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Silent recovery of native kidney function after transplantation in a patient with membranous nephropathy

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Abstract

Recurrence of membranous nephropathy (MN) is frequently seen after transplantation. However, there are no published data about the course of MN in the native kidneys after transplantation. Disease progression in almost all cases is assumed to be the 'natural' course after transplantation. We report on a patient suffering from end-stage renal disease due to MN. Eight years after transplantation, nephrectomy was performed due to chronic rejection and unexpectedly, partial recovery of native kidney function was noted. As far as we know, there is no other similar case reported in the literature. The potential impact of the immunosuppression, especially of calcineurin inhibitors, is discussed.

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Keywords: calcineurin inhibitors; kidney transplantation; membranous nephropathy; recovery of renal function

Background

Of all patients who receive a kidney transplant, 20–40% have glomerulonephritis as the cause of renal failure [1]. In patients with membranous nephropathy (MN), a recurrence rate of 30% is reported [2]. The management of recurrent MN is based on anecdotal reports and extrapolation of data on the management of native kidney MN. Spontaneous remissions, responses to, and failures with immunosuppressive treatment have all been reported. However, there are no published data about the course of MN in native kidneys after transplantation suggesting that further disease progression is the 'natural' course after transplantation. We report on a patient suffering from end-stage renal disease due to MN with unexpected recovery of native kidney

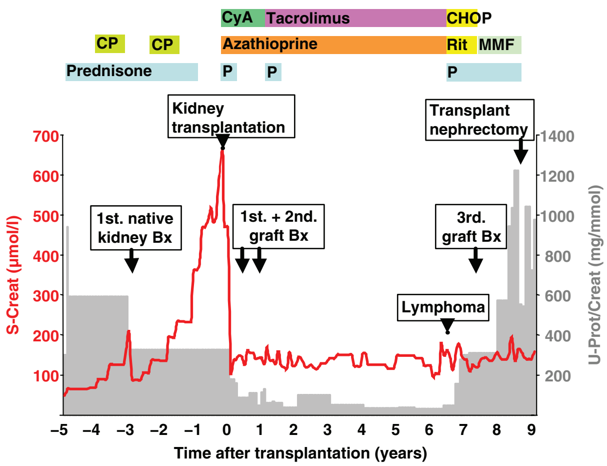

Fig. 1. Time course of membranous nephropathy in native kidneys and in a kidney graft (shown until graft nephrectomy). Serum creatinine (red line, µmol/l) and proteinuria [urine protein/urine creatinine (grey area, mg/mmol)] over time (years) before and after transplantation. P: prednisone; CP: cyclophosphamide; CyA: cyclosporine A neoral; CHOP: cyclophosphamide, doxorubicin, vincristine and dexamethasone; Rit: rituximab; MMF: mycophenolate mofetil; Bx: biopsy.

function and discuss the possible impact of immunosuppression (IS) on the outcome.

Case Report

In a nine-year-old girl suffering from a nephrotic syndrome, a kidney biopsy revealed MN stages (II) to III with proliferative crescents (Figures 1 and 2, Table 1). Secondary causes of MN such as a history of nonsteroidal anti-inflammatory agent usage, hepatitis B and C, other infections or a malignant tumour were ruled out.

In spite of therapy with prednisone and two courses of cyclophosphamide (2 mg/kg/day), proteinuria persisted and kidney function worsened steadily. Within 5 years, the kidneys failed [serum creatinine 7.9 mg/dl, estimated glomerular filtration rate (eGFR) by MDRD 8 ml/min/1.73 m^2] [4] and deceased-donor kidney transplantation was performed. The IS consisted of cyclosporine, azathioprine and prednisone. A graft biopsy at month 4 detected early recurrence of MN by immunofluorescence and interstitial rejection (Banff IA), which was treated by methylprednisolone (Figure 1, Table 1) [3]. A further graft biopsy at month 9 again revealed interstitial rejection (Banff IA) treated by methylprednisolone and by switching cyclosporine A to tacrolimus (Figure 1, Table 1) [3]. Thereafter, graft function remained stable (serum creatinine 1.6 mg/dl, eGFR by MDRD 39 ml/min/1.73 m^2) [4]. Six years later, a diffuse large B-cell lymphoma of the small bowel was diagnosed. Segmental resection was performed, and full remission was achieved after eight cycles of CHOP (cyclophosphamide, doxorubicin, vincristine and dexamethasone) in combination with eight doses of rituximab (375 mg/m^2). IS was stopped, and within 1 month proteinuria rose heavily from 0.15 to 2 g/day. A graft biopsy confirmed recurrence of MN without any signs of interstitial or vascular rejection

