

## A Case of Anti Glomerular Basement Membrane (GBM) Negative Goodpasture's Disease

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### Abstract

Goodpasture's disease is a fulminant rapidly progressive disease characterized by autoantibodies to the alpha-3 chain of type IV collagen (Goodpasture's antigen). It can present as a glomerulonephritis alone, or as a pulmonary-renal syndrome with alveolar haemorrhage. We report here a classical case of Goodpasture's disease presenting as a pulmonary-renal syndrome with serum anti-glomerular basement membrane (GBM) antibody negativity and positive perinuclear anti-neutrophil cytoplasm antibodies (p-ANCA).

### Introduction

Goodpasture's disease is a fulminant rapidly progressive disease characterized by autoantibodies to the alpha-3 chain of type IV collagen (Goodpasture's antigen) [1]. It can present as a glomerulonephritis alone, or as a pulmonary-renal syndrome with alveolar haemorrhage [2]. We report here a classical case of Goodpasture's disease presenting as a pulmonary-renal syndrome with serum anti-glomerular basement membrane (GBM) antibody negativity and positive perinuclear anti-neutrophil cytoplasm antibodies (p-ANCA).

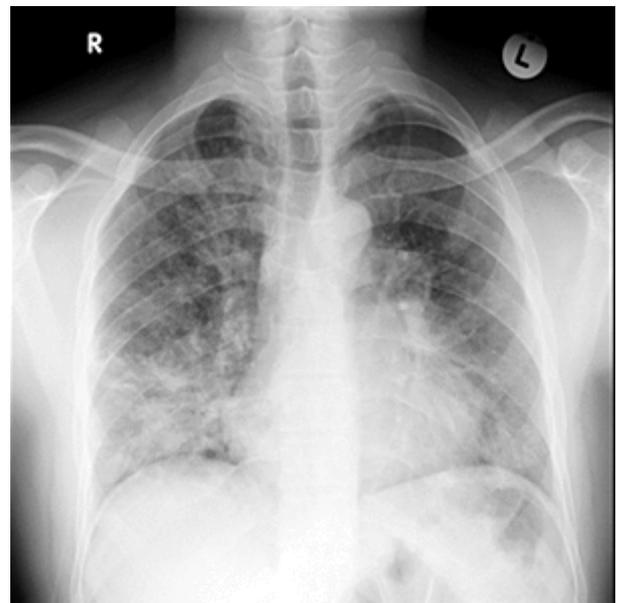
### Case Report

A 41-year-old black man presented to our hospital with a 5-day history of a tight chest, shortness of breath, a non-productive cough and pleuritic chest pain. He did not report any haemoptysis or constitutional symptoms. The patient was a lifelong non-smoker, and there were no relevant occupational or domestic exposures. He had no significant medical history except for a similar episode of shortness of breath a year previously that had been diagnosed by his general practitioner as post-infectious bronchospasm. He did not use any chronic medication, nor recreational drugs.

On examination he was found to be afebrile, pale and mildly tachypnoeic with a respiratory rate of 16 breaths per minute. Harsh breath sounds were heard in the right upper zone but no adventitious sounds were appreciated. Cardiovascular, abdominal and neurological examinations were unremarkable.

A chest X-ray (Figure 1) showed bilateral ground glass opacification, confirmed on high-resolution computerized tomography (CT) of the chest (Figure 2a). There was also an incidental finding of volume loss and saccular bronchiectasis in the left upper lobe (Figure 2b) resulting from an episode of previous pulmonary infection. Urine dipstick testing revealed 1+ blood and 2+ protein. His serum creatinine was 202  $\mu\text{mol/l}$ , and he had a normocytic anaemia with a haemoglobin of 9.9g/dl. Inflammatory markers were elevated (ESR 72, CRP 103.9). Pre- and post flow volume loops showed no

obstruction and mild restriction (forced vital capacity XX% predicted), and his diffusing capacity for carbon monoxide measured by the single breath technique was markedly elevated (129% of predicted).



**Figure 1:** Plain chest radiograph showing a bilateral ground glass opacifications with relative sparing of the left upper lobe.

