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CASE REPORT

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Sequential development of ANCA-associated vasculitis and anti-GBM disease: A report of two cases

Camille Le Moine[1] | **Noémie Jourde-Chiche**[2,3] | **Delphine Kemlin**[4] | **Benjamin Terrier**[3,5] | **Frédéric Vandergheynst**[1,3]

[1]Department of Internal Medicine. Hôpital Erasme, Brussels, Belgium

[2]Department of Nephrology, Hôpital de la Conception, Marseille, France

[3]French Vasculitis Study Group, Paris, France

[4]Department of Nephrology, Hôpital Erasme, Brussels, Belgium

[5]Department of Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases. Hôpital Cochin, Paris, France

Correspondence
Camille Le Moine, Department of Internal Medicine, Hôpital Erasme, 808 Route de Lennik, B-1070 Brussels, Belgium.
Email: camille.le.moine@erasme.ulb.ac.be

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Abstract

In case of AAV with kidney involvement, physicians should explore anti-GBM antibodies and be aware of the possible sequential development of AAV, especially with MPO-ANCA, and anti-GBM glomerulonephritis. This sequential disease history is associated with a poor renal outcome, highlighting the need for urgent diagnosis and management.

KEYWORDS

ANCA-associated vasculitis, anti-GBM disease, glomerulonephritis, myeloperoxidase

1 | INTRODUCTION

Double-positive vasculitis for ANCA and anti-GBM antibodies simultaneously is well described. Conversely, cases of sequential development of anti-GBM disease after ANCA-associated vasculitis are exceptionally reported. We describe 2 cases of ANCA-associated vasculitis followed by anti-GBM disease, suggesting that glomerular damages due to ANCA-associated vasculitis could induce an anti-GBM glomerulonephritis.

Antineutrophil cytoplasm antibodies (ANCA) targeting myeloperoxidase (MPO) are commonly found in antiglomerular basement membrane (GBM) disease. The association of small vessel vasculitis double positive for ANCA and anti-GBM antibodies occurring simultaneously is well described.[1,2] In contrast, sequential development of ANCA-associated vasculitis (AAV) followed by anti-GBM disease is rarely reported. Recently, evidence suggests that glomerular damages due to ANCA-associated glomerulonephritis could reveal sequestered epitopes of the GBM, inducing an anti-GBM immune response.

A survey across tertiary centers for the management of vasculitis affiliated to the French Vasculitis Study Group allowed us to identify two cases of AAV followed by

biopsy-proven anti-GBM disease: a 60-year-old man with eosinophilic granulomatosis with polyangiitis (EGPA) and a 23-year-old woman with granulomatosis with polyangiitis (GPA). Despite prompt management, adequate induction therapy, and plasma exchanges, the first case reached end-stage renal disease and the second case experienced a relapsing anti-GBM glomerulonephritis. The sequential occurrence of the two diseases is exceptionally reported in the literature, affecting preferentially elderly males with MPO-ANCA and a poor renal prognosis.

2 | CASE 1

A 60-year-old man with a history of asthma and chronic sinusitis presented a chronic nonproductive cough, recurrent fever, and limbs' neuropathic pain. Blood tests revealed persistent eosinophilia with mild inflammatory syndrome. Renal function and urine sediment were normal. Chest-computed tomography showed a diffuse interstitial lung disease with micronodules. Electroneuromyography revealed multiple mononeuropathy. Infectious serological tests and parasitological investigations were negative. Serum complement levels were normal. Antinuclear antibodies and serum cryoglobulins were negative. ANCA were positive, identified as MPO-ANCA. The patient was diagnosed with EGPA. High-dose glucocorticoids led to clinical improvement, allowing a slow tapering and withdrawal three years later.

