Clinical Kidney Journal

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LEADING EUROPEAN NEPHROLOGY

Clinical Kidney Journal, 2021, vol. 14, no. 1, 332–340

doi: 10.1093/ckj/sfaa139
Advance Access Publication Date: 6 September 2020
Original Article

ORIGINAL ARTICLE

Slowly progressive anti-neutrophil cytoplasmic antibody-associated renal vasculitis: clinico-pathological characterization and outcome

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ABSTRACT

Background. Although rapidly progressive glomerulonephritis is the main renal phenotype of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), slow renal disease progression is sometimes observed. These forms have been rarely discussed; we analysed their prevalence, clinico-pathological characteristics and outcome.

Methods. We screened patients with microscopic polyangiitis (MPA) and granulomatosis with polyangiitis followed at seven referral centres and selected those with estimated glomerular filtration rate (eGFR) reduction <50% over a 6-month period preceding diagnosis. Data regarding patient features and response to treatment were retrieved.

Received: 20.1.2020; Editorial decision: 25.5.2020

Results. Of 856 patients, 41 (5%) had slowly progressive renal AAV. All had MPA and all but one was P-ANCA/myeloperoxidase (MPO) ANCA-positive. At diagnosis, the median age was 70 years [interquartile range (IQR) 64–78] and extra-renal manifestations were absent or subclinical (interstitial lung lesions in 10, 24%). The median (IQR) eGFR was 23 mL/min/1.73 m^2 (15–35); six patients (15%) had started renal replacement therapy (RRT). All had proteinuria (median 1180 mg/24 h, IQR 670–2600) and micro-haematuria. Main histologic findings were extracapillary proliferation at chronic stages and glomerulosclerosis; following Berden's classification, 6/28 biopsies (21%) were 'focal', 1/28 (4%) 'crescentic', 9/28 (32%) 'mixed' and 12/28 (43%) 'sclerotic'. At last follow-up (median 32 months, IQR 12–52), 20/34 patients (59%) treated with immunosuppression had eGFR improvement >25% as compared with diagnosis, while 4/34 (12%) had started RRT.

Conclusions. AAV may present with slow renal disease progression; this subset is hallmarked by advanced age at diagnosis, positive MPO-ANCA, subclinical interstitial lung lesions and chronic damage at kidney biopsy. Partial renal recovery may occur following immunosuppression.

Keywords: ANCA, end-stage renal disease, glomerulonephritis, microscopic polyangiitis, rituximab, vasculitis

INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a necrotizing vasculitis characterized by small-vessel inflammation and circulating autoantibodies directed against proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA) [1]. Renal involvement is a major complication of the two main AAV variants, granulomatosis with polyangiits (GPA) and microscopic polyangiitis (MPA) [2, 3], and usually manifests with rapidly progressive glomerulonephritis (RPGN) [4]. This renal syndrome is hallmarked by a rapid decline in glomerular filtration rate (GFR), an active urinary sediment for the presence of erythrocyte casts and histological findings of pauci-immune necrotizing crescentic glomerulonephritis [5]. RPGN requires an early induction treatment with glucocorticoids and immunosuppressive drugs, e.g. cyclophosphamide or rituximab, to stop vasculitis activity and restore renal function [6].

Nevertheless, up to 30% of AAV patients with renal involvement have less aggressive manifestations than RPGN and some experience an indolent course with slow progression towards end-stage renal disease (ESRD) [5]. These 'slowly progressive' renal AAV forms have been rarely discussed in the literature [7], with only anecdotal cases reported to date [8–11]. Such peculiar phenotype probably accounts for a small proportion of AAV, but its recognition may be challenging, since manifestations are not typical for vasculitis and also occur in other more prevalent renal diseases. This can result in delayed or missed diagnosis, with progressive damage accrual. Furthermore, the optimal management and the outcome of these forms are unknown.

To address these points, we have screened a large multicentre cohort of AAV patients, in order to identify cases with slowly progressive renal course and analyse their prevalence, clinico-pathological features and outcome. We only considered patients with MPA and GPA and excluded those with eosinophilic granulomatosis with polyangiitis, since this AAV syndrome has further peculiar manifestations with uncommon and usually mild renal involvement [12]. Our ultimate goals were to raise awareness of this possible presentation of AAV and to explore whether these chronic and apparently irreversible cases have a chance of recovery.

