Transplant International

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.

Transplant International 2021; 34: 2895–2896

Key words
de novo MN, PLA2R staining, proteinuria

Received: 11 March 2021; Revision requested: 17 May 2021

doi:10.1111/tri.14164

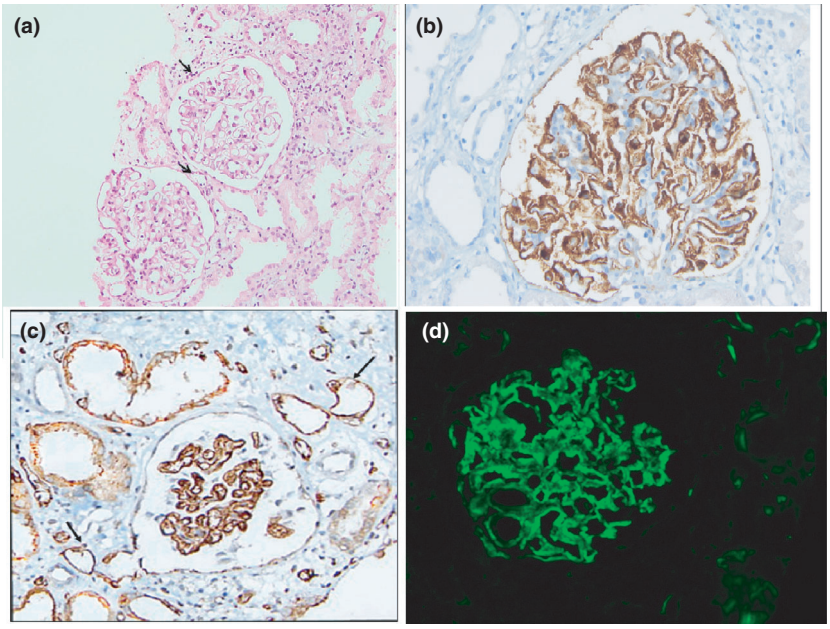

Figure 1 (a) Section shows two glomeruli with diffuse thickening of basement membranes. The peritubular capillaries show presence of lymphocytes (arrows). Haematoxylin and eosin, x200. (b) PLA2R granular positivity along glomerular basement membranes. (c) Linear C4d positivity in peritubular capillaries.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

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

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.

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

To see the answers, go to page 2910–2912

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