



Severe/uncontrolled asthma and overall survival in atopic patients with eosinophilic granulomatosis with polyangiitis

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ABSTRACT

Background: Although asthma, rhinitis/rhinosinusitis and peripheral eosinophilia are present in virtually all patients with eosinophilic granulomatosis with polyangiitis (EGPA), the role of atopy in these patients is not well defined.

Objective: To clarify the role of atopy in patients affected with EGPA.

Methods: Clinical, laboratory and standard spirometry data have been abstracted from medical records. Only patients who underwent skin and/or specific IgE testing for common aeroallergens before the vasculitic phase were included.

Results: Overall, 33.5% (63) of our patients underwent skin and/or specific IgE testing to aeroallergens. Atopy related to aeroallergens was confirmed in 22.3% (two-third of those tested), and was associated with more severe/uncontrolled asthma ($p < 0.001$), including a greater use of oral glucocorticoids for respiratory manifestations the year before the diagnosis of EGPA ($p = 0.013$). Atopic patients with EGPA had higher total serum IgE levels and less renal disease at EGPA diagnosis compared to non-atopic patients ($p < 0.05$). Among atopic patients, the majority had multiple sensitizations (76%); dust mite and grass pollen were the most common respiratory allergens identified. The number of allergens did not correlate with peripheral eosinophilia, total serum IgE, ESR, or measures of airway obstruction ($p > 0.05$ in all cases). The presence of atopy increased the risk of severe/uncontrolled asthma, but not the risk of severe vasculitis (Five Factor Score ≥ 1). Atopic patients had a better overall survival ($p = 0.027$).

Conclusion: In EGPA, atopy is associated with better prognosis and more severe/uncontrolled asthma manifestations in the year before the development of vasculitis, but not with more severe vasculitis at presentation.

1. Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss syndrome) is a rare systemic vasculitis occurring in patients with asthma and peripheral blood and tissue eosinophilia [1–3]. The clinical spectrum at diagnosis includes asthma and rhinitis, thought to be atopic manifestations, in addition to peripheral neuropathy; ear,

nose, and throat (ENT) involvement; skin lesions; lung infiltrates; and cardiomyopathy [4]. Adult-onset asthma is considered a central feature of EGPA; it is present in virtually all the patients and often requires high doses of oral corticosteroid (OCS) to be controlled [1–3]. However, features and severity of asthma remain understudied in EGPA compared to characterization of vasculitis [1–6].

In EGPA, the link between atopy, asthma and vasculitis is poorly

Abbreviations: ANCA, anti-neutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis with polyangiitis; MPO, myeloperoxidase; AIT, allergen immunotherapy; OCS, oral corticosteroids; ICS, inhaled corticosteroids; LABA, long acting beta-2 agonist; SABA, short acting beta-2 agonist; FEV1, forced expiratory volume in 1 s; FVC, Forced expiratory volume; FFS, Five Factor score; HR, hazard ratio; CI, confidence interval; SD, standard deviation; ACR, American College of Rheumatology; CHCC, Chapel Hill Consensus Conference; ERS/ATS, European Respiratory Society/American Thoracic Society

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understood. Atopy refers to the tendency to develop IgE-mediated diseases, including allergic rhinitis and asthma, which are associated with heightened immune responses to common inhaled allergens [7]. Although many physicians use the term atopy to indicate a generic predisposition to develop an allergic reaction, the demonstration of IgE-mediated sensitivity by means of skin prick test and/or the presence of serum specific IgE identifies those atopic patients with a specific tendency to type I allergic reactions [8]. Atopy is frequently identified in patients with asthma, and has been postulated to play a pathogenic role in the development of EGPA vasculitis, though the data remains unclear [9]. On the other hand, atopy has been shown to be associated with a more severe asthma requiring high-dose controller therapy in large inner-city asthma cohorts [10,11].

Although asthma, rhinosinusitis and peripheral blood hyper-eosinophilia are present in virtually all patients with EGPA during the prodromal phase of the disease, the role of atopy has not been widely explored in this syndrome [12–15]. Indeed, the natural history of EGPA is typically characterized by asthma initially, followed by increased peripheral eosinophil levels, and then vasculitis [16]. As part of the initial asthma work-up, allergy testing may be performed [16]. In this study, we retrospectively assessed the clinical and laboratory differences at diagnosis and overall survival between atopic versus non-atopic patients with EGPA who underwent a respiratory panel skin prick test and/or specific serum IgE detection before the diagnosis of EGPA.

2. Material and methods

2.1. Study design and case ascertainment

Following institutional review board approval, potential subjects were identified by computerized search of the Mayo Clinic Rochester records database from January 1, 1990 to August 1, 2017 to identify patients with EGPA, who had consented to review of their records. This study included only patients with EGPA who underwent allergy investigations (skin prick test or specific IgE panels) (Fig. 1). Patients had to meet the criteria of at least one of three EGPA classification schemes: American College of Rheumatology (ACR) classification criteria [17], Chapel Hill Consensus Conference (CHCC) definition [1], or Lanham criteria [13]. Subjects were classified as either atopic or non-atopic according to international guidelines [7]. Patients diagnosed or treated

for allergic bronchopulmonary aspergillosis were excluded.

