SAGE Open Medical Case Reports
Volume 6: 1–5

DOI: 10.1177/2050313X18807621
journals.sagepub.com/home/sco
SAGE

Membranous nephropathy followed by anti-glomerular basement disease: A case report and review of clinical presentation and treatment

Claudius Speer[1], Matthias Martin Gaida[2], Rüdiger Waldherr[2], Christian Nusshag[1], Florian Kälble[1] and Martin Zeier[1]

Abstract

Membranous nephropathy is a common cause of nephrotic syndrome in adults and can be primary or secondary through autoimmune disease, medication, infection, or malignancy. Rapidly progressive glomerulonephritis with crescent formation is rare in patients with membranous nephropathy. Thus, in cases with rapid decline in renal function, after excluding complications such as malignant hypertension, acute hypersensitivity interstitial nephritis, and bilateral renal vein thrombosis, the simultaneous occurrence of a superimposed glomerulonephritis should be considered. We report a 55-year-old man suffering from a biopsy-confirmed primary membranous nephropathy, who developed rapidly progressive glomerulonephritis with anti-glomerular basement membrane antibodies after being affected with membranous nephropathy for 8 years. The kidney biopsy revealed a concurrence of membranous nephropathy and anti-glomerular basement membrane disease. Clinical presentation and treatment of membranous nephropathy followed by anti-glomerular basement membrane disease are discussed based on our observation with promising follow-up.

Keywords

Glomerulonephritis, nephrology, rapid progressive glomerulonephritis, membranous nephropathy, pathology

Date received: 30 July 2018; accepted: 25 September 2018

Introduction

Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults and can be of primary origin or secondary in the context of autoimmune disease, medication, infection, or malignancy. Beck et al.[1] found that a majority of patients with idiopathic MN have antibodies against a conformation-dependent epitope in the M-type phospholipase A2 receptor (PLA2R), indicating that PLA2R is a major antigen in primary disease. The pathogenesis of secondary MN is multifactorial and poorly understood. The antigen thrombospondin type-1 domain-containing 7A (THSD7A) has been described to be associated with secondary MN through malignancy.[2] MN is morphologically characterized by diffuse thickening of the glomerular capillary basement membranes due to subepithelial immune complex deposits and complement activation, which leads to damage of the glomerular filter and consecutive proteinuria.

Anti-GBM disease is an autoimmune disorder, commonly associated with rapidly progressive glomerulonephritis (RPGN) and crescent formation in kidney biopsy as well as alveolar hemorrhage in 25%–50% of affected patients. Antibodies primarily targeting the non-collagenous domain 1 of α3 chain of type IV collagen (α3(IV)NC1) and α5(IV)NC1 are found in the glomerular and alveolar basement membranes.[3,4] The diagnosis is established by quantification of circulating anti-GBM antibodies and histological evaluation of the kidney biopsy. Early treatment is recommended due to high risks of severe pulmonary involvement and rapid decline in renal function.

The association of MN with anti-GBM disease has been assumed for the first time in 1974 by Klassen et al.[5] Few

[1]Department of Nephrology, Heidelberg University Hospital, Heidelberg, Germany
[2]Institute of Pathology, Heidelberg University Hospital, Heidelberg, Germany

Corresponding Author:
Claudius Speer, Department of Nephrology, Heidelberg University Hospital, 162 Im Neuenheimer Feld, D-69120 Heidelberg, Germany.
Email: Claudius.speer@med.uni-heidelberg.de

