Case Report: Absence of Clinically Significant Recurrent Diabetic Kidney Disease on Postmortem Biopsy 32 Years After Kidney Transplantation for Type 1 Diabetes

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INTRODUCTION

Patients with type 1 diabetes (T1D), particularly those who develop end-stage kidney disease (ESKD), are at high risk for premature death.1 Kidney transplantation improves mortality and quality of life over dialysis, even among diabetic patients.2 However, outcomes still remain worse among diabetic compared with nondiabetic transplant recipients,3,4 due to continued progression of microvascular and macrovascular complications.3

Graft survival in TID is primarily reduced due to death with functioning graft, though recurrence of diabetic kidney disease (DKD) posttransplantation is another important factor affecting outcomes.2,4 Nearly all transplanted kidneys from nondiabetic deceased donors to diabetic recipients demonstrate the pathological recurrence of DKD as early as 2 y posttransplant.5-11

We report a unique case of man who developed T1D at age 13, ESKD at age 47, deceased donor kidney transplantation at age 48, and death at age 80. He lived for 67 y after the onset of T1D. At his death, 32 y posttransplant, he maintained excellent allograft function without evidence of clinically significant recurrent DKD on postmortem biopsy. To our knowledge, this individual is one of the longest reported survivors of T1D and ESKD requiring a kidney transplant.

CASE DESCRIPTION

A 49-y-old Caucasian man (O positive; panel reactive antibody 0.0%; weight 80 kg, height 184 cm, body mass index 23.6 kg/m2) with ESKD from DKD associated with a 36-y history of T1D (diagnosed age 13) for which he had been maintained on peritoneal dialysis for 10 mo before transplantation received a neurologic determination of death, standard criteria donor kidney transplant (cytomegalovirus status: donor reactive, recipient reactive) in August 1988 in Vancouver, British Columbia (Table 1). The donor was a 17.6-y-old Caucasian male (O positive) who was otherwise healthy, on no home medications, and the cause of death was intracranial hemorrhage. Crossmatch was negative with no donor-specific antibody (donor HLA: A1—2, A2—32, B1—7, B2—44, DR1—2, DR2—unknown; recipient HLA: A1—3, A2—29, B1—44, B2—62, DR1—7, DR2—9). Recipient medical comorbidities at transplantation included hypertension. There were no intraoperative complications (cold ischemic time: 6 h 18 min; anastomosis time: 30 min). He received triple immunosuppressive therapy with cyclosporine, azathioprine, and prednisone without induction. The immediate postoperative course was uncomplicated, and he was discharged home on postoperative day 11. His nadir baseline creatinine was 60–80 µmol/L. He was started on insulin pump therapy immediately posttransplant and experienced excellent glycemic control. Prednisone was discontinued at the end of the first year and he was continued on cyclosporine and azathioprine.

His long-term posttransplant course was complicated by sequelae of diabetes and immunosuppressive therapy. Despite fastidious monitoring and control of his glucose levels (hemoglobin A1c, 6.2%–7.5% over the preceding 10 y), he still experienced numerous extrarenal complications related to his diabetes. These included progressive retinopathy with recurrent vitreous hemorrhages, cataracts, severe peripheral neuropathy, hypertension with orthostatic hypotension secondary to diabetic autonomic neuropathy with severe gait instability,
neurogenic bladder requiring a permanent in-dwelling catheter complicated by recurrent urinary tract infections (maintained on suppressive therapy), coronary artery disease requiring coronary artery bypass grafting and aortic valve replacement in 2015, diabetic foot ulcers, and severe peripheral vascular disease, resulting in bilateral below-knee amputations in 2016 and 2018. Immunosuppressive therapy complications included skin cancer (squamous cell carcinoma—penile shaft, 2006; basal cell carcinoma—forearm, 2019), osteoporosis with compression fractures, and recurrent infections. Azathioprine was stopped due to skin cancer in 2006, and he was maintained on cyclosporine monotherapy.

The recipient presented to hospital in January 2020 with a presumed acute viral pulmonary illness and subsequently died at age 80 with a functioning allograft (terminal creatinine 72 µmol/L; urine albumin to creatinine ratio 5.0 mg/mmol). Medications at admission included cyclosporine, ramipril, brimonidine, latanoprost, hydromorphone, nitrofurantoin, acacetaminophen, vitamin B₁₂, vitamin D, and insulin pump therapy. He also had excellent glycemic control with a terminal hemoglobin A₁c of 7.1%. Of interest, the recipient of the mate kidney died in 1998 also with a functioning allograft.

