Case Reports

Successful Renal Transplantation in Patients with Chronic Granulomatous Disease

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Chronic granulomatous disease (CGD) is a genetic disease caused by structural mutations in the enzyme NADPH oxidase that results in severe immunodeficiency. End-stage renal disease occurs in this patient population, and is often attributed to the necessary use of nephrotoxic anti-infectives. In this report, we present the experiences of two centers in transplantation of three patients with CGD: one transplanted with CGD, one cured of his CGD with bone marrow transplantation and who subsequently underwent kidney transplantation and one that received a kidney transplant prior to being cured of CGD via a sequential peripheral blood stem cell transplant (SCT). Each is unique in respect to pre-transplant disease status and underlying comorbidity. All three recipients have enjoyed excellent outcomes. Their courses demonstrate the absolute requirements for a multidisciplinary and compulsive approach before, during and after transplantation. These case reports also highlight the unexpectedly benign course of immunosuppressive therapy in this patient population.

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Introduction

Chronic granulomatous disease (CGD) is caused by one of several mutations that structurally alter the enzyme NADPH oxidase (1). The resulting phenotype is one of the immunodeficiency with affected individuals having serious recurrent bacterial and fungal infections and inflammatory granulomas. In this patient population, we have observed end-stage renal disease in approximately 3% of patients. The etiology is often multifactorial, attributed to the necessary use of nephrotoxic anti-infectives. Additionally, nephrotic range proteinuria may occur, and native renal kidney biopsies have demonstrated a variety of histologies including focal segmental glomerulosclerosis, membranous glomerulopathy (unpublished observations), chronic glomerulonephritis (2) and Henoch-Schonlein nephritis (3). Regardless of etiology, renal replacement therapy is required in many patients, and the occurrence of chronic life-threatening opportunistic infections would suggest that immunosuppression and renal transplantation would be contraindicated. A review of the literature has demonstrated only one other opportunity for renal transplantation in a patient with CGD, and in that case, the patient subsequently developed amyloidosis leading to graft loss at 66 months post-transplant (4).

In this report, we present the experiences of two centers in transplantation of three patients with CGD: one transplanted with CGD, one cured of his CGD with bone marrow transplantation and who subsequently underwent a kidney transplant and one patient that received a kidney transplant prior to being cured of CGD via a sequential peripheral blood stem cell transplant (SCT). Each is unique in respect to pre-transplant disease status and underlying comorbidity. All three recipients have enjoyed excellent renal function and outcomes and demonstrate the absolute requirements for a multidisciplinary and compulsive approach before, during and after transplantation. These case reports also highlight the unexpected benign course of immunosuppressive therapy in this patient population, and are the first reported in the English literature.

Case 1

RM was diagnosed with CGD, p47phox deficiency subtype, at age 10 months and presented to the National Institutes of Health at age 7 years. Associated with his primary diagnoses were multiple infections with atypical fungal and bacterial species, including Paecilomyces variota and Aspergillus fumigatus pneumonia necessitating prolonged treatment with amphoterin B and eventual pneumonectomy. He suffered severe hidradenitis suppurativa with hypertrophic granulation tissue, bacterial peritonitis and osteomyelitis. His chronic antimicrobial...
prophylaxis included itraconazole, vancomycin and trimethoprim/sulfamethoxazole. At age 15, he developed nephrotic range proteinuria (12 g/24 h). Renal biopsy revealed findings consistent with focal segmental glomerulosclerosis, with tubulointerstitial nephritis, moderate arteriosclerosis and severe nephrocalcinosis (the latter likely due to chronic drug toxicity). By February 2001, his creatinine clearance was 12 mL/min. Prior to initiation of dialysis, he presented for consideration for renal transplantation. At that time it was felt that the lack of data regarding transplantation in the CGD patient was a potential barrier to a successful outcome and that the patient would do better to optimize his renal status via dialysis.

The patient began peritoneal dialysis at age 19 which he tolerated poorly due to chronic anorexia, nausea and emesis, resulting in persistent weight loss and failure to thrive. He developed secondary hyperparathyroidism requiring total parathyroidectomy and autotransplantation. Given his progressive deterioration on dialysis, transplantation was reconsidered at age 21.

