Sequential development of pulmonary renal syndrome associated with c-ANCA 3 years after development of anti-GBM glomerulonephritis

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Introduction

There is evidence that there is an association between anti-glomerular basement membrane (anti-GBM) antibodies and anti-neutrophil cytoplasmic antibodies (ANCA) in the development of pulmonary renal syndrome (PRS) [1–7]. Whether these two distinct circulating auto-antibodies have some pathological interaction remains unclear. Studies have shown that 30% of patients with anti-GBM disease will test positive for ANCA [1,8]. There is evidence in these studies that the presence of both anti-GBM and ANCA auto-antibodies may lead to a better clinical course than in patients with anti-GBM disease alone regardless of c- or p-ANCA specificity. This suggests that dual positivity is not just an epiphenomenon, but may be pathologically linked.

Cases of vasculitis developing after anti-GBM disease have been reported, but it is uncertain whether these cases are incidental. We present here a case of anti-GBM glomerulonephritis where a patient had dual positivity of anti-GBM and c-ANCA/PR3 and then 3 years later developed c-ANCA/PR3 associated pauci-immune vasculitis. There are other cases in the literature where patients who have initially been diagnosed with anti-GBM disease subsequently develop p-ANCA/MPO PRS [2–4,7,9]. Most of these cases did not have dual positivity on initial presentation. Our case, included with others, supports a potential link in the underlying disease process leading to both anti-GBM disease and ANCA associated vasculitis that is not related to ANCA specificity.

Case report

An 86 year-old gentleman with a history of hypertension and benign prostate hypertrophy was seen by the nephrology service in April 2003 for non-oliguric renal failure. In January 2003, he developed a non-productive cough, rhinorrhea, dyspnoea, fatigue, chills and anorexia for 6 weeks. He went to another facility in March, at which time investigation revealed: urea 16.8 mmol/l, creatinine 259.3 µmol/l, urinalysis 1 + protein and 25–30 red blood cells. Previous labs in September 2002 revealed: urea 5.4 mmol/l and creatinine 91.5 µmol/l.

He was discharged from the hospital on levofloxacin for 7 days for a presumptive upper respiratory tract infection and referred back to his primary care physician for follow-up. He was seen several days later and was found to have worsening renal lab abnormalities: urea 42.8 mmol/l and creatinine 892.9 µmol/l. He had no further upper respiratory symptoms, but continued to complain of generalized fatigue. He had no fevers, chills, haemoptysis, haematuria, rash or arthritis. Other than the recent upper respiratory infection, he had no history of lung or sinus problems. His blood pressure was 164/80 mmHg, pulse 78 and he was afebrile. Physical exam revealed a mildly pale elderly gentleman with clear lungs, no evidence of oedema and no rash. Investigations revealed: white blood cell count 3.0 × 10⁹/l, haemoglobin 8.2 g/dl; urine analysis 3+ protein, 3+ blood, 5–10 white blood cells and too numerous to count red blood cells; spot protein/creatinine ratio was 2.32. C3 and C4 normal, ANA negative. c-ANCA titre 1:1280 and p-ANCA titre <1:20 (normal <1:20 for both). Enzyme-linked immunosorbent assay MPO antibody <5.0 EU/ml and PR3 antibody 57.5 EU/ml (normal <5 EU/ml for both). Anti-GBM titre 6.1 EU/ml (≤5.0 negative). (Table 1). Ultrasound of kidneys
revealed 11.2 cm right kidney and 12.0 cm left kidney with mild increased echogenicity and thinning of the cortex.

Renal biopsy revealed 27 non-sclerotic glomeruli and 2 globally sclerotic glomeruli (Figure 1). All non-sclerotic glomeruli were abnormal exhibiting prominent endo- and extra-capillary hypercellularity with cellular crescents in most glomeruli. Glomeruli contained neutrophils and fibrin deposition. The interstitium contained diffuse infiltrate of mononuclear cells and neutrophils with focal tubulitis. Tubular loss was estimated at 20% with accompanying interstitial fibrosis. Direct immunofluorescence contained 10 glomeruli showing intense linear staining of the glomerular basement membrane with IgG and patchy deposition of C3 (Figure 2). Fibrin stain showed bright staining in many of the crescents.

