Clinical reviews in allergy and immunology

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

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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.

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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

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

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

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

eosinophilic folliculitis[12] but also lymphomas (eg, cutaneous T-cell lymphoma) and Hodgkin disease.[23] The functional role of eosinophils in the pathogenesis of skin diseases remains largely unknown. Depending on the skin disease, a role in host defense, immunoregulation, and/or remodeling and fibrosis can be assumed. Specific cutaneous eosinophilic disorders are described below.

Eosinophilic cellulitis (Wells syndrome) and HES

As the name implies, Wells syndrome is characterized by an intense infiltration of eosinophils, extracellular granule deposition, and flame figures in the dermis. Patients present with recurrent episodes of acute pruritic dermatitis, seldom with blisters, painful edematous swellings, or persistent urticarial eruptions.[24] An increased expression of IL-5 has been reported in a number of cases. The cause is not known, but some patients had eosinophilic cellulitis in association with hematologic disorders, infections, or anti–TNF-α therapy. Corticosteroids are usually helpful in the treatment of Wells syndrome. Eosinophilic cellulitis can also occur as a cutaneous manifestation of HES. Other skin manifestations of HES are erythematous macules, papules or nodules, blisters, necrosis, ulcerations, purpura, lichenoid eruptions or urticarial lesions, and pruritus. The skin is affected in 37% of patients with HES.[25] Anti–IL-5 antibody therapy was shown to improve skin symptoms in patients with HES.[26] IL-5 producing clonal T cells has been identified in a subgroup of patients with HES. These T cells often exhibit an abnormal phenotype in as far as they have an either higher, lower, or absent expression of lineage-associated markers. Those patients usually present with cutaneous symptoms.[27]

Eosinophilic pustular folliculitis

Eosinophilic pustular folliculitis (EPF) presents as annular clusters of sterile follicular papules and pustules predominantly on the face and trunk that heal with postinflammatory hyperpigmentation but tend to recur periodically.[28] The histology shows a dense follicular and perifollicular infiltrate of eosinophils and scattered lymphocytes and sometimes follicular destruction. The classic type of EPF affects immunocompetent subjects. Meanwhile, 2 other subtypes of EPF have been identified. Infancy-associated EPF often involves the scalp. More commonly, EPF is seen in the context of immunosuppression. EPF has been reported in association with infections (in particular AIDS), medications, autoimmune diseases, and autologous peripheral blood stem cell and allogeneic bone marrow transplantation. A pathogenic role for eosinophils in response to fungi (*Malassezia* species), *Demodex* species mites, and bacteria has been suggested.

Drug reactions

Despite various cutaneous and histopathological presentations of drug reactions (eg, maculopapular rashes, erythema multiforme, acute generalized exanthematous pustulosis, and pseudolymphomatous and granulomatous drug reactions), the presence of eosinophils in the skin is a quite striking finding.[29] DRESS, also named hypersensitivity syndrome, presents with an acute, severe skin eruption that can develop from a maculopapular rash into erythroderma, as well as with fever, lymphadenopathy, hepatitis, blood eosinophilia, and other organ involvement caused by hypereosinophilia.[30] Eosinophils accompanied by other inflammatory cells are found in the skin and the lymph nodes. Severe hepatitis, in which eosinophilic infiltration or granulomas, as well as hepatocyte necrosis and cholestasis, are striking features, can result in

liver failure, accounting for the high mortality rate of 10%. The treatment is based on high-dose corticosteroids. Drugs known to cause DRESS are anticonvulsants, sulfa drugs, antimicrobial agents, anticancer drugs, nonsteroidal anti-inflammatory drugs, and antidiabetic agents.

AD

Tissue eosinophilia is a typical feature of AD. The numbers of eosinophils in the skin are usually modest (2.8 cells/mm^2; range, 0-90.3 cells/mm^2) and correlate with disease severity, as well as the degree of spongiosis in acute exacerbations and marked epidermal hyperplasia in chronic stages.[31] In addition to eosinophils, eosinophil-derived products, such as ECP, eosinophil-derived neurotoxin, and MBP, are present in increased amounts in the blood and skin of patients with AD. The measurement of ECP in serum is frequently used as a tool for monitoring AD activity and response to therapy.[32] Immunostaining with antibodies to MBP and ECP has demonstrated that eosinophil granule proteins are not only present inside eosinophils but also in the extracellular spaces, suggesting eosinophil degranulation. In biopsy specimens obtained from chronic AD lesions, intact eosinophils are located predominantly within the perivascular mononuclear cell infiltrate. In contrast, in the upper dermis extensive extracellular MBP deposition is observed in the near absence of intact eosinophils.[33] The presence of mostly disrupted eosinophils has been confirmed by using electron microscopic studies, which revealed various degrees of eosinophil degeneration ranging from intact eosinophils with granule abnormalities to intact eosinophils with abnormal granules and pseudopod-like extensions to eosinophils with degenerated cell, nuclear, or both membranes to free eosinophil granules.[34] Improvement of AD with both systemic and topical therapy is usually associated with a decrease in the numbers of eosinophils and other inflammatory cells in the skin. However, the administration of an anti–IL-5 antibody showed only moderate effects on clinical symptoms, although blood eosinophils were almost completely depleted.[35]

