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Letter to the Editor

The presentation of proteinuria in an adolescent with new-onset diabetes after heart transplantation

A 14-year-old girl presented with new-onset noninsulin-dependent diabetes mellitus for 5 years after a heart transplantation that was performed 7 years ago. The immunosuppressive agents that she received initially were tacrolimus, everolimus, and prednisolone, and she was maintained with cyclosporine and everolimus for the past 5 years. Treatment for her diabetes initially included oral hypoglycemic agents (OHAs), which was then switched to insulin therapy due to OHA-induced gastrointestinal upset. Overt proteinuria [urine protein/urine creatinine ratio (UPCR): 7.2 mg/mg; daily protein loss: 2.2 g] and massive pericardial effusion were detected 7 years after the heart transplantation. Laboratory data revealed normal renal function (creatinine: 0.5 mg/dl, estimated Glomerular Filtration Rate (eGFR) calculated using Schwartz formula: 117 ml/min/1.73 m^2), hyperglycemia (HbA1c: 9.0%), and hypoalbuminemia (2.3 g/dl). Immunological profiles analysis of ANA, IgA, IgG, IgM, C3, C4, and ASLO revealed results within the normal limit. The infection profile demonstrated negative results for HBV, HCV, HIV, and CMV infection. Biopsy of the cardiac muscle revealed neither cellular nor humoral rejection. There was also no retinopathy on ophthalmological examination. The differential diagnosis of proteinuria included diabetic nephropathy (DN), idiopathic nephrotic syndrome, and drug-induced nephropathy. Renal biopsy revealed diffuse moderate mesangial hypercellularity with moderate mesangial matrix expansion in the glomeruli (Fig. 1A). Electron microscopy demonstrated partial foot process effacement of podocytes with focally wrinkling changes (Fig. 1B) and irregular thickening of the glomerular capillary wall (400—700 nm) (Fig. 1C). There were trace levels of IgA, IgM, kappa and lambda light chains, linear and trace IgG, and negative C1q and C3c under immunostaining. Therefore, a diagnosis of diabetic glomerulopathy class IIa was established.

Due to the reported incidences of everolimus-induced proteinuria,[1] everolimus was replaced with mycophenolate mofetil and low-dose prednisolone (5—10 mg daily). Enalapril maleate (5 mg daily) was prescribed for controlling proteinuria and hypertension. After 1 month of treatment with these medications, the proteinuria decreased to the subnephrotic range (UPCR: 0.38 mg/mg), and the patient was discharged from hospital.

1. Discussion

The use of calcineurin inhibitors, mammalian target of rapamycin inhibitor (mTORi), and glucocorticoids is a predominant factor that causes the development of new-onset diabetes mellitus after transplantation (NODAT).[2] Worsened insulin resistance in puberty and post-transplant cytomegalovirus infection might also have contributed to the poor glucose control[2,3] and accelerated the development of DN in this patient. Bhalla et al. reported that the duration of the development of DN in the transplanted kidney of patients with pretransplant DM and NODAT is about 5.9 years.[2] However, the incidence of DN with macroalbuminuria in less than 5—6 years of diagnosis of diabetes in patients without renal transplantation is rare.

In addition, the atypical presentation of macroalbuminuria in patients with preserved renal function and absence of diabetic retinopathy is rare in the early stage of diabetic glomerulopathy. The patient's overt proteinuria may be explained by the nondiabetic finding of partial foot process effacement of podocytes associated with minimal changes of disease or mTORi toxicity.[4] The mechanism underlying the development of mTORi-induced proteinuria remains unknown. Dose-related proteinuria, incidences of nephrotic syndrome, renal histology of podocyte injury, and focal segmental glomerulosclerosis have been reported in the context of mTORi usage.[1,4] In the present case, the podocyte injury involved <50% of the area without glomerulosclerosis. Since diabetic

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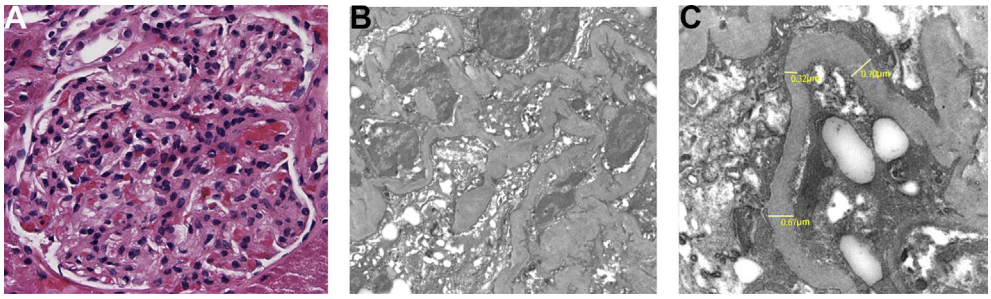

Figure 1 (A) The glomeruli show moderate mesangial hypercellularity with moderate mesangial matrix expansion. (B) Electron microscopically, partial foot process effacement (less than 50%) of podocytes is discernible with focally wrinkling change. (C) Irregularly thickening of glomerular capillary wall (400～700 nm) is noted. No prominent electron dense deposit can be seen in the mesangial, subendothelial and subepithelial regions.

glomerulopathy and mTORi toxicity play important roles in the etiology of glomerular proteinuria, it is difficult to differentiate based on the response to treatment with angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).[5] In our case, mTORi toxicity might have had the majority effect on proteinuria since a marked decreased proteinuria was noted after the withdrawal of mTORi for 1 month (UPCR: from 7.2 mg/mg to 1.02 mg/mg) and was improved in advance under ACEi treatment despite the patient's suboptimal diabetes control during this period.

In conclusion, it is difficult to diagnose mTORi-induced proteinuria in post-transplant pediatric patients with DN, and the diagnosis should not be based solely on renal histology. Reversal of proteinuria upon drug withdrawal helps the clinician to clarify the etiology before initiating further therapy. However, proteinuria should be closely monitored for the progression of DN after NODAT.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2018.11.001.

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