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Unraveling the Enigmatic Mysteries of a Rare Renal Disorder ANCA - Negative Pauci-Immune Glomerulonephritis

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Abstract: ***Background: ANCA-negative pauci-immune glomerulonephritis is a rare and intriguing form of glomerular inflammation that presents diagnostic and therapeutic challenges. This condition, characterized by rapidly progressive glomerular injury and crescent formation, occurs in approximately 10% of patients with systemic vasculitis. Despite the absence of detectable anti-neutrophil cytoplasmic antibodies (ANCA), patients exhibit histological features consistent with pauci-immune GN. The pathogenesis and optimal management of ANCA-negative pauci-immune glomerulonephritis remain largely unexplored. Methods: In this study, we present a comprehensive analysis of a case of ANCA-negative pauci-immune glomerulonephritis encountered in a 55-year-old normotensive, euglycemic woman. The patient's clinical presentation, laboratory findings, imaging results, treatment protocol, and response to therapy were thoroughly assessed. Additionally, we conducted a literature review to provide a broader perspective on the current state of knowledge regarding this rare condition. Results: The patient exhibited a myriad of symptoms, including fever, cough, weight loss, loss of appetite, bilateral pedal edema, decreased urine output, and breathlessness. Laboratory investigations revealed normocytic normochromic anemia, elevated creatinine and urea levels, hypokalemia, and an elevated total white blood cell count. Imaging studies demonstrated multiple lung cavities, and urine analysis showed numerous red blood cells and pus cells with klebsiella growth. Notably, all autoantibody tests, including C-ANCA, P-ANCA, ANA PROFILE, COMPLEMENTS C3, C4, and ANTI GBM ANTIBODY, were negative. The patient received an initial course of IV steroids, followed by oral prednisolone and cyclophosphamide therapy. Hemodialysis and PRBC transfusion were administered, and renal biopsy confirmed the presence of cellular crescents, consistent with pauci-immune glomerulonephritis. After six weeks of intensive treatment, the patient experienced complete renal recovery and a reduction in the size of lung cavities. Conclusion: ANCA-negative pauci-immune glomerulonephritis presents a unique and challenging clinical scenario due to its rarity and diagnostic complexities. Early recognition and initiation of immunosuppressive therapy, including steroids and cyclophosphamide, are critical in achieving favorable outcomes. This case report underscores the need for increased awareness and research to improve our understanding of the pathogenesis and management of ANCA-negative pauci-immune glomerulonephritis. Further investigations and case series are warranted to enhance the management of this distinct subset of glomerulonephritis and optimize patient outcomes.***

Keywords: ANCA-negative, pauci-immune glomerulonephritis, glomerular inflammation, systemic vasculitis, crescent formation, immunosuppressive therapy, lung cavities.

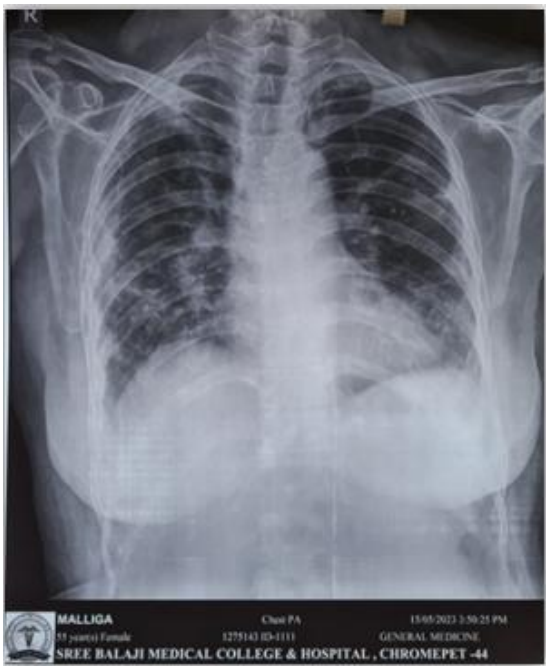
1. Introduction

Pauci-immune crescentic necrotizing glomerulonephritis (GN) is a type of glomerulonephritis characterized by rapidly progressive kidney inflammation. It is called "pauci-immune" because there is a lack of significant immune deposits in the glomeruli, which are the small blood vessels in the kidneys involved in filtering waste from the blood.

