Successful Management of Early Recurrent Focal Segmental Glomerulosclerosis after Renal Transplantation A Case Report and Brief Review of Literature.

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Abstract:
Focal segmental glomerulosclerosis (FSGS) recurs in 20-50 cases following transplantation and approximately half of these patients lose their grafts. We report a case of a 32-year-old man with idiopathic focal segmental glomerulosclerosis (FSGS) who underwent haploidentical live-related kidney transplantation with his 50-year-old mother as donor. He received induction with basiliximab and immunosuppression consisted of steroid, tacrolimus and mycophenolate mofetil (MMF). Two weeks after transplantation, patient presented with increasing creatinine and nephrotic range proteinuria. Renal allograft biopsy showed the histological features of FSGS in the graft by electron microscopy. He was treated with plasma exchange. Tacrolimus was continued and MMF was switched to oral cyclophosphamide. This resulted in remission of proteinuria from 9.9 to 0.91 g24hrs and stable graft function which are maintained at 6 months post transplant.

Keyword: Focal segmental glomerulosclerosis (FSGS), renal transplantation, plasma exchange, cyclophosphamide.

Introduction:
FSGS is the primary glomerular disease among 5-15% of renal allograft recipients (1). Recurrence of FSGS is observed in between 20 and 50% of the patients (2,3) with graft loss in 40 to 50% of those affected (4,5). Most (90%) recurrences occur early, within the first two years of transplantation and in most cases (80%) within the first month after transplantation and are characterized by the appearance of massive proteinuria and decline in graft function (3). Most patients with recurrent primary FSGS may have a substantial reduction in urine protein excretion and improvement in graft function after plasma exchange and intensified immunosuppression with oral cyclophosphamide/highdose cyclosporine and or rituximab along with angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) as per the evidence based on individual cases and uncontrolled series.
Case report:

<table>
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<th>LAB PARAMETER</th>
<th>PATIENT'S VALUE</th>
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| Urine examination             | *Urine protein – 3*<sup>+</sup>*  
|                               | *Urine WBC – 4/hpf, RBC – nil/hpf*  
|                               | *Urine culture – No growth*  
|                               | **24 hours urine protein – 9.9 gm** |
| Serum chemistry                | *Urea – 48 mg/dl*  
|                               | *Creatinine – 2.0 mg/dl*  
|                               | *Sodium – 140 mEq/L, Potassium – 3.0 mEq/L*  
|                               | *Albumin – 3.2 gm/dl*  
| Blood counts                  | *Hb – 9.0 gm/dl*  
|                               | *Total WBC count – 12300/cu.mm*  
|                               | *Platelet count – 2,20,000/cu.mm*  
|                               | *Peripheral smear – Microcytic, hypochromic anemia and no schistocytes*  
| Imaging of allograft kidney   | *Ultrasound transplant kidney – normal*  
|                               | *Colour Doppler transplant renal artery – normal*  
| Immunosuppressant drug levels | *Tacrolimus trough C0 – 4.5 ng/ml*  
|                               | *MPA (Area Under Curve) AUC – 48.5 mg h/L*  

| Renal allograft biopsy         | *Transplant glomerulitis, mild tubulitis with mild peritubular capillaritis and foci of tubular necrosis.* (FIGURE 2)  
|                               | *IF negative.*  
|                               | *C4d stains occasional peritubular capillary walls (<10%).*  

He was empirically pulsed with IV Methylprednisolone (1g, 500mg, 500mg respectively for three consecutive days) after initial renal allograft biopsy report mentioned in table (1) and immunosuppressive drugs were optimized as per the drug levels. Electron microscopy report was awaited and meanwhile his creatinine decreased to 1.7 mg/dl after the above treatment. He was followed regularly in the transplant outpatient clinic and his creatinine again increased to 2.0 mg/dl after 2 weeks of above treatment. By then, electron microscopy of renal allograft biopsy was reported as moderate endothelial injury and extensive podocyte foot process effacement (approximately 70-75%) with features suggestive of post renal transplant rapidly progressive recurrent of native kidney disease FSGS. So he was treated with plasma exchange (1.5 times plasma volume, replacement fluid as 60% - colloid fresh frozen plasma and albumin & 40% - crystalloid 0.9% normal saline) six sessions, initial 3 sessions daily and next 3 sessions on alternative days over ten days period. Also mycophenolate mofetil was changed to oral cyclophosphamide 2 mg/kg/daily for three months.
He had dramatic reduction in proteinuria to 0.91 gm/day from 9.9 gm/day after plasma exchange and cyclophosphamide therapy. Correspondingly, serum albumin increased to 4.2 mg/dl and also his graft function stabilized with creatinine of 1.6 mg/dl. He was subsequently followed with urine protein creatinine ratio weekly once for the first month post therapy and fortnightly for the next two months with all values below 0.9. His last urine protein creatinine ratio was 0.86 and creatinine was 1.57 mg/dl, 6 months post transplant (FIGURE 1 – Post transplant course and management). He is planned to follow up further with regular monitoring of graft function with urine protein and serum creatinine.

FIGURE 1

Discussion and Review of literature:
Recurrence is a major problem observed in renal transplantation for patients with FSGS and graft loss is inevitable in most patients if untreated. Recurrence is heralded by the sudden appearance of heavy proteinuria along with graft dysfunction, often within the first month after transplantation as noted in our case. As per the KDIGO transplant guidelines, it is suggested to screen for proteinuria in patients with primary kidney disease caused by FSGS at least daily for first week, then weekly for 4 weeks, every 3 months for the first year and every year thereafter (6). Ultrastructural examination of allograft biopsy is essential to show the extensive foot process effacement observed in such cases within first few weeks after transplant if there is strong suspicion of recurrent FSGS as routine light microscopy findings are not adequate to diagnose FSGS recurrence in the early period of 4 – 6 weeks post transplant and may delay the diagnosis and the treatment. As evident in our case, the light microscopy finding of the renal allograft biopsy did not have any underlying clue for recurrent FSGS, so as per the initial report, IV methylprednisolone was given considering acute cellular rejection. Ultrastructural report obtained after two weeks showed the features suggestive of recurrent FSGS and initiation of immediate treatment had helped dramatic improvement in our patient.

