Patients seeking alternatives to the long waiting list: a reality faced by transplant physicians

The United States is faced with an epidemic of kidney disease, with the prevalence of end-stage renal disease forecast to exceed 2 million by the year 2030. Kidney transplantation is the preferred method of renal replacement therapy for many patients. Currently, more than 76,000 candidates in the United States are on the waiting list for a kidney transplant (according to data from the Organ Procurement and Transplantation Network [OPTN] as of July 18, 2008), and that number is increasing daily. Conversely, only 16,626 kidney transplants were performed in 2007 (10,587 from deceased organ donors and 6,039 from live donors; according to OPTN data as of July 18, 2008). The median waiting time for a kidney from a deceased donor in the United States is 2 to 6 years, with longer waiting times predicted for the future. The disparity between availability of organs for transplantation and their demand will increase because the numbers of patients with chronic kidney disease are increasing as a result of the aging of the population and the increasing numbers of people with diabetes mellitus and hypertension.

We report 4 patients from our transplant center who traveled outside the United States to obtain a living donor kidney transplant. Each patient had undergone pretransplant evaluation and had been approved and placed on the waiting list for kidney transplantation in the United States. In each case, the transplant team was unaware that the patient had sought an organ outside the United States until the patient requested posttransplant care. Clinical information provided to the patients from the foreign transplant center was often limited and not in English. In each case, significant unexpected complications were associated with the transplant procedure.

Case Reports

Each patient in our case series obtained an allograft outside of the United States and experienced significant complications after the transplant procedure. The cases are described in detail here, including all information available from the transplant center.

Case 1: Posttransplantation Malaria

A 54-year-old white man with end-stage renal disease caused by unspecified glomerulonephritis came to our institution with fever and rigors 18 days after receiving a kidney transplant from a living unrelated donor in Pakistan. The patient had received a kidney transplant from a deceased donor in the United States 29 years earlier that had ultimately been lost to chronic
allograft nephropathy. The patient had returned to hemodialysis for 2 months before deciding to travel to Pakistan to purchase a kidney. He had not traveled outside the United States for 4 years before that and had no known exposure to infectious agents. The patient had been evaluated for transplantation in the United States and had recently been placed on the waiting list and designated status 1 by the United Network for Organ Sharing (UNOS). He had a high level of panel-reactive antibody, and his anticipated wait for a deceased donor organ was projected to be lengthy.

Unknown to the transplant team in the United States, the patient decided to travel to Pakistan with the assistance of a transplant broker he contacted via the Internet. The patient was matched by the broker to a living unrelated donor—a female donor who traveled from India to donate. Medical records were sent with the patient in English. The donor’s tissue typing was performed at the Pakistani transplant center, and the recipient’s tissue typing results were obtained from historic typing performed in the United States. The donor and recipient were matched for a single HLA-A and HLA-DR antigen and mismatched for 4 HLA antigens. Both donor and recipient were negative for antibodies to cytomegalovirus, hepatitis B virus, hepatitis C virus, and human immunodeficiency virus. Donor and recipient blood typing and cross-matching were performed at the Pakistani transplant center immediately before transplantation.

The patient was admitted to the hospital in Pakistan on December 31, 2006, and the transplant procedure was performed on January 7, 2007. Induction immunosuppressive therapy was not used, but a standard posttransplant immunosuppressive regimen was prescribed that included cyclosporine, mycophenolate mofetil, and prednisone. The dose of calcineurin inhibitor was adjusted on the basis of cyclosporin A levels 2 hours after dosing (C2 levels) in an attempt to avoid calcineurin nephrotoxicity. No intraoperative or perioperative complications were reported, and the nadir creatinine level was 1.5 mg/dL (to convert to micromoles per liter, multiply by 88.4) by 10 days after transplantation. The only obvious postoperative complication was an Escherichia coli infection of the urinary tract, which resolved with antimicrobial therapy. The patient was discharged with a ureteral stent in place 10 days after transplantation and a triple-drug regimen of cyclosporine, mycophenolate mofetil, and prednisone. He was instructed to have the ureteral stent removed 7 days after returning to the United States and was advised to have cyclosporine levels measured and routine laboratory tests done every 10 days for 3 months.

