Tryptophan immunoabsorption strongly reduces proteinuria in recurrent nephrotic syndrome

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Introduction

Nephrotic syndrome in patients with focal segmental glomerulosclerosis (FSGS) is characterized by heavy proteinuria. Because of a lack of efficient therapy, FSGS often leads to end-stage renal failure. Recurrence of FSGS and nephrotic syndrome is common after renal transplantation and has been reported in 15–55% of patients [1]. It has been suggested that the plasma of these patients contains one or more factors, which increase glomerular permeability to proteins. Plasma exchange and plasma-adsorption using protein A Sepharose cartridges have been used successfully so far. Supposedly, these plasma-treatments removed a factor(s) from plasma, which is (are) related to FSGS and the nephrotic syndrome. They were shown to effectively reduce proteinuria in FSGS [2–5]. In the present case, we performed immunoabsorption (IA) with a tryptophan-covered exchange column, which effectively reduced proteinuria. This is the first report of tryptophan-covered exchange columns in the treatment of FSGS. The patient was a kidney transplant recipient with FSGS and recurrent nephrotic syndrome.

Case

A 44-year-old male presented himself to the nephrologist in 1992 with idiopathic nephrotic syndrome. There was rapid progression to end-stage renal failure, and chronic haemodialysis became necessary the same year. A kidney biopsy was not taken. The patient received a cadaveric kidney allograft in June of 1998. Cold-ischaemic time was 16 h 55 min. HLA mismatch was: HLA-A, 2; HLA-B, 1; HLA-DR, 0. The age of the donor was 31 years. The initial graft function was excellent. On day 6 after transplantation, the serum creatinine increased and renal perfusion deteriorated. A kidney biopsy of the graft was performed. It showed acute rejection (Banff II). High-dose methyl prednisolone was given for 5 days; however, no improvement of renal function occurred. Rejection therapy was changed to include OKT-3. There was a decrease of the serum creatinine and normalization of renal perfusion. Cyclosporin A was changed to FK506. On discharge from the hospital (day 35 after transplantation) serum creatinine was 102 μmol/l and proteinuria was noticed (0.75 g/day). During the next 6 months proteinuria gradually increased. Seven months after the transplantation proteinuria had reached 27–35 g/day. The patient had massive oedema. There was profound hypalbuminaemia of 18 g/l. The serum creatinine had risen to 160 μmol/l and the serum urea was 20 mmol/l (normal 3.6–8.9 mmol/l). The urine sediment showed hyaline casts, but it was otherwise unremarkable. Another kidney graft biopsy was performed. Four of 21 glomeruli showed segmental glomerular sclerosis with adhesion of capillaries to Bowman’s capsule, swelling of epithelial cells, and accumulation of foam cells. Two of 21 glomeruli showed complete scarring. Some pre-glomerular capillaries showed media thickening with obliteration of the capillary lumen. FSGS was diagnosed and IA was started with 11 treatments given over a period of 17 days. During the first three sessions, 4 l of plasma (equal to 1.2 plasma volumes) were treated in each session, and during the following eight sessions 2 l of plasma (equal to 0.6 plasma volumes) were treated in each session, respectively. Over the following 3 weeks proteinuria decreased to 1.5–2.0 g/day (Figure 1). Serum albumin rose from 27 to 38 g/l (normal 37–53 g/l), serum creatinine fell to <100 μmol/l. Immunoglobulin G (IgG) fell from 30.24 g/l before IA to 1.89 g/l. One week after the last IA treatment, the patient developed bacterial pneumonia. He became bacteraemic. He required 6 days of treatment in the intensive care unit. Thereafter he made an uneventful recovery from the pneumonia.

About 1 month after the start of IA the patient was discharged from the hospital. Proteinuria was stable at

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1.5–2.0 g/day without IA. The graft perfusion was excellent by colour Doppler ultrasound. The serum creatinine was 160 μmol/l.

**Methods**

*Plasma protein adsorption*

The patient was treated with IA to tryptophan using the Haemomat-Plasmonat sytem (Diamed, Cologne, Germany). After the initial separation of plasma from corpuscular elements of blood, plasma was run through a column covered with a tryptophan-immobilized polyvinyl alcohol gel (TR 350, Asahi Medical, Japan) at a flow rate of 20 ml/min. Heparin was given for anticoagulation: 5000 I.E. as initial bolus, and 1000 I.E./h thereafter. In the first three treatment sessions, 41 of plasma were treated. In the following seven treatment sessions, 21 were treated (requiring approximately 4 and 2 h, respectively).

**Discussion**

It is now well established by several reports from different laboratories, that FSGS is often treatable by IA [3–5]. This applies to FSGS in renal transplants [3] and to FSGS in native kidneys [5]. The effects are attributed to removal of putative circulating factor(s), contributing to FSGS. This hypothesis has received support recently by the observation that isolated glomeruli in vitro when exposed to serum from patients with FSGS acquired increased glomerular permeability [6].

In the present case, the treatment of an FSGS-related recurrent nephrotic syndrome in a kidney transplant recipient using IA to a tryptophan column, dramatically improved proteinuria. To our knowledge, this has not been shown before. Franke et al. reported a child that was treated with a tryptophan column resulting in complete remission for 7 months. However, they did not communicate any data concerning proteinuria before and after IA to that column. Dantal et al. showed that IA using an anti-IgG IA column and IA on a protein-A column were equally effective in reducing proteinuria because of recurrent nephrotic syndrome after kidney transplantation. In fact, proteinuria fell by 83% and in some patients by more than 90%. In our patient proteinuria was reduced by 92% (from 25 to 2.0 g/day). Thus, the tryptophan column was equally effective with respect to the decrease in proteinuria. Dantal et al. treated 12.5 plasma volumes to achieve the effect mentioned above [5]; in our patient, we treated 8.25 plasma volumes. Thus, in our patient the tryptophan column appeared to be at least equally effective to the anti-IgG- and protein-A column. Treatment of more patients is necessary to confirm this observation. In our patient IgG decreased by 52% compared with 89% in the patients treated with the anti-IgG column (Figure 2). This supports the hypothesis that the involvement of immunoglobulins in causing the nephrotic syndrome of recurrent FSGS warrants further studies. In our study, the profound endogenous increase in IgG on day 35 was attributed to bacterial pneumonia.

Another aspect is economically important: the tryptophan column is approximately 15 times cheaper than the reusable protein-A and IgG column. In a newly diagnosed disease, where response to treatment (in this case reduction of proteinuria) is still uncertain, it might be economically wise to initiate IA with...
a tryptophan column unless response to treatment is verified.

In conclusion, we demonstrated that IA to tryptophan substantially decreased proteinuria in a patient with recurrent nephrotic syndrome as a result of FSGS in a kidney allograft. Whether removal of immunoglobulins or of another yet to be clarified factor leads to the reduction in proteinuria remains to be detected. Further studies with more patients are necessary to confirm our results.

References


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