

Persistent Eosinophilia is a Challenging Problem

Nahla AM Hamed*

Professor of Hematology, Faculty of Medicine, Alexandria University, Egypt

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*Corresponding author: Nahla AM Hamed, Professor of Hematology, Faculty of Medicine, Alexandria University, Egypt

Abstract

HE is defined as $>1.5 \times 10^9/L$ eosinophils in the blood on 2 examinations (interval >1 mo) and/or tissue HE defined by: eosinophils percentage in BM section exceeding 20% of all nucleated cells; and/or extensive eosinophilic tissue infiltration by pathologist opinion; and/or presence of marked deposition of eosinophil granule proteins (in the absence or presence of major tissue eosinophils infiltration).

Abbreviations: AEC: absolute eosinophil count; HE: Hypereosinophilia; ABPA: Allergic Bronchopulmonary Aspergillosis; B-ALL: Acute B-cell lymphoblastic leukemia; GVHD: Graft-Versus-Host Disease; BM: Bone Marrow; PB: Peripheral Blood; IL5: Interleukin 5; AML: Acute Myeloid Leukemia; LV: Lymphocytic Variant; Th2:T-cells have a helper type 2; EPPER: Eosinophilic, polymorphic, and pruritic Eruption Associated with Radiotherapy; MPN: Myeloproliferative Neoplasm; HES: Hypereosinophilic Syndrome; PDGFRA: Platelet-Derived Growth Factor Receptor Alpha; PDGFRB: Platelet-Derived Growth Factor Receptor Beta; FGFR1: Fibroblast Growth Factor Receptor 1; CEL-NOS: Chronic Eosinophilic Leukemia-Not Otherwise Specified; MDS: Myelodysplastic Syndrome; IgH: Ig Heavy Chain; EBV: Epstein-Barr virus

Introduction

Eosinophilia is defined as an AEC $>500/\mu L$ [1]. The severity of eosinophilia has been arbitrarily divided into mild (AEC: $500-1,500/mm^3$), moderate (AEC: $1,500-5,000/mm^3$), and severe (AEC: $>5,000/mm^3$) [2]. HE is defined as $>1.5 \times 10^9/L$ eosinophils in the blood on 2 examinations (interval >1 mo) and/or tissue HE. Subtypes of HE are hereditary (familial); primary (clonal/neoplastic) HE, secondary (reactive) HE; hypereosinophilic syndrome (HES) and HE of undetermined significance (HE_{us}) [3]. HE_{us} is a novel term in lieu of idiopathic hypereosinophilia [4]. Most eosinophilias are reactive [5].

1- Secondary (reactive) HE

Is characterized by proliferation of non-clonal, mature eosinophils [2]. HE is cytokine-driven in most cases [3]. It is typically caused by increased IL5 levels. Concomitant elevation in IL4 and IL13 can lead to associated hypergammaglobulinemia (Ig) E [2]. Elevated peripheral eosinophilia can be found in parasitic infection, significant atopic disease, drug hypersensitivity reactions, connective tissue disorders, malignancy, monogenic disorders of immune deficiency or dysregulation with prominent atopy, particularly in the pediatric age group and rare hypereosinophilic syndromes [6].

Infectious disease

Tissue invasive helminthes and burrowing ectoparasites commonly present with eosinophilia. Exclusively intraluminal parasites (e.g. adult tapeworms, protozoa) or those contained in

cystic structures (e.g. hydatid cyst, neurocysticercosis) are unlikely to cause eosinophilia [7]. Disseminated coccidioidomycosis and aspergillosis (when presenting as ABPA) are well-known fungal causes of eosinophilia. ABPA is an inflammatory airway disease promoted by presence of fungal-derived proteinases in the lungs, rather than a tissue invasive process. Histoplasmosis and tuberculosis can cause eosinophilia indirectly when they cause adrenal insufficiency. Eosinophilia in HIV may be due to infectious causes, eosinophilic pustular folliculitis, drug reactions (HAART or antimicrobials), malignancies, hypereosinophilic syndromes, toxins among others. HIV itself is thought to cause eosinophilia due a Th1-Th2 shift [7].

Immunologic

A. Few primary immunodeficiency disorders as Omenn syndrome, HyperIg E (Job's) syndrome, Dock8 deficiency, IPEX, and Zap70 deficiency are associated with high grade eosinophilia [8].

B. Marked eosinophilia occasionally seen in acute GVHD. Milder chronic GVHD has also been associated with eosinophilia, particularly following allogeneic stem cell transplantation; the associated eosinophilia has better outcomes and has no prognostic value [8].

