A case of PR3–ANCA-positive anti-GBM disease associated with intrarenal arteritis and thrombotic microangiopathy

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Abstract Coexistence of anti-glomerular basement membrane (anti-GBM) disease with anti-neutrophil cytoplasmic antibody (ANCA) is occasionally reported and termed “double positive” disease. Interestingly, the majority of “double positive” ANCA is myeloperoxidase (MPO)–ANCA, and some of the MPO–ANCA-positive cases reveal intrarenal arteritis indicating an ANCA-associated renal lesion. In contrast, proteinase 3 (PR3)–ANCA-positive “double positive” disease had rarely been reported, and as far as we know, none of the cases showed intrarenal arteritis. Herein, we report a case of PR3–ANCA-positive “double positive” anti-GBM disease presenting with pulmonary-renal syndrome and hemolytic uremic syndrome. The kidney biopsy showed crescentic glomerulonephritis, intrarenal arteritis, and thrombotic microangiopathy. This case newly describes PR3–ANCA-associated intrarenal arteritis in “double positive” anti-GBM disease.

Keywords Anti-glomerular basement membrane disease · Proteinase 3-anti-neutrophil cytoplasmic antibody · Double positive disease · Pulmonary-renal syndrome · Intrarenal arteritis · Thrombotic microangiopathy

Introduction

Anti-glomerular basement membrane (anti-GBM) disease and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis are two major causes of pulmonary-renal syndrome, which is characterized by rapidly progressive glomerulonephritis and diffuse alveolar hemorrhage [1, 2]. Anti-GBM disease is caused by autoantibody against glomerular and alveolar basement membrane, and is pathologically distinct from arteritis [1]. However, anti-GBM disease accompanied by arteritis was reported soon after the establishment of the concept of anti-GBM disease [2, 3], and after the generalization of ANCA assay, a substantial proportion (21.2–45.8%) of anti-GBM disease has been found to be positive for ANCA (Table 1) [4–11]. Therefore, ANCA is supposed to be responsible for the arteritis accompanied anti-GBM disease, and ANCA-positive anti-GBM disease is termed “double positive” disease.

Interestingly, the specific ANCA-type positive in “double positive” disease is almost always myeloperoxidase (MPO)–ANCA for unknown reason (68.4–100%; Table 1) [4–11], while proteinase 3 (PR3)–ANCA-positive “double positive” disease has been seldom reported [12–18]. Some MPO–ANCA-positive cases reveal intrarenal arteritis, which is histological observation theoretically specific for ANCA in “double positive” disease [19, 20]. In contrast, as far as we know, none of the PR3–ANCA-positive “double positive” disease has been reported with kidney biopsy-proven arteritis. Taken together, while MPO–ANCA is supposed to be involved in the renal pathogenesis of “double positive” disease, the significance of PR3–ANCA in “double positive” disease remains ambiguous.

Here, we report a PR3–ANCA-positive “double positive” disease presented with pulmonary-renal syndrome

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Table 1 Types of ANCA-positive in “double positive” anti-GBM diseases

No. of anti-GBM diseases	No. of “double positive” diseases (%)	Types of positive ANCA	Region	References
160	34 (21.2)	MPO; 25, PR3; 3	Europe	[4]
100	38 (38.0)	MPO; 25, MPO + PR3; 1, PR3; 12	North America	[5]
79	29 (36.7)	MPO; 25, PR3; 4	Europe	[6]
121	27 (22.3)	MPO; 22, MPO + PR3; 4, PR3; 1	Europe	[7]
24	11 (45.8)	MPO; 10, PR3; 1	Europe	[8]
205	63 (30.7)	MPO; 57, MPO + PR3; 4, PR3; 2	Asia	[9]
16	4 (25)	MPO; 4, PR3; 0	Asia	[10]
30	8 (26.6)	MPO; 8, PR3; 0	Europe	[11]

ANCA anti-neutrophil cytoplasmic antibody, GBM glomerular basement membrane, MPO myeloperoxidase, PR3 proteinase 3

and hemolytic uremic syndrome. Kidney biopsy revealed crescentic glomerulonephritis with linear immunoglobulin G deposition, intrarenal arteritis, and thrombotic microangiopathy. This case newly describes PR3-ANCA-associated intrarenal arteritis in “double positive” disease.

