Contents available at **PubMed**
www.anmm.org.mx

PERMANYER

Gac Med Mex. 2015;151:164-73

GACETA MÉDICA DE MÉXICO

ORIGINAL ARTICLE

Clinical characteristics of antineutrophil cytoplasmic antibody-associated vasculitis (AASV) in a respiratory diseases referral center in Mexico (1982-2010)

Luis Felipe Flores-Suárez and Marco A. Alba*
Primary Systemic Vasculitides Clinic, Instituto Nacional de Enfermedades Respiratorias (INER), Mexico, D.F., México

Abstract

Introduction: *Respiratory manifestations in antineutrophil cytoplasmic antibody-associated vasculitis (AASV) are common, though their suspicion is lower than expected in respiratory devoted centers, with few descriptions coming from them.* **Objective:** *To describe the clinical, paraclinical and radiological manifestations, plus the prognosis of AASV patients seen in a respiratory referral center in Mexico City.* **Material and methods:** *Retrospective review of patients with final diagnosis of AASV, based on the American College of Rheumatology criteria and the 1994 Chapel Hill Consensus Conference Nomenclature, from 1982 to 2010.* **Results:** *The characteristics of 74 granulomatosis with polyangiitis, 10 microscopic polyangiitis, and six eosinophilic granulomatosis with polyangiitis cases are described. Mean time elapsed from initial suspicion to definitive diagnosis was 30 months. As expected, respiratory findings dominated this cohort, but no significant differences were observed when compared to other series with AASV, except for a higher frequency of subglottic stenosis. After a mean follow-up of 22 months, 83% of patients were alive, with remission being achieved in 87% and response in 9%. Seven patients died, mostly from infectious complications. Conclusion: This study documents that airway manifestations in Mexican patients with AASV are similar to what has been previously described. However, time to diagnosis is long. Respiratory specialists should be more aware of the modes of presentation in AASV patients in order to facilitate their recognition.* (Gac Med Mex. 2015;151:164-73)

Corresponding author: *Luis Felipe Flores-Suárez, felipe98@prodigy.net.mx*

KEY WORDS: *ANCA-associated vasculitis. Airways. Lung.*

Introduction

Systemic vasculitides are a heterogeneous group of diseases characterized by an inflammation of the vascular wall that drives to its destruction and, consequently, to tissue ischemia[1]. Its diagnosis represents a real challenge, since not only are signs and symptoms diverse and wide, but also because other conditions not associated with the development of vascular inflammation have similar clinical characteristics, laboratory results and radiologic findings[2]. For these reasons, histological confirmation is crucial and advisable, although it is not always affordable[3].

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) are characterized by inflammation of small-diameter vessels, especially those from airways and kidneys[4]. Under this term, granulomatosis

Correspondence:
*Luis Felipe Flores-Suárez
Clínica de Vasculitis Sistémicas Primarias
Instituto Nacional de Enfermedades Respiratorias
Calzada de Tlalpan, 4502
Col. Sección XVI, Del. Tlalpan, C.P. 14000, México, D.F., México
E-mail: felipe98@prodigy.net.mx

Date of modified version reception: 16-01-2014
Date of acceptance: 19-05-2014

with polyangiitis (GPA [Wegeners]), microscopic polyangiitis (MPA) and eosinophilic GPA (EGPA [Churg-Strauss]) are grouped. The course of these conditions can be rapid and dangerous, with life-threatening manifestations or irreversible damage to the function of specific organs[5]. Therefore, establishing a timely diagnosis is crucial for optimal treatment to be started in order to achieve an adequate survival (currently, 80% at 5 years) and to reduce the probability of developing chronic irreversible lesions that significantly affect the quality of life of these patients[6-8].

Since these are considered rare diseases, and there are limited data on the subject in non-Caucasian populations, particularly in Latin America[9-12], the purpose of this study is to describe clinical, laboratory and radiologic manifestations, with an emphasis on the airways, as well as the observed prognosis in a retrospective series of 90 Mexican patients derived exclusively from a referral center for respiratory diseases.

Material and methods

A retrospective review was conducted with information obtained from the institutional admission registry and logs on discharge data, where the terms *granulomatosis, Wegener's granulomatosis, Wegener's disease, Wegener's syndrome, vasculitis, pulmonary vasculitis, lung-kidney syndrome, pneumorenal syndrome, alveolar hemorrhage, diffuse alveolar hemorrhage, pulmonary hemorrhage, microscopic polyangiitis, Churg-Strauss syndrome, pulmonary eosinophilia, eosinophilic pneumonitis, eosinophilic pneumonia, acute eosinophilic pneumonia, chronic eosinophilic pneumonia, Löffler syndrome, subglottic stenosis, idiopathic subglottic stenosis, tracheal stenosis and idiopathic tracheal stenosis* were identified. Clinical laboratory records were also searched, where the detection of ANCA-positive tests led to the review of the corresponding clinical record looking for relevant data. Once patients with these data were identified, two authors conducted an independent review of all cases. When there was disagreement with regard to the inclusion or not of cases for analysis, evidence was searched to support the presence of GPA, MPA or EGPA and a consensus was reached. In case of ANCA positive results, if there was another explanation (infection, neoplasm, use of drugs) or if the results were not reasonably justified, the case was not considered AAV-related.

