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Pregnancy-Related Human Leukocyte Antigen Sensitization Leading to Cardiac Allograft Vasculopathy and Graft Failure in a Heart Transplant Recipient: A Case Report

M. Ginwalla, M.J. Pando, and K.K. Khush

Division of Cardiovascular Medicine (M.G., K.K.K.), and Department of Pathology (M.J.P.), Stanford University School of Medicine, Stanford, California, USA.

Abstract

In this report, we present a heart transplant recipient who developed cross-reactive paternal and donor-specific human leukocyte antigen (HLA) class II antibodies during pregnancy, leading to accelerated cardiac allograft vasculopathy and severe allograft dysfunction 17 years after transplantation. This resulted in acute heart failure and ventricular arrhythmias requiring repeat heart transplantation.

Cardiac transplantation is a life-saving procedure for patients with end-stage cardiac disease with severe functional limitation who are refractory to medical therapy. An increasing number of transplant recipients are women of reproductive age or children who will reach reproductive age, which has led to a growing number of pregnancies in this group.¹ These pregnancies are high risk, with an increased prevalence of obstetric complications including pre-eclampsia, spontaneous abortions, low birth weight, and intrauterine growth retardation.² Fortunately, most pregnancies do not significantly affect allograft function. Although mild cellular rejection may occur, donor-specific human leukocyte antigen (HLA) sensitization rarely occurs following pregnancy.³

HLA sensitization, in general, results from blood transfusions, use of left ventricular assist devices, prior transplantation, or prior pregnancies. Heart transplant recipients sensitized to HLA have an increased risk of acute antibody-mediated rejection (AMR) and allograft vasculopathy leading to graft failure.⁴ We describe a patient who developed de novo cross-reactive HLA class II paternal and donor-specific antibodies following a normal pregnancy and delivery, leading to accelerated allograft vasculopathy and graft failure requiring repeat heart transplantation.

CASE REPORT

A 27-year-old woman underwent an orthotopic heart transplantation at the age of 10 years for familial cardiomyopathy. She had an uncomplicated posttransplantation course free from

rejection and opportunistic infections. The donor and recipient were both seropositive for cytomegalovirus (CMV). The patient had preserved left ventricular ejection fraction and normal coronary angiograms.

The patient became pregnant for the first time and had an uneventful pregnancy and delivery. Her immunosuppression comprised cyclosporine, azathioprine, and prednisone. Three months postdelivery, she presented with shortness of breath and lower extremity edema. Her echocardiogram showed an acute decrease in her ejection fraction from 58% to 25% with a restrictive filling pattern. Right-sided heart catheterization revealed elevated filling pressures and a low cardiac output of 2.2 L/min with a cardiac index of 1.5 L/min/m². Coronary angiography revealed significant cardiac allograft vasculopathy, with diffuse narrowing and tapering of the donor coronary arteries (Fig 1). An endomyocardial biopsy showed Grade 1R mild acute cellular rejection and immunofluorescence was negative for C4d staining. CMV polymerase chain reaction assay was negative. She was admitted to the cardiac intensive care unit and started on a dobutamine infusion. Azathioprine was changed to mycophenolate mofetil and she was treated with high-dose methylprednisolone. Because there was no improvement in her clinical status, she was empirically treated with 2 doses of intravenous immunoglobulin (IVIg) due to concern for acute AMR. This resulted in significant improvement in her clinical status. She was treated with oral medications for heart failure and discharged home with close clinical follow-up.

Examination of the antibody profile against HLA by single antigen bead assays showed that the patient had developed de novo donor-specific antibodies (DSAs). The strongest antibodies were directed against DQ5 and DQ6, which are both splits of the parent antigen DQ1 that was present on her cardiac allograft. Interestingly, her baby was typed as DQ6, part of the haplotype inherited from the father (Table 1). We hypothesized that allosensitization against the baby's DQ6 antigens triggered the development of new DSAs that cross-reacted with donor DQ1 antigens. Furthermore, retrospective analysis of a serum sample obtained at the time of the biopsy showed that the patient had strong antibodies to DQ5 and DQ6 (DQ1) by the complement-fixing C1q assay (MFIs = 10,000–25,000), demonstrating that these antibodies were likely cytotoxic.

Because the patient continued to have severe graft dysfunction and persistently elevated filling pressures despite optimal heart failure therapy, she was relisted for heart transplantation. Her panel of reactive antibodies (PRA) for HLA class I was 12% and for class II was 63% exclusively due to the antibodies to DQ1 at the time of transplantation listing. Due to her high risk of sudden cardiac death, she was provided with a defibrillator “life vest” jacket.

Subsequently, she was readmitted to the intensive care unit 5 months after her delivery with worsening fatigue, shortness of breath, and multiple aborted defibrillator vest shocks. Due to her high risk of arrhythmogenic sudden cardiac death, her waitlist status was upgraded to 1A. Eight days later, a compatible allograft became available, and she underwent successful retransplantation without a prospective crossmatch. Her explanted heart showed that the cause of her heart failure was severe occlusive cardiac vasculopathy (CAV), with only mild

acute cellular rejection (Grade 1A; Fig 2). The explanted heart was negative for AMR by C4D, C3D, and CD68 staining.

