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Letter to Editor

A Rare Relapse: Recurrence of Nephrotic Syndrome in an NPHS1 Mutation Post-Kidney Transplant

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To the Editor,

Renal transplantation is the most effective treatment for children with end-stage renal disease, offering the best long-term outcomes. However, recurrence of the primary disease can jeopardize graft survival, with post-transplant glomerulonephritis occurring in up to 45% of cases (1). In genetic forms of nephrotic syndrome, recurrence is considered rare, as the underlying defect is corrected with transplantation. Here, we present a case of recurrent focal segmental glomerulosclerosis after kidney transplantation in a patient with a heterozygous NPHS1 mutation, highlighting the need to better understand the mechanisms underlying post-transplant disease recurrence in genetic nephrotic syndrome.

A male patient was diagnosed with nephrotic syndrome at the age of 8 and underwent a renal biopsy at 13, confirming focal segmental glomerulosclerosis (FSGS). Genetic testing identified a p.Thr294Ile (c.881C>T) mutation in the NPHS1 gene. Despite multiple immunosuppressive treatments, the disease progressed to end-stage renal disease by age 20. He subsequently underwent a preemptive kidney transplant from his 55-year-old mother, who had normal renal function, with a 3/6 HLA match. Postoperatively, the patient received standard immunosuppressive therapy, including basiliximab, methylprednisolone, mycophenolate mofetil, and tacrolimus. The lowest serum creatinine level was 1.5 mg/dL within the first 10 days; however, by postoperative day 11, it increased to 1.9 mg/dL, raising concerns for graft dysfunction. Renal Doppler ultrasonography showed normal renal artery flow with a resistive index of 0.62. CMV-DNA was negative, and the spot urine protein-to-creatinine ratio was <300 mg/mg. Given these findings, recurrence of FSGS and de novo glomerulonephritis were initially ruled out.

By postoperative day 12, due to suspected cellular and humoral rejection, the patient was treated with intravenous methylprednisolone (250 mg/day for 3 days), anti-thymocyte globulin (600 mg total), and two plasmapheresis sessions with 12 units of fresh frozen plasma. By postoperative day 21, serum creatinine was 1.87 mg/dL, and the tacrolimus trough level was 8.2 ng/mL. At discharge, the immunosuppressive regimen was adjusted to extended-release tacrolimus (10 mg/day), mycophenolate mofetil (2000 mg/day), and prednisone (20 mg/day).

During follow-up, proteinuria increased to 1960 mg/mg, prompting the decision to perform a renal transplant biopsy at post-transplant month 3. At the time of the biopsy, the measured creatinine level was 2.0 mg/dL. Histopathological findings confirmed recurrent FSGS, leading to five plasmapheresis sessions and a single dose of rituximab (1000 mg). Losartan (100 mg/day) was initiated for its antiproteinuric effect. Maintenance immunosuppressive therapy was administered as extended-release tacrolimus (10 mg/day), mycophenolate mofetil (2000 mg/day), and prednisone (5 mg/day). The patient did not receive any additional doses of rituximab in the following period. Proteinuria gradually decreased, measuring 1000 mg/mg at one year and 380 mg/mg at two years post-transplant, while renal function remained stable (**Figure 1**). By the second year post-transplant, the patient's regimen included extended-release tacrolimus (5.5 mg/day), mycophenolic acid (1440 mg/day), and prednisone (5mg/day). Losartan (100 mg/day) was

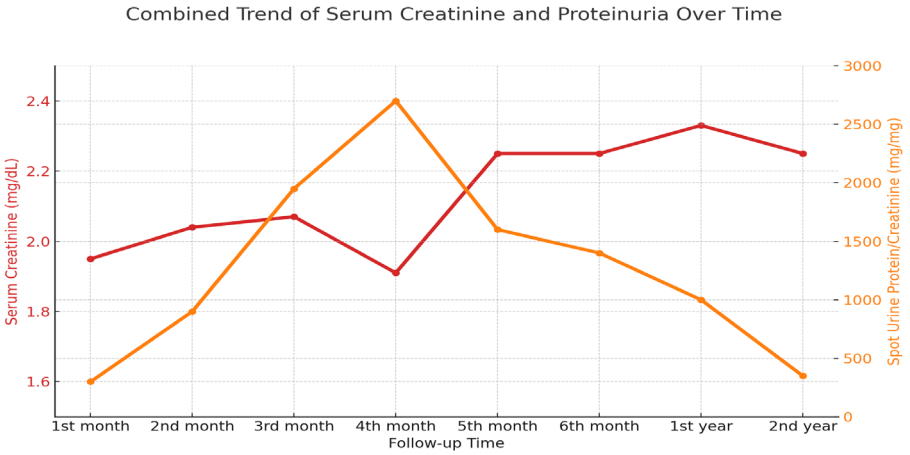

Figure 1. Combined trends of serum creatinine and spot urine protein/creatinine ratio over time after kidney transplantation, illustrating changes in renal function and proteinuria during follow-up.

continued for proteinuria management.

In patients with nephrotic syndrome, retrospective analyses of post-kidney transplant relapse cases show that relapses in genetic steroid-resistant nephrotic syndrome are very rare (2-4). In cases where relapse occurs, these relapses appear later compared to patients with non-genetic nephrotic syndrome, and they generally respond well to plasmapheresis treatment. Additionally, the kidney outcomes for these patients are typically good (4). However, the underlying mechanisms for the post-transplant relapse of genetic focal segmental glomerulosclerosis are not well understood. Circulating anti-nephrin antibodies may play a pathogenic role in the development of recurrent FSGS in patients with NPHS1 mutations but without NPHS2 mutations (5). Unlike previous reports where relapses occurred later, this case highlights the potential for early recurrence, underscoring the need for closer post-transplant monitoring in this subgroup. Nevertheless, the good prognosis was in line with the literature, as there was a response to plasmapheresis and no need for hemodialysis. In our case of a patient diagnosed with nephrotic syndrome due to an NPHS1 gene mutation, the occurrence of relapse in the early period post-transplant was unusual.

This case shows the early recurrence of FSGS after kidney transplantation in a patient with a heterozygous NPHS1 mutation, a phenomenon considered rare in genetic nephrotic syndrome. Despite the recurrence, the patient responded well to plasmapheresis and rituximab, with stable renal function and reduced proteinuria during follow-up. These findings demonstrates once the importance of close post-transplant monitoring and further research into the mechanisms of recurrence in genetic FSGS.

Sincerely,

DECLERATIONS

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