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Case Report

Collapsing FSGS in a Kidney Transplant Recipient on Sirolimus Following Treatment for Resistant CMV Viremia

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Abstract

Background: Proteinuria occurs commonly in transplant recipients treated with mechanistic target of rapamycin inhibitor (mTORi); although cause is unclear. Different mechanisms have been proposed such as podocyte injury due to the inhibitory effects of sirolimus on glomerular VEGF protein synthesis. Here, we describe a case of new-onset nephrotic range proteinuria and subsequent development of collapsing focal segmental glomerulosclerosis that occurred after conversion from tacrolimus to mTORi in a kidney transplant recipient in the setting of treating resistant CMV viremia.

Presentation: A 64-year-old woman with autosomal dominant polycystic liver and kidney disease underwent a second deceased-donor kidney transplant (November 2023). She was CMV high-risk (D+/R–) and initially demonstrated excellent allograft function. Six-months post-transplant, she developed severe CMV-viremia refractory to valganciclovir, requiring sequential therapy with ganciclovir, foscarnet, maribavir, letermovir, and adjunctive CMV immune globulin. Immunosuppression was reduced, including discontinuation of mycophenolate and conversion from tacrolimus to sirolimus.

Two months after initiating sirolimus, she abruptly developed nephrotic-range proteinuria (19 g/day) and a rapid increase in serum creatinine from baseline of 1.2 to 2.9 mg/dL. Renal transplant biopsy showed changes consistent with focal segmental glomerulosclerosis with features of collapsing glomerulopathy, and CMV immunostaining was negative. Sirolimus was discontinued and tacrolimus reintroduced, resulting in partial recovery of renal function and significant reduction in proteinuria.

Discussion: This case highlights sirolimus-associated collapsing FSGS as an important and potentially reversible cause of severe proteinuria in kidney transplant recipients. The clinical course underscores the need for careful monitoring of proteinuria following mTORi initiation.

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is a histopathologic pattern of glomerular injury characterized by segmental sclerosis of glomeruli and podocyte damage, leading to proteinuria and progressive kidney dysfunction. The collapsing variant of FSGS represents an especially aggressive subtype, defined by segmental or global collapse of glomerular capillary loops with overlying podocyte hypertrophy and hyperplasia. It is associated with rapid deterioration in renal function and poor prognosis, often progressing to end-stage kidney disease despite therapy [1,2].

Secondary forms of FSGS arise in association with various etiologies, including viral infections, medications, and systemic or adaptive factors. Viral infections such as HIV, parvovirus B19, cytomegalovirus (CMV), Epstein–Barr virus, and SARS-CoV-2 can cause nephrotic syndrome; medications, hyperfiltration states, and chronic allograft injury are other causes of secondary FSGS [3-6]. In renal transplant recipients, FSGS poses particular diagnostic and therapeutic challenges, as it can represent recurrence of primary disease, de novo glomerular injury, or medication-related toxicity.

Although the true incidence of collapsing FSGS in kidney allografts is low, it is associated with poor graft outcomes. Pathogenetically, collapsing FSGS reflects severe podocyte stress and dedifferentiation driven by actin cytoskeleton rearrangement, foot process effacement and slit diaphragm loss [7]. Viral infections may trigger podocyte injury through direct infection or cytokine-mediated toxicity, while medications can disrupt cellular homeostasis.

Among pharmacologic causes, mechanistic target of rapamycin (mTOR) inhibitors (previously also called mammalian target of rapamycin inhibitors); have emerged as an important contributor to de novo and recurrent FSGS in renal transplant recipients. Several studies have described the onset or exacerbation of proteinuria following conversion from calcineurin inhibitors (CNIs) to sirolimus or everolimus [8-11]. The pathophysiologic mechanisms remain incompletely understood but are thought to involve podocyte injury secondary to mTOR complex 2 inhibition, leading to decreased vascular endothelial growth factor (VEGF) synthesis, impaired Phosphoinositide 3-kinase (PI3K) signaling, and podocyte dedifferentiation and detachment [8-10]. Histologic findings in these cases often include features of collapsing glomerulopathy. Importantly, withdrawal of mTOR inhibitors has been associated with partial improvement in renal function and reduction in proteinuria, underscoring a potentially reversible form of podocyte injury [8].