Case report

Clinical history and laboratory data (Table 2)

A 59-year-old Asian single-living man was transported to our emergency department with an altered level of consciousness and hemoptysis. The patient had experienced

low-grade fever and general malaise for 4 months and revealed weight loss from 73 to 50 kg. Urine output had decreased for a few days. A few hours prior to the presentation, he had experienced progressive deterioration of general malaise and asked his relatives for help. They found the patient collapsed and coughing up blood and called for emergency assistance.

On presentation, his vital signs were as follows: Glasgow Coma Scale, 7 (1 for eyes, 2 for verbal, 4 for motor score); body temperature, 35.8 °C; blood pressure, 130/70 mmHg; pulse rate, 103/min; respiratory rate, 24/min; and arterial oxygen partial pressure on room air; 41.8 mmHg. Physical examination revealed conjunctival pallor, bilateral coarse rales, and decreased skin turgor.

Table 2 Laboratory findings on admission

Hematology			Biochemistry			Serology		
White blood cells	8.7×	10 ³ /μL	Total Protein	6.7	G/dL	Immunoglobulin G	1786	Mg/dL
Red blood cells	1.75×	10 ⁶ /μL	Blood urea nitrogen	321.7	mg/dL	Immunoglobulin A	355	mg/dL
Hemoglobin	4.5	g/dL	Creatinine	38.77	mg/dL	Immunoglobulin M	14	mg/dL
Hematocrit	15.3	%	Uric Acid	22.3	mg/dL	Anti-streptolysin O	445	IU/mL
Platelets	4.5×	10 ⁴ /μL	Sodium	143	mEq/L	Rheumatoid factor	14	IU/mL
Blood gas analysis			Potassium	7.8	mEq/L	Anti-neuclear antibody	<40	
pH	7.182		Chloride	101	mEq/L	MPO-ANCA	<10	EU/mL
pO ₂	41.8	mmHg	Calcium	7.2	mg/dL	PR3-ANCA	133	EU/mL
pCO ₂	18.2	mmHg	Phosphate	8.7	mg/dL	Anti-GBM-antibody	291	EU/mL
HCO ₃ ⁻	6.6	mmol/L	Lactate dehydrogenase	555	U/L	C3	78.1	mg/dL
Coagulation			Aspartate transaminase	14	U/L	C4	29.5	mg/dL
PT-INR	1.32		Alanine transaminase	11	U/L	ADAMTS-13	19.8	%
Fibrinogen	363	mg/dL	C reactive protein	6.46	mg/dL	ADAMTS-13 inhibitor	<0.5	BU/mL
D-dimer	6.99	μg/ml	Procalcitonin	7.24	ng/mL	Haptoglobin	12	mg/dL
Urinalysis			Iron	16	μg/dL			
RBC sediment	>100	HPF	TIBC	133	μg/dL			
UPCR	13.5	g/gCr	Ferritin	1642	ng/mL			

RBC red blood cell, UPCR urinary protein creatinine ratio, TIBC total iron binding capacity, CH50 total complement activity, MPO-ANCA myeloperoxidase-anti-neutrophil cytoplasmic antibody, PR3 proteinase-3, GBM anti-glomerular basement membrane, ADAMTS-13 a disintegrin and metalloprotease with thrombospondin type-1 repeats, member 13

Fig. 1 **a** Clinical course after admission. **b** Chest radiography (white arrows): (B1) on admission: pulmonary infiltrate with right lung field dominance and (B2) hospital day 18: resolution of pulmonary infiltration without nodular lesions or interstitial fibrosis. **c** Computed tomography of the chest (gray arrows): (C1) on admission: bilateral

ground-glass opacification and (C2) hospital day 8: widespread consolidation and mediastinal emphysema. *GBM* glomerular basement membrane, *PR3-ANCA* proteinase 3-anti-neutrophil cytoplasmic antibody, *CRP* C reactive protein, *PCT* procalcitonin, *Plt* platelets

