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Adrenocorticotrophic Hormone—Induced Remission of Pediatric Post-transplantation Recurrent Focal Segmental Glomerulosclerosis

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INTRODUCTION

Recurrence of focal segmental glomerulosclerosis (FSGS) after kidney transplantation occurs in up to 50% of cases and may lead to early graft failure.[1,2] In most patients, the exact biological mechanisms underlying recurrence are unknown and are likely multifactorial, which hampers targeted treatment. The majority of early post-transplantation nephrosis is presumed to be due to recurrence of the primary FSGS,[3] and evidence suggests that soluble factors play a role.[1,2,4] Despite multiple approaches to avoid FSGS recurrence in transplant patients, a uniform approach is not yet established.[2] This case report discusses the potential of adrenocorticotrophic hormone (ACTH) to treat post-transplantation disease recurrence in a pediatric patient.

CASE PRESENTATION

The study complied with the Declaration of Helsinki for investigations in human subjects. The Ethics Committee of the Sydney Children's Hospital Network (Sydney, Australia) approved the study. In line with good clinical practice guidelines and the national legislation, both parents provided written informed consent, and child gave informed assent.

The patient was first referred to our center when she was 2 years old, with a new diagnosis of steroid-sensitive nephrotic syndrome. She was referred from a rural center, having responded to steroids within 7 days. However, she relapsed when tapering steroids and then became unresponsive to both oral and high-dose i.v. corticosteroids. A renal biopsy was performed, which was suggestive of FSGS. After the diagnosis of steroid-resistant nephrotic syndrome (SRNS), the patient was commenced on cyclosporine (25 mg twice daily in addition to 60 mg/m^2 prednisone daily). Sequencing for a panel of genes associated with SRNS (Bristol, UK)[S1] was performed and did not reveal causative mutations. She received albumin infusions for symptomatic relief of her edema. After 4 months, her urine albumin:creatinine ratio (UAC) remained elevated (Figure 1), and she was changed from cyclosporine to an 8-week course of cyclophosphamide with weekly i.v. methylprednisolone.[S2] The patient responded partly to this protocol (Figure 1), but relapsed again after an upper respiratory tract infection. Rituximab was given without success. Immunosuppressive therapy was subsequently withdrawn, and indomethacin and an angiotensin-converting enzyme inhibitor were continued. The angiotensin-converting enzyme inhibitor was discontinued because of hyperkalemia, and tacrolimus was commenced. The symptomatic edema and proteinuria continued with anemia, low anti—thrombin 3 levels, low vitamin D, and elevated thyroid-stimulating hormone; therefore, prophylactic low—molecular-weight heparin was initiated as well as thyroxin, vitamin D, sodium bicarbonate supplements, iron, and erythropoietin supplementation. Albumin infusions were used to manage symptomatic edema. Proteinuria partially improved, but her kidney function deteriorated to end-stage kidney disease, and

