Diagnostic Complexities of Eosinophilia

Nathan D. Montgomery, MD, PhD; Cherie H. Dunphy, MD; Micah Mooberry, MD; Andrew Laramore, MD; Matthew C. Foster, MD; Steven I. Park, MD; Yuri D. Fedoriw, MD

• ***Context.***—**The advent of molecular tools capable of subclassifying eosinophilia has changed the diagnostic and clinical approach to what was classically called hypereosinophilic syndrome.**

Objectives.—**To review the etiologies of eosinophilia and to describe the current diagnostic approach to this abnormality.**

Data Sources.—**Literature review.**

Conclusions.—**Eosinophilia is a common, hematologic abnormality with diverse etiologies. The underlying causes can be broadly divided into reactive, clonal, and idiopathic. Classically, many cases of eosinophilia were grouped together into the umbrella category of hypereosinophilic syndrome, a clinical diagnosis of exclusion. In recent years, an improved mechanistic understanding of many eosinophilias has revolutionized the way these disorders are understood, diagnosed, and treated. As a result, specific diagnoses can now be assigned in many cases that were previously defined as hypereosinophilic syndrome. Most notably, chromosomal rearrangements, such as *FIP1L1-PDGFRA* fusions caused by internal deletions in chromosome 4, are now known to be associated with many chronic eosinophilic leukemias. When present, these specific molecular abnormalities predict response to directed therapies. Although an improved molecular understanding is revolutionizing the treatment of patients with rare causes of eosinophilia, it has also complicated the approach to evaluating and treating eosinophilia. Here, we review causes of eosinophilia and present a framework by which the practicing pathologist may approach this diagnostic dilemma. Finally, we consider recent cases as clinical examples of eosinophilia from a single institution, demonstrating the diversity of etiologies that must be considered.**

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Eosinophilia in the peripheral blood and in bone marrow biopsies is encountered frequently by practicing hematologists and hematopathologists. The clinical presentation and underlying etiologies are quite varied. In some cases, eosinophilia may be an incidental finding and prove benign and transient. However, in other cases, chronic eosinophilias may cause damage to a variety of organ systems.[1,2]

In broad terms, eosinophilias can be divided into reactive and clonal processes. In reactive eosinophilias, there is a polyclonal increase in the maturation and proliferation of eosinophils. Such cases may be triggered by allergy, infection, various medical conditions, or neoplasms. However, by definition, eosinophils cannot be part of a malignant clone in reactive eosinophilias. Conversely, clonal eosinophilias represent neoplasms in which eosinophils or their precursors are part of the malignant clone. Correct characterization of eosinophilia is critical because treatment is dependent on the underlying etiology.

Classically, hypereosinophilic syndrome (HES) represented a diagnosis of exclusion for patients who met certain clinical criteria. Specifically, HES required persistent eosinophilia, defined as an absolute eosinophil count (AEC) of at least 1500/μL (1.5×10^9/L) for 6 months or longer. These patients must have no identifiable parasitic, allergic, or other known cause of eosinophilia. The diagnosis also requires signs of organ involvement, most prominently the heart, which may develop valvular dysfunction leading to congestive heart failure.[2]

During the past several years, improved molecular understanding has allowed more specific classification of many cases that would once have been labeled within the broader umbrella of HES. In light of this increasingly complicated diagnostic picture, we review the diagnosis and treatment of eosinophilia and offer a framework by which the practicing pathologist may approach this diagnostic dilemma.

CLASSIFICATION AND DIAGNOSIS OF EOSINOPHILIAS

Reactive Eosinophilias

Most eosinophilias are reactive, polyclonal processes. In all these reactive processes, the increase in AEC appears to be mediated by cytokines, principally interleukin (IL) 5, which promotes proliferation of eosinophils and their precursors.[3] However, the underlying pathologic processes promoting increased cytokine production are varied, rang-

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From the Departments of Pathology and Laboratory Medicine, Division of Hematopathology (Drs Montgomery, Dunphy, Laramore, and Fedoriw); and Medicine, Division of Hematology and Oncology (Drs Mooberry, Foster, and Park), University of North Carolina School of Medicine, Chapel Hill.

