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RESEARCH ARTICLE

Childhood ANCA Positive Eosinophilic Granulomatosis with Polyangiitis

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Abstract

Eosinophilic granulomatosis with polyangiitis (EGPA) is an anti-neutrophil cytoplasmic antibody (ANCA) small and medium sized vasculitis. It is rare in childhood and its clinical presentation can be quite diverse. Objectives: to determine differences in clinical presentations, specific organ involvement and five factor score (FFS) between ANCA positive and ANCA negative cases. Methods: Descriptive statistical analysis was performed on Medline database up to June 2015 for childhood EGPA aged ? 18 years. Results: Sixty seven cases of childhood EGPA were identified with ANCA was measured in 35 cases (eight of them had positive results). In addition to the previous reported cases, we reported an eight years old female with severe asthma who presented with seizures and fingers' gangrene with positive ANCA, radiological paranasal sinus abnormalities and bilateral pulmonary infiltrates. Central nervous system and ocular involvement were significantly higher among ANCA positive cases. Asthma, pulmonary infiltrates, paranasal sinuses, renal, gastrointestinal and musculoskeletal involvements were more frequent in ANCA positive cases. Peripheral neuropathy and cardiac involvement were less frequent in ANCA positive cases. Five factor score (FFS) ? 1 was more frequent in ANCA positive cases. Conclusion: Hypereosinophila in severe asthma should raise the suspicion of EGPA especially if associated with pulmonary infiltrates or unusual multisystem affection. ANCA measurement could be used as a prognostic factor for EGPA.

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) which was formerly known as Churg-Strauss syndrome (CSS) is a rare primary systemic vasculitis affecting small and medium-sized blood vessels with marked peripheral eosinophilia in patient with severe asthma **(Churg and Strauss, 1951).** Classically, EGPA has three sequential phases: 1) The prodromal phase characterized by allergic rhinitis and asthma; 2) The eosinophilic phase with eosinophilic infiltration in multiple organs especially in the respiratory and gastrointestinal tract; and 3) the vasculitic phase in which a systemic vasculitis of the small and medium vessels develops, often with malaise, weight loss, and fever **(Vries and Tervaert, 2010).**

The pathogenesis of EGPA remains unknown. Several lines of evidence suggest genetic predisposition, which may entail inherited tendency to dysregulation of the cellular immune system **(Rust and Worrell, 2007).** Several exogenous triggering factors for disease onset or flares have been suspected. They include vaccinations, desensitizations, and drugs, such as macrolides, carbamazepine, quinine, and also anti-asthma agents, like leukotriene-receptor antagonists and omalizumab. Leukotriene-receptor antagonists and omalizumab often provide the opportunity for substantial tapering or withdrawal of corticosteroids in asthmatic patients, thereby unmasking an underlying 'formefruste' of EGPA, which had so far been controlled by corticosteroids **(Pagnoux et al., 2007; Bibby et al., 2010)**

The American College of Rheumatology developed criteria for the diagnosis of EGPA in 1990. Asthma (a history of wheezing or the finding of diffuse high pitched wheezes on expiration), eosinophils greater than 10 percent on the differential leukocyte count, mononeuropathy (including multiplex) or polyneuropathy, migratory or transient pulmonary opacities detected radiographically, paranasal sinus abnormality, biopsy containing a blood vessel showing the accumulation of eosinophils in extravascular area. The presence of 4 or more of these 6 criteria yielded a sensitivity of 85% and a specificity of 99.7% **(Masi et al., 1990).**

EGPA in childhood is rare and the clinical presentation can be quite diverse. Therefore, diagnosing EGPA in children may be difficult. However, early recognition of the disease is important, as delayed diagnosis can lead to severe organ involvement, and sometimes fatal outcome **(Zwerina et al., 2009).**

Material and methods

1. Literature Search and Data Collection

To evaluate the value of ANCA measurement in childhood EGPA, we searched PubMed database and Google search engine till June 2015 for childhood EGPA using the following terms: childhood CSS, ANCA positive vasculitis and allergic granulomatosis with polyangitis.