At the time he presented for transplantation, the patient was chronically ill appearing young man with multiple hypertrophic and purulent skin lesions. Laboratory analysis showed a serum creatinine of 12.8 mg/dL and BUN of 95 mg/dL. He had modest persistent hyperparathyroidism, hyperphosphotemia and hypocalcemia. A living unrelated donor was identified. Both the donor and recipient were counseled regarding the uncertain nature of the proposed transplant. Specifically, the requirement for lymphocyte directed immunosuppression combined with known neutrophil dysfunction was highlighted as having a potential for lethal immunoincompetence. Both the donor and recipient were enrolled in an Institutional Review Board approved Compassionate Exemption Protocol to facilitate informed consent.

In July 2003, RM underwent a technically uneventful living unrelated renal transplant. The patient received daclizumab induction, 2 mg/kg at transplant followed by 1 mg/kg every 2 weeks for five doses, and was maintained postoperatively on tacrolimus (trough blood levels 8–12 ng/mL), mycophenolate mofetil (MMF; 1 gtwice daily) and tapering doses of prednisone. In addition, he received viral, bacterial and fungal prophylaxis with acyclovir, 400 mg twice daily; trimethoprim/sulfa 800/160 mg, one twice daily and itraconazole, 100 mg daily. His postoperative recovery was complicated by drug induced hepatotoxicity attributable to cytochrome P450 CYP3A4 metabolized drugs including itraconazole and tacrolimus. A liver biopsy at that time revealed an overall pattern of cholestatic hepatitis but failed to implicate any specific drugs. Itraconazole, acyclovir and tacrolimus were discontinued and he responded appropriately to drug dose reduction. The patient tolerated gradual reintroduction of all his prophylactic and immunosuppressive medications although he continued to have chronic modest elevation of his liver enzymes.

This drug toxicity episode temporally preceded a borderline acute cellular rejection that was managed without bolus steroids but rather by re-establishment of therapeutic tacrolimus levels. Eventually, he was maintained on prednisone, 5 mg every other day; tacrolimus, 1 mg daily (leading to 24-h trough levels of 4 ng/mL due to coadministration of itraconazole) and MMF 500 mg twice daily. Over the ensuing year he returned to school full-time, gained weight and did not need to be hospitalized at any time for infection. Interestingly, his skin lesions improved markedly. At 1 year post-transplant, a protocol biopsy showed no evidence of rejection. His serum creatinine at that time was 1.2 mg/dL. At 603 days post-transplant, he was admitted to our service for an episode of acute rejection associated with tacrolimus levels of 1–2 ng/mL. This was managed with an increase in his immunosuppression to include prednisone 5 mg daily, tacrolimus 1 mg twice daily, MMF 1000 mg twice daily and a 1-week course of IVIG. Coincident with this hospitalization he was found to have a pneumonia that was successfully treated with IV ceftriaxone and linezolid. This was present on admission for the rejection episode and was not related to increased immunosuppression for the rejection. At the time of discharge, his serum creatinine was 1.5 mg/dL.

Case 2

GS, a 27-year-old male, was followed at the National Institutes of Health since adolescence with an established diagnosis of CGD, p22phox deficiency subtype. Similar to RM, he had multiple severe infections, including fungal pyelonephritis necessitating a right nephrectomy in 1988. He developed contralateral chronic renal insufficiency from multiple courses of amphotericin B. In 1999, he received a SCT from his HLA identical sister, which resulted in complete donor marrow engraftment. While this essentially cured his CGD, he developed chronic graft versus host disease (GVHD), which was chronically treated with cyclosporine and steroids. Attempts to wean him from cyclosporine were unsuccessful and calcineurin inhibitor nephrotoxicity precipitated end-stage renal failure.

