Slowly progressive glomerulonephritis in patients with ANCA-associated vasculitis (AAV)

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Introduction and objectives. Renal involvement in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is common and usually occurs in 70% of patients with granulomatosis with polyangiitis (GPA) and in almost 100% of patients with microscopic polyangiitis (MPA) [1]. Renal involvement in AAV is characterized by rapidly progressive renal failure and histologically by necrotizing crescentic glomerulonephritis. Anecdotal cases of AAV with slower progression to end-stage renal disease (ESRD) have been reported [2-6]. The purpose of this study is to better characterize the clinical phenotype of AAV patients with slow renal progression.

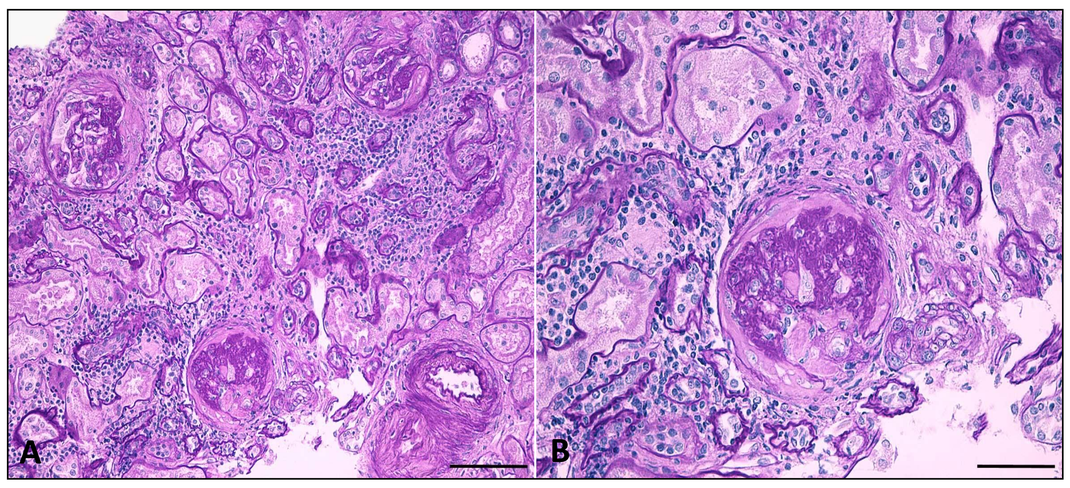
Methods. We included patients with a diagnosis of AAV, classified as GPA or MPA using Watts algorithm; their renal involvement had to be characterized by slow progression, i.e. reduction in eGFR>20% to <50% versus baseline over at least 6 months. All patients had to have a sufficient renal follow-up before and after AAV diagnosis (>6 months prior to and >6 months after diagnosis); the pre-diagnosis observation was required to confirm the slow disease progression.

Inclusion criteria
1. Diagnosis of ANCA-associated vasculitis, classified as GPA or MPA using Watts algorithm (EMEA algorithm)
2. Positive serology for ANCA (indirect immunofluorescence and/or ELISA)
3. Availability of kidney function tests and urine analysis over a period of at least 6 months before diagnosis (at least two tests)
4. Follow-up of at least 6 months after diagnosis
5. Kidney involvement characterized by a slow reduction of GFR (eGFR reduction >20% and < 50% over a period of at least 6 months; eGFR reduction > 50% was acceptable only over a disease duration longer than 6 months)
Exclusion criteria
1. AAV secondary to drugs, infections, tumors
2. AAV without kidney involvement
3. Renal presentation of AAV as nephritic syndrome/ RPGN

***Abbreviations**: AAV: ANCA-associated vasculitis; GPA: granulomatosis with polyangiitis; MPA: mycroscopic polyangiitis; eGFR: estimated glomerular filtration rate; RPGN: rapidly progressive glomerulonephritis.*