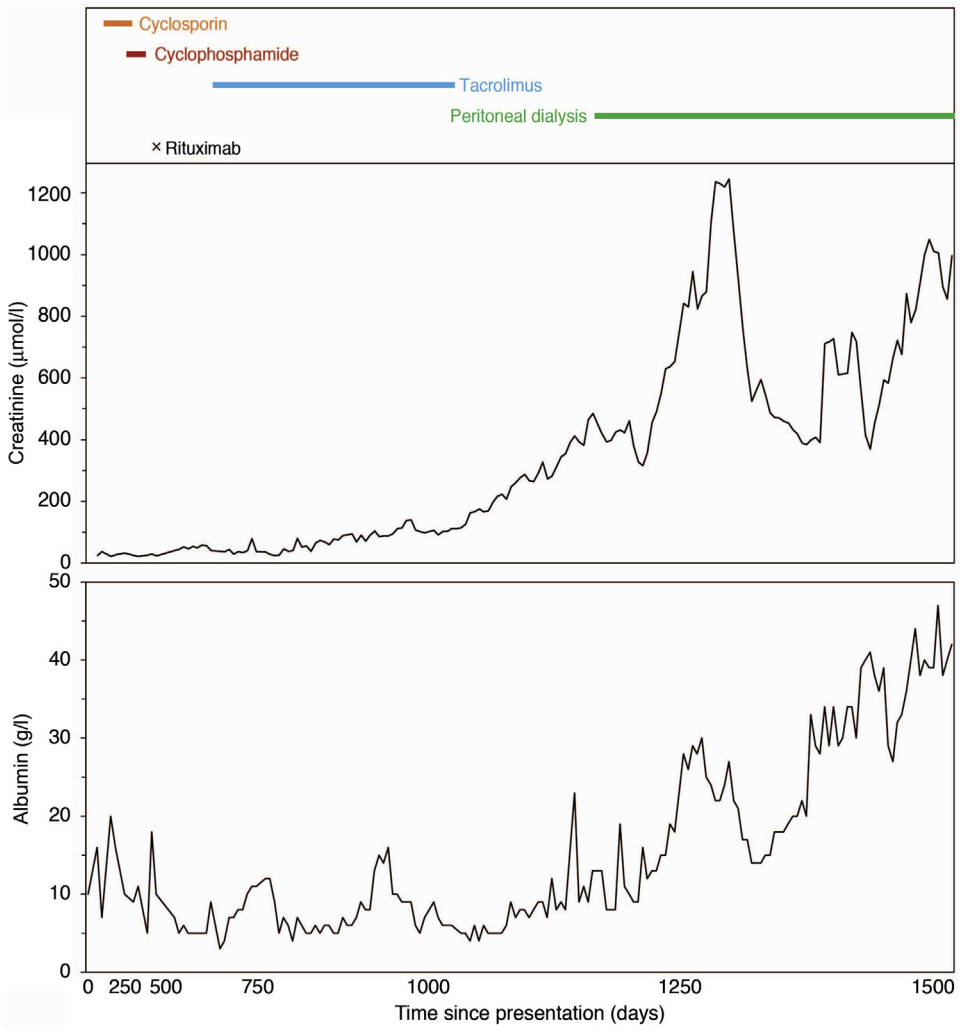

Figure 1. Overview of disease characteristics and treatment modalities from disease presentation until transplantation.

peritoneal dialysis was commenced at 3 years after the initial presentation. A year later, she received a deceased-donor kidney transplant. Her transplant immunosuppression regimen consisted of tacrolimus, mycophenolate, and prednisone with basiliximab at induction. She developed clinical disease recurrence immediately after transplantation (defined as UAC >1000 mg/mmol), and a renal biopsy showed FSGS and effacement of foot processes. She was treated with intensive plasma exchange and i.v. Ig in addition to 2 doses of rituximab (375 mg/m^2), with continuation of tacrolimus therapy (Figure 2). Moreover, she required multiple albumin infusions for symptom management. After these treatments, her serum creatinine remained stable, but serum albumin and urine UAC had not significantly improved (Figure 2). Remission (defined as UAC <25 mg/mmol and normalization of serum albumin) was not achieved and at 6 months post-transplantation when she was still receiving plasma exchange and i.v. Ig. Adrenocorticotrophic hormone therapy was initiated at a low dose of 0.3 mg subcutaneously twice a week (with continuation of her immunosuppression regimen), and she responded before further consideration of a dose increase. Her serum albumin increased from 11 to 26 g/l, and her UAC dropped from 1481 to 242 mg/mmol when plasma exchange and i.v. Ig were discontinued (Figure 2). Her serum albumin and UAC continued to normalize. She remained on the same dose for 6 months and was weaned off over 1 month. Four months after cessation of ACTH, she relapsed (as defined by UAC >1000 mg/mmol and a fall in serum albumin) and was recommenced on ACTH (Figure 2) at the same dose as soon as the drug was made available. Subsequently, she once again responded quickly to ACTH, which is ongoing. As she is now in remission (defined as UAC <25 mg/mmol), a further course of rituximab will be considered.

Complications of note during her disease progress and ACTH therapy were hypertension, low bone mineral density, and dyslipidemia. Supportive measures were taken, and at present she is still managed for

