Characteristics of dermatological patients with blood eosinophilia: a retrospective analysis of 453 patients

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ournal Prevence

57 ABSTRACT

58

BACKGROUND: Skin diseases associated with blood or tissue eosinophilia are
common. As their clinical manifestations are various, making the correct diagnosis
can be challenging. So far, dermatological patients with concomitant blood
eosinophilia have not been characterized.

OBJECTIVE: We aimed at investigating patterns of dermatological patients with
 concomitant blood eosinophilia in order to obtain information helpful for optimizing
 disease management.

METHODS: In this retrospective study, demographic and clinical data and diagnostic
test results of all patients presenting with dermatoses associated with blood
eosinophilia (DABE) referred to a university center from 2014 to 2018 were extracted
from the electronic patient charts and evaluated using descriptive and semantic map
analyses.

71 **RESULTS:** A total of 453 patients (51.4% females; mean age 58.4 ±21.7 years) were included and grouped according to blood absolute eosinophil counts: severe, ≥1.5 72 G/L (n=87; 19.2%), moderate, 1.0 – 1.49 G/L (n=73; 16.1%), and mild eosinophilia, 73 0.5 - 0.99 G/L (n=293; 64.7%). Most patients presented with chronic (64.6%), 74 generalized skin lesions (75.9%), and pruritus (88.1%). Statistical analyses revealed 75 three distinct patterns: 1. mild eosinophilia associated with localized skin disease, 76 age <50 years, history of atopy, diagnosis of eczema or infectious disease, 2. 77 moderate eosinophilia linked to generalized skin lesions, pruritus, age > 70 years, 78 and autoimmune bullous disease, and 3. severe eosinophilia associated with 79 diagnosis of hypereosinophilic syndromes, drug hypersensitivity or malignant 80 disesase. 81

- 82 **CONCLUSIONS**: Based on the pattern analysis of patients with DABE, a diagnostic
- 83 workup has been developed aiming at setting the correct differential diagnosis in a
- 84 feasible and effective manner.

85 Highlights box:

- 1. What is already known about this topic?
- To make a differential diagnosis of dermatoses associated with blood or tissue
- 88 eosinophilia is challenging as their manifestations are manifold. The underlying
- 89 mechanisms causing eosinophilia are classified into intrinsic and reactive ones.
- 90
- 91 2. What does this article add to our knowledge?
- 92 A pattern analysis of demographic, clinical and diagnostic test data of patients
- 93 presenting with dermatoses associated with blood eosinophilia revealed an
- 94 association of blood eosinophil levels with distinct clinical and diagnostic findings
- 95 and corresponding diagnoses.
- 96
- 97 3. How does this study impact current management guidelines?
- 98 The results of this study will help to optimize the diagnostic workup of
- 99 dermatologic patients presenting with blood eosinophilia and their therapeutic
- 100 management.
- 101
- 102 Key words:
- 103 Dermatosis, Eosinophilia, Hypereosinophilia, Skin, Pruritus, Dermatoses associated
- 104 with blood eosinophilia

105	Abbreviations:	
106	AEC	Absolute eosinophil count
107	BP	Bullous pemphigoid
108	CS	Corticosteroids
109	СТ	Computer tomography
110	C3	Complement 3
111	DABE	Dermatoses associated with blood eosinophilia
112	EGPA	Eosinophilic granulomatosis with polyangiitis
113	FIP1L1-PDGFRA	FIP1-like1-platelet-derived growth factor receptor alpha
114	GPA	Granulomatosis with polyangiitis
115	HES	Hypereosinophilic syndromes
116	lg	Immunoglobulin
117	IL	Interleukin
118	LDH	Lactate dehydrogenase
119	MRI	Magnet resonance imaging
120	PDGFRA/B	Platelet-derived growth factor receptor alpha/beta
121	SD	Standard deviation
122	WBC	White blood cells

123

124 INTRODUCTION

Skin diseases associated with eosinophilia either in the blood, tissue or both, are 125 common despite the fact that the skin does not harbor eosinophils under physiologic 126 conditions.¹ Eosinophil infiltration in the skin can typically be observed in allergic, 127 autoimmune bullous, and infectious diseases, but also in association with 128 hematologic diseases and tumors.¹⁻³ Cutaneous involvement is the most frequent 129 initial clinical manifestation of hypereosinophilic syndromes (HES) as it affects 69% 130 of patients.⁴ A pattern analysis of chronic pruritus patients revealed tissue 131 eosinophilia as a frequent histologic finding even if a diagnosis of an underlying skin 132 disease was lacking, whereas blood eosinophilia was frequently observed in 133 association with dermatological diseases.⁵ 134 135 Based on the pathomechanisms, eosinophilic diseases are classified in primary 136 (intrinsic) disorders with mutation or gene fusion-mediated clonal expansion of 137

eosinophils, and secondary, cytokine-mediated (extrinsic) disorders.⁶ Secondary 138 eosinophilic diseases are caused by an increased expression of eosinophil 139 hematopoietins that are produced by either T cells or tumor cells resulting in an 140 increased differentiation and survival of eosinophils.⁷ While eosinophilia associated 141 with allergic responses and asthma is often mediated by interleukin (IL) 3 and/or IL-5, 142 increased granulocyte-magrophage colony-stimulating factor levels are frequently 143 associated with malignant tumors or lymphoma.⁸⁻¹⁰ Recruitment of eosinophils to the 144 tissue is mediated by eotaxins.⁷ 145

146

The interest in eosinophilic dermatoses has increased attributed to research progress
and the development of novel anti-eosinophil therapies.¹¹ Since the clinical
presentation is multifaceted, the differential diagnosis of eosinophilic dermatoses is

still challenging in clinical practice. Elevated absolute eosinophil counts (AEC) in the

151 blood might be the first clue before further diagnostic steps are initiated and

152 histopathologic, imaging and laboratory results are available. For the differential

diagnoses of hypereosinophilia, algorithms have been developed.¹² However,

uniform recommendations on how to manage eosinophilic dermatoses or dermatoses

155 with associated blood eosinophilia (DABE) are not available.

156 In this study, we aimed at characterizing patients with peripheral blood eosinophilia

157 who were referred to a tertiary dermatology department for diagnostic workup and

treatment of their dermatoses, in order to identify patterns which might be helpful in

developing diagnostic algorithms and optimizing disease management.

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160 **METHODS**

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162 Study design and data collection

163 In this retrospective study, patients referred to the Department of Dermatology,

Inselspital, Bern University Hospital, between January 1, 2014 and August 31, 2018,

in whom AEC \geq 0.5 G/l had been detected were included. Based on the highest

individual AEC, patients were grouped according to clinically accepted cutoffs in

those with severe, AEC \geq 1.5 G/L (hypereosinophilia)¹³, moderate, AEC 1.0 – 1.49

168 G/L, and mild eosinophilia, AEC 0.5 – 0.99 G/L. The electronic patient charts of all

169 cases were reviewed and relevant data including follow-up data were extracted by

using a structured clinical report form (see **Table E1** in the Online Repository).

