Childhood-onset Eosinophilic Granulomatosis with Polyangiitis (formerly Churg-Strauss Syndrome): A Contemporary Single-center Cohort

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ABSTRACT. ***Objective.*** To date only 38 cases of childhood-onset eosinophilic granulomatosis with polyangiitis (cEGPA; formerly Churg-Strauss syndrome) have been reported. Additional patients with cEGPA could enhance the understanding of this rare and life-threatening condition. Our objectives were (1) to determine the frequency of specific organ system involvement; (2) to examine initial therapeutic regimen; and (3) to document disease and therapy-related morbidity in a contemporary cohort of patients with cEGPA.

Methods. Retrospective review of patients evaluated at the Cleveland Clinic between 2003 and 2011 who met either American College of Rheumatology or Lanham criteria for EGPA and whose age was < 18 years at symptom onset.

Results. Nine patients (8 female; 7 white) were identified. Median age at onset of rhinitis/asthma symptom was 13 years and median age at diagnosis of cEGPA was 15 years. All patients demonstrated eosinophilia, upper airway disease (allergic rhinitis, chronic sinusitis, and/or nasal polyps), and pulmonary involvement. Other frequently involved organ systems included musculoskeletal (67%), gastrointestinal (67%), cutaneous (67%), neurologic (56%), and cardiac (44%). Antineutrophil cytoplasmic antibody (ANCA) serologies were negative in all patients. The medications used most frequently for initial therapy included oral (44%) or intravenous corticosteroids (56%) and azathioprine (67%). Disease or therapeutic complications occurred in half of the cohort and included heart failure, stroke, and sequela from longterm, high-dose steroids.

Conclusion. Eosinophilia, in combination with upper airway, pulmonary, musculoskeletal, neurologic, and cardiac manifestations, is frequently observed in cEGPA. ANCA titers are often negative. Steroids are the mainstay of initial therapy but steroid-related side effects occur regularly. (First Release May 1 2013; J Rheumatol 2013;40:929–35; doi:10.3899/jrheum.120808)

Key Indexing Terms:
EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS
CHURG-STRAUSS SYNDROME
COHORT STUDY
PEDIATRIC VASCULITIS
ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, is a rare systemic necrotizing vasculitis with a prevalence of 10 to 13 patients per million people[1,2,3]. Classically, EGPA has been characterized as a triphasic illness with an initial prodrome of asthmatic and allergic rhinitis symptoms. These early atopic manifestations are followed by a period of peripheral hypereosinophilia, accumulation of extravascular eosinophils, and a final stage of systemic vasculitis[4]. Histological characteristics of the vasculitis include extravascular eosinophils, granuloma formation, and necrotizing changes in the small and medium-size vessels. Extrapulmonary involvement is common, with cutaneous, cardiac, and gastrointestinal (GI) manifestations often observed. In adult cohorts, the prevalence of antineutrophil cytoplasmic antibody (ANCA) present on serologic testing is variable, ranging from 40% to 78%[5,6]. The American College of Rheumatology (ACR) 1990 classification criteria for EGPA require that patients have 4 out of 6 of the following clinical findings: asthma, eosinophilia, mononeuropathy (including multiplex) or polyneuropathy, non-fixed pulmonary infiltrates on roentgenography, paranasal sinus abnormality, and biopsy containing a blood vessel with extravascular eosinophils[7]. Similarly, patients classified with EGPA according to Lanham criteria must have the 3 following criteria: asthma, peak peripheral blood eosinophil counts > 1.5×10^9/l, and systemic vasculitis involving 2 or more

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Accepted for publication February 4, 2013.

extrapulmonary organs[8]. Historically, treatment has been dependent on systemic corticosteroids and immunosuppressives, yet empirically the steroid-sparing agents typically effective in other forms of systemic vasculitis demonstrate lower rates of efficacy in EGPA.

