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【 CASE REPORT 】

Anti-glomerular Basement Membrane Disease with Antiphospholipid Syndrome

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Abstract:
A 48-year-old woman presented with a fever, microscopic hematuria, proteinuria, and rapid deterioration of the renal function. Pulmonary alveolar hemorrhaging and a high level of anti-glomerular basement membrane (GBM) antibodies (700 IU/mL) were observed. Based on her medical history and positive findings of serum lupus anticoagulant, anti-phospholipid antibody syndrome (APS) was suspected. A renal biopsy revealed cellular crescentic glomerulonephritis with thrombosis, suggesting anti-GBM disease with catastrophic APS. The patient was treated with pulse steroid therapy, plasma exchange, hemodialysis, and intravenous cyclophosphamide pulse therapy. To our knowledge, this is the first report of a patient with anti-GBM disease and APS.

Key words: anti-glomerular basement membrane disease, antiphospholipid syndrome, APS nephropathy, thrombotic microangiopathy, rapidly progressive glomerulonephritis

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Introduction

Anti-glomerular basement membrane (GBM) disease is a rare, life-threatening, small-vessel vasculitis in which circulating antibodies are directed against an antigen intrinsic to the GBM. Since both glomerular and pulmonary capillaries are injured by the antibodies, rapidly progressive glomerulonephritis (RPGN) occurs through glomerular necrosis and crescent formation, in addition to alveolar hemorrhaging (1).

Similarly, antiphospholipid syndrome (APS) is a rare autoimmune disorder characterized by the presence of circulating antiphospholipid antibodies (aPLs), vascular thrombosis, hypercoagulability, and pregnancy-related complications (2). Catastrophic APS (CAPS) is a severe form of APS that is characterized by diffuse thrombotic microangiopathy (TMA) (3).

Although there have been case reports of anti-GBM disease complicated with other diseases, such as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (4), membranous nephropathy (MN) (5), and immunoglobulin A (IgA) nephropathy (6), there have been no reports of cases of anti-GBM disease with APS.

We herein report a patient suffering from anti-GBM disease with APS who presented with RPGN, pulmonary hemorrhaging, TMA, and posterior reversible encephalopathy syndrome (PRES).

Case Report

A 48-year-old woman visited her physician with a complaint of a fever (temperature: 39℃) and was prescribed medications for the common cold. She revisited her physician one week later because the fever persisted. A blood examination and urine test revealed a white blood cell (WBC) count of 9,800/μL, C-reactive protein (CRP) level of 12.8 mg/dL, serum creatinine (sCr) level of 0.8 mg/dL, and urinary occult blood count of 3+. The patient was suspected of having pyelonephritis, and 500 mg of levofloxacin (LVFX) was administered daily. Due to her persistent fever, general

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Table. Laboratory Date on Admission.