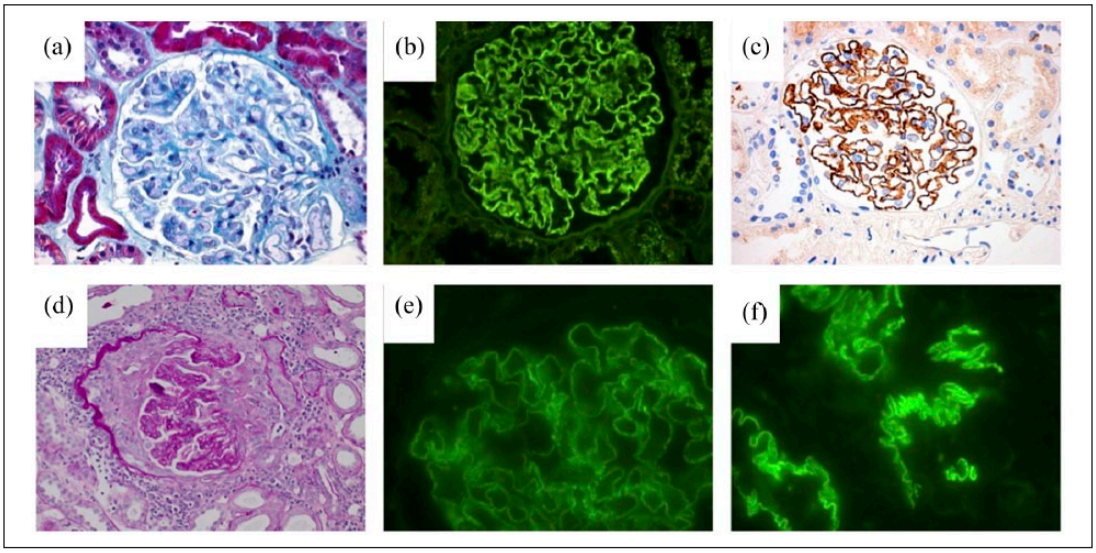

Figure 1. First biopsy 2009 (a–c) and second biopsy 2017 (d–f). The first kidney biopsy in 2009 revealed (a) a typical MN with thickening of glomerular basement membranes in the Masson trichrome stain, (b) diffuse granular IgG deposits in subepithelial localization, and (c) PLA2R-positivity. The current biopsy in 2017 disclosed an active crescentic GN (d; periodic acid Schiff (PAS) staining), with (e) finely granular and (f) co-existing linear IgG and C1q deposits along the GBM on immunohistology.

studies reported evidence that both, simultaneous and consecutive occurrence of MN and anti-GBM disease, can appear.[6–11] The precise pathogenesis is still unclear. It has been hypothesized that immune complex deposition in MN patients is responsible for the exposure of cryptic GBM epitopes, stimulating the formation of anti-GBM antibodies. There is no defined clinical feature or standardized algorithm in therapy. Here, we discuss a case of anti-GBM disease following MN and review the current literature in respect of clinical presentation and treatment options.

Case report

Clinical and laboratory features

We report a 55-year-old man with biopsy-confirmed MN (Figure 1(a)–(c)) 8 years ago and a preexisting chronic renal disease (CRD) KDIGO 2 with a baseline serum creatinine of 1.3 mg/dL and a protein/creatinine ratio of approximately 7 g/molCr. Retrospective immuno-histochemical analysis disclosed a diffuse granular positivity of PLA2R along the GBM (Figure 1(c)), whereas THSD7A was negative. The patient received angiotensin receptor blockers as medication without further immunosuppressive treatment.

Eight years after MN was diagnosed, the patient was admitted with a 4-week history of increasing exhaustion, myalgia, arthralgia, and peripheral edema in lower limbs. Initial laboratory studies revealed a serum creatinine level of 4.18 mg/dL and a blood urea nitrogen (BUN) level of 61.13 mg/dL. Analysis of urine disclosed a protein concentration of 0.85 g/L and a protein/creatinine ratio of 119 g/molCr. Urinary sediment revealed 50 erythrocytes and 5–10 leukocytes per high-power field. More than 50% of the erythrocytes were dysmorphic and several acanthocytes as well as red blood cell casts were visible. Serum complement 3 and 4 levels were normal, no myeloperoxidase (MPO) anti-neutrophil cytoplasmatic antibodies (ANCA), proteinase-3-specific (PR-3) ANCA, antinuclear antibodies (ANA), or anti-double stranded DNA antibodies (anti-dsDNA) were detected. Remarkably, anti-GBM antibodies were positive in the indirect immunofluorescence (titer 1:2560; standard value <1:10). Notably, the indirect immunofluorescence will detect non-anti-GBM anti-COLIV alpha chain directed antibodies as well, for what reason the combination of immunohistology, serology, and clinical manifestation is necessary for diagnosis.[12] Anti-PLA2R antibodies were not measured. In the thorax computed tomography (CT), no evidence of pulmonary hemorrhage was detected. Kidneys were of normal size with suitable arterial and venous perfusion on renal ultrasound.

In summary, we made the diagnosis of an acute on chronic kidney injury, suspicious of rapidly progressive glomerulonephritis. Thus, we decided to perform an early second biopsy.

