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## Case Series

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# Interest of a Kidney Biopsy to Rule out ANCA-Associated Renal Vasculitis in Glomerulonephritis Patients with a Positive ANCA

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## Keywords

ANCA-associated vasculitis · Kidney biopsy · Glomerulonephritis · Arteriosclerosis · Diabetes

## Abstract

Kidney biopsy is the gold standard for diagnosing glomerular kidney disease. Some authors debate the necessity of systematically performing kidney biopsies in ANCA-associated vasculitis (AAV) to confirm the diagnosis and assess the severity of renal damage. Nevertheless, kidney involvement is considered an organ-threatening disease requiring an aggressive immunosuppressive regimen. We present a series of 4 cases with a high clinical suspicion of ANCA-associated crescentic glomerulonephritis based on rising serum creatinine, presence of proteinuria and/or hematuria, and presence of ANCA with specificity against PR-3 or MPO. The main diagnosis, however, was arterionephrosclerosis without renal AAV. Certain comorbidities, such as diabetes and/or high blood pressure, can quickly mimic progressive glomerulonephritis. In addition, some patients with AAV do not have high creatinine, proteinuria, or hematuria levels. ANCA alone is not specific to AAV and has a poor positive predictive value. The main concern is to prevent the unnecessary, inappropriate complications of heavy immunosuppression, i.e., serious infections or risk of future malignancies. Kidney pathological confirmation is important in patients with no compatible extra-renal manifestations of AAV or any other possible renal diagnosis such as may be found in polyvascular disease or diabetic patients.

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## Introduction

Kidney biopsy (KB) is the gold standard for diagnosing glomerular disease [1]. The worldwide burden of diabetes mellitus [2] and high blood pressure [3] increases the number of patients who develop chronic kidney disease and proteinuria due to glomerular damage. These disorders can mimic certain other primary or secondary kidney diseases. In certain conditions, serum screening for immunological disorders and various antibodies may help define the diagnosis and avoid kidney biopsies [4], but this is not the case for all kidney diseases, one of which is ANCA-associated vasculitis (AAV) [5]. In various forms of AAV like granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis, extra-renal involvement can help to ascertain the clinical diagnosis. Nevertheless, kidney involvement can be isolated in a form called renal-limited vasculitis and associated with comorbidities such as diabetes or chronic hypertension.

Despite the fundamental role of pathological confirmation in the diagnosis of AAV and the importance of kidney function on patient survival [6, 7], renal biopsies are still not systematically performed. Some authors debate the necessity for systematic renal biopsies to confirm the diagnosis and assess the severity of renal damage [8]. However, kidney involvement in AAV is considered a severe or organ-threatening disease which affects the therapeutic decision [9]. Physicians' expertise and nephrology-center policies are often the substitutes for pathological investigation. Some authors recommend avoiding biopsies if there is a strong suspicion of AAV and positive PR3 or MPO ANCA antibodies [10, 11]. For example, only one-third of patients in the RAVE study underwent biopsies. Nevertheless, scientific societies strongly recommend performing biopsies at diagnosis [12] and, interestingly, the predictive negative value of biopsies is poorly understood [13]. Here, we present a series of 4 cases with a high clinical suspicion of ANCA-associated crescentic glomerulonephritis based on elevated serum creatinine (Scr), presence of proteinuria/hematuria, and presence of ANCA with specificity against PR-3 or MPO, whereas the biopsy findings were not compatible with AAV.