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Reprints: Yuri D. Fedoriw, MD, Department of Pathology and Laboratory Medicine, Division of Hematopathology, University of North Carolina School of Medicine, CB7525, Chapel Hill, NC 27599-7525 (e-mail: gfedoriw@unch.unc.edu).

ing from allergic responses to clonal expansion of IL-5 expressing cells. Reactive eosinophilias may also involve overproduction of additional cytokines, such as IL-3 and IL-4, which can lead to concomitant elevation of immunoglobulin (Ig) E in reactive eosinophilias.[4]

Eosinophilia Due to Allergic Reactions.—Among the reactive eosinophilias in the developed world, allergic reactions are most common, comprising approximately 80% of cases.[5] The mechanism underlying allergic eosinophilias, as with many reactive eosinophilias, involves an imbalance between helper T-cell subtypes, with increased production of IL-5 by T-helper 2 cells. Given its prevalence, clinicians and pathologists should rule out allergic etiologies, such as drug reactions, before proceeding to costly molecular tests for rare, molecularly defined eosinophilias (see below). Eosinophilia is an isolated hematologic finding in allergic reactions, although other cell counts may be abnormal in rare cases.[3] Although the clinical history will typically be informative, symptoms secondary to eosinophilia can themselves resemble allergic reactions, making the diagnosis more complicated. As such, confirmation with allergen skin testing or radioallergosorbent testing may prove helpful.

Eosinophilia Due to Parasitic Infections.—Parasitic infections represent the second most-common cause of eosinophilia in developed nations, comprising 8% of eosinophilias in one large European cohort.[5] Generally, the causative organism is a helminth, such as *Strongyloides* stercoralis. Less often, the culprit may be a single-celled protozoan. A thorough travel history can increase the clinical suspicion of these infections because many parasites are endemic in tropical and subtropical climates.[6] However, *Strongyloides stercoralis* may also be found in temperate climates, including in the southeastern United States.[6,7]

The diagnosis of parasitic eosinophilia ultimately requires identification of an infectious trigger, either directly by identifying ova or parasites or indirectly by appropriate serologies, which may vary dependent on travel history. At a minimum, the evaluation should consider strongyloidiasis, schistosomiasis, and filariasis.[8] In children, toxocariasis should also be considered. *Strongyloides stercoralis* can cause eosinophilia years after the initial infection because the organism is capable of autoinfection inside its host.[6] IgG serologies are appropriate diagnostic tests when stool studies are not revealing. Finally, when parasites are implicated, the level of eosinophilia is determined by the extent of tissue invasion, and only tissue parasites are likely to cause clinically important elevations in AEC.[9]

Eosinophilia Secondary to Various Medical Conditions.—Several medical conditions are also associated with reactive blood eosinophilia and should be ruled out before invasive diagnostic tests, such as bone marrow biopsies, are performed (Table 1). Foremost among these is adrenal insufficiency. For more than half a century, it has been recognized that some patients with Addison disease have blood eosinophilia.[10,11] This association exists because glucocorticoids inhibit eosinophil proliferation and survival,[12–14] an effect that is exploited clinically when steroids are used as treatment of reactive eosinophilias (see "Treatment of Eosinophilias" below). In adrenal insufficiency, the converse occurs; low glucocorticoid levels allow increased eosinophil proliferation and survival. This scenario is especially important in critically ill patients, in whom eosinophilia due to adrenal insufficiency is common.[15]

Table 1. Nonmalignant Medical Conditions Associated With Reactive Eosinophilia

Allergic reactions
Drug reactions
Asthma
Parasitic infections
Strongyloidiasis
Schistosomiasis
Filariasis
Toxocariasis
Metabolic abnormalities
Adrenal insufficiency
Humoral immunodeficiency
Hyperimmunoglobulin E syndrome (Job syndrome)
Wiskott-Aldrich syndrome
Hyperimmunoglobulin M syndrome
Immunoglobulin A deficiency
Pulmonary eosinophilias
Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)
Allergic bronchopulmonary aspergillosis
Chronic and acute idiopathic eosinophilic pneumonias
Autoimmune blistering skin diseases
Dermatitis herpetiformis
Bullous pemphigoid

Given the inverse relationship between glucocorticoid levels and eosinophil count, the standard evaluation of eosinophilia should include attention to clinical signs of adrenal insufficiency (orthostatic hypotension, skin discoloration); routine chemistries, which may be abnormal in Addison disease; and, in some cases, morning cortisol levels.

