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Case Report

Diffuse Glomerular Basement Membrane Lamellation in Post-Transplant IgA Nephropathy

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Diffuse glomerular basement membrane (GBM) lamellation, reminiscent of Alport's syndrome, has rarely, and exclusively, been reported in renal allografts from pediatric donors to adult recipients. We report on a similar lesion, identified in a 42-year-old male, who received a kidney from an unrelated 21-year-old living male donor. The disease of the recipient was unknown. Renal allograft biopsies were performed 3.5 and 4.8 years after the renal transplantation, due to massive proteinuria and serum creatinine elevation. The histological features of both biopsies were similar, but more advanced in the second biopsy. Glomerular mesangium was widened and had an IgA deposit in the first biopsy. In addition to the presence of mesangial electron dense deposits, the GBM showed diffuse lamellation and splintering on the subepithelial side, but no definite deposits. In the second biopsy, IgA deposits were extended to the peripheral capillary walls, but electron microscopic examination was not available. Two months after the second biopsy, the patient returned for hemodialysis.

Key Words: Allografts, IgA deposit, renal transplantation

INTRODUCTION

Irregular lamellation and splintering of the glomerular basement membrane (GBM), reminiscent of Alport's syndrome, have rarely been reported in renal allografts.[1-3] Although the pathogenesis is uncertain, hyperfiltration/hyperperfusion injury is held to be responsible for this lesion since it develops exclusively in pediatric kidneys transplanted into adult recipients.[4] Herein, we report a similar GBM lesion identified in an adult male with post-transplant IgA nephropathy, who received a kidney from an unrelated male adult.

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CASE REPORT

A 42-year-old male received a renal allograft from a 21-year-old, unrelated, healthy living donor on Dec. 20, 1989. The donor was screened for all tests, including a kidney function test, prior to transplantation. The patient had received hemodialysis for 19 months prior to transplantation. His original renal disease was unknown. Hepatitis B surface antigen was negative, and serology for the hepatitis C virus (HCV) was not performed. The post-operative course was uneventful without episodes of acute rejection. The patient received cyclosporine based double immunosuppression. In Oct. 1990, he was admitted to the hospital because of enterocolitis. The renal allograft had been functioning well and his serum creatinine level was 1.7 mg/dl. In Jul. 1993, the first allograft biopsy was performed due to massive proteinuria (3.1 g/24h). At that time his serum albumin was 3.6 g/dl, cholesterol 263 mg/dl and creatinine 1.9 mg/dl. A diagnosis of mild chronic rejection with glomerular segmental sclerosis and IgA nephropathy was made. After the biopsy, azathioprine and angiotensin II converting enzyme inhibitor were administered. His proteinuria had decreased to 0.8 g/24 h and serum creatinine maintained at 1.6 mg/dl. In Mar. 1994, he was admitted due to a subarachnoid hemorrhage. After surgery, he suffered from pneumonia, and his aspartate aminotransferase and alanine aminotransferase rose to 413 and 311 IU/l,

respectively. Tests for HCV PCR and anti-HCV antibodies were positive at that time. In Sep. 1994, his serum creatinine had elevated and proteinuria increased to 9.7g/24 h. In Nov. 1994, his serum creatinine had further elevated to 5 mg/dl, and urinary protein excretion was 10.4 g/24 h. His serum albumin decreased to 2.5 g/dl and his cholesterol was 573 mg/dl. A second allograft biopsy was performed. The diagnosis was acute superimposed on chronic rejection and IgA nephropathy. Two months after the second biopsy, he was returned to hemodialysis. The donor has had no kidney problems so far.

