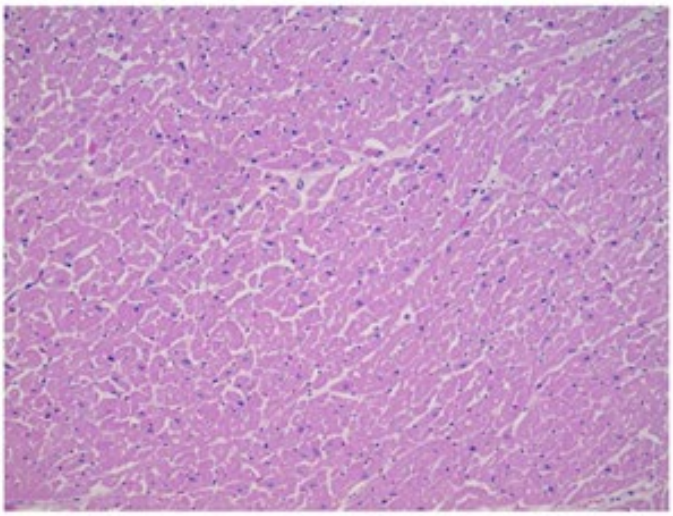

Figure 2: Heart Histo-and Lymphocytic Myocarditis. Vacuolation of Cardiomyocytes and Increased Number of Interstitial Cells, Especially Macrophages, Eosinophilic Granulocytes, and small Lymphocytes. Magnification 100x, H&E. (300 x 300 DPI)

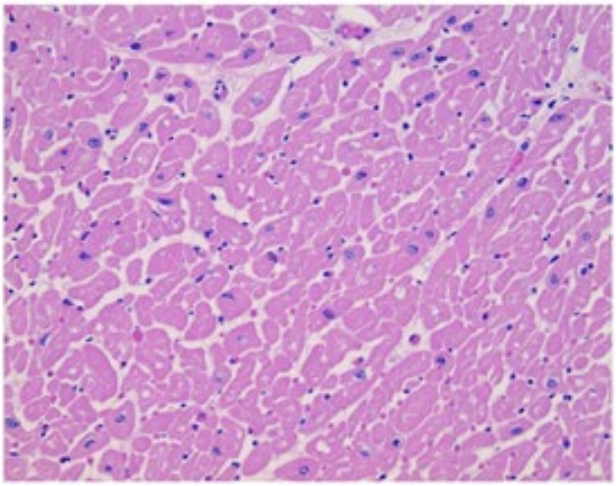

Figure 3: Heart, Close-Up Detail of Histo-and Lymphocytic Myocarditis. Vacuolation of Cardiomyocytes and Increased Number of Interstitial Cells, Especially Macrophages, Eosinophilic Granulocytes, and Small Lymphocytes. Magnification 200x, H&E. (300 x 300 DPI)

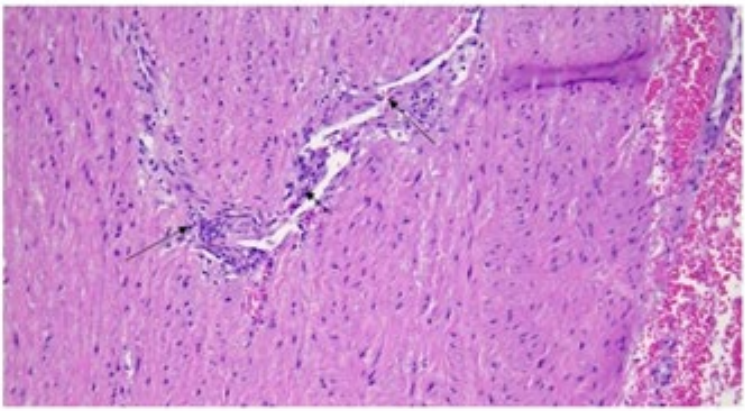

Figure 4: Detail from Figure 1. Vasculitis of Vasa Vasorum Aorta with Swelling of the Endothelial Cells and a Perivascular Accumulation of Macrophages, Eosinophil Granulocytes, and Lymphocytes. Magnification 100x, H&E. 72x37mm (300 x 300 DPI)