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CMV infection remains a major cause of morbidity in renal transplant recipients, especially in high-risk donor-seropositive/recipient-seronegative (D+/R–) combinations. Viral infections, particularly CMV, are also recognized as triggers of secondary and collapsing FSGS. Resistant CMV viremia may develop despite prophylactic therapy with valganciclovir and may further require second-line antivirals such as foscarnet or maribavir, in conjunction with CMV-specific immune globulin (Cytogam) [12]. CMV has been implicated in podocytopathy both by direct infection and through cytokine-mediated injury, and multiple case reports have described CMV-associated collapsing FSGS in both transplant and non-transplant settings [13,14].

Here, we present a unique case of collapsing FSGS in a kidney transplant recipient who developed nephrotic-range proteinuria after conversion from tacrolimus to sirolimus during treatment for resistant CMV viremia.

CASE PRESENTATION

A 64-year-old Caucasian woman with a history of autosomal dominant polycystic liver and kidney disease (ADPLKD) developed progressive chronic kidney disease, underwent a pre-emptive living-related kidney transplant in October 2010. Thereafter, developed progressive liver failure due to polycystic liver disease and in June 2022 she underwent a deceased-donor liver transplant (DDLT). Her creatinine prior to liver transplant was 1.7 mg/dl, but the post-liver transplant course was complicated by acute kidney injury superimposed on chronic kidney disease, ultimately requiring initiation of hemodialysis.

In November 2023, she received a second deceased-donor kidney transplant. The donor kidney had a kidney donor profile index (KDPI) of 43%. She was considered at high risk for CMV infection, as the donor was CMV seropositive and the recipient seronegative (D+/R–). Both recipient and donor were seropositive for EBV. She had low HLA risk with 0% calculated panel reactive antibody, and no donor specific antibody. At the time of the second kidney transplant, she received immunosuppression induction with Anti-Thymocyte globulin (total 3.75 mg/kg in 3 divided doses) and methylprednisolone given at 500 mg intra-op tapered down to 25 mg by post-op day 5 then came off steroids. Maintenance immunosuppression, with Tacrolimus (goal 10-12 ng/ml for first 2 months, the 6-8 ng/ml 2-6 months post-transplant) and mycophenolate 720 mg oral twice a day. Her serum creatinine posttransplant improved to a nadir of 1.1-1.2 mg/dL and urine protein-to creatinine ratio (UPCR) of 0.3– 0.4 g/g.

At 6 months post-transplant while on valganciclovir prophylaxis, she developed severe CMV viremia for which she received intravenous (IV) Ganciclovir for 1 week, without adequate response. Her CMV viral load at diagnosis was 5.0 log IU/ml and increased to 5.1 log IU/ml after a week of IV ganciclovir. CMV resistance testing sent at this time identified mutation in UL97 drug resistance; suggesting CMV virus resistance to ganciclovir but susceptible to foscarnet, cidofovir, maribavir and letermovir. She then received 3 weeks of intravenous (IV) foscarnet followed by 8 weeks of oral maribavir. Her CMV VL improved from a peak of 5.1 log IU/ml to 2.76 log IU/ml. A month later, CMV VL increased to 4.2 log IU/ml and CMV strain was then found to be resistant to Maribavir. At this time, she received a 2nd course of IV Foscarnet for 4 weeks and was started on letermovir and valganciclovir as outpatient treatment. Her CMV VL persisted in the 2.6-3.3 log IU/ml range for about 3 months. She then received intravenous CMV immune globulin (Cytogam) every 2 weeks for 4 doses. CMV viremia gradually resolved with this regimen; with CMV VL finally <2.0 log IU/ml after 5 months of initial diagnosis.

