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Cyclophosphamide as a Treatment for Focal Segmental Glomerular Sclerosis Recurrence in a Kidney Transplant Patient

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Statistical Analysis C
Data Interpretation D
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Conflict of interest: None declared

Patient: Female, 24-year-old
Final Diagnosis: Focal segmental glomerulosclerosis
Symptoms: Facia • lower extremity edema
Medication: —
Clinical Procedure: —
Specialty: Nephrology

Objective: Unusual or unexpected effect of treatment

Background: Primary focal segmental glomerular sclerosis (FSGS) frequently causes recurrence after kidney transplantation, leading to graft loss in half of the patients. Conservative treatment of FSGS is the main acceptable method due to the lack of randomized clinical trials. A few strategies are known to treat FSGS recurrence, such as plasmapheresis and intravenous immunoglobulin (IVIG), but failure to achieve remission may occur. In addition, some of these treatment strategies are more established in pediatric patients and lack evidence in adult patients.

Case Report: We describe the case of a 24-year-old woman who had a kidney transplant due to FSGS and was admitted to the hospital for an evaluation of lower-limb and facial swelling. Her kidney biopsy showed segmental glomerulosclerosis compatible with recurrence of FSGS. Her FSGS relapses were further confirmed by increase in serum creatinine and proteinuria. The patient had several FSGS relapses that were treated by different combinations of plasmapheresis, pulse steroid, mycophenolic acid, tacrolimus, prednisolone, IVIG, and IV rituximab. She did not respond to conventional therapy and was eventually treated successfully using cyclophosphamide and remained in remission afterward.

Conclusions: FSGS has a high recurrence rate after kidney transplantation. A few options to achieve remission have been investigated. In this report, we present the case of a young woman with FSGS recurrence after a kidney transplant, achieving remission successfully with cyclophosphamide. Cyclophosphamide can be used a treatment of FSGS recurrence in a transplanted kidney when all other options have been exhausted. Additional research is needed to assess the efficacy and safety profile of cyclophosphamide in such cases.

Keywords: Adult • Cyclophosphamide • Glomerulosclerosis, Focal Segmental • Kidney Transplantation • Renal Insufficiency

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Background

Focal segmental glomerulosclerosis (FSGS) is defined as segmental obliteration of the capillary lumina by the hyaline matrix component involving some of the nephrons [1]. It is considered the most frequent pathological lesions in adults with nephrotic syndrome [2]. FSGS is divided into 2 types based on the etiology of the disease. An idiopathic origin is regarded as primary FSGS. Causes of secondary FSGS include adaptive response of glomerular hypertension resulting from glomerulonephritis and diabetes mellitus, as well as hereditary/genetic glomeropathies (viral or drug-induced) and adaptive responses [3]. Moreover, primary FSGS is the only type related to recurrence in a transplanted kidney.

Treating FSGS conservatively is generally the main acceptable method due to the dearth of randomized clinical trials; however, kidney survival in non-nephrotic patients is significantly better than in nephrotic patients [4]. Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-II receptor blockers (ARBs) are beneficial in reducing proteinuria and improving long-term kidney function by controlling blood pressure [5]. Nonetheless, possible adverse effects such as hyperkalemia and acute kidney injury must be monitored. In addition to rennin-angiotensin system inhibition, lifestyle modifications are essential to achieve a goal of blood pressure less than 130/80 mmHg [5].

About 40-70% of patients with FSGS need dialysis within 10-20 years after diagnosis [3,6,7]. For patients reaching end-stage renal disease, kidney transplantation is the most suitable treatment option. However, primary FSGS has a recurrence rate of up to 30% [9]. Treatment of FSGS recurrence is challenging because of the limited treatment options. Plasmapheresis is the most common treatment and is reported to achieve remission in up to 63% of adults with recurrent FSGS following kidney transplantation [10]. Other medical treatment options include drugs such as calcineurin inhibitors, rituximab, and cyclophosphamide [1]. However, some of these options lack evidence in adult patients.

Herein, we present a case of an adult patient with FSGS treated by renal transplant who then developed a recurrence and was subsequently managed successfully with cyclophosphamide.

