Clinical reviews in allergy and immunology

Series editors: Donald Y. M. Leung, MD, PhD, and Dennis K. Ledford, MD

Organ-specific eosinophilic disorders of the skin, lung, and gastrointestinal tract

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Date of Original Release: July 2010. Credit may be obtained for these courses until June 30, 2012.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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List of Design Committee Members: Dagmar Simon, MD, Andrew Wardlaw, MD, PhD, and Marc E. Rothenberg, MD, PhD

Activity Objectives

1. To be able to identify the differential diagnosis of disorders associated with eosinophilic inflammation of the skin, lung, and gastrointestinal tract.
2. To understand the pathophysiology of disorders associated with eosinophilic inflammation of the skin, lung, and gastrointestinal tract.
3. To understand the mechanistic basis for the treatment of disorders associated with eosinophilic inflammation of the skin, lung, and gastrointestinal tract.

Recognition of Commercial Support: This CME activity has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: A. Wardlaw is on the Advisory Board for GlaxoSmithKline and receives research support from GlaxoSmithKline and Pfizer. M. E. Rothenberg is on the speakers' bureau for Merck; is a consultant for Merck, Centocor, Ception Therapeutics, Nycomed, and Array Biopharma; receives research support from the National Institutes of Health, the Food Allergy and Anaphylaxis Network, and the Dana Foundation; is on the Media Board for APFED; and is on the Executive Council for the International Eosinophil Society. D. Simon has declared no conflict of interest.

Eosinophils are multifunctional leukocytes that increase in various tissues in patients with a variety of disorders. Locally, they can be involved in the initiation and propagation of diverse inflammatory responses. In this review the clinical association of eosinophils with diseases of the skin, lung, and gastrointestinal tract is summarized. An approach to determining the causal role of eosinophils in these diseases is presented. Recent findings concerning molecular diagnosis, cause, and treatment are discussed. (J Allergy Clin Immunol 2010;126:3-13.)

Key words: *Asthma, cutaneous, dermatitis, eosinophilia, esophagitis, intestine, lung, respiratory, skin*

Eosinophils are multifunctional leukocytes implicated in the pathogenesis of numerous inflammatory processes, including infections (parasitic helminths, bacterial, and viral), nonspecific tissue injury, malignancy, and allergic diseases.[1] In response to a variety of stimuli, eosinophils are recruited from the circulation into the tissue, where they modulate immune responses through multiple mechanisms. Triggering of eosinophils by cytokines, immunoglobulins, and complement can lead to the release of an array of proinflammatory cytokines, such as chemokines, interleukins (eg, IL-2, IL-4, IL-5, IL-10, IL-12, IL-13, IL-16, and IL-18), TGF-α/β, lipid mediators (eg, platelet-activating factor and leukotriene C_4), free radicals, and mitochondrial DNA. These molecules have proinflammatory effects that include upregulation of adhesion systems, modulation of cellular trafficking, regulation of vascular permeability, mucus secretion, and smooth muscle constriction. In addition, eosinophils can initiate adaptive immunity by acting as antigen-presenting cells and secreting T_H cell chemokines. Furthermore, eosinophils can serve as major effector cells inducing tissue damage and dysfunction by releasing cytotoxic granule proteins, inflammatory lipid mediators, and mitochondrial DNA.[1] In this article we summarize the association of

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Supported in part by the National Institutes of Health National Institute of Allergy and Infectious Diseases, the Food Allergy and Anaphylaxis Network, the Food Allergy Project, the CURED Foundation, and the Buckeye Foundation (to M. E. R.).

Received for publication December 11, 2009; revised January 13, 2010; accepted for publication January 14, 2010.

Available online April 15, 2010.

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0091-6749/$36.00

doi:10.1016/j.jaci.2010.01.055

Abbreviations used
ABPA: Allergic bronchopulmonary aspergillosis
AD: Atopic dermatitis
AHR: Airway hyperresponsiveness
BP: Bullous pemphigoid
CSS: Churg-Strauss syndrome
DRESS: Drug reaction with eosinophilia and systemic symptoms
ECP: Eosinophilic cationic protein
EE: Eosinophilic esophagitis
EGID: Eosinophil-associated gastrointestinal disorder
EPF: Eosinophilic pustular folliculitis
GERD: Gastroesophageal reflux disease
HES: Hypereosinophilic syndrome
MBP: Major basic protein
SE: Severe exacerbation

eosinophils with diseases involving 3 tissues: the skin, respiratory tract, and gastrointestinal tract. Focusing on clinical data, we discuss differential disease diagnosis, therapy, and pathogenesis. A more detailed discussion of disease mechanisms and the detailed results of early eosinophil-targeted novel therapy are provided in another review in this issue.[2]

