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Nonrecurrent Early Post-Transplantation Focal Segmental Glomerulosclerosis

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Focal segmental glomerulosclerosis (FSGS) is one of the most common causes of nephrotic syndrome in adults, and the incidence of this diagnosis is increasing.1–4 This histological diagnosis can result from many conditions such as reflux nephropathy, significant obesity, or genetic mutations affecting structural elements of the glomerular filtration barrier. The idiopathic form of this disease is due to a circulating factor(s) that disrupt the glomerular filtration barrier, resulting in widespread podocyte foot process effacement (FPE) and proteinuria.5–7 Reported recurrence rates following the first kidney transplantation...
vary between 10% and 86%. Following a repeat transplantation, after an initial recurrence, the recurrence rate is approximately 90%. Recurrence post-transplantation can result in significantly premature graft loss. The circulating factor(s) responsible for idiopathic FSGS remain elusive.

Many investigators have proposed various clinical and or histological markers, or a combination thereof, to identify primary idiopathic FSGS. None of these have been able to predict recurrence following kidney transplantation with accuracy greater than 86%. Currently, the diagnosis of recurrent primary FSGS is made clinically, that is, development of proteinuria early after transplantation. However, in a number of patients, proteinuria develops later. The true specificity of disease recurrence following transplantation has not been examined.

We present 3 transplant recipients who developed early post-transplantation FSGS following transplantation (1 patient for the third time) who were found to have etiologies other than idiopathic FSGS. Being aware of these etiologies may prevent unnecessary therapy and also allow for better cohort definition, enabling identification of the elusive circulating factor(s).

**CASE 1**

A 23-year-old African American man was found to have hypertension, nephrotic range proteinuria, and advanced renal failure. His kidneys were small and atrophic bilaterally, precluding native kidney biopsy. There was no history of nephrotoxic agents or family history of kidney disease.

After 5 years on dialysis, he received a deceased donor kidney transplant from an 18-year-old African American donor. Implantation biopsy was without any abnormality. Immunosuppression was induced with alemtuzumab and maintained with dual therapy consisting of tacrolimus and mycophenolate mofetil. Because of concerns that he had primary FSGS, he was placed on a heightened post-transplantation monitoring regimen for albuminuria. The initial post-transplantation course was uneventful, with a normal protocol allograft biopsy at 4 months post-transplantation and normal urine albumin excretion. At 6 months post-transplantation, increasing albumin excretion peaking at 3.4 g/g creatinine with stable serum creatinine was noted. Allograft biopsy showed segmental sclerosis in 2 of 15 glomeruli, both of which had associated overlying podocyte reaction and protein resorption granules, with patchy mild mononuclear cell infiltrates involving less than 10% of the cortex with associated focal mild tubulitis. This was initially interpreted as clinically recurrent FSGS with borderline changes for rejection. Electron microscopy, however, showed largely intact podocyte foot processes.

Treatment for the borderline rejection consisted of 5 consecutive days of parenteral methylprednisolone with decreasing dosage, followed by a rapid oral prednisone taper to 5 mg over 7 days. Given the lack of podocyte FPE, no specific therapy for recurrent FSGS was undertaken. Losartan 25 mg daily was substituted for amlodipine 5 mg daily for blood pressure control.

A postrejection therapy follow-up biopsy sample was obtained 4 weeks later and was normal.
Albuminuria decreased gradually over the following 4 months to <1 g/g creatinine, then to <0.5 g/g creatinine over the subsequent 2 months and has remained in the range of 0.3 to 0.4 g/g creatinine over 2 years of follow-up (Figure 1). Blood pressure and renal function were stable throughout.

Given the unusual presentation, a thorough workup for secondary causes of FSGS was undertaken. This included apolipoprotein L 1 (APOL-1) testing of the recipient and donor. The recipient was homozygous for the average risk alleles, and the donor was homozygous for the high-risk allele G1.

