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Case Report

Transplantation and 6-Month Follow-up of Renal Transplantation from a Donor with Systemic Lupus Erythematosus and Lupus Nephritis

Michael S. Schwartzman*, Ping L. Zhang, Santosh Potdar, Sayeed K. Malek, Evan R. Norfolk, J. Edward Hartle, Cristen A. Weicker, Taher M. Yahya and John H. Shaw

Departments of Nephrology, Pathology and Transplant Surgery, Geisinger Medical Center, 100 North Academy Avenue, Danville, PA 17822, USA
** Corresponding author: Michael Schwartzman, msschwartzman@geisinger.edu*

Transplantation of kidneys with pre-existing glomerulonephritis (GN) has rarely been reported. Little is known of the subsequent evolution of donor pathology in the recipient. We report a transplant using a donor with systemic lupus erythematosus (SLE) and a history of remote acute renal failure but normal renal function at death. Although the screening harvest biopsy was unremarkable, time zero post-implantation renal biopsy showed evidence of lupus nephritis (LN). Sequential protocol biopsies demonstrated gradual resolution of the donor pathology, and renal function was stable despite severe cardiac disease in the recipient. Studies examining the role of functional and biopsy data on outcomes in expanded criteria renal transplantation are reviewed, and the limits of guidance from use of this data are discussed. Pre-existing mild GN may not be an absolute donor exclusion for candidates willing to accept expanded criteria donors. Use of expanded pool kidneys should be guided by functional, biopsy and demographic information, as no single factor alone predicts outcome.

Key words: Campath, expanded donor, kidney transplant, lupus nephritis

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Introduction

There were 8528 cadaver renal transplants (CRT) performed in the United States in 2002 (1). Approximately 1100 transplants are performed with kidneys meeting expanded donor criteria annually (2,3). United Network for Organ Sharing (UNOS) website data documents that in the year 2002, 1275 kidneys were recovered and not transplanted. Of these 1275 kidneys, 531 were discarded because of biopsy findings, 212 were discarded because of concerns about low creatinine clearance (CrCl), 151 under the general finding of organ unsatisfactory and another 237 because of either donor medical or social history or other and unknown reasons. UNOS reports that in the year 2002, 858 potential kidney donors were not recovered. Reasons cited for nonrecovery were poor function in 50%, organ unsatisfactory in 11.3%, donor medical or social history in 14.2% and biopsy findings in 1.7%. However, kidneys with mild glomerulonephritis (GN) such as IgA nephropathy are almost certainly occasionally unknowingly transplanted, as these conditions may be asymptomatic and undiagnosed during life and at the time of donor evaluation. Cadaver donor renal biopsy is not routinely performed unless donors meet criteria such as, age over 55 years, diabetes mellitus (DM), hypertension (HTN) or abnormal serum creatinine. When performed, such renal pathologic exams are routinely limited to light microscopy, and may not be interpreted by experienced or specialized renal pathologists. Therefore, it can be presumed that kidneys with mild glomerular disease are transplanted, but at an unknown rate. When glomerular disease is diagnosed in a recipient, it is typically presumed to be de-novo. The natural history of pre-existing GN in the new host is unknown. Even active mild severity GN may resolve once a kidney is transplanted to a host in whom specific immunologic injuries cannot continue.

Case Report

Recipient: A 63-year-old African American male with end-stage kidney disease (ESRD) due to Type 2 DM had been treated with maintenance hemodialysis. Blood type was AB, HLA type was A3, A74, B14, B47, DR1, DR3 and PRA was 0%. Underlying illnesses included atherosclerotic heart disease (ASHD), prior myocardial infarction (MI), cardiomyopathy with left ventricular ejection fraction (LVEF) 30% and depression. Weight was 68 kg. He received hemodialysis uneventfully for 18 months. Pre-transplant evaluation included negative studies for hepatitis B surface antigen, hepatitis B surface antibody, HIV, hepatitis C antibody, CMV IgG and CMV IgM. The patient consented for expanded criteria kidneys and received a CRT on 2/18/04 from a 56-year-old Hispanic female.