MATERIALS AND METHODS

Patients

We searched the medical records of AAV patients followed at seven vasculitis referral centres, namely the Nephrology Units of Parma University Hospital, Spedali Civili, Brescia, Policlinico San Matteo, Pavia, San Carlo Borromeo Hospital, Milano, San Gerardo Hospital, Monza, Italy and the Vasculitis and Lupus Clinic of the Addenbrooke's Hospital, Cambridge, UK. We screened patients classified as GPA or MPA according to the European Medicines Agency algorithm [13] who had renal involvement at diagnosis, defined as estimated GFR (eGFR) <90 mL/min/1.73 m^2 and urinalysis disclosing proteinuria and/or haematuria (Supplementary data, Table S1). Patients also had to be ≥18 years old at the time of diagnosis and had to have available ANCA test [indirect immunofluorescence and/or enzyme-linked immunosorbent assay (ELISA). AAV cases secondary to drugs, cancer, infections or other autoimmune disorders and patients who had received immunosuppressive therapy (prednisone >7.5 mg/day or equivalent, or any immunosuppressive agent) during the 6 months before diagnosis were excluded, in order to avoid any possible influence on renal disease progression.

We then selected patients with two or more renal function assessments performed within 6 months before diagnosis and analysed their GFR deterioration. Slow progression was defined as eGFR reduction >25% but ≤50% over the 6-month period preceding diagnosis. These limits allowed differentiation of slow renal course from RPGN, usually defined as eGFR reduction >50% in up to 3 months [5], and from kidney impairment with no significant progression. The medical history of patients with slow renal disease progression was reviewed in order to assess other potential causes of renal dysfunction, e.g. drugs, systemic illnesses, infections or any established kidney disease. After consensus was reached among three of the main investigators (G.T., S.G. and A.V.), we included those whose clinical course was not significantly influenced by any of these conditions. All patients signed an informed consent. The study was performed in accordance with the declaration of Helsinki and received approval from the Ethics Committee of the University of Firenze, Italy (protocol number 12097).

Data collection

The time of diagnosis corresponded to the first diagnostic renal biopsy or, if this was not available, to the occurrence of compatible clinical, laboratory or pathological findings, e.g. ANCA test. Data regarding demographic and clinical features were retrieved from medical records and disease activity was evaluated using the Birmingham Vasculitis Activity Score (BVAS) version 3 [14]. The patients' medical history was examined to assess the

presence of conditions associated with chronic kidney disease (CKD), i.e. atherosclerotic disease (clinically documented ischaemic heart disease, cerebrovascular disease or peripheral artery disease), diabetes and cardiovascular risk factors. To assess whether their prevalence was substantially different from that of the general population, data were compared with results of Italian and British national surveys (CuoreData, Il Progetto Cuore, Istituto Superiore di Sanità, www.cuore.iss.it by 29 July 2019; Heart and Circulatory Disease Statistics 2019, British Heart Foundation).

Renal parameters were collected starting from the first detection of renal disease, i.e. either eGFR <90 mL/min/1.73 m^2, proteinuria (urinary albumin-to-creatinine ratio >30 mg/g or 24 h-proteinuria >150 mg) or glomerular haematuria (>3 cells per high-power field, red cell casts on urine microscopic examination or >11 cells/μL on standard urinalysis). eGFR was calculated using the CKD Epidemiology Collaboration equation [15]. ESRD was defined as eGFR <15 mL/min/1.73 m^2 at two consecutive assessments or the need for renal replacement therapy (RRT). Kidney biopsies were examined by experienced local pathologists and classified according to the criteria proposed in 2010 by Berden *et al.* (see Supplementary Methods) [16].

The type of treatment was distinguished into one of the following: (i) no immunosuppressive therapy; (ii) regimens based on glucocorticoids and conventional immunosuppressive drugs other than rituximab, e.g. cyclophosphamide; and (iii) rituximab-based regimens. Outcome data were collected until last available follow-up, patient death or March 2019, and were assessed at Months 6, 12 and 24 after diagnosis and at last follow-up.

AAV remission was defined as absence of vasculitis activity (BVAS = 0). 'Renal response' was a composite of AAV remission (BVAS = 0) and eGFR improvement (≥25%) or stabilization as compared with diagnosis, with concomitant reduction of urinary abnormalities (≥50% at quantitative measurements). Those who reported either eGFR worsening (≥25%) or proteinuria increase (≥50% at quantitative measurements) as compared with diagnosis and those who started RRT failed to achieve response. Relapse was defined as any BVAS modification occurring after remission and 'renal worsening' as eGFR reduction (≥25%) or any other manifestation occurring after renal response.

Statistical analysis

Continuous variables, presented as median (interquartile range, IQR), were compared with the *t*-test or the Mann–Whitney test, where appropriate. Categorical variables, presented as *n* (%), were compared with the Chi-square test. Median eGFR and 24-h proteinuria at different time-points were compared using Friedman's test. All analyses were performed using Prism version 5. $P < 0.05$ were considered statistically significant.

