Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes

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Eosinophilia is an important indicator of various neoplastic and nonneoplastic conditions. Depending on the underlying disease and mechanisms, eosinophil infiltration can lead to organ dysfunction, clinical symptoms, or both. During the past 2 decades, several different classifications of eosinophilic disorders and related syndromes have been proposed in various fields of medicine. Although criteria and definitions are, in part, overlapping, no global consensus has been presented to date. The Year 2011 Working Conference on Eosinophil Disorders and Syndromes was organized to update and refine the criteria and definitions for eosinophilic disorders and to merge prior classifications in a contemporary multidisciplinary schema. A panel of experts from the fields of immunology, allergy, hematology, and pathology contributed to this project. The expert group agreed on unifying terminologies and criteria and a classification that delineates various forms of hypereosinophilia, including primary and secondary variants based on specific hematologic and immunologic conditions, and various forms of the hypereosinophilic syndrome. For patients in whom no underlying disease or hypereosinophilic syndrome is found, the term hypereosinophilia of undetermined significance is introduced. The proposed novel criteria, definitions, and terminologies should assist in daily practice, as well as in the preparation and conduct of clinical trials. (J Allergy Clin Immunol 2012;130:607-12.)

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Eosinophilia is observed in patients with various inflammatory and allergic conditions, as well as diverse hematologic malignancies.[1-3] In hematopoietic stem cell and myeloid neoplasms, eosinophils originate from a malignant clone, whereas in other conditions and disorders, (hyper)eosinophilia is considered a nonneoplastic process triggered by eosinophilopoietic cytokines or by other as yet unknown processes.[1-3] Peripheral blood eosinophilia can be transient, episodic, or persistent. In patients with chronic (persistent) eosinophilia, tissue infiltration and the effects of eosinophil-derived effector molecules might result in clinically relevant organ pathology or even in (irreversible) organ damage.[4-6] Notably, among a range of effects on multiple organs, endomyocardial fibrosis, thrombosis, or both might be life-threatening consequences in patients with sustained eosinophilia. In other patients eosinophilia can be persistent but does not lead to measurable organ dysfunction. In these patients the clinical course and outcome remain uncertain; therefore they should be followed for potential disease progression.

Several neoplastic conditions are associated with eosinophilia. Myeloid neoplasms variably accompanied by eosinophilia are chronic myeloid leukemia (CML), other myeloproliferative

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Abbreviations used

BM: Bone marrow
CEL: Chronic eosinophilic leukemia
FGFR: Fibroblast growth factor receptor
HE: Hypereosinophilia
HE_N: Primary (clonal/neoplastic) hypereosinophilia produced by apparently clonal (neoplastic) eosinophils
HE_R: Secondary (reactive) hypereosinophilia
HES: Hypereosinophilic syndrome
HE_{US}: Hypereosinophilia of undetermined significance
ICOG-EO: International Cooperative Working Group on Eosinophil Disorders
MDS: Myelodysplastic syndrome
MPN: Myeloproliferative neoplasm
PDGFR: Platelet-derived growth factor receptor
PDGFRA: Platelet-derived growth factor receptor α
PDGFRB: Platelet-derived growth factor receptor β
SM: Systemic mastocytosis
WHO: World Health Organization

neoplasms (MPNs), distinct variants of acute myeloid leukemia, rare forms of myelodysplastic syndromes (MDSs), some MDS/MPN overlap disorders, and a subset of patients with (advanced) systemic mastocytosis (SM).[7-9] These differential diagnoses have to be considered in cases of unexplained eosinophilia, especially when signs of myeloproliferation are present. In such patients a thorough hematologic workup, including bone marrow (BM) cytology, histology and immunohistochemistry, cytogenetics, molecular analyses, and staging of potentially affected organ systems, should be initiated. In patients with eosinophilic leukemia, hypereosinophilia (HE) is a consistent and predominant feature. Most serious complications of HE (ie, endomyocardial fibrosis, thrombosis, or both) are particularly prone to develop in these patients, especially in the setting of fusion genes involving platelet-derived growth factor receptor α *(PDGFRA)*. This is important clinically because imatinib is usually an effective therapy in patients with *PDGFRA* fusion genes and leads to complete hematologic and molecular remission in a high proportion of cases.[2,3,8-10]

During the past 2 decades, several different classifications of eosinophilic disorders have been proposed in various fields of medicine.[11-14] Although respective criteria and definitions partially overlap, no multidisciplinary global consensus has been developed. In addition, the recent identification of several new molecular and immunologic mechanisms lends greater understanding to the disorders and therefore to logical taxonomy.