CUTANEOUS EOSINOPHILIA

Eosinophil infiltration is found in a broad spectrum of skin disorders (Table I).[3] It is a characteristic feature of allergic diseases or parasitic infestations, but it is also observed in autoimmune diseases and hematologic diseases, as well as in association with tumors and bacterial or viral infections. Depending on the disease, eosinophils can be the predominant cell infiltrate, such as in eosinophilic cellulitis, or can be part of a mixed inflammatory infiltrate in the dermis, such as in eczematous reactions. Eosinophils can infiltrate the epidermis, presenting as eosinophilic spongiosis in particular in autoimmune bullous diseases, insect bite reactions, or acute contact dermatitis. Eosinophil infiltration of the deep dermis and subcutaneous fat tissue can be observed in eosinophilic cellulitis, parasitic infections, erythema nodosum, vasculitis, or lymphomas. Peripheral blood eosinophilia can be associated with tissue eosinophilia, such as in drug reactions with eosinophilia and systemic symptoms (DRESSs), atopic dermatitis (AD), or bullous pemphigoid (BP).

In hematoxylin and eosin–stained skin specimens, eosinophils are noticeable as round-shaped cells stuffed with coarse eosinophil granules. In subacute and chronic eczematous lesions, disrupted oval-shaped eosinophils might also be found. Extracellular deposits of granular proteins can be detected in varying amounts either as separate little granules or as a thin coating on collagen bundles. The latter are called flame figures and can typically be seen in eosinophilic cellulitis. Immunofluorescence staining with antibodies directed against eosinophilic cationic protein (ECP) or major basic protein (MBP) allows a more sensitive detection of eosinophils and extracellular granular protein depositions compared with hematoxylin and eosin staining.

Eosinophils do not enter the skin under physiological states. Mechanistically, cutaneous eosinophilia can be from a primary problem internal to the eosinophil or might be caused by stimuli outside the cell.[3] In either case increased production, recruitment, and/or survival of eosinophils is likely. Hematologic disorders affecting multipotent or pluripotent hematopoietic stem cells might involve the eosinophil lineage. In these diseases mutations that represent intrinsic defects in eosinophils cause eosinophil proliferation and tissue infiltration, including in the skin. Cutaneous manifestations are described as multiple erythematous papules, plaques, and nodules or generalized erythematous maculopapular eruptions often associated with pruritus. By means of cytogenetic and molecular techniques, a number of diseases formerly defined as idiopathic hypereosinophilic syndrome (HES) can now be classified as separate entities. Clonal eosinophilia is often associated with rearrangements involving the genes of the platelet-derived growth factors A and B, resulting in increased tyrosine kinase activity.[4] Notably, patients with HES caused by the fusion of the *PDFGFRA* and *FIP1L1* genes respond to imatinib therapy.[4]

More commonly, extrinsic eosinophilic disorders are observed, in which skin eosinophilia is caused by cytokine release by either T cells or tumor cells. Cytokines involved in the development of skin eosinophilia include IL-3, IL-5, and GM-CSF. The expression of IL-5 in association with eosinophilic skin disorders has been reported in patients with AD,[5,6] exanthematous drug reactions,[7] urticaria,[8] episodic angioedema with eosinophilia,[9] BP,[10] eosinophilic fasciitis,[11] eosinophilic folliculitis,[12] cutaneous T-cell lymphoma,[13] eosinophilic cellulitis,[14] and HES with skin involvement.[15] IL-3 expression has been detected in blister fluids of patients with BP.[16] In patients with Langerhans cell histiocytosis,[17] as well as in patients with AD, atopy patch test reactions, and cutaneous late-phase reactions, the expression of both IL-3 and GM-CSF has been shown.[16,18] Expression of the chemokine eotaxin has been observed in patients with AD,[19] drug reactions,[20] autoimmune-blistering diseases (eg, dermatitis herpetiformis and BP),[21] parasitic dermatoses,[22] and

TABLE I. A selection of diseases associated with skin eosinophilia

Intrinsic disorders	Extrinsic disorders
Mutations of hematopoietic stem cells	Cytokines released by T cells
Chronic eosinophilic leukemia	Allergic diseases
Acute myeloid leukemia	AD
Chronic myeloid leukemia	Urticaria
Myelodysplastic syndromes	Drug reactions
Idiopathic HES	Autoimmune diseases
	BP
	Dermatitis herpetiformis
	Infectious diseases
	HIV
	Ectoparasitosis
	Insect bites
	Erythema chronicum migrans
	Erythema toxicum neonatorum
	Hyper-IgE syndrome (Job syndrome)
	EPF
	Granuloma anulare
	Angiolymphoid hyperplasia with eosinophilia
	Eosinophilic fasciitis
	Eosinophilic cellulitis (Wells syndrome)
	HES
	Inflammatory clonal T-cell disease
	Cutaneous T-cell lymphoma
	Langerhans cell histiocytosis
	B-cell lymphomas
	Hodgkin lymphomas
	Acute T-cell leukemia/lymphoma