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# PULMONARY HEMORRHAGE AND CRESCENTIC GLOMERULONEPHRITIS IN A PATIENT WITH SEROPOSITIVE ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE AND ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODIES

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**SUMMARY** – Anti-glomerular basement membrane (anti-GBM) disease is an acute and life-threatening systemic autoimmune disorder. The coexistence of circulating anti-neutrophil cytoplasmic antibodies (ANCA) and anti-GBM disease, the so-called double-positive disease (DPD), is exceptionally rare. We report a unique case of DPD manifesting as pulmonary-renal syndrome (PRS) in a 46-year-old woman who first presented with clinical and radiological suspicion of pneumonia. Chest computed tomography scan later revealed bilateral alveolar hemorrhage. Kidney biopsy showed necrotizing crescentic (100% glomeruli) glomerulonephritis. On immunofluorescence microscopy, glomeruli were global linear positive for IgG, confirming anti-GBM disease. Double positivity was detected for circulating anti-myeloperoxidase ANCA (p-ANCA) and anti-GBM antibodies. Acute renal failure evolved rapidly. Therapeutic plasma exchange (TPE) and hemodialysis (HD) were initiated early in combination with intravenous pulse corticosteroid therapy followed by oral methylprednisolone and cyclophosphamide. Pulmonary hemorrhage resolved, but renal function could not be preserved. The patient remains HD dependent. This case report highlights that pulmonary symptomatology may be the leading clinical presentation of PRS, with initially normal renal function at DPD onset. Early recognition and diagnosis are therefore crucial to timely clinical intervention. The role of prompt kidney biopsy and initiation of TPE and HD in PRS must not be underestimated.

**Key words:** *anti-glomerular basement membrane (anti-GBM) disease, Goodpasture's syndrome, p-ANCA (anti-neutrophil cytoplasmic antibodies), pulmonary-renal syndrome, rapidly progressive glomerulonephritis with pulmonary hemorrhage*

## Introduction

Anti-glomerular basement membrane (anti-GBM) disease is a small vessel vasculitis mediated by in situ immune complex formation<sup>1</sup>. Anti-GBM disease clinically manifests as either Goodpasture's syndrome (GPS; the lungs and kidneys affected

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together), isolated anti-GBM glomerulonephritis, or isolated anti-GBM pulmonary hemorrhage. In the kidneys, anti-GBM disease usually presents as rapidly progressive glomerulonephritis (RPGN) and is suspected when detection of circulating or tissue-specific anti-GBM antibodies is associated with alveolar and/or glomerular involvement<sup>2,3</sup>.

In a subset of RPGN cases with crescentic changes, the rare presence of double-positive disease (DPD) is confirmed when both anti-GBM antibody and anti-neutrophil cytoplasmic antibodies (ANCA) are serologically detected<sup>4,5</sup>. Positivity for ANCA, predominantly anti-myeloperoxidase antibody (p-ANCA), is reported to occur in 10-40% of patients with anti-GBM disease<sup>4,6</sup>. The pathophysiological mechanism for this dual occurrence remains unclear. It is hypothesized that ANCA may play an important role in the development of anti-GBM disease by causing damage to the GBM and exposing the target antigen, thereby triggering production of anti-GBM antibodies<sup>7</sup>. The correct diagnosis and initiation of treatment may be delayed in some patients with DPD due to an atypical presentation of pulmonary-renal syndrome (PRS)<sup>8</sup>.

Herein, we describe a unique case of DPD manifesting as PRS. Contrary to previous reports, pulmonary symptomatology consisting of protracted cough and suspected bilateral pneumonia was the leading clinical presentation in this female patient with initially normal renal function. This report serves to remind clinicians that emphasis should be placed on prompt recognition of PRS, including kidney biopsy to confirm diagnosis, as well as timely initiation of treatment, including therapeutic plasma exchange (TPE) and hemodialysis (HD).