Autoimmune bullous diseases

BP is caused by an autoimmune response to structural components of junctional adhesion complexes, leading to damage of the dermal-epidermal junction with subepidermal blister formation.[36] Autoreactive B- and T-cell responses against the hemidesmosomal antigens BP180 and BP230 have been identified. IL-5 and eotaxin are abundant in blister fluids, and the production of IL-5 is associated with blood eosinophilia and significant eosinophil infiltration in the skin of patients with BP.[37] Eosinophils are thought to be implicated in blister formation by releasing toxic granule proteins (ECP and MBP) and proteolytic enzymes; however, the molecular mechanisms are not well understood. In dermatitis herpetiformis a specific cutaneous manifestation of gluten-sensitive enteropathy caused by anti-tissue transglutaminase antibodies, a neutrophilic infiltrate undermingled with eosinophils, is found in the papillary dermis. The expression of eotaxin in lesional skin and increased levels of serum ECP suggest a role for eosinophils in disease pathology.[21]

Neoplasms

In Langerhans cell histiocytosis, among the infiltrate of Langerhans cells, scattered or clustered eosinophils can be found in the papillary and deeper dermis, respectively.[38] Langerhans cells produce a broad spectrum of proinflammatory cytokines, such as

TABLE II. Eosinophilic lung diseases

Disease	Prevalence of disease	Degree of peripheral blood eosinophilia*	Comment
Asthma	Common	Mild (up to moderate in SEs and with nasal polyposis)	Eosinophils are most closely related to the phenotype of SEs.
Chronic obstructive pulmonary disease	Common	Mild	About 30% of patients have sputum eosinophilia, which is a marker of steroid responsiveness.
Eosinophilic bronchitis	Common (10% of chronic cough)	Mild	Patients present with nonproductive cough and steroid-responsive sputum eosinophilia.
Fungal airway colonization	Regarded as unusual but probably common in patients with more severe disease	Mild to moderate	Usually involves *Aspergillus fumigatus*, but other fungi are possible. ABPA is probably a florid expression of a common phenotype.
Eosinophilic pneumonia (EP)	Unusual	Moderate to severe	Acute presentations can have a variety of causes, including drug allergy and infection with helminths. Chronic EP is usually idiopathic.
CSS	Rare	Severe	Multisystem features and evidence of vasculitis and mononeuritis multiplex distinguish CSS from EP.
Idiopathic pulmonary fibrosis (IPF)	Unusual	Mild	Bronchoalveolar lavage eosinophilia is a feature of IPF and is thought to indicate poor prognosis.
Lung carcinoma	Common	Mild to severe	Lung carcinoma is an unusual cause of significant eosinophilia, generally in the context of extensive disease.
Infection with helminthic parasites	Common in countries where parasite infection is endemic	Severe	Such infections are associated with passage of larval forms through the lungs in association with acute infection. Loeffler syndrome is associated with ascariasis, *Ancylostoma* species, and *Strongyloides* species; visceral larva migrans with *Toxocara canis* or *Toxocara cati*; and tropical pulmonary eosinophilia with filarial parasites.

*Mild, 0.4 to 0.75×10^9/L; moderate, 0.75 to 1.50×10^9/L; severe, greater than 1.50×10^9/L.

GM-CSF, and chemokines and are thus likely to recruit and activate eosinophils directly or through stimulation of other cell types. Predominant T_H2 cytokine production by cutaneous T-cell lymphoma results in eosinophilia, extracellular granule protein depositions, and increased IL-5 levels in the skin, peripheral blood, or both.[39] Currently, it is not known whether the eosinophils modulate the proliferation of the malignant cells.

LUNG EOSINOPHILIA

Eosinophils are relatively rare in normal lungs, and therefore they stand out both in tissue and airway lumen samples when present in increased numbers. A number of lung diseases are associated with blood and tissue eosinophilia (Table II). The extent to which eosinophils cause tissue damage in these diseases remains controversial, but most evidence points to them as being proinflammatory effector cells in noninfectious disorders, in which they are prominent. The most common association, at least in industrialized countries, is with asthma and related airways diseases. Research into these conditions has resulted in much of our current understanding of the role of eosinophils in lung disease. These findings, as well as a summary of other eosinophil-associated lung conditions, will now be discussed in some detail.