Pathogenesis of recurrent FSGS:
The pathogenesis of FSGS is not fully understood, but there is a complex role of T cells, B cells, podocytes and circulating factors. There is considerable evidence for Th2 cytokine involvement in primary FSGS (7). This is supported by the observation of higher levels of cytoplasmic IL-13 mRNA in T cells from patients with...
relapsing FSGS compared to patients in remission [8]. Also, the soluble ST2 protein (sST2), a marker of Th2 cells predicted to be regulated by transcription factor c-maf, have been recently investigated in a population of patients with FSGS recurrence after transplantation [9]. However, despite the evidence for T-cell dysfunction in primary FSGS, treatments targeting T cells such as calcineurin inhibitors, anti-CD3, or anti-CD52 antibodies are not completely effective for the prevention or treatment of recurrent FSGS. Evidence of B-cell participation has also been recently provided, in the form of remission following treatment with rituximab (anti-CD20) in several case reports [10]. But the long term safety and prospective study of rituximab on the treatment is lacking. A critical advancement was the identification of circulating permeability factor by Savin’s group and has been isolated from sera of FSGS patients with increased glomerular permeability to albumin in vitro (isolated Sprague-Dawley rat model) [11], with an anionic charge and affinity for protein A and galactose which showed the utility of protein A adsorption and possible role of galactose respectively in the treatment of recurrent FSGS [12,13]. Various other circulating factors identified recently are soluble urokinase receptor (suPAR) [14], cardiotrophin like cytokine 1 [15] and angiopoeitin-like 4 [16] which have shown to activate podocyte injury. So the possible role of plasma exchange in removing the circulating factors for the management of recurrent FSGS is proposed in many studies. Permeability factor(s) exert direct effects on the nephrin and podocin or may alter phosphorylation of cellular proteins, influence the activity of serine proteases or induce of integrin-like kinase activity that leads to detachment of podocyte from GBM [13,17,18]. In spite of these tremendous advances in knowledge of permeability factors, they have major limitations to apply on clinical routine practice such as they are highly laborious, not readily available, lack specificity, sensitivity and precision and not validated by all centers.

**Risk factors of recurrent FSGS:**

The risk factors of recurrence FSGS are mentioned in the below table (2) *Conflicting risk factors*

**Treatment of recurrent FSGS:**

Treatment of recurrent FSGS is based on individual case reports and uncontrolled series and there are no randomized controlled trials available. Early initiation of plasma exchange has been shown to significantly reduce proteinuria as evident in our patient also and acts probably by removing circulating factors that alter glomerular permeability to protein [36,37]. But patients may present with recurrence of proteinuria after initial successful treatment with plasma exchange requiring additional exchanges, or even periodic, ongoing treatments. It is unclear regarding the duration of plasma exchange treatments required to reduce protein excretion, but one review found a median of nine treatments before there was a remission in proteinuria [36]. In our patient, after six sessions of plasma exchange, there was significant decrease in proteinuria from 9.9 gm/day to 0.91 gm/day. So, further plasma exchanges were not given as patient subsequently maintained urine protein creatinine ratio value below 1 on further close observation. In small case series, prophylactic plasma exchange during peri-transplant period has been reported in those with heavy proteinuria, but the data are not convincing on the effectiveness in preventing recurrent FSGS [38,39]. Staphylococcal protein A column adsorption has been used as an adjunct to plasma exchange [40].
Other option is to modify the immunosuppressive drugs to maintain the remission by adding either oral cyclophosphamide or cyclosporine as per the evidence based on several small case series. Cyclophosphamide given at a dose of 1-2 mg/Kg/day for a period of 8-12 weeks as a replacement of antimetabolites (Azathioprine, MMF) has helped in maintaining remission in several case series (41,42,43,44,45,46). In our patient, along with plasma exchange, MMF was replaced by cyclophosphamide for three months period. With the above treatment, he is able to maintain remission with stable graft function at 6 months post transplant. High-dose CsA (15 – 30 mg/kg/day, maintaining trough 200 – 300 ng/ml) may induce remission of proteinuria when used alone (47,48) or along with plasma exchange (49). Rituximab doses of 375 mg/m²/dose given once every one to two weeks, depending on the response) is tried in patients with relapse of recurrent FSGS with variable success (50,51,52,53,54). Galactose is found to improve proteinuria and stabilize eGFR in two case reports (55,56). Abatacept [soluble fusion protein that inhibits the T-cell protein, B7-1 (CD80)] was tried in four patients resistant to both plasma exchange and rituximab and found to have almost complete resolution of proteinuria (57). But the response is questionable as others did not find any benefit on abatacept therapy. For patients who do not respond to plasma exchange, or for patients who have non-nephrotic proteinuria, a reduction in proteinuria with an angiotensin-converting enzyme
inhibitor (ACE-I) and/or an angiotensin II receptor blocker (ARB) may be beneficial (6,34). Also ACE-I and ARB can be used as adjuvant drug along with plasma exchange and other therapies.

**Conclusion:**
FSGS can recur after transplant and early diagnosis by electron microscopy with early institution of therapy such as plasma exchange and others is found to have dramatic improvement of proteinuria and graft function.

**References:**


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