Journal of Nephrology (2022) 35:351–355
https://doi.org/10.1007/s40620-021-01165-0

LESSONS FOR THE CLINICAL NEPHROLOGIST

Membranous nephropathy in a patient with COVID-19 infection

Weiwen Guo[1] · **Puay Hoon Tan**[2] · **Shashidhar Baikunje**[1]

Received: 5 July 2021 / Accepted: 17 September 2021 / Published online: 7 October 2021

Keywords Case report · COVID-19 · Membranous nephropathy · PLA2R

Case description

A 29-year-old South Asian male presented with fever, myalgia and lower limb swelling of 3 days duration. Four weeks prior to presentation, he had been diagnosed with COVID-19 infection and was treated symptomatically in the community isolation facility.

He was diagnosed to have nephrotic syndrome with proteinuria of 8.71 g/24 h and serum albumin of 22 g/L. He also had acute kidney injury with peak serum creatinine of 145 µmol/L, estimated glomerular filtration rate (eGFR) of 65 mL/min per 1.73 m^2. Urinalysis revealed few dysmorphic red blood cells and presence of white blood cells. Antinuclear antibody, anti-double stranded DNA, antineutrophil cytoplasmic antibodies were negative. Hepatitis B, Hepatitis C and HIV screens were negative and ultrasound imaging showed normal kidneys.

Kidney biopsy showed 28 glomeruli with diffusely thickened capillary walls. Some glomeruli displayed segmental increases in mesangial cells amid expanded mesangial matrix. Masson-silver stains showed tiny fuchsinophilic subepithelial deposits and fine vacuolization of tangentially sectioned portions of the glomerular basement membranes (Fig. 1). Immunofluorescence showed 3 + finely granular staining for IgG along glomerular capillary walls, with focal weak segmental staining for anti-phospholipase A2 receptor (PLA2R) regarded as of uncertain significance (Fig. 2).

Electron microscopy revealed thickened glomerular basement membranes and subepithelial electron dense deposits. There was severe effacement of podocyte foot processes. Tubular epithelial cells displayed organelles of varying sizes, as well as few electron-dense particles measuring between 90 and 100 nm, which were considered suspicious, but did not display spikes and were hence not diagnostic of virions.

Subsequently, serum PLA2R antibody returned positive at a titer of 139.51 RU/mL. Workup for other causes of secondary membranous nephropathy was unrevealing.

Due to increasing COVID-19 infections at that time, immunosuppressive treatment was delayed. He was started on an angiotensin-converting-enzyme inhibitor which was titrated to the highest tolerated dose. The serum PLA2R antibody titer decreased to 106.32 RU/mL after 3 months. The patient declined further trending of PLA2R antibody titer.

After 8 months, the patient remained nephrotic with urine protein/creatinine ratio of 8.9 g/g, serum albumin of 23 g/L and serum creatinine of 129 µmol/L, eGFR 65 mL/min per 1.73 m^2. Clinical progress and laboratory results are shown in Table 1. Treatment options were rediscussed and immunosuppressive therapy was commenced with oral Cyclophosphamide at a dose of 2 mg/kg, together with Prednisolone 0.5 mg/kg. The patient declined checking of PLA2R antibody titer at the time of initiating immunosuppressive therapy.

Two months after starting immunosuppressive treatment, the patient showed partial clinical response. He was asymptomatic and serum creatinine improved to 100 µmol/L with eGFR 88 mL/min per 1.73 m^2. Serum albumin increased to 29 g/L and urine protein/creatinine ratio improved to 4.9 g/g. He subsequently returned to his home country for further follow-up.

✉ Weiwen Guo
guo.weiwen@singhealth.com.sg

[1] Department of Renal Medicine, Sengkang General Hospital, Medical Centre Level 9, 110 Sengkang E Way, Singapore 544886, Singapore

