Immunologic Overlap of Helper T-Cell Subtypes 17 and 22 in Erythrodermic Psoriasis and Atopic Dermatitis

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**IMPORTANCE** Psoriasis and atopic dermatitis (AD) are inflammatory diseases thought to be mediated by helper T-cell subtypes 1 and 2 (Th1 and Th2), respectively. Although psoriasis and AD show histopathologic differences during chronic disease, they are difficult to distinguish histologically during erythrodermic exacerbations.

**OBJECTIVE** To determine whether the immune phenotype of helper T cells can differentiate erythrodermic psoriasis and erythrodermic AD by studying skin biopsy specimens of patients with psoriasis and AD during erythrodermic and chronic disease phases.

**DESIGN, SETTING, AND PARTICIPANTS** We conducted a retrospective study using biopsy samples of psoriasis, AD, and erythroderma belonging to the surgical pathology files of the James Homer Wright Pathology Laboratories, Massachusetts General Hospital, and collected from January 1, 2004, through December 31, 2011. Samples were obtained from patients with chronic psoriasis (n = 20), chronic AD (n = 20), erythroderma subsequently diagnosed as psoriasis (n = 7), and erythroderma subsequently diagnosed as AD (n = 5). We evaluated immunohistochemical stains for CD3 and dual stains for CD4 and T-bet, GATA binding protein 3 (GATA3), signal transducer and activator of transcription 3 (STAT3), or basonucin 2 (BNC2), which are transcription factors reported to be specific and mutually exclusive for Th1, Th2, Th17, and Th22 cells, respectively. Two investigators independently counted CD3+ cells and dual-labeled CD4+/T-bet+, CD4+/GATA3+, CD4+/STAT3+, and CD4+/BNC2+ cells in 5 consecutive high-power fields.

**MAIN OUTCOMES AND MEASURES** We evaluated the percentage of Th1, Th2, Th17, and Th22 cells in CD3+ T cells and the Th1:Th2 ratio in chronic psoriasis, chronic AD, erythrodermic psoriasis, and erythrodermic AD.

**RESULTS** We found a significant difference in the Th1:Th2 ratio between chronic psoriasis and chronic AD (0.26 and 0.09, respectively; P = .005). However, we detected no significant difference in the percentage of Th1 (6.5% and 4.8%), Th2 (55.2% and 64.6%), Th17 (14.7% and 30.4%), and Th22 (3.8% and 3.3%) cells of CD3+ T cells or in the Th1:Th2 ratio (0.16 and 0.07) within biopsy specimens from patients with erythrodermic psoriasis and AD, respectively.

**CONCLUSIONS AND RELEVANCE** This study confirms the Th1- and Th2-skewed phenotype of chronic psoriasis and chronic AD, respectively. However, the immune phenotype, as determined by immunohistochemical analysis, cannot discriminate between these inflammatory diseases in the erythrodermic phase. These findings advance our understanding of the pathophysiological characteristics of erythroderma, psoriasis, and AD and may influence therapeutic decisions.
Psoriasis and atopic dermatitis (AD) are common inflammatory skin diseases with significant impairment of quality of life; traditionally, they have been thought to be mediated by polar helper T-cell subtypes 1 and 2 (T₈₁ and T₈₂), respectively. Clinically, acute exacerbations of psoriasis and AD can result in erythroderma, a severe dermatitis characterized by diffuse erythema and scaling. Erythroderma represents a state of immune dysregulation and is a potential dermatologic emergency in some cases. Thus, rapid diagnosis and therapeutic control of the disease is essential.

Although psoriasis and AD are broadly characterized by altered epidermal differentiation and infiltration of helper T and dendritic cells, they show distinct histopathologic changes in chronic disease, such as the presence of epidermal neutrophil microabscesses in psoriasis and dermal eosinophilic infiltrates in AD. In contrast, the nature of the underlying inflammatory dermatosis is notoriously difficult to determine during erythrodermic disease flares using routine histologic analysis because of overlapping histologic changes. This difficulty often results in numerous repeated biopsies and close clinical follow-up.

