

Case Report

Living-Related Kidney Transplant in Two Sets of Hla-Identical Twins

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Abstract

Organ transplantation between identical twins is a relatively rare event that has been performed for kidney, pancreas, small bowel, and liver transplants. Monozygotic twins have identical HLA genes that enable the theoretical opportunity of avoiding immunosuppressant medications following transplantation; and with it, the often-serious side effects and financial costs of these drugs. Published information on immunosuppressive management in this scenario is scant. We report two cases of Living Related Kidney Transplantation (LRKT) between identical twins and their immunosuppressive courses that followed transplantation, along with a review of the literature.

ABBREVIATIONS

LRKT: Living-related kidney transplant; cPRA: calculated Panel Reactive Antibody; HLA: Human Leukocyte Antigen; DSA: Donor Specific Antibody

INTRODUCTION

Solid organ transplantation between monozygotic twins is a rare operation performed by transplantation surgeons. Successful reports for kidney [1,2], pancreas [3], combined kidney-pancreas [4], small bowel [5, 6], and liver [7] have been documented, albeit in small numbers. Compared to transplantation between genetically mismatched pairs, the theoretical advantage to a patient receiving a monozygotic graft is the elimination of the need for immunosuppression, and with it, the removal of untoward side effects including osteoporosis, diabetes mellitus, renal insufficiency/failure, increased risk of infection, life-long increased risk for developing certain malignancies [8-10], as well as the financial costs of these medications.

Joseph E. Murray performed the first successful organ transplant, which happened to be a living-related kidney transplant between identical twins, in 1954 at Peter Bent Brigham Hospital in Boston, MA [1]. The recipient survived 9 years, without immunosuppression, before dying from a myocardial infarction [2]. With its success, the importance of the immunologic response and its role in transplantation and rejection was confirmed. Since

that time, a tremendous amount of resources and science have been devoted to the study of immunosuppression and the ability to wean immunosuppression in living-related kidney transplant recipients [11,12].

Since 1987, when the Organ Procurement and Transplantation Network began recording data pertaining to organ donation and transplantation in the United States, there have only been a total of 205 living-related kidney transplants between identical twins [13]. Information regarding immunosuppression in this population of patients is extremely limited. In this report, we will describe our experience with living-related kidney transplantation between two sets of identical twins and their immunosuppression management that followed.

CASE 1

A 19-year-old female with stage V chronic kidney disease secondary to severe acute neonatal renal failure caused by fetal twin-to-twin transfusion syndrome was referred for LRKT at our institution. Her medical history included hypertension and she had no history of previous surgeries. She was not yet on dialysis. She and her identical twin sister were both college students.

She had a calculated panel reactive antibody level (cPRA) of 2%. Initial Human Leukocyte Antigen (HLA) typing was performed using sequence-specific oligonucleotide (SSO) technique with Luminex testing for donor specific antibodies

(DSA) confirmed the patient and her twin were 6 antigen matches with no identified DSA. In addition to the HLA A, B and DR loci, they were also perfectly matched at the Bw, Cw and DQ loci. To further demonstrate that there were no allelic mismatches at these loci, further High Resolution HLA typing was performed using sequence-specific primer (SSP) technology. This confirmed that all alleles at the various HLA loci were also identical. At our multidisciplinary Selection Conference, we discussed that despite being HLA identical, there was a chance that different life experiences from her sister may have caused the patient to develop antibodies to unknown minor or non-HLA loci, which we were unable to test for. Based on this and after a review of the literature by the team, we decided to keep the recipient on mycophenolic acid (Myfortic®) alone as prophylactic immunosuppressant. At one year post transplant, we would consider stopping this as well if there were no rejection episodes.

The patient received a LRKT from a laparoscopically procured nephrectomy of her sister. She received no antibody induction therapy and had a rapid taper of methylprednisolone over three days (500 mg, 250 mg, and 125 mg). She was initiated on 720 mg of mycophenolic acid twice daily. Our center's usual protocol for immunosuppression involves alemtuzumab (Campath®) induction with steroid taper over three days, with tacrolimus and mycophenolic acid maintenance. She also received prophylactic antibiotic therapy consisting of acyclovir (donor and recipient were cytomegalovirus antibody negative), nystatin and sulfamethoxazole and trimethoprim (Bactrim®) for a period of 6 months. Post transplant, the patient did extremely well, with a baseline creatinine of 0.7 mg/dL (GFR 117 ml/min).

Approximately nine months post transplant, she was admitted for abdominal pain and diarrhea. Believing this may be a side effect of her immunosuppression, we stopped her mycophenolic acid. Further stool testing demonstrated that she was *C. difficile* positive, although we could not identify any other risk or causative factors. She was treated with a fourteen-day course of oral Vancomycin as she could not tolerate metronidazole. After treatment, we decided to permanently discontinue her mycophenolic acid. She is now over a year post transplant and has stable normal kidney allograft function with no rejection episodes.

