The relation between histopathological classification and renal outcome, ANCA subtype and treatment regimens in ANCA-associated vasculitis

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ABSTRACT

Objective. *ANCA-associated vasculitis (AAV) is associated with an increased risk of death and end stage renal disease (ESRD). The aim of this study was to examine the correlation between a histopathological classification and renal outcome and to describe the interaction with ANCA subtype and initial treatment.*

Methods. *Eighty-seven patients with AAV from 1999-2010 from two centres in Denmark were included in the study and had a 3-year follow-up. Data was collected retrospectively. The renal biopsies were reclassified into one of the following groups: crescentic, sclerotic, focal and mixed.*

Results. *Histopathologic groups were not associated with eGFR at three years. Age and baseline eGFR were independent prognostic for eGFR at three years. More patients in the crescentic group than in the mixed and focal groups developed ESRD (33%, 13% and 5% respectively). Patients reaching ESRD had fewer non-affected glomeruli (14 % vs. 34%, p=0.0014) and lower eGFR at baseline (7 vs. 21.7 ml/min/m^2, p<0.0001). At baseline MPO-ANCA positive patients were older, had more sclerotic glomeruli and had a lower eGFR after three years compared to PR3-ANCA positive patients. PR3-ANCA positive patients receiving plasma exchange (PE) improved eGFR more from baseline to three years than those not receiving PE (36 vs. 20 ml/min/m^2, p=0.01).*

Conclusion. *In our cohort most patients in the crescentic group and fewer in the focal group reached ESRD. Age and baseline eGFR are prognostic of renal function after 3 years, as also in the PR3-ANCA positive subgroup initial treatment with PE.*

Introduction

In anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) multiple organs can be affected. The kidney is involved in 75–90% of the cases often presenting as rapidly progressive glomerulonephritis (1). The disease has a major impact on patients' quality of life and increases the risk of death, particularly among those developing end stage renal diseases (ESRD). In a review article on renal vasculitis from 2004, the 1-year mortality untreated was 80% and the percentage of ESRD 20-25% among survivors (2). Sriskandarajan *et al*. found a significantly reduced risk of death and ESRD for patients with ANCA-associated glomerulonephritis in the period from 2003 to 2012, compared to 1988-2002 (3). They suggested this might be due to shorter diagnostic delay and better therapeutic regimens.

In 2010 Berden *et al*. published a classification of the histopathologic lesions in AAV (4). The lesions were divided into 4 groups: focal, crescentic, sclerotic and mixed based on the glomerular appearance. The predictive value for ERSD in this classification was validated in 100 patients with a follow-up for at least one year. Patients in the sclerotic group had an increased risk of ESRD and death compared to the other groups. Patients in the crescentic group had a higher percentage of renal recovery despite presenting with severely reduced renal function. Patients in the focal group presented with a better renal function, and patients in the mixed group had an intermediate outcome. Tubulo-interstitial fibrosis and atrophy did not increase the prognostic value. Validation studies of the classification have revealed conflicting results (5-8). None of the previous studies have evaluated the histopathological classification and the treatment regimen combined, and only a few have studied the influence of ANCA subtype.

The aim of the present study was to

examine the relation between the histopathologic classification and renal function in a cohort of Danish patients with AAV evaluated at baseline and after 3 years of follow-up, and to describe the interaction of ANCA subtype and the initial treatment on this relation.

Methods

All patients admitted to the Department of Nephrology, Aarhus University Hospital and the Regional Hospital of Viborg, diagnosed with renal AAV from 1999 to 2010, were included. Patients included were more than 18 years in age, ANCA-positive and anti GBM negative and had impaired renal function with estimated GFR (eGFR) <60 ml/min/1.73m^2 except from one patient with eGFR 83 ml/min/1.73m^2 and a kidney biopsy with crescentic glomerulonephritis in 5/8 glomeruli. A kidney biopsy was done at the time of diagnosis. The patients received an introductive therapy with oral prednisolone (1 mg/kg body weight/day) and approximately half of the patients were treated with i.v. methylprednisolone. All patients received oral cyclophosphamide (CYC) (2 mg/kg body weight) except one patient receiving i.v. pulse CYC, at presentation. Since 2007 all patients with eGFR <60 ml/min/1.73m^2 were offered plasma exchange (PE) in addition. Patients in remission were switched from CYC to maintenance therapy with either azathioprine (AZA) or mycophenolate mofetil and low dose prednisolone. More patients in the group treated with PE received AZA as maintenance therapy (75% *vs*. 30%) (9). Data was collected retrospectively by systemic review of all medical files. Estimated GFR at the time of diagnosis (baseline), at 3 months and 3 years after diagnosis were calculated according to the MDRD-formula. Two patients were lost to follow-up, because they both moved to another region. Acute kidney injury (AKI) was defined as the need for dialysis within the first week after presentation, and ESRD was defined as need for dialysis in more than 3 months at any time point during follow-up.