Kidney biopsy

The biopsy revealed predominantly circumferential cellular crescents with occasional segmental necrosis (Figure 1(d)). The immunofluorescent analysis showed granular, subepithelial IgG-positive immune complex deposits, in addition to areas with linear IgG and C1q positivity, indicating complement activation via the classical pathway through anti-GBM antibodies (Figure 1(e) and (f)). A mild tubular atrophy and interstitial fibrosis as well as mild arterio-arteriolosclerosis were noted. The diagnosis of an anti-GBM glomerulonephritis superimposed on preexisting MN could be established.

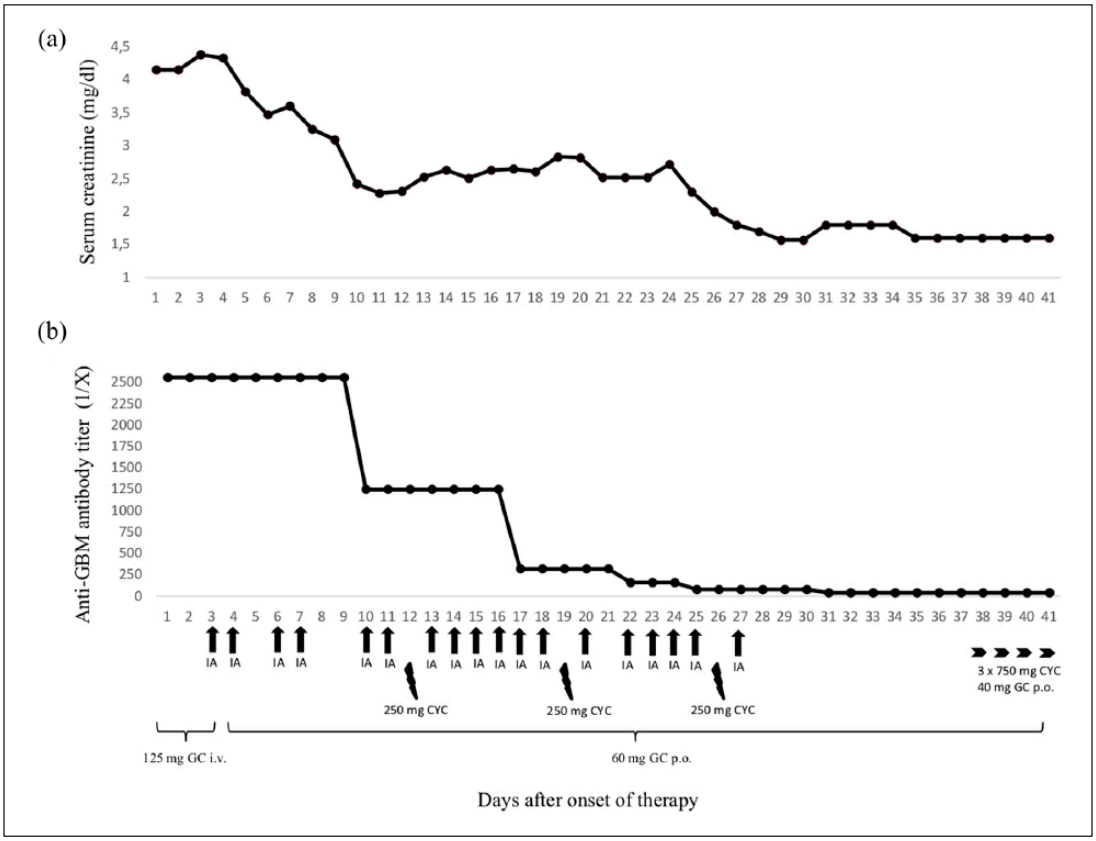

Figure 2. Therapy of MN followed by anti-GBM disease and progress of serum creatinine (a) and anti-GBM antibody titer (b). Initial treatment with 125 mg glucocorticoids (GC) for 3 days, followed by oral GC 60 mg per day. In addition, cyclophosphamide (CYC) i.v. once per week in a dose of 250 mg for three times was administered. Immunoadsorption (IA) was conducted 18 times. After 2 months the GC dose was reduced to 40 mg and the application of another three times cyclophosphamide 750 mg i.v. monthly for maintenance therapy was scheduled. (a) Kidney function improved after 1 month with serum creatinine declining from 4.2 to 1.6 mg/dL and (b) anti-GBM titers decreasing from 1:2560 to 1:80 during therapy.