Asthma and related airway diseases

There has been active debate about the role of eosinophils in asthma for at least the last 4 decades. Initially they were regarded as ameliorative cells able to dampen inflammatory responses, but this changed with the work of Seminario and Gleich,[40] who demonstrated that eosinophil basic proteins, particularly MBP, were toxic for bronchial epithelial cells and that MBP was present in large amounts in the airways of patients who had died from asthma. At the same time, controlled studies of bronchoscopy in patients with mild asthma demonstrated that a bronchoalveolar lavage eosinophilia tracked with active disease.[41] An assumption was made that the abnormal physiology that defines asthma (airway hyperresponsiveness [AHR]) and variable airflow obstruction was secondary to the airway eosinophilia. This hypothesis was underpinned by a persuasive paradigm that emerged in the 1990s that asthma was driven by activation in the bronchial mucosa of T_H2 lymphocytes, which, through the generation of IL-4, IL-5, and IL-13, are closely associated with blood and tissue eosinophilia both in human and animal models.[42-44] However, subsequent studies of induced sputum that allowed a more thorough examination of the relationship between airway inflammation and asthmatic airway dysfunction revealed at best a very

weak correlation between the degree of airway eosinophilia and the abnormal physiology. Conditions such as eosinophilic bronchitis, which presents as chronic cough, were identified in which airway eosinophilia occurred in the absence of airway dysfunction, and some asthmatic patients were identified who had airway dysfunction without eosinophilia.[45-47] Eosinophils are therefore neither necessary nor sufficient for an asthma-like airway dysfunction to be present.

Monoclonal antibodies against IL-5 have provided insight into the potential role of eosinophils in asthma. The drug that has been investigated in greatest detail is mepolizumab.[48] The first clinical efficacy study of mepolizumab was in a human allergen challenge model. This study demonstrated a marked reduction in blood and sputum eosinophil counts without any effect on either the early or late response or AHR. Although this was a small study, the interpretation of which was open to debate,[49] a larger trial of clinical asthma came to the same conclusion that eosinophils were not responsible for either the symptoms or physiological abnormalities that characterize asthma.[50] In this double-blind placebo-controlled study, 362 patients with moderate asthma were given 3 injections of drug 1 month apart. There was no difference in symptoms or lung function between the 2 groups. There was about a 50% reduction in severe exacerbations (SEs) in the 750-mg group, but the study was not powered to look at exacerbations, and this did not quite reach significance ($P < .061$). Of note, evidence of eosinophilic disease was not an entry criterion for the study, and sputum analysis was only undertaken in 37 patients. Another caveat to the conclusion that eosinophils are not causal in asthma pathophysiology is that although mepolizumab was very good at reducing blood and sputum eosinophil numbers, it only induced a modest (50%) reduction in bronchial wall eosinophil numbers.[50] Interestingly, this is similar to the effect of systemic steroids in refractory asthma, which have a marked effect on luminal eosinophils, but a much less marked effect on tissue eosinophils (Andrew Wardlaw, personal observation).[51] The reasons for this are not clear, but it suggests that IL-5 is more important in tissue-based eosinophil migration, whereas migration through the vascular endothelium into tissue is relatively IL-5 independent, with chemotactic stimuli perhaps being more important. This would be consistent with the observation that in contrast to 2-dimensional Boyden chamber–like assays, in a 3-dimensional model of tissue-based trafficking, migration in response to growth factors was more robust than migration in response to eotaxin.[52]

Do these clinical trials mean that eosinophils are not acting as effector cells in asthma? Two issues need to be considered.

First, in the above studies inclusion was not restricted to patients with eosinophilic disease. In patients with hypereosinophilic disease, many of whom had respiratory pathology, mepolizumab was highly effective in allowing a reduction in the dose of glucocorticoids required to control disease activity.[53]

Second, it depends what is meant by asthma. Clarifying this question requires a nuanced understanding of the pathophysiology of asthma and related airways diseases. Asthma was originally defined as marked variability in airflow obstruction over short (minutes) periods of time either spontaneously or in response to treatment, and this correlates very closely with the presence of AHR. Asthma symptoms of wheeze, chest tightness, and shortness of breath are closely related to this phenotype. However, over the last few decades, definitions of asthma have become more descriptive and have attempted to encompass the complete physiology seen in asthma and other airway diseases.[54] With the