### Case presentation

A 46-year-old woman, non-smoker, with an unremarkable past medical history, presented to an internist with cough and breathlessness on exertion lasting several days. She was prescribed oral antibiotic treatment, but her symptoms persisted and progressively worsened. Following an additional course of oral antibiotics for clinically and radiologically suspected bilateral pneumonia, the patient was hospitalized due to unrelenting febrile illness. At admission, she was tachycardic, febrile, eupneic at rest, mildly hypertensive, and had some inspiratory wheezing sounds bilaterally on chest

auscultation. Laboratory findings initially showed normal kidney function (creatinine 117  $\mu\text{mol/L}$ , urea 4.5 mmol/L), elevated erythrocyte sedimentation rate ( $>130$  mm/3.6 ks), raised inflammatory markers (L 11.78  $\times 10^9/\text{L}$ , neutrophils 83.2%, CRP 255.7 mg/L, fibrinogen 9.2 g/L), mild normocytic anemia (E 3.75  $\times 10^{12}/\text{L}$ , Hb 104 g/L, Hct 0.322 L/L, MCV 85.9 fL), proteinuria (1+) and erythrocyturia (2+), pathologic urine sediment (L 10-15, E 17-20, bacteria 1+), and normal total serum protein (76.6 g/L). Immunological tests revealed normal levels of rheumatoid factor (RF, 9.81), complement (C3 1.59, C4 0.40), and thyroid hormones (T3 4.51 pmol/L, T4 22.1 pmol/L, TSH 3.32 mIU/L). Positive thyroid antibodies (antiTG 543.37, antiTPO 963.87) indicated the presence of autoimmune disease (i.e., Hashimoto thyroiditis).

Chest X-ray and computed tomography scan of the thorax revealed bilateral hilar enlargement, with right-sided prominence, coarse reticular interstitial markings, and post-pneumonic changes at the right lung base. Concomitant broad-spectrum parenteral and oral antibiotic therapy was administered. Nevertheless, the patient continued to deteriorate. Acute renal failure rapidly ensued (creatinine 623  $\mu\text{mol/L}$ , urea 21.4 mmol/L), and she also developed hemoptysis. Repeat chest X-ray showed significant radiological progression, including perihilar alveolar-type infiltrates in the right lung field, suggestive of alveolar hemorrhage.

Aggressive therapy was promptly initiated. The first five days of hospitalization included daily HD and TPE (5% albumin and fresh frozen plasma) followed by intermittent sessions (total of 10 TPE and 11 HD). On day two, high dose immunosuppressive medication (intravenous methylprednisolone sodium succinate at 1 gram and oral cyclophosphamide at 250 mg after plasmapheresis) was administered for three days followed by standard tapering protocol. On day eight, oral steroids (methylprednisolone at 80 mg/day for five days) were started, then reduced to 60 mg daily until discharge. Antibiotics, as well as other supportive and symptomatic measures, including blood transfusions, were also given. Despite timely and aggressive treatment, renal impairment did not improve (urea 35.7, creatinine 667). Supplementary immunologic laboratory tests using indirect immunofluorescence were positive for both p-ANCA (33 U/mL) and anti-GBM (145 IU/mL). Thus, GPS was highly suspected and kidney biopsy was performed.

Light microscopy (Fig. 1 a-b) revealed diffuse necrotizing and crescentic glomerulonephritis with cellular crescents in 100% of glomeruli. There were also signs of severe acute tubular injury and moderate interstitial inflammation. There were no chronic changes. Direct immunofluorescence examination (Fig. 1 c) showed weak to 1+ positive linear staining along the glomerular basement membrane for IgG, C3, and lambda and kappa light chains. Electron microscopy analysis of a single glomerulus with necrosis and cellular crescent revealed diffuse effacement of podocyte foot processes and extensive podocyte cytoplasmic vacuolization. There were no significant immune deposits.