RESULTS

Patients

A total of 856 patients with primary AAV were screened. The cohort included 473 GPA cases (55%) and 383 MPA cases (45%) diagnosed between May 1999 and February 2018 (Figure 1). Renal involvement at diagnosis was reported among 615 patients (72%), of which 340 (55%) had MPA. Of the 258 patients with available pre-diagnosis tests, we did not assess the renal course of 11 who were taking immunosuppressive therapy already

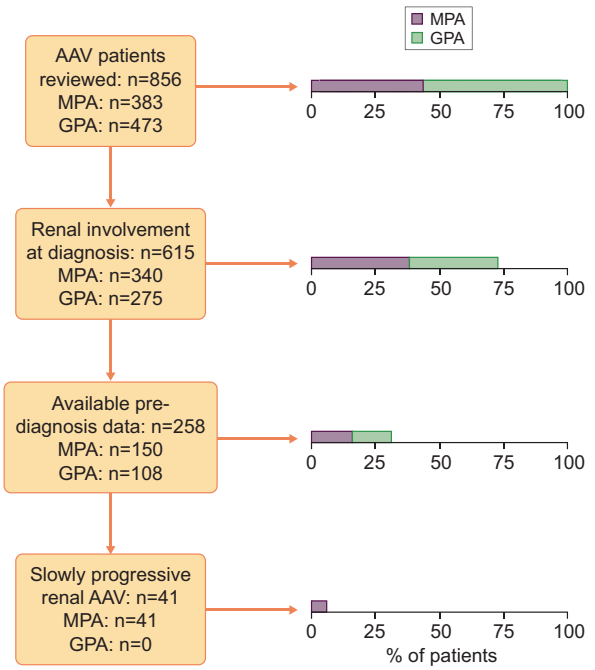

FIGURE 1: Study flow diagram. Renal involvement was defined as an eGFR <90 mL/min/1.73 m^2 and urinalysis disclosing proteinuria or haematuria. Pre-diagnosis data included renal function assessments performed over the 6-month period preceding diagnosis.

before diagnosis. Among the remaining, RPGN was recognized or could not be excluded in 173 (70%), while 27 (11%) had non-progressive kidney dysfunction with minor eGFR fluctuations. Moreover, six patients (2%) with slow renal disease progression were not included because this was attributed to other established causes, namely obstructive uropathy (1/6), severe cardiac failure (1/6), drug abuse (2/6) and chronic pyelonephritis (2/6).

We identified 41 patients who met the criteria for slowly progressive renal AAV. This group accounted for 5% of the screened cohort and for 17% of patients with pre-diagnosis tests. All had MPA, corresponding to 11% of the screened MPA cases (Figure 1).

Demographic and clinical features at diagnosis

At diagnosis, all but one had positive MPO-ANCA or 'perinuclear' pattern at immunofluorescence (P-ANCA) and 30 (73%) were >65 years (Table 1). Twenty-five patients (61%) had renal-limited vasculitis, while three (7%) had peripheral neuropathy confirmed by nerve conduction studies and two (5%) had non-granulomatous ear–nose–throat manifestations (otitis and serous nasal discharge).

Of the 26 patients with available chest high-resolution computed tomography (HRCT), 10 (38%) had radiological lung abnormalities according to the list of MPA-associated lung lesions by Yamagata *et al.* (see Supplementary Methods) [17]. The reported lesions were ground-glass opacities (5/10), interlobular septal thickening (4/10), honeycombing (3/10), nodular pattern (3/10), bronchiectasis (2/10) and reticular pattern (1/10). Four (40%) were current or former smokers, while none had a pre-existing lung disease, e.g. idiopathic interstitial pneumonia or infection. A clinico-radiological pattern corresponding to idiopathic pulmonary fibrosis was recognized in three cases (30%). Moreover, none experienced diffuse alveolar haemorrhage.

Table 1. Demographic and clinical characteristics of patients with slowly progressive ANCA-associated renal vasculitis at the time of diagnosis

	$n = 41$
Gender and age, *n* (%)	
Female	21 (51)
Age, median (IQR), years	70 (64–78)
<50 years	5 (12)
50–75 years	20 (49)
>75 years	16 (39)
Type of AAV, *n* (%)	
MPA	41 (100)
GPA	0
ANCA specificity, *n* (%)	
By indirect immunofluorescence	
P-ANCA alone	39 (94)
C- and P-ANCA	1 (3)
C-ANCA alone	1 (3)
By ELISA	
MPO-ANCA alone	37/39 (94)
MPO- and PR3-ANCA	1/39 (3)
PR3-ANCA alone	1/39 (3)
Clinical manifestations and organ involvement, *n* (%)	
Renal-limited vasculitis	25 (61)
Radiological lung abnormalities[b]	10/26 (38)
Diffuse alveolar haemorrhage	0
Idiopathic pulmonary fibrosis	3/26 (11)
Peripheral nervous system	3 (7)
Ear–nose–throat	2 (5)
Skin	1 (2)
BVAS, median (IQR)	6 (6–10)
Cardiovascular risk factors and comorbidities, *n* (%)	
Arterial hypertension	26 (63)
Diabetes	9 (22)
BMI ≥30 kg/m^2	6 (15)
Smoking history (current or former)	13 (32)
Atherosclerotic disease[c]	8 (19)

[a]P-ANCA means 'perinuclear' pattern, while C-ANCA refers to 'cytoplasmic' pattern.
[b]The presence of radiological lung abnormalities was evaluated in 26 patients who underwent HRCT of the lungs at diagnosis according to the list of MPA-associated lung lesions by Yamagata *et al.* (see Supplementary Methods) [17].
[c]Atherosclerotic disease was defined as the presence of at least one of the following documented conditions: coronary artery disease, cerebrovascular disease, peripheral arterial disease.
BMI, body mass index.