All individual medical records from identified patients were reviewed. Information on patient demographics, clinical manifestations, laboratory findings, histopathology, standard spirometry, allergy testing, radiology, and disease activity at baseline were retrieved. Manifestations at diagnosis were based on the treating physician's documentation. Laboratory findings at initial presentation at our institution were collected, using the data from testing closest to EGPA diagnosis but prior to initiation of treatment. Hyper-eosinophilia was defined as $> 10\%$ of the total white blood cell count and/or an absolute number of > 1500 cells/ μL . The date of first diagnosis was collected and all patients followed-up until August 1, 2017, or death. Patients were treated according to clinical need assessed by the treating physician, as already published by this group [3]. The study was approved by the institutional review board of Mayo Clinic, Rochester (MN).

2.2. Atopy definition

Atopic patients were defined as having a personal history of respiratory type I allergy as reported by an expert (Allergist/Immunologist or Pulmonologist) and at least one positive skin prick and/or specific serum IgE test result. Skin prick tests and serum specific IgE were performed for the most common indoor and outdoor allergens (grass pollen, trees, molds [*Alternaria tenuis*, *Aspergillus fumigatus*], dust mite [*Dermatophagoides farina*, *Dermatophagoides pteronyssinus*], ragweed [giant/short], cat hair, dog epithelium, horse epithelium, cockroach [German/American], mouse epithelium). Allergen sensitization was defined by a wheal at least 3 mm larger than that elicited by the glycerine control in the presence of a positive histamine control wheal or a specific IgE level of 0.35 kU/L or greater. All the patients withdrew the anti-histamine therapy at least 3 days before the date of skin prick testing, and none received daily glucocorticoid dose ≥ 10 mg at that time.

Non-atopic subjects were defined as those with negative skin or specific serum IgE testing. High total IgE and peripheral eosinophil levels were not considered surrogates for atopy, nor was drug hypersensitivity.

2.3. Severe/uncontrolled asthma and severe vasculitis definitions

The definition for severe/uncontrolled asthma was modified from the ERS/ATS (European Respiratory Society/American Thoracic Society) guidelines [18]. We thus defined severe/uncontrolled asthma as treatment as requiring either 1/continuous or near-continuous ($\geq 50\%$ of year) OCS or 2/high-dose inhaled corticosteroids and 2 of the following: an additional daily controller medication), asthma symptoms requiring SABA on daily or near daily basis, persistent airway obstruction ($\text{FEV1} < 80\%$ predicted, diurnal peak expiratory flow, variability $> 20\%$) one or more urgent care visits for asthma per year three or more OCS burst per year prompt deterioration with less than 25% reduction in OCS or ICS near fatal asthma event. Asthma assessment and pulmonary function tests (PFT) referred to the closest visit/PFT during the year before the diagnosis of EGPA vasculitis.

Data required to compute Five Factor score (FFS) [19] at EGPA diagnosis were also abstracted from the medical records. Vasculitis assessed at EGPA diagnosis was defined severe if FFS scored equal or greater than 1, according to what previously published [19].

2.4. Statistical analysis

Data are presented as means (SD) if normally distributed, or medians with interquartile range (IQR) if skewed. Statistical procedures included simple correlation analysis (Spearman's correlation), two-tailed Fisher exact test or chi-squared test for binary variables, as appropriate, and Mann-Whitney test for continuous variables.

Survival following the diagnosis of EGPA among patients with and

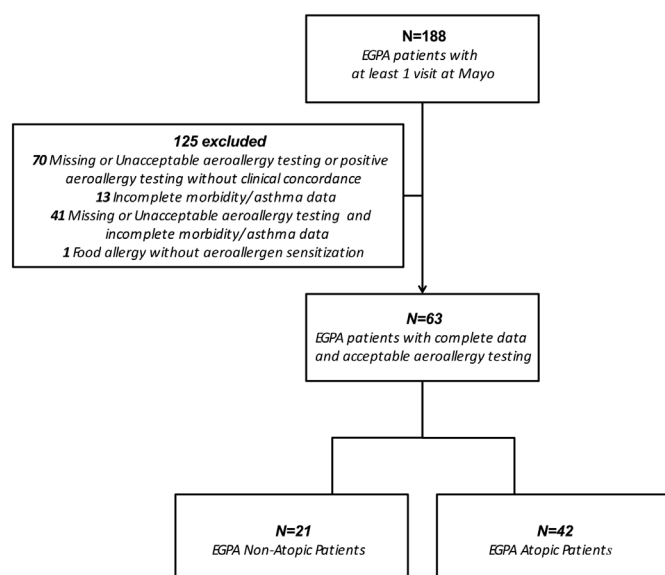


Fig. 1. Selection of participants for evaluation and skin and/or specific IgE testing to aeroallergens.

Table 1

Features of the studied patients by presence of atopy, collected at the time of Eosinophilic Granulomatosis with Polyangiitis diagnosis.

