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Serum cytokine and chemokine levels in patients with eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, or eosinophilic asthma

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Abstract

Objective.—The pathogenesis of eosinophilic granulomatosis with polyangiitis (EGPA) remains poorly understood, and may overlap with eosinophilic asthma and primary hypereosinophilic

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syndrome (HES). The aim of this study was to analyse a panel of serum cytokines and chemokines as markers of disease activity in patients with these conditions.

Methods.—The levels of 54 cytokines and chemokines were measured in the sera of 40 patients with active EGPA, 10 of these patients during inactive disease, 6 patients with HES, 8 with asthma, and 10 healthy controls. Serum cytokine/chemokines measured included interleukin (IL)-1α, 1β, 3, 4, 5, 6, 8, 13, 15, 17A, 17E(25), 18, 23 and 33, soluble IL-2 receptor alpha, eotaxin-1 (CCL11), -2 (CCL24) and -3 (CCL26), macrophage-derived chemokine (MDC/CCL22), macrophage inflammatory protein (MIP)-1a and -1b, and tumour necrosis factor (TNF)-α. Results were compared between disease and control groups using regression analysis, with Bonferroni correction for multiple comparisons (significant p-value ≤0.00093).

Results.—Significant differences were observed only in serum levels of MDC, IL-8, MIP-1a and -1b, TNF-α, each of which were lower in patients with active EGPA than in healthy controls ($p<0.0001$). Differences between patients with active disease and other disease groups did not reach significance. Paired comparisons between sera from patients with active or inactive EGPA showed no significant difference for any of the studied cytokines or chemokines.

Conclusion.—No clear difference in the serum levels of measured cytokines and chemokines helped distinguish between active EGPA or inactive EGPA, or other disease or control groups.

Keywords

eosinophilic granulomatosis with polyangiitis; cytokines; chemokines; asthma

Introduction

The main characteristics of eosinophilic granulomatosis with polyangiitis (EGPA; Churg-Strauss) include asthma with eosinophilia and vasculitic manifestations such as purpura. Early diagnosis of EGPA and the differentiation between EGPA and primary hypereosinophilic syndrome (HES) can be challenging but is important, as their therapeutic management and outcomes differ (1).

A few studies suggested that patients with EGPA may be distinguished from those with HES or eosinophilic asthma based on parameters other than ANCA, present in only 40% of EGPA patients, and histological evidence of vasculitis (1, 2). Immunophenotyping, T-cell clonal and cytogenetic studies, and molecular analyses to detect Fip1-like 1 (FIP1L1)–platelet-derived growth factor receptor-a (PDGFRA) gene fusion in the blood or bone marrow may help identify some patients with HES (3, 4). Studies on several serum eosinophilderived proteins and cytokines have led to variable, sometimes discordant, results (3, 5–11).

The aim of this study was to analyse a large panel of cytokines and chemokines in patients with EGPA, active or in remission, asthma or HES and controls.

Materials and methods

The levels of 54 cytokines and chemokines were measured in 40 patients with EGPA (including 10 tested twice, during active then inactive disease phases or the reverse), 6 patients with HES, 8 with asthma and 10 healthy controls.

Patients and controls

Patients with EGPA enrolled in this study have been previously entered in the Vasculitis Clinical Research Consortium (VCRC) Longitudinal Study, and satisfied the Chapel Hill nomenclature and/or the American College of Rheumatology classification criteria for EGPA (12, 13). At the time of this study, 170 EGPA patients had been enrolled in the VCRC Study; 40 of them with serum samples collected during active disease, as assessed by the site investigators at each visit (14), were randomly selected. Serum samples collected at the time of a visit in remission were also used for 10 of these 40 patients.