EGPA is uncommon in childhood. An examination of large contemporary databases reveals childhood-onset EGPA (cEGPA) accounts for less than 2% of all cases of pediatric vasculitis (CARRANet, ARChiVe unpublished data). Only 38 cases of cEGPA have been published, with most reports detailing experience with a single patient[9,10,11,12,13,14]. It is suspected that children with EGPA are less likely than adult patients to have positive ANCA titers, more likely to have pulmonary involvement, and suffer higher mortality rates[9]. However, conclusions drawn from these retrospective reports collected over the last 6 decades are potentially biased because of small patient numbers, non-uniform reporting of data elements, changes in diagnostic technologies over time, and advancements in treatment options. As an example, only 12 of the 33 patients in a review by Zwerina, *et al* had documented ANCA testing[9], likely because ANCA testing by immunofluorescence was not available until 1989[5], and their review covered case reports from 1951 until 2007. A contemporary review of cEGPA could be beneficial, given the heterogeneity of previous clinical data, lengthy timespan over which prior cases have been reported, and limited provider experience with cEGPA.

The primary goal of our study was to report the clinical characteristics of a cohort of patients with cEGPA evaluated at a single center since 2003. We examined the frequency of organ system involvement using contemporary diagnostic technologies. Secondary goals included determination of initial immunosuppressive regimens and documentation of disease and therapy-related morbidity in a contemporary cohort of patients with cEGPA. Comparison to previous reports in both adult-onset and childhood-onset EGPA was performed.

MATERIALS AND METHODS

Patient selection. Patients age 25 years or younger with EGPA seen between 2003 and May 2011 were identified by searching the electronic medical record for the *International Classification of Diseases*, 9th edition (ICD-9) code for Churg-Strauss syndrome (446.4) or vasculitis (447.6). The charts of these patients were reviewed to identify patients who manifested vasculitic symptoms prior to 18 years of age. Records were further examined to ensure they met classification criteria for EGPA. Since no validated classification criteria for cEGPA exist, 2 separate classification schema for EGPA were used: the ACR 1990 classification criteria and the Lanham criteria, described above. Exclusion criteria included failure to meet either of the accepted EGPA classification criteria or the presence of any other autoimmune process, infection, or malignancy.

Our study was approved by the Cleveland Clinic Institutional Review Board.

Demographic and disease-specific data. Specific clinical and laboratory elements were extracted from the charts of all patients who met inclusion criteria and did not meet exclusion criteria. Demographic criteria consisted of sex, ethnicity, and country of origin. Background information collected were age at onset of allergic symptoms, allergic symptoms prior to diagnosis of cEGPA, family history of atopy, constitutional symptoms prior to diagnosis, antileukotriene use prior to onset of vasculitis symptoms, peak relative and absolute eosinophil counts, and age at EGPA diagnosis. Laboratory values included serum immunoglobulin E (IgE) levels, ANCA status (including pattern and titer), antiproteinase 3 and antimyeloperoxidase titers, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell count, and hemoglobin and platelet counts at diagnosis. Upper airway involvement was defined as allergic rhinitis, sinusitis, nasal polyps, chronic otitis media, and subglottic stenosis, while pulmonary involvement was defined as asthma, non-fixed pulmonary infiltrates, pleural effusions, alveolar hemorrhage, laryngeal or tracheobronchial stenosis, or lung nodules. Pulmonary function testing results were reviewed for signs of restrictive lung disease [a reduction in total lung capacity below the 5th percentile of the predicted value, and a normal forced expiratory volume in 1 s adjusted for vital capacity (FEV_1/VC)][15], obstructive lung disease [defined as elevated forced vital capacity (FVC) and normal or low FEV_1], and mixed pattern and/or impaired carbon monoxide diffusion capacity (DLCO). Abnormal chest radiograph or computed tomography (CT) findings were recorded, including non-fixed infiltrates, nodules, effusions, or cavitary lesions. Cardiac involvement was defined as pericardial effusion, pericarditis, hypertrophic or dilated cardiomyopathy, valvular insufficiency, heart failure, myocardial ischemia or infarction, arrhythmia, or atrial or ventricular hypertrophy. Signs of GI involvement were defined as eosinophilic gastritis or eosinophilic esophagitis, abdominal pain, diarrhea, GI bleeding, or colitis. Neurologic involvement included mononeuritis multiplex, neuropathic pain, intracerebral hemorrhage, and cerebral infarction. Charts were reviewed for cutaneous signs including subcutaneous nodules, petechiae and/or purpura, erythema, livedo reticularis, and urticaria. Musculoskeletal manifestations were defined as myalgias, arthritis, arthralgias, or weakness. Renal disease was characterized by clinical diagnoses or proteinuria, microscopic hematuria, renal insufficiency, glomerulonephritis, hypertension, and renal failure. Histopathologic evidence of extravascular eosinophils, non-necrotizing vasculitis, necrotizing vasculitis, and granuloma formation was documented as evidence of EGPA. Review of immunosuppressive treatment regimens following diagnosis of cEGPA was also recorded on a biannual basis. Specific manifestations of disease and/or treatment morbidity were defined as intestinal perforation, intracranial hemorrhage, osteopenia, osteoporosis, vertebral fracture, cataracts, hypertension, diabetes, steroid myopathy, cytopenia, sepsis, mucosal candidiasis, amenorrhea, growth failure, and death. All clinical data were stored in the Research Electronic Data Capture database (REDCap)[16].

