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CASE REPORT

ADVANCED

CLINICAL CASE: ACC.23

Alert! Does Prolonged Temporary Support Induce an Immunological Response?

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ABSTRACT

Little is known about the development of human leukocyte antigen antibodies with use of the temporary transvalvular pump 5.5 mechanical circulatory support device. This case reports a patient who developed de novo antibodies prior to his heart transplantation and remains free of any episodes of rejection post transplantation to date. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2023;16:101877) Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 52-year-old African American man presented with cardiogenic shock with blood pressure of 89/63 mm Hg, heart rate of 110 beats/min with multiorgan dysfunction. His right heart catheterization revealed elevated filling pressures (right atrial of 15 mm Hg, wedge of 23 mm Hg, and cardiac index of 1.2). An attempt was made to improve his hemodynamics with dual inotropic therapy consisting of dobutamine 5 μg/kg/min and milrinone 0.5 μg/kg/min.

LEARNING OBJECTIVES

- To understand that tMCS devices might result in the development of de novo HLAs prior to transplantation.
- To highlight the need to conduct a prospective study to determine the incidence and the clinical significance of these antibodies and patients' outcomes following orthotopic heart transplantation.

PAST MEDICAL HISTORY

The patient has a history of nonischemic dilated cardiomyopathy, diabetes mellitus with a hemoglobin A_{1c} of 7.0, and obstructive sleep apnea on nighttime continuous positive airway pressure.

His hemodynamics on dual inotropic support consisted of blood pressure of 90/60 mm Hg with poor hemodynamics—right atrial pressure of 13 mm Hg, pulmonary capillary wedge pressure of

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

CPRA = calculated panel reactive antibody

HLA = human leukocyte antigen

tMCS = temporary mechanical circulatory support

25 mm Hg, cardiac index of 1.5, worsening hyponatremia and persistent renal dysfunction—warranting a Impella 5.5 placement as a bridge to heart transplantation. The axillary transvalvular pump site was evident of a small hematoma that did not require intervention. There were no signs of infection. All pulses were intact. The transvalvular pump had no alarms. The patient was noted to develop de novo class I and II anti-human leukocyte antigen (HLA) antibodies prior to his orthotopic heart transplantation.

The patient had no known history of blood transfusions. Furthermore, no blood products were administered at time of placement of the transvalvular pump or prior to transplantation. Prior to the transvalvular pump insertion, the patient's HLAs' calculated panel reactive antibody (CPRA) was 0%. HLAs were monitored weekly post transvalvular pump placement. On day 14 of admission, the patient was noted to have de novo class I and II antibodies with a CPRA of 56%. On follow-up, he developed further de novo HLA antibodies with CPRA rising to 88% (Table 1). The duration of transvalvular pump support was 48 days, and the device was removed at the time of transplantation.

DIFFERENTIAL DIAGNOSIS

The well-known sensitizing factors are high baseline PRA, female sex, prior transplantation, blood product transfusion,[1] pregnancy,[2] infection,[3,4] and durable left ventricular assist device insertion.[5-7] However, none of the known sensitizing factors were present in this patient.

INVESTIGATIONS

Class I and II anti-HLA antibodies testing with CPRA were done 7 days prior to transvalvular pump insertion; on days 7, 14, 21, 35, and 42 after transvalvular pump insertion; and 6 weeks after transplantation. A notable rise in the CPRA was recorded on day 14 after transvalvular pump insertion (Table 1). Post-transplant surveillance showed no signs of graft injury or episodes of rejection (Table 2).

MANAGEMENT

Due to the rise in the patient CPRA over 80%, the transplant team decided to induce the patient with anti-thymocyte globulin 4.5 mg/kg starting in the operating room. Intraoperatively, the patient received mycophenolate 1.5 g and methylprednisolone 1 g. Postoperatively, the patient was started on our standard immunosuppression regimen with tacrolimus to keep a target goal of 12-15 ng/mL in the first 3 months then 10-12 ng/mL for months 3-6. In addition, mycophenolate was kept at 1 g twice a day and prednisone was tapered off at 6 months.