[2] Division of Pathology, Singapore General Hospital, Singapore, Singapore

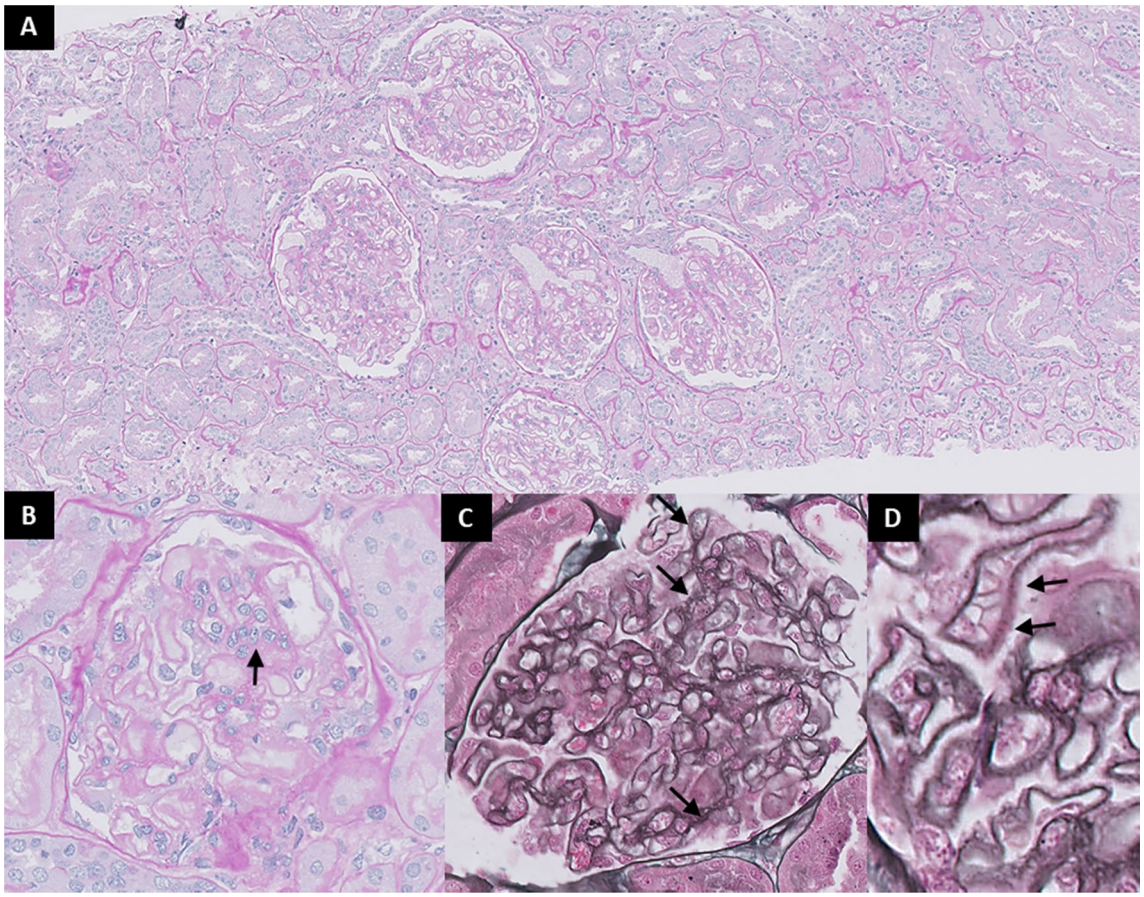

Fig. 1 **A** Several glomeruli with glomerular capillary wall thickening are seen (PAS × 100). **B** High magnification of a glomerulus with thickened glomerular capillary walls and a segmental increase in mesangial cells (6 cells, arrow), PAS × 400. **C** Masson-Trichrome silver stain shows vacuolization of tangentially sectioned glomerular capillary walls (arrows), PGMTx400. **D** Subepithelial fuchsinophilic deposits are present (arrows), PGMT × 600

Lessons for the clinical nephrologist

Kidney dysfunction in COVID-19 infection is commonly associated with acute tubular injury and collapsing glomerulopathy [1]. A recent case series [2] reported a wide spectrum of glomerular and tubular diseases, including two cases of membranous nephropathy, one of which was PLA2R positive. Two other cases of PLA2R positive membranous nephropathy after COVID-19 infection were mentioned in a case report [3]. However, most cases of membranous nephropathy associated with COVID-19 infection that have been reported were PLA2R negative [1, 2].

We report a case of PLA2R seropositive but biopsy-indeterminate membranous nephropathy with COVID-19 infection. PLA2R immunofluorescence staining in glomeruli was focal, segmental and weak, which could not be interpreted as definitively positive, and needed to be correlated with serological levels.

In one report of membranous nephropathy and acute kidney injury in COVID-19 infection, the author hypothesized that the development of immune deposits in membranous nephropathy could occur after a viral infection [4]. The target antigen in membranous glomerulopathy, PLA2R, is also expressed in the respiratory tract [5], potentially triggering anti-PLA2R immune response. Relapse in primary membranous nephropathy associated with inactivated vaccine against COVID-19 has also been reported [3].