Cases of EGPA occurring in children whose age ≤ 18 years old at presentation were included for analysis. Our literature search yielded 67 cases of childhood EGPA. ANCA was measured in 35 cases of them (**Zwerina et al., 2009; Mutsaers et al., 2013; Maritsi et al., 2011; Baildam et al., 2011; Moradinejad et al., 2010; Al-Ammar et al., 2009; Iglesias et al., 2014; Albahri et al., 2014; Gendelman et al., 2014; Razenberg et al., 2012; Liu et al., 2012; Basak et al., 2011; Demircin et al., 2010; Kawakami and Soma, 2009; Salerno et al., 2010; Yim et al., 2009; Ghaffar et al., 2011; Partal et al., 2004; Rabusin et al., 1998; Waseem et al., 2007; Hamdan et al., 2007; Martinez-Bone et al., 2008; Lu et al., 2008; Twardowsky et al., 2010; Sharma et al., 1996; Mpofu et al., 1995)** (Table 1).The following clinical and laboratory data, when available, was obtained: age, sex, different organs involvement, eosinophil percentage, serum IgE and ANCA status. Also, we reported an eight years old female with severe asthma who presented with seizures and fingers' gangrene (fig 1) with positive ANCA, radiological paranasal sinus abnormalities (fig 2) and bilateral pulmonary infiltrates (fig 3).

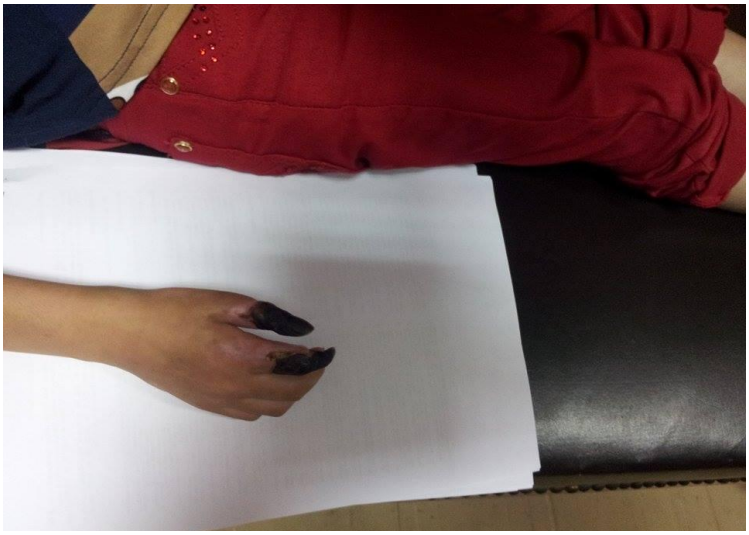

Fig 1: fingers' gangrene with line of demarcation

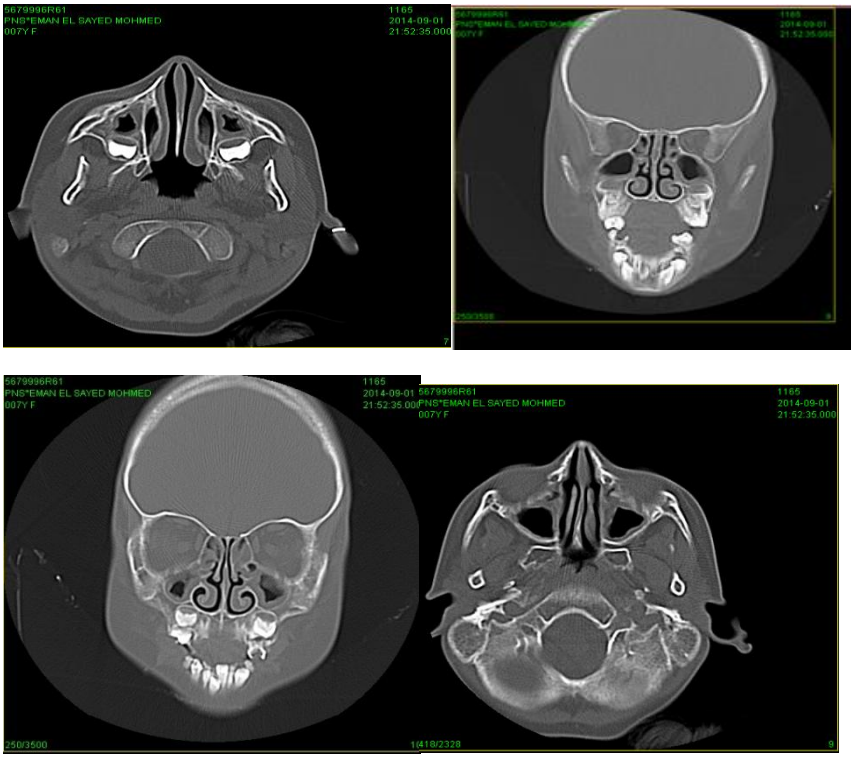

Fig 2: Paranasal sinuses CT showed mucosal thickening in both maxillary sinuses as well as the ethmoid air cells. Non pneumatized frontal sinuses and partially pneumatized sphenoid sinus