171 Missing data arised owing to the retrospective study design revealing variable

172 number of visits, diagnostic procedures and follow-up time.

173 The study was approved by the Ethics Committee of the Canton of Bern,

174 Switzerland. General informed consent had been obtained from all patients prior to

the study. All clinical investigations were conducted according to the principles of theDeclaration of Helsinki.

177

178 Statistical analyses

For descriptive purpose, continuous data were presented as means with standard deviations (SD), while categorical data as absolute numbers with percentages. In addition, Mann-Whitney U test and Kruskal-Wallis test were used to assess changes of eosinophilia levels across categories of nominal variables of interest, while Spearman's rank correlation was used to test for association with other continuous or ordinal variables. Patients with missing data were not included in the analysis. As this was an exploratory analysis, all p-values are simply provided in the tables as descriptive statistics and should not be interpreted as statistically significant or not.
The statistical analysis was performed with SPSS v. 26.0 (IBM Corp, Armonk, NY,
US).

189

190 Semantic map analyses

Associations among clinically relevant selected variables were analyzed in two 191 separate maps. The first one included patients' demographics (age and sex), blood 192 eosinophil counts, final diagnoses, pruritus, distribution of skin lesions, patient history 193 of atopic diseases and malignancy/cancer, use of antihypertensive drugs, results of 194 leucocyte and lactate dehydrogenase (LDH) levels, and serum protein 195 196 electrophoresis. The second map included presence of eosinophils in the skin, histologic pattern along with blood eosinophil counts and final diagnoses. 197 Both maps were generated by means of a data mining algorithm able to compute and 198 display the strongest correlations between each pair of variables taking into account 199 other covariates in the system.5,14,15 200 Briefly, multiple logistic regression models were fitted by taking each time, 201 sequentially, a variable as the outcome and the other as covariates. This process 202 203 was reiterated until all variables in the model were processed. Finally, a matrix of regression coefficients (B) is produced and system weights are then computed by 204 using inverse exponential transformation $[sign(B) * (1 - e^{-sign(B)*B})]$, mapping 205 associations in the interval (-1, 1). A mathematical filter, the maximum spanning 206 tree,¹⁶ which is a spanning tree connecting variables (nodes of a graph) having 207 maximum weight, was then applied to the matrix of weights and a semantic 208 connectivity map was generated. The maximum spanning tree selected only positive 209 associations ensuring normalized correlations in the interval [0, 1]. In addition, only 210

connections with a p-value <0.15 were considered by the algorithm in order to avoid

unstable associations. In the map, hubs of variables were detected, with straight lines

showing the strongest associations, while spatial proximity between variables

indicating patterns of direct correlations. The strength of associations can be

interpreted as mild, moderate, or strong for values <0.6, 0.6-0.79 and \ge 0.8

respectively.¹⁴ The semantic map analysis was carried out using MATLAB v.9.4

217 (MathWorks, Natick, MA, USA).

Journal Prevention

218 **RESULTS**

219

220 Patient demographics and history

A total of 453 patients (233 female, 51.4%) with a mean age of 58.4 years (SD: 21.7 years) fulfilled the inclusion criteria of AEC \geq 0.5 G/I. Demographics are summarized in **Table I**. Hypereosinophilia was noticed in 87 patients (19.2%), 73 patients (16.1%)

had moderate, and 293 patients (64.7%) had mild eosinophilia. The mean age was

higher in the hypereosinophilia group compared with the other groups.

In 40.2% (151/376) of the patients' electronic health records, concomitant and/or past

atopic diseases had been recorded. The history of neoplasia/cancer was most

frequently reported in the hypereosinophilia group (17/85 patients, 20%) compared to

other groups (**Table I**). Overall, 61.3% of patients with available data on concomitant

treatments (n=401) took at least one medication with a greater proportion (62/80,

231 77.5%) among those with hypereosinophilia compared to other patients (see **Table**

232 **E2** in the Online Repository).

233

Semantic map analyses show distinct clinical and histologic patterns of mild, moderate, and severe eosinophilia groups

236 In order to show the strongest associations among selected variables, semantic map analysis was applied. Interestingly, the groups with mild, moderate, and severe 237 (hyper-) eosinophilia are separated in different hubs suggesting distinct patterns of 238 clinical presentation, normal/abnormal blood parameters, patient history, and final 239 diagnoses (Figure 2). Mild blood eosinophilia seems to be more common at age <50 240 241 years, characterized by localized skin lesions and normal blood parameters (white blood cell (WBC) count, serum protein electrophoresis, LDH), associated with a 242 history of atopy and final diagnoses of infectious diseases and eczema. Moderate 243

blood eosinophilia is linked to pruritus and generalized skin lesions as well as
autoimmune bullous diseases. Autoimmune bullous diseases affect elderly patients,
and age >70 years is linked to abnormal serum protein electrophoresis rates and the
intake of antihypertensive drugs. Severe blood eosinophilia is associated with the
final diagnoses HES and drug hypersensitivity reaction and linked to the history and
final diagnoses of malignant diseases.

With focus on histopathologic results and final diagnoses, we again found three 250 distinct hubs separating mild, moderate, and severe blood eosinophilia (Figure 3). 251 The most common histopathologic patterns found was the eczematous/urticaria-like 252 pattern located in the center of the map. There is an association with mild 253 254 eosinophilia and the final diagnoses of eczema and infectious diseases. The histopathologic findings of eczematous/urticaria-like pattern plus skin eosinophil 255 infiltration on histology links to moderate eosinophilia and drug hypersensitivity 256 reaction as well as to autoimmune bullous diseases and subepidermal blistering. An 257 eczematous/urticaria-like pattern is also linked to severe eosinophilia, which is further 258 associated with the final diagnoses of malignant diseases. In this hub, HES are 259 associated with other specific epidermal/dermal/subcutaneous histopathologic 260 findings, while non-specific findings without tissue eosinophilia are connected to 261 psoriasis. 262

263

264 DABE are mainly generalized and associated with pruritus

Most patients (328/432 patients with available data, 75.9%) presented with lesions spread over the entire integument. Localized lesions were rare and mainly seen in the mild eosinophilia group (89/277 patients, 32.1%) (**Figure 1**, *A*). Pruritus was present in almost all patients (370/420, 88.1%) independent of AEC levels (**Figure 1**,

B). Pruritus on non-lesional skin that is particularly common in hematologic 269 malignancies,¹⁷ was only observed in a single case of our dermatological patient 270 cohort. The morphological spectrum of cutaneous lesions was broad with an 271 eczematous pattern being the most frequent one followed by blistering and urticarial 272 lesions (Figure 1, C). Chronic skin problems were recorded in 277/429 patients 273 (64.6%). To note, out of the patients with an acute exacerbation of their skin lesions 274 (152/429, 35.4%), 44 (29%) of these patients had hypereosinophilia accounting for 275 51% in the severe eosinophilia group (see **Table E3** in the Online Repository). 276 277