All kidney biopsies were re-evaluated by a single pathologist (SK), blinded for eGFR, ANCA subtype and treatment. Biopsies were classified into one of four groups according to the histopathological classification of ANCA-associated glomerulonephritis introduced by Berden *et al*. (4); those with more than 50% normal glomeruli were classified as focal, those with more than 50% sclerotic glomeruli were classified as sclerotic, those with more than 50% glomeruli with cellular crescents were classified as crescentic and the rest of the biopsies who did not met these criteria were classified as mixed (4). All biopsies were re-evaluated for tubulo-interstitial fibrosis (TIF) and atrophy (TA) by using a semi-quantitative measurement TIF/TA0 = 0%, TIF/TA1 = <25%, TIF/TA2 = 25–50% and TIF/TA3 >50% (10). In nine patients it was not possible to retrieve the kidney biopsies.

Statistical analyses

Results are expressed as geometric mean and ± 95% confidence interval, unless otherwise stated. Difference between histopathological lesions was evaluated by ANOVA for continuous variables and by Fisher's exact test for categorical variables. ANCA subtype and initial treatment were evaluated by Students *t*-test for continuous variables and by Fisher's exact test for categorical variables. Multivariable ANOVA performed to factors influencing eGFR, patients in dialysis was defined to have eGFR of 2 ml/min, and for those who died the last eGFR measured was carried forward. Time was not included as a variable. Normality was checked by inspecting QQ-plots of the residuals. *P*-values <0.05 were considered statistically significant. Data were analysed using Stata v. 13.1 (Lakeway Drive, Texas, USA).

Table I. Patient with ANCA associated vasculitis and decreased renal function stratified according to renal histologic lesion (Geometric means ± 95 CI or n).

	Crescentic n=24	Sclerotic n=3	Mixed n=30	Focal n=21	Unknown n=9	*p*-value
Age	63 (37-79)	64 (54-66)	65.5 (22-86)	60.5 (28-79)	68 (65-76)	0.57
Sex (female/male)	10/14	1/2	14/16	5/16	3/6	0.51
PR3-ANCA(n=49)	17 (35%)	1 (2%)	15 (33%)	12 (24%)	4 (13%)	0.44
MPO-ANCA(n=38)	7 (21%)	2 (5%)	15 (39%)	9 (24%)	5 (15%)	
ΔeGFR (BL-3y)	26.9 (17-43)	-	16.4 (6-43)	19.8 (15-25)	11.7 (3-41)	0.13*
ΔeGFR (3month-3y)	15.6 (11-21)	-	10.7 (6-20)	4.8 (1-20)	5.9 (0-23)	0.04*
ΔeGFR (BL-3month)	21.7 (13-35)	-	12.5 (6-24)	22.7 (14-37)	20 (-1-57)	0.89*
AKI baseline#	12 (50%)	1 (33%)	3 (10%)	2 (10%)	4 (44%)	0.004
Death	5 (21%)	0	7 (23%)	3 (14%)	3 (33%)	0.111
Number of glomeruli	10 [4-17]	12 [10-14]	11 [5-30]	13 [4-47]		
Not affected glomeruli (%)	13 [0-47]	8 [0-10]	21 [0-44]	63 [50-90]		0.001*
TIF (0/1/2)	7/15/2	0/0/3	2/18/10	7/13/1		0.013*
TA (0/1/2)	6/15/3	0/1/2	3/21/6	9/10/2		0.12*

*sclerotic not included; #within 1 week of diagnosis.

