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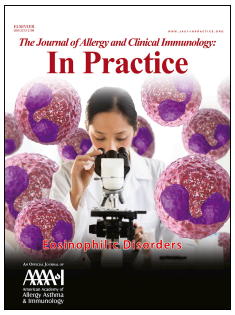

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Characteristics of dermatological patients with blood eosinophilia: a retrospective analysis of 453 patients

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ABSTRACT

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.

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 G/L (n=87; 19.2%), moderate, 1.0 – 1.49 G/L (n=73; 16.1%), and mild eosinophilia, 0.5 – 0.99 G/L (n=293; 64.7%). Most patients presented with chronic (64.6%), generalized skin lesions (75.9%), and pruritus (88.1%). Statistical analyses revealed three distinct patterns: 1. mild eosinophilia associated with localized skin disease, age <50 years, history of atopy, diagnosis of eczema or infectious disease, 2. moderate eosinophilia linked to generalized skin lesions, pruritus, age > 70 years, and autoimmune bullous disease, and 3. severe eosinophilia associated with diagnosis of hypereosinophilic syndromes, drug hypersensitivity or malignant disesase.

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

Highlights box:

1. What is already known about this topic?

   To make a differential diagnosis of dermatoses associated with blood or tissue eosinophilia is challenging as their manifestations are manifold. The underlying mechanisms causing eosinophilia are classified into intrinsic and reactive ones.

2. What does this article add to our knowledge?

   A pattern analysis of demographic, clinical and diagnostic test data of patients presenting with dermatoses associated with blood eosinophilia revealed an association of blood eosinophil levels with distinct clinical and diagnostic findings and corresponding diagnoses.

3. How does this study impact current management guidelines?

   The results of this study will help to optimize the diagnostic workup of dermatologic patients presenting with blood eosinophilia and their therapeutic management.

Key words:

Dermatosis, Eosinophilia, Hypereosinophilia, Skin, Pruritus, Dermatoses associated with blood eosinophilia

Abbreviations:

AEC	Absolute eosinophil count
BP	Bullous pemphigoid
CS	Corticosteroids
CT	Computer tomography
C3	Complement 3
DABE	Dermatoses associated with blood eosinophilia
EGPA	Eosinophilic granulomatosis with polyangiitis
FIP1L1-PDGFRA	FIP1-like1-platelet-derived growth factor receptor alpha
GPA	Granulomatosis with polyangiitis
HES	Hypereosinophilic syndromes
Ig	Immunoglobulin
IL	Interleukin
LDH	Lactate dehydrogenase
MRI	Magnet resonance imaging
PDGFRA/B	Platelet-derived growth factor receptor alpha/beta
SD	Standard deviation
WBC	White blood cells

INTRODUCTION

Skin diseases associated with eosinophilia either in the blood, tissue or both, are common despite the fact that the skin does not harbor eosinophils under physiologic conditions.[1] Eosinophil infiltration in the skin can typically be observed in allergic, autoimmune bullous, and infectious diseases, but also in association with hematologic diseases and tumors.[1-3] Cutaneous involvement is the most frequent initial clinical manifestation of hypereosinophilic syndromes (HES) as it affects 69% of patients.[4] A pattern analysis of chronic pruritus patients revealed tissue eosinophilia as a frequent histologic finding even if a diagnosis of an underlying skin disease was lacking, whereas blood eosinophilia was frequently observed in association with dermatological diseases.[5]

Based on the pathomechanisms, eosinophilic diseases are classified in primary (intrinsic) disorders with mutation or gene fusion-mediated clonal expansion of eosinophils, and secondary, cytokine-mediated (extrinsic) disorders.[6] Secondary eosinophilic diseases are caused by an increased expression of eosinophil hematopoietins that are produced by either T cells or tumor cells resulting in an increased differentiation and survival of eosinophils.[7] While eosinophilia associated with allergic responses and asthma is often mediated by interleukin (IL) 3 and/or IL-5, increased granulocyte-magrophage colony-stimulating factor levels are frequently associated with malignant tumors or lymphoma.[8-10] Recruitment of eosinophils to the tissue is mediated by eotaxins.[7]

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 blood might be the first clue before further diagnostic steps are initiated and 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 with associated blood eosinophilia (DABE) are not available.

