Case Report

A Case Report: Acute Myocardial Infarction, Coronal Arteritis and Myocarditis after BNT162b2 mRNA Vaccination against Covid-19

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Abstract: This is a case study of a 55-year-old patient who died four months after receiving the mRNA-vaccine BNT162b2 (Pfizer-BioNTech) against COVID-19 as a second dose, following an initial vaccination with the ChAdOx1 nCov-19 vector vaccine (AstraZeneca) two months earlier. The autopsy diagnosis revealed general atherosclerosis. The histopathologic analyses of cardiac tissue demonstrated the presence of a thrombus occluding the right coronary artery (RCA) without evidence of plaque rupture. As a substitute trigger of clotting, the RCA presented with characteristics of acute lymphocytic vasculitis that extended to vasa vasorum in the adventitia and vessels in adjacent adipose tissue. Microthrombi were occasionally detected in these small vessels. It was obvious that lymphocytic myocarditis had been a chronic ongoing process temporally distinct from acute myocardial infarction. The myocardium contained patchworks of fibrotic areas alongside foci of displaying acute inflammation and fresh myocyte damage. SARS-CoV-2 Spike protein, but not nucleocapsid protein was sporadically detected in vessel walls by immunohistochemical assay. The cause of death was determined to be acute myocardial infarction and lymphocytic myocarditis. These findings indicate that myocarditis, as well as thrombo-embolic events following injection of spike-inducing gene-based vaccines, are causally associated with a injurious immunological response to the encoded agent. Because of the fact that the immune response to a first gene-based vaccination is very low in comparison with the immune response to the second vaccination, the found adverse events has rather to be attributed to the mRNA-based second vaccination as to the initial vector-based one.

Keywords: mRNA vaccine; autopsy

1. Introduction

The enthusiasm that greeted the introduction of COVID-19 gene-based vaccines into the market concealed the existence of serious and significant adversities (Lai, Chua, et al., 2022; Menni et al., 2021). Early clinical studies and post-marketing data returned positive results concerning the safety of vaccination (Chan et al., 2022; Gee, 2021). However, a diversity of side effects have been observed (Lai, Chua, et al., 2022; Rosenblum et al., 2021; Wan et al., 2022), since mRNA-COVID-19 vaccines were approved including myocarditis (Abu Mouch et al., 2021; Oster et al., 2022). Carditis is not an uncommon vaccine-related side effect and is associated with influenza vaccinations (Cheng et al., 2016). The accumulation of case studies and case series has attracted the attention of international safety authorities, including the Centre for Disease Control and Prevention (CDC) (US-CDC, 2022) and the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency EMA (EMA, 2021).

After the COVID-19 vaccines were introduced into the market, multiple reports highlighted the accruing rate of vaccination-induced myocarditis and sudden myocardial infarction (AMI). Vaccine-induced myocarditis was more frequent among the young age groups between 12-18 years with higher rates in males (Baumeier et al, 2022, Karlstad et

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al., 2022, Schauer et al, 2022), whereas vaccine-related AMI affects the adults and aged population (Audrey & Chew, 2022; Chou et al., 2022; Karlstad et al., 2022; Kounis et al., 2022).

The approval of mRNA-based vaccines including BNT162b2 (Pfizer-BioNTech) for COVID-19 prevention among a younger population aged 16 years or older required post-marketing assessment for the newly incorporated population (Lamb, 2021). In a case-control study, the incidence of carditis in individuals receiving BNT162b2 vaccination (0.57 per 100,000 doses) was higher than that of individuals receiving the inactivated whole virus (CoronaVac; 0.31 per 100,000 doses) (Lai, Li, et al., 2022). Notwithstanding the dearth of reported risk of carditis in clinical trials, case reports of carditis have been accruing in various individuals receiving the mRNA-based vaccine worldwide (Audrey & Chew, 2022; Chou et al., 2022; Karlstad et al., 2022; Lai, Li, et al., 2022). The affected adolescents showed biochemical (elevated troponin-I) and radiological (MRI) evidence of either myocarditis or pericarditis shortly after receiving BNT162b2 vaccination (King et al., 2021; Marshall et al., 2021). Similarly, carditis was reported with other mRNA-based vaccines such as mRNA-1273 (Moderna) and the vector-based formula Ad26.COV2.S (Janssen) (M. Li et al., 2021; Nassar et al., 2021; Rosenblum et al., 2021; Sulemankhil et al., 2022). Other case reports highlighted the possibility of carditis in older persons who received the AstraZeneca vector COVID-19 vaccine (ChAdOx1-S/nCoV-19, AZD1222) (Hassanzadeh et al., 2022; Marsukjai et al., 2022).

Furthermore, myocardial infarction was reported in association with mRNA vaccinations both in the United States and Europe. Although the initial reports from mRNA-based vaccine trials reported minor side effects, serious thrombo-embolic events were reported after launching the various brands of mRNA-based vaccines. The reported cases of acute myocardial infarction (AMI) were represented by chest discomfort or shoulder pain within a few hours after receiving mRNA-1273 (Moderna) vaccine in the US (Boivin & Martin, 2021; Sung et al., 2021) and worldwide (Chatterjee et al., 2021; Maadarani et al., 2021). In Europe, the EMA approved two mRNA-based vaccines including BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) (Cavaleri et al., 2021). However, soon after the administration of mRNA vaccines on a large scale in Europe, accumulating evidence supported the link between AMI and mRNA-based vaccines including BNT162b2 (Pfizer-BioNTech) (Tajstra et al., 2021), and mRNA-1273 (Moderna) (Barsha et al., 2021; Klein et al., 2021). Given the catastrophic thrombo-embolic events, the vector-based vaccine Oxford-AstraZeneca was suspended in several European countries (Triggle, 2021; Wise, 2021). However, a report analyzing 23 fatalities in elderly people immediately after BNT162b2 COVID-19 immunization has raised concerns about the possibility that mRNA-based COVID-19 vaccination might have unanticipated serious results as well (Torjesen, 2021).

Further preclinical, autopsy and endocardial histopathologic studies confirmed the clinical case reports regarding the serious adverse effect of mRNA-based vaccines. Evidence from the *mouse* study concluded that accidental intravenous injection of mRNA-based vaccines can lead to myopericarditis, thus providing a possible explanation for the accumulating data from the case reports and highlighting a possible cause of the serious adversity that was not reported in the phase I-III studies (C. Li et al., 2021). Furthermore, an autopsy revealed features of myocarditis with significant heterogeneous inflammatory infiltrate in a 27-year-old healthy young man who presented to the emergency department (ED) with cardiopulmonary arrest a few days following the first dose of mRNA-1273 (Hoshino et al., 2022). In addition, another study showed evidence of eosinophilic myocarditis in three patients who received the BNT162b2 vaccine and presented with chest pain 14 days after the second dose (Frustaci et al., 2022). Therefore, myocarditis following mRNA-based vaccination is attributed to a hypersensitivity immune reaction that could pertain to the received vaccination.