Electron microscopy in our case revealed organelles of varying sizes in the tubular epithelial cells. They were considered suspicious, but did not display spikes and were hence not diagnostic of virions. Ultrastructural confirmation of coronavirus particles requires their localization within

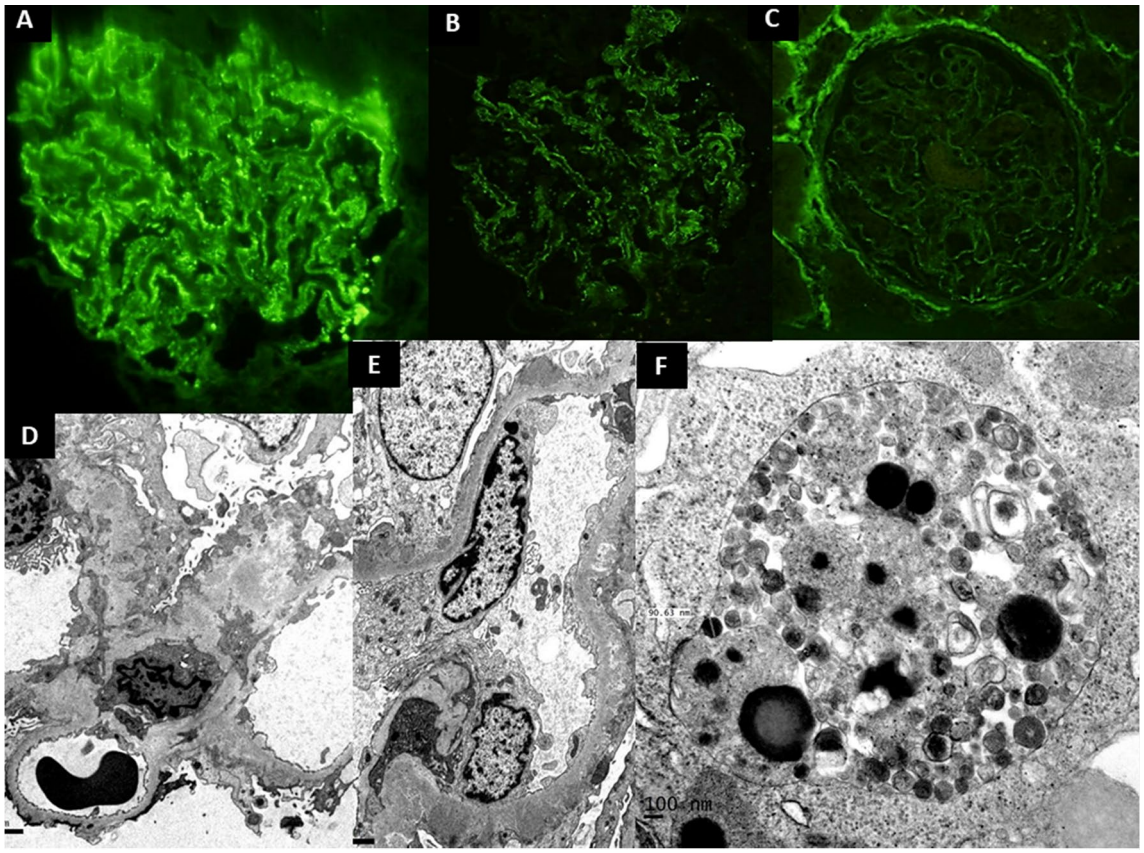

Fig. 2 Immunofluorescence for IgG **A** shows finely granular staining along glomerular capillary walls, while C1q **B** shows weaker reactivity. PLA2R shows weak segmental staining which was regarded of uncertain significance (**C**). Electron microscopy reveals extensive podocyte foot process effacement and intramembranous, mesangial (**D**) and subepithelial (**E**) electron dense deposits. Tubular epithelial cells disclosed electron dense structures, some measuring 90 nm, albeit without spikes and are not confirmatory for viral particles (**F**)

vacuoles rather than being in contact with cytosol, presence of spikes, outer membrane covering and internal dots indicating the nucleocapsid [6], which were not convincingly identified in our case. The finding was consistent with reported series [2], where no definitive SARS-CoV-2 virions were seen in glomerular or tubular cells, arguing against a direct viral infection of the kidneys.

Biopsy and serum PLA2R positivity has been associated with viral infections such as Hepatitis B [7] and Hepatitis C [8]. In our patient, it is likely that COVID-19 infection triggered the PLA2R antibody and membranous nephropathy.

Our case illustrates the challenges in the management of membranous nephropathy in the era of widespread COVID-19 infection. There is a paucity of data regarding the clinical course and outcomes of membranous nephropathy cases following COVID-19 infection. In view of increasing infection rates in the community, we decided on non-immunosuppressive treatment with close monitoring as our initial approach.

Experts have recommended delaying immunosuppression for membranous nephropathy patients with nephrotic syndrome and/or rising anti-PLA2R antibody titer, but without complications and with preserved glomerular filtration rate [9]. Our patient had decreasing serum PLA2R antibody titer at the third month and subsequently declined further trending of PLA2R antibody titer. He remained nephrotic after 8 months of non-immunosuppressive treatment, and was eventually started on immunosuppression based on clinical indications.