A transplant kidney allograft biopsy was performed on the day of death 6 h 5 min postmortem per the wish of the patient out of an altruistic desire to expand knowledge regarding DKD posttransplantation (Figure 1). The renal biopsy consisted of renal cortex and medulla, with 26 glomeruli sampled. Nine glomeruli were globally sclerosed, but 7 of these sclerosed glomeruli were in a subcapsular scar. Aside from diffuse autolysis, the glomeruli outside the subcapsular scar were histologically unremarkable and did not demonstrate mesangial sclerosis or discernible thickening of the glomerular basement membranes (GBMs). Other significant findings included moderate atherosclerosis, severe subendothelial arteriolar hyalinosis, and moderate interstitial fibrosis and tubular atrophy (including the subcapsular scar). Medial hyalinosis of the arteriolar walls was not present, and the interstitial fibrosis and tubular atrophy was patchy and not in a striped pattern. Features of T cells and antibody-mediated rejection were not present, and immunofluorescence microscopy for C4d was negative. Ultrastructural evaluation demonstrated global mild thickening of the GBMs without mesangial expansion and no duplication of the GBMs. The podocyte foot processes could not be evaluated due to the degree of autolysis. The glomerular features of DKD were mild (Renal pathology society

### TABLE 1. Timeline

| Year    | Event                                                                 |
|---------|-----------------------------------------------------------------------|
| 1952    | Diagnosis of type 1 diabetes (age 13)                                  |
| October 1987 | Progression to end-stage kidney disease and initiation of peritoneal dialysis (age 48) |
| August 1988 | Listing on the deceased donor kidney transplant waitlist               |
| August 1988 | Neurologic determination of death, standard criteria donor kidney transplant (age 49) |
| – initiation of immunosuppressive therapy with cyclosporine, azathioprine, and prednisone without induction |
| – initiation of insulin pump therapy |
| 1989    | Prednisone discontinued—maintained on azathioprine and cyclosporine   |
| 1991    | Vitreous hemorrhage                                                   |
| 2006    | Squamous cell carcinoma—azathioprine discontinued and maintained on cyclosporine monotherapy |
| 2002    | Osteopenia                                                            |
| 2011    | Neurogenic/diabetic bladder                                           |
| 2011    | Cataract extraction                                                   |
| 2012    | Osteoporosis                                                          |
| 2014    | Vitreous hemorrhage                                                   |
| June 2015 | Cataract extraction                                                   |
| July 2015 | Coronary artery disease and aortic stenosis requiring coronary artery bypass grafting and aortic valve replacement |
| December 2015 | Diabetic heel ulcer infection with *Staphylococcus aureus*             |
| January 2016 | *Escherichia hermannii* bacteremia and nonhealing left heel wound infection with left below-knee amputation |
| February 2016 | Hospital-acquired pneumonia                                           |
| October 2016 | Left below-knee amputation stump infection with *Staphylococcus aureus* |
| April 2018    | Ischemic right limb with gangrenous heel ulcer requiring peroneal and popliteal artery angioplasty with drug-eluting stent |
| June 2018    | Ischemic right foot with infected heel ulcer requiring right below-knee amputation |
| November 2018 | Parainfluenza virus 3 infection                                      |
| January 2019 | Basal cell carcinoma                                                  |
| July 2019    | Bacterial parotitis                                                   |
| January 2020 | Death with a functioning graft following admission to hospital with viral pneumonia (age 80)—postmortem renal allograft biopsy performed |

![FIGURE 1. A, The glomeruli were histologically unremarkable and did not demonstrate mesangial sclerosis. There was diffuse autolysis in the biopsy, which was most prominent in the tubular epithelial cells (PAS, x400). B, Severe subendothelial hyalinosis was present in several arterioles (PAS, x200). PAS, periodic acid-schiff.]
class I) and out of proportion to the more severe vascular and tubulointerstitial chronicity. Findings of chronic calcineurin inhibitor toxicity were not present, and the vascular findings may be related to hypertension rather than diabetes.