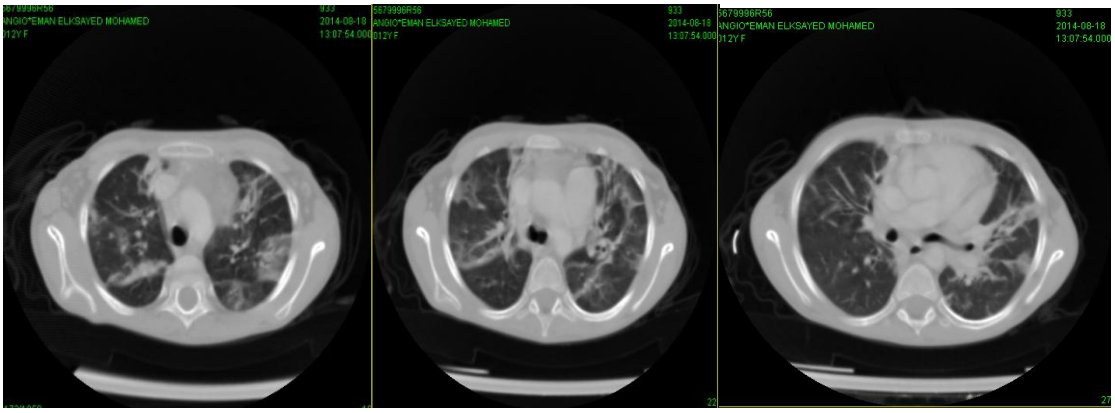

Fig 3: Chest CT showed bilateral pulmonary infiltrates with lower lobe predominance some of them are triangular shaped and pleural based.

2. Statistical Analysis

Testing was performed using SPSS 16.0. Shapiro-Wilk used to test distribution of data. Independent sample t test, Mann-Whitney U test and chi-square test were used to compare parametric, nonparametric and qualitative data respectively. A probability value of $P<0.05$ indicated statistical significance between groups.

Results

a)- Characteristics of ANCA positive cases (Table 1):

In addition to the 35 cases documented in literature to have childhood EGPA with documented ANCA measurement, we reported an eight years old female with ANCA positive EGPA. Within the documented cases, 9 (25%) were ANCA positive. Their mean ± standard deviation age was 12.11± 4.13 years. All had asthma, pulmonary infiltrates and eosinophilia (mean eosinophilic percentage 32.9 % ± 22.7%). Paranasal sinus abnormalities were reported in seven cases (77.8%), whereas skin manifestations were documented in six cases (66.6%). Other organs showed varied percentage of involvement such as musculoskeletal and gastrointestinal (55.6%), central nervous system (44.4 %), peripheral neuropathy and cardiac (33.3%). FFS ≥1 was reported in 5 cases (55.6%).

b) - Comparison of ANCA positive and ANCA negative cases (table 2)**:**

Central nervous system and eye involvement was significantly higher among ANCA positive cases (44.4% versus 7.4%, P=0.01). Asthma, paranasal sinuses involvement, pulmonary infiltrates, renal, gastrointestinal and musculoskeletal involvement were more frequent in ANCA positive cases but didn't reach statistical significance. Peripheral neuropathy and cardiac involvement were less frequent in ANCA positive cases but also didn't reach a significant value. Skin involvement was equaly involved in both groups (66.7%). FFS ≥ 1 was more frequent in ANCA positive cases (55.6% versus 40.7%, P=0.43). Both groups had no significant differences as regard age, gender, eosinophilic percentage and total serum IgE, (P = 0.98, 0.46, 0.98 and 0.191 respectively).

