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CASE REPORTS

Diagnosing and Treating ANCA-Associated Vasculitis within the COVID-19 Era: A Challenging Case Report

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Abstract

Introduction: Anti-neutrophil cytoplasmic antibody (ANCA)- associated vasculitis (AAV) is a rare group of systemic autoimmune diseases that primarily target small blood vessels. Renal manifestations often present as pauci-immune focal and segmental necrotizing crescentic glomerulonephritis (PI-NCGN), which can progress to acute or chronic kidney failure and multiorgan involvement. It is frequently associated with poor outcomes.

We report a case of PR3-positive ANCA-associated vasculitis complicated by rapidly progressive glomerulonephritis, acute kidney injury, and diffuse alveolar hemorrhage during the COVID-19 pandemic. This case highlights the diagnostic challenges of differentiating AAV from conditions associated with SARS-CoV-2 infection, as the clinical and radiological presentations of pulmonary-renal syndromes may overlap.

The findings underscore the importance of maintaining a comprehensive differential diagnosis in patients with pulmonary and renal involvement, particularly in the post-COVID-19 era, to ensure timely and accurate management of rare autoimmune conditions such as AAV.

Conclusion: ANCA-associated vasculitis (AAV) remains a diagnostic and therapeutic challenge, particularly in the post-COVID-19 era, where overlapping clinical and radiological features with SARS-CoV-2 complications can obscure timely identification. This case highlights the critical importance of maintaining a broad differential diagnosis in patients presenting with pulmonary-renal syndromes to differentiate AAV from more common conditions associated with COVID-19.

Keywords: ANCA-associated vasculitis, crescentic glomerulonephritis, acute kidney injury, plasma exchange, hemodialysis, pulmonary-renal syndrome.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA) - associated vasculitis (AAV) is a rare group of autoimmune, systemic vasculitis affecting small vessels, mainly capillaries, arterioles, and venules. [1-4]

Based on their histopathological and clinical spectrum, AAVs constitute three distinct entities: MPA, GPA, and EGPA. [1-4] Based on the serology findings, they are classified as PR3-positive, MPO-positive, or ANCA-negative vasculitis. [1-4]

It has an estimated prevalence of 200-400 cases per million people and an equal distribution among males and females. [1-3] Clinical presentation is heterogeneous, and multiple organ involvement is often present primarily renal and pulmonary involvement. Manifestations include

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constitutional symptoms like arthralgia, myalgia, fatigue, and malaise, as well as shortness of breath, wheezing, and hemoptysis. [1-4]

Kidney involvement with hematuria, proteinuria, hypertension, and occasionally interstitial nephritis are frequent, as well. [1-4] Purpuric and petechial lesions are the most common cutaneous manifestations. [1-4]

ENT involvement, including chronic rhinitis, otitis, sinusitis, and laryngitis, is frequently observed in GPA. [1-4] Neurological manifestations are less common and they typically include mononeuritis multiplex and symmetrical polyneuropathy. [5] Treatment consists of immunosuppressive therapy to induce remission and prevent relapses.

Case presentation

A 34-year-old woman presented to the Emergency Department with a two-week history of flank pain, abdominal discomfort and diarrhea, gross hematuria, bilateral lower extremities paresthesia, and a progressive decline in urine output.

On physical examination, high blood pressure (140/80 mmHg) and peripheral pitting edema were noted. The rest of her examination was unremarkable. She reported an eight-month history of recurrent and prolonged sinusitis with episodes of epistaxis, for which she had received antibiotics with some improvement, as well as polyarthralgia and anemia, for which she had seen a rheumatologist. Family medical history was insignificant.

A complete blood count (CBC) and a comprehensive metabolic panel revealed the presence of severe anemia (RBC = 2.46 x 106/uL, Hgb = 5.9 g/dl), elevated levels of serum urea = 161.6 mg/dl, creatinine = 4.92 mg/dl and uric acid = 7.9 mg/dl. Urinalysis was positive for protein (75 mg/dL) and red blood cells (>50 RBC/HPF). A 24-hour urine collection revealed an albuminuria of 1788 mg/24-h. G6PD levels were within normal range. Viral serology for Hepatitis B and C, HIV, and SARSCoV-2 was negative. The indirect Coombs test was positive. Immunological assays revealed elevated serum levels of PR3 = 76.84 U/ml and rheumatoid factor, RF = 35.2 UI/ml. The rest of the examinations were negative, including complement C3 and C4 levels, ENA panel, anti-ds-DNA, MPO, and ASLO.

A high-resolution chest CT (HRCT) showed decreased ventilation, more pronounced in the left inferior lobe and superior lobes bilaterally, with ground-glass opacities varying 1.5-2 cm in size, with a peripheral distribution. No evidence of pleural effusion was present.