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

METHODS

Study design and data collection

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 ≥ 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 ≥1.5 G/L (hypereosinophilia)[13], moderate, AEC 1.0 – 1.49 G/L, and mild eosinophilia, AEC 0.5 – 0.99 G/L. The electronic patient charts of all 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). Missing data arised owing to the retrospective study design revealing variable number of visits, diagnostic procedures and follow-up time.

The study was approved by the Ethics Committee of the Canton of Bern, Switzerland. General informed consent had been obtained from all patients prior to the study. All clinical investigations were conducted according to the principles of the Declaration of Helsinki.

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).

Semantic map analyses

Associations among clinically relevant selected variables were analyzed in two separate maps. The first one included patients' demographics (age and sex), blood eosinophil counts, final diagnoses, pruritus, distribution of skin lesions, patient history of atopic diseases and malignancy/cancer, use of antihypertensive drugs, results of leucocyte and lactate dehydrogenase (LDH) levels, and serum protein electrophoresis. The second map included presence of eosinophils in the skin, histologic pattern along with blood eosinophil counts and final diagnoses.

Both maps were generated by means of a data mining algorithm able to compute and display the strongest correlations between each pair of variables taking into account other covariates in the system.[5,14,15]

Briefly, multiple logistic regression models were fitted by taking each time, sequentially, a variable as the outcome and the other as covariates. This process 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 using inverse exponential transformation [$sign(B) * (1 - \mathrm{e}^{-\mathrm{sign(B)}*\mathrm{B}})$], mapping associations in the interval (-1, 1). A mathematical filter, the maximum spanning tree,[16] which is a spanning tree connecting variables (nodes of a graph) having maximum weight, was then applied to the matrix of weights and a semantic connectivity map was generated. The maximum spanning tree selected only positive associations ensuring normalized correlations in the interval [0, 1]. In addition, only connections with a p-value <0.15 were considered by the algorithm in order to avoid

212 unstable associations. In the map, hubs of variables were detected, with straight lines
213 showing the strongest associations, while spatial proximity between variables
214 indicating patterns of direct correlations. The strength of associations can be
215 interpreted as mild, moderate, or strong for values <0.6, 0.6-0.79 and ≥0.8
216 respectively.[14] The semantic map analysis was carried out using MATLAB v.9.4
217 (MathWorks, Natick, MA, USA).

RESULTS

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 ≥ 0.5 G/l. 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, 77.5%) among those with hypereosinophilia compared to other patients (see **Table E2** in the Online Repository).

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

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

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

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 malignancies,[17] was only observed in a single case of our dermatological patient cohort. The morphological spectrum of cutaneous lesions was broad with an eczematous pattern being the most frequent one followed by blistering and urticarial lesions (**Figure 1, *C***). Chronic skin problems were recorded in 277/429 patients (64.6%). To note, out of the patients with an acute exacerbation of their skin lesions (152/429, 35.4%), 44 (29%) of these patients had hypereosinophilia accounting for 51% in the severe eosinophilia group (see **Table E3** in the Online Repository).

Eczema is the most common dermatosis among DABE

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 diagnosed to have eczema including 79 patients (19%) with atopic dermatitis (see **Table E4** in the Online Repository). 56 patients (13.5%) had an autoimmune bullous disease, and 39 patients (9.4%) had a drug hypersensitivity reaction (**Figure 1, *D***). HES was diagnosed in 21 patients (5%). Intriguingly, in 5.5% of patients, the final diagnosis was psoriasis. An overall difference between eosinophil level and final diagnosis was found for eczema and infectious disease (mild eosinophilia), autoimmune-bullous disease (moderate eosinophilia), and HES (hypereosinophilia) (see **Table E4** in the Online Repository). When we searched for diagnoses such as granulomatosis with polyangiitis (GPA), eosinophilic GPA (EGPA), myeloproliferative neoplasia, human immunodeficiency virus infection, and hereditary diseases, we could not identify any of these.

Tissue eosinophilia is found in 75% of skin biopsies

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

Distinct blood parameter patterns in patients with moderate and severe eosinophilia

We also analyzed various blood parameters in order to identify associations with eosinophilia (see **Table E6** in the Online Repository). Pathologic results of WBC counts, LDH, and serum protein electrophoresis were more frequently observed in 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 (see **Table E6** in the Online Repository). Screening for the FIP1-like1-platelet-derived growth factor receptor α (FIP1L1-PDGFRA) fusion gene that has been associated with HES, was negative in all tested patients (n=8). For immunophenotyping of peripheral blood lymphocytes, flow cytometry using markers for CD4, CD5, CD6, CD7, CD8, CD10, CD26, CD27 and CD81 was performed.

