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Post Kidney Transplant Early Recurrence of Membranous Nephropathy with Significant Proteinuria: A Case Report

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Abstract:
Following kidney transplantation, membranous nephropathy recurs in a significant number of patients. It can recur either early or late post kidney transplantation. Early recurrence is less commonly reported as patients remain clinically asymptomatic and it is diagnosed only on protocol biopsies. Majority of post-transplant recurrence occurs late, when patients develop clinical features. In the current report, we describe a patient who developed recurrent membranous nephropathy within 3 months of transplantation with full-blown clinical picture, which is uncommon.

Key words: Membranous Nephropathy, kidney Transplant, recurrence, Anti-PLA2R, kidney biopsy.

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Introduction
Membranous Nephropathy (MN) is an immune-complex mediated glomerular disease that remains the leading cause of nephrotic syndrome (NS) in non-diabetic adults. It has traditionally been classified into two forms, i.e., primary and secondary. In the native kidney, primary MN (PMN) accounts for about 80% of cases and is mediated by circulating autoantibodies to phospholipase A2 receptors (anti-PLA2R) [1] and anti-thrombospondin type 1 domain-containing 7A (THSD7A). Secondary MN, on the other hand, accounts for 20% of cases and occurs secondary to systemic conditions like malignancy, infections, autoimmune disorders or medications. In either case, MN is characterized histologically by thickening of glomerular basement membranes (GBMs) on light microscopy (LM) with sub-epithelial deposits of IgG and C3 on electron microscopy (EM).

After transplantation, MN occurs in approximately 42% of patients and is associated with graft dysfunction leading to graft failure in 10% of patients. It can occur either *de novo* or as a result of disease recurrence. It can recur either early or late post kidney transplantation. Early recurrence is less commonly reported as patients remain clinically asymptomatic and it is diagnosed only on protocol biopsies. Majority of post-transplant recurrence occurs late, when patients develop clinical features. In either case, treatment involves the use of ACE inhibitors/ ARBs, calcineurin inhibitors, anti-proliferative agents and anti-CD20 monoclonal antibodies (rituximab). According to recent studies, rituximab [2] has been recommended as a first line therapy for post-transplant MN. For patients who do not respond to rituximab, cytotoxic agents like cyclophosphamide may be considered, provided anti-metabolic drugs like mycophenolate mofetil or azathioprine have been discontinued.
Herein, we describe a patient who developed recurrent MN within 3 months of transplantation with full-blown clinical picture, which is uncommon.

Case report:
A 52-year-old male diabetic and hypertensive for 15 years, received live-related kidney transplantation (LRRT) from brother in October, 2020. Patient' s primary disease was MN, diagnosed in 2013 following a kidney biopsy. His Serum Creatinine was 2.4 on presentation with proteinuria of 6 g/day and anti-PLA2R level of 30 RU/ml (Negative <14 U/ml). He was started on prednisolone, Tacrolimus and ACE inhibitors. Despite optimization of his

immunosuppressants, his disease progressed and he became dialysis dependent in four years. He remained on hemodialysis dependent for three years after which he underwent kidney transplantation. Following transplantation, his kidney functions returned to normal on 3rd postoperative day. His immunosuppressive medications included tacrolimus, 0.5 mg BD, mycophenolate mofetil, 500 mg BD and prednisolone 10 mg once a day. Patient remained compliant to medications. On follow-up visits, kidney functions and urine complete examination remained unremarkable with tacrolimus levels within therapeutic limits. After 3 months, in January 2021, the patient complained of frothy urine. Investigations showed 2+ proteinuria on urine complete examination with a spot urinary protein to creatinine ratio (uPCR) of 1.90. His viral serology was negative. Biopsy of transplanted kidney was taken and features were consistent with MN. The serum anti-PLA2R was positive. LM and immunofluorescence of transplanted kidney biopsy are shown in figure 1 and figure 2.

His immunosuppressive medications were continued and ACE inhibitor was added. Later on, due to poor response, 2 doses of 1g rituximab were given after 6 months of kidney transplantation that led to reduction of uPCR to 0.3 in next 3 months . Since then, the patient is asymptomatic and being followed up closely after every 4 weeks. His latest Serum Creatinine is 1.1mg/dl and uPCR is 0.42.