There was no skin rash or arthritis. Complete blood count revealed severe anemia associated with thrombocytopenia, and blood smear showed a large number of schistocytes. Blood chemistry revealed renal dysfunction associated with life-threatening hyperkalemia. The titer of anti-streptolysin O was elevated, and blood culture revealed *Streptococcus pyogenes*. Immunological studies revealed normal levels of immunoglobulins and complements, and negative anti-nuclear antibody and MPO-ANCA. In addition, the titer of PR3-ANCA and anti-GBM antibody was highly elevated. A disintegrin and metalloprotease with thrombospondin type-1 repeats, member 13 (ADAMTS-13) activity, were mildly decreased with no ADAMTS-13 inhibitor. Urinalysis revealed massive hematuria with red cell casts and a total protein-to-creatinine ratio of 13.5 g/gCr. Chest radiograph revealed infiltrative shadows in the right lung field without nodular lesion (Fig. 1b1). Computed tomography scan of the chest revealed bilateral consolidation interspersed with ground-glass attenuation

consistent with diffuse alveolar hemorrhage (Fig. 1c1), and the diagnosis of alveolar hemorrhage was confirmed by subsequent bronchoscopy.

Clinical course after admission (Fig. 1a)

The diagnoses of pulmonary-renal syndrome, hemolytic uremic syndrome, and sepsis were made, and the patient urgently implemented continuous renal replacement therapy and antibiotics. The day after admission, respiratory failure deteriorated, and the patient required mechanical ventilation. Since anti-GBM antibody and PR3-ANCA became evident on hospital day 4, plasma exchange (PEX) treatment was initiated. While PEX treatment effectively reduced the anti-GBM antibody and PR3-ANCA titers, alveolar hemorrhage and thrombocytopenia were not sufficiently resolved. Urgent methylprednisolone pulse therapy was considered; however, because of the concomitant sepsis, we elected to repeat PEX treatment. The alveolar

Fig. 2 Kidney biopsy findings. **a** Glomeruli revealing circumferential cellular crescents (*lower right*) and cellular crescents with ruptured Bowman's capsule (*upper left*; PAM staining $\times 100$). **b** Immunofluorescent evaluation revealing linear immunoglobulin G deposition. **c** Globally sclerosed glomeruli with Bowman's space segmentally occupied by acellular fibrous tissue (PAS staining $\times 200$). **d, g** An intrarenal arteriole with fibrin deposition and disruption of the internal

elastic lamina (**d**; Elastica-Masson staining $\times 200$, **f** immune histochemical staining for fibrinogen). **e** Intrarenal arteriole with mild fibrin deposition, partial distortion of the internal elastic lamina, and endothelial swelling with narrowing of the lumen (Elastica-Masson staining $\times 200$). **f** Interstitium with hemosiderin deposits (HE staining $\times 100$)

hemorrhage gradually worsened (Fig. 1c2), and a 3-day course of methylprednisolone 1-g pulse therapy was initiated on hospital day 8. The alveolar hemorrhage and thrombocytopenia improved after the initiation of corticosteroid therapy, and a kidney biopsy was performed to confirm the diagnosis of pulmonary-renal syndrome and hemolytic uremic syndrome.

Kidney biopsy findings

The kidney biopsy specimen contained 22 glomeruli with 6 globally sclerotic glomeruli. Most of the remaining glomeruli revealed circumferential cellular crescents (Fig. 2a), and some showed tuft necrosis and rupture of Bowman's capsules (Fig. 2a). Immunofluorescent examinations of glomeruli revealed linear deposition of immunoglobulin G (Fig. 2b), and electron microscopic examination excluded electron-dense deposition. The globally sclerotic glomeruli revealed segmental occupation of Bowman's space (Fig. 2c). Some arterioles revealed arteritis with fibrin

deposition and disruption of the internal elastic lamina (Fig. 2d, g). Other arterioles revealed mild fibrin deposition, partial distortion of the internal elastic lamina, and endothelial swelling with luminal narrowing (Fig. 2e). Interstitial necrotizing granulomatous inflammation was not detected. Hemosiderin was scattered in the interstitium (Fig. 2f). Based on these findings, we diagnosed the patient with anti-GBM disease associated with intrarenal arteritis and thrombotic microangiopathy.

