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CASE REPORT
Cardiovascular surgery

Sequential transplantation of the liver–kidney–heart from different donors: a case report

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Background Multi-organ transplantation has emerged as a viable treatment strategy for patients afflicted with multiple organ failure or significant organ dysfunctions. Despite the promising therapeutic outcomes, this approach also amplifies the risk of organ rejection, infection, or neoplastic growth. We present a unique case of a patient who sequentially underwent liver, kidney, and heart transplantation, all sourced from different donors. This case brings forth intriguing possibilities about the interplay between cardiovascular diseases and complications arising post-transplantation, thereby enriching our understanding of comprehensive transplant immunomodulation and cardiovascular disease prevention.

Case summary A 59-year-old male with chronic alcohol misuse developed liver cirrhosis in 2012 and subsequent kidney failure in 2018 due to alcoholic liver disease, type II diabetes, hyperlipidaemia, and severe hypertension. Subsequently, an incident of extensive transmural myocardial infarction (Killip III) warranted a heart transplant in 2022. Post-transplant, the patient was maintained on a standard immunosuppression regimen with regular post-operative follow-ups. No signs of rejection were noted 1-year post-final transplantation under standard immunosuppression.

Discussion The presented case exemplifies the potential and feasibility of sequential multi-organ transplantation. The multifaceted interplay between the transplanted organs and the immunosuppressive pharmaceuticals likely exert distinct influences on transplantation immune regulation, possibly diverging from the dynamics observed in single-organ transplantation. A comprehensive exploration of the mechanisms governing immune responses in the context of multi-organ transplantation could yield valuable insights for mitigating graft dysfunction. Furthermore, the rapid progression of atherosclerosis observed after liver and kidney transplantation necessitates further scrutiny to elucidate potential correlations with the post-transplantation state.

Keywords Case report • Heart transplantation • Multi-organ transplantation • Kidney transplantation • Liver transplantation • Immune rejection • Atherosclerosis

ESC curriculum 3.1 Coronary artery disease • 6.4 Acute heart failure • 7.5 Cardiac surgery • 8.4 Cardiovascular aspects in a diabetic patient

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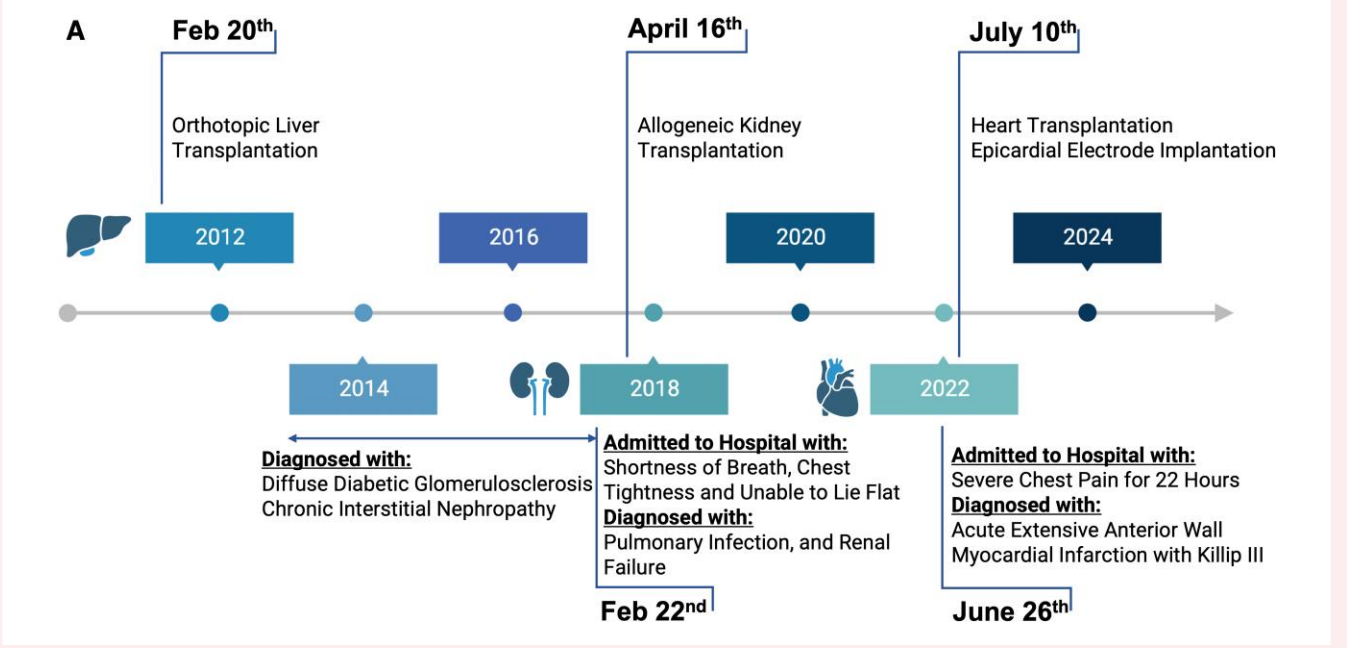
Learning points