Five months after glucocorticoids weaning, he developed an acute renal failure (creatinine serum level 7.2 mg/dl from 1.1 mg/dl previously) together with hematuria, mild proteinuria, elevated inflammatory parameters, and normal eosinophils count. High titers of MPO-ANCA (>200 UI/ml, N < 3.5 UI/ml) and anti-GBM antibodies (>200 UI/ml, N < 20 UI/ml) were detected. There was no alveolar hemorrhage on chest computed tomography. Kidney biopsy revealed a necrotizing and crescentic glomerulonephritis without rupture of Bowman's capsule, with IgG linear staining along the GBM on immunofluorescence (Figure 1), consistent with anti-GBM glomerulonephritis. He was treated with plasma exchanges, high-dose glucocorticoids, combined with rituximab, or cyclophosphamide (according to a double-blind randomized controlled trial). Anti-GBM antibodies were cleared, while MPO-ANCA remained detectable. Azathioprine was administered as maintenance therapy, replaced by rituximab because of digestive side effects. Unfortunately, despite treatment, kidney failure progressed to end-stage renal disease requiring dialysis.

3 | CASE 2

A 23-year-old woman with a history of chronic sinusitis, developed central diabetes insipidus with an enlarged pituitary gland on magnetic resonance imaging, bilateral renal pseudotumors and MPO-ANCA (6.3 UI/ml, N < 3.5 UI/ml) suggesting GPA. Renal function and urine sediment were normal. A biopsy of renal pseudotumor revealed a necrotizing glomerulonephritis with granulomatous inflammation, extracapillary proliferation, and fibrinoid necrosis-confirming GPA (Figure 2). Immunofluorescence was negative. In order to preserve her fertility, rituximab was administrated as induction therapy, with glucocorticoids, followed by an azathioprine-based maintenance therapy. Azathioprine-related gastrointestinal toxicity required replacement by methotrexate. The outcome was favorable with regression of renal masses and ANCA titers normalized. However, central diabetes insipidus persisted and was treated with desmopressin. Methotrexate combined with prednisone was continued as maintenance therapy for three years.

Four months after the end of maintenance therapy, she was admitted with fever, dyspnea, nonproductive cough, and weight loss. Biological findings showed an acute kidney injury (creatinine serum level 5.2 mg/dl from 0.9 mg/dl previously) with hematuria and mild proteinuria. Chest-computed tomography was normal. Renal ultrasound did not show any renal mass. Autoimmune panel showed high titers of anti-GBM antibodies (> 200 UI/ml) and transiently positive ANCA antibodies with a cytoplasmic staining pattern at a titer of 1/80 neither identified as PR3 nor MPO-ANCA.

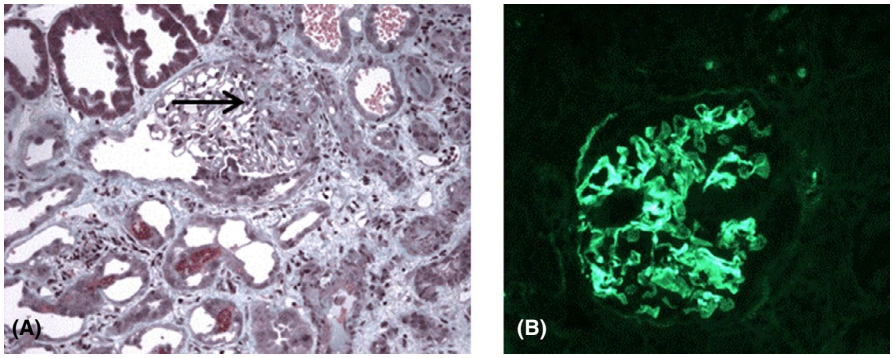

FIGURE 1 Microscopic pictures of a kidney biopsy. (A) Light microscopy reveals extracapillary proliferation along Bowman's capsule or crescents with interstitial fibrosis and tubular atrophy (Masson's trichrome staining). (B) Immunofluorescence reveals intense linear deposits of IgG along the GBM