278 Eczema is the most common dermatosis among DABE

279 Information on the final diagnosis was available in 416 cases, whereas for 37/453 patients (8.2%), a final diagnosis was not specified. 189 patients (45.4%) were 280 diagnosed to have eczema including 79 patients (19%) with atopic dermatitis (see 281 Table E4 in the Online Repository). 56 patients (13.5%) had an autoimmune bullous 282 disease, and 39 patients (9.4%) had a drug hypersensitivity reaction (Figure 1, D). 283 HES was diagnosed in 21 patients (5%). Intriguingly, in 5.5% of patients, the final 284 diagnosis was psoriasis. An overall difference between eosinophil level and final 285 diagnosis was found for eczema and infectious disease (mild eosinophilia), 286 autoimmune-bullous disease (moderate eosinophilia), and HES (hypereosinophilia) 287 (see **Table E4** in the Online Repository). When we searched for diagnoses such as 288 granulomatosis with polyangiitis (GPA), eosinophilic GPA (EGPA), myeloproliferative 289 neoplasia, human immunodeficiency virus infection, and hereditary diseases, we 290 could not identify any of these. 291

292

Tissue eosinophilia is found in 75% of skin biopsies

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294 Next, we were interested whether blood eosinophilia corresponds to eosinophil infiltration in the skin. The histopathological examination of skin biopsies revealed an 295 eosinophilic infiltrate in 233 out of 307 patients with available information (75.9%) 296 (see Table E5 in the Online Repository). The eczematous and urticaria-like pattern 297 was the most frequent one and reported in 58% (181/313) of the patients. To note, in 298 almost 10% of skin specimens, subepithelial blisters could be identified. In 25.2% of 299 patients (79/313), the histology did not reveal any specific findings. Among 195 300 available direct immunofluorescence results, linear deposits of immunoglobulin (Ig) G 301 or complement 3 (C3) along the basal membrane were the most frequent pathologic 302 finding often associated with moderate blood eosinophilia. Intercellular IgG or C3 303 304 deposits were detected in 18.5% of the patients (see Table E5 in the Online Repository). 305

306

307 Distinct blood parameter patterns in patients with moderate and severe 308 eosinophilia

We also analyzed various blood parameters in order to identify associations with 309 eosinophilia (see **Table E6** in the Online Repository). Pathologic results of WBC 310 counts, LDH, and serum protein electrophoresis were more frequently observed in 311 312 patients with moderate and severe blood eosinophilia. Bone marrow analyses (n=15) revealed abnormalities of the B cell (n=2), T cell (n=1) and mast cell (n=1) lineages 313 (see Table E6 in the Online Repository). Screening for the FIP1-like1-platelet-314 derived growth factor receptor α (FIP1L1-PDGFRA) fusion gene that has been 315 associated with HES, was negative in all tested patients (n=8). For 316 immunophenotyping of peripheral blood lymphocytes, flow cytometry using markers 317 for CD4, CD5, CD6, CD7, CD8, CD10, CD26, CD27 and CD81 was performed. 318

Aberrant T cells were identified in 12 and aberrant B cells in 3 out of 35 patients (see **Table E7** in the Online Repository).

321

322 Body imaging analyses such as X-ray (n=134), computer tomography (CT) scan (n=43), magnetic resonance imaging (MRI) (n=11), echocardiography (n=24) and 323 324 ultrasound (n=94) were done for diagnostic purposes, e.g. to identify solid tumors, lymphandenopathy or hepatosplenomegaly. While pathologic findings related to 325 eosinophilia on X-ray and sonography were reported in only 2 (1.5%) and 7 (7.4%) 326 patients, respectively, CT scan analysis revealed those in 11 patients (25.6%), with 327 no meaningful difference across the three groups (see Table E8 in the Online 328 Repository). 329

330

Topical and systemic corticosteroids (CS) are the most frequently applied therapies for DABE

We also analyzed the treatment modalities in our patient cohort. As our aim was to 333 develop an algorithm for diagnostic workup of DABE, we did not assess the clinical 334 and laboratory response to therapy in this study. Topical CS were the most frequently 335 provided substances for the treatment of DABE (Figure 1, E). For systemic 336 antiinflammatory/immunosuppressive therapy, oral CS, methotrexate, and ciclosporin 337 had been used in 152, 34 and 25 patients, respectively (see Table E9 in the Online 338 339 Repository). Patients with hypereosinophilia received systemic CS more frequently as compared to those with moderate and mild blood eosinophilia. In our study cohort, 340 37 patients had been treated with a total of 42 biologics, 23 for DABE directly or 341 indirectly targeting eosinophilic inflammation, and 19 for other diseases mainly 342 psoriasis (see Table E10 in the Online Repository). Biologics used included 343

- 344 mepolizumab, omalizumab, dupilumab, rituximab, adalimumab, ustekinumab,
- 345 secukinumab, and infliximab.

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347 **DISCUSSION**

Our study provides a detailed analysis of demographic, clinical, and diagnostic data 348 of patients presenting with cutaneous signs and symptoms who had concomitant 349 blood eosinophilia. Our results suggest that the level of blood eosinophilia is 350 associated with distinct clinical patterns in patients referred to a dermatological clinic. 351 Blood eosinophilia with or without tissue eosinophilia might be the first abnormality 352 that attracts attention in a diagnostic workup of dermatological patients. In view of the 353 broad spectrum of eosinophilic dermatoses that can be limited to the skin or be 354 associated with other organ involvements, a feasible diagnostic workup is required to 355 make the correct diagnosis.¹⁻³ 356 357 By applying semantic connectivity map analysis, the following associations between 358 blood eosinophilia and diagnoses were identified: 359 1. mild eosinophilia is associated with localized skin disease, age <50 years, 360 history of atopy, and a diagnosis of eczema or infectious disease, 361 moderate eosinophilia is linked to generalized skin lesions, pruritus, age >70 2. 362 years, and a diagnosis of autoimmune bullous disease, and 363 3. severe eosinophilia is associated with a diagnosis of HES, drug 364 hypersensitivity or malignant disease. 365 366 Although these correlations are of limited precision, they show that blood AEC 367 together with additional information such as age, distribution of skin lesions and other 368 blood parameters, might be helpful for planning further diagnostic steps. We added 369 conventional statistics to confirm and support the data gathered by semantic map 370 analysis. To note, missing data have not been amended in order to reflect patient 371 372 workup in real life. Additional features associated with hypereosinophilia that have

been identified by conventional statistical analyses, are older age, drug therapy,

374 specifically antihypertensives, a history of malignant diseases, as well as elevated