new insights gained by very targeted treatments, such as mepolizumab, there is a strong case to be made for returning to the original definition.[55] It is helpful in this regard to deconstruct airway disease into its component pathophysiological abnormalities, a process that is aided by an A to E classification system.[56] In this scheme A stands for the "asthma/AHR" phenotype, B for "bronchitis," C for "cough," D for "damage" (fixed airflow obstruction, bronchiectasis, and emphysema), and E for "extrapulmonary factors," such as adherence, comorbidity, and triggers. Eosinophils are found in the bronchitis phenotype and are most closely associated with the clinical phenotype of SEs, although they are also associated with cough, particularly in conditions such as eosinophilic bronchitis. As noted above, the majority of persons dying of asthma (the end result of untreated SEs), have marked eosinophilic inflammation.[57,58] Eosinophils were the best predictors of SE in a steroid reduction study, and approaches to management targeting the airway eosinophilia resulted in a marked reduction in SEs.[59,60] It therefore follows that the patients who are most likely to respond to antieosinophilic therapy are those with marked eosinophilic airway inflammation who also have SEs. This was confirmed in a study of 12 months' treatment with mepolizumab in patients with refractory eosinophilic asthma with SE as the primary outcome measure in whom a significant 40% reduction in SEs was observed.[61] Predictably, there was no effect on lung function, AHR, or day-to-day asthma symptoms, although there was an improvement in quality of life reflecting the effect of SEs on morbidity. Interestingly, there was no effect on exhaled nitric oxide levels, dissociating this biomarker from eosinophilic inflammation and clinical improvement. These findings were echoed in a study published at the same time of patients with marked eosinophilic airway disease (several did not have AHR) using a steroid-reduction design in which mepolizumab was found to be highly effective at reducing exacerbations. A marked and significant reduction in steroid dose was possible in the active group compared with that seen in the placebo group.[62] These studies represent direct evidence that eosinophils are causal in the pathogenesis of asthma-associated SEs. An important outcome of these findings is that eosinophilic airway disease (which will respond to antieosinophilic therapy) is a distinct, albeit overlapping phenotype from asthma, as defined by Nair et al.[62] Studies of antieosinophil agents therefore need to have inclusion criteria and outcome measures relevant to the eosinophilic bronchitis phenotype rather than the asthma/AHR phenotype (variable airflow obstruction, AHR, and symptoms). These patients are clinically recognizable in an airways disease clinic and can also be identified as an eosinophil inflammation–predominant cluster in an objective multidimensional analysis of asthma phenotype.[63] These studies also provide some insight into the pathogenesis of asthma SEs.[64] As noted above, the major effect of mepolizumab was to reduce the luminal eosinophilia with a modest effect on tissue eosinophil numbers. It suggests therefore that SEs are principally a luminal event with obstruction caused by blockage of bronchi with mucus and cell debris rather than smooth muscle–mediated bronchoconstriction. This would be consistent with the pathology of asthma mortality, in which mucus impaction is often the primary pathological cause of death. It would also explain why SEs are often relatively bronchodilator resistant. Focusing on luminal events in relation to SEs would also be consistent with the well-established importance of viral infections in triggering SEs, presumably through an interaction with the epithelium in the context of eosinophilic inflammation.[65]

Fungal allergy

One of the more common causes of lung eosinophilia is fungal colonization. The most florid expression of this is allergic bronchopulmonary aspergillosis (ABPA), the primary diagnostic criteria of which are asthma, proximal bronchiectasis, a positive skin prick test response, positive specific IgE and IgG levels to *Aspergillus fumigatus*, and a high total IgE level.[66] Blood eosinophilia and positive sputum culture for *A fumigatus* are secondary criteria. Classically, patients present with exacerbations of their asthma characterized by fleeting lung shadows, but this presentation is now unusual, possibly because of the increased use of potent high-dose inhaled steroids. Marked, significant blood and tissue eosinophilia helps guide diagnosis. A number of other molds can cause an ABPA-like picture, most of which are other *Aspergillus* or *Penicillium* species, and IgE sensitization to a range of fungi is common in patients with more severe asthma.[67,68] Two studies have shown that treatment with antifungal agents is beneficial in patients with ABPA, although both were small and the benefits were modest.[69,70] Relatively few patients with asthma and a positive specific IgE level to *A fumigatus* fulfill all the criteria for ABPA, although whether *A fumigatus* plays a significant part in their asthma in these circumstances is not clear. Interestingly, patients with severe asthma and fungal sensitization had a significant improvement in quality of life after treatment with itraconazole, although this class of drugs increases endogenous steroid levels, which is a confounding factor.[71]

Eosinophilic pneumonia

Eosinophilic pneumonia is an uncommon condition characterized by a marked peripheral blood and tissue/bronchoalveolar lavage eosinophilia and pneumonic lung shadowing. Patients can present acutely with breathlessness, hypoxia, general malaise, and sometimes fever and can be very unwell. They respond dramatically to high-dose systemic steroids.[72] Occasionally, presumably because of rapid trafficking of eosinophils into the lung, the peripheral blood values can be in the normal range. In cases such as drug allergy or parasitic infection, in which there is an identifiable cause, recurrence can usually be avoided, but many patients with idiopathic disease often have chronic eosinophilic pneumonia with recurrent relapse requiring long-term oral steroids. Relapse of eosinophilic pneumonia is often of slow onset and associated with airflow obstruction in the absence of wheeze or bronchodilator responsiveness suggestive of small airways disease. Relapses invariably respond well to high-dose oral steroids.

Churg-Strauss syndrome

Churg-Strauss syndrome (CSS) is a rare condition in which patients have asthma (which is often severe), marked peripheral blood eosinophilia, and evidence of a multisystem vasculitic disorder.[72,73] Upper airway symptoms are common, and mononeuritis multiplex, which is often slow to respond to treatment, is a characteristic feature. The cause is unknown, and the extent to which eosinophils are directly responsible for the tissue damage is unknown (trials of mepolizumab in this condition have not yet been reported). It is interesting, however, that neural damage is such a feature considering the neurotoxic properties of eosinophil-derived neurotoxin and the neurotrophic properties of eosinophils.[74,75] Treatment of the acute phase consists of potent immunosuppressants, including high-dose systemic steroids, cyclophosphamide, and azathioprine, although in the longer term low-dose oral steroids are often sufficient

to maintain remission. There is an association between treatment with leukotriene receptor antagonists and the onset of CSS, but this is generally considered to be coincidental, although a causal relationship has not been ruled out.[76]