Table 2. Renal characteristics of patients with slowly progressive ANCA-associated renal vasculitis

	$n = 41$
Renal function at diagnosis	
Serum creatinine, median (IQR), mg/dL	2.3 (1.8–3.4)
eGFR, median (IQR), mL/min/1.73 m^2	23 (15–35)
ESRD[a], *n* (%)	15 (37)
RRT, *n* (%)	6 (15)
Urinalysis at diagnosis[b]	
Proteinuria[c], *n* (%)	41 (100)
24-h proteinuria, median (IQR), mg/24 h	1180 (670–2600)
≥3500 mg/24 h, *n* (%)	5 (12)
Micro-haematuria[d], *n* (%)	41 (100)
Active urinary sediment[e], *n* (%)	2/14 (14)
Renal disease before diagnosis	
Time to diagnosis, median (IQR), months	13 (6–35)
Percent loss of eGFR from first assessment, median (IQR), %	53 (39–73)
Absolute loss of eGFR from first assessment, median(IQR), mL/min/1.73 m^2	25 (17–32)
Slope of eGFR reduction[f], median (IQR), mL/min/1.73 m^2/month	1.9 (1.0–3.1)
Renal biopsy category (Berden's classification)	$n = 28$
Focal, *n* (%)	6 (21)
Crescentic, *n* (%)	1 (4)
Mixed, *n* (%)	9 (32)
Sclerotic, *n* (%)	12 (43)

[a]ESRD was defined as eGFR <15 mL/min/1.73 m^2 established at two consecutive assessments or the need for RRT.
[b]For patients in ESRD, we considered the last available follow-up.
[c]Proteinuria was defined as either >150 mg/24 h or albumin/creatinine ratio >30 mg/g; 24-h proteinuria was available for 33 patients.
[d]Micro-haematuria was defined as either >3 cells per high-power field or >11 cells/μL on standard urinalysis.
[e]Urinary sediment was considered active in the presence of red cell casts.
[f]Slope of eGFR reduction was calculated dividing the absolute loss of eGFR from first assessment to diagnosis with the number of months elapsed between the two time points.

The prevalence of atherosclerotic disease and risk factors is shown in Table 1 and appeared similar to that reported by Italian and British national surveys on population of comparable sex and age.

Renal features and histology

At diagnosis, the median (IQR) eGFR was 23 mL/min/1.73 m^2 (15–35). Fifteen patients (37%) had ESRD and six (15%) required RRT (Table 2). All had haematuria and proteinuria (for those requiring RRT, we considered last available urinalysis). Five patients (12%) had urinary protein excretion ≥3500 mg/24 h but none showed further features of nephrotic syndrome.

The median (IQR) time elapsed from the first detection of renal abnormalities to diagnosis was 13 months (6–35); this was significantly longer among patients with ESRD than among those presenting with eGFR >15 mL/min/1.73 m^2, respectively, 38 months (IQR 13–52) and 8 months (IQR 6–16) ($P = 0.007$). Thirty-eight patients (93%) had three or more renal function assessments during the pre-diagnosis period. These values revealed that the eGFR decline had not occurred predominantly around diagnosis, as in RPGN. Rates of progression slightly varied between patients and between different observation periods for each patient (data not shown), but were consistent with gradual worsening. The evolution of eGFR during the 12 months preceding diagnosis is shown in Supplementary data, Figure S1.

All the 28 patients who underwent kidney biopsy had histology consistent with AAV. Extra-capillary proliferation was observed in 25 samples (89%); crescents were purely fibrous in 22 (78%) and cellular or fibro-cellular in three (11%). The median (IQR) proportion of glomeruli involved by extra-capillary proliferation was 31% (17–53%). Foci of fibrinoid necrosis were found in five cases (18%), while one (4%) had interstitial vasculitis with peri-glomerular infiltrates. Furthermore, all biopsies showed glomerulosclerosis, involving a median (IQR) proportion of 38% glomeruli (17–67), along with interstitial fibrosis and tubular atrophy of varying extent (Figure 2). Eight patients (28%) had severe arteriolar hyalinization. Of the six diabetic patients with available kidney biopsy, two had glomerular basement membrane thickening by light microscopy but none showed further diabetic nephropathy lesions. According to the histopathologic

