Anti-glomerular basement membrane disease complicated with posterior reversible encephalopathy syndrome and subcortical cerebral hemorrhage: a case report and review of the literature

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Abstract

A 71-year-old woman was hospitalized for the treatment of fatigue, fever, and cough. On admission, she showed increased serum inflammation markers, severe anemia, pulmonary hemorrhage, and advanced acute kidney injury requiring hemodialysis. Her serum anti-glomerular basement membrane (GBM) antibody titer was found to be extremely high on the 7th hospital day. She was eventually diagnosed with anti-GBM disease. She was treated with a combination of corticosteroid pulse therapy, oral prednisolone and cyclophosphamide, and plasma exchange, but continued to require maintenance hemodialysis for end-stage kidney disease. During her treatment, she suddenly developed headache, blindness, seizure, and consciousness disturbance. She was diagnosed by magnetic resonance imaging with posterior reversible encephalopathy syndrome (PRES) with subcortical cerebral hemorrhage. Both the PRES and cerebral hemorrhage subsided soon after control of her hypertension and reinforcement of immunosuppressive treatment. PRES, particularly when accompanied by cerebral hemorrhage, may cause irreversible and lethal neurological abnormalities, and nephrologists should, therefore, be aware of the potential risk of PRES in patients with anti-GBM disease. We discuss the current case in the light of the previous literature.

Keywords Anti-glomerular basement membrane disease · Cerebral hemorrhage · Pulmonary hemorrhage · Posterior reversible leukoencephalopathy syndrome · Rapidly progressive glomerulonephritis

Introduction

Anti-glomerular basement membrane (GBM) disease, also known as ‘Goodpasture syndrome’, especially when the lung is involved, is an autoimmune disorder mediated by the abnormal production of anti-GBM antibody, predominantly targeting the GBM and alveolar basement membrane. Anti-GBM disease typically results in kidney dysfunction and pulmonary disease [1], manifesting as rapidly progressive glomerulonephritis and pulmonary hemorrhage, with microscopic hematuria with proteinuria and increased serum creatinine and urea nitrogen in laboratory tests [2]. Advances in diagnostic serological tests and in the clinical understanding

of its pathogenesis and effective treatment strategies mean that anti-GBM disease-related pulmonary hemorrhage can generally be controlled by immunosuppressive treatment, while its early diagnosis and effective immunosuppression have reduced the number of patients developing end-stage kidney disease (ESKD) [3, 4]. However, even when patients are diagnosed promptly and treated appropriately with a combination of immunosuppressive drugs and plasma exchange, some patients still require temporary or permanent renal replacement therapy (RRT), and the renal recovery rate remains unsatisfactory, especially in patients with advanced acute kidney injury requiring RRT therapy at the time of initial admission [5].

Posterior reversible encephalopathy syndrome (PRES) is a manifestation of vasogenic brain edema evidenced by acute or subacute neurological signs and symptoms and distinctive neuroimaging findings confirmed by magnetic resonance imaging (MRI) [6, 7]. PRES predominantly affects the bilateral parieto-occipital regions and is usually reversible. The clinical symptoms of PRES typically include impaired

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visual acuity or blindness, headache, seizure, consciousness disturbance, and occasionally focal neurological deficits corresponding to the affected lesions of the brain. Recent reports have suggested that PRES is a more diverse disorder than previously considered, with the affected brain region not restricted to the occipital and posterior lobes but also involving a wider region including the cerebellum and other parts of the brain, such as the brainstem [7–10]. Notably, the neurological abnormalities caused by PRES are occasionally irreversible and lethal, especially in patients who develop brain hemorrhage and status epilepticus.

Here, we report a patient with anti-GBM disease with rapidly progressive glomerulonephritis (RPGN) and alveolar hemorrhage, who developed PRES and subcortical brain hemorrhage during the treatment for anti-GBM disease.