Clinical course after diagnosis (Fig. 1a)

The patient was weaned from mechanical ventilation after the 3-day course of methylprednisolone pulse therapy, and oral prednisolone of 40 mg per day was continued. Clinical symptoms, except for anuric renal failure, showed improvement and chest radiography revealed resolution without interstitial fibrosis (Fig. 1b2). Although dialysis treatment in outpatient setting was required, the patient was discharged in a good general physical status. We

administered intravenous cyclophosphamide 500 mg one month after, continued every month for three treatments, and then additional three treatments at 3-month intervals. Oral prednisolone was successfully reduced to 5 mg per day without any disease recurrence.

Discussion

The significance of ANCA in “double positive” disease has been widely examined, and several differences between “double positive” anti-GBM disease and “pure” anti-GBM disease have been evident. First, susceptible age of “double positive” disease is greater than “pure” anti-GBM disease, resembling ANCA-associated vasculitis [5–9]. This feature is proposed as sequential sensitization of GBM antigen following glomerular basement membrane destruction via ANCA-associated vasculitis, and the hypothesis is supported by cases showing positive conversion of anti-GBM antibody following ANCA-associated vasculitis [5, 8, 20–22]. Second, “double positive” disease

has a higher risk of relapse than “pure” anti-GBM disease [1, 8, 11]. This is supposed to be associated with disease nature that anti-GBM disease as a generally non-relapsing disease [1], while ANCA-associated vasculitis carries significant risk of relapse [2]. Third, one-third of “double positive” disease shows intrarenal arteritis, which is a histological observation theoretically specific for ANCA in “double positive” disease [7]. Considering these evidences, ANCA is supposed to have a critical role in “double positive” disease. However, all these knowledge are based on MPO-ANCA-positive “double positive” disease, and the significance of PR3-ANCA in anti-GBM disease remains largely unknown.

In contrast to MPO-ANCA-positive “double positive” disease, as far as we know, only 7 PR3-ANCA-positive cases are reported in detail (Table 3) [12–18]. All cases revealed crescentic glomerulonephritis with linear IgG deposition, while intrarenal arteritis was not documented; renal histology specific for PR3-ANCA in “double positive” disease was not evident in previously reported cases. Since intrarenal arteritis is only detectable in one-fourth of

Table 3 PR3-ANCA-positive “double positive” anti-GBM diseases

Age sex	Clinical presentation at biopsy (diagnosis)	Biopsy site	Kidney biopsy findings	Arteritis	Concomitant infection	Treatment	Outcome	References
68 M	RPGN (anti-GBM disease)	Kidney	CGN Linear IgG deposition	ND	Sepsis (<i>Staphylococcus aureus</i>)	CS, Cy, PEX	Sepsis Death	[12]
68 F	RPGN (anti-GBM disease)	Kidney	CGN Linear IgG deposition	ND	NTM (<i>Mycobacterium avium</i>)	CS	ICH Death	[13]
86 M	1st RPGN (anti-GBM disease) 2nd PRS (GPA)	1st Kidney 2nd Skin	CGN Linear IgG deposition	ND		CS, Cy, PEX	Death	[14]
60 M	1st hematuria (RLV) 2nd RPGN (anti-GBM disease)	1st Kidney 2nd Kidney	1st pauci-immune CGN 2nd CGN, Linear IgG deposition	ND	Pneumonia	CS, Cy, AZA	Remission	[15]
73 F	RPGN, Pulmonary nodule (GPA and anti-GBM disease)	Kidney Lung	CGN Linear IgG deposition	Lung		CS, Cy	ICH Death	[16]
50 F	PRS (GPA and anti-GBM disease)	1st Skin 2nd Kidney	CGN Linear IgG deposition	Skin	HCV carrier	CS, Cy, PEX	Remission	[17]
32 M	PRS (anti-GBM disease)	Kidney	CGN Linear IgG deposition	ND	Pulmonary tuberculosis (<i>Mycobacterium tuberculosis</i>)	CS, Cy, PEX	Remission	[18]
59 M	PRS (MPA and anti-GBM disease)	Kidney	CGN Intrarenal arteritis Linear IgG deposition	Kidney	Sepsis (<i>streptococcus pyogenes</i>)	CS, Cy, PEX	Remission	Present case