Interestingly, we were contacted by the center that transplanted the mate kidney of this recipient (see Case 2).

**CASE 2**

A 70-year-old Caucasian woman who developed end-stage renal disease (ESRD) attributed to hypertensive diabetic nephrosclerosis received a deceased donor kidney transplant after 2.5 years of dialysis. Her calculated panel reactive antibodies (cPRA) were 100%. Prior to transplantation, she underwent desensitization using plasma exchange (PLEX) and i.v. Ig. B-cell flow crossmatch was weakly positive at the time of transplantation. Induction was with antithymocyte globulin, and the patient was maintained on triple immunosuppressive therapy consisting of corticosteroids, mycophenolate mofetil, and tacrolimus. Post-transplantation she received rituximab and i.v. Ig and required a blood transfusion. One week post-transplantation there was an increase in donor-specific anti-human leukocyte antigen (HLA) antibodies (DSA). PLEX, i.v. Ig, and bortezomib were administered, followed by a decrease in DSA levels. Creatinine remained at baseline of 0.9 to 1.1 mg/dl. One year post-transplantation proteinuria was noted at 4.3 g/g creatinine. Previous levels were <0.35 g/g creatinine, with the most proximate level being 40 weeks before the detection of the nephrotic range proteinuria. Renal allograft biopsy showed de novo collapsing glomerulopathy with extensive FPE. Testing for HIV, Epstein-Barr virus, and Parvo virus was negative by polymerase chain reaction. The patient was started on an angiotensin receptor blocker. Her proteinuria increased to 10 g/g creatinine, at which point she underwent 5 sessions of PLEX and received additional rituximab and i.v. Ig. There was a transient decrease in proteinuria to 4.9 with stable graft function. Two months, later proteinuria increased to 11 g/g creatinine. Four months afterward, graft function began to deteriorate, with an increase in the baseline creatinine to 1.5 to 1.9 mg/dl, and 8 months later it was 4 mg/dl. A second allograft biopsy sample showed advanced focal and segmental sclerosis with no evidence of rejection but some findings suggestive of allograft pyelonephritis. An *Escherichia coli* urinary tract infection at that time was treated, with no improvement in renal function.

![Figure 2. Pathology of the 7-month post-transplantation kidney allograft biopsy from case 1: (a) light microscopy (original magnification ×40, periodic acid–Schiff) and (b) light microscopy (original magnification ×40, Jones), both showing segmental sclerosis in glomeruli with overlying podocyte reaction; and (c) electron microscopy photomicrograph demonstrating intact podocyte foot processes.](image-url)
function. Creatinine remained at 4.1 mg/dl and proteinuria consistently >20 g/g creatinine. The patient returned to maintenance hemodialysis 30 months post-transplantation.

**CASE 3**

A 40-year-old Caucasian man with ESRD from biopsy-proven FSGS at age 16 years received his third living donor kidney transplant. His 2 prior renal allografts had been diagnosed with recurrent FSGS, but their failures were slowly progressive.