Kidney biopsy revealed crescentic glomerulonephritis. Ten glomeruli were examined. Global sclerosis was observed in seven of them, and crescents were present in three of them. In the interstitial area, there were pronounced inflammatory lymphocytic infiltrates and tubular necrosis. Arteriolar hyalinosis was also observed.

IHC staining for IgG, IgM, IgG4, and C3d were negative, suggesting pauci-immune crescentic glomerulonephritis,

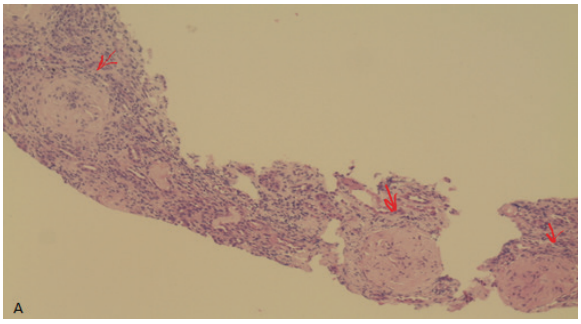

Fig. A. *Light microscopy of rapidly progressive glomerulonephritis (H&E staining). 3 glomeruli showing global sclerosis with all architectural landmarks and capillaries obliterated. There is marked interstitial inflammation.*

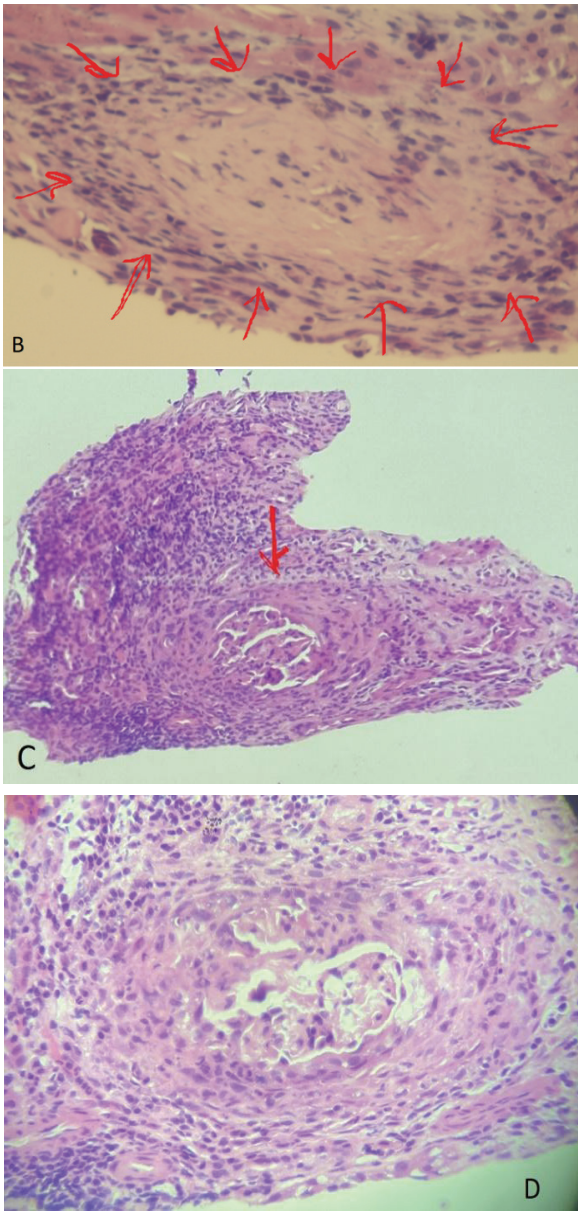

***Figure** B **- D.** (H&E staining). Light microscopy shows the vast destruction of Bowman's capsule.*
The glomerular tuft is collapsed by extra capillary cellular proliferation (crescents)

the sclerotic variant, with sclerosis in more than 50% of glomeruli.

In light of the clinical, radiological, and pathology findings, PR3-positive ANCA-associated vasculitis was diagnosed. During her hospital stay, her kidney function continued to deteriorate at a rapid pace, and she developed episodes of hemoptysis. Considering the urgent and rapidly progressive nature of her presentation and the multiple organ involvement, hemodialysis was initiated, as well as five sessions of plasmapheresis every 3 to 5 days. She was started on induction therapy with Cyclophosphamide and corticosteroids. She initially received a three-day course of high-dose pulse methylprednisolone (500 mg IV/daily) and was switched to 0.5 mg/kg/day of prednisone. She received Cyclophosphamide 500 mg IV for six rounds, three doses every two weeks, and the remaining three doses every three weeks until she was in complete remission. She was started on Azathioprine 2 mg/kg/daily as maintenance therapy, but after a few months, she developed HSV1-induced pancytopenia, and she was switched to mycophenolate mofetil 2g/daily.