In 1982, Davies et al. first described the presence of autoantibodies directed against neutrophil cytoplasmic targets. This discovery laid the foundation for understanding the role of autoantibodies in certain autoimmune diseases. Later, Van der Waude et al. conducted research on Wegener's granulomatosis, a form of vasculitis, and identified autoantibodies against ethanol-fixed neutrophils. This was followed by the work of Falk and Jennette, who described a perinuclear staining pattern of autoantibodies in patients with microscopic polyangiitis.

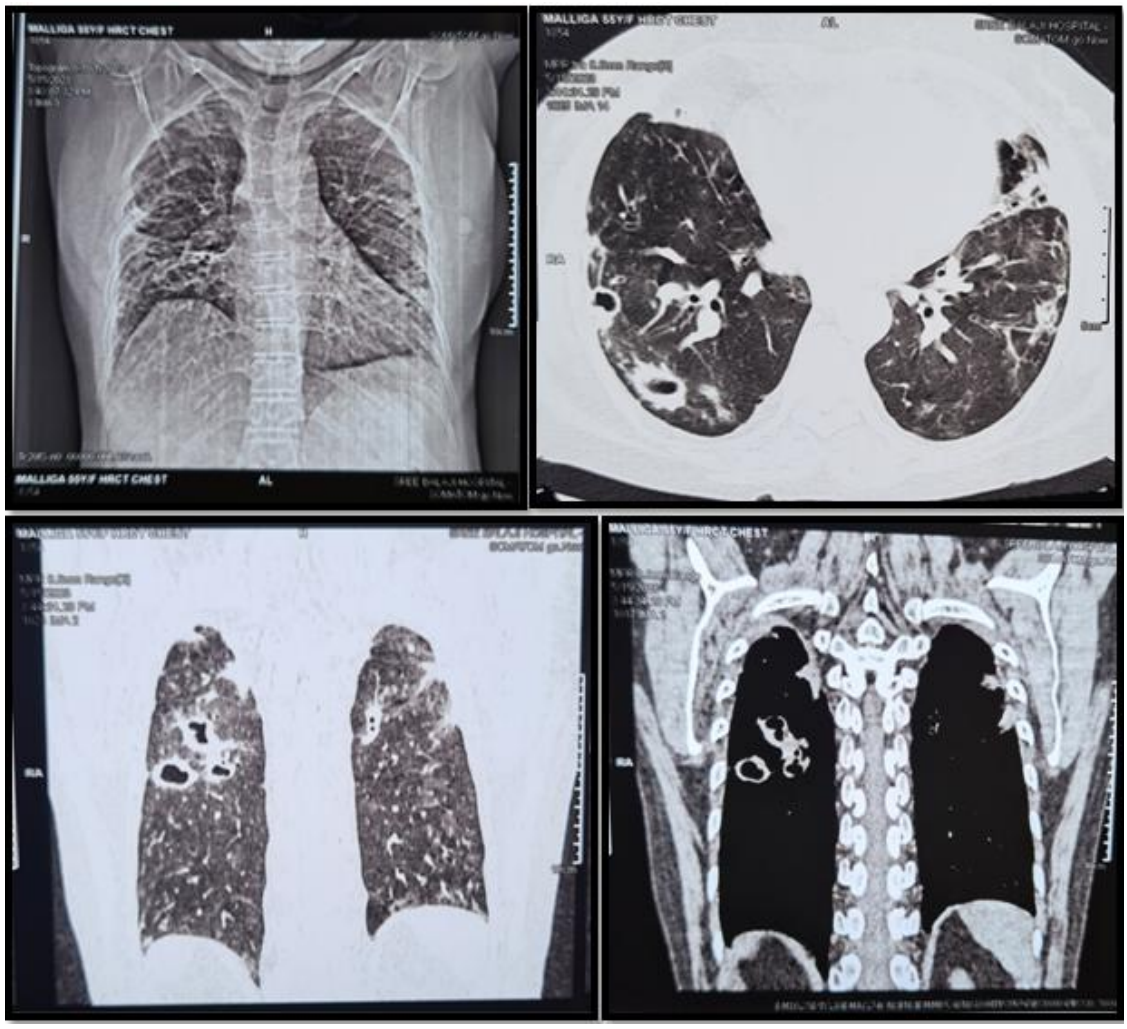
The identification of specific autoantibodies associated with pauci-immune glomerulonephritis has been significant in the diagnosis of this condition. Two specific autoantibodies, PR3-anti-neutrophil cytoplasmic antibody (ANCA) directed against proteinase 3, and MPO-ANCA directed against myeloperoxidase, have been found to be highly sensitive (91%) and specific (98%) for active pauci-immune vasculitis/glomerulonephritis. This means that the presence of these autoantibodies strongly suggests the presence of active disease.

