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1 **C-reactive protein as a diagnostic tool in differential diagnosis of hypereosinophilic**
2 **syndrome and ANCA-negative eosinophilic granulomatosis with polyangiitis**

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64 **Clinical implications:**

65 - In asthmatic patients with eosinophilia and systemic manifestations, a low serum C-
66 reactive protein level at diagnosis is suggestive of HES rather than EGPA.

67

68 *TO THE EDITOR:*

69

70 The differential diagnosis of hypereosinophilic syndrome (HES) and eosinophilic
71 granulomatosis with polyangiitis (EGPA) can be challenging in the context of asthma, blood
72 eosinophilia and systemic manifestations. EGPA (Churg-Strauss syndrome) differs from other
73 antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides by the constant presence
74 of asthma, blood eosinophilia, and presence of ANCAs (usually with myeloperoxidase
75 specificity, MPO/ANCAs) in only 30% or so of cases.¹⁻³

76 Patients with ANCAs are more likely to display a “vasculitis phenotype” and, conversely, a
77 non-negligible proportion of patients without ANCA reported in the largest series to date
78 lacked histologic evidence of vasculitis.¹⁻³ Moreover, the results of the recent MIRRA study
79 (demonstrating the benefit of mepolizumab in a significant proportion of EGPA patients with
80 relapsing or treatment-refractory disease) further suggest that some EGPA patients have an
81 “eosinophilic phenotype” rather than a “vasculitis phenotype”.⁴

82 To date, the clinical and biological characteristics of HES vs. EGPA have not yet been
83 described in a large group of patients. To address this question, we performed a retrospective,
84 observational, single-center study at Lille University Hospital. Both hospital discharge
85 (International Classification of Diseases, 10th Revision codes) and laboratory databases were
86 queried in order to screen all adult patients (aged 18 or over) diagnosed and/or treated
87 between 2006 and 2016 (see Supplemental Methods).

88 Of the 543 screened patients, 166 met our inclusion criteria (absolute eosinophil count [AEC]
89 >1G/L and a positive MPO/ANCA assay and/or manifestations related to organ damage
90 and/or dysfunction attributable to tissue hypereosinophilia, excluding asthma and ENT
91 manifestations without any exclusion criterion (Figure E1). Given the substantial clinical and
92 biological overlap between these two diseases, we compared the characteristics of patients

93 without using the conventional classification criteria of EGPA and HES.^{5,6} Included patients
94 were classified as follows: 18 MPO/ANCA+ patients with persistent asthma (Asth+ANCA+),
95 65 MPO/ANCA- patients with persistent asthma (Asth+ANCA-), and 83 MPO/ANCA-
96 patients without asthma (Asth-ANCA- patients). No patient was positive for anti-PR3 and no
97 asthma-free patient tested positive for ANCA. The patients' main demographic, clinical and
98 biological characteristics at diagnosis are summarized in Table I.

99 In the Asth+ANCA- group, 97%, 58% and 34% of the patients met the criteria for HES,⁵ the
100 American College of Rheumatology (ACR) criteria for EGPA,⁶ and the GERMOP/ERS
101 (Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires and European
102 Respiratory Society taskforce) criteria for EGPA,³ respectively, which highlights the overlap
103 between the conventional classification criteria (Table I). Lastly, 51% of Asth+ANCA-
104 patients met the criteria for hypereosinophilic asthma with systemic (non-vasculitic)
105 manifestations, which is in line with the recent report on the GERMOP/ERS cohort, in which
106 59% of ANCA- patients with asthma met these criteria.³

107 As reported by others,¹⁻³ Asth+ANCA- patients presented significantly less hematuria +
108 proteinuria > 0.2 g/day (2% vs. 22%, p=0.021) and mononeuritis multiplex (17% vs. 61%,
109 p=0.001) than Asth+ANCA+ patients, and they also showed a non-significant trend towards a
110 lower frequency of definite vasculitis (25%, vs. 56%, p=0.06) and alveolar hemorrhage (3%,
111 vs. 22%; p=0.054).

