**Case Report**

**Diffuse alveolar haemorrhage in ANCA-negative pauci-immune crescentic glomerulonephritis**

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**Abstract**

Pulmonary renal syndrome (PRS) is a combination of diffuse pulmonary haemorrhage and glomerulonephritis (GN). Though an established form of presentation in anti-neutrophil cytoplasmic autoantibody (ANCA)-associated GN and vasculitis, diffuse pulmonary haemorrhage is extremely unusual in those with ANCA-negative GN. We present here a case of a 76-year-old Hispanic female with stage IV chronic kidney disease (serum creatinine of 2 mg/dL), who presented with diffuse alveolar haemorrhage and nephritic syndrome. Less than 1 week prior to the full-blown PRS, she was treated for an apparent pneumonia as was evidenced by a right lower lobe infiltrate on her chest X-ray. Retrospectively, this was likely a focal pulmonary haemorrhage. ANCA were persistently negative, and the remainder of her immunologic workup was normal. Renal biopsy was diagnostic of crescentic pauci-immune GN. The patient required a ventilator and haemodialysis support (serum creatinine 6 mg/dL), and was successfully treated with methylprednisolone, cyclophosphamide and a total of six cycles of plasmapheresis. Once her oliguria resolved, the creatinine plateaued at 2.7 mg/dL. Our case illustrates that diffuse alveolar haemorrhage can be a distinct clinical feature even in patients with ANCA-negative pauci-immune crescentic glomerulonephritis.

**Keywords:** anti-neutrophil cytoplasmic autoantibodies; diffuse alveolar haemorrhage; pauci-immune crescentic glomerulonephritis; pulmonary renal syndrome

**Introduction**

Pulmonary renal syndrome (PRS) is a combination of diffuse pulmonary haemorrhage and glomerulonephritis (GN). Though an established form of presentation in anti-neutrophil cytoplasmic autoantibody (ANCA)-associated GN, diffuse pulmonary haemorrhage is unheard of in patients with confirmed ANCA-negative GN.
vealed diffuse necrotizing and crescentic pauci-immune 
GN (Figure 1).

The patient was treated with steroids, cyclophosphamide 
and a total of six cycles of plasmapheresis. Her clinical 
course was complicated with ventilator-associated pneu-
monia. After 20 days of intensive care treatment, her renal 
function improved. Haemodialysis was discontinued, and 
the patient was successfully extubated. Oral prednisone 
and cyclophosphamide were continued, and her creatinine 
plateaued at 2.7 mg/dL. Immunofluorescence (IF) testing 
for ANCAs was consistently negative at diagnosis and be-
fore the initiation of immunosuppressive therapy, and re-
mained negative during follow-up.

Discussion

PRS involves diffuse pulmonary haemorrhage with GN and 
can be seen in the setting of various immunologic disorders, 
such as ANCA-associated vasculitis, anti-glomerular base-
ment membrane disease, lupus and cryoglobulinaemia. 
Pauci-immune crescentic GN is basically a manifestation 
of ANCA-associated vasculitis, whereby ANCAs are di-
rected to proteinase 3 (PR3-ANCA) or myeloperoxidase 
(MPO-ANCA). However, as was in our patient, 10% of 
the patients with pauci-immune crescentic GN may lack 
ANCAs [1]. Furthermore, as the name suggest, the typical
renal histology in a case of ANCA-negative pauci-immune crescentic GN is of necrotizing GN associated with little or no glomerular staining for immunoglobulins. Overall, compared with ANCA-positive patients, ANCA-negative patients with crescentic GN have a higher level of proteinuria and poorer renal outcome, but less extra-renal involvement [2].

The usual extra-renal presenting symptoms of ANCA-negative crescentic GN are of vasculitic skin involvement, joint, and muscle involvement resulting in myalgia and arthralgia. In addition, nearly all the patients have atypical constitutional symptoms of fatigue, night sweats, weight loss and fever. Extra-renal involvement in the form of pulmonary infiltrates is rare in ANCA-negative GN. Case reports of pulmonary infiltrates with cavity lesions and bronchiolitis obliterans organizing pneumonia have been reported in the past [1,3]. Diffuse pulmonary haemorrhage is however extremely unusual in those with ANCA-negative GN. Part of this may be related to the underlying mechanism. In ANCA-positive cases, the autoantibodies (usually IgG) activate the neutrophils by binding to the Fab2 or Fc receptors. This would thus lead to endothelial cell apoptosis and necrosis manifesting as pulmonary haemorrhage in the lungs. On the other hand, the exact mechanism of pulmonary haemorrhage in ANCA-negative cases is unclear. Some of the extra-renal manifestations in ANCA-negative cases have been postulated to involve other unidentified autoantibodies or T-cell-dependent mechanisms, thus also leading directly or indirectly to a systemic neutrophilic activation [1]. This may have been the underlying pathophysiology of pulmonary haemorrhage in our patient. The fact that our patient responded well to plasmapheresis and other immunosuppressive therapies further supports this theory.

Due to ANCA negativity and atypical presenting symptoms, a delay in the diagnosis exposes the kidney to a chronic smouldering disease activity or rapid progression of irreversible renal lesions. One week prior to the acute renal failure, our patient presented with signs and symptoms of pneumonia. Retrospectively, the chest X-ray at that time was likely an early manifestation of localized pulmonary haemorrhage. Since signs and symptoms in vasculitis syndromes can wax and wane from time to time, it may also explain the patient’s initial symptomatic improvement, only to be later presenting as a full-blown PRS.

**Conclusion**

Pulmonary renal syndrome in the form of diffuse pulmonary haemorrhage is not limited to ANCA-associated glomerulonephritis/vasculitis but can occur in patients with ANCA-negative crescentic glomerulonephritis. The underlying immune mechanism may be related to an unidentified autoantibody or a T-cell-dependent mechanism.
Conflict of interest statement. None declared.

References

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