Eosinophilia is also observed in certain immunodeficiency syndromes, including hyperimmunoglobulin E syndrome, formerly known as Job syndrome. Both autosomal-dominant and autosomal-recessive forms of hyperimmunoglobulin E syndrome exist. Whereas autosomal-dominant hyperimmunoglobulin E syndrome is caused by mutations in *STAT3*, *DOCK8* and *TYK2* mutations are implicated in the comparatively rare autosomal-recessive forms of the disease.[16–18] Clinically, hyperimmunoglobulin E syndrome is defined by staphylococcal skin abscesses, recurrent pneumonias, and serum IgE levels greater than 10 times the upper reference limit.[18] Additional features of the autosomal-dominant form include retention of primary teeth, skeletal abnormalities, and a characteristic facial appearance.[19] Ninety-three percent of patients in one series had AECs more than 2 SD greater than the mean, indicating that eosinophilia is a consistent feature.[20] However, the elevation is typically only mild to moderate, with a mean peak AEC of 1162/μL in one series.[19] Eosinophilia may also be present in other immunodeficiencies associated with abnormal immunoglobulin levels, such as Wiskott-Aldrich syndrome, hyperimmunoglobulin M syndrome, and IgA deficiency.[21] As a result, immunoglobulin levels are recommended as part of the standard evaluation of unexplained eosinophilia.

The pulmonary eosinophilias are a diverse class of conditions that may also lead to elevated AEC. A full discussion of these disorders is beyond the scope of the present article, and the reader is referred to an excellent review on the subject.[22] In each of the pulmonary eosinophilias, patients present with pulmonary lesions that may be accompanied by blood eosinophilia. Of these, eosinophilic granulomatosis with polyangiitis, formerly known as Churg-Strauss syndrome, is associated with severe eosinophilia.[23] Clinical criteria of eosinophilic gran-

ulomatosis with polyangiitis include asthma, peripheral eosinophilia (>10% of nucleated cells), paranasal sinusitis, mononeuropathy multiplex, and pulmonary infiltrates.[24] Histologically, small-to-medium vessel vasculitis and granulomata are characteristic features that distinguish eosinophilic granulomatosis with polyangiitis from other eosinophilias.[25] Serologic evidence of antineutrophil cytoplasmic antibodies may also be informative, although it is not completely sensitive.[22]

Of the remaining pulmonary eosinophilias, allergic bronchopulmonary aspergillosis also merits special mention because it is associated with a very specific clinical picture. Patients typically have bronchiectasis associated with a history of either asthma or cystic fibrosis. Characteristic laboratory findings include increased serum IgE and *Aspergillus*-specific immunoglobulins.[22]

Finally, several dermatologic conditions, most notably bullous pemphigoid and dermatitis herpetiformis, can be associated with blood eosinophilia. In 2 separate series,[26,27] the incidence of peripheral blood eosinophilia in bullous pemphigoid was 50% and 50.9%, respectively. In most cases, the elevation is mild to moderate, with a median AEC of 1300/μL in patients with eosinophilia.[27] Both diseases have characteristic patterns of immunoglobulin deposition. Hemidesmosome-specific IgG is present in a linear pattern on epithelial basement membranes in bullous pemphigoid, and granular IgA deposition is observed in the papillary dermis of patients with dermatitis herpetiformis.[28] Histologically, both diseases are associated with characteristic patterns of dermal inflammation and subepidermal blistering. Given that some cases of blood eosinophilia will be explained by these conditions, referral to a dermatologist and skin biopsy are appropriate steps in patients with skin lesions associated with unexplained eosinophilia.