Case report

A 71-year-old woman was hospitalized for the treatment of fatigue, fever, and dry cough. She had been healthy and had no definite history of any disease requiring medical follow-up or treatment, except for transvaginal hysterectomy for endometriosis at 40 years of age. One month prior to admission, she developed fatigue, followed by high-grade fever and a dry cough. She visited a nearby hospital and was admitted for further evaluation. Laboratory data revealed a blood cell count of 10,600/ μ L, serum C-reactive protein (CRP) level 19.9 mg/dL, and serum creatinine level 11 mg/dL. Urine dip test showed 2+ proteinuria and 3+ hematuria. The results of urinary sedimentation were numerous red blood cells per high power field (HPF), white blood cells 3–5/HPF, and squamous cells 5–10/HPF. Chest X-ray showed an infiltrate in the left lung field, suggestive of bacterial pneumonia. The patient was initially treated with meropenem (0.5 g/day) and hemodialysis was initiated for her advanced acute kidney injury. However, her high-grade fever continued and serum levels of inflammatory markers remained high despite meropenem treatment for 7 days. In addition, her serum anti-GBM antibody titer measured on admission was found to be very high (457 U/mL), and she was, therefore, diagnosed with anti-GBM disease and transferred to our hospital for further treatment.

On hospitalization, the patient was alert with a blood pressure of 126/80 mmHg, heart rate 84 beats/min, respiratory rate 12/min, and body temperature 37.6 °C. Her oxygen saturation level was 98% under 2 L/min of oxygen supplementation by nasal cannula. Her height was 157 cm, body weight 55.8 kg, and body mass index 22.6 kg/m². On physical examination, her palpebral conjunctiva was anemic and pre-tibial pitting edema was present. There were no definite neurological findings at the time of admission.

Laboratory tests showed the following: blood hemoglobin level 5.2 g/dL, leukocyte count 10,650/ μ L with 85.4% neutrophils, serum albumin 1.9 g/dL, serum urea nitrogen 41 mg/dL, serum creatinine level 6.4 mg/dL, and CRP 16.5 mg/dL. Serum immunological tests showed normal serum levels of complements and immunoglobulins. Antinuclear antibody, serum double-stranded DNA, myeloperoxidase anti-nuclear cytoplasmic antibody (ANCA), and proteinase 3-ANCA were all negative. However, her anti-GBM antibody titer was above the upper measurable limit of the test (> 350 U/mL). Repeated blood culture tests were performed to rule out bacterial infection, but no bacteria were detected in any of the blood-culture bottles. Summary of blood and urine tests is shown in Table 1.

X-ray examination on admission showed infiltrates in the middle lung field and left hydrothorax (Fig. 1a). Additional chest computed tomography (CT) disclosed that the infiltrates were not detected 1 day before admission (Fig. 1b), indicating relatively new lesions and suggesting alveolar hemorrhage associated with anti-GBM disease. Ultrasonography showed no sign of bilateral kidney atrophy or masses and no hydronephrosis. Based on these findings, the patient was diagnosed with anti-GBM disease.

After admission, she received intravenous methylprednisolone pulse therapy (1000 mg/day for 3 days) from the first hospital day, followed by oral prednisolone 40 mg/day (0.7 mg/kg/day) from the second hospital day. She also underwent seven courses of plasma exchange. Chest CT on the 15th hospital day revealed enlarged infiltrates in the upper and middle lung lobes, although her serum CRP level was decreasing (Fig. 1c, d). She received further methylprednisolone pulse therapy (500 mg/day for 3 days). Bronchography was performed on the 20th hospital day, followed by confirmation of alveolar hemorrhage based on oozing and bloody bronchoalveolar lavage fluid from the right B2 in the right lung (Fig. 2). Cytology of the bronchoalveolar lavage fluid was negative. However, the patient suddenly developed blindness, headache, and seizure with consciousness disturbance on the 21st hospital day, together with right-sided hemiplegia, at 3 h after the 7th plasma exchange. At that time, her blood pressure had increased to 170/90 mmHg. MRI was performed on the 22nd hospital day, and both fluid-attenuated inversion recovery (FLAIR) and apparent diffusion coefficient images showed high-intensity areas in the bilateral parietal and occipital lobes (Fig. 3). T2*-weighted imaging indicated a subcortical cerebral hemorrhage in the left parietal lobe (Fig. 3). The patient was diagnosed with PRES.

We initiated intravenous anti-hypertensive (nicardipine) and anti-epileptic drugs (levetiracetam, 1000 mg/day) to prevent seizures and lower blood pressure level, together with further methylprednisolone pulse therapy (1000 mg/day for 3 days) followed by oral prednisolone (30 mg/day, 0.5 mg/