112 Ninety-nine percent of Asth-ANCA- patients met the criteria for HES and none of them met
113 the criteria for EGPA in absence of asthma. Moreover, their clinical profile was similar to that
114 of the international cohort of 188 HES patients, 64%, 54% and 37% of whom developed
115 dermatologic, pulmonary and gastrointestinal manifestations, respectively (vs. 69%, 44% and
116 38% in our study).⁷ Consequently, we considered Asth-ANCA- patients to be our reference

117 set for HES diagnosis. Conversely, MPO/ANCA being the strongest biomarker for EGPA,
118 Asth+ANCA+ patients were chosen as the reference set for EGPA diagnosis.

119 The highest median [IQR] serum CRP level was reported in Asth+ANCA+ patients (76.5
120 mg/L [58-130]) (Figure 1, A) and was similar to that measured in patients with MPO/ANCA+
121 patients with granulomatosis with polyangiitis or microscopic polyangiitis (85 [54-130];
122 $p=0.78$) (Figure 1, B). This suggests that a high CRP level is consistent with ANCA+
123 systemic vasculitis. The median serum CRP level was higher in Asth+ANCA+ patients than
124 in Asth+ANCA- patients (35.0 mg/L [8-73]; $p=0.028$). The same observation was previously
125 made in the French Vasculitis Study Group Cohort, with mean \pm standard deviation (SD)
126 serum CRP levels of 78.7 ± 62.4 and 58.5 ± 60.1 mg/L in ANCA+ and ANCA- patients,
127 respectively ($p=0.04$).²

128 The lowest median serum CRP level was reported in Asth-ANCA- patients (3.0 mg/L [0-12])
129 (Figure 1, A) and was similar to those recorded in patients with isolated eosinophilic asthma
130 with AEC $>1G/L$ (0 [0-5.2]; $p=0.11$) and in patients with asymptomatic unexplained
131 eosinophilia $>1G/L$ (0 [0-3]; $p=0.84$) (Figure 1, C). This suggests that a normal or slightly
132 elevated CRP level is expected in a high proportion of cases in which a diagnosis of EGPA
133 can be easily ruled out (i.e. no asthma and/or no systemic manifestations).

134 Both serum CRP values in Asth+ANCA+ and Asth-ANCA- groups differed significantly
135 from the median serum CRP level of Asth+ANCA- group (35.0 mg/L [8-73]; $p<0.001$ in a
136 Kruskal-Wallis test).

137 We next decided to evaluate the diagnostic value of the serum CRP level in Asth+ANCA-
138 patients (in which it is the most challenging to discriminate between HES and EGPA). We
139 considered Asth+ANCA+ group as the reference set for EGPA and Asth-ANCA- group as the
140 reference set for HES. On the receiver operating characteristic curve, the AUC [95%CI] for
141 serum CRP was 0.966 [0.907–0.993] (Figure E2). According to the Youden index, the best

142 cut-off value was <36 mg/L; this yielded a sensitivity of 94.8% [87.2; 98.6], a specificity of
143 93.7% [69.8; 99.8], and a PPV of 98.6% [91.6; 99.8] for the diagnosis of HES.

144 Interestingly, Asth+ANCA- patients with a serum CRP< 36mg/L were less likely to meet both
145 the ACR criteria for EGPA (37% vs. 83%; p<0.001) and the GERMOP/ERS criteria for
146 EGPA, 13 vs. 55% ; p<0.001), including definite vasculitis (10% vs. 38%; p=0.012), purpura
147 (3% vs. 28%; p=0.012) and mononeuritis multiplex (7% vs. 31%; p=0.016) (Table E1).

