CASE REPORT

Goodpasture's disease with late presentation of renal abnormality and anti-GBM autoantibody

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SUMMARY

Goodpasture's disease without circulating autoantibodies is a rare presentation of a rare diagnosis. We present the case of a man aged 17 years who had 3 hospital admissions over a 2-month period with haemoptysis and shortness of breath. Throughout his first 2 admissions, his renal function was normal and anti-glomerular basement membrane (GBM) antibodies were negative. CT pulmonary angiogram during his second admission revealed florid and diffuse alveolar infiltrates. However, high-resolution CT chest performed 4 weeks later showed complete resolution of these changes. On his third admission, he developed acute kidney injury. A repeat CT chest revealed the reappearance of initial findings and anti-GBM antibodies were now positive. Goodpasture's disease was subsequently confirmed with renal biopsy. Our case, with delayed onset of renal impairment, initial seronegativity for anti-GBM antibodies and relapsing and remitting CT findings, emphasises the need to consider this diagnosis in the setting of otherwise unexplained pulmonary haemorrhage.

BACKGROUND

Goodpasture's disease is a rare vasculitis, with an annual incidence in the UK of 0.5 cases per million. Ernest Goodpasture first recognised the disease in 1919, during an influenza epidemic, when a man aged 18 years developed pulmonary-renal symptoms.^{1 2} Goodpasture's disease is now recognised as an autoimmune disorder that characteristically presents as a triad of rapidly progressive glomerulonephritis, pulmonary haemorrhage and circulating anti-glomerular basement membrane (GBM) antibodies. Renal disease, with or without pulmonary involvement, is commonly encountered in anti-GBM disease. However, isolated pulmonary haemorrhage as the principal manifestation of this disease is uncommon.¹

We present an interesting case in which there was a delayed onset of renal involvement, and with it, a delayed detection of anti-GBM antibodies. This case is important as it suggests that anti-GBM antibody levels may not be detected in the early stages of disease, especially in the presence of normal renal function.

CASE PRESENTATION

A man aged 17 years was admitted to our hospital on three occasions over the course of nearly 2 months. He presented each time with haemoptysis and shortness of breath on exertion. He had lost 2 kg in weight over the past year. He did not have any risk factors for pulmonary embolism or

tuberculosis. There was no recent foreign travel and there was no history of epistaxis, mouth ulcers or joint swelling.

His medical history included a tonsillectomy at the age of 4 and a craniotomy and evacuation of a subdural empyema at the age of 12 following a nasal fracture. He was not taking any regular medication and had no known drug allergies. He did not have any significant family history. He was a non-smoker and had three pet dogs.

On first admission, he presented with a 4-day history of haemoptysis following symptoms of a mild upper respiratory tract infection. His oxygen saturations were 98% on room air and there were no abnormal respiratory signs. Blood tests including inflammatory markers, ESR and renal function were normal. D-dimer and HIV tests were negative. Vasculitis screen including ANCA and ANA were also normal and anti-GBM antibodies were not detected. His chest X-ray was reported as normal. Urine dipstick tests were negative. He was discharged with a respiratory clinic follow-up.

Five days after being discharged, he was readmitted with increased haemoptysis and worsening shortness of breath. His oxygen saturations were 91% on room air. Auscultation of the chest revealed fine bibasal crepitations. Blood tests showed normal renal function; however, CRP was slightly raised at 23.5 mg/L. Atypical pneumonia screen, sputum cultures and H1N1 swabs for influenza A were negative. CT pulmonary angiogram (CTPA) performed during this admission showed faint, bilateral alveolar infiltrates. He was treated with piperacillin/tazobactam, clarithromycin, oseltamavir, tranexamic acid and oral prednisolone 40 mg/day. He was discharged on a reducing regime of oral prednisolone and a follow-up high-resolution CT (HRCT) chest was requested as an outpatient.

On his third admission, 2 months after his first presentation, he was readmitted with worsening symptoms of haemoptysis and shortness of breath. His oxygen saturations on room air were 85%. Examination of the chest revealed fine crepitations throughout the lungs. White cell count was $12.1 \times 10^9/L$ and CRP was 91.5 mg/L. Renal function tests were initially normal, with urea 4.9 mg/dL and creatinine 75 $\mu\text{mol/L}$. However, this gradually deteriorated during admission with urea 12.2 mg/dL and creatinine 148 $\mu\text{mol/L}$. There were traces of blood and protein on urine dipstick tests. A repeat vasculitis screen was performed. ANCA and ANA were negative. However, ESR was elevated at 42 mm/hour and anti-GBM antibodies were now detectable at 26.4 EIA units (<0.9 =normal).

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INVESTIGATIONS

CTPA on second admission showed faint, bilateral, florid and diffuse alveolar infiltrate. Yet, HRCT chest 4 weeks later showed resolution of the above changes. During this time, our patient had been on a reducing regime of steroids, which might explain the resolution. During the third admission, a repeat CT chest was performed. This revealed a reappearance of the initial changes, and a worsening of these features (figure 1).

