CASE REPORT

Status epilepticus as the initial presentation of antibody-negative Goodpasture's syndrome

Ingrid PL Ting,¹ Saniah Abdul Halim,¹ Azreen Adnan,¹ Hasnan Jaafar²

¹Department of Medicine, University Sains Malaysia, Health Campus, Kubang Kerian, Malaysia

²Department of Pathology, University Sains Malaysia, Health Campus, Kubang Kerian, Malaysia

Correspondence to

Dr Ingrid PL Ting,
ingrid_tpl15@hotmail.com

Accepted 16 May 2017

SUMMARY

Goodpasture's syndrome is a rare pulmonary-renal disease. It is characterised by presence of auto-antibodies directed against the glomerular basement membrane (GBM) antigen. These antibodies that bind to the GBM antigens cause rapidly progressive glomerulonephritis. The alveolar basement membrane also contains similar antigen, leading to pulmonary haemorrhage in active disease. We report a case of a young man who initially presented with status epilepticus and later was found to have rapidly progressive glomerulonephritis with pulmonary haemorrhage. Serum anti-GBM antibody was negative but the renal biopsy confirmed the diagnosis by showing typical linear IgG along the GBM on immunofluorescent study. He was treated with plasmapheresis and high-dose steroid in combination with oral cyclophosphamide. His renal function normalised after treatment.

BACKGROUND

Goodpasture's syndrome is a rare autoimmune disease, occurs in approximately one case per million per year.¹ Its typical clinical manifestations are glomerulonephritis and pulmonary haemorrhage due to presence of antglomerular basement membrane (GBM) autoantibodies which are directed against the non-collagen domain 1 of the human alpha-3 chain of type IV collagen, also known as $\alpha3(IV)NC1$.²

Central nervous system (CNS) involvement is rarely reported and is primarily associated with CNS vasculitis.³⁻⁶ The initial presentation of neurological symptoms may mislead the diagnosis to primary CNS disorder especially in a case of antibody negative Goodpasture's syndrome. Thus, a high index of suspicion is required when the typical combination of pulmonary-renal syndrome is present, as delaying the diagnosis and treatment could cause severe organ failure with significant morbidity and mortality.

CASE PRESENTATION

A 16-year-old boy without any prior medical illness, presented with a first episode of recurrent generalised tonic seizures which progressed to status epilepticus and required mechanical ventilation. This was preceded by history of low-grade fever for 3 weeks associated with headache, nausea and vomiting. There was no other neurological manifestations, no symptoms to suggest connective tissue disease or family history of seizure. He was not on any medication or drug overused.

His vital signs were normal. There were no signs of vasculitic lesions, meningism or any neurological deficit. Lungs examinations revealed fine crepitation over both bases. Abdomen was soft and non-tender. Liver was just palpable and the Traube's space was dull.

INVESTIGATIONS

Blood investigations revealed high white cell count of $24.39 \times 10^9/L$, normal haemoglobin (12.5 g/dL) level and normal platelet ($424 \times 10^9/L$) count. Renal function test was abnormal with raised blood urea of 19.9 mmol/L and creatinine of 209 $\mu\text{mol/L}$. Repeated peripheral blood film did not show any features of microangiopathic haemolytic anaemia.

His head CT scan was normal. Lumbar puncture was performed to exclude meningoencephalitis. The cerebrospinal fluid (CSF) opening pressure was slightly raised of 28 cmH₂O but acellular with normal sugar and protein level. Other CSF tests to look for infection were negative. The brain MRI was also normal.

Urinalysis showed red blood cells >100/high power field and urine protein was 3+. Ultrasound of the kidneys showed normal bilateral kidney size. Anti-GBM antibody was negative. Perinuclear anti-neutrophil cytoplasmic antibody (P-ANCA), cytoplasmic anti-neutrophil cytoplasmic antibody (C-ANCA) and antinuclear antibody (ANA) were also negative. C3 0.08 g/L and C4 0.17 g/L were low.

