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Long-term plasmapheresis therapy in the management of focal segmental glomerulosclerosis recurrence after kidney transplantation

Gonzalo Ramirez-Guerrero [a], Angel M Sevillano Prieto [b,*], Fernando Jara-Vilugrón [c], Natalia Polanco Fernandez [b], Esther Gonzalez Monte [b], Ana Henandez Vicente [b], Lucia C Rodriguez Gayo [d], Manuel Praga Terente [b,d], Amado Andrés Belmonte [b]

[a] Department of Nephrology, Hospital Carlos Van Buren, Valparaiso. Street San Ignacio 725, Valparaíso, Chile
[b] Department of Nephrology, Hospital 12 de Octubre, Avda. de Córdoba, s/n Madrid, PC: 28041, Spain
[c] Department of Nephrology, Hospital Las Higueras, Alto Horno Street, Number 777, Talcahuano, Chile
[d] Department of Medicine, Universidad Complutense, Plaza Ramón y Cajal, Madrid, PC:28040, Spain

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ABSTRACT

The recurrence of primary focal segmental glomerulosclerosis (FSGS) after kidney transplantation (KT) appears in 30 % of the recipients. Sometimes it can cause the loss of the allograft. Although many treatments for this condition have been reported, 20 %–40 % of the affected patients are refractory or presents frequents relapses. In this paper we describe the evolution of three recipients treated with long-term plasmapheresis therapy after a recurrence of FSGS with a bad or incomplete response to other treatments. Although our findings require confirmation, long-term plasmapheresis could be a therapeutic option for this condition.

1. Introduction

Around 30 % of kidney transplantation recipients with renal failure secondary to FSGS develop a recurrence of the disease. The risk factors associated with recurrences are: younger recipient age, history of rapid progression to renal failure and the loss of a previously allograft from recurrence of the disease [1]. These recurrences are ominous, resulting in the loss of a half of the affected allografts after five years of follow up [2]. The lack of a full understanding of the FSGS recurrence pathophysiology and the limited number of clinical trials result in the absence of consensus on the most appropriated management of this condition. 20–40 % of these patients present relapses or are refractory under first line therapies [3,4]. In them, some authors have proposed long-term therapy with plasmapheresis, however reports are scarce and with short follow up times [5]. In this paper we present one of the longest series of recurrent primary FSGS after kidney transplantation in adults managed with chronic plasmapheresis therapy and their evolution.

2. Case Report/Case presentation

2.1. Case 1

53-year-old female recipient of a deceased-donor kidney transplantation due to a renal failure secondary to FSGS who achieved normal renal function after 12 days. On the first month after transplantation the patient presented a nephrotic syndrome, so a clinical diagnosis of FSGS recurrences was made. Seven plasmapheresis therapy exchanges were administered with a decrease of proteinuria under 1.5 g/day. Two years later the nephrotic syndrome reappeared. A graft biopsy was performed that showed calcineurin inhibitors toxicity, with no evidence of rejection or FSGS (electron microscopy were not available). Renin angiotensin aldosterone system blockade was started with a decrease of proteinuria from 6.4 g/day to 2 g/day. Eight months later proteinuria increased over 3.5 g/d, therefore a new allograft biopsy was performed that showed focal and global glomerulosclerosis in 2 and 6 of 18 glomeruli respectively. For this reason, 6 plasmapheresis exchanges and two doses of 1 g of rituximab were administered. Proteinuria initially decreased, but soon increased over 4 g/day. Long-term therapy with biweekly plasmapheresis exchanges were stablished, obtaining a normal renal function and the stabilization of proteinuria between 3 and 5 g/

* Corresponding author.
E-mail address: angelmanuel.sevillano@salud.madrid.org (A.M. Sevillano Prieto).

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day. Five years later plasmapheresis therapy was discontinued due to severe hypogammaglobulinemia. Shortly afterwards, proteinuria increased to 14 g/day and SCr to 1.7 mg/dl. Despite four boluses of 250 mg methylprednisolone and two doses of rituximab of 375 mg/m^2 no response was observed. Biweekly chronic plasmapheresis exchanges were re-started with intravenous immunoglobulin associated. With this treatment renal function improved to baseline, proteinuria dropped to 5 g/day and albuminemia rises to 4 g/dL. The patient was stable during 8 years. After this time, and despite of the intensification of plasmapheresis exchanges, proteinuria increased and a progressive loss of kidney function appeared. Renal replacement therapy was started 16 years after kidney transplantation Table 1.