Eosinophilia Associated With Solid Organ Malignancies.—Paraneoplastic eosinophilia is frequently observed in association with solid organ malignancies, with reported incidences ranging from 0.5% to 7%.[29–31] The phenomenon is not specific to any particular tumor type, and a broad spectrum of primary tumors have been implicated.[29–33] Instead, paraneoplastic eosinophilia appears to be closely related to tumor stage. In the mid-1940s, Isaacson and Rapoport[29] first noted that blood eosinophilia is a poor prognostic sign and, in almost all cases, is associated with advanced metastatic disease. Various mechanisms have been proposed to explain this association, including a response to tumor necrosis, an effect of bone marrow metastasis, and local stimulation by the tumor itself.[33] Granulocyte macrophage colony-stimulating factor, IL-3, and IL-5 have all been implicated, and some tumors are capable of producing these growth factors directly.[33,34] Consistent with these observations, eosinophilia may disappear after surgical excision and reappear with recurrence.[29] Because paraneoplastic eosinophilia is generally limited to advanced disease, high-resolution imaging to identify occult tumors is unlikely to provide high-yield diagnostic studies in most cases of unexplained eosinophilia.

Lymphocytic Variant HES.—As discussed above, classically, HES represented the poorly understood, idiopathic eosinophilias, which were often associated with a poor prognosis. However, in the past decade, the molecular mechanisms underlying 2 subtypes of HES have been elucidated. These well-characterized subtypes are lymphocytic variant HES, considered here, and myeloproliferative HES, considered below in the discussion of "Clonal Eosinophilias." Given the clinical definition of HES as an idiopathic eosinophilia, it may become appropriate to reclassify lymphocytic variant HES and myeloproliferative HES. However, for historic purposes, they are considered with other hypereosinophilic syndromes here.

Lymphocytic variant HES is caused by an expansion of abnormal or clonal T-helper–2 cell populations. Frequently, this expanded population may have an aberrant $CD3^-$, $CD4^+$ immunophenotype, although in other cases $CD3^+$, $CD4^-$, $CD8^-$ or $CD3^+$, $CD4^+$, $CD8^-$ T cells have been implicated.[4,35] Critically, eosinophils are not part of the malignant clone, but rather, their numbers increase reactively in response to the neoplasm.

Lymphocytic variant HES is not specifically recognized in the World Health Organization (WHO) classification, but recognition and reporting of this disorder is important because it may influence treatment. Patients with lymphocytic HES often have elevated serum thymus and activation-related chemokine and IgE levels, although these findings are neither sensitive nor specific.[36] Diagnosis is not standardized but requires demonstration that the observed eosinophilia is caused by an expanded population of T cells. This can be accomplished by demonstrating increased IL-5 expression from cultured T cells, abnormal immunophenotypes by flow cytometry, or identification of clonal T-cell populations by T-cell receptor rearrangement studies.[4]

Eosinophilia in Hodgkin Lymphoma.—Reactive eosinophilia is frequently observed in patients with lymphoma, often because of increased production of growth factors by the malignant cell population. In Hodgkin lymphoma, the reported incidence of blood eosinophilia is 15%.[37] Bone marrow and tissue eosinophilia are also common, although surprisingly, there is no strong correlation with peripheral eosinophil counts.[38,39] The incidence of tissue eosinophilia varies between types of Hodgkin lymphoma and is most common in mixed cellularity and nodular sclerosing forms of the disease.[39] As with many reactive eosinophilias, the mechanism appears dependent on increased IL-5, and possibly IgE, levels, both which may be produced directly by Reed-Sternberg cells.[40,41]

Eosinophilia in B-Cell and T-Cell Neoplasms.—Eosinophilia may also be associated with a variety of B-cell and T-cell neoplasms.[42–50] B-cell lymphoblastic leukemia (BLL) with eosinophilia is one such example. It is often associated with a characteristic cytogenetic abnormality t(5;14), which juxtaposes the *IL3* gene on chromosome 5 to the immunoglobulin heavy chain locus (IgH) on chromosome 14.[43–45] These cases are recognized in the 2008 WHO classification as *B lymphoblastic leukemia with t(5;14); IL3-IgH*."[51] This rearrangement implies a "reactive" eosinophilia, in which increased IL-3 expression by malignant, lymphoblastic clones provides a paracrine signal, driving polyclonal expansion of the eosinophils.[43–45]

Case reports have documented other chromosomal aberrations in BLL with eosinophilia.[47–50] In some cases, the same cytogenetic changes are found in cases of BLL without eosinophilia, making it unclear whether the association is diagnostically or clinically meaningful. The mechanism underlying eosinophilia is less clear with these alternative cytogenetic abnormalities, and some investigators suggest the eosinophils could actually be part of the malignant clone; in which case, these disorders would be

more appropriately classified as *clonal eosinophilias*. Definitive consideration of this question awaits cytogenetic and molecular analysis of eosinophils in a variety of B-cell leukemias/lymphomas.

