Successful treatment of focal segmental glomerulosclerosis (FSGS) after kidney transplantation with abatacept

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INTRODUCTION

Recurrence of primary FSGS after kidney transplantation occurs frequently, is difficult to treat and has been associated with decreased allograft survival. A circulating factor, probably soluble urokinase (suPAR) is assumed to cause FSGS. This permeability factor, be it suPAR or not, probably causes podocyte damage and proteinuria by inducing podocyte B7-1 (CD80) expression which leads to podocyte migration through inactivation of ß1-integrin. This pathophysiological concept provides the framework for a B7-1targeted therapy in FSGS.

CASE REPORT

A 26-year-old man with end-stage renal disease received a kidney transplantation from a deceased donor in October 2013 after having performed chronic peritoneal dialysis and hemodialysis for seven years. He had suffered from juvenile rheumatoid arthritis since early childhood. His primary renal diagnosis was unknown, but secondary amyloidosis due to rheumatic disease was suspected.

After an induction therapy with basiliximab the patient was treated with a standard immunosuppressive regime based on tacrolimus, mycophenolat mofetil (MMF) and steroids and CMV-prophylaxis with valgancyclovir.

On day eleven after transplantation he developed a nephrotic range proteinuria with a urinary protein-creatinine ratio (UPCR) of 3.34 g/g. An allograft biopsy showed ten normal glomeruli with negative immunohistology, and early recurrent primary FSGS was deemed to be the most likely diagnosis. Despite eight plasma exchange (PE) sessions over a period of three weeks proteinuria remained significantly elevated at around 3.5 g/g after an initial decline from 5.5 g/g (Fig.1).

A single dose of abatacept 10 mg per kg body weight was given. In order to avoid over-immunosuppression the dose of MMF was reduced from 1000 mg to 500 mg daily. Within the next three weeks, proteinuria decreased to 1.5 g/g, but then began to rise again to a peak value of 4.5 g/g over another three weeks.

A second allograft biopsy showed progressive disease with diffuse mesangial expansion (Fig. 2). Electron microscopy revealed dystrophic podocytes with flattened foot processes (Fig. 3). The patient was treated with further eight PE, leading to a reduction of proteinuria to around 3.0 g/g with a tendency to increase. Therefore, we decided to give a second dose of abatacept. This was followed by a rapid decline of proteinuria to 1 g/g and a further decline to 0.15 g/g in the following months..

Two weeks after the second dose of abatacept BK viremia was detected for the first time. BK viremia increased to 200000 copies/ml and JC viremia (6800 copies/ml) was detected additionally. After a further reduction of the immunsuppressive therapy JC-virus subsided whereas mild BK-viremia (10000 copies/ml) persisted. Regular EBV-DNA screening remained negative. Transplant function remained stable over the last 12 months (serum creatinine 1.4 mg/dl).

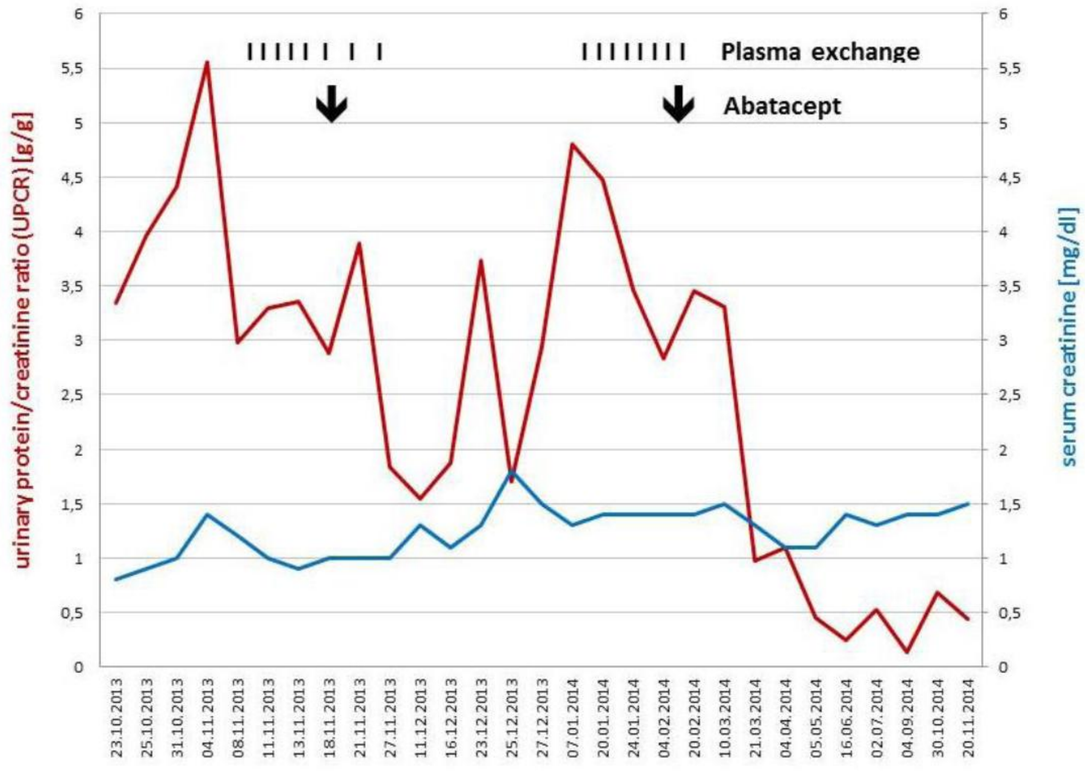

Fig. 1. Time course of serum creatinine and urinary protein/creatinine ratio in relation to plasma exchange and abatacept infusions.

