EXCEPTIONAL CASE

Recurrent focal segmental glomerulosclerosis apparently resistant to plasmapheresis improves after surgical repair of arteriovenous fistula aneurysms

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Abstract

Focal segmental glomerulosclerosis (FSGS) is a leading cause of end-stage renal disease and has a high recurrence rate after kidney transplantation, attributed to a circulating permeability factor. Plasmapheresis is the treatment of choice after recurrence to remove the circulating factor. We present a case of recurrent FSGS 6 years after transplantation. It is instructive because proteinuria did not respond to intensive plasmapheresis—combined with rituximab—until the possibility of ineffective apheresis secondary to multiple aneurysms in the arteriovenous fistula (AVF) was considered. Proteinuria improved soon after alternative access for plasmapheresis was secured and AVF aneurysms were surgically repaired.

Key words: arteriovenous fistula, FSGS, kidney transplantation, plasmapheresis, vascular access

Introduction

Focal segmental glomerulosclerosis (FSGS) is the most common primary glomerular disease leading to end-stage renal disease (ESRD). The majority of cases (80%) are idiopathic; the remainder are associated with genetic mutations, viral infections, drugs or adaptive conditions such as obesity and sickle cell anemia [1, 2]. The defining presentation is nephrotic-range proteinuria. FSGS tends to recur after kidney transplantation, sometimes within a few days. A circulating permeability factor—possibly serum soluble urokinase receptor—is postulated to explain the rapid recurrence in the transplanted kidney [3, 4]. Plasmapheresis with rituximab is the treatment of choice for relapsed FSGS [5].

Case report

A 37-year-old Asian man developed ESRD 11 years ago from primary FSGS, which was biopsy proven. A left upper arm brachial artery to cephalic vein arteriovenous fistula (AVF) was created and used for hemodialysis for 3 years prior to living unrelated kidney transplantation. Proteinuria recurred 10 days after transplantation and was treated with plasmapheresis and the addition of rituximab at 6 months posttransplant. The patient remained plasmapheresis dependent, with treatment frequency ranging from weekly to monthly. FSGS progressed slowly during the first 6 years after transplantation. Immunosuppression consisted of mycophenolate mofetil (MMF), tacrolimus and prednisone. The MMF dose was reduced at 5 years after transplantation

for polyomavirus BK viral infection, which resolved. Serum creatinine was <159 µmol/L (1.8 mg/dL), and the urine protein: creatinine ratio was ~1 (equivalent to 1 g/day proteinuria) until 7 years after transplantation, when progression started to accelerate. Kidney biopsy at the time showed diffuse severe degenerative changes of podocytes, including extensive effacement of foot processes. Six of 22 glomeruli had global or segmental glomerulosclerosis. Tubular atrophy and interstitial fibrosis involved 30% of kidney parenchyma. Antibody-mediated rejection was not seen. Moderate tubulitis and focal interstitial inflammation consistent with T-cell-mediated rejection (Banff class IA) were observed. Serum creatinine at the time of biopsy was 177 µmol/L (2 mg/dL) and proteinuria at the time of the biopsy was 7.7 g/24 h. Recurrent FSGS was felt to be the primary culprit for increased proteinuria. B7-1 staining of the biopsy specimen was negative, so the patient was not a candidate for abatacept [6]. Plasmapheresis frequency was increased from monthly to twice per week (one plasma volume exchanged with equal volume of 5% albumin each session) and two doses of rituximab (1000 mg each dose, 2 weeks apart) were given. He also received pulse solumedrol (500 mg/day for 3 days) for acute cellular rejection. Other medications include tacrolimus, mycophenolate, furosemide, losartan, darbepoetin and ferrous sulfate.

Access for plasmapheresis has been the left-sided brachiocephalic AVF established for hemodialysis 10 years ago. Over time, multiple aneurysms had developed along the AVF (Figure 1A). The cannulation points for apheresis were in the proximal aneurysm. Flow rates were in the range of 70–80 mL/min (1 mL/kg/min) with no pressure alarms. Imaging studies (ultrasound and venogram) confirmed stenosis of the cephalic vein as it entered the subclavian vein, but there was no central venous stenosis. Two attempts with balloon angioplasty followed by surgical excision of the stenotic portion of the cephalic vein several years prior had yielded no improvement in the aneurysms.

In spite of intensive plasmapheresis plus rituximab, proteinuria did not improve and serum creatinine continued to increase. IgM levels pre- and postprocedure (both drawn from the arterial access) were 24 and 10 mg/dL, respectively. Concerns about AVF recirculation reducing the effectiveness of plasmapheresis and long-term safety of the aneurysms were raised. After multidisciplinary discussion among nephrology, vascular surgery and transfusion medicine—with patient input and agreement—a tunneled catheter was placed in the right internal jugular vein to allow surgical repair of the AVF.