Paraneoplastic eosinophilia

It occurs in a variety of solid malignancies including, head and neck, lung, gastrointestinal, ovarian, and cervical cancer. Its

frequency is 0.5% to 7%. Eosinophilia is usually associated with advanced-stage disease. Its prognostic value and clinical significance is heterogeneous and vary (favorable, unfavorable or neutral) among tumor types [2]. About 25% of systemic mast cell disease is accompanied by peripheral eosinophilia [8] which is prognostically neutral and not affected by exclusion of FIP1L1-PDGFR α -positive cases [4]. Elevated AEC is present in non-Hodgkin's lymphoma (mostly of T-cell origin) (2-20%), adult T-cell leukemia/lymphoma (around 10%) and in B-ALL associated with t (5;14). The t (5;14) juxtaposes the IL3 gene (on chromosome 5) and IgH gene locus (on chromosome 14), resulting in enhanced IL3 transcription and consequent eosinophilia. Hodgkin's lymphoma, especially mixed cellularity or nodular sclerosis types, can present with PB or, less frequently, tissue or marrow eosinophilia. Eosinophils are recruited directly by Reed-Sternberg cells [2].

Endocrine

loss of endogenous adrenoglucocorticosteroids in Addison's disease, adrenal hemorrhage, or hypopituitarism can increase blood eosinophilia [8].

Other

Cholesterol embolization, typically after a vascular or intravascular procedure, EPPER characterized by tumor-associated blood eosinophilia and a cutaneous eosinophilic infiltrate, sarcoidosis, inflammatory bowel disease and other disorders associated with immune-dysregulation can be associated with marked eosinophilia [8].

2- Hereditary (familial) HE: there is familial clustering. No signs or symptoms of hereditary immunodeficiency, no evidence of a reactive or neoplastic condition/disorder underlying HE is present [3].

3-HE of undetermined significance (HEUS): Is diagnosed if there is no underlying cause of HE, no family history, no evidence of a reactive or neoplastic condition/disorder underlying HE, and no end-organ damage attributable to HE [3].

4- Clonal eosinophilia: Eosinophils represent the primary malignant clone and precursors. It can be found in the PB and/or BM. There are three main types of WHO-defined eosinophilia-associated myeloid neoplasms [2]:

- i. WHO-defined myeloid malignancies associated eosinophilia (eg. MDS, MPNs, MDS/MPNs, or AML).
- ii. Myeloid / lymphoid neoplasms with eosinophilia and rearrangements of PDGFRA, PDGFRB or FGFR1; or with PCM1-JAK2.
- iii. CEL, NOS [2].

WHO-defined myeloid malignancies associated eosinophilia

The classic example is AML with inv (16) or t (16;16) and AML with t (8;21). In the former, the increased numbers of abnormal eosinophils with characteristic large basophilic granules may suggest the diagnosis before cytogenetic results are available. In

the last, eosinophil precursors are increased in approximately one-third of patients, and blood eosinophilia may also be observed. Another characteristic is that blasts often have an aberrant CD13, CD34, CD19, PAX5, CD33 weak immunophenotype. In rare cases, clonal eosinophilia can also be associated with chronic myelogenous leukemia, chronic myelomonocytic leukemia, or MDS [5]. In de novo MDS, eosinophilia (and basophilia) predicted a significantly reduced survival and more frequent evolution to AML [4].

Myeloid / lymphoid neoplasms with eosinophilia and rearrangements of PDGFRA, PDGFRB or FGFR1; or with PCM1-JAK2

Myeloid / lymphoid neoplasms with PDGFRA rearrangement: A myeloid or lymphoid neoplasm, usually with prominent eosinophilia and presence of a FIP1L1-PDGFR α fusion gene or a variant fusion gene with rearrangement of PDGFRA [3].

Myeloid/lymphoid neoplasms with PDGFRB rearrangement: A myeloid or lymphoid neoplasm, often with prominent eosinophilia and sometimes with neutrophilia or monocytosis and presence of t (5;12)(q31;q33;p12) or a variant translocation or demonstration of an ETV6-PDGFRB fusion gene or rearrangement of PDGFRB [3].

Myeloid/lymphoid neoplasms with FGFR1 rearrangement: A MPN or myelodysplastic/MPN with prominent eosinophilia, and sometimes with neutrophilia or monocytosis or AML or precursor T-cell or precursor B-cell lymphoblastic leukemia/lymphoma or mixed phenotype acute leukemia (usually associated with PB or BM eosinophilia) and presence of t (8;13)(p11;q12) or a variant translocation leading to FGFR1 rearrangement demonstrated in myeloid cells, lymphoblasts, or both [3].

Myeloid/lymphoid neoplasms with PCM1-JAK2: a rare entity, there is t(8;9)(p22;p24.1) or a variant translocation leading to JAK2 rearrangement [3]. It is characterized by a prominent eosinophilia with BM findings of left-shifted erythroid predominance, lymphoid aggregates, and often myelofibrosis, at times mimicking PMF. It can also rarely present as T- or B-ALL and responds to JAK inhibition [9].

