Eosinophilia in Dermatologic Disorders

Elisabeth de Graauw, MD[a,b], Helmut Beltraminelli, MD[a], Hans-Uwe Simon, MD[b], Dagmar Simon, MD[a,*]

KEYWORDS

• Eosinophils • Atopic dermatitis • Drug hypersensitivity reaction
• Cutaneous lymphoma • Eosinophilic dermatitis • Hypereosinophilic syndromes

KEY POINTS

- Cutaneous eosinophil infiltration is observed in a broad spectrum of dermatologic disorders including allergic, autoimmune, infectious, and neoplastic diseases and can be associated with blood eosinophilia.
- The clinical presentation of eosinophilic dermatoses varies considerably, but pruritus is a common symptom.
- The diagnosis of eosinophilic dermatoses is usually based on histology, unless clinical signs and symptoms are unmistakable.
- The accumulation of eosinophils in the skin is reactive in most cases owing to the production of eosinophilopoietic cytokines by T cells or tumor/lymphoma cells.
- A potential pathogenic role of eosinophils in skin diseases has been attributed to host defense, immunoregulation, and fibrosis.

DERMATOLOGIC DISORDERS WITH EOSINOPHILIA

The presence of eosinophils in the skin is common in a broad spectrum of cutaneous disorders. To note, the skin lacks eosinophils under physiologic conditions. The clinical presentations of eosinophilic skin diseases are highly variable and include eczematous, papular, urticarial, bullous, nodular, and fibrotic lesions. Pruritus is a unique and striking feature of all of them, although not pathognomonic. In some patients presenting with itchy skin lesions, the disease can easily be diagnosed considering the patient history, age, clinical findings and distribution, for example, atopic dermatitis (AD),

The authors have nothing to disclose.
[a] Department of Dermatology, Inselspital, Freiburgstrasse, Bern CH-3010, Switzerland; [b] Institute of Pharmacology, University of Bern, Inselspital, Bern CH-3010, Switzerland
* Corresponding author. Department of Dermatology, Inselspital, Bern University Hospital, Bern CH-3010, Switzerland.
E-mail address: dagmar.simon@insel.ch

Immunol Allergy Clin N Am 35 (2015) 545–560
http://dx.doi.org/10.1016/j.iac.2015.05.005 **immunology.theclinics.com**
0889-8561/15/$ – see front matter

insect bites, larva migrans infection, and drug reactions. Moreover, inflammatory skin lesions are the most common clinical manifestation of hypereosinophilic syndromes (HES),[1,2] To confirm or make the correct diagnosis, biopsies from active skin lesions have to be taken for histologic, immunohistochemical, and immunofluorescence investigations, and in some cases polymerase chain reaction analysis to check for clonality of infiltrating cells. Eosinophils can easily be identified by hematoxylin and eosin staining in skin biopsies. Their numbers, localization, and degranulation, as well as tissue damage, might provide diagnostic clues for the dermatopathologist; for example, flame figures in Wells' syndrome, V-shaped eosinophilic infiltrate in arthropod reactions, and eosinophil lining and blister formation at the dermal–epidermal junction in bullous pemphigoid (BP). The eosinophilia can be restricted to the skin, but may be accompanied by blood eosinophilia, for example, in AD, BP and cutaneous T-cell lymphoma (CTCL), and involve other organs as well, such as in a drug reaction with eosinophilia and systemic symptoms (DRESS). Associated blood eosinophilia may be as high greater than 1.5×10^6/L, as in HES.

PATHOGENIC MECHANISMS MEDIATED BY EOSINOPHILS

Although eosinophils are encountered in many skin diseases, their functional role in the pathogenesis remains largely unclear. There is evidence that eosinophils might contribute to pathogen defense, regulate inflammatory responses, and induce fibrosis/remodeling.[3,4] According to their cytokine expression, functionally different subpopulations seem to exist: eosinophils that potentially regulate inflammatory responses and/or fibrosis.[5] Moreover, the cytokine pattern of eosinophils is distinct in allergic reactive, infectious, and autoimmune diseases, as well as in lymphomas/tumors.[5] Eosinophils have been demonstrated to form extracellular DNA traps (EET) in the skin and thus may play a role in host defense.[3,6] Thymic stromal lymphopoietin, a cytokine expressed by epithelial cells, for example, in AD and BP, stimulates eosinophils to release EETs that are able to kill bacteria.[7] Other mechanisms by which eosinophils may release granule proteins are degranulation and cytolysis.[8,9] In flame figures, granule protein deposition coating collagen fibers can be detected, suggesting a role of eosinophils in tissue damage.[10] Interestingly, tissue damage mediated by major basic protein seems to be limited by extracellular aggregation generating large, nontoxic amyloid plaques.[11] In eczematous lesions, a correlation between eosinophils expressing matrix metalloproteinase-9 with interleukin (IL)-17^+ T cells and remodeling has been reported.[12] Moreover, eosinophils might be involved in causing pruritus, because they can affect skin nerves directly.[13]

CLINICAL PRESENTATIONS OF DERMATOSES WITH EOSINOPHILIA

Eczematous Pattern

Atopic dermatitis

AD is a chronic inflammatory skin disease based on a genetic predisposition. The prevalence is as high as 20% in children and 10% in adults. Typically, AD presents with pruritus and excoriated eczematous skin lesions on the face, neck, and extensor sites of the extremities in infants, and subsequent lichenification at the flexural folds in children and adults (**Fig. 1**A). The pathogenesis is complex, including an impaired skin barrier function that promotes adaptive immune responses to environmental allergens, together with inadequate innate immune responses to microbes followed by colonization of *Staphylococcus aureus* and viral infections.[14] The diagnosis of AD is based on the clinical signs rather than diagnostic procedures, which may identify triggers. Approximately 80% of AD patients have increased total and specific