2.2. Case 2

47-year-old female recipient of kidney transplantation since 2009 due to a primary FSGS. On the 12th day after transplantation the patient presented proteinuria of 3.2 g/day and albuminemia of 3 g/dl, with normal renal function. Given the high suspicion of FSGS recurrence, 6 plasmapheresis exchanges and two doses of rituximab were administered. An initial decrease of proteinuria occurred, but quickly increased over 3,5 g/day. An allograft biopsy showed 4 of 11 glomeruli with focal sclerosis and adherences to the Bowman's capsule, so biweekly plasmapheresis exchanges was started. Partial remission was achieved, consequently this therapeutic scheme was maintained until April 2019, when the patient presented an infectious event. One month later, a significant rise in SCr (2.49 mg/dl) with biochemical nephrotic syndrome was observed. Once the infection was controlled long-term therapy with biweekly plasmapheresis exchange was stablished again. Although proteinuria continued over 5 g/day, a partial recovery of her kidney function (SCr 2 mg/dl) and albuminemia was observed. To date (October 2020), the patient is under the same plasmapheresis therapeutic scheme, maintaining stable renal function and proteinuria (Fig. 1).

2.3. Case 3

47-year-old man, with renal failure due to FSGS. In March 2015, he received his second kidney transplantation (the first was lost secondary to FSGF recurrence). Rituximab was added to induction therapy to prevent early recurrence of the FSGS. However, on 3rd day post-transplantation nephrotic syndrome were detected. A second dose of Rituximab on 14th day and 6 daily plasmapheresis exchanges were scheduled, achieving complete remission and a SCr of 1.6 mg/dL. The patient suffered three new recurrences on May 2015, December 2015 and March 2016, with a kidney biopsy showing FSGS after the first one (12 glomeruli, three of them with global glomerulosclerosis and 7 with focal glomerulosclerosis). All of the recurrences were treated with 5 or 6 daily plasmapheresis exchanges and 1 g of Rituximab. Complete remission was reached in the first and second recurrences, however only partial remission was achieved in the last one. Thus, long-term therapy with biweekly plasmapheresis exchanges was started. In January 2018 plasmapheresis exchanges were stopped secondary to a urinary tract infection. In march 2018, nephrotic syndrome appeared and kidney function enhanced (Scr 3 mg/dl). We decided to re-start chronic plasmapheresis exchange attaining a partial remission of the nephrotic syndrome but without an improve in the kidney function. In January 2019 after a respiratory tract infection with acute kidney injury PP therapy was cancelled. Renal replacement therapy was restarted in March 2019.

3. Discussion/Conclusion

Recurrence of primary FSGS is a common event and is associated with an increased risk of allograft failure [4]. In this manuscript we report on of the longest series with the longest follow up of adult kidney transplantation recipients with FSGS recurrence managed with long-term plasmapheresis therapy in the literature. All of our patients were diagnosed before transplantation with primary not-genetic FSGS and clinically presented with severe nephrotic syndrome with important proteinuria and deep hypoalbuminemia, being at least partially resistant to immunosuppressive therapy. The pathogenesis of recurrent FSGS is not well known. Shalhoub el al. in 1974 postulated that a circulating factor secreted by the interaction between B and T cells would be the responsible actor for the damage in the filtration barrier, targeting podocytes, causing cytoskeleton reorganization, pedicellar disappearance, podocitary loss and generating excessive glomerular permeability. The origin of this circulating factor is not yet specified [3]. Calcineurin inhibitors, rituximab and corticoids are considered the first line therapy in the disease because of their ability to suppress T cells, B cells and both of them respectively. In the resistant and refractory cases abatacept (an inhibitor of co-stimulation) and ofatuzumab (a more potent anti CD-20 that rituximab) has been used with different results [4]. In other way, plasmapheresis therapy seems one of the most effective treatments for FSGF management, achieving remission in a 65 % of the cases. Plasmapheresis is a low-selective procedure that allows removal of high molecules from the blood, included that possible circulating factor not yet identified [6]. An immunomodulatory role of plasmapheresis in FSGF recurrences has been proposed too [7]. For this reason, plasmapheresis is classified as category I in the American apheresis society guide in the management of FSGS recurrence [8,9]. Plasmapheresis therapy is usually stablished in an acute way [7], however, the utility of long-term plasmapheresis has been reported in pediatric population [5, 10]. The patients of our series are adult kidney transplantation recipients with a recurrence of FSGF and not satisfactory respond to first line therapy, added to the kidney transplantation immunosuppressive

Table 1
Summary of the patients under long term plasmapheresis therapy.

