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Review Article

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A Case Report of Posterior Reversible Encephalopathy Syndrome with Rapidly Progressive Glomerulonephritis Combined with Membranous Nephropathy

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Abstract: Rapidly progressive glomerulonephritis is a group of clinical syndromes, in which renal function of patient progressively deteriorates with pathological manifestation of extensive glomerular crescent formation. Among which, anti-glomerular basement membrane antibody glomerulonephritis is the rarest but the most aggressive subtype. This paper discusses a case of rapidly progressive glomerulonephritis combined with membranous nephropathy. There were posterior reversible encephalopathy syndromes during diagnosis and treatment. Diagnosis was confirmed in time by laboratory examination and renal pathology. Condition of the patient was alleviated through close work between all departments. This allowed us to further understand the case characteristics of rapidly progressive glomerulonephritis combined with membranous nephropathy, importance of effective prevention, and significance of various complications during treatment, so as to alleviate pain and improve prognosis in patient.

Keywords: Rapid progressive glomerulonephritis, Membranous nephropathy, Posterior reversible encephalopathy syndrome

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1 Clinical data

The patient is a 20-year-old female student, who was admitted to the hospital on 26th June 2018 due to chill for 2 weeks, fever and edema of both legs for 5 days. Two weeks before admission, the patient began to have chill and headache, no treatment was received. Five days before admission, the patient had cough with a small amount of white phlegm, accompanied by fever with body temperature up to 39°C. It was accompanied with poor appetite, edema at lower extremities with aggravation after activities; no foaming condition observed in urine, no lumbago and no gross hematuria. The patient visited local hospital and was diagnosed as "renal failure, anemia, acute tracheitis", and was prescribed with "methylprednisolone, cefoperazone sulbactam, vancomycin". The treatment was not effective, so the patient visited our hospital. The patient showed fatigue, poor appetite, poor sleep, no significant reduction in urine volume, no constipation and unknown weight changes.

She was healthy previously.

Physical examination: T 37.8°C, P 92 times/min, R 23 times/min, BP 117/76 mmHg, appeared to be anemic. Swollen eyelid, pale eyelid conjunctiva, with no yellow sclera. Breath sounds of both lungs were clear, with no dry and wet crackling breath sound heard. Heart rhythm was regular, hear rate was 92 beats/min, heart sound was solid, no murmur or pericardial friction sound was heard in auscultation area of heart valves. Abdomen was flat and soft, no lump was detected at liver and spleen under ribs, no abnormal mass was detected at entire abdomen. Mobile dullness was negative, there was no percussion pain in both kidney areas, and there

was no abnormal bowel sound. There was secondary depression edema at both lower limbs.

Auxiliary examination: test results before admission on 24th June 2018. Blood routine: white blood cell 10.15 × 109/L, red blood cell 2.89 × 1012/L, hemoglobin concentration 79.00 g/L, hematocrit 25.20%, neutrophil 72.60%, lymphocyte 15.30%, erythrocyte sedimentation rate 120 mm/h. Urine routine: urine protein 3+, occult blood 3+, pH6, urine specific gravity 1.010. Biochemical routine: urea 7.38 mmol/L, creatinine 154 μmol/L, uric acid 402 μmol/L, total protein TP 45.9 g/L, albumin ALB 19.6 g/L. Haemagglutination: PT 15.2 s, APTT 49.2 s, D-dimer 2.89 μg/ml. DS DNA: 38.95 IU/ml (normal value <30 IU/ml). Procalcitonin 0.15 ng/ml. Chest CT: increased bilateral lung markings and bilateral pleural effusion.

Thorough related examination after admission at 26th June 2018. Blood routine: white blood cell 9.28 × 109/L, hemoglobin concentration 72.00 g/L, hematocrit 21.90%, platelet number 394.00 × 109/L, neutrophil percentage 75.20%, lymphocyte percentage 15.00%, erythrocyte sedimentation rate 120 mm/h, hypersensitive C-reactive protein 104.98 mg/L. Urine routine: urinary protein 1+, occult blood 3+, pH5, urinary specific gravity 1.007, urine protein quantity: 693 mg/24h. Biochemical routine: BUN 9.64 mmol/L, Ccr 235 μmol/L, UA 434 μmol/L, Cys-C 2.26 mg/L, calcium 2.01 mmol/L, TP 49.82 g/L, ALB 20.55 g/L. Specific protein and complement: IgG 6.62 g/L, complement was normal. ANA and antinuclear antibody spectrum 3: all negative. ANCA combination: anti-GBM +, others were negative. IgG quantitative detection of anti-phospholipase A2 receptor antibody: 1069.99 RU/ml (+). Chest + full abdominal CT: no abnormality found on chest CT plain scan, a little fluid in pelvic cavity, left renal cyst was indicated. ECG and cardiac color ultrasound: no abnormality. Sputum culture: G-bacilli found by microscopy. Blood culture: no bacterial growth.