Comparison of cEGPA and adult-onset disease. Zwerina and colleagues reported differences between cEGPA and adult-onset disease[9]. We used the same 2 adult case series[5,6] from the review by Zwerina, *et al* as comparators to the cEGPA cohort. An additional PubMed search was performed to identify cases of cEGPA reported since publication of the prior study. Search terms included "Churg-Strauss," "allergic angiitis," or "allergic granulomatosis" in combination with "childhood," "children," "pediatric," "boy," or "girl." Clinical data from our present cohort and additional patient reports were summed with data from previous cases to find totals.

Statistical analysis. Calculations of prevalence and descriptive statistics were performed using Microsoft Excel. Frequency was calculated as the number of patients with a particular finding at any point over the observation period divided by the total number of patients within the cohort. Chi-square analysis and 2-tailed Fisher exact probability tests were used to assess for statistically significant differences between groups. P values < 0.05 were considered statistically significant.

RESULTS

Overall, 9 patients were diagnosed clinically with cEGPA during the study period. The median duration of followup

was 13 months. Eight patients fulfilled ACR criteria and 6 fulfilled the Lanham criteria. Five met both sets of criteria. Of the 3 patients who did not meet the Lanham criteria, 2 (Patients 4 and 5) failed to demonstrate involvement of 2 or more extrapulmonary organ systems and Patient 2 did not have a recorded peak absolute eosinophil count (AEC) > 1.5 × 10^9/l. Patient 6 met only 2/6 ACR criteria (asthma and eosinophilia > 10%), but met all 3 of the Lanham criteria. Eight patients were female and 7 were white. One patient was of Indian descent but resided in England. The remaining patients were citizens of the United States. The median age at cEGPA diagnosis was 15 years (range 10–23). All patients reported rhinitis or asthma symptoms beginning on average 5 years prior to diagnosis of cEGPA. Four patients had a family history of atopy and 4 patients had known antileukotriene use prior to diagnosis. Constitutional symptoms prior to diagnosis included fever (n = 3), fatigue (n = 3), and weight loss (n = 5). Table 1 details the demographic characteristics as well as the presence of specific classification criteria in the cohort.

Table 2 gives the frequency of organ-specific manifestations at the time of cEGPA diagnosis. At the time of diagnosis, all patients had upper airway disease and pulmonary involvement. Chronic or recurrent sinusitis was a frequent finding (n = 8), while other upper airway manifestations, including allergic rhinitis (n = 3) and nasal polyps (n = 3), were seen less frequently. A majority of patients had non-fixed pulmonary infiltrates (n = 6) on a radiograph or CT scan. Pulmonary nodules (n = 4) and pleural effusions (n = 2) were less common. Musculoskeletal findings, most commonly migratory arthralgias (n = 3), were frequent and present in 67% of patients. Sixty-seven percent of patients had GI symptoms attributed to their vasculitis, the most common being abdominal pain (n = 5). Eosinophilic esophagitis and gastritis were each found in 2 patients. Cutaneous manifestations were seen in 67% of patients. Cardiac manifestations, including pericardial effusion, dilated cardiomyopathy, valvular insufficiency, heart failure, and myocardial infarction (n = 1), were present at the time of diagnosis in 44% of patients. In the 3 patients with pericardial effusions, none underwent pericardiocentesis. Electrocardiographic abnormalities (n = 2) included left axis deviation and lateral ST depression, bradycardia, and premature ventricular complexes. Echocardiographic abnormalities noted in 4 patients included left ventricular dysfunction, dilation of the left ventricle, mild to moderate mitral regurgitation, and mild to large pericardial effusions. All 3 patients with valvular insufficiency had mild tricuspid regurgitation as well as mild to moderate mitral valve regurgitation, and 2 had mild pulmonary regurgitation. A majority of patients demonstrated neurologic involvement. Three patients had symptoms consistent with mononeuritis multiplex, while 2 had neuropathic pain. One patient had an ischemic stroke due to a thromboembolic event attributed to prior myocardial infarction and subsequent atrial fibrillation. Signs of renal vasculitis were not observed in this cohort.