Treatment and clinical follow-up

We initially started a therapy with pulse intravenous (i.v.) methylprednisolone 125 mg for 3 days, followed by oral prednisolone 60 mg per day. After receiving the results of the second biopsy, we administered cyclophosphamide (CYC) i.v. once per week in a dose of 250 mg for three times. In addition, immunoadsorption was conducted 18 times (Figure 2). Immunoadsorption was accomplished by semi-selective Globaffin columns on a Comtech centrifuge together with the ADAsorb device (Fresenius Medical Care). During each immunoadsorption treatment, 2.0-2.5 plasma volumes were processed.

The renal function improved and the serum creatinine concentration recovered to 2.5 mg/dL after 2 weeks (Figure 2(a)). The anti-GBM titer declined from initial 1:2560 to 1:1250 after 2 weeks (Figure 2(b)). The patient could be discharged after 3 weeks of hospitalization with a significantly improved kidney function (serum creatinine 2.6 mg/dL) and an anti-GBM titer of 1:320. Within the 2-month follow-up the patient presented with a serum creatinine of 1.6 mg/dL and an anti-GBM titer of 1:40. The protein/creatinine ratio was 9.5 g/molCr, indicating that MN was controlled as well. The prednisolone dose was reduced to 40 mg and three additional applications of CYC 750 mg i.v. monthly for maintenance therapy were scheduled (Figure 2).

Discussion

Clinical presentation of MN followed by anti-GBM disease

Endocapillary proliferation and crescent formation are rare in patients with primary MN, hence concurrence of another GN should be assumed. The connection between anti-GBM disease and primary MN is not co-incidental as both diseases have a common human leukocyte antigen (HLA)-determined predilection.[13] Thus, MN followed by anti-GBM disease rather represents diseases determined by each other than the coexistence of two different entities. There is some evidence that subepithelial immune complex deposits in MN may release antigenic GBM fragments, causing development of anti-GBM antibodies with crescentic formation.[5,7]

Since the first description of MN and anti-GBM disease in 1974 by Klassen et al.,[5] only few case reports have been published.[6–11,14] It seems to be important to distinguish between MN followed by anti-GBM GN and MN which follows an anti-GBM GN. Compared to MN followed by anti-GBM disease,[15] MN preceded anti-GBM GN appears to have an earlier onset of disease, an enhanced female gender distribution and a fairly good outcome with a recovery in most cases. In our case, MN was followed by anti-GBM disease. General symptoms are new onset of edema, myalgia, arthralgia, and rapid decline in kidney function. Only in one reported case, pulmonary involvement with hemoptysis in form of Goodpasture syndrome was described.[9] Subsequently, when confronted with the delineated constellation, anti-GBM and ANCA should be determined in peripheral blood and—second—kidney biopsy has to be considered.

Treatment and outcome

Patients with MN followed by anti-GBM disease have distinct clinical outcomes compared to primary anti-GBM disease. In all reported cases with MN followed by anti-GBM disease, the prognosis has been poor despite immunosuppressive therapy, with progression to end-stage renal disease (ESRD) or death.[6–11,14] Excluding the first reported case,[5] plasmapheresis combined with steroids and CYC were common therapeutic attempts. Due to the lack of precise data, the therapy of MN followed by anti-GBM disease is essentially based on expert opinion and experimental trials and not evidence-based.

We report a promising therapeutic approach in a patient with MN followed by anti-GBM disease. As initial therapy, we administered a pulse of i.v. methylprednisolone followed by immunoadsorption and CYC i.v. combined with oral steroids which is not standard of care in primary anti-GBM disease. It still remains elusive, if treatment of MN followed by anti-GBM disease requires the same therapy as primary anti-GBM disease. In comparison to previously reported cases, we chose immunoadsorption instead of plasmapheresis as it may be more efficient in removing pathogenic antibodies, enables the process of higher plasma volumes and is associated with decreased adverse effects compared to plasmapheresis. In addition, CYC was administered i.v. as induction and maintenance therapy compared to oral administration of CYC in other cases of MN followed by anti-GBM disease. There is increasing evidence that CYC i.v. therapy is equally effective as oral therapy and is associated with less toxicity due to reduced cumulative dose. In other diseases which are at least partly antibody-mediated such as ANCA-associated glomerulonephritis or lupus nephritis, i.v. cyclophosphamide was not inferior to oral administration with less adverse effects.[16–18]