Hematological values		**Serum biochemistry**		**Immunological studies**	
White blood cell count	12,600 /μL	Total protein	7 g/dL	C-reactive protein	26.1 mg/dL
Neutrophil	86 %	Albumin	2.5 g/dL	Complement 3	86.6 mg/dL
Lymphocyte	5 %	Aspartate amonotransferase	18 U/L	Complement 4	13.7 mg/dL
Monocyte	8 %	Alanine aminotransferase	13 U/L	Serum complement titer	33.1 U/mL
Eosinophil	1 %	Lactate dehydrogenase	194 U/L	Immunoglobulin G	2.068 mg/dL
Red blood cell count	325×10^4 /μL	Blood urea nitrogen	45 mg/dL	Immunoglobulin A	245 mg/dL
Hemoglobin	9.3 g/dL	Creatinine	5.37 mg/dL	Immunoglobulin M	45.8 mg/dL
Hematocrit	26.3 %	Uric acid	6.9 mg/dL	anti nuclear antibody	>1:160
Platelet count	45.6×10^4 /μL	Sodium	125 mEq/L	anti dsDNA antibody	11 U/mL
Urinalysis		Potassium	3.8 mEq/L	anti RNP antibody	21 U/mL
Protein	(1+)	Chloride	88 mEq/L	anti smith antibody	2.9 U/mL
Glucose	(-)	β2MG	11.99 μg/mL	anti SS-A antibody	118.7 U/mL
Occult blood	(3+)	**Venou blood gas**		anti SS-B antibody	17.4 U/mL
Red blood cell	>100 HPF	pH	7.42	anti Scl-70 antibody	2.8 U/mL
White blood cell	5~10 HPF	HCO_3^-	21.2 mmol/L	MPO-ANCA	<1.0 U/mL
Cast	RBS casts, granular casts	**Coagulation test**		PR3-ANCA	<1.0 U/mL
Urinary chemistry		PT-INR	1.24	anti GBM antibody (<7.0 U/mL)	700 U/mL
UP/UCr	1.27 g/gCr	APTT	45.0 s	anti-cardiolipin antibody	36 U/mL
Urinary β2MG	522 μg/L	FDP	19.8 μg/mL	Lupus anticoagulant	1.52 s
Urinary NAG	38.2 U/L	D-dimer	6.6 μg/mL	anti β2-GPI antibody	30 U/mL

HDL: high-density lipoprotein, HPF: high-power field, LDL: low-density lipoprotein, MCV mean corpuscular volume, MCHC: mean corpuscular hemoglobin concentration, RBC: red blood cell, UP/UCr: urinary protein/urinary creatinine ratio, β2MG: beta-2 microglobulin, NAG: N-acetyl-beta-D-glucosaminidase, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, FDP: fibrinogen degradation products, DNA: deoxyribonucleic acid, RNP: ribonucleoprotein, SS: Sjogren's syndrome, Scl: scleroderma, MPO: myeroperoxidase, PR3: proteinase 3, ANCA: antineutrophil cytoplasmic antibody, GBM: glomrular basement membrane, β2-GPI: beta-2-glycoprotein I

fatigue, vomiting, and gross hematuria despite five days of oral LVFX treatment, she was admitted to our hospital.

Although she had no history of kidney disease, her medical history revealed pregnancy-related complications (one spontaneous abortion and one stillbirth) and lower extremity venous thrombosis (for which oral aspirin was administered), which had not been investigated thoroughly before the admission. The laboratory tests on admission revealed findings of inflammation with an elevated WBC count of 12,600/μL and CRP level of 26.1 mg/dL. Her renal function had deteriorated rapidly, and the results of laboratory data were as follows: an sCr level of 5.37 mg/dL, blood urea nitrogen (BUN) level of 45 mg/dL, urinary protein creatinine ratio of 1.27 g/gCr, and urinary red blood cells (RBCs) > 100 cells /high power field; these results were consistent with the features of RPGN. A summary of the data on admission is shown in Table. On admission, her blood pressure (BP) was 107/89 mmHg, and her respiratory condition was stable. During the hospitalization, her BP was 110-120/70-80 mmHg without medications.

The patient's anti-GBM antibody titer was markedly elevated to 700 U/mL (normal range <7.0 U/mL), and computed tomography (CT) at admission showed bilateral renal swelling. In addition, ground-glass opacities, that suggested alveolar hemorrhaging, were observed in her right lung. Bronchoalveolar lavage (BAL) revealed alveolar hemorrhaging, leading to a diagnosis of anti-GBM disease. On the second day of admission, plasma exchange therapy (PEX) and pulse steroid therapy (methylprednisolone 1 g/day intravenously for 3 days) were initiated. From the second day of admission, aspirin was replaced with heparin. Hemodialysis therapy (HD) was started on the 4th day due to anuria, which had persisted from the day of admission. On the 8th day of admission, a sudden drop in her platelet (Plt) count (25,000 cells/μL) and anemia with associated schistocytes on the peripheral blood smear (Hb 6.2 g/dL) were observed. Furthermore, her levels of lactate dehydrogenase and D-dimer were 971 U/L and 17.5 ng/mL, respectively, and haptoglobin was <5 mg/dL. The patient was suspected of having TMA based on these findings.