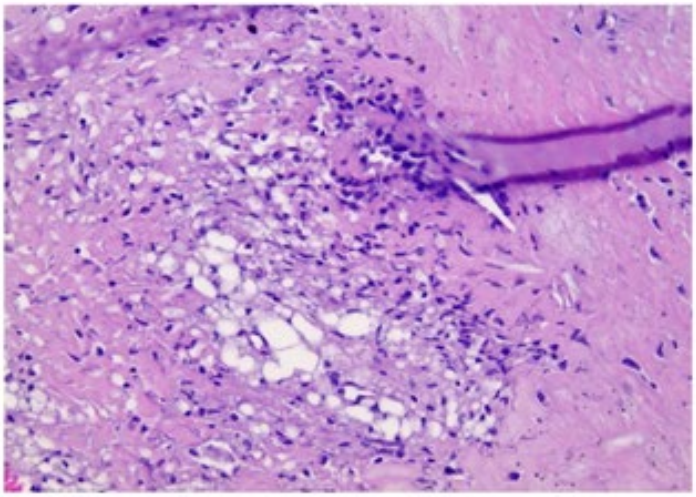

Figure 5: Greatest Detail from Figure 1 and 4. Vasculitis of Vasa Vasorum Aorta with Swelling of the Endothelial Cells and a Perivascular Accumulation of Macrophages, Eosinophil Granulocytes, and Lymphocytes. Magnification 200x, H&E. (300x300 DPI)

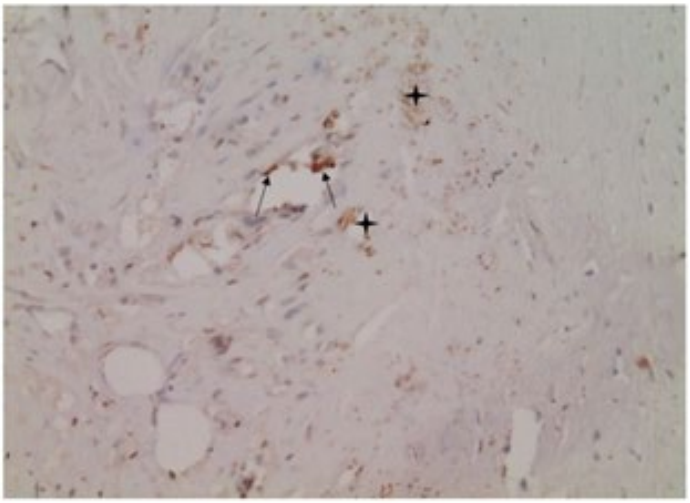

Figure 6: Vasa Vasorum Aortae. Granular Deposition of SARS-CoV2 Spike Subunit 1 in Endothelial cells (arrows) and Perivascular Macrophages (Stars). Magnification 200x, Immunohistochemistry. (300 x 300 DPI)

3. Discussion

As noted in Pfizer document 5.3.6, "Cumulative Analysis of Post-authorization Adverse Events Reports," 1,441 cardiovascular adverse events had been reported to Pfizer, including aortitis, pericarditis, and myocarditis [26]. The CDC website also holds the following notification regarding the causal relationship between vaccination with the COVID vaccines— genetic and protein-based, and the subsequent development of myocarditis and pericarditis: "Evidence from multiple monitoring systems in the United States and globally support a causal association for mRNA COVID-19 vaccines (Moderna or Pfizer-BioNTech) and myocarditis and pericarditis. Cases have occurred most frequently in young adult males within 7 days after receiving the second dose of an mRNA COVID-19 vaccine (Moderna and Pfizer-BioNTech)."

Myocarditis is now well recognized to be a serious adverse reaction associated with Pfizer's mRNA COVID-19 vaccine.

Studies have documented the presence of Spike protein and eosinophilic infiltration in cases of COVID-19 vaccine myocarditis [1,6,10-15]. Both of these features are present in this case as well. COVID-19 mRNA vaccines have also been implicated in acute hypersensitivity reactions, coagulopathy, cytokine storm, Takosubo Cardiomyopathy, Vasculitis, Aortitis, Pericarditis, and Myocarditis [4,7,10,11,18,27-31]. Any of these mechanisms could have played a role in the sequence of events, leading to aortitis, pericarditis, myocarditis, and ultimately catastrophic aortic dissection.

The pathogenesis of cardiac adverse events linked to COVID-19 mRNA vaccines is studied worldwide. Pfizer's 2022 COVID-19 vaccine internal document on myocarditis states that lipids may activate "immune responses" and "pro-inflammatory processes [32-35]." Additionally, the role of the COVID-19 mRNA vaccine LNP is to bring the mRNA to the cells for spike protein production. Animal models and studies since 2015 have shown that mRNA-LNP formulations can travel throughout the body and are not limited to the injection site [4,9,10,36]. Studies also show that in several cases in which immunohistochemical staining and biopsy were performed, Spike protein is found to be accompanied by evidence of inflammatory responses in the heart tissue of myocarditis cases after COVID-19 vaccinations, including in the aorta of the young man whose case we present herein [1,4,7,34].

In 2023, Twenty-one Yale physicians published a COVID-19 vaccine myocarditis cytokine research study that details the various cytokine immune responses seen in the cohort of 23 young patients with myocarditis after mRNA vaccine. This study states, "the LNP component of the vaccine alone was found to be highly inflammatory." The study also suggests that "the LNP delivery platform in synergy with vaccine-vectored antigens is more likely the driver of an exaggerated immune cytokine response driving cardiac pathology after vaccination in susceptible individuals [4]."