375 WBC count and serum LDH levels.

376

As shown on the semantic map, even localized skin lesions can be associated with mild blood eosinophilia. Examples are infectious dermatoses such as cutaneous larva migrans or scabies. The finding that acute manifestations of skin lesions were more frequently observed in the group with severe eosinophilia, is likely related to the fact that drug hypersensitivity reactions are often accompanied by high AEC.¹⁸

Pruritus is a striking symptom of DABE. Eosinophils that express IL-31 can directly
contribute to pruritus as shown in bullous pemphigoid (BP).¹⁹ In addition, eosinophils
are capable of generating many other typical pathological and clinical features of
DABE.²⁰⁻²⁷ For instance, they can amplify type 2 inflammation (e.g. in atopic
dermatitis), contribute to blister formation (e.g. in BP) and damage blood vessels
(e.g. in EGPA).^{21,24,27}

389

390 Tissue and/or blood eosinophilia reflect a systemic process that is either primary (intrinsic) caused by a clonal expansion of eosinophils or reactive due to a cytokine-391 mediated increased production, activation and survival of eosinophils.^{6,13} Clonal 392 eosinophilia can be part of various myeloid neoplasms and stem cell neoplasms, for 393 instance, chronic eosinophilic leukemia, hematopoietic neoplasms with eosinophilia 394 and abnormalities in PDGFRA, PDGFRB or FGFR1, myelodysplasic syndrome or 395 aggressive systemic mastocytosis.²⁸ Therefore, patients with skin lesions, severe 396 blood eosinophilia in addition to fever, weight loss, fatigue, malaise, and 397 398 hepatosplenomegaly require immediate workup in order to identify the underlying

disease and other organ involvement.²⁹ On the other hand, by producing 399 eosinopoietins, neoplastic disorders such as B- and T-cell lymphomas/leukemias, 400 Hodgkin's disease, Langerhans cell histiocytosis and solid tumors can cause 401 secondary eosinophilia.^{28,30} Eosinophilic dermatosis associated with hematologic 402 malignancies is mainly observed in patients with chronic lymphocytic leukemia. IL-5-403 producing T cells that are reactive to malignant B cells have been hypothesized to 404 trigger eosinophil accumulation and activation, and subsequent skin 405 manifestation.^{31,32} Moreover, skin inflammation and pruritus are predominant findings 406 in patients with eosinophilia attributed to aberrant T cells producing IL-5.³³⁻³⁵ Indeed, 407 in our study, we could identify dermatological patients with blood eosinophilia in 408 409 association with malignant diseases. Although the number of cases was small, this observation indicates how important a thorough diagnostic workup is. 410 411

In our patient cohort, severe blood eosinophilia was also linked to the diagnosis of 412 HES. A careful diagnostic workup of dermatological patients presenting with severe 413 eosinophilia is mandatory in view of the fact that they frequently present with 414 cutaneous signs and symptoms first.^{4,17} In HES, these are polymorphic, ranging from 415 416 eczema and urticaria to ulcers or vasculitis, and are usually not pathognomonic for different subtypes.^{13,29} Notably, mucosal ulcerations have been recognized a distinct 417 feature of patients with myeloproliferative HES, in particular FIP1L1-PDGFRA-418 positive HES.²⁹ 419

420

Histopathological examination of skin biopsies providing information on the
inflammatory pattern, absence or presence and distribution of eosinophils seem
crucial for the differential diagnosis of DABE. Although not pathognomonic, some
findings are indicative for certain diagnoses, e.g. flame figures in eosinophilic

425	cellulitis/dermatitis (Wells' syndrome) or eosinophilic vasculitis in eosinophilic
426	granulomatosis with polyangiitis. ¹ To confirm the diagnosis, further investigations are
427	required depending on the clinical manifestations and age.
428	

To treat DABE, CS were most frequently used as first line treatment before other immunosuppressive or immunomodulatory substances were initiated. Biologics such as mepolizumab, omalizumab, dupilumab and rituximab were applied for different DABE that all were attributed to reactive eosinophilia. Because of the retrospective study design, it was not possible to clarify the association between the use of other biologics and eosinophilia, if it was either related to therapy of severe disease, e.g. psoriasis,³⁶ or immunomodulatory/immunosuppressive effects.

436

Based on our pattern analysis, we suggest a diagnostic workup of patients with

438 DABE (Figure 4). A correct clinical, laboratory, histopathological and molecular

diagnosis together with an improved understanding of the pathogenic role of

eosinophils in DABE will be crucial to identify those patients that are candidates for

targeted, anti-eosinophil therapies. Further studies are needed to validate and refine

442 our proposed diagnostic algorithm in larger groups of patients.

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553 FIGURE LEGENDS

554 FIGURE 1. Characteristics of patients with dermatoses associated with blood

eosinophilia. Graphs show (A) frequency of localized or generalized distribution of
skin lesions (n=432), (B) presence of pruritus (n=420), (C) clinical morphology of skin
lesions, (D) final diagnoses and their frequencies (n=416), and (E) treatments applied
in the study population. HES: Hypereosinophilic syndromes.

FIGURE 2. Semantic map showing the strongest connections among blood
eosinophil levels, age, diagnoses as well as selected variables of diagnostic
test results. The numbers on connecting lines indicate normalized correlations
(between 0 and 1). The line thickness corresponds to the strength of association
(thin, <0.6; medium, 0.6-0.79; thick, >0.8).
FIGURE 3. Semantic map showing the strongest connections among blood

eosinophils levels, histopathological patterns and diagnoses in patients with
dermatoses associated with blood eosinophilia. The numbers on connecting lines
indicate normalized correlations (between 0 and 1). The line thickness corresponds
to the strength of association (thin <0.6; medium 0.6-0.79; thick >0.8).

FIGURE 4. Diagnostic workup in patients with dermatoses associated with
 blood eosinophilia. Diagnostic procedures and common findings in patients with
 mild, moderate and severe blood eosinophilia grouped by absolute eosinophil counts

of 0.5 - 0.99 G/L, 1.0 - 1.49 G/L, and ≥ 1.5 G/L, respectively. To note, the sequence and extent of diagnostic procedures may vary in clinical practice depending on the patient status.