Her BP was 154/110 mmHg, and her peripheral arterial oxygen saturation (SpO_2) was 90% on room air. In addition, she developed exacerbated alveolar hemorrhaging (Fig. 1), convulsions, an altered level of consciousness, and a reticular rash. She was therefore transferred to the intensive-care unit (ICU), and intravenous cyclophosphamide pulse therapy (IVCY, 350 mg/day) was administered.

Repeat plain CT revealed a reticular region of high absorbance, a notch on the left kidney, and suspected renal infarction. In addition, we were unable to exclude the possibility of microscopic cerebral infarction. Multiple organ dysfunction similar to CAPS could not be denied based on the presence of renal failure, convulsions, and respiratory status deterioration. Therefore, her condition was considered likely to be due to CAPS, and anticoagulation therapy was initiated. On the same day, heparin was replaced with nafamostat me-

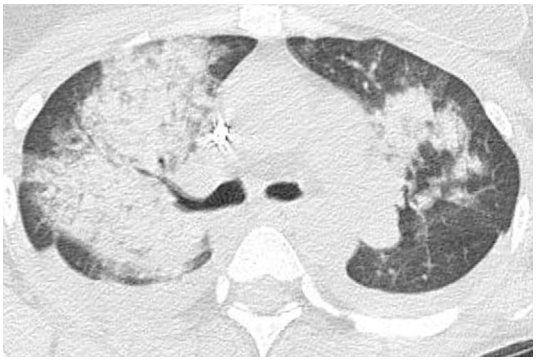


Figure 1. CT on the 8th day after admission showed diffusely distributed ground-glass opacities and severe alveolar hemorrhaging in both lung fields.

sylate, and continuous hemodiafiltration (CHDF) was initiated. Although there was the risk of her developing immune-mediated heparin-induced thrombocytopenia because of heparin therapy, no heparin-dependent antibodies were detected. Because of the severity of the alveolar hemorrhaging and the possibility of CAPS, Plt transfusion was performed to maintain a Plt count >50,000 cells/μL. Furthermore, RBC transfusions were conducted repeatedly when necessary.

Following convulsions, her BP increased to a maximum of 206/108 mmHg. Since reversible changes were observed on brain magnetic resonance imaging (MRI), she was diagnosed with PRES. Thereafter, her BP was controlled to approximately 130/80 mmHg with the administration of antihypertensive drugs.

In total, 6 and 3 courses of the IVCY (350 mg/day) and pulse steroid therapy were administered biweekly and weekly, respectively, followed by ongoing oral steroid therapy. After confirming a seronegative result for anti-GBM antibodies (6.4 U/mL) and improvement in TMA, PEX (36 cycles in total) was discontinued.

On day 15 of admission, the patient was discharged from the ICU, and a renal biopsy was performed on the 24th day of admission. Periodic acid Schiff (PAS) staining revealed the circumferential formation of cellular crescents in all glomeruli and fibrinoid necrosis associated with the rupture of Bowman's capsule in 11 of 20 glomeruli. Infiltration of inflammatory cells was similarly observed in the tubulointerstitium and peritubular capillaries. Erythrocytic casts and other cellular casts were observed in the urinary tubules, and vacuolar degeneration was noted in the tubular epithelium (Fig. 2A-C). Immunofluorescence (IF) revealed immunoglobulin G (IgG) and complement component 3 (C3) deposition in a linear pattern along the glomerular capillaries (Fig. 2F, G), and thrombi were observed in the arterioles (Fig. 2D, E). Electron microscopy revealed that the thrombi were amorphous, villous, and fluffy, with patchy electron-dense fluctuations (Fig. 2H). Based on the renal biopsy findings, the patient was diagnosed with anti-GBM disease and APS. In addition, her APS was considered to meet the criteria for CAPS because thrombosis was observed in the renal tissue.