TREATMENT

He was extubated after 3 days of admission but was reintubated 48 hours afterwards due to pulmonary haemorrhage and respiratory failure. His renal function deteriorated and required haemodialysis. Diagnosis of rapidly progressive glomerulonephritis with pulmonary-renal syndrome was made and Goodpasture's syndrome was suspected. Renal biopsy was planned, however his condition was unstable, and thus the procedure was postponed. Plasmapheresis was initiated and continued for three cycles. He was also started on intravenous methylprednisolone 1 g daily for 3 days followed by oral prednisolone 60 mg daily. Oral cyclophosphamide 100 mg daily was added for optimisation of immunosuppression. He recovered well and was discharged home 2 weeks later. His kidney function normalised at hospital discharge.

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To cite: Ting IPL, Abdul Halim S, Adnan A, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-219628

Figure 1 H&E section of renal biopsy. (A) Two glomeruli exhibiting mesangial cell proliferation. No tubular changes, interstitial infiltrates or fibrosis seen. The vessel is unremarkable. (B) The glomeruli shows mesangial cell proliferation and synechiae adhesion. Original magnifications, (A) $\times 100$ and (B) $\times 400$.

OUTCOME AND FOLLOW-UP

Subsequently, renal biopsy was performed during the follow-up visit. A total of eight glomeruli were seen and five of them were normal except for three glomeruli that showed mesangial cell proliferation and synechiae adhesions. No features of vasculitis, tubular changes, interstitial infiltrates, fibrosis, glomerulosclerosis, cellular or fibrous crescents identified. No features of Wegener granulomatosis such as lymphocytic aggregates with granuloma formation. There was no histological evidence of vascular or glomerular intracapillary thrombi to suggest thrombotic microangiopathy (figure 1).

Immunofluorescent study showed linear IgG on glomerular basement membrane (figure 2).

He completed 3 months of oral cyclophosphamide and the prednisolone was tapered off after 1 year of therapy. During follow-up, his renal function remained normal and the urinalysis showed no evidence of red blood cell cast.

DISCUSSION

Goodpasture's syndrome in adult has a bimodal age distribution; the first peak occurs between the ages of 20 and 30 years old, whereas the second peak is usually around 60 and 70 years. In the younger age group, male is the more commonly affected, whereas in older patients, males and females are equal in distribution.⁷ Our patient's age of onset is younger than the common peak age group.

The pathogenesis of disease is multifactorial and may be triggered by environmental exposure to hydrocarbon, tobacco smoke, cocaine inhalation and metallic dust. Viral respiratory infection is also postulated to be one of the culprit.⁸

Figure 2 Immunofluorescence microscopy demonstrating linear deposition of IgG.

Goodpasture's syndrome may be associated with concomitant extra pulmonary–renal involvement in 10%–30% of cases.³ Only four cases of CNS vasculitis associated with Goodpasture's syndrome have been reported in the literature.^{3–6} All patients described had recurrent seizures with or without haemoptysis. Their brain MRI showed either lacunar type of infarct⁴ or multifocal cortical ischaemia in the occipital and parietal lobes.^{3,5,6}

Rydel *et al*⁴ suggested the role of anti-GBM antibodies in development of CNS vasculitis in Goodpasture's syndrome. Even though brain biopsy is the gold standard diagnostic investigation, most of the previous reports have made diagnosis without biopsy, but based mainly on clinical and radiological features that consistent with vasculitis, in combination with good neurological response after immunosuppressive therapy.^{3–6}

In our case, the patient presented with status epilepticus, but there were no specific changes of vasculitic infarct seen on brain MRI. Cerebral angiogram would be helpful to ascertain the diagnosis of vasculitis. Other possible explanation for the cause of seizure could be due to acute metabolic derangement related to kidney failure. The slightly raised CSF pressure with normal CSF content may occur as a consequence of status epilepticus due to failure of cerebral autoregulation.

Posterior reversible encephalopathy syndrome (PRES) is another cause of seizure that needs to be considered in immune-mediated disease. Combination of symptoms such as headache, seizure, focal neurological signs and vasogenic oedema in the posterior region of the brain are the characteristics of PRES. Presence of hypertension, uraemia and concomitant use of immunosuppressive therapy increase the likelihood of PRES. The underlying hypothesis is attributed to impairment of blood–brain barrier and cerebral autoregulation.⁹ In our patient, diagnosis of PRES is unlikely as his blood pressure was within normal limit, no prior used of immunosuppressive agents and there was no MRI evidence of vasogenic cerebral oedema.