Due to refractory CMV viremia her immunosuppressive regimen was modified; mycophenolate was discontinued at the time of CMV viremia diagnosis; and maintenance dose prednisone 5 mg daily started. Tacrolimus dose initially reduced to a goal of 4-6 ng/ml; but then switched to Sirolimus (goal of 4-6 ng/ml); 3-months after CMV viremia diagnosis, due to persistently positive CMV levels. Her CMV titer at the time of switching to Sirolimus was 3.2 log IU/ml.

Two months after switching to sirolimus, serum creatinine gradually rose from baseline of 1.4 mg/dl to 2.9 mg/dL and proteinuria (UPCR) increased from 1 g/g to a peak of 19 g/g. CMV viral load at this time was negligible at <2.3 detected log IU/ml. A renal allograft biopsy was performed. Due to concern for proteinuria induced from mTORi, sirolimus was discontinued and tacrolimus was reintroduced. Histopathologic examination of the kidney biopsy demonstrated focal segmental glomerular collapse and sclerosis with overlying podocyte hypertrophy and hyperplasia, consistent with collapsing FSGS (Figure 1). There were mild interstitial fibrosis and tubular atrophy, along with mesangial matrix proliferation. Electron microscopy revealed extensive

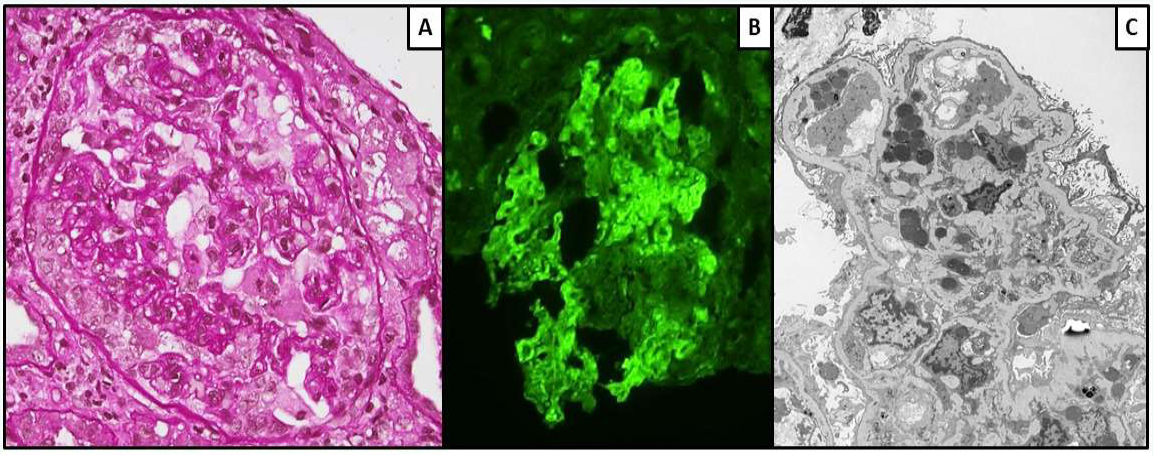

Figure 1: The renal biopsy showed glomeruli with collapse (A, PAS) and immunofluorescence studies revealed a glomerulosclerotic type staining pattern with IgM (B). Diffuse foot process effacement was seen in electron microscopic studies (C). These changes are typical of collapsing FSGS.

podocyte foot process effacement, confirming severe podocytopathy. Immunohistochemical staining for CMV was negative, making direct viral cytopathic effect within the allograft less likely. CMV immunostains were negative. Within 10 days of switching back to tacrolimus from sirolimus creatinine improved to 2.5 mg/dL, proteinuria fell to ~5 g/g. About 6 weeks later graft function improved to creatinine 2.1 mg/dL and UPCR 2 g/g. At the last follow up tests (1-year post kidney allograft biopsy); the Creatinine was 1.8 mg/dl and proteinuria was 0.75 g/g. The detailed timeline from time of transplant to last follow up in terms of creatinine, proteinuria, CMV infection, biopsy timing and medication changes is shown in Figure 2.