No remarkable improvement was observed in her renal function despite the intensive treatments. CHDF was performed during the patient' stay in the ICU, and after leaving the ICU, three-times-weekly maintenance HD was provided owing to the persistent anuria. Therefore, a vascular shunt was created on the 28th day of admission. After confirming an improvement in the status of alveolar hemorrhaging and TMA, the anticoagulation therapy was switched to aspirin and oral warfarin (Fig. 3). She was diagnosed with APS based on the relevant criteria [lupus anticoagulant, anticardiolipin antibodies, and anticardiolipin β2-glycoprotein I (β2-GPI) antibodies] after discharge and experienced no recurrence during the follow-up period.

Discussion

The patient was diagnosed with anti-GBM disease and APS based on the clinical course, laboratory data, and renal biopsy findings. To our knowledge, this is the first reported case of anti-GBM disease with APS.

Anti-GBM disease was identified in this case based on the renal biopsy findings, such as crescent formation in all glomeruli and an IF pattern revealing a linear pattern of IgG and C3 in the basement membrane. The prevalence of pathological findings of the kidney in APS reportedly is as follows: arteriosclerosis (75%), fibrous intimal hyperplasia (75%), tubular thyroidization (75%), and TMA (31%) (7). According to a previous report, the types of glomerular lesions in APS vary among cases, such as MN, focal segmental glomerulosclerosis, and membranoproliferative glomerulonephritis, and the induction of a specific lesion by APS is caused by vascular endothelial injury (8). Unlike Plt/fibrin thrombi, the thrombi observed in APS nephropathy (APSN) are amorphous, villous, and fluffy with patchy electron-dense fluctuations on electron microscopy (9, 10). In the present case, APSN was established based on the thrombi observed by Masson's trichrome staining in addition to the thrombi with fluffy patches of fluctuating density on electron microscopy.

The present patient was also suspected of having CAPS. The reported preliminary classification criteria for CAPS are as follows: (i) Evidence of involvement of three or more organs, systems, and/or tissues; (ii) development of manifestations simultaneously or within a week; (iii) confirmation by histopathology of small vessel occlusion in at least one organ or tissue; and (iv) laboratory confirmation of the presence of aPLs (lupus anticoagulant and/or anticardiolipin antibodies). The definite diagnosis of CAPS requires meeting all four criteria, but probable CAPS is defined based on the following: (a) all four criteria except for the involvement of only two organs, systems, and/or tissues; (b) all four criteria except for the absence of laboratory confirmation at least six weeks apart due to the early death of a patient never tested for aPLs before the catastrophic APS; (c) criteria (i), (ii),

