ORIGINAL ARTICLE

ANCA-positive vasculitis: Clinical implications of ANCA types and titers

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Summary

Introduction: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis is an autoimmune disease that can affect multiple organs, the kidney being one of the most affected. Apart from the diagnostics value of ANCA, they have also been advocated as biomarkers of the disease activity. Recently, the genetic changes found in polyangiitis associated with serine-protease proteinase 3 (PR3)-ANCA or myeloperoxidase (MPO)-ANCA raised the possibility of immune-pathogenic and therapeutic differences.
Objective: To identify differences in the number of relapses, inflammatory markers, outcomes and renal histology related to the types of ANCA. To analyze the implications of ANCA titers in prognosis.
Method: A retrospective observational study in a Portuguese tertiary hospital.
Results: There were no differences in the progression of renal function, histological pattern and initial treatment with regard to ANCA subtypes. As for the evaluated parameters, there were no significant differences according to the types of ANCA, except for mean CRP values within the normal range, which was 6.3±1.3 mg/L for MPO-ANCA and 12.4±10.14 mg/L for PR3-ANCA (p=0.04). We found that 66.7% of the MPO-ANCA-positive showed no relapses *versus* 40% in the case of PR3-ANCA-positive. There was no correlation between the ANCA titers at presentation, during remission, and in the last evaluation, and the number of relapses.
Conclusion: PR3-ANCA patients have a mean CRP value within the normal range significantly higher than that of MPO-ANCA patients (p=0.04), which seems to reveal greater inflammatory activity in the first.

Keywords: anti-neutrophil cytoplasmic antibody-associated vasculitis, peroxidase, serine proteases.

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Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis is an autoimmune disease that can affect different organs and present multiple symptoms. This group includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA) and vasculitis limited to the kidney (KLD, Kidney Limited Disease).[1,2] In addition to these, ANCA are also detected in other vasculitic diseases, such as drug-induced systemic vasculitis and other autoimmune diseases.[3]

The term "ANCA-associated vasculitis" (AAV) combines histological and clinical similarities, the widespread use of ANCA antibodies as a diagnostic marker, and its pathogenic potential. The main fluoroscopy staining patterns are diffuse granular cytoplasmic (C-ANCA) and perinuclear (P-ANCA); the first is due to the presence of autoantibodies bound to serine-protease proteinase 3 (PR3-ANCA), while the latter can be caused by antibodies against many antigens, including myeloperoxidase (MPO-ANCA), which is the most frequent in AAV.[4]

The role of ANCA in the diagnosis of AAV is indisputable, and these antibodies have been advocated as biomarkers of disease activity.[5] The complexity of the role of ANCA is associated with the plurality of genetic, epigen-

etic and environmental factors.[6] Genetic differences in polyangiitis caused by PR3-ANCA and MPO-ANCA may have immune-pathogenic and therapeutic implications.[7]

The kidney is one of the organs most affected in AAV. In GPA and MPA, there is renal involvement in about 71-88% of cases, and 25% in EGPA.[2] Rapidly progressive renal failure is the most typical kidney presentation, combining a rapid deterioration in renal function with micro or macro hematuria and often with non-nephrotic proteinuria.[1] About 35% of these patients require dialysis at presentation.[8]

Renal biopsy is recommended in order to confirm the diagnosis and prognosis of kidney damage.[1] The percentage of normal glomeruli is a powerful predictor, possibly the best predictor of histologic outcomes in the short and long term.[9] Nevertheless, renal disease activity indicators, such as increased serum creatinine and/or presence of hematuria, and the value or worsening of proteinuria and erythrocyte cylinders in urine, have been identified.[10]

In short, ANCA antibodies have a central involvement in the pathogenesis of these vasculites, but little is known about their prognostic value at the date of diagnosis and progression in the course of disease. Thus, we intend to identify differences in the number of relapses, inflammatory markers, outcomes and renal histologic pattern found with the different types of ANCA (PR3-ANCA, MPO-ANCA). In addition, we intend to analyze the implications of ANCA titers at baseline and their progression over the course of disease, including the number of relapses presented by patients.