Pathologic findings

The biopsy findings of the first and second biopsies were similar, but the second biopsy showed more advanced lesions. In the first biopsy, a total of 14 glomeruli were present, as indicated by light microscopy. Five glomeruli were obsolete and another five showed segmental sclerosis. In the nonsclerotic glomeruli, the glomerular mesangium was mildly enlarged and the glomerular basement membrane was irregularly thickened. Tubules were mildly atrophic, and this was associated with mild interstitial fibrosis. Fibrous intimal thickening of interlobular and arcuate arteries was mild. Immunofluorescence revealed 4 glomeruli, showing positive staining of IgG (+/+++) and IgA (+/+++) in the mesangium (Fig. 1). Two glomeruli were examined by electron microscopy. GBM disclosed lamellation and splintering on the subepithelial side and occasional electron dense granules, occupying about 30% and 50% of the glomerular capillary loops, respectively. The subendothelial area was focally widened with new GBM formation. Epithelial foot processes were focally effaced with microvillous transformation (Fig. 2). Electron dense deposits were present in the mesangium (Fig. 3).

In the second biopsy, a total of 7 glomeruli were present, three showed global sclerosis and four showed segmental sclerosis. There was severe tubular atrophy and interstitial fibrosis. A moderate degree of mononuclear cell infiltrate was present in the nonfibrotic interstitium with invasion of the nonatrophic tubules. Arteriolar hyalinosis was mild. On immunofluorescence, IgG

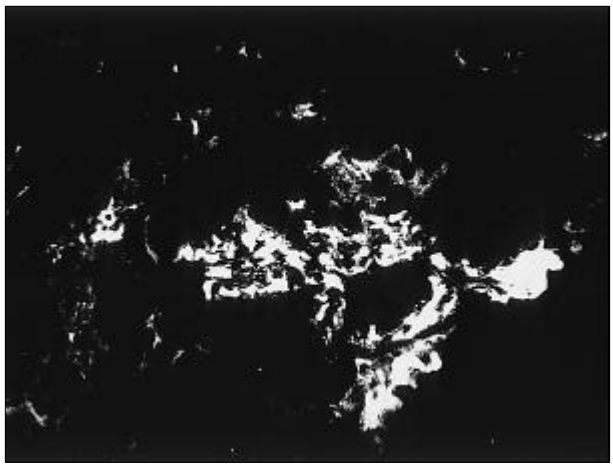

Fig. 1. Mild mesangial IgA deposit is present in the first biopsy (Immunofluorescence, × 200).

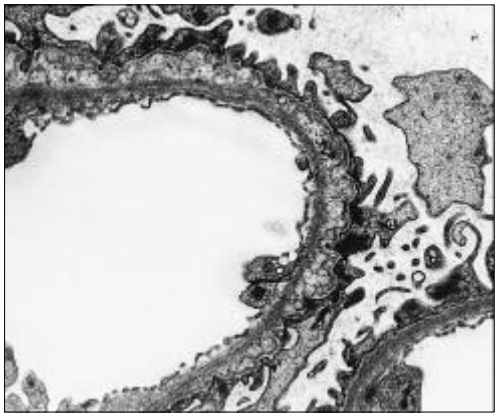

Fig. 2. The glomerular basement membrane shows diffuse irregularity, lamellation and granular, electron dense materials in the subepithelial area. Visceral epithelial cells show foot process effacement and microvillous transformation (Original magnification, × 5,200).

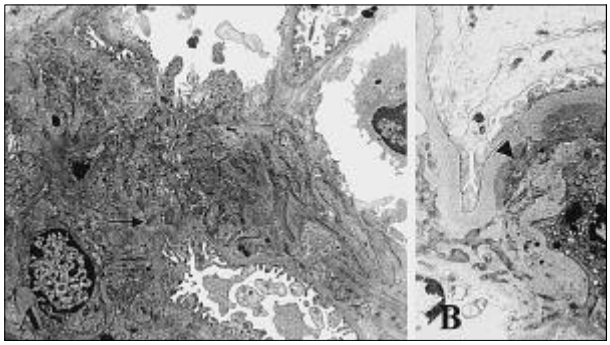

Fig. 3. The glomerular mesangium contains several discrete, small (A, arrow, × 3,900) and large (B, arrowhead, × 5,200) electron dense deposits.

