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Acute kidney injury associated with anti-glomerular basement membrane (anti-GBM) antibody disease — a clinical case

ABSTRACT

In differential diagnosis of causes of acute kidney injury presenting as nephritic syndrome, several causes should be taken into account, including diseases associated with depositions of immune complexes, systemic vasculitis, as well as rare causes such as anti-glomerular basement membrane (anti-GBM) antibody disease. This article presents a clinical case of a patient with this diagnosis. We present and discuss the current standard of diagnostic and therapeutic management, along with associated controversies and perspectives for future therapies for this disease.

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Keywords: anti-GBM, rapidly progressive glomerulonephritis, Goodpasture's syndrome

INTRODUCTION

Anti-glomerular basement membrane (anti-GBM) antibody disease is a relatively rare condition (incidence 0.5–1/million population), associated with the presence of autoantibodies against the non-collagenous α3 chain domain of type IV basement membrane collagen (anti-GBM). It is estimated to cause 1–2% of all glomerulonephritis and 10–15% of rapidly progressive glomerulonephritis with crescents (rapidly progressive GN).

It is estimated that 95% of patients undergoing renal biopsy show cellular crescent formation, and the presence of crescents in more than 50% of glomeruli is found in up to 80% of patients [1]. Anti-GBM disease can present as isolated kidney disease or as pulmonary-renal syndrome (PRS), manifested additionally by pulmonary hemorrhages. The co-occurrence of diffuse alveolar hemorrhage, rapidly progressive glomerulonephritis, and anti-GBM autoantibodies is called the Goodpasture syndrome (GS), after Dr Ernest W. Goodpasture. In 1919, he was the first to describe two cases of simultaneous pulmonary and renal involvement. GS accounts for approximately 20% of cases of PRS and occurs in 40–60% of patients with anti-GBM disease [1–3]. The condition has a high mortality rate of up to 47% despite immunosuppressive treatment.

A bimodal distribution of age of onset is observed, with peaks in the third, sixth, and seventh decades of life. Patients under 30 years of age have a higher propensity for pulmonary hemorrhage comorbidity, while patients over 50 years more often may have isolated glomerulonephritis (ESRD). In the younger age group, there is a slight prevalence of the disease among men, while in the older age group, the disease is more prevalent among women. Attention is also drawn to the simultaneous occurrence of anti-GBM and anti-ANCA antibodies (approximately 47% of cases) [4], which may affect patients' long-term prognosis. The cornerstone of anti-GBM disease treatment is rapid removal of pathogenic autoantibodies and inhibition of their production to prevent further organ damage. The case presented below illustrates a complete diagnostic and therapeutic management of renal-limited anti-GBM disease in an elderly patient, from its first symptom.

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CASE DESCRIPTION

An 89-year-old patient, a retired mechanical engineer, with chronic coronary syndrome, who underwent coronary angioplasty (in 2010) and cataract surgery, with benign prostatic proliferation, osteoarthritis, and suspected glaucoma was transferred to the Department of Nephrology, Transplantology and Internal Medicine at the University Clinical Centre in Gdansk from an internal medicine ward of a district hospital. The reason for the transfer was a suspicion of rapidly progressive glomerulonephritis. The patient was taking solid medication: nebivolol (5 mg), rosuvastatin (5 mg), acetylsalicylic acid (75 mg), and doxazosin (2 mg).

During his sanatorium treatment in September 2023, a change in urine color (to dark brown/brown) was first noticed. In addition, increasing general weakness, lack of appetite, decreased urine output, nausea with vomiting, and joint pain appeared. Laboratory investigations revealed acute kidney injury with an increase in creatinine cocncentration from 1 mg/dL (January 2023) to 3.25 mg/dL and an increase in C-reactive protein (CRP) concentration (102 mg/L). Urinalysis showed proteinuria, and erythrocyturia (fresh erythrocytes 5–10 per vision field partially leached erythrocytes 50–70 per vison field.). His urine culture was negative. Abdominal ultrasound described both kidneys length at 120 mm, with increased echogenicity and swelling of the cortical layer.

Given the above, the patient was referred to the internal ward where, despite the treatment administered, a rapid rise in creatinine to 7.48 mg/dl (eGFR 7 mL/min/1.73 m^2 according to the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) and obstruction with stasis in the pulmonary circulation was observed. Renal replacement therapy with hemodialysis from vascular access *via* a temporary catheter was then initiated. After a positive pANCA antibody result of 1:10 and a negative cANCA result, the patient was transferred to the Department of Nephrology with a diagnosis of acute kidney injury and suspected rapidly progressive glomerulonephritis in the course of systemic vasculitis.

On admission, the patient was in moderate general condition, cardiovascularly fit but with respiratory failure, requiring passive oxygen therapy. On physical examination, the following abnormalities were noted: temperature of 37 °C, respiratory effort, reduced alveolar murmur over the lower half of the right lung and at the base of the left lung, blood pressure of 150/80 mmHg, and edema of both lower limbs. In addition to elevated renal failure parameters, investigations showed CRP 176 mg/dl, macrocytic anemia (Hgb 8.6 g/dL, reduced Htc 26.6%, MCV 100.4 fl), hypoalbuminemia (23 g/L), reduced corrected calcium (8.5 mg/dL), elevated iPTH (232 pg/mL), and erythrocyturia with leukocyturia and proteinuria (uPCR 3693 mg/g). A high-resolution computed tomography (HR CT) scan of the chest showed stasis in the pulmonary circulation, a large amount of fluid in the right pleural cavity, inflammatory and non-inflammatory changes above the fluid in the right lung, but no obvious ground-glass-type lesions. A pigtail drain was placed due to dyspnea and a significant amount of pleural fluid in the left pleural cavity.