Table 1. Overview of the morphological findings in native biopsies and in the renal transplant

Biopsies	First native kidney	Zero hour	First Tx	Second Tx	Third Tx	Tx–Nx	Second native kidney
Time before and after Tx	Year-3	Day 0	Month 4	Month 9	Year 7	Year 8	Year 10
No glomeruli for LM	14/2 obsolescent	3/0	16/0	20/0	29/12 obsolescent		23/12 obsolescent
Diagnosis	MN with crescents in 3/12 glomeruli	Normal	MN + rejection	Rejection[a]	MN	End-stage contracted kidney with vascular rejection	MN with crescents and fibrin in 3/11 glomeruli
Interstitial fibrosis	100%	0%	30%	50%	60%		70%
Tubular atrophy	50%	0%	20%	60%	60%		70%
Inflammation	Slight	Absent	Banff IA	Banff IA	Massive focal in scars		Medium
Arteriolar hyalinosis	No	No	Minimal	Minimal	Minimal		Severe (partly: CNI type)
IF/IHC peripheral deposits	IgG, C3 very weak	No	IgG, IgM, IgA positive C3 negative	IHC[a] in paraffin: C5b-9 minimal	IgG, IgM, IgA, C3, C4, C5b-9	nd	IgG, IgM, IgA, C1q, C3, C4, C5b-9 and fibrinogen
Electron microscopy	MN stages II and III	nd	nd	nd	nd	nd	MN stages II and III

Tx: transplant, Nx: nephrectomy, No: number, LM: light microscopy, MN: membranous nephropathy, IF: immunofluorescence, IHC: immunohistochemistry, nd: not done, CNI: calcineurin inhibitor, Ig: immunoglobulin, C: complement.
[a]In the second biopsy, MN could not be diagnosed by the use of paraffin for IHC.

