CASE REPORT

Double-seropositive anti-nuclear cytoplasmic antibody and anti-glomerular basement membrane disease complicated with posterior reversible encephalopathy syndrome: a case report and literature review

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ABSTRACT

We report a case of rapidly progressive glomerulonephritis caused by anti-glomerular basement membrane (GBM) disease accompanied by positive anti-nuclear cytoplasmic antibody (ANCA) presenting central nervous system involvement in a 43-year-old female. She was treated with combination therapy consisting of corticosteroid pulse therapy, oral prednisolone, cyclophosphamide, plasma exchange, and hemodialysis for end-stage kidney disease. During the treatment, she suddenly developed seizures and consciousness disturbance. She was diagnosed with posterior reversible encephalopathy syndrome (PRES) by magnetic resonance imaging and an IgG oligoclonal band was found in the cerebrospinal fluid, which suggested that there were potentially abnormal antibodies outside the central nervous system, leading to vasculitis or endothelial injury. The PRES was quickly controlled by anti-hypertensive agents and reinforcement of immunosuppressive treatment. According to the literature review, patients with double-seropositivity for ANCA and anti-GBM antibodies are predisposed to PRES; therefore, nephrologists should take precautions due to the potential risk of PRES in these patients. (Am J Transl Med 2022. 6(4):177-184).

Keywords: Anti-glomerular basement membrane disease; Anti-nuclear cytoplasmic antibody; Posterior reversible encephalopathy syndrome; Vasculitis

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.CASE PRESENTATION

A 43-year-old female patient sought medical help for intermittent foamy urine and gross hematuria for about 1 month and persistent edema of the eyelids and lower extremities for 1 week. One month prior to presentation, the patient had suffered from foamy urine and severe tea-like urine, without urinary tract irritation or dysuria. Symmetrical pitting edema of the face and lower extremities developed gradually, accompanied by a decrease in urine output to 100 ml per day, with nausea, fatigue, abdominal pain, and diarrhea 3–6 times per day. There were no other symptoms. On physical examination, the patient had an anemic appearance, decreased breathing sounds bilaterally in the lower lungs without rales, a soft abdomen without tenderness, shifting dullness (+), and severe pitting edema of the lower extremities. The remainder of the physical examination yielded no additional abnormalities. On admission, the urine dipstick indicated proteinuria (3+) and hematuria (3+). Urinary sediment analysis indicated numerous red blood cells per high-power field (HPF), white blood cells 5–10/HPF, and squamous cells 5–10/HPF. Laboratory data revealed elevated serum creatinine (15.4 mg/dl), elevated C-reactive protein (CRP) (126 mg/L), and decreased hemoglobin (50 g/L).

The patient was transferred to our department due to

Table 1. Previous case reports of anti-GBM disease with PRES

No.	Gender	Age	Scr	CRP	ANCA	HT	PH	Treatment	Ref.
1	M	27	HD	N/A	(-)	(+)	(+)	OC+CTX	12
2	M	23	6.6	8	(-)	(+)	(+)	CTX+PE (12 sessions)	13
3	F	22	HD	N/A	(-)	(+)	(+)	MP+OC+CTX+PE (9 sessions)	14
4	F	22	9.5	5.5	(-)	(+)	(+)	MP+OC+CTX+PE (8 sessions)	15
5	F	22	1.7	N/A	(-)	(+)	(+)	MP+CTX+PE (5 sessions)	16
6	M	24	HD	8.2	(-)	(+)	(-)	MP+CTX+PE (6 sessions)	17
7	F	36	4.7	13.8	(-)	(-)	(-)	MP+OC+CTX+PE (5 sessions)	18
8	F	71	11	19.9	(-)	(+)	(+)	MP+OC+CTX+PE (7 sessions)	11
9	F	29	5.5	N/A	p-ANCA(+)	(-)	(-)	MP+OC+CTX+PE	19
10	M	21	12.5	N/A	(-)	(+)	(+)	MP+OC+CTX	20
11	F	14	19.5	N/A	(-)	(+)	(+)	OC+CTX+ PE (14 sessions)	21
12	F	33	2.79	26.48	(-)	(+)	(-)	MP+OC+CTX+PE (22 sessions)+RTX(600mg 1 session)	22
Our case	F	43	15.4	12.1	MPO(+)	(+)	(+)	OC+CTX+PE (13 sessions)	Present

Note: ANCA anti-nuclear cytoplasmic antibody, CRP C-reactive protein, CTX cyclophosphamide, HT hypertension, MP methylprednisolone, MPO myeloperoxidase anti-nuclear cytoplasmic antibody, NA not applicable, OC oral corticosteroid, p-ANCA perinuclear anti-neutrophil cytoplasmic antibodies, PE plasma exchange, PH pulmonary hemorrhage, RTX rituximab, Scr serum creatinine (mg/dl).

