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Eosinophilic disorders

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Eosinophilic inflammatory responses occur in association with multiple disorders. Although the initial cause and the affected organs vary among the different eosinophilic disorders, there are only 2 major pathways that mediate eosinophilia:

(1) cytokine-mediated increased differentiation and survival of eosinophils (extrinsic eosinophilic disorders), and (2) mutation-mediated clonal expansion of eosinophils (intrinsic eosinophilic disorders). Independent from the original trigger, the most common cause of eosinophilia is the increased generation of IL-5-producing T cells. In some cases, tumor cells are the source of eosinophil hematopoietins. The intrinsic eosinophilic disorders are characterized by mutations in pluripotent or multipotent hematopoietic stem cells leading to chronic myeloid leukemias with eosinophils as part of the clone. Here, we propose a new classification of eosinophilic disorders on the basis of these obvious pathogenic differences between the 2 groups of patients. We then discuss many known eosinophilic disorders, which can be further subdivided by differences in T-cell activation mechanisms, origin of the cytokine-producing tumor cell, or potency of the mutated stem cell. Interestingly, many subgroups of patients originally thought to have the idiopathic hypereosinophilic syndrome can be integrated in this classification. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Allergy, classification, eosinophilia, eosinophils, eosinophilic disorders, infection, IL-5, leukemia, lymphoma, hypereosinophilic syndrome, tumors

Eosinophils are generated in the bone marrow and can be found in the peripheral blood, where they represent 1% to 5% of the leukocytes with an upper limit of $0.4 \times 10^9/L$.¹ Some laboratories list higher upper values, in particular in children (as high as $0.75 \times 10^9/L$). Eosinophils

Abbreviations used

Abl:	Abelson
ABPA:	Allergic bronchopulmonary aspergillosis
DRESS:	Drug reactions with eosinophilia and systemic symptoms
GVHD:	Graft-versus-host disease
Jak:	Janus kinase
PDGFRA:	Platelet-derived growth factor receptor α
PDGFRB:	Platelet-derived growth factor receptor β

reside in the hematopoietic and lymphatic organs such as the bone marrow, spleen, lymph nodes, and thymus. In addition, eosinophils physiologically migrate in digestive tract organs (with the exception of the esophagus),² the female reproductive tract,^{3,4} and the mammary gland.⁵ Their physiologic function is unknown. Eosinophils can easily be identified in blood and tissues because of their strong affinity to the acidic dye eosin, a characteristic that actually helped Paul Ehrlich discover them in 1879.⁶ Since this time, eosinophils have generated significant interest because they occur in increased numbers in association with multiple diseases, most frequently with infections and allergies. This article is an attempt to provide an overview about eosinophilic disorders. A better understanding of the cellular and molecular bases of these diseases allowed incorporating them into a new pathobiologically oriented classification scheme, in which we focus on the question what causes eosinophilia.

A NEW CLASSIFICATION OF EOSINOPHILIC DISORDERS

Many earlier classifications of eosinophilic diseases were generated according to the site of eosinophilic infiltration associated with organ damage and dysfunction. This resulted in several disease terms such as *eosinophilic dermatitis*, *gastroenteritis*, *pneumonia*, or *fasciitis*. Other classifications are based on the numbers of blood eosinophils (eg, hypereosinophilic syndrome). However, research efforts combined with new technologies and therapeutic tools have led to a better understanding of the pathogenetic aspects of eosinophilia in the last 2

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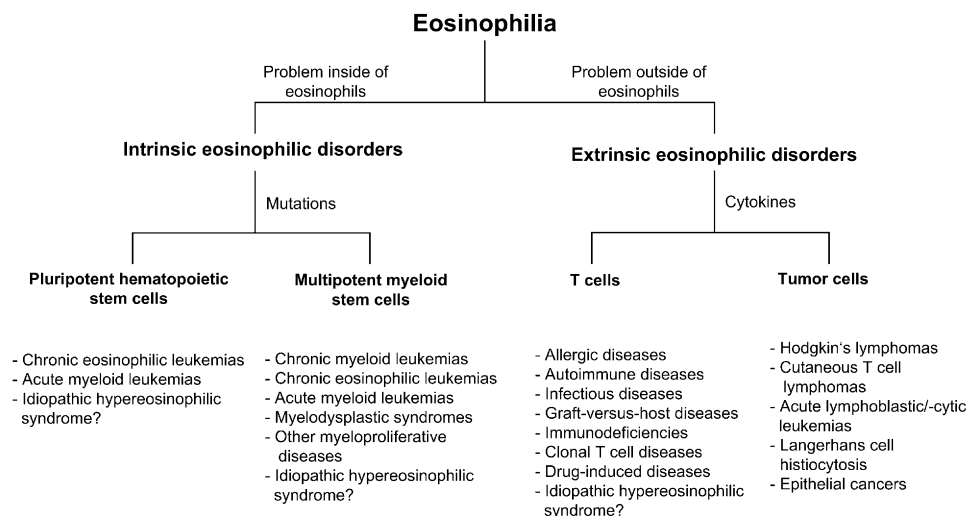


FIG 1. Classification of eosinophilic disorders. Eosinophilia is either mediated by cytokines (in particular IL-5) or a consequence of mutations in hematopoietic stem cells leading to predominant eosinophil differentiation. Interestingly, even patients with idiopathic (hyper)eosinophilia can be integrated in this simple scheme as soon as information regarding cytokine expression and/or the imatinib response is available.

decades. Because of the unknown functions of the eosinophils within the pathogenesis of most eosinophilic diseases, however, the value of eosinophil numbers for clinical practice is limited at the moment. Nevertheless, we believe it is still timely to ask for similarities and differences in the development of eosinophilia in the many known eosinophilic disorders.

In the new classification, we ask a simple question: is the primary cause of eosinophilia located within the eosinophils (and/or eosinophil precursors) themselves or in other cells (Fig 1)? Similar to allergic diseases, which can be divided in IgE-mediated (extrinsic) and non-IgE-mediated (intrinsic) diseases, we use in this article the terms *extrinsic* and *intrinsic eosinophilic disorders* to indicate whether the primary cause of eosinophilia is inside or outside the eosinophil lineage.

Intrinsic eosinophilic disorders mainly represent hematologic disorders affecting multipotent or pluripotent hematopoietic stem cells that at least partially involve the eosinophil lineage. In contrast, in extrinsic eosinophilic disorders, cells not belonging to the eosinophil lineage, release cytokines that trigger eosinophilia. The eosinophilia in these extrinsic diseases is therefore often considered reactive. Because the released cytokines directly activate eosinophils and/or eosinophil precursors, they are also called eosinophil hematopoietins (IL-5, IL-3, and GM-CSF).

After answering the first question whether an intrinsic or an extrinsic cause is responsible for the development of the eosinophilia, further pathogenic thoughts can be undertaken, and additional questions should be asked. In intrinsic eosinophilic disorders, cytogenetic procedures and/or molecular genetic analysis may help to establish an accurate diagnosis. In extrinsic eosinophilic disorders, the identification of the responsible cytokines and the cytokine-producing cellular sources is the next step. If

the molecular mechanisms leading to increased cytokine production are understood, the primary causes of eosinophilia can often be concluded. Besides serving as a guide in this article, the classification proposed here might be useful to establish an algorithm to diagnose accurately patients with eosinophilia (Fig 2 provides a frame for such an effort) and to select the most effective treatments for them in the future.

In the following, we mention multiple eosinophilic disorders and incorporate them in the new classification scheme. It was not the purpose of this article to summarize our current knowledge regarding pathogenesis and treatment of each disorder in detail. As with all classifications, it is difficult to consider each disorder in 1 category only for the following reasons: (1) the current understanding of the pathogenesis does not allow a clear incorporation; (2) the results of diagnostic procedures have not been described until now; and (3) more than 1 cause of eosinophilia may drive the disease. In spite of these problems, we hope to provide a simple approach to describe the existing huge variety of eosinophilic disorders that is often confusing, in particular for nonspecialists or individuals who are newly interested in the field.

INTRINSIC EOSINOPHILIC DISORDERS

Eosinophilic disorders resulting from mutations in pluripotent hematopoietic stem cells

Chronic eosinophilic leukemias belong to a special group of chronic myeloid leukemias, in which eosinophil differentiation is dominant, resulting in blood eosinophil counts of greater than $1.5 \times 10^9/L$.⁷ However, other lineages are also affected, because the disease is the result of a mutation in a pluripotent hematopoietic stem cell.