One week after returning to the United States, the patient was evaluated in the emergency department for fever and rigors. His oral temperature was 103°F (39°C), but the rest of the physical examination was unrevealing. The laboratory tests showed anemia, and a serum creatinine level of 1.9 mg/dL. Liver enzyme levels were slightly elevated. Upon hospital admission, malarial parasites were noted on a peripheral blood smear by a laboratory technician. The blood parasite screen revealed Plasmodium vivax, with 1.5% parasitemia. The patient was treated successfully for uncomplicated P vivax malaria with 14 days of oral chloroquine and primaquine. No further complications occurred, and the patient continues to experience a stable posttransplant course on standard triple-drug immunosuppression, with serum creatinine levels of 1.4 to 1.6 mg/dL.

Case 2: Posttransplantation Tuberculosis, Deep Venous Thrombosis, Lymphocele, and Ureteral Stricture

A 42-year-old female resident of Saudi Arabia was temporarily living in the United States and receiving routine care for chronic kidney disease at our nephrology center. The patient had a history of end-stage renal disease due to chronic glomerulonephritis of unclear origin and had been evaluated and accepted for deceased donor transplantation in Saudi Arabia. She had a history of chronic hypertension and hyperparathyroidism and hyperlipidemia, but no history of hepatitis, liver disease, heart disease, cancer, or tuberculosis. She also had no known history of Bacille Calmette-Guérin (BCG) vaccination. A skin test for tuberculosis before transplantation was negative.

The patient, unbeknownst to her nephrologists in the United States or Saudi Arabia, traveled to the Philippines to obtain a living unrelated kidney transplant on March 17, 2006. The patient underwent an incidental open cholecystectomy at the time of kidney transplantation. The immediate postoperative course was uneventful, except for the receipt of 6 units of packed red blood cells in the perioperative period, presumably necessitated by intraoperative hemorrhage. The patient was discharged 7 days after transplantation, taking cyclosporine, mycophenolate mofetil, and prednisone for maintenance immunosuppression. It is not known whether induction immunosuppressive therapy was given. Medical records were not supplied by the Philippine transplant center.

Upon discharge from the transplant center, the patient claimed that she noted increased swelling in her right lower extremity. The swelling in the right lower extremity worsened on return to the United States, and she came to our transplant center with severe ipsilateral leg swelling, leg pain, and acute renal failure. A magnetic resonance imaging examination revealed a large lymphocele and superficial thrombosis in the right femoral vein and deep venous thrombosis in the external iliac vein extending into the transplant renal vein. In addition, retroperitoneal lymphadenopathy was noted. She was admitted to the hospital and underwent...
percutaneous lymphocele drainage and thrombolysis of the deep vein thrombosis with infusion of tissue-plasminogen activator for several days. Thrombolysis resulted in resolution of the leg edema and improvement in renal function.

A biopsy of an enlarged mesenteric lymph node revealed necrotizing granulomas that ultimately cultured positive for *Mycobacterium tuberculosis*. The serum was negative for cryptococcal antigen and coccidiodymosis antibody. The patient was treated with a 4-drug antitubercular regimen consisting of isoniazide, rifampin, ethambutol, and pyrazinamide. After drainage of the lymphoceles, thrombolysis, anticoagulation, and initiation of antituberculous therapy, the patient regained excellent renal function, measured by a serum creatinine level of 1.1 mg/dL. Three months later though, she came back with an increase in serum level of creatinine to 3.0 mg/dL, which was ultimately found to be due to a long-segment ureteral stricture thought to be unrelated to the tuberculosis. The patient underwent surgical repair of the ureteral stricture via ureteropyelostomy of the native right ureter to the renal transplant pelvis. After correction of the ureteral stricture, she did well, with a stable serum creatinine level of 1.1 to 1.3 mg/dL, and she was discharged back to her physicians in Saudi Arabia.

**Case 3: Posttransplantation Acute Rejection**

A 56-year-old Chinese woman, resident of the United States, with end-stage renal disease due to diabetic nephropathy traveled to China to undergo live donor transplantation from a remote relative. She did not discuss the intent to travel to China for transplantation with her physicians. In addition to renal disease, the patient had a history notable for myocardial infarction followed by coronary revascularization in 2005, and internal carotid artery stenosis resulting in left-sided cerebrovascular accident and treated by carotid endarterectomy. Her medical history was also notable for chronic hepatitis B and hepatitis C infection. A liver biopsy showed minimal portal and lobular inflammation without evidence of portal fibrosis or periportal bridging. Despite multiple medical comorbidities, the patient had been deemed a suitable candidate for kidney transplantation and she was activated on the kidney transplant waiting list at UNOS status 1 in 2005. In addition, she had 6 children and a husband who were willing potential live donors.

