



Double Whammy: Monoclonal Gammopathy Induced ANCA-associate Glomerulonephritis

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ABSTRACT

ANCA-associated vasculitis (AAV) is an inflammatory condition affecting small blood vessels, characterized by necrosis of glomeruli in the kidneys. It is driven by an autoimmune response in which anti-neutrophil cytoplasmic antibodies (ANCA) target proteins in neutrophils, primarily myeloperoxidase (MPO) and proteinase 3 (PR3) (1). This autoimmune reaction leads to neutrophil activation and degranulation, causing vascular endothelial damage (2). Monoclonal gammopathy (MG) involves the clonal proliferation of plasma cells or B-lymphocytes, producing a monoclonal immunoglobulin (M-protein). MG can range from benign conditions, such as monoclonal gammopathy of undetermined significance (MGUS), to malignant disorders like multiple myeloma (MM) and Waldenström's macroglobulinemia (WM). The presence of MG can result in the deposition of abnormal proteins in various organs, including the kidneys, potentially inducing an autoimmune response and leading to AAV. While the exact mechanism remains unclear, it is hypothesized that these abnormal proteins may trigger immune responses that result in ANCA production and subsequent glomerular inflammation.

Keywords: crescentic necrotizing glomerulonephritis, ANCA-associated glomerulonephritis, Monoclonal gammopathy, Nephrotic range proteinuria.

INTRODUCTION

Patients with AAV typically present with hematuria, proteinuria, and renal impairment, with some developing rapidly progressive glomerulonephritis (RPGN). Systemic symptoms such as fever, malaise, weight loss, and signs of vasculitis (e.g., purpura, arthritis) may also be present.

Diagnostic evaluation includes testing for ANCA (anti-MPO or anti-PR3), detection of monoclonal proteins in serum or urine (via serum protein electrophoresis, immunofixation, or serum free light chain assays), and assessment of renal function. A kidney biopsy is crucial for diagnosing AAV, typically revealing pauci-immune necrotizing and crescentic glomerulonephritis.

Treatment of AAV primarily involves immunosuppressive therapy, including:

- Corticosteroids (e.g., prednisone)
- Cyclophosphamide or rituximab
- Plasma exchange (plasmapheresis) in severe cases

For underlying MGUS, treatment may not be necessary if the condition is stable. However, if MM or another malignancy is present, treatment may include chemotherapy, targeted therapy, or stem cell transplantation. Supportive care, including blood pressure management, fluid balance, and addressing complications such as infections, is also essential.

PROGNOSIS AND FOLLOW-UP

The prognosis of AAV induced by MG depends on factors such as the severity of renal involvement, response to treatment, and the nature of the underlying plasma cell disorder. Early diagnosis and aggressive treatment are essential for improving outcomes. Regular follow-up is necessary to monitor renal function, disease activity, and potential treatment-related complications. This typically involves periodic blood tests, urine analyses, and imaging studies as needed. A multidisciplinary approach involving nephrologists, hematologists, and rheumatologists is essential for effective diagnosis and treatment.

CASE REPORT

A 76-year-old woman presented to Marshfield Medical Center in Weston, WI, with fatigue and poor appetite persisting for three months. Two months prior, she underwent an abdominal aortic aneurysm repair with endograft placement and bilateral stenting of the common iliac arteries. Her serum creatinine had increased from 1.09 mg/dL to 3.67 mg/dL over this period, indicating worsening kidney function. Nephrology evaluation revealed nephrotic-range proteinuria of 3.285 g/dL, an albumin creatinine ratio (ACR) of 2,008 mg/dL, and the presence of MPO-ANCA. Additional laboratory work showed IgG monoclonal gammopathy, with an elevated kappa-lambda ratio of 1.82 (normal range: 0.26–1.65) and a high kappa free light chain level of 25.92 mg/dL (normal range: 0.33–1.94 mg/dL). The patient's renal function continued to decline, accompanied by peripheral edema and an estimated glomerular filtration rate (eGFR) of 14 mL/min. Laboratory data are summarized in Table 1.

