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 of 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 2007;119:1291-300.)

Key words: Allergy, classification, eosinophila, eosinophilic disorders, infection, IL-5, leukemia, lymphona, 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. Some laboratories list higher upper values, in particular in children (as high as 0.75 \times 10^9/L). Eosinophils 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), the female reproductive tract, and the mammary gland. 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. 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 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 $1.5 \times 10^9/L$. However, other lineages are also affected, because the disease is the result of a mutation in a pluripotent hematopoietic stem cell.
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.

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. 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.

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 monocyes, also show increased differentiation. Numerous 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 Bain and updated by Gotlib et al. 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. Marked eosinophilia is often associated with cytogenetic evolution and either represents the accelerated phase of the disease or occurs during acute transformation. 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

![Diagram of algorithm to diagnose eosinophilic disorders](image-url)
eosinophilia. 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. 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.

Myelodysplastic syndromes are a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective and inadequate hematopoiesis. In some cases, it was directly demonstrated that eosinophils are part of the neoplastic clone and that the mutation occurred in a multipotent myeloid stem cell. 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. 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. 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.

### EXTRANSPORTOSINOPHILIC DISORDERS

**T cell–mediated eosinophilias**

**Allergic diseases.** Common diseases are allergic rhinoconjunctivitis, asthma, eosinophilic esophagitis, and atopic dermatitis. Moreover, in most patients with primary eosinophilic gastrointestinal disorders, evidence for IgE-mediated allergic sensitization mechanisms exists. Eosinophilic pancreatitis is rare and usually occurs together with eosinophilic gastroenteritis. In childhood, food allergy and allergic colitis are common. 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. 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. Eosinophils may contribute to inflammation by causing tissue damage and subsequently organ dysfunction, but also by the generation of cytokines and lipid mediators. In addition, they have been implicated in tissue remodeling processes as a consequence of tissue damage. 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. Reasons for that were seen in an insufficient reduction of eosinophils in the bronchial mucosa and in persistent T-cell activation. Similarly, anti–IL-5 antibody treatment failed to improve symptoms significantly in atopic dermatitis. 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. Studies are underway to investigate the effect of anti–IL-5 antibody treatment in patients with eosinophilic esophagitis.

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 antineutrophil cytoplasmic antibodies point to the possibility that autoimmune mechanisms contribute to the disease, although no direct evidence exists for such an assumption. In allergic bronchopulmonary aspergillosis (ABPA), patients cannot eliminate the fungus because of pre-existing epithelial cell damage and subsequently develop an allergy against Aspergillus. 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. 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. 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.

**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
involved in the development of cutaneous and pulmonary fibrosis in these patients. 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.

In primary biliary cirrhosis, eosinophilia is a common and distinctive feature that might be useful in the diagnosis of the disease. In liver biopsies of these patients, increased IL-5 mRNA was detected. A striking tissue eosinophilia has also been reported in Riedel invasive fibrous thyroiditis, but not in other autoimmune forms of thyroiditis. 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).

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. 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. 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.

Infectious diseases. TH2 inflammatory responses are induced by helminths (worms; Table I). 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. 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. IL-5 has been shown to be sufficient to cause helminth infection–mediated eosinophilia.

Eosinophilia was also seen in response to *Plasmodium falciparum* infection. Ectoparasitic infections can also be associated with eosinophilia. For instance, in scabies presenting with bullae, dermal eosinophilia has been observed. Similarly, arthropod bites often cause dermal eosinophilia. In contrast, unicellular protozoa usually induce TH1-type inflammatory responses that are not associated with eosinophilia.

Interestingly, eosinophil granule proteins have been implicated in antibacterial immunity. In addition, eosinophils express LPS receptors on their surface. 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 rhinosinusitis and atopic dermatitis. *Pseudomonas* infection in lung transplant recipients associated with pulmonary eosinophilia has also been reported. *Borrelia* infections may cause erythema chronicum migrans, which is characterized by a mixed inflammatory cellular infiltrate, including eosinophils. In addition, some patients with eosinophilic fasciitis were shown to be infected with *Borrelia burgdorferi*. Moreover, exacerbations of chronic obstructive pulmonary disease might be caused by bacterial infections that further increase inflammatory cell infiltration, including eosinophils.

Eosinophilia in association with viral infections is not common. However, when virus-specific T cells are generated in a TH2 environment, they can also release IL-5 and therefore trigger eosinophilia. This may explain why viral respiratory tract infections are an important cause of asthma exacerbations. 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 TH2 cytokines and eosinophil numbers. It is possible but not proven that eosinophil granule proteins are involved in such cases to neutralize the virus. Moreover, exacerbations of chronic obstructive pulmonary disease might be caused by viral infections that further increase inflammatory cell infiltration, including eosinophils.