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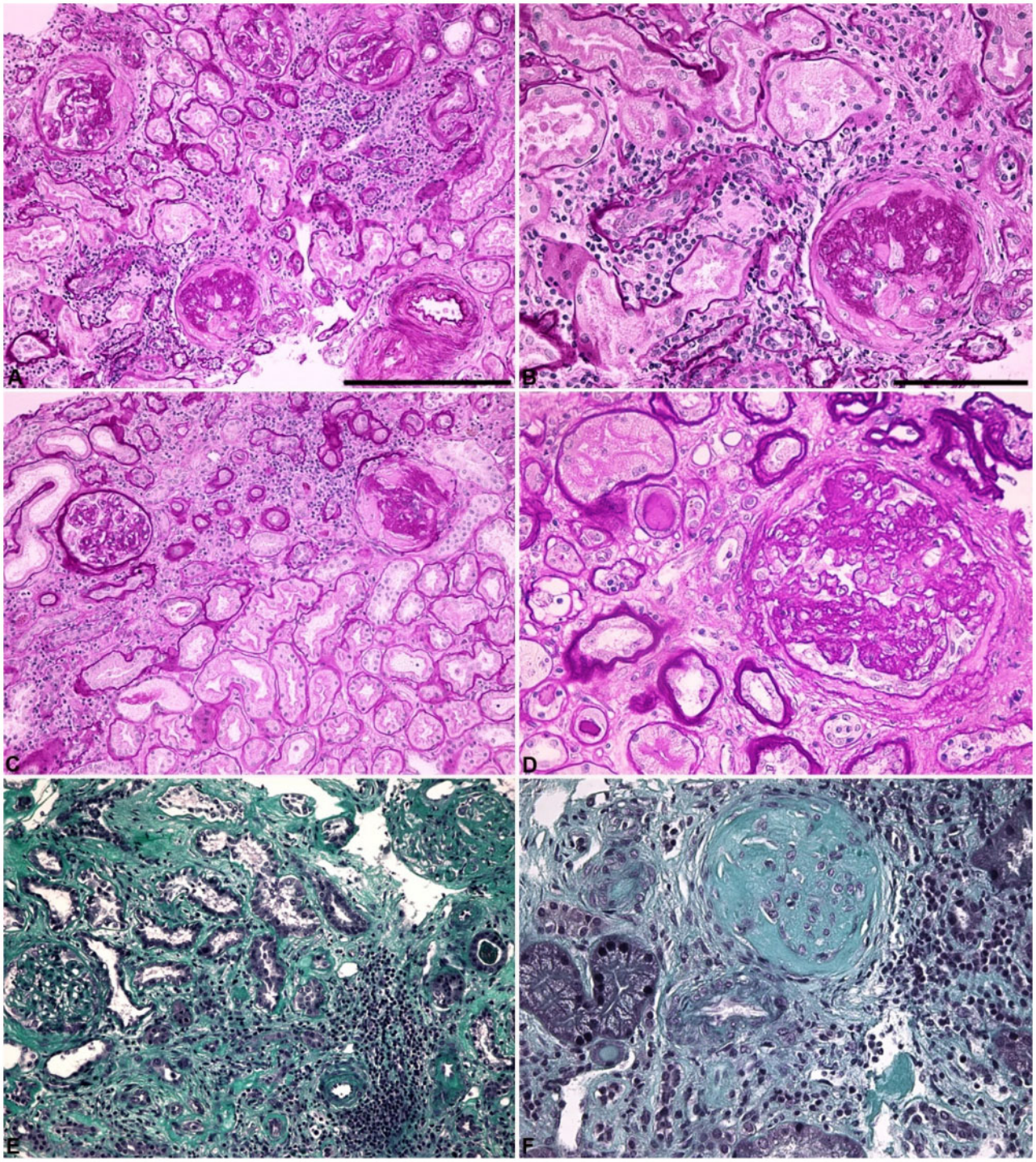

FIGURE 2: Representative renal histology. Renal biopsy specimens of patients with slowly progressive ANCA-associated renal vasculitis: (**A**) low-power view showing diffuse glomerular and tubulointerstitial chronic inflammatory and fibrotic lesions, particularly fibrous crescents in all the examined glomeruli. (**B**) High-power view of one of the glomeruli seen in (**A**), showing a circumferential fibrous crescent and a periglomerular, tubulointerstitial mononuclear cell infiltrate. (**C**) Low-power view image disclosing chronic glomerular as well as mildly active glomerular lesions, and a chronic tubulointerstitial inflammatory infiltrate. (**D**) High-power view showing a glomerulus with shrinkage of the capillary tuft and initial extra-capillary proliferation; tubular atrophy is also evident. (**E**) Low-power view showing hyaline changes in medium-sized and small vessels, glomerulosclerosis, tubulointerstitial inflammation and diffuse interstitial fibrosis. (**F**) High-power view of a globally sclerosed glomerulus and chronic tubulointerstitial infiltrate. (**A**–**D**): periodic acid–Schiff staining, (**E** and **F**): Masson trichrome staining. Original magnification, ×20 in (**A**), (**C**) and (**E**), ×40 in (**B**), (**D**) and (**F**). Scale bars are 150 μm in (**A**) (which also applies to **C** and **E**), and 75 μm in (**B**) (which also applies to **D** and **F**).