The study period was from 1982 to 2010, and the site was the National Institute of Respiratory Diseases (INER – *Instituto Nacional de Enfermedades Respiratorias)* of Mexico, which is a referral center for pulmonary and otorhinolaryngologic diseases that serves primarily non-medically insured patients from the metropolitan area of Mexico City and neighboring states, mainly from central and southern regions of the country, athough patients are referred from the entire nation. Additionally, any patient can request medical care in the Respiratory Emergencies Unit due to problems associated with this organ system, with no previous reference being mandatory.

Classification of the different AAVs was established based on the ACR 1990 definitions for GPA[13] and EGPA[14]. Since there are no ACR classificatory criteria for MPA, the use of the definition by the 1994 Chapel Hill Consensus Conference for vasculitides nomenclature was decided for this type of vasculitis[15].

Based on a pre-established 400-variable electronic report form elaborated by the investigators, data on gender, age at diagnosis, initial diagnosis suspected by the referring clinician (primary care or first treating physician at the INER, an emergency, internal medicine or pneumology specialist), initial symptoms at diagnosis and disease- and treatment-related complications were collected. Additionally, initial histopathological results and laboratory data including hemoglobin, serum creatinine, erythrocyte sedimentation rate (ESR) and C-reactive protein levels, as well as white-cell count, with the corresponding differential test, and platelet counts were collected. Simple x-ray and computed tomography (CT) findings were also recorded.

Manifestations collected by organ systems included:

- Articular, when patients experienced arthritis or joint pain
- Cutaneous: presence of cutaneous ulcers of non-infectious origin or due to venous stasis o chronic arterial insufficiency, palpable purpura, cutaneous nodules, gangrene and, in mucosae, oral persistent ulcers.
- Ocular: corneal ulcers, episcleritis, scleritis, nasolacrimal obstruction, proptosis or orbital masses, uveitis or retinal vasculitis.
- Of the nervous system: it was divided into peripheral in case of sensitive or motor peripheral polyneuropathy or mononeuritis multiplex and central involvement for cerebral infarctions, intracranial granulomatous lesions, aseptic meningitis, pachymeningitis and external ophthalmoplegia.
- Gastrointestinal: intestinal infarction or ischemic ulcers, with evidence of upper or lower gastrointestinal (GI) tract bleeding.

Table 1. Demographic characteristics*

	GPA	MPA	EGPA	Total
Number of patients (%)	74 (82)	10 (11)	6 (7)	90
Males/females (%)	30/44 (40.5/59.5)	1/9 (10/90)	4/2 (67/33)	35/55 (39/61)
Age at diagnosis (years ± SD)	42 ± 12 years	47 ± 11 years	34 ± 15 years	42 ± 12 years
Follow-up in months (range)	21 ± 32 (0.3-198)	19 ± 18 (1.0-46.8)	47 ± 56 (6-148)	22 ± 33 (0.3-1.98)
Alive (%)	61 (82)	9 (90)	5 (83)	75 (83)
Dead (%)	7 (9.5)	0 (0)	0 (0)	7 (8)
Lost to follow-up (%)	6 (8)	1 (10)	1 (17)	8 (9)

*Rounded percentages are shown.

- Cardiac; myocarditis or pericarditis.
- Renal: hematuria (excluding other origin), acute renal failure associated with rapidly progressive glomerulonepfhritis with nephritic syndrome or proteinuria not explained by other causes.
- Otorhinolaryngologic: hemorrhagic persistent crusting or nasal ulcers, rhinitis, anosmia, sinusitis, epistaxis, turbinate erosion, otic fullness, otitis media or internal, tinnitus, otorrhea, facial paralysis, saddle nose deformity, conductive or sensoryneural hearing loss with no established cause.
- From airways and lungs: subglottic and/or tracheal stenosis, severe persistent asthma of unexplained cause, alveolar hemorrhage, pulmonary nodules or cavitation and bronchial or pleural thickening.

To describe the results of treatment, the definitions proposed by the European League Against Rheumatism (EULAR), i.e., remission, response, relapse and presence of refractory disease, were used[16]. Disease activity and chronic damage were measured using the Disease Extent Index (DEI)[17] and the Vasculitis Damage Index (VDI)[18], respectively. Briefly, a patient was considered to be in remission when a stable treatment was maintained (with no change in the dose or the number of immunosuppressants or corticosteroids) and no data on AAV were found. Response was defined as a 50% decrease in the DEI, in addition to absence of new clinical manifestations. Reappearance of AAV manifestations once remission was achieved was considered to be relapse, which could be serious, when the reinitiating of manifestations had a severity that could be life- or organ-threatening, or mild, when it did not represent a threat to life or to a specific organ function. Finally, refractory patients were defined as those whose activity measured with the DEI increased within the first 4 weeks after starting treatment following the diagnosis or as lack of response after six weeks on therapy. For the description of imaging characteristics of the CT scans, the definitions of the international glossary, published in 1996, were used[19].

Statistical analysis

The results of continuous variables were presented as means ± standard deviations (SD), and those of categorical variables, as percentages. Data comparison was performed with Student's t-test for continuous variables and the chi-square test for categorical variables, using the software package PAWS statistics, version 18 (SPSS, Inc. 2009, Chicago, Illinois). Statistical significance was established at p-values < 0.05.

