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Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis in Mexican Population: Clinical Phenotype, Autoantibody Profile and Renal Characteristics

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Abstract

Objective: To describe the clinical, serological characteristics, and renal histology in Mexican patients with anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV).

Methods: Forty patients with diagnosis of AAV and renal biopsy, followed at a tertiary care center in Mexico City from 2002-2012 were retrospectively studied. Demographics, comorbidities, clinical, laboratory variables, disease activity, mortality, renal variables and histological classes were analyzed. Additionally, 50 patients with AAV, and a control group (other systemic vasculitis, systemic lupus erythematosus, infections, healthy subjects) were studied transversally to assess the prevalence of specific antibodies (ANCA, MPO, PR3, cathepsin G, lysozyme, lactoferrin, BPI and elastase), and their association with clinical manifestations.

Results: Granulomatosis with polyangiitis (GPA) was the predominant phenotype, and median age at diagnosis was 53 years. High disease activity (BVAS/GPA=24), general symptoms (98%), renal (80%), pulmonary (63%), and ear, nose and throat (ENT) (58%) involvement were frequent at diagnosis. Renal damage was present at diagnosis (serum creatinine 3.9 mg/dl, estimated glomerular filtration rate 16 ml/min, 24 hr proteinuria 2.5 g, 15% on dialysis). The most prevalent renal histological class was sclerotic (58%), followed by mixed (32%), focal (8%), and crescentic (2%). No significant differences were found between histological classes in comorbidities, clinical, renal and laboratory variables, or survival. The main ANCA immunofluorescence pattern was C-ANCA (68%), followed by X-ANCA (22%), and P-ANCA (18%). PR3-ANCA (high sensitive) was the most frequent antibody, positive in 86%, while positivity for MPO-ANCA was observed in 18%. ANCA positivity was more frequent in patients with AAV than the control group ($p<0.001$). Antibodies directed to minor targets were infrequent in patients with AAV (2%). No significant correlations were identified between autoantibodies and clinical manifestations.

Conclusion: GPA phenotype, C-ANCA and PR3-ANCA positivity, high disease activity, chronic renal damage, general symptoms, ENT and lung involvement at diagnosis distinguish our population with AAV.

Keywords: ANCA; Vasculitis; Mexican; Ethnicity; Clinical phenotype; Autoantibodies; Renal histology

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitides (AAV) are infrequent, chronic, multi systemic autoimmune diseases characterized by the presence of vasculitis and necrosis affecting predominantly small vessels. The main phenotypes of AAV are granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Disease patterns including clinical manifestations, serology and disease activity may vary among different regional and ethnic backgrounds.

Geographical differences in the incidence and expression of AAV have been demonstrated in Japan, Europe and North America [1]. The incidence and the prevalence of GPA are significantly higher in northern Europe (Norway and Germany), while MPA is predominant is southern Europe (Spain) [2]. Annual incidence of AAV is similar between Japan and UK (around 22/million adults). In Japan, MPA is the main subtype (83%), whereas GPA is more frequent in UK (66%), following the latitude theory of AAV. Moreover, P-ANCA and/or MPO-ANCA positivity predominates in Japanese patients (>80%), whereas two-thirds of patients in the UK are C-ANCA and/or PR3-ANCA positive [1]. African Americans with pauci-immune glomerulonephritis are younger and more often MPO-ANCA positive compared to Caucasians [3]. A study from China demonstrated that patients with GPA were predominantly MPO-ANCA positive and this antibody was associated with multiorgan involvement and higher levels of serum creatinine than PR3-ANCA patients with GPA [4].

Antibodies specific for other neutrophil antigens, such as cathepsin G, lysozyme, lactoferrin, bacterial permeability increasing protein (BPI), and elastase have been observed in specific clinical scenarios. Anti-elastase are present in drug-associated vasculitis and in cocaine-induced nasal destruction. Anti-BPI is present in C-ANCA-positive patients that are negative for MPO-ANCA and PR3-ANCA antibodies. Anti-cathepsin G has been found in Sjögren´s syndrome and pediatric GPA. Anti-lactoferrin and anti-lysozyme can be present in drug-induced vasculitis and other autoimmune diseases [5,6]. The low prevalence of these antibodies that are not routinely determined has limited conclusions regarding their clinical significance.