Method

A retrospective study of 29 patients followed at the Nephrology Service of Centro Hospitalar do Porto, Hospital de Santo António, between 1997 and 2014, identified with AAV with renal involvement.

All patients had renal biopsies confirming the diagnosis, and disease criteria were based on international recommendations (EUVAS): history of chronic inflammatory disease for at least 4 weeks ruling out other potential causes, such as infection or malignancy, and support of histological features on biopsy and/or enzyme-linked immunosorbent assay (ELISA) positive for PR3 or MPO antibodies.[11]

Remission was considered as the absence of symptoms, i.e., Birmingham vasculitis activity score (BVAS)=0, under a low dose of prednisolone (≤ 10 mg/day) for at least 6 months.[12]

Major relapse was defined as recurrence or *de novo* appearance of disease activity threatening a vital organ or the patient's life, and which could not be treated solely with increased doses of corticosteroids. Minor relapse, in turn, corresponded to other activities of the disease.[11,13] Proteinuria at presentation was classified, based on a 24-hour urine sample, into nephrotic (≥ 3.5 g/24h), non-nephrotic (300 mg/24h to 3.5 g/24h), and microalbuminuria (30 to 300 mg/24h).

Up to six values were selected for changes in titers of ANCA antibodies, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and indicators of renal injury and dysfunction at time intervals of about 4 months, during remissions of each patient. Again, the same parameters for each recurrence.

ANCA and antinuclear antibodies titers were obtained using ELISA method. BVAS score was calculated using Calculater – V3[14] software, considering the symptoms described in the patient's clinical process.

Chi-square and Fisher tests were used in the analysis of categorical variables, nonparametric Mann-Whitney test was used to compare two independent samples, and Kruskal-Wallis test allowed to compare differences between variables with more than two independent samples using SPSS 22.0 software. The results were considered statistically significant at the significance level of 5% (p=0.05).

Results

Of the 29 patients, at admission, 24 were positive for MPO-ANCA and only five for PR3-ANCA; 18 had ANCA titers ≥ 1/640, nine had titers at 1/320, and two ≤ 1/80. As for histology in renal biopsy, 14 revealed a progressive pattern, five had sclerotic pattern, and 10 a mixed pattern. Other demographic data as well as the outcomes are shown in Table 1.

Of the 15 patients on renal replacement therapy, three underwent renal transplantation while the rest remained on hemodialysis. Mortality rates were 0% after 1 year of follow-up, one death (3.4%) after 3 years, and three deaths (10.3%) after 7 years.

In renal histology of PR3-ANCA-positive patients, 80% (n=4) showed a progressive pattern, while 20% (n=1) had a sclerotic pattern. Among the MPO-ANCA-positive patients, 41.7% (n=10) revealed a progressive pattern, 41.7% (n=10) a mixed pattern and 16.7% (n=4) had a sclerotic pattern.

Regarding ANCA titers at presentation, 75% (n=18) of the MPO-ANCA-positive had ANCA ≥ 1/640, while 25% (n=6) presented 1/320. As for the PR3-ANCA-positive patients, 60% (n=3) showed titers at 1/320 and 40% (n=2) showed titers ≤ 1/80.

Regarding the number of relapses, 40% (n=2) of the PR3-ANCA-positive did not recur, and 60% (n=3) had relapsed once. Among the MPO-ANCA-positive, 66.7%

TABLE 1 Demographic data of the sample and events.