Case Report

A 24-year-old woman had been diagnosed with primary FSGS at age 10 years; nephrotic syndrome was noted on biopsy as primary FSGS. The patient was found to have primary steroid-resistant nephrotic syndrome and was started on peritoneal dialysis (PD). Three years later, she received a single-kidney transplant from a living non-related donor; her post-transplant kidney function was normal. She was started on mycophenolic acid (MMF), tacrolimus, and prednisolone after the transplant. The patient was compliant with her medications, but 2 years later she presented with bilateral lower-limb edema and facial puffiness. Her serum creatinine (SCr) had an almost 3-fold increase from her baseline of 60-70 umol/L. The initial kidney ultrasound (US) revealed mild increased size and echogenicity of the transplanted kidney (**Figure 1A**), as well as an increase in resistive index of the main renal artery (**Figure 1B**). A biopsy showed borderline changes for acute T cell-mediated rejection and features consistent with recurrent/de novo FSGS (**Figure 2A**). The pathological features included only 1 out 5 glomeruli with global glomerulosclerosis, 6 glomeruli with segmental sclerosis, mild interstitial fibrosis, and tubular atrophy. After excluding secondary causes of FSGS, the patient was treated by plasmapheresis in addition to pulse steroid and responded well, with SCr level returning to baseline. Three years later,

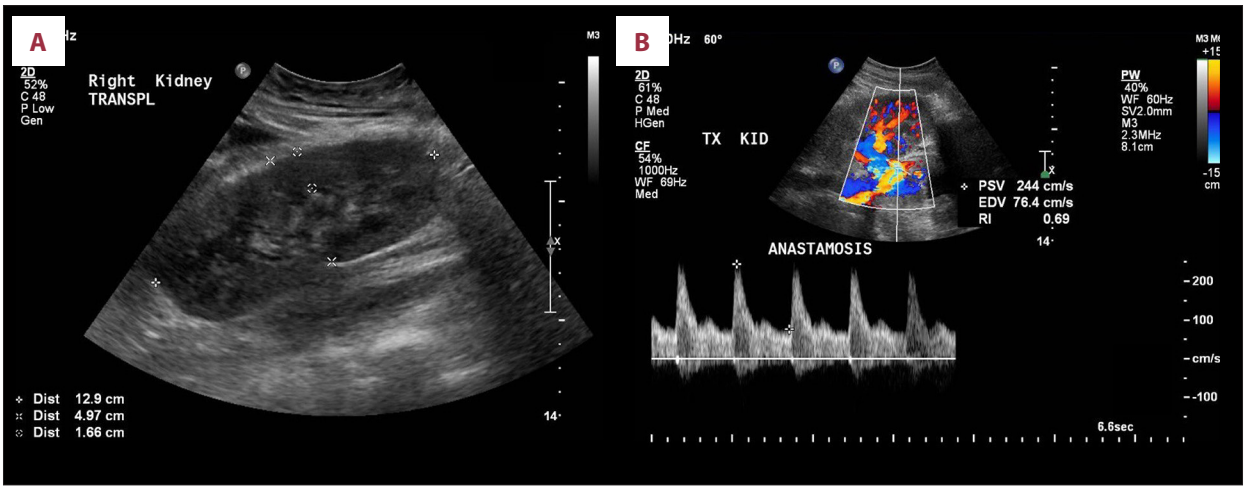

Figure 1. Renal ultrasound showing: (**A**) Increased size and echogenicity of transplanted kidney. (**B**) Increase in resistive index of the main renal artery.