- The potential protective effect of liver and kidney transplants, along with sustained immunosuppressive therapy, may combine to prolong the lifespan of organs after multi-organ transplantation.
- The rapid progression of atherosclerosis after liver and kidney transplantation warrants further investigation to determine whether it is related to post-transplantation status.
- The success of multi-organ transplant management lies in minimizing cross-reactive immune responses and preserving organ function. This includes determining optimal immunosuppressant dosages, maintaining regular clinical follow-ups, and closely monitoring the health of the transplanted organs.

Introduction

Multi-organ transplantation has become an effective yet rare treatment for patients with multi-organ failure or significant organ dysfunctions.[1,2] Successful long-term cases are with increased risks of organ rejection, infection, or cancer in post-operation patients.[3] Here, we reported a case of triple-organ transplantation for a patient experiencing significant organ dysfunctions over time. These transplantations include liver, kidney, and heart, which were carried out sequentially from different donors. He was treated with conventional immunosuppressive therapy with no evidence of rejection or dysfunction of any organ 1 year after his heart transplant. In addition, the rapid progression of atherosclerosis in this patient following his second organ transplantation indicates a potential link between standard post-transplantation treatments and cardiovascular diseases, which were rarely discussed in previous studies.

Summary figure



Case presentation

A 59-year-old male presented with a history of chronic abdominal distension and lower limb oedema, intermittent respiratory symptoms, and a recent episode of altered mental status after a meat meal. He was later diagnosed with decompensated alcoholic liver cirrhosis, hepatic encephalopathy, and hepatorenal syndrome. He had a history of type II diabetes mellitus for 14 years. Initial attempts to control his blood sugar levels involved the use of oral Glucobay (acarbose tablets) but were unsuccessful in maintaining stable glucose levels. Subsequently, a regimen combining short-acting and long-acting insulin was initiated subcutaneously. But the blood glucose control is still suboptimal control with fluctuations. The patient has also been diagnosed with hypertension for 13 years, which has been managed with metoprolol and amlodipine. Alongside the above conditions, the patient has had a history of hyperlipidaemia for many years (diagnosed externally, the age of onset is unknown) and has been smoking for over 30 years, averaging more than 20 cigarettes a day. The patient intermittently used statin drugs, but compliance was sporadic and poor.

He was admitted to The General Hospital of the Chinese People's Armed Police Forces (CAPF) and underwent orthotopic liver transplantation without HLA cross-matching on 20 February 2012. Methylprednisolone (MP) [500 mg intravenous (i.v.)] was administered during the surgery and maintained with a triple immunosuppressive regimen [tacrolimus (FK506), mycophenolate mofetil (MMF), and prednisone]. The patient was later discharged on MP 4 mg/day and

