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LETTER TO THE EDITOR

Is eosinophil cationic protein (ECP) a new predictor for assessing disease control in chronic spontaneous urticaria?

Dear Editor,

Chronic spontaneous urticaria (CSU) is mostly a mast cell (MC)-driven disease, but the interaction of skin MCs with other cells such as monocytes, basophils, neutrophils, T-lymphocytes and eosinophils plays a role in its pathogenesis.[1] The role of eosinophils in the pathogenesis of CSU is not fully understood; however, histological studies have shown that eosinophil infiltration correlates with high disease activity.[2–4] Eosinophils and MCs engage in bidirectional communication, with reciprocal activation and degranulation in CSU. MC-mediated cytokine release triggers eosinophil infiltration into CSU lesions followed by the production of stem cell factor from eosinophils which promotes the proliferation and differentiation of MCs and may contribute to the persistence of high numbers of MCs at the site of wheals and in nonlesional skin.[4] Furthermore eosinophil-derived proteins, such as the major basic protein (MBP) and eosinophil cationic protein (ECP), can induce MC degranulation via Mas-related G protein-coupled receptor-X2, thus perpetuating the inflammatory cycle.[4]

In previous studies, deposition of MBP and ECP in the skin has been observed in CSU, delayed pressure urticaria,[5] solar urticaria,[6] cold urticaria, and dermographic urticaria.[7] Lorenzo et al.[8] identified a correlation between eosinophil proteins and the severity of urticaria, demonstrating that serum levels of ECP were significantly related to the severity of CSU. However, no studies have evaluated the association between eosinophil proteins and disease control.

In this retrospective cross-sectional study, we analyzed the electronic or written records of patients diagnosed with CSU between 2018 and 2022 in an Allergy and Immunology Department in Türkiye. Patients whose urticaria could not be controlled despite standard single-dose of second-generation H1-antihistamines (sgAHs) and whose dosage was increased to fourfolds were included in the study. Exclusion criteria were: isolated inducible urticaria, atopic dermatitis, severe systemic and infectious disease, concomitant neoplastic disease, pregnancy and use of systemic steroids and immunosuppressives.

The patients were treated with fourfolds of sgAHs for 4 weeks and response to treatment was evaluated by the urticaria control test (UCT) (UCT scores ≥ 12 [well-controlled urticaria] and UCT < 12 [poor disease control]). Serum ECP levels were measured (Siemens Immulite device [clia, chemmulinescence method]) only at one-time inclusion before the escalation of antihistamines. Receiver operating characteristic (ROC) curve analysis was performed to define an optimal cut-off value for serum ECP. The study protocol was approved by the local ethics committee of our hospital.

The response rate to updosed antihistamines in 342 patients (85 male, 257 female) with CSU with a duration of disease ranging from 5 to 36 months was 43.9%. When responder and nonresponder groups were compared, there was no statistical difference in terms of age, gender, autoimmunity rate, and total IgE, tryptase and C-reactive protein levels. However, disease duration and D-dimer, eosinophil count and ECP levels were statistically higher in the nonresponder group (Table 1). While no correlation was found between peripheral eosinophil count and UCT, ECP was found to be inversely correlated with UCT ($p < 0.001$, $r = -0.247$) (Figure 1). In ROC analysis, an ECP cut-off value of 37.8 ng/mL for prediction of poor urticaria control was obtained. The sensitivity and specificity of the ECP measurement in determining urticaria control were 65.1% and 65.3%, respectively.

Lorenzo et al.[8] reported that serum ECP levels were increased both in symptomatic and asymptomatic patients with CSU, but they did not correlate ECP levels with peripheral eosinophil counts. In that study,[8] the ECP cut-off value was very close to our study (in symptomatic CSU 37.77 ± 12.60 μg/L versus in asymptomatic CSU 11.75 ± 2.68 μg/L; $p = 0.0001$). Saleh et al.[9] examined the correlation between urticaria activity score and eosinophil-

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TABLE 1 Comparison of characteristics between responders and nonresponders to updosed antihistamine treatment.

	Responder *n*: 192 UCT ≥ 12	Nonresponder *n*: 150 UCT < 12	*p* Value
Age (years), mean ± SD	40.32 ± 14.160	43.21 ± 15.073	0.458
Gender female, *n* (%)	139 (72.4)	118 (78.7)	0.183
BMI mean ± SD (kg/m^2)	28.11 ± 5.35	27.84 ± 5.85	0.210
Disease duration months, median (min–max)	12.00 (2–84)	24.00 (1–120)	**<0.001**
Presence of angioedema, *n* (%)	106 (55.5)	100 (67.1)	**0.030**
Autoimmune markers			
ANA positivity, *n* (%)	30 (16)	31 (20.9)	0.239
ENA positivity, *n* (%)	27 (16.8)	19 (14.5)	0.713
Anti-TPO positivity, *n* (%)	26 (13.9)	21 (14.4)	1.000
Anti-thyroglobulin positivity, *n* (%)	20 (10.7)	12 (8.3)	0.299
Total IgE (IU/mL), median (min–max)	143.50 (1–3552)	124.00 (1–1522)	0.293
Tryptase (μg/L), median (min–max)	5.86 (1.00–15.80)	5.64 (1.00–13.70)	0.169
CRP (mg/dL), median (min–max)	3.00 (0.2–59.0)	3.00 (0.2–26.9)	0.172
D-dimer (mg/L), median (min-max)	0.33 (0.19–4.30)	0.56 (0.19–7.98)	**<0.001**
Eosinophil/μL, median (min–max)	110 (0–1580)	140 (0–1900)	**0.003**
ECP (ng/mL), median (min–max)	28.50 (2.85–172.00)	47.25 (4.80–200.0)	**<0.001**

Note: ENA panel is a blood test that looks for antibodies to six or seven different proteins in the body (anti-Ro, anti-La, anti-Sm [anti-Smith antibody], anti-RNP [anti-ribonucleoprotein], anti-Jo-1, anti-Scl70, anti-centromere). Bold values are statistically significant.