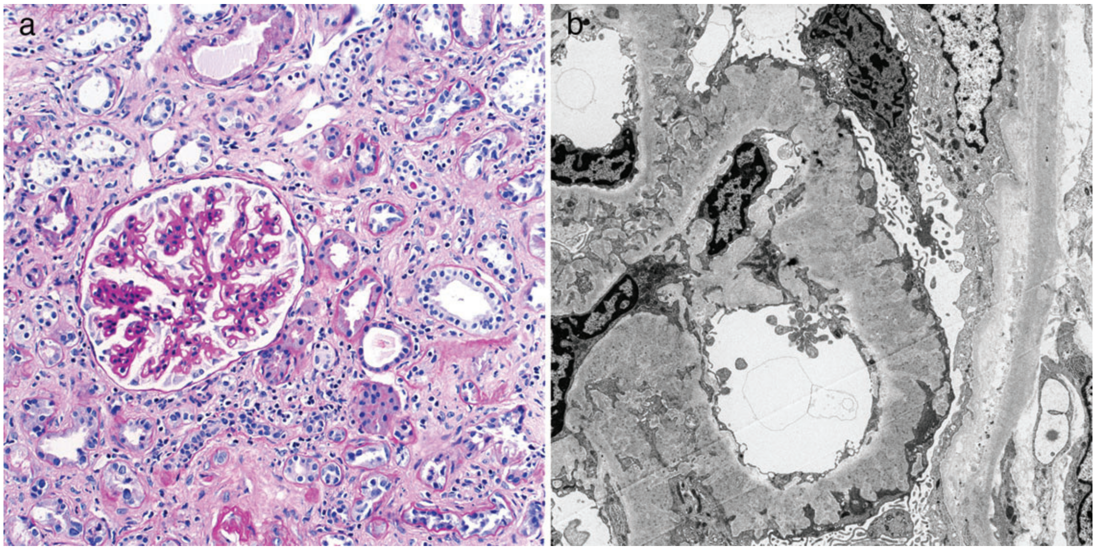

Fig. 2. First native kidney biopsy performed 3 years before transplantation: (**A**) glomerulus with thickened basement membranes embedded in a tubulo-interstitial space showing tubular atrophy, fibrosis and scattered inflammatory infiltrates (PAS, ×200); (**B**) peripheral capillary loops with subepithelial deposits partly separated by spike or surrounded by newly formed basement membrane (EM, ×3300).

(Figures 1 and 3, Table 1). Four months after chemotherapy, mycophenolate was added to prednisone. During the next 2 years, serum creatinine increased slightly and kidney graft hydronephrosis due to ureter stenosis was diagnosed and treated by ureter catheter insertion. Five months later, the patient suffered from pain in the graft region and, surprisingly, Doppler ultrasound showed no perfusion of the graft. The immediate surgical exploration revealed a blue graft without perfusion. Misled by only a slight increase in serum creatinine (1.9 mg/dl, eGFR by MDRD 34 ml/min/1.73 m^2) [4], graft nephrectomy was not performed despite the disastrous finding. Severe acute rejection was assumed and treated with methylprednisolone. Three days later, serum creatinine remained unchanged but magnetic resonance angiography confirmed the absence of any perfusion. However, as a surprising additional finding, both native kidneys showed contrast agent elimination (Figure 4). Graft nephrectomy was performed, serum creatinine actually remained stable and proteinuria was unchanged. Histologically, end-stage vascular rejection of the kidney and ureter was seen (Figure 1, Table 1). Over the next 2 years, proteinuria increased and kidney function worsened. Therefore, 13 years after the first biopsy a second biopsy of the native kidneys was performed (serum creatinine 4.7 mg/dl, eGFR by MDRD 9 ml/min/1.73 m^2) [3] and revealed MN very similar to the first biopsy (Figure 5, Table 1). Twelve days later, dialysis had to be started. The patient died unexpectedly 2 months later due to central venous embolism.

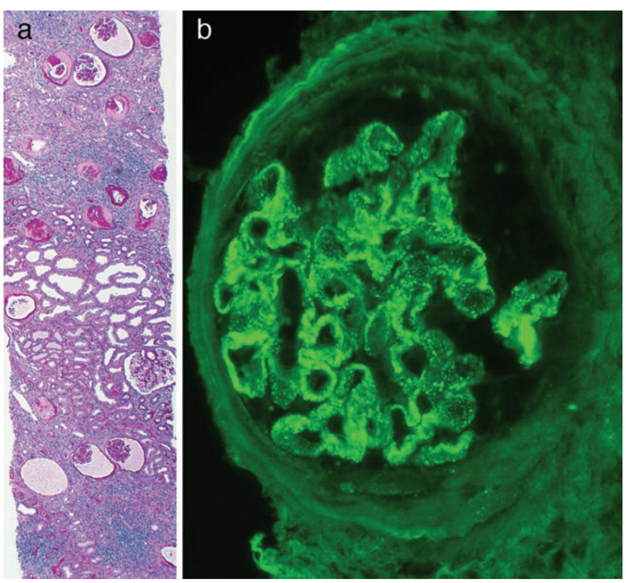

Fig. 3. Third graft biopsy performed 7 years after transplantation: (**A**) overview of the biopsy with severe scarring, glomerular obsolescence and collapse, and one hypertrophic glomerulus surrounded by hypertrophic tubules (PAS, ×40); (**B**) collapsed glomerulus with granular IgG deposits in the loop periphery (immunofluorescence, ×250).