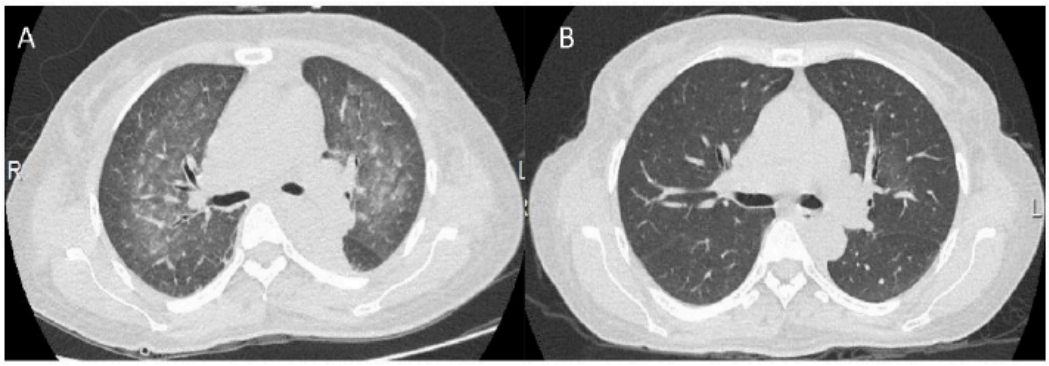

Figure 1. Chest computed tomography (CT) images. The images were obtained at the time of admission (A)and after one month of treatment (B).

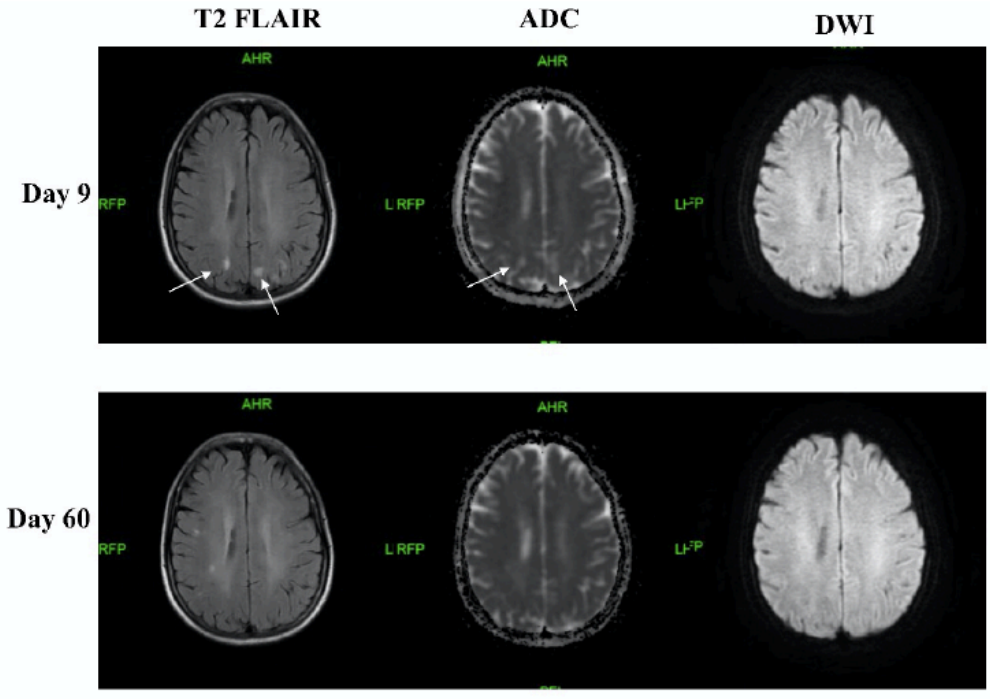

Figure 2. Serial changes in brain magnetic resonance imaging findings. Representative magnetic resonance images of T2 FLAIR, ADC measured by DWI, and DWI were obtained on the 9th and 60th hospital days. The white arrows mark the lesion in the bilateral frontoparietal occipital white matter.

rapid-onset renal insufficiency. Her anti-glomerular basement membrane (GBM) antibody titer was higher than the upper limit of normal (>400 IU/L), myeloperoxidase anti-nuclear cytoplasmic antibody (MPO) antibody was positive, anti-nuclear antibody (ANA) titer was 1:320, and anti-centromere antibody

was 3+; in addition, the case was complicated by hypocomplementemia. However, perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA), cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA), and anti-double-stranded DNA (dsDNA) antibody remained negative throughout the treatment period. Lysed and malformed red blood cells were found in the peripheral blood, with enlarged, lightly stained central areas. The laboratory data on admission, including complete blood count, serum biochemistry, serum immunological tests, infection-related tests, and coagulation tests, are presented in **Table 1**. Repeated blood cultures were performed to rule out a bacterial infection, and no bacteria were detected in any of the blood cultures. X-ray examination on admission revealed infiltrates in the middle lung field and bilateral hydrothorax. Chest computed tomography (CT) indicated that the infiltrates were not detected 1 week before admission, and the new-onset lesions were suggestive of alveolar hemorrhage associated with anti-GBM disease **(Figure 1**). Based on these findings, the patient was diagnosed with the double-seropositive anti-GBM disease.

