Case report

New conditions in heart transplantation in persistence of SARS-CoV-2

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Abstract: Heart transplantation is a treatment of choice for patients with severe heart failure. Infection transmission from a donor to a recipient remains a prominent problem in organ transplantation. However, the risk of SARS-CoV-2 transmission through nonlung organ transplantation is still unclear. In the article we present a case of a 28-year-old pregnant woman who developed heart failure soon after recovery from SARS-CoV-2 infection in the third trimester of gestation. In the postpartum period the disease worsened and the patient required cardiac transplantation. We examined the recipient's heart and diagnosed left ventricular noncompaction cardiomyopathy. Immunohistochemical analysis showed the SARS-CoV-2 antigen expression in the donor's heart before transplantation and after the surgery the endomyocardial biopsy was taken. Moreover, an ultrastructural assessment of the endomyocardial specimen revealed endothelial and pericyte injury and single particles on the surface of endothelium consistent with SARS-CoV-2. Recent findings were associated these damages with SARS-CoV-2 infection. The present study describes the rare case of SARS-CoV-2 transmission from donor to recipient through a heart transplant and resulting in endothelial cell and pericyte activation and humoral immune response activation.

Keywords: SARS-CoV-2 infection; immunohistochemical and ultrastructural myocardial studies; heart transplantation; virus transmission

1. Introduction

The first heart transplant was performed in 1967, since then it has remained the definitive treatment for patients with end-stage heart failure (HF). Patients with pre-existing heart conditions are more susceptible to SARS-CoV-2 infection and are at a higher risk of morbidity and mortality. Therefore, it is not surprising that during SARS-CoV-2 pandemic, there was an increasing number of patients with organ transplants who suffered from COVID-19 [1]. Since these patients received immunosuppression therapy, the course of the disease was more severe.

2. Case presentation

The patient, a 28-year-old pregnant woman at the 34th week of gestation, was diagnosed with SARS-CoV-2 infection and had bilateral pneumonia. Ten days after recovery, the patient started to experience HF symptoms: shortness of breath, swelling in the legs, ankles, and feet, and heart palpitations. On clinical examination, the following data were determined: bilateral interstitial pneumonia

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and hydrothorax; sinus tachycardia and nonspecific T-wave; significant chamber dilation and signs of left ventricular (LV) hypertrophy; LV ejection fraction was 37% (Table 1).

Table 1. - Clinical data of the recipient.

A period of time	A period of treatment	Data of examination
34th week of gestation	First complaints developed and patient was managed at home.	- SARS-CoV-2 infection and had bilateral pneumonia. - In 2 weeks patient recovered from COVID-19 but due clinical manifestation of heart failure patient was admitted to the local hospital.
39th week of gestation	Patient moved to our Centre	- Patient gave a birth to a healthy baby by cesarean section.
3 weeks after delivery	Heart failure ICU	- HFrEF, ECMO implantation - Included in the heart transplant waiting list
18 days after ECMO implantation	Heart failure ICU	Heart transplantation, ECMO explantation
8 days after heart transplantation	Heart transplantation clinical department	EMB results were as following: acute cellular rejection (ACR (0R)) and antibody-mediated rejection (pAMR2 (I+, H+)).
20 days after heart transplantation	Heart transplantation clinical department	EMB results were as following: signs of humoral rejection (pAMR2 (I+, H+)).
34 days after heart transplantation		EMB results were as following: ACR (1R/1A) and pAMR0.

At the 39th week of gestation the healthy newborn was delivered by cesarean section.

In the post-partum period, the patient still had symptoms of HF: dyspnea on exertion, edema of ankles and feet, high level of N-terminal pro-B-type natriuretic peptide (NT-proBNP) of 3506 pg/mL, progressive decline in LV ejection fraction to 17%. Concomitant infection resulted in an aggravation of HF symptoms, e.g. recurrent atrial flutter.

Because of the end-stage HF, the patient was eventually transferred to extracorporeal membrane oxygenation (ECMO). To define HF origin, the right ventricular endomyocardial biopsy (EMB) was carried out.