One year after UNOS listing, the patient disappeared from our transplant center. She reappeared in January 2007 with a new living donor kidney transplant and severe acute renal failure. An English translation of the Chinese hospital records was provided by the transplant center. The records stated the patient received a “living-related” donor allograft in November 2006. The donor was a 19-year-old woman who was a distant relative of a half-sister. The donor was blood type O and the recipient was blood type A. Donor and recipient were matched for 1 HLA-A antigen and 1 HLA-DR antigen. The kidney appeared to function well for the first 3 weeks after transplantation, with urine volumes of 1600 to 2000 mL daily and a nadir serum creatinine level of 80 μmol/L (0.9 mg/dL). The immunosuppressive regimen consisted of cyclosporine 100 mg twice a day and azathiprine 75 mg twice a day. No evidence indicated that serum cyclosporine levels had been monitored postoperatively. Approximately 3 weeks after transplantation, urine output and renal function declined abruptly. The patient was reported to have evidence of fluid overload and cardiac ischemia developed. Hemodialysis was initiated in China, although no renal biopsy was performed. No antirejection therapy was administered, and corticosteroids were not prescribed. In addition, the dose of cyclosporine was lowered in order to treat “delayed renal function.” She was discharged with the recommendation to seek professional therapy in a transplantation center in the United States.

On presentation to the emergency department at our institution, her creatinine level was 9.7 mg/dL, her serum level of urea nitrogen was 142 mg/dL (to convert to millimoles per liter, multiply by 0.357), and her potassium level was 5.9 mEq/L. The patient was admitted to the hospital, treated with methylprednisolone, and a renal biopsy revealed acute interstitial nephritis and intimal arteritis, Banff grade III. Hemodialysis was initiated and the patient received methylprednisolone and eventually thymoglobulin with no improvement in renal function. Ultimately, chronic hemodialysis was started, and the patient has recently been reevaluated to determine her candidacy for listing for a deceased donor organ in the United States.

**Case 4: Posttransplantation Hemorrhage, Renal Failure, Disseminated Intravascular Coagulation, and Death**

A 33-year-old Hispanic female resident of the United States with end-stage renal disease due to chronic glomerulonephritis was listed with our transplant center as a UNOS status 1. She decided, without discussion with her nephrologist, to travel to Mexico to undergo live kidney transplantation from a sister. The family did not clarify the reasons for her choice of transplant center. According to the Mexican hospital records (provided in Spanish) and reports of the family, no operative or peritransplant complications occurred, and she was doing quite well for the first 5 days after transplantation. Her creatinine level decreased from 13 to 4 mg/dL. On the fifth day after transplantation, hypertension, oliguria, and pain over the right iliac fossa developed suddenly. Based on these symptoms, she was empirically administered 3 doses of methylprednisolone,
which improved the pain over the right iliac fossa, although the renal function was not known. She was then discharged from the hospital in Mexico to a hotel adjacent to the hospital on December 24, 2006.

Within a few days of discharge, on December 28, the patient came back to the hospital with oliguria, hypertension, and pain over the right iliac fossa. She also had bruising over the left flank and severe pain on palpation of the right side of the abdomen. The laboratory findings showed a white blood cell count of 14800/µL, a serum level of urea nitrogen of 165 mg/dL, and a creatinine level of 6 mg/dL. The hemoglobin level was 4.5 g/dL with a hematocrit of 13%. An ultrasound revealed a large perirenal hematoma, but no obvious site for the bleeding was noted during the imaging. Exploratory surgery was performed via a midline incision, and a large peritransplant hematoma was drained. Brisk bleeding at the site of the vascular anastomosis was noted in the hospital records. The area around the anastomosis was packed with sterile pads, although no attempted surgical repair of the bleeding site was reported.

The patient’s mental status began to deteriorate during the next few days, and disseminated intravascular coagulation was diagnosed on the basis of the hemogram. Multiple transfusions of blood, fresh frozen plasma, cryoprecipitate, and platelets were administered during this admission, but the patient’s condition continued to deteriorate. An area of full-thickness necrosis had developed on her anterior abdominal wall at the nexus of her transplant incision and midline. The patient continued to bleed through her incision and through this area of necrosis during her admission. As the patient became completely obtunded, the family became increasingly worried for her safety. The family ultimately transferred the patient from the hospital in Mexico to our facility on January 16, 2007. On arrival at our facility, the patient was obtunded, had severe renal failure, and was extremely acidic. She was emergently intubated on arrival, but was noted to have fixed and dilated pupils and eventually died.