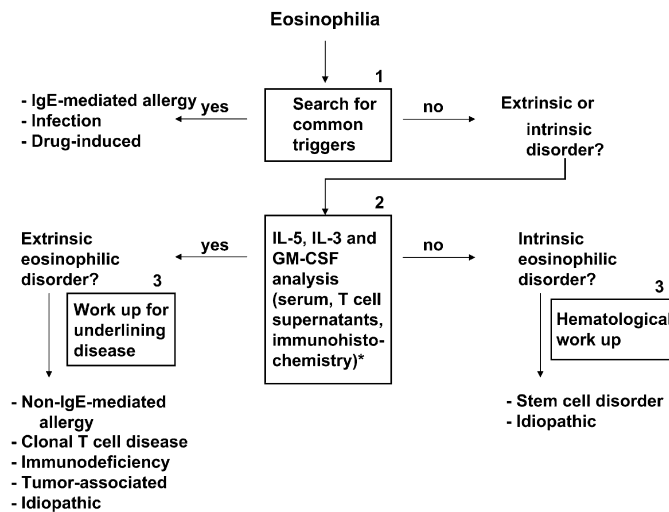


FIG 2. A proposed algorithm to diagnose eosinophilic disorders. In the first step (step 1), patients should be screened for common triggers of eosinophilia. If no likely cause of eosinophilia is identified, a potential involvement of eosinophil hematopoietins should directly be investigated (step 2). Unfortunately, if no cytokine levels can be detected in serum, an extrinsic eosinophilic disorder cannot be excluded, and no routine assays are currently available regarding *in vitro* cytokine production by T cells (*). If there is evidence for a cytokine-driven process, specialized laboratories (immunology-oriented) should be contacted to identify the cytokine-producing cell, and a tumor should be excluded (step 3). Similarly, if the cytokine analysis is negative, further diagnostic procedures should also be performed by specialized laboratories (hematology-oriented) to answer the question whether a stem cell disorder might be the underlying cause of eosinophilia (step 3).

Several defined entities have been described. Chromosomal translocations related to breakpoints on chromosome 8p11 result in fibroblast growth factor receptor 1 fusion genes with increased kinase activity causing the so-called *8p11 syndrome*. This type of leukemia has a particular poor prognosis and frequently transforms into acute myeloid leukemia within 1 to 2 years after diagnosis.⁸

Another tyrosine kinase with increased activity as a consequence of gene fusion represents platelet-derived growth factor receptor α (*PDGFRA*). *PDGFRA* is fused to a gene called Fip1-like 1 (*FIP1L1*) as a result of an 800-kb interstitial deletion on chromosome 4q12.⁹ The gene fusion has been identified in eosinophils but also in multiple hematopoietic lineages, including neutrophils, monocytes, lymphocytes, and mast cells. These observations suggest that the *FIP1L1*-*PDGFRA*-associated eosinophilic leukemia is a clonal disorder arising from a pluripotent hematopoietic stem cell. This type of leukemia responds well to the tyrosine kinase inhibitor imatinib.⁹ The transition of *PDGFRA*-associated chronic eosinophilic leukemia into acute myeloid leukemia has been reported.¹⁰ Many of the patients with *PDGFRA*-associated chronic eosinophilic leukemia have previously been classified as having idiopathic hypereosinophilic syndrome. In the presence of a clone with a defined gene fusion, however, the designation of idiopathic hypereosinophilic syndrome is no longer appropriate. It should also be noted that, although the *FIP1L1*-*PDGFRA* gene fusion was found in mast cells, these patients do not meet the World Health Organization criteria for systemic mastocytosis.¹¹

Eosinophilic disorders resulting from mutations in multipotent myeloid stem cells

In the chronic myeloid leukemias with eosinophilia, eosinophils are part of the clone. Only in a subgroup of patients, eosinophil numbers reach levels that meet the criteria for eosinophilic leukemia. This is because eosinophil differentiation is often not as prominent and other myeloid cells, such as monocytes, also show increased differentiation.¹² Several defined entities have been described. Chromosomal translocations related to breakpoints on chromosome 5q33 are common and represent the basis for the formation of platelet-derived growth factor receptor β (*PDGFRB*) fusion genes. The different chromosomal rearrangements found in association with *PDGFRB*-associated chronic myeloid leukemia have been summarized by Bain¹² and updated by Gotlib et al.¹⁰ *PDGFRB* gene fusions result in increased tyrosine kinase activity, and imatinib therapy has been successful in most patients. Evolution to acute myeloid leukemia has been reported in some cases.

Patients with Philadelphia chromosome–positive breakpoint cluster region–Abelson (*ABL*)–associated chronic myeloid leukemia usually have absolute eosinophilia.¹³ Marked eosinophilia is often associated with cytogenetic evolution and either represents the accelerated phase of the disease or occurs during acute transformation.¹² *ABL* was also found as a fusion gene together with the transcription factor E26 transformation-specific sequence variant gene 6 (*ETV6*), a genetic rearrangement that also resulted in chronic myeloid leukemia associated with

eosinophilia.¹⁴ ABL is a tyrosine kinase, and patients respond to imatinib if no additional mutation within the ABL gene causing imatinib resistance is present.

Chromosomal translocations related to breakpoints on chromosome 8 were also reported in association with pericentriolar material 1–Janus kinase (*Jak*) 2 gene fusions.¹⁵ In some cases, eosinophilia has been observed, suggesting that increased tyrosine kinase activity of Jak2 can mediate eosinophilia. This does not appear to be surprising, because Jak2 has previously been characterized as an essential element in IL-5 signal transduction in eosinophils.¹⁶

Myelodysplastic syndromes are a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective and inadequate hematopoiesis.¹⁷ In some cases, it was directly demonstrated that eosinophils are part of the neoplastic clone^{18,19} and that the mutation occurred in a multipotent myeloid stem cell.¹² Eosinophils have also been characterized as part of the malignant clone in other myeloproliferative diseases, such as polycythemia vera, essential thrombocythemia, and agnogenic myeloid metaplasia.^{10,12} The exact molecular genetic abnormalities resulting in eosinophilia in these disorders remain to be determined.

A number of patients with the idiopathic hypereosinophilic syndrome were responsive to imatinib, but no evidence for a genetic rearrangement was obtained.⁹ This raises the possibility that such patients have a rearrangement, or at least overexpression, of a gene encoding a tyrosine kinase. It is likely that all patients with idiopathic hypereosinophilic syndrome who are responsive to imatinib actually have chronic myeloid leukemia or chronic eosinophilic leukemia.^{11,12}

EXTRINSIC EOSINOPHILIC DISORDERS

T cell-mediated eosinophilias

Allergic diseases. Common diseases are allergic rhinoconjunctivitis,²⁰ bronchial asthma,²¹ eosinophilic esophagitis,²² and atopic dermatitis.²³ Moreover, in most patients with primary eosinophilic gastrointestinal disorders, evidence for IgE-mediated allergic sensitization mechanisms exists.²⁴ Eosinophilic pancreatitis is rare and usually occurs together with eosinophilic gastroenteritis.²⁵ In childhood, food allergy and allergic colitis are common.²⁶ Tissue and blood eosinophilia is a characteristic feature of most of these patients. Eosinophils have been found to correlate with disease activity in groups of patients, but not necessarily in every patient.²⁷ Eosinophilia (and IgE production) is driven by allergen-activated T_H2 cells that generate large amounts of T_H2 cytokines (eg, IL-4, IL-5, IL-13). For eosinophilia, IL-5 is the most critical cytokine mediating increased eosinophil differentiation, activation, and survival.²⁸ Eosinophils may contribute to inflammation by causing tissue damage and subsequently organ dysfunction, but also by the generation of cytokines and lipid mediators.²⁹ In addition, they have been implicated in tissue remodeling processes as a consequence of tissue damage.³⁰ Eosinophils interact either directly (cognate

interactions) or indirectly (via the release of soluble factors) with multiple immune and structural cells.

