Early Diabetic Nephropathy in a Pediatric Renal Transplant Recipient Leading to End Stage Renal Disease

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Abstract

Limited data is available on post-transplant diabetes mellitus (PTDM) and diabetic nephropathy in the pediatric population. Annual prevalence of diabetes and diabetic nephropathy in the general pediatric population is on the rise. In the non-transplant pediatric population, diabetic nephropathy occurs 10-15 years after the diagnosis of diabetes mellitus (DM). As per our knowledge, this is the first reported pediatric case of diabetic nephropathy that occurred within 3 years of the diagnosis of PTDM, and also developed end stage renal disease within 7 years. Prognosis was worse due to poor compliance with the medication, antibody-mediated rejection and diabetic nephropathy leading to end stage renal disease (ESRD). Patient is currently on dialysis.

Keywords: Diabetes mellitus; Chronic kidney disease; Glomerulo nephritis

Abbreviations

DM: Diabetes Mellitus; PTDM: Post Transplant Diabetes Mellitus; ESRD: End Stage Renal Disease; CKD: Chronic Kidney Disease; MPGN: Membrane Proliferative Glomerulo Nephritis; FSGS: Focal Segmental Glomerulo Sclerosis; HbA1C: Hemoglobin A1C

Case Presentation

21-year old Hispanic female with end stage renal disease (ESRD) due to membrane proliferative glomerulo nephritis type 2 (MPGN). At 14 years of age, she received a deceased donor renal transplant. The donor was a healthy 17 year old female who died from a gunshot wound. Donor kidney biopsy was not performed. Pre-transplant period was significant for glucocorticoid-induced insulin-dependent diabetes mellitus that resolved after discontinuation of the steroids. One month post-transplant, she developed gluco corticoid- and tacrolimus-induced type 1 diabetes mellitus, poorly controlled (Hemoglobin A1C averaged 10%). Three years post-transplant, patient developed nephrotic-range proteinuria and microscopic hematuria. Serum complements were normal suggesting non-recurrence of the MPGN, and the serum creatinine was stable at 0.8mg/dL. (Laboratory results, Graphs 1-3 and Tables 1 and 2). Patient was started on enalapril with
little improvement in the proteinuria. Patient also had persistent hypertension that was controlled with amlodipine and enalapril. Fundoscopic exam showed no evidence of diabetic retinopathy. A graft biopsy was performed to rule out MPGN type 2 recurrence, de novo glomerulopathy, diabetic nephropathy, or rejection. The biopsy showed basement membrane thickening and mesangial expansion with focal nodularity, consistent with de novo diabetic nephropathy. There was isolated mesangial complement 3 (C3) staining that was non-specific for MPGN. There were no signs of rejection or de novo glomerulopathy. BK virus staining was negative. Patient continued to have poorly controlled DM and non-adherence to the medications. The graft function deteriorated and a repeat biopsy showed worsening of the diabetic nephropathy, secondary focal segmental glomerulosclerosis (FSGS), and chronic antibody-mediated rejection (Figures 1A and B,2,3,4A,B,C and D) with transplant glomerulopathy. Patient progressed to end-stage renal disease and hemodialysis was initiated.

The risk factors for the development of DM in this patient included a maternal history of DM, pre-transplant glucocorticoid-induced DM, and post-transplant glucocorticoid- and tacrolimus-induced DM. Her poor compliance with the insulin regimen resulted in early progression to diabetic nephropathy leading to end stage renal disease.

**Discussion**

The risk of PTDM is well defined in adults but much less understood in pediatric population. In the adult population, the incidence of de novo PTDM varies between 2% and 53%, of which 4-25% are renal transplant recipients [1]. Based on previous studies, 2–35% of children develop PTDM after renal transplantation [2-4].

Incidence of DM is higher in transplant patients compared to the
general population. Adult risk factors associated with the development of PTDM are age >40 years, obesity, metabolic syndrome, family history of diabetes mellitus, cadaveric graft, and Afro-American or Hispanic race. Hepatitis C infection and the use of glucocorticoids, tacrolimus and sirolimus are risk factors as well [1,5,6]. Pediatric studies have shown that the risk factors for PTDM are older age, obesity (Body Mass Index BMI ≥ 30) and cytomegalovirus (CMV) naïve recipients who receive a CMV positive graft. Small studies have shown that a family history of diabetes and peri- transplant hyperglycemia are also risk factors for the development of PTDM [2].

The occurrence of PTDM is usually within the first six months following transplantation and is generally reversible [7]. In the non-transplant pediatric population, diabetic nephropathy usually develops within 10-15 years after the diagnosis of DM. In the pediatric population, it is uncommon to develop diabetic nephropathy within 4-5 years of the diagnosis of DM [8,9]. The development of PTDM is a major clinical concern following kidney transplantation and has been shown to be strongly associated with reduced graft function, increased cardiovascular morbidity and lower patient survival among adult recipients [4,9-11]. In the pediatric population, few small studies have shown no direct significant association of PTDM with graft dysfunction or patient mortality. There is scarce data available on PTDM in pediatric population leading to graft loss [4].

Calcineurin inhibitors lead to DM by decreasing glucose uptake, reducing insulin release or reducing insulin gene expression. Among calcineurin inhibitors, tacrolimus is more diabetogenic by 30-50% compared to cyclosporine and its effect is not dose dependent. Tacrolimus is still the preferred immunosuppressant drug due to its superior efficacy and safety despite the risk of diabetes [12-14]. Glucocorticoids cause DM by increasing glyconeogenesis, increasing insulin resistance, reducing insulin release, or depressing beta cell function.

The choice of immunosuppressant and the obesity are the only modifiable risk factors reaching significance. Corticosteroids dose reduction has been shown to significantly improve glucose tolerance during the first year after transplantation. In patients with PTDM, tacrolimus to cyclosporine conversion therapy has shown variable results. However, any dose reduction or change of immunosuppressive regimen should be weighed against the risk of rejection, patient’s medication tolerance and side effects [14-17].

Post-transplant serum glucose should be monitored on a regular basis and if abnormal, a glucose tolerance test should be performed. Based on the transplant center incidence and prevalence of PTDM, it is reasonable to obtain a monthly fasting blood glucose and HbA1C, at least for the first few months after transplant. Prompt referral to the Endocrinology service is essential to instruct the patients on home glucose monitoring, carbohydrate counting and insulin administration, if needed. Patients need to be educated on the importance of glyemic control and lifestyle modification. If there are signs of proteinuria or graft dysfunction in an adolescent or young adult patient with PTDM, diabetic nephropathy should be considered in the differential diagnosis.

References