Discussion

In our analysis, Out of 67 childhood EGPA cases reported in literature, ANCA was measured in 35 cases in addition to our case. ANCA was positive in 25% of cases with documented ANCA**.** EGPA positive ANCA and EGPA negative ANCA were comparable in many but not all aspects. First of all; age, sex, eosinophilic percentage and serum IgE levels were not significantly different between ANCA positive and ANCA negative cases. Second, a wide range of vasculitic manifestations involving multiple anatomic sites and tissues was observed. Interestingly, the association between ANCA positivity and the anatomic site of vasculitic involvement was particularly noticed which means presence of correlation between the laboratory biomarkers and the clinical disease phenotype. A phenotype was previously defined as "observable characteristics" of disease subtypes ranging from clinical presentation, triggering factors to therapeutic responses **(Zedan et al., 2015).** Current analysis revealed that the prevalence of individual organ involvement (clinical disease phenotype) is different among ANCA positive and ANCA negative cases. ANCA positive cases showed more significant involvement of central nervous system and eyes when compared with ANCA negative cases (P=0.01).). Our 8 years old female patient presented with seizure which was proved to be secondary to PR3-ANCA positive EGPA. This finding goes hand in hand with a larger adult study done in 2013 and included 383 adult cases which showed more frequent involvement of central nervous system and eyes in ANCA positive cases **(Comarmond et al., 2013).**

The initiating mechanisms driving granuloma formation or triggering ANCA-mediated vasculitis in certain organs have still not been clearly determined. However, it is clear that T cells are off balance in ANCA associated vasculitis **(Lamprecht et al., 2005; Gómez-Puerta et al., 2009).** Thus, this specific organ involvement might be related to different T-cell phenotype and pro-inflammatory cytokine response, together with a specific genetic background.

In the current study, ANCA positive cases when compared with ANCA negative showed more frequent organ involvement; lower airways (Asthma and pulmonary infiltrates 100% versus), paranasal sinuses disease

(77.8%), musculoskeletal (55.6%), gastrointestinal (55.6%) and renal (22.2%) involvement. Whereas peripheral neuropathy and cardiac involvement were less frequent than in ANCA negative cases. However, these differences were not statistically significant.

Despite the relatively small number of our study group in pediatric population, clinical differences according to ANCA status are consistent in most aspects with several adult studies. The French Vasculitis Study Group [FVSG] in 2005 evaluated 112 patients and showed that ANCA-positive patients had more frequent renal disease and peripheral nerve involvement and a lower frequency of cardiac involvement. However prognosis at 3 years follow-up didn't differ between both groups **(Sablé-Fourtassou et al., 2005).** Another larger study conducted by the FVSG in 2013 showed significantly more frequent ear, nose and throat manifestations, peripheral nerve involvement, and renal disease in ANCA-positive patients, while ANCA-negative patients had significantly more frequent cardiomyopathy. Vasculitis relapses occurred significantly more in ANCA-positive than in ANCA-negative patients but with higher mortality rates in the ANCA negative **(Comarmond et al., 2013).** Also Homeister et al., stated that 75% of EGPA patients with glomerulonephritis were ANCA-positive while ANCA-negative patients tend to develop cardiac and lung involvements **(Homeister et al., 2013).** In 2014, Sokolowska et al., published a single Polish center experience and showed that ANCA positive patients had more frequent renal involvement, skin manifestations and peripheral neuropathy but less frequent cardiac involvement **(Sokolowska et al., 2014).**

Based on ANCA status, some authors hypothesized the existence of two disease subsets with different clinical manifestations and, possibly, pathogenetic mechanisms **(Radice et al., 2013).** Other mechanisms determining specific organ damage were related in part to the inflammatory mediators and the role of antiphospholipid-related hypercoagulability and thrombosis **(Agmon-Levin et al., 2013).** However, others hypothesized that some EGPA patients who were ANCA-negative at diagnosis possibly undergo seroconversion to ANCA positivity at some point upon the development of glomerulonephritis or some other specific systemic involvement **(Rowaiye et al., 2015).**

The principle that ANCA associated vasculitis in children is clinically distinct is essential to the categorization of patients according to organ involvement and hence to the morbidity and clinical outcome of patients. Since CNS involvement is a major determinant of severity, morbidity and mortality in patients with vasculitis **(Alba et al., 2011),** the association between ANCA positivity and CNS involvement in EGPA patients could be informative. In addition it has been previously suggested that treatment may have to be adapted according to ANCA status **((Comarmond et al., 2013).** Hence, the addition of ANCA positivity to the EGPA FFS might makes a sense.