Although IL-5 is critical for the development of eosinophilia in these diseases, anti-IL-5 antibody treatment did not have any effect on airway hyperresponsiveness and symptoms in patients with asthma.^{31,32} Reasons for that were seen in an insufficient reduction of eosinophils in the bronchial mucosa³³ and in persistent T-cell activation.³⁴ Similarly, anti-IL-5 antibody treatment failed to improve symptoms significantly in atopic dermatitis.³⁵ Unfortunately, no information is available whether and to what extent the antibody treatment reduced eosinophil numbers in the skin of these patients. In contrast with these negative findings, the size of nasal polyps in chronic rhinosinusitis patients decreased on a single injection of an anti-IL-5 antibody in patients with elevated baseline IL-5 levels in nasal secretions.³⁶ Studies are underway to investigate the effect of anti-IL-5 antibody treatment in patients with eosinophilic esophagitis.³⁷

There are several additional allergic diseases in which autoimmune and/or infectious antigens may contribute to T-cell activation and subsequent eosinophilia. For instance, in Churg-Strauss syndrome, the presence of anti-neutrophil cytoplasmic antibodies point to the possibility that autoimmune mechanisms contribute to the disease, although no direct evidence exists for such an assumption.³⁸ In allergic bronchopulmonary aspergillosis (ABPA), patients cannot eliminate the fungus because of pre-existing epithelial cell damage and subsequently develop an allergy against *Aspergillus*.³⁹ Therefore, patients have bronchial asthma or cystic fibrosis first, and subsequently develop ABPA. Kimura disease is an uncommon chronic inflammatory disorder frequently associated with hypereosinophilia that involves subcutaneous tissue, predominantly in the head and neck region. The pathogenesis includes IL-5–releasing T cells, which might be activated by different etiologic factors, including allergic, autoimmune, and infective causes.⁴⁰ Only approximately 70% of the patients with chronic eosinophilic pneumonia exhibit evidence for an IgE-associated disease, suggesting that nonallergic mechanisms exist in at least a subgroup of patients.⁴¹ IL-5 expression by T cells or mononuclear cells has been demonstrated in all these disorders.

In a significant subgroup of patients with allergic rhinoconjunctivitis, bronchial asthma, eosinophilic esophagitis, and atopic dermatitis, IgE-mediated mechanisms are not evident, and relevant allergens cannot be identified. These forms are often called *intrinsic*. The cellular infiltrate of the affected tissues in these diseases is very similar compared with the IgE-associated forms, and the eosinophilia is also driven by IL-5–producing T_H2 cells.^{42–44}

Autoimmune diseases. Because these diseases are often associated with a T_H1-associated inflammatory response, eosinophilia is not frequently observed. However, evidence for eosinophil activation has been obtained in patients with systemic sclerosis, because elevated serum levels of major basic protein and extracellular major basic protein depositions in skin and lung tissues were observed in some patients. This suggests that eosinophils might be

TABLE I. Drugs associated with DRESS

Drug group	Drug examples
Aromatic anticonvulsants	Carbamazepine
	Phenobarbital
	Phenytoin
	Primidone
Nonaromatic anticonvulsants	Lamotrigine
	Valproic acid
	Gabapentin
	Benzodiazepines
Anticancer drugs	Allopurinol
Antimicrobial agents	Minocycline
	Terbinafine
	Nitrofurantoin
	Isoniazid
Sulfa drugs	Abacavir
	Sulfonamides
	Dapsone
	Sulfasalazine
Nonsteroidal anti-inflammatory drugs	Oxicam
	Thalidomide
Antihypertensive drugs	Captopril
	Diltiazem
Antidiabetics	Sorbinil

involved in the development of cutaneous and pulmonary fibrosis in these patients.⁴⁵ Because eosinophilic fasciitis is associated with fibrosis, it is often classified together with systemic sclerosis. Eosinophil-mediated tissue damage might play a role in the initiation phase of the disease, and a role for IL-5 has been demonstrated.⁴⁶

In primary biliary cirrhosis, eosinophilia is a common and distinctive feature that might be useful in the diagnosis of the disease.⁴⁷ In liver biopsies of these patients, increased IL-5 mRNA was detected.⁴⁸ A striking tissue eosinophilia has also been reported in Riedel invasive fibrous thyroiditis, but not in other autoimmune forms of thyroiditis.⁴⁹ Eosinophilia may also be present in dermatomyositis, systemic lupus erythematosus, and Sjögren syndrome, but most frequently it indicates an allergic reaction in these disorders, in particular to drugs (see *drug-induced diseases*).⁵⁰

Eosinophilia of the dermis but also of the epidermis with or without associated peripheral blood eosinophilia is a quite common finding in various autoimmune skin diseases (pemphigoid, pemphigus, epidermolysis). These diseases are characterized by the presence of autoimmune antibodies, which are believed to contribute to blister formation. High levels of IL-5 were found in blister fluids from patients with pemphigoid.⁵¹ In palmoplantar pustulosis, a common chronic skin disease with predominant neutrophil infiltration in the epidermis, large numbers of eosinophils are present in the subpustular area.⁵² In autoimmune progesterone dermatitis, which is characterized by an immune reaction against endogenous progesterone, a perivascular dermal mixed cellular infiltration, including lymphocytes and eosinophils, has been described.⁵³

Infectious diseases. T_H2 inflammatory responses are induced by helminths (worms; Table I).⁵⁴ These responses

are characterized by IgE antibody production and eosinophilia; both have been implicated in mediating protective immunity to the parasites. Indeed, a role of eosinophils in immunity to *Schistosoma trematodes* has been demonstrated.⁵⁵ However, in other helminth infections, the assumed protective role of eosinophils has not been confirmed in experimental *in vivo* systems. In contrast, there is little doubt that eosinophils contribute to tissue damage and therefore to the pathogenesis of these infections.⁵⁴ IL-5 has been shown to be sufficient to cause helminth infection-mediated eosinophilia.⁵⁶

Eosinophilia was also seen in response to *Plasmodium falciparum* infection.⁵⁷ Ectoparasitic infections can also be associated with eosinophilia. For instance, in scabies presenting with bullae, dermal eosinophilia has been observed.⁵⁸ Similarly, arthropod bites often cause dermal eosinophilia.⁵⁹ In contrast, unicellular protozoa usually induce T_H1-type inflammatory responses that are not associated with eosinophilia.⁵⁴

Interestingly, eosinophil granule proteins have been implicated in antibacterial immunity.⁶⁰ In addition, eosinophils express LPS receptors on their surface.⁶¹ Therefore, it has been proposed that they also participate in antibacterial immunity, although eosinophilia in association with bacterial infections is not common. However, *Staphylococcus*-derived superantigens may activate T cells in chronic rhinosinusitis⁶² and atopic dermatitis.⁶³ *Pseudomonas* infection in lung transplant recipients associated with pulmonary eosinophilia has also been reported.⁶⁴ *Borrelia* infections may cause erythema chronicum migrans, which is characterized by a mixed inflammatory cellular infiltrate, including eosinophils.⁶⁵ In addition, some patients with eosinophilic fasciitis were shown to be infected with *Borrelia burgdorferi*.⁶⁶ Moreover, exacerbations of chronic obstructive pulmonary disease might be caused by bacterial infections that further increase inflammatory cell infiltration, including eosinophils.⁶⁷

Eosinophilia in association with viral infections is not common. However, when virus-specific T cells are generated in a T_H2 environment, they can also release IL-5 and therefore trigger eosinophilia.⁶⁸ This may explain why viral respiratory tract infections are an important cause of asthma exacerbations.⁶⁹ Moreover, respiratory syncytial virus infections are the most common cause of lower respiratory tract disease in infants that is associated with a marked increase of T_H2 cytokines and eosinophil numbers.⁷⁰ It is possible but not proven that eosinophil granule proteins are involved in such cases to neutralize the virus.⁷¹ Moreover, exacerbations of chronic obstructive pulmonary disease might be caused by viral infections that further increase inflammatory cell infiltration, including eosinophils.⁶⁷

HIV-1 infections are also associated with T_H2 responses after disease progression.⁷² However, it remains unclear whether the virus itself induces cytokine production in T cells or whether the cytokine balance is changed because of the developing immunodeficiency (see Immunodeficiencies). The pulmonary eosinophilia in lung transplant recipients associated with Coxsackie virus infection might

also be related to the immunodeficient stage of the patients.⁶⁴ Cutaneous disease associated with human T-lymphotropic virus type 1 infection demonstrates a mixed cellular dermal infiltrate, including eosinophils. A transition in a cutaneous T-cell lymphoma (see *tumors originated from hematopoietic cells*) often occurs after a cutaneous prodromal phase.⁷³

In chronic rhinosinusitis, eosinophilia is related to fungal infections with certain molds (eg, *Alternaria*) present in the nasal and paranasal cavities. In healthy control individuals, these molds are unable to trigger eosinophilia.⁷⁴ *Alternaria*-specific IL-5–expressing T cells have been demonstrated in patients with chronic rhinosinusitis.⁷⁵ Colonization of the respiratory tract with *Aspergillus fumigatus* is usually benign, but may trigger eosinophilia in patients with ABPA (see *allergic diseases*). Similarly, a pathogenic role of the opportunistic yeast *Malassezia* has been postulated in atopic dermatitis, because a large proportion of these patients develops *Malassezia*-specific IgE antibodies.⁷⁶ Whether *Malassezia* is able to trigger eosinophilia in patients with atopic dermatitis is unknown.