On physical examination, the patient had elevated blood pressure (149/78 mmHg), normal temperature (36.5°C), and bilateral leg edema. Cardiovascular and pulmonary examinations were unremarkable. Her hemoglobin was low at 9.7 g/dL, and urine analysis showed

microscopic hematuria, though no RBC casts or acanthocytes were detected. Other laboratory results are detailed in Table 1. The patient had an elevated erythrocyte sedimentation rate (78 mm/h) and C-reactive protein (49 mg/dL), with negative anti-glomerular basement membrane antibodies and hepatitis B and C serologies.

Abdominal ultrasound of the kidneys revealed normal-sized kidneys with no evidence of obstruction or structural kidney disease. A renal biopsy revealed segmental and global glomerulosclerosis, prominent fibrinous necrosis in the loops and interstitial small arteries (Fig. 1), and pauci-immune glomerulonephritis on immunofluorescence. No monoclonal protein deposition was found in renal tissue. Bone marrow aspiration and biopsy revealed a small clone of plasma cells, comprising less than 3% of the cellular components. A diagnosis of monoclonal gammopathy of renal significance (MGRS) was considered.

Given the clinical findings, ANCA results, and renal biopsy, the patient was started on prednisone and cyclophosphamide for AAV with crescentic glomerulonephritis. Supportive measures, including blood pressure control, were initiated, and follow-up with nephrology was arranged.

DISCUSSION

The coexistence of AAV and MG is exceedingly rare, with few documented cases. The diagnosis of AAV is supported by positive ANCA serology and kidney biopsy findings of crescentic glomerulonephritis. MG is confirmed through serum immunofixation electrophoresis, serum free light chain assays, and bone marrow examination. In this case, renal biopsy did not reveal amyloid deposition or abnormal plasma cell infiltration, consistent with MGRS rather than direct kidney involvement by MG.

Esnault et al. (6) reported that patients with monoclonal immunoglobulin deposition disease (MIDD) might be ANCA-positive. Although AAV is uncommon in hematologic malignancies, Cil et al. (7) detected ANCA positivity in 8 of 60 patients with Hodgkin's lymphoma but in none of 119 non-Hodgkin's lymphoma patients. Nocente et al. (8) described a case of Sweet's syndrome associated with IgG-lambda monoclonal gammopathy and P-ANCA positivity, suggesting that neutrophil antigen fragmentation may contribute to ANCA production.

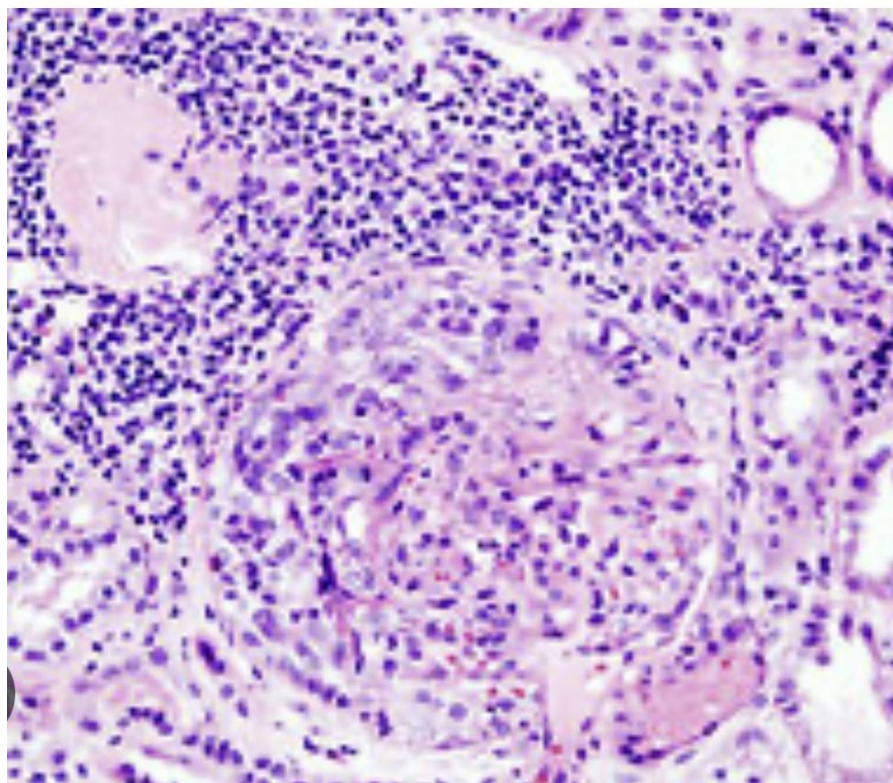
Conte et al. (9) reported Henoch-Schönlein purpura (HSP) in a patient with MM, although HSP is not typically ANCA-positive. These cases suggest a possible association between ANCA and MG, although the nature of this relationship remains unclear. The simultaneous occurrence of AAV and MG may be coincidental or may involve a shared underlying immune dysregulation, warranting further study.