To update and refine the criteria and definitions for eosinophilic disorders and to merge classifications in a multidisciplinary consensus, we organized the Year 2011 Working Conference on Eosinophil Disorders and Syndromes (Vienna, Austria; May 27-28, 2011). Experts from the fields of immunology, allergy, hematology, pathology, and molecular medicine contributed to this project. All faculty members actively participated in preconference and postconference discussions (from October 2010 to August 2011). The final outcomes of these discussions were formulated into consensus statements and into a contemporary multidisciplinary classification of eosinophilic disorders and related syndromes together with proposed criteria that are summarized in this article.

BIOLOGY OF EOSINOPHILS AND NORMAL LABORATORY VALUES

Under normal physiologic conditions, eosinophil production is tightly controlled by the cytokine network.[4,5,8] The normal eosinophil count in peripheral blood ranges between 0.05 and 0.5 $\times$ 10^9/L. Normal values for BM eosinophils also have been proposed, and in textbooks normal values of eosinophils in BM aspirates commonly range between 1% and 6%. Eosinophils are not normally present in other human tissues and organs, with the exception of the thymus, spleen, lymph nodes, uterus, and gastrointestinal tract from the stomach through the large intestine. The normal physiologic range of eosinophils in these organs is less well defined.[4-6,15]

Similar to other leukocytes, eosinophils originate from $CD34^+$ hematopoietic precursor cells.[4,5,8] The most potent growth factors for eosinophils are IL-5, GM-CSF, and IL-3.[4,5,8] These eosinophilopoietic cytokines are primarily produced by activated T lymphocytes, mast cells, and stromal cells and trigger not only growth but also activation of normal and neoplastic eosinophils.[4-6] Apart from these classical growth regulators, several other cytokines and chemokines also trigger eosinophil growth and/or function. Reactive eosinophilia is mainly caused by eosinophilopoietic cytokines (IL-3, IL-5, and GM-CSF), whereas clonal eosinophils typically are derived from progenitors containing mutations in oncogenic tyrosine kinase receptors, such as *PDGFRA*, platelet-derived growth factor receptor β *(PDGFRB)*, or fibroblast growth factor receptor 1 *(FGFR1)*, or other acquired (cyto)genetic lesions.[7-10] Eosinophils produce and store a number of biologically active molecules in their granules, such as eosinophil peroxidase, eosinophil cationic protein, major basic protein, and numerous cytokines, including TGF-β.[4-6] Under various conditions, eosinophils are activated to release their mediators and thereby influence tissue homeostasis and integrity. In the setting of massive and persistent activation, eosinophils cause profound changes in the microenvironment, often with resultant fibrosis, thrombosis, or both and thus severe organ damage.[4-6] In patients with such persistent eosinophil activation, tissue specimens might show marked deposition of eosinophil granule proteins, even in the absence of a massive eosinophil infiltrate.[4-6] Recommended stains for visualization and enumeration of eosinophils in organ sections are May-Grunwald-Giemsa and Wright-Giemsa. In the normal BM the eosinophil count ranges between 1% and 6%. Eosinophils are also detectable in the normal mucosal layers of the stomach, small and large bowels, uterus, thymus, spleen, and lymph nodes, but only a few robust studies comparing eosinophil numbers in normal and inflamed organs are available. Other healthy tissues do not contain eosinophils, and no eosinophil-derived proteins can be detected.[15]

DEFINITION AND CLASSIFICATION OF HE

Traditionally, peripheral blood eosinophilia has been divided into mild (0.5-1.5 $\times$ 10^9/L), marked (>1.5 $\times$ 10^9/L), and massive (>5.0 $\times$ 10^9/L) eosinophilia. As noted previously, eosinophilia can be transient, episodic, or persistent (chronic). The proposal of this expert panel is that the term HE should be used when marked and persistent eosinophilia has been documented or marked tissue eosinophilia is observed (Table I). The faculty also agreed that the term persistent applies to peripheral blood eosinophilia recorded on at least 2 occasions with a minimum time interval of 4 weeks (except when immediate therapy