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Acute Humoral Rejection 12 Days Post-Heart Transplantation with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Antigen Expression in Myocardial Tissue: A Clinical Case

Kalp Naklinden 12 Gün Sonra Miyokard Dokusunda Şiddetli Akut Solunum Sendromu Koronavirüs 2 (SARS-CoV-2) Antijen Ekspresyonu ile Akut Hümoral Rejeksiyon: Klinik Bir Olgu

ABSTRACT

The development of acute humoral rejection (AMR) in transplanted organs remains a highly relevant and unresolved issue. This study presents a clinical case of heart transplantation (HT) in a patient with hypertrophic cardiomyopathy transitioning to a restrictive phenotype amid chronic lymphocytic myocarditis. Following HT, the patient developed nosocomial pneumonia, necessitating a reduction in immunosuppressive therapy. On the 12th day post-transplantation, the patient experienced a sudden hemodynamic collapse, which proved fatal. Autopsy examination revealed acute humoral rejection with a predominance of CD16+ cells in the infiltrate, exhibiting high expression of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Spike protein on the endothelium and CD16+ cells. Further investigation is required to clarify the role of SARS-CoV-2 in potentially exacerbating AMR development.

Keywords: Acute humoral rejection, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), cardiac surgery, heart failure, heart transplantation, immunohistochemical study, morphological study

ÖZET

Nakledilen organlarda akut humoral rejeksiyon (AMR) gelişimi oldukça önemli ve çözülmemiş bir sorun olmaya devam etmektedir. Bu çalışmada, kronik lenfositik miyokarditin ortasında restriktif fenotipe geçiş yapan hipertrofik kardiyomiyopatili bir hastada kalp transplantasyonu (HT) yapılan klinik bir vaka sunulmaktadır. HT sonrasında hastada nozokomiyal pnömoni gelişmiş ve immünosupresif tedavinin azaltılması gerekmiştir. Nakil sonrası 12. günde, hasta ani bir hemodinamik kollaps yaşadı ve bu durum ölümcül oldu. Otopsi incelemesi, infiltratta CD16+ hücrelerinin baskın olduğu, endotel ve CD16+ hücrelerinde Şiddetli Akut Solunum Sendromu Koronavirüs 2 (SARS-CoV-2) Spike proteininin yüksek ekspresyonunu sergileyen akut humoral rejeksiyonu ortaya çıkarmıştır. SARS-CoV-2'nin AMR gelişimini potansiyel olarak şiddetlendirmedeki rolünü açıklığa kavuşturmak için daha fazla araştırma yapılması gerekmektedir.

Anahtar Kelimeler: Akut humoral rejeksiyon, şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2), kalp cerrahisi, kalp yetmezliği, kalp transplantasyonu, immünohistokimyasal çalışma, morfolojik çalışma

CASE REPORT
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Heart transplantation (HT) is one of the treatment methods for patients with end-stage heart failure that is refractory to optimal medical therapy. Despite significant advances in the management of patients post-HT, graft rejection remains a significant problem in transplantation.

According to the National Society of Heart and Lung Transplantation, acute humoral rejection (antibody-mediated rejection, AMR) is characterized by a transplant rejection reaction based on histological and immunopathological criteria.[1]