M male, F female, RPGN rapidly progressive glomerulonephritis, CGN crescentic glomerular nephritis, ND not detected, CS Corticosteroid, Cy cyclophosphamide, PEX plasma exchange, ICH intracerebral hemorrhage, AZA azathioprine, PRS pulmonary-renal syndrome, GPA granulomatosis with polyangiitis, RLV renal limited vasculitis, MPA microscopic polyangiitis

“pure” ANCA-associated glomerulonephritis [23], this accumulation of intrarenal arteritis negative cases supposed to be a coincidence. However, there remains a slight possibility that the PR3–ANCA was false-positive in “double positive” disease.

The prevalence of false-positive PR3–ANCA, which is serologically positive PR3–ANCA without vasculitic disease, is higher than previously expected; 9.7–24.3% of PR3–ANCA positivity [24, 25]. False-positive cases are associated with autoimmune diseases, malignancies, and infections, such as *Staphylococcus aureus* endocarditis and mycobacterial infection [24, 25]. Among the PR3–ANCA-positive “double positive” disease, 3 cases had these particular infections, *S. aureus* septicemia [12] and mycobacterium infection [13, 18], indicating false-positive PR3–ANCA. In contrast to these cases, our case newly describes PR3–ANCA-associated intrarenal arteritis, renal histology specific for PR3–ANCA, in “double positive” disease.

The present case revealed some histological signs suggestive of ANCA-associated vasculitis in addition to the arteritis. Glomerular lesions revealed different phases of crescentic glomerulonephritis which are less commonly seen in “pure” anti-GBM disease [26], including highly active circumferential cellular crescents (Fig. 2a) and global sclerosis with segmental occupation of Bowman’s space (Fig. 2c). Interstitium revealed hemosiderin deposits (Fig. 2f), which reflect old interstitial hemorrhage [2]. In contrast, interstitial granulomatous lesion, rare but characteristic lesion of ANCA positivity [23], was not detected. We speculate that these renal histological findings are consistent with the clinical history of 4-month preceding physical symptoms culminating in sudden-onset alveolar hemorrhage and anuric renal failure. Chest radiographs showing neither nodular lesions nor pulmonary fibrosis (Fig. 1b2) also support that alveolar hemorrhage as pulmonary lesion of anti-GBM disease. Taken together, the renal PR3–ANCA-associated vasculitis might precede and subsequently develop pulmonary-renal syndrome via anti-GBM antibody in the present case. While MPO–ANCA-associated vasculitis are the majority of glomerular disease preceding anti-GBM disease, IgA nephritis [20], membranous nephropathy [20], and PR3–ANCA-associated vasculitis [15] cases are also reported to precede anti-GBM disease. Moreover, subclinical elevations of MPO–ANCA and PR3–ANCA titer are reported to evoke anti-GBM disease [27]. These suggest that PR3–ANCA-associated vasculitis might cause sequential development of anti-GBM disease.