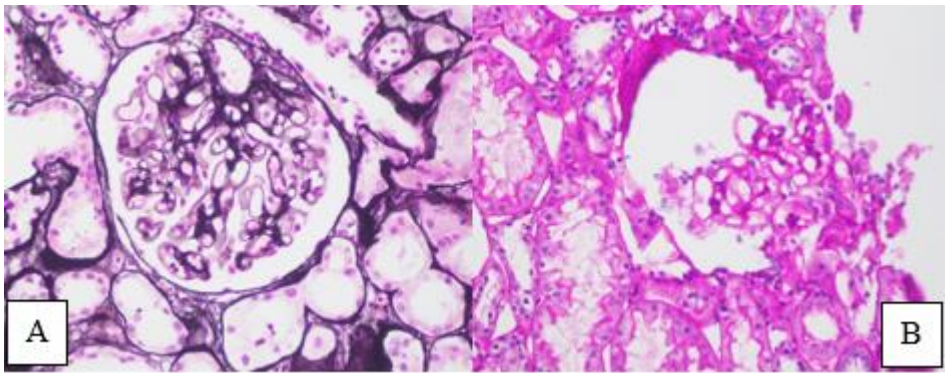

Figure 1: Light microscopy (A) JMS (B) PAS Stain .
Thickening of glomerular basement membranes (GBM) along with spikes on silver stain are visible in this post transplant patient.

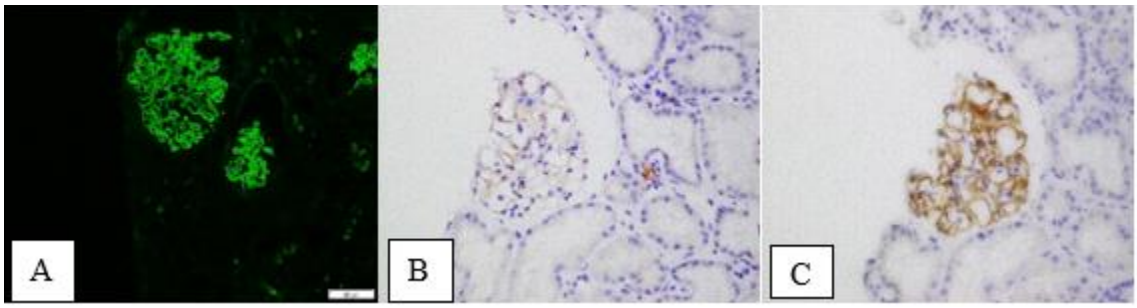

Figure 2: Immunofluorescence of the patient transplanted kidney biopsy with membranous nephropathy.(A)Positive IgG along with GBM (B) Positive IgG4 along the GBM and
(C) Positive anti-PLA2R antibodies.

Discussion:

Recurrence of MN can occur either early after transplantation, i.e., within first 6 to 12 months post- transplantation, or late, i.e., around 5 years of transplan.[3] Early recurrence is typically diagnosed on protocol biopsy, as these patients do not manifest any clinical features. LM and immunofluorescence can be normal with diagnosis made entirely on EM, that shows fusion of foot processes of podocytes and sub-epithelial electron dense deposits. Pathogenesis for early recurrence involves deposition of circulating anti-PLA2R antibodies that were present at the time of transplantation. Late-onset recurrence, on the other hand, is diagnosed in patients who are symptomatic with progressive proteinuria. Histological features resemble those of MN in native kidney and pathogenesis involves post-transplant production of new anti-PLA2R antibodies. There is sufficient evidence from previous reports that recurrence is more commonly seen with live donors than deceased ones because of genetic predisposition and presence of circulating factors like anti- PLA2R.[4] While at the same time, few other studies suggested that it is more

common in cadaveric transplantation. There is a strong correlation between anti-PLA2R titers and risk of PMN recurrence. Patients showing persistence or recurrence of ant-PLA2R, have a more aggressive disease that will have a poor response to immunosuppressants and takes longer time to achieve remission.

In this case, although patient developed early recurrent MN but surprisingly showed typical clinical features and significant proteinuria of 1.90 g which is a feature of late recurrence. Live donation and possibility of positive anti-PLA2R at the time of transplantation seem to be the contributing factors in this aggressive form of early recurrence. Apart from steroids, calcineurin inhibitors and anti-proliferative agents, that are often used as immunosuppressive therapy after transplantation, rituximab has also shown promising results in patients with PMN. This was also evident in our case where patient responded to two doses of rituximab.

Conclusion

Although there is a high risk of recurrence of MN after kidney transplantation, especially in case of live donation, but this does not preclude live donor kidney transplantation. Recurrent MN shows good response to rituximab along with ACE inhibitors and conventional post-transplant immunosuppressants.

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