Table 1 Laboratory data on admission

				Normal range
<i>Complete blood count</i>		<i>Serum immunological tests</i>		
White blood cell count, / μ L	10,650	C3, mg/dL	131	73–138
Neutrophils, %	85.4	C4, mg/dL	40	11–31
Hemoglobin, g/dL	5.2	CH50, U/mL	60	32–58
Platelets, $\times 10^4/\mu$ L	360	Immunoglobulin G	1112	861–1747
<i>Serum biochemistry</i>		Immunoglobulin A	211	93–393
Total protein, g/dL	5.3	Immunoglobulin M	46	50–269
Albumin, g/dL	1.9	Rheumatoid factor	< 5	≤ 15
Total bilirubin, mg/dL	0.4	Anti-nuclear antibody	0.6	≤ 10
Aspartate aminotransferase, U/L	17	Anti-double stranded DNA antibody	Negative	
Alanine aminotransferase, U/L	9	Myeloperoxidase-ANCA, U/mL	< 1.0	< 3.5
Lactate dehydrogenase, U/L	280	Proteinase 3-ANCA, U/mL	< 1.0	< 3.5
Creatine phosphokinase, U/L	22	Anti-GBM antibody	≥ 350	
Blood urea nitrogen, mg/dL	41	Procalcitonin	1.84	< 0.5
Creatinine, mg/dL	6.37	<i>Infection-related tests</i>		
Uric acid, mg/dL	4.6	HBs antigen	Negative	
Sodium, mmol/L	135	HBs antibody	Negative	
Potassium, mmol/L	3.8	TPHA	Negative	
Chloride, mmol/L	97	RPR	Negative	
Magnesium, mg/dL		HTLV-1 antibody	Negative	
Calcium, mg/dL	7.2	T-SPOT	Negative	
Phosphorus, mg/dL	2.7	<i>Coagulation</i>		
Amylase, U/L	34	PT-INR	1.20	
Lipase, U/L	19	APTT, sec	32.8	
Triglyceride, mg/dL	154	Fibrinogen, mg/dL	600	
LDL-cholesterol, mg/dL	49	<i>Blood gas analysis</i>		
HDL-cholesterol, mg/dL	17	pH		
C-reactive protein, mg/dL	16.5	pO ₂ (Oxygen 2L/min, nasal canula), mmHg	114.5	
Glucose, mg/dL	118	pCO ₂ , mmHg	32.8	
HbA1c, %	5.3	HCO ₃ ⁻ , mmol/L	24.8	

ANCA anti-neutrophilic cytoplasmic antibody, APTT activated partial thrombin time, HBs hepatitis B surface, C complement, CH hemolytic complement, DNA deoxyribonucleic acid, GBM glomerular basement membrane, HDL high-density lipoprotein, 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

kg/day) and cyclophosphamide (25 mg/day) to suppress disease activity. One day after initiating the anti-epileptic drug, her consciousness became almost normal and her blindness resolved 2 days later. The increased signal intensity on FLAIR images was significantly attenuated on the 27th hospital day and had disappeared completely on the 48th hospital day (Fig. 3).

No kidney biopsy was performed in the present case, because it was apparent that she was suffering from anti-GBM disease, and that anti-GBM antibody-related glomerulonephritis was the probable cause of her RPGN, based on the high serum anti-GBM antibody titer, concomitant alveolar hemorrhage, high serum CRP level, and progressive advanced renal failure with severe microscopic hematuria. Indeed, the high level of anti-GBM disease

activity meant that the patient missed the opportunity for a kidney biopsy, but she received hemodialysis every other day and plasma exchange on non-hemodialysis days. Furthermore, advanced kidney disease requiring RRT at the time of initial admission has been reported not to recover [5]. Because the patient's kidney function was very poor at the time of her transfer, her kidney function did not recover and she continued to require maintenance hemodialysis even after the anti-GBM disease activity had been successfully suppressed by anti-immunosuppressive drugs and other treatments.

The patient was finally discharged with virtually no neurological sequelae on the 67th hospital day. Six months after discharge, she continued to receive maintenance hemodialysis with no relapse of her anti-GBM disease or PRES, under

Fig. 1 X-ray films and chest computed tomography. Chest X-ray (a) and computed tomography (CT) images (b) obtained at the time of admission. Chest CT images of two slices obtained on the 15th hospital day (c, d)

Fig. 2 Bronchography image on 20th hospital day. Bronchography image showed oozing from B2 in the right lung

5 mg/day of oral prednisolone therapy. The patient's clinical course is summarized in Fig. 4.

