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TRANSPLANT QUIZ

Recurrent proteinuria with graft dysfunction: a diagnostic and clinical conundrum

Abhilash Chandra[1], Kiran Preet Malhotra[2], Namrata S. Rao[1] & Amit Kumar Singh[1]

1 Department of Nephrology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India
2 Department of Pathology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India

Correspondence
Namrata S. Rao, Department of Nephrology, 4th floor, OPD building, Dr. Ram Manohar Lohia Institute of Medical Sciences, Vibhuti Khand, Gomti Nagar, Lucknow 226010, India.
Tel.: 91-9454360872;
fax: 91-522-6692029;
e-mail: snamratarao@yahoo.co.in

CASE REPORT

The index case is a 45-year old male with unknown cause for native kidney disease, who received a kidney from his wife. Antithymocyte globulin (ATG) was used for induction, and tacrolimus, mycophenolate mofetil and prednisolone were prescribed for maintenance. His baseline serum creatinine was 0.9 mg/dl. Two years after the transplant, the patient developed 3+ proteinuria on routine urinalysis with stable graft function. His 24-hour urinary protein was 2.3 grams, serum albumin was 3.0 g/dl, and the total cholesterol was 251 mg/dl. The tacrolimus C0 levels were maintained between 6 and 8 ng/ml range. Allograft biopsy revealed diffuse thickening of glomerular basement membranes, with the immunofluorescence showing 2+ granular positivity along the loops for IgG and C3. Further, tissue staining for PLA2R and THD7A were both negative. Also, no donor-specific antibodies (DSA) were detected, and serum PLA2R antibody assay was also negative. The patient was managed conservatively with losartan 50 mg and atorvastatin 20 mg, with subsequent reports of proteinuria of 1.5-2.0 grams/day. After 52 months of renal transplant, the patient presented with a serum creatinine of 2.06 mg/dl and proteinuria of 6.8 grams/day. A repeat allograft biopsy revealed thickened glomerular basement membranes with spikes on silver staining. (Figure 1a) Further, immunofluorescence studies showed 2+-3+ granular positivity for IgG, C3, with the added findings of C4d positivity on the peritubular capillaries and tissue PLA2R positivity on the basement membranes by immunohistochemistry. (Figures 1b-d) The biopsy also revealed peritubular capillaritis and acute tubular injury. Antibodies to donor Class II (HLA DR) were positive with a mean fluorescence intensity (MFI) of 6885, but serum PLA2R antibodies remained negative. Based on these findings, the patient was treated with pulse methylprednisolone, 5 sessions of plasma exchange at 40 ml/kg with 5% human albumin and fresh frozen plasma replacement, intravenous immunoglobulin (at 100 mg/kg × 5) and rituximab (two doses of 1 g 2 weeks apart). Subsequently, the serum creatinine settled to 1.6 mg/dl, and DSA reduced to < 500 MFI. Three months after discharge, the serum creatinine is 1.5 mg/dl, 24-hour urine protein is 982 mg/day and follow-up DSA remains negative.

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de novo MN, PLA2R staining, proteinuria

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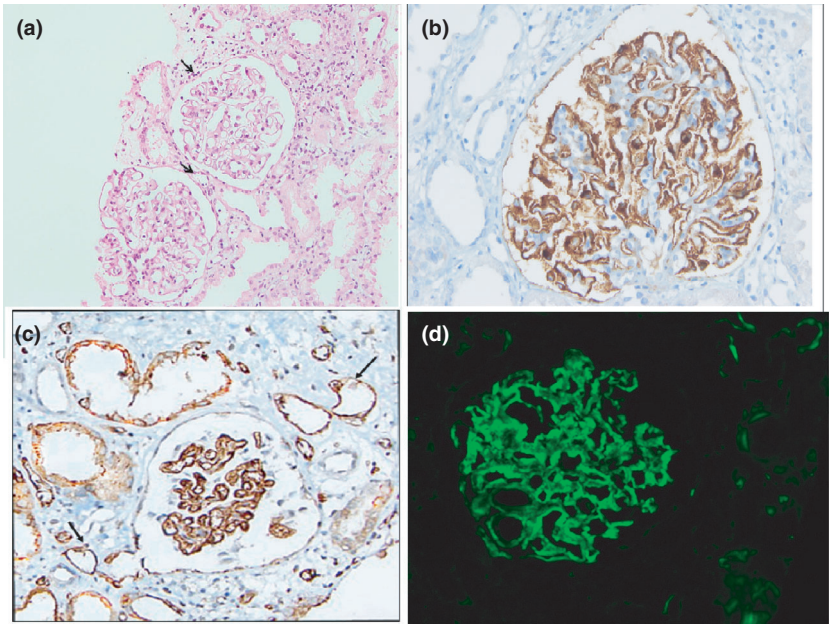

Figure 1 (a) Section shows two glomeruli with diffuse thickening of basement membranes. The peritubular capillaries show presence of lymphocytes (arrows). Haematoxylin and eosin, x200. (b) PLA2R granular positivity along glomerular basement membranes. (c) Linear C4d positivity in peritubular capillaries. (d) Immunofluorescence for IgG.