On histological examination of EMB sample, moderate myocyte degeneration was observed. Immunohistochemical study identified the following cell types: CD3+ activated T lymphocytes (5 per 1 mm^2); CD68+ macrophages (16 per 1 mm^2); enterovirus VP1 positive cardiomyocytes (5-20%); HHV-6 positive lymphocytes. The cytomegalovirus antigen was not detected. Endothelial activation was confirmed by the expression of VWF, VEGF, and C1q, but HLA-DR was negative. Thus, we concluded the absence of myocarditis signs in EMB specimen. On the other hand, we found the markers of humoral immunity activation and endothelial cell activation. These symptoms could be linked to post-COVID-19 syndrome.

Orthotopic heart transplantation (HTX) was carried out after 18 days of ECMO therapy. For HTX, we used the bicaval technique under extracorporeal circulation, and myocardial protection was provided with custodiol cardioplegia. According to our local protocol all donors and recipients were examined to rule out the COVID-19 before the HTX: swab PCR tests and thoracic CT scans were performed in both of them prior to the surgery. During the surgery, a polypoid white formation of size 2x0.7 cm was found in the donor atrium. It was removed together with a 0.4x0.3 cm fragment of myocardium. After histological examination, this case was diagnosed with polypoid fibrolipoma (Figure 1A, 1B).

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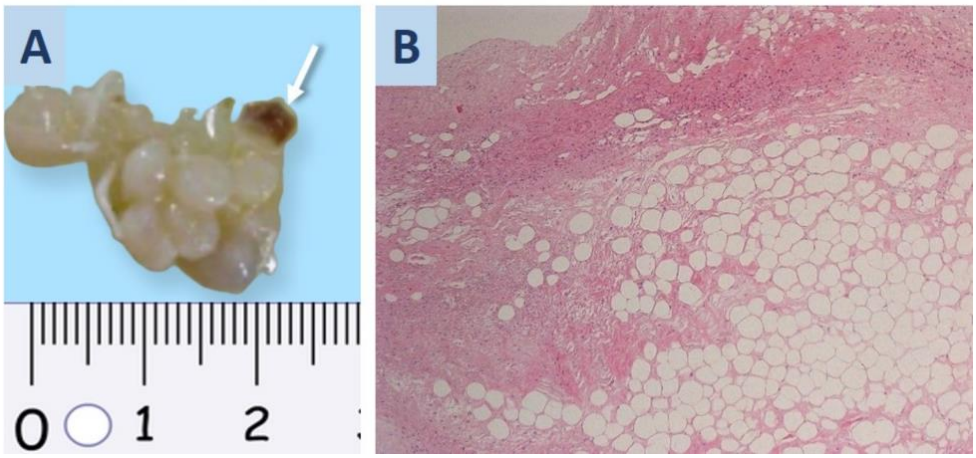

Figure 1. A. Polypoid fibrolipoma in donor left atrium, the arrow indicates the myocardial site. **B.** Fibrous and adipose tissue structure of fibrolipoma; hematoxylin-eosin staining; x100.

The explanted heart was globular, weighed 387 g, and had a size of 11.0x11.0x6.0 cm. Coronary arteries were without stenosis. As can be seen from the figure (Figure 2A), the ventricular cavities were affected by excessive trabeculation, and mural thrombi were distinguished in the intertrabecular spaces. The thickness of the apical and mid-ventricular regions of posterior and lateral walls of LV was 0.6 cm. The thickness of trabeculated myocardium was 1.6 cm. In the cross-section, the myocardium was homogeneous and was brown in a color.

Histologically the myocardium showed signs of parietal thromboendocarditis of 2-3 weeks with fibrin deposition, lymphocytic infiltration, and granulation tissue. Microscopic examination of 15 sections of LV free wall found two samples with lymphocytic infiltrates (10 and 23 cells per 1 mm^2). The report diagnosed LV noncompaction cardiomyopathy, acute focal myocarditis, parietal thromboendocarditis of LV. The latter possibly as part of post-COVID-19 syndrome. However, immunohistochemical study did not reveal SARS-CoV-2 antigen expression.

After heart transplantation the recipient was managed with triple-drug immunosuppression: Tacrolimus, mycophenolic acid and steroids. In the recent weeks before the HTX she was treated for multi-drug resistant bacterial pneumonia with different schemes of I.V. antibacterial treatment. It was decided not to prescribe the induction therapy, considering her recent recovery from infectious complications, the duration on the ECMO support, initiation of triple-drug immunosuppression after HTX to minimize the risk for the infection development.