Characteristic	Non-Atopic (N = 21)	Atopic (N = 42)	Total (N = 63)	p value
Age, years, mean(SD)	48.1 (3.7)	47.3(2.6)	47.6 (16.9)	0.754
Sex, female	11/21 (52%)	20/42 (48%)	31/63 (49%)	0.793
Ethnicity, Caucasian†	21/21 (100%)	41/42 (98%)	62/63 (98%)	1.000
Active or former smokers, n (%)	7/21 (33%)	16/42 (38%)	23/63 (37%)	0.786
Gastroesophageal reflux, n (%)	3/20 (15%)	7/36 (19%)	10/56 (18%)	1.000
BMI, kg/m ² , mean (SD)	25.39 (5.86)	25.70 (6.38)	25.59 (6.15)	0.867
Obesity, (BMI ≥ 30 kg/m ²)	3/18 (17%)	5/34 (15%)	8/52 (15%)	1.000
Clinical manifestation EGPA				
Ear, Nose and Throat	20/21 (95%)	38/42 (90%)	58/63 (92%)	0.657
Peripheral Nervous System	14/21 (67%)	26/41 (63%)	40 (63%)	1.000
Central Nervous System	2/21(10%)	4/42 (10%)	6/63 (10%)	1.000
Skin	12/21 (57%)	22/42 (53%)	29/62 (54%)	0.793
Heart	3/21 (14%)	6/42 (14%)	9/63 (14%)	1.000
Renal	7/21 (33%)	4/42 (10%)	11/63 (17%)	0.032
Chest abnormalities at X ray or CT scan*	13/21 (62%)	30/42 (71%)	43/63 (68%)	0.567
Pulmonary Infiltrate	12/21 (57%)	26/41 (63%)	38/62 (61%)	0.784
Pleural Effusion	5/21 (24%)	10/34 (29%)	15/55 (27%)	0.761
Diffuse Alveolar Hemorrhage	1/21 (5%)	1/42 (2%)	2/63 (3%)	1.000
Gastrointestinal	6/21 (29%)	11/42 (26%)	17/63 (27%)	1.000
Joints	5/21 (24%)	10/42 (24%)	15/63 (24%)	1.000
Rhinitis/rhinosinusitis, n (%)	20/21 (95%)	38/42 (93%)	58/63 (92%)	1.000
Delay between rhinitis/rhinosinusitis and EGPA diagnosis, median, years	4.7 [2.0–17.9]	9.0 (2.8–14.2)	8.0 [2.6–14.1]	0.354
Sinus surgery, n (%)	12/21 (57%)	22/39 (56%)	51/60 (85%)	1.000
Asthma, n (%)	21/21 (100%)	42/42 (100%)	63/63 (100%)	1.000
Delay between asthma and EGPA diagnosis, median, years	3.0 [1.3–5.0]	6.0 [2.0–14.1]	3.0 [1.9–13.3]	0.127
Biopsy, performed, n (%)	20/21(95%)	34/41(83%)	54/62 (87%)	0.247
Biopsy, positive, n (%)	14/20 (70%)	25/34 (74%)	39/54 (72%)	1.000
Lung, n (%)	3/20 (15%)	7/34 (21%)	10/54 (19%)	0.728
Kidney, n (%)	1/20 (5%)	2/34 (6%)	3/54 (6%)	1.000
Heart, n (%)	2/20 (10%)	1/34 (3%)	3/54 (6%)	0.548
Sural nerve, n (%)	1/20 (5%)	7/34 (21%)	8/54 (15%)	0.233
Skin, n (%)	8/20 (40%)	14/34 (42%)	22/54 (40%)	1.000
Others, n (%)**	3/20 (15%)	5/34 (15%)	8/54 (15%)	1.000
FFS ≥ 1, n (%)	10/21 (52%)	9/40 (23%)	19/61 (31%)	0.079
Positive p-ANCA/MPO-ANCA, n (%)	7 (33%)	14 (56%)	21/59	1.000
Eosinophils peak median, cells/10 ⁹ /L	3.53 [2.14–6.80]	5.65 [2.03–17.48]	4.50 [2.14–11.21]	0.172
ESR, median, mm/h	22 [8, 54]	22 [10, 60]	22 [9, 58]	0.916
Total serum IgE, IU/mL	55.4 [13.5–178.3]	185.5 [79.7–596.0]	160 [49.6–584.5]	0.035

Continuous variables were compared between groups using Mann-Whitney *U* test or Student's *t*-test. Categorical variables were compared between groups using Fisher's exact test.

†All but one patient (Hispanic) were Caucasian.

SD: standard deviation, EGPA: eosinophilic granulomatosis with polyangiitis; p-ANCA/MPO-ANCA: perinuclear anti-neutrophil cytoplasmic antibody/myeloperoxidase anti-neutrophil cytoplasmic antibody; FFS: Five Factor score; ESR: erythrocyte sedimentation rate.

*Chest abnormalities on imaging: ground-glass opacities and consolidations, pulmonary infiltrates, pulmonary nodules and micronodules, interlobular septal thickening; bronchial wall thickening and/or bronchial dilatation; diffuse alveolar hemorrhage.