Discussion

We herein report a patient with anti-GBM disease with RPGN and pulmonary hemorrhage, who developed PRES with subcortical cerebral hemorrhage presenting with

Fig. 3 Serial changes in head magnetic resonance imaging findings. Representative magnetic resonance images of DWI, ADC measured by DWI, FLAIR, and T2* obtained on the 22nd, 27th, and 48th hospital days. Increased signal intensities in the bilateral cortical and subcortical regions of the occipital and parietal lobes were observed on the 22nd hospital day, which gradually subsided after adequate blood pressure control. Subcortical cerebral hemorrhage was also confirmed by T2*. ADC apparent diffusion coefficient, DWI diffusion-weighted imaging, FLAIR fluid-attenuated inversion recovery

blindness, headache, and seizure with consciousness disturbance, and right-sided hemiplegia. Her anti-GBM disease activity was suppressed and her pulmonary hemorrhage and PRES were suppressed by a combination of intravenous methylprednisolone pulse therapy, oral prednisolone and cyclophosphamide, plasma exchange, and anti-epileptic and anti-hypertensive agents, but she continued to need maintenance hemodialysis for RPGN-related irreversible ESKD.

We found seven previous case reports of anti-GBM disease accompanied by PRES in the literature [11–17]. The clinical characteristics of these cases and the current case are summarized in Table 2. The age of the seven cases ranged between 24 and 36, much younger than our case. Both male and female were equally affected. Most patients had hypertension at the onset of PRES and six out of seven cases eventually developed acute kidney injury requiring permanent RRT. Only the current case was complicated by subcortical cerebral hemorrhage leading to right-sided hemiplegia; however, it has been reported that 10–25% of cases of PRES may be accompanied by intracranial hemorrhage, including subarachnoid hemorrhage [18, 19]. The duration between the onset of anti-GBM disease and PRES varied, from within 1–4 months. Some developed PRES soon after starting immunosuppressive treatment, while others develop during tapering of immunosuppressive drugs. Collectively, many of the cases who developed PRES were younger, develop advanced kidney injury requiring RRT, and complicated concomitant hypertension. Because there has been no report that directly compared the clinical features of patients with anti-GBM disease who developed PRES and

Fig. 4 Clinical course during hospitalization. SBP, systolic blood pressure; BUN, blood urea nitrogen; CPA, cyclophosphamide; CRP, C-reactive protein; CT, computed tomography; CTR, cardiothoracic ratio; GBM, glomerular basement membrane; MRI, magnetic resonance imaging, mPSL, methylprednisolone; PE, plasma exchange; PRES, posterior reversible encephalopathy syndrome; PSL, prednisolone; RBC, red blood cells

those without PRES, much more case reports are needed to detail the underlying mechanism related to the development of PRES in patients with anti-GBM disease.

Regarding the pathophysiology of PRES, two possible causes have been proposed: (1) a rapid increase in arterial blood pressure, particularly accompanied by hypervolemia, beyond the upper limit of cerebral blood flow autoregulation with or without vasospasm; and (2) endothelial dysfunction including increased permeability of the blood–brain barrier by endogenous and exogenous toxins [1, 2, 20]. In the current case, the patient's arterial blood pressure was increased and fluctuated around the time of PRES onset, although cardiothoracic ratio as a surrogate marker of intravascular volume had been within acceptable range (Fig. 4). The explanation for the high blood pressure at the time of PRES could be not by increased intravascular volume but by activated sympathetic nervous system and renin–angiotensin–aldosterone system, probably mediated by sustained uremic condition and inflammation by anti-GBM disease. Furthermore, the patient underwent a total of seven courses of plasma exchange using albumin and fresh frozen plasma and four transfusions of red blood cells prior to the development of PRES, and it is possible that these transfusions may have promoted the development of PRES due to hypervolemia and vasospasm [21]. Furthermore, previous reports suggest that patients with advanced kidney disease and uremic condition are prone to develop PRES [7, 9]. Although the detailed mechanisms are still unknown, uremic toxins accumulated as a result of the patient's rapidly progressive

kidney disease may have caused endothelial dysfunction, accounting for the development of PRES, as in the present case. Or some researchers speculate that not uremic toxins, but hypertension itself associated with advanced kidney disease may contribute to the endothelial dysfunction, followed by PRES. Further studies are necessary to clearly determine why some of the cases with anti-GBM disease develop PRES.