148 In the present study, serum CRP levels collected at diagnosis and in absence of confounding
149 factors (like corticosteroids), differ between Asth+ANCA+, Asth+ANCA- and Asth-ANCA-
150 patients. A previous study unsuccessfully tried to differentiate between EGPA and HES by
151 considering levels of CRP and many other biomarkers; this failure was probably due to the
152 small number of patients, and the fact that 60% of patients were taking corticosteroids at the
153 time of evaluation.⁸ The disparity between the literature data and our results might be due to
154 the heterogeneity of eosinophilic disorders encompassed within the diagnosis of “EGPA”, and
155 notably HES in which a low serum CRP is expected at diagnosis and during follow-up.

156 To conclude, in asthmatic patients with eosinophilia and systemic manifestations, our results
157 suggest that a low serum CRP level at diagnosis is suggestive of HES rather than EGPA.

158

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- 187

188 **FIGURE LEGENDS**

Study groups: Eo >1G/L and systemic symptoms

I. Asth+ANCA+ patients (n=16)

II. Asth+ANCA- patients (n=59)

III. Asth-ANCA- patients (n=77)

Selected control groups

IV. MPO-ANCA+ MPA/GPA (n=35)

V. Eosinophilic asthma (Eo >1G/L) (n=22)

VI. Asymptomatic unexplained Eo >1G/L (n=19)

189

190 **FIGURE 1.** CRP levels in the study groups (A) and control groups (B-C).

191 Asth+ANCA+, patients with persistent asthma and positive MPO/ANCA assays (n=16);

192 Asth+ANCA-, patients with persistent asthma and negative MPO/ANCA assays (n=59);

193 Asth-ANCA-, asthma-free patients with negative MPO/ANCA assays (n=77); MPO+

194 MPA/GPA, MPO/ANCA+ patients with granulomatosis with polyangiitis or microscopic

195 polyangiitis (n=35); Eo. Asthma, isolated eosinophilic asthma (n=22); Asympt. Blood Eo.,

196 asymptomatic unexplained blood eosinophilia (n=19).

197 Boxes: median [interquartile range]; error bars: 10th-90th percentiles. * p = 0.028 *** p <

198 0.001; ns, non-significant.