Due to deterioration of renal function, creatinine progressively increased and anti-GBM was (+). Rapidly progressive glomerulonephritis was considered. Renal puncture biopsy was performed. Combined with clinical examination, the renal pathology was consistent with anti-glomerular basement membrane glomerulonephritis (crescent formation) with membranous nephropathy (phase II), to be confirmed by electron microscopy. Combined with clinical and light microscopic results, electron microscopic diagnosis was consistent with anti-glomerular basement membrane glomerulonephritis combined with stage II membranous nephropathy (as shown in Figure 1). After hormone shock therapy combined with cyclophosphamide shock therapy and plasma catheterization, condition of the patient was stable. Renal function and other indicators improved significantly. There was no fever. Blood pressure was stable. In the morning of 14th July 2018, the patient had a sudden serious seizure and was transferred to ICU for further diagnosis and treatment. After being transferred to ICU, epilepsy attack and temperature rose again, and life support treatments such as anti-epilepsy, sedation, tracheal intubation and ventilator assisted respiration were given. After the transfer to ICU, causes of fever and epilepsy were investigated and relevant tests were carried out. Blood culture: negative. Four sputum culture: 1 respiratory tract normal flora and 3 *Pseudomonas aeruginosa*. Procalcitonin: normal. G test + GM test on 17th July: G test ((1-3)-β-D glucan): 183.5 pg/ml (normal 0–60), GM test negative. On July 19, G test < 10 pg/ml, GM test was negative. Thorough lumbar puncture and cerebral spinal fluid examination: Pan's test, red blood cell, Cl and cerebral spinal fluid protein were all normal, no *Cryptococcus neoformans* was detected by ink staining, no bacterium was detected by Gram's staining, no acid fast bacterium was detected by acid fast staining, and no bacterial growth in basic culture media. On 14th July 2018, lung CT scan showed double pneumonic lesions and bilateral pleural effusion, presented advancement when compared to the scan on 3rd July 2018. Brain CT showed multiple low-density lesions in bilateral frontal and parietooccipital lobes. Brain MRI showed abnormal signals in bilateral frontal, parietal, occipital and left temporal cortex, indicating angiogenic brain edema. Re-examination was recommended. Bilateral middle and anterior cerebral arteries were fine, indicating that there were secondary changes. There was no obvious abnormality in brain magnetic resonance venography. Consultation was obtained from neurology department, occurrence of posterior reversible leukoencephalopathy syndrome was considered, and cefoxitin was given for treatment of pneumonia while antiepileptic drugs, deep sedation brain protection, diuresis were given for treatment of epilepsy. Upon stable condition, the patient was transferred to our department to continue anti-infection and anti-epilepsy treatments, and sufficient amount of hormone treatment. Renal function of the patient

was stable. Brain MRI of the patient was re-examined. FLAIR sequence: parts of sulcus signal were slightly higher, improvement was noticed when compared to original scan. The patient was discharged and followed up for one year. At present, renal function of the patient is normal, albumin increases to 45.97 g/L, urinary protein decreases to 146 mg/D, anti-phospholesterase A2 receptor Antibody IgG quantitative test is negative, and anti-GBM is negative. There is no recurrent epileptic attack. Brain MRI: ventriculus system slightly expands, combination with clinical examination is requested. The patient has stopped hormone, cyclophosphamide and valproate treatments, condition of the patient is stable.

