Case Report

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Case Report: Secondary Membranous Nephropathy with ANCA-related Focal Necrotizing Glomerulonephritis

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1. Abstract

Antineutrophil cytoplasmic antibodies (ANCA) are the serological hallmark of some idiopathic systemic vasculitis, Pauci-immune necrotizing and crescentic glomerulonephritis (NCGN) is a frequent component of ANCA-associated vasculitis. Up to now, a few rare cases of concurrent membranous nephropathy (MN) and ANCA-associated vasculitis have been reported. Herein, we report a case of a young woman who exhibited moderate proteinuria and tested positive for myeloperoxidase (MPO) and perinuclear anti-ANCA (p-ANCA), diagnosed with ANCA-associated vasculitis combined with membranous nephropathy by kidney biopsy. Notably, the patient displayed no systemic vasculitis response, no crescent formation, only focal necrosis and a slightly damaged kidney--proteinuria and hematuria with normal renal function. Therefore, the less common AAV type of renal-limited vasculitis (RLV) is under consideration. Because of the PLA2R staining was negative and the subtype of IgG on immunofluorescence was dominated by IgG3 deposition rather than IgG4, the patient was diagnosed with secondary MN. Treatment with corticosteroids combined with mycophenolate mofetil (MMF) led to complete remission of proteinuria. Our case is a rare case with normal renal function among other cases, and this case report discusses that for patients with high clinical suspicion, even if the symptoms are not obvious and the renal function is stable, prompt diagnosis and active therapy should be performed to avoid delaying the condition.

2. Keywords:
ANCA-associated vasculitis (AAV), membranous nephropathy (MN), corticosteroids, rituximab, case report

3. Introduction

ANCA-associated vasculitis (AAV) is an autoimmune disease that affects multiple systems, mainly including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and renal-limited vasculitis (RLV) with MPO and proteinase 3 (PR3) as the main target antigens [1]. The common pattern of kidney injury is pauci-immune NCGN in all of ANCA-related glomerulonephritis. MN is classified into idiopathic and secondary, the most common pathological type of nephrotic syndrome in adults, characterized by subepithelial immune complex deposition and glomerular basement membrane thickening. About 80% of MN is idiopathic, and systemic lupus erythematosus (SLE), infections, drugs, and malignancy are important factors affecting secondary MN. [2] Cases of AAV combined with MN have been occasionally observed and are characterized by pauci--immune NCGN and electron-dense deposition under electron microscopy with poor prognosis. [3] There is a lack of systematic research on this disease, and most diagnosis and treatment strategies are based on clinical experience and case reports. Therefore, we describe a rare case of AAV combined with secondary MN. The patient without systemic vasculitis performed only proteinuria, hematuria and sustained stable renal function with rare pathological features. Even though the patient had normal renal function and no other organ involvement, we continued active treatment, and eventually, the patient's proteinuria became negative.

4. Case report

A 36-year-old unmarried female was admitted to our hospital with proteinuria and lower extremity edema for 20 days. The patient presented with normal urine output and blood pressure and was examined in the clinic for 3+ urinary protein. Microscopic examination of the urinary sediment showed 15-20 erythrocytes/HP. Still, the patient denied experiencing nocturia, painful urination, gross hematuria, skin rash, arthralgia, oral ulcers, photosensitivity, hair loss, or significant changes in urine volume. She denied a history of hepatitis, purpura, diabetes mellitus, surgery, trauma, blood transfusion, food and drug allergies, unknown history of vaccinations, and no family history of kidney disease or immune disease. She had no history of medications such as