Graft-versus-host diseases. Graft-versus-host diseases (GVHDs) frequently develop after allogeneic hematopoietic stem cell transplantation. GVHDs are initiated when immunocompetent T cells from the graft react against the immunocompromised host via recognition of alloantigens. The skin, liver, and gastrointestinal tract represent the major target organs of GVHDs. Eosinophilia has been observed in association with chronic GVHDs, in particular in chronic gastrointestinal GVHD and in chronic cutaneous GVHD.⁷⁷ The latter might be accompanied by an eosinophilic fasciitis.⁷⁸ Donor-derived, alloreactive IL-5–producing T cells are thought to trigger eosinophilia in chronic GVHDs.⁷⁹ Eosinophilia has also been observed in some cases of acute GVHD, in particular in kidney transplant recipients.⁸⁰ In general, however, acute GVHD is thought to be a T_H1-mediated disorder.⁷⁷

Immunodeficiencies. Several primary and secondary immunodeficiencies are frequently associated with eosinophilia, which is mediated by IL-5–producing T cells. Whether such T_H2 cells actually mediate the immunodeficiency or whether they develop because of T_H1 deficiency is often unclear. T-cell activation and eosinophilia might also be triggered by infections in these patients. In the following, we mention a few examples of such disorders. Omenn syndrome is an autosomal recessive form of severe combined immunodeficiencies. Because of mutations in the recombination genes, the T cells exhibit only a highly restricted T-cell receptor heterogeneity and are of the T_H2 phenotype.⁸¹ The hyper-IgE syndrome is another rare genetic immunodeficiency; however, the underlining gene defects are unknown.⁸² Peripheral blood eosinophilia is a common finding in these patients. Interestingly, a case of hyper-IgE syndrome with a cytokine-producing T-cell clone has recently been reported.⁸³ Chronic granulomatous disease is another rare immunodeficiency caused by a genetic defect in the nicotinamide adenine dinucleotide phosphate oxidase in which an eosinophilic inflammatory response can point to its diagnosis.⁸⁴

TABLE II. Parasitic helminth infections associated with eosinophilia

Phylum	Species
Cestode	<i>Mesocostoides corti</i> *
	<i>Hymenolepis diminuta</i>
Nematode	<i>Angiostrongylus</i> species*
	<i>Anisakis</i> species
	<i>Ascaris lumbricoides</i>
	<i>Ancylostoma</i> species
	<i>Baylisascaris</i> species
	<i>Brugia</i> species*
	<i>Enterobius vermicularis</i>
	<i>Heligmosomoides polygyrus</i>
	<i>Litomosoides</i> species*
	<i>Nippostrongylus</i> species*
	<i>Onchocerca</i> species*
	<i>Strongyloides</i> species*
	<i>Toxocara</i> species
	<i>Trichinella</i> species*
	<i>Trichuris</i> species
Trematode	<i>Wuchereria bancrofti</i>
	<i>Fasciola</i> species
	<i>Schistosoma</i> species*

*Eosinophil-mediated protection has been observed in animal or human models; data are from reference 54.

Moreover, in patients with AIDS, eosinophilia is a frequent finding (see *Infectious diseases*). In addition, drug-induced immunodeficiency associated with eosinophilia has been observed in transplant recipients.^{85,86} Similarly, immunosuppressive anti-CD52 antibody therapy was related to severe eosinophilia (see *Drug-induced diseases*).⁸⁷

Inflammatory clonal T-cell diseases. In a subgroup of patients originally diagnosed as having idiopathic eosinophilia, IL-5–producing clonal T cells with abnormal immunophenotypes were observed. These T cells exhibit either lower or higher expression of lineage-associated markers, such as CD2, CD3, CD4, CD5, CD6, CD7, or CD8.⁸⁸ In some cases, a marker can be completely absent, resulting in, for instance, CD3⁺CD4⁺⁸⁹ or CD3⁺CD4⁺CD8⁺ T cells.⁹⁰ Because these T cells can easily be detected in blood (and tissues), monitoring their numbers over time is possible. The numbers of the abnormal T cells are often stable over years, and patients usually have an inflammatory skin disease. In some cases, however, the clonal T cells may transform into a T-cell lymphoma.⁹¹

It has been suggested to categorize these patients as a defined subgroup of the idiopathic hypereosinophilic syndrome termed *lymphocytic variant of the hypereosinophilic syndrome*.⁹² However, it is debatable whether the designation of idiopathic hypereosinophilic syndrome is still appropriate for these patients because of the following reasons: (1) the cause of the eosinophilia is no longer idiopathic, and (2) there are patients who exhibit a T-cell clone with associated eosinophilia, but the eosinophil numbers do not reach the level of $>1.5 \times 10^9/L$. Therefore, we suggest designating this disorder *inflammatory*

clonal T-cell disease associated with eosinophilia. In addition, it is possible that patients exist in whom the IL-5-producing T-cell clone exhibits a normal immunophenotype. Clearly, such patients should also be included in this disease group.

Drug-induced diseases. Eosinophilia is a characteristic feature in drug hypersensitivity reactions. The manifestations range from maculopapular rashes of the skin to severe life threatening drug reactions with eosinophilia and systemic symptoms (DRESS).⁹³ Drugs associated with DRESS are aromatic anticonvulsants and other anti-epileptics, sulfonamides, allopurinol, nonsteroidal anti-inflammatory drugs, and antibiotics (Table II).⁹⁴ T cells are thought to be activated by these drugs via a specific pathomechanism called *pharmacologic interaction with immune receptors* (p-I concept). The interaction between the drug and the T-cell receptor does not necessarily require covalent binding of the drug to a carrier molecule.⁹⁵ Drugs may even bypass antigen-presenting cells and directly stimulate memory T cells.⁹⁶ It is possible but not proven that the agents causing the L-tryptophan syndrome (eosinophilia-myalgia syndrome)⁹⁷ and the Spanish toxic oil syndrome⁹⁸ stimulate T cells according to the p-I concept. Nevertheless, increased levels of IL-5 were found in L-tryptophan syndrome.⁹⁹ A classical IgE-mediated allergy against human insulin has been reported in association with eosinophilia.¹⁰⁰

IL-2 therapy is sometimes provided to patients with cancer or AIDS and can cause hypereosinophilia in blood¹⁰¹ that might be a result of the expansion of IL-5-producing T cells. Infusion of GM-CSF in patients with AIDS induced blood and bone marrow eosinophilia,¹⁰² suggesting increased eosinophil differentiation. Anti-TNF- α antibody therapy may disturb the T_H1/T_H2 balance, resulting in atopic dermatitis.¹⁰³ Anti-CD52 therapy is used in chronic lymphocytic leukemia but can also cause severe immunodeficiency associated with severe eosinophilia (see *Immunodeficiencies*).⁸⁷ The cytokine release syndrome is a potential side effect of antibody therapies; however, the release of eosinophil hematopoietins and consequent eosinophilia has not been reported. Anti-CD20 antibody therapy was accompanied with mild transient blood eosinophilia of unknown mechanism.¹⁰⁴

Idiopathic eosinophilia. There are conditions in which increased IL-5 expression by T cells can be detected but the reason for T-cell activation remains obscure. These patients may also not show evidence for a clonal T-cell expansion.⁸⁸ Patients with eosinophilic dermatitis fall into this group of patients.¹⁰⁵ If they exhibit eosinophil numbers of greater than $1.5 \times 10^9/L$, these patients could be diagnosed as having idiopathic hypereosinophilic syndrome. There are other subgroups of this syndrome in which there is evidence for a T cell-mediated and IL-5-driven mechanism, such as episodic angioedema¹⁰⁶ and hereditary eosinophilia.¹⁰⁷