**DISCUSSION**

Recurrent DKD posttransplantation has been reported as early 2 y posttransplant with histologic changes characterized by mesangial sclerosis, GBM thickening, and glomerular neovascularization.\(^6\)\(^,\)\(^7\)\(^,\)\(^9\)\(^,\)\(^12\) One study of 14 diabetic kidney transplant recipients reported that the histologic diagnosis of recurrent DKD was made on average 97 mo (range, 41–154 mo) after transplantation, was accompanied by both proteinuria and abnormal renal function, and was associated with a higher rate of graft failure.\(^10\) Other authors have reported that although uncommon, graft loss due to recurrent DKD does occur.\(^5\) Among a cohort of T1D kidney transplant recipients reported back in 1989, 40% were alive and 32% of the primary grafts were functioning at 10 y.\(^5\) Mortality and graft longevity have improved over the past several decades, though they remain reduced compared with nondiabetic transplant recipients.\(^4\)\(^,\)\(^8\) Kim et al\(^8\) reported a survival rate of 74% versus 95% among diabetic versus nondiabetic patients at 10 y. A more recent study of 2383 T1D patients in Finland found that the median survival was 15.9 y after a successful transplant, 11.2 y if transplant function was lost, and 2.9 y if they remained on dialysis.\(^4\)

Posttransplant hyperglycemia and abnormal glomerular angiogenesis have been proposed as mechanisms responsible for recurrent DKD.\(^7\)\(^,\)\(^12\) Strict glycemic control, achieved through intensive insulin therapy, has been demonstrated to reduce the risk of developing microvascular and macrovascular complications and slow the progression of existing complications.\(^13\)\(^,\)\(^14\) This is supported by a prospective randomized study that evaluated the impact of glycemic control on 5-y posttransplant allograft biopsies from T1D transplant recipients.\(^12\) The authors demonstrated a 2-fold increase in the volume fraction of mesangial matrix per glomerulus, greater GBM widening, and a 3-fold increase in arteriolar hyalinosis, suggesting a causal relationship between posttransplant hyperglycemia and important lesions of recurrent DKD.\(^12\) Nyumura et al\(^7\) reported that glomerular neovascularization, represented by increased number and area of capillaries, occurs as an early lesion in recurrent DKD and that posttransplant hyperglycemia was a significant risk factor for recurrent DKD.

Despite the use of intensive insulin therapy and insulin pumps, no form of exogenous insulin therapy has been able to sustain euglycemia as effectively as a functioning pancreas.\(^15\)\(^,\)\(^16\) Simultaneous pancreas kidney transplant slows the progression of microvascular and macrovascular disease, reduces mortality, and improves quality of life, in addition to rendering a patient free of both insulin and dialysis.\(^15\)\(^,\)\(^17\) Simultaneous pancreas kidney is generally considered superior to deceased donor kidney transplant alone, though excellent outcomes have been reported after living donor kidney transplantation, primarily due to elimination of dialysis.\(^15\)\(^,\)\(^17\) Pancreas after kidney transplant appears to combine the advantages of pancreas and living donor kidney transplantation, resulting in the greatest survival benefit.\(^16\)

It is remarkable that this patient developed numerous diabetic complications including both microvascular and macrovascular diseases, but the donor kidney was protected from the development of DKD. In addition to excellent blood pressure and glycemic control, several explanations may account for this recipient’s protection against DKD. First, transplanted kidneys are denervated at the time of the surgery that may abort the glomerular hyperfiltration typically seen in DKD.\(^18\) Second, although DKD is traditionally considered a nonimmune disease, there is growing evidence that immunologic and inflammatory mechanisms play a significant role in the development and progression of DKD.\(^19\) Third, steroid withdrawal may have reduced the risk of recurrent DKD.\(^20\) Fourth, there is growing recognition that diabetic complications represent heterogeneous disease phenotypes, highlighting the importance of clarifying the complex pathophysiology of DKD.\(^21\) In a study of nontransplant diabetic patients who underwent kidney biopsy, approximately half were found to have DKD and half had non-DKD.\(^21\) Finally, we cannot underestimate the importance of HLA matching, recipient adherence to immunosuppressive therapy, or the possibility that the donor kidney may have had a protective genotype against the development of DKD.\(^22\)

In summary, we report one of the oldest survivors of T1D and ESKD requiring a kidney transplant, who died with a functioning graft 32 y posttransplant, and on postmortem biopsy had only mild changes associated with diabetes without evidence of clinically recurrent DKD. This case demonstrates that kidney allografts in T1D recipients can remain free of clinically significant recurrent DKD into the fourth decade posttransplant. A better understanding of the pathophysiology of recurrent DKD posttransplantation may have important therapeutic implications for improving management, mortality, and graft longevity in diabetic transplant recipients.

**ETHICAL CONSIDERATIONS**

Written informed consent was obtained from the patient’s spouse for this case report.

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