

4. Kottek M, Yuen ML. Public health risks from asbestos cement roofing. *Am J Ind Med* 2022;65:157–61.
5. Autoimmunity and Asbestos Exposure - PMC [cited January 17, 2023]. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4022069/>
6. Caza TN, Hassen SI, Dvanajscak Z, Kuperman M, Edmondson R, Herzog C, *et al.* NELL1 is a target antigen in malignancy-associated membranous nephropathy. *Kidney Int* 2021;99:967–76.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, transform, and build upon the work non-commercially, as long as

appropriate credit is given and the new creations are licensed under the identical terms.

How to cite this article: Sundaram B, Pathak N, Ambrose MM, Papou SM. NELL-1 as a Target Antigen in Asbestosis Associated Membranous Nephropathy — A Case Report. *Indian J Nephrol.* 2025;35:103-5. doi: 10.25259/IJN_65_2024

Received: 07-02-2024; **Accepted:** 03-03-2024;
Online First: 04-06-2024; **Published:** 04-01-2025

DOI: 10.25259/IJN_65_2024



Concomitant Histological Features of Membranous Nephropathy and Anti-Neutrophil Cytoplasmic Antibody Associated Vasculitis

Abstract

The simultaneous occurrence of vasculitic glomerulonephritis and membranous nephropathy is unusual. We report two cases that presented to our outpatient department with rapidly progressive renal failure. On evaluation, in one patient, anti-myeloperoxidase (MPO) titers were high, and renal biopsy was suggestive of concurrent necrotizing and diffuse crescentic anti-MPO anti-neutrophil cytoplasmic antigen-associated glomerulonephritis with the circumferential cellular crescent formation and membranous glomerulopathy. He responded to plasmapheresis followed by maintenance immunosuppression with oral cyclophosphamide. Another patient was treated with Methylprednisolone and two doses of rituximab. Both the patients showed marked symptomatic improvement and became dialysis independent with stable creatinine at 3 months.

Keywords: *Anti-neutrophil cytoplasmic antibody associated Vasculitis, Crescentic glomerulonephritis, Membranous nephropathy, Plasmapheresis, Rapidly progressing renal failure*

Introduction

Membranous nephropathy (MN) is histologically characterized by subepithelial immunoglobulin deposits and complement.¹ Vasculitic or crescentic glomerulonephritis is rarely seen in MN except in systemic lupus erythematosus.^{2,3} There are only a few cases with Wegener's granulomatosis that combine MN and crescentic glomerulonephritis.⁴ Our knowledge of the immunopathogenesis, clinical features, treatment and outcomes of this unusual combination of membranous nephropathy and vasculitic or crescentic glomerulonephritis is limited. We report two patients who had concomitant necrotizing crescentic anti-MPO (Myeloperoxidase) associated glomerulonephritis and MN.

Case Reports

Case 1

A 58-year-old man with no known comorbidities presented with nonspecific pain abdomen. On evaluation, he was found to have hypertension, Serum creatinine - 3.4 mg/dl) and hematuria. At 12 days, his serum creatinine worsened to 10 mg/dl, and his anti MPO titres were >200 RIU/ml. Renal biopsy [Figure 1] suggested crescentic glomerulonephritis with IgG deposits. He was treated with a methylprednisolone pulse and four sessions of plasmapheresis. He required three sessions of hemodialysis, and was started on prednisolone and

oral cyclophosphamide. At 3 months, he became dialysis independent.

Case 2

A 51-year-old lady with no known comorbidities presented with acute febrile illness decreased urine output, and generalized swelling of the body. On evaluation, she was found to have hypertension and serum creatinine of 1.4 mg/dl. Over two weeks, she had rapidly worsening creatinine to 10 mg/dl and required hemodialysis. Her anti MPO titre were >200 RIU/ml. Renal biopsy suggested crescentic glomerulonephritis [Figure 2] with IgG deposits. She was given a methylprednisolone pulse and two doses of rituximab. At 3 months, she became dialysis independent. The clinical and renal biopsy findings and treatment details of both patients are mentioned in Table 1.