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propylthiouracil and hydralazine. After hospital admission, the physical examination revealed mild edema of the lower limbs. Laboratory findings were as follows: albumin 30.0 g/L; the results of urinalysis were: 24-hour urine collection between 1341-2617 mg/24 h; microscopic examination of the urinary sediment showed 3-5 erythrocytes/HP; serum creatinine 0.6 mg/dL; erythrocyte sedimentation rate (ESR) 10 mm/h; C-reactive protein (CRP) <3.1 ug/ml; p-ANCA positive, MPO 103.9 RU/ml; urine light chain LAMBDA 54 mg/L, light chain KAPPA 71 mg/L. The patient results were negative for antinuclear antibody (ANA), anti-double-stranded DNA (ds-DNA), and anti-Smith antibody (anti-Sm). Additional serology tests did not show significant abnormalities, including PR3, immune globulin, complement, serum anti-phospholipase A2 receptor (PLA2R) antibody, anti-glomerular basement membrane (GBM) antibody, hepatitis B surface antigen, hepatitis C virus, blood and urine immunofixation electrophoresis, and tumor markers. Chest computed tomography (CT) showed a faint 4 mm. nodule in the lower lobe of the left lung. There were no significant abnormalities in the heart, large blood vessels, or mediastinal lymph nodes. No bilateral pleural effusions were observed. Impressions at admission: nephritic syndrome. Owing to the presence of MPO and p-ANCA, a renal biopsy was performed and light microscopy showed (Figure 1A) segmental sclerosis in 1/45 (2.2%) glomeruli, fibrinous necrosis in one capillary loop, mild interstitial fibrosis, and slight focal inflammatory cell infiltration (mainly mononuclear cells). The tubules showed casts, and mild tubule interstitial fibrosis. There is no crescent formation and proliferation of mesangial cells. No definite lesion was found in the vessels. Immunofluorescence showed (Figure 1B): diffuse, globular to capillary loops and a few mesangial areas positive or IgG (3+), IgA (2+), IgM (2-3+), C3 (3+), C1q (2+), C4 (2+), light chain Kappa (3+), Lambda (3+), IgG was mainly IgG3 (3+) positive. Notably, the PLA2R staining was negative. Electron microscopy (Figure 1C) revealed extensive fusion of foot processes, large numbers of electron-dense material deposits were seen in the mesangial area and subepithelial with basement membrane reaction. The pathologic diagnosis was (1) ANCA-related vasculitis; (2) membranous nephropathy and pathology suggested MN in stage I. Therefore, we diagnosed MN complicated with AAV, nephritic syndrome.

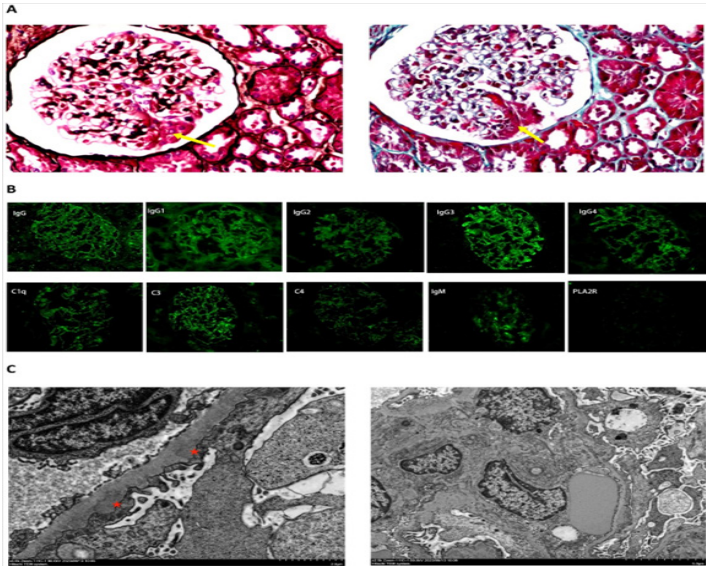

Figure 1: A Light microscopy: Crinkled capillary loops and fibrinoid necrosis formation were observed under light microscopy(arrows in inset). (a: PASM+HE 40×10; b: Masson 40×10). (B) Immunofluorescence: IgG, IgG1, IgG2, IgG3, IgG4, IgM, C3, C1q, and C4 were deposited in capillary loops and a few mesangial areas. (Immunofluorescence × 400). (C) Electron microscopic: More electron-dense deposits were seen in the mesangial region and numerous small subepithelial electron-dense deposits with basement membrane reactions (stars in inset).