However, it's important to note that approximately 10% of cases with systemic vasculitis may test negative for ANCA. In these cases, other diagnostic methods and clinical evaluations are necessary to establish a diagnosis.



2. Case Report

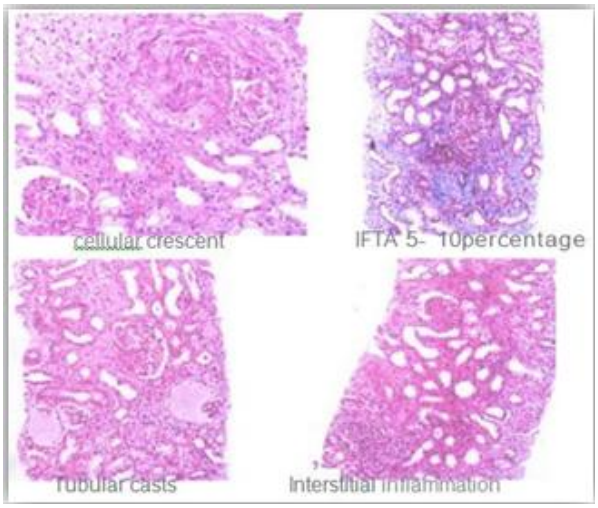
A 55-year-old homemaker with no significant medical history presented with a persistent fever for over a week, accompanied by a non-productive cough that had been troubling her for more than two weeks. The patient also reported experiencing weight loss and loss of appetite for more than three months, which prompted concern. In addition, she developed bilateral pitting pedal edema over three days, leading to decreased urine output and breathlessness, both of which had onset within the last two days.



Clinical Evaluation and Investigations: Upon examination, the patient showed signs of pallor and bilateral pitting pedal edema. Routine investigations revealed normocytic normochromic anemia, elevated creatinine (ranging from 3.7 to 7.8) and urea levels (74 to 176), as well as an elevated ESR of 136. Hypokalemia and an elevated total white blood cell count (more than 18000) were also observed. Urine analysis revealed the presence of numerous red blood cells and pus cells, with klebsiella growth detected in the culture.

To rule out tuberculosis, sputum AFB, gram staining, culture sensitivity, CBNAAT, and bronchoalveolar lavage tests

were conducted, and all yielded negative results. Autoantibody tests, including C-ANCA, P-ANCA, ANA PROFILE, COMPLEMENTS C3, C4, and ANTI GBM ANTIBODY, were all negative as well, indicating ANCA-negative status.



Treatment and Outcome: Given the severity of the clinical presentation and diagnostic uncertainty, the patient was initiated on IV steroids (Inj. Methyl prednisolone 1g for 3 days), followed by oral prednisolone 1mg/kg. Subsequently, cyclophosphamide therapy was commenced at 50mg once daily. Additionally, the patient underwent 11 cycles of hemodialysis and received 7 units of PRBC transfusion under nephrologist consultation to manage the deteriorating renal function. Hypokalemia was corrected, and IV antibiotics were administered to address the infection.

A renal biopsy was performed, revealing the presence of cellular crescents, raising the possibility of pauci-immune glomerulonephritis. After six weeks of intensive treatment, the patient showed remarkable improvement, with complete recovery of renal function and a reduction in the size of the lung cavities observed on HRCT Chest. To maintain disease remission, the patient is currently on maintenance cyclophosphamide therapy.

3. Discussion

ANCA (anti-neutrophil cytoplasmic antibodies) testing is an important diagnostic tool for identifying certain types of systemic vasculitis, particularly those associated with pauci-immune glomerulonephritis. As you mentioned, ANCA testing can detect two main types of staining patterns on ethanol-fixed human neutrophils: cytoplasmic (cANCA) and perinuclear (pANCA). These staining patterns are associated with specific antigens, primarily PR3 (protease 3) for cANCA and MPO (myeloperoxidase) for pANCA.

