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En Bloc Cadaver Kidney Transplantation From a 9-Month-Old Donor to an Adult Recipient: Maturation of Glomerular Size and Podocyte in the Recipient

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Background. Favorable outcomes of en bloc pediatric donor kidney transplantation to adult recipients are attributed primarily to grafting of twice the nephron mass of a single kidney. **Methods.** The kidneys of a 9-month-old male infant were transplanted en bloc in a 56-year-old man. Biopsies were performed 1 hour postreperfusion, 6 months and 3.5 years posttransplant. **Results.** Warm and cold ischemia times were 21 and 426 minutes, respectively. The recipient was released from hemodialysis 10 days posttransplant and discharged 91 days posttransplant when serum creatinine was 0.9 mg/dL. At 4 years and 9 months posttransplant, serum creatinine was 1.0 mg/dL, and estimated glomerular filtration rate was 58.0 mL/min per 1.73 m^2. The grafts increased in size until they reached adult size by 3 months posttransplant. The glomerular area and volume, respectively, increased from 5.9×10^3 μm^2 and 0.34×10^6 μm^3 at 1 hour postreperfusion to 14.9×10^3 μm^2 and 1.27×10^6 μm^3 at 3.5 years posttransplant, both of which were less than half of adult size. At 1 hour postreperfusion, podocytes were structurally immature. At 6 months posttransplant, podocyte immaturity was still evident. At 3.5 years posttransplant, podocytes were mature. **Conclusions.** These findings suggest that podocytes and glomerular size of pediatric donor kidneys can continue to mature in adult recipients at rates appropriate for donor age when transplanted en bloc. The maturational levels of podocytes and glomeruli may also be a factor involved in favorable outcomes of en bloc pediatric donor kidney transplantation.

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There is a worldwide shortage of kidneys for transplantation. The use of cadaveric pediatric donor kidneys is a potential approach to expand the donor pool. Early attempts of kidney transplantation from a pediatric donor to an adult recipient yielded variable outcomes, influenced by donor age or weight, and the use of either single-kidney or en bloc approach.[1,2] Over the last 2 decades, the outcomes of cadaveric pediatric donor kidney transplantation have significantly been improved, owing in part to the active practice of en bloc transplantation.[3] Recent single-center and multicenter series have reported long-term graft survival or function of en bloc pediatric donor kidneys either comparable or superior to single-kidney transplants or living adult donor kidneys.[4-11] Favorable outcomes of en bloc pediatric donor kidney transplantation are attributed primarily to grafting of a larger renal volume and twice the nephron mass of a single kidney.

We performed en bloc cadaver kidney transplantation from a 9-month-old infant to an adult recipient. We report biopsy findings up to 3.5 years posttransplant and discuss their significance in the context of literature.

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T.H. performed transplantation, biopsies and clinical care, analyzed the findings, and wrote the article. H.S. assisted Dr. Hirukawa in transplantation, biopsies, clinical care, and data analysis. F.N. a pediatric nephrologist, interpreted biopsies with particular attention to podocyte structure and assisted Dr. Hirukawa in reviewing literature. M.F. supervised the entire process until article submission. T.K. was the immediate supervisor of Drs. Hirukawa and Suzuki. He supervised transplantation, clinical care and data analysis, laid out the blueprint of the article structure and edited the article. All authors have approved the submitted version of the article.

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CASE DESCRIPTION

Donor

The donor was a 9-month-old male infant with an estimated weight of 8 kg who died from acute epidural hematoma caused by head injury. There was no other significant organ injury.

Recipient

The recipient was a 56-year-old man who was 170 cm tall and weighed 60 kg. At 28 years of age, he developed proteinuria and started outpatient visits with a diagnosis of chronic glomerulonephritis of unknown cause. At 41 years of age, his conditions reached end-stage renal failure, and hemodialysis was introduced. At 56 years of age, he became the number one candidate on the kidney transplantation waiting list and was hospitalized at the Tokai University Hospital, Isehara, Japan. There were 2 HLA mismatches.