## Case Report/Presentation

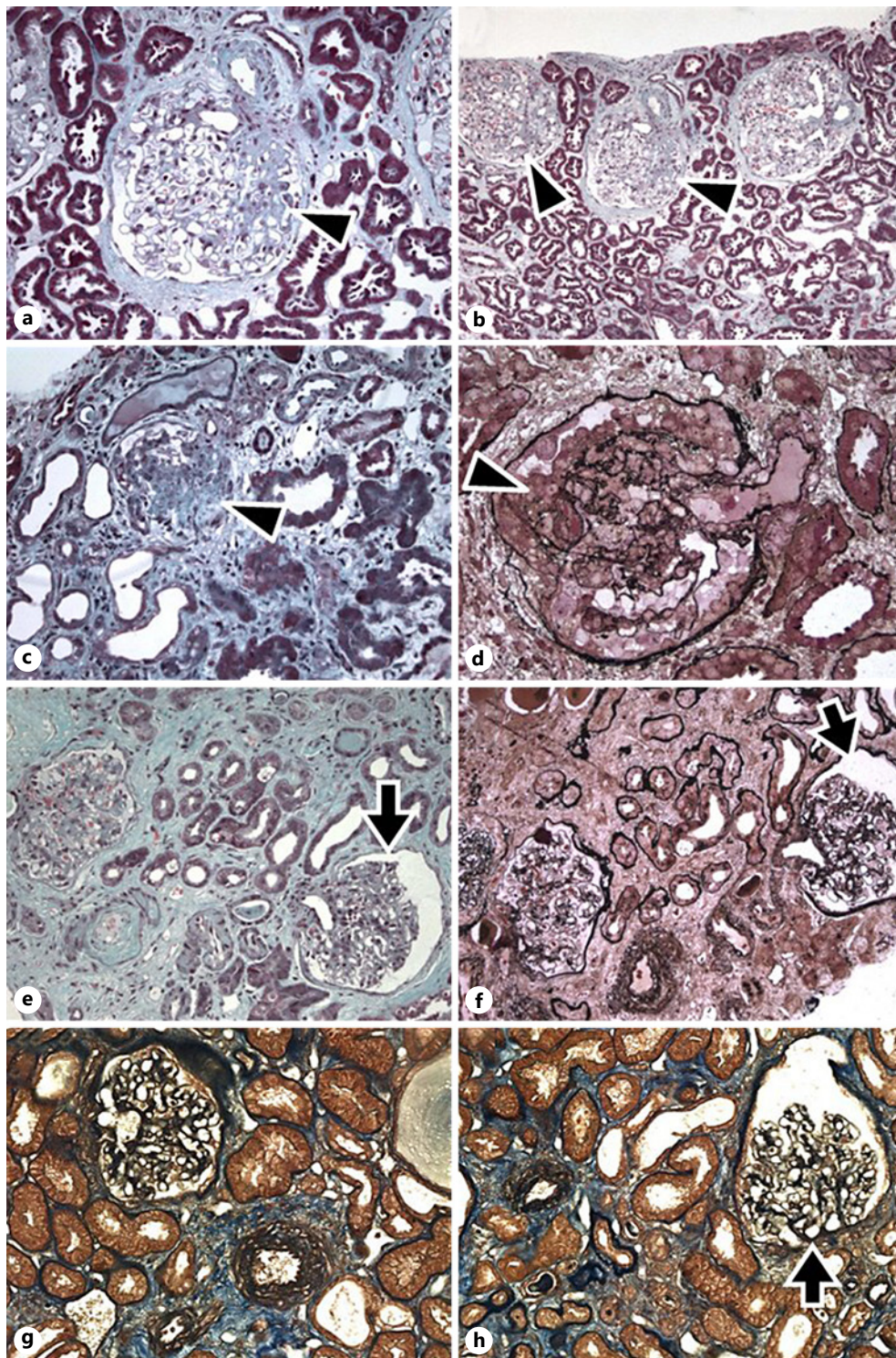
Patient 1 was hospitalized in our unit for acute kidney injury (AKIN 1). The patient was a 74-year-old man with a history of smoking and high blood pressure for 10 years, and diabetes for 5 years. At first, he had been hospitalized at a secondary care hospital for weight loss and asthenia with an inflammatory syndrome (CRP 150 mg/L). He presented urinary retention treated with urinary catheterization. Further exploration found pericarditis, and colchicine was introduced with a good outcome. Three weeks later, he came to the emergency department with fever and arthralgia, an inflammatory syndrome, and urinary retention. Urinary catheterization was set up and could not be withdrawn. In addition, a whole-body CT scan found lower interstitial lung infiltration and the PET-scan found few small hypermetabolic mediastinal nodes. The patient's clinical status improved with antibiotics and he was discharged. One month later, he benefitted from trans-urethral resection of the prostate but, one month later, the arthralgia without arthritis and the inflammatory syndrome returned. At admission, his serum creatinine level had risen sharply within a month (83–128  $\mu\text{mol/L}$ ) associated with proteinuria, but hematuria was uninterpretable due to chronic urinary catheterization. An immunologic test was made and ANCA was positive with MPO antibody specificity. Corticosteroid 0.5 mg/kg was promptly started, and the patient was transferred to our unit for a KB. One day after admission, while awaiting the pathological results (steroid pulse 500 mg  $\times$  3 and rituximab 375 mg/m<sup>2</sup>  $\times$  4), the patient's