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

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 ultrasound (n=94) were done for diagnostic purposes, e.g. to identify solid tumors, lymphandenopathy or hepatosplenomegaly. While pathologic findings related to eosinophilia on X-ray and sonography were reported in only 2 (1.5%) and 7 (7.4%) patients, respectively, CT scan analysis revealed those in 11 patients (25.6%), with no meaningful difference across the three groups (see **Table E8** in the Online Repository).

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

mepolizumab, omalizumab, dupilumab, rituximab, adalimumab, ustekinumab, secukinumab, and infliximab.

DISCUSSION

Our study provides a detailed analysis of demographic, clinical, and diagnostic data of patients presenting with cutaneous signs and symptoms who had concomitant blood eosinophilia. Our results suggest that the level of blood eosinophilia is associated with distinct clinical patterns in patients referred to a dermatological clinic. Blood eosinophilia with or without tissue eosinophilia might be the first abnormality that attracts attention in a diagnostic workup of dermatological patients. In view of the broad spectrum of eosinophilic dermatoses that can be limited to the skin or be associated with other organ involvements, a feasible diagnostic workup is required to make the correct diagnosis.[1-3]

By applying semantic connectivity map analysis, the following associations between blood eosinophilia and diagnoses were identified:

1. mild eosinophilia is associated with localized skin disease, age <50 years, history of atopy, and a diagnosis of eczema or infectious disease,
2. moderate eosinophilia is linked to generalized skin lesions, pruritus, age >70 years, and a diagnosis of autoimmune bullous disease, and
3. severe eosinophilia is associated with a diagnosis of HES, drug hypersensitivity or malignant disease.

Although these correlations are of limited precision, they show that blood AEC together with additional information such as age, distribution of skin lesions and other blood parameters, might be helpful for planning further diagnostic steps. We added conventional statistics to confirm and support the data gathered by semantic map analysis. To note, missing data have not been amended in order to reflect patient workup in real life. Additional features associated with hypereosinophilia that have

been identified by conventional statistical analyses, are older age, drug therapy, specifically antihypertensives, a history of malignant diseases, as well as elevated WBC count and serum LDH levels.

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]

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-mediated increased production, activation and survival of eosinophils.[6,13] Clonal eosinophilia can be part of various myeloid neoplasms and stem cell neoplasms, for instance, chronic eosinophilic leukemia, hematopoietic neoplasms with eosinophilia and abnormalities in PDGFRA, PDGFRB or FGFR1, myelodysplasic syndrome or aggressive systemic mastocytosis.[28] Therefore, patients with skin lesions, severe blood eosinophilia in addition to fever, weight loss, fatigue, malaise, and hepatosplenomegaly require immediate workup in order to identify the underlying

disease and other organ involvement.[29] On the other hand, by producing eosinopoietins, neoplastic disorders such as B- and T-cell lymphomas/leukemias, Hodgkin's disease, Langerhans cell histiocytosis and solid tumors can cause secondary eosinophilia.[28,30] Eosinophilic dermatosis associated with hematologic malignancies is mainly observed in patients with chronic lymphocytic leukemia. IL-5-producing T cells that are reactive to malignant B cells have been hypothesized to trigger eosinophil accumulation and activation, and subsequent skin manifestation.[31,32] Moreover, skin inflammation and pruritus are predominant findings in patients with eosinophilia attributed to aberrant T cells producing IL-5.[33-35] Indeed, in our study, we could identify dermatological patients with blood eosinophilia in association with malignant diseases. Although the number of cases was small, this observation indicates how important a thorough diagnostic workup is.

In our patient cohort, severe blood eosinophilia was also linked to the diagnosis of HES. A careful diagnostic workup of dermatological patients presenting with severe eosinophilia is mandatory in view of the fact that they frequently present with cutaneous signs and symptoms first.[4,17] In HES, these are polymorphic, ranging from 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 feature of patients with myeloproliferative HES, in particular FIP1L1-PDGFRA-positive HES.[29]

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

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

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.

Based on our pattern analysis, we suggest a diagnostic workup of patients with 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 our proposed diagnostic algorithm in larger groups of patients.

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FIGURE LEGENDS

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.