Differences in clinical phenotypes have also been described. For example, there is lower frequency of renal involvement in Japanese patients with GPA (12-63%) compared to over 70% in patients with GPA from Germany and USA [1]. The severity of kidney damage, as well as differences in therapy, influence the distribution of the renal histopathological classes among populations, as shown in the studies that have validated the histopathological classification of ANCA-associated glomerulonephritis proposed by Berden et al. [7,8]. Also, variations in the prevalence of interstitial lung disease between Asia and Europe have been described, with a higher prevalence of this manifestation in Asian countries probably associated with the predominance for MPO-ANCA positivity in this geographic region [2].

Few studies have assessed the characteristics of Mexican patients with AAV [9-12]. A study that compared Hispanics (Mexican ancestry) and Caucasians with AAV living in the same geographical area in Chicago showed that Hispanics present with a more severe disease activity, more damage, and a higher prevalence of renal involvement and kidney insufficiency requiring dialysis than Caucasians [13].

Because AAV is infrequent in non-Caucasians, and differences in disease expression among ethnic backgrounds exist, we aimed to describe the clinical and serological characteristics, as well as renal histology in Mexican patients with AAV from a single center.

Patients and Methods

Clinical and renal histologic characteristics

We retrospectively studied all patients with diagnosis of AAV, followed at the Department of Immunology and Rheumatology of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, a tertiary care center in Mexico City, from January 2002 to December 2012. Our center is a referral Institution for mainly uninsured patients from all over the country. Inclusion criteria were: diagnosis of GPA or MPA according to definitions from the 2012 revised Chapel Hill Consensus Conference [14], availability of a kidney biopsy, and positivity for ANCA, MPO or PR3-ANCA antibodies. Information was retrieved from the medical records. Patients with EGPA, secondary forms of vasculitis, anti-glomerular basement membrane disease, lupus nephritis or IgA-nephropathy, and patients with missing data were excluded. Patients that had diagnosis of GPA or MPA and diabetes mellitus with a renal biopsy showing diabetic nephropathy were also excluded.

Demographics and comorbidities were considered at diagnosis of vasculitis. Clinical and laboratory variables were also analyzed at the time of AAV diagnosis, and included: antibodies (ANCA by indirect immunofluorescence assay, anti-PR3 and anti-MPO by ELISA), erythrocyte sedimentation rate (ESR), and high sensitivity C-reactive protein (hsCRP). Organ manifestations were only registered if symptoms could be ascribed to active vasculitis. Disease activity was scored using the Birmingham Vasculitis Activity Score specific for GPA (BVAS/GPA) [15], while prognosis was assessed using the Five-Factor Score (FFS) at diagnosis [16]. Mortality and causes of death were recorded during follow-up.

Renal variables included, serum creatinine, 24-hour urine protein excretion, protein/creatinine ratio, estimated glomerular filtration rate (eGFR), using MDRD formula [17], and dialysis requirements at diagnosis of AAV.

Forty patients with renal biopsy were included. In every case, one section of the kidney biopsy core was formalin fixed and paraffin embedded, 2 μm sections were stained with haematoxylin and eosin (H&E), periodic acid-Schiff, Masson's trichrome stain and Jone's methenamine silver stain. Direct immunofluorescence was performed on 3 μm frozen sections that were exposed to antibodies against IgG, IgM, IgA, kappa, lambda, C1q, C3c, albumin and fibrinogen. All biopsies were reviewed and scored by two pathologists who were unaware of the clinical and laboratory information. Based on the pathological classification of ANCA-associated glomerulonephritis [7], all biopsies were evaluated and classified according to one of the four main categories (i.e. focal, crescentic, mixed or sclerotic). The percentage of normal glomeruli, tubular atrophy, interstitial infiltrate and interstitial fibrosis were also assessed.

