

Case Report

Plasmapheresis in Refractory FSGS

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Abstract

Focal segmental glomerulosclerosis (FSGS) is one of the commonest causes of glomerulonephritis related end stage renal disease. FSGS can be primary or secondary and its management varies. Patients with primary FSGS who present with nephrotic syndrome need treatment with glucocorticoids alone or in combination with other immunosuppressive drugs such as calcineurin inhibitors, cyclophosphamide or mycophenolatemofetil. Alternative therapies that have been tried in refractory FSGS include rituximab and plasmapheresis. Most of the literature regarding plasmapheresis is recurrent FSGS in renal transplant patients. To the best of our knowledge, there is very limited data on plasmapheresis in refractory FSGS in the native kidneys. Herein we report a case of refractory FSGS in native kidneys that failed to respond to all immunosuppressive therapy and finally responded to regular plasmapheresis.

Keywords

- Focal segmental glomerulosclerosis
- Plasmapheresis
- Rituximab
- Renal transplant

ABBREVIATIONS

FSGS: Focal Segmental Glomerulosclerosis; MMF: Mycophenolatemofetil; NR: Normal Range; SuPAR: Soluble Urokinase Plasminogen Activator Receptor; UPCI: Urine Protein Creatinine Index

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is a histopathologic pattern, rather than a disease. It can be primary or secondary (genetic diseases, infection, drug-induced, obesity and previous injury resulting in hyperfiltration of remaining viable nephrons) [1]. Adults with primary FSGS present with nephrotic syndrome in more than 70% in those cases where as secondary FSGS presentation is more frequent indolent, with asymptomatic sub-nephrotic proteinuria without hypoalbuminemia or oedema and progresses over years. Distinguishing between primary and secondary FSGS is important as their management varies. The incidence of FSGS has risen from 3 to 13 fold over the past 20 years and it is present in 20%-25% of adult patients with idiopathic GN [2]. Most recent data from United States Renal Data System reported glomerulonephritis related end stage renal disease with a total incidence of 6.5%, in which primary FSGS accounted the most at 2.1% [3]. The rate of spontaneous complete remission among FSGS patients with nephrotic syndrome is unknown but is probably less than 10% and more likely to occur among patients with normal kidney function and sub-nephrotic range proteinuria. Factors that influence response to treatment and prognosis include the severity and duration of proteinuria, severity of renal dysfunction and histologic findings like the degree of tubulointerstitial fibrosis, but the most reliable prognostic indicator remains the patient's response to treatment

[4]. Untreated FSGS patients with nephrotic syndrome have a five-year renal survival rate of 60 to 90%, and 10-year renal survival rates of 30 to 55% [5]. Heavy proteinuria (>10 g/day), in unresponsive treatment, is associated with an even worse prognosis, with most patients progressing to end stage renal disease within five years [5].

Herein we report a 24 year old patient with primary FSGS who presented in 2009 with severe nephrotic syndrome, and developed multiple relapses despite on standard first and second line therapy for FSGS including rituximab. She eventually achieved remission after regular plasmapheresis and remains in complete remission.

CASE PRESENTATION

A 24 year old Chinese lady presented to another institution in September 2009 lower limb swelling of two weeks associated with frothy urine. She denied any fever, sore throat, haematuria, connective tissue disease symptoms and no history of taking over the counter or traditional complementary medication. Clinical examination revealed bilateral pitting oedema up to knees another systemic examination was unremarkable. Laboratory investigations showed serum sodium 140 mmol/L (NR 136-145), potassium 4.0 mmol/L (NR 3.5-5.1), urea 3.4mmol/L (NR 2.5-6.7) and creatinine 70 µmol/L (NR 50.4-98), albumin 17g/L (NR 38-54), total cholesterol 8.4mmol/L (NR<5.18), triglycerides 5.4mmol/L (NR<1.7), low density lipoprotein cholesterol 4.0 mmol/L (NR<3.80) and high density lipoprotein cholesterol 3.2 mmol/L (NR>1.20). Her urinalysis revealed protein 3+, RBC negative and urine to protein creatinine index (UPCI) of 0.8 g/mmol (NR<0.02). She was diagnosed as nephrotic syndrome and a renal biopsy confirmed minimal change disease and was