The patient underwent hemodialysis sessions for a couple of weeks, but eventually, her kidney function improved, and she was weaned off dialysis. She is currently in complete remission.

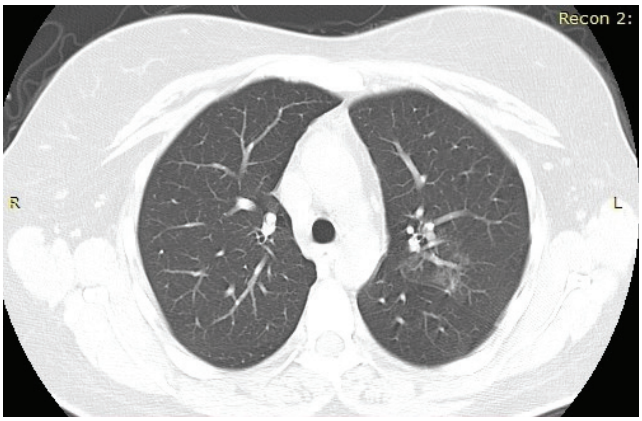

Figure. E. Chest CT scan after plasma exchange.

Discussion

The pathogenesis of AAV is complex and not fully elucidated. Genetic, environmental, and infectious factors have all been implicated in initiating an abnormal immune response, leading to the formation of autoantibodies (ANCA) directed against one of two neutrophil proteins, PR3 and MPO. [1-4]

PR3 and MPO are mainly found within neutrophil primary granules and lysosomes of monocytes. [1-4] Despite their presence in other autoimmune diseases or healthy individuals, ample evidence points to ANCA's pathogenicity. [1-4]

Neutrophils are key players in AAV pathogenesis, as they are both targets of autoimmunity and one of the primary effector cells. [1-4] Neutrophil priming implies an amplified neutrophil response to activating stimuli and represents a crucial step in the pathogenesis of AAV. [1,4]

It has been postulated that loss of B and T cell's immunologic tolerance to PR3 or MPO leads to the development of autoantibodies (ANCA) that, in turn, promote activation of neutrophils, adherence to the microvascular endothelium of the renal and respiratory system and other organs, ultimately inducing inflammation and tissue injury. [1-4] Monocytes and macrophages are important effector cells, contributing to the ongoing inflammation and granuloma formation. [1,2,4] Their pro-inflammatory and pro-fibrotic cytokines are instrumental in both acute and chronic injury. [1,2,4]

Radiological findings in HRCT include solid pulmonary nodules of varying size, usually of bilateral distribution, mainly in subpleural regions. [7-12] Focal "halo sings" surrounding solid nodules can also be appreciated in HRCT. [7-12] Central cavitation, without calcifications, may be present, and it is more prominent in larger nodules. [7-12] Air-space consolidations, ground-glass opacities (GGO), and mosaic attenuation patterns corresponding to areas of diffuse alveolar hemorrhage and vascular inflammation can be noted, as well. [7-12] They commonly present as diffuse, patchy opacities. [7-12] Occasionally, centrilobular nodules and a tree-in-bud pattern can be visualized. [7-12] Bronchial wall thickening and peri-bronchovascular interstitial thickening may be evident. [7-12] Pleural effusions and wedge-shaped consolidations may be present in some cases, representing possible pulmonary infarcts. [13]

Bronchial involvement with decreased ventilation, more pronounced in the left inferior lobe and superior lobes bilaterally, was observed in our patient. Ground-glass opacities measuring 1.5-2 cm with a peripheral distribution were noted. No evidence of pleural effusion was present. Considering that ground-glass opacities were a ubiquitous finding in HRCT of patients with COVID-19 and our patient presented in the midst of the COVID-19 pandemic, the differential diagnosis was challenging, as the radiological findings initially suggested a potential COVID-19 infection.

Kidney involvement is very prevalent in AAV and is considered an important predictor of mortality, associated with a 50% risk of death or ESKD at five years in patients presenting with an eGFR < 50 ml/min. [14] It is characterized by rapidly progressive glomerulonephritis (RPGN) with proteinuria, microscopic hematuria, and rapid decline of kidney function in a few days to months. [14] Kidney biopsy typically shows the presence of pauci-immune focal necrotizing crescentic glomerulonephritis. [14]

Nevertheless, the biopsy findings were typical of pauci-immune crescentic glomerulonephritis, the sclerotic variant with more than 50% of glomeruli showing global sclerosis. Crescents were found in 3 out of 10 glomeruli. Overall, the clinical, laboratory, and histopathological findings all pointed to a diagnosis of PR3-positive ANCA vasculitis.