ANCA serologies were negative in 8 patients and unknown in 1 patient. All patients had a peak serum AEC > 500 × 10^6 cells/l (median 7010 × 10^6 cells/l); 8 patients had peak serum AEC > 1500 × 10^6 cells/l. Serum IgE levels were significantly elevated in the 7/8 patients with a documented IgE level (median 803 kU/l). ESR were elevated in 4 patients at diagnosis (median 25 mg/dl) and CRP values were abnormal in only 3 patients at diagnosis.

Imaging and other diagnostic investigations were performed frequently in these patients. All patients had both plain chest radiographs and CT imaging of the lungs. Seven

Table 1. Demographic characteristics and frequency of classification criteria for eosinophilic granulomatosis with polyangiitis (EGPA) in 9 children with EGPA.

Characteristic	Patient 1	2	3	4	5	6	7	8	9	Total/Mean
Sex	F	F	F	M	F	F	F	F	F	11% M
Race	White	White	White	White	Asian	White	NR	White	White	78% White
Age at onset of rhinitis/asthma, yrs	16	0.25	8	14	13	13	11	13	3	10
Age at CSS diagnosis, yrs	16	12	23	15	15	17	12	14	10	15
Asthma	Y	Y	N	Y	Y	Y	Y	Y	Y	8/9
Peak serum AEC (× 10^6/l)	14400	520	8547	5900	8800	8120	2000	11500	2190	6886
Eosinophilia (ACR/Lanham†)	Y/Y	Y/N	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	8/9
Neuropathy	N	Y	Y	N	N	Y	N	Y	Y	5/9
Non-fixed pulmonary infiltrates	N	Y	Y	Y	Y	N	Y	N	Y	6/9
Paranasal sinus abnormality	Y	Y	Y	Y	Y	N	Y	Y	Y	8/9
Abnormal biopsy	Y	Y	Y	Y	Y	N	N	Y	Y	7/9
2 extrapulmonary organs*	Y	Y	Y	N	N	Y	Y	Y	Y	7/9
Meets ACR CSS criteria	Y	Y	Y	Y	Y	N	Y	Y	Y	8/9
Meets Lanham CSS criteria	Y	N	Y	N	N	Y	Y	Y	Y	6/9

† Requires AEC > 1500 × 10^6/l. * Systemic vasculitis involving 2 or more extrapulmonary organs. ACR: American College of Rheumatology; AEC: absolute eosinophil count; CSS: Churg-Strauss syndrome; NR: not recorded.

Table 2. Frequency of organ-specific involvement at time of diagnosis in 9 children with eosinophilic granulomatosis with polyangiitis (EGPA).