Recently, T₈₁₇ cells, a distinct subtype of CD4⁺ helper T cells that are responsible for the production of interleukin 17 (IL-17) and IL-22, have been identified and have shown evidence of immunologic overlap between these disorders. Increased numbers of T₈₁₇ cells have been demonstrated in psoriatic skin, which has led to the development of T₈₁₇ antagonists for the treatment of psoriasis. In addition, elevated levels of circulating T₈₁₇ cells have been identified in patients with AD. Studies have also shown significantly increased expression of IL-17 in acute skin lesions of AD. The T₈₂₂ cells make up another distinct subset of helper T cells. Whereas T₈₂₂ cells produce most of the IL-22 in normal human skin and in AD, T₈₁, T₈₁₇, and T₈₂₂ cells are all believed to contribute to the production of IL-22 in psoriasis. Despite these findings, the helper T-cell phenotype has not been specifically characterized during erythrodermic disease flares. We sought to determine whether the helper T-cell immune phenotype could discriminate between psoriasis and AD in the erythrodermic phase of the disease.

In an effort to further explore the pathophysiological similarities and differences between psoriasis and AD, we examined skin biopsy samples from patients with chronic psoriasis and AD and from patients with erythroderma who were subsequently diagnosed as having psoriasis or AD. We carefully evaluated the immunohistochemical staining characteristics of T cells using antibodies to specific T₈₁, T₈₂, T₈₁₇, and T₈₂₂ cell transcription factors (T-bet, GATA binding protein 3 [GATA3], signal transducer and activator of transcription 3 [STAT3], and basonuclin 2 [BNC2], respectively). The specific aims of this study were to confirm the T₈₁- and T₈₂-skewed immune phenotypes of chronic psoriasis and AD, respectively, and to determine whether T₈₁₇ or T₈₂₂ cells predominate in clinically erythrodermic exacerbations. Such information could help to guide therapeutic intervention.

### Methods

#### Case Selection

This study was approved by the institutional review board of Massachusetts General Hospital, Boston. Patient data were de-identified. Biopsy specimens of psoriasis and AD collected from January 1, 2004, through December 31, 2011, were selected retrospectively from the surgical pathology files of James Homer Wright Pathology Laboratories, Massachusetts General Hospital. Specifically, 20 biopsy specimens of chronic psoriasis from 18 patients and 20 biopsy specimens of chronic AD from 17 patients were included. In addition, biopsy specimens from patients with erythroderma who were subsequently diagnosed as having psoriasis (n = 7) or AD (n = 5) underwent evaluation; these biopsy specimens will be termed "erythrodermic psoriasis" and "erythrodermic AD" hereinafter. Biopsy specimens from these patients during the chronic phase of the disease were included within the total number of chronic psoriasis or chronic AD biopsy specimens. Overall, 52 skin biopsy specimens from 43 patients underwent evaluation. Demographic data, including patient sex and age at the time of biopsy, were collected.

#### Histologic Evaluation

Hematoxylin-eosin–stained 5-µm sections of the formalin-fixed, paraffin-embedded skin biopsy specimens were reviewed to assess the presence of histologic features that included hyperkeratosis, hypogranulosis, acanthosis, spongiosis, vesiculation, microabscess formation, papillary vascular proliferation, and perivascular inflammatory infiltrate. In addition, we noted the composition (ie, lymphocytes and/or eosinophils) of the perivascular inflammatory infiltrate.

#### Immunohistochemical Analysis

We evaluated immunohistochemical stains for CD3 and dual stains for CD4 and T-bet, GATA3, STAT3, or BNC2 for all biopsy specimens. The immunohistochemical staining was performed using a commercially available autostaining device (Autostainer Plus; Dako North America, Inc) according to the manufacturer’s protocol. After deparaffinization, monoclonal antibodies against CD3 (Dako North America, Inc) or CD4 (Biocare Medical) and T-bet (Invitrogen), GATA3 (Sigma-Aldrich Co), STAT3 (LSBio), or BNC2 (Sigma-Aldrich Co) were applied to 5-µm tissue sections. The CD3⁺ cells and dual-labeled CD4⁺/T-bet⁺, CD4⁺/GATA3⁺, CD4⁺/STAT3⁺, and CD4⁺/BNC2⁺ cells in the dermal inflammatory infiltrate were counted in 5 consecutive high-power fields (original magnification ×400) independently by two of us (A.P.M. and R.M.N.). A dual-labeled cell was defined by the presence of cytoplasmic staining for CD4 (brown chromogen) and nuclear staining for the interrogated transcription factor (blue chromogen). The mean number of cells counted per high-power field was used to calculate the percentage of dual-stained T₈₁, T₈₂, T₈₁₇, and T₈₂₂ cells among CD3⁺ T cells.