Results

Study population

Eighty-seven ANCA positive patients with kidney biopsies verified pauci-immune glomerulonephritis were included. Forty-nine patients (56%) were MPO-ANCA positive and 38 (44%) were PR3-ANCA positive. The patients were 22 to 86 years of age with a mean age of 62.9 years. The male-female ratio was 3:2. Twenty-two patients (25%) were dialysis-dependent within the first week after diagnosis, and 18 patients (21%) were still in dialysis after 3 month. Twenty-six patients (30%) received PE.

Eighteen patients (21%) died (Table I). The percentage of deaths was lower in the focal group (14%), and higher in the crescentic and mixed group (21% and 23%, respectively).

Histopathology

35% of the patients were in the mixed group, 3% in the sclerotic group, 24% in the focal group and 28% in the crescentic group (Table I). The total number of glomeruli was 4 to 47 in the biopsies, with a median of 10-13 in the all the groups (Table I).

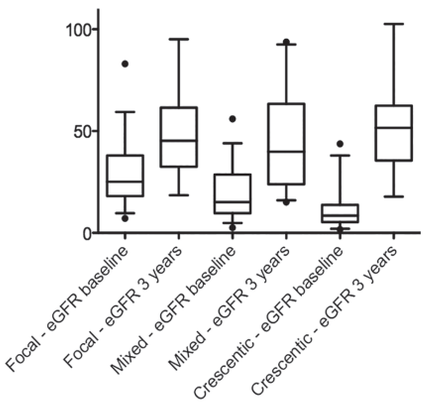

Fig. 1. Box-plot with eGFR at baseline and at three years in the different histopathological groups.
At baseline the focal group has the highest eGFR and the crescentic group has the lowest eGFR (24.5 *vs*. 8,9 ml/min, p=0.001). After 3 years follow-up there are no differences between the groups (p=0.22). Boxes represent 25%-75% percentiles with median value outlined and whiskers representing min-max values.

Table II. Patient with ANCA associated vasculitis and affected renal function according to reaching ESRD.

	Non ERSD (n=71)	ERSD (n=16)	p-value
Age	62.8 (28-86)	65.6 (22-81)	<0.56
Sex (female/male)	28/43	5/11	0.78
eGFR baseline	21.7 (1-83)	7.0 (1-18)	<0.0001
Histologic type *	16/2/26/20/7	8/1/4/1/2	0.05
MPO/PR3	31/40	7/9	1.0
No PE/PE	48/23	13/3	0.37
Not affected glomeruli (%)	34.2(0-90)	14.0(0-67)	0.0014
Sclerotic glomeruli (%)	11.6(0-78)	16.8(0-76)	0.049
TIF (0/1/2)#	14/37/13	2/9/3	0.92
TA (0/1/2)#	16/39/9	2/8/4	0.34

#Fisher's exact test; *crescentic/sclerotic/mixed/focal/not done.

Table III. Patients with PR3+ ANCA associated vasculitis and affected renal function stratified by initial treatment.

	No PE (n=33)	PE (n=16)	p-value
Age	60.5 (22-83)	57.6 (40-79)	0.47
Sex(female/male)	10/23 6/10	0.75	
eGFR baseline	23.3 (1-83)	16.1 (6-33)	0.20
eGFR 3 years	51.7 (19-95)	52.6 (24-94)	0.89
ΔeGFR (BL-3years)	19.5 (-13-50)	36.4 (15-61)	0.01
Histologic type*	10/1/10/9/3	6/0/5/4/1	

*Crescentic/sclerotic/mixed/focal/not done.