Repeat serological tests for both anti-GBM and p-ANCA were positive, consistent with a diagnosis of DPD. The patient's condition and renal function began to improve (i.e., urea 15.4, creatinine 474, L 3.2, CRP 23.4, fibrinogen 2.1). She was discharged following a reducing course of oral steroids (60 mg of methylprednisolone) and oral cyclophosphamide (150 mg). Six months later, repeat immunological tests were negative. In the meantime, however, renal function had progressively deteriorated. At the latest follow-up approximately two years after initial presentation, the patient was still on chronic HD treatment given her severe renal failure (creatinine 799  $\mu\text{mol/L}$ , urea 22.8 mmol/L, and potassium 6.5 mmol/L).

## Discussion

GPS is a rare disease, occurring in 0.5 to 1 case per million inhabitants per year<sup>6,9</sup>. It is diagnosed in 10-20% of all patients with RPGN and has a poor prognosis with a high mortality rate<sup>10</sup>. GPS is characterized by the presence of circulating anti-GBM antibodies; in 20-35% of patients, p-ANCA is present simultaneously<sup>6</sup>. The low prevalence of DPD may be due to under-recognition of the coexistence of these autoantibodies<sup>4</sup>. Antibody testing should therefore be performed at the same time for both anti-GBM and ANCA in patients with renal disease<sup>6</sup>.

In previous research, GPS has been found to be associated with other autoimmune diseases. The case described above also had positive serum anti-thyroid antibodies (i.e., autoimmune thyroiditis). Ara *et al.* demonstrated a high prevalence of serum anti-thyroid antibodies in patients (45% or 16/35) with anti-GBM antibody-mediated disease, thus suggesting a possible pathologic link between the two entities<sup>11</sup>.

