Case Report

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Focal Segmental Glomerulosclerosis in a 32-Year-Old Kidney Allograft after 7 Years without Immunosuppression

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Abstract
In kidney allografts, focal segmental glomerulosclerosis (FSGS) has been described as recurrent, de novo, or a histological variant of chronic transplant glomerulopathy. We describe a unique case of de novo FSGS in a renal transplant not accompanied by any feature of rejection in a patient who had not been immunosuppressed for several years. A 58-year-old woman received a histoidentical living-related kidney transplant for end-stage renal disease due to chronic pyelonephritis. Twenty-four years after the transplant she voluntarily discontinued all immunosuppressive medication. Seven years later she presented with nephrotic syndrome, mild renal failure, and positive serology for hepatitis C virus (HCV) antibody. The kidney transplant biopsy disclosed de novo FSGS. Features of acute or chronic rejection, including chronic transplant glomerulopathy, were not seen. The pathogenesis of this lesion is probably related to sustained and prolonged glomerular hyperfiltration; alternatively, HCV infection may have triggered or accelerated the appearance of FSGS.

Introduction

In native kidneys, focal segmental glomerulosclerosis (FSGS) is classified as primary or secondary [1]. In transplant kidneys, FSGS is classified as recurrent FSGS [2], as a morphological variant of chronic transplant glomerulopathy [3], or as de novo FSGS [4]. We report herein a case of de novo FSGS in a 32-year-old allograft after 7 years without immunosuppression.

Case Report

The patient was a 58-year-old white woman who presented with nephrotic syndrome. The patient had multiple episodes of urinary tract infection during her childhood. The diagnosis of chronic pyelonephritis was rendered 40 years ago and, at that time, an intravenous pyelogram showed severe, bilateral renal atrophy. Due to recurrent infections, a right nephrectomy and subsequently, 32 years prior to this admission, a left nephrectomy were performed. Pathologic examination of the removed kidneys confirmed the diagnosis of chronic pyelonephritis. That same year she received a cadaveric kidney transplant; however, due to surgical complications, the graft was lost and subsequently removed. Four months later she received a histoidentical living-related kidney transplant from her twin sister. There was no discrepancy in body size between the donor and recipient, who weighed 58 and 61 kg, respectively. Immunosuppression consisted of radiotherapy for the perioperative period plus methylprednisolone (10 mg every other day) and azathioprine (75 mg every

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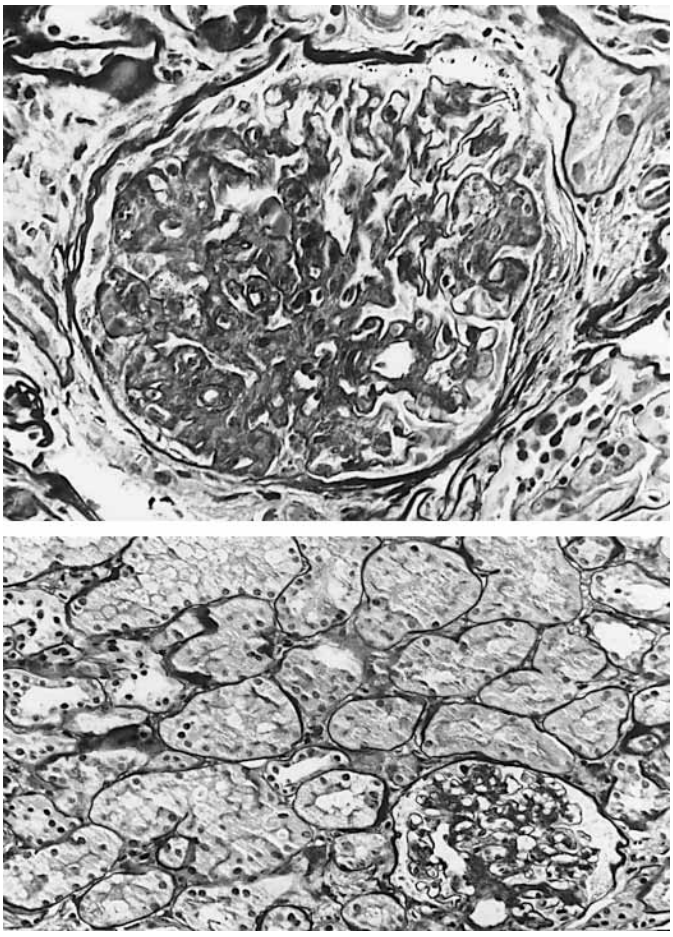