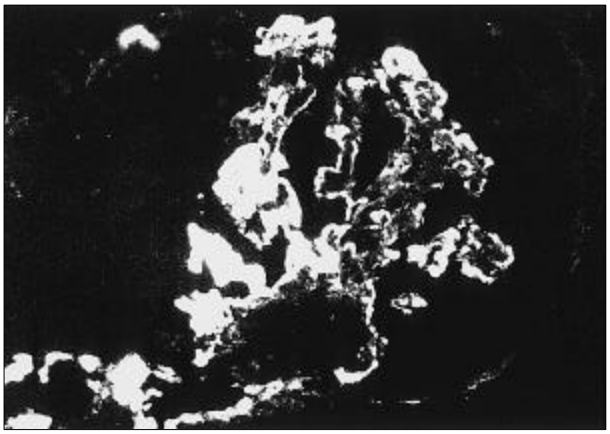

Fig. 4. Moderate amount of peripheral and mesangial IgA deposits are seen in the second biopsy (Immunofluorescence, × 200).

and IgA deposits were present in the mesangium, and along the peripheral capillary walls (Fig. 4). IgM and C3 deposits were minimally present in the mesangium. No glomeruli were found by electron microscopy.

DISCUSSION

GBM can be duplicated or lamellated in various conditions. GBM lamellation has been reported in native kidneys, including Alport's syndrome,[5] and in renal allografts,[6,7] but is mostly focal and mild. Diffuse GBM lamellation is rare and has been exclusively reported in Alport's syndrome and renal allografts.[1-4] In renal allografts, all seven age-documented transplant cases were reported in pediatric kidneys transplanted into adult recipients.[2,4] The present case demonstrates that a similar GBM lesion can develop in an adult kidney.

Although the pathogenesis of the GBM lesion was uncertain in this patient, hyperfiltration/hyperperfusion injury is the most probable pathogenetic mechanism, as in pediatric kidneys. The percentage of glomerulosclerosis and the degree of interstitial fibrosis were high, and the patient had a nephrotic range proteinuria. However, the patient's clinical course was complicated by other injuries, which suggests that other factors might also play a role. The first possibility is IgA nephropathy. Lamellation of the lamina densa has been reported in primary IgA nephropathy, which tends to be focal, but is more extensive in children.[8-10] GBM lamellation seems to be common in post-transplant IgA nephropathy. We additionally identified focal lamellation in three cases, including 2 recurrent forms, out of 43 cases examined by electron microscopy. It seems plausible that IgA nephropathy took part in the evolution and/or progression of this lesion, with peripheral capillary wall deposits and an increase in proteinuria.

Another possibility is hepatitis C viral infection. Hepatitis C infection can be associated with membranoproliferative features and GBM duplication. However, the GBM lesion was present in the first biopsy, whereas symptomatic viral infection, with positive serology, manifested between the first and second biopsies. The possibility of membranous nephropathy superimposed on IgA nephropathy was also excluded, because glomerular capillary wall deposits were not observed either by immunofluorescence or electron microscopy. This lesion was different from transplant glomerulopathy characterized by subendothelial widening containing fluffy material and doubling of the lamina densa.[6,7] Although a similar GBM lesion was reported in a transplant recipient treated with antilymphocyte globulin,[1] this patient had no history of antilymphocyte globulin treatment until the second allograft biopsy had been performed. The least possible explanation of all is the presentation of donor's hidden Alport's syndrome. Prior to, and following the transplant, the donor had no problems with kidney function. Moreover, the GBM lesion did not have a characteristic "basket-weave" pattern.

Taken together, GBM lamellation develops by several mechanisms including intrinsic structural or metabolic abnormality, hemodynamic derangement, or reaction to immune complex deposition, as a result of epithelial and endothelial injuries causing failure of GBM maintenance. In this patient, more than one mechanism seemed to operate in the production of the GBM lesion. No matter what underlying mechanism was involved in the GBM lamellation, the structural GBM abnormality may contribute to filtration derangement, nephrotic range proteinuria, and poor prognosis. To uncover the development of this

peculiar GBM alteration, electron microscopy should be mandatory in renal allografts, and information on more such cases should be accumulated.

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