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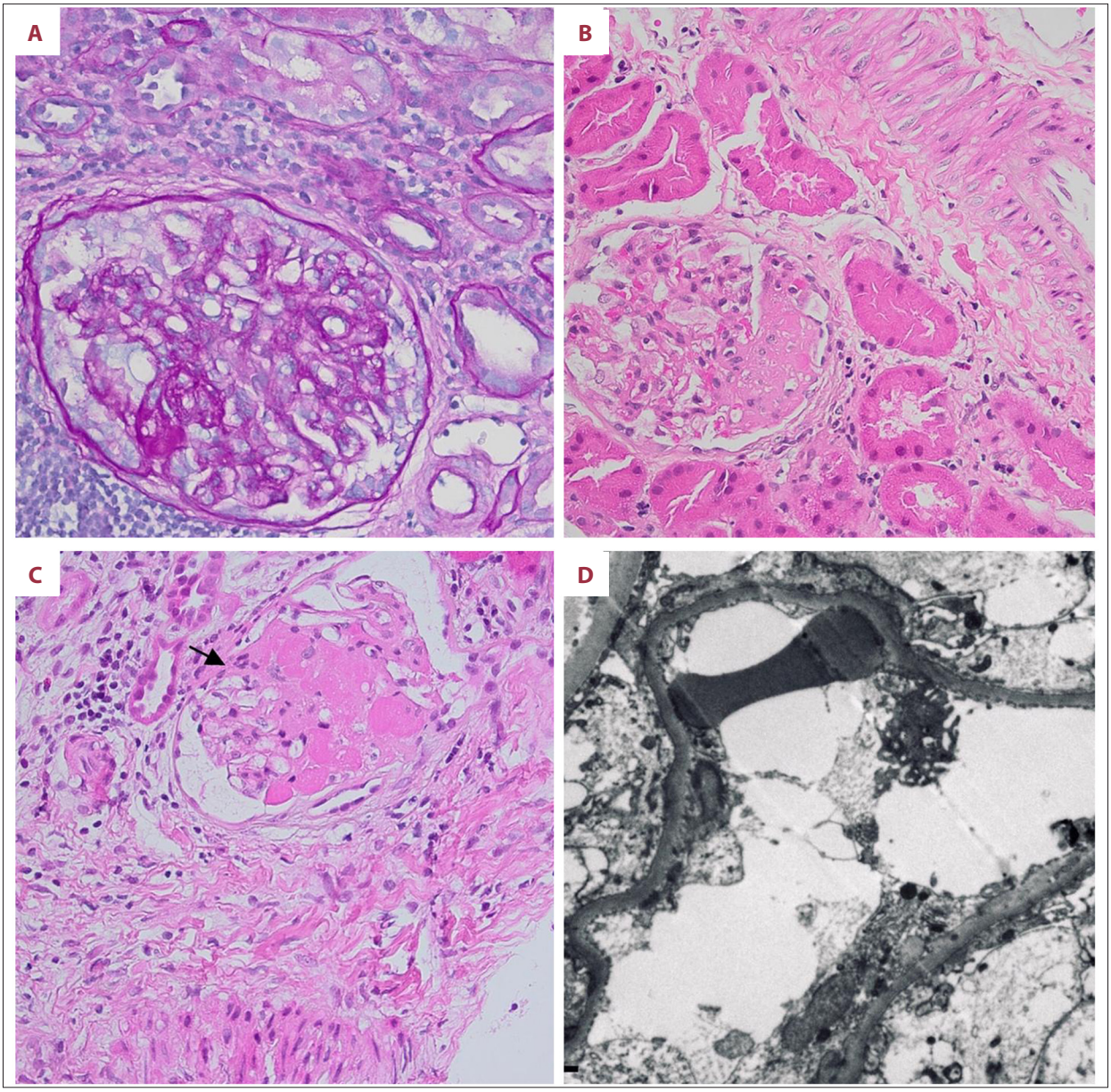

Figure 2. (**A**) In August 2016, an image representative of a glomerulus involvement by segmental sclerosis: segmental obliteration of a capillary loop segment with associated expansion of mesangial matrix by hyaline matrix, in a non-characteristic localization appearing red, PAS stain, ×400. A capsular adhesion of the corresponding segment is present. (**B**) In May 2019, the image demonstrates glomeruli involvement, in a non-characteristic localization, by segmental sclerosis and capsular adhesion, H&E stain, ×400. (**C**) In May 2019, the image demonstrates a corticomedullary glomerulus involvement by segmental sclerosis and capsular adhesion, H&E stain, ×400. (**D**) An electron microscopic image demonstrates effacement and fusion of podocyte foot processes over long segments (>90%) of the glomerular basement membranes, EM, ×2000.