Controls included subjects who had no vasculitis and followed in the Respirology and Immunology Clinic (Hospital, Hamilton) with i) asthma (n=8), previously documented with pulmonary function tests; and ii) HES (n=6). Patients with HES fulfilled the Chusid criteria for diagnosis of idiopathic HES, needed to have blood eosinophil count >1,500 per microliter for ≥6 months and eosinophilia-related organ involvement or dysfunction, with no other identifiable secondary cause of eosinophilia (15). Healthy controls (n=10) were volunteers, non-smokers, with no abnormality on metacholine test (done for another reason than the study), and not on any glucocorticoids or other immunosuppressive treatment. Local IRBs (Mount Sinai Hospital, Toronto and St. Joseph's healthcare center, Hamilton) approved the study and informed consents were obtained from all participants in the study.

Laboratory measurements

Blood samples (one 7 ml blood vial) were collected and centrifugated on site and the serum extracted and aliquoted in labelled vials, stored at −80°C before being sent to Calgary (Multiplexing Eve technologies, Calgary, AL) for analysis. Frozen serum samples from patients with EGPA were sent from the VCRC Biospecimen Repository, and those from patients with asthma, HES and controls directly from the Hamilton clinic.

Serum cytokine/chemokine measurements were performed in duplicates using customised Human Plex Cytokine/Chemokine Panels (Multiplexing Eve technologies, Calgary, AL; discoveryassay.com) that allowed the simultaneous analysis of interleukin ((IL)-1α, 1β, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12 (p40 and p70), 13, 15, 17a, 17E(25), 18, 23 and 33, IL-1 receptor antagonist (IL-1ra), soluble CD40 ligand (sCD40L), soluble IL-2 receptor alpha (sIL-2Rα), eotaxin-1 (CCL11), -2 (CCL24) and -3 (CCL26), GRO-Pan (chemokine ligand CXCL1/2/3/GRO), macrophage-derived chemokine (MDC/CCL22), macrophage inflammatory protein (MIP)-1α and -1β, monocyte chemotactic protein-3 (MCP-3), soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), interferon (IFN)-α2 and -γ, IFN-γ-inducible protein (IP)-10, FMS-like tyrosine kinase 3 ligand (Flt-3L), thymic stromal lymphopoietin (TSLP), thymus and activation-regulated chemokine (TARC), monocyte chemoattractant protein-1 (MCP-1), tumour necrosis factor (TNF)-α and

-β, TNF-related apoptosis-inducing ligand (TRAIL), transforming growth factor (TGF)-α, regulated on activation, normal T cell expressed and secreted (RANTES), platelet-derived growth factor (PDGF)-AA and -BB, epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) A, fibroblast growth factor (FGF)-2, granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), soluble form of receptor for advanced glycation end products (sRAGE) and fractalkine (using the Human Cytokine 41-plex Discovery Assay, Custom 1-Plex Kit & Assay service; Human Cytokine Custom 7 Plex Kit & Assay Service; and the HNDGMAG-36K Human Neurodegenerative P3 Custom 2 Plex Kit & Assay Service).

Statistics

The numbers of enrolled patients and controls were based on study feasibility, with a recruitment period running from March 2012 to March 2015. Laboratory values are given as median [interquartile range (IQR)]. Cytokine/chemokine levels, according to groups (active EGPA *vs.* asthma, HES or controls), were compared using SAS PROC LIFEREG, which allowed for the analysis of normal and log-normal censored cytokine data. Cytokine/chemokine levels were also compared in the 10 patients with EGPA who had serum samples collected at the times of active disease and in remission, using paired Mann-Whitney tests. The Bonferroni correction was used for adjustment to *p*-values for multiple comparisons, with only *p*-values ≤0.00093 considered significant (16). Analyses were performed using SAS Software v. 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

At the time of serum sampling, for the 40 patients with EGPA with active disease (mean age 50.7±16.2 years, 17 male patients, 4 have had detectable ANCA), mean eosinophil count was 7,270±11,260/mm3; 31 were taking glucocorticoids and 22 on another immunosuppressive agent (combined with glucocorticoids in 18 of them). At the time of repeat serum sampling in remission, for 10 of these EGPA (mean age 47.6±11.4 years, 3 male patients, 1 have had detectable ANCA), 9 were on glucocorticoids, with 5 of them also on another immunosuppressive agent.