Since there was a significant elevation in the c-ANCA levels and since the anti-GBM level was only borderline elevated, there was a concern prior to the biopsy that the patient had a pauci-immune vasculitis vs anti-GBM disease. There are false negatives in enzyme-linked immunosorbent assay up to 13% as well as false negatives in western blotting techniques for the detection of anti-GBM [10,11]. It also appears to be a characteristic of patients with dual positivity to have lower titres of anti-GBM than in patients with positive anti-GBM alone [8]. The diagnosis of anti-GBM disease was determined given the intense linear staining of the glomerular basement membrane, severe activity in the biopsy and the lack of other disease entities in this patient that can also cause linear staining such as diabetes mellitus, systemic lupus erythematosus and multiple myeloma.

The patient was initiated on haemodialysis and started on IV methylprednisolone for 3 consecutive days and then high-dose prednisone daily. Cyclophosphamide and plasmapheresis were started after biopsy results returned. Plasmapheresis was limited to 3 sessions after anti-GBM levels returned to <5 EU/ml almost immediately. After 2 months of therapy, the patient had not been able to come off dialysis and he was taken off all immunosuppressants.

He had been relatively stable until one year later where he developed haemoptysis. His evaluation included a bronchoscopy, which revealed negative cultures and no evidence of bronchial alveolar haemorrhage. Anti-GBM antibody levels were <1 EU/ml (As of 3/06: normal <20.9). C-ANCA titre was elevated at 1:640 while p-ANCA remained <1:20 (normal <1:20 for both). PR3 antibody remained elevated also at >320 EU/ml (normal <5 EU/ml) (Table 1).

Three years after his initial presentation, he presented with gross haematuria and haemoptysis. Computed tomography of the chest revealed diffuse bilateral alveolar air space infiltrates, and bronchoscopy revealed diffuse bloody secretions in the central airways without clearing after lavage. Pathology revealed many haemosiderin latent macrophages and all cultures were negative. A punch skin biopsy of a rash found on his lower extremities revealed acute purpuric haemorrhage. CT of the sinuses revealed right mastoid opacification. CT of the abdomen and pelvis and cystoscopy revealed no cause of his haematuria. Lung and kidney biopsy were not pursued due to his overall clinical condition.

Plasmapheresis was initiated for 2 weeks and the patient was given IV methylprednisolone for 3 days.

Table 1. Antibody levels

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<tr>
<td>C-ANCA (titre)</td>
<td>1:1280</td>
<td>1:640</td>
<td>1:640</td>
<td>1:120</td>
<td>1:20</td>
<td>1:120</td>
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<tr>
<td>P-ANCA (titre)</td>
<td>&lt;1:20</td>
<td>&lt;1:20</td>
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<td>MPO (EU/ml)</td>
<td>&lt;5.0</td>
<td>&lt;5.0</td>
<td>&lt;5.0</td>
<td>&lt;5.0</td>
<td>&lt;5.0</td>
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<tr>
<td>PR3 (EU/ml)</td>
<td>57.5</td>
<td>36.0</td>
<td>&gt;320.0</td>
<td>&gt;320.0</td>
<td>115.7</td>
<td>&lt;5.0</td>
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<tr>
<td>Anti-GBM Ab (EU/ml)</td>
<td>6.1</td>
<td>&lt;5.0</td>
<td>&lt;5.0</td>
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C-ANCA, cytoplasmic anti-neutrophil cytoplasmic antibodies; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; PR3, proteinase-3; MPO, myeloperoxidase.

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He was then initiated on prednisone and oral cyclophosphamide. His haemoptysis, gross haematuria and rash resolved. He developed thrush and progressive anorexia. The patient decided to discontinue all medical therapy and he expired soon after.