Discussion

Immunoglobulin deposits are usually absent in the glomeruli of patients with anti neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis. It is proposed that ANCA does not damage the glomerulus directly. Still, neutrophils activated by ANCA integrate into capillary walls and release several protein-degrading enzymes, and, finally, these pathological changes may cause necrosis to glomerular capillary walls.⁵ Membranous glomerulopathy has subepithelial

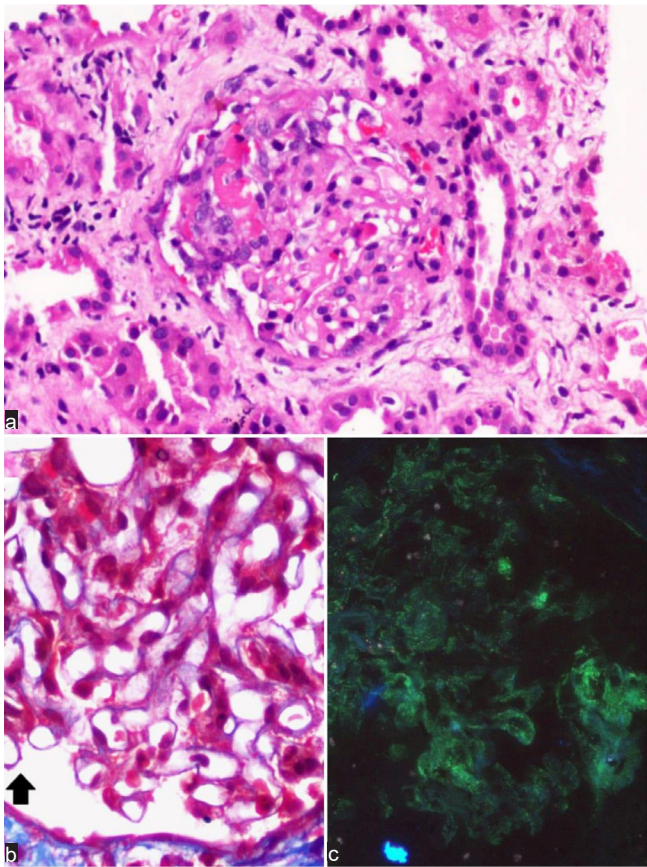


Figure 1: (a and b) Glomerulus showing segmental fibrinoid necrosis and cellular crescent formation (Hematoxylin and Eosin stain) with concomitant segments of capillary wall thickening and subepithelial fuscinophilic deposits (bold black arrow in b), Masson trichrome stain), original magnifications X40. (c) Immunofluorescence microscopy depicting global fine granular (3+ intensity staining for IgG), original magnifications X40.