Autoantibodies

From June 2014 to June 2015, 50 consecutive outpatients with diagnosis of AAV (GPA, MPA, EGPA or renal-limited vasculitis) according to definitions from the 2012 revised Chapel Hill Consensus Conference [14] were recruited at the Rheumatology consult of our Institution. The comparative control group comprised 10 patients with systemic vasculitis other than AAV (7 with takayasu's arteritis, 2 with behçet's disease and 1 with crioglobulinemia); 10 patients with systemic lupus erythematosus (SLE); 10 patients with infections without autoimmune disease (2 with tuberculosis, 3 with HIV/AIDS, 1 with bacterial endocarditis and 4 with bacterial infections), and 13 healthy subjects.

Evaluation of the patients with AAV included disease activity (BVAS/GPA), physician's global assessment (PGA), laboratory tests and treatment information.

All serum samples were tested for ANCA-IgG by indirect immunofluorescence (IIF) on ethanol fixed human neutrophils (NOVA Lite ANCA; INOVA Diagnostics, San Diego, USA). Serum screening dilution was 1:20 (Beeline 220s, HTZ; London, UK). Staining patterns were identified as perinuclear (P-ANCA), granular cytoplasmic (C-ANCA) and delineated atypical (X-ANCA). Atypical or P-ANCA patterns were confirmed in formalin fixed neutrophils substrate and antinuclear antibodies were ruled-out (INOVA Diagnostics, San Diego, USA).

Specific autoantibodies (IgG isotype) included: MPO, PR3 (QUANTA Lite; INOVA Diagnostics, San Diego, USA), high sensitive-PR3, cathepsin G, lysozyme, lactoferrin, BPI and elastase (Orgentec Diagnostika GmbH; Mainz, Germany). All tests were analyzed according to the manufacturer's recommendations in a DSX System (DYNEX Technologies). The cut-off values were previously determined in 55 healthy subjects (90th percentile).

The hospital institutional review board approved the study and all patients provided written informed consent.

Statistical analysis

Descriptive statistics include n, percent and median with 25-75 percentiles. Differences between groups were evaluated with the Student t test or Mann-Whitney U test for continuous variables, and Chi-square test or Fisher's exact test for categorical variables. Comparisons between histologic classes were done with the Kruskall-Wallis test. Logistic regression was used in multivariate analyses to evaluate associations between significant variables ($p \leq 0.10$) identified

from bivariate analyses. OR and 95% confidence intervals (CI) were calculated. Patient survival was assessed by life-table analysis using the Kaplan-Meier method. Differences in survival were calculated using the log-rank test. Correlations of antibodies and clinical manifestations were assessed using Spearman's correlation test with Bonferroni correction. Exact p-values are reported and a two-sided p-value of ≤0.05 was considered statistically significant. All analyses were done using Stata software (Stata Corp; College Station, Texas USA), version 12.0.

Results

Clinical and renal histologic characteristics

We studied 40 patients with AAV; 23 (58%) female gender (1.3:1 female to male ratio), 35 (88%) had diagnosis of GPA and 5 (12%) of MPA. In 35/40 renal biopsy was performed at diagnosis of vasculitis, therefore, disease duration was 0 months (minimum 0 and maximum 43 months). Age at diagnosis was 53 years (37-58), and the most prevalent comorbidity was arterial hypertension, present in 16 (41%).

Most of the patients were ANCA positive at diagnosis (98%); C-ANCA staining pattern was positive in 88%, while P-ANCA was observed in 18% and atypical X-ANCA in 35%. PR3-ANCA positivity was present in 77% and MPO-ANCA in 17%.

Disease activity according to BVAS/GPA at diagnosis was 24 (16-25), while FFS was 2 points (1-2). The most frequent clinical manifestations were general (98%), renal (80%), pulmonary (63%), ear, nose and throat (ENT) (58%). Patients had a median of 4 (2-6) organs affected according to BVAS/GPA categories.