Table 3. Treatment and outcome of patients with slowly progressive ANCA-associated renal vasculitis at Months 6 and 12 after diagnosis (baseline) and at last follow-up

n (%)	Baseline *n* = 41	Month 6 *n* = 41	Month 12 *n* = 33	Last follow-up *n* = 41
Type of treatment				
No immunosuppressive therapy	4 (10)	4 (10)	4 (12)	4 (10)
Conventional immunosuppressive therapy	23 (56)	23 (56)	18 (55)	19 (46)
Rituximab-based therapy	14 (34)	14 (34)	11 (33)	18 (44)
ESRD[a]	15 (37)	10 (24)	5 (15)	12 (29)
RRT	6 (15)	7 (17)	4 (12)	10 (24)
Renal outcome in patients treated with immunosuppression[b]		*n* = 34	*n* = 28	*n* = 34
Response	–	32 (94)	23 (82)	23 (68)
Improved GFR (≥25%)[c]	–	25 (73)	19 (68)	20 (59)
Stable GFR (<25%)	–	7 (21)	4 (14)	3 (9)
No response/progression	–	2 (6)	5 (18)	11 (32)
RRT	–	1 (3)	1 (4)	4 (12)

[a]ESRD was defined as eGFR <15 mL/min/1.73 m^2 established at two consecutive assessments or the need for RRT.
[b]Patients requiring RRT at the time of treatment start were excluded from the analysis.
[c]In this subgroup of patients, the median (IQR) absolute eGFR increase was 14 mL/min (14–21) while the median (IQR) percent eGFR increase was 52% (34–65%). Conventional immunosuppressive therapy included regimens based on glucocorticoids and immunosuppressive agents other than rituximab. Renal response was defined as absence of vasculitis activity and documentation of improved or stabilized renal function as compared with baseline, with concomitant improvement of urinary abnormalities.

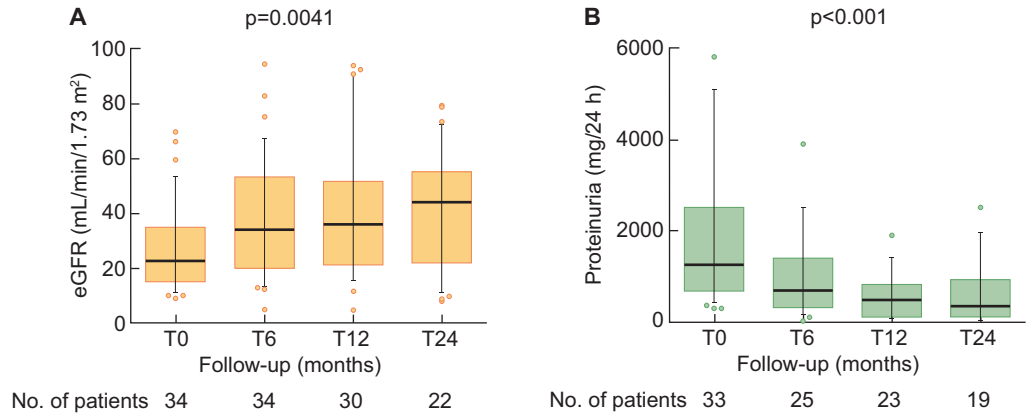

FIGURE 3: Evolution of eGFR and proteinuria after diagnosis. The plots show eGFR (**A**) and 24-h proteinuria (**B**) of patients with slowly progressive ANCA-associated renal vasculitis at diagnosis (T0) and at Months 6 (T6), 12 (T12) and 24 (T24) after diagnosis. Patients who required RRT at T0 or did not receive immunosuppressive therapy were excluded from the analysis. Data showed a significant increase in median eGFR and a significant decrease in median 24-h proteinuria over the first 24 months after diagnosis (respectively, $P = 0.0041$ and $P < 0.001$ using Friedman's test). The boxes indicate the 25th–75th percentile, the bar inside the boxes indicates the median, the whiskers indicate the 10th–90th percentile and the dots the outliers.

classification, 6 biopsies (21%) were 'focal', 1 (4%) 'crescentic', 9 (32%) 'mixed' and 12 (43%) 'sclerotic' (Table 2).