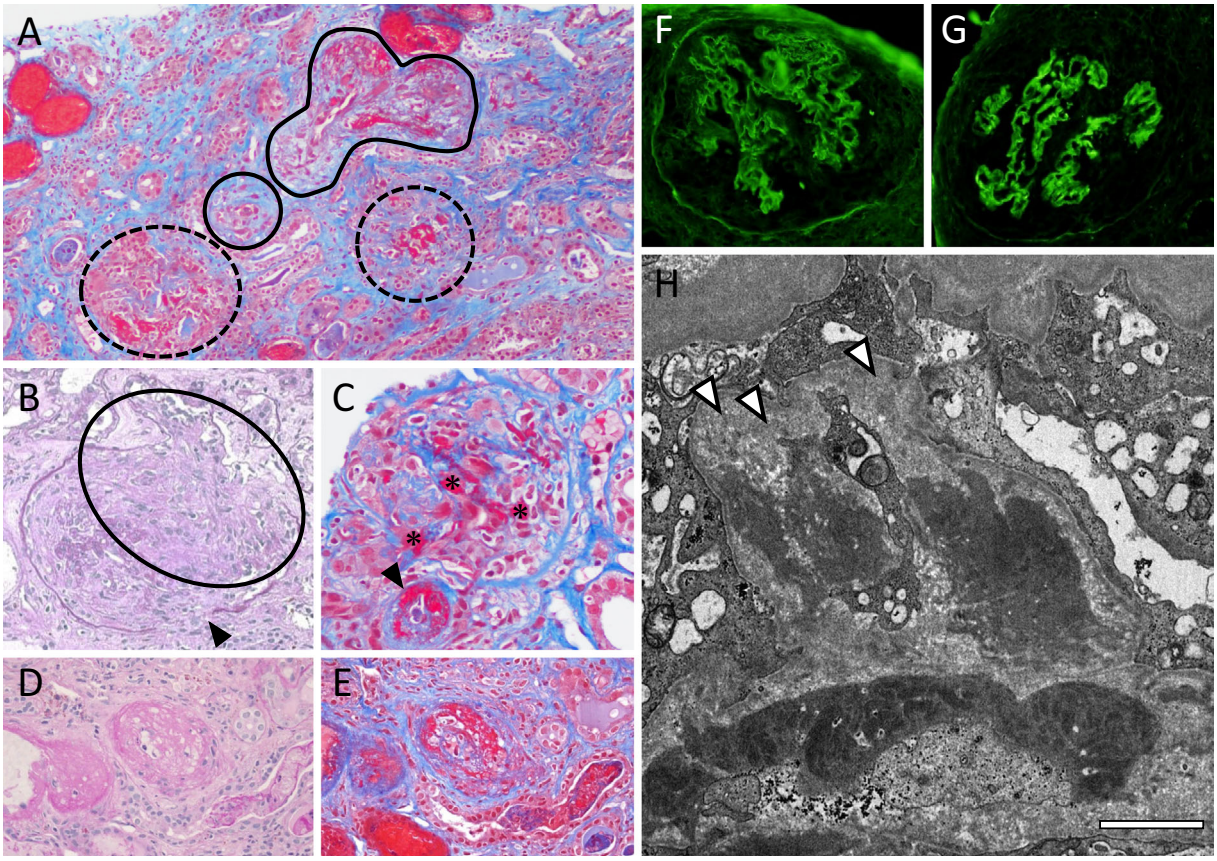
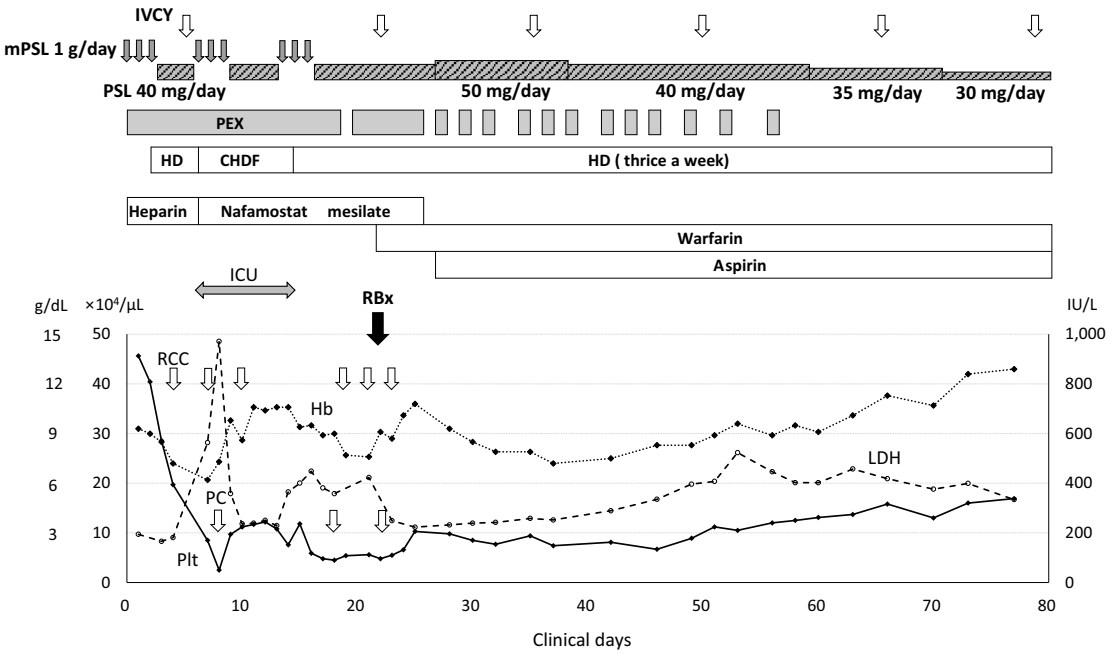