The most prevalent specific manifestations according to each category of the BVAS/GPA were: fever (80%), rise in creatinine/fall in creatinine clearance (78%), hematuria (75%), arthritis (53%), alveolar hemorrhage (48%), pulmonary infiltrates (43%), nasal crusts (38%), purpura (30%), and sensory peripheral neuropathy (25%).

Baseline serum creatinine was 3.9 mg/dl (2.6-4.3), eGFR 16 ml/min (11-22), and 24 hr proteinuria 2.5 g (1.9-3). Five patients (13%) were on dialysis at diagnosis, (1 with mixed and 4 with sclerotic histological class).

The most prevalent renal histological class was sclerotic (23 patients, 58%), followed by mixed (13 patients, 32%), focal (3 patients, 8%) and crescentic (1 patient, 2%). No significant differences were found between histological classes when comorbidities, clinical (including disease activity), renal, and laboratory variables were analyzed.

In all renal biopsies, independent of the histological class, percentage of normal glomeruli was 22% (11-60), tubular atrophy 30% (15-59), interstitial fibrosis 30% (20-50) and interstitial infiltrate 15% (10-30%).

Six patients (15%) died during follow-up (4 with sclerotic class, 1 with focal, and 1 with mixed class). Median length of follow-up time was 24 months (minimum 6, maximum 96). Survival in patients with sclerotic class was 100% and 66% at 1 and 5 years respectively; whereas in patients with non-sclerotic class it was 93% at 1 and 5 years. No difference in overall survival was found between groups (p=0.55 log-rank). Causes of death were infectious, pneumonia in four patients and sepsis in two. Table 1 summarizes clinical and renal characteristics at diagnosis.

Characteristic	N (%)
Demographics and comorbidities	
Female gender	23 (58)
Age at diagnosis—years	53 (37-58)
GPA	35 (88)
MPA	5 (12)
Diabetes	3 (8)
Dyslipidemia	6 (15)
Arterial hypertension	16 (41)
Smoking	7 (18)
Clinical variables	
BVAS/GPA	24 (16-25)
FFS at diagnosis	2 (1-2)
General	39 (98)
Cutaneous	15 (38)
Mucous membranes/Eyes	7 (18)
Ear, nose and throat	23 (58)
Cardiovascular	0
Gastrointestinal	0
Pulmonary	25 (63)
Renal	32 (80)
Nervous system	12 (30)
Renal variables	
Renal histological class	
Focal	3 (8)
Crescentic	1 (2)
Mixed	13 (32)
Sclerotic	23 (58)
Baseline serum creatinine—mg/dl	3.9 (2.6-4.3)
eGFR (MDRD) ml/min at diagnosis	16 (11-22)
Proteinuria (gr/24 h)	2.5 (1.9-3)
Protein/creatinine ratio	2.7 (2-3.2)
Dialysis at diagnosis	5 (13)
Laboratory variables at diagnosis	
ANCA positive (any pattern)	39 (98)
C-ANCA positive	35 (88)
P-ANCA positive	7 (18)
X-ANCA positive	14 (35)

Anti-PR3 positive—n +/n tested (%)	27/35 (77)
Anti-MPO positive—n +/n tested (%)	6/35 (17)
hsCRP—mg/l	3 (2-4.5)
ESR—mm/h	65 (46-94)

Table 1: Clinical and renal characteristics at diagnosis. GPA: Granulomatosis with Polyangiitis; MPA: Microscopic Polyangiitis; BVAS/GPA: Brirmingham Vasculitis Activity Score for GPA; FFS: Five Factor Score; eGFR: Estimated Glomerular Filtration Rate; Anti-MPO: Anti-Myeloperoxidase Antibody; Anti-PR3: Anti-Proteinase 3 Antibody; hsCRP: high sensitivity C - reactive protein; ESR: Erythrocyte Sedimentation Rate.