At baseline five times as many patients in the crescentic group had AKI (50%) compared to patients in the mixed (10%) and focal group (10%) (p<0.004). Patients in the focal group had approximately three times higher eGFR at baseline (p<0.001) (Fig. 1), which coincided with a higher percentage of non-affected glomeruli (p<0.001) compared to the other groups (Table I). Histopathological group at presentation was not associated with eGFR after three years (p=0.22) (Fig. 1). There was no statistical significant difference in change in eGFR (ΔeGFR) from baseline to 3 month and from baseline to 3 years between the four histopathological groups, but ΔeGFR from 3 month to 3 years were three times higher in the crescentic group compared to the focal group, and 1.5 times higher than in the mixed group (p<0.04) (Table I).
Eight of the 24 patients (33%) in the crescentic group reached ESRD. In the focal and mixed group only 1/20 (5%) and 1/7 (13%) (p<0.05) reached ESRD at any point during the 3 years follow-up, respectively (Table II). Compared to patients with preserved renal function, the patients who reached ESRD had a three times lower eGFR at baseline (7.0 *vs*. 21.7 ml/min) (p<0.001), fewer non-affected glomeruli (14% *vs*. 34.2%, p<0.001) and more sclerotic glomeruli in the biopsy (17% *vs*. 12%) (p<0.04) (Table II). There were no differences in the degree of tubulo-interstitial fibrosis or atrophy between patients reaching ESRD and patients who did not. In a multivariate model with eGFR at 3 years as the independent variable, and age, baseline eGFR and histopathological groups as dependent variables, only age and baseline eGFR had significant prognostic value (r^2=0.85, p<0.01) (data not shown). No interaction or collinearity was shown between the variables.
In the mixed group approximately seven times as many patients had tubulo-interstitial fibrosis grade 2 (TIF 2) (33%) compared to the focal group (5%) and four times as many as patients in the crescentic group (8%) (p<0.013) (Table I). Patients in the crescentic and focal group had approximately the same number of TIF 0. All the patients in the sclerotic group had TIF2. TIF and TA were in a linear regression model related to age (r^2=0.12, p<0.01 and r^2=0.10, p<0.01, respectively) but not to histopathological group or eGFR at baseline.

ANCA subtype
The mean age of MPO-ANCA positive patients was 10 years older than the PR3-ANCA positive patients. There were no differences in gender and eGFR at baseline between MPO- and PR3-ANCA positive patients, but after three years the MPO-ANCA positive patients had a significantly lower eGFR (31.1 ml/min/1.73 m^2 *vs*. 49.3 ml/min/1.73 m^2, p<0.003). The MPO-ANCA positive patients had more than twice as many sclerotic glomeruli, three times as many TA2 lesions (p<0.004) and seven times as many TIF2 lesions (p<0.0001) compared to PR3-ANCA positive patients. There was no difference in the number of non-affected glomeruli between the two groups (data not shown).

Treatment
There were no differences in age, gender, eGFR or histopathological group at baseline when comparing patients who received initial treatment with PE to patients who did not receive PE. Patients receiving PE had a non-significant tendency to a higher increase in

Table IV. Results of different validations study of the histopathological classification of AAV.

	Nationality	Age, mean (range)	n. of patients	PR3/MPO	Plasma exchange	n. of glomeruli, mean	Subgroups (F/C/M/S)	Risk for ESRD	% ESRD	% deaths	Follow-up time (years, mean)
Berden *et al*. (2010)	European	62.6 (20.4-80.7)	100	45%/47%	nd	14.8 (10-49)	16%/**55%**/16%/13%	S>M>C>F	25-35%	25%	1
Ellis *et al*. (2013)	American (82% caucasian)	58	76	82% ANCA positivity	0%	29	26%/24%/**36%**/14%	S>M=C>F	32%	8%	1
Nohr *et al*. (2013)	Canadian	60 (14-89)	67	31%/58%	nd	>10	21%/**35%**/32%/11%	S>M>C=F	nd	12%	1
Moroni *et al*. (2015)	Italian	58.8±16.3 (sd)	93	39%/46%	13%	>10	21%/30%/**39%**/10%	S=C>M=F	33%	15%	5
Ford *et al*. (2014)	Australian	66 (8-87)	120	100% ANCA positivity	15%	22±14 (sd)	28%/28%/28%/17%	S>M>C>F	33%	13%	3,4
Hilhorst *et al*. (2013)	The Nederlands	61.0	221	51%/49%	nd	>10	**49%**/26%/24%/0%	C=M>F	nd	nd	8,5
Chang *et al*. (2011)	Chinese	57.2 (15-81)	121	11%/89%	5%	25.7±10.4 (sd)	27%/**44%**/20%/9%	S>C=M>F	25%	nd	2,9
Quintana *et al*. (2014)	UK and Spain	62.1	136	38%/56%	nd	18 (8-40)	26%/23%/**39%**/13%	S>M=C>F	24%	20%	2,5
Kristensen *et al*. (2015)	Danish	62.9 (22-86)	87	44%/56%	30%	11.5 (4-47)	24%/28%/**35%**/3%	C>M>F	18%	21%	3