History and findings	Specific information of attention	
	•	
Demographics	Sex	
	Age	
Medical history	Malignant diseases	
	Atopic diseases	Atopic dermatitis, bronchial asthma, allergic rhinitis/conjunctivitis, polyposis nasi, eosinophilic esophagitis
	Medication	Antibiotics, antihypertensives, diuretics, antidepressants, non-steroidal anti- inflammatory drugs, proton pump inhibitors, antiepileptic/psychotropic drugs
Skin manifestation	Distribution	
	Eczematous	
	Blistering	
	Urticarial	
	Cellulitis	
	Vasculitis	
	Mucosal affection	
	Pruritus	
Final diagnosis	Acute exacerbation	Atopic dormatitic, other oczama
	Drug hypersonsitivity	
	Autoimmune builous disease	pemphigoid, pemphigus, epidermolysis bullosa acquisita
	Vasculitis	
	Malignant diseases	
	Infectious diseases	
	Hypereosinophilic syndromes	
	Psoriasis	
	Other diseases	
Dermatopathology results	Skin eosinophilia	
	Histologic pattern	Eczematous/ urticarial, subepithelial blisters, other epidermal/ dermal/ subcutaneous patterns, unspecific findings
	Direct Immunofluorescence	Linear IgG or C3, intercellular IgG or C3, linear IgM, linear IgE, other/unspecific findings
	Autoantibodies	Indirect Immunofluorescence, BP180/BP230 autoantibodies
Laboratory results	Peak absolute eosinophil count	
	White blood cell counts	
	Lymphocytes	
	Liver function	LDH, ALAT, ASAT
	Renal function	Creatinine
	Serum protein electrophoresis	
	Tryptase	
	Autoantibodies	ANA, ANCA
	Total Immunoglobulin E (IgE)	· · · · · · · · · · · · · · · · · · ·
	Sx-1 (specific IgE to mix of 8	
	environmental allergens)	
	Bone marrow analysis	B cell abnormalities T cell abnormalities Mastocytosis
	Immunophenotyping	CD4/CD8 ratio, aberrant T cells/Sézary cells, aberrant B cells

Table E1. Information extracted from electronic patient charts

	FIP1L1-PDGFRA	
Body imaging	X-ray	
	CT scan	
	MRI	
	Echocardiography	
	Ultrasound	
Drug therapy	Topical	Corticosteroids, calcineurinnhibitors
	Systemic	Corticosteroids, methotrexate, ciclosporin,
		biologics, other treatments

Ig: immunoglobulin; C3: complement 3; BP: bullous pemphigoid; LDH: lactate dehydrogenase; ASAT/ALAT: aspartate aminotransferase/alanine aminotransferase; ANA: antinuclear antibodies; ANCA: anti neutrophil cytoplasmic antibodies; PDGFRA: Platelet-derived growth factor receptor alpha; CT: computer tomography; MRI: magnet resonance imaging

, ny; MR: ma

TABLE E2. Detailed information on patients history and concomitant medication in the study population, overall and by blood eosinophil levels

			Eosinophilia (G/L)						P**	
		≥	≥1.5 1.0-1.49 0.5-0.99 Total							
		N*	%	N*	%	N*	%	N*	%	
Malignant disease	No	68	80.0	63	88.7	266	94.7	397	90.8	<0.001
	Yes	17	20.0	8	11.3	15	5.3	40	9.2	
lf yes, type	Solid	8	47.1	5	62.5	13	86.7	26	65.0	0.06
	Lymphoma	6	35.3	2	25.0	2	13.3	10	25.0	
	Hematologic	3	17.6	1	12.5	0	0.0	4	10.0	
Atopic diseases***	No	47	58.8	43	60.6	135	60.0	225	59.8	0.90
	Yes	33	41.3	28	39.4	90	40.0	151	40.2	
At least one medication	No	18	22.5	36	51.4	101	40.2	155	38.7	0.10
	Yes	62	77.5	34	48.6	150	59.8	246	61.3	
Antibiotics	No	68	84.0	62	88.6	221	89.1	351	88.0	0.28
	Yes	13	16.0	8	11.4	27	10.9	48	12.0	
Antihypertensive drugs	No	35	43.2	52	75.4	143	57.4	230	57.6	0.42
	Yes	46	56.8	17	24.6	106	42.6	169	42.4	
If yes, type****	ACE inhibitors	25	54.3	10	58.8	37	35.6	72	43.1	0.02
	Ca antagonists	13	28.3	5	29.4	30	28.8	48	28.7	0.96
	Angiotensin-II-Receptor-	3	6.5	2	11.8	40	38.5	45	26.9	<0.001
	Antagonists									
	Beta Blocker	17	37.0	4	23.5	46	44.2	67	40.1	0.25
Diuretic drugs	No	56	70.0	57	81.4	178	71.5	291	72.9	0.65
	Yes	24	30.0	13	18.6	71	28.5	108	27.1	
Antidepressants	No	60	75.9	62	89.9	214	85.9	336	84.6	0.15
	Yes	19	24.1	7	10.1	35	14.1	61	15.4	
NSAID	No	63	78.8	62	89.9	202	80.8	327	82.0	0.72
	Yes	17	21.3	7	10.1	48	19.2	72	18.0	
PPI	No	56	70.0	59	85.5	201	80.7	316	79.4	0.17
	Yes	24	30.0	10	14.5	48	19.3	82	20.6	
Antiepileptics/psychotropic	No	72	90.0	66	95.7	240	96.4	378	95.0	0.048
drugs	Yes	8	10.0	3	4.3	9	3.6	20	5.0	

ACE: angiotensin-converting enzyme, Ca: calcium, NSAID: nonsteroidal anti-inflammatory drug, PPI: protonpump inhibitor

* Patient numbers in the total cohort (N=453): ≥1.5 G/L, N=87; 1.0-1.49 G/L, N=73; 0.5-0.99 G/L, N=293; Patients with missing data were not included in the analysis.

**Mann-Whitney U test and Kruskal-Wallis test were used to assess changes of eosinophilia levels across categories of nominal variables.

***Atopic diseases include atopic dermatitis, bronchial asthma, allergic rhinitis/conjunctivitis, polyposis nasi.

****Multiple drugs were possible.

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			Eosinophilia (G/L)									
			≥1.5 1.0-1.49 0.5-0.99						otal	P**		
		N*	%	N*	%	N*	%	N*	%			
Distribution	Generalized	74	88.1%	66	93.0%	188	67.9%	328	75.9%	<0.001		
	Localized	10	11.9%	5	7.0%	89	32.1%	104	24.1%			
Eczematous	No	18	22.0%	11	15.5%	97	35.3%	126	29.4%	0.001		
	Yes	64	78.0%	60	84.5%	178	64.7%	302	70.6%			
Blistering	No	66	79.5%	53	74.6%	228	83.2%	347	81.1%	0.19		
	Yes	17	20.5%	18	25.4%	46	16.8%	81	18.9%			
Urticarial	No	62	74.7%	66	93.0%	248	90.5%	376	87.9%	0.003		
	Yes	21	25.3%	5	7.0%	26	9.5%	52	12.1%			
Cellulitis	No	80	96.4%	70	98.6%	274	100.0%	424	99.1%	0.003		
	Yes	3	3.6%	1	1.4%	0	0.0%	4	0.9%			
Vasculitis	No	76	91.6%	71	100.0%	271	98.9%	418	97.7%	0.003		
	Yes	7	8.4%	0	0.0%	3	1.1%	10	2.3%			
Mucosal affection	No	75	89.3%	69	97.2%	264	96.0%	408	94.9%	0.06		
	Yes	9	10.7%	2	2.8%	11	4.0%	22	5.1%			
Pruritus	No	7	8.4%	8	11.3%	35	13.2%	50	11.9%	0.26		
	Yes	76	91.6%	63	88.7%	231	86.8%	370	88.1%			
Acute	No	41	48.2%	47	68.1%	189	68.7%	277	64.6%	0.004		
exacerbation	Yes	44	51.8%	22	31.9%	86	31.3%	152	35.4%			

Table E3. Distribution, morphology and exacerbation of skin lesions and pruritus inthe study population, overall and by blood eosinophil levels

*Patient numbers in the total cohort (N=453): ≥1.5 G/L, N=87; 1.0-1.49 G/L, N=73; 0.5-0.99 G/L, N=293; Patients with missing data were not included in the analysis.