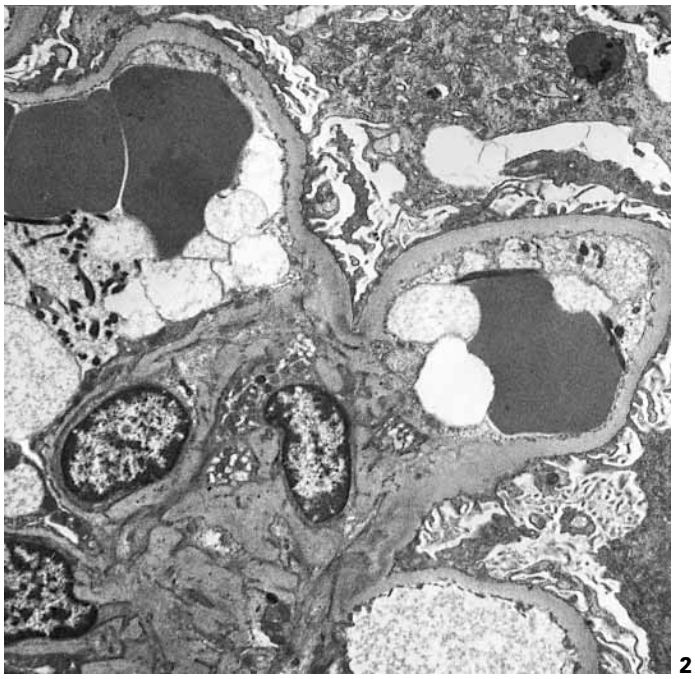

Fig. 1. a A glomerulus displaying segmental sclerosis and hyalinosis. The uninvolved glomerular capillaries are unremarkable. Periodic acid-Schiff. × 1,165. **b** Most areas of the kidney biopsy do not show any significant changes. Periodic acid-Schiff. × 590.

Fig. 2. Electron microscopic examination shows mild mesangial sclerosis and hypercellularity. There is also segmental effacement of the foot process. Features of chronic transplant glomerulopathy or electron dense deposits are not seen. Electron microscopy. × 5,700.

other day). Seven years ago, believing that the transplanted kidney would continue to function well, as it had for the preceding 24 years, and out of a growing fear of the systemic complications of continuous immunosuppression, she voluntarily discontinued all immunosuppressive medications. During the current admission her physical examination was unremarkable except for a mild periorbital edema and marked pitting edema of her lower extremities. Her blood pressure was normal. Her hematocrit was 35%, hemoglobin 11.3 mg/dl, WBC 11,000/μl, platelets 324,000/μl, sodium 139 mEq/l, potassium 4.3 mEq/l, chloride 108 mEq/l, bicarbonate 24 mEq/l, BUN 43 mg/dl, serum creatinine 1.6 mg/dl, serum protein 6.1 g/dl, serum albumin 3.0 g/dl, ALT 52 U, AST 29 U, alkaline phosphatase 200 U, and cholesterol 359 mg/dl. Serum protein electrophoresis showed polyclonal hypergammaglobulinemia. The urinary analysis was normal except for 4+ proteinuria. The 24-hour urinary protein collection was 3.9 g in a urine volume of 4,450 ml. ANA was positive at a 1/320 dilution with a centromere pattern. The serum complement levels were normal. Serum studies for Sm, RNP, ds DNA, SSA, SSB, ANCA, rheumatoid factor and cryoglobulins were all negative. Anti-HCV was positive, and the presence of HCV was confirmed by PCR. All HIV testing was negative. A circulating permeability factor was not looked for. Renal ultrasound showed a transplanted kidney of normal size and mild hydronephrosis. Cystoscopy was normal.

Kidney biopsy was performed and showed both cortical and medullary tissue with 21 glomeruli. Four glomeruli displayed segmental sclerosis with some of the segmentally sclerotic areas also showing hyalinosis (fig. 1). Four other glomeruli were globally sclerotic, and the remaining ones were unremarkable. The tubulointerstitial compartment displayed areas of mild tubular atrophy, associated with mild interstitial fibrosis and mononuclear inflammatory cell infiltrates, but was otherwise unremarkable. There was mild focal fibrous thickening of arterial intima. The immunofluorescent studies revealed three open glomeruli displaying only segmental staining for IgM and C3. Electron microscopy revealed two open glomeruli which displayed normal glomerular basement membrane and an absence of electron dense deposits, albeit with segmental foot process effacement (fig. 2); a third one was globally sclerotic. Features of acute rejection, chronic rejection including chronic transplant glomerulopathy, or immune-mediated glomerulonephritis (GN) were not seen. The patient was started on enalapril 10 mg/day, but refused methylprednisolone therapy.

