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, antiphospholipid 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

Introduction
Anti-glomerular basement membrane (anti-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 leukoencephalopathy syndrome (PRES).

Case Report
A 48-year-old woman visited her physician with a complaint of a fever (temperature: 39°C) 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)
Bronchoalveolar lavage (BAL) revealed alveolar hemorrhaging and swelling. In addition, ground-glass opacities, which suggested pulmonary edema, were observed on the admission CT at admission showed bilateral renal enlargement, a notch on the left kidney, and suspected renal infarction. Multiple organ dysfunction syndrome (MODS) was considered likely to be occurring similar to CAPS could not be denied based on the presence of microscopic cerebral infarction. Multiple organ dysfunc-
tion. 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.

was administered daily. Due to her persistent fever, general 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 which had persisted from the day of admission. On the 8th day of admission, a sudden drop in her platelet (Plt) count of 1.27 g/gCr, and urinary red blood cells (RBCs) > 100 mmHg, and her respiratory condition was stable. During the hospitalization, her BP was 110-120/70-80 mmHg without medications.

### Table. Laboratory Data on Admission.

| Hematological values | Serum biochemistry | Immunological studies |
|----------------------|--------------------|-----------------------|
| White blood cell count | Total protein: 7 g/dL | C-reactive protein: 26.1 mg/dL |
| Neutrophil | Albumin: 2.5 g/dL | Complement 3: 86.6 mg/dL |
| Lymphocyte | Aspartate aminotransferase: 18 U/L | Complement 4: 13.7 mg/dL |
| Monocyte | Alanine aminotransferase: 13 U/L | Serum complement titer: 33.1 U/mL |
| Eosinophil | Lactate dehydrogenase: 194 U/L | Immunoglobulin G: 2.068 mg/dL |
| Red blood cell count | Blood urea nitrogen: 45 mg/dL | Immunoglobulin A: 245 mg/dL |
| Hemoglobin | Creatinine: 5.37 mg/dL | Immunoglobulin M: 45.8 mg/dL |
| Hematocrit | Uric acid: 6.9 mg/dL | anti nuclear antibody >1:160 |
| Platelet count | Sodium: 125 mEq/L | anti dsDNA antibody: 11 U/mL |
| Urinalysis | Potassium: 3.8 mEq/L | anti RNP antibody: 21 U/mL |
| Protein | 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 | Venous blood gas | anti SS-B antibody: 17.4 U/mL |
| Red blood cell | pH: 7.42 | anti Scl-70 antibody: 2.8 U/mL |
| White blood cell | HCO₃⁻: 21.2 mmol/L | MPO-ANCA: <1.0 U/mL |
| Cast RBS casts, granular casts | Na⁺: 138.3 mmol/L | PR3-ANCA: <1.0 U/mL |
| Urinary chemistry | PT-INR | anti GBM antibody (<7.0 U/mL): 700 U/mL |
| UP/UcR | APTT | anti-cardiolipin antibody: 36 U/mL |
| Urinary β2MG | FD | Lupus anticoagulant: 1.52 sec |
| Urinary NAG | 2-MG | anti β2-GPI antibody: 30 U/mL |

HDL: high-density lipoprotein, HDL: high-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, FD: fibrinogen degradation products, DNA: deoxyribonucleic acid, RNP: ribonucleoprotein, SS: Sjogren’s syndrome, SC: scleroderma, MPO: myeloperoxidase, PR3: proteinase 3, ANCA: antineutrophil cytoplasmic antibody, GBM: glomerular basement membrane, β2-GPI: beta-2-glycoprotein I
On the same day, heparin was replaced with nafamostat mesylate, 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, red blood cell 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, B, 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’s 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), 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
related vasculitis. In the present case, the presence of aPLs anti-GBM antibody as well as the development of ANCA ruptured GBM, which may result in the production of 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 was secondary 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 IV CY 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).

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