The first transplant was a living donor transplant from his mother. Early complications included 2 biopsy-proven acute cellular rejection episodes that were successfully treated, and 2 thrombotic events. These consisted of renal vein thrombosis, requiring thrombectomy, and lower extremity deep vein thrombosis. Because of these 2 events, lifelong anticoagulation was commenced. Eight months after the first kidney transplantation, the patient had increasing serum creatinine and proteinuria. A biopsy sample showed FPE and swollen visceral epithelial cells. Proteinuria progressed, and at 2 years post-transplantation the biopsy sample showed established FSGS lesions with diffuse FPE. Graft function continued to decline slowly, with ongoing heavy proteinuria. At 10 years post-transplantation a biopsy sample continued to show similar features but with worsening interstitial fibrosis and tubular atrophy. In preparation for a second transplant, imaging revealed an allograft renal cell carcinoma, and the patient underwent an allograft nephrectomy 1 month prior to receiving his second living donor transplant. At the time of the second transplantation, the inferior vena cava (IVC) was noted to be occluded by thrombus but with good collateral drainage. The second transplant functioned well initially. The protocol 3-month post-transplantation allograft biopsy revealed moderate segmental podocyte FPE that was interpreted as early recurrent FSGS with low-level albuminuria (213–617 mg/g). Conservative therapy was undertaken. At 1 year, the albuminuria increased to 1386 mg/g and the protocol biopsy showed 60% FPE. By 2 years, albuminuria progressed to 3494 mg/g and the protocol biopsy revealed 70% to 80% FPE with 1 of 12 glomeruli exhibiting a segmental scar with foam cells and an adhesion to the Bowman capsule. Based on these findings, a course of PLEX was undertaken, but there was no significant response. Rituximab was considered but not administered, given the lack of response to the PLEX. Albuminuria fluctuated between 2 and 4 g/g creatinine over the remainder of the life of the allograft. Eight years after this second transplantation, the patient underwent an allograft nephrectomy with simultaneous living donor transplant. This combined procedure was undertaken because of the finding on computed tomographic venography that the iliac veins and IVC were occluded and that the venous pedicle of the second allograft was the only feasible location to attach the third kidney allograft.

For this third transplant, the patient underwent our center’s current standard conditioning for high-risk FSGS recipients. This consisted of 2 doses of

![Figure 3. Trends of serum creatinine, random albumin/creatinine ratio, 24-hour albumin excretion, and serum albumin from case 3. IVC, inferior vena cava.](image-url)
rituximab (1 g each) and 4 sessions of PLEX prior to transplantation and careful follow-up of post-transplantation albuminuria. The donor was a 68-year-old man with treated hypertension.

The patient’s post-transplantation course was complicated by slow graft function and fluctuating proteinuria punctuated by repeated episodes of acute kidney injury (Figure 3). On post-transplantation day 3, because of increasing albuminuria, PLEX was initiated. A day 4 renal allograft biopsy showed acute tubular injury and focal (20%–30%) FPE. With subsequent decline in albuminuria, PLEX was discontinued on day 5.

Graft function and albuminuria continued to fluctuate, and a biopsy sample 50 days after transplantation showed negligible FPE. At this time, because of the age of the donor and the donor-derived chronic vascular changes noted in the allograft, belatacept was substituted for tacrolimus. Despite this, there was still ongoing suboptimal renal function and fluctuating albuminuria. Four months post-transplantation, biopsy showed focal FPE with proteinuria of 2890 mg/24 h (Figure 4).

At this 4-month visit, given the past medical history of veno-occlusive disease and the atypical post-transplantation course, other potential causes of suboptimal graft function and proteinuria were investigated. Despite a normal renal allograft ultrasound and Doppler not revealing renal vein thrombosis or abnormal resistive indices, we proceeded with an inferior venacavogram. A successful balloon venoplasty of the occluded vena cava was accomplished (Figure 5). The pressure gradient from the external iliac vein to the right atrium decreased from 11 to 12 mm Hg to 5 to 6 mmHg. Following this, renal allograft function improved dramatically, with normalization of urine albumin excretion. Two months later, to avoid possible restenosis, a repeat cavogram was performed with stenting of the inferior vena cava (Figure 5).

At the 2-year protocol visit, the patient continued to have normal urine albumin excretion. The protocol 2-year post-transplantation biopsy sample showed intact podocyte foot processes.