Yale's cytokine myocarditis study referenced Genentech's 2022 study on cytokines in RNA-LNP vaccines, which explains that certain mRNA vaccine components, contaminants, or artifacts in synergy with the lipids are able to elicit inflammatory factors that can lead to cytokine release syndrome (CRS) [9]. Genentech's study also states, "…RNA vaccines against COVID-19 (mRNA-1273 by Moderna and BNT162b2 by BioNTech/Pfizer)—which use modRNA with a greatly reduced innate immunostimulatory activity—still elicit systemic adverse events in patients following initial intramuscular administration [10]."

In the case of this 34-year-old young man presented herein, at the family's request after his untimely passing following his mRNA COVID-19 vaccine, his perimortem serum was also examined in 2022. His findings of an acute inflammatory cytokine response with concurrent elevations in IL-1 and IL-18 are consistent with Yale's 2023 cytokine myocarditis research study and Johns Hopkins's 2022 cytokine and myopericarditis study as well [9].

There is now a large body of evidence showing that young and previously healthy individuals have experienced life-changing and life-threatening adverse events subsequent to COVID-19 mRNA vaccination [7,11,27,28,30-32,37-45] For example, in 2022, Patone et al. stated, "The risk of vaccine-associated myocarditis is consistently higher in younger men, particularly after a second dose of mRNA-1273…" The study continues, "An important consideration for this group is that the risk of myocarditis after a second dose of mRNA-1273 was higher than the risk after infection [46]." Covid-19 vaccine myocarditis long-term outcomes cannot be predicted; however, studies have shown residual Late Gadolinium Enhancement (LGE) "likely reflecting myocardial fibrosis" in both adults and children following COVID-19 vaccine myocarditis [47]. Myocardial fibrosis could potentially result in a focus for arrythmias later in life.

However, currently, a standard method of reporting myocarditis and cardiac adverse events, incidence rate, and follow-up findings does not exist, but gaps do exist in many current studies. For instance, myocarditis patients selected for research studies typically restrict the inclusion of patients who have presented with myocarditis within 7 to 14 days of vaccination, and many only include myocarditis cases that take place after the second dose. Yet, it has been shown that myocarditis incidence after COVID-19 vaccination is often known to take place after the first dose, and it can take place within 28 days and sometimes up to 90 days after the second dose [46,48,49].

We should also point out that many studies include only myocarditis participants with raised troponin levels, even though elevated troponin levels have been reported as an unreliable biomarker of myocarditis [44,45,50-52]. For instance, the pathology of the young man whose medical case we present herein shows raised myoglobin markers without raised troponin markers, possibly due to the insufficient period of time from the onset of cardiac damage to his demise, which may not have allowed for the anticipated rise in troponin.

It should be said that in cases of fatality after recent COVID-19 vaccinations, without autopsy and histopathological examinations, a complete patient diagnosis and accurate reporting of the true incidence of vaccine-linked fatal injury, including cardiac events, may not be known.

Again, the biological markers and the sophisticated imaging techniques described above have revealed even subclinical cases or asymptomatic cases. Still, it is important to remember that not all cities and communities have access to this testing, and many cases will remain undetected. In the case presented herein and in the relevant data, we found that the above factors can exclude even serious myocarditis cases from research studies, and we also learned that cases may go undetected, untreated, and excluded from statistical analysis [47,51].

Several studies have recommended advanced cardiac testing in all patients with cardiac symptoms such as chest pain, palpitations, or shortness of breath following mRNA vaccination.

Our findings and the case presentation herein highlight the need for these in-depth cardiac studies both in the hospital setting during patient assessment and the in-depth histopathology testing at autopsy in unfortunate fatality cases of those who were recently vaccinated. Thorough testing must be performed in both instances to better inform public policy and, ultimately, avoid future patient harm.

The benefit of risk appraisal of COVID-19 vaccination is determined by public health agencies, which are expected to inform the public of emerging safety data as it is made available to afford complete informed consent. Especially in the case of a novel therapy with global implications, but also in the case of all novel vaccines or therapies, without complete data, these safety concerns cannot be fully known, and timely regulatory

investigations and actions important for public health may be delayed or not appreciated. This case review and our findings emphasize that without the described thorough investigations, accurate safety data cannot be realized, and in fact, the safety data is likely impacted by information gaps in the reporting.

4. Materials and Methods-Histology and Immunohistochemistry

4.1 Routine Histology

Formalin-fixed tissues were routinely processed, and paraffin-embedded tissues were cut into 5 µm sections and stained with hematoxylin and eosin (H&E) for histopathological examination.