Autoantibody profile

Fifty patients with AAV were studied transversally (40 with GPA, 4 with MPA, 3 with EGPA, and 3 with renal-limited vasculitis); 31 (62%) were female and 19 (38%) were male (1.6:1 ratio); age was 52 years (41-64), and disease duration was 3 years (2-5).

Disease activity according to BVAS/GPA at the time of the evaluation was 3 (minimum 0, maximum 14); ENT, neurologic and renal were the most prevalent clinical manifestations, present in 28%, 24% and 16%, respectively. General symptoms were present in 14%, while cutaneous, mucous membranes/eyes and pulmonary manifestations were present in ≤ 10%.

In patients with AAV, serum creatinine was 1.1 mg/dl (0.8-1.8); leukocytes 7.7 x10^3/ mm^3 (5.5-10.7); hemoglobin 13.5 g/dl (12.3-14.6), and platelet count 262 K/ ul (212-321). Anemia was present in 9 (18%), while leukopenia and thrombocytosis were infrequent (2%).

At the moment of the evaluation, 41 (82%) patients were receiving prednisone, dose of 10 mg/d (5-15); 28 (56%) azathioprine, dose of 100 mg/d (75-150); 4 (8%) were receiving IV monthly cyclophosphamide at a dose of 875 mg (750-1000), and 3 (6%) methotrexate, dose of 12.5 mg/week (10-17.5). Median ESR and hsCRP was 7 mm/hr (4-22), and 0.3 mg/dl (0.2-1.8), respectively.

Patients with AAV were older than controls (51.5 vs 31 years, p<0.001). ANCA positivity was more frequent in patients with AAV than controls (p < 0.001). As expected by the GPA predominance over the other forms of AAV, the main ANCA IIF staining pattern was C-ANCA, present in 34 (68%) of the patients vs 6 (14%) of the controls (p < 0.001), followed by X-ANCA in 11 (22%) of the patients and 2 (5%) of controls (p<0.01), and P-ANCA in 9 (18%) and 1 (2%), respectively (p=0.01). Positivity for two different ANCA IIF staining patterns was observed in 11 (22%) of patients and 1 (2%) of controls (p=0.005). Seven patients (14%) presented high ANCA titers (>1:160), compared to 5 (12%) of the controls (p=0.76); none of the healthy subjects was ANCA positive. Twenty-tree patients (46%) were positive for PR3-ANCA, compared to 4 (9%) of controls (p<0.0001), while high-sensitivity PR3-ANCA was positive in 43 (86%) of patients and in 21 (55%) of controls (p=0.002), and MPO-ANCA in 9 (18%) and 5 (12%), respectively (p=0.56). In multivariate analysis, age (OR 1.08, 95% CI 1.03-1.13, p=0.02), and ANCA positivity (OR 15, 95% CI 3.90-57.59, p < 0.0001) were independent variables associated with AAV.

Antibodies directed to minor targets were infrequent in our patients with AAV. Elastase, BPI, and cathepsin G were positive in 1 patient with EGPA who was C-ANCA positive; while lactoferrin was positive in 1 GPA patient with C-ANCA and X-ANCA staining patterns, and lysozyme in none. Both patients were negative for MPO and PR3-ANCA. In the control group, 1 patient with SLE was positive for elastase and cathepsin G, and 1 only for cathepsin G; 1 with infection (diabetic foot) was positive for elastase and BPI, and 1 with HIV was positive for BPI and cathepsin G. Two more patients with infections (1 with pyelonephritis and 1 with endocarditis) were positive for BPI, and 2 for elastase (1 with HIV and histoplasmosis and 1 with disseminated tuberculosis).

No significant correlations were identified between specific autoantibodies and clinical or laboratory variables. A positive correlation was found between PGA and BVAS/GPA (r=0.83, p < 0.0001), hsCRP and BVAS/GPA (r=0.51, p=0.03), and hsCRP and PGA (r=0.66, p > 0.0001).