#### Statistical Analysis

We used the χ² test and unpaired t test for categorical data and continuous variables, respectively. We compared the interob-
server variability of the cell counts performed on immunohistochemical stains with a paired t test. \( P < .05 \) was considered statistically significant.

**Results**

**Clinical Features and Histologic Evaluation**

We found no significant difference in the sex distribution or the mean age of patients with chronic psoriasis and chronic AD (Table 1) or of patients with erythrodermic psoriasis and erythrodermic AD (Table 2). Biopsy specimens of chronic psoriasis and chronic AD showed distinct histologic features (Table 1). Hypogranulosis, acanthosis, neutrophilic microabscess formation, and papillary dermal capillary proliferation were significantly associated with chronic psoriasis. In contrast, spongiosis, vesiculation, and the presence of perivascular eosinophils were significantly associated with chronic AD (Table 1 and Figure 1). However, we detected no significant difference in these features between erythrodermic biopsy specimens from patients subsequently diagnosed as having psoriasis or AD (Table 2 and Figure 2).

**Immunohistochemical Analysis**

We detected no statistically significant difference between the mean counts (per 5 consecutive high-power fields) of dual-labeled cells (CD4+/T-bet+, CD4+/GATA3+, CD4+/STAT3+, and CD4+/BNC2+ cells) obtained by the 2 evaluators (A.P.M. and R.M.N.). A significant difference was detected in the mean count (per 5 consecutive high-power fields) of CD3+ cells (\( P < .001 \)); the mean of the differences of these counts was 9.4. Discordant cases were limited to cases of chronic psoriasis and chronic AD and were resolved by results of a consensus examination.

A significant difference in the mean \( T_{H1}:T_{H2} \) ratio among chronic psoriasis and chronic AD lesions was detected (0.26 and 0.09, respectively; \( P = .005 \); Table 1). In addition, we found a significantly greater percentage of \( T_{H1} \) cells in chronic psoriasis compared with chronic AD (12.3% and 4.3%, respectively; \( P < .001 \); Table 1 and Figure 1). However, we found no significant difference in the percentages of \( T_{H2}, T_{H17} \), or \( T_{H22} \) cells among chronic lesions of either phenotype (Table 1 and Figure 1). In comparison, we found no difference in the percentages of \( T_{H1}, T_{H2}, T_{H17} \), and \( T_{H22} \) cells or in the \( T_{H1}:T_{H2} \) cell ratio among biopsy specimens of erythrodermic psoriasis and AD lesions (Table 2 and Figure 2).

**Discussion**

Psoriasis and AD are common inflammatory skin diseases that result from multiple genetic and environmental factors and are typically characterized by a chronic relapsing course. These diseases share some similarities in pathogenesis, such as altered differentiation of keratinocytes and abnormal cutaneous infiltration of lymphocytes and dendritic cells, but distinct clinical and histologic features can generally distinguish these diseases in their chronic phases; for example, epidermal neutrophil microabscesses are seen in biopsy specimens of psoriasis, whereas dermal eosinophil infiltrates are character-
istic of AD. Exacerbations can occur in both diseases and result in erythroderma, a severe condition characterized by generalized erythema and scaling of the skin. Erythroderma results from immune dysregulation, which culminates in a complex interaction of cytokines, chemokines, and intercellular adhesion molecules and leads to the infiltration of inflammatory cells to the skin and increased turnover of keratinocytes. Diffuse exfoliation of the skin is life threatening because significant loss of proteins, amino acids, and nucleic acids through the skin may cause high-output cardiac failure, fluid and electrolyte imbalances, and hypothermia. Loss of epidermal cells, their barrier function, and their innate immunemolecules contributestosusceptibilitytoinfection and septicemia. Thus, rapid diagnosis and therapeutic controlofthediseaseareimportant.