Treatment and outcome

All patients received supportive therapy according to clinical status. Seventeen (41%) were already taking angiotensin-converting enzyme inhibitors and angiotensin receptor blockers before diagnosis. After diagnosis was made, 37 patients (90%) were treated with immunosuppression. Twenty-three (56%) received glucocorticoids alone (5/23) or combined with cyclophosphamide (14/23), mycophenolate mofetil (2/23) and azathioprine (2/23), while 14 (34%) were administered a rituximab-based regimen. Two received rituximab alone because of contraindications to glucocorticoids (diabetes and atherosclerotic disease); they had eGFR ≤15 mL/min/1.73 m^2 and a 'sclerotic' pattern at kidney biopsy. Moreover, four patients (10%) were not treated with immunosuppression because they had no active extra-renal disease and their renal recovery was considered unlikely.

The median (IQR) follow-up after diagnosis was 32 months (12–52). Table 3 describes the renal outcome of the 34 patients who received immunosuppression and did not require RRT at treatment start. At Month 6, 32 (94%) had achieved renal response and 25 (73%) reported eGFR improvement as compared with diagnosis. Haematuria improved or subsided in all patients while proteinuria showed initial decrease (Figure 3B).

At last follow-up, renal response was maintained among 23 patients (68%), of which 20 (59%) had eGFR improvement as compared with diagnosis. Eleven (32%) had progressed and four of them (12%) had started RRT; these patients had eGFR <15 mL/min/1.73 m^2 already at diagnosis and a 'sclerotic' pattern at kidney biopsy. The remaining six whose biopsy was classified as

'sclerotic' had partial renal function improvement as compared with diagnosis, with median (IQR) eGFR risen from 14 mL/min/1.73 m^2 (12–19) to 20 mL/min/1.73 m^2 (18–27) ($P = 0.05$). The evolution of eGFR through the first 24 months after diagnosis is shown in Figure 3A.

The groups treated with rituximab-based and rituximab-free immunosuppressive regimens reported similar rates of response (Supplementary data, Table S2). Moreover, both patients who received rituximab monotherapy had eGFR improvement at Month 6 and at last follow-up (respectively, 9 and 45 months after diagnosis). None of those who started RRT became RRT-free. Moreover, all patients who did not receive immunosuppressive therapy progressed to or remained in ESRD.

Among patients with a follow-up of at least 12 months, 10/27 (37%) experienced a renal worsening with eGFR decline >25% after an initial response. Six also had worsening proteinuria and haematuria. Moreover, ANCA were positive in all but their titre was increased in only two as compared with previous assessments. One patient had concomitant progression of pulmonary fibrosis demonstrated by HRCT. No significant differences in clinical and demographic features were observed between this group and the remaining (data not shown). Five underwent retreatment or started a new therapy (rituximab) on the suspicion of renal relapse, and four achieved again renal response.

Active extra-renal manifestations improved after treatment in all patients. Interstitial lung lesions were found during follow-up in four who had not previously undergone HRCT. Moreover, one reported neurosensory hearing loss that significantly improved with rituximab.

Nine patients (22%) died after a median (IQR) of 20 months (6–48). None experienced a concomitant vasculitic flare or had treatment-related adverse events that could have caused death. The identifiable causes of death were pulmonary embolism (1/9), hepatic insufficiency due to viral infection (1/9), intestinal perforation (1/9) and pulmonary oedema due to heart failure (2/9).

DISCUSSION

Renal involvement in AAV includes a broad spectrum of manifestations that range from RPGN, the most common and severe one, to less aggressive forms [5]. In this study, we characterized a peculiar subset of AAV patients, hallmarked by slow progression of renal disease at presentation. Among a large multicentre cohort of GPA and MPA patients, we found that 5% had a slow rather than rapid renal course, with gradual renal function deterioration and mild-to-moderate urinary abnormalities. All were classified as MPA and most had advanced age, positive MPO-ANCA and few or no vasculitic symptoms, while the most frequent extra-renal manifestation was subclinical interstitial lung disease. Renal histology showed predominance of chronic damage and scarce active lesions. However, despite a poor renal prognostic profile, most patients treated with immunosuppression had partial renal recovery at short- and long-term follow-up.

To our knowledge, this is the first study that systematically assesses slowly progressive renal AAV. The recognition of this phenotype suggests that AAV occasionally presents with indolent renal progression and scarce vasculitic features, particularly among elderly patients. In such a clinical scenario, it may be hard to suspect AAV. It also seems conceivable that a proportion of patients with this AAV form has been overlooked, as their renal disease was probably attributed to CKD of non-specific aetiology, e.g. 'nephrosclerosis' or 'hypertensive kidney disease' [18]. In order to identify these cases early, ANCA should be tested soon after detection of CKD, especially among patients with urinary abnormalities, progression despite nephroprotective therapy and interstitial lung lesions. The ANCA status also helps to decide on kidney biopsy and to evaluate its findings. Along with diffuse chronic damage and some vascular changes compatible with nephrosclerosis, i.e. arteriolar hyalinosis, our patients had pauci-immune extracapillary proliferation, mainly at chronic stages. We believe that these findings, although non-specific, are consistent with renal AAV in ANCA-positive patients and suggest that vasculitis contributes to renal damage in these forms, even if more traditional factors could also play a role.