Blood transfusion, plasma exchange (PE), continuous renal replacement therapy, and oral prednisone (1 mg/kg/day) were administered. Chest CT on the sixth day of hospitalization revealed enlarged infiltrates in the upper and middle lung lobes. However, the patient suddenly developed three episodes of seizure with disturbance of consciousness on the ninth day of hospitalization, 24 hours after PE treatment. During the first attack, her blood pressure was 150/90 mmHg. Her left limb was elevated, and she lost consciousness for about 5 minutes, with involuntary twitching of both limbs. The second and third attacks were similar to the first. Seizures were treated and stopped by intravenous injection of diazepam within 5 minutes. After the attacks, the patient was confused and reported accompanying muscle pain and headache, without any residual neurological sequelae. A brain CT scan showed no obvious lesions. Magnetic resonance imaging (MRI) of the brain showed multiple patches of lesions. Axial T1 fluid-attenuated inversion-recovery sequences (T1-FLAIR) showed low signals in the bilateral frontoparietal occipital white matter. T2 fluid-attenuated inversion recovery sequences (T2-FLAIR) showed predominantly subcortical abnormal T2 signals in the bilateral frontoparietal white matter. Some lesions had a high signal on diffusion-weighted imaging (DWI) (b=1000) and a high apparent diffusion coefficient (ADC). The patient was diagnosed with posterior reversible encephalopathy syndrome (PRES) (**Figure 2**). Except for steroid therapy, anti-hypertensive and anti-epileptic drugs were administered. There were no abnormal neurological manifestations in the following 3 months. The patient continued to require maintenance hemodialysis 3 times per week, and anti-GBM antibody was negative at 4 months after disease onset.

DISCUSSION

We present a patient with the double-seropositive anti-GBM disease with rapid progressive glomerulonephritis (RPGN) and pulmonary hemorrhage (i.e., Goodpasture's disease) who developed PRES with seizures and consciousness disturbance. Anti-GBM disease complicated with central nervous system involvement has scarcely been reported in the literature. The patient's systemic discomfort was alleviated by combination therapy consisting of oral prednisolone, cyclophosphamide (CTX), PE, and anti-epileptic and anti-hypertensive agents, and she became reliant on maintenance hemodialysis for RPGN-related irreversible end-stage kidney disease (ESRD).

Goodpasture's disease is an organ-specific autoimmune disease that is mediated by anti-GBM antibodies against the alpha 3 chain of type IV collagen epitope (a3 [IV]) (Borza et al., 2000). The disease presents as acute renal failure and is often accompanied by pulmonary hemorrhage.

Several case reports and review articles demonstrated the relationship between anti-GBM antibodies and ANCA. This phenomenon has been called a double-seropositive anti-GBM disease or anti-GBM/ANCA cross-over disease. About 10–30% of patients are double seropositive, usually for p-ANCA or anti-MPO. The pathogenesis of the double-seropositive anti-GBM disease is currently unclear; however, there is an accepted hypothesis that ANCA can indirectly induce the production of reactive oxygen species and increase proteolysis. A previous study found that patients with double-seropositive anti-GBM disease had high serum creatinine, a high proportion of patients required initial renal replacement therapy, and they had low 1-year renal survival. Another study claimed that double-positive patients were more likely to recover from being dialysis-dependent after treatment (McAdoo et al., 2017). A large cohort of patients with anti-GBM disease from China was investigated, and ANCA positivity was a predictor of mortality in Goodpasture's disease (HR, 4.43; 95% CI, 1.72–11.38). Furthermore, neurological manifestations differentiated patients with double-seropositive anti-GBM disease from patients with typical isolated anti-GBM vasculitis (Jia et al., 2022).