DISCUSSION

The U.S. Food and Drug Administration approved the use of temporary mechanical circulatory support (tMCS) devices, most notably the Impella 5.5 and Impella CP (ABIOMED), in refractory heart failure and as a bridge to orthotopic heart transplantation.[8] In addition, the new 2018 heart allocation system, resulted in increased use of tMCS as bridging devices.[9] There is evidence that durable left ventricular assist devices can promote anti-HLA antibody

TABLE 1 Patient Timeline During Hospitalization

Timeline	Calculated Panel Antibody (%)	Calculated Panel Antibody > 10,000 and/or C1q + (%)	Class I and Class II Antigens
Pretransvalvular pump 5.5 (7 days prior to insertion)	0	0	None
Impella 5.5 insertion			
Post- transvalvular pump 5.5 day 7	0	0	None
Day 14	56	0	Cw: 2, DR: 53
Day 21	65	0	DR: 53, DQ: 5, DP: 5, DP: 11
Day 28	88	0	DR: 51, DR: 53, DQ: 5, DQ: 6, DP: 5, DP: 6, DP: 11
Day 35	88	0	A: 69, DR: 51, DR: 53, DQ: 5, DQ: 6, DP: 5, DP: 6, DP: 11
Day 42 Sample used for virtual crossmatch	88	0	A: 69, DR: 51, DR: 53, DQ: 5, DQ: 6, DP: 5, DP: 6, DP: 11
Orthotopic heart transplantation			
Post-TX HLA 6 weeks	70	NA	DR: 51, DR: 53, DP: 5, DP: 11 No DSAs

C1q = complete binding assay; DSAs = donor specific antibodies; HLA = human leukocyte antigen; NA = not available; TX = transplantation.

TABLE 2 Post-Transplant Surveillance

11 Days postop	TTE LVEF 60%-65%
2 Weeks postop	EMB OR, AMR 0 MMDx no AMR or TCMR
6 Weeks postop	AlloSure <0.12% EMB OR, AMR 0 MMDx no AMR or TCMR HLA negative for DSAs
10 Weeks postop	AlloSure <0.12% AlloMap 20
5 Months postop	AlloSure <0.12% AlloMap 22
6 Months postop	AlloSure <0.12% AlloMap 24 HLA negative for DSAs

AMR = antibody mediated rejection; EMB = endomyocardial biopsy; LVEF = left ventricular ejection fraction; MMDx = molecular microscope diagnostic system; postop = postoperative; TCMR = T-cell mediated rejection; TTE = transthoracic echocardiogram; other abbreviations as in Table 1.

production, which tends to decline after transplant, and are often not immunologically detrimental. Device recipients are often thought to become sensitized because of exposure to blood products at time of implantation of the device.[10] Sensitization has also been attributed to the host-device biomaterial interaction, which induces aberrant T-cell activation and B-cell hyperactivity.[5-7] Yet, little is known about the ability of these temporary devices to promote production of de novo anti-HLA antibodies and the downstream effects on patients receiving orthotopic heart transplantation. In our case, the rise in the patient's CPRA post transvalvular pump 5.5 insertion without the presence of other sensitizing factors supports the hypothesis that tMCS devices have the potential to promote development of de novo anti-HLA antibodies in recipients. To fill this gap of knowledge, a prospective study is needed to determine whether temporary devices promote production of de novo anti-HLA as it would likely change pre-transplant monitoring of these type of patients.

FOLLOW-UP

At 6 months post transplantation, the patient has had no episodes of rejection on surveillance biopsies, no hospitalizations, and has not developed any post-transplant donor-specific antibodies. The patient has also had a consistent AlloSure score of <0.12% and a range of AlloMap scores of 20-24 (Table 2). Additionally, apart from the 2 standard of care biopsies in our protocol at weeks 2 and 6 after transplantation, the patient has not required any further biopsies for concerns of rejection. The patient remains on routine immunosuppression and comes in monthly per standard of care for post-transplant follow-up.

CONCLUSIONS

Similar to the experience with durable left ventricular assist devices, the tMCS device, transvalvular pump 5.5, may result in the development of new HLAs. Further studies measuring HLAs in patients requiring tMCS are needed to determine the incidence and clinical significance of these antibodies and outcomes following heart transplantation.

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