**Mann-Whitney U test was used to assess changes of eosinophilia levels between categories of nominal variables.

		Eosinophilia (G/L)									
		≥1.5	1.	0-1.49	0.5	5-0.99	Т	otal			
	N*	%	N*	%	N*	%	N*	%			
Eczema***	28	32.2%	30	42.3%	131	50.8%	189	45.4%	0.009		
Drug hypersensitivity	12	13.8%	10	14.1%	17	6.6%	39	9.4%	0.04		
Autoimmune bullous disease***	12	13.8%	18	25.4%	26	10.1%	56	13.5%	0.004		
Vasculitis***	2	2.3%	0	0.0%	4	1.6%	6	1.4%	0.62		
Malignant diseases***	6	6.9%	1	1.4%	6	2.3%	13	3.1%	0.09		
Infectious diseases***	0	0.0%	1	1.4%	14	5.4%	15	3.6%	0.03		
Hypereosinophilic syndromes***	20	23.0%	1	1.4%	0	0.0%	21	5.0%	<0.001		
Psoriasis	0	0.0%	0	0.0%	23	8.9%	23	5.5%	<0.001		
Other diseases***	7	8.0%	10	14.1%	37	14.3%	54	13.0%	0.30		

TABLE E4. Final diagnoses of patients with dermatoses associated with bloodeosinophilia, overall and by blood eosinophil levels

*Patient numbers in the total cohort (N=453): ≥1.5 G/L, N=87; 1.0-1.49 G/L, N=73; 0.5-0.99 G/L, N=293; Patients with missing data were not included in the analysis.

**Pearson's X² test or Fisher's exact test where required.

***Diagnoses included were (n for severe/moderate/mild eosinophilia group):

- Eczema (n=189): Atopic dermatitis (15/19/45), other eczema (13/11/86)
- Autoimmune bullous disease (n=56): Bullous pemphigoid (12/15/21), Pemphigus (0/1/5), Epidermolysis bullosa acquisita (0/2/0)
- Vasculitis (n=6): Urticarial vasculitis (1/0/3), Wegener Granulomatosis (0/0/0), vasculitis not further specified (1/0/1)
- Malignant diseases (n=13): Cutaneous T-cell lymhoma (5/1/3), solid tumor (0/0/2), myeloprliferative disease (0/0/0), neoplastic disease not further specified (1/0/1)
- Infectious diseases (n=15): Parasites (0/0/4), HIV (0/0/0), infectious diseases not further specified (0/1/10)
- Hypereosinophilic syndromes (n=21): m-HES (1/0/0), I-HES (5/1/0), HES not further specified (14/0/0)
- Other diseases (n=54): dyskeratosis follicularis Darier (1/0/0), panniculitis (2/0/0), ulcerative colitis (1/0/0), endocrine diseases (0/0/4), rheumatologic diseases (0/0/3), unspecified conditions (3/10/30)

TABLE E5. Histological findings, direct and indirect immunofluorescence (IF) and serum BP180/230 auto-antibody analyses in the study population, overall and by blood eosinophil levels

			Eosinophilia (G/L)						P**	
			≥1.5	1.	0-1.49	0.5	5-0.99	Т	otal	
		N*	%	N*	%	N*	%	N*	%	
Skin	No	16	22.2%	6	12.2%	52	28.0%	74	24.1%	0.11
eosinophilia	Yes	56	77.8%	43	87.8%	134	72.0%	233	75.9%	
Histologic	Eczematous/ urticarial	49	70.0%	23	44.2%	109	57.1%	181	57.8%	0.31
pattern	Subepithelial blisters	8	11.4%	10	19.2%	12	6.3%	30	9.6%	0.04
	Other epidermal/ dermal/	10	14.3%	1	1.9%	12	6.3%	23	7.3%	0.13
	subcutaneous patterns									
	Non-specific findings	3	4.3%	18	34.6%	58	30.4%	79	25.2%	0.001
Direct IF***	Total	56		30		109		195		
	No pathologic findings	22	39.3%	4	13.3%	46	42.2%	72	36.9%	0.31
	Linear IgG or C3 +	12	21.4%	15	50.0%	21	19.3%	48	24.6%	0.28
	Intercellular IgG or C3 +	13	23.2%	4	13.3%	19	17.4%	36	18.5%	0.48
	Linear IgM +	7	12.5%	1	3.3%	4	3.7%	12	6.2%	0.04
	Linear IgE +	6	10.7%	1	3.3%	2	1.8%	9	4.6%	0.02
	Other/unspecific findings	0	0.0%	6	20.0%	22	20.2%	28	14.4%	0.001
Indirect IF	Negative	8	61.5%	4	36.4%	20	74.1%	32	62.7%	0.20
	Positive	5	38.5%	7	63.6%	7	25.9%	19	37.3%	
BP180/BP230	Not detectable	19	59.4%	12	57.1%	36	65.5%	67	62.0%	0.05
	BP180 +	10	31.3%	5	23.8%	7	12.7%	22	20.4%	
	BP230 +	1	3.1%	0	0.0%	8	14.5%	9	8.3%	
	BP180/230 +	2	6.3%	4	19.0%	4	7.3%	10	9.3%	

Ig: Immunoglobulin; C3: Complement 3; BP: Bullous pemphigoid

*Patient numbers in the total cohort (N=453): ≥1.5 G/L, N=87; 1.0-1.49 G/L, N=73; 0.5-0.99 G/L, N=293;Patients without tested parameters were not included in the analysis.

**Mann-Whitney U test and Kruskal-Wallis test were used to assess changes of eosinophilia levels across categories of nominal variables. For the histology, specific p-values were calculated for each subtype.