Results

One hundred and two patients with a final diagnostic of GPA, MPA or EGPA (Churg-Strauss) were identified between 1982 and 2010. Of them, in 12 cases, no complete information was available or could not be classified according to the employed instruments and definitions and, therefore, they were excluded. The numbers of patients diagnosed per decade were the following: 2 from 1982 to 1989, 9 from 1990 to 1999, 67 from 2000 to 2009 and 12 in the year 2010. Mean age at diagnosis was 42 ± 12 years (range: 17-68) and the female:male ratio was 1.5:1. The most common diagnosis was GPA (82%). Demographic characteristics are presented in table 1. The time elapsed between the first symptoms and diagnosis was 30 ± 62 months (range: 0.3-414 months). With regard to initially suspected diagnoses, it is important mentioning that, in spite of the long period between the onset of disease and the establishment of the correct diagnosis, a related disease (polyarteritis nodosa)

was suspected only in one of the cases, whereas some other autoimmune pathology (including ocular inflammatory disease, pulmonary interstitial disease, lupus erythematosus or generalized or rheumatoid arthritis) was suspected in 21% of the cases.

Clinical manifestations

The initial symptom was cough in 18 patients (20%), dyspnea, rhinorrhea or fever in 15 cases (16.6% each), joint pain in 8 (8.8%), otorrhea or otic fullness in 7 (7.7%), hearing loss or red eyes or eye pain in 4 (4.4% each), dysphonia in 3 (3.3%) and mouth ulcers in 1 (1.1%). At the moment of diagnosis, 50 patients had general symptoms: 34 (37.8%) had fever; 25 (27.8%), weakness: 21 (23.3%), weight loss (mean of 10 kg in two months), and 8 (8.9%), nocturnal diaphoresis. Sixty-two percent of the cases had involvement in more that one organ (eyes, lungs, joints, skin, kidneys or peripheral nerves), although, as expected, the respiratory tract was the most frequently involved. Baseline average DEI was 5.27 ± 2.9 (range: 2-13). Extrapulmonary symptoms included joint manifestations (arthritis or joint pain) in 37 cases (41%), renal manifestations (acute renal failure or nephritic syndrome) in 22 (24%), ocular inflammatory manifestations (episcleritis, scleritis, uveitis or orbital mass) in 21 (23%), cutaneous manifestations (purpura palpable or cutaneous ulcers) in 14 (15%), peripheral nervous system manifestations (sensitive or motor neuropathy or mononeuritis multiplex) in 13 (14%) and GI tract (hematochezia) and central nervous system manifestations (cerebral infarction) in 2 (2%).

Airways manifestations

Airway involvement was present in 85 patients (94%) and it was the only documented manifestation in 32 (35.5%). Those affecting the upper airway were present in 67 patients, while lungs were affected in 39 cases (43%).

The most common symptom at diagnosis in the entire retrospective series was dyspnea, usually mild, in 58% of the cases. Otorhinolaryngologic manifestations included cough (49%), purulent rhinorrhea (33%), nasal congestion (31%), sinusitis (30%) and each one of the following was present in < 25% of the cases: epistaxis, dysphonia, anosmia, rhinitis, turbinate erosion and facial paralysis. In 18 cases (20%) there was hemoptisis, which was the main pulmonary symptom. Eight patients (9%) required mechanical ventilation because their respiratory condition was serious and life-threatening. Table 2 shows entirely the upper and lower airways initial manifestations.

With regard to symptoms and signs characteristically associated with each one of the AAVs, some were identified and were present only in GPA. Saddle nose deformity and subglottic stenosis (SGS) were found exclusively in this disease; to classify its seriousness, the system proposed by Myer et al.[20] was used by employing flexible nasofibrolaryngoscopy: grade I, up to 50% luminal obstruction; grade II, 51 to 70%; grade III, more than 70% with any luminal caliber observed, and grade IV, absence of luminal patency. There were 23 patients with SGS; 18 grade I, 2 grade II and 3 grade III. Other manifestations exclusive in GPA were: hearing loss in 20 patients (27%), otitis media in 14 (19%), otic fullness in 9 (12%), mouth ulcers in 9 (12%), otorrhea in 6 (8%) and facial paralysis in 3 (4%).

Paraclinical diagnostic assessment

Radiology

All patients had at least one chest x-ray and/or high resolution computed tomography (HRCT). These data are shown in table 3. Radioopacities or parenchimal infiltrates were the most common findings, present in simple x-ray or HRCT in 22% of the patients with GPA, 50% of the patients with MPA and in all patients with EGPA.

Laboratory data

The results of the initial laboratory tests are shown in table 4. Anemia (hemoglobin < 12 g/dl) was documented in 36/89 (40%) subjects, ESR > 30 mm/h in 20/63 (32%), thrombocytosis > 450,000/µl in 13/38 (15%), leukocytosis in 23/88 (26%), serum creatinine > 15 mg/dl in 12/89 (13.5%) and eosinophilia > 1,500/µl in 7/86 (8%). The only, but expectable and obvious difference in these parameters between all three AAVs was eosinophilia, present in 83% of the patients with Churg-Strauss; it was also found in GPA (3%), but in no patients with MPA ($p < 0.0001$). In 67 patients (74%), the ANCA levels were measured by indirect immunofluorescence (IIF), and antigenic specificities against proteinase 3 (PR-3) and myeloperoxidase (MPO) were determined by enzime-linked immunosorbent assay (ELISA) in 30 (34.4%). It is important pointing out that these tests by both methods were regularly introduced in our center in 2009, ever since the creation of the Primary Systemic Vasculitides Clinic. Previously, in