In this study, detailed histopathologic analyses of the heart were undertaken in a 55-year old patient who deceased four months after mRNA vaccine booster. The cause of death as stated at autopsy was acute myocardial infarction and lymphocytic myocarditis

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associated with spike protein detected in the respective tissue. The results indicate that both myocarditis and thromboembolic events derived from a hyperinflammatory, excessive immune response to the mRNA-vaccine BNT162b2 (Pfizer-BioNTech) against COVID-19.

2. Materials and Methods

Materials and methods comply were exactly as described in Mörz, 2022 as follows:

Formalin-fixed and paraffin-embedded tissues were routinely cut into 5-µm sections and stained with haematoxylin and eosin (H & E) for histopathological examination. Immunohistochemical staining was conducted on a fully automated immunostaining system Ventana Benchmark (Roche). An antigen retrieval Ultra CC1 (Roche Ventana) was used for every antibody. The dilution factors and incubation times for all antibodies used are summarized in Table 1. SARS-CoV2 positive tissues were used as a control for the antibodies against SARS-CoV2-epitopes as well as in vitro transfected positive control samples (see hereafter). The slides were examined with a light microscope (Nikon ECLIPSE 80i) and representative images were captured by the camera system Motic® Europe Motic MP3.

Table 1. Antibodies.

Target antigen	Manufacturer	Clone	Dilution	Incubation time
CD4	Zytomed	SP35	Ready to use	30 minutes
CD8	Zytomed	C8/114B	Ready to use	40 minutes
CD61	Medac	2f2	1:50	45 minutes
SARS-CoV2-Subunit 1	ProSci	9083	1:500	30 minutes
SARS-CoV2-Nucleocapsid	ProSci	35-720	1:500	30 minutes

2.1. Preparation of positive control samples

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), 10% FCS (Gibco) 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 1h with 2 ml of fresh medium containing the injection solutions directly from the original bottles diluted to the respective vaccination dose. This was 1:500 dilution in the case of BNT162b2 Pfizer/Biotech), 1:100 dilution in cases of mRNA-1273 (Moderna), AstraZeneca (Vaxzevria), 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.

The preparation of tissue blocks from transfected cells: 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) and harvested with 10 ml of PBS/10% FCS and washed 2x with PBS and centrifugation at 280xg for 10 min each. Cell pellets were fixed overnight in 2 ml in PBS/4% Formalin at 8°C, then washed in PBS once. The remaining cell pellets after centrifugation were dissolved 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 agarose fixed cell pellets were stored in 4% Formalin/PBS till subjection to routine paraffin embedding parallel to tissue samples.

2.2. Case presentation and description

2.2.1. Autopsy presentation

A 55-year-old male patient was vaccinated with the ChAdOx1 nCov-19 vector vaccine (AstraZeneca) in May 2021, and with BNT162b2 mRNA vaccine (Pfizer-BioNTech

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COMIRNATY) in July 2021, according to a copy of the vaccination book. The patient died in November 2021. An autopsy diagnosis was general atherosclerosis. The cause of death was acute myocardial infarction and lymphocytic myocarditis. The lumen was occluded with a platelet thrombus on an atherosclerotic bed in the right coronary artery. This condition was associated with a significant lymphocytic vasculitis of the vasa vasorum.

2.2.2. Autopsy

The family of the patient sought and approved the autopsy since the patient's symptoms before passing away were unclear. Standard procedures were followed throughout the autopsy, including a macroscopic and microscopic examination. All parenchymatous tissues were examined histopathologically.

3. Results

3.1. Autopsy findings

Anatomical Specifications: Body weight, height, and specifications of body organs are summarized in Table 2.

Table 2. Anatomical Specifications.

Item	Measure
Body weight	105 kg
Hight	180 cm
Heart weight	640 g
Left heart hypertrophy	20 mm
Right heart hypertrophy	8 mm
Brain weight	1540 g
Liver weight	2710 g
Spleen weight	190 g
Left kidney weight	210 g
Right kidney weight	215 g

Cardiac tissue: Autopsy findings showed left ventricular myocardial hypertrophy, consecutive right ventricular hypertrophy, and bilateral nodular adrenal hyperplasia with adenoma-like features. The posterior cardiac wall showed myocardial fibrosis with coarse spots and features of acute myocardial infarction (6 x 5 cm). Ectasia of atria and ventricles was noticed (sign of acute and chronic circulatory insufficiency and central dysregulation).

Coronaries: Histopathological examination of the coronary arteries showed severe and moderately stenosed arteriosclerotic right coronary artery with a 1 cm long plaque at a distance of 1 cm from aortic origin. Moderate to moderately stenosed arteriosclerosis of the Left anterior descending artery was noticed. The circumflex branch of the left coronary artery showed features of atherosclerosis with mild stenosis.

Vascular tissue: Histopathological examination revealed moderate arterio-arteriolosclerosis of the renal arteries, cervical arteries, cerebral basal arteries, thoracic aorta, ascending aorta, and aortic arch as well as high-grade nodular arteriosclerosis of the abdominal aorta and iliac arteries. In addition, there was lymphocytic vasculitis of the vasa vasorum and lumen-occlusive platelet thrombus in histological examination. Furthermore, there were features of lymphocytic myocarditis.

Other tissues: Tissue congestion was noticed including features of acute pulmonary edema, brain edema (mild), pituitary, larynx, pharynx, bronchial mucosa, lungs, spleen, kidneys, liver (acute and chronic), and prostate. Histological features of kidney shock were identified. Urine bladder ectasia was identified (distorted urinary bladder). The cerebral dentate nucleus showed evidence of fresh necrosis.