***Multiple findings were possible.

TABLE E6. Laboratory analyses of blood and bone marrow in the study population, overall and by blood eosinophil levels

			Eosinophilia (G/L)							
		≥1.5 1.0-1.49					5-0.99	-	Total	
		N*	%	N*	%	N*	%	N*	%	
White blood cell counts	Normal	43	50.0%	48	68.6%	240	82.2%	331	73.9%	<0.001
	Elevated	42	48.8%	21	30.0%	49	16.8%	112	25.0%	
	Decreased	1	1.2%	1	1.4%	3	1.0%	5	1.1%	
Lymphocytes	Normal	65	75.6%	56	81.2%	236	81.1%	357	80.0%	0.27
	Elevated	3	3.5%	2	2.9%	11	3.8%	16	3.6%	
	Decreased	18	20.9%	11	15.9%	44	15.1%	73	16.4%	
LDH	Normal	28	50.0%	20	46.5%	80	67.8%	128	59.0%	0.008
	Elevated	28	50.0%	23	53.5%	38	32.2%	89	41.0%	
ALAT/ASAT	Normal	71	88.8%	57	89.1%	211	86.5%	339	87.4%	0.51
	Elevated	9	11.3%	_7	10.9%	33	13.5%	49	12.6%	
Creatinine	Normal	52	62.7%	49	73.1%	173	71.8%	274	70.1%	0.35
	Elevated	30	36.1%	18	26.9%	68	28.2%	116	29.7%	
	Decreased	1	1.2%	0	0.0%	0	0.0%	1	0.3%	
Serum protein	Normal	8	23.5%	7	53.8%	43	55.8%	58	46.8%	0.004
electrophoresis	Dysproteinemia	26	76.5%	6	46.2%	34	44.2%	66	53.2%	
Tryptase	Normal	23	92.0%	12	100.0%	22	88.0%	57	91.9%	0.65
	Elevated	2	8.0%	0	0.0%	3	12.0%	5	8.1%	
ANA	Normal	26	83.9%	10	71.4%	45	73.8%	81	76.4%	0.34
	Elevated	5	16.1%	4	28.6%	16	26.2%	25	23.6%	
ANCA	Normal	28	100.0%	8	100.0%	35	97.2%	71	98.6%	0.50
	Elevated	0	0.0%	0	0.0%	1	2.8%	1	1.4%	
Total Immunoglobulin E	Normal	13	28.9%	4	12.9%	30	31.6%	47	27.5%	0.39
(IgE)	Elevated	32	71.1%	27	87.1%	65	68.4%	124	72.5%	
Sx-1 (specific IgE to mix of	Normal	17	58.6%	9	56.3%	30	60.0%	56	58.9%	0.87
8 environmental allergens)	Elevated	12	41.4%	7	43.8%	20	40.0%	39	41.1%	
FIP1L1-PDGFRA + cells	Not detected	8	100.0%	0	0.0%	0	0.0%	8	100.0%	nc
	Detected	0	0.0%	0	0.0%	0	0.0%	0	0.0%	
Bone marrow analysis	No pathologic	10	83.3%	0	0.0%	1	33.3%	11	73.3%	0.03
	findings									
	B cell	2	16.7%	0	0.0%	0	0.0%	2	13.3%	
	abnormalities									
	T cell	0	0.0%	0	0.0%	1	33.3%	1	6.7%	
	abnormalities									
	Mastocytosis	0	0.0%	0	0.0%	1	33.3%	1	6.7%	

LDH: lactate dehydrogenase, ASAT/ALAT: aspartate aminotransferase/alanine aminotransferase, ANA: antinuclear antibodies, ANCA: anti neutrophil cytoplasmic antibodies

*Patient numbers in the total cohort (N=453): ≥1.5 G/L, N=87; 1.0-1.49 G/L, N=73; 0.5-0.99 G/L, N=293; Patients without tested parameters were not included in the analysis.

**Mann-Whitney U test and Kruskal-Wallis were used to assess changes of eosinophilia levels across categories of nominal variables, while Spearman's rank correlation was used for ordinal variables.

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TABLE E7. Results of immunophenotyping of peripheral blood lymphocytes in 35 patients with dermatoses associated with blood eosinophilia by blood eosinophil levels

		E	Eosinophilia (G/L)		
		≥1.5	1.0-1.49	0.5-0.99	
		N=23	N=4	N=8	
CD4/CD8 ratio	Increased	7	0	3	
	Normal	4	0	2	
	Decreased	1	0	0	
Aberrant T cells	/Sézary cells	11	0	1	Ċ
Aberrant B cells		2	1	0	

		Eosinophilia (G/L)						P**		
			≥1.5	1.0-1.49		0.5-0.99		Total		
		N*	%	N*	%	N*	%	N*	%	
X-ray	Normal	24	72.7%	11	57.9%	64	78.0%	99	73.9%	0.54
	Pathologic findings									
	unrelated to eosinophilia	8	24.2%	8	42.1%	17	20.7%	33	24.6%	
	related to eosinophilia***	1	3.0%	0	0.0%	1	1.2%	2	1.5%	
CT scan	Normal	6	37.5%	5	62.5%	8	42.1%	19	44.2%	0.28
	Pathology findings									
	unrelated to eosinophilia	4	25.0%	1	12.5%	8	42.1%	13	30.2%	
	related to eosinophilia***	6	37.5%	2	25.0%	3	15.8%	11	25.6%	
MRI	Normal	0	0.0%	1	33.3%	1	20.0%	2	18.2%	0.42
	Pathologic findings								6	
	unrelated to eosinophilia	2	66.7%	2	66.7%	3	60.0%	7	3.6%	
	related to eosinophilia***	0	0.0%	0	0.0%	1	20.0%	1	9.1%	
	Tumor	1	33.3%	0	0.0%	0	0.0%	1	9.1%	
Echocardiography	Normal	7	77.8%	2	100.0%	12	92.3%	21	87.5%	0.45
	Pathologic findings	2	22.2%	0	0.0%	1	7.7%	3	12.5%	
Ultrasound	Normal	15	46.9%	8	61.5%	25	51.0%	48	51.1%	0.58
	Pathologic findings									
	unrelated to eosinophilia	13	40.6%	4	30.8%	21	42.9%	38	40.4%	
	related eosinophilia***	3	9.4%	1	7.7%	3	6.1%	7	7.4%	
	Tumor	1	3.1%	0	0.0%	0	0.0%	1	1.1%	

TABLE E8. Body imaging findings in the study population, overall and by blood eosinophil levels

CT: computer tomography; MRI: magnetic resonance imaging

*Patient numbers in the total cohort (N=453): ≥1.5 G/L, N=87; 1.0-1.49 G/L, N=73; 0.5-0.99 G/L, N=293; Patients without imaging examinations were not included in the analysis.

**Mann-Whitney U test and Kruskal-Wallis were used to assess changes of eosinophilia levels across categories of nominal variables.

***Pathologic findings related to eosinophilia: X-ray: Lymphadenopathy in cutaneous T-cell Lymphoma, pulmonal metastasis of solid tumor (urogenital carcinoma); CT scan: subcutaneous tumor, lymphadenopathy in HES; generalized lymphadenopathy (N=3), lymphadenopathy and splenomegaly in cutaneous T cell lymphoma, splenomegaly in drug hypersensitivity reaction, adrenal gland metastasis of solid tumor (renal carcinoma); MRI: phlegmonous subcutaneous infection with toxic cellulitis; ultrasound: lipomatous pancreatitis associated with neoplastic disease, lymphadenopathy in cutaneous T cell lymphoma (N=3), splenomegaly in drug hypersensitivity reaction, lymph node metastasis of solid tumor (urogenital carcinoma), phlegmonous subcutaneous infection with toxic cellulitis.