Eight days post-HTX, the patient had the first EMB and its examination detected the following rejection grade of the cardiac graft: acute cellular rejection (ACR (0R)) and antibody-mediated rejection (pAMR2 (I+, H+)). Twenty days post-HTX, signs of humoral rejection (pAMR2 (I+, H+)) persisted in the second EMB sample. Pathomorphological analysis of both EMB samples (8 and 20 days) additionally found hypertrophic, polymorphic, perivascular cells with large nuclei (Figure 2B, 2C, 2D). We described these cells as activated endothelial cells because of CD34 expression, the SARS-CoV-2 antigen was also positive. However, the ddPCR did not confirm the SARS-CoV-2 RNA presence in the EMB sample. Ultrastructural study was performed only for the second EMB (20 days post-HTX).

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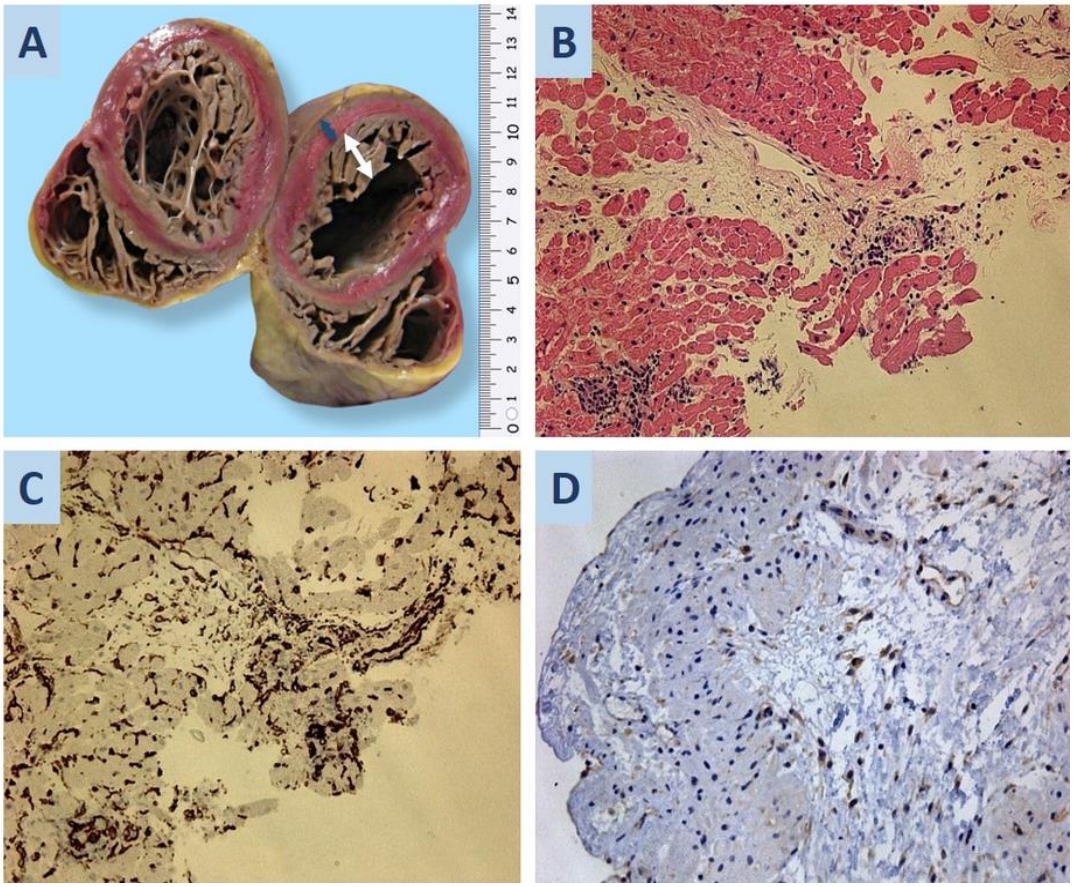

Figure 2. A. Noncompact myocardium of the left ventricle: the blue arrow shows the thickness of the compact layer (0.6 cm), the white arrow–non-compact layer (1.6 cm). **B**. Second EMB of the donor heart: it's visible infiltrative vasculitis, macrophages in the lumen of blood vessels, hematoxylin-eosin staining; x200. C. Immunohistochemical staining shows CD34 expression in the large, polymorphic endothelial cells; x200. D. SARS-CoV-2 S-protein expression in the cytoplasm of large, polymorphic endothelial cells; x200.