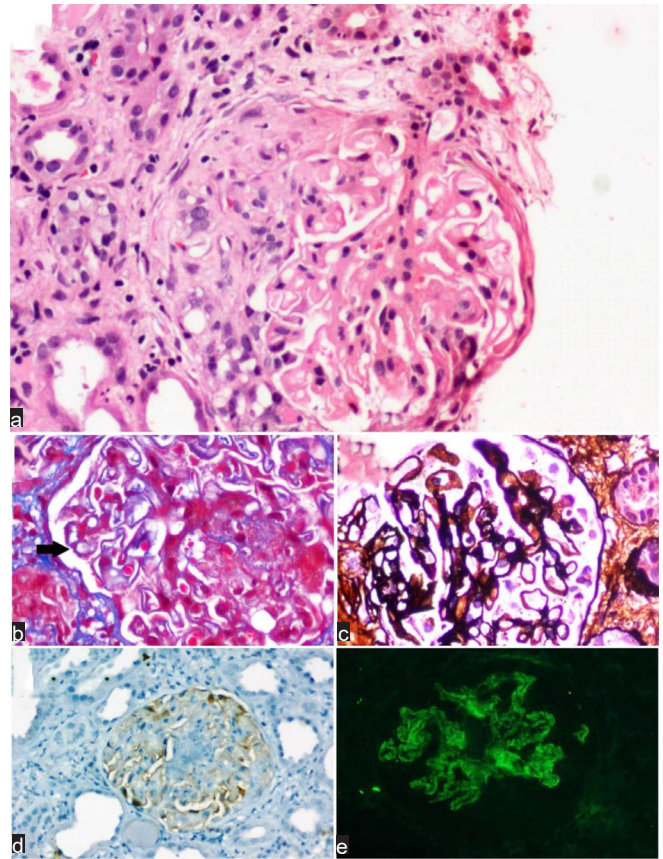


Figure 2: (a) Glomerulus showing circumferential fibro cellular crescent formation, Hematoxylin and Eosin stain, (b) concomitant segments of capillary wall thickening and subepithelial fuscinophilic deposits (bold black arrow) Masson trichrome stain, (c) Segments of structural capillary wall abnormalities with spike formation, Jones methenamine silver stain, (d) PLA2R immunohistochemistry shows faint non diagnostic staining of podocytes(interpreted to be negative), original magnifications X40. (e) Immunofluorescence microscopy depicting global fine granular (3+intensity staining for IgG), original magnifications X40. PLA2R: phospholipase A2 receptor.

Table 1: Clinical features, renal biopsy findings, Treatment details and outcomes

	Case 1	Case 2
Age/Gender	58/M	51/F
Mode of presentation	RPRF	RPRF
BP at presentation (mm Hg)	160/100	150/100
Index serum creatinine (mg/dl)	3.5	1.5
Serum creatinine (mg/dl) at the time of biopsy at 10 days	10.2	9.6
Urine routine	RBC-8, Protein-2+	RBC-10, Protein-3+
24 hour urine protein/creatinine ratio	3.9	7.8
Serum albumin (gm/dl)	4.1	2.5
Anti MPO titres RIU/ml	>200	>200
Anti GBM	Not done	Negative
Complements	Normal	Normal
Renal biopsy		
No. of glomeruli	11	10
Globally sclerosed glomeruli	2	2

Contd.

Table 1: Contd.

	Case 1	Case 2
Glomeruli with active vasculitic lesions	8 glomeruli showed circumferential cellular with crescent formation	2 -glomeruli showed circumferential cellular crescents 5-glomeruli showed with fibrous crescent formation 1-glomerulus showed fibro cellular crescent
Tubular changes	Diffuse acute tubular necrosis, many tubules show intraluminal RBC casts	Diffuse acute tubular necrosis
Intersitium	40% fibrosis	50-60% fibrosis
Immunofluorescence	IgG (2+) membranous pattern	IgG (3-4+) membranous pattern
IHC for PLA2R	Not done	Negative
Treatment details		
Induction	MP pulse (Day 1-1 gram, Day 2 – 500 mg and Day 3- 500 mg) Plasmapheresis	MP pulse (Day 1-1 gram, Day 2 – 500 mg and Day 3- 500 mg) Rituximab (1 gram two weeks apart)
Maintenance immunosuppression	Pred/oral cyclophosphamide (1 mg/kg body weight)	Rituximab 1 gram at 4, 8, 12 and 16 months
Hemodialysis requirement	Yes	Yes
Serum creatinine (mg/dl) at 3 months	2	2.5
At 3 months - Off hemodialysis	Yes	Yes
Complications		
Catheter related	Nil	Nil
Plasmapheresis related	Nil	Not applicable
Dialysis related	Nil	Nil
Immunosuppression related	Nil	Nil

ANCA: Anti neutrophil cytoplasmic antibody; GBM: Glomerular basement membrane; MP: Methyl prednisolone; MPO: Myeloperoxidase; Pred: Prednisolone; RPRF: Rapidly progressing renal failure, BP: Blood pressure, IHC: Immunohistochemistry, PLA2R: Phospholipase A2 receptor.