Organ System	%	Organ System	%
Upper airway	100	Cutaneous	67
Allergic rhinitis	33	Subcutaneous nodules	11
Sinusitis	89	Petechiae	11
Nasal polyps	33	Ecchymosis	33
Chronic otitis	11	Urticaria	11
Pulmonary	100	Other	33
Asthma	89	Neurologic	56
Non-fixed infiltrates	67	Mononeuritis multiplex	33
Pleural effusion	22	Neuropathic pain	22
Alveolar hemorrhage	22	Cerebral infarction	11
Lung nodules	44	Cardiac	44
Musculoskeletal	67	Pericardial effusion	33
Migratory polyarthralgias	33	Dilated cardiomyopathy	22
Arthritis	22	Valvular insufficiency	33
Myalgias	22	Heart failure	22
Weakness	11	Abnormal electrocardiogram	22
Gastrointestinal	67	Myocardial ischemia	11
Eosinophilic esophagitis	22	Myocardial infarction	11
Eosinophilic gastritis	22	Abnormal echocardiogram	44
Abdominal pain	56	Renal	0
Diarrhea	33		
Colitis	33		

patients were found to have abnormal chest radiographs, while all patients had abnormal chest CT. The most frequent initial chest CT findings were non-fixed pulmonary infiltrates (n = 6), lung nodules (n = 4), ground-glass opacities (n = 2), and pleural effusions (n = 2). No cavitary lesions were noted.

Pulmonary function testing (PFT) results were abnormal in 78% of patients. PFT revealed an obstructive pattern in 5 patients, mixed pattern in 1 patient, and restrictive disease and impaired DLCO in 1 patient. Four patients underwent bronchoscopy, which was normal in 2 patients. In the remaining 2 patients, bronchoalveolar lavage revealed eosinophilia and/or increased red blood cells and hemosiderin-laden macrophages consistent with pulmonary hemorrhage. No patient showed signs of laryngeal or tracheobronchial stenosis.

Table 3 summarizes results of 48 biopsies performed in 9 patients with cEGPA. Biopsies with normal results (n = 23) were not included on the table. Twenty-one biopsies had evidence of extravascular eosinophils, 2 had non-necrotizing vasculitis, 1 had necrotizing vasculitis, and 1 had evidence of granuloma formation. Lung biopsies were most frequently abnormal (7/7 patients). Fifty percent of transbronchial lung biopsies were abnormal and all open-lung biopsies were abnormal (6 open-lung biopsies in 6 patients). Esophagogastroduodenoscopy and colonoscopy were both performed in 5 patients. Sixty percent of these patients had biopsy findings consistent with EGPA. In addition, 2 of 4 bone marrow biopsies were abnormal, identifying eosinophilia. Of note, Patients 6 and 7 did not have biopsy findings consistent with EGPA but still met EGPA classification criteria. Patient 6 met Lanham criteria by having asthma, peak peripheral blood eosinophil counts > 1.5×10^9/l (peak AEC = 8120), and systemic vasculitis involving 2 or more systems (cardiac, GI, renal, and musculoskeletal system involvement). Patient 7 met the ACR criteria (asthma, eosinophilia > 10%, non-fixed pulmonary infiltrates, and sinus disease) and Lanham criteria (asthma, peak AEC = 2000, with cardiac and GI system involvement).

All patients were initially treated with oral or intravenous corticosteroids. Seven patients were treated with azathioprine during followup. Four patients were treated with methotrexate (2 oral; 2 subcutaneous). Patients were also treated with intravenous and oral cyclophosphamide (4 patients), rituximab (2 patients), omalizumab (1 patient), mycophenolate mofetil (2 patients), and hydroxychloroquine (1 patient). Of the 3 patients with at least 3 years of treatment, all continued to require daily oral corticosteroids to control their vasculitis. Table 4 illustrates treatment regimens for all subjects.

Complications related to disease or therapy were noted in 5 patients. Patients 6 and 8 experienced heart failure due either to eosinophil infiltration of the myocardium or to vasculitic damage. Therapy-related adverse events included cytopenias in 2 patients (Patients 6 and 9) treated with cyclophosphamide as well as steroid-related osteoporosis in 2 patients (Patients 3 and 6) and cataracts in 2 patients (patients 2 and 6). Patient 6 was treated with oral prednisone

Table 3. Biopsy results in 9 children with eosinophilic granulomatosis with polyangiitis (EGPA).