blood pressure was 110/70 mm Hg. A KB was performed and complete immunosuppressive therapy was begun due to the indication for emergency treatment in this clinical situation with ANCA positivity. The main pathological findings (Fig. 1a, b) were irregular thickness of glomerular basement membrane, focal segmental glomerulosclerosis of hilar pole associated with mesangial expansion, absence of crescent formation, and moderate fibrosis. It was also noted that the large arteries showed marked intimal fibroplasia and severe arteriolar hyalinosis in a few places. Glomerular immunofluorescence was negative. Diabetic nephropathy with arterionephrosclerosis was diagnosed. Finally, joint pain was considered due to uric acid elevation and treated with colchicine and allopurinol, with good clinical improvement. After receiving the renal histology results, we decided to stop the immunosuppressive therapy. The kidney function was stable 13 months after the biopsy without maintaining treatment (Table 1).

Patient 2 was a 41-year-old man who, notably, had a history of drug abuse (cannabis, cocaine, and heroin). No data were available regarding his baseline kidney function. High blood pressure was found during a systematic medical visit and the biological assessment revealed a high creatinine value. As the patient's blood pressure was over 180/110 mm Hg with blurred vision, he was admitted to our unit. His Scr on admission was 173  $\mu\text{mol/L}$ . In addition, he had nephrotic-range proteinuria of 4 g/g associated with hematuria. Intravenous hypertensive therapy was begun, and his blood pressure went down to below 130/80 mm Hg and proteinuria decreased to 0.21 g/g. He had no extra-renal complaints, and the total body CT scan found only mucosal thickening of bilateral maxillary and left sphenoid sinuses. There was no lung involvement. The brain MRI only gave a lacunar picture with doubts on ischemic microangiopathy without the typical aspect of vasculitis. Although the clinical presentation may well have been due to severe hypertension, the ANCA positivity with MPO antibody specificity associated with mucosal thickening of sinuses, hematuria, and initial nephrotic proteinuria gave rise to a KB. The pathological kidney finding was focal and segmental glomerulosclerosis with synechiae and slight mesangial hypercellularity. Some areas presented acute tubular injury. Interstitial and vascular intimal fibrosis were marked according to age. Immunofluorescence revealed diffuse mesangial IgM deposits. The pathological diagnosis was focal segmental glomerulosclerosis. We strongly suspected that this was the result of drug consumption.

As the patient's glomerulonephritis had worsened 2 years later, a second biopsy was performed. The pathological conclusion was the same with several protein droplets in hypertrophied podocytes (Fig. 1c, d). The patient had end-stage renal disease a few weeks after (Table 1). Cocaine abuse was linked to the outcome.

Patient 3 was a 65-year-old man with a previous history of smoking and diabetes for 10 years without diabetic retinopathy. He reported silica exposure. His Scr had risen within 2 months (135–165  $\mu\text{mol/L}$ ) and his arterial pressure was 136/73 mm Hg at admission. He complained of knee arthralgia, atypical intermittent chest pain, and hearing loss for a few months. The physical examination found distal symmetrical neuropathy which was confirmed on the nerve conduction test. A CT scan of the sinuses and chest was performed and found an aspect of bronchiolitis without typical vasculitis involvement in those areas. As he had proteinuria, microscopic hematuria, and ANCA MPO antibody positivity in association with these atypical symptoms and an absence of diabetic retinopathy, we decided to perform a KB in order to differentiate between diabetic nephropathy and renal limited vasculitis. The histology (Fig. 1e, f) revealed a wrinkled glomerular basement membrane in 2 glomeruli without extracapillary proliferation and 10 sclerosed glomeruli associated with severe interstitial fibrosis with tubular atrophy and intimal fibrosis with mild obliteration of the vascular lumen, compatible with arterionephrosclerosis. Glomerular immunofluorescence was negative. Finally, distal sensory neuropathy was attributed to diabetes and the patient's



**Fig. 1.** Optic microscopy. The arrowhead shows FSGS glomerulus and the arrow represents an ischemic glomerulus. Patient 1: hilar variant of FSGS with mesangial expansion in continuity associated with arteriolar hyaline thickening, Masson trichrome stain.  $\times 200$  (a); Masson trichrome stain.  $\times 100$  (b). Patient 2: FSGS with a small acute tubular necrosis area and interstitial fibrosis marked for age, Masson trichrome stain.  $\times 100$  (c); silver stain.  $\times 200$  (d). Patient 3: ischemic glomerulus with marked interstitial fibrosis and increased arteriolar medial layer, Masson trichrome stain.  $\times 100$  (e); silver stain.  $\times 100$  (f). Patient 4: ischemic glomerulus with increased medial layer, Masson trichrome stain.  $\times 100$  (g); Masson trichrome stain.  $\times 100$  (h).