		Eosinophilia (G/L)							P**	
		≥1.5		1.0-1.49		0.5-0.99		Т	otal	
		N*	N* %		%	N*	%	N* %		
Topical CS	No	9	10.3%	8	11.6%	47	16.7%	64	14.6%	0.10
	1st line	78	89.7%	61	88.4%	229	81.5%	368	84.2%	
	2nd line	0	0.0%	0	0.0%	5	1.8%	5	1.1%	
Systemic CS	No	45	51.7%	47	68.1%	192	68.6%	284	65.1%	0.01
	1st line	38	43.7%	19	27.5%	81	28.9%	138	31.7%	X
	2nd line	4	4.6%	3	4.3%	6	2.1%	13	3.0%	
	3rd line	0	0.0%	0	0.0%	1	0.4%	1	0.2%	
Methotrexate	No	80	93.0%	66	95.7%	257	91.1%	403	92.2%	0.32
	1st line	4	4.7%	0	0.0%	5	1.8%	9	2.1%	
	2nd line	1	1.2%	3	4.3%	19	6.7%	23	5.3%	
	3rd line	1	1.2%	0	0.0%	1	0.4%	2	0.5%	
Ciclosporin	No	79	91.9%	62	89.9%	272	96.1%	413	94.3%	0.04
	1st line	5	5.8%	3	4.3%	1	0.4%	9	2.1%	
	2nd line	1	1.2%	4	5.8%	9	3.2%	14	3.2%	
	3rd line	1	1.2%	0	0.0%	1	0.4%	2	0.5%	
Biologics	No	83	96.5%	64	92.8%	253	89.7%	400	91.5%	0.048
	1st line	2	2.3%	1	1.4%	4	1.4%	7	1.6%	
	2nd line	1	1.2%	2	2.9%	12	4.3%	15	3.4%	
	3rd line	0	0.0%	2	2.9%	13	4.6%	15	3.4%	
Other treatments	No	46	52.9%	55	75.3%	0	0.0%	101	63.1%	0.003
	Yes	41	47.1%	18	24.7%	0	0.0%	59	36.9%	

TABLE E9. Antiinflammatory treatment used in the study population, overall and by blood eosinophil levels

CS: corticosteroids

*Patient numbers in the total cohort (N=453): ≥1.5 G/L, N=87; 1.0-1.49 G/L, N=73; 0.5-0.99 G/L, N=293; Patients with missing data were not included in the analysis.

**Mann-Whitney U test was used to assess changes of eosinophilia levels between categories of nominal variables, comparing treatment use vs. no use.

TABLE E10. Specification of therapy with biologics applied in 37 patients with dermatoses associated with blood eosinophilia

Biologic	Number of	Final diagnosis	Number of
	patients*		patients
Mepolizumab	7	L-HES	1
		Bullous pemphigoid	6
Omalizumab	7	Bullous pemphigoid	2
		Atopic dermatitis	2
		Urticaria vasculitis	1
		Indolent systemic mastocytosis	1
		Chronic pruritus, urticarial factitia	1
Dupilumab	5	Atopic dermatitis	5
Rituximab	4	L-HES	1
		Pemphigus foliaceus	2
		Mucocutaneous pemphigus	1
Adalimumab	8	Hidradenitis suppurativa	2
		Psoriasis arthritis	1
		Psoriasis	3
		Lichen planus	1
		Juvenile idiopathic arthritis	1
Ustekinumab	7	Psoriasis	7
Secukinumab	3	Psoriasis	3
Infliximab	1	Pyoderma gangraenosum	1

L-HES, lymphocytic variant of hypereosinophilic syndrome

* Some patients received more than one biologic.

TABLE I: Demographics of and history of neoplasia/cancer and atopic diseases in the study population at time of eosinophilia assessment, overall and by blood eosinophil levels

		Eosinophilia (G/L)									
		≥1.5		1.0-1.49		0.5-0.99		Total			
		N*=87	%	N*=73	%	N*=293	%	N*=453	%		
Sex	Male	45	51.7%	25	34.2%	150	51.2%	220	48.6%	0.31	
	Female	42	48.3%	48	65.8%	143	48.8%	233	51.4%		
Age (years)	Mean,	64.5	20.5	55.6	22.7	57.3	21.5	58.4	21.7	0.03	
	SD										
	< 50	20	23.0%	31	42.5%	99	33.8%	150	33.1%		
	50 - 69	24	27.6%	18	24.7%	95	32.4%	137	30.2%		
	≥ 70	43	49.4%	24	32.9%	99	33.8%	166	36.6%		
Max. eosinophilia	Mean,	2.8	2.1	1.2	0.1	0.7	0.1	1.2	1.2	-	
(G/L)	SD										
History of malignant	No	68	80.0%	63	88.7%	266	94.7%	397	90.8%	<0.001	
diseases	Yes	17	20.0%	8	11.3%	15	5.3%	40	9.2%		
History of atopic	No	47	58.8%	43	60.6%	135	60.0%	225	59.8%	0.90	
diseases***	Yes	33	41.3%	28	39.4%	90	40.0%	151	40.2%		

SD: standard deviation.

*Patients with missing data were not included in the analysis.

**Mann-Whitney U test was used to assess changes of eosinophilia levels between categories of nominal variables, while Spearman's rank correlation was used for continuous variables.

***Includes atopic dermatitis, bronchial asthma and allergic rhinitis or conjunctivitis/polyposis nasi.





Demographics Final diagnoses Clinical history and features Blood eosinophilia Diagnostic test results

ABD: autoimmune-bullous diseases; Antihyp: antihypertensive drugs; Diag: final diagnosis; Eos: eosinophilia; gen: generalized; HES: hypereosinophilic syndromes; Hist: patient history; hyp: hypersensitivity; infect: infectious diseases; LDH: lactate dehydrogenase; Leuco: leucocytes; loc: localized; Malign: malignant diseases; SPE: serum protein electrophoresis





ABD: autoimmune-bullous diseases; Diag: final diagnosis; Eczem/urtic: eczematous/urticarial; Eos: eosinophilia; Epid: epidermal/dermal/subcutaneous patterns; HES: hypereosinophilic syndromes; Histop: histopathological pattern; hyp: hypersensitivity; infect: infectious diseases; Malign: malignant diseases; Subepit blist: subepithelial blisters



AEC, absolute eosinophil count; BP, bullous pemphigoid; CT, computer tomography; H&E, hematoxylin and eosinin staining; HES, hypereosinophilic syndrome; IF, immunofluorescence; LDH, lactate dehydrogenase; WBC, white blood cell count

FIGURE 4