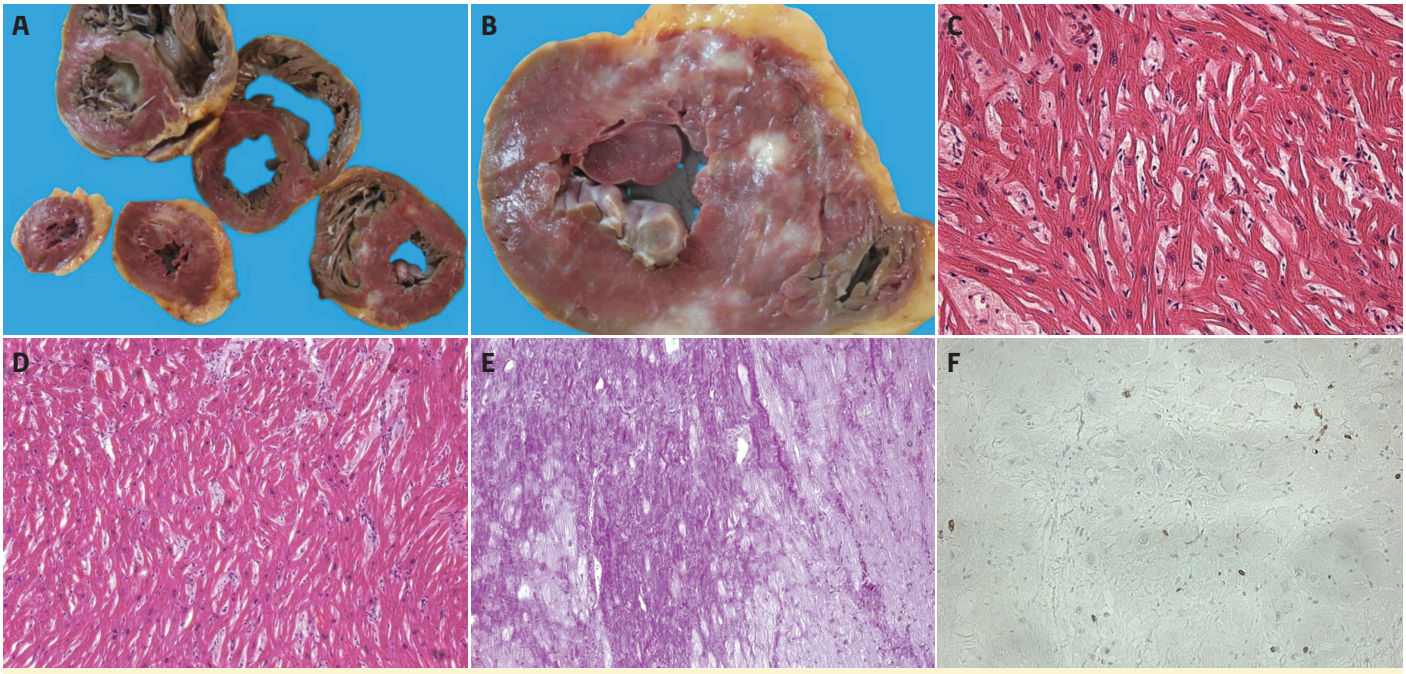

Figure 1. Morphological examination of the recipient's heart after transplantation. (A, B) Transverse sections of the heart, 1-1.5 cm thick along the long axis: scars predominantly identified in the interventricular septum. (C, D) Disarray of myocardial fibers and mononuclear infiltration in the interstitium with aggressive cell invasion into the sarcoplasm of cardiomyocytes; H&E staining; C – x200, D – x100. (E) Focal myocardial sclerosis and perimyocardial fibrosis-netting; Van Gieson's staining, x100. (F) Immunostaining with CD3 antibody: more than 14 CD3+ cells detected per 1 mm2 of myocardium; x200.

The American Society of Transplantation defines AMR as manifesting through graft dysfunction, elevated levels of donor-specific antibodies (DSA), histological evidence of acute capillary injury, and immunohistochemical evidence of antibody-mediated damage.[2]

Case Report

Cardiological symptoms manifested in the patient at the age of 23, characterized by syncopal episodes. Echocardiographic examination revealed hypertrophic cardiomyopathy (HCM). The patient received disease-modifying and symptomatic therapy, maintaining a high tolerance for physical exertion.

At the age of 42, the patient experienced two episodes of Coronavirus Disease 2019 (COVID-19) infection, each accompanied by bilateral polysegmental pneumonia, affecting 60% and 70% of the lung parenchyma, respectively. Seven months after the last episode of COVID-19, the patient began to experience a reduced tolerance for physical exertion, characterized by dyspnea when walking up to 20 meters. Magnetic resonance imaging (MRI) showed significant enlargement of both atria and pronounced fibrotic changes in the interventricular septum and left ventricle extending to the papillary muscles. Echocardiography indicated diastolic dysfunction of the myocardium with preserved systolic function. Both atrial fibrillation and transient intraventricular block were observed.

Given these findings, the patient's cardiac pathology was deemed a combination of hypertrophic and restrictive cardiomyopathy phenotypes. Cardiac amyloidosis was excluded based on biopsy of the colonic mucosa and cardiac MRI findings. Owing to the progression of chronic heart failure, a heart transplantation was performed.