F: Focal; C: Crescentic; M: Mixed; S: Sclerotic; ESRD: End stage renal disease; nd: no data.

eGFR from baseline to 3 years ($p<0.07$) (data not shown). PR3-ANCA positive patients receiving PE had a twice as high increase in eGFR from baseline to 3 years ($p=0.01$) compared to PR3-ANCA positive patients not receiving PE (Table III). Plasma exchange did not seem to affect the number of patients reaching ESRD, which is not surprising with the few outcomes.

Discussion

We retrospectively analysed outcome of 87 patients with AAV with a follow-up of 3 years. Patients in the focal group had the highest eGFR at presentation, but after 3 years there were no differences in eGFR between the histopathological groups. Most patients in the crescentic group and fewest in the focal group reached ESRD. Age and eGFR at presentation was of prognostic value as well as initial treatment with PE in the group of patients with PR3-ANCA positive vasculitis.

Several studies have evaluated the histopathological classification introduced by Berden *et al*. in 2010. The percentage of patients in the 4 histopathological groups differs among the validation studies, for example the percentage of patients in the sclerotic group differs from 0–17%. In the other 3 groups the percentage differs from 20-40% (Table IV). The differences might not be surprising, with a complete agreement between pathologists of 43% in a study testing reproducibility of the classification (11). Berden *et al*. have the highest number of patients in the crescentic group (55%), which probably reflects a selection bias, as their cohort are included in randomised treatment studies (MEPEX (12) and CYCAZAREM (13)) which does not reflect the pattern of patients in the daily clinic. In the present study the majority of the patients were in the mixed group, which is in agreement with other studies (5, 8, 14) (Table IV). In all the validation studies the patients came from a single or few centres. The generalisability of the histopathological classification might be decreased because patients from selected populations are compared to patients from the general population. In a recent study it was found that patients with granulomatosis with polyangiitis or microscopic polyangiitis in randomised clinical trials (RCT) and observational cohorts showed important differences that should be considered when comparing results based on these study populations (15). Patients from RCT were older at diagnosis by almost 10 years and had more frequent and severe kidney disease. After adjusting for age and glomerular filtration rate, the relapse and mortality rate were higher for patients in RCT than patients in cohort studies (15).

We had the majority of patients in the mixed group, which may be a consequence of the fact that we did not have a lower limit for numbers of glomeruli in the kidney biopsies and therefore maybe more patient are placed in the mixed group. Moroni *et al*. (14) also had the majority of patients in the mixed group, despite that they only included patients with more than 10 glomeruli in the kidney biopsy. They have a higher percentage of ESRD compared to our study (33% vs 18%). This may be explained by the higher percentage of patients in the sclerotic group.

In our cohort patients in the focal group had the highest eGFR at presentation and the highest percentage of non-affected glomeruli, which is in agreement with most validation studies (5-8, 11, 16). We found no differences between the 4 groups according to mean change in eGFR from baseline to three years follow-up. Other stud-

ies found that patients in the crescentic group had a higher improvement in eGFR after one year follow-up (4, 7). In agreement with other studies (8) we found that after three years follow-up, age and baseline eGFR was independent predictors of eGFR, and that histopathological group did not add further prognostic value.