**Other sites of biopsy (equal or less than 2 patients each): gastrointestinal tract, paranasal sinuses, bladder, testes, muscles.

without atopy was estimated using Kaplan-Meier methods. Survival rates between groups were compared using the Log-rank test. Cox regression models were used to adjust the relation between atopy and outcome for patient's age and sex. P values from Cox regression models were computed using the likelihood ratio test.

Analyses were performed using JMP, version 4.0 (SAS Institute Inc., Cary, North Carolina). P values < 0.05 were considered significant.

3. Results

3.1. Prevalence of atopy

Overall, 33.5% of the Mayo cohort of EGPA patients underwent skin and/or specific IgE testing to aeroallergens (Fig. 1). Sixty-three patients with EGPA were included, with a mean age of 47.6 (± 16.9); 49% female, and 98% Caucasian. Clinical and laboratory characteristics are summarized in Table 1. Skin prick tests and specific IgE determinations were performed in 56 and 18 patients, respectively; both skin prick and specific IgE testing was performed in 11.

A respiratory atopic background was identified in 22.3% of

patients (n = 42, two third of those tested), while asthma was present in 100% and rhinitis/rhinosinusitis in 92%.

3.2. Clinical manifestations

The spectrum of organ involvement at the time of diagnosis of vasculitis was similar in atopic and non-atopic patients, except renal involvement was more frequent in non-atopic patients (33% versus 10%) (Table 1). Sixty-three patients were on oral corticosteroids in the year before their diagnosis of vasculitis (76% in the atopic group and 43% in the non-atopic group p = 0.013). No patients were on immunosuppressants. The prevalence of rhinitis/rhinosinusitis and asthma were similar in the two groups. Approximately half of the patients with rhinosinusitis underwent surgery to control nasal polyposis, with similar proportions in both atopic and non-atopic patients. Although atopy tended to be associated with a longer history of rhinitis/rhinosinusitis and asthma before the diagnosis of EGPA, the delay between diagnosis of rhinitis/rhinosinusitis or asthma and the diagnosis of vasculitis did not differ between groups (p = 0.354 and p = 0.127, respectively). No difference in chest abnormalities at imaging at the

time of diagnosis was observed between atopic and non-atopic patients, and only two patients had documented diffuse alveolar hemorrhage at presentation, one in each group. Prior corticosteroid use did not correlate with the presence or absence of pulmonary infiltrates. The majority of the patients underwent to organ biopsy, with the histological confirmation of EGPA diagnosis in about 72% of patients, with no difference between the two groups in the overall incidence of diagnosis and by single organs.

Incidence of obesity, smoking status, gastrointestinal reflux, and asthma flare before the diagnosis of EGPA was similar in the two groups (Supplementary Table 1).

Elevated p-ANCA detected by immunofluorescence and/or MPO-ANCA detected by ELISA was noted in 36% and peripheral blood eosinophilia in 100% of the overall cohort, without difference between the two groups. Serum IgE levels were elevated in the whole cohort at 160 IU/mL [49.6–584.5] (normal < 100IU/mL), but significantly more so in the atopic group at 185.5IU/mL (versus 55.4IU/mL in the non-atopic group) ($p = 0.035$) (Table 1, Supplementary Fig. 1).

3.3. Pulmonary function tests, asthma severity and respiratory treatment

While there was no statistically significant difference in the FEV1/FVC (Forced expiratory volume in the first second/Forced vital capacity) and FEV1 between atopic and non-atopic patients in pulmonary function tests performed during the year preceding the diagnosis of EGPA (Table 2, Supplementary Fig. 1, Supplementary Table 1), severe/uncontrolled asthma was much more frequent in atopic patients (74%) compared to non-atopic patients (24%, $p < 0.001$). Seven and four patients in the atopic group received specific allergen immunotherapy and omalizumab, respectively. None of the patients received any immunosuppressive therapy other than OCS during the year before the diagnosis of vasculitis. One or more hypersensitivity reactions to drugs were reported in more than 50% in both groups ($p = 0.429$).

In the year preceding the diagnosis of EGPA, the numbers on inhaler therapy for asthma were similar for the two groups, but the use of OCS for respiratory symptoms was significantly higher in the atopic subset 76% versus 43% ($p = 0.013$), although the mean dosage of OCS did not significantly changed between the two groups.

3.4. Sensitization to aeroallergens and its relation to asthma and vasculitis

Skin testing and allergen-specific IgE evaluation demonstrated sensitization to multiple antigens in the majority of the atopic subset (76% of patients with ≥ 2 allergens) (Fig. 2). The most common allergens were dust mite and grass pollen (both detected in 24), then trees, mold, ragweed and cat dander. Among atopic patients, those with severe asthma were not sensitized to a higher number of allergens ($p > 0.05$) (Fig. 2). The number of allergens did not correlate with peripheral eosinophilia, total serum IgE, ESR, or measures of airway obstruction ($p > 0.05$ in all cases) (Supplementary Fig. 2).

The presence of atopy increased the risk of severe/uncontrolled asthma (by 20 fold in atopic EGPA patients with at least 1 positive aeroallergen), but not the risk of severe vasculitis (defined as Five Factor Score ≥ 1) [19] at univariate analysis (Table 3). The risk of severe/uncontrolled asthma remained higher in atopic patients also when atopy group was defined by ≥ 2 , ≥ 3 , or ≥ 4 positive aeroallergens (Table 3).