Given the rarity of AAV coexisting with MG, renal biopsy remains critical for diagnosis. Both AAV and MG are more common in elderly patients and can lead to acute kidney injury, potentially progressing to end-stage renal disease (ESRD) requiring renal replacement therapy. Screening for AAV and MG should be considered in elderly patients with renal dysfunction. In this case, treatment focused on AAV given the absence of significant plasma cell infiltration in the kidney.

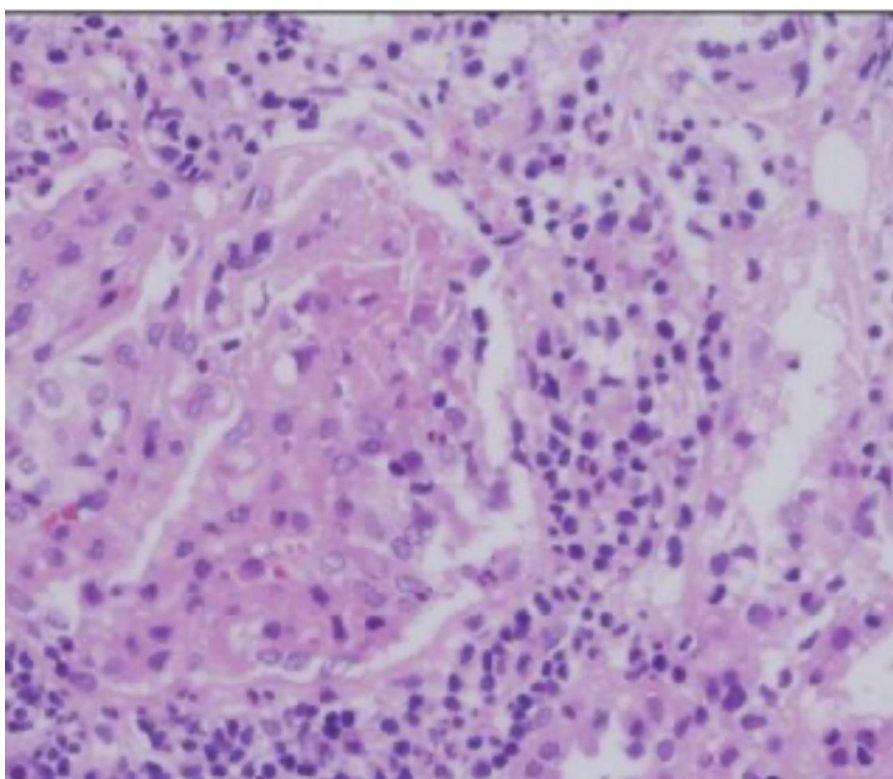
Regular follow-up is essential to monitor renal function, disease activity, and treatment-related complications. A multidisciplinary approach is crucial for managing these complex cases, involving nephrologists, hematologists, and rheumatologists.

