Remission of post-transplant focal segmental glomerulosclerosis with angiotensin receptor blockers

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ABSTRACT

Recurrence of focal segmental glomerulosclerosis (FSGS) is common after kidney transplantation. Plasmapheresis (PP) is considered to be the most effective treatment; however, results are variable and relapse is common after stopping plasmapheresis. Here, we report an unusual case of recurrent FSGS, who achieved complete remission with angiotensin receptor blocker therapy.

Key words: Focal segmental glomerulosclerosis, kidney transplant, recurrence

Introduction

Focal segmental glomerulosclerosis is the second most common cause of idiopathic nephrotic syndrome (NS) in adults.[1] Kidney transplantation in patients with FSGS has a recurrence rate of 20–40% after first transplant and up to 50–80% in subsequent transplants.[2-4] Plasmapheresis has been used as mainstay of therapy for recurrence; however, most patients relapse after cessation of plasmapheresis. Graft survival is inferior to those without recurrence and spontaneous remission is rare.[3-5] Here, we report a case of posttransplant recurrent FSGS, who was successfully managed with addition of angiotensin receptor blockers (ARBs) without plasmapheresis.

Case Report

A 52-year-old male with end-stage kidney disease (ESRD) on maintenance hemodialysis since May 2011 presented to us in July 2011. His basic disease was unknown. On evaluation, he had bilaterally small kidneys with urine output of only 200–300 ml/day. His spot urine protein/creatinine ratio was 13.5. His sister was found suitable as a prospective donor. He underwent kidney transplantation on August 2, 2011, with triple immunosuppression consisting of tacrolimus (TAC), mycophenolate mofetil, and prednisolone without antibody induction. Initially, he had good urine output and creatinine decreased to 1.6 mg on day 4; however, on postoperative day 5, patient became oliguric. Renal Doppler was normal, so a kidney biopsy was done on day 6, and hemodialysis was initiated. Biopsy revealed changes of acute cellular rejection (ACR, Banff IB) with acute tubular necrosis (ATN). Patient received three doses of intravenous methylprednisolone 500 mg, but his urine output and kidney function did not improve and he was continued on dialysis. A repeat kidney biopsy on day 16 revealed focal ATN without inflammation and patient was continued on dialysis. A third kidney biopsy was done on day 30 in view of nonrecovering renal failure, which showed recovering ATN and changes of calcineurin inhibitor toxicity. TAC doses were reduced and subsequently his urine output increased and renal functions gradually improved. He

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achieved a minimum creatinine of 1.3 mg/dl at 2 months of transplant. In his next visit after 2 weeks, patient developed swelling over feet. A 24 h urine collection confirmed proteinuria of 11.8 g/day. At this time, his serum albumin was 1.7 mg/dl, and creatinine, 1.4 mg/dl. A repeat kidney biopsy was done at 3 months, which revealed segmental sclerosis in 3/22 glomeruli on light microscopy (LM). There was no interstitial inflammation or tubular atrophy/interstitial fibrosis (IFTA) in biopsy [Figure 1a]. Immunofluorescence (IF) revealed trace to 1+ positivity of IgM. Electron microscopy revealed diffuse foot process effacement confirming the diagnosis of recurrent FSGS [Figure 1d]. Patient was explained about the need of PP; however, he did not agree for the same. Hence, his prednisolone dose was increased to 30 mg/day and tab telmisartan 40 mg/day was added, which was gradually increased to 120 mg/day. TAC levels were kept between 6 and 8 ng/ml. Prednisolone was gradually tapered to 7.5 mg/day over next 6 months. With this treatment, there was a gradual improvement in proteinuria, which decreased to 600 mg/day at the end of 1 year and creatinine remained between 1.2 and 1.4 mg/dl. Serum albumin also increased to 3.2 g. After 1 year, proteinuria again increased to 2 g/day on reducing telmisartan to 40 mg/day, as he had hypotension and dizziness. A repeat kidney biopsy revealed global sclerosis in 3/19 glomeruli, segmental sclerosis with hyalinosis in 6 glomeruli, synechia formation in 3 glomeruli, and IFTA in 10–15% of the cortical area [Figure 1b and c]. There was no tubulitis or interstitial inflammation and IF was unremarkable. Biopsy findings suggested that despite control of proteinuria and apparently normal serum creatinine, the histological changes continued to progress. At this time again, treatment with plasmapheresis and rituximab was discussed with patient, however he was not willing. Subsequently, his prednisolone was increased to 20 mg/day and telmisartan to 120 mg/day. This resulted in gradual improvement in proteinuria to 500 mg/day over the next 1 year. Now, after completion of 4 years of transplant, patient is doing well with serum creatinine of 1.4–1.5 mg/dl, and proteinuria between 250 and 500 mg/day. His current immunosuppression includes tab prednisolone 7.5 mg/day, mycophenolate sodium 360 mg twice daily, and TAC 1 mg twice daily (level 4–5 ng/ml). In addition, patient is receiving telmisartan 120 mg/day.