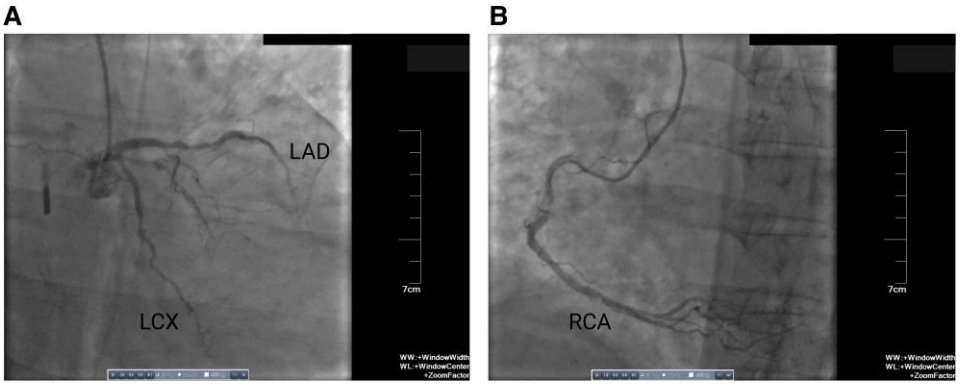


Figure 1 Coronary angiography performed prior to heart transplantation. (*A*) In the left anterior descending artery, there were proximal to mid-segment lesions with diffuse narrowing, showing a maximum of 95% stenosis and 99% stenosis at the distal end, with TIMI 3 grade blood flow in the distal part. In the left circumflex artery, arteriosclerosis was observed with 90% stenosis in the mid-segment, complete occlusion in the distal segment, and TIMI 0 grade blood flow distally. (*B*) In the right coronary artery, arteriosclerosis was observed with 70–80% stenosis in the mid-segment and TIMI 3 grade blood flow distally. The coronary artery exhibited right dominance. LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

tacrolimus 4 mg/day (with a trough level of 10–15 ng/mL during this period). The patient's liver function recovered by the 16th day (Alanine transaminase 23 U/L and total bilirubin 20.9 μmol/L).

The patient was initially found to have escalating proteinuria levels, reaching 4+ in 2014. He was then diagnosed with diffuse diabetic glomerulosclerosis and chronic interstitial nephritis in 2018, but the condition did not receive sufficient attention. However, in February 2018, due to symptoms of chest tightness and shortness of breath, he was admitted to The General Hospital of the CAPF. He was diagnosed with lung infection and renal failure, with significantly worsened renal function (creatinine: 551 μmol/L, blood urea nitrogen: 31.47 mmol/L, and proteinuria: +++). After 2 months of dialysis, he underwent a kidney transplant on 16 April 2018. Methylprednisolone (1000 mg i.v.) was given during the surgery. He was later discharged on oral MP (12 mg/day), enteric-coated mycophenolate sodium (EC-MPS; 1080 mg/day), and tacrolimus (6 mg/day, with a trough level of 7.9–11.5 ng/mL during this period). The patient's kidney function recovered by Day 3 [serum creatinine 106 μmol/L and glomerular filtration rate (GFR) 68.2 mL/min/1.73m^2].

From 2012 to 2021, encompassing both liver and kidney transplants, cardiac enzyme tests and electrocardiogram (ECG) remained normal. After the liver transplant, a chest computed tomography indicated left heart enlargement, minor pericardial effusion, and coronary artery calcification. Post-kidney transplant in 2021, ECG detected ST-T segment changes in the left ventricle, suggesting potential ischaemia or infarction, but heart function appeared largely normal with an ejection fraction (EF) of 63%. However, the patient's condition deteriorated in 2022. In January, ECG findings pointed to a first-degree atrioventricular block and signs of widespread infarction. In June, the patient was admitted to the hospital due to chest pain lasting for 22 h and was diagnosed with acute extensive myocardial infarction (Killip III). An echocardiogram showed thinning of the left ventricular anterior wall and anterior septal wall, an apical left ventricular aneurysm measuring about 52 mm × 40 mm, and a reduced EF of 27%, well below the normal value. Additionally, the patient had small amounts of mitral and tricuspid regurgitation and a small amount of pericardial effusion. The pre-operational coronary angiogram showed the patient had significant coronary artery disease, as evidenced by ~95% stenosis in the left anterior descending artery (LAD) and 90% stenosis complete occlusion in the distal segment of the left circumflex artery (LCX) (*Figure 1A*). The right coronary artery (RCA) also showed 70–80% stenosis (*Figure 1B*). Lipid-lowering drugs (statins) and aspirin enteric-coated tablets combined with ticagrelor for antiplatelet therapy were combined and systematically used during his hospitalization.