Variable		Result
Average age (years) - diagnosis (M±sd)		58.38±17.45 (30-87)
Gender (n;%)		
Women		55.2% (16)
Men		44.8% (13)
Mean follow-up in years (M±sd)		4.11±3.34 (1.5-12) Med=3.0
Serum creatinine at baseline (mg/dL) (M±sd)		5.2±2.98 (1.74-13) Med=4.6
CRP at baseline (mg/L) (M±sd)		36.36±54.23 (0.9-181) Med=9.5
ESR at baseline (mm/h) (M±sd)		87.2±21.32 (46-126) Med=89.0
BVAS at baseline (M±sd)		16.52±3.97 (12-29)
Types of ANCA (n;%)		
MPO		82.76% (24)
PR3		17.24% (5)
ANCA titers (n;%)	≥1/640	62.1% (18)
	1/320	31.0% (9)
	≤1/80	6.9% (2)
ANA (n;%)	Positive	48.3% (14)
	Progressive	48.3% (14)
Histological patterns of biopsy (n;%)	Sclerotic	17.2% (5)
	Mixed	34.5% (10)
Proteinuria at baseline (n;%)	Non-nephrotic	27.6% (8)
	Nephrotic	31.0% (9)
	Microalbuminuria	34.5% (10)
	Absent	6.9% (2)
Microscopic hematuria at baseline (n;%)	Present	96.6% (28)
Renal symptoms at baseline (n;%)	Present	44.8% (13)
Pulmonary symptoms at baseline (n;%)	Present	31.0% (9)
Number of relapses (n;%)	0	62.1% (18)
	1	31.0% (9)
	>2	6.8% (2)
Initial treatment (n;%)	Corticosteroids + cyclophosphamide	58.6% (17)
	Corticosteroids + cyclophosphamide + plasmapheresis	41.4% (12)
	RRT	60% (15)
Outcome (n;%)	Remission	28.0% (7)
	Death	12.0% (3)

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BVAS: Birmingham vasculitis activity score; ANCA: anti-neutrophil cytoplasmic antibody; MPO: myeloperoxidase; PR3: proteinase; ANA: antinuclear antibodies; RRT: renal replacement therapy; Med: median; M: mean; sd: standard deviation.

(n=16) did not recur, 25% (n=6) had one relapse, and 8.4% (n=2) showed at least two relapses.

50% (n=12) of the MPO-ANCA-positive patients had renal involvement at presentation, and 29.2% (n=7) had pulmonary involvement. There was one MPO-ANCA-positive patient who presented renal and pulmonary symptoms simultaneously. Among the PR3-ANCA-positive patients, only one (20%) had renal involvement at the time of diagnosis, and two (40%) had pulmonary involvement (p>0.05).

Regarding BVAS presentation, the mean value of creatinine at baseline and at the last evaluation, and the mean value of ESR at baseline and intervals, there were no statistically significant differences in terms of types of ANCA (p>0.05) (Table 2). The same was true for CRP value at baseline. The mean value of CRP within the intervals for MPO-ANCA-positive patients was 6.3±6.4 mg/L (Med=5.00), while for PR3-ANCA-positive individuals it was 12.4±10.1 mg/L (Med=8.00), with a p=0.04 (Table 2).

TABLE 2 List of types of ANCA antibodies with the mean values for BVAS at baseline, creatinine at baseline, creatinine at last evaluation, CRP at baseline, CRP within the interval, ESR at baseline and ESR within the interval.

	MPO (M, sd)	PR3 (M, sd)	p
BVAS at baseline	16.1 (4.03)	18.6 (3.2)	0.171
Serum creatinine at baseline (mg/dL)	5.3 (3.1)	4.7 (2.6)	0.885
Serum creatinine at last evaluation (mg/dL)	4 (2.2)	2.4 (2.1)	0.347
CRP at baseline (mg/L)	37.3 (58.1); Med=7.9	32 (33.7); Med=16.3	0.106
CRP within interval (mg/L)	6.3 (6.4); Med=5.0	12.4 (10.1); Med=8.0	0.04
ESR at baseline (mm/h)	85.3 (20.3); Med=88.0	97 (27.4); Med=100.5	0.317
ESR within interval (mm/h)	47.6 (28); Med=42.0	38.5 (27.7); Med=25.5	0.701

BVAS: Birmingham vasculitis activity score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ANCA: anti-neutrophil cytoplasmic antibody; MPO: myeloperoxidase; PR3: proteinase; M: mean; sd: standard deviation; Med: median.