As shown in Figure 1 and Table I, for the 54 cytokines and chemokines measured, the only significant differences between active EGPA and the other groups were observed in serum levels of MDC, IL-8, MIP-1a, and -1b, TNF-α ($p<0.0001$ for the global comparison between groups), which were especially lower than in healthy controls.

Paired comparisons between sera from patients with active or inactive EGPA showed no significant difference for any of the studied cytokines or chemokines (Table II).

Discussion

This study failed to identify specific and distinct cytokine and chemokine differences between patients with EGPA or control groups, which may have provided new insights into disease pathophysiology or been of interest for diagnostic purpose. Only the levels of MDC, IL-8, MIP-1a and -1b, and TNF-α, which are mainly produced by macrophages and

are pro-inflammatory (17–19), were found to differ between patients with active EGPA and controls, but no clear difference was observed between active or inactive EGPA, or *versus* patients with HES or asthma.

In a few previous studies with a more limited panel of cytokines or chemokines, eotaxin-1 levels were found to be increased in subjects with asthma and/or sinusitis compared with HES and normal controls, as well as serum IL-10 levels in patients with EGPA, either active or in remission compared to normal controls. Serum eosinophil cationic protein, IL-5, IL-25, RANTES, TRAIL, VEGF or eotaxin-3 (CCL26) were increased in a few studies in patients in active EGPA, but some of these were also increased in patients with asthma or other eosinophilic conditions (6–10). However, and similarly to our findings, none of the several serum biomarkers examined in Khoury *et al.* or Dejacco *et al.*, including IL-10 or eotaxin-3, were found useful in differentiating between subjects with EGPA (definite or probable) and HES with asthma (3, 5). The reasons for these variable findings between studies remain unclear. Our findings could also suggest that, whereas most emphasis in the pathophysiology of EGPA has been given to eosinophils and some cytokines, more should possibly be given to macrophages and neutrophils, and treatments should not be determined based only on cytokine levels.

Caution must be exercised in interpreting the results of studies on serum levels of cytokines and chemokines in EGPA. Treatment may affect levels of several cytokines. The use of glucocorticoids was associated with a lower level of eotaxin-3 in the sera of patients with EGPA in the study by Dejacco *et al.,* but levels of TARC were not affected in the study by Khoury *et al.* (3, 5). The measurements of serum cytokines and chemokines may also be technically challenging, due to conservation methods and glycoprotein degradation *ex vivo*. There are currently no FDA-approved cytokine measurement kit, and no international units to which existing kits could be calibrated towards (20). No reference ranges were available for the cytokines and chemokines tested with the kits used in this study. Other techniques, such as the measurement of gene expression in peripheral blood cells or single nucleotide polymorphisms, may be more reliable and suitable to analyse cytokines and chemokines in these conditions. Urine levels, rather than serum levels, of cytokines or chemokines may also be more informative, at least in patients with renal involvement. Finally, sample sizes are small, due to the rarity of EGPA, and only 10% of our EGPA patients have had detectable ANCA, which limited the power of this study and prevented us from conducting any meaningful subgroup analysis (*e.g.* to compare patients with EGPA on glucocorticoids or not), and some clinical information were lacking for control groups, including on treatments.