Morphological examination of the explanted heart revealed a symmetric type of HCM with disarray of myocardial fibers involving over 15% of the area of the interventricular septum and left ventricle. Cardiomyocyte hypertrophy and nuclear polymorphism were noted, along with the presence of secondary active chronic lymphocytic myocarditis (Figure 1).

Pre-transplant human leukocyte antigen (HLA) antibodies were not detected. The patient received the Sputnik Light vaccine 40 days before the heart transplantation. Polymerase chain reaction (PCR) testing of nasopharyngeal swabs conducted before and after heart transplantation returned negative results. Additionally, post-mortem PCR testing on the donor was negative. The immunoglobulin M (IgM) titer for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in the recipient following heart transplantation was undetectable, while the IgG titer remained high.

ABBREVIATIONS

AMR	Acute humoral rejection
HCM	Hypertrophic cardiomyopathy
HLA	Human leukocyte antigen
HT	Heart transplantation
IgM	immunoglobulin M
MRI	Magnetic resonance imaging
PCR	Polymerase chain reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

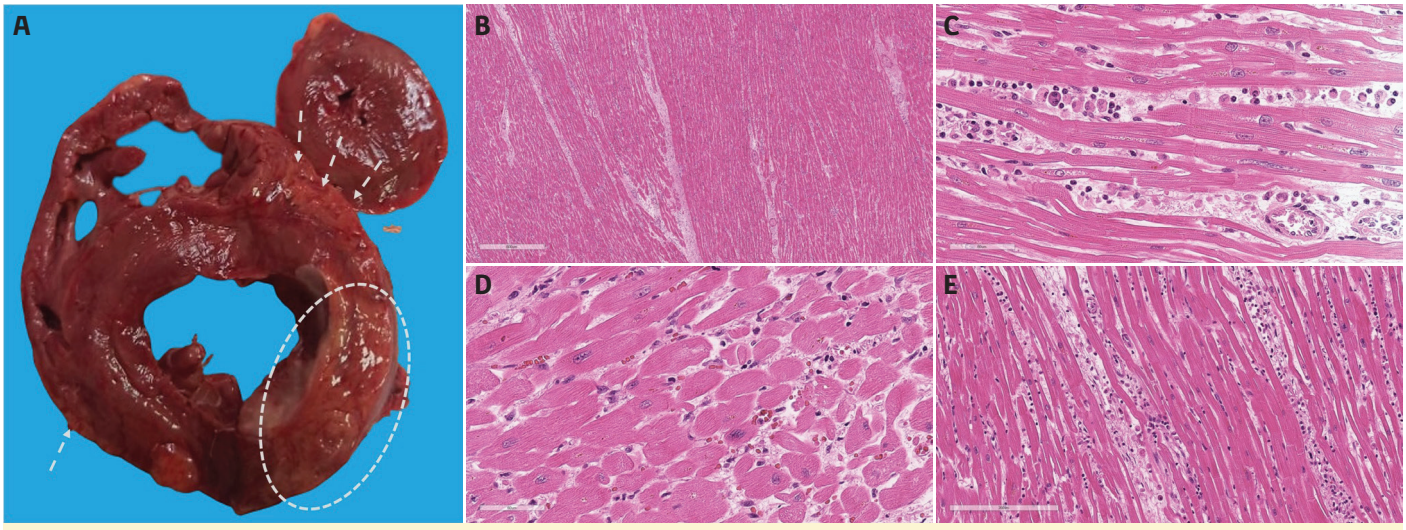

Figure 2. Morphological examination of the donor heart after transplantation (autopsy examination). (A) Transverse section of the ventricles: multiple lighter protruding areas with loss of fibrous structure observed against a fibrous reddish-brown myocardium (indicated by dashed arrows and a dashed oval). (B) Left ventricular myocardium: prominent perimyocardial mononuclear infiltrates, stromal edema; x40. (C) Left ventricular myocardium: marked edema, erythrocytic extravasation, mononuclear infiltration; x200. (D, E) Interventricular septum myocardium with pronounced mononuclear infiltrates, subtotal desquamation of vascular endothelium, stromal edema, and numerous erythrocytic extravasations, D – x200, E – x100. B-E – H&E staining.