DISCUSSION

Collapsing focal segmental glomerulosclerosis (FSGS) in kidney allografts can result from diverse etiologies, including recurrent FSGS disease, viral infections, drug toxicity, and ischemic or immunologic injury. In this patient, the differential diagnosis included cytomegalovirus (CMV)–associated glomerulopathy, and/or sirolimus-related podocyte injury. The close temporal association between sirolimus initiation and the onset of nephrotic-range proteinuria, followed by marked improvement after drug withdrawal, strongly supports sirolimus-induced glomerulopathy as the primary etiology. Her CMV viremia had resolved before nephrotic range proteinuria developed, immunohistochemistry for CMV was negative, and no other hemodynamic or pharmacologic insult was identified. The pattern of rapid proteinuria rise within 8 weeks of sirolimus conversion and rate of recovery upon discontinuation mirrors previously described cases of mTOR inhibitor–associated podocytopathy [8,15,18].

The nephrotoxic effects of mechanistic target of rapamycin inhibitors (mTORi) on podocytes are increasingly recognized. Sirolimus inhibits mTOR complex 2 (mTORC2), a key regulator of cell growth and cytoskeletal organization, leading to disruption of podocyte structure and function. Letavernier and colleagues demonstrated that sirolimus exposure decreases WT1 gene expression and downregulates podocyte vascular endothelial growth factor (VEGF) synthesis leading to endothelial dysfunction, loss of fenestrations, increased podocyte stress resulting in altered cytoskeletal organization and dedifferentiation rather than apoptosis [8,9]. Podocytes subsequently lose markers of differentiation such as nephrin, and detach from the glomerular basement membrane, producing segmental collapse and sclerosis—the histologic hallmarks of collapsing FSGS. In addition, sirolimus impairs endothelial–podocyte axis and glomerular reparative pathways, aggravating glomerular injury [16,17].

Other nephron segments may also be affected. Oroszlán et al. demonstrated that sirolimus and everolimus downregulate cubilin and megalin in proximal tubular cells, reducing albumin endocytosis and contributing to tubular proteinuria [19]. Thus, mTOR inhibition can cause proteinuria through both podocyte-specific injury and impaired tubular reabsorption. Although transient hemodynamic changes from calcineurin inhibitor withdrawal could explain mild proteinuria, they cannot account for the observed collapsing morphology or the reversibility after sirolimus discontinuation. The biopsy in this case—showing glomerular collapse, podocyte hypertrophy and hyperplasia, and extensive foot process effacement—is found in mTOR inhibitor–related collapsing podocytopathy.