Data summarizing the antibody profile in patients with AAV and controls is shown in (Table 2).

Variable	Patients	Controls	p
	n=50	n=43	
Age—years	51.5 (21-85)	31 (18-77)	<0.001
Female—n (%)	31 (62)	27 (63)	1
ANCA 1:20—n (%)	43 (86)	8 (19)	<0.001
ANCA 1:40—n (%)	34 (68)	6 (14)	<0.001
ANCA 1:80—n (%)	15 (30)	6 (14)	0.08
ANCA > 1:160—n (%)	7 (14)	5 (12)	0.76
C-ANCA—n (%)	34 (68)	6 (14)	<0.001
P-ANCA—n (%)	9 (18)	1 (2)	0.01
X-ANCA—n (%)	11 (22)	2 (5)	0.01
Anti-PR3 positive—n (%)	23 (46)	4 (9)	<0.0001
Anti-PR3 high sensitive positive—n + /n tested (%)	43 (86)	21/38 (55)	0.002
Anti-MPO positive—n (%)	9 (18)	5 (12)	0.56
Elastase positive—n +/n tested (%)	1 (2)	4/38 (11)	0.16
BPI positive—n +/n tested (%)	1 (2)	4/38 (11)	0.16
Cathepsin G positive—n +/n tested (%)	1 (2)	3/38 (8)	0.31
Lactoferrin positive—n (%)	1 (2)	0	1
Lysozyme positive—n (%)	0	0	-

Table 2: Autoantibody profile in patients with AAV and controls. ANCA: Anti-Neutrophil Cytoplasmic Antibodies; C-ANCA: Cytoplasmic Staining Pattern; P-ANCA: Perinuclear Staining Pattern; X-ANCA: Atypical Staining Pattern; anti-PR3: anti-proteinase 3 antibody; anti-MPO: anti-myeloperoxidase antibody; BPI: Bactericidal Permeability Increasing protein.

Discussion

We describe the characteristics of Mexican patients with AAV in two different scenarios. In the first one, patients were analyzed at diagnosis of vasculitis, when multiple organ involvement, high disease activity and renal damage were present. At this point, the main renal histological class was sclerotic in more than half of our patients, with no differences between histological classes regarding clinical, serological manifestations and survival. Secondly, patients were assessed during disease course to evaluate the prevalence of ANCA and antibodies specific for other neutrophils antigens. C-ANCA and PR3-ANCA were the predominant profile, while the antibodies to minor targets were infrequent, without correlation with specific clinical manifestations.

Our data regarding predominance of female gender, age, and main clinical manifestations at diagnosis (ENT, lung, renal and peripheral nervous system) corresponds well with the characteristics described in a report from Latin-American (Chilean) patients with GPA and MPA, where ENT involvement was present in 38-57%, lung in 28-62%, renal in 68-78%, and peripheral nervous system in 17-59% [18]. High frequency of constitutional symptoms (>90%), and high serum creatinine at diagnosis (4 mg/dl) were also identified in 80 German patients with AAV [19]. It is worth pointing out the high frequency of alveolar hemorrhage at diagnosis in 48% of our patients, as defined by BVAS/GPA. Previous studies have also described high incidences of this severe manifestation [20]. Our findings of frequent ENT involvement at diagnosis and predominant chronic renal histological lesions differ from the ones reported by Rahmattulla et al. [21], where the presence of ENT involvement was associated with prognostically favorable renal biopsy findings (focal class, less interstitial fibrosis and tubular atrophy), and better renal function.

A FFS of 2 points at diagnosis was present in our patients, mostly due to the renal items, since gastrointestinal and cardiac manifestations were not observed. Despite the 5-year survival of 40% expected for this score, 66% and 93% of our patients with sclerotic and the other histological classes respectively, were alive at 5 years, similar to the 5-year survival reported in patients from the Limburg Renal Registry cohort [22]. As in our study, other authors have described no significant differences in patient survival among histological classes [23]. This should be interpreted cautiously, since the purpose of our study was to assess the differences in the renal histological classes rather than to make conclusions regarding the survival and outcome of our population.

