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Case Report

Structural and Histopathologic Changes in Renal Allografts from an Infant Donor

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Abstract

Prognosis of a renal allograft is dependent on many factors, including but not limited to recipient's age, sex, and size. One underreported finding in an adult patient receiving a pediatric allograft is splitting and lamellation of the glomerular basement membrane, similar to that seen in Alport's syndrome. Histological and ultrastructural changes must be monitored after transplant, and changes can be detected using light microscopy and electron microscopy. These changes are believed to be due to hyperperfusion and high filtration pressures in an immature pediatric kidney. Despite these anomalies, pediatric allografts are comparable to adult allografts in regard to intermediate and long-term prognosis. In this report, we describe the case of a 20-year-old man who received an en-bloc kidney transplant from a 9-month-old female, with resultant hematuria, subnephrotic range proteinuria and glomerular basement membrane changes.

Keywords: Allograft; Alport-like; Hematuria; Pediatric; Renal; Ultrastructure

Introduction

Renal allograft from pediatric donors is an emerging method to increase the organ donor pool for adult patients with end-stage renal disease. The incidence of proteinuria and glomerular damage is higher in adults receiving pediatric donors than vice-versa; however, pediatric donor kidneys have still been found comparable to adult donor kidneys with regards to intermediate and long-term prognosis and graft survival [1]. Adults who received pediatric kidneys < 10 years old had a higher incidence of pediatric donor glomerulopathy, characterized by Alport-like changes in the Glomerular Basement Membrane (GBM) consisting of splitting and lamellation [2].These changes are most commonly seen in Electron Microscopy (EM) analysis of biopsies taken after transplant. De novo post-transplant glomerular disease in pediatric donor kidneys is believed to be related to hyperperfusion injury of the young kidney [3]. In this report, we describe the case of a pediatric kidney donor in an adult recipient that led to Alport-like changes in the GBM.

Case Report

A 20-year-old male with history of end-stage renal disease secondary to bilateral renal hypoplasia received en-bloc bilateral kidneys from a 9-month-old female donor. Immunosuppression with methylprednisolone and alemtuzumab was used. The right kidney was pink and well-perfused, while the left kidney took time to change color, likely due to vasoconstriction. Doppler signal was present after administration of heparin/verapamil injection. After surgical intervention and recovery, the patient was released on belatecept, myfortic, and prednisone. At follow-up 295 days after transplant, serum creatinine was 4.1 mg/dL, compared to baseline of 1.5-2.0 mg/dL. Serum albumin was normal, but urinalysis showed proteinuria (225.2 mg/dL) and 2+ hematuria. Prospera was positive (11.82% dd-cfDNA). A decision was made to perform a renal allograft biopsy. The biopsy showed acute cellular rejection, Banff grade IB, and acute tubular injury. Paraffin

sections stained with H&E, trichrome, and methenamine silver contained renal medulla and cortex with evidence of focal segmental mesangial expansion and hypercellularity (Figure 1). Interstitial inflammatory cell infiltrate of lymphocytes, plasma cells, eosinophils, and rare neutrophils was also noted (Figure 2). There was prominent tubulitis with rare tubular red blood cell casts. Mild interstitial fibrosis was seen. The arteries and arterioles were unremarkable. Direct immunofluorescence was negative except for segmental C3 glomerular staining. EM showed evidence of glomerular mesangial expansion, as well as lamellation of the GBM similar to Alport's syndrome (Figure 3). Some areas of the capillary basement membranes were extremely thin, measuring only 100-140 nm (Figure 4). All basement membranes, including glomerular, peritubular capillary, and collecting tubules were found to be laminated. Despite a history of acute cellular rejection, the patient stated he was doing well and has had no concerns. The patient maintains good hydration and urinates regularly without issue. With treatment, follow-ups have shown reductions in serum creatinine (2.80 mg/dL) and improvement of proteinuria (23.2 mg/dL) and hematuria. A subsequent biopsy performed 2 months later showed improvement of acute cellular rejection. Two of the glomeruli demonstrated segmental sclerotic lesions on light microscopy. Ultrastructurally, the glomeruli examined were unremarkable with no evidence of GBM lamellation.