The collection of data and presentation of these cases and this study was approved by the Mayo Clinic Institutional Review Board (IRB# 18-007788) and are
consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

**DISCUSSION**

These cases illustrate the difficulty, and possible pitfalls, in making a diagnosis of recurrent FSGS. In the first case, the pretransplantation probability of FSGS was moderate. There was no native biopsy sample and no clear history of nephrotic syndrome. The increasing proteinuria and the light microscopic findings of 2 of 15 glomeruli with segmental lesions, and reactive podocytes made the diagnosis of recurrent primary idiopathic FSGS likely. This constellation of findings, in many centers including our own, would have resulted in initiation of PLEX with or without high-dose corticosteroids to treat what would be bona fide FSGS, be it recurrent or de novo. The rapid turnaround of electron microscopy (EM) results that showed intact podocyte foot processes allowed a pause and rethinking of what this clinical scenario represented. Early recurrent FSGS presents with diffuse FPE, generally with normal glomerular histology on light microscopy. S6, S7 This case had the opposite findings: namely, FSGS lesions noted on LM, but intact foot processes on EM in the setting of new-onset and worsening proteinuria. The response to a short course of corticosteroids to treat the borderline cellular rejection was also unlikely to have resulted in resolution of recurrent or de novo FSGS.

So why did this patient develop this increasing albuminuria? Why did it resolve with a short course of corticosteroids? We postulate that the patient was doing well until his 4-month visit, which included a reassuring protocol biopsy. Subsequent to this, there could have been a transient decrease in tacrolimus levels resulting in the borderline cellular rejection that was noted on the biopsy sample. The activation of the immune system targeting the renal allograft with allograft inflammation would have resulted in increased inflammatory cytokines, including interferon-γ and tumor necrosis factor-α. S8 Tumor necrosis factor-α–related pathways have been implicated in FSGS previously. S9–S12 With the homozygosity of the high-risk APOL-1 alleles, the podocytes would have been susceptible to this inflammatory milieu, S13–S15 and some of them succumbed, resulting in the increased proteinuria and the segmental lesions that were seen on the biopsy sample. The cell-mediated injury may not have been diffuse in our case, given the patchy nature of cellular rejection and as such may not have resulted in widespread diffuse FPE. It may also have been very transient or improving prior to the biopsy, possibly due to increased levels of the immunosuppressants, and was not picked up at the time of the biopsy. In the mate kidney that was placed in a highly sensitized patient with increasing DSA, the more diffuse pattern of injury commensurate with the humoral response may have resulted in widespread podocyte dysfunction resulting in the collapsing FSGS. A similar presentation was previously reported in a transplant recipient. S16

APOL-1 has surfaced as a genetic variant that partially explains the increased risk of hypertensive ESRD associated with FSGS in the African American population, as well as in other populations in West

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**Figure 5.** Photographs from the cavogram of case 3 (a) occluded inferior vena cava (IVC) with guidewire traversing the obstruction, (b) after IVC dilation, and (c) after IVC stenting.
Africa or with West African heritage. Patients who are homozygous for 2 high-risk alleles either G1 or G2 or a combination of both are at increased risk for ESRD from FSGS and hypertension (odds ratio = 10.5, 95% confidence interval = 6.0–18.4, and odds ratio = 7.3, 95% confidence interval = 5.6–9.5, respectively). These patients are also at increased risk for HIV-associated nephropathy (HIVAN) with a lifetime risk of ESRD of 50% versus 4%, respectively.

APOL-1 is expressed in many tissues and is present in the circulation. That the constitutive APOL-1 in the kidney is responsible for increased risk of dysfunction was alluded to by the finding that kidneys from donors who expressed 2 high-risk alleles had shorter graft survival irrespective of the recipients’ APOL-1 status.

Our patient was homozygous for the average risk (wild-type or reference) allele and the donor kidney was homozygous for the high-risk allele (G1), providing further evidence that the intrinsic APOL-1, independent of the circulating form, confers risk.

