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Letter to the Editor

Rapidly progressive glomerulonephritis due to coexistent anti-glomerular basement membrane and anti-myeloperoxidase antibody

Dear Editor,

Rapidly progressive glomerulonephritis (RPGN) is usually accompanied by microscopic glomerular crescent formation with progression to renal failure within weeks to months. RPGN is relative rare and affecting 10%–15% of patients with glomerulonephritis (GN).[1,2] The antineutrophil cytoplasmic antibodies (ANCA)-associated RPGN are responsible for more than 80% of the cases. On the other hand, type 4 double-antibody positive diseases are extremely rare, account less than 1% of RPGN, and have features of both type 1 and 3 (Table 1A and B). Here, we report a clinical case of RPGN proved by renal biopsy (Fig. 1) and serological test. We confirmed this rare double antibodies positive type 4 RPGN in this patient.

A 57-year-old female patient did not have any relevant medical history. She complained of sudden onset of shortness of breath and productive cough with blood-tinged sputum for one day. The patient had multiple ecchymosis and petechial on her both upper limbs. Her eyes were congested with evidence of uveitis. Her body temperature was 37°°C. Her blood pressure was 165/95 mmHg, heart rate 90 beats per minute, and respiratory rate 23 breaths per minute. Her renal function test was abnormal with elevated serum blood urea nitrogen 103 mg/dL and creatinine 11.15 mg/dL on admission. Complete blood count showed that she had normocytic anemia with hemoglobin of 8.9 g/dL. Urinalysis revealed microscopic hematuria with red blood cells 20–25 cells per high power field and mild proteinuria. Complement component C3 was 93.10 mg/dL and C4 19.10 mg/dL. The serum titer of myeloperoxidase antineutrophil cytoplasmic antibodies (P-ANCA) was 1:80 (positive), anti-glomerular basement (GBM) membrane antibody level was 337 μg/L (positive), but cytoplasmic antineutrophil cytoplasmic antibody (C-ANCA) was negative. The chest X-ray showed no obvious pulmonary infiltrates. Percutaneous renal biopsy was performed on 10th admission day, revealing 13 cellular crescents (61.9%), 2 fibrous crescents (9.5%), and 6 globally sclerotic glomeruli (28.6%) in 21 glomeruli (Fig. 1). Immunofluorescence microscopy disclosed no specific immunoglobulin or complement deposition. The diagnosis of pauci-immune crescentic glomerulonephritis with double antibodies positive disease was made.

The "double antibodies positive" disease is characterized by coexisting presentation of both ANCA and anti-GBM antibodies.[1,2,5,7–12] It was first reported by O'Donoghue et al., in 1989.[1] The prevalence of "double positive" was 5%–14% in patients with ANCA–associated systemic vasculitis (AASV),[2,3] 20%–40% in those with anti-GBM disease[4] and 2% in patients presented with RPGN.[3] Previous study revealed that "double positive" disease has characteristics similar to those of AASV with multisystem involvements.[5] On the other hand, a linear or fine granular deposition of IgG or C3 along the glomerular capillary wall under direct immunofluorescence stain was found (Table 1B),[4–6] which suggesting that the pathological features of the 'double positive' are similar to those with anti-GBM disease.[6,7] Our

Table 1A Classification of Rapidly Progressive Glomerulonephritis (RPGN).

Type	Percentage of RPGN cases
Type 1: Anti-GBM antibodies mediated	≤10%
Type 2: Immune complex	≤40%
Type 3: Pauci-immune	≤50%
Type 4: Double antibodies positive	Rare

Abbreviation: Anti-GBM: Anti-glomerular basement membrane. Adopted from Merck manuals, professional edition, 2016. https://www.merckmanuals.com.

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Table 1B Brief summary of clinical cases of RPGN with double positive antibodies.

No. of cases reported	Sex/Age	Clinical manifestations	Renal IF findings	ANCA	Authors & references
1	M/63	Watery diarrhea, non-oliguria	Linear	p-ANCA	Chan PS[7]
1	F/80	Fatigue, weight loss and hemoptysis.	Not available	p-ANCA	Almouradi T[8]
4	M/78	Case 1: pulmonary fibrosis, fever and cough.	3 linear, 1 not available	p-ANCA	Nakabayashi K[9]
	M/64	Case 2: pulmonary fibrosis, hemoptysis and shortness of breath			
	M/72	Case 3: myalgia, arthralgia and low grade fever			
	F/42	Case 4: Raynaud's phenomenon, edema, proteinuria and hematuria.			
2	M/73	Case 1 & 2: Cough, hemoptysis,	1 linear, 1 not available	Case 1 p-ANCA	Zoysa J[10]
	M/43	proteinuria and hematuria.		Case 2 c-ANCA	
1	M/75	Anuria acute renal failure, low grade fever and weight loss.	Pauci-immune initially and linear deposits 3 years later	p-ANCA	Serratrice J[11]
1	M/23	Pulmonary-renal syndrome	Linear	p-ANCA	Verburgh CA[12]
3	F/59	Case 1: hemoptysis, shortness of breath oliguria and fever	Linear	c-ANCA	O'Donoghue DJ[1]
	F/64	Case 2: cough, erythematous rash and weight loss			
	F/59	Case 3: fatigue, arthralgia, and hemoptysis.			