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3.2. Immunohistochemical analyses

The immunohistochemical staining of the right cardiac artery (RCA) tissue showed thrombus formation on atherosclerotic bases (Figure 1A) along with arteritis in the media with lymphocytic and histiocytic infiltration (Figure 1B) as well as periarteritis in the adventitia (Figure 1C) with CD4 T helper cell and CD8 killer cell infiltration (Figure 2, 3) at the level of the thrombus formation. The intima of the RCA showed inflamed atherosclerotic plaques with lymphocytic infiltration (Figure 4). SARS-Cov2-Spike protein was detected by DAB immunostaining (Figure 5) but SARS-Cov2-nucleocapsid protein was not (Figure 6). Thrombus formation, rich in platelets and lymphocytes, was detected in the lumen of the RCA (Figure 7, 8), the attributed small coronary vessels (arteritis) (Figure 10), and blood capillaries (periarteritis) (Figure 9) at the level of the occluded thrombus of the RCA.

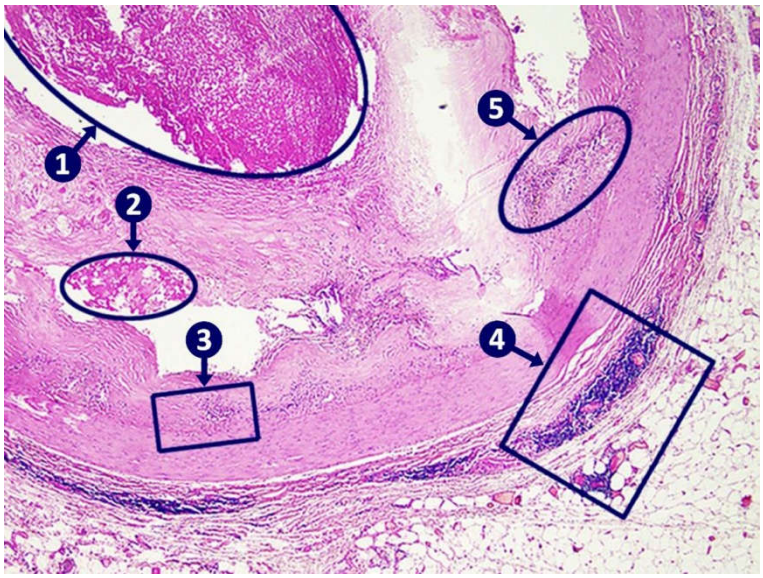

Figure 1A. H & E 24x Cross-section through the right coronary artery at the level of the thrombus. 1 Thrombus; 2 Atherosclerotic plaque; 3 Arteritis; 4 Periarteritis; 5 Photoarea of SARS-CoV2- Spike and nucleocapsid immunohistochemistry**.**

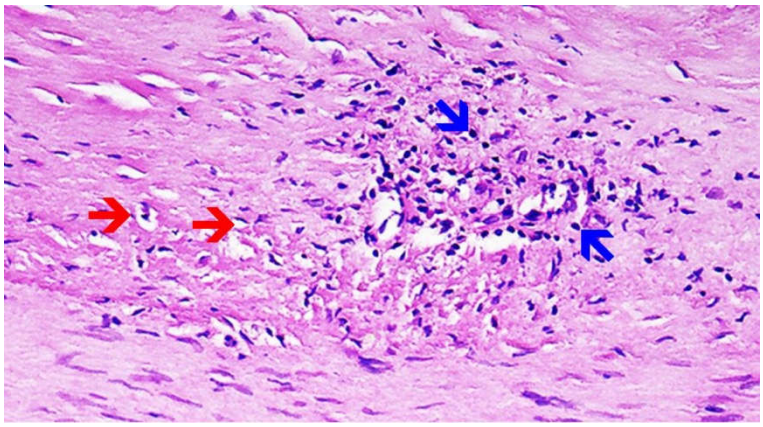

Figure 1B. H & E 200x Arteritis in the media of the right coronary artery at the level of the thrombus Enlargement of the specimen from Figure 1A, zone No. 3. Blue arrows: Lymphocytes (examples); Red arrows: Histiocytes (examples)**.**

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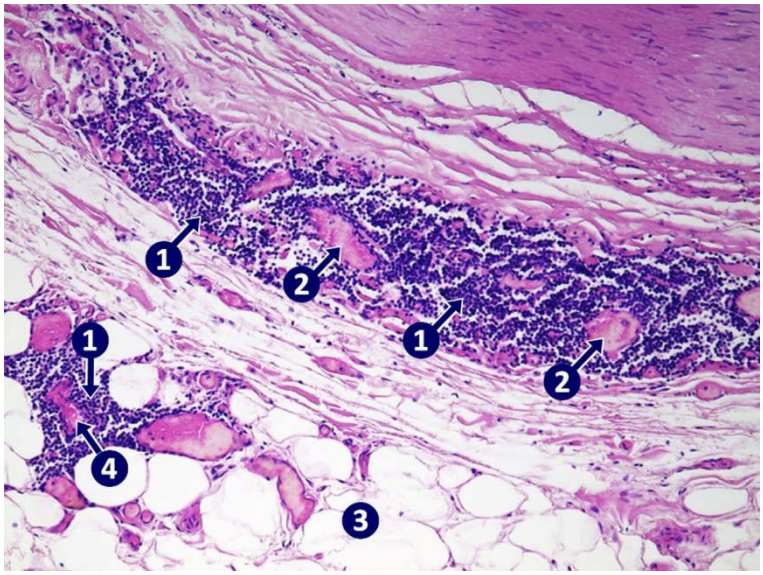

Figure 1C. H & E 100x Periarteritis in the adventitia of the right coronary artery at the level of the thrombus and arteritis in the surrounding adipose tissue Enlargement of the specimen from Figure 1A, zone No. 4. 1 Lymphocytes: Sharply demarcated dark blue cells; 2 Periarteritis (vasae vasorum) in the adventitia; 3 Adipose tissue; 4 Vasculitis one small vessel in the adjacent adipose tissue**.**

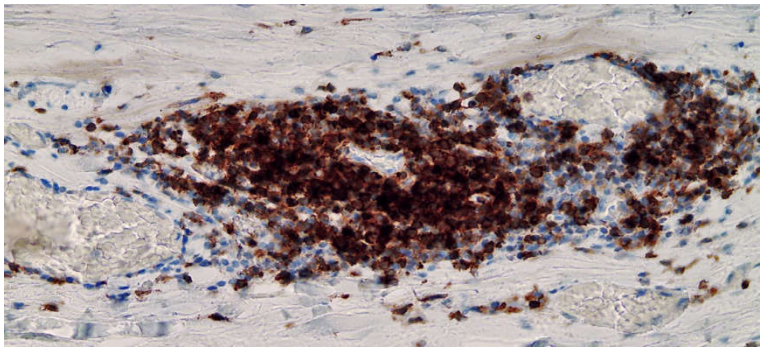

Figure 2. CD4 200x Periarteritis in the adventitia of the right coronary artery at the level of the thrombus, zone No. 4 Figure 1 A. T helper cells: Brownish granular deposits of DAB; T Killer cells: Blue cells.