Table 2. Respiratory tract manifestations at the moment of diagnosis*

	GPA (n = 74)	MPA (n = 10)	EGPA (n = 6)	Total (n = 90)
Dyspnea	40 (54)	6 (60)	6 (100)	52 (58)
Cough	30 (40.5)	8 (80)	6 (100)	44 (49)
Sinusitis	26 (35)	–	1 (17)	27 (30)
Nasal cogestion	24 (32)	2 (20)	2 (33)	28 (31)
Purulent rhinorrhea	24 (32)	3 (30)	3 (50)	30 (33)
SGS	23 (31)	–	–	23 (26)
Nasal crusting	21 (28)	–	–	21 (23)
Epistaxis	16 (22)	2 (20)	1 (17)	19 (21)
Wheezing	15 (20)	3 (30)	1 (17)	19 (21)
Rhinitis	15 (21)	1 (10)	2 (33)	18 (20)
Dysphonia	15 (20)	–	–	15 (17)
Hemoptisis	13 (18)	5 (50)	–	18 (20)
Laryngeal stridor	13 (18)	–	–	13 (14)
Hyposmia/anosmia	5 (7)	–	–	5 (6)
Chest pain	2 (3)	2 (20)	–	4 (4)
Tracheomalacia	2 (3)	–	–	2 (2)
Tracheal fistula	1 (1)	–	–	1 (1)
Bronchial stenosis	1 (1)	–	–	1 (1)
Asthma	–	–	6 (100)	6 (7)

*All patients had more than one manifestation. Percentages presented rounded.

some cases only ANCA IIF measurement was performed. Therefore, there were disagreements between the number of tests by IIF and ELISA. Positivity by IIF was established as that in ≥ 1:40 dilution, and for ANCA MPO and PR-3 in > 20U/ml for each, according to the manufacturer (Eroimmun, Lübeck, Germany). The results were considered positive for antinuclear antibodies at a > 1:160 dilution by IIF; the results were positive in 20 patients. Additionally, 13 patients tested positive for rheumatoid factor, within a range from 27 to 288 U/ml.

Histopathology

One-hundred and nineteen biopsies were performed in 59 patients: 109 in 51 patients with GPA, 4 in 3 patients with MPA and 6 in 5 patients with Churg Strauss (EGPA). In 33 patients, 2 or more biopsies were performed. Only in one MPA and one Churg-Strauss case, in kidney and lung, respectively, biopsies showed the classical features of these AAVs, i.e., pauci-immune necrotizing glomerulonephritis with crescents in the case of MPA and small vessel vasculitis with abundant eosinophilic infiltration in the case of EGPA. In GPA, histology was considered to be positive when the combination of granulomatous inflammation composed by a mixture of neutrophils, lymphocytes and/or eosinophils, vasculitis of small vessels and geographic necrosis occurred. The ratio of positive biopsy specimens over the total number of performed biopsies was, for each site, the following: orbital tissue: 2/3; nasal mucosa: 18/38; oral cavity: 4/7; subglottis: 4/12; trachea or bronchi: 4/18; lung: 8/14; kidney: 1/3; skin: 4/6; peripheral nerve: 1/1; breast: 1/1, and other (bone marrow, muscle): 0/6.

Treatment and outcome

Treatment consisted of methylprednisolone pulses in 25 cases (27.8%): 22 patients received three 0.5 or 1 g methylprednisolone boluses, whereas one patient

Table 3. Radiologic findings at diagnosis*

	GPA	MPA	EGPA	Total
X-ray				
– Micronodular pulmonary infiltrates	12 (16)	4 (40)	5 (83.3)	21 (23)
– Pulmonary nodules	16 (21.6)	–	–	16 (18)
– Cavitated nodules	7 (9)	–	–	7 (8)
– Pleural effusion	2 (3)	–	–	2 (2)
CT				
– Alveolar hemorrhage	1 (1)	1 (10)	–	2 (2)
– Pulmonary nodules	12 (16)	1 (10)	1 (16)	14 (16)
– Cavitated nodules	5 (7)	–	–	5 (5.5)
– Pleural effusion	2 (3)	–	–	2 (2)
– Bronchiectasis	1 (1)	–	1 (17)	2 (2)
– Pulmonary abscess	1 (1)	–	–	1 (1)
– Mediastinal adenopathy	1 (1)	1 (10)	–	2 (2)
– Interstitial infiltrate (ground glass)†	4 (5)	3 (30)	2 (33)	9 (10)
– Interstitial infiltrate (honeycombing/fibrosis)‡	–	1 (10)	1 (17)	2 (2)
– Pulmonary infarction	–	1 (10)	–	1 (1)

*All patients had more than one radiologic manifestation. Percentages presented rounded.
†Hazy increased attenuation that respects vascular margins and adjacent bronchi.
‡Grouped cystic air spaces with thickened, well-defined walls, usually subpleurally located, with a diameter ranging from 0.3 to 1 cm.

received 5 pulses and another 6. Of the subjects reported in this series, 84.4% received oral prednisone (n = 76; average ± SD: 50 ± 15 mg/day; range: 20-80 mg/day) and 66.7%, cyclophosphamide (n = 60; 17 cases orally, 11 intravenously and in the rest no administration route was specified). In the case of the oral route, average cumulative dose was 29 ± 12.2 g (range: 13.5-47 g), and for the intravenous route (mean: 7 ± 2 boluses), 14 ± 12.3 g (range: 0.5-30 g). Other used immunosuppressants were: methotrexate in 40%