As outlined above, the patient had a significantly improved kidney function in the 2-month follow-up with serum creatinine declining from 4.2 to 1.6 mg/dL, anti-GBM titers decreasing from 1:2560 to 1:40 and a protein/creatinine ratio of 9.5 g/molCr during therapy (Figure 2). Independent of therapy, the outcome of these patients seems to be primarily influenced by immediate diagnosis and treatment.[6–11] An adverse outcome was associated with high initial serum creatinine, oligoanuria, a high percentage of circumferential crescents and high titers of anti-GBM antibodies.[6–11] In previously reported cases, the onset of induction therapy is not invariably defined. Notably, serum creatinine before treatment was a mean of 9.9 mg/dL in reported cases and most patients showed oligoanuria, whereas our patient presented a serum creatinine of 4.18 mg/dL and unaltered diuresis, indicating an initiation of treatment in an earlier phase of disease.[6–11,14]

In summary, our case report revealed effectiveness of administered therapy although it cannot be definitively clarified if different treatment patterns, earlier onset of induction therapy, or combination of both are causal for favorable outcome and larger case series are needed for confirmation.

Conclusion

We report a promising approach to treatment in a patient with MN followed by anti-GBM disease. Early diagnosis and immediate treatment appear to be essential to achieve a favorable outcome. This case report underlines the fact that an early second biopsy should be considered in MN patients with an unusual clinical course.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

References

1. Beck LH Jr, Bonegio RGB, Lambeau G, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med* 2009; 361(1): 11–21.
2. Beck LH Jr. PLA2R and THSD7A: disparate paths to the same disease? *J Am Soc Nephrol* 2017; 28(9): 2579–2589.
3. Saus J, Wieslander J, Langeveld JP, et al. Identification of the Goodpasture antigen as the alpha 3(IV) chain of collagen IV. *J Biol Chem* 1988; 263(26): 13374–13380.

4. Hudson BG, Tryggvason K, Sundaramoorthy M, et al. Alport's syndrome, Goodpasture's syndrome, and type IV collagen. *N Engl J Med* 2003; 348(25): 2543–2556.
5. Klassen J, Elwood C, Grossberg AL, et al. Evolution of membranous nephropathy into anti-glomerular-basement-membrane glomerulonephritis. *N Engl J Med* 1974; 290(24): 1340–1344.
6. Moorthy AV, Zimmerman SW, Burkholder PM, et al. Association of crescentic glomerulonephritis with membranous glomerulonephropathy: a report of three cases. *Clin Nephrol* 1976; 6(1): 319–325.
7. Richman AV, Rifkin SI and McAllister CJ. Rapidly progressive glomerulonephritis. Combined antiglomerular basement membrane antibody and immune complex pathogenesis. *Hum Pathol* 1981; 12(7): 597–604.
8. Kurki P, Helve T, von Bonsdorff M, 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(2): 134–137.
9. Thitiarchakul S, Lal SM, Luger A, et al. Goodpasture's syndrome superimposed on membranous nephropathy. A case report. *Int J Artif Organs* 1995; 18(12): 763–765.
10. Nayak SG and Satish R. Crescentic transformation in primary membranous glomerulopathy: association with anti-GBM antibody. *Saudi J Kidney Dis Transpl* 2007; 18(4): 599–602.
11. Imtiaz S, Alswaida A, Rehman H, et al. Transformation of membranous into anti-GBM nephritis. *Indian J Nephrol* 2012; 22(5): 370–373.
12. Hellmark T and Segelmark M. Diagnosis and classification of Goodpasture's disease (anti-GBM). *J Autoimmun* 2014; 48–49: 108–112.
13. Fisher M, Pusey CD, Vaughan RW, et al. Susceptibility to anti-glomerular basement membrane disease is strongly associated with HLA-DRB1 genes. *Kidney Int* 1997; 51(1): 222–229.
14. Agodoa LCY, Striker GE, George CRP, et al. The appearance of nonlinear deposits of immunoglobulins in Goodpasture's syndrome. *Am J Med* 1976; 61(3): 407–413.
15. Basford AW, Lewis J, Dwyer JP, et al. Membranous nephropathy with crescents. *J Am Soc Nephrol* 2011; 22(10): 1804–1808.
16. De Groot K, Harper L, Jayne DR, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2009; 150(10): 670–680.
17. Haubitz M, Schellong SG, Göbel U, et al. Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitis and renal involvement: a prospective, randomized study. *Arthritis Rheum* 1998; 41(10): 1835–1844.
18. Houssiau FA, Vasconcelos C, D'Cruz D, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum* 2002; 46(8): 2121–2131.