Chronic obstructive pulmonary disease

Tobacco smoking–associated chronic obstructive pulmonary disease is often a disease that is contrasted with asthma with a more neutrophilic and $CD8^+$ T cell–associated pathology. However, just as some asthma is noneosinophilic, quite a lot of chronic obstructive pulmonary disease is characterized by eosinophilic airway inflammation, particularly during exacerbations.[77] These patients are often more steroid responsive than their noneosinophilic counterparts.[78]

Parasitic lung disease

A number of helminthic parasites have a larval stage that passes through the lung and causes respiratory symptoms.[79,80] The exact pattern of illness varies with the parasite with various acronyms (Table II). Generally, the condition looks like a combination of asthma and eosinophilic pneumonia with low-grade fever, dry cough, chest discomfort, shortness of breath, wheeze, and occasionally hemoptysis. The chest radiograph classically shows lung shadowing that can be pneumonic in appearance and often lasts from a few days to weeks. Parasites can sometimes be identified in lung tissue samples. Tropical pulmonary eosinophilia caused by infection with filarial parasites can produce a more chronic illness with lethargy and anorexia in association with asthma-like symptoms and occasionally mediastinal lymphadenopathy, cavitation, and pleural effusion.

EOSINOPHILIC GASTROINTESTINAL DISORDERS

Eosinophils are present throughout the healthy gastrointestinal tract, except for the esophagus, which typically contains no eosinophils.[1] Eosinophil-associated gastrointestinal disorders (EGIDs) are characterized by a high level of eosinophils within isolated or multiple segments of the gastrointestinal tract. Over the past decade, there has been a striking increase in the incidence of primary EGIDs, as well as a robust increase in data linking the development of EGIDs to atopy. The most common form of EGID is eosinophilic esophagitis (EE), which is characterized by a relatively high level of eosinophils within the esophagus (without an acid-induced cause).[81] Other forms of EGIDs include eosinophilic gastritis, eosinophilic enteritis, eosinophilic colitis, and eosinophilic gastroenteritis. These disorders are less frequent than EE, but their pathogenesis and treatment are somewhat similar. Clinically, patients with EGIDs often have failure to thrive (especially in pediatrics), dysphagia, vomiting, abdominal pain, and/or diarrhea.[82] Patients with EE often present with symptoms that mimic gastroesophageal reflux disease (GERD). The number of eosinophils per high-power field required to diagnose an EGID has not been uniformly agreed upon, which can make the diagnosis of EGID challenging. For this reason, an experienced pathologist knowledgeable with the number of eosinophils typically found in the gastrointestinal tract at their medical center is essential for interpreting biopsy specimens in patients with suspected EGIDs. Agreed on criteria for the diagnosis of EGIDs are currently being pursued. The diagnostic criteria for EE established at the First International Gastrointestinal Eosinophilic Research Symposium is greater than 15 eosinophils per high-power field

noted in at least one of 4 biopsy specimens when GERD is ruled out.[81] The quantity and distribution of gastrointestinal eosinophils in pediatric patients without apparent pathologic disease has been reported,[83] although the application of these data to the diagnosis of EGID has not been established. In addition to the increased eosinophil numbers, the usual morphology of the gastrointestinal tract is typically disrupted in patients with EGIDs. Depending on the location of the eosinophil accumulation, additional manifestations might include the presence of eosinophilic microabscesses, disruption of the surface epithelium cryptitis, basilar hypertrophy, or lamina propria fibrosis.[84] Although the presence of increased eosinophil numbers and disruption of the typical gastrointestinal tract morphology are crucial for the diagnosis of EGID, the isolated presence of gastrointestinal eosinophilia is not sufficient. The differential diagnosis for gastrointestinal eosinophilia is broad and includes EGIDs, HES, collagen vascular disease, inflammatory bowel disease, and parasitic or fungal infection; disease differentiation based on primary or secondary causes is useful (Table III). To diagnose an EGID, the patient must have a biopsy specimen and clinical presentation consistent with the EGID; other causes of gastrointestinal eosinophilia (eg, parasitic infection and drug hypersensitivity) must be ruled out. This review will focus on primary EGIDs not associated with known causes for the eosinophilic inflammation.