Bronchoscopy and bronchoalveolar lavage were performed during his second admission. This did not reveal any abnormalities other than a growth of *Klebsiella* on culture.

During the third admission, an ultrasound scan of the renal tract was performed. This showed bilateral enlarged kidneys and increased cortical echogenicity with loss of the corticomedullary differentiation, suggestive of parenchymal disease.

DIFFERENTIAL DIAGNOSIS

Our patient was initially treated for atypical pneumonia with macrolide antibiotics. Other possible differentials included hypersensitivity pneumonitis and consequently, he was treated with a course of prednisolone.

TREATMENT

Our patient was treated with piperacillin/tazobactam, clarithromycin and oral prednisolone 60 mg/day. Following the detection of anti-GBM antibodies, he was transferred to a specialist tertiary centre for further management. Renal biopsy was performed which showed a necrotising glomerulonephritis with crescents, which confirmed the diagnosis of anti-GBM disease. He received plasma exchange, intravenous methylprednisolone and cyclophosphamide.

OUTCOME AND FOLLOW-UP

He made an excellent recovery and was discharged on a reducing course of oral steroids and is to have monthly cyclophosphamide infusions.

DISCUSSION

The hallmark in the pathogenesis of anti-GBM disease is the formation and deposition of anti-GBM antibodies along the glomerular and alveolar basement membranes. These autoantibodies target epitopes in the NC1 domain of the α -3 chain of type IV collagen. Type IV collagen is a major component of the glomerular basement membrane, thus damage to this leads to impairment of its ultrafiltration properties.^{3–5} Hence, autoimmunity against these epitopes remains crucial in causing an acute kidney injury. This hypothesis is well supported by the

limited number of cases that report normal renal function in the presence of detectable anti-GBM antibody levels.^{6–11} Clinically, a delay in appearance of anti-GBM antibodies in serum may, therefore, correlate significantly with delayed renal involvement.

However, it is proposed that the development of pulmonary haemorrhage in Goodpasture's disease may be subjected to a non-specific lung injury, in addition to the presence of autoantibodies. This additional injury increases the alveolar–capillary permeability, thus exposing the antigen to the autoantibodies. Respiratory infection (influenza, bacterial infection), fluid overload, high concentrations of inspired oxygen, inhalation of toxins (volatile hydrocarbons, gasoline vapours) and smoking have been recognised as potential triggers.^{2 12–15} It may be that very low levels of circulating anti-GBM antibodies, in the presence of an additional trigger, are sufficient to cause an alveolar injury, which then manifests itself as alveolar haemorrhage. In other words, pulmonary haemorrhage without clinically evident glomerulonephritis, which is seronegative at the same time, may represent early anti-GBM antibody disease. Our patient initially presented with haemoptysis and no active renal involvement, as evidenced by a normal urine dipstick and normal renal function blood tests. It not until his third admission, with relapse of his symptoms, that glomerulonephritis and anti-GBM antibodies were detected. We believe that concurrent respiratory infection may have been the additional precipitant to trigger florid pulmonary disease in our patient. One similar case with delayed appearance of antibodies and delayed renal involvement has been reported.¹ It is debatable whether these cases represent a poorly understood variant of anti-GBM disease that primarily involves the lungs and is not associated with early detectable antibodies. However, we suggest that haemoptysis paired with lack of glomerulonephritis and undetectable anti-GBM antibodies should still prompt physicians to consider this diagnosis.

Failure to detect serum anti-GBM antibodies may also be representative of scientific limitations and technical constraints of the commonly used laboratory assays rather than actual negativity. Cases of biopsy-proven anti-GBM disease have been reported whereby anti-GBM antibodies were undetectable using ELISA or western blotting technique, but instead confirmed using a high-sensitivity biosensor system.¹⁶ Therefore, we postulate that negativity for these antibodies should not exclude the diagnosis of anti-GBM disease, as low levels may not be detectable in the early stages or by standard analytical techniques. From our case and review of the literature, we stress that respiratory physicians should be highly vigilant of this rare diagnosis in the presence of isolated alveolar haemorrhage, despite negative autoantibody results.

Figure 1 CT pulmonary angiogram during the second admission showed florid and diffuse alveolar infiltrates (left image). High-resolution CT 4 weeks later, after a course of oral steroids, was normal (middle image). A third CT was performed 4 weeks after the second, when our patient was readmitted with worsening symptoms. This showed a recurrence and worsening of initial changes (right image).

Learning points

- This case demonstrates that early Goodpasture's disease can be seronegative and clinically associated with a preserved renal function. Physicians should be aware of this presentation when investigating similar cases. We stress the importance of repeating anti-glomerular basement membrane (GBM) antibody levels in patients with ongoing symptoms.
- Physicians should also be aware that standard laboratory techniques may not identify low circulating levels of anti-GBM antibodies.
- Steroids could play a role in blinding typical radiological findings in cases of Goodpasture's disease.

Contributors EAB identified and managed the case, performed a literature search and drafted and revised the report. She is the guarantor. SS identified the case, did the literature search and drafted and revised the report. RY revised the report.

Competing interests None declared.

Patient consent Obtained.

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