That immune-mediated mechanisms are involved in kidney disease pathogenesis among these patients is further supported by the renal function improvement observed in a substantial proportion of cases following immunosuppressive therapy. Notably, renal response was also achieved by those who repeated treatment for possible renal relapse. Kidney impairment is usually considered irreversible in nephrosclerosis, where risk factor control aims at preventing progression, while timely immunosuppression may lead to renal recovery in AAV. Whether slowly progressive renal AAV should be treated with immunosuppression rather than with supportive care only is not an easy question, since the long duration of renal disease with diffuse sclerosis and few active lesions discourages treatment. Our study could not provide evidence to solve this dilemma, but the high frequency of renal response we reported is in favour of immunosuppression.

The choice of management appears particularly intricate for patients with severe renal function impairment and a 'sclerotic' pattern at kidney biopsy, i.e. the subgroup with the worst prognosis [19–21]. However, as shown in our cohort and in previous experiences [22], some achieve renal stabilization with partial recovery, thus neither for these cases should immunosuppression be *a priori* excluded. It seems reasonable that these patients be treated with light regimens and reduced glucocorticoid dose. With reagard to this, we reported two cases that experienced sustained improvement after rituximab monotherapy, which could represent a valid therapeutic option for comorbid patients.

Although we screened a large number of GPA patients, granulomatous manifestations were never found among slowly progressive renal AAV cases, while MPO-ANCA strongly characterized this group. These findings suggest a distinct pathogenic process underlying the slow renal course, likely orchestrated by MPO-ANCA. These autoantibodies have been shown to be nephritogenic, causing crescentic glomerulonephritis when injected in murine models [23]. Moreover, MPO ANCA-positive vasculitis is associated with more chronic damage at kidney biopsy than PR3-ANCA-positive vasculitis [24, 25]. This has been related to a possible diagnostic delay due to less extra-renal involvement in MPO-ANCA-positive patients that would allow active lesions to turn into chronic ones. Hauer *et al.* also proposed that the process of renal sclerosis is enhanced in MPO-ANCA-positive vasculitis and occurs already at early stages [25]. Mechanisms that could explain this pattern have not been explored; however, MPO-ANCA triggers lung fibrosis in MPA and could have similar effects in the kidney [26, 27]. Slowly progressive renal AAV could represent a disease subset in which MPO-ANCA promote more renal sclerosis than vasculitis, with consequent mild manifestations, slow progression and chronic damage accrual. The reason why most MPO-ANCA-positive patients develop RPGN and a small proportion has slowly progressive renal disease is elusive; future studies are needed to compare these two different subsets, e.g. by exploring differences in genetic profiles and ANCA epitopes.

Our study has limitations, mainly related to its retrospective nature and the absence of established definitions to discriminate slowly progressive renal disease from more typical forms of renal involvement, such as RPGN. However, the criteria we chose to define slowly progressive renal AAV, although arbitrary, were quite stringent and in our opinion sufficient to differentiate this presentation from other renal syndromes. Further strengths of the study are the large size of the AAV cohort and the availability of long-term follow-up data.

In conclusion, AAV may present with slowly progressive renal disease. This patient subset has MPA phenotype, MPO-ANCA positivity, advanced age at diagnosis and subclinical extra-renal involvement, mainly interstitial lung disease. There is a danger of missed or delayed diagnosis for these cases, with markedly increased ESRD risk, and ANCA test is crucial for their recognition. Despite chronic renal injury, immunosuppressive treatment may allow partial renal recovery and thus should be considered in these forms.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

ACKNOWLEDGEMENTS

We gratefully acknowledge Dr Maria Nicastro for providing the renal biopsy images, and Professor Carlo Buzio for having inspired this study.

FUNDING

None of the authors has received any kind of financial support for this study.

AUTHORS' CONTRIBUTIONS

G.T. and A.V. made substantial contributions to study conception and design. G.T., A.V., S.G., M.L.U., D.G., M.A.C., P.G.V., M.C., P.E., C.M., F.A., F.M., L.M., A.P., G.M., G.G., R.A.S., G.E. and D.R.W.J. made substantial contributions to acquisition of data. G.T., A.V., A.B., P.R., G.E. and D.R.W.J. made substantial contributions to analysis and interpretation of data. All authors were involved in drafting the article or revising it critically for important intellectual content, and gave final approval of the version of the article to be published.

CONFLICT OF INTEREST STATEMENT

None of the authors has any kind of conflict of interest with the publication of this manuscript. The results of this study have not been previously published, in whole or part, except in abstract format.

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