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Exceptional Case

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Successful long-term management of recurrent focal segmental glomerulosclerosis after kidney transplantation with costimulation blockade

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ABSTRACT

Recurrence of primary focal segmental glomerulosclerosis (FSGS) occurs in up to 50% of patients after kidney transplantation and is associated with poor allograft outcome. Novel therapeutic concepts directly target podocyte function via B7-1 with inconsistent response. We present the case of a 19-year-old patient with recurrent primary FSGS early after living donor kidney transplantation. Plasmapheresis and rituximab did not induce remission. Repetitive abatacept administration was able to achieve partial remission. Maintenance immunosuppression was subsequently switched to a belatacept-based calcineurin inhibitor-free immunosuppression, resulting in sustained complete remission with excellent allograft function throughout a follow-up of >56 months.

Keywords: B7-1, belatacept, focal segmental glomerulosclerosis, kidney transplantation, nephrotic syndrome, recurrence

BACKGROUND

Primary focal segmental glomerulosclerosis (FSGS) represents a major challenge after kidney transplantation due to a high rate of recurrence and poor allograft outcome [1]. There is no consensus on optimal therapeutic concepts for prevention and management of recurrence. A novel approach using inhibition of the T-cell costimulatory protein B7-1 has shown partial or complete remission [2]; however, subsequent investigations with B7-1 blockade could not reproduce this finding [3]. Here we report a case of successful long-term remission with abatacept and subsequent belatacept-based immunosuppression.

CASE REPORT

A 19-year-old patient presented for living donor kidney transplantation due to primary FSGS (further information in Supplementary data). On post-operative day (POD) 4, the patient

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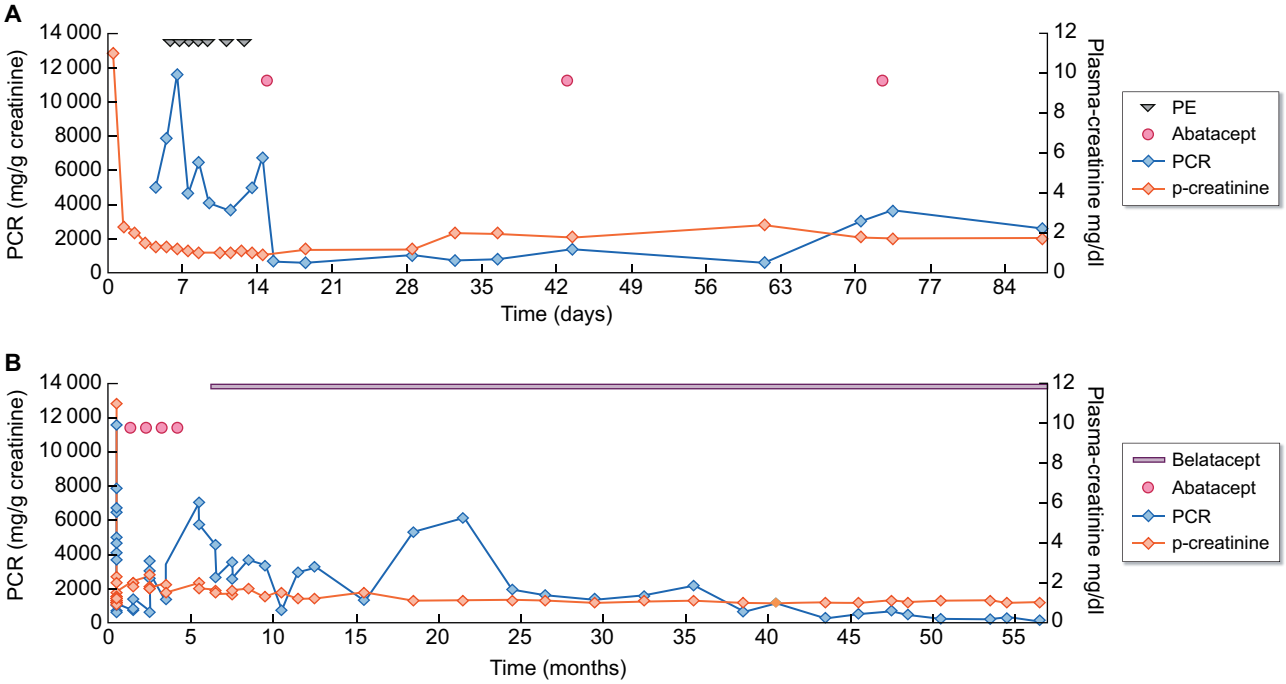