Table E1. Information extracted from electronic patient charts

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	
	Acute exacerbation	
Final diagnosis	Eczema	Atopic dermatitis, other eczema
	Drug hypersensitivity	
	Autoimmune bullous disease	Autoimmune bullous disease: bullous 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

	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

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	
If 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-Antagonists	*3*	*6.5*	*2*	*11.8*	*40*	*38.5*	*45*	*26.9*	*<0.001*
	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 drugs	No	72	90.0	66	95.7	240	96.4	378	95.0	0.048
	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: proton-pump 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.

Table E3. Distribution, morphology and exacerbation of skin lesions and pruritus 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*	%	
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 exacerbation	No	41	48.2%	47	68.1%	189	68.7%	277	64.6%	0.004
	Yes	44	51.8%	22	31.9%	86	31.3%	152	35.4%	

*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.

TABLE E4. Final diagnoses of patients with dermatoses associated with blood eosinophilia, 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*	%	
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

*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 X^2 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), l-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		0.5-0.99		Total		
		N*	%	N*	%	N*	%	N*	%	
Skin eosinophilia	No	16	22.2%	6	12.2%	52	28.0%	74	24.1%	0.11
	Yes	56	77.8%	43	87.8%	134	72.0%	233	75.9%	
Histologic pattern	Eczematous/ urticarial	49	70.0%	23	44.2%	109	57.1%	181	57.8%	0.31
	Subepithelial blisters	8	11.4%	10	19.2%	12	6.3%	30	9.6%	0.04
	Other epidermal/ dermal/ subcutaneous patterns	10	14.3%	1	1.9%	12	6.3%	23	7.3%	0.13
	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)								P**
		≥1.5		1.0-1.49		0.5-0.99		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 findings	10	83.3%	0	0.0%	1	33.3%	11	73.3%	0.03
	B cell abnormalities	2	16.7%	0	0.0%	0	0.0%	2	13.3%	
	T cell abnormalities	0	0.0%	0	0.0%	1	33.3%	1	6.7%	
	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.

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

		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
Aberrant B cells		2	1	0

TABLE E8. Body imaging findings 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*	%	
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%	

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.

TABLE E9. Antiinflammatory treatment used 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*	%	
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%	
	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%	

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 patients*	Final diagnosis	Number of 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)								P**
		≥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, SD*	*64.5*	*20.5*	*55.6*	*22.7*	*57.3*	*21.5*	*58.4*	*21.7*	0.03
	< 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 (G/L)	*Mean, SD*	*2.8*	*2.1*	*1.2*	*0.1*	*0.7*	*0.1*	*1.2*	*1.2*	-
History of malignant diseases	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%	
History of 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%	

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.