There are several case reports that describe worsening proteinuria

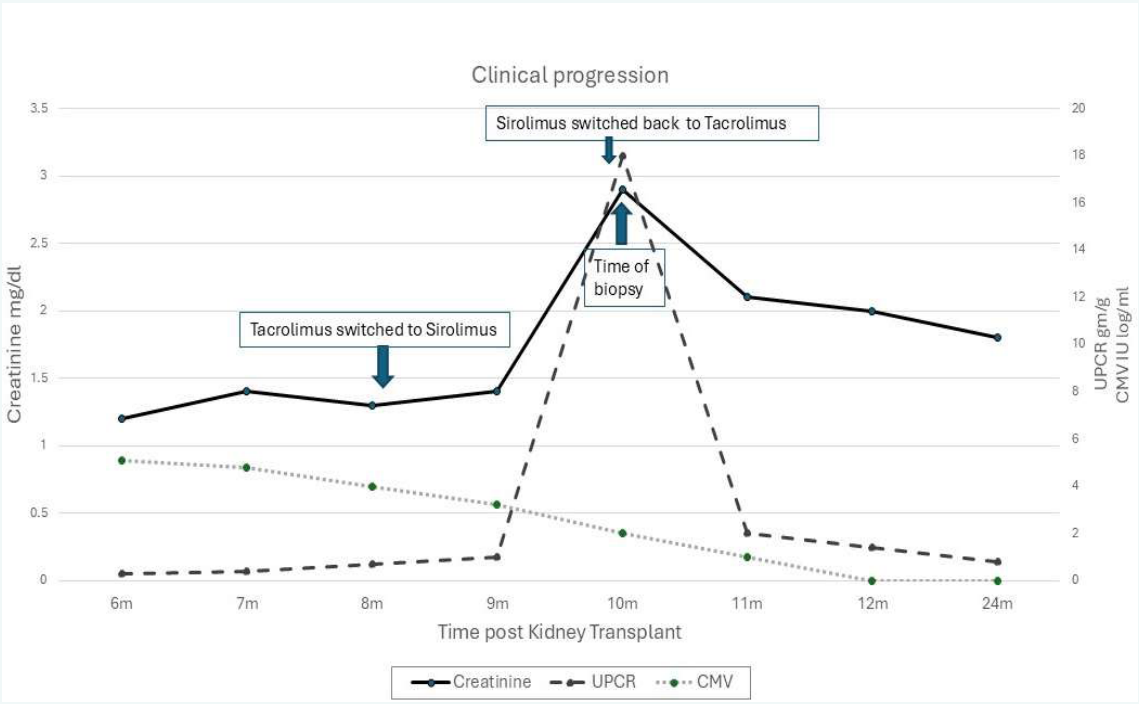

Figure 2: Clinical course showing trends of serum creatinine, proteinuria and CMV viral load

in setting of mTOR inhibitor use, but to our knowledge there are very few case reports of collapsing variant of FSGS attributed to Sirolimus. Dogan et al., reported collapsing glomerulopathy following conversion from tacrolimus to sirolimus in a renal transplant recipient, with improvement in renal function and proteinuria after cessation of sirolimus [15]. Diekmann et al., described de novo FSGS associated with mTOR inhibitors, emphasizing the reversibility of the lesion once the drug was withdrawn [19]. Letavernier et al., and Hanna et al. documented comparable findings of sirolimus- and everolimus associated FSGS and nephrotic proteinuria [8,11]. Our patient's presentation—rapid development of nephrotic-range proteinuria after mTORi initiation, biopsy-confirmed collapsing glomerulopathy, and functional improvement after returning to calcineurin inhibitor therapy—is consistent with these reports. A distinguishing feature of our case is the preceding resistant CMV viremia, which initially confounded the diagnosis. Patel et al., published a case report of collapsing FSGS secondary to CMV infection [14,15]. However, the absence of viral inclusions, negative CMV immunostaining, and occurrence during virologic remission argue against CMV-induced podocytopathy in our case [14].

Recognition of this adverse effect has broader clinical importance. The mTOR inhibitors are now widely used not only in kidney transplantation but also in heart, liver, and lung transplants, and in nontransplant conditions such as malignancy and tuberous sclerosis complex. Proteinuria is a known but often underappreciated toxicity of mTOR inhibitors. Failure to monitor and address this complication can result in irreversible glomerular scarring and renal dysfunction. Early identification and discontinuation of the offending agent can lead to partial or complete recovery of renal function, as demonstrated in this case. Routine surveillance of urine protein excretion should therefore be incorporated into follow-up protocols for patients receiving sirolimus or everolimus, based regimens.

CONCLUSION

In conclusion, this case illustrates a rare but significant complication of sirolimus therapy—collapsing FSGS in a renal allograft—likely mediated by podocyte injury and dedifferentiation. The temporal pattern, biopsy findings, and reversibility upon drug withdrawal strongly support causality. As mTOR inhibitors gain broader therapeutic application, clinicians must remain vigilant for this complication and monitor renal function and proteinuria closely to prevent irreversible injury.

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