Figure 2. **A biopsy of the kidney. Light microscopic findings and electron microscopy. (A, C, and E) Masson trichrome staining, (B and D) Periodic acid–Schiff (PAS) staining, (F and G) Immunofluorescence staining of Immunoglobulin G (IgG) and complement component 3 (C3). (A) A cellular crescent with fibrinoid necrosis (black dotted circle); lesion of the arterioles with fibrinoid necrosis and luminal narrowing (area marked in black) (magnification ×100). (B) A glomerulus with fibrinoid necrosis, extravasation of fibrin, and rupture of Bowman's capsule (arrowheads), forming a cellular crescent (black circle) (magnification ×200). (C) Thrombosis of the afferent arteriole (arrowhead) and partial necrosis of the glomerulus with deposition of fibrin (*) and fragmented erythrocytes (magnification ×200). (D) and (E) the same arteriole (magnification ×400). Fibrin precipitation, edematous intimal thickening, and bleeding are apparent in the arterioles. Microthrombus formation is observed in the arteriolar lumen. Congestion of the peritubular capillaries is marked and widespread. (F) and (G) strong staining of IgG (F) and C3 (G) in a linear pattern along the glomerular basement membrane. (H) Electron microscopy findings (magnification ×4,000 scale bar: 2 μm). Thrombi are observed as fluffy and patchy electron density fluctuations associated with endothelial damage (arrowheads).**

and (iv); or (d) criteria (i), (iii), and (iv) and the development of a third event after over a week but within a month, despite anticoagulation therapy (11). CAPS damages multiple organs, such as the kidneys, lungs, brain, heart, and skin, at a high rate. The prevalence of organ failure was as follows: kidneys, via renal failure in 77%; lungs, via alveolar hemorrhaging in 12%; and brain, via convulsion in 15% (12). In the present case, probable CAPS was suspected based on the initial clinical symptoms (renal failure, respiratory status deterioration, and convulsions) and presence of aPLs. In addition, renal pathology showed thrombi; however, anti-GBM nephritis may have been involved in the renal failure and alveolar hemorrhaging. The convulsions spontaneously attenuated, and the abnormal signal on brain MRI disappeared. Therefore, the patient was diagnosed with PRES. Similarly, PRES has been reported as a potential complication of CAPS (13). Although the aforementioned four diagnostic criteria were satisfied, not only CAPS but also anti-GBM disease or high blood pressure were considered potential causes of the multiple organ disorders. Thus, it was difficult to establish the diagnosis of CAPS.

Given the present patient's history of deep vein thrombosis and recurrent pregnancy loss, this patient had supposedly suffered from APS before admission. Supporting evidence regarding the complication of APS with anti-GBM disease is unavailable. The patient had no history of infection or exposure to organic solvents that could have triggered anti-GBM disease. The complication of these two diseases might have



Anti GBM antibody (U/mL)	700	551.6	109.6	85.5	34.6	23.9	16.3	8.4	6.4	9.0		7.6
Hpt (mg/dL)	98.6	<5	62.7	6.7	108.2		92.4			69.5		94.8
CRP (mg/dL)	26.1	11.6	6.2	2.1	4.4	1.4	2.3	1.3	0.9	0.7	0.5	0.4

