Evaluation and Differential Diagnosis of Persistent Marked Eosinophilia

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KEYWORDS

- Eosinophilia • Hypereosinophilic syndrome • *FIP1L1-PDGFRA*
- Lymphocytic hypereosinophilic syndrome (L-HES)
- Myeloproliferative hypereosinophilic syndrome (M-HES)

KEY POINTS

- The causes of peripheral blood eosinophilia are varied, ranging from benign eosinophilia to malignancy; a careful history and physical examination along with directed clinical evaluation may help determine the cause.
- Although drug allergy is the most common cause of hypereosinophilia in the United States, parasitic diseases are the most common cause worldwide.
- Hypereosinophilic syndrome is a diagnosis of exclusion; however, it should be considered in patients with peripheral eosinophilia of unknown cause, because delay in diagnosis may result in end-organ damage.
- In recent years, advances in molecular diagnostics have improved the ability of physicians to identify and treat hypereosinophilic syndrome.

EOSINOPHIL BIOLOGY

In order to better appreciate the implications of eosinophilia and eosinophilic tissue infiltration, it is helpful to have an understanding of eosinophil development, structure, and function. Eosinophils are terminally differentiated granulocytes derived in the bone marrow from CD34+ hematopoietic stem cells.[1] Cytokines integral to the transition from progenitor cells to eosinophils include interleukin (IL)-3, IL-5, and granulocyte-macrophage colony–stimulating factor (GM-CSF); IL-5 also participates in regulation of other aspects of eosinophil function, including release of mature cells from the

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bone marrow and migration into tissue.[2] Progression toward the eosinophil lineage is directed by several key transcription factors, including GATA-binding protein 1 (GATA-1), PU.1, interferon consensus–binding protein, and CCAAT-enhancer binding proteins.[3] The half-life of eosinophils in the peripheral blood is approximately 18 hours, and under normal circumstances they represent only 1% to 5% peripheral blood leukocytes. However, their survival is significantly prolonged after recruitment into tissue, where they represent a more substantial proportion of the cellular population.[3,4]

Eosinophils have a characteristic morphology, with bilobed nuclei and numerous cytoplasmic granules that bind to the dye eosin, leading to a distinct pink coloration of the cytoplasm on microscopy.[5,6] Their specific granules contain hydrolytic enzymes and cationic granule proteins including major basic protein (MBP), eosinophil peroxidase, eosinophil-derived neurotoxin (EDN), and eosinophil cationic protein.[6] These proteins are responsible for many fundamental activities of eosinophils. Specific granules also contain cytokines, chemokines, and growth factors, such as CC chemokine ligand 5 (CCL5)/regulated on activation, normal T cell expressed and secreted (RANTES), CCL11/eotaxin, GM-CSF, IL-2, IL-4, IL-5, IL-6, IL-13, transforming growth factor alpha, and tumor necrosis factor alpha.[6] As these mediators are preformed and do not require de novo synthesis, activated eosinophils can respond rapidly to changes in the environment, promoting efficient cellular recruitment and coordinated immune responses.

Understanding the normal mechanisms of eosinophil development and proliferation is essential for identifying the derangements in these pathways that lead to eosinophilia. Similarly, knowledge of eosinophil function provides a framework for comprehension of the abnormalities that can occur in the setting of increased eosinophil number or activity.

EOSINOPHILIA

Eosinophilia is defined as an increase in the peripheral absolute eosinophil count (AEC). There are defined categories including mild (AEC from 500–1500/mm^3), moderate (AEC 1500–5000/mm^3), and severe (AEC >5000/mm^3).[7] The clinical impact of eosinophilia is variable. The severity of symptoms does not always correlate with the degree of eosinophilia; some patients with substantial peripheral eosinophil increases remain asymptomatic, whereas others with mild eosinophilia have severe complications.[8] The fact that blood eosinophil counts may not be representative of eosinophilic tissue infiltration may be partially responsible for this. Eosinophil counts in tissue are generally higher than those present in peripheral blood, and the release of preformed mediators in associated tissue often leads to the clinical manifestations and complications of eosinophilia.[9] The discrepancy between degree of eosinophilia and manifestation of clinical symptoms may also be explained by differences in the degree of eosinophil activation. Studies of members of an asymptomatic family with hypereosinophilia (2000–5000 eosinophils/mm^3) showed that they had relative lack of eosinophil activation (decreased serum levels of EDN and MBP, and decreased surface expression of CD25) compared with those with nonfamilial hypereosinophilic syndrome (HES).[10]

The causes of eosinophilia are varied, and are further explored later in this article. It is essential to systematically approach patients who present with unexplained eosinophilia, because the treatments may vary by cause and the urgency of management may be guided by the presence or absence of end-organ manifestations. A detailed discussion of end-organ manifestations associated with eosinophilia is provided by Akuthota and Weller elsewhere in this issue.