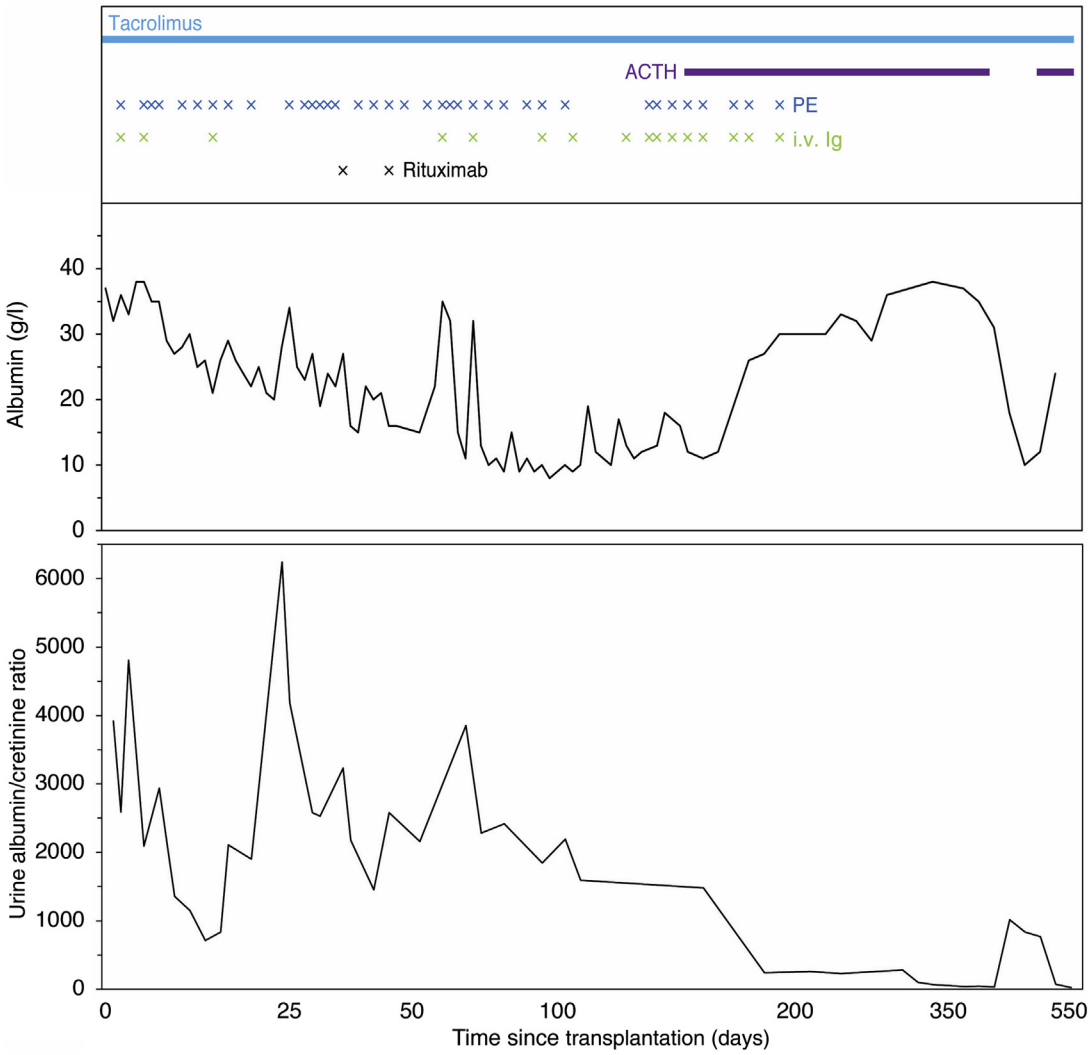

Figure 2. Overview of disease characteristics and treatment modalities from transplantation until present. ACTH, adrenocorticotrophic hormone; PE, plasma exchange.

these comorbidities. Moreover, her blood BK-virus counts increased after the second course of ACTH, which was managed with exchange of mycophenolate mofetil for leflunomide. Her current creatinine level is 31 μmol/l, and a recent glomerular filtration rate was measured (Tc-99m diethylene triamine pentaacetate) at 111 ml/min per 1.73 m^2. Despite the complex disease progression and multiple intensive therapies, she describes her quality of life as excellent.

DISCUSSION

Stratification of pediatric patients with FSGS according to phenotype and genotype now allows much better risk prediction for recurrence of disease post-transplantation. Patients with a known genetic cause of SRNS have negligible disease recurrence, compared to those without an identified cause with SRNS (~30% recurrence) or initially SSNS and subsequent SRNS (~90% recurrence).[5] Recurrence of FSGS may be more common after live donation compared to deceased donation.[S3]

Recurrence is typically managed with a regimen of plasma exchange and rituximab, although this regimen is known to fail in ~50% of cases.[S4] In this report, we successfully treated FSGS recurrence with ACTH s.c. injections twice weekly for both induction of remission after FSGS recurrence post-transplantation as well as the second relapse. To the best of our knowledge, this is the first case report of ACTH use in a child with FSGS recurrence after kidney transplantation.

We have reviewed the use of ACTH in renal transplant patients in Table 1.[6,7,S5–S8] To illustrate our case further, 2 retrospective reviews have looked at the use of ACTH gel in resistant FSGS in adults.[6,7] Alhamad *et al*. reported outcomes of ACTH treatment in 20 adults with post-transplantation FSGS (15 were recurrent disease) after treatment failure of therapeutic plasma exchange and/or rituximab. There was