Hemodialysis therapy was continued, while diuretic treatment was intensified, achieving a reduction in edema, stasis in the pulmonary circulation, resolution of dyspnea, and full respiratory capacity. Empirical antibiotic therapy (ceftriaxone) was also administered. On the fourth day of hospitalization, anti-glomerular basement membrane antibodies showed to be positive in high titer (> 1:2560). On this basis, anti-GBM disease was diagnosed. Plasmapheresis treatment was administered (seven times in total), alternating with hemodialysis treatments. In addition, a total of three pulses of methylprednisolone were administered *i.v.* (1.0 g each), followed by oral prednisone at a dose of 60 mg/day. Moreover, a tunneled dialysis catheter was implanted, and the first dose of cyclophosphamide was administered *i.v.* (600 mg), with no early complications observed. Due to anemia, a total of two units of red blood cell concentrate (RBC) were transfused, and an additional 3000 units/week of epoetin alfa were administered.

The treatment resulted in clinical improvement, resolution of dyspnea, reduction in inflammatory parameters (decrease in CRP from 230 to 32 mg/L), and increase in hemoglobin concentration (from 7.8 to 9.4 g/dL). Due to persistently high anti-GBM antibody titers (1:2560), treatment with glucocorticoids and cyclophosphamide was continued (initially scheduled for infusions every three weeks for the next three months). The patient, dependent on renal replacement therapy and in good

general condition, was discharged home under the care of the on-site dialysis center and the Day Unit of the Nephrology Department in Gdansk.

DISCUSSION

The case described here illustrates a less typical course of anti-GBM disease, confined to the kidney, in a patient in advanced age. The picture of nephritic syndrome with rapid progression of renal failure and the presence of anti-glomerular basement membrane antibodies in high titers allowed for a rapid diagnosis and immediate implementation of treatment based on the 2021 Kidney Disease Improving Global Outcomes (KDIGO) recommendations.

This treatment consisted of a cycle of therapeutic plasmapheresis to eliminate pathogenic anti-GBM antibodies, with concomitant high-dose corticosteroids (3 × 1.0 g methylprednisolone *i.v.*, followed by prednisone at 1 mg/kg) [5]. The KDIGO guidelines recommend treatment with oral cyclophosphamide at a dose of 2–3 mg/kg, but due to the center's experience in the treatment of ANCA-positive systemic vasculitis, it was decided to provide intravenous cyclophosphamide at 14–21-day intervals. According to our experience, this treatment is therapeutically effective and, at the same time, associated with good therapy tolerance and a reduction in the total drug dose. In differential diagnosis of acute kidney injury presenting with nephritic syndrome, one of the diagnostic tools, in addition to a profiled immunological diagnosis, is renal biopsy. However, this procedure should not delay treatment decisions. According to the authors of the guidelines, a preliminary result of renal biopsy based on histopathological examination with immunofluorescence evaluation should be available within 24 hours, which is usually not possible in practice. In addition, performing a renal biopsy in the setting of acute kidney injury requiring renal replacement therapy is associated with significantly higher risk of hemorrhagic complications [6]. Because of the above limitations, in the case of our patient, a diagnostic renal biopsy was not chosen, and the final diagnosis was based on the clinical picture and the result of immunological tests.

The available literature highlights the co-occurrence of anti-GBM disease with systemic vasculitis or membranous nephropathy [7]. This implies an increased prevalence of anti-GBM and anti-ANCA antibodies, especially those directed against myeloperoxidase (anti-MPO) [8]. In observational studies, "double-positive" patients had a higher incidence of pulmonary complications, while on the other hand, they were statistically more likely to be independent of renal replacement therapy in response. It is likely that such cases also require a prolonged period of induction and maintenance treatment for remissions, analogous to the treatment of ANCA-positive systemic vasculitis [8].

In the case presented here, pANCA antibodies were confirmed in low titer (1:10) at the first hospital, which initially suggested microscopic vasculitis. Low levels of ANCA can be detected even many years before the appearance of anti-GBM antibodies and before the onset of clinical symptoms. It was therefore hypothesized that ANCA antibodies may induce glomerulonephritis which modifies or reveals epitopes in GBM, triggering the formation of anti-GBM antibodies. Nishibata *et al.* showed that proteases released from ANCA-activated neutrophils can "digest" type IV collagen and subsequently expose α-3(IV)NC), which results in the formation of autoantibodies [9, 10].

From 60 to 90% of patients survive the acute phase of the disease with appropriate treatment. Anti-GBM antibodies usually disappear after 2–3 weeks of effective treatment. Outcomes are worse if renal failure is present at the start of treatment (especially with GFR < 15 mL/min and the need for dialysis). In such cases, up to 50% of patients remain dialysis-dependent and require chronic renal replacement therapy [11].

Anti-GBM disease relapses are rare and should be treated as in first-line treatment. As an alternative to cyclophosphamide, mycophenolate mofetil, or rituximab are considered. Imlifidase (a cysteine protease derivative of the IgG degrading enzyme) may become a potential new therapeutic option (currently under investigation). In a pilot study, its use was associated with a higher rate of independence from dialysis [12].

The case we have presented shows that prompt diagnostic management and early effective therapeutic intervention are necessary in any patient with acute kidney injury and nephritic syndrome. It is important to remember that anti-GBM disease should be considered

in differential diagnosis in addition to more common causes, such as ANCA-associated systemic vasculitis. It is also worth noting that both diseases can coexist, which has prognostic and therapeutic significance [13].

ARTICLE INFORMATION AND DECLARATIONS

Ethical statement:

Consent of the bioethics committee was not required.

Author contributions:

I acknowledge the substantive contribution of the authors listed

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None.

Conflict of interest:

The authors report no conflict of interest.

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