In the operating theatre, the patient underwent complete revision of the aneurysmal left AVF (Figure 1B) to continue using his nondominant arm, instead of creating a new AVF on the right. Revision was accomplished via an 8 cm resection of the proximal aneurysmal portion of the AVF adjacent to the brachial artery, coupled with plication of the distal portion of the aneurysmal AVF. The distal venous end of the AVF was transected, the revised fistula was tunneled towards the axilla and an anastomosis was performed between this distal segment and the axillary vein to decompress the outflow obstruction in the cephalic vein (Figure 1C).

We observed a rapid reduction in proteinuria after plasmapheresis access was changed to the tunneled catheter, then the repaired AVF after wound healing. The mean urine protein: creatinine ratio for the 4 months prior to surgery was 7.7, approximately equivalent to 8 g/day ($n = 9$), and decreased to 3.5 (equivalent to 3.5 g/day) in the 4 months after switching plasmapheresis access and aneurysm repair ($n = 17$). This represents a statistically significant change ($P < 0.05$, t-test). The timeline for this patient's course is shown in Figure 2. Plasmapheresis was performed twice weekly for 2 months, then transitioned to a weekly schedule,

Fig. 1. Photographs of the left arm aneurysms (A) before revision, (B) during revision and (C) after revision.

which has maintained the improved level of proteinuria and stable serum creatinine [221 µmol/L (2.5 mg/dL)] for 1 year.

Discussion

We postulate that plasmapheresis was more effective through the tunneled catheter and subsequently the revised AVF than through the aneurysmal fistula, where blood was likely in a more static reservoir, leading to recirculation and ineffective removal of the circulating permeability factor. International registry data show that AVFs (and arteriovenous grafts) are used in only 4% of apheresis procedures worldwide and therefore are potentially less familiar to many physicians overseeing apheresis. AVFs are used when plasmapheresis access is needed over many months or years, as in our case [7]. Aneurysm development is not an uncommon complication of AVFs for hemodialysis, and multiple options exist for surgical management [8, 9]. Recirculation is a known complication of dialysis through AVFs; it is not always detected by conventional measurements and the presence of intra-access strictures is a risk factor [10]. Although there is no definitive proof of recirculation in our case, other therapeutic options had been exhausted and the size of the aneurysms posed a safety risk. We do not believe that the improvement in
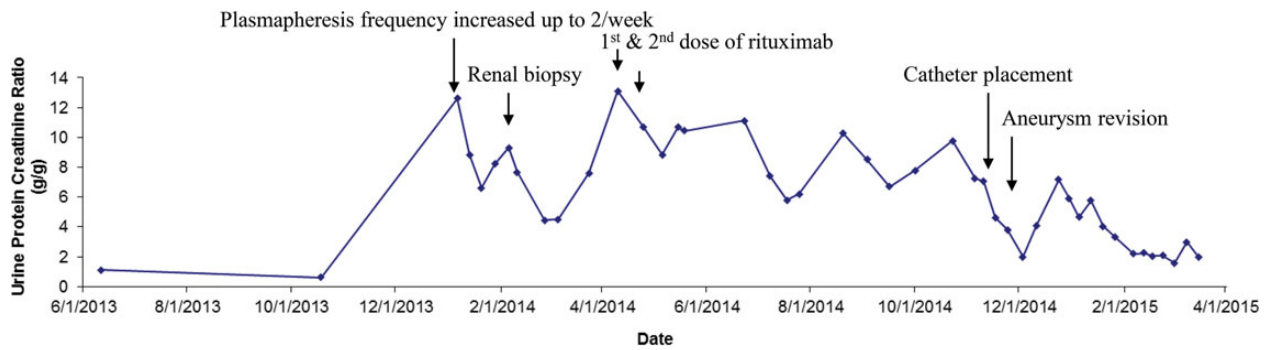
Fig. 2. Proteinuria measured as the urine protein : creatinine ratio, which approximates proteinuria in grams per 24 h. Dates of increased frequency of plasmapheresis, kidney biopsy, rituximab therapy, catheter placement and aneurysm revision are indicated on the timeline.

proteinuria is attributable to rituximab therapy administered 8 months prior to aneurysmal repair, since response to rituximab typically occurs within 4 months [11]. There was no other change in immunosuppression other than a slightly higher tacrolimus trough level. The rapid improvement in proteinuria after changing plasmapheresis access in this case provides more support to the circulating factor theory. The residual proteinuria despite more effective plasmapheresis is likely the result of adaptive glomerular changes from permanent damage such as podocyte detachment, podocyte apoptosis and glomerular sclerosis [2].

Close communication between nephrologists, apheresis practitioners and vascular surgery is key to the management of patients with kidney disease who require plasmapheresis. Ineffective exchange attributable to recirculation within an aneurysmal AVF should be considered if patients with recurrent FSGS fail to respond to intensified plasmapheresis and rituximab.

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Conflict of interest statement

This manuscript has not been previously submitted elsewhere except in abstract format. The authors do not have any conflict of interest to disclose.

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