Tumor cell-mediated eosinophilias

Tumors originated from hematopoietic cells. Besides the eosinophilic or myeloid leukemias, in which

eosinophils are part of the malignant clone (see *Intrinsic eosinophilic disorders*), eosinophilia can be driven by the production of eosinophil hematopoietins, which are generated by lymphoid cells. For instance, blood and tissue eosinophilia is often associated with Hodgkin disease, and the generation of IL-5 by Reed-Sternberg cells has been demonstrated.¹⁰⁸ In primary cutaneous T-cell lymphoma and Sézary syndrome, blood and dermal eosinophilia are also frequently observed. The lymphoma cells were shown to produce IL-5 in these disorders.^{109,110} Other types of lymphoid malignancies have been associated with eosinophilia, such as acute lymphoblastic leukemia with a translocation between chromosomes 5 and 14.^{111,112} It is likely that a gene encoding an eosinophil hematopoietin is overexpressed in these patients. Indeed, in patients with acute B lymphocytic leukemia, a translocation between chromosomes 5 and 14 resulted in the juxtaposition of the IL-3 gene and the immunoglobulin heavy-chain gene, resulting in large production of IL-3 and subsequent eosinophilia.¹¹³

Langerhans cell histiocytosis is caused by a clonal proliferation of dendritic cells with Langerhans cell characteristics and associated eosinophilia. It is characterized by a lesional cytokine storm caused by Langerhans cell-T-cell interactions, the latter producing IL-5.¹¹⁴

Solid tumors. Blood and tissue eosinophilia may be observed in patients with tumors of epithelial cell origin.¹¹⁵ In at least some published reports, the tumor cells were identified as a cellular source of IL-5 and/or IL-3. Examples are tumors of the thyroid gland,¹¹⁶ stomach,¹¹⁷ liver,¹¹⁸ and bladder.¹¹⁹ The role of eosinophils under these conditions remains unclear.

CONCLUSION

In this article, we propose a simple classification scheme of eosinophilic disorders (Fig 1). Eosinophilia might be caused either by mutations in eosinophil precursors or by overexpression of eosinophil hematopoietins. Among the eosinophil hematopoietins, IL-5 appears to be the most prominent. In some cases, IL-3 contributes or is dominant.¹²⁰ GM-CSF appears to play a less important role but has often been shown to be expressed in *in vitro* activated eosinophils. The expression of eosinophil hematopoietins by eosinophils was not discussed in this article because it is unclear whether this phenomenon plays a role in driving eosinophilia *in vivo*. It should also be noted that, although eosinophil hematopoietins are important for the development of blood eosinophilia, additional chemotactic factors, such as eotaxin and/or RANTES, seem to be required for eosinophil tissue infiltration.¹²¹

The simple distinction between cytokine-dependent and cytokine-independent mechanisms seems to be possible in the diagnostic evaluation of most patients with eosinophilia (Fig 2) and results in therapeutic consequences. However, the exact molecular mechanism in individual patients may not always be obvious. For instance, although T-cell activation is evident, its

mechanism cannot be determined, and the eosinophilia remains idiopathic. Similarly, hypereosinophilic patients may respond to imatinib, suggesting the presence of an eosinophilic leukemia, but the exact molecular mechanism cannot be determined. Thus, in these cases, some information regarding the pathogenesis is available and even sufficient for therapeutic decisions. Clearly, with the accumulating knowledge regarding the pathogenesis of eosinophilia, fewer and fewer patients should be diagnosed with idiopathic hypereosinophilic syndrome, and the redefinition of this term should be considered in the near future.

REFERENCES

- Osgood EE, Brownlee IE, Osgood MW, Ellis DM, Cohen W. Total differential and absolute leukocyte counts and sedimentation rates. *Arch Int Med* 1939;64:105-20.
- Straumann A, Simon HU. The physiological and pathophysiological roles of eosinophils in the gastrointestinal tract. *Allergy* 2004;59:15-25.
- McMaster MT, Newton RC, Dey SK, Andrews GK. Activation and distribution of inflammatory cells in the mouse uterus during the preimplantation period. *J Immunol* 1992;148:1699-705.
- Robertson SA, Mau VJ, Hudson SA, Tremellen KP. Cytokine-leukocyte networks and the establishment of pregnancy in the mouse. *J Reprod Fertil* 1997;107:265-77.
- Gouon-Evans V, Rothenberg ME, Pollard JW. Postnatal mammary gland development requires macrophages and eosinophils. *Development* 2000;127:2269-82.
- Ehrlich P. Beiträge zur Kenntnis der granulierenden Bindegewebszellen und der eosinophilen Leukocyten. *Arch Anat Physiol* 1879;166-9.
- Bain B, Pierre R, Imbert M, Vardiman JW, Brunning RD, Flandrin G. Chronic eosinophilic leukaemia and the hypereosinophilic syndrome. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. *World Health Organization classification of tumours: pathology and genetics of tumours of haematopoietic and lymphoid tissues*. Lyon: IARC Press; 2001. p. 29-31.
- Ollendorff V, Guasch G, Isnardon D, Galindo R, Birnbaum D, Pebusque MJ. Characterization of FIM-FGFR I, the fusion product of the myeloproliferative disorder-associated t(8;13) translocation. *J Biol Chem* 1999;274:26922-30.
- Cools J, DeAngelo DJ, Gotlib J, Stover EH, Legare RD, Cortes J, et al. A tyrosine kinase created by the fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med* 2003;348:1201-14.
- Gotlib J, Cross NCP, Gilliland DG. Eosinophilic disorders: molecular pathogenesis, new classification, and modern therapy. *Best Pract Res Clin Haematol* 2006;3:535-69.
- Bain BJ. Relationship between idiopathic hypereosinophilic syndrome, eosinophilic leukemia, and systemic mastocytosis. *Am J Haematol* 2004;77:82-5.
- Bain BJ. Cytogenetic and molecular genetic aspects of eosinophilic leukemias. *Br J Haematol* 2003;122:173-9.
- Spiers ASD, Bain BJ, Turner JE. The peripheral blood in chronic granulocytic leukaemia. *Scand J Haematol* 1977;18:25-38.
- Keung YK, Beaty M, Steward W, Jackle B, Petnat M. Chronic myelocytic leukemia with eosinophilia, t(9;12)(q34;p13) and ETV6-ABL gene rearrangement: case report and review of the literature. *Cancer Genet Cytogenet* 2002;138:139-42.
- Reiter A, Walz C, Watmore A, Schoch C, Blau I, Schlegelberger B, et al. The t(8;9)(p22;p24) is a recurrent abnormality in chronic and acute leukemia that fuses PCMI to Jak2. *Cancer Res* 2005;65:2662-7.
- Simon HU, Yousefi S, Dibbert B, Levi-Schaffer F, Blaser K. Apoptotic signals of granulocyte-macrophage colony-stimulating factor are transduced via Jak2 tyrosine kinase in eosinophils. *Eur J Immunol* 1997;27:3536-9.
- Steensma DP, Tefferi A. The myelodysplastic syndrome(s): a perspective and review highlighting current controversies. *Leuk Res* 2003;27:95-120.
- Ma SK, Wong KF, Chan JK, Kwong YL. Refractory cytopenia with t(1;7), +8 abnormality and dysplastic eosinophils showing intranuclear Charcot-Leyden crystals: a fluorescence in situ hybridization study. *Br J Haematol* 1995;90:216-8.
- Imai Y, Yasuhara S, Hanafusa N, Ohsaka A, Enokihara H, Tomizuka H, et al. Clonal involvement of eosinophils in therapy-related myelodysplastic syndrome with eosinophilia, translocation t(1;7) and lung cancer. *Br J Haematol* 1996;95:710-4.
- Ying S, Durham SR, Barkans J, Masuyama K, Jacobson M, Rak S, et al. T cells are the principal source of interleukin-5 mRNA in allergen-induced rhinitis. *Am J Respir Cell Mol Biol* 1993;9:356-60.
- Robinson DS, Hamid Q, Ying S, Tsigopoulos A, Barkans J, Bentley AM, et al. Predominant Th2-like bronchoalveolar T-lymphocyte population in atopic asthma. *N Engl J Med* 1992;326:298-304.
- Straumann A, Bauer M, Fischer B, Blaser K, Simon HU. Idiopathic eosinophilic esophagitis is associated with a Th2-type allergic inflammatory response. *J Allergy Clin Immunol* 2001;108:954-61.
- Simon D, Vassina E, Yousefi S, Kozlowski E, Braathen LR, Simon HU. Reduced dermal infiltration of cytokine-expressing inflammatory cells in atopic dermatitis after short-term topical tacrolimus treatment. *J Allergy Clin Immunol* 2004;114:887-95.
- Rothenberg ME. Eosinophilic gastrointestinal disorders (EGID). *J Allergy Clin Immunol* 2004;113:11-28.
- Cay A, Imamoglu M, Cobanoglu U. Eosinophil pancreatitis mimicking pancreatic neoplasia. *Can J Gastroenterol* 2006;20:361-4.
- Hill SM, Milla PJ. Colitis caused by food allergy in infants. *Arch Dis Child* 1990;65:132-3.
- Bousquet J, Chanez P, Lacoste JY, Barnéon G, Ghavanian N, Enander I, et al. Eosinophilic inflammation in asthma. *N Engl J Med* 1990;323:1033-9.
- Sanderson CJ. Interleukin-5, eosinophils, and disease. *Blood* 1992;79:3101-9.
- Rothenberg ME, Hogan SP. The eosinophil. *Ann Rev Immunol* 2006;24:147-74.
- Kay AB, Phipps S, Robinson D. A role for eosinophils in airway remodelling in asthma. *Trends Immunol* 2004;25:477-82.
- Leck MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyperresponsiveness, and the late asthmatic response. *Lancet* 2000;356:2144-8.
- Kips JC, O'Connor BJ, Langley SJ, Woodcock A, Kerstjens HA, Postma DS, et al. Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study. *Am J Respir Crit Care Med* 2003;167:1655-9.
- Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-IL-5 only partially depletes numbers in asthmatic airway. *Am J Respir Crit Care Med* 2003;167:199-204.
- Buttner C, Lun A, Spletstoeser T, Kunkel G, Renz H. Monoclonal anti-interleukin-5 treatment suppresses eosinophil but not T cell function. *Eur Respir J* 2003;21:799-803.
- Oldhoff JM, Darsow U, Werfel T, Katzer K, Wulf A, Laifaoui J, et al. Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. *Allergy* 2005;60:693-6.
- Gevaert P, Lang-Loidolt D, Lackner A, Stammberger H, Staudinger H, van Zele T, et al. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. *J Allergy Clin Immunol* 2006;118:1133-41.
- Stein ML, Collins MH, Villanueva JM, Kushner JP, Putnam PE, Buckmeier BK, et al. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol* 2006;118:1312-9.
- Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome: clinical study and long-term follow-up of 96 patients. *Medicine (Baltimore)* 1999;78:26-37.
- Greenberger PA. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol* 2002;110:685-92.
- Meningaud JP, Pitak-Arnop P, Fouret P, Bertrand JC. Kimura's disease of the parotid region: report of 2 cases and review of the literature. *J Oral Maxillofac Surg* 2007;65:134-40.
- Jederlinic PJ, Sicilian L, Gaensler EA. Chronic eosinophilic pneumonia: a report of 19 cases and a review of the literature. *Medicine (Baltimore)* 1988;67:154-62.