3.5. Atopy and overall survival

At last follow-up (median 55 months, 25%–75% IQR 19–136 months), we registered six deaths (10% of the cohort), two in the atopic group and four in the non-atopic group. Overall, the survival rate of this cohort was 98.4% at 12 months, 96.8% at 24 months and 95.2% at 60 months. The cause of death was only available in three patients, all of whom died of non-inflammatory cardiovascular artery disease (none of

Table 2

Features of the studied patients by presence of atopy, collected the year before the Eosinophilic Granulomatosis with Polyangiitis diagnosis.

Characteristic	Non-Atopic (N = 21)	Atopic (N = 42)	Total (N = 63)	p value
Severe/uncontrolled Asthma*	5/21 (24%)	31/42 (74%)	36/63 (57%)	< 0.001
Pulmonary Function Tests				
FEV1/FVC, value	67.1 (3.5)	66.2 (2.1)	66.5 (11.5)	0.834
FEV1, value	2.3 (0.5)	2.5 (1.1)	2.5 (1.0)	0.491
FEV1, %	76.3 (18.9)	74.4 (35.4)	74.9 (24.0)	0.821
Respiratory Therapy				
Daily OCS, n (%)	9/21 (43%)	32/42 (76%)	41/63 (65%)	0.013
Daily ICS, n (%)	17/21 (81%)	29/42 (69%)	46/63 (63%)	0.380
Daily LABA, n (%)	9/21 (31%)	21/40 (52%)	30/61 (49%)	0.592
≥ 1 times/week	17/21 (81%)	30/41 (73%)	47/62 (76%)	0.550
SABA, n (%)				
Previous/current Immunotherapy, n (%)**	0/21 (0%)	7/42 (17%)	7/63 (11%)	0.041
Previous/Current Omalizumab, n (%)**	0/21 (0%)	4/35 (11%)	4/56 (7%)	0.287
Previous/current drug hypersensitivity, n (%)**	13/21 (62%)	21/42 (50%)	34/63 (54%)	0.429

Continuous variables were compared between groups using Mann-Whitney U test or Student's t-test. Categorical variables were compared between groups using Fisher's exact test.

OCS: oral corticosteroids, ICS: inhaled corticosteroids, LABA: long acting beta2 agonist, SABA: short acting beta2 agonist, FEV1: forced expiratory volume in 1 s. FVC: Forced expiratory volume.

#Modified definition of severe/uncontrolled asthma from ERS/ATS (European Respiratory Society/American Thoracic Society) guidelines [14]: the latest definition for severe asthma was not applicable as Asthma Control Questionnaire and the Asthma Control Test scores were not systematically collected in patients during the visit. We thus defined severe asthma as treatment with continuous or near-continuous ($\geq 50\%$ of year) oral corticosteroid (major criteria) and/or requirement for treatment with high-dose inhaled corticosteroids (major criteria) and/or requirement for additionally daily treatment with a controller medication (minor criteria), asthma symptoms requiring SABA on daily or near daily basis (minor criteria), persistent airway obstruction (FEV1 < 80% predicted, diurnal peak expiratory flow, variability > 20%) (minor criteria), one or more urgent care visits for asthma per year (minor criteria), three or more OCS burst per year (minor criteria), prompt deterioration with less than 25% reduction in OCS or ICS (minor criteria), near fatal asthma event (minor criteria). One or two major criteria and at least two minor criteria are required.

**these data refers not only to the year before EGPA diagnosis, but to the past medical history of the patient before EGPA diagnosis.

these patients had a documented myocarditis, and none had active vasculitic disease at the time of death (Supplementary Table 2 for more details).

Treatment approach of vasculitis was the same in all patients during the follow-up; the use of cyclophosphamide and other disease modifying immunosuppressants was reserved for more severe cases, and OCS were reduced to the lowest dosage as soon as possible. All the patients with a FFS ≥ 1 at diagnosis were treated adding cyclophosphamide or another immune suppressants, while for patients with FFS = 0 patients were treated with only corticosteroids (33%) or adding immune suppressants (67%). Treatments were similar in the two groups ($p > 0.05$ for all comparisons): oral and/or intravenous glucocorticoids were used in all patients; oral cyclophosphamide was used in 6 (29%) patients in the non-atopic group and in 8 (19%) in the atopic group; rituximab was used in 1 patient in each group (5% and 2% respectively); azathioprine in 9 (43%) and 14 (33%) of non-atopic and atopic patients, respectively; methotrexate in 5 (24%) and 11 (26%) of non-atopic and atopic patients, respectively. Mycophenolate mofetil