Table 4. Laboratory results at the moment of diagnosis

Parameter (mean ± SD)	GPA	MPA	EGPA	Total
ESR, mm/h	21.5 ± 14.7	26.7 ± 14.7	14 ± 22	21.77 ± 15.1
C-reactive protein, mg/dl	46.6	2.6 ± 3.73	0.56 ± 0.46	3.77 ± 6.32
Hemoglobin, g/dl	12.6 ± 2.7	11.15 ± 2.6	14.37 ± 2.3	12.6 ± 2.7
Platelets x 10^3/mm^3	334 ± 174	371 ± 134	390 ± 155	342 ± 168
White blood cells x 10^3/mm^3	8.8 ± 4	10.2 ± 5	12 ± 5.1	9.1 ± 4.3
Eosinophils x 10^3/mm^3	0.25 ± 0.51	0.17 ± 0.11	3.9 ± 3.1	0.5 ± 1.3
Creatinine (mg/dl)	1.2 ± 1.5	1 ± 0.9	0.9 ± 0.17	1.2 ± 1.3
ANCA by IIF*	53 (71)	10 (100)	4 (66.7)	67 (74)
C-ANCA†	41 (77)	5 (50)	0	46 (68.7)
P-ANCA†	5 (9.4)	5 (50)	1 (25)	11 (17.9)
ANCA by ELISA*	23 (31)	7 (70)	1 (16.7)	30 (34.4)
PR-3-ANCA†	15 (65.2)	0 (0)	0 (0)	15 (48.4)
MPO-ANCA†	5 (21.7)	7 (100)	0 (0)	12 (38.7)

*Number of patients with ANCA determination.
†Number of patients with positive result.

of the cases (36 individuals; minimum dose: 10 mg/week; maximum dose: 30 mg/week; average: 21.9 ± 5.3), azathioprine in 47.8% (43 cases; minimum dose: 75 mg/day; maximum dose: 150 mg/day; average: 120 ± 27.3), rituximab in 10% (n = 9; average: 2 g total dose), mycophenolate mofetil in 3.3% (n = 3), trimethoprim sulfamethoxazole in 18.9% (n = 17, all at doses of 800/160 mg thrice weekly), and for *Staphylococcus aureus* erradication in nasal mucosa chronic carriers, topical mupirocin was used in 19 patients (21.1%). Thirty patients required surgical treatment, all of them diagnosed with GPA. Eighteen patients underwent resection of the subglottic larynx stenotic segment affected by granulomatous inflammation. This procedure was complemented with frequent mechanical dilatations and topical mitomycin c applications on all four quadrants of the stenotic area. Nine patients required a tympanostomy with ventilation tubes insertion for the treatment of otitis media. Finally, 14 individuals required a tracheostomy for airway protection.

Treatment-related adverse events were observed in 63.3% (n = 57) of the patients; corticosteroids were responsible in 43% (n = 39). The most common adverse events were corticosteroid-induced systemic arterial hypertension (16.7%) and diabetes mellitus (7.8%), as well as Cushing syndrome, which was established by the presence of hirsutism, acne, facial fullness, abdominal striae, dorsal hump and proximal muscular weakness. In some cases, the first two above mentioned most common complications were also present as part of other manifestations of the syndrome.

During the follow-up, 7 patients (7.8%) died and 8 (8.9) were lost, i.e., stopped attending regularly to the control medical visit for over a year. In one sigle case, the cause of death was deemed to be directly associated with disease activity (massive hemoptisis in a patient with MPA). Two patiens died from non vasculitis-related causes (necrosant pancreatitis and upper GI tract hemorrhage). Four patients died due to septic shock. It is probable that AAV treatment contributed to the development of sepsis in two cases, since it occurred 0.5 and 2 months after the diagnosis, during the phase of highest immunosuppression due to the treatment (remission induction)[21]. The two other patients with septic shock died after 7 and 52 months follow up.

Of all 82 patients with complete follow-up until data collection, 72 (87%) achieved remission and 7 (9%) staisfactory response, whereas 3 (4%) cases were treatment-refractory. Relapses were observed in 33 patients (40%), with 15 of them experiencing at least two episodes of disease activity. Average time from diagnosis to first relapse was 27.5 ± 19.8 months (range: 1.71). Most patients who relapsed (28 [85%] patients) did it with the same manifestation their disease had started. Upper and lower respiratory tract relapses were observed in 14 (42%) and 7 (21%) patients, respectively. Final indices of disease extent and chronic damage (mean ± SD) were 3.14 ± 2.9 and 3.12 ± 2.5, respectively. At the end of the follow-up period, 82% of the patients (n = 68) had a damage score > 0 (VDI = 1 in 15% [n = 13]; VDI = 2 in 19% [n = 16]; VDI = 3 in 9% [n = 8]; VDI ≥ 4 in 37% [n = 31]. Most frequent chronic damages documented in the VDI were the following: hearing loss in 24% of the patients (n = 20; 19 diagnosed with GPA and 1 with MPA), sadle nose deformity in 23% (n = 19, all with GPA), SGS requiring surgery in 22% (n = 18, all GPA), peripheral neuropathy in 17% (n = 14; 7 GPA, 3 MPA and 4 EGPA cases), chronic dyspnea in 15% (n = 13; 3 MPA cases and the rest, GPA) and unilateral blindness in 10% (n = 9, all with GPA).