Considering the poor prognosis of vasculitis, we needed to treat the patient proactively to prevent the disease's rapid progression despite her early manifestation of vasculitis with predominant renal damage. According to the 2021 KDIGO guidelines, the patient had no vital organ involvement, had normal renal function, and no pregnancy history, we prescribed induction therapy consisting of oral prednisone 40 mg/day combined with MMF 0.75 mg bid. After one month of follow-up, the 24-hour proteinuria quantification remained high at 2373 mg/24 h, and MPO was 23.4 RU/ml. Since proteinuria was still high, 100 mg of losartan qd was administered orally. After four months, p-ANCA became negative, MPO levels decreased to 17.3RU/ml, 24-hour proteinuria was 2871 mg/24 h, and renal function remained normal, allowing for a gradual reduction of corticosteroid dosage. After the 11th month of follow-up, 24-hour proteinuria quantification decreased to 198 mg/24 h, albumin was 41.9 g/L, MPO levels elevated to 79.2 RU/ml, and renal function remained stable. Subsequently, in the 14th month, 24-hour proteinuria turned negative (32.9 mg/24 h), MPO continued to rise to 103.5RU/ml, although renal function was normal. The titer of MPO kept increasing, although the renal function was stable, and there was no sign of recurrence. To prevent relapse and minimize the side effects of the medication with long-term corticosteroids and MMF application, the treatment regimen was adjusted to rituximab (375 mg/m2) as maintenance therapy. One month after rituximab injection, the 24-hour proteinuria level was 116 mg/24 h, while MPO levels continued to rise to 117.7 RU/ml. Four months later, the 24-hour proteinuria level decreased to 57 mg/24 h, creatinine remained stable at 59 μmol/L, and the MPO titer was 74.2 RU/ml. After 6 months of rituximab treatment, the 24-hour proteinuria level was 109 mg/24 h, and the MPO titer was 92.2 RU/ml. The patient was followed up for 21 months without any adverse effects, proteinuria achieved complete remission, and renal function was maintained at normal level (Figure 2). We are currently on maintenance therapy with 500 mg of rituximab every six months and plan to keep treatment for 2-3 years.

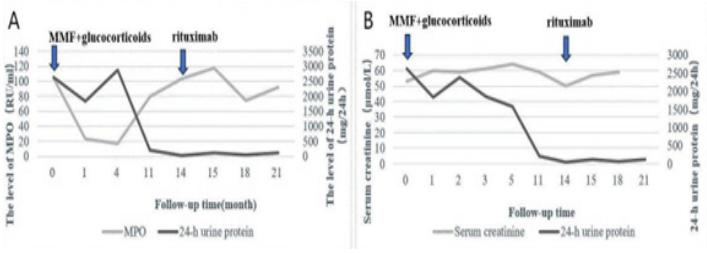

Figure 2: Photo of changes in patient-related indicators.

(A): 24-hour urine protein quantification graph versus creatinine change at 21 months of patient follow-up. Proteinuria quantification showed a decreasing trend, and complete remission was achieved; the creatinine level did not progress.
(B): Graph of the relationship between 24-hour proteinuria quantification and MPO titer changes in the patient, with a decreasing trend of both proteinuria and MPO titer.

5. Discussion

In this case, the laboratory and pathological results of the patient were consistent with the characteristics of secondary membranous nephropathy, especially PLA2R is useful to distinguish between primary or secondary MN. According to the medical history, she had no chronic infections such as hepatitis B and C, and no clinical manifestations of rheumatoid arthritis or SLE. She also had no history of cancer or medication. Therefore, we needed to consider an association with AAV. The patient tested MPO and P-ANCA were double-positive by enzyme-linked immunosorbent assay (ELISA) and immunofluorescence, which suggested that false-positives seem unlikely. Pathological report showed fibrinoid necrosis instead of the crescent, which was supposed to be an early renal manifestation of AAV. However there was no abnormality of renal function and no other target organ involvement, we considered this patient to be a special type of AAV called RLV. RLV is not the classical type of AAV, which refers to vasculitis confined to the kidney, has fibrinoid necrosis in the vascular wall of the kidney, accompanied by inflammatory cell infiltration, and manifests solely as hematuria, proteinuria, or combined with renal insufficiency. ANCA-positive RLV may lack systemic manifestations of AAV, such as rash, sinusitis, and pulmonary nodules, [4,5] which is consistent with our case. This may be early renal damage in vasculitis, if not treated proactively, may progress to classic ANCA-associated glomerulonephritis, which presents with rapid deterioration of renal function. [6] ANCA-associated glomerulonephritis typically presents as pauci-immune NCGN, which is characterized by glomerular necrosis and crescent formation in the absence of significant intracapillary proliferation and glomerular immune complex deposit.[7,8] 80% of untreated patients have a high mortality rate, while 90% who receive treatment within the first year eventually have a good prognosis. [9]