Discussion

To our knowledge, we report on the first case of recovery of native kidney function after kidney transplantation in a patient suffering from ESRD due to MN. The course of MN was uncommon, due to the young age of the patient, the rapid progression of the disease and the presence of crescents in the first biopsy. However, if and to what extent the peculiar characteristics of the native disease contributed to the unusual course remains unclear. Treatment recommendations depend on the risk for progression that depends on renal function and proteinuria. Unfortunately, for high-risk patients there are limited data concerning different therapy modalities as for our patient [5]. Our patient received two courses of cyclophoshamide and steroids, obviously without a benefit.

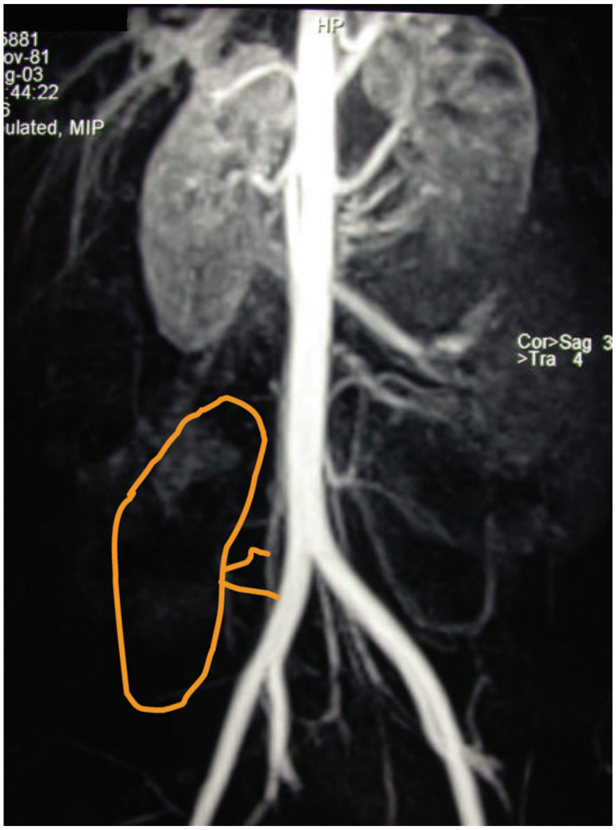

Fig. 4. MR Angiography Abdomen before graft nephrectomy: Kidney graft and vessels in the right fossa iliaca not visible due to the absence of perfusion (cartoon in orange shows place of graft). Contrast elimination of both native kidneys.

