Co-existing post-transplant membranous nephropathy and diabetic nephropathy: A case report

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Abstract
Membranous nephropathy (MN) is a glomerular disease commonly found in transplanted kidneys. The natural history of MN post-transplant is unpredictable and spontaneous remission is uncommon. Diabetic nephropathy (DN) is also commonly seen in patients with prolonged new onset diabetes mellitus after transplant (NODAT). However, there have been no previous reports of co-existing MN and DN in transplanted kidneys. We herein report a case of a 53-year-old male with early post-transplant proteinuria and microscopic hematuria due to MN with subsequent clinical spontaneous remission. Due to the early onset of disease after transplant and presence of serum anti-phospholipase A2 receptor (anti-PLA2R) antibody, the evidence suggests primary recurrent MN in this patient. He was then diagnosed with NODAT, with fair glycemic control with oral hypoglycemic agents. Sixteen years after remission, he developed recurrent proteinuria and progressive impairment of renal function. The allograft biopsy revealed both MN and DN. Both diseases may have contributed to the development of glomerular pathology in this patient.

1. Introduction
Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults and is one of the most frequent glomerular diseases found in the post-transplant period [1] leading to poor allograft survival [2]. New onset diabetes mellitus after transplant (NODAT) has been reported to occur in 4–25% of renal transplant recipients [3–8] and may lead to diabetic nephropathy (DN), which results in lower allograft and patient survival [4,5,9–15]. However, there have been no previous reports of co-existing of MN and DN in transplanted kidneys. Here, we report a case of co-existing post-transplant MN with DN as a complication of NODAT.

2. Case report
A 53-year-old Thai male with end-stage renal disease (ESRD) due to hypertensive nephropathy received an HLA-identical allograft renal transplant from his brother in February 1997. He had no prior history of diabetes mellitus (DM) but his mother was a diabetic. Induction treatment with methylprednisolone 1000 mg, 500 mg, and 250 mg was given on days 0, 1 and 2, respectively. The maintenance immunosuppressive regimen consisted of cyclosporine A 350 mg/day and prednisolone 20 mg/day. His post-operative period was uneventful and allograft function was excellent.

Within four months after the transplant, his serum creatinine level rose from 1.2 mg/dL to 3.3 mg/dL. Allograft biopsy was performed and showed no signs of graft rejection. Cyclosporin-induced nephrotoxicity was diagnosed since the highest cyclosporin trough level reported was 414 ng/ml (Fig. 1A). After the dosage of cyclosporin was lowered, the serum creatinine level decreased to 1.6 mg/dL (Fig. 1B).

In 1998, he developed DM, which was controlled with glipizide 5 mg/day and sitagliptin 100 mg/day resulting in fair glycaemic control with HbA1c levels between 6.3% and 8.1% (Fig. 1C). His systolic blood pressure varied between 130 and 160 mmHg and diastolic blood pressure varied between 80 and 110 mmHg (Fig. 1D).

In 1999, urinalysis during follow up revealed proteinuria with a urine protein of 2.8 g/day, RBC 5–10/HPF with no cellular casts. Allograft biopsy revealed thickening of the glomerular capillary walls in all glomeruli. A diagnosis of MN and hyaline
arteriosclerosis was made. Enalapril was given to control proteinuria with poor response. He had spontaneous clinical remission after 4 years of treatment (Fig. 1E).

In 2014, he presented with pitting edema in both legs, and positive dipstick proteinuria. The UPCR was 1.85 g/g, serum albumin of 3.29 g/dL, cholesterol of 185 mg/dL and anti-phospholipase A2 receptor (anti-PLA2R) was detected in the serum. Renal ultrasonography revealed a normal appearance of the renal allograft. HBsAg, anti-HBs, Anti-HCV and anti-HIV were negative. Allograft biopsy was performed and showed thickened capillary wall and expanded mesangial matrix in the glomeruli (Fig. 2A), weak linear IgG deposition on immunofluorescence (Fig. 2C) and thickened basement membrane (510–614 nm.) on electron microscopy (Fig. 2D), compatible with diabetic nephropathy, class 2[16]. In addition, granular deposits of IgG along the capillary wall (Fig. 2C) corresponded with spikes on light microscopy and foci of electron lucent and dense deposits in subepithelium and intramembrane (Fig. 2D), all features of membranous nephropathy. C4d was negative in the peritubular capillaries but positive in glomerular capillaries (Fig. 2B).