deposits of immunoglobulins and complement, with microscopic changes in the glomerular basement membrane, including spike and bubbling formations. The association of membranous nephropathy and vasculitic/crescentic glomerulonephritis is found in fewer than 5% of cases of membranous nephropathy, usually with anti-PR3 antibodies.⁶ Tse *et al.* reported 10 cases of MN superimposed with vasculitic glomerulonephritis; four were ANCA-positive.⁶ Their kidney function recovered with immunosuppressive therapy and plasma exchange, except for one patient in whom the renal pathological findings were especially severe. Nasr *et al.* reported 14 patients with membranous glomerulonephritis (MGN) and ANCA-associated glomerulonephritis (ANCA-GN) and identified the rate of crescent formation as a risk factor for developing ESRD.⁷ This unusual combination of MN with vasculitic/crescentic glomerulonephritis, although often idiopathic,^{8,9} can occur in association with systemic lupus erythematosus and anti-GBM antibodies,¹⁰ and ANCA-positive or negative systemic vasculitis. MN complicated by vasculitic glomerulonephritis appears to have a more aggressive clinical course than membranous nephropathy alone. Nakada *et al.* reported a case of concurrent MPO-/PR3-Negative ANCA-GN and membranous glomerulopathy.¹¹ At present, any association between MN and ANCA-GN

is unclear. Matsumoto *et al.* postulated a hypothesis that MPO is highly cationic; it can bind to anionic surfaces such as GBM or endothelial cells and possibly behave as a planted antigen. In anti MPO- GN, MPO released from neutrophils could be localized on the glomerular capillary walls, where it could interact with MPO-ANCA. This might explain why membranous glomerular lesions were induced during MPO-ANCA-associated GN.¹² On the other hand, Nasr *et al.*⁷ suggested that the concurrence of MN and ANCA-GN may just be by chance because they occur together too infrequently to be related pathologically.

Our first patient received plasmapheresis followed by maintenance immunosuppression with cyclophosphamide as per methylprednisolone plasma exchange (MPEX),¹³ a randomized controlled trial by Szpirt *et al.*¹⁴ and CYCLOPS trials.^{15,16} The second patient received a methylprednisolone pulse followed by two doses of Rituximab based on induction trials in ANCA vasculitis like rituximab in ANCA associated vasculitis (RAVE) and rituximab versus cyclophosphamide in ANCA associated vasculitis (RITUXIVAS).¹⁷⁻¹⁹ She was planned to continue rituximab for maintenance immunosuppression based on the maintenance of remission using rituximab in ANCA associated vasculitis (MAINRITSAN) trial.²⁰ Currently, both patients are dialysis independent, but they require long-

term follow-up for relapses or worsening renal functions. Lack of serum PLA2R levels in both patients, IgG subclassification, and tissue PLA2R in one patient were limitations of this study.

The association of MN and vasculitic/crescentic glomerulonephritis is rare and appears to have a more aggressive clinical course compared to membranous nephropathy alone. Early detection and treatment will have a good prognosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Conflicts of interest

There are no conflicts of interest.

**Chilaka Rajesh¹, Utkarash Mishra¹ Sanjeet Roy²,
Rizwan Alam¹, Selvin Sundar Raj Mani¹, Jeethu
Joseph Eapen¹, Athul Thomas¹, Suceena Alexander¹,
Santosh Varughese¹, Vinoi George David¹**

Departments of ¹Nephrology, ²Pathology, Christian Medical College,
Vellore, Tamil Nadu, India

Corresponding author:

Vinoi George David, Department of Nephrology, Christian Medical
College, Vellore, Tamil Nadu, India. Email: vinoigd@hotmail.com