Table 1. Review of ACTH use in kidney transplant patients

Study	N	Mean age (y)	Inclusion	Intervention	Outcome
Alhamad *et al.*[7]	20	49	*De novo* or recurrent FSGS resistant to TPE and rituximab	ACTH analogue gel 80 units s.c. injection twice weekly	Complete or partial remission in 50%
Anwar *et al.*[S5]	1	23	Case report	ACTH analogue s.c. injection 80 units twice weekly	Partial remission
He *et al.*[S6]	6	37	Effect of short-term ACTH administration on lipid profile and kidney function	ACTH analogue i.m. injection 1 mg/d for 4 days	Beneficial for lipid profile and kidney function
Grafals *et al.*[6]	14	41	Retrospective study on effect of ACTH in FSGS after transplantation	ACTH analogue gel 80 units twice weekly	Complete or partial remission in 36%
Markell *et al.*[S7]	3	48	Case series	ACTH analogue gel 80 mg twice weekly	Partial remission in 66%
Mittal *et al.*[S8]	1	80	Case report	ACTH analogue s.c. injection 40 mg then 80 mg twice weekly	Complete remission

ACTH, adrenocorticotropic hormone; FSGS, focal segmental glomerulosclerosis; TPE, therapeutic plasma exchange.

a significant reduction in UAC noted after the use of ACTH gel, and 50% of patients achieved complete or partial remission.[7] Similar results with a slightly lower response rate (36%) in a group of 14 adults were reported by Grafals *et al.*[6] (Table 1). A systematic review performed in 2016 about the efficacy and safety of ACTH therapy concluded that data are lacking for ACTH use in (adult) FSGS patients.[8] On the contrary, a systematic review performed to investigate the efficacy in idiopathic nephrotic syndrome in children and young adults showed a response rate of 71%.[9] Moreover, Tumlin *et al.* showed a higher response rate with the use of ACTH in combination with tacrolimus,[S9] which might explain the success of our therapy. Rituximab may be effective to consolidate remission.[S10]

The mechanism of ACTH therapy is thought to be nonspecific, with both immune-modulatory as well as steroid-like effects. Historically, ACTH has been used for the treatment of nephrotic syndrome in children[S11] but was replaced by oral steroids, which are now widely used as first-line therapy for nephrotic syndrome. However, the steroidal and nonsteroidal effects of ACTH have brought this drug back to the forefront. ACTH has been reported to be efficacious to varying degrees in many resistant glomerular diseases, including FSGS in adults and children,[S12,S13] as well as a variety of other diseases such as infantile spasms, multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus.[S14] The proposed "nonsteroidal" mechanisms of actions of ACTH include direct protection of podocytes as well as systemic immunomodulation effects, potentially through action on the mineralocorticoid 1 receptor.[S15] The variability in response rates could be explained by the phenotypic and genetic heterogeneity in underlying diagnoses and is likely multifactorial.

Graft survival is significantly reduced with FSGS disease recurrence. For example, Pardon *et al.* saw a cumulative graft survival rate of 57% with FSGS recurrence versus 82% without recurrence.[S16] Other studies have reported a 5 times higher relative risk of graft failure in FSGS disease recurrence.[S17] Even partial remission of FSGS seems beneficial to prevent graft loss. In the study of Troyanov *et al.*, hazard ratios for graft loss for complete and partial remission compared to no remission were 0.23 and 0.48, respectively. The cumulative graft survival rates over 15 years of complete, partial, and no remission were 80%, 70%, and 20%, respectively.[S18]

From our case report, it is impossible to draw definitive conclusions about efficacy, but we would suggest consideration of ACTH use in FSGS recurrence post-transplant where standard therapy has been ineffective. More studies are needed to define the efficacy, optimal duration, and dosing of ACTH in children for this indication. In conclusion, in treatment of resistant FSGS disease recurrence and post-transplantation, ACTH therapy should be considered in children, as our case demonstrates that it is a safe and effective treatment option.

Because FSGS disease recurrence is associated with significant graft loss and complications of intensified immunosuppression, a guideline for FSGS disease recurrence is crucial (Table 2). Based on our findings, we propose that ACTH should be considered in disease recurrence of FSGS post-transplantation if other methods fail. Moreover, relapses could occur after cessation of therapy, and warrant further studies. Future studies should investigate the potential of ACTH in children with FSGS recurrence and the safety of long-term use (Table 2).

Table 2. Teaching points and perspectives for ACTH use in pediatric transplant patients

Recurrence of FSGS after renal transplantation is common and reduces allograft survival significantly
ACTH can be a safe and effective treatment option for therapy-resistant recurrent FSGS in pediatric transplant recipients
Future studies should investigate the potential of ACTH in children with FSGS recurrence and the safety of long-term use

ACTH, adrenocorticotropic hormone; FSGS, focal segmental glomerulosclerosis.

DISCLOSURE

All the authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

AR and EC participated in the design and data collection of the case report and drafted the manuscript. SK, SEK, and HJM designed the treatment plan and gave significant input to the manuscript including literature review. All authors approved the final version of the manuscript before submission.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary References.

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