**Table 1.** Patient characteristics

Patient	Sex	Age	Clinical and biological assessment					Pathological			Treatment		Follow-up after biopsy							
			tobacco	HBP	diabetes mellitus	basal creatinine	Scr	PCR (ACR)	HU	ANCA specificity <sup>‡</sup>	suspected extra-renal involvement	total glomeruli, number	GS, n (%)	intimal fibrosis	conclusion	IS induction	CEI or ARB	time, month	serum creatinine	ANCA specificity
1	M	74	Yes	Yes	Yes	83	128	1.65 (50%)	N/A	MPO (68)	Articular pain	13	2 (15)	+++	Arterionephrosclerosis diabetic nephropathy	Yes	Yes	13	104	MPO (12)
2	M	41	Yes	No	Yes	ND	173	0.21	+	MPO (130)	None	42	14 (33)	+++	FSGS	No	Yes	24	ESRD	MPO (497)
		43					390	4.7 (100%)	+	MPO (497)		9	4 (44)	++	FSGS with proteinuric tubular injury					
3	M	65	Yes	No	Yes	135	165	1.8 (35%)	+	MPO (24)	Articular pain	PNS 13	10 (77)	+++	Arterionephrosclerosis	No	Yes	25	178	MPO (54)
4	M	82	No	Yes	Yes	157	260	0.07	+	PR3 (78)	None	20	3 (15)	++	Arterionephrosclerosis	No	Yes	23	273	ND

Clinical and biological assessment was made at biopsy day. Semi-quantitative assessment for pathological finding: + = sparsely (<25% of cortical area); ++ = moderate (25–50% of cortical area); +++ = important (>50% of cortical area).  
HBP, high blood pressure; PCR, protein to creatinine ratio; ACR, albumin to creatinine ratio; HU, hematuria (positive if superior to 20,000/mL); ANCA, anti-neutrophil cytoplasm antibody; MPO, myeloperoxidase; PR3, proteinase 3; PNS, peripheral nervous system; GS, glomerulosclerosis; FSGS, focal segmental glomerulosclerosis; CEI, converting-enzyme inhibitor; ARB, angiotensin renin blockade; ESRD, end-stage renal disease; N/A, not applicable; ND, not done.  
<sup>‡</sup>ELISA rate in UI/mL (positivity >5 UI/mL).

kidney function remained stable 25 months after the biopsy (Table 1). Silica exposure was the reason for MPO positivity.

Patient 4 was an 82-year-old man with a history of high blood pressure and diabetes. He was referred to our unit because his Scr had risen progressively within 8 months (from 157 to 260  $\mu\text{mol/L}$ ). Arterial pressure was 110/57 mm Hg and was associated with 2 g/day of proteinuria, micro-hematuria, and a positive ANCA PR-3 antibody. No extra-renal manifestations were found. In the absence of clinical symptoms, we did not proceed with any medical imaging other than kidney ultrasound. In this context, renal limited vasculitis was suspected. Biopsy findings (Fig. 1g, h) revealed 3 sclerosed glomeruli, 3 with a wrinkled irregular glomerular basement membrane and absence of proliferation. Moderate interstitial fibrosis and intimal fibrosis with duplication and thickening of media were also found. Glomerular immunofluorescence revealed nonsignificant C3 mesangial deposition. The conclusion was arterionephrosclerosis. The increase in Scr was due to the evolution of chronic kidney disease. The kidney function remained stable 23 months after the biopsy and proteinuria dropped with a renin-angiotensin system inhibitor (Table 1).