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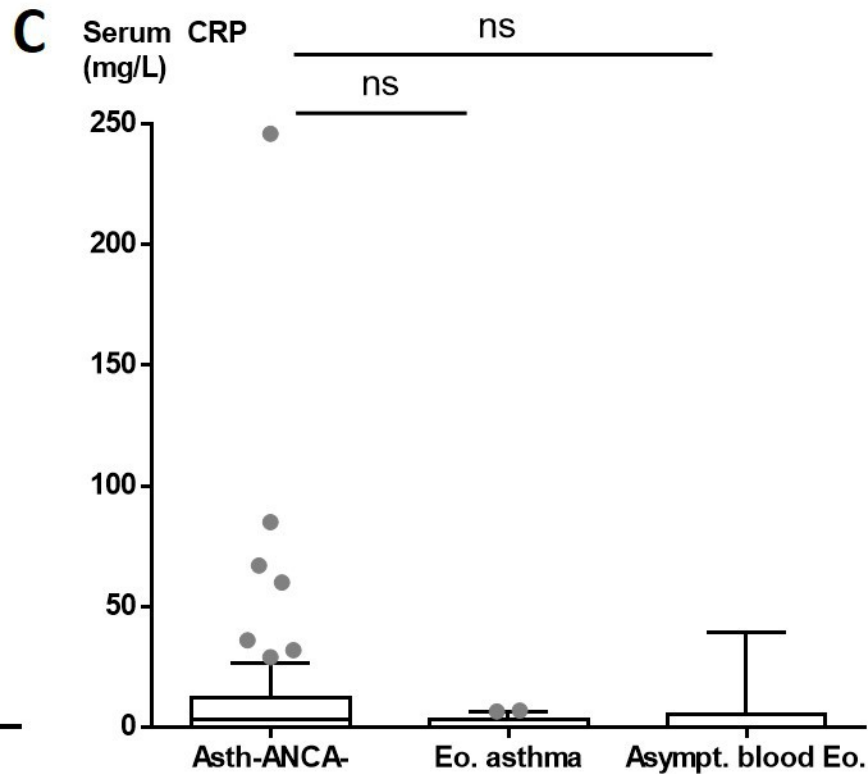
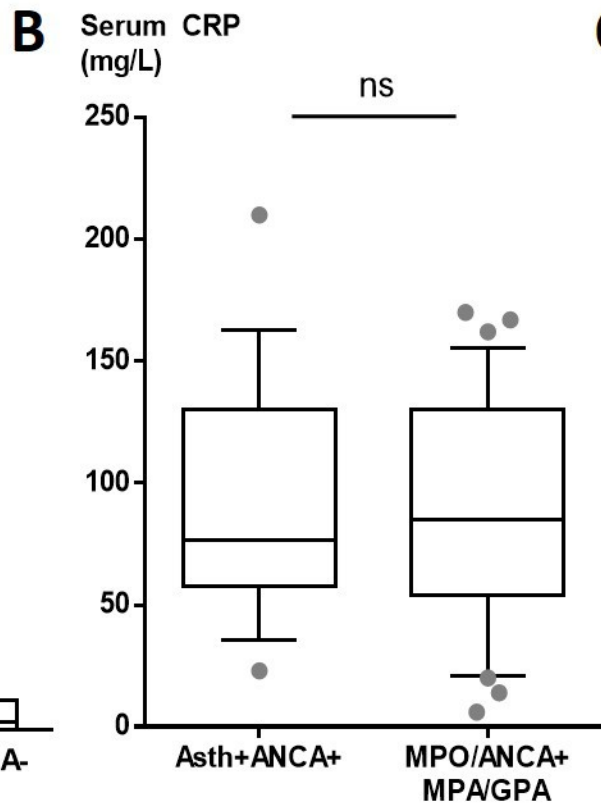
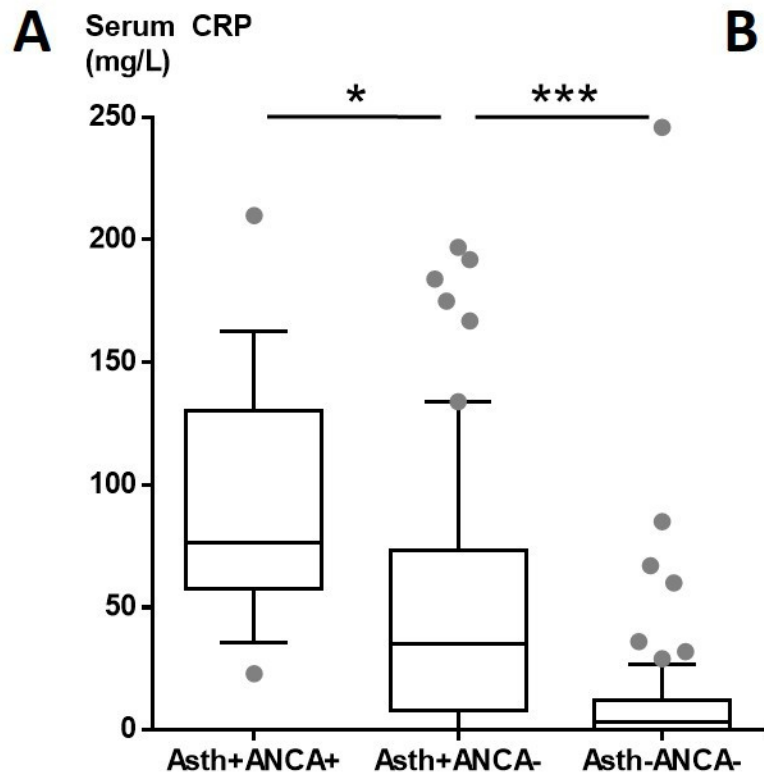


