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Case Report

Double-Positive Anti-GBM and ANCA Vasculitis: 2 Case Reports and Review of the Literature

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Abstract

Double-Positive Patients (DPPs), characterized by the simultaneous presence of Anti-Neutrophil Cytoplasmic Antibody (ANCA) and anti-Glomerular Basement Membrane (anti-GBM) antibodies, represent a rare subset in systemic vasculitis.

We present two cases of DPPs with renal involvement and review the existing literature to elucidate the clinical characteristics, histopathological findings, management strategies, and prognostic outcomes associated with this condition. Both cases exhibited renal involvement with rapidly progressive glomerulonephritis, requiring renal replacement therapy. Renal biopsies confirmed crescentic glomerulonephritis with features of both anti-GBM disease and ANCA-associated vasculitis. Management included high-dose glucocorticoids, cyclophosphamide, and consideration of plasma exchanges.

Double-positive ANCA and anti-GBM vasculitis pose challenges in management and prognosis. Further research is essential to improve therapeutic strategies for this rare and heterogeneous condition.

More Information

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Introduction

Double Positive Patients (DPPs), characterized by the simultaneous presence of anti-neutrophil cytoplasmic antibody (ANCA) and anti-glomerular basement membrane (anti-GBM) antibodies, represent a rare subset in systemic vasculitis [1]. DPPs exhibit a unique clinical and immunological profile, with prevailing myeloperoxidase (MPO)-ANCA antibodies and occasional cases of triple positivity [2]. DPPs present with multi-organ symptoms with renal involvement similar to their single-positive counterparts [1,3,4]. Renal histopathology reveals features of both anti-GBM disease and ANCA-associated vasculitis. Despite aggressive immunosuppression, DPPs often experience diminished renal recovery, challenging traditional therapeutic approaches [5,6]. Prognostic outcomes remain conflicting, underscoring the need for larger and standardized studies. We present these cases to underscore the renal involvement in DPPs and the importance of a clearer understanding of the factors influencing outcomes in this specific patient population.

Case reports

Case 1

A 79-year-old female with a history of inflammatory arthralgia affecting the small joints of the hands presented with oliguria, hematuria, proteinuria, and elevated serum creatinine levels. She had no previous history of autoimmune diseases, diabetes, and hypertension. Physical examination revealed no overt signs of systemic vasculitis, respiratory symptoms, or hemoptysis. Laboratory investigations indicated renal involvement.

Investigations: Laboratory tests revealed elevated serum creatinine (1043 µmol/l), microscopic hematuria, proteinuria (8 g/g), and normal serum complement levels. ANCA testing was positive for anti-MPO antibodies (100 AU/ml), and anti-GBM was also positive (544 U/ml). Anti-DNA antibodies, Anti-Ro/SSA antibodies, anticardiolipin, and anti-β2glycoprotein-1 were negative.

Renal ultrasound showed normal-sized kidneys measuring 11 cm in the long axis with good corticomedullary differentiation.

CT scan showed no diffuse alveolar hemorrhage.

Renal biopsy confirmed crescentic glomerulonephritis The biopsy sample contained a total of 11 glomeruli. Among them, five exhibited crescent formation, including three with cellular crescents and two with fibrocellular crescents. Additionally, two glomeruli were sclerotic, while

the remaining glomeruli showed mesangial proliferation. Interstitial fibrosis and tubular atrophy were noted in 25% - 50% of the renal parenchyma. Tubular necrosis was also evident. Immunofluorescence demonstrated global linear deposits of IgG, C3, Kappa, and Lambda in glomeruli. Additionally, focal granular deposits of C1q, C3, and IgM were observed. Notably, extra-glomerular focal granular deposits of IgG and C3 were present in peritubular areas (Figure 1).

The white arrows indicate a glomerulus with extra capillary hypercellularity forming circumferential cellular crescents with rupture of Bowman's capsule and retracted flocculus.

Treatment: The patient was initiated on high-dose glucocorticoids (1 g each day for 3 days) and cyclophosphamide for induction therapy (500 mg). A renal replacement therapy was initiated at the presentation. The patient was treated with TMP/SMX to lower the infectious risk.

Follow-up: Regular follow-up appointments were scheduled to monitor disease activity, adjust immunosuppressive therapy, and address potential complications. After an 8-month follow-up, the patient's clinical course was marked by the onset of end-stage chronic kidney disease and initiation of dialysis.

Case 2

A 52-year-old female with a history of chronic sinusitis presented with elevated serum creatinine levels. She had no previous history of autoimmune diseases, diabetes, or hypertension. Physical examination revealed no respiratory symptoms or hemoptysis. Laboratory investigations indicated renal involvement.