Treatment of AAV consists of a two-step approach: an induction therapy to achieve clinical remission and a maintenance therapy to maintain remission. [3,4,13,15]

Combined therapy with glucocorticoids and an immunosuppressive agent has been traditionally used to induce remission. [3,4,13,15] A three consecutive day IV pulse of methylprednisolone, then switched to oral prednisone of 1 mg/kg/daily, has been generally used. [3,4,13,15] Nevertheless, new studies advocate the adoption of reduced-dose and rapid tapering glucocorticoid protocols. [3,4,13,15] They have been shown to be non-inferior to more traditional, slower-tapering regimens and associated with fewer side effects. [3,4,13,15]

Cyclophosphamide is an alkylating agent that, for decades, has been the cornerstone of induction therapy in AAV. It is associated with 75% to 90% remission rates at three to six months, respectively. [3,4,13,15] Both oral and intravenous administration have been used. However, the intravenous route at weeks 0, 2, 4, and every three weeks is preferred as it leads to less exposure and smaller cumulative doses of Cyclophosphamide. [3,4,13,15]

Rituximab is a chimeric monoclonal anti-CD20 antibody used to induce remission in combination with glucocorticoid therapy. [3,4,13,15] Cyclophosphamide remains the preferred agent in organ and life-threatening diseases, including severe kidney disease and diffuse alveolar hemorrhage (DAH). [3,4,13,15] In these patients, the use of plasmapheresis to aid in removing immune complexes from serum has also been advocated. [3,4,13,15]

Currently, rituximab is considered first-line therapy following induction with rituximab or Cyclophosphamide, as studies show it is associated with lower relapse rates. [3,4,13,15] Azathioprine, mycophenolate mofetil (MMF), and methotrexate can be used as alternatives, coupled with low-dose steroids. [15] Patients remain on maintenance immunosuppression for two to four years. [15]

In our patient, considering the severe kidney involvement, as well as the development of diffuse alveolar hemorrhage, we opted for the use of plasmapheresis, five sessions in total every 3 to 5 days, and induction therapy with pulse glucocorticoids for three consecutive days, then switched to a reduced-dose steroid regimen and intravenous Cyclophosphamide, for a total of six doses until achieving complete remission. As rituximab is not reimbursed in Albania, she was started on Azathioprine as maintenance therapy and subsequently switched to mycophenolate mofetil (MMF) due to adverse effects associated with Azathioprine. She remains in complete remission.

Conclusion

This is one of the first documented cases in our country where the complete recommended therapeutic regimen has been successfully implemented to achieve remission in ANCA vasculitis. Initially, the radiological findings were suggestive of a COVID-19 infection, a common diagnostic challenge during the pandemic era. The overlap of imaging findings between COVID-19 and other systemic diseases with pulmonary involvement posed a significant obstacle in the differential diagnosis.

Prompt diagnosis followed by a targeted and aggressive treatment approach, including the rare use of plasmapheresis in our institution, was pivotal in achieving complete remission. This case emphasizes the importance of considering a broad differential diagnosis and the potential utility of plasmapheresis in severe ANCA vasculitis with DAH, even in resource-limited settings.

COI Statement: This paper has yet to be submitted in parallel, presented fully or partially at a meeting, podium, or congress, published, or submitted for consideration beforehand.

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Abbreviations

ANCA - Anti-Neutrophil Cytoplasmic Antibody; AAV - ANCA - Associated Vasculitis; PI-NCGN - Pauci-Immune Focal and Segmental Necrotizing Crescentic Glomerulonephritis; GPA - Granulomatosis with Polyangiitis; MPA - Microscopic Polyangiitis; EGPA - Eosinophilic GPA; ENT - Ear, Nose and Throat; RBC - Red Blood Cell; HPF - High Power Field; G6PD - Glucose-6-Phosphate Dehydrogenase; HIV - Human Immunodeficiency Virus; SARSCoV2 - Severe Acute Respiratory Syndrome Coronavirus 2; PR3 - Antimicrobial Proteins Proteinase 3; RF - Rheumatoid Factor; ENA - Extractable Nuclear Antigen; DNA - Deoxyribonucleic Acid; ds - double stranded; MPO - Myeloperoxidase; ASLO - Antistreptolysin O; HRCT - High-Resolution Chest CT; IHC- Immunohistochemistry; IgM – Immunoglobulin M: IgG - Immunoglobulin G; IgE - immunoglobulin E; H&E - Haematoxylin & Eosin: PR3 - Proteinase 3; RPGN - Rapidly Progressive Glomerulonephritis; DAH - Diffuse Alveolar Hemorrhage; CD20 - Cluster of Differentiation 20; MMF - Mycophenolate Mofetil;

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