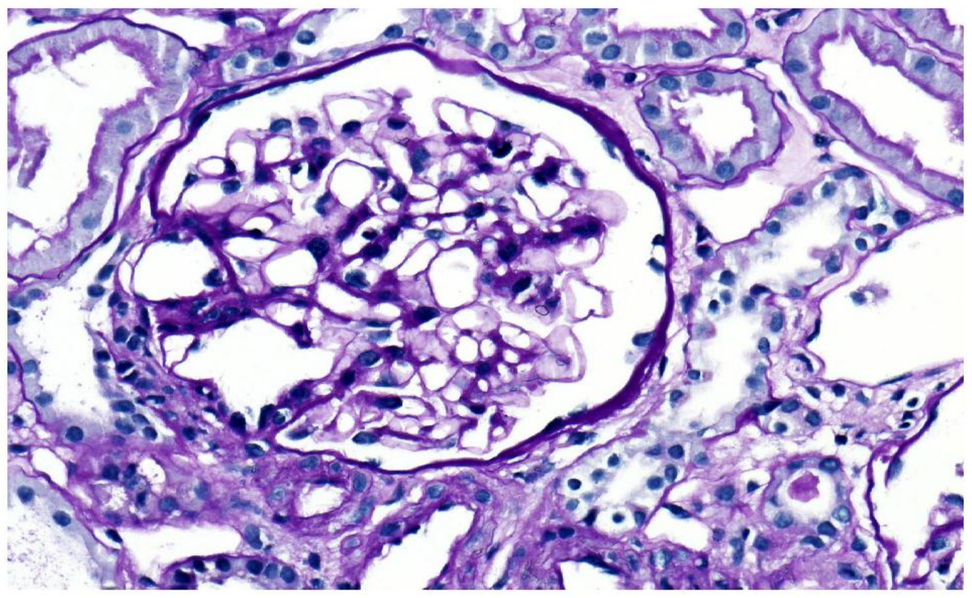

Fig. 2. Light microscopy showing mild mesangial matrix expansion and an increase in mesangial cell number with focal accentuation (PAS, 200x).

ABATACEPT: PROPOSED MODE OF ACTION

Abatacept is a fusion molecule of a modified cytotoxic T lymphocyte-associated antigen 4 - (CTLA-4) extracellular domain and a constant-region fragment of human IgG1. Abatacept and its sister molecule belatacept bind to B7-1and B7-2 on antigen-presenting cells, thereby blocking T cell activation, and are currently licensed for the treatmentof rheumatoid arthritis and the prevention of rejection in kidney transplantation. The rationale for the use of abatacept in recurrent FSGS was the observation that B7-1 is expressed de novo on podocytes in proteinuric kidney diseases. B7-1 causes inactivation of β1-integrin via competition between its cytoplasmic tail and talin for binding to β1-integrin. Inactivation of β1-integrin will subsequently cause detachment of foot processes and proteinuria.

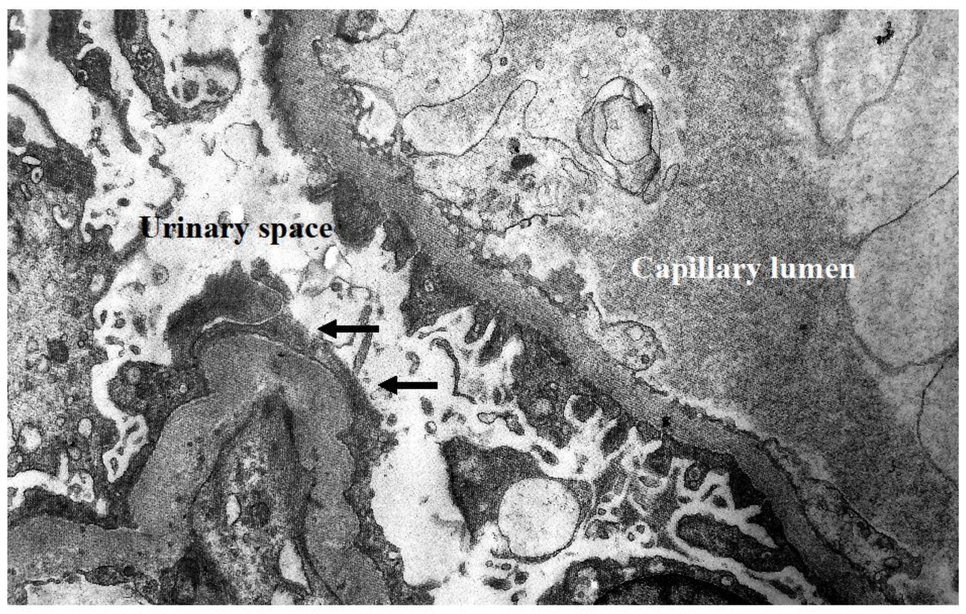

Fig. 3. Electron microscopy of the renal biopsy reveals partial effacement and flattening of podocyte foot processes (⬅). The glomerular basement membrane is regular. No immune complex deposits are detected (4000x).

DISCUSSION

Although we cannot exclude a possible role of PE treatment, we believe that remission of proteinuria in our patient was caused by abatacept. The debate is ongoing on whether CTLA4Ig fusion molecules are effective in the treatment of recurrent FSGS or other proteinuric diseases.

If B7-1 blockade proves to be effective, an immunosuppressive protocol based on belatacept should be considered for patients who suffer from primary FSGS undergoing renal transplantation. The risk of viral infection in kidney transplant recipients treated with abatacept on top of full immunosuppression and plasma exchange is a matter of concern. Careful monitoring and judicious management of immunosuppressive therapy are warranted.

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