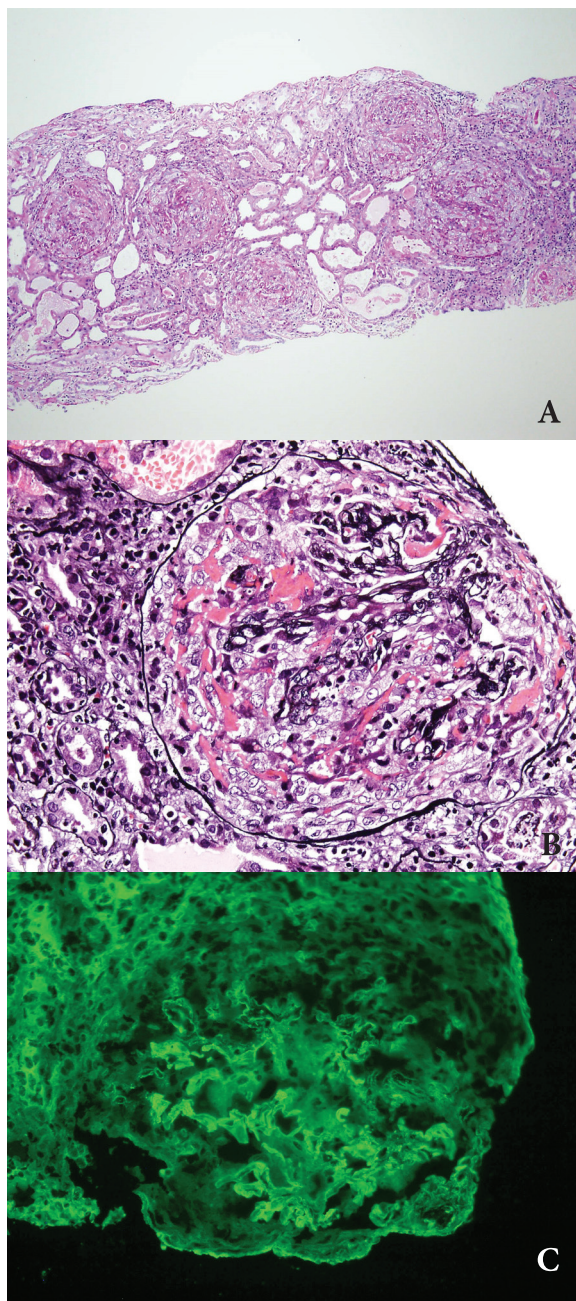


Fig. 1. Photomicrograph of kidney biopsy by: (a) light microscopy on low magnification showing the renal cortex with diffuse crescentic glomerulonephritis and acute tubular injury (Periodic acid-Schiff stain,  $\times 100$ ), (b) light microscopy on high magnification showing a glomerulus with cellular crescent and necrosis (Jones stain,  $\times 400$ ), and (c) direct immunofluorescence microscopy revealing a single glomerulus with weak linear positivity for IgG along the glomerular basement membrane (direct immunofluorescence,  $\times 400$ ).

Poor prognostic factors in GPS include advanced renal failure at presentation (i.e., high initial serum creatinine level) and crescents present in more than 50% of glomeruli<sup>12</sup>. Although the patient presented here had proteinuria, erythrocyturia, and pathologic urine sediment together with pulmonary symptoms at the beginning of the disease, the renal function was normal, but rapidly deteriorated to acute renal failure. On renal biopsy, crescents were seen in 100% of the observed glomeruli. Given that GPS is associated with high mortality rate, kidney biopsy is recommended in every patient with pulmonary symptoms and urine abnormality (proteinuria, erythrocyturia, and pathologic urine sediment)<sup>13</sup>. If the biopsy confirms GPS, aggressive treatment is indicated (TPE, steroids and immunosuppressive therapy).

Overall survival of patients with GPS with dialysis-dependent renal failure at initial presentation has been reported to be 65% at one year follow-up, whereas renal survival was poor at 8%<sup>14</sup>. Lindic *et al.* summarized a small case series of patients with DPD in which those with serum creatinine concentration < 500  $\mu\text{mol/L}$  (i.e. a single patient) on admission had a 100% one-year patient and renal survival, respectively, in comparison to levels > 500  $\mu\text{mol/L}$  (i.e., 7 patients) with 57% and 0% survival, respectively<sup>15</sup>. In the latter group, as in the current case, renal function did not recover regardless of aggressive treatment with methylprednisolone, TPE, and cyclophosphamide<sup>15</sup>.

Lung involvement in GPS, such as pulmonary hemorrhage (PH), appears to be associated with exposure to several inhaled pulmonary irritants, such as tobacco smoking<sup>2</sup>. It has also been postulated that infection may initiate anti-GBM antibody production, leading to alveolar and/or renal damage as some cross-reactivity is reportedly shared between group A type 12 streptococcal cell membrane and human GBM<sup>16</sup>. The patient described herein was a lifetime non-smoker, had a protracted respiratory infection, and later developed PH, thus lending support to the infection-associated hypothesis.

Optimal treatment of patients with DPD remains unclear. In addition to immunosuppressive therapy, the removal of immune complexes in GPS involves TPE, a method that was first used in the early 1970s<sup>10</sup>. TPE is currently considered a grade 1B recommendation in patients who are at presentation dialysis independent, 1C when diffuse alveolar hemorrhage is present, and 2B if there is dialysis dependence at presentation without

diffuse alveolar hemorrhage<sup>17</sup>. Both circulating anti-GBM and p-ANCA antibodies became undetectable following TPE in the described patient, who was initially dialysis independent. In addition, pulmonary symptoms and radiological lung changes showed improvement. However, notwithstanding prompt and aggressive treatment, renal function could not be recovered and the patient remained HD dependent.

Relapse or recurrence of disease activity is possible in PRS, presenting as PH and detectable serum p-ANCA many months after clinical remission with negative anti-GBM antibodies<sup>15</sup>. In a case detailed by Klasa *et al.*, life-threatening relapse involving intrapulmonary hemorrhage, reappearance of serum anti-GBM antibody, and hematuria, occurred following a five-year remission<sup>18</sup>. Patients with DPD seem to have higher recurrence rates than those with anti-GBM antibodies alone<sup>19</sup>. Therefore, close and long-term follow-up is imperative due to the relapsing nature of the ANCA component of the disease<sup>15,19</sup>.