Thrombotic microangiopathy such as thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome in association with immune-related disorder is another differential diagnosis of seizure. However, there were no hallmark of the disease found in our patient such as microangiopathic haemolytic anaemia, thrombocytopenia or renal biopsy evidence of vascular thrombi.

Interestingly, the choroid plexus and the glomerular basement membrane share some similarities in its morphology, biochemical and molecular composition.^{10–12} Anti-GBM antibodies that were present in the serum as well as from the kidney of a patient diagnosed with Goodpasture's syndrome were also found in choroid plexus. These antibodies were capable of inducing a glomerulonephritis and pulmonary disease as well as inflammation in the choroid plexus. The finding indicates that a similar immune attack exists in both structures.¹³ The injury to choroid plexus may be the cause of raised CSF pressure and seizure.

Diagnosis of Goodpasture's syndrome usually can be made by a detection of circulating anti-GBM antibodies. However, in rare cases, the anti-GBM antibodies are absent, making the diagnosis challenging. Negative anti-GBM antibody test has been described in many series.^{14–17} The absence of circulating anti-GBM antibodies can be explained by its half-life, which is longer in the kidney as compared with those in circulation. The antibodies may have disappeared from circulation during the time of blood taking.¹⁸ Another possible reason for a negative test is that the antibodies may have reacted at different antigen or epitopes and not with the usual epitope $\alpha 3(\text{IV})\text{NC1}$ regions.¹⁸ The predominance of IgG4 autoantibodies subtype is another reason for negative anti-GBM antibody test which was seen in four cases. This can be detected with IgG subclass specific tests

or kidney biopsy.¹⁸ A newer biosensor techniques may improve the sensitivity of detection of circulating anti-GBM antibodies.¹⁹ However, this technique is used in research and is not widely available for routine clinical used.

A more definitive diagnosis can be made by examination of the biopsied kidney under electrofluorescent microscopy, which is typically characterised by crescentic glomerulonephritis with linear immunofluorescent staining of IgG on the glomerular basement membrane. The finding is pathognomonic of Goodpasture's syndrome.^{7 20} In our case, the renal biopsy finding of linear IgG immunofluorescent staining on the basement membrane was still present, even though the biopsy was done 1 month after the treatment. In such case of severe pulmonary–renal involvement, one would expect to see the histological features of crescentic glomerulonephritis. However, these features were absent in our patient, either due to insufficient glomeruli obtained during renal biopsy or to the effect of immunosuppressive medications that were given prior to the biopsy. In focal crescentic glomerulonephritis such as Goodpasture's syndrome, only 5%–25% of glomeruli are involved especially in the early phase of the disease. Thus, more than 20 glomeruli are required for examination under light microscopy for adequate visualisation of crescents.²¹

There are three major components in the treatment of Goodpasture's syndrome; plasmapheresis, immunosuppressive therapy and removal of offending agents. Plasmapheresis helps to remove the circulating antibodies, whereas the immunosuppressive therapy using combination of high-dose corticosteroid and cyclophosphamide prevents new antibody release and rebound hypersynthesis.^{20 22 23} Our patient received plasmapheresis, intravenous methylprednisolone 1 g daily for 3 days followed by oral prednisolone 1 mg/kg in tapering dose and cyclophosphamide 100 mg daily. Treatment described has greatly improved the prognosis of the disease.²⁴

Learning points

- ▶ Neurological symptom is a rare manifestation of Goodpasture's syndrome.
- ▶ In any patient presented with pulmonary–renal syndrome, a high index of suspicion of Goodpasture's syndrome and a rapid clinical diagnosis is required to prevent progression to end-stage renal and pulmonary disease.
- ▶ The possible variant of negative antiglomerular basement membrane antibody makes the diagnosis even more difficult to establish.
- ▶ Renal biopsy is the gold standard diagnostic test but treatment should not be delayed in a case when renal biopsy cannot be carried out immediately.

Contributors IPLT and AA comanage the patient and wrote the manuscript. SAH wrote the manuscript together with IPLT and AA. HJ contribute in histopathology renal biopsy of the patient.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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