FIGURE 1: (**A**) Clinical course of allograft function and proteinuria in the initial period following transplantation. (**B**) Long-term clinical course of allograft function and proteinuria. PCR, protein/creatinine ratio.

developed nephrotic range proteinuria, which continued to rise up to 11 589 mg/g creatinine on POD 7 while allograft function remained excellent [plasma creatinine 1.2 mg/dL, estimated glomerular filtration rate (eGFR) 87 mL/min/1.73 m^2]. Renal vein thrombosis was excluded. Suspicious of early recurrence of FSGS, plasmapheresis was initiated on POD 4 and continued daily for the next 5 days and then every other day until POD 13. Under this treatment, proteinuria stabilized at around 4000 mg/g creatinine. A first kidney biopsy performed on POD 14 did not show any pathology, and in particular no signs of podocytopathy. On POD 15, abatacept 500 mg was administered, which lead to a rapid decrease in proteinuria (Figure 1A). Due to neurotoxic side-effects related to tacrolimus a switch to cyclosporine was necessary on POD 16. The patient was dismissed with excellent allograft function (plasma creatinine 1.2 mg/dL) and proteinuria <1000 mg/g creatinine.

Over the next weeks, allograft function slowly deteriorated. A second kidney biopsy performed on POD 61 revealed podocyte foot effacement on electron microscopy, confirming the diagnosis of podocytopathy, in clinical context consistent with the diagnosis of recurrent FSGS. Abatacept was continued every 4–6 weeks for a total of four doses, furthermore, rituximab 375 mg/m^2 was given on POD 73. In due course, the patient was switched to a belatacept-based immunosuppression with subsequent taper of cyclosporine. Pre-transplant Epstein–Barr virus-seropositivity was confirmed prior to conversion.

Although proteinuria was undulating for 2 years after transplantation with another peak at 18–22 months, no clinical signs of nephrotic syndrome were evident. Follow-up biopsies were declined by the patient. During long-term follow-up of currently 5 years, allograft function has remained excellent with an eGFR of >90 mg/dL (plasma creatinine 1.0 mg/dL) and clinically insignificant proteinuria (130 mg/g creatinine, albumin to creatinine ratio 72 mg/g) on maintenance immunosuppression with belatacept, mycophenolate and prednisolone (Figure 1B).

DISCUSSION

The present case demonstrates the lymphocyte costimulatory molecule B7-1 to be a target for drug therapy and supports evidence for a pathophysiologic role of B7-1 in recurrent FSGS. Expression of B7-1 has been shown in murine and human podocytes in proteinuric disease [4]. By interacting with the regulation of the actin cytoskeleton, B7-1 leads to podocyte foot process effacement and proteinuria. However, staining for B7-1 in podocytes is not consistently reproducible and the prognostic value to date remains unclear (further discussion in Supplementary data).

In 2013, Yu *et al.* successfully used the B7-1 inhibitor abatacept to induce partial or complete remission in five patients with FSGS [2]. These patients achieved remission after one or two doses of abatacept. Our patient required four repetitive administrations of abatacept every 4–6 weeks to achieve and maintain partial remission. Switch of maintenance immunosuppression to belatacept, showing a 2-fold higher binding affinity to B7-1, allowed for complete remission and excellent allograft function over a follow-up of >56 months. This is in line with the notion that patients with belatacept maintenance immunosuppression have lesser recurrence of FSGS, compared with a calcineurin inhibitor (CNI)-based immunosuppression [5]. Although these data provide evidence for sustained long-term remission under B7-1 inhibition with belatacept, a previous case series has not shown an effect of B7-1 inhibition with either abatacept or belatacept [3].

A limitation to our case is the overlap of initial therapeutic approaches [plasma exchange (PE), rituximab, CNI] and initiation of B7-1 inhibition that compromises dissociation of effects (see also Supplementary data). However, most of the patients reported in the studies of Yu *et al*. and Delville *et al*. also had received PE and/or rituximab previously [2, 3]. The main difference to our case is treatment duration, as complete remission was only achieved with repetitive applications of high-affinity B7-1 inhibitor belatacept over many months, making it unlikely to be an effect of PE, rituximab or CNI use.

In conclusion, we hereby report a first case of sustained long-term remission of recurrent FSGS by costimulation blockade in a renal transplant recipient using maintenance immunosuppression with belatacept. Hence, in case of limited response to plasmapheresis and/or rituximab, conversion to belatacept-based immunosuppression may be considered.

PATIENT CONSENT

The patient gave informed consent to publish this case.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

None declared.

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