On 10 July 2022, the patient, diagnosed with coronary atherosclerotic heart disease, acute extensive anterior wall myocardial infarction with Killip III, and left ventricular apical wall aneurysm formation, underwent heart transplantation without HLA cross-matching (*Figure 2A–C*). The recipient's HLA-A alleles are HLA-A*02 and HLA-A*32, HLA-B alleles are HLA-B*44 and HLA-B*40, HLA-DRB1 alleles are HLA-DRB1*08 and HLA-DRB1*09, and HLA-DQB1 alleles are HLA-DRB1*06 and HLA-DQB1*03, without panel reactive antibody (PRA)-I and PRA-II detected. Due to the constraints of ischaemic time for the donor heart and the fact that the degree of HLA match does not affect the early survival of the transplanted heart, international guidelines do not require routine HLA typing before transplantation.[4] Methylprednisolone (500 mg i.v.) was administered during the transplant, and the patient was later discharged on MP (10 mg/day), EC-MPS (1000 mg/day), and tacrolimus (3 mg/day, with trough levels of 12–15 ng/mL during this period). The patient's heart function recovered by Day 3, and his liver and kidney function remained stable.

The patient tested negative for PRAs before kidney and heart transplants, suggesting he had not developed a persistent immune response against the previously transplanted organs. After his heart transplant, a very low level of donor-specific antibodies (DSAs) was found (*Figure 2D*), which correlated with the absence of clinical features of rejection.

The patient is scheduled for regular follow-up visits, during which basic functional assessments of the transplanted organs are conducted mainly through liver enzyme tests, urinalysis, cardiac enzyme tests, and ECG. Throughout these periods, no significant abnormalities or early signs of rejection have been detected.

Discussion

Feasibility of sequential multi-organ transplantation

Sequential liver, kidney, and heart transplantation requires a complicated series of surgical procedures, especially with multiple different

