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

Case presentation

A 76-year-old Hispanic female with a past medical history of hypertension, diabetes mellitus, hypercholesterolaemia and chronic kidney disease (stage IV; baseline creatinine 2.0 mg/dL) presented with a 3-day history of fever, productive cough and pleuritic chest pain. Physical examination was remarkable for decreased air entry in her right lung base. Chest X-ray revealed right lower lobe infiltrates, and the patient was treated for community-acquired pneumonia. She demonstrated symptomatic improvement after 3 days of intravenous antibiotics and was therefore discharged from the hospital on the third day. The patient was advised to complete the course of oral antibiotics and to be followed up as an outpatient in the clinic.

Two days later, she presented to the emergency department with worsening shortness of breath. On examination, her respiratory rate was 22 breaths/minute, pulse 98 beats/minute and blood pressure 154/80 mmHg. The patient’s oral temperature was 39°C, and she had diffuse bilateral crackles on her lung examination. Chest X-ray showed bilateral patchy infiltrates (Figure 1). The patient was now started on intravenous vancomycin and ceftriaxone. The basic laboratory panel was suggestive of an acute-on-chronic renal failure with nephritic syndrome (Table 1). Her condition worsened over the next 24 h as she developed massive haemoptysis and severe hypoxaemia, requiring intubation. Posterior bronchoscopy revealed diffuse alveolar haemorrhage with bleeding predominantly in the lower lobes. Blood culture, respiratory culture and urine culture showed no growth, and no organisms were isolated from the bronchoalveolar lavage. Antinuclear antibody (ANA) was 1:80, and the remainder of the immunology panel was essentially normal (Table 1).

In view of PRS, the patient was started on steroids (methylprednisolone pulse of 1 g for 3 days). By the third hospital day, haemodialysis had to be initiated for worsening renal failure and oliguria (creatinine 6 mg/dL). Repeat immunology panel was unchanged from the previous values, and therefore, a renal biopsy was performed. It re-
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 pneumonia. 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 before the initiation of immunosuppressive therapy, and remained 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 basement membrane disease, lupus and cryoglobulinaemia. Pauci-immune crescentic GN is basically a manifestation of ANCA-associated vasculitis, whereby ANCAs are directed 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

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**Fig. 1.** (a) Diffuse bilateral patchy infiltrate. Bronchoscopy revealed diffuse alveolar haemorrhage. One week prior to this chest X-ray, the infiltrate was limited to the right lower lobe and hence the suspicion of community-acquired pneumonia. (b) Light microscopy: segmental cellular crescent with rupture of the glomerular basement membrane (GBM) at 4 o’clock position resulting in fibrin extravagation into Bowman’s space 7–11 o’clock position. Eleven of 15 non-sclerotic glomeruli were involved with cellular crescents, 5 glomeruli displayed global sclerosis and 8 glomeruli displayed segmental scars with evidence of fibrocellular or fibrous crescents. These findings equate to severe activity and moderate chronicity. (c) Immunofluorescence for fibrin: segmental staining of the glomerular tuft, associated with rupture of the GBM resulting in fibrinoid necrosis. The immunofluorescence findings of trace to 1+ segmental to global granular mesangial staining for IgM and C3 as well as the segmental staining for fibrin supported a diagnosis of pauci-immune crescentic glomerulonephritis. (d) Vascular cross section: moderate arteriosclerosis. No evidence of vasculitis. Final diagnosis: diffuse necrotizing and crescentic pauci-immune glomerulonephritis.
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 cavitary 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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