

---

*Case report*

## **Recurrent focal segmental glomerular sclerosis after kidney transplantation**

Ristoska Bojkovska Nadica<sup>1</sup>, Kuzmanovska Dafina<sup>1</sup>, Tasic Velibor<sup>1</sup>, Sahpazova Emilija<sup>1</sup> and Spasovski Goce<sup>2</sup>

<sup>1</sup>Department of Nephrology, Children's Clinic, University of Skopje, R. Macedonia

<sup>2</sup>Department of Nephrology, University of Skopje, R. Macedonia

---

### **Abstract**

Renal transplantation is the optimal mode of treatment for end-stage renal disease in the pediatric population. Compared with dialysis, transplantation is offered to the children with chronic renal failure as best chance for obtaining normal growth and neurophysiologic development.

We present a case of 13 years old girl who had clinical and laboratory symptoms of nephrotic syndrome since her 1 year of age. She underwent renal biopsy which showed histopathology of focal segmental glomerular sclerosis (FSGS). The therapy with steroids, cyclosporin and cyclophosphamid did not show any result of remission of the disease.

At her 6-year of age she progressed to terminal renal insufficiency and commenced with peritoneal dialysis treatment for the next 2,5 years. In her 9 year of age she obtained her first living donor kidney transplantation in Thessalonica (Greece). One year after transplantation a high proteinuria with an increased serum creatinine and hypertension was observed. She underwent graft biopsy and the recurrence of the primary disease (FSGS) was confirmed. The treatment of these progressive recurrent FSGS has included pulse corticosteroid therapy and immunoadsorption. The severe course of the disease ended up with a rapid loss of graft function and development of chronic transplant nephropathy and end stage renal disease at 3 years after transplantation. A treatment with an automatic peritoneal dialysis was instituted and a look into the future and possible second transplantation is considered.

Recurrence of the FSGS in renal transplant recipients is an important cause of allograft dysfunction. Dilemma, which might be raised in this case is the time of treatment with renal replacement therapy and pretransplant work, as well as pretransplant work up in order to possibly improve the graft survival.

**Key words:** live donor transplantation; FSGS recurrence; treatment

---

### **Introduction**

Focal segmental glomerulosclerosis (FSGS) is the most frequent cause of intractable proteinuria in children and is a major cause of progressive chronic kidney disease [1]. Approximately 30% of patients with idiopathic FSGS recur after renal transplantation and in very young pediatric recipients and in patients with a rapid course of the disease from Caucasian origin there is a higher risk of recurrence.

It is worrisome complication for pediatric nephrologist because of its high rate of incidence, the subsequent graft loss and inability to predict its occurrence. Hence, an early diagnosis and adequate treatment are considered as crucial issue. Plasmapheresis and immunoadsorption with protein A columns have been used successfully in induction of the remission of proteinuria and the disease itself.

In addition, patients having recurrence of FSGS in the first year after transplantation with rapid loss of their graft are at very high risk (>80%) of having recurrences in the subsequent grafts.

Recurrence of FSGS with proteinuria can occur within hours of transplantation and is associated with diffuse effacement of the foot processes [1]. Recent advances in molecular genetics of FSGS led to the identification of several genes responsible for coding proteins of the podocyte and are localized in the glomerular diaphragm where they play role in the control of glomerular permeability.

Living-related donors are not recommended for renal transplantation in children with FSGS in many centers because of the high incidence of recurrence. However, the dilemma is arisen in the societies where there is no other choice than living-related transplantation.

## Case report

We present a case of 13 years old girl with clinical and laboratory symptoms of nephrotic syndrome since her 1 year of age. She underwent renal biopsy which showed histopathology of focal segmental glomerulosclerosis. The therapy with steroids, cyclosporin and cyclophosphamid did not achieve any substantial degree of remission of the disease.

At her 6 of age she progressed to terminal renal insufficiency and started her treatment with peritoneal dialysis for the next 2,5 years. In 2002 (at her 9 years of age), living donor kidney transplantation has been performed in Thessalonica (Greece). However, she did not receive preoperative immunoadsorption or other preconditioning regimen. The maintenance therapy consisted of cyclosporin, mycophenolat mofetil and steroids. Early recurrence of the nephrotic syndrome was clinically defined as a development of massive proteinuria ( $>40$  mg/m<sup>2</sup>/day) and hypoalbuminemia ( $<2,5$  g/l). She underwent graft biopsy and the recurrence of the primary disease (FSGS) was confirmed with a diffuse foot process effacement and/or glomerulosclerosis in the graft histology. The recurrence of the primary disease (FSGS) started at one year after transplantation with a high proteinuria (up to 4 g/l), elevated serum creatinine and urea levels and a therapy resistant hypertension.

The treatment of these progressive recurrent FSGS has included pulse corticosteroid therapy (methylprednisolone 250 mg/m<sup>2</sup>/day) for the first 3 days and then the dose was tapered at the level of the previous one. Immunoabsorption sessions (n=10) were conducted over the next 4 weeks.

## Discussion

We present a case report of a 13 years old girl with an extremely early onset of the original nephrotic syndrome as 1,5 year of age. The histology of the first renal biopsy showed initial focal segmental glomerulosclerosis. The therapy with steroids and cyclophosphamide did not show any improvement in the disease progression. The patient developed edema and hypertension, under a condition of overt proteinuria of 1,5-2g/l. In parallel there was manifestation of a classical nephrotic syndrome with hyperlipidemia (triglycerides 14,4 mmol/l), while serum creatinine and urea were still maintained within the normal range. At her 2 years of age a therapy with Cyclosporine (150 mg/m<sup>2</sup>) and steroids 30 mg/m<sup>2</sup> according to the internationally adopted protocols for FSGS in pediatric patients was administered.