CEL, NOS: a MPN [10] characterized by eosinophil count $>1.5 \times 10^9/L$; not meeting WHO criteria for BCR-ABL1-positive chronic myeloid leukemia, PV, ET, PMF, CNL, CMML, or atypical CML; no rearrangement of PDGFRA, PDGFRB, or FGFR1; no PCM1-JAK2, ETV6-JAK2, or BCR-JAK2 fusion gene; the blast cell count in the PB and BM is less than 20%, and inv(16)(p13.1q22), t(16;16)(p13;q22) and other diagnostic features of AML are absent; there is a clonal cytogenetic or molecular genetic abnormality, or blast cells are $\geq 2\%$ in the PB or $>5\%$ in the BM [3]. The prognosis of WHO-defined CEL-NOS is poor. Acute transformation may develop [4]. It can only be reliably separated from idiopathic HES by the presence of increased blasts in BM and or PB, or proof of clonality [10].

5-HES: AEC $>1.5 \times 10^9/L$ must persist for at least 6 mo, together with organ damage and/or dysfunction attributable to tissue HE; Exclude reactive eosinophilia; (LV) HES (cytokine-producing, immunophenotypically-aberrant T-cell population); CEL, NOS;

WHO-defined myeloid malignancies associated eosinophilia (e.g., MDS, MPNs, MDS/MPNs, or AML); eosinophilia-associated MPNs or AML/ALL with rearrangements of PDGFRA, PDGFRB, or FGFR1 or with PCM1-JAK2 and other disorders or conditions causing organ damage [3]. HE-related organ damage means organ dysfunction with marked tissue eosinophil infiltrates and/or extensive deposition of eosinophil-derived proteins (\pm marked tissue eosinophils) and 1 or more of the following: fibrosis (lung, heart, digestive tract, skin, and others); thrombosis with or without thromboembolism; cutaneous (including mucosal) erythema, edema/angioedema, ulceration, pruritus, and eczema; and peripheral or central neuropathy with chronic or recurrent neurologic deficit. Other organ system involvement (liver, pancreas, kidney, and other organs) are less common. HES can manifest in 1 or more organ systems [4]. If there is no tissue damage; HE_{US} is the preferred diagnosis [3]. HES are considered a provisional diagnosis until a cause of HE is discovered [3].

(LV) HES: Peripheral blood eosinophilia is sustained by clonal T helper 2 cells, which may display different phenotypes, such as CD3-/CD4+, CD3+/CD4-/CD8- and CD3+/CD4+/CD8- (2) and a normal component of the T-cell receptor complex. Additional immunophenotypic abnormalities include elevated CD5 expression on CD3-CD4+ cells, and loss of surface CD7 and/or expression of CD27 [4]. Increased serum IgE levels can also be present [2]. These patients typically have cutaneous signs and symptoms as the primary disease manifestation [4]. Clinical manifestations can involve all tissue or organs affected in other types of HE [11] including superficial adenopathy, rheumatologic, gastrointestinal, pulmonary, neurologic, and cardiovascular [4].

Diagnosis of LV HES 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 [2]. An indolent disease course is usually observed. However, patients may infrequently develop either T-cell lymphoma or Sezary syndrome. Accumulation of cytogenetic changes (e.g. partial 6q and 10p deletions, trisomy 7) in T-cells, and proliferation of lymphocytes with the CD3-CD4+ phenotype have been observed with progression to lymphoma [4]. A case of lymphocyte variant hypereosinophilia was reported in a patient with chronic active EBV infection but the causal relationship between EBV and this subtype of eosinophilia is unclear [4].

Practical Points

A. In developing countries, eosinophilia is most commonly associated with infectious processes such as helminth-associated and fungal conditions, while in developed countries; eosinophilia is most commonly associated with allergic conditions such as drug reactions [7].

B. Eosinophilia in the context of an acute illness points toward autoimmune, parasitic (e.g. acute schistosomiasis), or fungal (e.g. coccidiomycosis) or other non-infectious etiology as the cause of the illness since peripheral eosinophil counts is suppressed during acute bacterial and viral infections [1].

C. In critically ill patients, eosinophilia due to adrenal insufficiency is common [5].

D. *Strongyloides stercoralis* can cause eosinophilia years after the initial infection because the organism is capable of autoinfection inside its host.

E. Chromosomal abnormalities carrying an intermediate or poor prognosis are significantly higher in patients with eosinophilia or basophilia (compared to patients with neither) [4].

F. In HES, with evolving life-threatening end-organ damage, the diagnosis can be made immediately to avoid delay in therapy [3].

G. A complete medication history of over the counter medications, supplements, herbal preparations, and vitamins; any medication known to induce eosinophilia should be taken [8].

H. In workup of HE, rule out reactive (secondary) causes first. If negative, parallel or sequential testing for a primary (clonal) eosinophilia should be undertaken. Evaluation includes morphologic analysis of the PB and BM, immunohistochemistry (eg, CD117, tryptase, and CD25 in systemic mastocytosis), flow cytometric immunophenotyping for myeloid, B- and/or T-lymphocyte markers, and cytogenetic/molecular/genetic testing. Idiopathic HES is a diagnosis of exclusion and requires the presence of organ damage [3,12].

Conclusion

A detailed understanding of classification schemes of eosinophilic disorders can be better translated into therapeutic implications.

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