The present case also revealed hemolytic uremic syndrome and thrombotic microangiopathy resolved by the intensive treatment. They concurrently occur in autoimmune diseases [28], and several cases associated with

ANCA-associated vasculitis [29], “pure” anti-GBM antibody disease, and “double positive” disease have been reported [30]. In most of these cases, as well as present case, ADAMTS-13 activity is moderately decreased and the ADAMTS-13 inhibitor is negative [28–30]. Therefore, hemolytic uremic syndrome and thrombotic microangiopathy are supposed to develop following severe vascular endothelial damage [29]. In the present case, typical arteriolar and/or glomerular intracapillary thrombosis was a seldom detected. However, while it was difficult to clearly distinguish thrombotic microangiopathy from arteritis, the swelling of endothelial cells with narrowing of the arteriolar lumen (Fig. 2f) was compatible with associated thrombotic microangiopathy [29]. Because of the concurrent sepsis, we initially performed PEX treatment. The PEX treatment reduced the anti-GBM antibody and PR3–ANCA titers, as expected; the resolution of hemolytic uremic syndrome was not achieved until the initiation of corticosteroid therapy.

In conclusion, while MPO–ANCA is the majority of ANCA in “double positive” disease, the present case revealed that PR3–ANCA also plays a significant role in “double positive” disease. When anti-GBM disease is contracted, accompanied by intrarenal arteritis, evaluation of coexisting PR3–ANCA, not only MPO–ANCA, is required.

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Compliance with ethical standards

Conflict of interest We have no financial or other supports and no conflict of interest.

Research involving human participants The study is carried out in accordance with the Helsinki Declaration of 1964.

Privacy protection for the patient To protect the patient privacy, identifying information including names, initials, or hospital numbers, are not described in manuscript and figures.

References

1. Pusey CD. Anti-glomerular basement membrane disease. *Kidney Int.* 2003;64:1535–50.
2. Gómez-Puerta JA, Bosch X. Anti-neutrophil cytoplasmic antibody pathogenesis in small-vessel vasculitis: an update. *Am J Pathol.* 2009;175:1790–8.
3. Nakabayashi K, Fujioka Y, Arimura Y, 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.
4. Short AK, Esnault VL, Lockwood CM, et al. Anti-neutrophil cytoplasm antibodies and anti-glomerular basement membrane