Results. A total of 25 patients were identified by searching the AAV databases of 5 different Northern Italian nephrology centres. At first detection of pathological eGFR values, all patients had urinary abnormalities (e.g. hematuria and proteinuria). The median time from the first pathological eGFR value to AAV diagnosis was 13 months (interquartile range, IQR 9-34). At diagnosis, the median age was 72 years (IQR 67-79), the median creatinine 3.4 mg/dL (IQR 2.1-4.5). 25/25 patients were P-ANCA and/or MPO-ANCA positive. 9/25 patients (36%) had interstitial lung lesions and 3/25 (12%) peripheral neuropathy. Only 2 patients had alveolar hemorrhage (*Table 1*). AAV-related glomerulonephritis was histologically confirmed in 15/25 patients. 9/15 patients (60%) had a sclerotic form and 6/15 (40%) a mixed form according to Berden's classification (*Figure 1*); no case was classified as focal or crescentic; no one had fibrinoid necrosis (*Table 2*).

Figure 1:



Representative renal biopsy findings from one patient slowly progressive ANCA-associated glomerulonephritis. Fibrous crescents can be observed in most glomeruli. Significant interstitial inflammation and fibrosis, along with tubular atrophy, is also observed. Periodic acid Schiff staining. A 20x, B 40x .

Table 1:

Age at diagnosis- years, median (IQR)	72 (67-79)
Male/female- n. (%)	12/13 (48%/52%)
MPA- n. (%)	25 (100%)
GPA- n. (%)	0 (0%)
ANCA positivity- n. (%)	
Indirect Immunofluorescence	
C-ANCA	0/25 (0%)
P-ANCA	25/25 (100%)
ELISA	
MPO-ANCA	25/25 (100%)
PR3-ANCA	0/25 (0%)
C-reactive protein- mg/L , median (IQR)	3.9 (2.0-11.3)
ESR- mm/h, median (IQR)	56 (38-100)
C3- mg/dL, median (IQR)	100 (88.3-106)
C4- mg/dL, median (IQR)	32.9 (20.7-39.0)
Anti-GBM positivity- n. (%)	0 (0%)
ANA positivity- n. (%)	25/32 (78%)
Clinical manifestations- n. (%)	
Constitutional symptoms	2/25 (8%)
Renal-limited vasculitis	14/25 (56%)
Pulmonary involvement	9/25 (31%)
Severe (alveolar hemorrhage, pulmonary fibrosis)	2/25 (8%)
Peripheral neuropathy	3/25 (12%)
ENT involvement	0/25 (0%)
Skin involvement	0/25 (0%)
Other	4/25 (16%))
BVAS at diagnosis, median (IQR)	5 (5-12)

At diagnosis 5/25 patients had already reached ESRD, and 20/25 had varying degrees of renal failure. Main renal parameters at the time of diagnosis are shown in the table below.

Table 2:

Renal characteristics at diagnosis- median (IQR)	
Serum Creatinine – mg/dl	3.4 (2.1-4.5)
eGFR– ml/min per 1.73 m2	18.5 (12.0-28.6)
ESRD requiring RRT- n. (%)	5/25 (20%)
Median time from the first pathological GFR to AAV	13 (9-34)
diagnosis- months median (IQR)	1.18 (0.67-2.60)
Proteinuria- g/24 h	4/25 (12%)
Nephrotic range proteinuria- no.(%)	18/25 (72%)
Microhematuria- n. (%)	4/25 (16%)
Active urinary sediment- n. (%)	
Renal biopsy, no.(%)	15/25 (60%)
Focal	0/15 (0%)
Crescentic	0/15 (0%)
Mixed	6/15 (40%)
Sclerotic	9/15 (60%)

21/25 patients received immunosuppression (5/21 steroid therapy, 5/21 steroids plus conventional immunosuppressive drugs, 11/21 rituximab). Twelve months after diagnosis, 10 of the 21 treated patients had renal function improvement, 5/21 had stable renal function and 2/21 worsened renal function.

Conclusions. A subset of AAV has a slowly progressive course. This subset usually has an MPA phenotype, is MPO-ANCA positive and has few extra-renal manifestations except for a high prevalence of interstitial lung disease. Renal histology usually shows sclerotic or mixed phenotypes. Treatment of this patient subset may dampen progression of AAV-related renal disease.

References

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