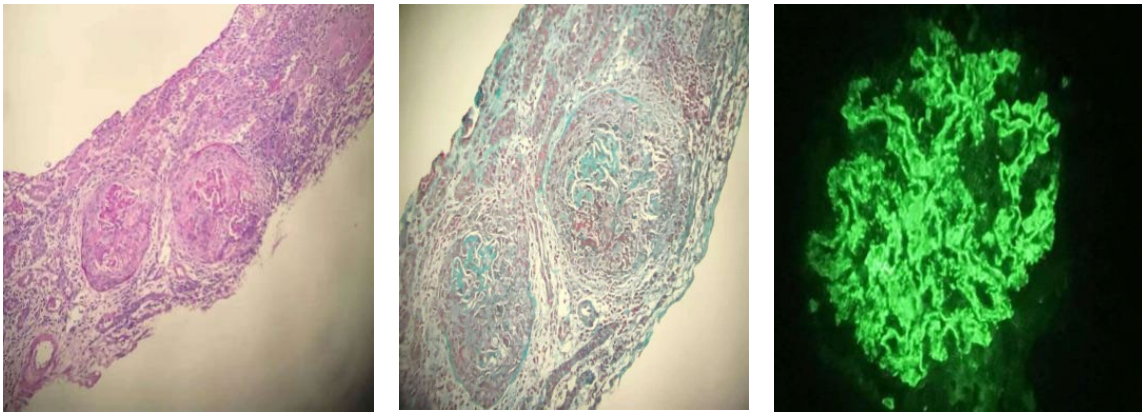

Figure 1. Renal pathology

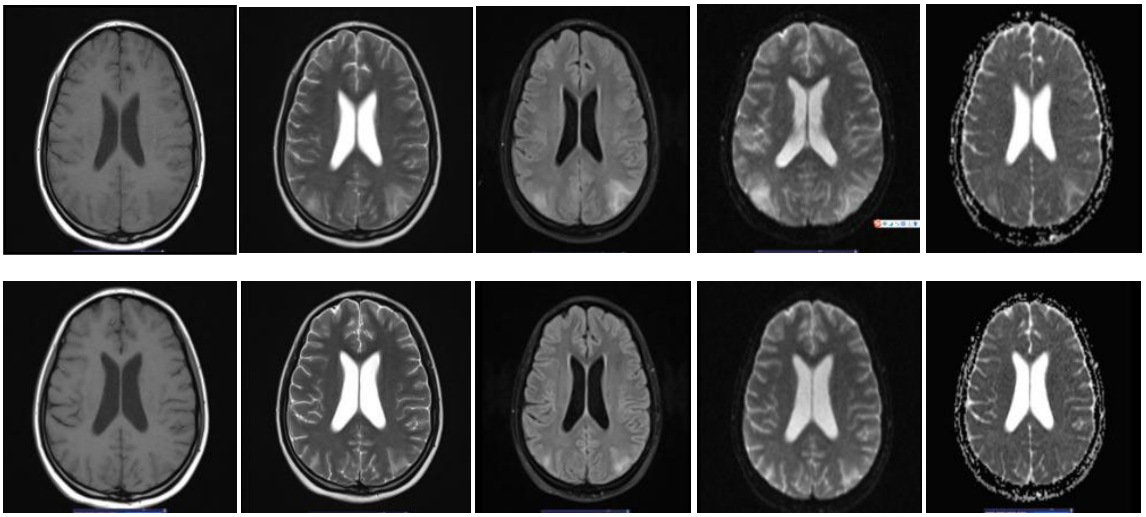

Figure 2. Brain MRI changes (upper: 20th July 2018 ~ lower: 26th July 2018)

2 Discussion

Nephritis is one of the most common types of kidney disease. At present, clinical pathogenesis and specific pathogenesis of this disease have not been fully elucidated[1]. Rapidly progressive glomerulonephritis is a group of glomerulonephritis characterized by progressive deterioration of proteinuria, hematuria and renal function. Its pathological change is characterized by formation of crescent bodies. According to anti-neutrophil cytoplasmic antibody (ANCA) in serum, anti-glomerular basement membrane (anti-GBM) antibody and renal pathological fluorescence, this disease can be classified into anti-GBM antibody type, immune complex deposition type and less immune complex deposition type. Clinically, this disease is more aggressive with more complications. If not treated in time, it will progress within a short period of time and lead to end-stage renal disease and even death. If it is treated in time, prognosis can be significantly improved[2]. Anti-GBM disease is often associated with ANCA-related vasculitis. According to research reports, clinical manifestation in patient with both ANCA and anti-GBM glomerulonephritis is more serious than those patient with only anti-GBM disease, and that

the prognosis effect is poor[3]. Clinically, combination with IgA nephropathy and membranous nephropathy is also possible. Wang Jinquan[4] et al. analyzed the clinical pathological characteristics of patients with anti-glomerular basement membrane disease combined with IgA nephropathy or membranous nephropathy in Nanjing General Hospital. The investigators found that clinical manifestation, laboratory examination, pathological indicators and prognosis of patients with IgA nephropathy or membranous nephropathy were better than that of patients with only anti-GBM antibody disease. In this paper, anti-GBM antibody of the patient was positive, whereas anti-phospholipase A2 receptor antibody IgG quantitative detection showed 1069.99 ru/ml. Combined with renal pathology, GBM disease combined with membranous nephropathy was considered.