Investigations: Laboratory tests revealed elevated serum creatinine (1361 µmol/l) and normal serum complement levels. ANCA testing was positive for anti-PR3 antibodies (50 AU/ml). Anti-GBM was also positive (500 U/ml). Anti-DNA antibodies, Anti-Ro/SSA antibodies, anticardiolipin, and anti-β2glycoprotein-1 were also negative.

Renal biopsy confirmed crescentic glomerulonephritis the biopsy sample contained a total of 14 glomeruli. Among them, 6 exhibited crescent formation, including four with cellular crescents and two with fibrocellular crescents. Additionally, four glomeruli were sclerotic, while the remaining glomeruli showed mesangial proliferation. Interstitial fibrosis and tubular atrophy were noted in 25% - 50% of the renal parenchyma. Immunofluorescence showed focal granular deposits of IgG/IgM and fibrinogen.

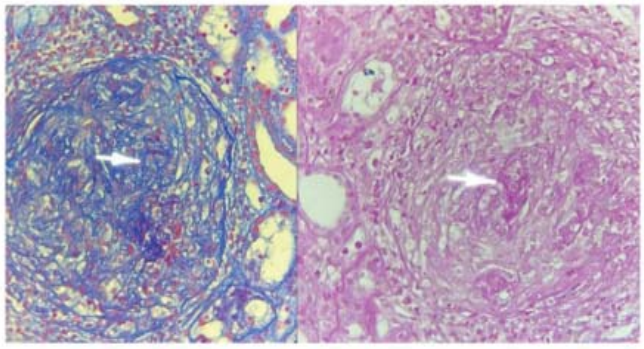

Figure 1: Kidney biopsy microscopy image (x40).

CT scan showed no diffuse alveolar hemorrhage.

Treatment and outcome: The patient was also initiated on high-dose glucocorticoids (1g each day for 3 days) and cyclophosphamide (500 mg) for induction therapy, followed by maintenance with azathioprine. Additionally, renal replacement therapy was initiated temporarily. The patient was also treated with TMP/SMX to lower the infectious risk.

Follow-up: Regular follow-up appointments were scheduled to monitor disease activity, adjust immunosuppressive therapy, and address potential complications. After 2 years of follow-up, the patient's clinical course was marked by the onset of end-stage chronic kidney disease and initiation of dialysis.

Discussion

We report two cases of patients with crescentic glomerulonephritis that tested positive for both anti-glomerular basement membrane and ANCA antibodies also known as double-positive vasculitis.

The double-positive ANCA and anti-Glomerular Basement Membrane (GBM) antibody-associated vasculitis is a rare entity of systemic vasculitis characterized by the presence of both ANCA and anti-GBM antibodies [1]. Double-Positive Patients (DPPs) display a mixed phenotype in terms of clinical, biological, and therapeutic aspects.

The incidence of double-positive ANCA/anti-GBM vasculitis is estimated at 0.6 cases per million inhabitants [1,2].

The usual age of onset in patients with AAV and anti-GBM overlap is later in life consistent with the demographic profile of ANCA-associated vasculitis (AAV) [2,7].

The sex ratio of patients with double-positive vasculitis appears to be close to 1, indicating a nearly equal distribution between genders [8].

It is noteworthy that myeloperoxidase (MPO)-ANCA antibodies are more prevalent than proteinase 3 (PR3)-ANCA antibodies in DPPs [2].

The first and second patients in our study were positive for P-ANCA and C-ANCA, respectively.

However, rare cases of triple positivity, involving anti-glomerular basement membrane (anti-GBM), anti-

myeloperoxidase (anti-MPO), and anti-proteinase 3 (PR3) antibodies, have been reported [2].

The two populations of antibodies associated with these conditions exhibit antigenic distinctiveness. This distinction arises from the specific molecular structures and characteristics inherent to each antibody type.

ANCA primarily recognizes antigens present in the cytoplasm of neutrophils, such as proteinase 3 (PR3) or myeloperoxidase (MPO) [9]. On the other hand, anti-GBM antibodies target epitopes within the glomerular basement membrane [10].

The antigenic dissimilarity is further underscored by the diverse clinical manifestations associated with these antibodies. ANCA-associated vasculitis (AAV) often involves small vessel inflammation, affecting various organs like the kidneys and lungs [11]. In contrast, anti-GBM antibody-associated diseases, such as Goodpasture's syndrome, predominantly manifest as glomerulonephritis and pulmonary hemorrhage [10].