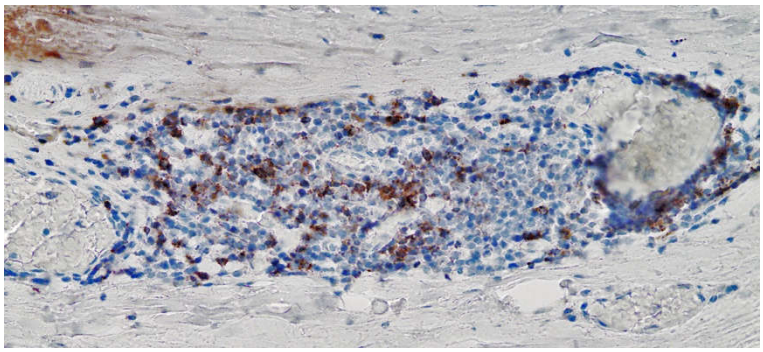

Figure 3. CD8 200x Periarteritis in the adventitia of the right coronary artery at the level of the thrombus, zone No. 4 Figure 1 A. T helper cells: Blue cells; T Killer cells: Brownish granular deposits of DAB.

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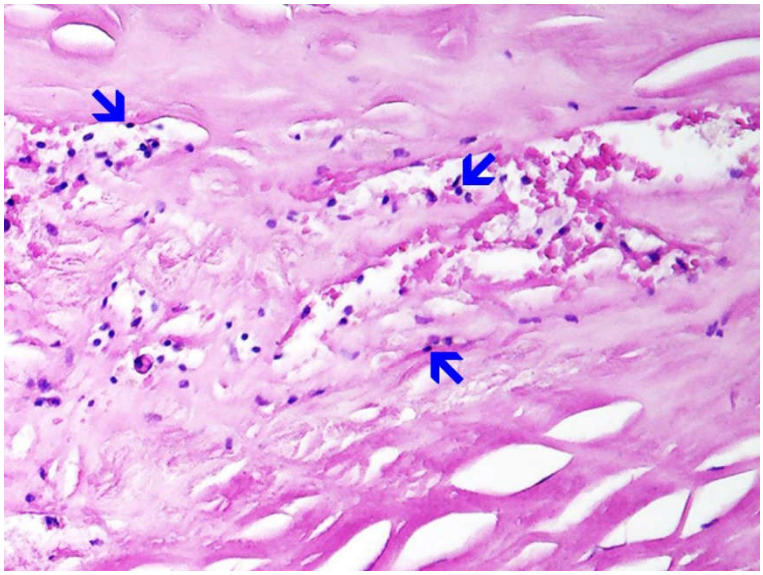

Figure 4. H & E 100x Inflamed Arteriosclerotic plaque in the intima of the right coronary artery at the level of the thrombus. Blue arrows: Lymphocytes (examples).

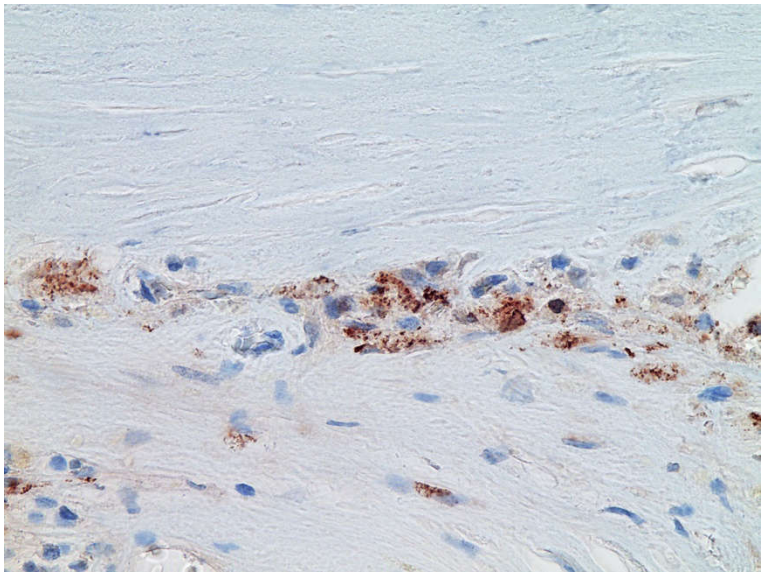

Figure 5. SARS-CoV2-Spike protein 400x Arteritis of the right coronary artery at the level of the thrombus zone. No. 5, Figure 1A. Spike protein: Brownish granular deposits of DAB

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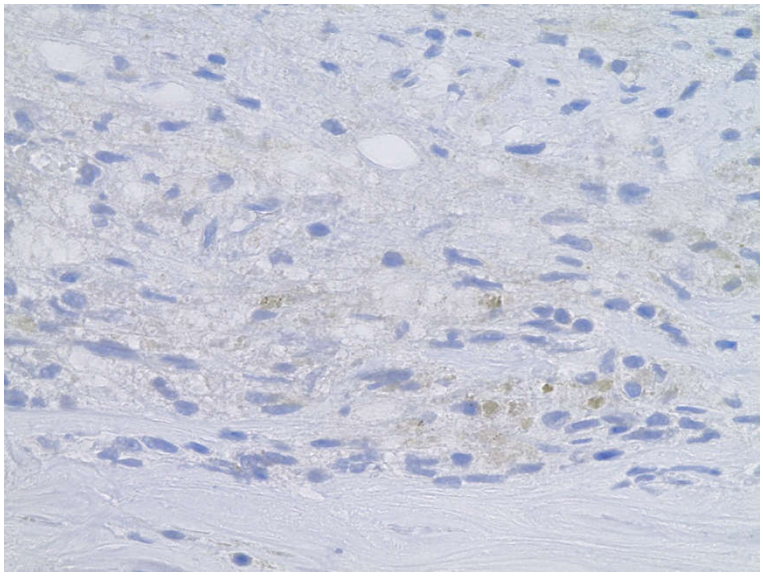

Figure 6. SARS-CoV2-Nucleocapsid protein 400x Arteritis of the right coronary artery at the level of the thrombus zone No. 5, Figure 1A. No detection (of DAB) of nucleocapsid protein.