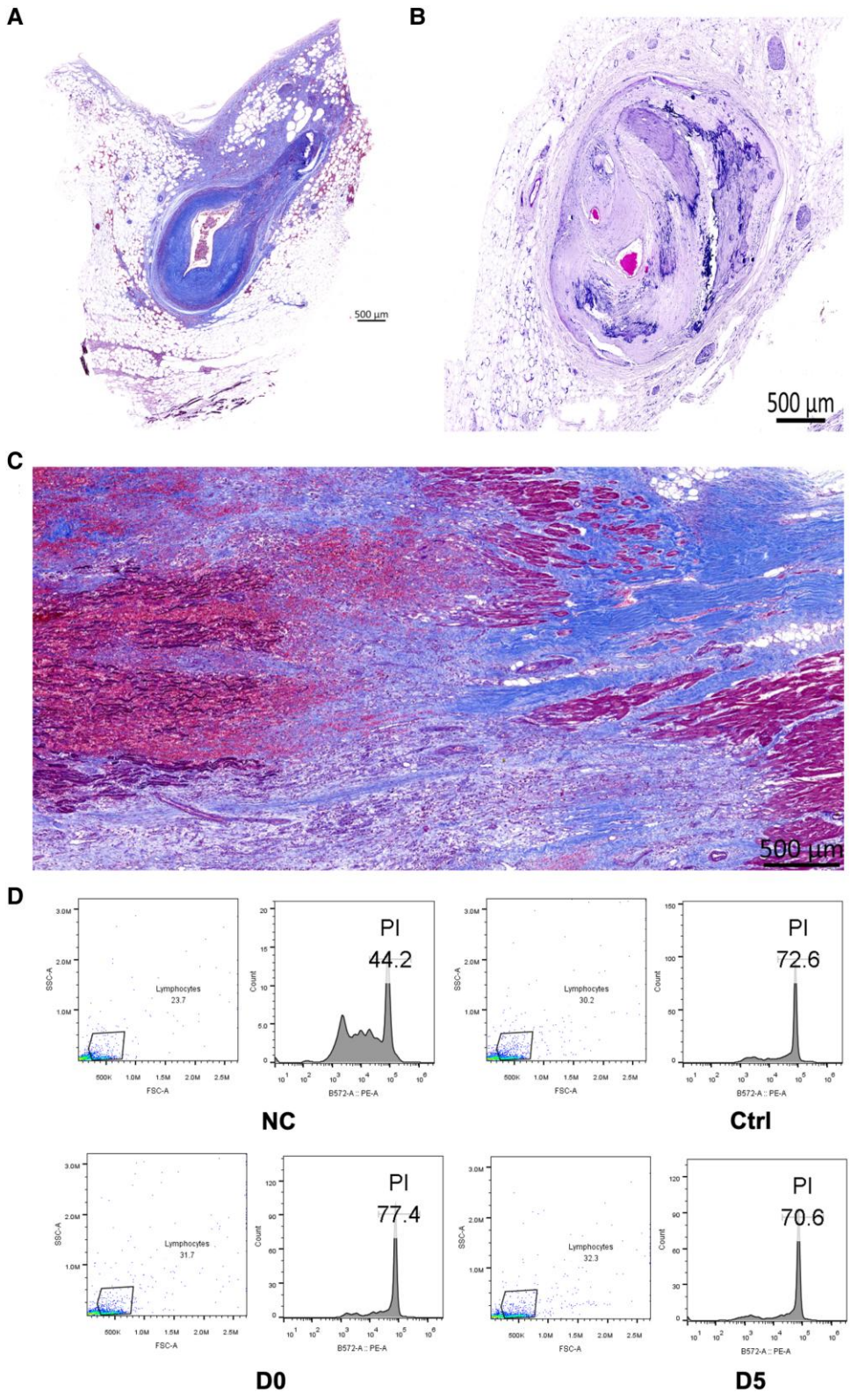


Figure 2 (*A*) H and E stain of the left anterior descending artery, which reveals severe stenosis with obstruction and thickening of the vascular intima. (*B*) H and E stain of the distal part of the left circumflex artery, which reveals near-complete obstruction due to atherosclerotic plaque. (*C*) Masson stain of the large infarcted area at the anterior wall of the left ventricle, massive intramyocardial bleeding, infiltration of inflammatory cells, and formation of collagen fibres. (*D*) Donor frozen peripheral blood mononuclear cells mixed with donor peripheral blood mononuclear cells (NC), complement only (Ctrl), recipient D0 serum with complement (D0), and recipient D5 serum with complement (D5). Donor-specific antibody was quantified using flow cytometry. NC, negative control; Ctrl, control; PI, propidium iodide; FSC-A, forward scatter area; B572-A, B572 area; PE-A, phycoerythrin area.

organ donors involved and intermittent procedures over several years.[1,2,5] In such patients, long-term immunosuppressive therapy is unavoidable and increases the risk of infections, tumours, and cardiovascular disease. In addition, immunosuppressive drug resistance might develop, necessitating higher doses and increasing the risk of rejection and graft failure. However, several reports of successful cases,[1,2,5] including the one we present here, have demonstrated the feasibility of multi-organ transplantation.

Although the heart does not possess immune privilege, combined transplantation with the liver or kidney might result in reduced immune response or induced immunological tolerance. Liver transplantation has been reported to induce immune tolerance in some cases. Kushwaha reported that a heart-after-liver transplant *from the same donor* significantly downregulated the immune response against the heart.[6] Whether the same result could be expected in multi-organ transplantation from *different donors* is unknown. In our patient, the presence of the liver graft might contribute to the negative PRA documented after the liver and kidney transplants and in the low level of DSA after heart transplantation.

The liver may contribute to the development of immune tolerance through special immune-regulation properties of its sinusoidal endothelial cells (ECs).[6] Liver ECs express scavenger receptors that remove circulating antigens and result in a lower level of DSAs in liver transplant patients.[7] Liver ECs expressing HLA classes I and II and co-stimulatory molecules also act as antigen-presenting cells (APCs) to induce regulatory effects by inducing IL-10 signalling pathway.[7] In addition, FasL and Bim (Bcl-2 family member) were upregulated when liver ECs were stimulated by antigen, which separately induced the apoptosis of donor antigen-activated $CD4^+$T cells[8] and reactive $CD8^+$T cells.[9] These special immune tolerance properties of liver ECs provide a potentially new perspective on immune therapy.

Kidney transplants may also play a role in developing an immune-tolerant state after multi-organ transplantation. Renal parenchymal cells can initiate the development of immune tolerance after MHC-matched kidney–heart transplantation.[10]

Transplantation tolerance usually implies 'the specific absence of a destructive immune response to a transplanted tissue in the absence of immunosuppression'.[11] However, a low level of circulating antibodies does not mean a complete absence of the immune response or the induction of tolerance. Donor-specific antibodies could be absorbed into the donor organs, showing low levels of circulating DSA in the recipient before rejection.[12] Therefore, evaluation of DSA-secreting cells is essential for the comprehensive understanding of the patient's immune response to the donor organs.