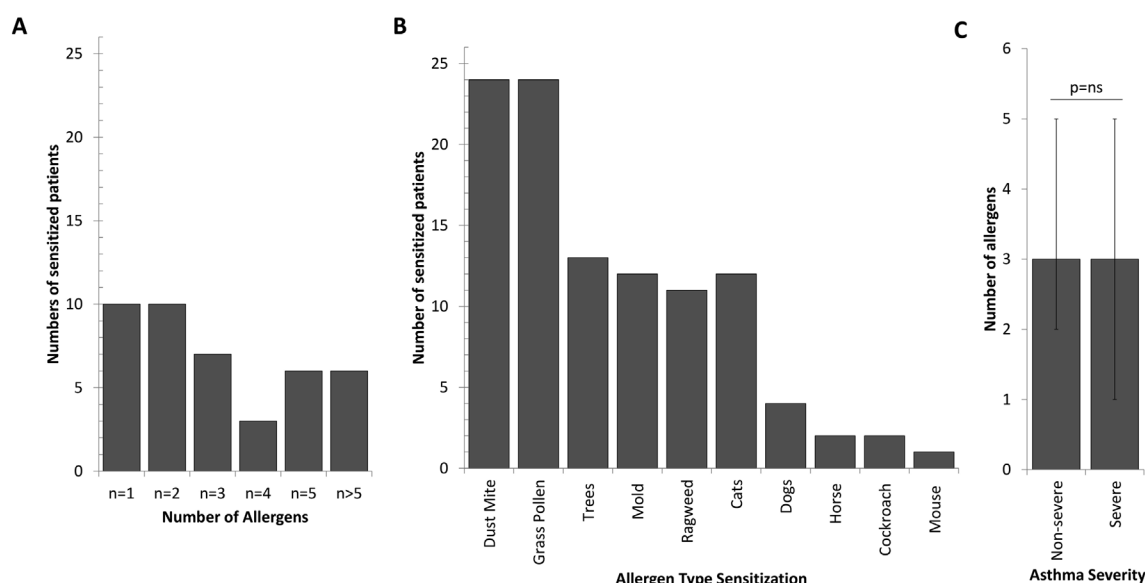


Fig. 2. Sensitization profile of atopic patients with eosinophilic granulomatosis with polyangiitis (n = 42). (A) Number of patients by number of allergen sensitization. (B) Number of patients by allergens type. (C) Number of allergens in patients severe/uncontrolled asthma versus non-severe/controlled at diagnosis.

and hydroxyurea were both used in 1 (5%) patient in non-atopic group and 2 (5%) patients in atopic group (both 5%); 6-mercaptopurine was used in 1 (5%) patients in the non-atopic group and interferon-alpha in 2 (5%) patients in atopic group. Mepolizumab was used in 1 patient in each group (5% and 2% respectively).

Atopy detected before the diagnosis of EGPA portended a better overall prognosis after adjustment for age and sex, and significantly associated with better patient survival (Log rank test $p = 0.027$) (Fig. 3).

4. Discussion

Our findings show that atopy, considered as the demonstration of skin and/or specific IgE to aeroallergens consistent with the clinical history of the patient, is associated with more severe/uncontrolled asthma in EGPA, including increased use of OCS for respiratory symptoms, the year before the diagnosis of vasculitis. The majority of atopic patients with EGPA have multiple sensitizations as opposed to a single sensitization. Atopic patients with EGPA also have higher serum IgE levels and less vasculitic renal disease at EGPA diagnosis versus

non-atopic patients. A better overall survival was observed in atopic patients compared to non-atopic. According to what previously published [12,20], atopy was eventually confirmed in a minority of the EGPA patients followed-up at Mayo (approximately 22%).

Asthma is one of the main clinical challenges of EGPA, usually predating the vasculitic phase by several years [4,16,20]. In our cohort, 57% had severe/uncontrolled asthma at diagnosis, similar to what has been previously reported [20,21]. Here we demonstrate that asthma was worst in atopic patients. This finding suggests that the presence of atopy could predispose to severe asthma, regardless of the pathogenic implication that the underlying atopic condition may or may not have for EGPA development. The clinical relevance of this is that primary allergic sensitization to aeroallergens in patients who subsequently develop vasculitis increases the likelihood of severe/difficult-to-control asthma. Consequently, in order to achieve better control of asthma, avoidance of aeroallergens and optimal allergy management should be an important focus of the clinical management of patients with EGPA.

A minority of the patients received allergen immunotherapy (AIT) or omalizumab before the onset of overt vasculitis. Omalizumab may have a corticosteroid-sparing effect in EGPA patients with asthmatic

Table 3

Odds ratios for aeroallergens sensitization, risk of severe/uncontrolled asthma and risk of severe vasculitis in patients with EGPA.