He tolerated dialysis poorly, and had worsening of his constitutional symptoms including shortness of breath, nausea and fatigue. He presented for renal transplantation in May 2001 with a calculated creatinine clearance of approximately 12 mL/min. His bone marrow donor was not available to serve as a kidney donor. Again, the decision to proceed with transplantation was accompanied by extensive discussions related to the unknown morbidity associated with transplantation in this setting. He too was enrolled in an Institutional Review Board approved Compassionate Exemption Protocol to facilitate informed consent.

In October 2001, the patient underwent a technically uncomplicated living related renal transplant from a haploidentical sister. At the time of admission, he was taking
cyclosporine 125 mg twice daily and prednisone 2.5 mg, alternating with 20 mg every other day for suppression of his GVHD. He received a modest steroid taper and MMF without a change in his cyclosporine dose. The patient had a postoperative pseudomonal urinary tract infection that responded to oral levofloxacin. Standard antimicrobial prophylaxis included trimethoprim/sulfa 800/160 mg three times weekly, valganciclovir 450 mg daily and nystatin oral suspension four times daily. At discharge, his BUN was 18 mg/dL and creatinine was 0.8 mg/dL. His maintenance immunosuppression was eventually weaned to MMF 500 mg twice daily, cyclosporine 125 mg twice daily and prednisone 10 mg every other day. At present, over 3 years post-transplant, he is clinically stable with a BUN of 7 mg/dL and a creatinine of 1.1 mg/dL. He has not required readmission for opportunistic infection and his GVHD has abated.

Case 3

AA was born in 1966 and until 8 years of age, she experienced only minor infections. At that time, she presented with recalcitrant pulmonary infiltrates. At age 16, she developed anemia and thrombocytopenia, which normalized after splenectomy. At age 19, she presented with a cervical septic lymphadenitis, and CGD was diagnosed. Subsequent testing revealed a p47phox deficiency genotype. Two years later, she developed inflammatory bowel disease, which progressed despite intensive pharmacotherapy and necessitated colectomy 9 years later. At that time hypertensive disease with myocardial and renal impairment became a progressive problem and kidney transplantation was considered.

Her older unaffected sister was found to be HLA- and ABO-identical. After thorough consultation with hematologists, a nephrologist and a transplant surgeon, the patient underwent sequential renal and SCT from her sister. In April 2001, a successful renal transplantation was performed using tacrolimus and MMF. There was immediate graft function without any rejection episodes or post-transplant infections.

Hematopoietic SCT with G-CSF mobilized peripheral stem cells from her sister was performed 4 weeks post-transplant. After conditioning with fludarabine 30 mg/m²/day, days −10 to −5, busulfan 4 mg/kg/d, days −4 and −3 together with rabbit anti-thymocyte globulin (Thymoglobulin®) 2 mg/kg/day, days −4 to −1, 3.3 million CD 34+ cells/kg were given un-manipulated. Immunosuppression with tacrolimus and MMF was continued as prophylaxis against GVHD. The patient’s total white count never dropped below 0.2 × 10⁹/L, platelets never under 100 × 10⁹/L and she was only transfused with 2 units of erythrocytes. Engraftment with ANC >0.5 × 10⁹/L occurred on day +12. The SCT course was uneventful and the patient was discharged on post-transplant day 14 without any signs of GVHD. At the outpatient clinic she received two courses of antiviral treatment for CMV viremia.

Mycophenolate mofetil was discontinued at 3 months post-SCT and tacrolimus was gradually tapered from 11 months and discontinued at 13 months after SCT. At that time she had only 35% donor T cells. Due to threatened stem cell rejection she received 5 × 10⁶ CD3+ cells/kg 13.5 months, and 1 × 10⁶ CD3+ cells/kg 16 months after SCT without side effects. Thereafter she gradually had increasing donor chimerism and is today >99% donor positive in all cell lineages. She developed auto-immune neutropenia with neutrophil specific antibodies against HNA-1b at 22 months after SCT. This is gradually improving without treatment coincident with increasing donor chimerism.

A flow cytometry test for activity of the NADPH oxidase at 3 months after SCT showed completely normal results. She is currently doing well 4 years after SCT, is cured of CGD, has normal renal function, was recently married and is studying to become a nurse.