As for nonrenal episodes, he had tuberculous peritonitis at 40 years of age. At 55 years of age, he had angina pectoris and underwent percutaneous coronary intervention with a drug-eluting stent indwelled in the left anterior descending coronary artery. He was a type C hepatitis virus carrier with unknown route of infection.

Transplantation

Both kidneys were retrieved en bloc, and the proximal ends of the abdominal artery and inferior vena cava were oversewn. The distal ends of the abdominal aorta (6 mm long) and inferior vena cava (6-7 mm long) were anastomosed end-to-end to the external iliac artery and vein of the recipient, respectively, in the right iliac fossa. The donor ureters (10 cm long) were anastomosed to the recipient bladder according to Politano-Leadbetter ureteral reimplantation procedure using 4.8-French double-J stents. Surgery was completed without applying excessive pressure on the grafts or blood vessels. Warm ischemia time was 21 minutes, and cold ischemia time was 7 hours and 6 minutes. Biopsy was performed 1 hour after reperfusion.

Postoperative Clinical Course

Immunosuppressant therapy consisted of cyclosporine, basiliximab, mycophenolate mofetil, and methylprednisolone. Targeted trough of cyclosporine was 150 to 250 ng/mL for the initial 1 month, 100 to 150 ng/mL in the subsequent 2 to 3 months, and less than 100 ng/mL thereafter.

The first urine output occurred 7 days posttransplant. The recipient was released from hemodialysis 10 days posttransplant. Later, the recipient developed low bladder capacity-associated reflux urinary tract infection and had a urine leak from the ureterovesical anastomosis sites. These conditions were improved by ceftazidime administration and catheter indwelling, respectively.

Serum creatinine was 10.1 mg/dL on the day of transplantation (Figure 1A). At 91 days posttransplant, serum creatinine was 0.9 mg/dL (Figure 1A), and the recipient was discharged from the hospital.

Postdischarge Clinical Course

Blood pressure was well controlled with 20 mg olmesartan per day. Protocol renal biopsy was performed at 6 months posttransplant.

Around 3.5 years posttransplant, serum creatinine was 0.9 to 1.3 mg/dL (Figure 1A), and estimated glomerular filtration rate (eGFR) (according to the Modification of Diet in Renal Disease equation modified for Japanese[12]) was 45.4 to 68.6 mL/min per 1.73 m^2 (Figure 1B). Because cyclosporine trough was slightly high at 140 to 160 ng/mL, biopsy was performed for differential diagnosis of immunosuppressant-induced nephropathy and chronic allograft nephropathy. Because biopsy results suggested immunosuppressant-associated nephropathy and urinary analysis showed no signs of rejection, the immunosuppressant dose was adjusted. Since then, renal function was stable with a serum creatinine of 1.0 to 1.2 mg/dL (Figure 1A) and eGFR of 49.8 to 58.0 mL/min per 1.73 m^2 (Figure 1B).

At 4 years and 9 months posttransplant, serum creatinine was 1.0 mg/dL (Figure 1A), and eGFR was 58.0 mL/min per 1.73 m^2 (Figure 1B).

Graft Size

The graft size was periodically determined by ultrasonography. An increase in size was apparent 15 days posttransplant (right kidney, 77 × 39 vs 58 × 31 mm 2 days posttransplant; left kidney, 80 × 43 vs 67 × 38 mm 2 days posttransplant). The size reached about 10 × 5 cm 3 months posttransplant (right kidney, 100 × 45 mm; left kidney, 101 × 53 mm) and remained stable upon the last determination at 24 months posttransplant (right kidney, 101 × 44 mm; left kidney, 99 × 52 mm).

Biopsy Findings

Biopsies were performed 3 times in the upper areas of the right kidney using a 16G needle, and 4-μm sections were examined with periodic acid-Schiff staining.

The first biopsy was performed 1 hour after reperfusion, and 35 glomeruli were identified. The glomerular planar area (mean ± SD) was 5.94 ± 2.17 × 10^3 μm^2 (Figure 2). The glomerular volume determined by the Weibel-Gomez method[13,14] was 0.34 × 10^6 μm^3 (Figure 2). Glomeruli showed no injury (Figures 3A and B). Visceral epithelial cells were cuboidal and lined more than half of the circumference of the glomerular tuft (Figure 3A). Some tubular epithelial cells showed turbidity and enlargement, and some had detached from the basement membrane (Figure 3B).