Variables	Severe/Uncontrolled Asthma ^a		Severe Vasculitis (FFS ≥ 1) ^a	
	Odds Ratio (95% CI)	p value	Odds Ratio (95% CI)	p value
Atopy status at index date				
≥ 1 aeroallergens (versus no sensitization)	20.78 (4.96–86.97)	< 0.001	0.38 (0.12–1.18)	0.139
≥ 2 aeroallergens (versus no sensitization)	14.87 (3.41–64.88)	< 0.001	0.39 (0.11–1.32)	0.215
≥ 3 aeroallergens (versus no sensitization)	15.11 (3.22–70.83)	< 0.001	0.36 (0.10–1.36)	0.192
≥ 4 aeroallergens (versus no sensitization)	11.33 (3.04–63.08)	0.006	0.24 (0.04–1.41)	0.139

^a Two separate outcomes were considered: the risk of severe/uncontrolled asthma as defined by ATS/ERS guidelines and the risk of severe vasculitis as defined by Five Factor Score (FFS) ≥ 1 . Separate analyses were performed, considering atopy as having ≥ 1 positive aeroallergens (versus no sensitization), ≥ 2 positive aeroallergens (versus no sensitization), ≥ 3 positive aeroallergens (versus no sensitization), and ≥ 4 positive aeroallergens (versus no sensitization) and a positive patient history consistent with allergy testing. Modified definition of severe/uncontrolled asthma from ERS/ATS (European Respiratory Society/American Thoracic Society) guidelines¹⁴: the latest definition for severe asthma was not applicable as Asthma Control Questionnaire and the Asthma Control Test scores were not systematically collected in patients during the visit. We thus defined severe asthma as treatment with continuous or near-continuous ($\geq 50\%$ of year) oral corticosteroid (major criteria) and/or requirement for treatment with high-dose inhaled corticosteroids (major criteria) and/or requirement for additionally daily treatment with a controller medication (minor criteria), asthma symptoms requiring SABA on daily or near daily basis (minor criteria), persistent airway obstruction (FEV1 < 80% predicted, diurnal peak expiratory flow, variability > 20%) (minor criteria), one or more urgent care visits for asthma per year (minor criteria), three or more OCS burst per year (minor criteria), prompt deterioration with less than 25% reduction in OCS or ICS (minor criteria), near fatal asthma event (minor criteria). One or two major criteria and at least two minor criteria are required.

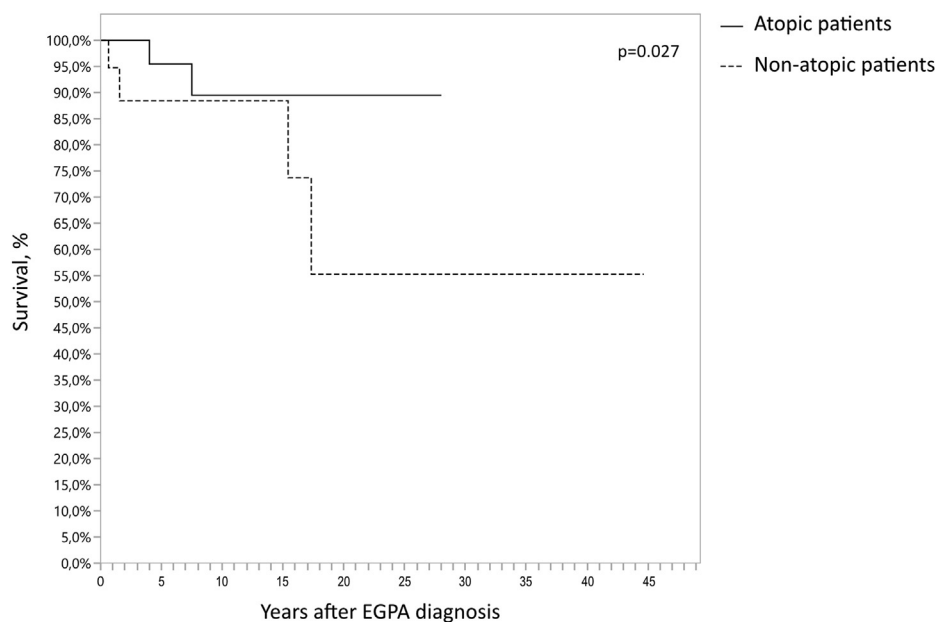


Fig. 3. Age- and sex-adjusted patient survival by presence of atopy. Atopic patients with EGPA ($n = 42$; solid line) compared with non-atopic ones ($n = 21$; dashed line). Hazard ratio for atopy 0.12, 95%CI: 0.01–0.79, $p = 0.027$ adjusted for age and sex.

and/or sinonasal manifestations [22,23], but reducing the glucocorticoid dose may also increase the risk of severe vasculitis flares, which raises the question of the safety of omalizumab in patients with EGPA. However, there is no formal evidence that the severity of asthma in EGPA can be influenced by this treatment or by AIT as for allergic asthma [24]. These treatments are a flag of allergic asthma: all of the patients in our cohort treated with one of these agents, in fact, belong to the atopic group and were treated with omalizumab or AIT because of the subtle allergic respiratory condition. Accordingly, higher levels of total serum IgE have been found in atopic compared to non-atopic patients. Our findings thus confirm the previous study reporting an higher levels of total IgE in allergic patients with EGPA [12]. Interestingly, non-atopic patients in our cohort had a higher prevalence of renal involvement than their atopic counterparts. The significance of this observation is unclear and needs to be validated in a larger cohort of patients.