The primary therapy for EGPA is systemic glucocorticoids. An additional immunosuppressive agent is typically added in patients with more advanced or refractory disease and in those whose disease flares with tapering of systemic glucocorticoids. Choosing among these agents is largely dependent on the disease severity and response to treatment **(Bosch et al., 2007; Sinico et al., 2007).**

In conclusion, in our view the published evidence from case reports suggests a possible association between ANCA positivity, specific organ involvement, and the prognosis of EGPA. The most convincing finding is the significant involvement of central nervous system and eye in ANCA positive cases when compared with ANCA negative cases. Coupled with prior evidence showing that ANCA positive cases tend to have poor prognostic factors (FFS $\geq$1) more frequently than ANCA negative cases, we believe that ANCA positivity could be added to the prognostic factors of EGPA. Since it is obvious that many patients in the vasculitic phase do not respond to standard therapy, early diagnosis is essential. Thus, we believe that, hypereosinophila in difficult to control (severe) asthma should raise the suspicion of EGPA especially if associated with pulmonary infiltrates or unusual multisystem affection. Further research studies are needed to detect different disease phenotypes, the underlying disease pathogenesis and the exact role of ANCA.

No conflict of interests

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Tables

Table 1: Demographic characteristics of ANCA positive and ANCA negative cases:

	Case	Age	Sex	ANCA	EO% or count	IgE	A	S	L	PNS	H	GIT	K	Skin	Ms	CNS & eye
1	**Our case**	8	f	+ve	8%	15	+	+	+	+	-	+	+	+	-	+
2	**Mutsaers et al., 2013**	13	F	+ve	67%	5035	+	+	+	+	-	+	-	+	+	+
3	**Maritsi et al., 2011**	16	F	+ve	40.9%	3200	+	+	+	-	-	+	-	+	+	_
4	**Baildam et al., 2011**	14	f	+ve	$61600\times10^{6/l}$	NR	+	-	+	-	+	+	+	+	-	+
5	**Moradinejad et al., 2010**	16	F	+ve	42%	157	+	+	+	-	+	-	-	-	+	+
6	**Al-ammar et al., 2009**	10 y	F	+ve	60%	NR	+	+	+	-	-	-	-	-	-	-
7	**Zwerina et al., 2009**	4	F	+ve	10%	679	+	-	+	-	-	-	-	-	-	-
8	**Zwerina et al., 2009**	12	M	+ve	21%	1822	+	+	+	+	+	+	-	+	+	-
9	**Zwerina et al., 2009**	16	F	+ve	15%	93	+	+	+	-	-	-	-	+	+	_
10	**Iglesias et al., 2014**	10	F	-ve	17.6%	2169	+	+	+	+	+	+	-	+	-	-
11	**Albahri et al., 2014**	17	F	-ve	61%	1080	+	+	+	+	+	-	-	-	+	-
12	**Gendelmane et al., 2013**	16	F	-ve	$14400\times10^{6/l}$	NR	+	+	-	-	*	*	*	*	*	*
13	**Gendelmane et al., 2013**	12	F	-ve	$520\times10^{6/l}$	NR	+	+	+	+	*	*	*	*	*	*
14	**Gendelman et al., 2013**	23	F	-ve	$8547\times10^{6/l}$	NR	-	+	+	+	*	*	*	*	*	*
15	**Gendelman et al., 2013**	15	M	-ve	$5900\times10^{6/l}$	NR	+	+	+	-	*	*	*	*	*	*