Sreih et al. reported higher frequency of renal involvement in Hispanic patients (Mexican ancestry) compared to Caucasians (85% vs 48%), with similar characteristics than our population regarding renal function and BVAS/GPA at presentation, but more patients with dialysis requirements (31.8% versus 13% in our study) [13]. The most frequent renal histological class in our analysis was sclerotic, opposite to other single-center studies and multicentric clinical trials that have validated the histological classification, where sclerotic class was absent or very infrequent [7,22,24,25]. A study that analyzed the histopathological classification in 156 Australian patients reported 20 cases (17%) with sclerotic class, and concluded that the sclerotic patterns are the lesions more reliably identified by pathologists [26]. A possible explanation for the predominance of sclerotic class in our population is a delay in diagnosis or referral to specialized medical centers due to socioeconomic reasons.

The distribution of the four renal histological categories is similar in Europe, Canada, India and China, with crescentic class being the dominant, whereas in Japan the focal class predominates, and in USA the mixed [7,23,27-33]. The presence of impaired renal function, and the low percentage of normal glomeruli (<25%) in our population are factors known to be associated with poor renal outcome [25,34,35].

Predominance for GPA, C-ANCA and PR3-ANCA in our population is similar to the phenotype of European patients with AAV. Antibodies to minor targets were infrequent in our patients with AAV, similar to the findings reported by Talor et al. [5]; therefore, we were unable to find a correlation with specific clinical manifestations. The utility of testing for antibodies to minor antigens is to explain immunofluorescence reactivity for ANCA in the absence of MPO and PR3-ANCA positivity.

Recent focus has been directed on the study of potential biomarkers in AAV. Among the candidate's biomarkers are those related to B and T cells, markers of vascular damage or activation, and organ-specific markers. Promising biomarkers identified are MMP-2, MMP-3, MMP-9, TIMP-1, VEGF, CXCL13 (BCA-1), complement pathway, and high mobility group box 1 (HMGB1) [36,37].

The IL-33/ST2 (suppression of tumorigenicity 2) pathway has been subject of recent studies, especially in patients with cardiovascular and pulmonary diseases, but also in systemic infection and inflammation. IL-33 binds to ST2, a member of the IL-1 receptor family that mediates important Th2 functions. A recent study of 139 AAV patients and 62 controls, found that newly diagnosed AAV had higher soluble ST2 levels than controls, and these levels were significantly higher in active newly diagnosed AAV patients than in patients in remission, whereas IL-33 levels were also higher in AAV than controls, but no difference was found in active patients compared to patients in remission, suggesting a potential role for serum soluble ST2 as a biomarker of activity in AAV [38]. To date, no single biomarker has met high sensitivity or specificity to justify its clinical usefulness.

The present study has some limitations. First, the reduced number of patients, although the sample represents a single center, numbers are small. Second, our patients belong to a tertiary care center, where cases with a more severe spectrum of the disease are referred; therefore the results might not be representative of the entire Mexican population with AAV. Last, no conclusions about the predictive value of the histological classification for renal outcome can be derived from our study, since treatment, remission, and relapses were not assessed in follow-up, and due to limited number of patients in each histological class. Nevertheless, we consider that our study adds valuable information about the expression of AAV in Mexican patients, both at diagnosis and during the course of the disease with regard to clinical, serologic and renal histologic characteristics.

In conclusion, GPA was the most frequent AAV in our population; constitutional, ENT, lung and renal involvement were the predominant clinical manifestations. Sclerotic renal histological class was the most frequent, without differences between histological classes regarding clinical, serological manifestations and survival. These data suggest that our patients present severe disease activity, and high prevalence of renal involvement and damage. Prospective studies are needed to assess long-term outcomes in Mexican patients with AAV.

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Conflicts of interest

The authors declare no conflicts of interest.

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