In summary, the potential protective effect of liver and kidney transplants, sustained immunosuppressive therapy, and regulated clinical follow-ups may combine to prolong the lifespan of organs after multi-organ transplantation.

The rapid progression of myocardial infarction

Although our patient was known to have atherosclerosis, its rapid progression over the 10 years of his follow-up caught our attention. Histopathology showed symmetrical sclerosis of his LAD (*Figure 2A*) and nearly complete obstruction of the LCX, indicating a progression of atherosclerosis (*Figure 2B*). The anterior wall of the left ventricle was infarcted with massive intramyocardial bleeding, inflammatory cell infiltration, and collagen fibre formation (*Figure 2C*). Thus, we concluded that the rapid progression of atherosclerosis was mainly due to pre-existing atherosclerosis and was not related to any unusual immune response that might have affected a native organ.

When patients with pre-existing atherosclerosis undergo organ transplantation and receive sustained immunosuppressive therapy, the risks of severe cardiovascular diseases, such as acute myocardial infarction, may increase. Tacrolimus, a common immunosuppressive medication used in our patient, can affect the function of endothelial colony-forming cells (ECFCs), a subgroup of endothelial progenitor cells.[13] Damaged ECFCs, with diminished vascular reparation, proliferation, migration, tube formation ability, and enhanced inflammatory responses, could result in a higher risk of cardiovascular diseases.[13] In addition, tacrolimus is also instrumental in increasing the blood lipids, reducing bile secretion, and thus affecting the progression of atherosclerosis.[14]

The problem of metabolic disorders, especially the dynamic remodelling of lipid homeostasis, followed by liver transplantation, is another crucial factor in developing post-transplant cardiovascular disease.[15] Liver transplant recipients usually have a higher pro-atherogenic lipoprotein profile, including higher IFN-ɣ and vascular cell adhesion molecules, and a decreased level of protective serum IL-10 concentration.[16,17] Hepatic fibrosis–induced oxidative stress, vascular inflammation, and development of post-liver transplantation endothelial dysfunction also contribute to metabolic disorders after liver transplantation.[16,17]

In conclusion, this case draws attention to the accelerated atherosclerosis observed after multi-organ transplantation, which may be influenced by a multitude of factors. The rapid progression from atherosclerosis to acute myocardial infarction in this patient may have been impacted by his post-transplantation condition and treatments. This underscores the importance of vigilant post-transplant management, particularly in patients already at risk of cardiovascular disease. Close follow-up, frequent diagnostic testing, identification of exacerbating factors and signs of deterioration, and the careful selection and dosing of immunosuppressive drugs can all be instrumental in reducing the worsening and degree of cardiovascular disease post-transplantation. However, we must exercise caution in drawing definitive causation from a single instance. The potential connection invites further study to optimize comprehensive management strategies, such as rigorous medication monitoring and control of metabolic syndrome, to mitigate the risk of atherosclerosis progression. This complex interplay necessitates further exploration to foster a more nuanced understanding of these dynamics.

Lead author biography

The author is affiliated with the Department of Transplantation of The Second Affiliated Hospital of Hainan Medical University, serving as Chairman of Dialysis Transplantation Society of Chinese Biomedical Engineering and holding memberships in various prestigious medical associations such as the Organ Transplantation Branch of the Chinese Medical Association, the Transplantation Medicine Committee of the Chinese Research Hospital Association. Additionally, he is recognized as an expert by National Advanced Individual in the Health System. He has led groundbreaking research projects including China's first ABO-incompatible kidney transplant, two National Natural Science Foundation projects, and seven major provincial and ministerial-level scientific research projects.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

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Consent: This study was conducted in accordance with the ethical guidelines of the Institutional Review Board of the Second Affiliated Hospital of Hainan Medical University. All participants provided informed consent prior to participation, and their confidentiality and anonymity were protected throughout the study. We hereby affirm that a comprehensive consent form has been duly completed and signed by the patient prior to the submission of the manuscript. We have ensured that the consent form utilized is compliant with the COPE guidelines on Ensuring Consent for Publishing Medical Case Reports. Further to this, we have also obtained the patient's consent using the *European Heart Journal – Case Reports* Patient Consent Form. If a request is made, we stand ready to make this consent form available to the journal editor.

Conflict of interest: None declared.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

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