Donor: A 56-year-old Hispanic female, blood type A+, HLA A30, B18, B41, DR4, DR17 sustained a CVA and became brain dead on 2/17/04. Past medical history included systemic lupus erythematosus **(**SLE), Type 2 DM, ASHD and coronary bypass grafting, and a previous history of acute renal failure requiring hemodialysis 2 years prior to death. This was attributed to acute tubular necrosis (ATN) from biliary sepsis. There was no history of cytotoxic therapy for lupus nephritis (LN). Maintenance medications included prednisone, aspirin, clopidrogel, glyburide, citalopram and pantoprazole. Two days prior to death, BUN was 23 and serum creatinine 0.8 mg/dL. Glomerular filtration rate (GFR) by formula estimation was 67 mL/min. Routine urinalysis was dipstick negative for protein. Donor was CMV IgG positive. Kidney function was well preserved up to harvesting and there was no documented hypotension. The right kidney was 11.0 cm × 6.4 cm, and the left kidney 11.2 cm × 6.5 cm. Biopsies were obtained from each kidney at the time of harvest and were interpreted by the harvesting hospital pathologist on call. The right kidney tissue showed that 1/25 glomeruli were globally sclerosed. There was no evidence of ATN, interstitial fibrosis or GN. The left kidney showed 5/40 glomeruli were globally sclerosed, and there was evidence of interstitial inflammation and fibrosis interpreted as mild chronic interstitial nephritis. The right kidney was used for transplantation, but the left kidney was discarded. Review of the renal biopsy at the transplant center showed focal proliferative LN (Figure 1A). The tissue was prepared for electron microscopy (EM) by transferring from the formalin fixed paraffin block into 3% glutaraldehyde for 48 h. After fixation, the tissue was post-fixed in osmium tetroxide, embedded in resin, then sectioned and stained with uranyl acetate and lead citrate. EM findings included moderate amounts of electron dense mesangial deposits, and occasional large but scattered subendothelial deposits. Rare intramembranous deposits were identified (Figure 1B).

Post-transplant: The allograft warm ischemic time was 45 min and the cold ischemic time was 12 h and 15 min. The patient received induction with Campath-1H 30 mg and methylprednisolone 1000 mg intravenously (IV) day 1, and was begun on prednisone 20 mg daily plus tacrolimus. The patient did not require dialysis post-transplant. Serum creatinine began to decline on day 5 and achieved a nadir of 1.5 mg/dL on day 70 post-transplant. Prednisone was tapered to 5 mg daily by week 8 post-transplant. On day 150 and 151 the serum creatinine was 1.6 and 1.7 mg/dL corresponding to calculated GFR of 49 and 46 mL/min. A protocol biopsy was performed on day 21 and again on day 100 post-transplant. The patient was treated for serious ventricular arrhythmias on day 120 post-transplant and was found to have sustained further reduction in cardiac function with fall in LVEF to 20%. He was treated for congestive heart failure on several occasions.

Renal pathology day 21: Eight glomeruli were identified, of which none showed global or segmental sclerosis. Mild mesangial expansion and mild mesangial cell hypercellularity were observed, as well as focal proliferation (Figure 1C). There were no crescents or segmental necrotizing features. Focal mild interstitial fibrosis, and tubular atrophy were seen. Features of mild residual tubular cell injury including diminished brush borders and tubular dilation were present. Immunofluorescence (IF) staining showed granular capillary loop staining for IgG 3+, IgA 1+, IgM 1+, C3 3+, C1q 2+, lambda 2+ and kappa 2+. By EM, mesangial and rare subendothelial deposits were identified (Figure 1D), but these appeared less significant than in the pre-transplant biopsy. These changes were consistent with improving World Health Organization (WHO) Class 3 LN.

Renal pathology day 100: Glomeruli were not identified in the routine H&E sections. Tissue from the EM blocks cut at 1 μm and stained with toluidine blue revealed minimal mesangial expansion, but no focal proliferation (Figure 1E). On IF staining, IgG was 2+, IgM was 1+, IgA was negative, C3 2+, C1q 1+, kappa 2+ and lambda 2+; overall the intensity of staining was less than that was on day 21. EM evaluated four glomeruli. There was no foot process effacement, proliferation or crescent formation. Scattered mesangial and rare subendothelial deposits were observed, fewer in number than on the previous biopsy (Figure 1F). These changes were consistent with resolving WHO Class 3 LN.