As for proteinuria, nine (37.5%) of the MPO-ANCA-positive individuals had microalbuminuria, six (25%) had non-nephrotic proteinuria, and nine (37.5%) had nephrotic proteinuria. Among the PR3-ANCA-positive patients, two (40%) did not have proteinuria, one (20%) had non-nephrotic proteinuria, and two (40%) had nephrotic proteinuria. An identical distribution of these variables between the two types of ANCA was found.

At the end of follow-up, 65% (n=13) of MPO-ANCA-positive patients were on renal replacement therapy, 20% (n=4) were in remission, and 15% (n=3) died. 40% (n=2) of the PR3-ANCA-positive patients were under treatment with renal replacement therapy, and 60% (n=3) were in remission.

In the last assessment of ANCA titers, we obtained the following values: 31% (n=9) were negative, 34.5% (n=10) showed titers ≤ 1/80, 13.8% (n=4) had titers equal to 1/160 and 13.8% (n=4) had titers ≥ 1/320; two other patients did not have ANCA counts (Table 3).

TABLE 3 Progression of ANCA titers (first assessment *vs.* last assessment) and relative and absolute frequencies of relapse by ANCA titers at presentation.

		ANCA titers at presentation		
		≥1/640 (n,%)	≥1/640 (n,%)	≥1/640 (n,%)
Last ANCA titers evaluated	Negative	6 (35.3)	2 (25)	1 (50)
	≤1/80	6 (35.3)	3 (37.5)	1 (50)
	1/160	3 (17.6)	1 (12.5)	0
	≥1/320	2 (11.8)	2 (25)	0
Total number of relapses	0	12 (66.7)	6 (66.7)	0
	1	4 (22.2)	3 (33.3)	2 (100)
	2	1 (5.6)	0	0
	3	1 (5.6)	0	0

ANCA: anti-neutrophil cytoplasmic antibody.

Despite the non-applicability of statistical tests, by analyzing the frequency displayed as Table 3, we found that patients with higher ANCA titers at presentation became negative more often and had a greater decline over the course of the evaluation.

With regard to the relationship between relapses and ANCA titers at presentation, based on the frequency analysis presented on Table 3, we have not found a correlation between the ANCA titers and relapses, i.e., lower ANCA titers are not predictors of non-recurrence. The same is true for ANCA titers during remission and at the last evaluation.

Discussion

ANCA antibodies have an indisputable role in the diagnosis of AAV.[5] In a study conducted by Lionaki et al., most of the patients with KLD were MPO-ANCA-positive (81%), while in patients with destructive lesions of the upper airway PR3-ANCA prevails (94%). Thus, when vasculitis expands from limited to the kidney to a form that involves the gastrointestinal or respiratory tract, the frequency of MPO-ANCA decreases at the expense of increased PR3-ANCA.[15]

In our study, where all patients had renal involvement, 82.8% of patients were MPO-ANCA-positive, which is in line with the results found in other studies. However, only 50% of patients with MPO-ANCA showed renal involvement at presentation. 40% of the PR3-ANCA-positive patients presented with pulmonary involvement.

Positive ANCA titers have a sensitivity and specificity of about 90% for the diagnosis of pauci-immune focal necrotizing glomerulonephritis. The specificity of ANCA for MPO and PR3 can be detected in 85-90% of patients.[16] This result supports the role of ANCA antibodies in the pathogenesis of vasculitis, with several clinical and genetic evidence, and tests backing it up.[5,16] Serum determina-

tion of ANCA titers in the assessment of disease activity remains a controversial topic in different studies. A meta-analysis conducted by Rainer Birck et al. concludes that, in the literature, serum monitoring ANCA titers is characterized by great clinical and methodological heterogeneity, and only a minority of studies is designed optimally to evaluate the accuracy of this parameter.[17] In an article, Salama and Rees[16] state that in some randomized prospective clinical trials and meta-analyzes neither the presence nor the titers of MPO or PR3 antibodies consistently correlate with disease activity or clinical response to treatment, and they are not predictors of clinical relapse.