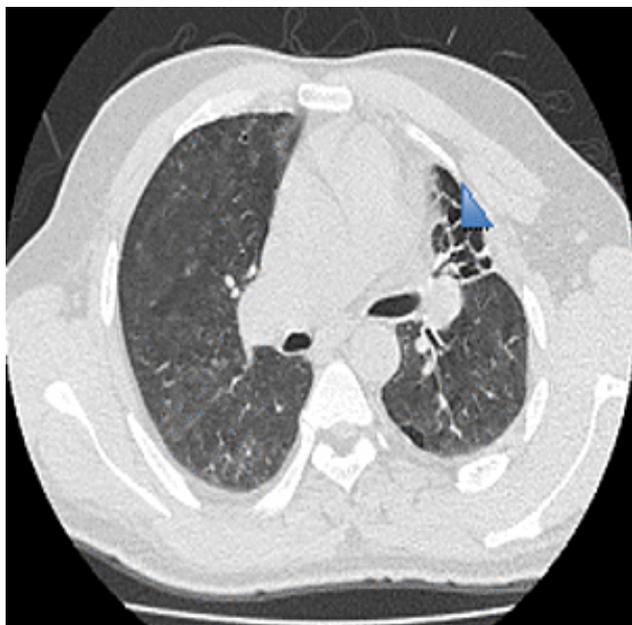
The patient underwent flexible bronchoscopy, with return of a progressively bloody bronchoalveolar lavage (BAL) (Figure 3), confirming the diagnosis of alveolar haemorrhage. Serological studies including HIV, hepatitis B and C panels, complement levels (C3, C4), anti-proteinase-3 (cytoplasmic anti-neutrophil cytoplasm antibodies (c-ANCA) and anti glomerular basement membrane (GBM) antibodies were negative. Anti-myeloperoxidase antibodies (anti-

MPO) (also known as perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA)) were positive.

was initiated (after a negative tuberculosis GeneXpert<sup>®</sup> MTB/RIF test on BAL) due to the high prevalence of tuberculosis in South Africa.



**Figure 2a:** High-resolution CT chest showing patchy ground glass infiltrates predominantly in the right upper lobe, with volume loss and pleural thickening of the left upper lobe.



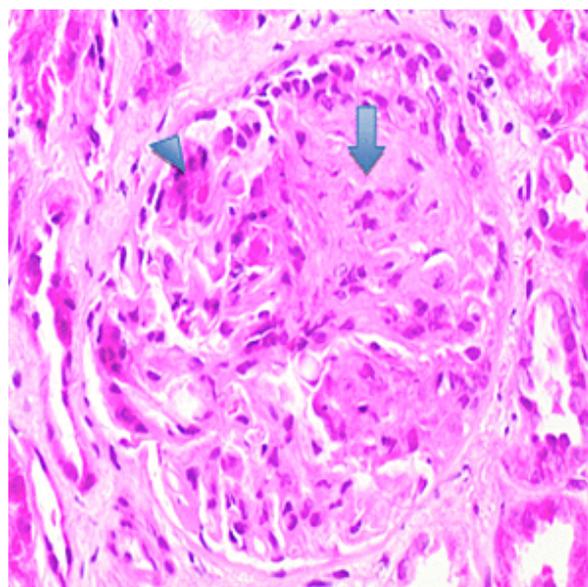
**Figure 2b:** CT chest showing fibrocystic change and volume loss of the left upper lobe (arrowhead)

Urine microscopy revealed a red blood cell casts in keeping with rapidly progressive glomerulonephritis. The patient was pulsed with methylprednisone 500mg intravenously (IV) daily for 3 days, followed by oral prednisolone at a dose of 1mg/kg daily. Isoniazid prophylaxis



**Figure 3:** Bloody bronchoalveolar lavage

Ultrasound-guided renal biopsy yielded 2 cores of renal cortex with 16 glomeruli. Despite serum anti-GBM antibody negativity, the diagnosis of Goodpasture's disease was confirmed by demonstrating the histological features of a rapidly progressive glomerulonephritis (RPGN) with cellular and fibrocellular crescent formation (Figure 4a), with linear deposition of IgG and of C3 at the GBM on immunohistochemistry (Figure 4b).