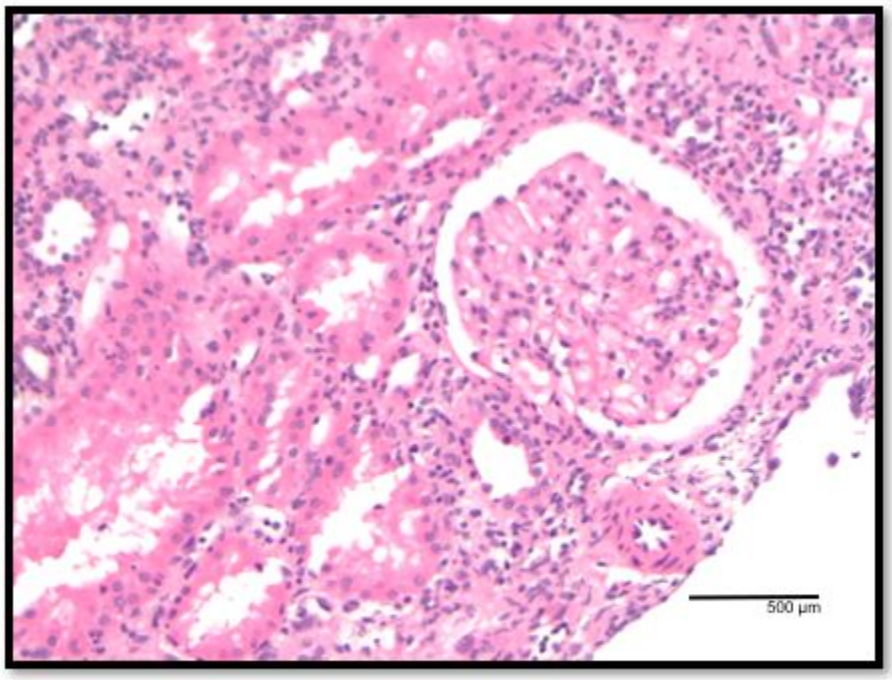

Figure 1. Light microscopy of pediatric renal allograft showing focal segmental mesangial expansion and hypercellularity, as well as prominent interstitial inflammation.

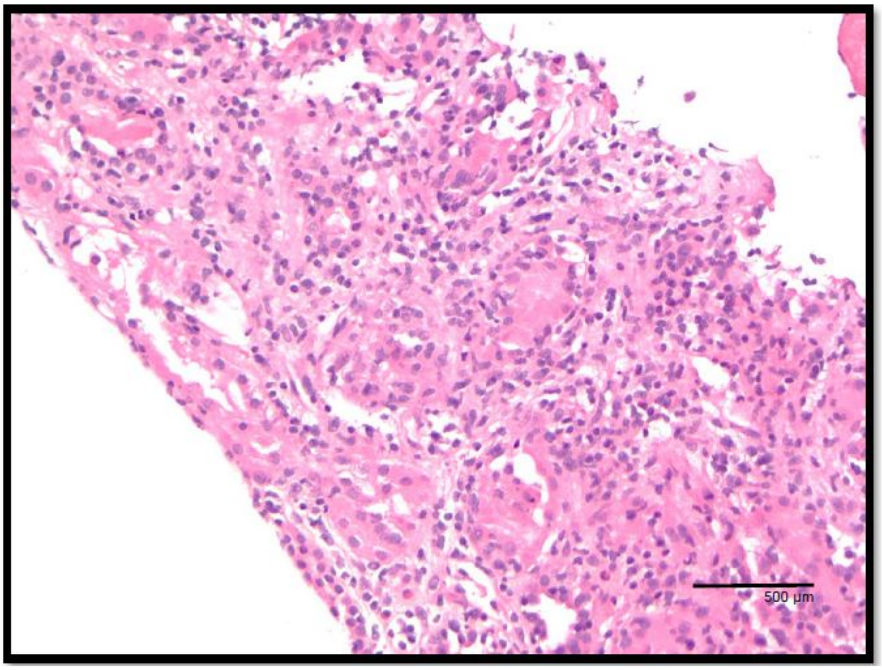

Figure 2. Interstitial inflammation and tubulitis of pediatric renal allograft.