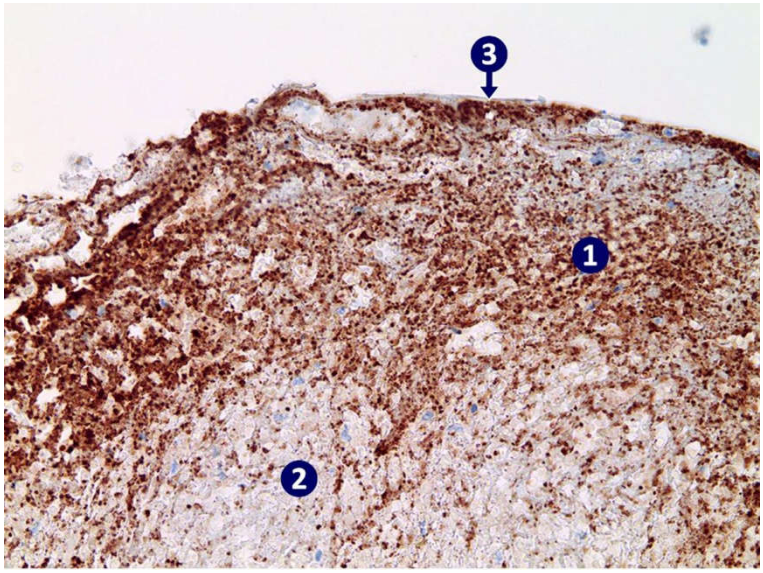

Figure 7. CD61 200x Right coronary artery: Thrombus with zonal formation. Thromboytes: Brownish granular deposits of DAB; The denser the brownish granular deposits of DAB occur, the higher the proportion of platelets. 1 Zone with high platelet percentage; 2 Zone with lesser platelet percentage; 3Endothelium.

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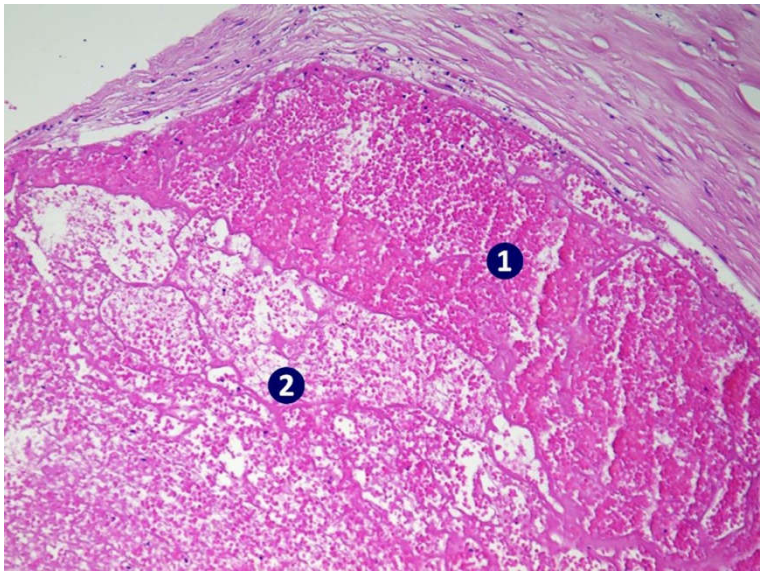

Figure 8. H & E 100x Right coronary artery: Thrombus with zonal formation. 1 Zone with high platelet percentage**;** 2**.** Zone with lesser platelet percentage**.**

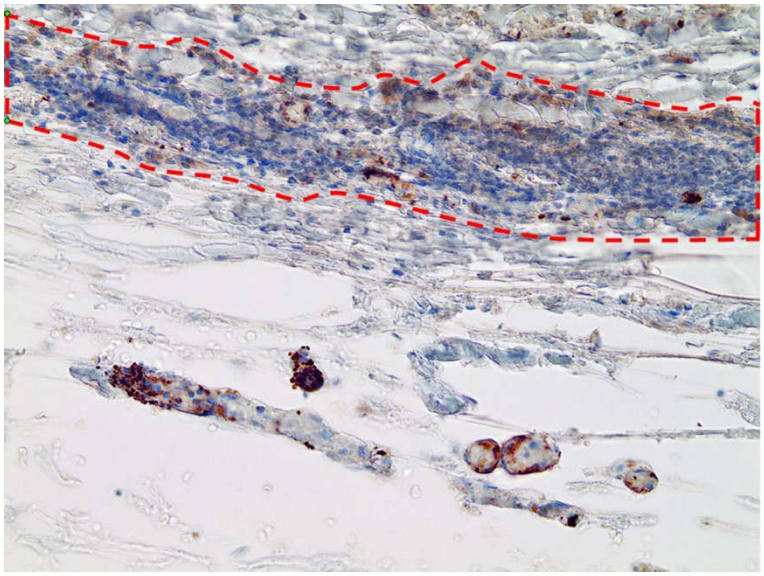

Figure 9. CD61 200x Periarteritis with capillary thrombosis at the level of the occluded thrombus of the right coronary artery. Zone marked red: Periarteritis; Blue cells: Lymphocytes; Linked Thrombocytes: Brownish granular deposits of DAB; The denser the granules appear, the higher the proportion of platelets**.**

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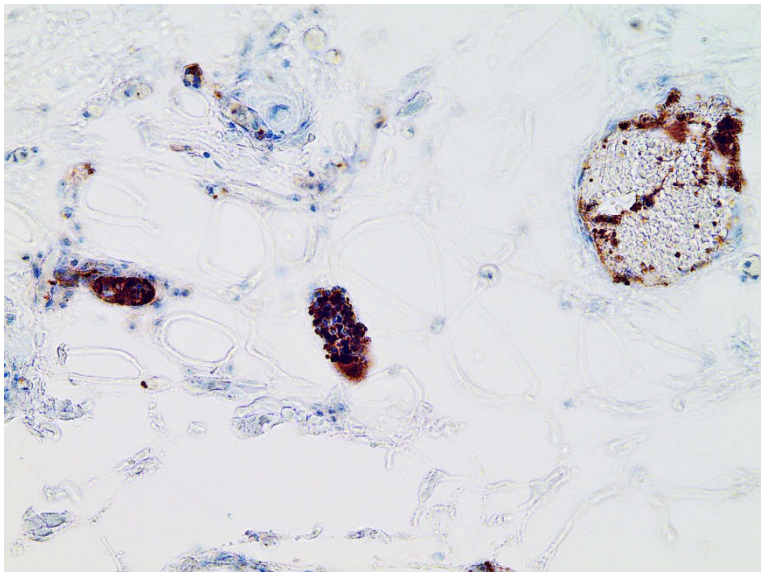

Figure 10. CD61 200x Periarteritis with small Vessels thrombosis at the level of the occluded thrombus of the right coronary artery (Enlargement of the specimen from Figure 1A, zone No. 4). Blue cells: Lymphocytes; Thrombocytes: Brownish granular; deposits of DAB; The denser the granules appear, the higher the proportion of platelets**.**

Examination of the myocardium showed evidence of extensive reticular fibrosis (Figure 11A, 11B) and of myocarditis (Figure 12A, 12B). SARS-Cov2-Spike protein was detected in the myocardium by DAB immunostaining (Figure 13) but again not the SARS-Cov2-nucleocapsid protein (Figure 14).