CASE 2

The second case was a set of male twins, 36 years of age. The recipient suffered from end stage renal disease secondary to congenital prune-belly syndrome with urinary tract anatomical anomalies, and had started on hemodialysis approximately one month prior to transplantation. He had a history of right nephrectomy and urostomy as an infant with subsequent closure. In addition, he had an orchiopexy and a history of stage I colon cancer in the left transverse colon for which he underwent resection four years prior. He also had a history of previous transfusions.

Similar to the first case, low resolution and high resolution HLA typing were performed which confirmed HLA loci and allelic congruency with no DSA. His cPRA was 58%. Based on our previous experience, we decided to place this patient on half dose mycophenolic acid (360 mg twice daily) indefinitely.

Post transplant, the patient has done well, with a baseline creatinine of 1.1 mg/dl (GFR 86 ml/min). He is now over 6 months post transplant and has had no rejection or infectious episodes.

DISCUSSION

In 1986, Tinley et al. [2] published a review of 30 transplantations between identical twins performed at the Peter Bent Brigham Hospital, where the first pioneering transplant between identical twins was performed in 1954. Follow-up extended 27 years and demonstrated a 25-year patient survival rate of around 65% and a graft survival rate of around 55%. Graft survival was 84% at 1 year and 72% at 5 years.

Following this review in 1986, there were only a few small articles on the topic of renal transplantation between identical twins [14-16]. With regards to immunosuppression, one of these articles describes the use of steroids in the short-term (6 weeks) to prevent ischemic-reperfusion injury [15] and another used steroids with azathioprine or cyclosporine for long-term prevention of recurrent glomerulonephritis or rejection [14].

With the lack of more recent information available on the topic, Kessarar *et al.* [17], in 2008, published their review of results from 120 patients in the United States and United Kingdom who received monozygotic twin kidney transplants from 1988-2004. Graft survival was 99.17% and 88.96% in the US group at 1 and 5 years, respectively, and 83.3% and 75% in the UK group during the same follow-up period. Patient survival was 100% and 97.01% in the US group at 1 and 5 years, respectively, and 100% in the UK group during the same 5-year follow-up period. These results demonstrate that both graft and patient survival have obviously improved greatly since the early Boston series [2], likely due to advanced HLA-testing, improvements in preservation and operative techniques, and better management of immunosuppression for rejection and recurrence of original disease.

Interestingly, in terms of immunosuppression, 68% of patients in the United States were discharged on some form of immunosuppression. There was, however, no statistically significant difference in graft survival between those patients that had maintenance immunosuppression and those that did not ($p= 0.12$). Furthermore, there were fewer patients on immunosuppression at follow-up compared with the time of transplantation [17].

The results demonstrated by Kessarar *et al* raise questions surrounding the proper immunosuppressive course following renal transplantation between identical twins. Given the results above, one must ask whether immunosuppression is necessary at all. It is a common belief that monozygotic twins share 100% of the genes and thus will not require immunosuppression. However, this is not always the case. Gringas *et al* explain that a number of intrauterine effects and genetic mechanisms may result in phenotypic, genotypic, and epigenetic differences between monozygous twins (18). Also, as mentioned earlier, differential life experiences may cause a recipient to develop antibodies to minor or non-HLA antigens, which may possibly impact graft survival. As part of the Collaborative Transplant Study, Opelz, et al (19), describe worse graft survival among sensitized (PRA >50%)

kidney transplant recipients who received HLA identical sibling allografts, compared to non-sensitized recipients, suggesting some modality of as yet undiagnosed immunological injury. As such, the clinical scenario in which immunosuppression should be used following transplantation between identical twins is not entirely straightforward. This has led to calculated immunologic risk monitoring in some instances in order to determine when immune suppressant medications can be withdrawn [12].

Arguments for withdrawing immune suppression therapy are obvious and stem from the widely known side effects of these medications [8-10]. If these medications can be deemed unnecessary they should be stopped. However, given the scarcity of information regarding immunosuppressive management in identical twin LRKT, this decision can be quite difficult, as the concern for rejection remains a critical issue. The decision likely must be made for each individual patient.

In our report, each twin received minimal immunosuppression at the start of transplantation without induction therapy. In Case 1, maintenance therapy was continued with mycophenolic acid, however, due to a subsequent *C. difficile* infection immunosuppression was stopped at nine months post-transplant. It is possible that she did not need any immunosuppression from the start and her infection was precipitated by her being on it. She has done well and has been kept off immune suppression without subsequent sequelae. In Case 2, we describe a gentleman that has been managed on half-dose mycophenolic acid since transplant. Since he had a relatively high cPRA we are somewhat cautious about withdrawing his immunosuppression and will bear close watching.

As suggested by Kessar et al. [17], as well as studies examining the true genetic relationship between monozygotic twins [18] and immune suppression management in these individuals [12], the choice of whether to provide immunosuppression in identical twin LRKT and what type of medications to use is not clearly defined. Our experience hopefully adds to the collective experience on which future decisions on this subject can be made. For now, until further immunological advancements are made, immunosuppressive medications must be tailored to individual patients based on their clinical scenario, which will include genetic and immunologic results, underlying kidney disease, concomitant disease or infection, and other factors such as age and gender which may all influence graft survival.

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