However, despite its significance in diagnosing ANCA-associated vasculitis, approximately 10% of patients with systemic vasculitis test negative for ANCA. This group of patients with ANCA-negative vasculitis has been studied less frequently than those who test positive for ANCA.

One study by Hedger et al. investigated 35 patients with ANCA-negative rapidly progressive glomerulonephritis and found that they had fewer airway symptoms compared to ANCA-positive patients. However, no other significant differences were observed between these two subgroups of patients.

In another multicentric retrospective observational study by Eisenberger et al., 20 cases of ANCA-negative vasculitis were identified. The renal histology in these patients revealed a high percentage of active glomerular lesions, mainly cellular crescents, but glomerular necrosis was present in a smaller proportion of cases. Additionally, chronic tissue damage with glomerulosclerosis and diffuse interstitial fibrosis were already present at diagnosis and were more prominent in ANCA-negative patients compared to historical ANCA-positive patients.

Indeed, emerging evidence from both human and experimental studies suggests that ANCA (anti-neutrophil cytoplasmic antibodies) play a pathogenetic role in vasculitic processes, rather than just being diagnostic markers. The following mechanisms have been proposed:

1) Priming and Activation of Neutrophils: TNF-alpha can prime neutrophils, leading to the expression of cell surface MPO and PR-3. Subsequent interaction between ANCA and these primed neutrophils can result in endothelial damage, neutrophil transmigration, and degranulation, ultimately leading to necrotizing vasculitis.
2) Anti-Endothelial Cell Antibodies (AECA): In ANCA-negative vasculitis, AECA has been implicated as having a causal role. Some patients with ANCA-negative glomerulonephritis have been found to be positive for AECA. Autoantibodies targeting endothelial antigens have been detected, and the presence of specific AECA autoantibodies has been associated with higher prevalence of skin rash, thrombocytosis, and disease severity.
3) Circulating Angiopoietin-2: Elevated levels of circulating angiopoietin-2, a marker of endothelial cell detachment, have been observed in systemic vasculitides with renal involvement. Angiopoietin-2 has been suggested to play a role in mediating endothelial cell damage.
4) Intrinsic Podocyte Defect: Studies in conditional knockout mouse models have demonstrated that specific podocyte deletion of the VHL (Von Hippel-Lindau) gene can lead to crescentic glomerulonephritis without ANCA positivity.
5) The VHL protein product interacts with hypoxia-inducible factor 1 (HIF-1), which regulates several factors implicated in glomerular damage, including TNF-alpha, VEGF-A, and the chemokine receptor 4 (CXC-R4).

These findings highlight the complex interplay between various components of the immune system, endothelial cells, and podocytes in the pathogenesis of vasculitis. Further research is needed to fully understand the mechanisms involved and identify potential therapeutic targets for ANCA-negative vasculitis.

4. Conclusion

Patients who present with ANCA-negative vasculitis and pauci-immune glomerulonephritis often exhibit significant systemic involvement, indicating a more severe form of the disease. In these cases, the renal lesions are characterized by focal proliferation with crescents, which are a histological feature indicating severe kidney injury. Additionally, chronic tubulointerstitial changes may be observed, indicating long-standing damage.

The treatment approach for ANCA-negative vasculitis with pauci-immune glomerulonephritis typically involves immunosuppressive drugs. Corticosteroids, such as prednisone, are commonly used as the initial therapy to suppress the immune response. Cyclophosphamide, a potent immunosuppressant, is often added to the treatment regimen to induce remission. Mycophenolate mofetil (MMF) is another immunosuppressive medication that may be used as an alternative or in combination with cyclophosphamide. These medications have shown significant improvement in prognosis and help manage the disease by suppressing the immune system and reducing inflammation.

However, it is important to note that the exact pathogenesis of ANCA-negative vasculitis with pauci-immune glomerulonephritis is not fully understood. Further research is needed to elucidate the underlying mechanisms and identify specific diagnostic markers for this particular group of patients. Advancements in understanding the disease's pathogenesis can potentially lead to the development of targeted therapies and more precise diagnostic tools, improving patient outcomes.

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