Discussion

This study contributes to increase the information on AAV in Latin America, with the results demonstrating that, in general, Mexican patients have clinical, biochemical and imaging presentation similar to that reported in the rest of the American continent. Although we are aware that we are not offering seminal discoveries, this work has the following strengths: it is one of the few originating entirely in a respiratory center and it is the first to provide data in this setting in Latin America.

An aspect of the present that should be highlighted is the average time between the initial symptoms and final diagnosis, which was 30 months, a figure similar to that observed in a previous study conducted in Mexico in a Rheumatology Department[9]. This period is longer than those reported in countries with centers specialized in these diseases[22-25], where the average between symptoms onset and final diagnosis is 4-6. This is, at least in part, the result of a lack of specific diagnostic criteria for AAVs, which is one of the most important problems in this context. The ACR classification criteria and the Chapel Hill Consensus Conference on the nomenclature of vasculitis are useful only in standardized cases and for clinical research purposes[26]. Currently, there is an ongoing international effort, with stringent metodolgy, for the development of diagnostic criteria (Diagnosis and Classification of Vasculitis [DCVAS])[27], which is highly necessary.

There are 3 recent series on these conditions in the region[10-12]. The first, conducted in Chile and reported in 2005, included 123 patients: 65 with MPA and 58 with GPA, over an 11-year period[11]. Overall mortality reported in this study was 10% higher than ours. The most recent series is from Brazil; it is limited to GPA and is the one with the larger number of patients with this condition reported in our region, with a total of 123[10]. Respiratory symptoms were dominant, as in our study, and patients were under the care of Rheumatology and Pneumology Deparments, although the exact number treated in each department was not defined. As with the Chilean series, mortality was higher than ours and was distributed equally between infectious complications, chronic complications due to the disease, and a combination of both causes. In 2007, we reported what in its time was the largest series of patients with GPA in Latin America[9]. In this study, conducted in a tertiary care center specialized in internal medicine, one fourth of all 65 patients treated at the Rheumatology Department, over a period of nearly 30 years, had pulmonary symptoms; the most frequent were in the upper airway, occurring in three quarters of the subjects.

Previous studies have reported an incidence of alveolar hemorrhage of 5-45% in GPA[22,28,29] and 15-55% in MPA[30,31]. This manifesration is much less common in EGPA, since it occurs only in 4% of the patients[32]. Acute mortality associated with this serious manifestation is approximately 60% and is 6-fold higher than in patients with vasculitis but without the presence of diffuse alveolar hemorrhage[24,33]. In the Chilean series, the number of patients with diffuse alveolar hemorrhage is noteworthy, since it exceedes the number observed by us; it is even more frequent in GPA than in MPA, which is in contrast with reports from different geographic regions where these conditions are more common[22,28-32]. Probably this explains the higher rate of observed mortality. On the other hand, in contrast with data of an epidemiological study conducted in Peru[12], GPA appears to be more frequent than MPA in our country, which was observed both in the center where the study published in 2007 was conducted[9] and in our center.

Most descriptions of respiratory disease are inserted in data cohorts originating in Nephrology or Rheumatology Units[23,24,31,34,35], and only few reports are derived exclusively from centers specialized in respiratory care[36-38]. When clinical manifestations observed in the largest AAV observed group, the GPA group, are compared with those derived from a series studied in a center specialized in respiratory diseases, comprised by 77 Caucasian patients with an average age of 46.5 years[36], we find SGS to be more frequent in our study (31 vs. 2.5%), whereas cough (40 vs. 78%), rhinitis (20 vs. 42%), hemoptisis (17 vs. 39%) and chest pain (3 vs. 32%) were less frequent. As in other series[10,36,39-41], the most common radiologic findings were infiltrates or radio-opacities and pulmonary masses or nodules (Table 5).

To establish vasculitis histological diagnosis, the highest yield was obtained with lung (57% positive) and nasal mucosa (47%) biopsies; this last percentage, close to 50%, is higher to those reported in other series, which combined approach, in best case scenario, 25 or 30%. Although paranasal sinuses or nasal mucosa samples are easily accessible and have a wide range of safety, the sensitivity described for biopsies at this level is low. In a previous description of 126 biopsies from 70 patients with GPA, only 16% of upper airway specimens (paranasal sinuses, nose and subglottis) showed the vasculitis-necrosis-granuloma triad[42]. Conversely, lung biopsy is frequently diagnosed in centers with experience and highly skilled pathologists, but it requires an invasive procedure, not always feasible, given the conditions of many patients. In a report of 87 open lung biopsies in 67 patients with GPA, 90% of the specimens had demonstrable vasculitis[28]. In our series, a good alternative to obtain histological confirmation was orbital tissue and the oral cavity.