References

- Glasscock RJ, Adler SG, Ward HJ, Cohen AH. Primary glomerular disease. In Brenner BM, Rector FC Jr, ed. *The Kidney*, 3rd edn. Saunders, Philadelphia; 1986. p. 929–1013. <http://nek.istanbul.edu.tr:4444/ekos/TEZ/25496.pdf>
- Pasquali S, Banfi G, Zucchelli A, Moroni G, Ponticelli C, Zucchelli P. Lupus membranous nephropathy: Long-term outcome. *Clin Nephrol* 1993;39:175–82.
- Schwarz MM. Membranous glomerulonephritis. In: Heptinstall RH, ed. *Pathology of the Kidney*, 4th edn. Little, Brown, Boston; 1992. p. 559–626. https://link.springer.com/chapter/10.1007/978-0-387-31127-2_2
- Gaber LW, Wall BM, Cooke CR. Coexistence of anti-neutrophil cytoplasmic antibody-associated glomerulonephritis and membranous glomerulopathy. *Am J Clin Pathol* 1993;99:211–5.
- Bosch X, Guilabert A, Font J. Antineutrophil cytoplasmic antibodies. *Lancet* 2006;368:404–18.
- Tse WY, Howie AJ, Adu D, Savage CO, Richards NT, Wheeler DC, et al. Association of vasculitic glomerulonephritis with membranous nephropathy: A report of 10 cases. *Nephrol Dial Transplant* 1997;12:1017–27.
- Nasr SH, Said SM, Valeri AM, Stokes MB, Masani NN, D'Agati VD, et al. Membranous glomerulonephritis with ANCA-associated necrotizing and crescentic glomerulonephritis. *Clin J Am Soc Nephrol* 2009;4:299–308.
- Kwan JT, Moore RH, Dodd SM, Cunningham J. Crescentic transformation in primary membranous glomerulonephritis. *Postgrad Med J* 1991;67:574–6.
- James SH, Lien YH, Ruffenach SJ, Wilcox GE. Acute renal failure in membranous glomerulonephropathy: A result of superimposed crescentic glomerulonephritis. *J Am Soc Nephrol* 1995;6:1541–6.
- Kurki P, Helve T, von Bonsdorff M, Törnroth T, Pettersson E, Riska H et al. Transformation of membranous glomerulonephritis into crescentic glomerulonephritis with glomerular basement membrane antibodies. Serial determinations of anti-GBM before the transformation. *Nephron* 1984;38:134–7.
- Nakada Y, Tsuboi N, Takahashi Y, Yoshida H, Hara Y, Okonogi H, et al. A case of concurrent MPO-/PR3-negative ANCA-associated glomerulonephritis and membranous glomerulopathy. *Case Reports in Nephrology* 2015;2015:316863.
- Matsumoto K, Honda H, Shibata T, Sanada D, Wada Y, Ashikaga E et al. MPO-ANCA crescentic glomerulonephritis complicated by membranous nephropathy: MPO demonstrated in epimembranous deposits. *NDT Plus* 2009;2:461–5.
- de Lind van Wijngaarden RA, Hauer HA, Wolterbeek R, Jayne DR, Gaskin G, Rasmussen N, et al. Clinical and histologic determinants of renal outcome in ANCA-associated vasculitis: A prospective analysis of 100 patients with severe renal involvement. *J Am Soc Nephrol* 2006;17:2264–74.
- Szpirt WM, Heaf JG, Petersen J. Plasma exchange for induction and cyclosporine a for maintenance of remission in Wegener's granulomatosis--a clinical randomized controlled trial. *Nephrol Dial Transplant* 2011;26:206–13.
- de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL et al. EUVAS (European Vasculitis Study Group). Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: A randomized trial. *Ann Intern Med* 2009;150:670–80.
- Jha V, Ganguli A, Saha TK, Kohli HS, Sud K, Gupta KL, et al. A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy. *J Am Soc Nephrol* 2007;18:1899–904.
- Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. European vasculitis study group. rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010;363:211–20.
- Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. RAVE-ITN research group. rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010;363:221–32.
- Jones RB, Furuta S, Tervaert JW, Hauser T, Luqmani R, Morgan MD, et al. European vasculitis society (EUVAS). Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial. *Ann Rheum Dis* 2015;74:1178–82.
- Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al. French Vasculitis Study Group. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med*. 2014 Nov 6;371(19):1771-80. doi: 10.1056/NEJMoa1404231. PMID: 25372085.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, transform, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

How to cite this article: Rajesh C, Mishra U, Roy S, Alam R, Raj Mani SS, Eapen JJ, et al. Concomitant Histological Features of Membranous Nephropathy and Anti-Neutrophil Cytoplasmic Antibody Associated Vasculitis. *Indian J Nephrol*. 2025;35:105-8. doi: 10.25259/IJN_140_2024

Received: 24-03-2024; Accepted: 17-04-2024;
Online First: 15-07-2024; Published: 04-01-2025

DOI: 10.25259/IJN_140_2024