Patient	Gender	Age at onset of FSGS (years)	Time to renal failure (years)	Age at KT (years)	Time to FSGS recurrence after KT	FSGS therapy different to PP	PP therapy	FSGS evolution	Kidney allograft evolution	Complications
1	F	53	0	53	1 month	Rituximab + IVIg + CC bolus	Biweekly for 5 years and for 8 years	Partial Remission hypoalbuminemia recovery	Renal failure after 16 years	Hypogammaglobulinemia.
2	F	39	9	47	12 days	Rituximab	Biweekly for 10 years and for 1 years	Partial Remission hypoalbuminemia recovery	11 years of follow up. Scr of 2.3 mg/dl	Hypogammaglobulinemia Pulmonary infection
3	M		2	47	3 days	IVIg + Rituximab	Biweekly for 3 years	Partial Remission hypoalbuminemia recovery	Renal failure after 4 years	Hypogammaglobulinemia and urinary tract infection

Abbreviations: F:Female, M: Male; IS: immunosuppressive; KT: kidney transplantation; IVIg: intravenous immunoglobulins; PP: Plasmapheresis; CC: corticosteroids.

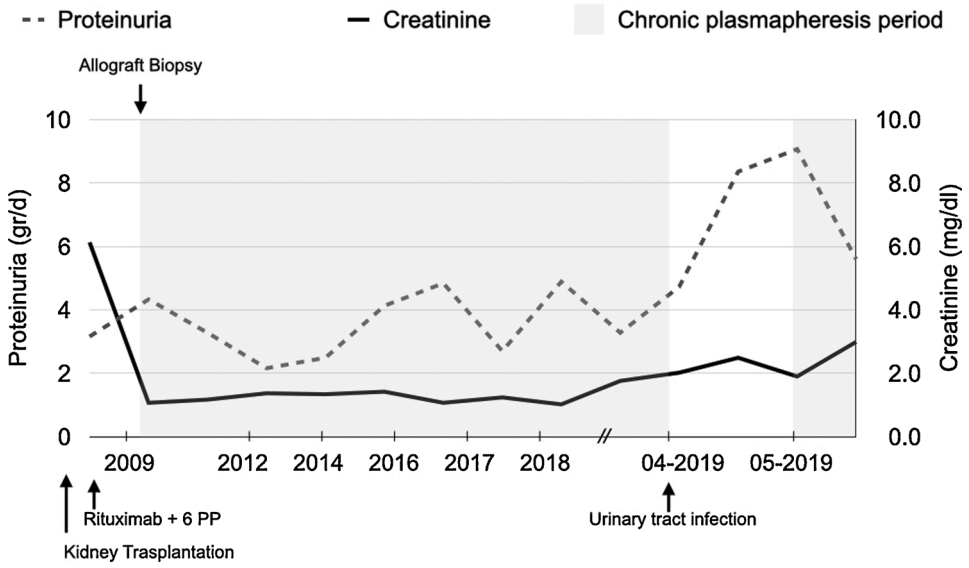

Fig. 1. Clinical evolution of patient 2.

regimen usually employed in our department (corticosteroids, mycophenolic acid and tacrolimus). That led us to stablish a therapeutically scheme based in long-term (generally biweekly) plasmapheresis exchanges. Usually, 1–1.5 plasma volume exchanges per procedure was performed using as replacement fluid albumin. If hypogammaglobulinemia appear, frozen plasma was employed as replacement fluid. After the start of plasmapheresis our patient's evolution was satisfactory. In that way, although only partial remission was achieved, a quite long renal survival was attending (16, 11 and 4 years in cases one, two and three respectively). The temporal relationship, with occurrence of relapses after plasmapheresis discontinuation and remissions when it was re-started, seems a probe of the utility of this therapy. The main concerns of plasmapheresis therapy are the need of a vascular access to performance it, and the appearance of adverse events (infection and hypogammaglobulinemia) like was observed in our patients. In conclusion, treatment with long-term plasmapheresis could be a weapon in the treatment of patients with frequent relapses or resistant FSFG recurrences after kidney transplantation.

Statement of ethics

Subjects have given their written informed consent to publish their case.

Author contributions

Research idea and study design: GRG, AMSP, FGV; Data acquisition: GRG; Data analysis/interpretation: GRG, AMSP; Supervision or mentorship: NPF, MPT, LRG, AAB; Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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