4.2 Immunohistochemistry

Immunohistochemical staining was performed on the heart, vasa vasorum, and aorta using a fully automated immunostaining system (Ventana Benchmark, Roche). An antigen retrieval (Ultra CC1, Roche Ventana) was used for every antibody. The target antigens and dilution factors for the antibodies used are summarized in Table 1. Incubation with the primary antibody was carried out for 30 min in each case. Tissues from SARS-CoV-2-positive COVID-19 patients were used as a control for the antibodies against SARS-CoV-2-spike and nucleocapsid. Cultured cells that had been transfected in vitro (see hereafter) served as a positive control for the detection of vaccine-induced spike protein expression and as a negative control for the detection of nucleocapsid protein. The slides were examined with a light microscope (Nikon ECLIPSE 80i).

Table 1. Primary antibodies used for immunohistochemistry. Tissue sections were incubated 30 min with the antibody in question, diluted as stated in the table.

Target Antigen	Manufacturer	Clone	Dilution	Incubation Time
CD3 (expressed by T-Lymphocytes)	Cytomed	ZM-45	1:200	30 min
CD68 (expressed by monocytic cells)	DAKO	PG-M1	1:100	30 min
SARS-CoV-2-Spike subunit 1	ProSci	9083	1:500	30 min
SARS-CoV-2-Nucleocapsid	ProSci	35–720	1:500	30 min

Table 1: Primary Antibodies Used for Immunohistochemistry

4.3. Preparation of Positive Control Samples for the Immunohistochemical Detection of the Vaccine-Induced Spike Protein Cell Culture and Transfection

Cell culture and transfection: Ovarian cancer cell lines (OVCAR-3 and SK-OV3, CSL cell Lines Service, Heidelberg, Germany) were grown to 70% confluence in flat bottom 75 cm^2 cell culture flasks (Cell star) in DMEM/HAMS-F12 medium supplemented with Glutamax (Sigma-Aldrich, St. Louis, MO, USA), 10% FCS (Gibco, Shanghai, China) and Gentamycin (final concentration 20 µg/mL, Gibco), at 37 °C, 5% CO_2 in a humidified cell incubator. For transfection, the medium was completely removed, and cells were incubated for 1 h with 2 mL of fresh medium containing the injection solutions directly from the original bottles, diluted 1:500 in the case of BNT162b2 (Pfizer/Biotech) and 1:100 in cases of mRNA-1273 (Moderna), Vaxzevria (AstraZeneca), and Jansen (COVID-19 vaccine Jansen). Then, another 15 mL of fresh medium was added to the cell cultures, and cells were grown to confluence for another 3 days.

Preparation of tissue blocks from transfected cells: The cell culture medium was removed from transfected cells, and the monolayer was washed twice with PBS, then trypsinized by adding 1 mL of 0.25% Trypsin-EDTA (Gibco), harvested with 10 mL of PBS/10% FCS, and washed 2× with PBS and centrifugation at 280× g for 10 min each. Cell pellets were fixed overnight in 2 mL in PBS/4% Formalin at 8 °C and then washed in PBS once. The cell pellets remaining after centrifugation were suspended in 200 µL PBS each, mixed with 400 µL 2% agarose in PBS solution (precooled to around 40 °C), and immediately transferred to small (1 cm) dishes for fixation. The fixed and agarose-embedded cell pellets were stored in 4% Formalin/PBS till subjection to routine paraffin embedding in parallel to tissue samples.

5. Conclusion

Administration of COVID-19 mRNA vaccinations should be carefully weighed on an individual basis with a full understanding of evolving safety risk data, including potential subclinical disease. Unrecognized complications could prove especially harmful in the younger population under age 39, such as the tragic case we present.

Competing Interests

None. The authors have no financial relationships with any organizations that might have an interest in the submitted work.

Use of Artificial Intelligence

None. No AI was used in this case review.

Contributorship

Eduardo Balbona, Author and corresponding author and editor-accepts full responsibility for the finished work and/or the conduct of the study, has access to the data, and controlled the decision to publish.

Eduardo Balbona, Heather Hudson, Michael Morz, and Janci Lindsay - Authors, each ontributed to the conception or design of the work; or the acquisition, analysis, or interpretation of

data for the work; revising it critically for important intellectual content; Final approval of the version to be published; Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data Sharing Statement

All data relevant to the case review are included in the article or uploaded as supplementary information.

Ethical Approval Information, Institution, and Number(s)

Not applicable. This case review did not involve a living human research participant and thus did not require ethics approval. According to the Saxonian State Chamber of Medicine (Ethikkommission Landesärztekammer Sachsen), no explicit ethical approval is required for autopsy case reports as long as informed consent was obtained from the entitled person (next of kin or family) and all data has been anonymized.

Patient Consent

The patient's family gave written consent to publish this case review and figures/images.

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