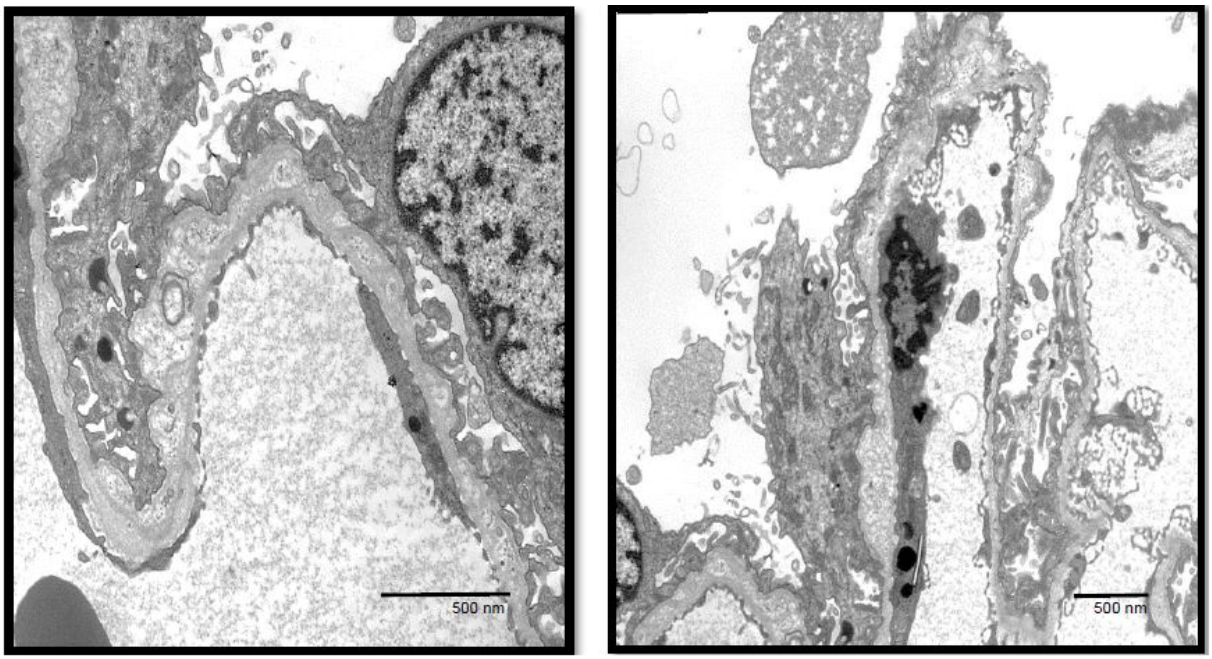

Figure 3. EM of different sites of the GBM with splitting and laminations, similar to that seen in Alport's syndrome.