DISCUSSION

In this report, we present a heart transplant recipient who developed de novo HLA sensitization during pregnancy due to cross-reacting paternal and DSAs leading to rapid development of CAV and new-onset allograft dysfunction.

According to data from the US National Transplantation Pregnancy Registry, 50%–86% of pregnant solid organ transplant recipients produce a successful live birth. Pregnancy in a transplant recipient carries a potential risk of allograft rejection. These episodes are usually mild and require no treatment.³ HLA sensitization may occur during pregnancy but the incidence is unknown because antibody levels are not monitored routinely.⁵

Recently, it has been shown that de novo DSAs that develop after transplantation may result in acute AMR and are associated with poor survival.⁶ AMR involves the development of antibodies against donor vascular endothelial antigens that contribute to the development of cardiac allograft vasculopathy—the main cause of mortality beyond the first year after cardiac transplantation. Known risk factors for development of CAV also include dyslipidemia, diabetes, hypertension, and CMV infection. There is a complex interplay between immunologic and nonimmunologic factors that ultimately result in endothelial injury and an exaggerated repair response. These processes manifest pathologically as fibroelastic intimal proliferation and luminal stenosis, which can be diagnosed clinically using coronary angiography and intravascular ultrasound.⁷

Our patient had remained free of cellular rejection and CAV for 17 years prior to her pregnancy. Two months after delivery she developed accelerated allograft vasculopathy and graft failure. Although her endomyocardial biopsy was negative for capillary C4d staining, HLA typing and antibody screen revealed the development of de novo antibodies against the paternal antigen DQ6, which cross reacted with DQ5, both of which are splits of the donor antigen DQ1. These antibodies were also found to be C1q positive, which does not always correlate with C4d staining. C1q was detected using the complement-fixing assay using HLA single antigen beads. C1q-positive antibodies appear to be more highly correlated with AMR after heart transplantation than antibodies detected solely with the immunoglobulin (IgG) single antigen bead assay.⁸

Per the International Society for Heart and Lung Transplantation consensus conference on AMR, AMR is considered a pathological diagnosis and is diagnosed by histological parameters including activated endothelial cells, intravascular macrophages, and immunophenotypic evidence of capillary C4d deposition.⁹ Although our patient did not have histological evidence of AMR or immunophenotypic staining for C4d, HLA antibody testing revealed the development of de novo paternal-specific antibodies that cross reacted with donor antigens and likely led to clinical graft dysfunction. Her clinical response to IVIg therapy further indicated that AMR was the primary cause of her graft dysfunction.

The only other documented case of a patient developing de novo DSAs and paternal-specific antibodies after pregnancy was reported by O'Boyle et al. Their patient developed HLA class II DSAs and paternal-specific antibodies after a spontaneous miscarriage resulting in AMR. However, in their case, the patient's coronary arteries were normal without evidence of CAV.⁵

Our case demonstrates that HLA sensitization can occur during pregnancy in transplant recipients, despite immunosuppression, and can result in AMR. These patients may develop DSAs despite negative immunophenotypic studies. If sensitization has occurred, therapies such as plasmapheresis and IVIg may result in clinical improvement. Pregnancies in transplant recipients are high risk and require close maternal and fetal surveillance not only during pregnancy but for at least several months after delivery through coordinated care between maternal-fetal medicine specialists and transplantation personnel. In conclusion, our study highlights the risk of pregnancy in transplant recipients. We speculate that transplant recipients may benefit from pre-emptively monitoring DSAs during pregnancy or for several months after delivery to prevent postpregnancy complications.

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Fig 1. Coronary angiogram images showing moderate CAV with diffuse narrowing of the donor coronary arteries. **(A and B)** Left main, left anterior descending, and left circumflex coronary arteries. Left anterior oblique and right anterior oblique projections. **(C)** Right anterior oblique projection of the right coronary artery.

Fig 2. Section of an allograft coronary artery showing occlusive transplant vasculopathy (**A**) with a severely reduced lumen (**B**). (**A**) H&E staining. (**B**) EVG staining.

Table 1

HLA Typing of the Patient, Her Husband, Their Baby, and the Heart Transplant Donors

	HLA-A		HLA-B		HLA-DR		HLA-DQ	
Patient	A24	A32	B*35:08	B*35:02	DR11	X	DQ7	X
Baby	A3	A32	B7	B*35:02	DR15	DR11	DQ6	DQ7
Father	A3	A24	B7	B39	DR15	DR8	DQ6	DQ4
Donor no. 1	A2	X	B44	X	DR6	DR7	DQ1	DQ2
Donor no. 2	A2	A26	B14	B73	DR7	DR11	DQ2	DQ3