Discussion

Expanded donor criteria include donor age >60 years, donor age >50 plus creatinine >1.5 mg/dL or donor age >50 plus HTN and death by stroke (CVA). Other categories of donor kidneys for which concern about long-term outcomes exists includes donors with ATN and previously normal renal function, kidneys with prolonged cold ischemia time, nonheart beating donors, donors with DM and donors with Stage 1 (GFR > 90) or mild Stage 2 (GFR 60–90) chronic kidney disease (CKD).

Over a 14-month period from late 1999 to 2001, UNOS reported outcomes at 1 year for 3444 harvested kidneys in which renal biopsies were performed as part of the evaluation of suitability for transplantation (2). Of these kidneys, the most frequent reasons cited for nonuse were biopsy findings (38%) followed by poor organ function (14.8%). Biopsy reports included information about % glomerular sclerosis (GS), with no data regarding interstitial fibrosis, arteriolar hyalinosis or arteriosclerosis. Biopsy needle gauge and number of glomeruli per biopsy sample were not known, and IF and EM were not performed in this setting. Higher % of GS were correlated with female sex, death from CVA and age over 60 years. HTN and CrCl under 80 mL/min were correlated with GS > 20% as opposed to GS <20%. Of 860 kidneys discarded for issues of either high % GS or CrCl <80 mL/min, 129 kidneys actually had either CrCl > 80 mL/min or GS <20%. Specific renal