However, a recent study showed the possible implication of intermolecular epitope spreading in the production of anti-glomerular basement membrane antibodies in anti-neutrophil cytoplasmic antibody-associated vasculitis [12].

In contrast to anti-GBM patients, DPPs are characterized by multiple organ involvement. Signs involving the ear, nose, and throat, ophthalmological, neurological, articular, and cutaneous manifestations can be observed [3,5,13].

Our first patient presented inflammatory arthralgia affecting the small joints of the hands while the second one presented chronic sinusitis typical of the GPA (Granulomatosis with polyangiitis).

Renal involvement in DPPs is similar to their single-positive counterparts presenting with rapidly progressive glomerulonephritis [1,3,4]. Serum creatinine levels in double-positive disease are higher than in either anti-GBM disease or AAV alone [2,8].

Our patients presented with high creatinine levels (1043 and 1361 µmol/l).

Also, Many studies have shown that DPPs' need for dialysis is more important than single single-positive patients [2,4,8].

Our 2 patients required renal replacement therapy at presentation.

Moreover, the frequency of pulmonary involvement, represented in Intra-alveolar hemorrhage, is comparable to that of patients with circulating anti-GBM antibodies realizing a typical pulmonary-renal syndrome [8,14]. As early as 2003, Levy, et al. reported intra-alveolar hemorrhage in 44% of cases [15].

The histological findings in patients with Double-Positive Vasculitis (DPPs) can vary but often include features indicative of both anti-Glomerular Basement Membrane (anti-GBM) disease and ANCA-associated vasculitis (AAV) represented in crescentic glomerulonephritis.

In a study involving fifty-four DPPs and anti-GBM simple positive patients who underwent renal biopsy, McAdoo and al [8] observed no difference in the proportion of crescentic glomeruli between the 2 groups but a tendency for more sclerotic glomeruli in DPPs and a higher degree of interstitial fibrosis and tubular atrophy.

Immunofluorescence identifies linear deposits of IgG and/or C3 in 75 to 80% of cases. The absence of deposits (pauci-immune) was found in only 5 to 8% of cases [1,4,8].

These findings correlate with our two reported cases.

Management of DDPs is similar to single-positive patients with the initiation of high-dose glucocorticoids associated with cyclophosphamide and Plasmatic Exchanges (PE).

Plasma exchanges were not used in our two patients due to practical limitations.

Despite treatment with high-dose glucocorticoids and cyclophosphamide, our two patients progressed to end-stage chronic kidney disease requiring dialysis within a timeframe respectively of 8 months and 2 years.

The PEXIVAS study questioned the use of PE in patients with ANCA-associated vasculitis. This landmark trial, published in 2020, demonstrated that plasma exchange did not significantly reduce the incidence of End-Stage Kidney Disease (ESKD) or death in patients with severe AAV compared to standard therapy. Consequently, in clinical practice, the decision to use plasma exchange is often individualized.

However, considering the severity of renal involvement and other extra-renal manifestations in double-positive patients, the potential benefit of plasma exchanges should be reconsidered [16].

As for rituximab, it has been rarely used in Double Positive Patients (DPPs). A case report by Taam, et al. demonstrated an improvement in renal function and a negativization of Anti-MBG and ANCA levels after the administration of grams of rituximab at a 15-day interval [17].

In terms of prognosis, many studies have delved into the outcomes of individuals with dual positivity, yielding conflicting results. Some investigations have suggested favorable prognoses compared to their counterparts with single-positive anti-GBM disease [6,18,19]. Conversely, other research has posited that those who are double positive may face outcomes on par with or even worse than single-positive patients [5,6].

A significant constraint in those studies is the relatively modest sample sizes in many of these investigations. The statistical power of such studies may be compromised due to this limitation, making it challenging to draw definitive conclusions from the findings. Moreover, the heterogeneity in disease severity at the time of presentation further complicates the interpretation of results. Instances where the percentage of patients dependent on dialysis at the point of diagnosis spans from 0% to 100% highlight the variability in the clinical spectrum of these cases [8].

Conclusion

Double-positive vasculitis characterized by the coexistence of Anti-GBM and MPO-ANCA exhibits clinical manifestations similar to their single-positive counterparts dominated by rapidly progressive glomerulonephritis. The existing body of literature on double-positive cases presents a mosaic of findings, reflecting the challenges and complexities inherent in studying a relatively rare and heterogeneous condition. The conflicting nature of the outcomes underscores the need for more extensive studies to unravel the intricacies surrounding dual positive vasculitis.

Consent for publication

Informed consent was obtained from all the patients

Ethical approval

Ethical approval is not required at our institution for publishing a case report in a medical journal.

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