Published in final edited form as:

Semin Hematol. 2012 April ; 49(2): 111–112. doi:10.1053/j.seminhematol.2012.01.004.

Eosinophilia: Introduction

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Since the first descriptions of “unexplained eosinophilia” in the early 1900s,^{1,2} the etiology and pathogenesis of eosinophilia in human disease has provoked controversy. This stems, in part, from the fact that the end results of eosinophilic inflammation in tissues are often similar regardless of the underlying cause. In 1975, Chusid et al published their landmark paper defining “the hypereosinophilic syndrome” (HES) on the basis of three criteria: (1) a persistent eosinophilia of 1,500/ μ L for 6 months, or death before 6 months associated with signs and symptoms of hypereosinophilic disease; (2) a lack of evidence for parasitic, allergic, or known causes of eosinophilia; and (3) presumptive signs of organ involvement.³ Although they recognized at the time that this broad case definition included patients with a variety of disorders, including chronic eosinophilic leukemia and eosinophilic collagen vascular diseases, it is only recently that the molecular and immunologic tools have become available to begin to dissect out the underlying etiologies of “idiopathic” HES.

The 1996 description of a patient with HES, in whom the eosinophilia was driven by expansion of an abnormal CD3⁺ CD4⁺ T-cell population producing interleukin-5 (IL-5),⁵ provided the first demonstration of a defined etiology of the eosinophilia in a patient with presumed “idiopathic” HES. Aberrant T-cell populations were subsequently documented in a larger series of patients,⁶ and the so-called “lymphocytic variant” is now known to account for 10% to 15% of patients presenting with HES.⁶ The next major advance in HES diagnosis was certainly the identification of the fusion tyrosine kinase, FIP1L1-platelet-derived growth factor alpha (PDGFRA).⁴ Not only did this discovery confirm earlier suspicions that some patients with HES have chronic eosinophilic leukemia despite normal cytogenetic analysis, but it provided a rationale for the success of targeted therapy with imatinib in these patients. Similar to the lymphocytic variant, PDGFRA-associated my-eloproliferative neoplasms account for a minority of patients presenting with a clinical picture consistent with HES.

Although these advances in our understanding of the etiology of HES coupled with the development of novel and effective therapies, including monoclonal antibodies to IL-5⁸ and tyrosine kinase inhibitors, have dramatically altered the treatment and prognosis of patients with HES, they have also led to increased confusion in the definition and nomenclature of eosinophilic disorders.⁷ Clearly, with the availability of therapies that reduce morbidity and mortality (when initiated before the development of irreversible organ pathology), it is no longer appropriate to wait 6 months to make a diagnosis of HES. Less certain is whether

disorders of defined etiology that present in a way that is clinically indistinguishable from “idiopathic” HES should be classified as variants of HES or removed from the definition as they are identified. Reliable means of assessing eosinophil-associated end organ pathology are also lacking. As the number of agents targeting specific pathways and molecules continues to increase, it will become increasingly important to identify and classify patients in a way that facilitates rational therapeutic choices.

This issue of *Seminars in Hematology* provides a state of the art review of eosinophil biology and pathogenesis, as well as a guide to the diagnosis and management of a variety of eosinophilic disorders. Ongoing difficulties and controversies in the classification of eosinophilic disorders are also discussed.

Acknowledgments

This work was supported by the Division of Intramural Research, NIAID, NIH.

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