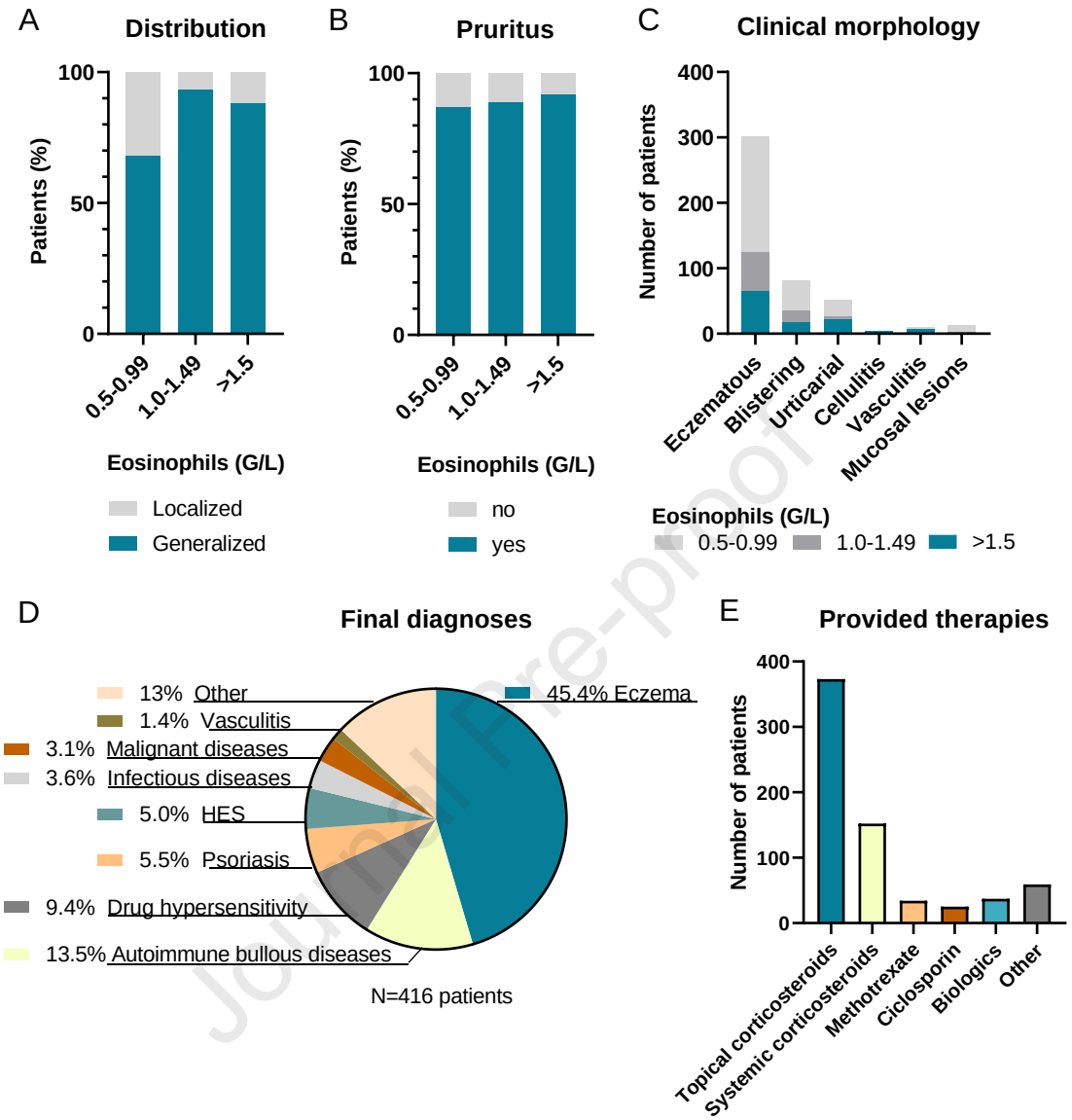
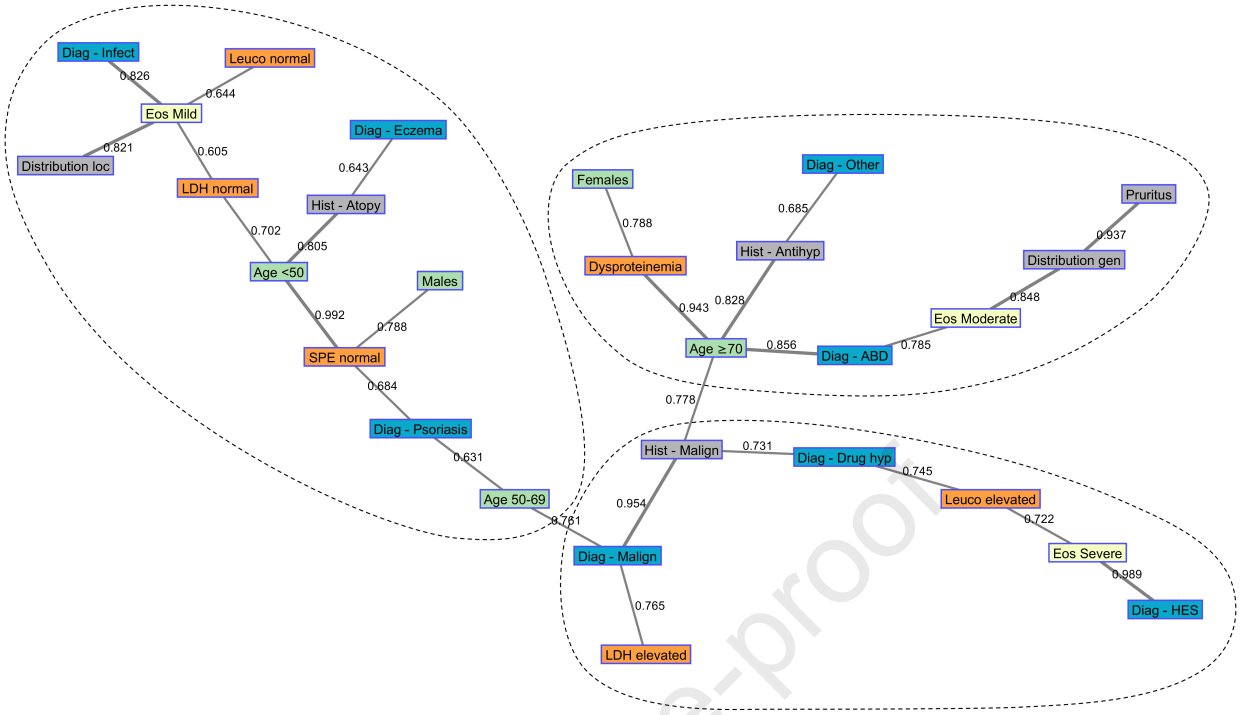