We found clear signs of the ultrastructural remodeling of blood capillaries. Many endothelial cells were irregularly shaped, with uneven and indented luminal surface and large, irregular nuclei protruding into the lumen of the blood capillary (Figure 3A). The cytoplasm was packed with numerous membrane vesicles, both plasma membrane-bound and unbound, thus indicating activation of the endothelium (Figure 3B). Pericyte processes were in close contact with the capillaries. As endothelial cells, pericyte processes contained abundant vesicles and vacuoles up to 1 μm in size (Figure 3C).

Cytoplasmic vacuolization can be transient or irreversible, the latter is usually observed in the cells infected with bacterial or viral agents. The lumen of the part of the capillaries was completely obstructed by fibrillar material of moderate electron density, presumably fibrin (Figure 3D). In some of the capillaries, macrophages containing multiple phagocytic vacuoles were detected (Figure 3E). While most of cardiomyocytes retained normal ultrastructural organization, some of them showed the signs of necrotic death, e.g. rupture of the plasma membrane and release of intracellular organelles (Figure 3F).

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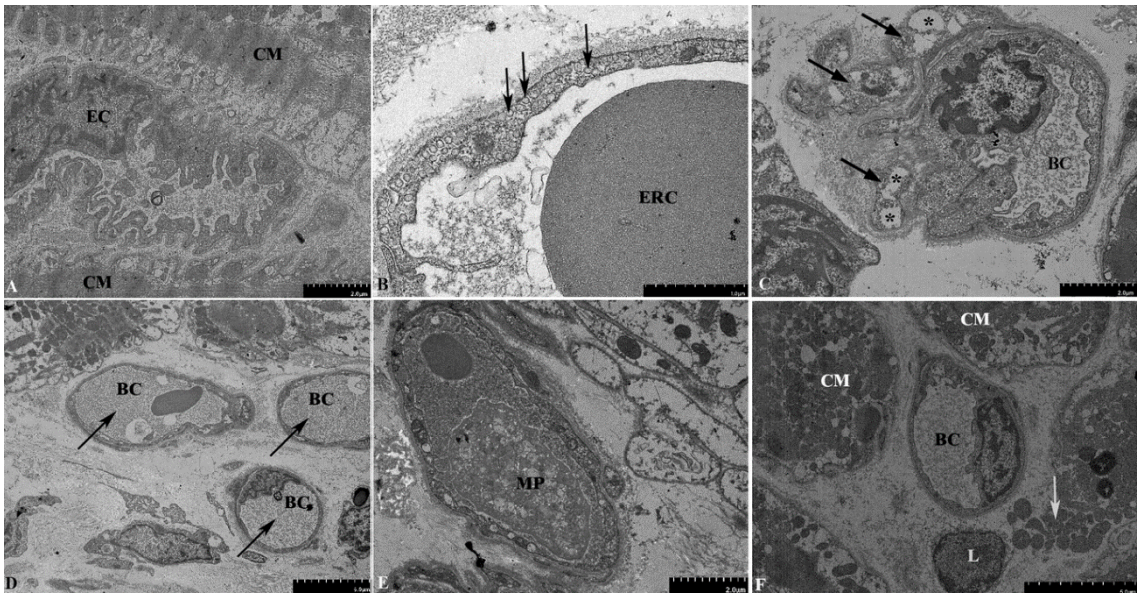

Figure 3. Electron microscopy examination of the second EMB of the donor heart. A. Irregularly shaped endothelial cells, with an indented luminal surface and irregular nuclei protruding into the lumen of the blood capillary. B. A huge number of membrane vesicles in the cytoplasm of endothelial cell (arrows). C. Pericyte processes (arrows) in close contact with the blood capillary. The processes contain vacuoles up to 1 μm in size (asterisks). D. Obstruction of the capillary lumens by a fibrillar material of medium electron density, presumably fibrin (arrows). E. Macrophage containing multiple phagocytic vacuoles in the capillary lumen. F. Necrosis of cardiomyocyte, with a rupture of the plasma membrane and the release of intracellular organelles into the extracellular space (arrows). Abbreviations: EC–endothelial cell, CM–cardiomyocyte, BC–blood capillary, ERC–erythrocyte, MP–macrophage, L–lymphocyte.

In one section, we found a 100 nm round particle with clear signs of morphological similarity to the SARS-CoV2 virion, being associated with the apical surface of the endothelial cell (Figure 4A). Some of the aforementioned ultrastructural changes found in EMB are known to be histopathological features of AMR [2].