Berden *et al*. described the patients in the crescentic group with the lowest eGFR at presentations but with a good change of renal function recovery and a reduced risk of developing ESRD compared to the patients in the mixed and sclerotic group (4). We found that patients in the crescentic group had the worse renal survival and reached ESRD more often than patients in the mixed and focal group. In general most studies agree that the patients in the sclerotic group has the highest risk of developing ESRD and the patients in the focal group has the lowest risk of developing ESRD, but there is disagreement in the mixed and crescentic group (Table IV). The total percentage of patients reaching ESRD in the different validations studies is quite similar with a range from 24-35%, despite the differences in number of patients in the 4 histopathological subgroups (Table IV). Despite having more MPO-ANCA positive patients, the percentage of ESRD in the Chinese study is not higher than the rest of the studies. The definitions of ESRD vary in the validation studies. In some studies no definition are given, whereas others define it as need for dialysis with or without time frame, or eGFR less than 15 ml/min/m^2. In our study only 18% reached ESRD. This may be explained by our definition of ESRD, which is the need for dialysis for more than 12 weeks, or maybe the low number of patients in the sclerotic group. The different definitions complicate the comparability of the studies.

In Berden's cohort the percentage of death is 25% after 1 year follow-up (4). The rest of the studies have death rates between 8-21%, but different follow-up time (Table IV). There is a tendency that the patients in the studies with the lowest death rates are younger. The higher death rate in Berden's cohort might be because the patients came partly from the MEPEX study, where all patients had serum-creatinine higher than 500 μmol/l.

In most studies there was an equal distribution of ANCA subtypes (Table IV), except for the Asian study with more MPO-ANCA positive patients. None of the validations studies has analysed the prognosis of AAV based on different ANCA subtypes. We found that the MPO-ANCA positive patients had more chronic glomerular lesions and were older of age. There is an ongoing discussion on whether MPO-AAV and PR3-AAV are two different disease entities (17), and maybe we cannot compare patients with different ANCA subtype. It is also difficult directly to compare results between patients from different ethnic groups because there are known differences in disease manifestations (17). In our study all the patients were Caucasian.

Thirty percent of our patients were initially treated with plasma exchange. In the other validation studies the frequency varied from 0 to 15% (Table IV). We found, that PR3-ANCA positive patients had a higher increase in eGFR when induction therapy was supplemented with PE. In part of the present cohort, we have earlier demonstrated that the 1 year risk of ERSD was reduced in PR3-ANCA positive patients treated with PE (9). Estimated GFR improved more in 1 year among PE treated patients compared to patients who did not receive PE (36.1 vs. 19.7 ml/min/m^2, p=0.03) (9). In the present study, we found that PR3-ANCA positive patients who received PE also had a better 3 year outcome with a higher increase in eGFR indicating that the improvement in eGFR during induction therapy is a stabile gain over time, which might hopefully be an indicator of improved long-term outcome. This effect is independent of histopathological group at presentation

Berden *et al*. (4) found that including tubulo-interstitial parameters did not improve the prognostic value of the histopathological classification on eGFR at follow-up. We found that patients in the mixed group had more severe tubulo-interstitial fibrosis compared to focal and crescentic patients, but no differences between the four groups according to tubular atrophy. No differences were found in tubulointerstitiel lesions in patients reaching ESRD compared to those not reaching ESRD, which is in agreement with other studies (6, 7). Others found that inclusion of tubulointerstitiel fibrosis and atrophy may enhance the prognostic value of the histopathological classification (5, 11). It had been demonstrated earlier that the severity of tubulo-interstitial fibrosis is an independent predictor of long term outcome of renal function (18) and that tubular atrophy, tubular necrosis and interstitial infiltrates could predict renal function (19). Overall there is no agreement on the value of including tubuluinterstitiel lesions in the classification.

Strength of the present study is the attempt to estimate the influence of ANCA subtype and PE on the outcome and interplay with the histological classification. Limitations in our study include the relative small number of patients and the retrospective design and the use of historic controls for estimating the effect of PE. Using accessible kidney biopsies even though with low number of glomeruli might induce a bias with misclassification of the histopathological group. Sixteen patients had less than 8 glomeruli in the kidney biopsy, but they had the same distribution between histopathological groups compared to patients with more than 8 glomeruli in the biopsy. On the other hand it might be strength that the study reflects daily clinical practice. In nine patients (10%) it was not possible to re-evaluate the biopsy. Their baseline data was comparable to the rest of the cohort and probably not inducing bias.

Our results are not all in accordance with the results of the original work by Berden *et al*. in 2010. We find it necessary to do more and bigger studies especially on how different treatment regimens and ANCA subtype interacts with the prognosis of AAV.

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