42. Walker C, Bode E, Boer L, Hansel TT, Blaser K, Virchow JC. Allergic and nonallergic asthmatics have distinct patterns of T-cell activation and cytokine production in peripheral blood and bronchoalveolar lavage. *Am Rev Respir Dis* 1992;146:109-15.
43. Simon HU, Yousefi S, Schranz C, Schapowal A, Bachert C, Blaser K. Direct demonstration of delayed eosinophil apoptosis as a mechanism causing tissue eosinophilia. *J Immunol* 1997;158:3902-8.
44. Akdis CA, Akdis M, Simon D, Dibbert B, Weber M, Gratzl S, et al. T cells and T cell-derived cytokines as pathogenic factors in the non-allergic form of atopic dermatitis. *J Invest Dermatol* 1999;113:628-34.
45. Cox D, Earle L, Jimenez SA, Leiferman KM, Gleich GJ, Varga J. Elevated levels of eosinophil major basic protein in the sera of patients with systemic sclerosis. *Arthritis Rheum* 1996;38:939-45.
46. Viallard JF, Taupin JL, Ranchin V, Leng B, Pellegrin JL, Moreau JF. Analysis of leukemia inhibitory factor, type 1 and type 2 cytokine production in patients with eosinophilic fasciitis. *J Rheumatol* 2001;28:75-80.
47. Yamazaki K, Nakadate I, Suzuki K, Sato S, Masuda T. Eosinophilia in primary biliary cirrhosis. *Am J Gastroenterol* 1996;91:516-22.
48. Nagano T, Yamamoto K, Matsumoto S, Okamoto R, Tagashira M, Ibuki N, et al. Cytokine profile in the liver of primary biliary cirrhosis. *J Clin Immunol* 1999;19:422-7.
49. Heufelder AE, Goellner JR, Bahn RS, Gleich GJ, Hay ID. Tissue eosinophilia and eosinophil degranulation in Riedel's invasive fibrous thyroiditis. *J Clin Endocrinol Metab* 1996;81:977-84.
50. Kargi A, Bavbek N, Kaya A, Kosar A, Karaaslan Y. Eosinophilia in rheumatologic diseases: a prospective study of 100 cases. *Rheumatol Int* 2004;24:321-4.
51. Wakugawa M, Nakamura K, Hino H, Toyama K, Hattori N, Okochi H, et al. Elevated levels of eotaxin and interleukin-5 in blister fluid of bullous pemphigoid: correlation with tissue eosinophilia. *Br J Dermatol* 2000;143:112-6.
52. Eriksson MO, Hagforsen E, Lundin IP, Michaelsson G. Palmoplantar pustulosis: a clinical and immunohistological study. *Br J Dermatol* 1998;138:390-8.
53. Rasi A, Khatami A. Autoimmune progesterone dermatitis. *Int J Dermatol* 2004;43:588-90.
54. Klion AD, Nutman TB. The role of eosinophils in host defense against helminth parasites. *J Allergy Clin Immunol* 2004;113:30-7.
55. Sturrock RF, Kimani R, Cottrell BJ, Butterworth AE, Seitz HM, Siongok TK, et al. Observations on possible immunity to reinfection among Kenyan schoolchildren after treatment for *Schistosoma mansoni*. *Trans R Soc Trop Med Hyg* 1983;77:363-71.
56. Coffman RL, Seymour BW, Hudak S, Jackson J, Rennick D. Antibody to interleukin-5 inhibits helminth-induced eosinophilia in mice. *Science* 1989;245:308-10.
57. MacDonald SM, Bhisutthibhan J, Shapiro TA, Rogerson SJ, Taylor TE, Tembo M, et al. Immune mimicry in malaria: *Plasmodium falciparum* secretes a functional histamine-releasing factor homolog in vitro and in vivo. *Proc Natl Acad Sci U S A* 2001;98:10829-32.
58. Ansarin H, Jalali MH, Mazloomi S, Soltani-Arabshahi R, Setarehshenas R. Scabies presenting with bullous pemphigoid-like lesions. *Dermatol Online J* 2006;12:19.
59. Wood C, Miller AC, Jacobs A, Hart R, Nickloff BJ. Eosinophilic infiltration with flame figures: a distinctive tissue reaction seen in Wells' syndrome and other diseases. *Am J Dermatopathol* 1986;8:186-93.
60. Lehrer RI, Szklarek D, Barton A, Ganz T, Hamann KJ, Gleich GJ. Anti-bacterial properties of eosinophil major basic protein (MBP) and eosinophil cationic protein (ECP). *J Immunol* 1989;142:4428-34.
61. Plötz SG, Lentschat A, Behrendt H, Plötz W, Hamann L, Ring J, et al. The interaction of human peripheral blood eosinophils with bacterial lipopolysaccharide is CD14 dependent. *Blood* 2001;97:235-41.
62. Zhang N, Gevaert P, van Zele T, Perez-Novo C, Patou J, Holtappels G, et al. An update on the impact of *Staphylococcus aureus* enterotoxins in chronic sinusitis with nasal polyposis. *Rhinology* 2005;43:162-8.
63. Cardona ID, Cho SH, Leung DY. Role of bacterial superantigens in atopic dermatitis: implications for future therapeutic strategies. *Am J Clin Dermatol* 2006;7:273-9.
64. Yousem SA. Graft eosinophilia in lung transplantation. *Hum Pathol* 1992;23:1172-7.
65. Berger BW, Clemmensen OJ, Ackerman AB. Lyme disease is a spirochetosis: a review of the disease and evidence for its cause. *Am J Dermatopathol* 1983;5:111-24.
66. Granter SR, Barnhill RL, Hewins ME, Duray PH. Identification of *Borrelia burgdorferi* in diffuse fasciitis with peripheral eosinophilia: borreliac fasciitis. *JAMA* 1994;272:1283-5.
67. Papi A, Luppi F, Franco F, Fabbri LM. Pathophysiology of exacerbations of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2006;3:245-51.
68. Coyle AJ, Erard F, Bertrand C, Walti S, Pircher H, Le Gros G. Virus-specific CD8+ cells can switch to interleukin 5 production and induce airway eosinophilia. *J Exp Med* 1995;181:1229-33.
69. Busse WW, Gern JE. Viruses in asthma. *J Allergy Clin Immunol* 1997;100:147-50.
70. Becker Y. Respiratory syncytial virus (RSV) evades the human adaptive immune system by skewing the Th1/Th2 cytokine balance toward increased levels of Th2 cytokines and IgE, markers of allergy: a review. *Virus Genes* 2006;33:235-52.
71. Slifman NR, Loegering DA, McKean DJ, Gleich GJ. Ribonuclease activity associated with human eosinophil-derived neurotoxin and eosinophil cationic protein. *J Immunol* 1986;137:2913-7.
72. Clerici M, Shearer GM. A Th1->Th2 switch is a critical step in the etiology of HIV infection. *Immunol Today* 1993;14:107-11.
73. Whittaker SJ, Ng YL, Rustin M, Levene G, McGibbon DH, Smith NP. HTLV-1-associated cutaneous disease: a clinicopathological and molecular study of patients from U.K. *Br J Dermatol* 1993;128:483-92.
74. Sasama J, Sherris DA, Shin SH, Kephart GM, Kern EB, Ponikau JU. New paradigm for the roles of fungi and eosinophils in chronic rhinosinusitis. *Curr Opin Otolaryngol Head Neck Surg* 2005;13:2-8.
75. Shin SH, Ponikau JU, Sherris DA, Congdon D, Frigas E, Homburger HA, et al. Rhinosinusitis: an enhanced immune response to ubiquitous airborne fungi. *J Allergy Clin Immunol* 2004;114:1369-75.
76. Fischer Casagrande B, Flückiger S, Tengvall Linder M, Johansson C, Scheynius A, Cramer R, et al. Sensitization to the yeast *Malassezia sympodialis* is specific for extrinsic and intrinsic atopic eczema. *J Invest Dermatol* 2006;126:2414-21.
77. Schaffer JV. The changing face of graft-versus-host disease. *Semin Cutan Med Surg* 2006;25:190-200.
78. Janin A, Socie G, Devergia A, Aractingi S, Esperou H, Verola O, et al. Fasciitis in chronic graft-versus-host disease: a clinicopathologic study of 14 cases. *Ann Intern Med* 1994;120:993-8.
79. Jacobsen DA, Schechter T, Seshadri R, Thormann K, Duerst R, Kletzel M. Eosinophilia correlates with the presence or development of chronic graft-versus-host disease in children. *Transplantation* 2004;77:1096-100.
80. Basara N, Kiehl MG, Fauser AA. Eosinophilia indicates the evolution to acute graft-versus-host disease. *Blood* 2002;100:3055.
81. Aleman K, Noordzij JG, de Groot R, van Dongen JJM, Hartwig NG. Reviewing Omenn syndrome. *Eur J Pediatr* 2001;160:718-25.
82. Grimbacher B, Holland SM, Gallin JI, Greenberg F, Hill SC, Malech HL, et al. Hyper-IgE syndrome with recurrent infections: an autosomal dominant multisystem disorder. *N Engl J Med* 1999;340:692-702.
83. Simon HU, Seger R. Hyper-IgE syndrome associated with an IL-4-producing γ/δ + T-cell clone. *J Allergy Clin Immunol* 2007;119:246-8.
84. Jaggi P, Freeman AF, Katz BZ. Chronic granulomatous disease presenting with eosinophilic inflammation. *Pediatr Infect Dis J* 2005;24:1020-1.
85. Jezior D, Boratynska M, Halon A, Kusztal M, Rabczynski J, Szyber P, et al. Biopsy eosinophilia as a predictor of renal graft dysfunction. *Transplant Proc* 2003;35:2182-5.
86. Meleg-Smith S, Gauthier PM. Abundance of interstitial eosinophils in renal allografts is associated with vascular rejection. *Transplantation* 2005;79:444-50.
87. Wolff D, Steiner B, Stilgenbauer S, Kahl C, Leithausen M, Junghans C, et al. Treatment with campath-1H for relapsed chronic lymphocytic leukemia after allogeneic peripheral blood stem cell transplantation does not abrogate the development of chronic GVHD. *Eur J Haematol* 2004;72:145-8.
88. Simon HU, Plötz SG, Dummer R, Blaser K. Abnormal clones of T cells producing interleukin-5 in idiopathic eosinophilia. *N Engl J Med* 1999;341:1112-20.