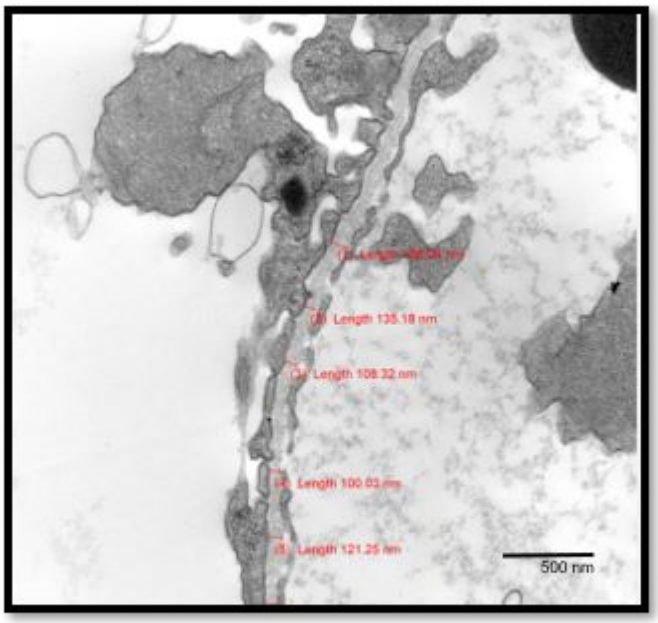

Figure 4. EM of the pediatric allograft 295 days after transplantation, showing extremely thin areas of the GBM.

Discussion

In analysis of renal allograft transplant, decline of kidney function is multifactorial. Potential loss of a renal allograft can include rejection or infection, but more subtle changes may occur in patients who receive an age, sex, or size-mismatched kidney [4]. In this report, we describe the case of a 20-year-old male receiving bilateral en bloc kidneys from a 9-month-old female. Previous studies have shown that although a relatively uncommon occurrence, de novo glomerulopathy post-transplant in older recipients of pediatric donors is not unheard of. Nadasdy et al [3] reported six cases of diffuse irregular lamellation of the GBM from pediatric donors < 6 years old. These changes occurred as early as 10 weeks after transplantation and were accompanied by severe proteinuria and varying degrees of diffuse mesangial expansion. No such findings were found in transplants from adult donors. Similarly, electron microscopy performed by Choung et al [2] found diffuse changes in the GBM in pediatric allografts. Research has shown various events happen after transplantation. In one study, the average GBM thickness at 1-hour post-transplant was significantly thinner in donor-recipient mismatch groups compared to controls. However, at 1-year post-transplant, there was no significant difference in thickness of the GBM between the two groups [5]. Other studies have shown that pediatric allografts increase to adult size by 3 months post-transplant, but glomerular area and volume remain less than half of adult size 3.5 years post-transplant, despite mature podocytes. There are currently several theories as to why such ultrastructural changes occur. Transplantation of the kidney results in denervation and insufficiency of the hemodynamic autoregulation system, leading to GBM stretching due to acute increased blood flow from a larger recipient into the pediatric kidney. However, the basement membrane soon returns to baseline due to the myogenic response and the effects of angiotensin II [6,7]. Hyperperfusion leading to increased filtration may also explain why pediatric grafts grow to adult size only months after transplant. Pediatric kidneys have relatively insufficient nephron units for adult recipients; with high filtration pressure, kidneys grow to adult size and the GBM begins to split and laminate. Splitting and lamination may be explained by repetitive glomerular endothelial and podocyte cell injury secondary to the hyperperfusion. The inner glomerular cells continue growing and differentiating. After several years, the filtration barrier matures and reaches normal adult levels [8]. Additionally, the second biopsy in our case showed evidence of Focal Segmental Glomerulosclerosis (FSGS). Nadasdy et al [3] had previously reported evidence of FSGS in three adult recipients of pediatric allografts; however, only one of these was found to be non-recurrent. To the best of our knowledge, there is very limited literature regarding de novo FSGS in pediatric allografts. We hypothesize that this change occurs due to glomerular hyperfiltration, similar to the way GBM lamellation occurs.

Conclusion

Numerous factors may affect the function and survival of a renal allograft. High skepticism is required in adults receiving pediatric donor kidneys; knowledge of the unique changes seen in pediatric grafts is important in determining the success of a renal transplant. Histological and ultrastructural analysis is required and are best seen with biopsy looked at under Light Microscopy (LM) and Ultrastructurally (EM). In this case, insufficient time has passed to determine whether the pediatric renal allograft will return to baseline function. However, more research is needed to determine the pathophysiologic changes seen in pediatric renal transplantation and its causes.

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