Our patient had partial clinical response after 2 months of immunosuppressive treatment. The lack of PLA2R antibody titer trend posed a limitation to our management of the patient. Without the evaluation of PLA2R antibody titer at the start of immunosuppression, we cannot conclude

Table 1 Laboratory Data

Laboratory test	Admission	3 months	6 months	8 months	10 months	Reference
Serum biochemistry						
Sodium, mmol/L	142	142	140	142	140	136–146 mmol/L
Potassium, mmol/L	3.7	4.3	4.0	4.2	4.7	3.5–5.1 mmol/L
Chloride, mmol/L	109	110	109	111	107	98–107 mmol/L
Bicarbonate, mmol/L	26.1	24.2	25.5	27.5	24.7	19–29 mmol/L
Urea, mmol/L	4.1	5.1	4.3	4.8	5.6	2.7–6.9 mmol/L
Creatinine µmol/L	145	121	119	129	100	59–104 µmol/L
eGFR, mL/min/BSA	56	70	71	65	88	> 60
Glucose, mmol/L	6.4	5.4	5.3	5.6	6.4	3.0–11.0
Total protein, g/L	45					68–85 g/L
Albumin, g/L	22	31	29	23	29	40–51 g/L
Urine protein/Cr ratio g/g	7.5	11.9	7.7	9.2	4.9	< 0.2
Urine protein 24-h g/day	8.71					< 0.13 g/day
Lipid						
Total cholesterol, mmol/L	7.66					< 5.2 mmol/L
HDL, mmol/L	0.92					> 1.6 mmol/L
LDL, mmol/L	5.25					< 2.6 mmol/L
Triglycerides, mmol/L	3.28					< 1.7 mmol/L
Serology						
HBs antigen	Negative					
HCV Antibody screen	Negative					
HIV Antigen	Negative					
Complement C3, G/L	1.59					0.9–1.8 G/L
Complement C4, G/L	0.51					0.1–0.4 G/L
Antinuclear antibody	Negative					
Anti dsDNA IU	0.83					< 25 IU
Anti MPO RU/mL	< 2.0					< 20 RU/mL
Anti PR3 RU/mL	< 2.0					< 20 RU/mL
Anti-phospholipase A2 receptor (ELISA), RU/mL	139.51	106.32				< 14 RU/mL
Monoclonal gammopathy screen	Negative					

whether the improvement was due to treatment or immunological remission.

The clinical course of the patient and trend of PLA2R antibody titer remain useful guides for considering initiation of immunosuppressive treatment for cases of membranous nephropathy after COVID-19 infection.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40620-021-01165-0.

Acknowledgements We acknowledge support by Sengkang General Hospital Renal Department and Singapore General Hospital Pathology Division.

Funding There were no specific funding sources relevant to this manuscript.

Declarations

Conflict of interest The authors have no conflict of interest to declare.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Written consent was obtained from the patient for publication of this case report and accompanying images.

Data availability All data are incorporated into the article and its online supplementary material.

References

1. Nasr SH et al (2021) Kidney biopsy findings in patients with COVID-19, kidney injury, and proteinuria. Am J Kidney Dis 77(3):465–468. https://doi.org/10.1053/j.ajkd.2020.11.002
2. Kudose S et al (2020) Kidney biopsy findings in patients with COVID-19. J Am Soc Nephrol 31(9):1959–1968. https://doi.org/10.1681/ASN.2020060802
3. Aydin MF et al (2021) Relapse of primary membranous nephropathy after inactivated SARS-CoV-2 virus vaccination. Kidney Int. https://doi.org/10.1016/j.kint.2021.05.001
4. Miao J, Fidler ME, Nasr SH, Larsen CP, Zoghby ZM (2021) Membranous nephropathy in a patient with coronavirus disease 2019 (COVID-19): a case report. Clin Nephrol Case Stud 9(01):11–18. https://doi.org/10.5414/cncs110379
5. Granata F et al (2010) The role of mast cell-derived secreted phospholipases A2 in respiratory allergy. Biochimie 92(6):588–593. https://doi.org/10.1016/j.biochi.2010.02.030 ((**Elsevier**))
6. Miller SE, Brealey JK (2020) Visualization of putative coronavirus in kidney. Kidney Int 98(1):231–232. https://doi.org/10.1016/j.kint.2020.05.004
7. Xie Q et al (2015) Renal phospholipase A2 receptor in hepatitis B virus-associated membranous nephropathy. Am J Nephrol 41(4–5):345–353. https://doi.org/10.1159/000431331
8. Larsen CP, Messias NC, Silva FG, Messias E, Walker PD (2013) Determination of primary versus secondary membranous glomerulopathy utilizing phospholipase A2 receptor staining in renal biopsies. Mod Pathol 26(5):709–715. https://doi.org/10.1038/modpathol.2012.207
9. Bomback AS, Canetta PA, Ahn W, Ahmad SB, Radhakrishnan J, Appel GB (2020) How COVID-19 has changed the management of glomerular diseases. Clin J Am Soc Nephrol 15(6):876–879. https://doi.org/10.2215/CJN.04530420