Anti-GBM disease accompanied by PRES is rarely reported, and we found only 12 previous cases in the literature (Tsuneyoshi et al., 2020). The clinical characteristics of these cases and the current case are summarized in Table 1 (Abenza-Abildua et al., 2009; Camara-Lemarroy et al., 2015; Cha et al., 2017; Ge et al., 2015; Gittins et al., 2004; Gutierrez-Sanchez et al., 2012; Lahmer et al., 2012; Nisar et al., 2019; Ozkok et al., 2012; Preul et al., 2009; Taniguchi & Hanaoka, 2021). The ages of the eight cases ranged from 14 to 71 years, and most of the patients were much younger than our case. Males and females were equally affected. The time between the onset of anti-GBM disease and PRES varied from under 1 month to 4 months. Most patients had hypertension at the onset of PRES and received CTX or PE treatment, which was thought to contribute to the development of PRES. Our case did not receive CTX or PE before PRES was developed, which may exclude the influence of these therapeutic agents. Only our current case and the case reported by Taha Nisar et al. were complicated by ANCA positivity, with MPO and p-ANCA positivity, respectively. Most of the cases required permanent dialysis or renal replacement therapy.

PRES refers to a disorder of vasogenic cerebral edema generally associated with hypertension and predominantly involving the bilateral parieto-occipital regions; the frontoparietal regions have also been reported to be involved (Fugate & Rabinstein, 2015). The pathophysiological changes underlying PRES are not fully understood. Hyper-perfusion of cerebral blood flow and endothelial dysfunction are thought to be two key factors in the pathogenesis of PRES, especially in the context of renal failure, blood pressure fluctuations, the use of cytotoxic drugs, autoimmune disorders, or eclampsia (Burnett et al., 2010; Fujieda et al., 2011; Li et al., 2012).

In our case, the patient was double seropositive for ANCA and anti-GBM antibodies, and lumbar punction was performed after her seizures. An oligoclonal IgG band was detected in the cerebrospinal fluid at the same location as in the peripheral blood, suggesting that abnormal antibodies outside the central nervous system caused the seizure. Therefore, we hypothesized that vasculitis may cause local damage to the vascular wall, which may destroy the integrity of the vascular wall, allowing anti-GBM antibodies or other autoimmune antibodies to cross the inflammatory vascular wall into the cerebrospinal fluid and cause PRES.

In summary, we report a patient with the double-seropositive anti-GBM disease with RPGN and alveolar hemorrhage accompanied by PRES that developed during the therapeutic course. We found evidence that anti-GBM antibodies or other autoantibodies might be able to transfer into the central nervous system because of vasculitis or endothelial injury. More attention should be paid to anti-GBM disease, which can be accompanied by nervous system injury. Further studies

are needed to elucidate the mechanism underlying the coexistence of double-seropositive anti-GBM disease and PRES.

ETHICAL STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this study and any accompanying images.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no competing interests.

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Supplement table 1. Laboratory data on admission

				Normal range
Complete blood count		Serum immunological tests		
White blood cell count, $\times 10^4/\mu L$	7.51	C3, mg/dL	0.885	0.9-1.8 g/L
Neutrophils, %	84.5	C4, mg/dL	0.271	0.1-0.4 g/L
Hemoglobin, g/dL	50	Immunoglobulin G	11.1	7-16 g/L
Platelets, $\times 10^4/\mu L$	244	Immunoglobulin A	2.86	0.7-4 g/L
Serum biochemistry		Immunoglobulin M	0.744	0.4-2.3 g/L
Total protein, g/dL	58	Rheumatoid factor	< 2.0	< 30 U/ml
Albumin, g/dL	25.5	Anti-nuclear antibody	1:320	Negative
Total bilirubin, mg/dL	8.54	Anti-double stranded DNA antibody	Negative	
Aspartate aminotransferase, U/L	10	Myeloperoxidase-ANCA, U/mL	positive	
Alanine aminotransferase, U/L	18	Proteinase 3-ANCA, U/mL	Negative	
Blood urea nitrogen, mg/dL	25.81	Anti-GBM antibody	> 400	
Creatinine, umol/L	1232.2	Infection-related tests		
Uric acid, umol/L	358.6	HBs antigen	Negative	
Sodium, mmol/L	132.52	HBs antibody	Positive	
Potassium, mmol/L	4.8	TPHA	Negative	
Chloride, mmol/L	101.18	RPR	Negative	
Calcium, mg/dL	1.94	HTLV-1 antibody	Negative	
Phosphorus, mg/dL	2.04	T-SPOT	Negative	
Triglyceride, mg/dL	0.82	Coagulation		
LDL-cholesterol, mg/dL	1.79	PT-INR	1.22	0.8-1.15
C-reactive protein, mg/dL	126	APTT, sec	32.5	25-35 sec
Glucose, mg/dL	4.81	Fibrinogen, mg/dL	94.1	0-5.0 ug/mL

Note: ANCA anti-neutrophilic cytoplasmic antibody, APTT activated partial thrombin time, HBs hepatitis B surface, C complement, DNA deoxyribonucleic acid, GBM glomerular basement membrane, HTLV-1 human T lymphotropic virus-1, LDL low-density lipoprotein, RPR, rapid plasma reagin, PT-INR prothrombin time-internationalized ratio, TPHA Treponema pallidum hemagglutination