In our study, we observed that there is no pattern of relationship between ANCA titers and the number of relapses. Even patients with negative ANCA titers during remission had recurrences. Regarding the progression of ANCA titers from the date of diagnosis to the last evaluation, these tended to decline or remain constant regardless of the clinical outcome of patients.

According to Savige et al. ANCA titers are often high at presentation, declining with treatment and eventually becoming negative in many patients, after 6 months or so of treatment. According to the authors, several studies show that an increase in ANCA titers precedes, between 3 and 6 months, at least half of the relapses;[18] however, they do not mention the possibility of increases occurring in patients with negative titers. However, in a meta-analysis conducted by Gunnar Tomasson et al. and in the study performed by Sidy Seck et al., both the increase and persistence of ANCA titers during remission of vasculitis were no more than moderate predictors of recurrence risk, which led to the conclusion that routine assessment of ANCA titers does not affect significantly the estimated clinical risk.[5,19] But once again the possibility of relapse with negative or declining ANCA titers is not evaluated.

In our cohort, the MPO-ANCA-positive patients had mean CRP values within the intervals significantly lower than those of PR3-ANCA-positive patients; also, 66.7% of the MPO-ANCA-positive showed no recurrence *versus* 40% among the PR3-ANCA-positive. This can translate a stronger inflammatory response in PR3-ANCA-positive patients and thus justify the observation by Sophia Lionaki et al.[15] In her article, ANCA antibody specificity was predictive of relapse. Our group of PR3-ANCA patients had almost twice the probability to have recurrences than the MPO-ANCA patients (p=0.04). The authors conclude that classifications and diagnostic systems that incorporate ANCA specificity provide a more useful tool for predicting recurrences than the pathological clinical categories alone.

Given that the course of disease after initial treatment is highly variable, and the fact that markers such as ANCA titers and non-specific inflammatory markers (CRP and ESR) have limitations, the research of new biomarkers is fundamental. Monach et al., among others, have identified three biomarkers, CXCL13, MMP-3 and TIMP-1, which stand out due to their ability to distinguish active AAV better than other reference markers studied, including CRP and ESR.[20]

Renal morphology of ANCA-negative patients with pauci-immune focal glomerulonephritis is indistinguishable from that of ANCA-positive patients according to Salama and Rees, raising the question of what the etiology of injury in the absence of these antibodies is. Thus, it seems highly likely that additional factors are required for AAV expression, leading to the need to analyze the role of newer described autoantibodies as well as their specificities for LAMP-2, plasminogen and moesin.[16]

In our study, we did not verify differences in serum creatinine at baseline, final serum creatinine and BVAS at baseline for the different types of ANCA. This is in line with other studies, namely the study by Clara Day et al., which did not reveal a correlation between levels of creatinine at baseline and ANCA subtypes.[21]

A study of 100 biopsies from patients with glomerulonephritis associated with ANCA antibodies stressed that the histologic classification at presentation is correlated with outcomes. Patients with sclerotic glomerulonephritis have worse renal function at diagnosis, with no significant improvement at 5 years. If more than 50% of the kidney is sclerotic, immunosuppression does not appear useful. Patients with focal disease and good renal function at baseline maintain good function after 5 years of treatment. Patients with classic progressive pattern present with rapidly progressive glomerulonephritis and worse renal function. However a considerable improvement is found after 5 years.[8] In our review we found no differences between histological patterns and ANCA subtypes, which can be justified by a small number of cases.

Flossmann et al. found no differences in survival of patients with GPA and MPA.[22] Again, noting that we did not classify our patients as small vessel vasculitis subtype, our results are in line with those obtained in the study mentioned above, since there were no differences in outcomes relative to ANCA subtype.

Immunosuppressive therapy has significantly improved the prognosis, and the mortality rate has decreased as a result of an improvement in treatment strategies. In the study by Yong-Xi Chen et al., with 101 patients, the mortality rate at 1 year was 18.8%, and 32.9% at 5 years.[23]

In the study by Day et al., with 390 patients including cases of AAV and renal involvement, 18% of patients at 5 years required renal replacement treatment and 40% died.[21] In our study, the mean follow-up was 4.1 years (1.5-12 years) with a median of 3 years, during which 60% of patients underwent renal replacement therapy, and 12% died. Although the mean follow-up was shorter than in other studies, our mortality rates are low: 0% at 1 year follow-up, one death (3.4%) after 3 years, and three deaths (10.3%) after 7 years.