In summary, this study found no major differences in the serum levels of a large panel of cytokines and chemokines that could distinguish between patients with active or inactive EGPA, HES or asthma. Conversely, these data may suggest that clinical and biological overlaps exist between these conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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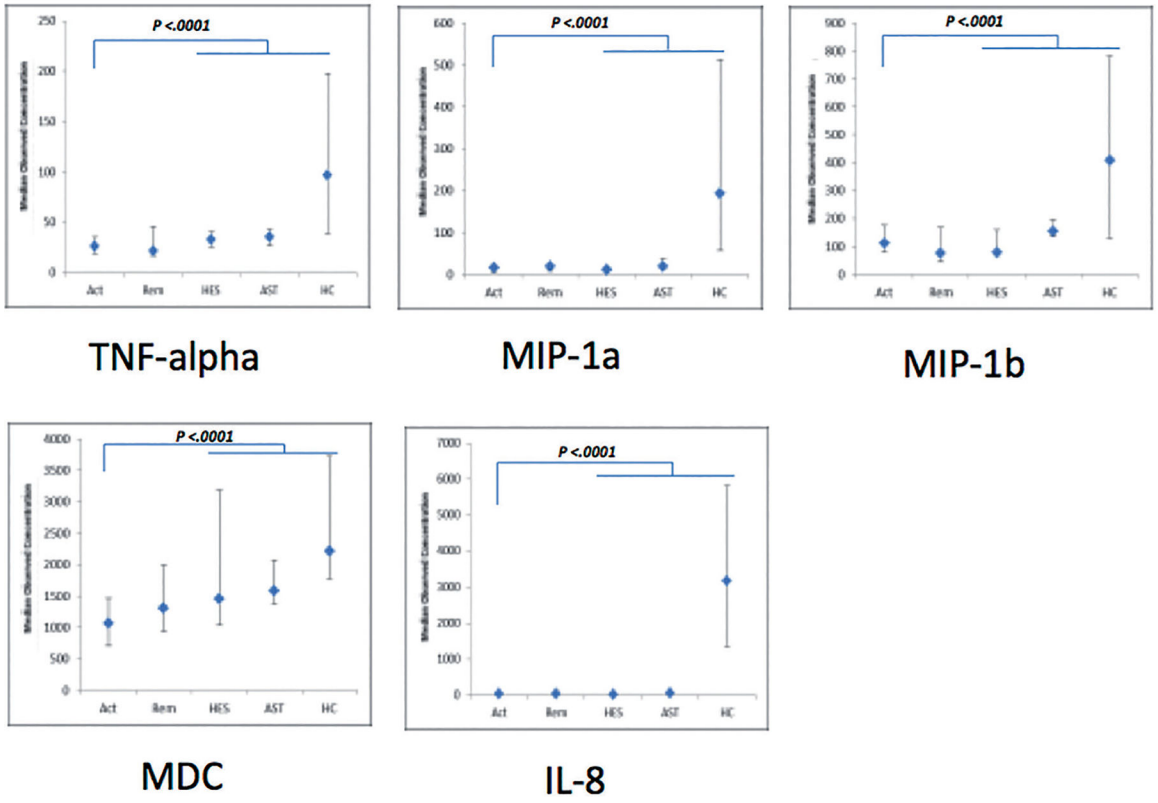

Fig. 1.

Serum levels (median [interquartile range (IQR)]; pg/ml) of the 5 cytokines and chemokines with a significant overall difference ($p \leq 0.00093$) between patients with active EGPA [Act] and asthma [AST], hypereosinophilic syndrome [HES] or controls [HC]). Serum values for the 10 patients with EGPA also tested during remission [Rem] are indicated (but were compared only to the patients with active EGPA, using paired Mann-Whitney tests - cf. Table.

Table I.

Main results of the logistic regression for all tested cytokines and chemokines (comparisons between values in patients with active eosinophilic granulomatosis with polyangiitis [EGPA] *vs.* other 3 groups – hypereosinophilic syndrome [HES], healthy controls and asthma patients).

	Group	Coefficients (intercept)	Standard error	*p*-value	Overall *p*-value
MDC*	EGPA	6.9624	0.0935		
	HES	0.4851	0.2589	0.0609	0.0002
	Controls	0.8064	0.2091	0.0001	
	Asthma	0.5817	0.2290	0.0111	
IL-8	EGPA	3.5016	0.1596		
	HES	−0.2476	0.4418	0.5752	<0.0001
	Controls	4.1536	0.3568	<0.0001	
	Asthma	0.5723	0.3909	0.1431	
MIP-1a	EGPA	2.3123	0.1993		
	HES	0.2962	0.5496	0.5900	<0.0001
	Controls	3.0718	0.4440	<0.0001	
	Asthma	0.9132	0.4863	0.0604	
MIP-1b	EGPA	4.7136	0.1420		
	HES	0.1706	0.3933	0.6646	0.0008
	Controls	1.2732	0.3176	<0.0001	
	Asthma	0.5134	0.3479	0.1401	
TNF-α	EGPA	3.2469	0.1197		
	HES	0.5696	0.3314	0.0857	<0.0001
	Controls	1.2551	0.2676	<0.0001	
	Asthma	0.4480	0.2932	0.1265	
Flt-3L					0.0020
EGF					0.0022
RANTES					0.0022
IFNy					0.0027
MCP 1					0.0028
IL-17A					0.0033
TRAIL					0.0033