HIV-1 infections are also associated with TH2 responses after disease progression. 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

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Drug examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatic anticonvulsants</td>
<td>Carbamazepine, Phenobarbital, Phenytoin, Primidone</td>
</tr>
<tr>
<td>Nonaromatic anticonvulsants</td>
<td>Lamotrigine, Valproic acid, Gabapentin, Benzodiazepines, Allopurinol</td>
</tr>
<tr>
<td>Anticancer drugs</td>
<td>Minocycline, Ticarcillin, Terbinafine, Nitrofurantoin, Isoniazid, Abacavir</td>
</tr>
<tr>
<td>Antimicrobial agents</td>
<td>Sulfonamides, Dapsone, Sulfasalazine, Pseudomonas infection</td>
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<tr>
<td>Sulfa drugs</td>
<td>Dapsone, Sulfasalazine</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Oxicam, Thalidomide, Sulfasalazine</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>Captopril, Diltiazem</td>
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<tr>
<td>Antidiabetics</td>
<td>Sorbinil</td>
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TABLE II. Parasitic helminth infections associated with eosinophilia

<table>
<thead>
<tr>
<th>Phylum</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cestode</td>
<td><em>Mesocestoides corti</em></td>
</tr>
<tr>
<td></td>
<td><em>Hymenolepis diminuta</em></td>
</tr>
<tr>
<td></td>
<td><em>Angiostrongylus species</em></td>
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<tr>
<td></td>
<td><em>Anisakis species</em></td>
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<tr>
<td></td>
<td><em>Ascaris lumbricoides</em></td>
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<tr>
<td></td>
<td><em>Ancylostoma species</em></td>
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<tr>
<td></td>
<td><em>Baylisascaris species</em></td>
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<tr>
<td></td>
<td><em>Brugia species</em></td>
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<tr>
<td></td>
<td><em>Enterobius vermicularis</em></td>
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<tr>
<td></td>
<td><em>Heligmosomoides polygyrus</em></td>
</tr>
<tr>
<td></td>
<td><em>Litomosoides species</em></td>
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<tr>
<td></td>
<td><em>Nippostrongylus species</em></td>
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<tr>
<td></td>
<td><em>Onchocerca species</em></td>
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<tr>
<td></td>
<td><em>Strongyloides species</em></td>
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<tr>
<td></td>
<td><em>Toxocara species</em></td>
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<tr>
<td></td>
<td><em>Trichinella species</em></td>
</tr>
<tr>
<td></td>
<td><em>Trichuris species</em></td>
</tr>
<tr>
<td></td>
<td><em>Wuchereria bancrofti</em></td>
</tr>
<tr>
<td></td>
<td><em>Fasciola species</em></td>
</tr>
<tr>
<td></td>
<td><em>Schistosoma species</em></td>
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</tbody>
</table>

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

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

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. *Alternaria*-specific IL-5–expressing T cells have been demonstrated in patients with chronic rhinosinusitis. 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. Whether *Malassezia* is able to trigger eosinophilia in patients with atopic dermatitis is unknown.

*Graft-versus-host disease.* Graft-versus-host diseases (GVHDs) frequently develop after allogeneic hematopoietic stem cell transplantation. GVHDs are initiated when immunocompromised 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. The latter might be accompanied by an eosinophilic fasciitis. Donor-derived, alloreactive IL-5–producing T cells are thought to trigger eosinophilia in chronic GVHDs. Eosinophilia has also been observed in some cases of acute GVHD, in particular in kidney transplant recipients. In general, however, acute GVHD is thought to be a T<sub>H</sub>1-mediated disorder.

**Immunodeficiencies.** Several primary and secondary immunodeficiencies are frequently associated with eosinophilia, which is mediated by IL-5–producing T cells. Whether such T<sub>H</sub>2 cells actually mediate the immunodeficiency or whether they develop because of T<sub>H</sub>1 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<sub>H</sub>2 phenotype. The hyper-IgE syndrome is another rare genetic immunodeficiency; however, the underlining gene defects are unknown. 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. 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.

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. Similarly, immunosuppressive anti-CD52 antibody therapy was related to severe eosinophilia (see Drug-induced diseases).

**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. In some cases, a marker can be completely absent, resulting in, for instance, CD3<sup>−</sup>CD4<sup>+</sup> or CD3<sup>+</sup>CD4<sup>−</sup>CD8<sup>−</sup> T cells. 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.

It has been suggested to categorize these patients as a defined subgroup of the idiopathic hypereosinophilic syndrome termed lymphocytic variant of the hypereosinophilic syndrome. 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 × 10<sup>9</sup>/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). Drugs associated with severe life threatening drug reactions with eosinophilia 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). Drugs associated with DRESS are aromatic anticonvulsants and other anti-epileptics, sulfonamides, allopurinol, nonsteroidal anti-inflammatory drugs, and antibiotics (Table II). 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. Drugs may even bypass antigen-presenting cells and directly stimulate memory T cells. It is possible but not proven that the agents causing the L-tryptophan syndrome (eosinophilia-myalgia syndrome) and the Spanish toxic oil syndrome stimulate T cells according to the p-I concept. Nevertheless, increased levels of IL-5 were found in L-tryptophan syndrome. A classical IgE-mediated allergy against human insulin has been reported in association with eosinophilia.

IL-2 therapy is sometimes provided to patients with cancer or AIDS and can cause hypereosinophilia in blood 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, suggesting increased eosinophil differentiation. Anti-TNF-α antibody therapy may disturb the Th1/Th2 balance, resulting in atopic dermatitis. Anti-CD52 therapy is used in chronic lymphocytic leukemia but can also cause severe immunodeficiency associated with severe eosinophilia (see Immunodeficiencies). 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.

**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. Patients with eosinophilic dermatitis fall into this group of patients. If they exhibit eosinophil numbers of greater than 1.5 × 10^6/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 angioedema and hereditary eosinophilia.

**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. 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. Other types of lymphoid malignancies have been associated with eosinophilia, such as acute lymphoblastic leukemia with a translocation between chromosomes 5 and 14. 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.

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.

**Solid tumors.** Blood and tissue eosinophilia may be observed in patients with tumors of epithelial cell origin. 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, stomach, liver, and bladder. 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. 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.

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.

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