Thirty-four days post-HTX, we performed the third EMB for recurrent assessment of the rejection grade. They were defined as follows: ACR (1R/1A) and pAMR0.

In the postoperative period, LV function was preserved, and sinus rhythm was maintained during the follow-up period.

Additionally, we performed the retrospective immunohistochemical study of polypoid fibrolipoma from the donor heart to determine the expression of SARS-CoV-2 antigen and define the carrier of SARS-CoV-2. SARS-CoV-2 antigen was present only in the donor heart (Figure 4B). Heart recipient's explanted heart histological examination showed no signs of being infected with SARS-CoV-2, as far as, COVID-19 diagnosis was also ruled out prior to HTx. There were no diagnosed COVID-19 cases in patients or healthcare practitioners who were in contact with recipient while she was awaiting transplantation. After the surgery recipient stayed in the individual patient room and advanced sanitary conditions were organized based on the hospital's protocol.

At the same time, donors' organs came from the other hospitals. While the acute COVID-19 diagnosis was ruled out on the day before the transplantation. COVID-19 myocarditis was diagnosed after the heart transplantation in the recipient's history. It was suggested that she was infected with SARS-CoV-2 from the heart transplant donor whose heart was histologically examined only after HTx, looking to exclude the transplant rejection.

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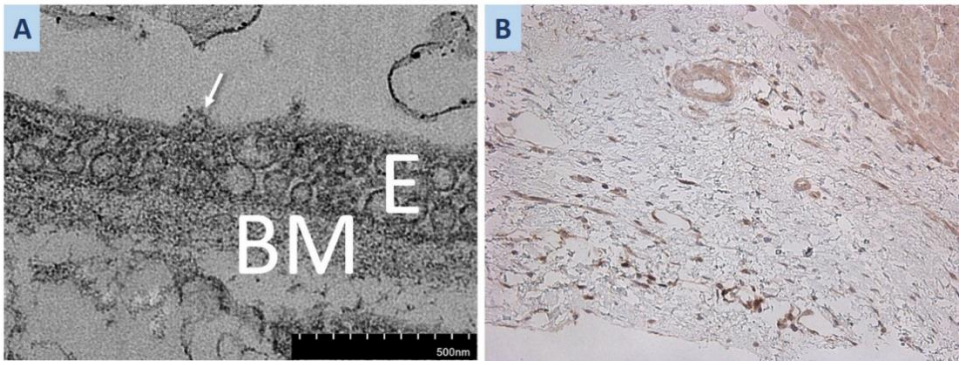

Figure 4. A. Second EMB of the donor heart. Round 100 nm particle with clear signs of morphological similarity to the SARS-CoV2 virion (arrow), associated with the apical surface of the endothelium. B. SARS-CoV-2 S-protein expression in the cytoplasm of endothelial cells of the polypoid fibrolipoma myocardial site; x100. Abbreviations: E–endothelium, BM–basal membrane.

3. Discussion

According to the reviews summarizing the aspects of COVID-19 in the transplant patients, the median intervals from transplantation to the diagnosis were from 26 months till 10 years [3, 4].

Cases of SARS-CoV-2 infection in the peritransplant period are scarce. Qin et al. described a liver transplant recipient presented with the perioperative COVID-19 that was not detected upon admission [5].

Proven transmission of SARS-CoV-2 from donor to recipient have been rarely documented. Several studies have described transplantation of nonlung organs from SARS-CoV-2 recovered donors into uninfected recipients without virus transmission [6-11]. Moreover, transplanting from the SARS-CoV-2 infected donors did not result in the recipient infection either [12-16]. On the other hand, the proven transmission of SARS-CoV-2 by lung transplantation have been reported [17, 18]. In both cases, donors were asymptomatic and had a negative results of nasopharyngeal swab PCR SARS-CoV-2 testing. Thus, during the pandemic years, there was an increasing amount of literature on parenchymal organ transplantation from the SARS-CoV-2 positive donors. Only in the case of a lung transplant, the recipient developed COVID-19 after the transplantation. However, the risk of SARS-CoV-2 transmission through organ donation remains underestimated.