Patient	Lung	Gastrointestinal	Bone Marrow	Other
1				Skin: eosinophilic granuloma
2	Eosinophilic pneumonia	Extravascular eosinophilis		Sinus: extravascular eosinophils Sural nerve: chronic axonopathy
3	Eosinophilic pneumonia	Eosinophilic vasculitis		
4	Extravascular eosinophils			
5	Extravascular eosinophils			
6	Hemosiderin-laden macrophages		Normal	
7			Normal	Myocardium: normal Sinus: polyps
8	Eosinophilic pneumonia and vasculitis		Eosinophilia	
9	Eosinophilic vasculitis	Eosinophilic gastroenteritis	Eosinophilia	

Table 4. Immunosuppressive medications used in childhood eosinophilic granulomatosis with polyangiitis (EGPA).

	Month After Diagnosis					
Patient	0–6	7–12	13–18	19–24	25–36	> 36
1	IV CS Oral CS AZA	Oral CS AZA HCQ	Oral CS AZA HCQ	IV CS Oral CS Oral MTX IV CYC	IV CS Oral CS Oral MTX IV CYC	
2	IV CS Oral CS AZA	Oral CS AZA				
3	Oral CS AZA Omalizumab	AZA Omalizumab	AZA Omalizumab	Oral CS AZA Omalizumab	Oral CS AZA Omalizumab	Oral CS AZA Omalizumab
4	Oral CS SC MTX	Oral CS SC MTX	Oral CS AZA	Oral CS AZA	Oral CS Rituximab	
5	IV CS Oral CS MMF					
6	Oral CS AZA Oral CYC	Oral CS AZA				
7	Oral CS Oral MTX AZA	Oral CS MMF	Oral CS MMF			
8	IV CS Oral CS AZA Oral CYC	Oral CS AZA				
9	IV CS Oral CS SC MTX IV CYC	IV CS Oral CS Oral CYC Rituximab				

CS: corticosteroids; CYC: cyclophosphamide; AZA: azathioprine; MTX: methotrexate; MMF: mycophenolate mofetil, HCQ: hydroxychloroquine; SC: subcutaneous; IV: intravenous.

75 mg daily for months prior to her initial visit to our center, and had steroid-induced vertebral fractures, diabetes, steroid myopathy, mucosal candidiasis, and cerebral infarction.

Comparison of adult and childhood-onset EGPA. The 9 pediatric patients from our series and 5 other single childhood case reports from the literature were added to the case series of childhood-onset EGPA from Zwerina, *et al*[9]. The differences in clinical features of cEGPA that were noted with the additional 14 childhood cases compared with Zwerina's retrospective case series (n = 33) were less cardiac involvement (29% vs 52%), fewer biopsy findings with vasculitis (36% vs 83%) and granulomas (7% vs 41%), and lower mortality (0% vs 18%). Males were less likely to have childhood-onset EGPA ($p < 0.001$).

Table 5 shows the clinical characteristics of 47 children with EGPA compared to 205 adult patients with EGPA[5,6]. Compared to adults, children with EGPA were significantly more likely to have lung involvement ($p < 0.001$), pulmonary infiltrates ($p = 0.02$), cardiac disease ($p = 0.01$), and GI involvement ($p = 0.02$). Additionally, children were significantly less likely to have musculoskeletal, peripheral nervous system, or renal disease. No differences were noted in frequencies of asthma and sinusitis, although there was a trend toward greater risk of mortality in children (13% vs 5%; $p = 0.10$).

DISCUSSION

EGPA is a systemic necrotizing vasculitis of unknown etiology that typically presents in middle-aged adults with asthma. EGPA is extremely rare in childhood. Zwerina and colleagues reviewed 33 cases of cEGPA reported since 1951[9]. The primary goal of our study was to add to the literature by reporting the clinical characteristics of 9 patients who presented with symptoms of systemic vasculitis before the age of 18 years and who were eventually diagnosed with EGPA.

All patients in our cohort had eosinophilia, upper airway disease, and lung involvement. Sixty-seven percent had musculoskeletal findings, most commonly migratory arthralgias, 56% had neurologic involvement, 67% had GI involvement (most with abdominal pain), 67% had skin involvement, and 44% had cardiac involvement. Unlike Zwerina's case series and 2 published adult series, none of the patients in our series had positive ANCA serologies.

Table 5. Comparison of adult- and childhood-onset eosinophilic granulomatosis with polyangiitis (EGPA).