Quiz

1. All of the following are true regarding PLA2R staining in MN except:

A. 70-80% of primary MN is mediated by circulating anti-PLA2R antibodies
B. Positive anti-PLA2R MN have been reported with sarcoidosis and liver autoimmune disease
C. Clearance of anti-PLA2R antibodies is a pre-requisite to transplantation in primary MN
D. Presence of PLA2R staining supports a diagnosis of de novo MN as opposed to recurrent MN
E. Tissue PLA2R staining carries a higher sensitivity

Explanation: Membranous nephropathy (MN) in the renal allograft can be either de novo or recurrence of primary disease. Tissue staining for phospholipase A2 receptor (PLA2R) helps in this differentiation, due to its high sensitivity and specificity for primary and recurrent MN. [1,2] In the last few years, de novo MN has been described in association with and after episodes of antibody-mediated rejection (ABMR). [3,4] The detection of positive PLA2R staining in cases of ABMR-associated MN is extremely rare. Previous reports on PLA2R positive de novo MN with concomitant ABMR are scant. [1,5] Larsen *et al* described one patient of de novo MN with positive tissue PLA2R staining. [1] This patient had concomitant BK nephritis, with C4d positivity, though other features of ABMR were not documented. Another report by Manolopoulou *et al* described a young male recipient of a deceased donor kidney, who developed an episode of ABMR with associated PLA2R positive MN, responding to antirejection therapies. [5] We hypothesize that in our case, the patient was likely to be a case of de novo MN, possibly with immune reactivity against unknown donor antigens, and the development of subsequent ABMR represents a continuum in the pathogenesis of de novo MN, as the proteinuria and graft dysfunction settled simultaneously upon management of humoral rejection. Subsequent PLA2R positivity might also reflect secondary exposure of hidden antigens.

2. One of the following is not considered a risk factor for de novo MN?

A. Post-transplant malignancy
B. Hepatitis B and C infections
C. Circulating class 2 donor-specific antibodies
D. High titres of anti-PLA2R antibodies prior to renal transplant

Explanation: Several risk factors have been associated with de novo MN including hepatitis B, C, post-transplant malignancies, ureteral obstruction, drugs and recurrent IgA nephropathy. High titres of anti-PLA2R antibodies prior to transplant are associated with recurrent MN, in the early post-transplant period. [1,2] Presence of PLA2R staining and antibodies suggests primary and recurrent MN, as opposed to de novo MN. However, certain secondary causes of MN, such as sarcoidosis, hepatitis B and C and liver autoimmune diseases, are associated with PLA2R

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staining. It is very rare to find PLA2R staining to be positive in cases of MN associated with antibody-mediated rejection (supposedly, de novo MN). Only three cases of PLA2R positive MN associated with antibody-mediated rejection have been described till date. [1,5, present case].

3. Which statement is not true regarding de novo MN associated with antibody-mediated rejection?

A. Histologic findings of mesangial hypercellularity, peritubular capillaritis, C4d deposits and transplant glomerulopathy are found concomitant to changes of membranous nephropathy in cases of de novo MN
B. The predominant subtype found on immunofluorescence is IgG1
C. The prognosis of de novo MN is generally good and allograft loss is very rare
D. Presence of de novo MN is a contraindication to retransplantation.

Explanation: Light microscopic changes of de novo MN can include some mesangial proliferation and signs of antibody-mediated rejection. IgG1 subtype predominates in de novo MN associated with antibody-mediated rejection. The prognosis of de novo MN often depends on its underlying aetiology. De novo MN seen in association with ABMR, especially chronic forms, is associated with unfavourable renal outcomes. There is no strong evidence for the use of enhanced immunosuppression, including rituximab. [2,3] The favourable outcome in the short term, as seen in the present case, is probably related to the lack of chronic changes. The presence of de novo MN per se does not preclude retransplantation.

4. Immunofluorescent staining for IgG4 subtype in a case of membranous nephropathy supports a diagnosis of which categories of MN?

A. Primary MN and IgG4 related disease
B. Primary and recurrent MN
C. Secondary and de novo MN
D. Antibody-mediated rejection associated MN

Explanation: Data from previous studies suggest that IgG subtyping can help in distinguishing recurrent from de novo MN, especially in situations where native kidney biopsy was never performed. Primary and recurrent MN show predominantly IgG4 subtype while cases of secondary and de novo MN, including MN associated with antibody-mediated rejection, show predominance of IgG1 and IgG2 subtypes [1,2].

Authorship

A.C: managed the patient and revised the manuscript. K.P.M: analysed the kidney biopsy specimen and revised the manuscript. N.R: managed the patient and wrote the manuscript. A.K.S: collected data and involved in case management.

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Conflicts of interest

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