### Discussion/Conclusion

We hereby report a series of patients clinically suspected of having AAV, although renal vasculitis was not confirmed after pathological investigation. All had hematuria (though the first patient had a confounding factor with urethral catheterization). The main pathological diagnosis was arterionephrosclerosis (3 out of 4), and all patients had several cardiovascular risk factors and were mostly diabetic (3 out of 4). None of them had interstitial inflammation. Two patients presented suspected extra-renal involvement but, after exploration, other diseases (uric acid and diabetes) were revealed.

In the literature, the positive predictive value of a KB for diagnosing AAV is well known [14]. The main difficulty is to assess laboratory abnormalities for the diagnosis of renal AAV. Jennette et al. [15] studied a cohort of patients with biopsy-proven crescentic glomerulonephritis in North Carolina. They found patients with normal kidney function and/or absence of proteinuria [15]. Furthermore, ANCA alone is not specific to AAV. One study found a positive predictive value of only 34.4% [5]. Interestingly, another study found that higher ANCA levels and more affected organ systems were associated with a diagnosis of AAV [16]. In that study, higher ANCA numbers with a time cut-off above 4 were associated with a decrease in the area under the curve discrimination index for diagnosing AAV. In addition, different conditions can lead to ANCA positivity without any clinical argument for AAV, such as certain other inflammatory, malignant, and infectious diseases for which immunosuppression is contraindicated [17]. The risk of an isolated biological assessment is that patients who do not need it may be treated with an immunosuppressive regimen.

Another difficulty in assessing AAV is the association with preexisting cardiovascular diseases such as hypertension and diabetes. These two chronic diseases can cause kidney disease with glomerular damage. One large cohort study of 10,000 patients found a decline in eGFR in men with diabetes mellitus of 2.7 mL/min/1.73 m<sup>2</sup> per year (95% CI: 2.3–3.1) and 2.1 mL/min/1.73 m<sup>2</sup> per year (95% CI: 1.8–2.5) in women, but some patients can have a fast decline in eGFR in just a few weeks [18]. In addition, 13–30% of diabetic patients had hematuria [19] and, sometimes, with red cell casts [20]. These conditions can mimic progressive glomerulonephritis and only pathological analyses of the glomeruli can help to confirm the final diagnosis. But when the glomeruli are either normal or scarred, with significant interstitial fibrosis, it may be difficult to make the difference between chronic arterionephro-

sclerosis or quiet/undersampled AAV. We believe that intensive creatinine follow-up for a few months could help us avoid failing to diagnose AAV.

On the other hand, a recent study found a subset of AAV patients with slowly progressing kidney disease [21]. These patients represented 5% of their cohort, exclusively microscopic polyangiitis, mostly with MPO positivity at 94%, 3% PR3, and 3% double positivity. The clinical presentation was mild proteinuria (1,180 mg/24 h, median (IQR) (670–2,600)), and all patients had microscopic hematuria but only 14% with red cell cast. Most of them had renal limited vasculitis (61%) and a sclerotic form of Berden's classification (43%). Some patient had cardiovascular risk factors (63%). These different conditions suggest the difficulty of making a diagnosis of AAV based only on clinical and biological tests. The limitations of our case report include the short longitudinal follow-up of two of our patients, the absence of red cell cast analyses, and for patient 1, induction treatment started before obtaining the pathological results, although creatinine was stable at the latest follow-up.

Our cases highlight the fundamental role of kidney biopsies in managing AAV in patients with positive ANCA and kidney injury in the absence of other life-threatening organ involvement or comorbidities suggesting other diagnoses. Histological assessment is the gold standard for confirming vasculitis but is also important from a prognostic viewpoint. In our opinion, immunosuppressive therapy should not be undertaken without pathological confirmation via a KB in patients with no compatible extra-renal manifestations or other comorbidities that may suggest other causes of renal involvement. More prospective studies are required to explore the pivotal role of kidney biopsies in therapeutic decision-making, mainly for renal-limited vasculitis.

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### Statement of Ethics

Patients' electronic medical records and clinical correspondence were analyzed during routine clinical practice. Our local Research Ethics Committee approved the use of all patient data (IRB number 191002). All patients had given written informed consent for the publication of this case report and any accompanying images.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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### Author Contributions

F.G., O.M., C.A., and P.A. looked after the patients; contributed to the acquisition, analysis, and interpretation of data; and drafted the manuscript. H.P. and L.D. contributed to the pathological analyses.

### Data Availability Statement

The data used to support the cases are included within the article.

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