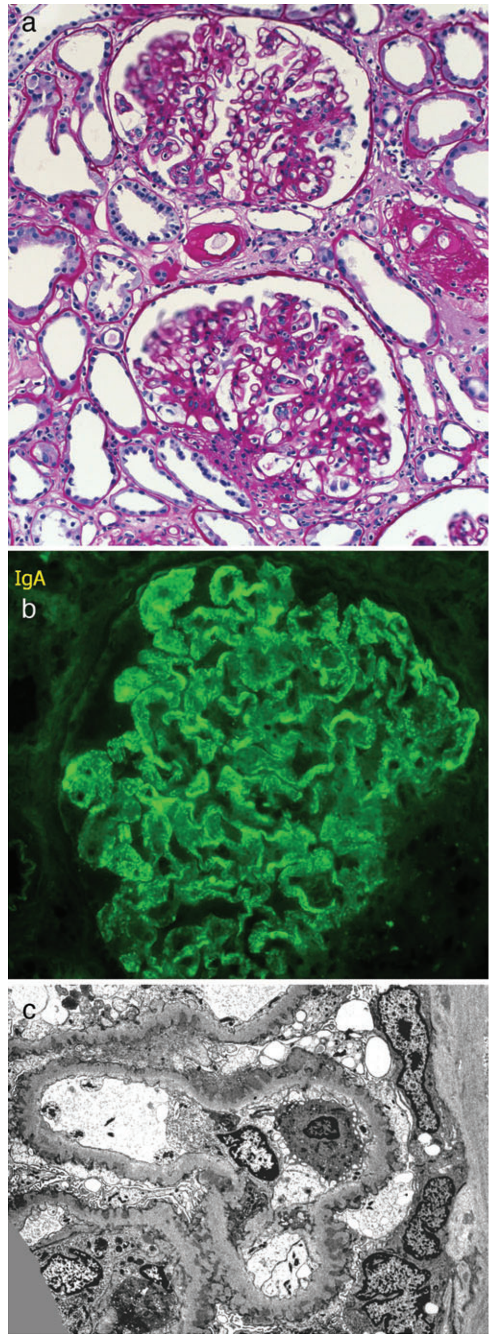

Fig. 5. Second native kidney biopsy performed 2 years after graft nephrectomy: (**A**) two hypertrophic glomeruli with thickened basement membranes and slightly increased mesangial matrix. Note: arteriolopathy of the CNI type (PAS, ×200); (**B**) glomerulus with granular peripheral deposits for IgA. Identical deposits were seen for other antigens and complement factors (immunofluorescence, ×250); (**C**) thickened peripheral glomerular capillary loops with subepithelial deposits separated by spikes (EM, ×2200).

After transplantation, we are not able to assess exactly when and to what extent the native kidneys started to contribute to the 'global' kidney function. Cattran *et al*. showed that cyclosporine may be effective in reducing both the rate of renal deterioration and proteinuria in patients with MN [6]. Praga *et al*. reported on a reduction in the risk for deteriorating renal function and greater decrease in proteinuria in patients with MN treated with tacrolimus [7]. In our patient after stopping tacrolimus, a marked increase of proteinuria was seen indicating that tacrolimus (and previously cyclosporine) could have contributed to the remission of MN in the native kidneys. The assumption that proteinuria originated from the native kidneys is based on similar histologies in graft biopsies and on persisting proteinuria after graft nephrectomy. However, an increase of proteinuria after calcineurin inhibitor (CNI) interruption is relatively common not only in MN but also in other proteinuric nephropathies. The reduction of proteinuria does not invariably mean that therapy is effective in improving the disease and that its interruption is associated with a recurrence of glomerular injury. Changes in urinary protein excretion may simply rely on the vasoconstrictive effect of CNI on renal blood flow. After treatment for posttransplant lymphoproliferative disease (PTLD), CNI was not reintroduced because of the risk of relapse of PTLD. This could explain why the native kidneys failed thereafter.

In contrast to a possible effect of CNIs on MN in the native kidneys, CNIs could not prevent recurrence of MN in our patient's graft. Schwarz *et al*. found, in a retrospective analysis, that the occurrence of *de novo* MN could not be prevented by cyclosporine and was not resolved by further steroid medication [8]. However, it is probably not valid to transfer the situation of *de novo* MN to recurrent MN. Therefore, currently we do not know if CNI-based IS is beneficial in MN after transplantation.

In published studies, rituximab in idiopathic MN has a significant effect on reduction of proteinuria [9,10]. The occurrence of proteinuria during rituximab therapy for PTLD implicates that the B-cell depleting therapy had no positive effect on the further course of our patient's MN.

It remains controversial how and when to restart immunosuppressive therapy after PTLD [11]. Generally, we stop maintenance IS as long as a patient is treated by chemotherapy and restart carefully with low doses of mycophenolate or sirolimus in combination with prednisone. In spite of this approach, our patient lost her graft by vascular rejection. Misled by a nearly stable serum creatinine, the rejection remained unrecognized until the patient had symptoms. A hint could have been hydronephrosis of the graft: stenosis of the ureter was caused by vascular rejection as seen histologically [12].

Certainly, our case of recurrence of native kidney function 8 years after kidney transplantation in a patient suffering from MN is an extreme rarity. The impact of CNIs in this unusual course of MN after transplantation remains unclear. The role of newer therapy regimens, such as anti-CD20 antibodies, on MN has to be further studied.

Conflict of interest statements. None declared.

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