The second biopsy was performed at 6 months posttransplant and 21 glomeruli were identified. The glomerular planar area (mean ± SD) was 9.43 ± 4.08 × 10^3 μm^2 (Figure 2A). The glomerular volume was 0.69 × 10^6 μm^3 (Figure 2B). Glomeruli showed no injury (Figure 3C). About half of the circumference of the glomerular tuft was lined with cuboidal visceral epithelial cells, and adjoining of more than 5 visceral epithelial cells was evident. Interstitial infiltration and tubular atrophy were observed (ci2 and ct2, respectively, by the Banff classification; Figure 3D). No tubulitis, glomerulitis, or intimal arteritis was recognized.

The third biopsy was performed at 3.5 years posttransplant, and 11 glomeruli were identified. The glomerular planar area (mean ± SD) and volume were 14.18 ± 6.64 × 10^3 μm^2 (Figure 2A) and 1.27 × 10^6 μm^3 (Figure 2B) both of which were less than half of that of adult glomeruli (32.27 ± 4.44 × 10^3 μm^2 and 4.35 × 10^6 μm^3, respectively; Figure 2). Glomeruli showed no injury (Figure 3E). There was no podocyte layer surrounding the tuft. Some arteriolar hyalinosis

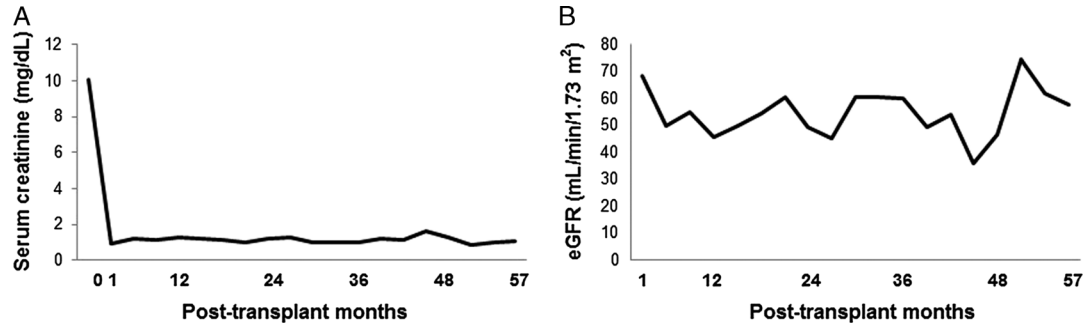

FIGURE 1. Posttransplant serum creatinine and eGFR. A, Serum creatinine was determined on the day of transplantation (posttransplant month 0) and up to 57 months posttransplant. B, eGFR was determined according to the Modification of Diet in Renal Disease equation modified for Japanese at 1 month posttransplant and up to 57 months posttransplant.

was recognized (ah1 by the Banff classification; Figure 3F). The degree of interstitial infiltration and tubular atrophy were unchanged as compared with the findings seen 6 months posttransplant.

DISCUSSION

We transplanted en bloc the kidneys of a 9-month-old infant in an adult recipient. The clinical course was stable and uneventful throughout 4 years and 9 months of posttransplant follow-up with no proteinuria or a significant reduction in renal function.

The grafted kidneys increased in size and reached adult size by 3 months posttransplant. In general, en bloc pediatric donor kidneys increase in size rapidly in larger recipients.[15,16] Nghiem et al[15] reported a twofold increase in graft volume in 3 to 6 months and a threefold increase in 6 months posttransplant in adult recipients of en bloc kidneys; the donors were 5- to 60-month-old with a mean weight of 10.8 kg, and the recipients had a mean weight of 76.5 kg. Lau et al[16] revealed a greater than 30% increase by 6 months posttransplant in length of en bloc kidneys from 9- to 49-month-old donors in 7.5- to 16.7-year-old pediatric recipients.

