

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

PLA2R Related Primary Membranous Nephropathy In A Hepatitis C Positive Patient

Authors: Raja Ramachandran*¹, Ashok Kumar Yadav*¹, Vinod Kumar*¹, Ashwani Varma*², Sunil Taneja³, Ritambhra Nada², Krishan Lal Gupta¹, Vivekanand Jha^{4,5}

¹Department of Nephrology, Postgraduate Institute of Medical Education and Research, Chandigarh, India
²Department of Histopathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India
³Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India
⁴Department of Nephrology, Oxford University, Oxford, UK; ⁵Executive Director, The George Institute for Global Health, New Delhi, India
*Equal contribution as 1st author.

Communicating Author

Prof Vivekanand Jha,
Department of Nephrology,
Oxford University, Oxford, UK;
Executive Director, The George Institute for Global Health, New Delhi, India.
Email: vjha60@gmail.com

Sir,

A 58-year old non-diabetic female with history of hypertension presented with swelling of both lower limbs and facial puffiness of 5-month duration. Evaluation revealed nephrotic syndrome (proteinuria 2.8 g/day, bland urinary sediment, serum albumin 1.6 g/dL) and normal kidney function (serum creatinine 0.63 mg/dl). The kidney biopsy was suggestive of membranous nephropathy with enhanced staining for M-type phospholipase A2 receptor (PLA₂R). Anti-hepatitis C virus (HCV) antibody was positive, with 38,90,243 IU/ml of HCV RNA (genotype 3). The serum antibody to PLA₂R (aPLA₂R) was 236 RU/mL. The patient was started on telmisartan, atorvastatin, diuretics, warfarin, sofosbuvir and ribavirin. The HCV RNA became undetectable (< 50 IU/ml) at 2 months. The aPLA₂R after 2 months of antiviral therapy came down to 4.67 RU/mL. However, the nephrotic syndrome persisted. A repeat aPLA₂R done 9 months after initial presentation showed a rise (117.62 RU/mL). At this time, a diagnosis of aPLA₂R related MN was made, cyclical cyclophosphamide and steroids¹ was started and patient achieved complete clinical remission. The proteinuria became undetectable; serum albumin was 3.69 g/dl and repeat aPLA₂R 0.0019 RU/ml 8 months after starting the therapy. The patient remains in remission after 5 months of stopping immunosuppressive therapy, and the HCV viral load remains undetectable (13 months after stopping antivirals).

The present case highlights the fact that not all MN in hepatitis C positive patients are virus related. *Larsen et al.* reported enhanced staining for PLA₂R in 64% of HCV associated MN.² The studies describing PLA₂R in MN with hepatitis B and/or C infection are limited by lack of sequential antibody monitoring after treating infection.^{2,3,4} In the index case, the NS failed to abate despite successful treatment of hepatitis C infection. Interestingly, the aPLA₂R came down during the anti-viral treatment but reappeared, perhaps due to the serum-glomerular dynamics,^{5,6} well described in the past. The clinical and serological remission with immunosuppressive treatment clearly demonstrates the primary nature of the disease. Alternatively, the virus could be acting as a trigger for producing antibodies.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Reference:

1. Ramachandran R, HN H, Kumar V, Nada R, Yadav AK, Goyal A, et al. Tacrolimus combined with corticosteroids versus Modified Ponticelli regimen in treatment of Idiopathic Membranous Nephropathy: Randomized control trial. *Nephrology (Carlton)*. 2016;21(2):139-46.
2. Larsen CP, Messias NC, Silva FG, Messias E, Walker PD. Determination of primary versus secondary membranous glomerulopathy utilizing phospholipase A2 receptor staining in renal biopsies. *Mod Pathol*. 2013; 26(5): 709-15.
3. Xie Q, Li Y, Xue J, Xiong Z, Wang L, Sun Z, Ren Y, Zhu X, Hao CM. Renal phospholipase A2 receptor in hepatitis B virus-associated membranous nephropathy. *Am J Nephrol*. 2015;41(4-5):345-53.
4. Qin W, Beck LH, Zeng C, et al. Anti-Phospholipase A2 Receptor Antibody in Membranous Nephropathy. *Journal of the American Society of Nephrology*. 2011;22(6):1137-1143.
5. Ramachandran R, Kumar V, Nada R, Jha V. Serial monitoring of anti-PLA2R in initial PLA2R-negative patients with primary membranous nephropathy. *Kidney Int*. 2015;88(5):1198-9.
6. van de Logt AE, Hofstra JM, Wetzels JF. Serum anti-PLA2R antibodies can be initially absent in idiopathic membranous nephropathy: seroconversion after prolonged follow-up. *Kidney Int* 2015; 87: 1263–1264.