Since the coexistence of AAV with MN is relatively rare, we summarized the global cases of AAV combined with MN (table S1). Most patients present with renal insufficiency, with only three patients[6,10] (including our case) having normal creatinine levels. Most cases showed crescentic glomerulonephritis, but that percentage of crescentic is not 100%, [11] indicating that not all patients form crescent. Immunofluorescence results show a predominance of IgG3 and C3 deposition, with IgA and IgM slightly deposition. In all cases, subepithelial electron-dense deposits were visible by electron microscopy.[11,12] This reinforces the uniqueness of our case. Although there are a few case reports of AAV combined with MN, the exact pathogenesis is unclear. Our review of the studies revealed that surindran [13] suggested that it is the result of a coincidence, but it has been reported that AAV may also result in MN. [3,14] In 2009, a scholar [6] found that MPO deposition was observed by immunofluorescence in patients with AAV combined with MN. MPO could bind to GBM or endothelial cells and co-localization with IgG as membranous pattern,[15] play a part as a pathogenic antigen, leading to the formation of subepithelial immune complexes, [6,16] These results suggested that the secondary MN was caused by MPO-ANCA immune-complex. [6,17] Therefore, MPO, but PLA2R, is the therapeutic antigen. Our results were consistent with the majority of cases as secondary MN, so we considered that AAV might cause MN. Most of the therapy was corticosteroids and cyclophosphamide (CTX). Although the renal function was steady and no acute vasculitis change was found in admission, a rapid exacerbation is possible. Thus, a combination of glucocorticoid and immunosuppressant was applied, despite no crescent formation and normal renal function. The patient responds well to the treatment and has only recurrent elevation of MPO titer, there is a relevance between the titer and the activity of the disease? The Birmingham Vasculitis Activity Score (BVAS) indicated that the ANCA titer is correlated with disease activity, suggesting a possibility of recurring disease.[18] However, relying solely on ANCA titer to predict recurrence and formulate a treatment plan is inadequate.[19] Then, to follow up and continued maintenance treatment with rituximab 500 mg every six months for 3 years. However, discontinuing the drug after 3 years or needing long-term follow-up to adjust the medication is uncertain, and we need to evaluate the patient's condition further.

Table 1: Clinical and laboratory characteristics of 98 patients with ANCA-associated vasculitis combined with MN

Literature	Publish time	no	Age (years)	ANCA	24-h proteinuria (g/24 h)	Serum creatinine (μmol/L)	Treatment options	ESRD
Gaber etc.1	1993	1	64	C - ANCA	1.6	301	GC + CTX	0
Kanaharaet al.2	1997	1	47	MPO	5.76	97	GC + CTX	0
Tse etc.3	1997	4	57.3 (30 to 70)	C-ANCA(2) P-ANCA(2)	1.5 to 10.0	120 to 1220	GC + CTX(3)	1
							Untreated (1)	
Taniguchi et al.4	1999	1	68	MPO	1.26	128	GC	0
Dwyer et al.5	2001	2	67, 69	MPO	0.56	130 ~ HD	GC(1)	1
					7.16		GC + CTX(1)	