Figure 3. Clinical course. The time course of this patient is shown. IVCY: intravenous cyclophosphamide pulse therapy, mPSL: methylprednisolone, PSL: prednisolone, PEX: plasma exchange therapy, HD: hemodialysis, CHDF: continuous hemodiafiltration, Plt: platelet, Hb: hemoglobin, LDH: lactate dehydrogenase, GBM: glomerular basement membrane, Hpt: haptoglobin, CRP: C-reactive protein, ICU: intensive-care unit, RBx: renal biopsy, RCC: red cell concentrate, PC: platelet concentrate

been incidental, or a severe status of APS might have played a role in inducing anti-GBM disease. Alternatively, the onset of anti-GBM disease may have caused a more severe manifestation of APS. It is unclear if the anti-GBM antibody and APS caused tissue damage via independent mechanisms or if there was a causal relationship between the two pathologies. Recently, numerous cases of anti-GBM antibody nephritis with low levels of ANCA over a year before its onset have been reported (14). The pathophysiology is considered to involve ANCA activating cells, mainly neutrophils, and making them adhere to vascular endothelial cells. Inflammatory cytokines and complement activation are similarly involved in this mechanism and cause damage to the capillary walls, eventually resulting in rupture and necrosis of the basement membrane. Consequently, the anti-GBM antibody is supposedly produced by exposing the pathogenic epitopes of the GBM (15). Regarding APS, aPLs activate monocytes, macrophages, and vascular endothelial cells through phospholipid-binding proteins, such as β2-GPI. These activated cells produce tissue factors, adhesion factors, and inflammatory cytokines that impair endothelial cells (16). Therefore, aPLs induce vascular endothelial damage and rupture of the GBM, which may result in the production of anti-GBM antibody as well as the development of ANCA-related vasculitis. In the present case, the presence of aPLs was recognized before the kidney function deterioration. Although the triggering factor for the activation of aPLs is unclear, the vascular endothelium was damaged by these activated aPLs. Consequently, the epitope sites on the GBM were exposed, and anti-GBM antibody was secondarily produced, as previously reported (15).

TMA accompanies various conditions, including autoimmune diseases (systemic lupus erythematosus and systemic sclerosis among others), malignancies, drug reactions, and infections. A previous report showed that TMA can occur concurrently with anti-GBM antibody-positive RPGN. TMA is also reported to be caused by the cytopathic effect of aPLs on the vascular endothelium and activation of the complement system by aPLs in APSN (17). Therefore, TMA is considered more likely to occur in cases of anti-GBM disease with APSN, and careful attention should be paid to the increased risk of TMA in such cases. Furthermore, the cause of thrombocytopenia may be associated with anti-GBM nephritis and severe hypertension (18). The thrombocytopenia in the present case may thus have resulted from the combined superposition of anti-GBM nephritis and TMA due to severe hypertension and APS.

There is no established treatment for severe cases of anti-GBM disease or APS, and these conditions are associated with a high mortality rate and rapid worsening of the general condition. A previous report found that patients (with a Cr level of ≥5.66 mg/dL) who required dialysis and were

treated with PEX and immunosuppressants for anti-GBM disease showed a 1-year survival rate of 65% and 1-year renal survival rate of 8%. In addition, all patients who required immediate HD and had 100% glomerular crescents on a renal biopsy remained dialysis-dependent (19). Although our present case was diagnosed with anti-GBM disease and APS with severe symptoms, including rapidly progressive renal failure, alveolar hemorrhaging-induced respiratory failure, TMA, and PRES, she was successfully stabilized with PEX, steroid therapy, and IVCY in the acute phase of this condition. Anticoagulation therapies are crucial for APS, and certain symptoms, such as central nervous system symptoms and renal thrombus on CT, were compatible with CAPS in this case; however, the patient developed alveolar hemorrhaging and severe thrombocytopenia. Therefore, the dose of the anticoagulants had to be reduced. Specifically, anticoagulation therapy was conducted while evaluating her general condition in order to determine whether or not she had alveolar bleeding and systemic thrombosis.