Our study has several limitations. Since this is a retrospective study, with consultation of physical and computer medical records, there may have been misinterpretations of data consulted, inducing bias especially in the calculation of BVAS and in the evaluation of symptoms presented by the patient at baseline. Another imitation is the fact that the evaluations of patients were not conducted in a uniform manner with assessment intervals at an average of four months. During remissions, the average assessment intervals increased, and therefore measurements may be under- or overvalued. Furthermore, since this is a study of patients followed only by the nephrology service, there may be differences in the severity of the disease, types of ANCA antibodies and outcomes presented compared with the general population with AAV. A major limitation of our study was the small number of patients, which prevented us from obtaining statistical significance in the comparison of several variables among each other, a limitation inherent to the rarity of the disease.

Conclusion

The vast majority of patients with AAV and renal involvement are MPO-ANCA-positive (82.76%). Although there is no relationship between ANCA titers and the number of relapses, we found that PR3-ANCA-positive patients may occasionally be more likely to relapse, even if not statistically significantly. The fact that MPO-ANCA-positive patients have a mean CRP value within intervals significantly lower than PR3-ANCA-positive patients allows us to infer a greater inflammatory activity of the latter that tends to support this hypothesis. Regarding the progression of ANCA titers from the date of diagnosis to the last evaluation, these tended to decline or remain constant regardless of the clinical outcome of patients. New prospective studies that assess other markers would be of extreme interest, including CXCL 13, MMP-3 and TIMP-1 during disease activity and in response to treatment of AAV, in addition to the markers usually studied (securities ANCA, CRP and ESR), as well as the role of autoantibodies to LAMP-2, plasminogen and moesin.

Resumo

Vasculite ANCA positiva: implicações clínicas dos tipos e dos títulos de ANCA

Introdução: a vasculite associada aos anticorpos anticitoplasma de neutrófilos (ANCA) é uma doença autoimune que pode acometer vários órgãos, sendo o rim um dos mais afetados. Além dos ANCA serem marcadores de diagnóstico, foram também defendidos como marcadores de atividade. Recentemente as alterações genéticas encontradas entre as poliangeítes serina-protease 3 da proteinase (PR3)-ANCA ou mieloperoxidase (MPO)-ANCA levantam a possibilidade de diferenças imunopatogênicas e terapêuticas.
Objetivos: identificar diferenças quanto a número de recidivas, marcadores inflamatórios, desfechos e histologia renal relativamente aos tipos de ANCA. Analisar implicações dos títulos de ANCA no prognóstico.
Método: estudo retrospectivo observacional em hospital terciário português.
Resultados: não se verificaram diferenças quanto à evolução da função renal, ao padrão histológico e ao tratamento inicial relativamente aos subtipos de ANCA. Nos parâmetros analíticos avaliados, não se verificaram diferenças significativas relativas aos tipos de ANCA, à exceção do valor médio de PCR no intervalo que foi de 6,3±1,3 mg/L nos MPO-ANCA e 12,4±10,14 mg/L nos PR3-ANCA (p=0,04). Verificamos que 66,7% dos MPO-ANCA positivos não apresentaram recidivas *versus* 40% dos PR3--ANCA positivos. Não se verificou nenhuma correlação entre os títulos de ANCA à apresentação, durante a remissão e na última avaliação com o número de recidivas.
Conclusão: os indivíduos PR3-ANCA apresentaram um valor médio de PCR nos intervalos superior aos indivíduos MPO-ANCA (p=0,04), o que parece evidenciar uma maior atividade inflamatória nos primeiros.

Palavras-chave: vasculite associada a anticorpo anticitoplasma de neutrófilos, peroxidase, serina proteases.

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