**Figure 4a:** Renal biopsy with fibrocellular crescent (thick arrow) and necrotic lesion (arrowhead) on H&E stain

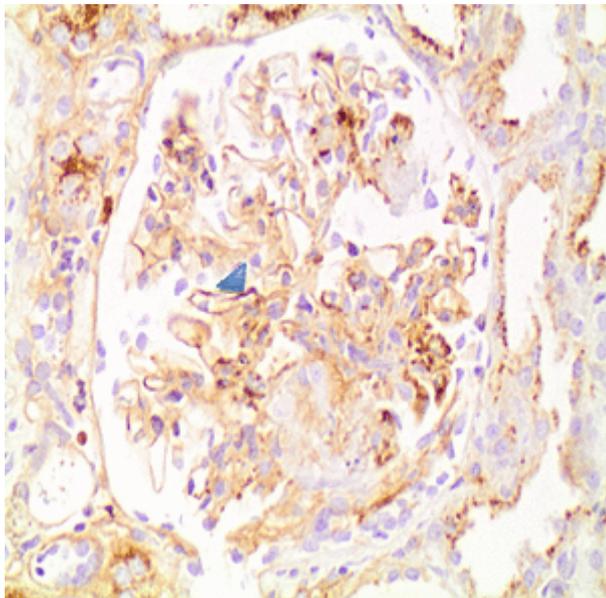


Figure 4b: Linear IgG deposits along the GBM (arrowhead) on immunohistochemistry

Discrete necrotizing foci were also seen. The patient was subsequently treated with 750mg IV cyclophosphamide and plasmapheresis as per the KDIGO working group guidelines [2]. In total, he received 8 sessions of plasma exchange. His renal function stabilized and improved during his hospital admission, and no further episodes of alveolar haemorrhage were noted. He was discharged on oral prednisone with a prolonged taper over 6 months, with two further doses of IV cyclophosphamide administered as an outpatient at monthly intervals. At his 2 month follow-up, he remains well with a serum creatinine of 119  $\mu\text{mol/l}$ , a stable haemoglobin and clear chest x-ray. A repeat p-ANCA was negative.

## Discussion

Goodpasture's disease is a rare condition with an estimated annual incidence of 0.5-1 per million [2]. There is a paucity of published reports describing anti-GBM negative Goodpasture's disease, a clinical situation that causes diagnostic difficulty [3]. Our centre uses standard ELISA techniques to detect circulating anti-GBM antibodies. Cases yielding false negative results with this assay have been described in the literature where the diagnosis was made on renal biopsy [4]. The limitations of this diagnostic assay may be a feasible explanation for our patient's antibody negative disease.

Approximately 20-30% of patients with anti-GBM disease are "double antibody positive" with anti-GBM antibodies and ANCA (typically p-ANCA) – however, they do not seem to have a different clinical course from patients with anti-GBM alone [5]. Our patient, who was p-ANCA positive, had discrete necrotizing foci on his renal biopsy suggesting vasculitic glomerular damage. A possible reason for

this phenomenon is that the vasculitis creates lesions that expose basement membrane, facilitating the formation of anti-GBM antibodies as a secondary phenomenon [6].

Factors predicting renal survival in anti-GBM disease include: serum creatinine and the need for dialysis at presentation, and the percentage of glomerular crescents observed on biopsy [7]. As demonstrated by our case, early presentation and diagnosis with rapid institution of treatment is associated with a favourable outcome. Patients with moderate to severe disease who do not require dialysis upon presentation generally respond well to therapy, with recovery being maintained during long-term follow-up

Plasmapheresis may be stopped when the circulating antibody is no longer detectable, typically after 10-14 treatments [2]. Serial anti-GBM antibody titers could not be measured in this case thus it was difficult to determine the duration and role of plasmapheresis in this patient. His clinical improvement, serum creatinine stabilization and the opinion of an expert nephrologist were relied upon to determine the duration of treatment.

## Conclusion

Early diagnosis and appropriate medical management of anti-GBM disease is important to ensure kidney survival. In the situation of anti-GBM antibody negativity, and in the appropriate clinical context, renal biopsy demonstrating linear deposition of immunoglobulin along the GBM and crescentic glomerulonephritis remains the gold standard to make a diagnosis of anti-GBM disease [8]. Plasmapheresis and immunosuppression with high-dose corticosteroids and cyclophosphamide are the mainstays of treatment.

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