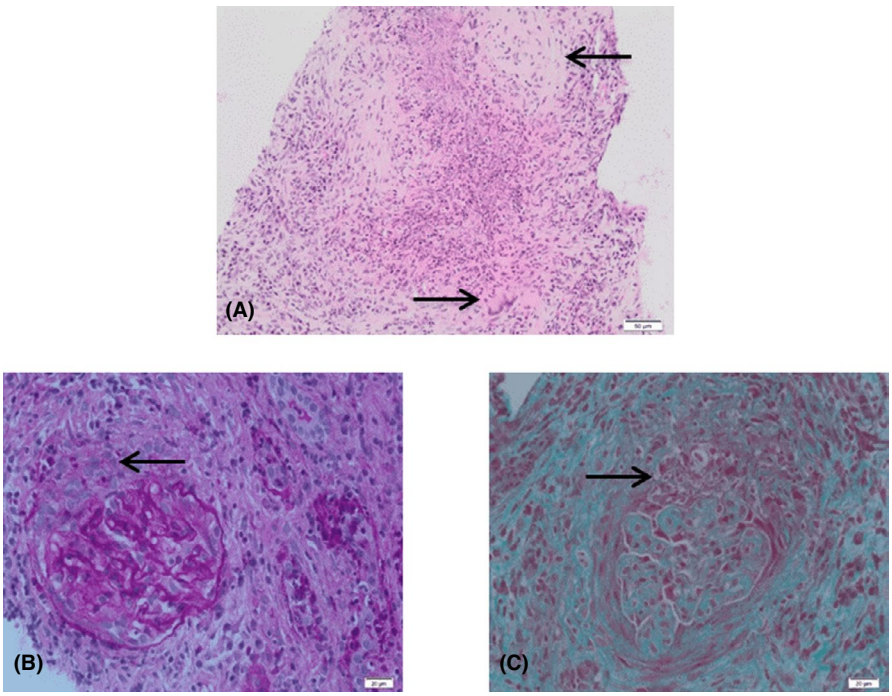

FIGURE 2 Microscopic pictures of a kidney biopsy. (A) Light microscopy reveals granulomatous inflammation with multinucleated giant cells, fibrinoid necrosis (hematoxylin and eosin staining), and (B) extracapillary proliferation along Bowman's capsule or crescents (periodic acid Schiff staining) with (C) interstitial fibrosis (Masson's trichrome staining)

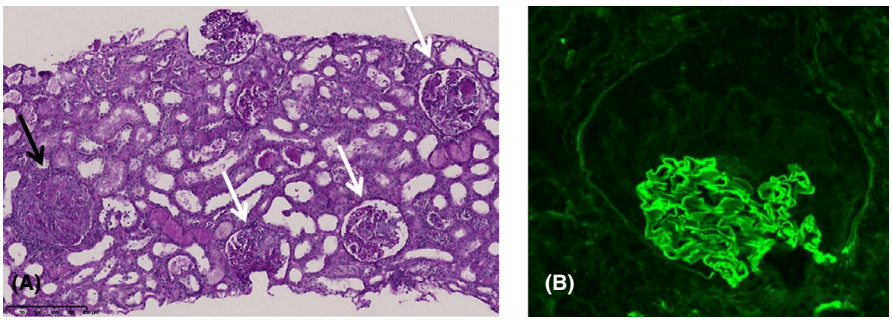

FIGURE 3 Microscopic pictures of a kidney biopsy. (A) Light microscopy reveals 25 glomeruli: 3 sclerotic (black arrow) and 14 partially crescentic (white arrows) (periodic acid Schiff staining). (B) Immunofluorescence reveals intense linear deposits of IgG along the GBM

Kidney biopsy revealed a crescentic glomerulonephritis with IgG linear deposits along the GBM on immunofluorescence (Figure 3), establishing the diagnosis of anti-GBM disease. The patient was treated with plasma exchanges, high-dose glucocorticoids, and rituximab. Clinical status and renal function improved.

Unfortunately, six months later she experienced a relapse of anti-GBM glomerulonephritis with an acute renal failure (creatinine serum level 2.2 mg/dl from 1.4 mg/dl previously) and high titers of anti-GBM antibodies (148 UI/ml). ANCA were negative. A second line of immunosuppressive therapy by high-dose glucocorticoids and intravenous cyclophosphamide was initiated, with iterative plasma exchanges. Anti-GBM antibodies titers decreased progressively but remained detectable. Treatment combining progressively tapered-prednisone and oral cyclophosphamide was pursued without further renal function deterioration. Her actual stabilized glomerular filtration rate is 52 ml/min/1.73 m² (creatinine serum level 1.3 mg/dl).