she presented with symptoms similar to the first episode of recurrence. Her SCr was within her normal baseline, but urine analysis was positive for proteinuria. On admission, laboratory findings included decreased albumin (21 g/L) and 24-h urine collection with a protein level of 5.2 g/day. Renal US images revealed a mild degree of hydronephrosis of the transplanted kidney, without stones, focal masses, or perinephric collection. The kidney size was estimated to be 12×5.1 cm with cortical thickness of 1.3 cm (**Figure 3**). A biopsy was planned immediately, which revealed segmental glomerulosclerosis in 4 out of 8 glomeruli, mild arteriolar hyalinosis, minimal interstitial fibrosis, and tubular atrophy, showing a recurrence of FSGS without evidence of acute active cellular rejection (**Figure 2B-2D**). She was treated initially with 9 sessions of plasmapheresis in

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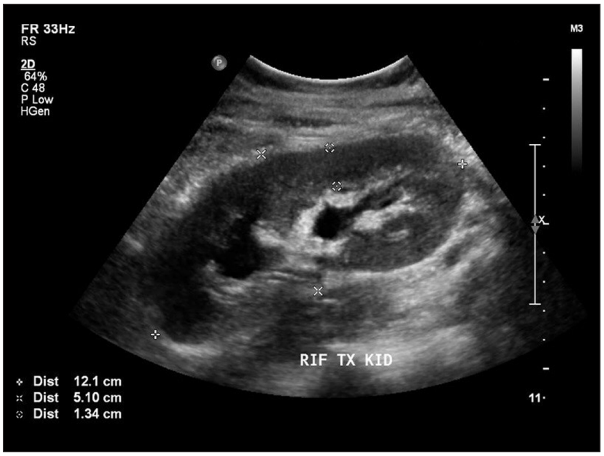

Figure 3. Renal ultrasound the transplanted kidney with a size of 12×5.1 cm and cortical thickness of 1.3 cm.

combination with intravenous immunoglobulin (IVIG) and pulse steroid. The patient did not respond, and proteinuria persisted, exceeding 5 g/day; therefore, she was started on IV rituximab 375 mg. After the first dose, the patient responded well, with complete remission of FSGS noted by absence of proteinuria, improvement of albumin level (46 g/L), and reduction of 24-h urine protein to 145 mg/day. The patient was discharged on tacrolimus, and another dose of IV rituximab 375 mg was administered 1 week later. One month later, she experienced bilateral optic atrophy as an adverse effect of tacrolimus; thus, she was switched to cyclosporine. Two months after the second recurrence, repeated 24-h urine protein was 12.8 g/day, but the renal profile was normal. The patient was admitted as a case of FSGS recurrence and started on plasmapheresis and received 5 consecutive sessions, which reduced proteinuria to 6.2 g/day. She was discharged to continue 2 session per week of plasmapheresis for 3 months. During the second month of the planned plasmapheresis, the patient developed anasarca, and repeated 24-h urine protein was more than 20 g/day. Since her condition did not improve after plasmapheresis and administration of rituximab, cyclophosphamide was added to the plasmapheresis that she already was receiving, after discussion and informed consent. She was started on daily oral cyclophosphamide 100 mg, in addition to discontinuation of MMF. At 17 days after starting cyclophosphamide, her symptoms improved, and proteinuria fell to 0.7 g/day (**Figure 4** demonstrates the timeline of FSGS disease, relapses, and medication regimen). She was discharged on the same dose of cyclophosphamide, prednisolone 10 mg, and cyclosporine 75 mg. Three months later, she had completed a 3-month course of cyclophosphamide, and MMF was resumed. Subsequently, on regular follow-up, she remained in partial remission, with proteinuria ranging from 0.5 g/day to 0.8 g/day.

Discussion

There are few options to treat FSGS recurrence after kidney transplantation. Many studies have noted evidence to support plasma exchange in treating primary recurrent FSGS. Plasma exchange has been shown to ameliorate proteinuria, improve kidney function, and prevent allograft loss [11]. Rituximab's role in preventing and treating the recurrence of FSGS was not fully established; however, rituximab achieved a significant decrease in proteinuria and recurrence rate as prophylactic therapy in high-risk patients [12].