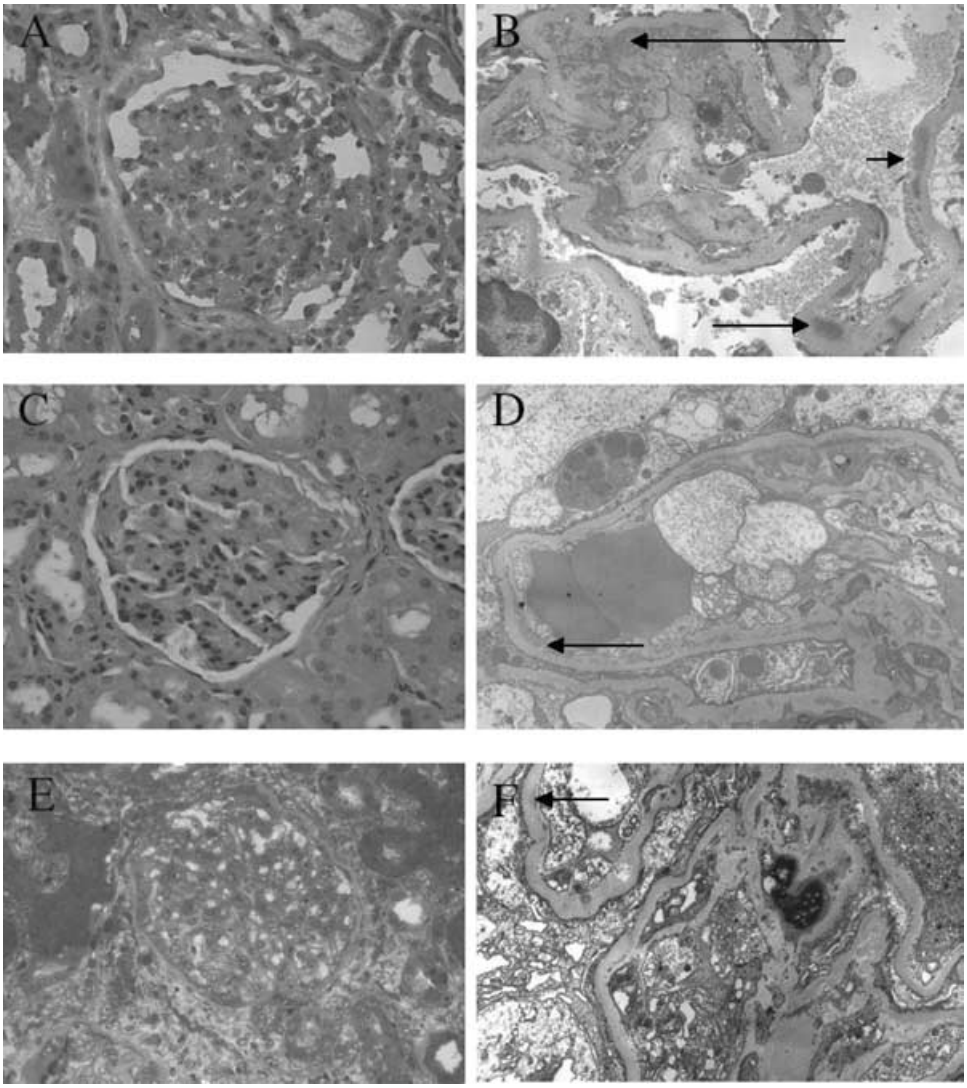

Figure 1: Prior transplant biopsy—frozen section tissue for light microscopy (HE, 400×) (A) and electron microscopy (EM, 3000×) (B); The first post-transplant biopsy—light microscopy (HE, 400×) (C) and electron microscopy (EM,3000×) (D); The second post-transplant biopsy—light microscopy (Toluidine blue stain on thick section of EM, 400×) (E) and electron microscopy (EM, 3,000×) (F).

diagnosis on these patients with Stage 1 or Stage 2 CKD was not established or reported from the limited biopsy information obtained at harvesting. In this study, % GS alone was not predictive of 1-year transplant outcomes, whereas % GS combined with CrCl at harvest did correlate with 1-year functional outcomes.

In another study (4), donor wedge biopsies were performed on either one or both kidneys prospectively in a series of 200 donors between 1993 and 1996. Follow-up of 387 recipients in total and 228 biopsied kidneys was available. A single pathologist graded the severity of GS, tubulointerstitial fibrosis and arteriolonephrosclerosis. Twenty-seven percent of donors were older than 50 years. Thirty-six percent of donors died of CVA. The single strongest predictor of short- and long-term function was donor age. Higher degrees of GS on biopsy were associated with lower functional outcomes, but % GS was not a significant predictor of either short- or long-term graft survival or graft function when donor age was factored in the multivariate regression analysis.

A study by Karpinski et al. (5) examined outcomes of expanded criteria CRT as a function of both biopsy findings and donor CrCl. Sixty-five donors meeting expanded criteria and in which biopsies were performed after 1994 were included. Biopsies were reviewed by renal pathologists, and graded for severity of GS, interstitial fibrosis, tubular injury, hyaline arteriolosclerosis and arterial sclerosis. Outcomes were compared to an age and disease matched cohort of normal donor CRT recipients. One-year graft and patient survival did not differ in recipients of expanded or normal pool kidneys. Both DGF and rejection were more frequent in recipients of expanded criteria kidneys. CrCl was lower in recipients of expanded donor kidneys at all time points. Higher scores for donor pathology were correlated with more DGF and lower CrCl. Vascular pathology showed the highest correlations with DGF and lower

CrCl, and was more predictive than % GS. Interestingly, CrCl <100 mL/min vs. >100 mL/min was not predictive of donor biopsy pathology. The combination of CrCl <100 mL/min and vascular pathology score of 3 (severe) was most predictive of lower function at 1 year.

Escofet et al. (6) reported on biopsy findings and long term followup in 210 CRT from which wedge renal biopsies were available at the time of implantation. 129 of 210 biopsies showed 0% GS, 42 of 210 showed 0.1–10% GS, 22 of 210 showed 10.1–20% GS and 17 of 210 showed >20% GS. In this study, only 33% of all donors were aged >55 years. Interestingly, 43% of donors over age 55 years had 0% GS. Thirteen percent of donors under age 55 had >10% GS. All kidneys were used for transplantation. Long-term allograft function was highly correlated with % GS and with acute rejection episodes, but not with donor age or DGF. Their model showed that a 10% increase in GS had the same effect on allograft function as one episode of acute rejection, or a 30-year increment in donor age.