Table I. General characteristics of patients with blood eosinophilia >1 G/L and systemic manifestations

	Asth+ANCA+ (n=18)	<i>p</i> value (1)	Asth+ANCA- (n=65)	<i>p</i> value (1)	Asth-ANCA- (n=83)
Sex, male/female	11/7	ns	24/41	0.025	49/34
Age (years)	59 [49;63]	ns	48 [43;58]	0.002	60 [39;72]
CRITERIA FOR HES					
HES criteria	18 (100%)	ns	63 (97%)	ns	82 (99%)
Blood eosinophilia \geq 1.5 G/L at \geq 2 examinations	18 (100%)	ns	63 (97%)	ns	80 (96%)
Tissue eosinophilia	5 (28%)	0.003	47 (72%)	ns	63 (76%)
Clonal eosinophilia and/or myeloproliferative disorder	0	ns	1 (2%)	ns	9 (11%)
Abnormal circulating T-cells (lymphocytic variant HES)	0	ns	2 (3%)	ns	7 (8%)
CRITERIA FOR EGPA					
\geq 4 of the 6 1990 ACR criteria	15 (83%)	ns	38 (58%)	<0.001	1 (1%)
GERMOP/ERS revised nomenclature					
EGPA criteria (polyangiitis)	18 (100%)	<0.001	22 (34%)	na	na
Definite vasculitis	10 (56%)	0.06	16 (25%)	<0.001	2 (2%)
Strong surrogate of vasculitis	0	ns	0	ns	0
Mononeuritis multiplex	11 (61%)	0.001	11 (17%)	0.075	4 (5%)
MPO-ANCA	18 (100%)		0		0
Hypereosinophilic asthma with systemic (non-vascularitic) manifestations	na	na	33 (51%)	na	na
GENERAL MANIFESTATIONS					
Fever $>38^{\circ}\text{C}$	7 (39%)	ns	20 (31%)	<0.001	2 (2%)
Asthenia	14 (78%)	ns	42 (65%)	0.003	30 (36%)
Myalgia	6 (33%)	ns	11 (17%)	ns	7 (8%)
Arthralgia	7 (39%)	ns	18 (28%)	ns	14 (17%)
LUNG MANIFESTATIONS					
History of asthma	na		na		9 (11%)
Persistent asthma at diagnosis	18 (100%)	ns	65 (100%)	na	na
Duration of asthma at diagnosis (years)	4.5 [1.25;9.75]	ns	4 [1.5;19.5]	na	na
Allergic asthma	4 (22%)	ns	24 (37%)	na	na
Lung infiltrates	9 (50%)	ns	34 (52%)	<0.001	11 (13%)
Pleural effusion	2 (11%)	ns	13 (20%)	ns	11 (13%)