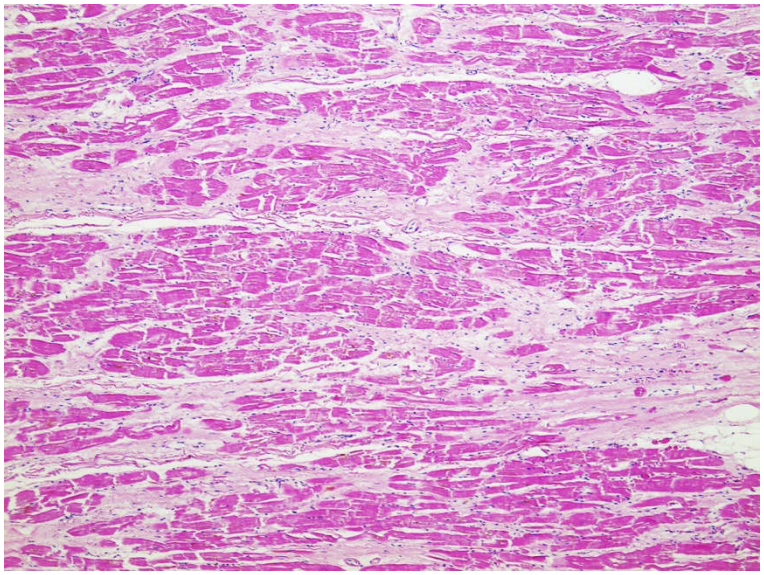

Figure 11A. H & E 40x Myocardium with reticular extensive fibrosis. Magenta: Cardiomyocytes**;** Blue cells: Lymphocytes**.**

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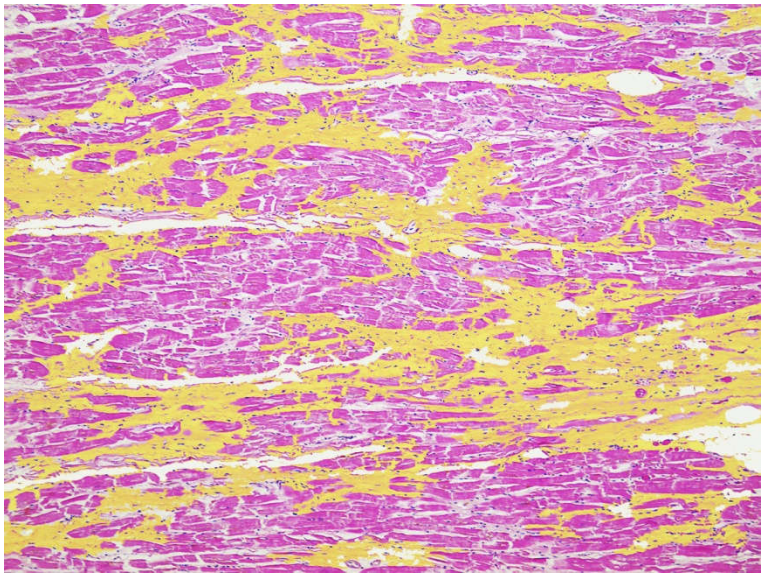

Figure 11B. H & E 40x Myocardium with reticular exten-sive fibrosis, digitally highlighted in yellow of Figure 11A. Yellow:Fibrosis**;** Magenta: Cardiomyocytes**;** Blue cells:Lymphocytes**.**

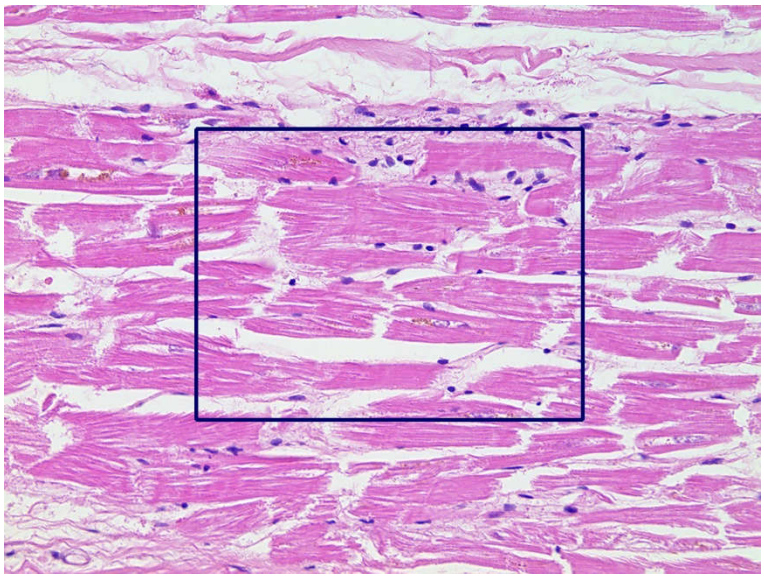

Figure 12A. H & E 200x Myocarditis overview.