Inflammatory dermatoses, including psoriasis and AD, cause approximately 60% of cases of erythroderma, and clinical and histologic diagnosis of the underlying cause of erythroderma is difficult. Diffuse exfoliation of the skin is life threatening because significant loss of proteins, amino acids, and nucleic acids through the skin may cause high-output cardiac failure, fluid and electrolyte imbalances, and hypothermia. Loss of epidermal cells, their barrier function, and their innate immune molecules contributes to susceptibility to infection and septicemia. Thus, rapid diagnosis and therapeutic control of the disease are important. Inflammatory dermatoses, including psoriasis and AD, cause approximately 60% of cases of erythroderma, and clinical and histologic diagnosis of the underlying cause of erythroderma is difficult. In fact, no reports to date have identified reliable histopathologic features capable of distinguishing the underlying dermatosis in patients presenting with erythroderma that would enable prompt, appropriate, and specific therapy.

Psoriasis and AD have been thought to be mediated by TH1- and TH2-polarized immune responses, respectively. The distinct helper T-cell subtypes TH1 and TH2 are distinguished by the cytokines they produce. Interferon γ, the main proinflammatory cytokine produced by TH1 cells, activates macrophages directly and via antibody production. Uncontrolled proinflammatory TH1 responses can perpetuate autoimmune diseases and lead to excess tissue damage. The TH2 cytokines IL-4, IL-5, and IL-13 stimulate IgE-dependent reactions that activate mast cells and eosinophils. Thus, TH2 cells are implicated in allergic diseases.

However, this TH1/TH2 paradigm has been revised recently as additional helper T-cell subsets, including TH17 and TH22, have been described, providing new insight into our understanding of basic immunologic pathways. TH17 cells are characterized by the production of IL-17, IL-22, and interferon γ and have been implicated in the production of neutrophil, T-cell, and dendritic cell chemokines and the regulation of antimicrobial peptides in keratinocytes. Interleukin 17 expression has been demonstrated in lesional psoriatic skin (although absent in nonlesional skin) and within the peripheral circulation of patients with psoriasis. Subsequent studies have demonstrated increased numbers of TH17 cells within acute AD lesions and within the peripheral blood of patients with AD. Furthermore, the percentage of circulating TH17 cells correlated with increasing severity of disease among patients with AD. However, IL-17 production by TH17 cells is significantly greater in lesional skin from patients with psoriasis compared with those with AD, possibly owing to inhibition of TH17 cells by cytokines produced by TH2 cells in AD. This finding is supported by the observation that levels of antimicrobial peptides are decreased in the skin of patients with AD and by the clinical observation of the increased rate of infection in patients with AD compared with those with psoriasis.

Although TH17 cells produce IL-22, TH22 cells produce most of the IL-22 present in human skin. Significantly increased numbers of TH22 cells are present in chronic AD lesions compared with psoriasis lesions, and the number of TH22

### Table 2. Clinical and Pathologic Features of Erythrodermic Psoriasis and AD

<table>
<thead>
<tr>
<th>Feature</th>
<th>Erythrodermic Psoriasis</th>
<th>Erythrodermic AD</th>
<th>P Value</th>
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<td>Demographic</td>
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<td>Female sex, No. (%) of patients</td>
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<td>Age, mean (range), y</td>
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<td>Hyperkeratosis/parakeratosis</td>
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<td>5/5 (100)</td>
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<td>Acanthosis</td>
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<td>Spongiosis</td>
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<td>&gt; .99</td>
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<td>.47</td>
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<td>Papillary dermal capillary proliferation</td>
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<td>3/5 (60)</td>
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<td>Perivascular eosinophils</td>
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<td>4/5 (80)</td>
<td>.42</td>
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<td>Papillary dermal fibrosis</td>
<td>1/7 (14)</td>
<td>0/5 (0)</td>
<td>&gt; .99</td>
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**Abbreviations:** AD, atopic dermatitis; TH, T helper cell.