Supportive treatment with ACEI and statin were given. The patient still had persistent proteinuria of 5 g/day and a serum creatinine level of 2.2 mg/dL (CKD-EPI eGFR 33 ml/min per 1.73 m²) at the last follow up. In addition, there was no clinical evidence of diabetes mellitus or kidney disease in the sibling donor post-transplantation after 17 years follow up.

3. Discussion

We present this case of co-existing MN and DN in a transplant patient. One year after transplantation he developed NODAT, the most common complication in renal transplant patients [5,10] and has been reported to occur in 4–25% of recipients [3–8]. The cause of NODAT in this patient was thought to be due to the side effects of the immunosuppressive agents including cyclosporine A and prednisolone [5,10,15,17–24] combined with a family history of DM. In previous studies, the familial history of DM along with race, age, genetic background, previous glucose intolerance, obesity, hepatitis C virus, and cytomegalovirus infection were risk factors of NODAT [25,26]. The patient’s NODAT was fairly controlled with oral hypoglycemic agents.

Two years after transplantation, he developed proteinuria and microscopic hematuria. Allograft biopsy revealed thickening of the glomerular capillary walls in all glomeruli, consistent with the histopathological features of MN [27]. From previous reports, recurrent MN occurred earlier than de novo MN (15.58 ± 19.13 vs 49.27 ± 32.71 months), our patient was therefore considered as recurrent MN, which has been reported to occur in 2.5% of transplanted patients [28]. Such a significant difference suggests that different mechanisms are involved in the physiopathology of these diseases. For de novo MN, HCV and donor-specific antibody seem to be the important etiologic factors [28,29]. Since no known etiologies of MN including viral infection, malignancy,
autoimmune disease or cryoglobulinemia have been identified to date, we believe he has idiopathic MN. In addition, the allograft biopsy also revealed hyaline arteriosclerosis, which can be found in hypertensive nephropathy, calcineurin inhibitor nephrotoxicity, or DN. Enalapril was given to control proteinuria but without response. He had spontaneous clinical remission after 4 years of treatment. Spontaneous remission of idiopathic MN has been observed among transplant patients and is a well-known feature [29–31].

Seventeen years after transplant, he presented with leg edema and recurrent proteinuria. The differential diagnoses were recurrent MN, DN, and transplant glomerulopathy. Allograft biopsy revealed histopathological features of both MN and DN. The hepatitis and HIV viral studies were negative except for anti-phospholipase A2 receptor (PLA2R) antibody which was detected in the serum. Anti-PLA2R antibody is a biomarker that can be used to differentiate between idiopathic and secondary MN [32–35]. Therefore, it was more likely that the patient had idiopathic recurrent MN. In this patient, DN was identified 16 years after the diagnosis of NODAT. In previous studies, NODAT has been reported to cause DN approximately 5.9 years after transplantation [36].

Even though MN and DN are common in the post-transplant period, co-existence of MN and DN has yet to be reported. Post-transplant spontaneous remission of MN can be observed, but MN may lead to poor allograft survival [2]. Long standing DM after kidney-transplant causes significant pathological injury to the allograft, resulting in lowered allograft and patient survival [4,5,9–15]. The United States Renal Data System (USRDS) has clearly stated the relationship between NODAT and a 63% increase in graft failure and an 85% increase in mortality [37]. Individually, MN and DN have a negative impact on allograft survival. We believe that having both MN and DN may contribute to an even worse outcome than having either disease alone.

In native kidneys, all patients with MN should receive best supportive care, including treatment with ACEI/ARB, lipid lowering agents, and adequate control of blood pressure [38]. The use of immunosuppressive therapy should be considered on an individual basis [39]. In this case, supportive care and immunosuppressive therapy were already given. It is well known that immunosuppressors are needed to avoid graft rejection, but their beneficial effects on post-transplant MN have not yet been validated [31].

References