89. Cogan E, Schandené L, Crusiaux A, Cochaux P, Velu T, Goldman M. Brief report: clonal proliferation of type 2 helper T cells in a man with the hypereosinophilic syndrome. *N Engl J Med* 1994;330:535-8.
90. Simon HU, Yousefi S, Dommann-Scherrer CC, Zimmermann DR, Bauer S, Barandun J, et al. Expansion of cytokine-producing CD4-CD8-T cells associated with abnormal Fas expression and hypereosinophilia. *J Exp Med* 1996;183:1071-82.
91. Simon HU, Plötz SG, Simon D, Dummer R, Blaser K. Clinical and immunological features of patients with interleukin-5-producing T cell clones and eosinophilia. *Int Arch Allergy Immunol* 2001;124:242-5.
92. Klion AD, Bochner BS, Gleich GJ, Nutman TB, Rothenberg ME, Simon HU, et al. Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report. *J Allergy Clin Immunol* 2006;117:1292-302.
93. Roujeau JC. Clinical heterogeneity of drug hypersensitivity. *Toxicology* 2005;209:123-9.
94. Wolf R, Matz H, Marcos B, Orion E. Drug rash with eosinophilia and systemic symptoms vs toxic epidermal necrolysis: the dilemma of classification. *Clin Dermatol* 2005;23:311-4.
95. Pichler WJ. Pharmacological interaction of drugs with antigen-specific immune responses: the p-i concept. *Curr Opin Allergy Clin Immunol* 2002;2:301-5.
96. Pichler WJ. Direct T-cell stimulations by drugs: bypassing the innate immune system. *Toxicology* 2005;209:95-100.
97. Dicker RM, James N, Cunha BA. The eosinophilia-myalgia syndrome with neuritis associated with L-tryptophan use. *Ann Intern Med* 1990;112:957-8.
98. Rigau-Perez JG, Perez-Alvarez L, Duenas-Castro S, Choi K, Thacker SB, Germain JL, et al. Epidemiologic investigation of an oil-associated pneumonic paralytic eosinophilic syndrome in Spain. *Am J Epidemiol* 1984;119:250-60.
99. Owen WF, Petersen J, Sheff DM, Folkerth RD, Anderson RJ, Corson JM, et al. Hypodense eosinophils and interleukin-5 activity in the blood of patients with eosinophilia-myalgia syndrome. *Proc Natl Acad Sci U S A* 1990;87:8647-51.
100. Nagai Y, Mori T, Abe T, Nomura G. Immediate-type allergy against human insulin associated with marked eosinophilia in type 2 diabetic patient. *Endocr J* 2001;48:311-6.
101. Silberstein DS, Schoof DD, Rodrick ML, Tai PC, Spry CJ, Davis JR, et al. Activation of eosinophils in cancer patients treated with interleukin-2 and interleukin-2-generated LAK cells. *J Immunol* 1989;142:2162-7.
102. Groopman JE, Mitsuyasu RT, DeLeo MJ, Oette DH, Golde DW. Effect of recombinant human granulocyte-macrophage colony-stimulating factor on myelopoiesis in the acquired immunodeficiency syndrome. *N Engl J Med* 1987;317:593-9.
103. Chan JL, Davis-Reed L, Kimball AB. Counter regulatory balance: atopic dermatitis in patients undergoing infliximab infusion therapy. *J Drugs Dermatol* 2004;3:315-8.
104. Bonnekoh B, Schulz M, Franke I, Gollnick H. Complete remission of a primary cutaneous B-cell lymphoma of the lower leg by first-line monotherapy with the anti-CD20-antibody rituximab. *J Cancer Res Clin Oncol* 2002;128:161-6.
105. Plötz SG, Simon HU, Darsow U, Simon D, Vassina E, Yousefi S, et al. Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis. *N Engl J Med* 2003;349:2334-9.
106. Butterfield JH, Leiferman KM, Abrams J, Silver JE, Bower J, Gonchoroff N, et al. Elevated serum levels of interleukin-5 in patients with the syndrome of episodic angioedema and eosinophilia. *Blood* 1992;79:688-92.
107. Rioux JD, Stone VA, Daly MJ, Cargill M, Green T, Nguyen H, et al. Familial eosinophilia maps to the cytokine gene cluster on human chromosomal region 5Q31-q33. *Am J Hum Genet* 1998;63:1086-94.
108. Gruss HJ, Herrmann F, Drexler HG. Hodgkin's disease: a cytokine-producing tumor: a review. *Crit Rev Oncogenesis* 1994;5:473-538.
109. Ionescu MA, Rivet J, Daneshpouy M, Briere J, Morel P, Janin A. In situ eosinophil activation in 26 primary cutaneous T-cell lymphomas with blood eosinophilia. *J Am Acad Dermatol* 2005;52:32-9.
110. Borish L, Dishuck J, Cox L, Mascali JJ, Williams J, Rosenwasser LJ. Sezary syndrome with elevated IgE and hypereosinophilia: role of dysregulated cytokine production. *J Allergy Clin Immunol* 1993;92:123-31.
111. Tono-oka T, Sato Y, Matsumoto T, Ueno N, Ohkawa M, Shikano T, et al. Hypereosinophilic syndrome in acute lymphoblastic leukemia with a chromosomal translocation [t(5q;14q)]. *Med Pediatr Oncol* 1984;12:33-7.
112. Hogan TF, Koss W, Murgo AJ, Amato RS, Fontana JA, VanScoy FL. Acute lymphoblastic leukemia with chromosomal 5:14 translocation and hypereosinophilia: case report and literature review. *J Clin Oncol* 1987;5:382-90.
113. Meeker TC, Hardy D, Willman C, Hogan T, Abrams J. Activation of the interleukin-3 gene by chromosome translocation in acute lymphocytic leukemia with eosinophilia. *Blood* 1990;76:285-9.
114. Laman JD, Leenen PJM, Annels NE, Hogendoorn PCW, Egeler RM. Langerhans-cell histiocytosis "insight into DC biology." *Trends Immunol* 2003;24:190-6.
115. Lowe D, Jorizzo J, Hutt MSR. Tumour-associated eosinophilia: a review. *J Clin Pathol* 1981;34:1343-8.
116. Geisinger KR, Steffee CH, McGee RS, Woodruff RD, Buss DH. The cytomorphologic features of sclerosing mucoepidermoid carcinoma of the thyroid gland with eosinophilia. *Am J Clin Pathol* 1998;109:294-301.
117. Horie S, Okubo Y, Suzuki J, Isobe M. An emaciated man with eosinophilic pneumonia. *Lancet* 1996;348:166.
118. Fridlender ZG, Simon HU, Shalit M. Metastatic carcinoma presenting with concomitant eosinophilia and thromboembolism. *Am J Med Sci* 2003;326:98-101.
119. Dibbert B, Daigle I, Braun D, Schranz C, Weber M, Blaser K, et al. Role for Bcl-xL in delayed eosinophil apoptosis mediated by granulocyte-macrophage colony-stimulating factor and interleukin-5. *Blood* 1998;92:778-83.
120. Vassina EM, Yousefi S, Simon D, Zwicky C, Conus S, Simon HU. cIAP-2 and survivin contribute to cytokine-mediated delayed eosinophil apoptosis. *Eur J Immunol* 2006;36:1975-84.
121. Rothenberg ME. Eosinophilia. *N Engl J Med* 1998;338:1592-600.