*Includes 7 specimens from patients with erythrodermic psoriasis and 5 from patients with erythrodermic AD.*
Figure 1. Histologic Features in the Inflammatory Phenotypes of Chronic Psoriasis and Atopic Dermatitis (AD)

Chronic Psoriasis | Chronic AD
--- | ---
![Image](A) | ![Image](B)

Epidermal neutrophilic microabscesses and a papillary dermal vascular proliferation are more commonly seen in psoriasis (A). Spongiosis and perivascular eosinophils are more commonly seen in AD (B) (A and B, hematoxylin-eosin, original magnification ×200). More CD4+/T-bet+ cells (helper T-cell subtype 1 [T H1]) are present within the inflammatory infiltrate of psoriasis (C) compared with AD (D). However, no difference is seen in the percentage of CD4+/GATA3+ cells (T h2 cells) within the inflammatory infiltrate of psoriasis (E) and AD (F). In addition, chronic psoriasis (G) and chronic AD (H) have no significant difference in the percentage of CD4+/STAT3+ cells (T h17 cells) and no significant difference in the percentage of CD4+/BNC2+ cells (T h22 cells) in psoriasis (I) and AD (J).

Positive staining is indicated by dual cytoplasmic (brown chromogen, eg, for CD4) and nuclear (blue chromogen, eg, for BNC2) positivity within a cell (C-J, original magnification ×400). BNC2 indicates basonuclin 2; GATA3, GATA binding protein 3; and STAT3, signal transducer and activator of transcription 3.
Figure 2. Histologic Features in Erythrodermic Psoriasis and Erythrodermic Atopic Dermatitis (AD)

Biopsy specimens of erythrodermic psoriasis (A) and erythrodermic AD (B) show overlapping histologic features (A and B, hematoxylin-eosin, original magnification ×200). No significant difference is seen in the inflammatory phenotype present in erythrodermic psoriasis and erythrodermic AD as evaluated by the percentage of CD4+/T-bet+ cells (helper T-cell subtype 1 [T H1]; C and D, respectively), CD4+/GATA3+ cells (T H2 cells; E and F, respectively), CD4+/STAT3+ cells (T H17 cells; G and H, respectively), or CD4+/BNC2+ cells (T H22 cells; I and J, respectively). Positive staining is indicated by dual cytoplasmic (brown chromogen, eg, for CD4) and nuclear (blue chromogen, eg, for BNC2) positivity within a cell (C-J, original magnification ×400). BNC2 indicates basonuclin 2; GATA3, GATA binding protein 3; and STAT3, signal transducer and activator of transcription 3.
cells present in AD lesions correlates with disease severity. In addition, increased circulating T_{H2} cells have been demonstrated in patients with psoriasis, and IL-22 is believed to play a critical role in epidermal acanthosis of psoriatic skin. Despite an overlap in pathophysiological characteristics, T_{H17} cells appear to work in concert with T_{H1} cells to cause psoriasis, whereas AD is mediated primarily by T_{H2} cells. As such, T_{H17} antagonists are currently under investigation for the treatment of chronic psoriasis. Results from clinical trials have shown promising results and are informing our understanding of the pathogenesis of psoriasis.

In this study, we sought to determine whether distinct helper T-cell subtypes can be detected in biopsy specimens from patients with chronic psoriasis and AD and aid in the diagnosis of the underlying disease process in patients with erythroderma. We studied biopsy specimens from patients with chronic psoriasis and AD and biopsy specimens from patients with erythroderma who were diagnosed as having psoriasis or AD on results of subsequent biopsies (erythrodermic psoriasis and erythrodermic AD, respectively). However, we hypothesized that the immune profile of the inflammatory infiltrate present in erythrodermic lesions would overlap because the clinical and histopathologic features in these patients are very similar. In fact, this investigation confirms that, although distinct histologic features are characteristic of psoriasis and AD in the chronic setting (ie, hypogranulosis, acanthosis, and epidermal neutrophilic microabscesses are suggestive of psoriasis, whereas vesiculation and perivascular eosinophils are suggestive of AD) (Table 1), no histologic finding studied can reliably distinguish these diseases in the setting of erythroderma (Table 2). An interesting observation was the presence of eosinophils in cases of chronic psoriasis and AD, both with increased frequency during erythrodermic disease exacerbations (Tables 1 and 2). Although the presence of eosinophils within the inflammatory infiltrate typically is associated with AD, eosinophils may be identified in lesions of psoriasis, particularly in the setting of severe or erythrodermic disease.