We recognize some limitations to our study: its retrospective nature, lack of standardized data collection, the fact that many physicians were involved in the care of included patients, including initial diagnostic approach, subsequent assessment for this purpose, definitive diagnostic confirmation, subsequent treatment and, finally, the collection of data during the follow-up. These problems have to be recognized in order to later have them corrected, particularly in a center where the reference bias entails, at least partially, a higher probability of attendance or reference of patients with these conditions, in addition to an inherent responsibility, given the characteristics of the center, of timely diagnosis and treatment to be achieved. In conclusion, this study documents that, in general, AAVs airway manifestations in Mexicans are similar to those described in the literature. Diagnosis remains a challenge. This applies not only to our geopraphic area, where AAVs appear to be less frequent than in others, but also in hospitals without units dedicated to the care of patients with these conditions. Focusing our

Table 5. Comparison of the main clinical manifestations and radiologic findings in several GPA cohorts*

	Current study (n = 74)	Stone et al.[39] (n = 180)	De Souza et al.[10] (n = 134)	Cordier et al[36] (n = 77)	Lohrmann et al.[40] (n = 38)	Lee et al[41] (n = 30)
Ethnicity	Mexican Mestizo	White/African American	Mestizo	Caucasian	Caucasian	Asian
Period	1982-2010	2000-2002	1999-2009	1967-1989	1993-2003	1993-2001
Origin	Mexico	U.S.A.	Brazil	France	Germany	Korea
Center of reference	Pneumology/ Otorhinolaryngology†	Rheumatology‡	Rheumatology/ Pneumology†	Pneumology‡	Rheumatology†	Pneumology†
Dyspnea	40 (54)	–	–	43 (56)	–	4 (13)
Cough	30 (40.5)	–	–	60 (78)	–	15 (50)
Sinusitis	26 (35)	84 (47)	97 (72)	35 (45)	–	–
Nasal congestion	24 (32)	–	–	–	–	11 (37)
Nasal crusting	21 (28)	106 (59)	111 (83)	–	–	–
Purulent rhinorrhea	24 (32)	–	72 (54)	–	–	2 (7)
SGS	23 (31)	21 (11)	15 (11)	2 (2.5)	–	–
Hearing loss	20 (27)	41 (23)	33 (25)	17 (22)	–	–
Epistaxis	16 (22)	–	–	11 (14)	–	–
Rhinitis	15 (20)	–	–	32 (42)	–	–
Otitis	14 (19)	–	23 (17)	24 (31)	–	–
Hemoptisis	13 (18)	–	54 (40)	30 (39)	–	4 (13)
Chest pain	2 (3)	–	–	25 (32)	–	–
Bronchial stenosis	1 (1)	–	–	13 (17)	–	–
Pulmonary infiltrates	16 (22)	52 (29)	43 (32)	41 (53)	9 (24)	7 (23)
Pulmonary nodules or masses	16 (22)	56 (31)	53 (40)	53 (69)	35 (92)	27 (90)
Cavitated nodules	7/16 (43)	–	23/53 (43)	26/53 (49)	–	13/27 (48)
Pleural efussion	2 (3)	–	–	–	5 (13)	–
Pleural opacities	–	–	–	9 (12)	6 (16)	4 (13)
Bronchiectasis	1 (1)	–	–	–	6 (16)	–
Thoracic adenopathy	1 (1)	–	–	1 (1)	5 (13)	–

*Data at diagnosis used for this comparative table. All studies used the ACR classification criteria[13]. The number is shown with percentages in parenthesis.
†Monocenter.
‡Multicenter.

country and Latin America in general, further studies are needed in order to expand the interest, knowledge and skills of clinicians to suspect AAV and, consequently, improve treatment and prognosis for these patients.

