Eosinophilia in Hematologic Disorders

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KEYWORDS

• Eosinophilia • PDGFRA • PDGFRB • Chronic eosinophilic leukemia
• Hypereosinophilic syndrome • Imatinib

KEY POINTS

- Eosinophilia can subtend a broad differential diagnosis of acute or chronic, benign or malignant disorders.
- Suspecting an eosinophilia-associated myeloid neoplasm is important for prompt initiation of effective therapy.
- Molecular characterization of eosinophilia-associated myeloid neoplasms is critical for selecting the most appropriate targeted therapy.

INTRODUCTION

The upper limit of normal for eosinophils in the peripheral blood is 3% to 5%, corresponding to an absolute eosinophil count (AEC) of 350 to 500/mm^3.[1] The severity of eosinophilia has been arbitrarily divided into mild (AEC 500–1500/mm^3), moderate (AEC 1500–5000/mm^3), and severe (AEC >5000/mm^3),[1,2] although the practical significance of this stratification is unclear.

Many different conditions can underlie a finding of eosinophilia. A first broad distinction should be made between reactive and clonal eosinophilia. The first condition is characterized by the proliferation of polyclonal, mature eosinophils and can be sustained by benign or malignant disorders. In the second, eosinophils represent the primary malignant clone, and precursors can be found in the peripheral blood or bone marrow. As an additional category, idiopathic hypereosinophilic syndrome (HES) is a diagnosis of exclusion in patients with sustained eosinophilia and evidence of end-organ damage. It is important to identify the correct type of eosinophilia in a timely manner because a delay in referral and treatment can have profoundly detrimental

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consequences on patient outcomes. This review discusses the diagnostic approach to eosinophilia from the hematologist's perspective, including elements of suspicion, diagnostic tests, and current treatment approaches for eosinophilia-associated myeloid neoplasms (MN-eos).

REACTIVE EOSINOPHILIA

Reactive eosinophilia is typically caused by increased levels of interleukin (IL)-5. Concomitant elevation in IL-4 and IL-13 can lead to associated hypergammaglobulinemia E (hyper-IgE).[3] In Western countries, reactive eosinophilia is most commonly caused by allergic conditions, whereby increases in IL-5 are mediated by T-helper 2 cells. A detailed clinical history and prick or radioallergosorbent tests usually allow prompt diagnosis and appropriate treatment.[4] In developing countries, the main cause of eosinophilia is invasive parasitic infections (most commonly helminths). A thorough travel history is crucial to elicit clinical suspicion and subsequent testing.[5] Other medical conditions that can present or associate with eosinophilia include a variety of pulmonary, dermatologic, or gastrointestinal disorders,[6] adrenal insufficiency,[7,8] and more rare entities such as hyper-IgE syndrome[9] or Wiscott-Aldrich syndrome.[10] A systematic review of these disorders is offered elsewhere in this issue.

REACTIVE EOSINOPHILIA OF HEMATOLOGIC AND ONCOLOGIC INTEREST

Cancer cells are capable of secreting granulocyte-/monocyte-colony stimulating factor, IL-3, and IL-5, which stimulate the proliferation of polyclonal eosinophils.[11,12] Paraneoplastic eosinophilia occurs in a variety of solid malignancies including, but not limited to, head and neck, lung, gastrointestinal, ovarian, and cervical cancer. Its frequency is 0.5% to 7%.[13] Eosinophilia is usually associated with advanced-stage disease and its prognostic value seems to vary (favorable, unfavorable, or neutral) among tumor types. However, the available data on the clinical significance of tumor-associated tissue eosinophilia are limited and heterogeneous.[14]

Hodgkin lymphoma, especially the mixed cellularity or nodular sclerosis types, can present with peripheral blood or, less frequently, tissue or marrow eosinophilia. Eosinophils are recruited directly by Reed-Sternberg cells. Acute B-cell lymphoblastic leukemia (B-ALL) associated with t(5;14) can also present with eosinophilia. The t(5;14) juxtaposes the IL-3 gene (on chromosome 5) and the immunoglobulin heavy chain (IgH) gene locus (on chromosome 14), resulting in enhanced IL-3 transcription and consequent eosinophilia. Around 10% of cases of adult T-cell leukemia/lymphoma are associated with reactive, IL-5-mediated peripheral blood eosinophilia, and 2% to 20% of patients with non-Hodgkin lymphoma (mostly of T-cell origin) present with elevated AEC (eosinophilia in lymphoproliferative disorders is reviewed in Ref.[15]).

LYMPHOCYTE VARIANT HYPEREOSINOPHILIC SYNDROME

In lymphocytic variant (LV) HES, peripheral blood eosinophilia is sustained by clonal T-helper 2 cells,[16] which may display different phenotypes, such as $CD3^-/CD4^+$, $CD3^+/CD4^-/CD8^-$, and $CD3^+/CD4^+/CD8^-$. Increased serum IgE levels can also be present. Diagnosis of LV HES, which is not a World Health Organization (WHO)-defined entity, is not standardized. Demonstration of a clonally rearranged T-cell receptor, direct observation of cytokine production by cultured T cells, or a finding of elevated TARC (a T-helper 2 cytokine) may be helpful in supporting the diagnosis. Up to one-fourth of patients with LV HES ultimately develop an overt T-cell malignancy.[17]