Discussion

In Goodpasture’s/PRS syndrome, anti-type IV collagen disease with predominance of anti-GBM antibodies to \( \alpha 3 \) (IV) NC1 has been proposed as the pathophysiological mechanism by which patients develop glomerulonephritis and pulmonary haemorrhage [12,13]. In pauci-immune vasculitis, ANCA appears to have a direct role in the pathogenesis of Wegener’s and microscopic polyangiitis [14]. Even in the presence of dual positivity, there appears to be no direct cross-reactivity between these antibodies supporting the concept that both anti-GBM disease and ANCA vasculitis are two separate pathological entities [15]. However, it has been postulated that either ANCA-related vasculitis or the underlying processes causing the vasculitis leads to exposure or alterations to the basement membrane that leads to autoimmune reactivity [1,6,15]. More specifically, it has been speculated that anti-GBM glomerulonephritis/PRS may be initiated by ANCA-related protease damage or exposure of epitopes of \( \alpha 3 \) (IV) collagen in the glomerular basement membrane [16]. Potential inciting events include: infection, toxin exposure, renal injury, neoplasia, neoantigens and endogenous antigens [4,12,17].

There are reports that dual positivity in anti-GBM disease leads, at least for some patients, to a different clinical course. Generally patients who are on dialysis due to anti-GBM disease do not have significant renal recovery regardless of therapy [12]. On the other hand there is evidence that for some patients with dual positivity, there has been significant renal recovery after initiating dialysis [1,8]. Although anti-GBM disease can rarely recur, ANCA-associated vasculitis has a recurrence rate of 30–60% depending on the antibody and disease [18–20]. There is evidence that there are higher relapses when dual positivity of ANCA and anti-GBM auto-antibodies exists compared with anti-GBM alone [6,8]. Given the potential risk of relapse, there is a benefit in monitoring ANCA levels in this subgroup of patients. There may also be other clinical consequences of a systemic vasculitis in patients with dual positivity. There are some patients who have evidence of extra-glomerular vasculitis as well as other clinical involvement outside the pulmonary and renal systems [1,8]. All these differences support the concept that dual positivity may lead to a mix of vasculitis and anti-GBM disease.

Patients with dual positivity are more likely to have a p-ANCA pattern and a higher specificity to MPO vs PR3 [1,6,8,12]. Reports by Peces et al. [4] and Vanhille et al. [21] identified cases of MPO-ANCA associated vasculitis developing sequentially after anti-GBM disease. However, in both cases, ANCA was negative on initial presentation. One could argue that these two patients may have had two separate diseases occurring completely independently of each other. On the other hand, the case from Verburgh et al. [7] reveals a case of anti-GBM with dual positivity of anti-GBM and p-ANCA/MPO auto-antibodies leading to PRS and then the development 5 years later of p-ANCA/MPO associated PRS. Our case is similar, and both cases suggest that the ANCA positivity may be pathogenic in anti-GBM disease with dual positivity rather than an incidental finding and can lead clinically to vasculitis. Although MPO specificity is the predominant pattern found in dual positivity, our case suggests that this phenomenon can be seen either with MPO or PR3 suggesting an injury leading to glomerular membrane damage and anti-GBM disease is not related to specific ANCA positivity or PR3/MPO specificity. This phenomenon may also be unrelated to a specific vasculitis such as Wegener’s or microscopic polyangiitis, but rather to a more generalized injury in conjunction with a complex immune response.

Our case is unique in that it is the first reported case of the sequential development of dual positivity anti-GBM glomerulonephritis and then c-ANCA/PR3 vasculitis years later. Dual positivity with anti-GBM and ANCA is well known but the pathological connection of both auto-antibodies is still questionable. Our case suggests that there is some pathological interaction albeit perhaps a more generalized injury connecting these two diseases rather than an epiphenomenon. This phenomenon is related to both c- or p-ANCA and PR3 or MPO specificity. It also appears that this pathological connection may ultimately lead to significant clinical differences. Given our case, patients with dual positivity with c-ANCA/PR3 on initial presentation may need continued close monitoring for detection of PRS.

Conflict of interest statement. None declared.

References


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