	Adult-onset: 1989 to 2004[5]; 1995 to 2002[6]	Childhood-onset: 1951 to 2007[9], Cases 1995–2012[10–14], This Series	p
Type of Study	Multicenter retrospective	Case series retrospective	
No.	205	47	
Age, mean yrs	48	12	
Male/female ratio	0.87:1	0.36:1	< 0.001
Eosinophilia	Present	Present	
ANCA (% positive)	78/205 (38)	6/24 (25)	0.066
Clinical features (%)			
Asthma	200/205 (98)	43/47 (91)	NS
Sinusitis	139/205 (77)	30/41 (75)	NS
Lung	120/205 (59)	43/47 (91)	< 0.001
Pulmonary infiltrates	73/112 (65)	39/47 (83)	0.02
Pleural effusion	25/112 (22)	7/47 (15)	NS
Heart	54/205 (26)	21/47 (45)	0.01
Pericarditis	28/112 (25)	12/47 (26)	NS
Cardiomyopathy	27/112 (24)	16/47 (34)	NS
Mitral valve insufficiency	Not erported	6/47 (13)	—
Musculoskeletal			
Arthralgia	42/112 (37)	12/45 (27)	NS
Myalgia	60/112 (54)	10/45 (22)	0.001
Skin	107/205 (52)	31/46 (67)	0.11
Peripheral nervous system	141/205 (69)	18/45 (40)	< 0.001
Gastrointestinal involvement	56/205 (27)	22/47 (47)	0.02
Renal	43/205 (21)	6/46 (13)	NS
Biopsy findings (%)			
Vasculitis	53/95 (56)	29/43 (67)	NS
Extravascular eosinophilia	50/95 (53)	35/43 (81)	0.001
Granuloma	17/95 (18)	13/43 (30)	0.10
Deaths	6/112 (5)	6/47 (13)	0.10

ANCA: Antineutrophil cytoplasmic antibody; NS: nonsignificant.

Seven of the 9 patients had at least 1 histologic finding characteristic of EGPA. As in Zwerina, *et al*, all patients in our cohort received daily corticosteroids in addition to a steroid-sparing immunosuppressive agent. All patients with > 18 months of treatment recorded continued to require daily oral corticosteroids.

To date, the therapeutic options in EGPA have been extrapolated from experience obtained with other forms of vasculitis. However, the EGPA phenotype and pathophysiology is notably different from other chronic vasculitides such as Takayasu arteritis and microscopic polyangiitis. In EGPA, chronic eosinophil activation leads to infiltration and damage of organ parenchyma[17]. It would follow that successful control of the cytokine pathway controlling eosinophil activation would yield successful therapeutic results. Potential targets would include immunoglobulin E, interleukin 5, and CTLA-4. Fortunately, pharmacologic agents have been developed that target these potential sites of eosinophil activation and offer the promise of more specific therapy for EGPA in both children and adults. Although we are not able to make conclusions about effective treatment from our small case series, controlled studies of novel agents are needed to reduce the rates of steroid-related adverse effects and the risk of mortality in cEGPA.

There are several limitations to this study. First, this cohort was largely retrospective and primary data were not collected in standardized fashion. Also, our selection of cases was biased by retrospectively searching electronic medical records for the ICD-9 codes for Churg-Strauss syndrome (446.4) or vasculitis (447.6). We may have overlooked other patients who have not yet been diagnosed with EGPA, but would meet ACR or Lanham criteria for EGPA. Another limitation is that several of these patients made only 1 or 2 visits to our center over the followup period. Finally, our center serves a quaternary care center for children with chronic vasculitis, and it is possible that the children we have described represent a subgroup of patients with more severe cEGPA.

We detailed the clinical findings in a contemporary group of 9 children with EGPA and highlighted critical differences between adult and childhood-onset EGPA. These data add to the existing literature on pediatric EGPA. Evidence shows that children with EGPA are dependent on daily systemic corticosteroids for control of their disease, and side effects from therapy are common. International, multicenter clinical trials examining more specific therapeutic options are required to reduce burden of disease- and therapy-related sequela in children with this rare and life-threatening disease.

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