Anti-GBM antibody is the direct cause of anti-GBM nephritis. Its main target antigen is the NC1 domain of type IV collagen 3-chain (-3 (IV) NC1). Some antibody can also recognize 4- and 5- chain. The above target antigens are not exposed under normal condition, but may be exposed following lung or kidney injury, resulting in production of auto-antibodies[5]. Cui Zhao and Zhao Minghui[6] found that affinity maturation process of anti-GBM antibody may has been completed when clinical symptoms appear, however serum antibody affinity may be different in different patient. The affinity degree can determine the degree of pathological kidney damage, suggesting that affinity of anti-GBM antibody plays an important role in the pathogenesis of anti-GBM antibody-related diseases. Membranous nephropathy is a common kidney disease in adults, while the incidence of anti-GBM antibody glomerulonephritis is very low. The relationship between the two diseases remains uncertain, thus the possibility of simultaneous occurrence of the two unrelated diseases cannot be eliminated. At present, the mechanism of anti-GBM antibody disease combined with membranous nephropathy is still unclear. It is speculated that exposure of auto-antigens caused by injury of basement membrane leads to formation of anti-GBM antibodies, or that increased permeability caused by basement membrane damage leads to deposition of sub-epithelial immune complexes, resulting in membranous nephropathy[8]. In 2012, guideline by Kidney Disease Improving Global Outcomes (KDIGO) recommends that glucocorticoid combined with cyclophosphamide (CTX) and plasma exchange should serve as the main treatment for type I acute nephritis[9]. Patients with primary glomerulonephritis are usually treated with standard anti-GBM disease therapy. At present, laboratory test of the patient shows obvious improvement after treatment with hormone, cyclophosphamide and plasma exchange. Anti-phospholipase A2 receptor antibody shows significant decline, and anti-GBM antibody becomes negative, from strong positive to weak positive.

Posterior reversible encephalopathy syndrome (PRES) is a group of neuroimaging syndromes with main symptoms being headache, visual disorder, epileptic attack, consciousness disorder and mental disorder. Lesion is mainly symmetrical involvement of posterior white matter. Active treatment often results in reversible clinical manifestations and clinical neuroimaging. Characteristic imaging features of conventional RPES are symmetrical diffuse edema in posterior part of brain, most often involve the parietooccipital lobe of posterior circulation, and possibly brainstem, cerebellum, basal ganglia and frontal lobe[10,11]. Literatures reported that the common causes of PRES include hypertension, eclampsia/pre-eclampsia, immunosuppressive agent, chemotherapy drug, cytotoxic drug, immune system disease, kidney disease and serious infection[12,13]. A recent case report reported occurrence of PRES during application of bortezomib[14]. Systemic lupus erythematosus also occurred, but anti-glomerular basement membrane antibody type glomerulonephritis was not reported. There are two types of mechanisms, the first is the theory of automatic regulation collapse and over-perfusion of cerebral vessels, the other is the theory of vasospasm and insufficient perfusion. Although the two theories are relatively in contrast, they ultimately explicate a similar change: angiogenic edema. Angiogenic edema can also arise even when blood pressure is not high. Compared with brain CT, brain MRI can more accurately reflect changes of brain white matter. Treatment should actively control blood pressure, discontinue epilepsy, reduce brain edema, stop or reduce cytotoxic drug, and actively treat basic disease as well as provide symptomatic support treatment. Following timely treatment, clinical symptom and imaging change of most patients completely recover within 1–2 weeks, with no neurological sequelae. However, some patients mat not acquire complete reversal. Cerebral hemorrhage, cerebral infarction and other imaging changes suggest irreversible lesion

and poor prognosis, and patients with serious disease may die[15]. In this paper, epileptic seizures occurred in the patient during diagnosis and treatment, when the primary disease was under control and blood pressure was stable. At such, hormone and cyclophosphamide cytotoxic drugs were used in the patient. The patient also had pulmonary infection. Considering that posterior encephalopathy syndrome of the patient was related to drugs and infection, hormone and cyclophosphamide treatment of the patient were not stopped but reduced in dose in order to prevent recurrence of the primary disease. After active control of infection and epilepsy, posterior encephalopathy syndromes of the patient improved with no seizure occurred. High possibility of PRES induced by infection was considered.

In clinical detection of anti-glomerular basement membrane antibody glomerulonephritis, presence of other glomerulonephritis should be examined. Symptoms should be identified in time and indicators should be observed closely. Examination should not merely focus on renal function, albumin and urinary protein, but monitoring of indexes such as brain CT, lung CT, infection indicator, blood pressure, and input and output volume should also be enhanced. Early diagnosis and treatment should be taken place in order to avoid co-occurrence of complications and other organ injuries. In this study, collaborated diagnosis and treatment from different departments allowed early diagnosis and early treatment in the patient, which improved prognosis of the patient.

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