The size increase of glomeruli lagged behind the rapid enlargement of the grafted kidneys. The glomerular area and volume increased by 60% and 100%, respectively, in the first 6 months posttransplant. Then, the rates of increase declined to 50% and 84% in the subsequent 3 years to 3.5 years posttransplant when the glomerular area and volume were still less than half of adult size.

Structural maturation of glomeruli was slower than the size increase. Biopsies at 1 hour postreperfusion and 6 months posttransplant revealed that a significant part of the circumference of the glomerular tuft was lined with cuboidal visceral epithelial cells or podocytes, and more than 5 podocytes adjoined. Such structure and disposition of podocytes are characteristics of their immaturity.[17] Thöny et al[17] laid out the criteria that subdivide the postnatal glomerular maturation into 3 stages. Stage 1 is characterized by fully formed glomeruli with at least half of the circumference of the tuft lined with cuboidal podocytes. Stage 2 glomeruli have less than half of the circumference of the tuft lined with podocytes, with at least 5 podocytes adjoining. Stage 3 glomeruli have no podocyte layer surrounding the tuft. According to these criteria, the glomeruli on the present 1 hour postreperfusion biopsy were at stage 1, those on the 6-month posttransplant biopsy were at Stage 2, and those on the 3.5-year posttransplant biopsy were at Stage 3.

The observed glomerular size and structure are normal for the age of the donor who would have been 4 years and

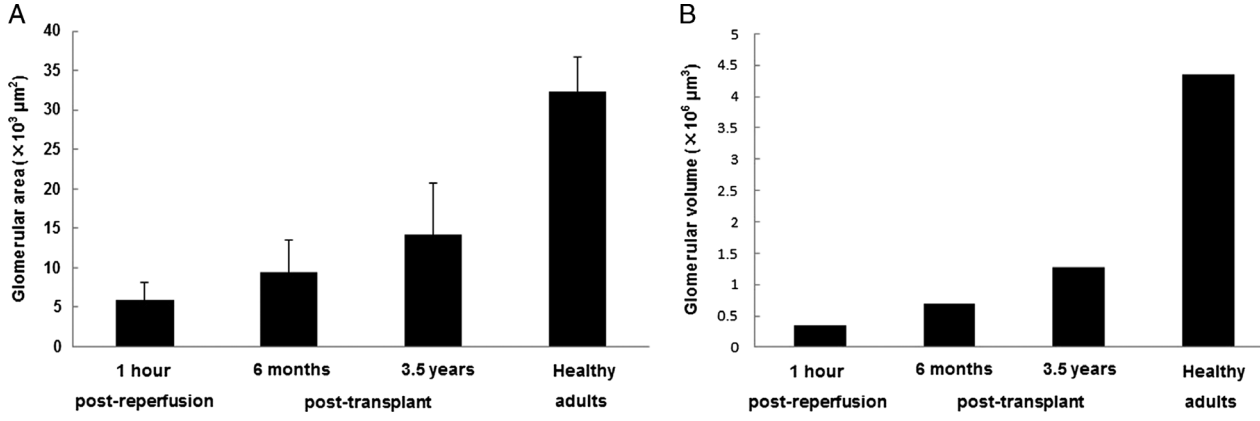

FIGURE 2. Glomerular size. A, The glomerular planar area was determined in μm^2 using WinRoof ver. 7.0.0 imaging analysis software (Mitani Corporation, Tokyo, Japan) in 35, 21, and 11 glomeruli identified on periodic acid-Schiff-stained 4-μm sections of biopsy samples collected 1 hour after reperfusion, and 6 months and 3.5 years posttransplant, respectively. The glomerular area of healthy adults is presented as a reference. Values are mean ± SD. B, The glomerular volume was determined in μm^3 in 35, 21, and 11 glomeruli identified on biopsies sampled at 1 hour after reperfusion, and 6 months and 3.5 years posttransplant, respectively, by the Weibel and Gomez method[12,13] using the formula, glomerular volume = mean glomerular area$^{1.5}$ × (1.38/1.01), where 1.38 is the shape coefficient for a sphere and 1.01 is the size distribution coefficient assuming a 10% coefficient of variation. The glomerular volume of healthy adults is presented as a reference.