- antibodies: two coexisting distinct autoreactivities detectable in patients with rapidly progressive glomerulonephritis. *Am J Kidney Dis.* 1995;26:439–45.
5. Hellmark T, Niles JL, Collins AB, et al. Comparison of anti-GBM antibodies in sera with or without ANCA. *J Am Soc Nephrol.* 1997;8:376–85.
 6. Segelmark M, Hellmark T, Wieslander J. The prognostic significance in Goodpasture's disease of specificity, titre and affinity of anti-glomerular-basement-membrane antibodies. *Nephron Clin Pract.* 2003;94:c59–68.
 7. Levy JB, Hammad T, Coulthart A, et al. Clinical features and outcome of patients with both ANCA and anti-GBM antibodies. *Kidney Int.* 2004;66:1535–40.
 8. Rutgers A, Slot M, van Paassen P, et al. Coexistence of anti-glomerular basement membrane antibodies and myeloperoxidase-ANCAs in crescentic glomerulonephritis. *Am J Kidney Dis.* 2005;46:253–62.
 9. Yang R, Hellmark T, Zhao J, et al. Antigen and epitope specificity of anti-glomerular basement membrane antibodies in patients with goodpasture disease with or without anti-neutrophil cytoplasmic antibodies. *J Am Soc Nephrol.* 2007;18:1338–43.
 10. Kitagawa W, Imai H, Komatsuda A, et al. The HLA-DRB1*1501 allele is prevalent among Japanese patients with anti-glomerular basement membrane antibody-mediated disease. *Nephrol Dial Transplant.* 2008;23:3126–9.
 11. Lindić J, Vizjak A, Ferluga D, et al. Clinical outcome of patients with coexistent antineutrophil cytoplasmic antibodies and antibodies against glomerular basement membrane. *Ther Apheresis Dial.* 2009;13:278–81.
 12. Neary P, Kadlubowski M, Thomson D, et al. Antiglomerular basement membrane disease with cANCA positivity without pulmonary involvement. *Nephrol Dial Transplant.* 1996;11:693–5.
 13. Kalluri R, Meyers K, Mogyrosi A, et al. Goodpasture syndrome involving overlap with Wegener's granulomatosis and anti-glomerular basement membrane disease. *J Am Soc Nephrol.* 1997;8:1795–800.
 14. Desai A, Goldschmidt RA, Kim GC. Sequential development of pulmonary renal syndrome associated with c-ANCA 3 years after development of anti-GBM glomerulonephritis. *Nephrol Dial Transplant.* 2007;22:926–9.
 15. Andrassy M, Sis J, Waldherr R, et al. The patient with C-ANCA/PR3-ANCA-positive crescentic pauci-immune glomerulonephritis and recurrence of nephritic sediment. *Nephrol Dial Transplant.* 2008;23:2084–7.
 16. Clyne S, Frederick C, Arndt F, et al. Concurrent and discrete clinicopathological presentations of Wegener granulomatosis and anti-glomerular basement membrane disease. *Am J Kidney Dis.* 2009;54:1116–20.
 17. Mulpuru S, Touchie C, Karpinski J, et al. Coexistent Wegener's granulomatosis and Goodpasture's disease. *J Rheumatol.* 2010;37:1786–7.
 18. Waqar K, Sonia Y, Syed FM. Double positive Goodpasture's syndrome with Concomitant Active Pulmonary Tuberculosis. *Saudi J Kidney Dis Transpl.* 2013;24:783–8.
 19. Arimura Y, Minoshima S, Kamiya Y, et al. A case of Goodpasture's syndrome associated with anti-myeloperoxidase antibodies. *Intern Med.* 1992;31:239–43.
 20. Serratrice J, Chiche L, Dussol B, et al. Sequential development of perinuclear ANCA-associated vasculitis and anti-glomerular basement membrane glomerulonephritis. *Am J Kidney Dis.* 2004;43:e26–30.
 21. Verburgh CA, Bruijn JA, Daha MR, et al. Sequential development of anti-GBM nephritis and ANCA-associated Pauci-immune glomerulonephritis. *Am J Kidney Dis.* 1999;34:344–8.
 22. O'Connor K, Fulcher D, Phoon RK. Development of anti-glomerular basement membrane disease after remission from perinuclear ANCA-associated glomerulonephritis in a patient with HLA susceptibility. *Am J Kidney Dis.* 2010;55:566–9.
 23. Vizjak A, Rott T, Koselj-Kajtna M, et al. Histologic and immunohistologic study and clinical presentation of ANCA-associated glomerulonephritis with correlation to ANCA antigen specificity. *Am J Kidney Dis.* 2003;41:539–49.
 24. Knight A, Ekblom A, Brandt L, et al. What is the significance in routine care of c-ANCA/PR3-ANCA in the absence of systemic vasculitis? A case series. *Clin Exp Rheumatol.* 2008;26:S53–6.
 25. McAdoo SP, Hall A, Levy J, et al. Proteinase-3 antineutrophil cytoplasm antibody positivity in patients without primary systemic vasculitis. *J Clin Rheumatol.* 2012;18:336–40.
 26. Kluth DC, Rees AJ. Anti-glomerular basement membrane disease. *J Am Soc Nephrol.* 1999;10:2446–53.
 27. Olson SW, Arbogast CB, Baker TP, et al. Asymptomatic autoantibodies associate with future anti-glomerular basement membrane disease. *J Am Soc Nephrol.* 2011;22:1946–52.
 28. Matsuyama T, Kuwana M, Matsumoto M, et al. Heterogeneous pathogenic processes of thrombotic microangiopathies in patients with connective tissue diseases. *Thromb Haemost.* 2009;102:371–8.
 29. Chen SF, Wang H, Huang YM, et al. Clinicopathologic characteristics and outcomes of renal thrombotic microangiopathy in anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis. *Clin J Am Soc Nephrol.* 2015;10:750–8.
 30. Watanabe H, Kitagawa W, Suzuki K. Thrombotic thrombocytopenic purpura in a patient with rapidly progressive glomerulonephritis with both anti-glomerular basement membrane antibodies and myeloperoxidase anti-neutrophil cytoplasmic antibodies. *Clin Exp Nephrol.* 2010;14:598–601.