Abbreviations: Anti-TPO, anti-thyroperoxidase; BMI, body mass index; CRP, C-reactive protein; ECP, eosinophil cationic protein; ENA panel, extractable nuclear antigen panel; IQR, interquartile range; max, maximum; min, minimum; SD, standard deviation; UCT, urticaria control test.

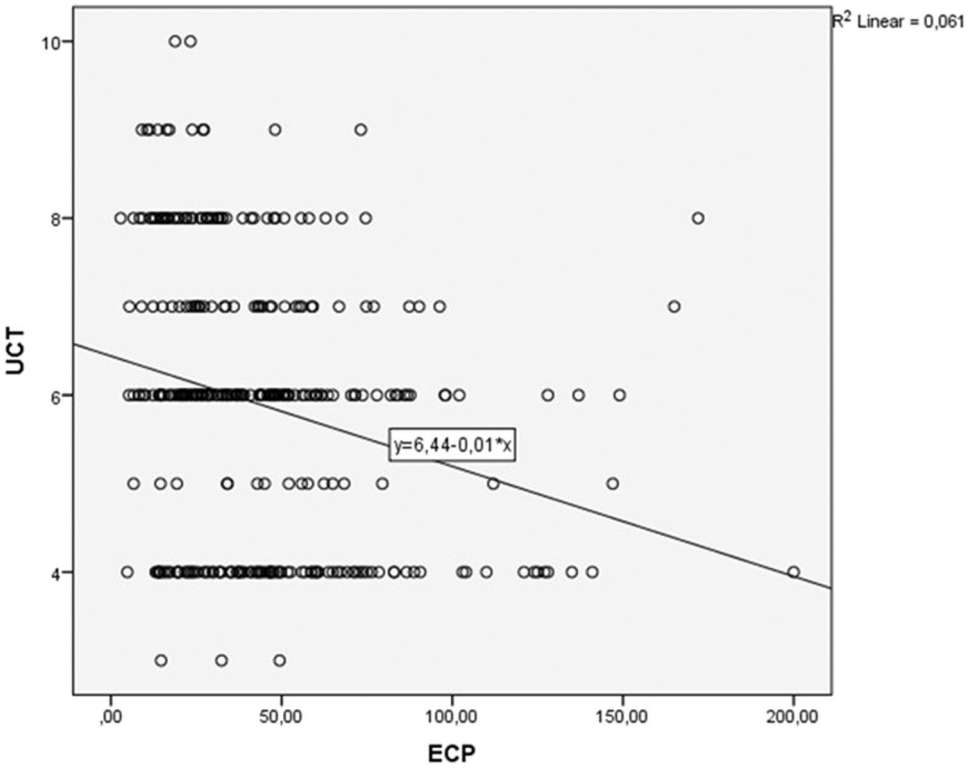


FIGURE 1 The relationship between baseline urticaria control test (UCT) and eosinophil cationic protein (ECP) was measured by Pearson's correlation. A very weak but significant negative correlation was found between these parameters ($r = -0.247$, $p < 0.001$).

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derived neurotoxin (EDN), one of the mediators released from eosinophils such as ECP, and found a positive correlation[9]; serum EDN has 70% sensitivity and 60% specificity for CSU with 66.9% accuracy.

Our findings align with previous research indicating that eosinophil infiltration in CSU lesions is associated with higher disease activity and plays a role in the pathogenesis of CSU. Specifically, we observed that elevated levels of ECP, a marker of eosinophil inflammatory activity, are linked to poor control of urticaria, reflecting increased disease severity. Therefore, we propose that serum ECP levels can serve as a predictive marker for poor antihistamine response, with a suggested cut-off value of 37.8 ng/mL.

KEYWORDS

allergy, eosinophil cationic protein, mast cells, urticaria

AUTHOR CONTRIBUTIONS

Concept: Özge Atik, Şeyma Özden, and Fatma Merve Tepetam. *Design*: Özge Atik, Emek Kocatürk, and Şeyma Özden. *Data collection or processing*: Özge Atik, Fatma Merve Tepetam, and Şeyma Özden. *Analysis or interpretation*: Özge Atik, Emek Kocatürk, and Şeyma Özden. *Literature search*: Özge Atik and Fatma Merve Tepetam. *Writing*: Özge Atik, Fatma Merve Tepetam, and Emek Kocatürk.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable—no new data is generated.

ETHICS STATEMENT

All authors consented to publication. This study protocol was reviewed and approved by [Süreyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital Ethical Committee], Approval Number [209]. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent form was obtained from the patients who participated in the study.

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