16	**Gendelman et al., 2013**	15	F	-ve	$8800\times10^{6/l}$	NR	+	+	+	-	*	*	*	*	*	*
17	**Gendelmane t al., 2013**	17	F	-ve	$8120\times10^{6/l}$	NR	+	-	-	+	*	*	*	*	*	*
18	**Gendelman et al., 2013**	12	F	-ve	$2000\times10^{6/l}$	NR	+	+	+	-	*	*	*	*	*	*
19	**Gendelmane t al., 2013**	14	F	-ve	$11500\times10^{6/l}$	NR	+	+	-	+	*	*	*	*	*	*
20	**Gendelmane t al., 2013**	10	f	-ve	$2190\times10^{6/l}$	NR	+	+	+	+	*	*	*	*	*	*
21	**Femke et al., 2012**	12	M	-ve	50%	2901	+	-	+	-	+	+	-	+	-	-
22	**Liu et al., 2012**	9	M	-ve	30.7%	1258	+	-	+	-	-	-	-	+	+	-
23	**Basak et al., 2011**	10	F	-ve	59%	NR	+	-	+	+	-	-	-	+	+	-
24	**Demircin et al., 2010**	2	M	-ve	12%	1640	+	-	+	-	-	-	-	+	-	-
25	**Kawakami and Soma,2009**	10	F	-ve	17%	2000	+	-	-	+	-	-	-	+	-	-
26	**Salerno et al., 2009**	14	F	-ve	15.2%	356	+	+	+	+	-	+	-	-	-	-
27	**Zwerina et al., 2009**	13	F	-ve	32%	<100	+	+	-	-	-	-	-	+	-	-
28	**Zwerina et al., 2009**	17	M	-ve	63%	895	+	+	-	+	-	-	-	+	-	-
29	**Zwerina et al., 2009**	14	F	-ve	36%	3477	+	+	+	-	+	-	-	-	-	-
30	**Zwerina et al., 2009**	15	F	-ve	32%	1701	+	+	+	-	-	+	-	+	-	-
31	**Zwerina et al., 2009**	10	F	-ve	35%	NR	+	-	+	-	+	+	-	+	-	-
32	**Zwerina et al., 2009**	15	F	-ve	29%	3228	+	-	+	+	+	+	-	+	-	-
33	**Zwerina et al., 2009**	7	F	-ve	19%	NR	+	+	+	-	-	-	-	-	-	-
3	**Zwerina et**	6	F	-ve	28%	NR	+	+	+	-	-	-	-	-	-	-

4	**al., 2009**														
35	**Zwerina et al., 2009**	2	M	-ve	12%	1640	+	+	+	-	-	-	-	+	+	-
36	**Partal et al., 2004**	10	F	-ve	40%	NR	+	-	+	-	-	+	+	-	+	+

***Gendelmanet al., 2013 reported 4 cases with heart, 6 with GIT, none with kidney, 6 with skin, 6 with musvloskletal and 1 with CNS involvement.** A, asthma; Eo, eosinophils; GIT, gastrointestinal tract; H, heart; K, kidney; L, lung; Ms, musculoskeletal; PNS, mononeuritis multiplex; S, sinusitis. Nine cases have positive ANCA.

Table 2: Demographic characteristics and frequency of organ involvement in childhood CSS, ANCA positive and ANCA negative cases:

Clinical feature	ANCA positive	ANCA negative	P value
Number (%)	9 (25%)	27 (75%)	**0.003**
Age (mean ±SD)	12.11 ± 4.13	12.14 ± 4.6	0.98
Gender Female N (%) **Male N (%)**	8 (88.9) 1 (11)	21 (77.8) 6 (22.2)	0.46
Eosinophilc % (mean ±SD)	32.9 % ± 22.7%	32.6 % ± 16.5%	0.98
Serum IgE(median and IQR)	679 and 310	1640 and 1547	0.191
Asthma N (%)	9 (100)	26 (96.3)	0.56
Sinus disease N (%)	7 (77.8)	25 (69.4)	0.53
Pulmonary infiltrate N (%)	9 (100)	21 (77.8)	0.121
Peripheral neuropathy N (%)	3 (33.3)	12 (44.4)	0.5
Cardiac involvement N (%)	3 (33.3)	10 (37)	0.8
GIT involvement N (%)	5 (55.6)	13 (48.1)	0.7
CNS & eye involvement N(%)	4 (44.4)	2 (7.4)	**0.01**
Kidney involvement N (%)	2 (22.2)	1 (3.7)	0.08
Skin involvement N (%)	6 (66.7)	18 (66.7)	1
Muscle-skeletal involvement N (%)	5 (55.6)	11 (40.7)	0.43
FFS FFS≥1 N(%)	5 (55.6)	11 (40.7)	0.43

CSS, Churg-Strauss Syndrome; ANCA,antineutrophil cytoplasmic antibody;CNS,central nervous system;GIT, gastrointestinal tract; FFS, five factor score. N,number; %,percentage; IQR, inter quartile range; P value considered significant if < 0.05. CNS and eye involvement are more frequent in ANCA positive cases.

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