In this paper we provided an allergenic sensitization profile of the atopic patients affected by EGPA and showed that the majority of patients are poly-sensitized. In agreement with a previous retrospective study of Bottero et al., dust mite was the most frequent antigens found positive in EGPA patients [12], but our findings showed that grass pollen sensitization was also commonly found in these patients, followed by trees and molds. Ragweed pollen, which was responsible of 25% of seasonal worsening of respiratory symptoms in a previous Italian cohort of EGPA patients [12], was found to be positive in 17% of our patients. This result may also be explained by a spread of short ragweed in Southern Europe in the last decades [25], compared to the United States [26]. In distinction to other studies of allergic asthma [10,11], in this cohort of asthmatic EGPA patients, having multiple sensitizations did not correlate with asthma severity, and just the presence of atopy increased the risk of severe/uncontrolled asthma. This may probably reflect the different pathogenic mechanisms existing in allergic asthma and asthma occurring in EGPA patients. Furthermore, our findings clearly showed that atopy have an independent course from vasculitis severity in EGPA. This observation further defines the role atopy in EGPA, which is linked to asthma but not to vasculitis, likely being one of the mechanisms triggering asthma exacerbation and/or supporting persistent airways inflammation. Although the observed discrepancies between atopic and non-atopic EGPA patients deserve confirmation in larger cohorts, our results differ from previous

studies describing the prevalence of atopy in EGPA without any implication on asthma and vasculitis severity [12,14,15,20].

In this cohort, non-atopic patients with EGPA had a worse overall survival. A positive history for atopy may be useful to identify a subset of patients with a better outcome. To date, a comprehensive tool called FFS has been proposed to evaluate the prognosis and guide therapy of ANCA-associated vasculitis (including EGPA) [19]. Atopy is not included in this score, and might have a role in further defining the risk stratification for EGPA. This observation, even with its limitations inherent to the retrospective nature of the investigations, the relatively small number of events (death) and patients for this analysis, integrates well with the significant association of atopy with severe/uncontrolled asthma and the lack of association with severe vasculitis. In other words, the atopic subset of patients with EGPA has worse asthma but a better survival compared to non-atopic patients with EGPA. This may be consistent with a more Th2-oriented immune profile of atopic patients with EGPA compared to non-atopic ones, with the immune system being directed more towards an allergic rather than inflammatory response [8,27]. On the other hand, the higher proportion of patients taking OCS in order to control asthma before EGPA diagnosis might have dampened the inflammatory response toward a less aggressive EGPA, or perhaps atopy condition may have induced the patients to seek medical attention more frequently, leading to a closer medical follow-up which might have contributed to a better monitoring of the general health status of the patients affected.

This study has strengths and limitations. The limitations include its retrospective nature: clinical information was not systematically obtained by the treating physicians following an established protocol. However, this is a monocentric cohort, and patients with EGPA are principally managed by pulmonologists and or allergists/immunologists. This potentially allows for more robust data collection and a harmonization of the standard clinical management of patients' asthma and atopy. We selected only those patients who underwent a complete allergy evaluation and testing, thus allowing a reliable estimation of the role of atopy in EGPA. On the other hand, only a minority of EGPA patients of our cohort could have been included; ascertainment bias, classification error, survivor treatment selection and other biases cannot be completely excluded. However, the results reflect a real life setting of this specific subset of patients and therefore should have relevance for routine patient care.

We acknowledge that our study may be underpowered to detect prognostic differences between small subsets defined by the presence of atopy. However, despite this limited statistical power, atopy gave a positive signal of effect to predict survival, thus suggesting its potential utility. Because this study is based on retrospective review of data recorded in the clinical record and we focused only of those patients who underwent to a complete allergy visit and testing, we might involuntarily have selected a particular subset of patients. In fact, allergy testing is usually performed only in those patients who have allergic symptoms. If we would have included the other patients of our cohort not tested for atopy in the “non-atopic” group, for instance, assuming that no allergy tests means no allergy symptoms (and thus no indication to allergy testing), the survival analysis would have been extremely significant in favor of atopy (i.e. 2 deaths in atopic group versus 19 deaths in non-atopic group). However, our choice reflects a *real life* setting (in particular that one seen more frequently by allergists and pulmonologists than by nephrologist or rheumatologists) and therefore should have relevance for routine patient care. Future studies with more comprehensive data related to aeroallergen sensitization in larger populations are needed to confirm the significance of atopy in EGPA suggested by our observations.

Moreover, all the data about allergy and asthma were collected before the vasculitis onset, without the possibility of any interference of immunosuppressive therapy on the OCS dose, nor the possibility to receive OCS for different reasons than asthma. We could not completely exclude that OCS *per se*, and not atopy, might be the reason why our findings did show that atopy may not prevent a more severe vasculitis. Future studies will clarify this point.

Finally, the patients included in this study were predominantly white; therefore, one should be cautious when generalizing the present findings to other ethnic groups or study settings.

In conclusion, our report demonstrates that in EGPA, atopy is associated with more severe/uncontrolled asthma manifestations in the year before the development of vasculitis, but not with more severe vasculitis. The atopic subset of patients with EGPA has a better overall survival compared to non-atopic patients. Clinicians should be aware of these findings, in order to investigate the history of atopy in patients with EGPA. Further studies are needed to assess whether atopy can identify individuals who will have more severe asthma throughout the course of their disease.

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Disclosure statement for all authors

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.rmed.2018.07.017>.

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