Discussion

Patients with end-stage renal disease who are in need of a kidney transplant are waiting extraordinarily long times to receive a deceased donor organ. These lengthy delays are fueling desperate attempts at earlier transplantation. We described 4 patients who left the United States to receive a kidney transplant. In each case, a nephrologist at our transplant center was following up with the patient, and 3 of the patients had been placed on the waiting list with a UNOS status of 1. None of the patients discussed their interest in transplantation outside of the United States with the transplant center. Furthermore, the patients were not asked about their knowledge of alternative means of obtaining a transplanted organ such as transplantation at a foreign transplant center or the practice of “transplant tourism.” In each case, an adverse outcome was experienced, which in one case led to the death of the transplant patient.

The disparity between the need for and the availability of kidneys for transplantation is growing and leading many patients to seek alternatives to the lengthy wait for a deceased donor organ in the United States. In many cases, the alternatives include solicitation of altruistic donors through personal advertisements and Internet sites, altruistic live donation from relatives living outside the United States, and purchase of organs at foreign transplant centers.

The purchase of organs involves a practice called transplant tourism, defined as the practice of patients seeking organ transplantation in countries where donors are potentially exploited, such as through paid living donation.' It is often difficult to identify patients that have purchased an organ. Indeed only 1 of the patients in our case series admitted to the purchase of an organ. Several transplant societies as well as the World Health Organization and the United States Institute of Medicine have condemned the practice of transplant tourism.'

Despite national and international condemnation, the growing disparity between the need for and the availability of organs will inevitably result in an increasing trend of transplant tourism.

International transplant centers that provide organ transplantation for purchase are readily accessed through several Internet sites. Commercialization has extended to solid organ “transplant brokers,” who, for a fee, will match a recipient with a live donor. All-inclusive packages with airfare, meals, lodging, and transplant services are provided. In many cases, the organ donor is a willing participant who is in need of financial compensation. In other cases, the organ donor is an unwilling participant, and prisoner executions for the purpose of providing organs have been reported. The cost to the recipient for the purchase of an organ has been estimated to range from US$15 000 to US$70 000, depending on the transplant center.’ Potential recipients might feel that this is a low price compared with the psychosocial and medical costs associated with remaining on dialysis. Therefore the temptation to circumvent the long waiting times for an organ will inevitably result in greater interest of patients in transplant tourism.

Not all cases of desperation involve the practice of transplant tourism. Indeed, many foreign hospitals will transplant an organ from a live donor who is not paid for their organ. One of the patients in our case series went to a hospital in Mexico for her transplant. The reasons she did not have the transplant performed in the United States are not clear, as she was unable to communicate upon her return to our transplant center.
Although many transplant centers outside the United States provide excellent surgical and medical care for transplant donors and recipients, the market of transplantation involving organ sales or involving limited adherence to UNOS guidelines is growing. The transplantation of organs at transplant centers without rigorous oversight can lead to limited donor and recipient evaluations and limited follow-up after transplantation. Transmission of infectious diseases such as malaria and tuberculosis, as seen in our patients, is possible when donors are from regions in which those transmissible diseases are endemic. Indeed, several reports have described donor transmission of both malaria and tuberculosis. Management of acute rejection might also be risky at transplant centers with limited availability for monitoring immunosuppressive drug levels or limited tools for diagnostic evaluations. Diagnosis and treatment of surgical complications can be compromised in centers that do not have transplant expertise.

On the basis of our experience, we propose that all patients evaluated and listed for transplantation be offered advice about the risks of transplantation at a center that does not have rigorous oversight or that participates in transplant tourism. The risks include transmission of infectious diseases, transmission of noninfectious donor-related diseases, limited surgical and medical expertise, limited pretransplant evaluations of recipient and donor, and limited postoperative follow-up at the transplanting center. In addition, the ethical issues involved in the practice of transplant tourism should be discussed with the patient. The selection of donor and recipient pairs may be compromised to the detriment of both donor and recipient. These centers might also have limited ability to care for their complications or adverse outcomes such as acute rejection. Patients should be informed in an open, nonjudgmental manner so as to maintain their trust and maintain the relationship between the physician and the patient.

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If patients pursue organ transplantation at a transplant center that participates in organ trafficking, the patients should be encouraged to return to their physician when they get back to the United States and be monitored for potential medical and surgical complications. It must be noted though that some transplant physicians may not be willing to provide care for patients who received an organ through transplant tourism.

References