The immunosuppressive therapy after transplantation initially comprised a four-component regimen: basiliximab (day 0), prednisolone, tacrolimus (starting day 3), and mycophenolate. The postoperative period was complicated by the development of non-coronavirus-related nosocomial pneumonia, which necessitated the discontinuation of basiliximab on day 4 and the omission of mycophenolic acid. Tacrolimus levels were within the target range (12.2 ng/mL) on day 10 post-transplantation.

Laboratory testing showed mild leukocytosis in the peripheral blood from days 6 to 10 after the transplantation, likely related to prednisone therapy. No other significant abnormalities were found in the results of laboratory and instrumental studies.

On day 12 post-transplantation, the patient experienced a sudden and severe hemodynamic collapse, leading to resuscitation efforts that proved unsuccessful. Autopsy examination of the donor heart revealed multiple mosaic non-coronarogenic myocardial necroses, hemorrhages, marked stromal edema, and significant mononuclear infiltration in all cardiac chamber walls (within the stroma and vessel lumens), as well as desquamated endothelium of intramyocardial vessels (Figure 2).

Immunohistochemical examination showed that the infiltrate predominantly consisted of CD16+ cells, with fewer CD3+ T lymphocytes and CD68+ macrophages. High expression of the C1q and C4d complement components and SARS-CoV-2 Spike protein were detected on endothelial cells and CD16+ cells (Figure 3). These findings led to the conclusion that the patient's death was due to an antibody-mediated humoral rejection crisis (AMR 3).

Immunohistochemical examination followed our institution's protocol.[3] The antibodies used included anti-CD16 (rabbit polyclonal antibody, DAKO, Denmark; dilution 1:50), anti-CD3 (rabbit polyclonal antibody, DAKO, Nottingham, UK; dilution 1:100), anti-CD68 (mouse monoclonal antibody, clone PG-M1; DAKO, Carpinteria, CA, USA; dilution 1:25), C1q (rabbit monoclonal antibody, clone JU99-33; Diagnostic BioSystems, Slough, UK; dilution 1:100), C4d (rabbit polyclonal antibody, ThermoFisher, USA; dilution 1:40), and SARS-CoV-2 Spike protein (rabbit polyclonal antibody; GeneTex, Hsinchu City, Taiwan; dilution 1:100).

Discussion

The early development of a humoral rejection crisis can occur within the first month post-transplantation, typically within one to two weeks, due to de novo production of donor-specific antibodies or increased production of pre-formed DSA. This early type of humoral rejection is commonly associated with allograft dysfunction and manifests as hemodynamic disturbances.[4,5]

Symptoms of acute antibody-mediated rejection include systolic and diastolic dysfunction of the right and/or left ventricle, exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, elevated jugular venous pressure, edema, and abdominal distension. AMR is linked to hemodynamic compromise in 10-47% of cases. The symptoms and signs of hemodynamic impairment vary widely, and the spectrum of graft dysfunction can range from reduced ejection fraction to cardiogenic shock, necessitating resuscitative measures.[6-8]

The main morphological manifestations of acute humoral rejection include intravascular endothelial activation, mononuclear infiltrates in vessel lumens, infiltrative vasculitis and perivasculitis, stromal edema, and in cases of AMR3, hemorrhage, muscle fiber necrosis, and leukocyte infiltration. Pronounced leukocyte infiltration was not observed in our study.

The COVID-19 pandemic has prompted questions regarding the potential link between coronavirus infection and AMR.