Abbreviation: IF: immunofluorescence; ANCA: anti-neutrophil cytoplasmic antibody; RPGN: rapidly progressive glomerulonephritis.

patient had RPGN with extra-renal manifestations of hemoptysis and uveitis, showing 80% of cellular crescents with pauci-immune deposits under direct immunofluorescence staining in the examination of specimens from renal biopsy. These features represented the unique presentation of our patient as compared to those reported in the literature (Table 1B).[1,2,4–12]

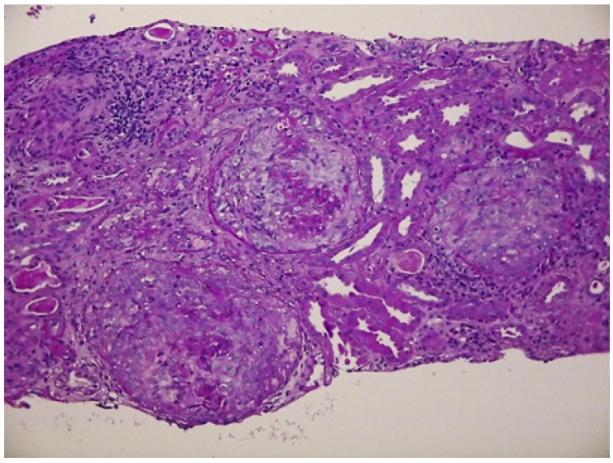

Figure 1. The pathologic features of renal biopsy revealed multiple glomerular cellular crescent formations (H & E stain, 400X).

The renal outcome is generally unfavorable in "double positive" disease.[5,7–12] Levy et al. reported that 68% of their patients require dialysis at presentation, none of them recover renal function.[5] Furthermore, patients with serum creatinine greater than 500 μmol/L also do not achieve renal recovery. In addition, a high percentage (>85%) of glomeruli with crescents is implicated as a poor prognostic factor in Chinese patients with "double positive" disease.[6] Immunosuppressive therapy and plasmapheresis are the standard treatment strategy in management of RPGN. But, advocacy of an aggressive immunosuppressive therapy versus more conservative treatment should be taken into consideration of the above-mentioned poor prognostic factors. This strategy would not put the poor renal survival patients at a risk of excessive immunosuppression.

Conflicts of interest

All contributing authors declare no conflicts of interest.

References

1. O'Donoghue DJ, Short CD, Brenchley PE, Lawler W, Ballardie FW. Sequential development of systemic vasculitis with anti-neutrophil cytoplasmic antibodies complicating anti-glomerular basement membrane disease. *Clin Nephrol* 1989; **32**:251–5.

2. Jayne DR, Marshall PD, Jones SJ, Lockwood CM. Autoantibodies to GBM and neutrophil cytoplasm in rapidly progressive glomerulonephritis. *Kidney Int* 1990;**37**:965—70.
3. Chen PS, Chi H, Huang FY, Peng CC, Chen MR, Chiu NC. Clinical manifestations of Kawasaki disease shock syndrome: a case-control study. *J Microbiol Immunol Infect* 2015;**48**:43—50.
4. Bosch X, Mirapeix E, Font J, Borrellas X, Rodriguez R, López-Soto A, et al. Prognostic implication of anti-neutrophil cytoplasmic autoantibodies with myeloperoxidase specificity in anti-glomerular basement membrane disease. *Clin Nephrol* 1991;**36**(3):107—13.
5. Levy JB, Hammad T, Coulthart A, Dougan T, Pusey CD. Clinical features and outcome of patients with both ANCA and anti-GBM antibodies. *Kidney Int* 2004;**66**:1535—40.
6. Zhao J, Yang R, Cui Z, Chen M, Zhao MH, Wang HY. Characteristics and outcome of Chinese patients with both anti-neutrophil cytoplasmic antibody and antiglomerular basement membrane antibodies. *Nephron Clin Pract* 2007;**107**:c56—62.
7. Chan PS, Leung MH. Sequential occurrence of anti-glomerular basement membrane disease 9 years after anti-neutrophil cytoplasmic antibody-associated vasculitis. *Oxf Med Case Rep* 2016;**2016**:91—3.
8. Almouradi T, Hart P, Muram-Zborovski T. An 80-year-old female with double positive disease: case report and brief review of literature. *Am J Case Rep* 2013;**14**:30—3.
9. Nakabayashi K, Fujioka Y, Arimura Y, Fukuoka T, Marumo T, Umino M, et al. Anti-glomerular basement membrane (anti-GBM) disease accompanied by vasculitis that was not positive for antineutrophil cytoplasmic antibodies to myeloperoxidase and proteinase 3: a report of two cases and the incidence of anti-GBM disease at one institution. *Clin Exp Nephrol* 2011;**15**:504—13.
10. De Zoysa J, Taylor D, Thein H, Yehia M. Incidence and features of dual anti-GBM-positive and ANCA-positive patients. *Nephrology (Carlton)* 2011;**16**:725—9.
11. Serratrice J, Chiche L, Dussol B, Granel B, Daniel L, Jego-Desplat S, et al. Sequential development of perinuclear ANCA-associated vasculitis and anti-glomerular basement membrane glomerulonephritis. *Am J Kidney Dis* 2004;**43**:e26—30.
12. Verburgh CA, Bruijn JA, Daha MR, van Es LA. Sequential development of anti-GBM nephritis and ANCA-associated Pauci-immune glomerulonephritis. *Am J Kidney Dis* 1999;**34**:344—8.

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