Whether or not anti-GBM antibodies can directly injure the basement membrane of cerebral vessels, thus leading to PRES and cerebral hemorrhage, remains unclear. Anti-GBM antibodies inducing RPGN and pulmonary disorders usually target the $\alpha 3$ chain of type IV collagen, which is expressed exclusively in the GBM and alveolar basement membrane, while the $\alpha 1$ and $\alpha 2$ (but not the $\alpha 3$) chains are components of the basement membrane in the cerebral vessels. It is, therefore, unlikely that anti-GBM antibodies directly induced injury of the basement membrane or breakdown of the blood–brain barrier leading to PRES and cerebral hemorrhage in this case. However, one previous case report showed that CNS vasculitis was histologically proven in a patient with anti-GBM disease, indicating possible role of anti-GBM antibody in the brain vessel [22]. Hence, further studies are necessary to determine whether anti-GBM antibody directly acts on basement membrane in the brain.

The reason for the persistently high serum anti-GBM antibody titer despite aggressive immunosuppressive treatment after hospitalization should be elucidated. Because the upper limit of the detection kit we used for serum anti-GBM

Table 2 Previous reports of anti-GBM disease with PRES

No	References	Age	Sex	Serum Cr at presentation (mg/dL)	RRT	Max CRP (mg/dL)	AHT	PH	CH	Treatment	OC	CP	Plasma Ex
1	Abenza-Abildua et al. [11]	27	M	HD	mHD	N/A	(+)	(+)	(-)	(-)	30 mg/day	150 mg/day	N/A
2	Gutiérrez-Sánchez et al. [13]	22	F	HD	N/A	N/A	(+)	(+)	(-)	1 g × 3 days	60 mg/day	1 mg/kg/day	9 sessions
3	Ozkok et al. [14]	22	F	9.5	mHD	5.5	(+)	(+)	(-)	1 g × 3 days	1 mg/kg/day	750 mg	8 sessions
4	Lahmer et al. [12]	23	M	6.6	KTx	8	(+)	(+)	(-)	1 g × 5 days	(-)	1 g × 6 course	12 sessions
5	Camara-Lemarroy et al. [15]	22	F	1.7	mHD	N/A	(+)	(+)	(-)	0.5 g × 3 days	(-)	720 mg	5 sessions
6	Ge et al. [16]	24	M	HD	mHD	8.2	(+)	(-)	(-)	0.5 g × 3 days	(-)	10 mg/kg/2 weeks	6 sessions
7	Cha et al. [17]	36	F	4.7	mHD	13.8	(-)	(-)	(-)	0.5 g × 3 days	60 mg/day	1 mg/kg/day	5 sessions
8	Present case	71	F	11	mHD	19.9	(+)	(+)	(+)	1 g × 3 days, 3 sessions	40 mg/day	25 mg/day	7 sessions

AHT arterial hypertension, CH cerebral hemorrhage, Cr creatinine, CP cyclophosphamide, Ex exchange, GBM glomerular basement membrane, HD hemodialysis, KTx kidney transplantation, mHD maintenance hemodialysis, mPSL methylprednisolone, NA not applicable, OC oral corticosteroid, PH pulmonary hemorrhage, PRES posterior reversible encephalopathy syndrome

antibody measurement was 350 U/mL, the result of the anti-GBM antibody titer was returned to us as > 350 U/mL over the first few weeks. The actual value of her serum anti-GBM titer was expected to be extremely high above the upper limit of 350 U/mL, although we were unable to know the actual value. We think that the actual value of the serum anti-GBM antibody titer insidiously decreased during the first few weeks and then around the time of the onset of RRES, the actual titer decreased below 350 U/mL and we were able to know the actual value. Accordingly, we used serum C-reactive protein level as a marker of activity of anti-GMB disease during the hospitalization until the serum anti-GBM antibody titer decreased less than 350 U/mL. However, C-reactive protein is not a direct marker of anti-GBM disease and can elevate in various disease conditions including infection and other inflammatory disorders. Hence, it is an urgent need to get a new anti-GBM detection kit that can determine a higher value of anti-GBM antibody.

In summary, we report a patient with anti-GBM disease with RPGN and alveolar hemorrhage, accompanied by PRES and subcortical hemorrhage during the therapeutic course. Although we could not find a causal association between anti-GBM antibodies and PRES, this case highlights the need to be aware that PRES may develop in patients with rapidly progressive kidney diseases, such anti-GBM disease, associated with increased and fluctuating arterial blood pressure and the accumulation of uremic toxins, and necessitating extensive treatments with plasma exchange and red blood cell transfusions. Further case series and observational studies may be needed to elucidate the mechanism underlying the possible coexistence of anti-GBM disease and PRES.

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Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Informed consent Written informed consent was obtained from the patient for submitting this case report to English language journals.

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