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Suwabe et al.6	2005	1	68	MPO	6.97	265	GC + CTX	0
Zhan Yongli et al.[i]	2006	1	72	P-ANCA+MPO	1.5	455	GC + CTX	0
Nasr et al.[ii]	2009	14	58.7	C-ANCA(5) P-ANCA(7) P-ANCA+	6.5	79 to 787	GC + CTX(11)	5
			(37-79)	C-ANCA(1)	(0.8 to 16)		GC+CTX + PLX(1)	
				Atypical(1)			Untreated (2)	
Matsumoto et al.[iii]	2009	1	Not available	MPO	Not available	53	GC + CTX	Not available
Zhou Guangyu et al.[iv]	2011	4	51.5	MPO(3)	3.9 to 6.3	228-347	GC + CTX (3)	1
			(49-64)	PR3(1)			GC(1)	
Watanabe et al.[v]	2011	1	79	MPO	3.5	Not available	GC	Not available
Surindran et al.[vi]	2012	1	56	MPO	14	1185	GC + CTX + PLX	0
Shimada et al.[vii]	2013	1	73	MPO	2.3	477	GC	1
Kanodia et al.[viii]	2014	1	48	MPO	Not available	806	GC + CTX	0
Thajudeen et al.[ix]	2014	1	30	MPO	5.6	274	GC + CTX	0
Jin Ling et al.[x]	2014	5	65	MPO(4)	4.9	255	GC + CTX	0
Hu et al.[xi]			(62-69)	PR3(1)	(3.6 to 6.8)	(198 to 262)	GC + CTX	
	2014	1	51	MPO	5.28	124		0
Barrett et al.[xii]	2014	8	66.6	MPO(6)	5.64	288	GC(1)	2
			(55-82)	P-ANCA(2)	(1 to 14)	(97 to 504)	GC + CTX(4)	
							GC+CTX+RITUX(2)	
							GC+ CTX + PLX (1)	
Zou et al.[xiii]	2015	27	42.4± 17.7	MPO(25)	3.84±2.35	566.6±455.3	GC + CTX (15)	13
				PR3(2)			GC+CTX + PLX(10)	
							Untreated (2)	
Balafa et al.[xiv]	2015	1	58	P-ANCA	8	653	GC + CTX + PLX	0
Ren Feif eng[xv]	2015	1	58	P-ANCA+MPO	2. 16	145.7	GC + CTX	0
Bian et al.[xvi]	2015	1	52	P-ANCA+MPO	3.08	166	GC + CTX	0
Carrara etc.[xvii]	2016	1	34	MPO	Not available	371	GC + RITUX + PLX	0
Moinuddin etc.[xviii]	2016	1	50	P-ANCA+MPO	1.6	194	GC + Azathioprine	0
P'ng et al.[xix]	2017	1	55	MPO	2.57	732	GC + CTX + PLX	1
Manabe et al.[xx]	2017	1	19	MPO	Not available	106.1	GC	0
Yang Le et al.[xxi]	2018	1	67	P-ANCA+MPO	4.1	125.4	Untreated	0
Tominaga et al. [xxii]	2018	2	52,63	MPO (2)	0.316	175.916	Not available	Not available
					Not available	64.532		
Nikolopoul ouet al. [xxiii]	2019	7	64.8 (34 to 74)	MPO-ANCA(6)	1.23	361	CTX+GC+PLX(1) GC+ CTX+RITUX(3) GC+ MMF(2) GC+CTX(1)	2

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Menghan Gao etc.[xxiv]	2020	1	62	PR3(1)	(0.08 to4.28)	(86 to 877)	GC+Mizoribine	0
				MPO	7.09	79		
Yu et al. [xxv]	2020	1	53	p-ANCA+MPO	4.8	324.4	GC+CTX+PLX+HD	0
Zhu et al. [xxvi]	2021	1	57	ANCA	1.247	130	GC+CTX	0
Zhang et al. [xxvii]	2021	1	33	MPO	5.24	297	PLX+CTX+GC	0
Our Case	2023	1	36	p-ANCA+MPO	2.617	53	GC+MMF	0

6. Conclusion

In summary, we report a relatively rare case of AAV combined with secondary MN, and atypical vasculitis damage. The patient also had uncommon symptoms, and no systemic vasculitis response. She only had renal involvement and was characterized by focal necrosis, absence of crescent formation, and no deterioration of renal function, but she presented proteinuria with hematuria. Although the patient's kidney function was stable, we still treated her actively, and a significant reduction in proteinuria was observed following active treatment. For this reason, our article would like to remind medical professionals that observation may delay the patient's condition; timely initiation of therapy is critical to prevent kidney progression to renal failure.

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