The duration of the original nephrotic syndrome prior to development of ESRD was in a course of 4 years. We started peritoneal dialysis for 2,5 years (1 year CAPD and 1,5 year APD). She had four peritonitis episodes with staphylococcus aureus. She underwent living related kidney transplantation from her mother at 9 years of age with an excellent graft function of 90  $\mu$ mol/l. However, recurrent proteinuria developed 8 months posttransplantation. Kidney graft biopsy was performed and didn't

show any significant changes apart from mild interstitial inflammation. The therapy was switched to Prograf instead of Cyclosporine A. One year after transplantation we had already established severe persistent nephrotic syndrome and a deterioration of the graft function, with serum creatinine level 350  $\mu$ mol/l. A new graft biopsy confirmed recurrent FSGS of the renal allograft. A bolus methylprednisolone therapy for 3 days and immunoabsorption sessions for two weeks were started. Only a partial remission was obtained within the next six months. There was persistent nephrotic proteinuria and elevated degradation products. Moreover, the patient had an episode of graft rejection and shortly thereafter, she lost her graft function and was put on automated peritoneal dialysis.

Steroid-resistant nephrotic syndrome with FSGS is one of the most frequent lesions leading to renal transplantation in children. The recurrence of the disease is 20-40% in renal allografts and graft failure in 40-50% of patients with recurrence occur early after transplantation [2,3].

Living-related transplants are not recommended for children with FSGS in many centers, because of the high rate 20-30% of recurrence that is hard to predict, and the 30-50% rate of graft loss [4]. Unfortunately, in our country there is no possible choice of cadaveric transplantation yet. Hence, in cases when recurrent nephrotic syndrome is suspected clinically, an immediate graft biopsy is essential to confirm the recurrence and to differentiate a possible acute rejection.

An aggressive anti-rejection therapy should be started for patients experiencing graft rejection. On the other hand, an additional difficulty in managing recurrent FSGS is that it is hard to predict and hard to prevent [5]. The duration of the disease, the interval on dialysis and many peritonitis episodes made very hard decision for timing of the kidney transplantation [5]. It might have been better if we could have waited some more years on peritoneal dialysis, because of a possible acute rejection that could not have been excluded. The patient had cyclosporine nephrotoxicity early in the beginning, and we had to change the therapy switching it to tacrolimus. The serum creatinin and urea reached high levels several months after Prograf<sup>®</sup> was commenced.

Aggressive anti-rejection therapy should be initialised for patients experiencing graft rejection. Recently, rituximab, primarily indicated for treatment of lymphoma, has been successfully used in cases of immediate post transplant recurrence of FSGS [6]. Rituximab is a high-affinity-specific antibody against the CD20+ antigen. It is a chimeric monoclonal antibody composed of human immunoglobulin IgG1 heavy chain and kappa light chain constant regions and variable light and heavy chain murine regions. By targeting CD20 on precursor B cell we can decrease the production of activated B cell and limit antibody production. Rituximab directly inhibits B-cell proliferation and induces cellular apoptosis through the binding of complement. On the other hand, complement mediates cytotoxicity and antibody-dependent cell-mediated cytotoxicity.

The doses may vary between 375 mg/m<sup>2</sup> per dose at weekly intervals for 6 weeks and a single dose of 375 mg/m<sup>2</sup> which might result in a rapid clearing of circulating CD 20-positive B cells. Intermittent immunoadsorption combined with B cell depletion by rituximab treatment induced prolonged reduction of proteinuria in a high-risk patient for recurrence of FSGS in the graft [6].

### Conclusions

Recurrence or onset of de novo disease in the renal allograft is an important cause of allograft dysfunction. Recurrence in patients who develop ESRD secondary to FSGS can occur early, within days or weeks after transplantation (as it was in the present case). Treatment of recurrent FSGS has included high doses methylprednisolon, in combination with plasmapheresis and eventually combined with rituximab. However, randomized studies are required to establish new therapy for improvement and establishing therapy for graft rejection in patients with FSGS. The recurrence of the FSGS in renal transplant recipients is not only an important cause of allograft dysfunction but also a dilemma, as raised in our case on when the time of treatment with renal replacement therapy and pretransplant work should be initialised,

as well as the pre/posttransplant work up in order to possibly maintain the graft function and a survival.

*Conflict of interest statement.* None declared.

### References

1. Gian Marco Ghiggeri, Michele Carraro, Flavio Vincenti *et al.* Recurrent Focal glomerulosclerosis in the era of genetics of podocyte proteins: theory and therapy. *Nephrol Dial Transplant* 2004; 19: 1036-1040.
2. Hae Li Cheong, Hye Won Han, Hye Won Park, Li Soo Ha, Kyu Sup Han, Hyun Soon Lee, Sang Joon Kim, Yong Choi. Early recurrent nephrotic syndrome after renal transplantation in children with focal segmental glomerulosclerosis. *Nephrol Dial Transplant* 2000; 15: 78-81.
3. Richard N.Fine *et al.* Recurrence of nephrotic syndrome /focal segmental glomerulosclerosis following renal transplantation. *Pediatr Nephrol* 2007; 496-502.
4. First MR *et al.* Living-related donor transplants should be performed with caution in patients with focal segmental glomerulosclerosis. *Pediatr Nephrol* 1995; 9: S40-42.
5. Therese C Jungraithmay, Monika Bulla, Jurgen Dippell *et al.* Primary focal segmental glomerulosclerosis - Long-term outcome after pediatric transplantation. *Pediatr Transplant* 2005; 9(2): 226-31.
6. Terje Apeland, Anders Hartmann *et al.* Rituximab therapy in early recurrent focal segmental sclerosis after renal transplantation, *Nephrol Dial Transpl* 2008; 23: 2091-2094.