References

1. Watts RA, Scott DG. Recent developments in the classification and assessment of vasculitis. Best Pract Res Clin Rheumatol. 2009;23(3): 429-43.
2. Molloy ES, Langford CA. Vasculitis mimics. Curr Opin Rheumatol. 2008;20(1):29-34.
3. Hunder GG, Arend WP, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Introduction. Arthritis Rheum. 1990;33(8):1065-7.
4. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised international chapel hill consensus conference nomenclature of vasculitides. Arthritis Rheum. 2013;65(1):1-11.
5. Khan SA, Subla MR, Behl D, Specks U, Afessa B. Outcome of patients with small-vessel vasculitis admitted to a medical ICU. Chest. 2007;131(4):972-6.
6. Gaffo AL. Diagnostic approach to ANCA-associated vasculitides. Rheum Dis Clin North Am. 2010;36(3):491-506.
7. Flossmann O, Berden A, de Groot K, et al. Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis. 2011;70(3):488-94.
8. Basu N, McClean A, Harper L, et al. The characterisation and determinants of quality of life in ANCA associated vasculitis. Ann Rheum Dis. 2014;73(1):207-11.
9. Flores-Suárez LF, Villa AR. Spectrum of Wegener granulomatosis in a Mexican population. Ann N Y Acad Sci. 2007;1107:400-9.
10. de Souza FH, Radu Halpern AS, Valente Barbas CS, Shinjo SK. Wegener's granulomatosis: experience from a Brazilian tertiary center. Clin Rheumatol. 2010;29(8):855-60.
11. Cisternas M, Soto L, Jacobelli S, et al. Manifestaciones clínicas de la granulomatosis de Wegener y la poliangeítis microscópica en Santiago-Chile , 1990-2001. Rev Med Chile 2005;133: 273-8.
12. Sánchez Torres A, Acevedo Vásquez E, Sánchez Schwartz C, et al. Epidemiología de las vasculitis sistémicas primarias en una población latinoamericana. Reumatología. 2005;21:145-50.
13. Leavitt RY, Fauci AS, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum. 1990;33(8):1101-7.
14. Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum. 1990;33(8): 1094-100.
15. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum. 1994;37(2):187-92.
16. Hellmich B, Flossmann O, Gross WL, et al. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis. 2007;66(5):605-17.
17. de Groot K, Gross WL, Herlyn K, Reinhold-Keller E. Development and validation of a disease extent index for Wegener's granulomatosis. Clin Nephrol. 2001;55(1):31-8.
18. Exley AR, Bacon PA, Luqmani RA, et al. Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. Arthritis Rheum. 1997;40(2): 371-80.
19. Austin JH, Muller NL, Friedman PJ, et al. Glossary of terms for CT of the lungs: recommendations of the Nomenclature Committee of the Fleischner Society. Radiology. 1996;200(2):327-31.
20. Myer CM 3rd, O'Connor DM, Cotton RT. Proposed grading system for subglottic stenosis based on endotracheal tube sizes. Ann Otol Rhinol Laryngol. 1994;103(4 Pt 1):319-23.
21. Charlier C, Henegar C, Launay O, et al. Risk factors for major infections in Wegener granulomatosis: analysis of 113 patients. Ann Rheum Dis. 2009;68(5):658-63.
22. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med. 1992;116(6):488-98.
23. Anderson G, Coles ET, Crane M, et al. Wegener's granuloma. A series of 265 British cases seen between 1975 and 1985. A report by a sub-committee of the British Thoracic Society Research Committee. Q J Med. 1992;83(302):427-38.
24. Hissaria P, Cai FZ, Ahern M, Smith M, Gillis D, Roberts-Thomson P. Wegener's granulomatosis: epidemiological and clinical features in a South Australian study. Intern Med. J 2008;38(10):776-80.
25. Takala JH, Kautiainen H, Malmberg H, Leirisalo-Repo M. Wegener's granulomatosis in Finland in 1981-2000: clinical presentation and diagnostic delay. Scand J Rheumatol. 2008;37(6):435-8.
26. Rao JK, Allen NB, Pincus T.Limitations of the 1990 American College of Rheumatology classification criteria in the diagnosis of vasculitis. Ann Intern Med. 1998;129(5):345-52.
27. Luqmani RA, Suppiah R, Grayson PC, Merkel PA, Watts R. Nomenclature and classification of vasculitis - update on the ACR/EULAR diagnosis and classification of vasculitis study (DCVAS). Clin Exp Immunol. 2011;164 Suppl 1:11-3.
28. Travis WD, Hoffman GS, Leavitt RY, Pass HI, Fauci AS. Surgical pathology of the lung in Wegener's granulomatosis. Review of 87 open lung biopsies from 67 patients. Am J Surg Pathol. 1991;15(4):315-33.
29. Haworth SJ, Savage CO, Carr D, Hughes JM, Rees AJ. Pulmonary haemorrhage complicating Wegener's granulomatosis and microscopic polyarteritis. Br Med J (Clin Res Ed). 1985;290(6484):1775-8.
30. Lauque D, Cadranel J, Lazor R, et al. Microscopic polyangiitis with alveolar hemorrhage. A study of 29 cases and review of the literature. Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). Medicine (Baltimore). 2000;79(4):222-33.
31. Guillevin L, Durand-Gasselin B, Cevallos R, et al. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. Arthritis Rheum. 1999;42(3):421-30.
32. Comarmond C, Pagnoux C, Khellaf M, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. Arthritis Rheum. 2013;65(1):270-81.
33. Green RJ, Ruoss SJ, Kraft SA, Duncan SR, Berry GJ, Raffin TA. Pulmonary capillaritis and alveolar hemorrhage. Update on diagnosis and management. Chest. 1996;110(5):1305-16.
34. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. Medicine. 1999;78(1):26-37.
35. Reinhold-Keller E, Beuge N, Latza U, et al. An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. Arthritis Rheum. 2000;43(5):1021-32.
36. Cordier JF, Valeyre D, Guillevin L, Loire R, Brechot JM. Pulmonary Wegener's granulomatosis. A clinical and imaging study of 77 cases. Chest. 1990;97(4):906-12.
37. Szczeklik W, Sokolowska B, Mastalerz L, et al. Pulmonary findings in Churg-Strauss syndrome in chest X-rays and high resolution computed tomography at the time of initial diagnosis. Clin Rheumatol. 2010; 29(10):1127-34.
38. Homma S, Matsushita H, Nakata K. Pulmonary fibrosis in myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitides. Respirology. 2004;9(2):190-6.
39. Stone JH, Wegener's Granulomatosis Etanercept Trial Research Group. Limited versus severe Wegener's granulomatosis: baseline data on patients in the Wegener's granulomatosis etanercept trial. Arthritis Rheum. 2003;48(8):2299-309.
40. Lohrmann C, Uhl M, Schaefer O, Ghanem N, Kotter E, Langer M. Serial high-resolution computed tomography imaging in patients with Wegener granulomatosis: differentiation between active inflammatory and chronic fibrotic lesions. Acta Radiol. 2005;46(5):484-91.
41. Lee KS, Kim TS, Fujimoto K, et al. Thoracic manifestation of Wegener's granulomatosis: CT findings in 30 patients. Eur Radiol. 2003;13(1):43-51.
42. Devaney KO, Travis WD, Hoffman G, Leavitt R, Lebovics R, Fauci AS. Interpretation of head and neck biopsies in Wegener's granulomatosis. A pathologic study of 126 biopsies in 70 patients. Am J Surg Pathol. 1990;14(6):555-64.