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CASE REPORT

De Novo Membranoproliferative Glomerulonephritis III in a renal transplant patient: Case report and review of the literature

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Summary

Idiopathic membranoproliferative glomerulonephritis (MPGN) is a rare cause of renal failure with a cumulative incidence of 0.3% of all ESRD and 4% of all primary glomerulonephritis for types I and II. Membranoproliferative glomerulonephritis type III is more uncommon and idiopathic de novo MPGN III in a renal transplant patient has not been reported. We present the case of a 57-year old white female patient with a diagnosis of lithium toxicity as cause of end stage renal disease (ESRD) who developed MPGN III in her allograft 6 years after a renal transplant. Despite treatment, she progressed to ESRD within four and a half years from the time of diagnosis.

Introduction

Membranoproliferative glomerulonephritis is an uncommon cause of glomerulonephritis with an incidence of 1.9 per million people [1]. The mean age of onset ranges from 8 to 30 years [2]. It lacks unique serological markers or pathognomonic features, and is defined histologically [3].

Secondary MPGN has been associated with autoimmune diseases, thrombotic microangiopathies, chronic infections and transplant glomerulopathy [4]. Three forms have been defined based on electron microscopy (Table 1) [5–7].

Type III MPGN is the rarest, and recurrence has been reported only as two separate case reports [8,9]. Idiopathic de novo MPGN III has not been previously reported.

To understand MPGN III and its development after transplant better, we describe the case of a female patient, who developed MPGN III in the allograft 6-years after transplant.

Case report

A 57-year old white female patient presented in June 1995 with a serum creatinine of 2.3 mg/dl. Her urinalysis showed 1 + protein and no hematuria. She had taken lithium from 1979 to 1989 for bipolar disorder and her ESRD was attributed to lithium toxicity. Past medical history was significant for hypertension. Family history was noncontributory. She underwent a native kidney biopsy in March 1999 when her serum creatinine increased to 4.4 mg/dl (Fig. 1a–d).

The light microscopy (LM) showed 13 glomeruli. Nine were globally sclerosed. Protein reabsorption droplets were present within the tubules. There was extensive interstitial fibrosis and tubular atrophy with moderate, patchy chronic

Table 1. Three forms of MPGN.

Type	Age of onset (years)	Histological findings	Incidence	Incidence of recurrence (%)
Type I	5–76	Characterized by discrete immune deposits in the mesangium and subendothelial space.	0.3%	20–30
Type II	4–34	Also called dense deposit disease. Characterized by continuous dense ribbonlike deposits along the glomeruli, tubules and Bowman's capsule.	0.03%	50–100
Type III	3–66	Similar to type I but subepithelial deposits are prominent and there is complex disruption of glomerular basement membrane with large lucent areas.	Unknown	Unknown (2 cases to date)

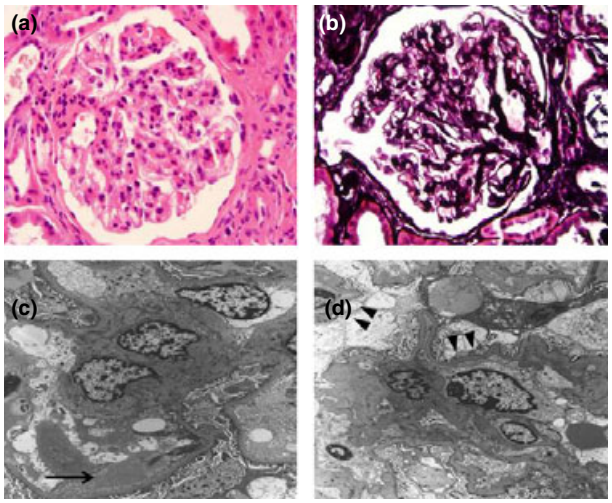

Figure 1 Native Kidney Biopsy. (a) The native kidney biopsy shows a relatively unremarkable glomerulus with only mild mesangial hypercellularity (Hematoxylin and Eosin stain; 40×). (b) There is no evidence of capillary loop duplication or ''spike'' formation on the Jones' methanamine silver (b, 40× magnification) stain. (c, d) Transmission electron microscopy of the native kidney biopsy shows segmental effacement of the podocyte foot processes (arrowhead). The glomerular basement membrane is of normal thickness with accentuated wrinkling. There is a single subendothelial electron dense deposit (arrow). Notably, no subepithelial electron dense deposits are seen (7700× magnification).

interstitial inflammation. Severe arteriolosclerosis and arteriosclerosis were evident. Trichrome, Periodic Acid-Schiff and silver stains confirmed these findings.