4 | DISCUSSION

We report two cases of MPO-AAV characterized by the development 3 years later of anti-GBM glomerulonephritis: a first case of EGPA without initial renal involvement and a second case of atypical GPA with renal pseudotumors and a pauci-immune crescentic glomerulonephritis. Since the initial clinical presentation of these 2 cases was suggestive of AAV, anti-GBM disease was not considered at first and anti-GBM antibodies were not searched at that time. However, circulating anti-GBM antibodies are found in approximately 10% of cases of AAV.[2] In addition, low titers of anti-GBM antibodies can be found years before the onset of any clinical feature of anti-GBM disease.[3] The sequential occurrence of these vasculitis suggests a pathophysiologic involvement of ANCA in the development of anti-GBM disease. Glomerular inflammation related to AAV could induce damage of the GBM, revealing sequestered epitopes of type IV collagen leading to a phenomenon

TABLE 1 Literature cases of sequential development of AAV and anti-GBM disease

	Case 1	Case 2	Case report 1	Case report 2	Case report 3	Case report 4
Case reports	**French Vasculitis Study Group**	**French Vasculitis Study Group**	**Wahls et al. (1987)**	**Serratrice et al. (2004)**	**Chan PSJ, Leung MH. (2016)**	**Yamazaki et al. (2012)**
Gender	Male	Female	Male	Male	Male	Male
Age at AAV diagnosis (years)	60	23	70	72	54	74
AAV diagnosis	EGPA	GPA	Limited GPA	MPA	MPO-AAV	Anti-MPO-AAV
			Lung biopsy-proven			
ANCA	Anti-MPO	Anti-MPO	NA	Anti-MPO	Anti-MPO	Anti-MPO
Anti-GBM antibodies	NA	NA	NA	Negative	Negative	NA
AAV with initial renal involvement	No	Yes, not requiring dialysis	No	Yes, not requiring dialysis	Yes, with temporary dialysis	no
Serum creatinine at AAV diagnosis (mg/dl)	0.8	0.9	NA	1.7	2	NA
Kidney biopsy	No	Yes	No	No	NA	NA
Induction therapy for AAV	Methylprednisolone	Methylprednisolone	No	Methylprednisolone	Methylprednisolone	NA
		Rituximab	No	Cyclophosphamide	Cyclophosphamide	
					Plasma exchange	
Maintenance therapy for AAV	Prednisone	Azathioprine	No	Prednisone	Azathioprine	NA
		Prednisone	No		Prednisone	
Age at anti-GBM disease diagnosis (years)	63	27	70	75	63	78
Serum creatinine at anti-GBM disease diagnosis (mg/dl)	8.9	5.2	16.3	NA	12	16.9
Anti-GBM antibodies	Positive	Positive	Positive	Positive	Positive	Positive
Kidney biopsy-proven anti-GBM disease	Yes	Yes	Yes	Yes	Yes	Yes
ANCA	Positive	Negative	NA	Positive	Negative	Positive
Time period between the 2 diagnoses (years)	3	3	0.5	3	9	4
Induction therapy for anti-GBM disease	Methylprednisolone	Methylprednisolone	Methylprednisolone	Methylprednisolone	Methylprednisolone	Methylprednisolone

(Continues)

TABLE 1 (Continued)

Case reports	Case 1	Case 2	Case report 1	Case report 2	Case report 3	Case report 4
	French Vasculitis Study Group	**French Vasculitis Study Group**	**Wahls et al. (1987)**	**Serratrice et al. (2004)**	**Chan PSJ, Leung MH. (2016)**	**Yamazaki et al. (2012)**
	Rituximab or cyclophosphamide	Rituximab	Cyclophosphamide	Cyclophosphamide	Cyclophosphamide	Plasma exchange
	Plasma exchange	Plasma exchange	Plasma exchange	Plasma exchange	Plasma exchange	
Maintenance therapy for anti-GBM disease	Azathioprine	Azathioprine	Prednisone	Prednisone		
	Prednisone	Prednisone				
Dialysis-free survival	No	Yes	No	No	No	No
Overall survival	Yes	Yes	Yes	Yes	No, death <30 days after diagnosis	No, death >30 days after diagnosis
Anti-GBM disease relapse-free survival	Yes	No, treated by cyclophosphamide and plasma exchange	NA	NA	/	/

Abbreviations: MPA, microscopic polyangiitis; NA, not available.