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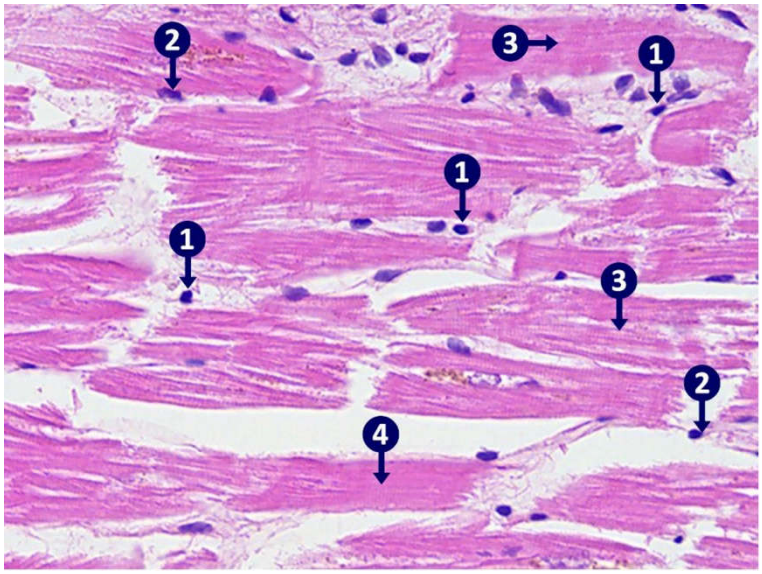

Figure 12B. H & E 400x Myocarditis Enlargement of the specimen from Figure 12A. Magenta: Cardiomyocytes; 1 Lymphocytes (examples); 2 Histiocytes (examples); 3Z-band damages (examples); 4Cardiomyocyte with loss of nucleus and eosin red cytoplasm as a typical sign of dying cardiomyocytes**.**

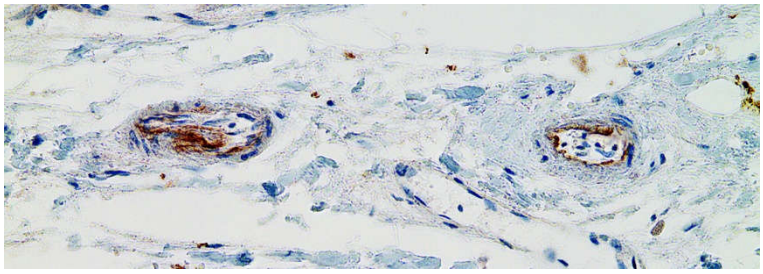

Figure 13. SARS-CoV2-Spike protein 200x Myocardium cross-section small vessels. Spike protein: Brownish granular deposits of DAB predominantly in the vessel wall.

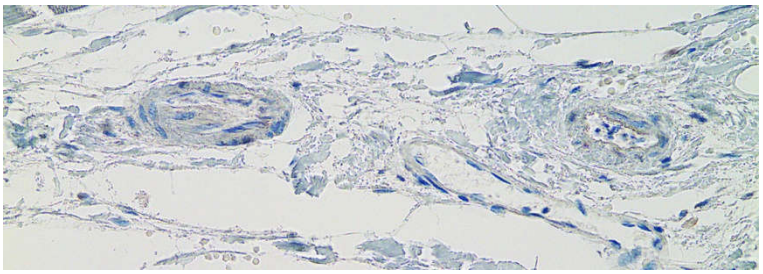

Figure 14. SARS-CoV2-Nucleocapsid protein 200x Myocardium cross-section small vessels. No detection (of DAB) of nucleocapsid protein.

3.3. Autopsy-based diagnosis

The final diagnosis was acute myocardial infarction (I21.9), arteritis of the right coronary artery and acute myocarditis (I40.9), and generalized atherosclerosis (I70.9). The identification of SARS-CoV-2 spike protein on the endothelial surface correlates the findings with the host immune response to the received vaccine. A recent infection with SARS-CoV-2 could be excluded as the source of the spike protein based on the absence of concomitantly expressed nucleocapsid protein.

4. Discussion

Mass vaccination of the whole population is considered the sole safe and effective solution to halt the progress and spread of the severe acute respiratory syndrome

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coronavirus 2 (SARS-CoV-2). The reluctance of people to get immunizations is a major challenge. The fear of getting immunization is fuelled in part by concerns. Myopericarditis is a particularly serious and potentially fatal side effect. The incidence of myopericarditis was reported to be approximately 40.6 cases per million second doses mainly in young males between 12-29 years who received mRNA COVID-19 vaccine (Gargano et al., 2021). It is important to bear in mind that fundamental facets of the immunogenicity and adverse effects of gene-based vaccines have not been properly explored (McDonald et al., 2021). The lack of secondary pharmacodynamic investigations and safety pharmacology research serves as a cornerstone for this assumption (European Medicines Agency (EMA), 2022).

The autopsy study of a 55-year-old deceased person revealed evidence of thrombus formation in the large RCA, small arterial branches, and arterial capillaries that could not be attributed to atherosclerosis plaque rupture. Moreover, there was inflammatory cell infiltration including CD4 and CD8 T cells and histiocytes which is typical of an autoimmune reaction. The histopathological examinations revealed the extensive presence of scattered fibrotic areas, indicating that cardiac cell necrosis had occurred at these sites during a time period well preceding death. The abundance of small fibrotic scars, in combination with fresh inflammatory lesions,, as revealed in this study, has never been described in any cardiac affliction hithertofore.

A crucial finding, in this study, was the detection of spike protein by immunohistochemistry in the vascular and cardiac tissue in the absence of the nucleocapsid protein. Similar findings were reported in other case studies and biopsy examinations (Baumeier et al., 2022; C. Li et al., 2021, Mörz, 2022). These findings indicate that the leading cause of the immunological reaction (myocarditis with lymphocytic infiltration and thromboembolic features) is related to the gene-based vaccination and not to an acute infection with the SARS-CoV-2 virus. Since the initial vaccination of the patient was conducted with the ChAdOx1 nCov-19 vector vaccine , followed by the second vaccination with the BNT162b2 mRNA vaccine, it has to be considered how far each of the two vaccines contributed to the adverse events of the vaccination found during autopsy and histological examination. In this regard it has to be taken into account that the spike antibody response after an initial vaccination with the ChAdOx1 nCov-19 vector vaccine is very low in comparison to the response to a second dose of either the ChAdOx1 nCov-19 vector vaccine or the BNT162b2 mRNA vaccine (Shrotri, 2021). Therefore, and because of the fact that the patient suffered the adverse events after the second but not after the first gene-based vaccination, the histopathological findings should be attributed to the last gene-based vaccination with the BNT162b2 mRNA vaccine.

Further, accumulating evidence indicates the association between mRNA-based vaccination and the occurrence of myocarditis (Kawamura et al., 2022; Lai, Li, et al., 2022; X. Li et al., 2022; Mishra et al., 2022b; Mörz, 2022). Myocardial hypertrophy and extensive fibrosis are the major findings made in endomyocardial biopsy studies (Choi et al., 2021; Hoshino et al., 2022). In addition, myocardial cell death in the form of degeneration, apoptosis, and necrosis was observed in a preclinical study when the mRNA vaccine was injected directly intravenously (C. Li et al., 2021). In concurrence with the literature, the present study detected unusual, scattered areas of myocardial fibrosis that may be related both to microthrombotic vascular occlusion and to direct immunological damage, but certainly not to atherosclerosis plaque rupture (Alkarithi et al., 2021; Kim et al., 2019; Ludewig et al., 2002).