No single cell-surface marker is specific for T_{H1}, T_{H2}, T_{H17}, or T_{H22} cells, and immunohistochemical staining for secretory cytokines has inherent limitations, such as significant background staining, because these molecules are secreted by the producing cell, and intracellular and membrane-bound expression levels are typically low. Therefore, we performed dual immunohistochemical staining for CD4, a marker of helper T cells, and transcription factors reported to be specific and mutually exclusive for T_{H1}, T_{H2}, T_{H17}, and T_{H22} cell subtypes (T-bet, GATA3, STAT3, and BNC2, respectively). Dual-stained CD4+T-bet+ cells, CD4+/GATA3+ cells, CD4+/STAT3+ cells, and CD4+/BNC2+ cells were counted independently by 2 investigators, with similar results. A significant difference was detected in the mean T_{H1}/T_{H2} ratio of the dermal inflammatory infiltrate among chronic psoriasis and chronic AD lesions. Specifically, greater numbers of T_{H1} cells were found in chronic psoriasis and greater numbers of T_{H2} cells were found in chronic AD, confirming the T_{H1}- and T_{H2}-skewed helper T-cell phenotype of these diseases. However, this difference was not detected in biopsy specimens from patients with erythrodermic psoriasis and acute AD. In addition, we found no significant difference in the percentage of T_{H17} and T_{H22} cells (among CD3+ T cells) within the inflammatory infiltrate in biopsy specimens from chronic psoriasis vs chronic AD or erythrodermic psoriasis vs erythrodermic AD. Thus, these results reveal significant overlap in the types of helper T-cell subtypes present within the infiltrate of psoriasis and AD. Similar to previous reports, our findings suggest that T_{H17} and T_{H22} cells are involved in the pathophysiological characteristics of psoriasis and AD and that the functional overlap of these helper T-cell subtypes may be responsible for the overlap in histologic features seen on skin biopsy specimens from patients with erythroderma.

Although our results suggest an overlap in the role of T_{H17} and T_{H22} cells in the pathogenesis of erythroderma, we evaluated only the quantity of helper T-cell subtypes present with lesions of psoriasis and AD, and slight variability in the number or type of inflammatory cells present on each consecutive 5-μm tissue section may have affected our analysis. Furthermore, we did not evaluate the relative functionality of the helper T cells, that is, the amount of cytokine production present within the inflammatory infiltrate. Future studies may include investigation of the helper T-cell cytokine signature present in erythrodermic psoriasis and AD lesions with in situ hybridization or molecular techniques.

**Conclusions**

This study has determined that an overlap in the types of helper T-cell subtypes is present in erythrodermic psoriasis and AD, but distinct differences in the profile of secreted cytokines may exist. Such results may help to determine whether psoriasis or AD is the underlying cause of a patient’s erythroderma, thereby allowing for the prompt initiation of the appropriate therapy. Moreover, these experiments may elucidate cytokines that are important for regulating the helper T-cell phenotype that results in the clinical and histopathologic erythrodermic phenotype. These findings could lead to the use of new therapeutic strategies to improve the morbidity and mortality of patients with severe erythrodermic psoriasis and AD, such as the use of IL-17 antagonists for both diseases or the development of new monoclonal antibodies aimed at altering the helper T-cell phenotype during erythrodermic disease exacerbations. Overall, additional experiments to clarify our understanding of the pathophysiological characteristics of psoriasis and AD, especially the mechanisms that account for erythrodermic exacerbations, may allow for more informed and targeted therapeutic decisions.
Acquisition, analysis, or interpretation of data: Moy, Kroshinsky, Duncan, Nazarian.

Drafting of the manuscript: Moy, Nazarian.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Moy.

Obtained funding: Nazarian.

Administrative, technical, or material support: Moy, Murali, Kroshinsky.

Study supervision: Duncan, Nazarian.

Conflict of Interest Disclosures: None reported.

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