Group	Coefficients (intercept)	Standard error	*p*-value	Overall *p*-value
TARC				0.0045
sCD40L				0.0061
IL-4				0.0143
IL-1a				0.0172
IL-6				0.0382
IL-15				0.0432
IFNa2				0.0527
GCSF				0.0646
sVCAM1				0.0670
sIL2Ra				0.0775
GM-CSF				0.0905
TNF-β				0.0914
MCP 3				0.0942
IL-13				0.1142
IL-12P40				0.1262
IL-3				0.1334
IP10				0.1459
Eotaxin 1				0.1623
IL-5				0.2068
Fractalkine				0.2699
PDGF AA				0.3184
IL-12P70				0.3255
IL-1β				0.3673
TGF-α				0.3816
Eotaxin 3				0.4991
sICAM-1				0.4992
GRO pan				0.5152
IL-23				0.5305
IL-1RA				0.6700
IL-17E				0.6758
TSLP				0.7127

	Group	Coefficients (intercept)	Standard error	*p*-value	Overall *p*-value
IL-33					0.7218
FGF 2					0.7317
IL-9					0.7586
IL-18					0.8022
VEGF A					0.8363
IL-2					0.8882
IL-7					0.8890
PDGF BB					0.9312
IL-10					0.9485
Eotaxin 2					0.9601
sRAGE					0.9774

*
see text (Methods) for full extended names of cytokines/chemokines.

Complete results with regression coefficients (intercept) for each group are listed only for the five cytokines and chemokines with a significant overall difference ($p \leq 0.00093$; complete results for all cytokines and chemokines are in online Suppl. Table I).

Table II.

Results of the paired comparisons between levels of cytokines and chemokines in the 10 patients with eosinophilic granulomatosis with polyangiitis (EGPA) who had serum samples collected at times of active disease and in remission, using paired Mann-Whitney tests.

Cytokine / chemokine	*p*-value	Cytokine / chemokine	*p*-value
PDGF AA	0.00169	IFNγ	0.26454
ARC	0.01576	**TNF-α**	0.27956
IL-12P40	0.02486	IL-17E	0.29593
sIL2Ra	0.04222	IL-2	0.31585
IL-23	0.04373	Fractalkine	0.32735
IL-8	0.04452	MCP 1	0.33087
IL-15	0.04731	**MIP-1a**	0.37405
IL-33	0.05093	IL-13	0.39866
GM-CSF	0.08015	GCSF	0.42138
sVCAM 1	0.09238	IL-5	0.51945
IFNa2	0.11867	EGF	0.52008
TNF-β	0.12970	IL-1B	0.53870
IL-17A	0.13732	MCP 3	0.54557
RANTES	0.14018	IL-18	0.59630
TSLP	0.15760	FGF 2	0.64492
IL-9	0.15770	sCD40L	0.67339
IL-6	0.15822	IL-10	0.70935
IL-4	0.17291	TRAIL	0.79040
IL-12P70	0.17938	sICAM 1	0.81553
IL-1a	0.18349	IL-1RA	0.84591
IP10	0.18436	TGF-α	0.88472
Eotaxin 1	0.18738	Eotaxin 2	0.88541
GRO pan	0.20302	**MDC**	0.88642
IL-7	0.21781	Eotaxin 3	0.89439
Flt3L	0.22748	IL-3	0.92451
sRAGE	0.23766	**MIP-1B**	0.99501
VEGF A	0.25910	PDGF BB	0.99915

No difference reached the significant *p*-value of ≤0.00093, including for the five cytokines and chemokines (in bold) whose levels differed between patients with active EGPA *vs.* healthy controls, patients with asthma or hypereosinophilic syndrome.