Electron microscopy (EM) showed segmental effacement of the podocyte foot processes involving approximately 10% of the capillary loop surface area. There was diffuse wrinkling of the glomerular basement membrane (GBM). Lipid droplets were noted within the podocyte cytoplasm. A single subendothelial, granular deposit was seen. Mesangial and subepithelial deposits were not seen. There was no evidence of GBM duplication.

The extensive wrinkling of the glomerular basement membrane was suggestive of focal segmental glomerulosclerosis FSGS but nonspecific. The single, granular, subendothelial deposit was of unclear significance.

She underwent a pre-emptive 1-haplotype but zero-antigen mismatched (HLA recipient A1,3; B35,62; DR4,8) living related kidney transplant from her son on February 1, 2000. Both the recipient and donor were cytomegalovirus seronegative. She received rabbit antithymocyte globulin (rATG, Thymoglobulin) 125 mg (1.5 mg/kg) for a total of four doses. She was maintained on azathioprine 200 mg daily, cyclosporine (400 mg orally twice daily decreased to 75 mg twice daily based on trough levels) and prednisone, which was tapered to 5 mg/day by post-transplant week 18. Her creatinine post-transplant was 1.4 mg/dl.

In December 2005, a urine protein creatinine ratio estimated a protein excretion rate of 2.1 g/day which was confirmed with a 24-h urine collection. Because of the diagnosis of lithium toxicity as the cause of ESRD, excellent HLA match and stable serum creatinine, a biopsy was deferred, and losartan 50 mg orally twice daily was started.

By April 2006, she developed worsening edema, hypertension, proteinuria to 5.3 g/day and creatinine increased to 1.8 mg/dl. In June 2006, she underwent an allograft biopsy (Fig. 2a–d). There were diffuse subepithelial and focal subendothelial and mesangial electron dense deposits with focal areas of GBM duplication. Immunofluorescence (IF) showed granular capillary loop staining for IgG and C3. Staining for C4d was negative, and no anti-HLA antibodies were detected in the serum. Workup was negative for hepatitis B, C and HIV serologies. A two-dimensional echocardiogram to rule out infective endocarditis showed no evidence of vegetations. Computed tomography (CT) of the chest, abdomen and pelvis ruled out any visceral infection or neoplasm. She was afebrile and had a normal white blood cell count. Additional evaluation including, coagulation factors, platelet count and complement fractions were within normal limits. Collectively, these findings were interpreted as MPGN type III.

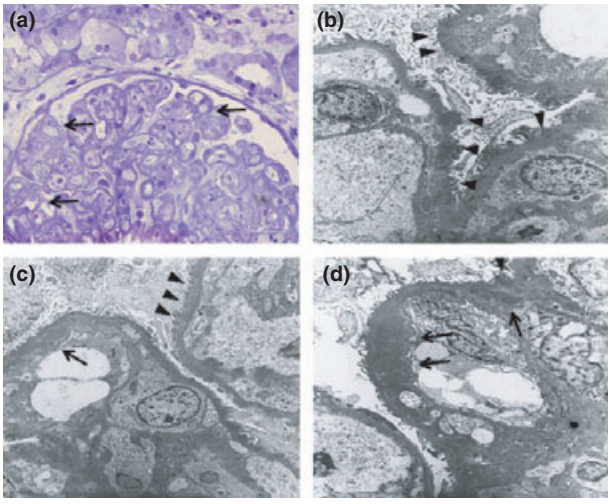

Figure 2 Allograft Kidney Biopsy. (a) Toluidine blue-stained plastic section (60× magnification) of the allograft biopsy shows a lobular appearing glomerulus with duplication of the capillary loops (arrows). (b, c, & d) Transmission electron microscopy of the allograft kidney biopsy demonstrates diffuse thickening of the glomerular basement membrane by subepithelial/intramembranous (arrowheads), and subendothelial (arrows) electron dense deposits. The deposits have no discernable substructure. Focally, the glomerular basement membrane is duplicated. Significant podocyte foot process effacement is seen. These findings support the diagnosis of membranoproliferative glomerulonephritis type III (b, d 10,000× and c 6,250× magnification).