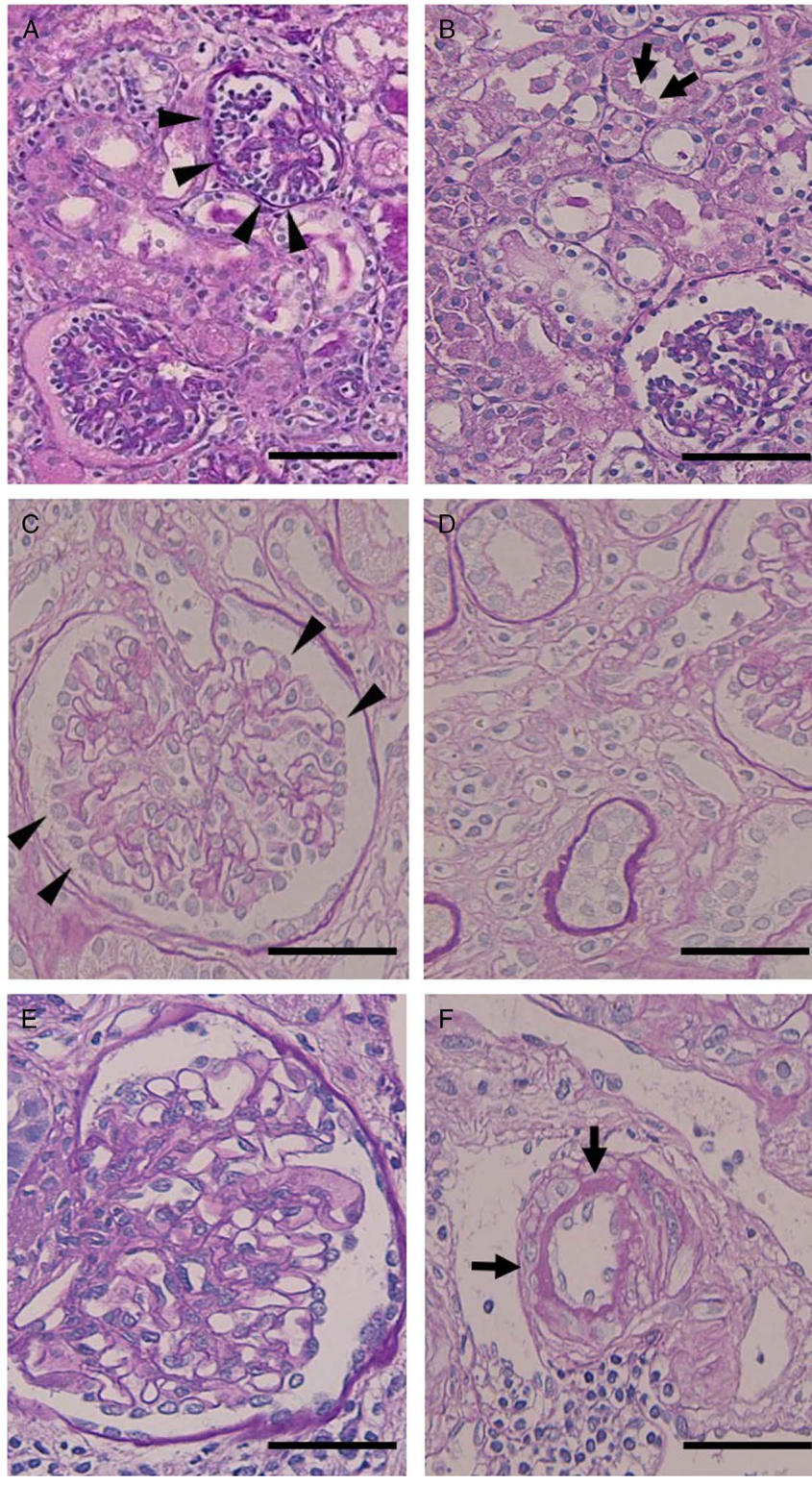

FIGURE 3. Renal biopsy. A, One hour postreperfusion. Visceral epithelial cells are cuboidal and line more than half of the circumference of the glomerular tuft (arrow heads). B, One hour postreperfusion. There are tubular epithelial cell turbidity, enlargement and detachment from the basement membranes (arrows). C, Six months posttransplant. Visceral epithelial cells line about half of the circumference of the glomerular tuft. Adjoining of more than 5 visceral epithelial cells is evident (arrow heads). D, Six months posttransplant. Interstitial infiltration and tubular atrophy are recognizable (ci1 and ct2, respectively, by the Banff classification). E, Three and half years posttransplant. Glomeruli have no visceral epithelial cell layer lining the circumference of the glomerular tuft. F, Three and half years posttransplant. Arteriolar hyalinosis is evident (arrows; ah1 by the Banff classification). Staining was periodic acid-Schiff. Bar represents 50 μm. Magnification, ×200.

5 months of age at 3.5 years posttransplant. Souster and Emery[18] determined the glomerular size in fetuses and infants up to 5 years of age and concluded that glomeruli increase in size immediately after birth and, thereafter, the size increase

slows down, reaching about 12×10^3 μm^2 at 2 years of age. Moore et al[19] extended their observations to 16 years of age and showed that glomeruli continue to increase in size slowly even at this age, noting that the glomerular size correlates better with age than with height, weight or body mass index. Podocyte structure and disposition also continue to change for some time after birth, reaching stage 3 by 25 to 36 months of age.[17] Our biopsies revealed all 3 stages of postnatal glomerular maturation within 3.5 years of posttransplant period. Thus, our findings indicate that glomeruli of the en bloc kidneys from the present 9-month-old donor matured at rates appropriate for donor age rather than in response to the increased workload imposed by the larger recipient.