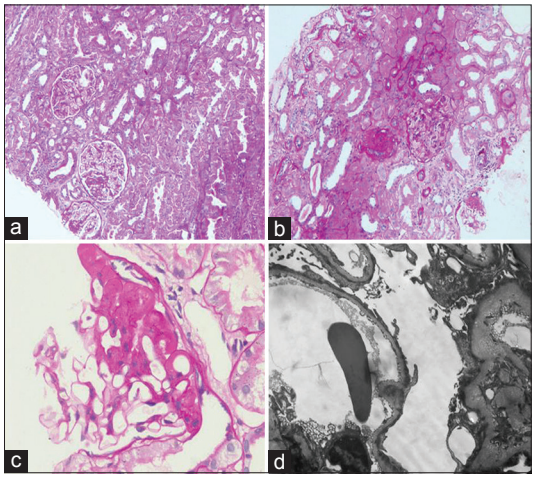

Figure 1: (a) By light microscopy, the initial biopsy show focal segmental glomerulosclerosis; however, no tubular atrophy or interstitial fibrosis was noted (b) by light microscopy, the following biopsy show focal segmental glomerulosclerosis, occasional globally sclerosed glomerulus along with mild patchy tubular atrophy occupying 10–15% of the sampled cortex (c) higher magnification of the 5th allograft biopsy show lesion of segmental sclerosis with hyalinosis and synechiae formation (d) electron microscopy performed on 4th allograft biopsy show extensive foot process effacement

Discussion

Recurrence of FSGS after kidney transplantation is widely reported. The risk factors for recurrence are early age of presentation of NS, rapid progression to ESRD, presence of mesangioproliferation in kidney biopsy, and retransplant, etc.[2,3,6] Recurrence of FSGS may be early or late. Early recurrence is more common, occurs within few days of transplant and is associated with massive proteinuria and delay in treatment may lead to rapid deterioration of renal function. The late recurrence occurs weeks to months after transplant.[2-4] Kidney biopsy within few days after transplant is normal on LM, except the presence of diffuse foot process effacement in electron microscopy. Late biopsies reveal features of focal segmental and global sclerosis.[2-4] Another feature of recurrent FSGS found in some reports is higher chances of acute rejection and ATN.[7] Our patient had delayed graft function and initial biopsies within 1 month revealed changes of ACR and ATN without any segmental sclerosis. However, as kidney function improved, patient was found to have heavy proteinuria with hypoalbuminemia and kidney biopsy at 3 months confirmed recurrence of FSGS [Figure 1a and d]. Our patient did not have pretransplant biopsy, so there was a possibility of *de novo* FSGS; however, *de novo* FSGS usually presents late. One series found that the mean time of diagnosis of *de novo* FSGS after transplantation was 57 months.[8]

Plasmapheresis has been shown to be most effective treatment for recurrent FSGS. Most studies demonstrate remission rates between 50% and 60% with PP, but most patients relapse after stopping PP, suggesting that such treatment induces transient rather than sustained remission[4,5,9] and graft survival is significantly inferior to patients without recurrence.[10] It is possible that, despite initial remission of proteinuria, the histological changes continue to progress. Our patient had progression of histological changes at 1 year, despite control of proteinuria and normal renal function.

Some reports have advocated intensifying immunosuppression, for example, replacement of azathioprine with cyclophosphamide or using high doses of cyclosporine.[11,12] However, these strategies have been found effective in only some patients. Angiotensin-converting enzyme inhibitors (ACEIs) are shown to reduce proteinuria in one case report, but in this report ACEIs were used with PP.[13]

Our patient responded to the slight increase in dose of corticosteroids, and use of ARB without PP and is doing well after 4 years of transplant.

Savin *et al*. demonstrated that a circulating factor of 30–50 ka protein is associated with increased permeability to albumin in rats.[14] Wei *et al*. demonstrated that soluble urokinase-type plasminogen activator receptor (suPAR) is most likely this factor; however, more recent work has shown that suPAR is not correlated with proteinuria in recurrent FSGS and increased levels are found in other causes of proteinuria as well as other diseases.[15]

To summarize, this case report highlights two things: first and foremost is that some patients with post-transplant FSGS might respond to mild increase in steroid doses and optimal use of ACE inhibitors/ARB without PP and second despite the clinical response, the histological lesions may continue to progress.

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Conflicts of interest
There are no conflicts of interest.

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