In conclusion, DPD is a very rare autoimmune disorder with high rates of morbidity and mortality. Screening for both anti-GBM and ANCA antibodies, in addition to kidney biopsy, should be undertaken in patients presenting with lung involvement and urine abnormalities. Renal function, however, may not be impaired at onset of DPD. Pulmonary infiltrates (i.e., alveolar hemorrhage) on radiological work-up may be initially misdiagnosed as pneumonia, thus delaying proper diagnosis. Early recognition of PRS, even in atypical presentations, is necessary to initiate aggressive therapeutic management (TPE, steroids and immunosuppressive therapy, as well as HD for renal failure when indicated) in a timely manner. Careful monitoring over the long-term is crucial due to the higher relapse rates in patients with DPD than in those with anti-GBM antibodies alone.

#### **Informed consent:**

Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images or figures related to this case report.

#### **Author disclosure statement:**

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## Sažetak

## PLUĆNO KRVARENJE I GLOMERULONEFRITIS S POLUMJESECIMA U PACIJENTU SA SEROPOZITIVNOM ANTIGLOMERULARNOM BOLESTI BAZNE MEMBRANE I ANTI-NEUTROFILNIM CITOPLAZMIČNIM ANTITIJELIMA

K. B. Sreter, D. Pavlović, M. Tomić, P. Šenjug i D. Galešić Ljubanović

Bolest protiv glomerularne bazalne membrane (anti-GBM) je akutna i po život opasna sistemska autoimuna bolest. Pojava cirkulirajućih antitijela na citoplazmu granulocita (engl. *anti-neutrophil cytoplasmic antibody*, ANCA) u bolesnika sa anti-GBM glomerulonefritom, tako zvana dvostruko pozitivna bolest (engl. *double-positive disease*, DPD), je vrlo rijetka. Prikazujemo 46 godišnju bolesnicu u koje je prvo klinički i radiološki postavljena sumnja na upalu pluća, a koja se kasnije manifestirala sa pulmo-renalnim sindromom (PRS) odnosno DPD. Kompjutorskom tomografijom pluća dokazano je alveolarno krvarenje. Biopsijom bubrega dokazan je nekrotizirajući glomerulonefritis (100 % glomerula). Imunofluorescencija je pokazala pozitivne linearne IgG depozite, što odgovara anti-GBM glomerulonefritisu. U bolesnice su dokazana antitijela na mijeloperoksidazu p-ANCA i antitijela na glomerularnu bazalnu membranu. Liječena je terapijskom izmjenom plazme (engl. *therapeutic plasma exchange*, TPE), hemodijalizom te kombinacijom parenteralne pulsne terapije kortikosteroidima, kasnije oralnom primjenom metilprednisolona i ciklofosfamida. Došlo je do regresije krvarenja u plućima ali se bubrežna funkcija nije oporavila, zbog čega smo nastavili s redovitim hemodijalizama. Ovaj prikaz bolesnice pokazuje kako u DPD, plućna simptomatologija može biti vodeći simptom PRS sa urednom bubrežnom funkcijom u početku. Rano prepoznavanje i dijagnoza su značajni za pravovremeni početak liječenja. Potrebno je naglasiti značaj rane biopsije bubrega, ranog početka TPE te po potrebi i nadomještanje bubrežne funkcije hemodijalizom.

Ključne riječi: *bolest protiv glomerularne bazalne membrane (anti-GBM), Goodpasturov sindrom, p-ANCA (anti-neutrofilna citoplazmatska protutijela), pulmo-renalni sindrom, brzoprogresivni glomerulonefritis s plućnom hemoragijom*