started on oral prednisolone 1mg/kg and although there was some response to steroids, she relapsed in December 2009 when the dose of steroids was tapered and went to another institution for a second opinion. Mycophenolatemofetil (MMF) was added and oral prednisolone was increased to 50mg daily. Despite this, she did not respond and therefore presented to our institution for a third opinion. We switched MMF to oral cyclosporine A 100mg b.d. and performed a repeat renal biopsy in May 2010 which showed FSGS. Unfortunately she developed acute kidney injury with cyclosporine A and was started on intravenous cyclophosphamide in July 2010. However, she developed recurrent pneumonia after receiving one month of cyclophosphamide and therefore maintained on steroids only. She was diagnosed with endobronchial tuberculosis after bronchoscopy and CT thorax and treated anti-tuberculous therapy. All immunosuppressive agents were withheld that time except oral prednisolone. After 2 months of intensive phase of tuberculosis treatment, she received intravenous rituximab but did not respond and remained oedematous with her serum albumin ranging between 16-20 g/L and nephrotic range proteinuria. Subsequently in August 2011, we reintroduced cyclosporine A and MMF later in view of poor response. However, she still remained active not even achieving partial remission; therefore we switched cyclosporine A to tacrolimus in 2012 and titrated the dose to achieve therapeutic level. Despite being on triple therapy and therapeutic doses of tacrolimus and dual anti-proteinuric agents (perindopril and spironolactone) she still remained nephrotic. Eventually she was initiated on regular plasmapheresis via an arteriovenous fistula in Jan 2015 initially three sessions/week and had a good response within three months. We therefore tapered plasmapheresis to twice/weekly and two months later to once weekly. She is currently on plasmapheresis fortnightly since December 2015 and remains in complete remission. Since starting plasmapheresis, her UPCI reduced remarkably from an average of 0.5-0.8 g/mmol to 0.05-0.08 g/mmol with serum albumin level from less than 20 g/L previously to current level of 38 g/L, with a stable creatinine of 100 μ mol/L. She is now on fortnightly plasmapheresis in addition to prednisolone 10 mg/day and tacrolimus 2mg b.d. and remains in complete remission.

DISCUSSION

Initial therapy in patients with FSGS includes renin angiotensin aldosterone blockade along with good blood pressure control, however, nephrotic patients rarely achieve remission without immunosuppressive therapy [6]. In patients with nephrotic syndrome, a course of prednisone is recommended until complete remission is attained and tapered slowly over 4-6 months. In steroid dependent or steroid-resistant FSGS, ciclosporin A can be used and maintained for 1-2 years after remission is achieved. A calcineurin inhibitor or MMF can be considered as first line immunosuppressive therapy in patients contraindicated for steroids [7]. Cyclophosphamide may be considered in patients who shown a partial response to prednisone and who show extensive interstitial fibrosis and/or vascular disease on renal pathology that put them at higher risk of calcineurin nephrotoxicity. Rituximab has been reported with some success in adult patients with steroid-dependent but not steroid resistant FSGS. Kronbichler et al in 2013 reported all

five patients treated with rituximab achieved sustained complete remission and additional immunosuppression was able to be withdrawn in multiple relapsing steroid-dependent nephrotic syndrome due to FSGS [8]. However, our patient did not respond to rituximab presumable because she was steroid resistant.

To the best of our knowledge, there are only few studies on plasmapheresis in native kidney FSGS patients. The limited role for plasmapheresis in the treatment of primary FSGS is based on the finding of unidentified plasma factors in patients with recurrent FSGS post renal transplant [9]. Recently, soluble urokinase plasminogen activator receptor (suPAR) was identified in a majority of patients with FSGS. Increased plasma levels of suPAR lead to increased β_3 integrin activation, causing podocyte dysfunction and effacement [10]. Many studies regarding suPAR and its subtypes are ongoing still. Ponticelli demonstrated that both 63% of adult patients with recurrence of FSGS post renal transplantation achieved complete or partial remission of proteinuria [11]. A systematic review published in 2016 reported remission rates (both partial and complete) of 71 % with plasmapheresis in recurrent post-transplant FSGS [12]. However, the applicability of data from transplant recipients to patients with native kidney primary FSGS is unclear. There are controversial reports regarding benefits of plasmapheresis in treating primary FSGS. Mitwalli reported a 72.7 or 73% remission rate when plasmapheresis was performed in addition to corticosteroids and cyclophosphamide in 11 patients with steroid-resistant primary FSGS [13]. Contemporary uncontrolled study by Feld et al., reported a relatively poor response rate with plasmapheresis, with only two of eight patients experiencing transient improvement in proteinuria [9]. Oliveira reported a case of late rescue from end stage renal disease due to FSGS when plasmapheresis was combined with low dose during haemodialysis treatment [14]. Since 2007, there is paucity of literature regarding plasmapheresis in native refractory primary FSGS. Our patient failed to respond to all immunosuppressive therapy and it's the rationale for the use of plasmapheresis. She achieved remission after regular plasmapheresis with dramatic improvement symptoms, serum albumin and UPCI.

We conclude that plasmapheresis could be a beneficial refractory native FSGS. However, since there is limited data on the long-term effects of such an approach, plasmapheresis should only be considered in patient who has failed to respond to conventional treatment.

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