In the third case, the converse regarding the pre- and post-transplantation probability of FSGS was present. The pretransplantation probability of recurrent FSGS was very high, given a native kidney disease that was diagnosed clinically and histologically and 2 prior renal allografts with clinical and histological findings of FSGS; hence the pretreatment with PLEX and rituximab. The post-transplantation findings on biopsy were less typical of what we frequently see. The FPE was focal and not diffuse, the proteinuria fluctuated, and renal function was erratic and suboptimal. One plausible explanation that could be proposed for the lack of diffuse FPE in this and similar situations is that this was partially treated FSGS by the pretransplantation PLEX and rituximab, post-transplantation PLEX, and the standard triple immunosuppression therapy needed for an allograft. The suboptimal renal allograft function could also be attributed to an older and hypertensive donor kidney showing minor vascular changes and resulting in oversensitivity to tacrolimus. Noted, however, was the lack of improvement with the transition to belatacept and discontinuation of the calcineurin inhibitor tacrolimus.

The significant improvement in renal function and albuminuria following venoplasty and subsequent stenting of the inferior vena cava, with documented improvement in the venous pressure gradient, is evidence that the dysfunction was due to venous hypertension. It is known that renal vein thrombosis manifests with heavy proteinuria, the mechanism being an elevation in intraglomerular pressure and increase in transcapillary filtration pressure gradient. Partial occlusion or other causes of elevated venous pressures such as right-sided heart failure can also lead to similar findings.

Could this patient’s prior 2 allografts have been affected by a similar phenomenon? In contrast to the current allograft, the prior renal allografts had good renal function for extended periods of time. Also, the progression of proteinuria and the diffuse podocyte FPE was more in keeping with recurrent FSGS. Could this patient develop recurrent late FSGS? Time will tell. This case does highlight the difficulty in investigating venous hypertension as the cause of renal allograft dysfunction. There is no reliable noninvasive means of assessing renal vein pressures. We rely on renal allograft ultrasound with Doppler to assess venous flow and to exclude occlusion. Echocardiography can assess right-sided heart pressures and in turn may reflect elevated venous pressures, although only if a more central origin is the cause. The only reliable means of measuring renal vein pressure is via venography. Venography is invasive and carries risks of the procedure as well as contrast exposure. Thus, there is considerable hesitation in proceeding with such invasive testing.

We demonstrated that even in the setting of biopsy findings of FSGS and a post-transplantation state with careful follow-up, there is difficulty in identifying recurrent FSGS due to a circulating permeability factor. An incorrect labeling of a case has implications for the individual patient being treated and for studies attempting to identify the circulating permeability factor. For the patient, this may result in unnecessary therapy with associated comorbidity, cost, and possible failure to identify a treatable condition. For investigators, this will result in study groupings that include heterogeneous cases, increasing the likelihood of identifying markers that are in common pathways for proteinuric renal disease or podocyte injury, and may not identify the circulating permeability factor(s).

In conclusion, donor derived APOL-1 high-risk alleles intrinsic to the renal allograft, and not the recipient, confer risk of proteinuria and development of FSGS lesion in the kidney. These allografts may be susceptible to the injurious effects of both the cellular and humoral arms of the immune system. Venous hypertension can mimic recurrent FSGS and, in the correct circumstance, warrants invasive testing. Scrutiny of FSGS cohorts is imperative in the quest to identify the circulating permeability factor(s).

**DISCLOSURE**

All the authors declared no competing interests.
Renal Trapping in Accidental Metformin Intoxication

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Metformin is widely used as an antihyperglycemic drug to treat patients with type 2 diabetes. Because metformin is renally excreted and not metabolized, it can accumulate in patients with renal insufficiency and cause lactic acidosis, known as metformin-associated lactic acidosis (MALA). 1,2 The reported incidence of MALA ranges from 3 to 10 per 100,000 patient-years and is associated with a high mortality rate. However, the full clinical context or metformin blood concentration is often not reported, making it challenging to distinguish metformin-associated from metformin-induced lactic acidosis (MILA), respectively. 1

Normally, metformin shows 2-compartment pharmacokinetics with a terminal half-life of 20 hours, suggesting the existence of a deeper compartment. 2 After oral administration to mice, accumulation of metformin was observed in the gut, kidneys, and liver. 3 After 6 to 8 weeks of metformin therapy given to drug-naive patients with type 2 diabetes, the