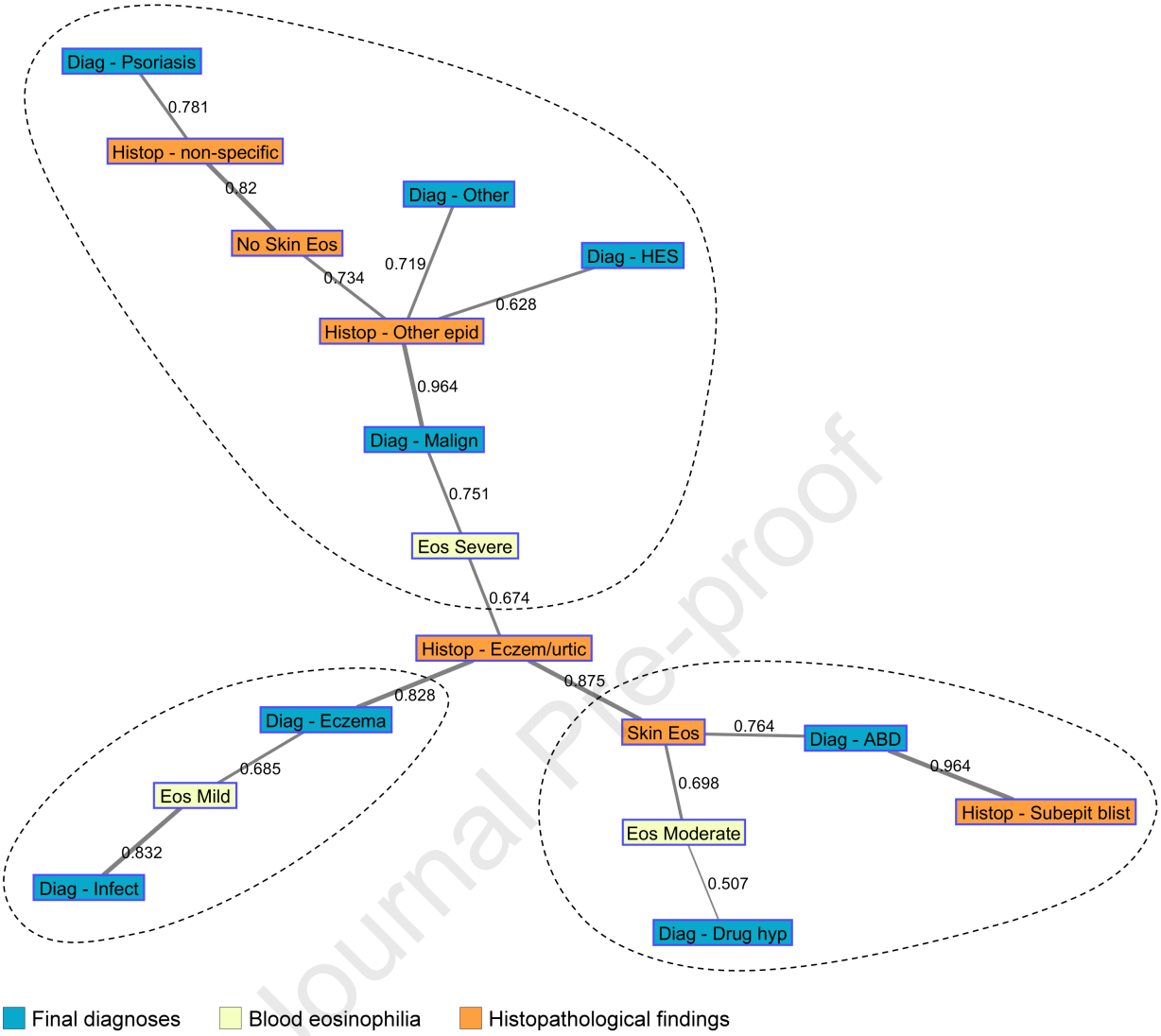