The present case of anti-GBM disease had concurrent APS, which made it difficult to understand and treat the patient's condition. Both an early diagnosis and intensive treatment are important; however, more cases need to be accumulated in order to establish an optimal treatment for this condition.

The authors state that they have no Conflict of Interest (COI).

References

1. McAdoo SP, Pusey CD. Anti-glomerular basement membrane disease. Clin J Am Soc Nephrol **12**: 1162-1172, 2017.
2. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. N Engl J Med **346**: 752-763, 2002.
3. Adhikari A, Chisti MM, Bastola S, Kc O. Rare case of catastrophic antiphospholipid syndrome with spontaneous intracranial haemorrhage. BMJ Case Rep **12**: 3227171, 2019.
4. 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 **66**: 1535-1540, 2004.
5. Basford AW, Lewis J, Dwyer JP, Fogo AB. Membranous nephropathy with crescents. J Am Soc Nephrol **22**: 1804-1808, 2011.
6. Longano A. Concurrent anti-GBM disease and IgA glomerulonephritis. Pathology **51**: 336-338, 2019.
7. Nochy D, Daugas E, Deoz D, et al. The intrarenal vascular lesions associated with primary antiphospholipid syndrome. J Am Soc Nephrol **10**: 507-518, 1999.
8. Sinico RA, Cavazzana I, Nuzzo M, et al. Renal involvement in primary antiphospholipid syndrome: retrospective analysis of 160 patients. Clin J Am Soc Nephrol **5**: 1211-1217, 2010.
9. Jennette JC, D'Agati VD, Olson JL, Silva FG. Heptinstall's pathology of the kidney. 7th ed. Wolters Kluwer, Alphen aan den Rijn, Netherlands, 2014: 739-782.
10. Fischer MJ, Rauch J, Levine JS. The antiphospholipid syndrome. Semin Nephrol **27**: 35-46, 2007.
11. Asherson RA, Cervera R, de Groot PG, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus **12**: 530-534, 2003.
12. Rodriguez-Pinto I, Moitinho M, Santacreu I, et al. Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of 500 patients from the International CAPS Registry. Autoimmun Rev **15**: 1120-1124, 2016.
13. Renard D, Dutrav A, Le Quellec A, Milhaud D. Reversible posterior leukoencephalopathy syndrome in catastrophic antiphospholipid syndrome. Cerebrovasc Dis **24**: 141-143, 2007.
14. Olson SW, Arbogast CB, Baker TP, et al. Asymptomatic autoantibodies associate with future anti-glomerular basement membrane disease. J Am Soc Nephrol **22**: 1945-1952, 2011.
15. Serratrice J, Chiche L, Dussol B, et al. Sequential development of perinuclear ANCA-associated vasculitis and anti-glomerular basement membrane glomerulonephritis. Am J Kidney **43**: e26-e30, 2004.
16. Matsuura E, Shen L, Matsunami Y, et al. Pathophysiology of β2-glycoprotien I in antiphospholipid syndrome. Lupus **19**: 379-384, 2010.
17. Terryn W, Benoit D, Van Loo A, et al. Goodpasture's syndrome associated with autoimmune thrombotic thrombocytopenic purpura-an unusual case. Nephrol Dial Transplant **22**: 3672-3673, 2007.
18. Manabe S, Banno M, Nakano M, et al. A case of PR3-ANCA-positive anti-GBM disease associated with intrarenal arteritis and thrombotic microangiopathy. CEN Case Rep **6**: 39-45, 2017.
19. Levy JB, Turney AN, Rees AJ, Pusey CD. Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasmas exchange and immunosuppression. Ann Intern Med **134**: 1033-1042, 2001.