This is in contrast to the findings of Uemura et al[20] who investigated the growth of glomeruli of pediatric donor kidneys transplanted in adult recipients as single, rather than en bloc, allografts. They reported an increase in the greatest glomerular dimension from 122 ± 8 μm at 1 to 2 months posttransplant to 169 ± 23 μm at 3 to 12 months posttransplant in adult recipients of single-kidney grafts from pediatric donors with a mean age of 27.6 months.[20] These values of glomerular size correspond to those reported by Moore et al[19] for the age of 2 to 3 years and 14 to 15 years, respectively. Glomeruli of pediatric donor kidneys, therefore, have capacity to accelerate their size increase beyond the rate appropriate for donor age when forced by twice as much workload as that of en bloc transplantation.

Such "forced and accelerated" glomerular enlargement in single-kidney pediatric donor transplants may be more similar to accelerated glomerular enlargement in preterm neonatal kidneys[21] than to compensatory glomerular hypertrophy in adult kidneys. In preterm kidneys, glomeruli at various developmental stages are exposed to a dramatic increase in blood flow. Sutherland et al[21] revealed accelerated glomerular enlargement in preterm neonatal kidneys. Mean glomerular area increased in preterm kidneys, averaging over 5×10^3 μm^2 compared with approximately 4×10^3 μm^2 in gestational controls, and was 34×10^3 μm^2 in one oligonephronic neonate.[21] However, the occurrence of glomerular enlargement in preterm kidneys cannot be fully accounted for by reduced nephron mass because preterm kidneys are endowed with as much, if not greater, nephron mass as that of en bloc pediatric donor kidneys. Moreover, the imposed workload is smaller than that in adult recipients. One of the major differences between preterm and pediatric donor kidneys is the maturity of podocytes, the glomerular constituent most sensitive to increased filtration. Podocytes of preterm kidneys are immature and prone to injury when exposed to the birth-associated blood flow increase. Those of pediatric donor kidneys are also immature, depending on donor age. Yet, podocytes of 9-month-old donor kidneys can sustain the higher blood flow in adult recipients without being injured when transplanted en bloc. The podocyte maturational level, therefore, may be another factor that spares glomeruli from injurious "forced and accelerated" glomerular enlargement and later graft loss.