FIGURE 1

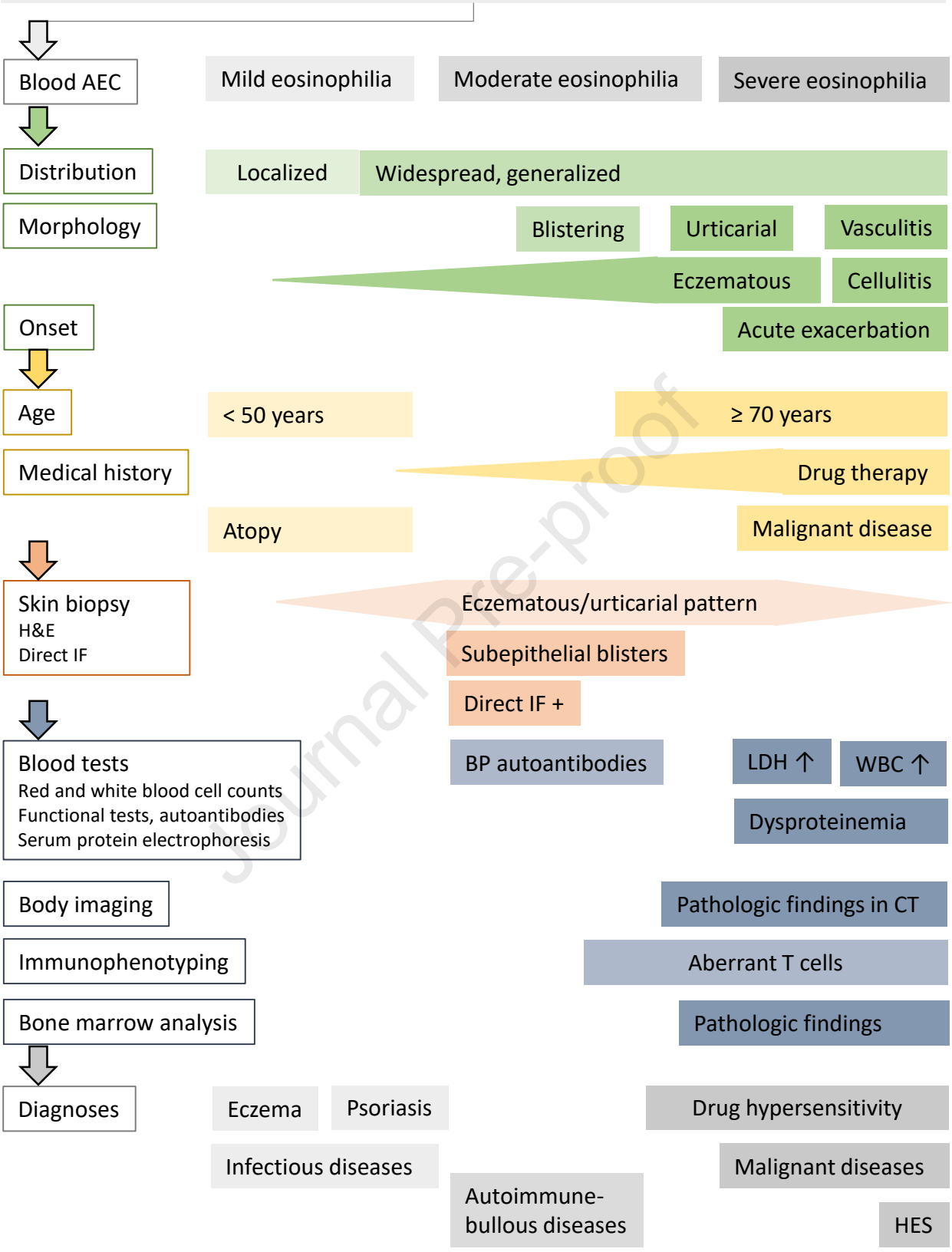


Demographics | Final diagnoses | Clinical history and features | Blood eosinophilia | Diagnostic test results

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