In the present report, we used immunohistochemistry to determine the expression of SARS-CoV-2 antigen in the cardiac transplant and in the recipient's heart before HTX. We found that transplant was SARS-CoV-2 positive, while the explanted heart did not contain viral antigens. Taken together, our observations suggest that, in the present case, SARS-CoV-2 spread from donor to recipient. However, it cannot be completely ruled out that the residual recipient virus could have certainly infected the transplanted heart. At the same time, there are research findings that using hearts from COVID-19–positive donors can be safe and effective [19, 20]. However, more information is needed regarding selecting COVID-19–positive donor.

The ability of SARS-CoV-2 to persist in the tissues and duration of persistence remains an unresolved question. Long-term SARS-CoV-2 persistence in the upper respiratory samples was detected on the fourth-fifth month post-symptom onset [21]. It is a common knowledge that patients on immunosuppressive therapy were more susceptible to the prolonged persistence of SARS-CoV-2. The longest (over 8 months) viral shedding from the SARS-CoV-2 positive nasopharyngeal swab was documented in a patient with non-Hodgkin lymphoma [22]. Viremia in this patient was associated with COVID-19 relapses and was accompanied by a decrease in CD8+ T-lymphocyte count. A kidney transplant recipient also was prolonged (2 months) positive results of SARS-CoV-2 testing [23].

In our study, SARS-CoV-2 persisted in the myocardium up to 34 days after HTX. This conclusion was based on results of the third EMB (34 days post-HTX), where signs of endotheliitis were not found.

Mycophenolate mofetil and steroids can be prescribed for the myocarditis treatment [24, 25]. We suggested that the other reason behind no heart failure development of the transplanted heart was

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in the steroid management that was a part of standard post-transplant immunosuppression protocol [26].

Electron microscopic assessment of EMB in the post-HTX period revealed pericyte alteration. Pericytes were discovered in 1873 by the French scientist Charles-Marie Benjamin Rouget and were originally called Rouget cells [27]. Pericytes are found within the basement membrane of the capillary and surround the endothelial cells. Pericytes contact with endothelial cells by cytoplasmic processes and are considered to stabilize the vessel wall and control endothelial cell proliferation. Pericytes are present in a variety of tissue types, e.g. lung, heart, and nervous tissue. There, they regulate blood flow, angiogenesis, and neovascularization, maintain the blood-brain barrier and tissue hemostasis, and participate in inflammation. The distinct feature of pericytes is their ability to differentiate into other cell types under external stimuli, e.g. adipocytes, chondrocytes, fibroblasts, vascular cells, and other cells of mesenchymal origin [28].

Vascular cells and immune cells circulating in the vascular system are known targets of different viruses. Moreover, the viral capacity to enter the blood flow and produce viremia is crucial for the viral spread. Results of several studies on cellular and organoid models clearly demonstrated that pericytes could be infected by SARS-CoV-2 [29, 30]. However, the data from patients are scarce. Pericyte infection by SARS-CoV-2 was reported for heart and brain tissue [31, 32].

Angiotensin-converting enzyme 2 (ACE2) is a receptor enabling SARS-CoV-2 entry into the cell, and its expression was found in endothelial cells and pericytes [33]. However, endothelial cells express ACE2 at a very low level, while pericytes had the highest level of ACE2 expression [34]. This corroborates the idea that human pericytes are the key target for SARS-CoV-2 infection [35]. Pericyte injury leads to capillary endothelial cell dysfunction, thus causing microvascular dysfunction and microvasculopathy. Moreover, patients with cardiovascular conditions had an elevated level of ACE2 expression that increased the risk of a severe course of COVID-19 [36].

Under pathological conditions, cardiac pericytes can detach from the vascular wall and differentiate into myofibroblasts. This process results in increased vascular permeability and inflammation, and ultimately contributes to interstitial fibrosis and destabilization of the vascular wall [37, 38]. For that reason, cardiac pericytes can serve as a therapeutic target in the treatment of HF and other diseases [39].

Electron microscopy of EMB has demonstrated round particle with clear signs of morphological similarity to the SARS-CoV2 virion, being associated with the apical surface of the endothelial cell. Fox SE et al. [40] also showed particles consistent with SARS-CoV-2 presented within a cardiac endothelial cell. On the other hand, reliable detection of coronavirus virions using electron microscopy is challenging because of the structural similarity between virions and intracellular structures [41].

In this study, we conducted an analysis of reported cases of coronavirus transmission during heart transplantation as documented in the literature. Our objective was to examine the incidence and outcomes of such transmissions. The findings of our analysis are summarized in the table below, providing valuable insights into the occurrence and implications of coronavirus transmission in the context of heart transplantation. By systematically reviewing and synthesizing the available data, we aimed to contribute to the existing knowledge on this critical aspect of transplantation medicine.