Discussion

CGD is a rare immune disorder which occurs in approximately 1 in 200 000 live births in the United States (1,5). The primary genetic defect is caused by mutation on one of four genes, the most common being the x-linked gene gp91phox, which is also the most severe form. The three other known mutations p22phox, p47phox and p67phox, are autosomal recessive and tend to lead to clinically less severe disease. The mutation causes a failure of the NADPH oxidase enzyme complex in phagocytic cells to produce adequate reactive oxygen intermediates to promote intracellular killing (6). In addition to the decreased immune response to engulfed organisms, these patients have dysregulation of the inflammatory response which is demonstrated clinically by their tendency to form noncaseating granulomas, manifested in the skin and subcutaneous soft tissues, as well as in the lungs and other viscera. The underlying mechanism of this aberrance is not well elucidated (7).

Patients generally present early in life with recurrent infections of the lungs, skin, soft tissues and abdominal viscera. The majority of these infections are caused by a few catalase-positive organisms including S. aureus, B. cepacia, S. marcescens, Nocardia species and Aspergillus species (8). Many of these infections can be refractory to treatment and life-threatening despite surgical debridement and protracted courses of aggressive antibiotic therapy. Drug-related toxicity from these repeated and often prolonged courses of antibiotics can result in liver failure, pulmonary fibrosis and renal failure. Amphotericin B, a frequently used therapy for Aspergillosis, has known renal impairment in between 7% and 83% of users (9). It tends to be progressive in nature and is dose related. Nephrotoxicity
results from direct tubular injury as well as vasoconstriction caused by amphotericin (10).

One treatment option for CGD is allogeneic bone marrow transplant. While this has the potential to be curative, GVHD and renal dysfunction are not uncommon complications. The incidence of chronic renal insufficiency after bone marrow transplant ranges from 0.8% to 9.5%. This may be due in part to post-radiation nephropathy, thrombotic microangiopathy, immune-complex deposition, previ- ous infections or nephrotic treatments related to other concomitant medical conditions, and in most cases is likely multifactorial.

From the perspective of patient safety, there was ongoing concern for all these three patients that the need for T-cell suppression would result in an unacceptable level of overall immunosuppression in patients with a pre-existing immunodeficiency. In CGD, patients have little to no effective phagocytic cell population. In addition, in GVHD, the immune system appears to be affected with deficiencies in both humoral and cellular immunity. However, this concern has not been borne out over the postoperative course in any patient even when transplantation was performed prior to curative CGD therapy. Of interest, in RM, therapeutic levels of immunosuppression have resulted in a considerable decrease in granuloma formation and a marked improvement in the cutaneous manifestations of the disease. We hypothesize that the etiology of these lesions may best be considered as the result of dysregulated immunity as opposed to immunosuppression per se. Similarly, the addition of MMF to GS’s regimen has substantially reduced his GVHD, and in AA the need for immunosuppression has been eliminated through tolerance. Most importantly, none of these patients has had serious or recurrent infections since transplantation.

The post-transplant immunocompetence of these three patients likely differs. RM has clearly demonstrated an ability to mount an allograft rejection on two occasions, thus the lesion of CGD does not appear to alter the allogeneic response substantially. Conversely, patients that have received bone marrow transplants and proceeded to renal transplantation from a donor other than their bone marrow donor infrequently reject suggesting that allograft immunocompetence is less robust following bone marrow transplant (11,12). Consistent with this, GS has not had a rejection episode. In AA, the ideal situation of tolerance has been achieved as it is known to occur after a tolerated bone marrow transplant (13). However, unlike most reported cases, in this case the marrow replacement was gradual due to the reduced intensity conditioning and followed the renal transplant.

The prior literature has reported only one case involving organ transplant in a CGD patient (4). There is no reference in this Spanish report as to the genetic variant of CGD that the patient possessed. As our patients have had either the p47phox or the p22phox deficiency subtypes, it is not clear whether the results can be extrapolated to other genotypes. Nevertheless, the current report confirms and expands upon the prior report that renal transplantation is possible and perhaps a preferred therapy in patients with CGD.

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