She was treated with prednisone 60 mg/day and MMF 500 mg twice daily which replaced azathioprine. Spironolactone 25 mg/day, aspirin 81 mg/day and dipyridamole 50 mg thrice daily were started.

Prednisone was tapered to 10 mg/day over 3 months. Cyclosporine was stopped in November 2006 secondary to an increasing serum creatinine and no prior evidence of rejection, and MMF was increased to 1000 mg twice daily but later decreased to 500 mg twice daily secondary to diarrhea.

Her proteinuria decreased to 700 mg/day by August 2007. The serum creatinine remained stable at approximately 2.5 mg/dl until 2008 but worsened to 4.2 by December 2010.

Discussion

We believe this to be the first reported case of de novo MPGN III in a renal transplant recipient based on the following. The native kidney biopsy showed no mesangial hypercellularity, accentuated lobular appearance, or capillary loop duplication. The IF stains were negative for C3, IgG, IgA, IgM, C1q and C4d. There was only one granular subendothelial electron dense deposit seen and no coexisting subepithelial electron dense deposits making the diagnosis of MPGN type III unlikely. The finding of capillary loop wrinkling in the setting of proteinuria, hypertension and thickened vessels is most consistent with secondary focal segmental glomerulosclerosis likely related to hypertensive renal disease. In contrast, the positive glomerular IgG and C3 stains, negative C4d stain, absence of anti-HLA antibodies and the EM findings on the transplant kidney biopsy of diffuse subepithelial and focal subendothelial and mesangial electron dense deposits are characteristic of MPGN type III.

Serial biopsies have not been reported but based on the relentless progression, histological changes of MPGN III would not resolve. Thus, although there was a delay from the time of presentation to biopsy of her native kidney it is unlikely we missed a diagnosis of MPGN in the native kidney.

Successful treatment of an inciting infection usually leads to resolution of MPGN. In comparison, the outcome is poor in patients with idiopathic MPGN. Approximately 50% of patients progress to ESRD within 10 years of diagnosis [5,10–12].

A potential limitation is that we did not absolutely exclude all infectious etiologies such as protozoal disease, mycoplasma or tuberculosis that may be associated with MPGN. However, she had an unremarkable echocardiogram, CT of the abdomen and pelvis and the patient progressed to ESRD relatively slowly.

Another potential limitation is that we did not assess deficiencies or inhibitors of complement factor H or I. These have been associated with Type II MPGN. Tests for factor H and I are not routinely available. In addition, the patient has returned to dialysis and is not a re-transplant candidate; so we could not justify testing for these potential abnormalities.

The prognosis in idiopathic MPGN depends on the level of proteinuria, renal function at presentation, the presence or absence of hypertension and crescents or tubulointerstitial disease on biopsy. The risk of progression correlates more closely with the severity of tubulointerstitial disease rather than with the degree of glomerular damage [3,11]. The LM in our patient showed moderate tubulointerstitial fibrosis without crescents.

Treatment is aimed at decreasing proteinuria and slowing progression of renal disease using angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists and vitamin D such as we used. Other treatments for idiopathic MPGN are controversial and include corticosteroids, immunosuppressives, antiplatelet regimens and plasma exchange. Our patient developed MPGN III while on cyclosporine and prednisone that only transiently responded to MMF, increased steroids and antiplatelet agents. She did not receive plasma exchange.

The efficacy of the various therapeutic regimens for MPGN is difficult to assess because of the small number of patients and short-term nature of published controlled trials. Most trials include patients with all three types of MPGN, making the analysis of treatment results more difficult. Eculizumab, a C5a inhibitor, has shown some promise for dense deposit disease [13]. This expensive medicine was not available at our facility.

In summary, we believe we have reported the first case of de novo MPGN III in a renal transplant patient. This occurred without obvious inciting events, and progressed to ESRD despite immunosuppression and the use of established anti-proteinuric therapy. This case provides insight into the causes and pathophysiology of this uncommon disease.

Authorship

All authors contributed to the data collection and writing of the paper.

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