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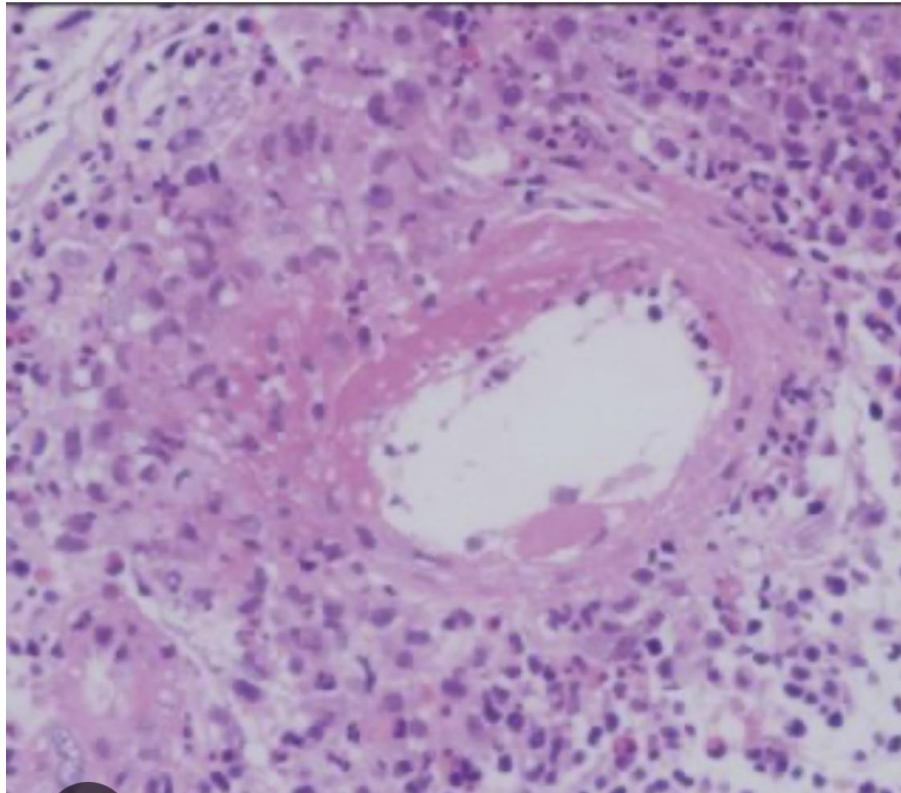
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Crescentic glomerulonephritis caused by AAV (ANCA-associated vasculitis)



Tubulitis and interstitial infiltration caused by ANCA-associated vasculitis (AAV)



Infiltration by neutrophils of the walls of small blood vessels caused by AAV.

Table 1: Patient's laboratory data

Laboratory data	Normal range
BUN 53 mg/dl	(6-20mg/dl)
Creatinine 3.67 mg/dl	(1.0 mg/dl)
K/L ratio 1.82	(0.26 – 165 mg/dl)
KFLC 25.92 mg/dl	(0.33 – 1.94 mg/dl)
LFLC 14.27mg/dl	(0.57 – 2.63 mg/dl)
IgG levels 2,328 mg/dl	(617 – 1,344 mg/dl)
ANCA (+)	Negative
MPO H>8.0 AI	(0.0 – 0.9 AI)
HGB 9.7 grams/L	(12-15 grams/L)
Urine	
RBCs 51-100 PHF	(0.0 – 3 PHF)
Protein/creatinine ratio 3,285 mg/ml	(0.0 – 0.165 mg/dl)
UACR 2,008 mg/ml	(0.0 30 ug/ml)

BUN – blood urea nitrogen, K/L – kappa – lambda ratio, KFLC – kappa free light chain, LFLC – lambda free light chain, ANCA – anti-neutrophil cytoplasmic anti-bodies, MPO – myeloperoxidase, HGB – hemoglobin, RBCs – red blood cells, UACR – urine albumin creatinine ratio