As for the functional capacity of en bloc pediatric donor kidneys, Sureshkumar et al,[6] for example, showed that eGFR was consistently higher in adult recipients of en bloc pediatric kidneys than in those of living adult kidneys throughout 8-year posttransplant period; mean donor age was 16.9 months for pediatric donors and 40.1 years for adult donors. In addition, en bloc pediatric donor kidneys appear to have a greater functional reserve than single adult donor kidneys. Marañes et al[22] compared responses of GFR and plasma flow to intravenous amino acid overload between adult recipients of single adult donor kidneys and those of en bloc kidneys from pediatric donors with a mean age of 17 months. These functional parameters increased in the recipients of en bloc pediatric donor kidneys, but not in those of single adult donor kidneys.[22] In healthy infants, eGFR is about 80 mL/min per 1.73 m^2 at 8 to 12 weeks of age and reaches adult levels by approximately 2 years of age.[23] Thus, the en bloc kidneys from the present 9-month-old donor likely had a filtration capacity not far from that of adult donor kidneys.

In contrast to the natural history of en bloc pediatric donor transplants, the "forced and accelerated" glomerular enlargement in single-kidney pediatric donor transplants can have certain impact on graft survival over time. Studies have reported poorer graft survival of single-kidney pediatric donor transplants in adult recipients than that of en bloc transplants. Bresnahan et al[4] reported that the survival of kidneys from 0 to 5-year-old donors in adult recipients was better with en bloc than with single-kidney transplantation. Pelletier et al[5] showed that the survival in adult recipients of en bloc kidneys from donors less than 21 kg was comparable to that of ideal donors, whereas single-kidney transplants were at an increased risk of graft loss. Kayler et al[7] found that in adult recipients, the survival of en bloc kidneys from pediatric donors weighing 10 to 34 kg was similar to that of ideal standard criteria donor kidneys, whereas the survival of single-kidney transplants from adult donors was comparable to that of nonideal standard criteria donor kidneys. Bhayana et al[9] described that 5-year survival in adult recipients of kidneys from 0- to 5-year-old donors was comparable between en bloc and single-kidney transplants; however, 10-year graft survival was better with en bloc than with single-kidney transplants. Al-Shraideh et al[11] reported that 60-month graft survival was better with en bloc than with single-kidney transplants in adults receiving kidneys from 5-year-old or younger donors.

Recent studies have consistently reported encouraging outcomes of en bloc pediatric donor kidney transplantation.[4-11] In terms of size-mismatch kidney transplantation from very young and small donors to adult recipients, some studies have recommended that the choice between en bloc and single-kidney transplantation be based on donor age,[24-26] donor weight,[10] or relative size of the donor and recipient.[27,28] Hidden behind the age-based recommendations may be the podocyte maturational level of donor kidneys. Cadaver kidneys from a pediatric donor have a potential to benefit 2 individuals. Examination of available posttransplant biopsies may provide key information that helps us find ways to make the best use of precious pediatric donor kidneys.

Biopsies revealed a few lesions. One hour after reperfusion, tubular epithelial cell turbidity and enlargement, and some detachment were observed, indicating the occurrence of acute tubular necrosis. These lesions are likely secondary to ischemia-reperfusion injury that occurs inevitably in kidney transplantation. Protocol biopsy performed at 6 months posttransplant showed occasional interstitial infiltration and tubular atrophy. There was no tubulitis, glomerulitis, or intimal arteritis. These lesions are likely secondary to reflux urinary tract infection because the recipient developed reflux

urinary tract infection prior to this biopsy. At 3.5 years posttransplant, arteriolar hyalinosis was recognized. Arteriolar hyalinosis is most likely a result of chronic calcineurin inhibitor toxicity since cyclosporine trough was slightly high and no immune deposits were apparent.[29,30]

Our biopsy findings have some limitations. We examined limited numbers of glomeruli. Additionally, it is likely that the first biopsy sampled the outer or mid-cortex, whereas the other 2 biopsies sampled the mid-cortex or medulla. The age-dependent patterns of glomerular growth, however, are similar in the cortex and medulla,[18,19] and our biopsies revealed a glomerular growth pattern matching donor age.

In conclusion, our present findings indicate that glomeruli of very young pediatric donor kidneys can maintain glomerular and podocyte maturation at rates appropriate for donor age when transplanted en bloc in adult recipients. The maturational levels of podocytes and glomeruli may be one of the factors underlying favorable outcomes of en bloc pediatric donor kidney transplantation.

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