Approximately 40% of kidneys from donors over age 55 years undergo biopsy (2), whereas younger donors are rarely subjected to biopsy. Normal creatinine may mask mild CKD; serum creatinine may be normal owing to hyperfiltration in the presence of mild structural renal disease. Left–right discordance of biopsy findings was present in 43% of patients in the UNOS study (2), with sampling issues raised in this regard. Sampling issues occasionally cloud interpretation of biopsy results, particularly when a high GS score is found in a donor with normal CrCl and second samples reveal lower GS scores. Biopsies from scar or otherwise nonrepresentative areas do occur and may result in nonuse of otherwise acceptable kidneys. Therefore, current biopsy use guidelines may result in underreporting of CKD in younger donors, and potentially overestimate disease severity in older donors.

Despite the risks of sampling error, donor biopsies can provide a useful context for interpreting pathology in post-transplant biopsies performed either by protocol or for changes in allograft function. D'Agati and Cohen (7) suggested that donor biopsies may become the 'standard of care' for assessment of the suitability of kidneys for transplantation and estimation of functional potential. The universal use of donor biopsies is likely to reveal more frequent but milder donor pathology than is currently known to be present. There is currently no evidence base for guidelines on assignment of kidneys with mild pathology, and certainly no guidelines for the use of donor kidneys with mild GN.

An extensive review of the literature reveals only rare reports on kidney transplants involving the use of donors with pre-existing GN. We reviewed a case report summarizing the use of kidneys from a donor with a history of LN for two recipients (8). Five years prior to death, a 26-year-old female with SLE had WHO class IV/V LN. After treatment, the patient entered remission, and was free of clinical evidence of active LN until her death. At the time of death, the serum creatinine was 0.6 mg/dL. A donor light microscopic evaluation revealed no evidence of LN, with 0/13 glomeruli showing sclerosis. Nevertheless, EM evaluation revealed both subepithelial and mesangial deposits, and IF showed full house immunoglobulins to be present. Final donor biopsy result was WHO class II/V LN. In one recipient, biopsy at week 7 showed significant decreases in the intensity of the IF staining, and by 3 years, there was no residual evidence of persistence of any features of LN. In the other recipient, no biopsies were performed, but stable 3-year function with absence of proteinuria and hematuria were reported.

Suzuki et al. (9) investigated the background incidence of IgA nephropathy in kidney donors in Japan. A prospective series of donor biopsies was performed between 1992 and 1999 in Tokyo. Five-hundred-ten of 561 consecutive donor kidneys underwent 0-h biopsy (447 living and 64 cadaveric). Sixteen of 510 or 3.1% had both mesangial IgA and C3 deposits. Of these, eight exhibited minor glomerular abnormalities, whereas five showed focal and three diffuse proliferative GN. An additional 66 patients had IgA deposits without C3 deposition; of these, 5 showed focal and 1 diffuse proliferative GN, whereas 55 showed only minor glomerular abnormalities. Thus, 2.7% (14 of 510) of transplants were performed from donors with significant and previously undiagnosed IgA nephropathy despite usual donor evaluations.

Thin basement membrane nephropathy (TBMN) is a relatively common genetic disorder, which may be present in donor kidneys. The frequency of this finding varies with the definitions of TBMN and normal range for GBM thickness. In some cases TBMN may represent an early stage of Hereditary Nephritis. Steffes et al. (10) studied 118 kidney donor biopsies for GBM thickness by EM. Mean GBM thickness for 59 females was 326 nM, and for 59 males was 373 nM. Twenty-one of 118 kidneys had GBM thickness <300 nM, consistent with TBMN range. Of these, 21 of 23 were females. Microscopic hematuria is more common in females, probably owing to having normally thinner GBM. Dische (11) measured glomerular basement membrane thickness in a variety of kidneys including 41 donor nephrectomy biopsies, defining TBMN range as <330 nM. Two of 41 donors exhibited GBM thickness consistent with TBMN. GBM thickness in clinical TBMN varied from 206 to 335 nM, with a mean = 296 nM (11). Dische (12) also reported another series of 76 kidney donors, in which 7.5% (5 of 76) had TBMN defined as GBM thickness <330 nM and 1.4% (2 of 76) possible TBMN based on GBM thickness between 330 and 340 nM.

The patient who is the subject of this report has a very good short-term outcome despite severe recipient cardiac disease using a kidney from a donor with LN. The mate kidney from this pair was rejected for based on the donor

history and the biopsy finding of 20% GS. Sequential post-transplant biopsies demonstrated regression of the donor pathology, and renal function was acceptable and stable.

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