EE

The esophagus normally does not contain eosinophils, and therefore the finding of esophageal eosinophils denotes pathology. In addition to EE, many disorders are accompanied by eosinophil infiltration in the esophagus, such as GERD, eosinophilic gastroenteritis, parasitic and fungal infections, inflammatory bowel disease, HES, esophageal leiomyomatosis, myeloproliferative disorders, carcinomatosis, periarteritis, allergic vasculitis, scleroderma, and drug injury.[85] EE is classified into primary and secondary subtypes, with the primary subtype including the atopic, nonatopic, and familial variants and the secondary subtype including one composed of systemic eosinophilic disorders (eg, HES) and another composed of noneosinophilic disorders (Table III). Primary EE has also been called idiopathic EE or allergic esophagitis. The sibling recurrence risk ratio has been estimated to be greater than 50-fold,[86] and the familial form of EE is noted in about 10% of patients.[87]

The cause of EE is poorly understood, but food allergy has been implicated. In fact, most patients have evidence of food and aeroallergen sensitization as defined by skin prick tests, allergen-specific IgE tests, or both; however, only a minority have a history of food-induced anaphylaxis.[88] Evidence suggests that esophageal eosinophilic inflammation is mechanistically linked with pulmonary inflammation based on the finding that delivery of specific allergens or the T_H2 cytokine IL-13 to the lungs of mice induces experimental EE.[89,90] Reports of increased eosinophil levels in the esophagus of patients with seasonal allergic rhinitis with hypersensitivity to grass have been published.[91] Recent studies have found a strong relationship between atopy and EE.[92-94] Indeed, patients with EE commonly report variable seasonal symptoms. In addition to eosinophil numbers, T-cell and mast cell numbers are increased in esophageal mucosal biopsy specimens, suggesting chronic T_H2-associated inflammation.[95] Exposure to antigen through an epicutaneous route primes for marked eosinophilic inflammation in the esophagus triggered by only a single respiratory antigen exposure.[96] IL-5 is required for

TABLE III. Categories of EGIDs*

Eosinophil-associated esophagitis
  Primary EE (>15 eosinophils per high-power field without GERD)
    Atopic
    Nonatopic
    Familial
  Secondary
    Eosinophilic disorders
      Eosinophilic gastroenteritis
      HES
    Noneosinophilic disorders
      Iatrogenic
      Infection (typically helminthic)
      GERD
      Esophageal leiomyomatosis
      Connective tissue disease (scleroderma)
Eosinophil-associated gastroenteritis
  Primary (mucosal, muscularis, and serosal forms)
    Atopic
    Nonatopic
    Familial
  Secondary
    Eosinophilic disorders
      HES
    Noneosinophilic disorders
      Celiac disease (typically not responsive to gluten avoidance alone)
      Connective tissue disease (scleroderma)
      Iatrogenic
      Infection (typically helminthic)
      Inflammatory bowel disease
      Vasculitis (CSS)
Eosinophil-associated colitis
  Primary eosinophilic colitis (also allergic colitis of infancy)
    Atopic
    Nonatopic
  Secondary
    Eosinophilic disorders
      Eosinophilic gastroenteritis
      HES
    Noneosinophilic disorders
      Celiac disease
      Connective tissue disease (scleroderma)
      Iatrogenic
      Infection
      Inflammatory bowel disease
      Vasculitis (CSS)

this eosinophilic inflammation, suggesting a T_H2-dependent mechanism. Notably, overexpression of IL-5 induces EE, and neutralization of IL-5 completely blocks allergen or IL-13–induced EE in mice.[89,90,97]

A landmark advance in EE research is the recent genome-wide microarray profile analysis of esophageal tissue.[98] Investigators compared gene transcript expression in esophageal tissue of patients with EE, patients with chronic esophagitis (typical of GERD), and healthy subjects. Notably, dysregulated expression of approximately 1% of the human genome led to the identification of an EE genetic signature. Interestingly, eotaxin-3 was the most overexpressed gene in patients with EE, and levels correlated with disease severity, a finding that has now been independently replicated.[99] Furthermore, a single nucleotide polymorphism in the eotaxin-3 gene was overrepresented in patients with EE compared with control subjects. Interestingly, mice

with a genetic ablation of the eotaxin receptor (CCR3) were protected from the development of experimental EE. Notably, eotaxin-3 has been shown to be produced by esophageal epithelial cells and induced by the T_H2 cytokine IL-13, which is also markedly overexpressed in the esophagus of patients with EE.[100] Taken together, these results strongly implicate eotaxin-3 in the pathogenesis of EE and offer a molecular connection between T_H2 inflammation and the development of EE.

A specific food allergen avoidance trial is often indicated for patients with atopic EE, and if unsatisfactory or practically difficult (when patients are sensitized to many allergens), a diet consisting of an elemental (amino acid–based) formula is often advocated. Interestingly, it has been shown that an elemental diet has the potential to reduce the number of eosinophils in the esophageal biopsy specimens and improve symptoms in patients with primary EE (allergic or nonallergic subtypes).[101] Patients on elemental diets frequently require a surgically placed gastrostomy tube to achieve adequate caloric support. Glucocorticoids (systemic or topical) have also been used with satisfactory results. Systemic glucocorticoids are used for acute exacerbations, whereas topical glucocorticoids are used to provide chronic control. A study that followed patients with EE for 10 years supports the efficacy of continuing corticosteroids and food elimination therapy for EE.[101] When using topical steroids, we recommend the use of a metered-dose inhaler without a spacer and having the patient swallow the medicine to promote deposition on the esophageal mucosa. The toxicity associated with inhaled glucocorticoids (eg, adrenal suppression) is unlikely to be seen with swallowed fluticasone because of first-pass hepatic metabolism after gastrointestinal absorption. However, about 10% of patients treated with topical fluticasone have esophageal candidiasis. Although the metered-dose inhaler is recommended with topical fluticasone, another study has shown the success of using an oral suspension of budesonide in patients with EE who were unable to use inhalers.[102] In the first placebo-controlled double-blind trial in patients with EE, swallowed topical fluticasone was demonstrated to be effective in inducing disease remission, including reduction in eosinophil, mast cell, and CD8 T-cell levels, as well as the degree of epithelial hyperplasia.[103] Notably, only half of the patients responded to topical glucocorticoids, and 10% responded to placebo. A recent study also showed the promising effect of anti-human–IL-13 antibody in an animal model of IL-13–induced airway and esophageal eosinophilia.[104] In addition, in 2 open-label trials humanized anti–IL-5 mAb therapy has been shown to be helpful in small numbers of patients.[105,106] Larger-scale trials are currently underway. Finally, even if GERD is not present, neutralization of gastric acidity with proton pump inhibitors might improve the symptoms and degree of esophageal pathology.