The second histopathological finding was T cell infiltration including, but not limited to, CD3+, CD4+ and CD8+ T cells, cytotoxic cells, and macrophages (Baumeier et al., 2022). Another study found mainly CD68 positive macrophages and CD3 T cells (Nguyen et al., 2021). Eosinophilic infiltration was reported in an endomyocardial biopsy study in 3 patients who proved clinically and laboratory to have post-vaccination myocarditis, thus suggesting a hypersensitivity reaction to the vaccine. The study proposed the formation of new antigens from macromolecules of cardiomyocytes and the mRNA-based vaccine or one of its components (Frustaci et al., 2022). Another study found eosinophilic cells

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infiltration along with T cells and macrophages in an autopsy study, thus supporting the hypersensitivity nature of post-vaccination myocarditis (Hoshino et al., 2022). Neutrophils and histiocytes were predominant in the case of isolated atrial myocarditis (Choi et al., 2021). This study concurred with the literature on the presence of T lymphocyte infiltration with the predominance of CD4+ T helper cells suggesting the autoimmune nature of myocarditis (Alberto Kölliker Frers et al., 2020).

Differences observed in the various studies possibly stem from temporal deviations in the course of events. Endothelial damage is likely the common initial trigger of injurious events. Intramuscularly applied mRNA vaccines are known to rapidly reach the bloodstream (C. Li et al., 2021), from whence they will be taken up by the endothelium (Theoharides, 2022). Indeed, spike protein has repeatedly been detected on endothelial cells following mRNA COVID-19 vaccination (Xia, 2021) and this must be assumed to initiate an immune attack on the vessel wall with resulting vasculitis and thrombus formation.

It is noteworthy that immune-mediated thrombotic events must be expected to further be propelled by the direct activation of platelets by the spike protein produced by endothelial cells that line the vessel walls (Chatterjee et al., 2021; Flower et al., 2021; Mishra et al., 2022; Sung et al., 2021). This could explain the occurrence of "white" thrombi with the typical thick sheaths of platelet lining (see Fig. 7 and 8). These "early" events likely cause vessel damage and leakage of the vaccines to surrounding tissue cells, where their uptake will spark destructive auto-attack processes. A most remarkable finding in this study relates to the simultaneous occurrence of fresh lesions (Fig. 11A and 11B) alongside with aged lesions (fibrotic areas). This indicates that tissue damage is inflicted continuously over time (Alkarithi et al., 2021; von Hundelshausen et al., 2021).

The high incidence of post-vaccination serious side effects soon after receiving the second or third mRNA vaccine dose (Hoshino et al., 2022; Nguyen et al., 2021; Sung et al., 2021) emphasizes that mRNA vaccine booster doses represent a culprit responsible for the exaggerated immune response. Repeated exposure to the mRNA-encoded protein allows the elicited antibodies to bind and activate complement-mediated mechanisms including histamine release, activation of neutrophils and histiocytes, and a direct cytotoxic action (Bhakdi and Tranum-Jensen, 1983; Jiang et al., 2022; Meng et al., 2021).

The current study has demonstrated the presence of thrombus formation not only in the lumen of the RCA but also in the vasa vasorum and capillaries of the RCA itself (Fig. 7-9). These findings, to the best knowledge of the author, have never been described in the literature and cannot be attributed to atherosclerotic plaque rupture. The abundance of inflammatory cells points to the autoimmune nature of the event (Frustaci et al., 2022; Hoshino et al., 2022) that most probably is triggered by the spike protein whose expression is induced in endothelial and myocardial cells. The parallel presence of aged and fresh myocardial lesions indicates that tissue damage occurs repeatedly over extended periods, probably in response to vaccination boosters.

It is now known that post-vaccination thromboembolic events occur at an alarming incidence following COVID vaccination. Thrombosis in the left anterior descending coronary artery (LAD) was found in an 86-year-old male patient who collapsed immediately after receiving the first dose of the BNT162b2 mRNA vaccine, (Tajstra et al., 2021). Several case studies reported the occurrence of thromboembolic events and coronary artery occlusion that necessitated emergency coronary intervention (Chatterjee et al., 2021; Flower et al., 2021; Mishra et al., 2022a; Sung et al., 2021). Other thromboembolic events were reported in association with mRNA-based vaccines including thrombotic thrombocytopenia that resemble heparin-induced thrombocytopenia (von Hundelshausen et al., 2021) and hypersensitivity myocarditis (Kounis syndrome) (Kounis et al., 2022; Memon et al., 2015).

Most recently, results of an excellent cohort study have appeared focusing on cardiovascular effects, particularly myocarditis and pericarditis events, after BNT162b2 mRNA COVID-19 vaccine injection in 301 Thai adolescents. Moreover, cardiovascular effects were found in 29.24% of patients, ranging from tachycardia, palpitation, and myopericarditis (Mansanguan et al., 2022). The clinical presentation of myopericarditis after

vaccination was usually mild, with all cases fully recovering within 14 days. The authors rightly noted, however, that mid- to long-term adverse consequences arising in the wake of fibrotic scar formation could not be excluded, and careful follow-up studies are urgently needed.

5. Conclusion

The results of the presented histopathological analyses strongly suggest an autoimmune origin of myocarditis, arteritis and AMI in a patient who had received the ChAdOx1 nCov-19 vector vaccine (AstraZenca) initially, followed by a second vaccination with the BNT162b2 mRNA vaccine (Pfizer-BioNTech) against COVID-19. The compelling consideration of a causal link between the gene-based-vaccinations and the diagnostic findings stems from the detection of SARS-CoV2-Spike protein in the absence of SARS-CoV-2 nucleocapsid in the cardiac tissue, the occurrence of vasculitis and perivasculitis with thrombus formation at multiple sites, infiltration of the myocard by inflammatory cells, and the simultaneous presence of reticular scarred tissue alongside with sites of ongoing cell destruction. In the particular case it has to be considered that the manifest adverse events have to be attributed rather to the second gene-based vaccination with the BNT162b2 mRNA vaccine, which has been applied as a booster to the earlier vaccination with the ChAdOx1 nCov-19 vector vaccine, due to the assumption of a comparably low immune response commonly found after an initial gene-based vaccination against Covid-19. Thus, further investigations into the possibility that adverse events following application of gene-based vaccines may derive from an excessive immune response are urgently called for.

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