The table presents a comprehensive overview of the cases reviewed, including relevant clinical details, outcomes, and pertinent observations (Table 2).

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Table 2. - Analysis of Reported Cases of Coronavirus Transmission during Heart Transplantation.

Authors	Cases	Proof of coronavirus in a donor	Proof of coronavirus in a recipient	Complication
Shin Lin et al [42]	5 cases of heart transplantation from COVID-19-positive donors	NP RT-PCR: positive (0-1 days prior) Bronchoalveolar lavage PCR test – positive (0 days) Blood IgG spike – positive (0 days)	None	1 case - primary graft dysfunction 4 case – none or nonspecific complication
Jashari R. et al [43]	2 cases of heart transplantation from COVID-19-positive donors	NP RT-PCR: positive (0 days prior) PCR test on the myocardium and heart valves – negative	PCR of the cardio-vascular tissues – negative	None
Castro-Varela A. et al [44]	6 cases of heart transplantation from COVID-19-positive donors	NP RT-PCR: positive (1-7 days prior)	NP RT-PCR: negative	3 - primary graft dysfunction 1 - diffuse myocyte injury, pericarditis. Death.
Eichenberger E.M. et al [45]	9 cases of heart transplantation from COVID-19-positive donors	NP RT-PCR: positive (1-7 days prior)	NP RT-PCR: negative	1 - detection of coronavirus antigens in the myocardium using IHC 1 – massive hemorrhage and coronary thrombosis
Vaidya, G. N. et al. [46]	177 cases of heart transplantation from COVID-19-positive donors	NP RT-PCR: positive (0-14 days prior)	NP RT-PCR: negative	6 - primary graft dysfunction 9 - death
Neidlinger N. A. et al. [47]	1 cases of heart transplantation from COVID-19-positive donors	Stool PCR positive (3 days prior) NP RT-PCR: negative (0 days prior)	NP RT-PCR: negative	None
Madan S. et al. [48]	150 cases of heart transplantation from COVID-19-positive donors	NP RT-PCR: negative (0-2 days prior)	NP RT-PCR: negative	23 - Mortality Cumulative Kaplan-Meier Estimates primary graft dysfunction – no data

Abbreviations: NP RT-PCR - nasopharyngeal swab reverse transcription PCR

Based on the cumulative findings of previous studies, it can be inferred that in the majority of cases, heart transplantation was performed within 0-7 days after the last positive nasopharyngeal swab. However, PCR testing of myocardial tissue was conducted only in isolated instances. Similarly, post-transplantation endomyocardial biopsy (EMB) analysis for coronavirus antigens was carried out in only a few cases. Despite this limited data, none of the patients exhibited systemic coronavirus infection following heart transplantation.

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Furthermore, the presence of coronavirus infection in the donor did not impact the outcomes of the recipients in any of the reported cases. Thus, heart transplantation from donors with coronavirus infection appears to be a relatively safe procedure rather than a risky one. Nevertheless, patients in such scenarios require more thorough postoperative monitoring to ensure their well-being.

4. Conclusions

The present report describes the unique case of SARS-CoV-2 transmission from donor to recipient during HTX, followed by activation of vascular wall cells (endothelial cells and capillary pericytes) and humoral immunity. We suggest examining all post-transplant EMBs to exclude the SARS-CoV-2 transmission in the transplanted heart, especially in those with the signs of humoral rejection.

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Declarations Ethical Approval: The research was approved by the local ethics committee (protocol No. 2209-20 dated September 21, 2020 and a new protocol No. 1131-22 dated November 28, 2022 as part of dissertation research), and was conducted in compliance with the Declaration of Helsinki.

Abbreviations

ACR	acute cellular rejection
AMR	antibody-mediated rejection
CD	cluster of differentiation
EF	ejection fraction
EMB	endomyocardial biopsy
ECMO	extracorporeal membrane oxygenation
HF	heart failure
HLA-DR	Human Leukocyte Antigen DR isotype
HHV	Human Herpes Virus
HTX	heart transplantation
LV	left ventricle
PCR	polymerase chain reaction
RNA	ribonucleic acid
VEGF	vascular endothelial growth factors
VWF	von Willebrand factor

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