Eosinophilic gastritis and gastroenteritis

In contrast to the esophagus, the stomach and intestine have readily detectable baseline eosinophils under healthy conditions, confounding the diagnosis of EGID involving these tissues. For the purposes of this review, eosinophilic gastritis, enteritis, and gastroenteritis are grouped together because they are similar clinically and because there is a lack of information available concerning their pathogenesis; however, it is likely that they are indeed distinct processes in most patients. These diseases are characterized by the selective infiltration of eosinophils in the stomach, small intestine, or both with variable involvement of the esophagus, large intestine, or both. It is now appreciated that many

diseases are accompanied by eosinophilia in the stomach, such as infection (parasitic and bacterial) including *Helicobacter pylori*, periarteritis, inflammatory bowel disease, allergic vasculitis, HES, myeloproliferative disorders, scleroderma, drug injury, and drug hypersensivity.[82] Similar to EE, these disorders are classified into primary and secondary subtypes. The primary group includes the atopic, nonatopic, and familial variants, whereas the secondary subtype contains 2 groups, one composed of systemic eosinophilic disorders (eg, HES) and another composed of noneosinophilic disorders (Table III). Primary eosinophilic enteritis, gastritis, and gastroenteritis have also been called idiopathic or allergic gastroenteropathy. Primary eosinophilic gastroenteritis involves multiple disease entities subcategorized into different types based on the level of histologic involvement: mucosal, muscularis, and serosal forms.[107] Of note, either layer of the gastrointestinal tract can be involved; as such, endoscopy and biopsy results can be normal in patients with the muscularis, serosal, or both subtypes.

Although these diseases are idiopathic, an allergic mechanism has been suggested.[108] Indeed, increased total IgE and food-specific IgE levels have been detected in most patients. On the other hand, focal erosive gastritis, enteritis, and occasionally esophagitis with prominent eosinophilia, such as the dietary (food) protein–induced enterocolitis and dietary protein enteropathy, are characterized by negative skin test results and absent specific IgE.[109] Most patients have positive skin prick test responses to a variety of food antigens but do not have typical anaphylactic reactions, which is consistent with a delayed-type food hypersensitivity.

In clinical studies increased production of T_H2-associated cytokines (eg, IL-4 and IL-5) by peripheral blood T cells has been reported in patients with eosinophilic gastroenteritis.[108] Furthermore, lamina propria T cells derived from the duodenum of patients with EGID preferentially secrete T_H2 cytokines (especially IL-13) when stimulated with milk proteins.[110] IgA deficiency has also been associated with eosinophilic gastroenteritis; perhaps this could be related to the associated increased rate of atopy or to an occult gastrointestinal infection in these patients. Eosinophilic gastroenteritis and the dietary protein–induced syndromes (enterocolitis, enteropathy, and colitis) might represent a continuum of EGID with similar underlying immunopathogenic mechanisms. In addition, eosinophilic gastroenteritis can frequently be associated with protein-losing enteropathy.[111]

Eliminating the dietary intake of the foods implicated by skin tests (or measurement of allergen-specific IgE levels) has variable effects, but complete resolution is generally achieved with elemental diets.[111] Once disease remission has been obtained by means of dietary modification, the specific food groups are slowly reintroduced (at approximately 3-week intervals for each food group), and endoscopy is performed every 3 months to identify disease status. Drugs such as sodium cromoglycate, montelukast, mycophenolate mofetil (an inosine monophosphate dehydrogenase inhibitor), ketotifen, suplatast tosilate, and "alternative Chinese medicines" have been suggested but are generally not successful. However, a publication reported a successful long-term remission of eosinophilic gastroenteritis after montelukast treatment.[112] In our institution an appropriate therapeutic approach includes a trial of food elimination if sensitization to food is found by means of skin tests, measurement of specific IgE levels, or both. If no sensitization is found or if specific food avoidance is not feasible, elemental formula feedings are initiated.