Discussion

In native kidneys, FSGS is classified as primary (95%) or secondary (5%). The secondary forms of FSGS have been observed in a wide variety of conditions, including HIV infection, heroin addiction, vesicoureteral reflux, sickle-cell hemoglobinopathy, conditions associated with diminished renal mass, or with post-inflammatory scarring [1].

FSGS can also be seen in transplanted kidneys. In this context, FSGS is traditionally classified as recurrent FSGS [2], a variant of chronic transplant glomerulopathy [3], or de novo FSGS [4]. FSGS causing end-stage renal disease may recur in kidney transplants; this best characterized form of FSGS in renal transplant has characteristic features, including a prevalence in young African American males, early onset, progressive course, and a relatively high frequency of recurrence noted in 20–30% of patients [2, 3]. Chronic transplant glomerulopathy, which is pathogenetically related to chronic rejection at the glomerular capillary structures, can be seen in up to 7 and 25% of renal allografts after 1 and 10 years, respectively [3]. Chronic transplant glomerulopathy displays a wide spectrum of glomerular changes, including focal segmental sclerosis [5, 6]. FSGS in transplanted kidneys not related to preexisting FSGS or to chronic rejection is defined as de novo FSGS. De novo FSGS remains a poorly defined entity. Although Cheigh et al. [4] reported FSGS as a cause of heavy proteinuria and allograft dysfunction in up to 8.7% of transplant patients followed for up to 43 months after transplant, in many of these cases FSGS is probably not of de novo type.

We believe that our patient has all the characteristic features of de novo FSGS. The transplant biopsy showed FSGS without features of acute or chronic rejection, including chronic transplant glomerulopathy. In addition, the kidney came from a histoidentical twin, and the previous renal disease in this patient was chronic pyelonephritis, which precludes the consideration of recurrent FSGS. In spite of recent-onset nephrotic syndrome, the transplanted kidney had been functioning well in the preceding 32 years, even without any immunosuppression for the last 7 years. In this regard, this case represents the longest recorded survival, without immunosuppressive therapy, of a kidney transplant with fairly normal renal function.

The pathogenesis of de novo FSGS has not been elucidated. Primary FSGS in native kidneys has been thought to be related to a circulating factor that is toxic to the glomerulus [7]. This non-immunoglobulin molecule of approximately 50 kD increases the permeability of glomeruli to albumin [7] and although it was not measured in our patient, it could have been involved in the pathogenesis of the GN. In both native and transplanted kidneys, FSGS may develop from the background of renal tissue loss characterized by severe chronic tubulointerstitial damage secondary to hydronephrosis and intrarenal reflux of urine [1]. However, this pathogenetic pathway does not seem to play a role in this case, since there was only mild hydronephrosis by ultrasound; in addition, tubulointerstitial damage and urine reflux were not present.

Our patient tested positive for anti-HCV antibodies, and many types of glomerular lesions have been described in patients with HCV infection. The most common is membranoproliferative GN, but diffuse, focal, mesangial proliferative and membranous GN have also been reported, with or without mixed cryoglobulinemia [8]. Whether some cases of FSGS are pathogenetically related to HCV infection remains obscure. Cosio et al. [9] demonstrated a significantly higher prevalence of anti-HCV antibodies in patients with FSGS in native kidneys compared with diabetic patients. They attributed this increased prevalence to a previous history of drug abuse among their patients, and further supported the previous concept that there was no association between HCV and FSGS [9]. In renal transplant patients, the prevalence of anti-HCV antibodies is high (10–26%) [10], but de novo FSGS in biopsy is quite rare. This discrepancy indicates that HCV infection may not play a pathogenetic role in de novo FSGS.

Finally, the de novo FSGS in this patient may be secondary to glomerular hyperfiltration induced by diminished renal mass and resulting increased glomerular capillary pressure and plasma flow. This self-perpetuating process leads to expansion of extracellular matrix, followed by endothelial and mesangial cell proliferation with glomerular dysfunction manifested clinically as proteinuria, systemic hypertension and progressive renal failure. Several promoters of cell growth have been shown to stimulate mesangial and epithelial cell proliferation in kidneys with reduced mass including angiotensin II, endothelin-1, platelet-derived growth factor, interleukin-1, tumor necrosis factor and transforming growth factor-β [11]. Although virtually all renal transplant recipients suffer from the same condition of reduced renal mass as our patient, few have kidneys lasting as long (31 years). Thus, hyperfiltration for a protracted period of time may have led to the development of FSGS.

In summary, we report the de novo occurrence of FSGS in a kidney transplanted from a histoidentical living-related donor. The emergence of this disorder appears to be due to many years of function with a reduced renal mass.

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