64. Dahinden CA, Kurimoto Y, Wirthmuller U. Growth factors, lipid mediators and effector cells. *J Lipid Mediat* 1990;2(suppl):S129-36.
65. Hosken NA, Shibuya K, Heath AW, Murphy KM, O'Garra A. The effect of antigen dose on CD4⁺ T helper cell phenotype development in a T cell receptor- $\alpha\beta$ -transgenic model. *J Exp Med* 1995;182:1579-84.
66. Ring J, Darsow U. Idiopathic anaphylaxis. *Curr Allergy Asthma Rep* 2002;2:40-5.
67. Dybendal T, Guttormsen AB, Elsayed S, Askeland B, Harboe T, Florvaag E. Screening for mast cell tryptase and serum IgE antibodies in 18 patients with anaphylactic shock during general anaesthesia. *Acta Anaesthesiol Scand* 2003;47:1211-8.
68. Golden DB. Patterns of anaphylaxis: acute and late phase features of allergic reactions. *Novartis Found Symp* 2004;257:101-10; discussion 10-5, 57-60, 276-85.
69. Cheifetz A, Smedley M, Martin S, Reiter M, Leone G, Mayer L, et al. The incidence and management of infusion reactions to infliximab: a large center experience. *Am J Gastroenterol* 2003;98:1315-24.
70. Stallmach A, Giese T, Schmidt C, Meuer SC, Zeuzem SS. Severe anaphylactic reaction to infliximab: successful treatment with adalimumab—report of a case. *Eur J Gastroenterol Hepatol* 2004;16:627-30.
71. Dreyfus DH, Randolph CC. Characterization of an anaphylactoid reaction to omalizumab. *Ann Allergy Asthma Immunol* 2006;96:624-7.
72. Leung DY, Sampson HA, Yunginger JW, Burks AW Jr, Schneider LC, Wortel CH, et al. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 2003;348:986-93.
73. Duplay D. Physician's desk reference. 58th ed. Montvale (NJ): Thomson PDT; 2004.
74. Gomez FP, Marrades RM, Iglesia R, Roca J, Barbera JA, Chung KF, et al. Gas exchange response to a PAF receptor antagonist, SR 27417A, in acute asthma: a pilot study. *Eur Respir J* 1999;14:622-6.
75. Danko G, Sherwood JE, Grissom B, Kreutner W, Chapman RW. Effect of the PAF antagonists, CV-3988 and L-652,731 on the pulmonary and hematological responses to guinea pig anaphylaxis. *Pharmacol Res Commun* 1988;20:785-98.
76. Duschl A, Muller T, Sebald W. Antagonistic mutant proteins of interleukin-4. *Behring Inst Mitt* 1995;87-94.
77. Beckmann MP, Schooley KA, Gallis B, Vanden Bos T, Friend D, Alpert AR, et al. Monoclonal antibodies block murine IL-4 receptor function. *J Immunol* 1990;144:4212-7.
78. Lee SY, Huang CK, Zhang TF, Schofield BH, Burks AW, Bannon GA, et al. Oral administration of IL-12 suppresses anaphylactic reactions in a murine model of peanut hypersensitivity. *Clin Immunol* 2001;101:220-8.
79. Frossard CP, Steidler L, Eigenmann PA. Oral administration of an IL-10-secreting *Lactococcus lactis* strain prevents food-induced IgE sensitization. *J Allergy Clin Immunol* 2007;119:952-9.
80. Zhu D, Kepley CL, Zhang M, Zhang K, Saxon A. A novel human immunoglobulin Fc γ Fc ϵ bifunctional fusion protein inhibits Fc ϵ RI-mediated degranulation. *Nat Med* 2002;8:518-21.
81. Zhang K, Kepley CL, Terada T, Zhu D, Perez H, Saxon A. Inhibition of allergen-specific IgE reactivity by a human Ig Fc γ -Fc ϵ bifunctional fusion protein. *J Allergy Clin Immunol* 2004;114:321-7.
82. Bachelet I, Munitz A, Levi-Schaffer F. Abrogation of allergic reactions by a bispecific antibody fragment linking IgE to CD300a. *J Allergy Clin Immunol* 2006;117:1314-20.
83. Ong CJ, Ming-Lum A, Nodwell M, Ghanipour A, Yang L, Williams DE, et al. Small molecule agonists of SHIP1 inhibit the phosphoinositide 3-kinase pathway in hematopoietic cells. *Blood* 2007;May 14 [epub ahead of print].
84. Buchanan AD, Green TD, Jones SM, Scurlock AM, Christie L, Althage KA, et al. Egg oral immunotherapy in nonanaphylactic children with egg allergy. *J Allergy Clin Immunol* 2007;119:199-205.
85. Nash SD, Steele PH, Kamilaris JS, Pons L, Kulis M, Lee LA, et al. Oral peanut immunotherapy for peanut allergic patients. *J Allergy Clin Immunol* 2007;119(suppl):S158.

Correction

With regard to the June 2007 article entitled "Eosinophilic disorders" (*J Allergy Clin Immunol* 2007;119:1291-300), the citations of Table I and Table II in the text were reversed. The reference to Table I in the text of the article actually refers to Table II, and the reference to Table II actually refers to Table I.