of epitope spreading with the production of anti-GBM antibodies and the development of anti-GBM glomerulonephritis.[1,2] This sequence beginning by an overt flare of AAV should be distinguished from the entity of small vessels vasculitis double positive for ANCA and anti-GBM antibodies occurring simultaneously. Subclinical elevated ANCA before the onset of anti-GBM disease have been reported. In a case-control study involving serum samples (some of which collected more than five years before the diagnosis of anti-GBM disease) of 30 patients diagnosed with anti-GBM disease, Olson et al. found a significantly higher percentage of disease subjects with detectable ANCA (>1 UI/ml) in multiple serum samples over time before the onset of anti-GBM disease compared with matched healthy controls for age, gender, and race.[3] By contrast, the sequential development of the two diseases has exceptionally been reported previously and limited to 4 other cases (Table 1).[4-7] They reveal a male predominance with an advanced age at AAV diagnosis and a MPO-ANCA subtype predominance, which is characterized—in the setting of isolated AAV—by a higher frequency of kidney involvement.[8] Renal prognosis is poor after biopsy-proven anti-GBM disease development, since only one patient remained dialysis-free. In this latter case, kidney function remained stable despite the persistence of anti-GBM antibodies and recurrent anti-GBM glomerulonephritis, which is infrequent in contrast to AAV. Given the patient's young age, the concern of avoiding gonadal failure, and despite the lack of evidence of noninferiority of this induction therapy, rituximab was preferred to cyclophosphamide.

In case of double-positive vasculitis, a renal involvement is systematically observed and the kidney function seems to be more severely impaired. Serum creatinine level is significantly higher than in isolated AAV in which renal improvement is more frequently observed through immunosuppressive therapy.[9] According to different studies comparing the prognosis of these double-positive patients to patients with isolated anti-GBM antibodies, we can observe conflicting results. Some studies suggest a better outcome in terms of renal prognosis [10,11] but other studies have failed to demonstrate similar results.[1,12] In 1996, Heeringa et al. demonstrated an aggravation of anti-GBM nephritis in case of immunization with MPO-ANCA in a murine model.[13] In 2017, McAdoo et al. reported more chronic kidney damages with sclerotic glomeruli, interstitial fibrosis, and tubular atrophy in cases with double-positive vasculitis compared with isolated anti-GBM disease. Nevertheless, the prognosis does not seem to be worse. Indeed, they observed a better renal outcome.[10] In addition, these double-positive patients may have had an atypical presentation leading to a delayed diagnosis, and thus delayed initiation of an immunosuppressive therapy and plasma exchange. Furthermore, renal prognosis of double-positive vasculitis

presenting concomitantly ANCA and anti-GBM antibodies and sequential occurrence of the 2 vasculitis have to be distinguished from each other.

Anti-GBM antibodies should be monitored since the diagnosis of AAV and during the follow-up of the patients, guiding toward the onset of an associated anti-GBM disease and leading to a prompt management which could improve renal survival. The onset of these 2 uncommon distinct diseases, occurring distinctly by 3 to 4 years delay, cannot be the result of chance only, assuming a causal relation between the 2 diseases. However, further work is necessary to understand the involvement of AAV in the occurrence of anti-GBM disease, including its immunopathogenic mechanism.

5 | CONCLUSION

In case of diagnosis of AAV or anti-GBM disease, the presence of both ANCA and anti-GBM antibodies should be routinely explored. The few reported cases—including ours—highlight the existence of sequential occurrence of AAV and anti-GBM disease, in which an anti-GBM response following kidney damage due to the AAV is suspected. They are characterized by exclusively MPO-ANCA, old age, and poor renal outcome, characteristics not shared by our second patient. A close monitoring of ANCA and anti-GBM antibodies and the maintenance of a long-term immunosuppressive therapy are important to prevent the potential development of an anti-GBM glomerulonephritis and a dialysis-dependent renal failure.

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CONFLICT OF INTEREST

None of the authors have any conflict of interest associated with the work presented in this manuscript.

AUTHOR CONTRIBUTIONS

All authors had access to the data and played a role in writing the manuscript. This manuscript is the authors' own original work, which has not been previously published elsewhere.

INFORMED CONSENT

The participants have consented to the submission of the case reports to the journal.

DATA AVAILABILITY STATEMENT

Not applicable to this article.

ORCID

Camille Le Moine https://orcid.org/0000-0002-8199-6772

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