Alveolar hemorrhage	4 (22%)	0.054	2 (3%)	ns	0
Eosinophilic count \geq 25% in bronchoalveolar lavage	3 (17%)	ns	10 (15%)	ns	7 (8%)
ENT MANIFESTATIONS					
Chronic rhinosinusitis	15 (83%)	ns	51 (78%)	<0.001	19 (23%)
Nasal polyposis	9 (50%)	ns	35 (54%)	<0.001	7 (8%)
CARDIAC MANIFESTATIONS					
Myocarditis	0	ns	9 (14%)	0.015	1 (1%)
Myocardial infarction due to coronary arteritis	0	ns	1 (2%)	ns	0
Pericarditis	2 (11%)	ns	16 (25%)	0.005	5 (6%)
Endomyocardial fibrosis	0	ns	2 (3%)	ns	2 (2%)
Deep venous thrombosis/pulmonary embolism	0	ns	3/1 (5%/2%)	ns	6/1 (7%/1%)
RENAL MANIFESTATIONS					
Hematuria + proteinuria > 0.2 g/day	4 (22%)	0.021	1 (2%)	ns	0
Biopsy-proven necrotizing or crescentic glomerulonephritis	2 (11%)	ns	1 (2%)	ns	0
Creatinine > 150 μ mol/L	1 (6%)	ns	1 (2%)	ns	0
GASTROINTESTINAL MANIFESTATIONS					
Abdominal pain	4 (22%)	ns	18 (28%)	ns	22 (27%)
Diarrhoea	1 (6%)	ns	14 (22%)	ns	19 (23%)
Pancreatitis	0	ns	2 (3%)	ns	4 (5%)
Eosinophilic gastroenteritis (biopsy-proven)	0	ns	7 (11%)	ns	13 (16%)
Ischemic colitis	0	ns	0	ns	2 (2%)
Ascites	0	ns	3 (5%)	ns	4 (5%)
NEUROLOGIC MANIFESTATIONS					
Mononeuritis multiplex	11 (61%)	0.001	11 (17%)	0.075	4 (5%)
Distal polyneuropathy	1 (6%)	ns	11 (17%)	ns	5 (6%)
Inflammatory lesions of cerebral white matter	0	ns	0	ns	3 (4%)
Cerebral vasculitis	1 (6%)	ns	3 (5%)	ns	1 (1%)
Ischaemic stroke (without vasculitis)	1 (6%)	ns	5 (8%)	ns	5 (6%)
CUTANEOUS MANIFESTATIONS					
Palpable purpura	5 (28%)	ns	10 (15%)	<0.001	0
Digital necrosis	0	ns	0	ns	1 (1%)
Splinter hemorrhage	0	ns	1 (2%)	ns	1 (1%)
Livedo racemosa	1 (6%)	ns	0	ns	1 (1%)
Erythematous papules, plaques, and/or nodules	0	ns	14 (22%)	0.005	39 (47%)
Urticaria	0	ns	9 (14%)	ns	15 (18%)

Angioedema	1 (6%)	ns	8 (12%)	ns	8 (10%)
BIOLOGICAL CHARACTERISTICS					
Absolute eosinophil count (G/L)	6 [4.2-11.3]	ns	4.2 [2.4-10.6]	0.07	2.7 [2-6.2]
Eosinophils > 10% of leukocytes	17 (94%)	ns	61 (94%)	ns	82 (99%)
Elevated serum tryptase (2)	0	ns	4 (12%)	ns	10 (15%)
Elevated serum IgE (2)	6 (75%)	ns	42 (74%)	ns	34 (61%)
Elevated serum vitamin B12 (2)	0	ns	1 (2%)	ns	6 (11%)
Serum CRP (mg/L) (3)	76.5 [23-131]	0.03	35 [8-73]	<0.001	3 [0-12]

ACR, American College of Rheumatology; ANCA, antineutrophil cytoplasmic antibodies; Asth+ANCA+, patients with persistent asthma and positive MPO/ANCA assays; Asth+ANCA-, patients with persistent asthma and negative MPO/ANCA assays; Asth-ANCA-, asthma-free patients with negative MPO/ANCA assays; EGPA, eosinophil granulomatosis with polyangiitis; ENT, ear nose and throat; ERS, European Respiratory Society; GERMOP, Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires; HES, hypereosinophilic syndrome; IgE, immunoglobulin E; MPO, myeloperoxidase; na, not applicable; ns, non-significant.

(1) Adjusted p values are given for intergroup comparisons -adjacent columns- of each variable

(2) The serum tryptase level was available for n=3/34/66 patients in Asth+ANCA+, Asth+ANCA-, Asth-ANCA- patients respectively, with data on IgE in n=8/57/56 and data on vitamin B12 in 8/42/55.

(3) The serum CRP level was available without cofounding factors for n=16/59/77 patients in Asth+ANCA+, Asth+ANCA-, Asth-ANCA- patients respectively. The mean±SD CRP levels were 92.6 ±49.6 mg/L in Asth+ANCA+ and 53.2 ±54.2 mg/L in Asth+ANCA-.