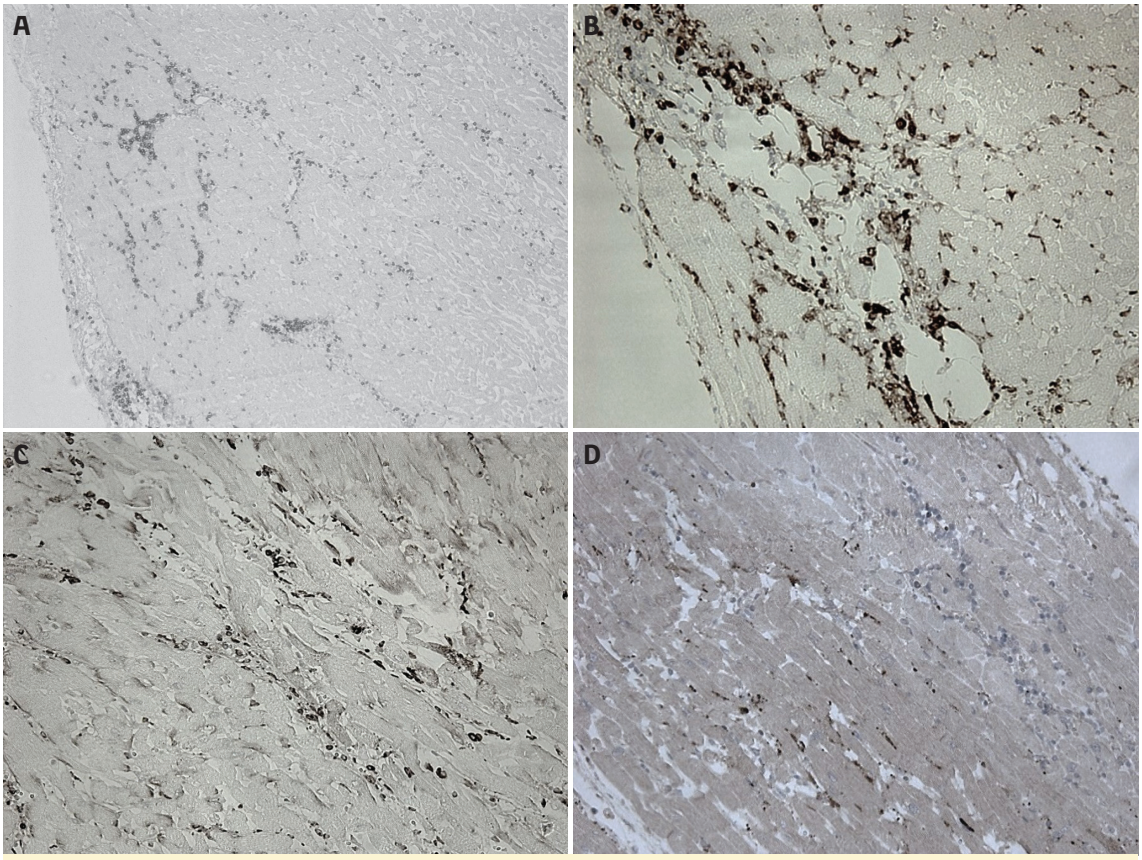

Figure 3. Immunohistochemical examination of the donor heart (autopsy examination). (A) Immunostaining with CD3; x100. (B) Immunostaining with CD16. (C) Immunostaining with C1q complement component. (D) Immunostaining with SARS-CoV-2 Spike protein; B-D -x200.

For example, a study by Bottio T. et al.[9] found that the risk of developing fatal complications was higher in recipients diagnosed with the novel coronavirus infection in the immediate postoperative period.

The risk of developing humoral transplant rejection is heightened directly, irrespective of symptom severity, antiviral treatment, or vaccination status.[10] However, determining the specific impact of the novel coronavirus infection on the increased risk of a widespread humoral rejection crisis is challenging due to the scarcity of published data.

In the case described, the reduction of immunosuppressive therapy may have influenced the development of AMR3. This highlights the importance of carefully identifying risk factors for transplant rejection and cautiously reducing immunosuppressive therapy in the presence of postoperative infectious processes.

Additionally, the presence of a large number of CD16+ cells in the myocardial infiltrate, some expressing SARS-CoV-2, suggests a potential role of the coronavirus in inducing a humoral rejection crisis. Conversely, the persistence of SARS-CoV-2 in CD16+ cells may reflect the post-acute phase of COVID-19, as demonstrated in our previous research.[11]

Conclusion

The persistence of SARS-CoV-2 in endothelial cells and CD16+ cells may increase the risk of developing and progressing a humoral rejection crisis. More extensive studies are necessary to explore the relationship between prior COVID-19 infection and the development of AMR to improve our understanding of the pathogenesis of the virus's impact on the myocardium and subsequently enhance patient treatment outcomes.

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