Our patient received multiple sessions of plasmapheresis, 2 doses of rituximab, and steroids, but she had another FSGS recurrence within 3 months. Moreover, a meta-analysis demonstrated that FSGS recurrence after kidney transplant can be treated with the combination of rituximab and plasmapheresis, which helped achieve remission in 72.7% of the cases [13]. Nonetheless, rituximab has shown beneficial outcomes in adults with FSGS recurrence after transplant, but there is no consensus on the exact dose or duration. Some patients have been reported to achieve complete remission after 2 doses [14], but others may require 3 or 4 doses [15]. Due to a lack of substantial evidence of the efficacy and safety of repetitive rituximab use, a trial of cyclophosphamide to save the graft improved our patient's symptoms and resolved her proteinuria.

Cyclophosphamide is a nitrogen mustard drug; its main effect is DNA alkylation [16]. The drug affects Th2 cytokines like IL-4 and IL-10 by increasing the secretion in the blood and decreases interferon-gamma secretion [17]. However, the exact mechanism by which cyclophosphamide achieves its immunomodulatory

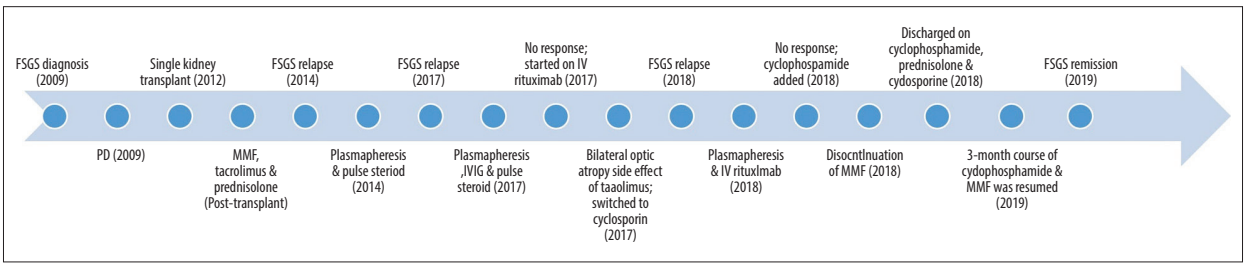

Figure 4. Timeline of FSGS disease, relapses, and medication regimen. FSGS: focal segmental glomerulosclerosis. PD – peritoneal dialysis; MMF – mycophenolic acid; IVIG – intravenous immunoglobulin.

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effects is unclear. Theories include type I interferons induction, regulatory T cell elimination, and reducing rejection risk by decreasing the sensitivity of host cells to donor T cells [17].

When used in patients with FSGS with native kidneys, cyclophosphamide has shown beneficial outcomes in achieving partial or complete remission [18]. Experts differ regarding use of cyclophosphamide in cases of FSGS recurrence after kidney. In the pediatric population, a case series of cyclophosphamide use in 11 children showed that 9 of them achieved remission, with 7 becoming free of disease [19]. Moreover, another case series on 6 children with recurrent FSGS treated with a combination of cyclophosphamide and plasma exchange resulted in complete remission in 3 patients, while the rest had partial remission [20]. On the other hand, there is limited data in adult patients treated with cyclophosphamide for FSGS recurrence after kidney transplantation. A case report by Hristea et al describes a case similar to ours, in which the patient received plasmapheresis and rituximab, while cyclophosphamide was used to consolidate the outcomes rather than solely treating recurrence [21].

Our patient received plasmapheresis, rituximab, and steroids, without significant remission. Cyclophosphamide was initiated, which resulted in partial remission. The effect of cyclophosphamide alone was not studied before; nonetheless, our patient received cyclophosphamide after exhausting the other options, but FSGS recurrence was eventually treated successfully.

A limitation of this case report is that the patient's improvement started almost 4 months after starting rituximab, which may be the reason for achieving remission.

Conclusions

FSGS has a high recurrence rate after kidney transplantation. A few options to gain remission are investigated. In this report, we present the case of a young woman with FSGS recurrence after kidney transplant, achieving remission successfully with cyclophosphamide. Further randomized controlled trials are needed to evaluate the efficacy and safety of this method.

Conflict of Interest

None.

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