The management of eosinophilic gastroenteritis, in addition to an amino acid–based diet, includes the following: systemic and

topical steroids, noncorticosteroid therapy, and management of other EGID complications (eg, iron deficiency and anemia).[113] Anti-inflammatory drugs (systemic or topical steroids) are the main therapy if diet restriction has failed or is not feasible. There are several forms of topical glucocorticoids designed to deliver drugs to specific segments of the gastrointestinal tract, such as budesonide tablets (Entocort EC; Prometheus Laboratories, Inc, San Diego, Calif) designed to deliver drug to the ileum and proximal colon. In severe cases refractory or dependent on glucocorticoid therapy, intravenous alimentation or immunosuppressive antimetabolite therapy with azathioprine or 6-mercaptopurine are alternatives. Finally, even if GERD is not present, neutralization of gastric acidity with proton pump inhibitors can improve symptoms and the degree of esophageal and gastric pathology.

Eosinophilic colitis

Eosinophils accumulate in the colons of patients with a variety of disorders, including infection (pin and dog hookworms), eosinophilic gastroenteritis, allergic colitis of infancy, drug reactions, and vasculitis (eg, CSS and inflammatory bowel disease).[114] Dietary protein–induced proctocolitis of infancy syndrome (also known as allergic colitis of infancy) is the most common cause of blood in the stool in the first year of life.[115] Similar to other EGIDs, these disorders are classified into primary and secondary types (Table III), with the primary type including the atopic and nonatopic variants composed of systemic eosinophilic disorders (eg, HES) and the other by noneosinophilic disorders.

Eosinophilic colitis is usually a non–IgE-associated disease. In fact, some studies point to a T lymphocyte–mediated process, but the exact immunologic mechanisms responsible have not been identified.[116] It has been reported that allergic colitis of infancy might be an early expression of protein-induced enteropathy or protein-induced enterocolitis syndrome. Cow's milk and soy proteins are the most frequently implicated foods in allergic colitis of infancy, but a variety of food proteins can also provoke the disease. Interestingly, this condition can more commonly occur in infants exclusively breast-fed and can even occur in infants fed with protein hydrolysate formulas.

Treatment of eosinophilic colitis varies primarily depending on the disease subtype. Eosinophilic colitis of infancy is generally a benign disease. On removal of the offending protein in the diet, the gross blood in the stools typically resolves within days, but occult blood loss might persist longer. Treatment of eosinophilic colitis in older subjects usually requires medical management because IgE-associated triggers are usually not identified. Drugs such as montelukast, sodium cromoglycate, and histamine receptor antagonists are typically not successful. Anti-inflammatory drugs, including aminosalicylates and systemic or topical glucocorticoids, appear to be efficacious, but careful clinical trials have not been conducted. There are several forms of topical glucocorticoids designed to deliver drugs to the distal colon and rectum, but eosinophilic colitis usually involves the proximal colon. In severe cases alternative therapy includes intravenous alimentation or immunosuppressive therapy with azathioprine or 6-mercaptopurine.

SUMMARY

Eosinophilic tissue diseases are a heterogeneous group of diseases that include common conditions, such as asthma and AD; less common but regularly diagnosed diseases, such as EE; and rare diseases, such as eosinophilic pneumonia and CSS. The eosinophilia in these diseases might be associated with allergy to common aeroallergens but include rarer causes of eosinophilia, such as drug allergy and (in nonindustrialized countries) parasitic infection. However, in many patients with eosinophilic tissue disease, the cause remains elusive. Eosinophilic tissue disease is almost invariably highly responsive to glucocorticoids, which are the mainstay of treatment. True steroid resistance is rare, although in refractory diseases in which the inflammation is peripheral, systemic as opposed to topical steroids are often required. Apparent steroid resistance in eosinophilic disease should always raise questions about adherence to treatment. Although usually effective, systemic steroid therapy is limited by toxicity, providing the impetus for better antieosinophil drugs. Promisingly, anti–IL-5 strategies appear to be well tolerated and effective and provide strong clues about the role of eosinophils in various tissue diseases. To optimally use these drugs, we need to recognize that eosinophilic tissue diseases have distinct features. For example, in the case of the lung, asthmatic patients that might benefit from anti-eosinophil–directed therapy have a selective phenotype, including marked blood and/or sputum eosinophilia, nasal polyposis, and patterns of recurrent severe steroid responsive exacerbations. Taken together, emerging concepts have been presented that highlight the seriousness of eosinophil-associated tissue diseases, the potential role of eosinophils in these processes, and appropriate approaches to differential diagnosis and therapy.

What do we know?
- **Eosinophilia (in the blood and tissue) is often associated with distinct diseases of the skin, lung, and gastrointestinal tract.**
- **In a subset of these diseases (now including some forms of severe asthma), eosinophils are key effector cells responsible for tissue pathology and clinical symptoms, at least in part.**

What is still unknown?
- **We must determine how to identify eosinophil-mediated disease processes in individual patients.**
- **There are several therapeutic agents that target eosinophil-selective pathways, eosinophils, or both directly, but efficacy of these drugs has not yet been agreed on, and they are only available via clinical trials.**

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