By comparison, eosinophilia in patients with adult T-cell leukemia/lymphoma is more clearly reactive. The mechanism in these cases is conceptually similar to that of lymphocytic variant HES.[52] However, in cases of adult T-cell leukemia/lymphoma, the cells expressing IL-5 represent a truly clonal, neoplastic population.

Large studies evaluating the incidence of blood eosinophilia in association with non-Hodgkin lymphoma have not, to our knowledge, been conducted. Smaller studies have estimated the incidence as anywhere from 2% to 20%, depending on tumor type, with eosinophilia occurring more frequently in T-cell lymphomas than it does in B-cell lymphomas.[42,53] Bone marrow eosinophilia is also observed in association with non-Hodgkin lymphoma and is likely more common than peripheral eosinophilia is.[53]

Clonal Eosinophilias

Eosinophilias Associated With Myeloid Leukemias.—Many cases of clonal eosinophilia represent a variant of a well-characterized myeloid neoplasm. In these cases, eosinophils may represent one of several expanded populations derived from the malignant clone. The classic example of this group of eosinophilias is recognized in the WHO classification as *acute myeloid leukemia (AML) with abnormal eosinophils and inv(16) or t(16;16)*.[51] In the WHO framework, the characteristic cytogenetic changes are sufficient for the diagnosis. Both inv(16) and t(16;16) result in fusion of *CBFB* and *MYH11*,[54] either by inversion within a single chromosome 16 or by translocation between homologs. Both rearrangements can be detected by karyotype, fluorescence in situ hybridization (FISH), or reverse transcription-polymerase chain reaction spanning the breakpoint region. In addition to structural changes involving *CBFB*, "second-hit" mutations, promoting cell division or cell survival, appear to be necessary for leukemogenesis.[54]

Although no longer required for diagnosis, several morphologic features are characteristic of AML with abnormal eosinophils and inv(16) or t(16;16). As the WHO nomenclature implies, the marrow typically demonstrates increased numbers of abnormal eosinophils with characteristic, large, and basophilic granules (Figure 1, A and B).[51] This finding may suggest the diagnosis before cytogenetic results are available.

Similar to AML with inv(16) or t(16;16), AML with t(8;21) is associated with eosinophilia and falls within the broader WHO category of *AML with recurrent genetic abnormalities*. The t(8;21) is among the most-common translocations associated with AML, occurring in 7% to 16% of cases, depending on the series.[55,56] The rearrangement produces a fusion transcript between *RUNX1* (also known as *AML1*) and *RUNX1T1* (also known as *ETO*). *RUNX1* is a core binding factor subunit, and the *RUNX1-RUNX1T1* fusion disrupts the core binding factor function, leading to transcriptional repression of *RUNX1* target genes.[57] Eosinophil precursors are increased in approximately one-third of patients, and blood eosinophilia may also be observed.[58,59] In these cases, t(8;21) is present in eosinophils, indicating that these cells are part of the malignant clone.[58,60] Another characteristic of this disease is that blasts in AML with t(8;21) often have an aberrant $CD13^+$, $CD34^+$, $CD19^+$, $PAX5^+$, CD33 weak immunophenotype, although this finding is not required in the WHO framework.[42]

In rare cases, clonal eosinophilia can also be associated with chronic myelogenous leukemia, chronic myelomonocytic leukemia, or myelodysplastic syndromes.[61] Therefore, these diagnoses should be considered and excluded in the bone marrow evaluation of eosinophilia. Particularly relevant are myeloid neoplasms associated with t(5;12) translocations. These neoplasms respond to tyrosine kinase inhibitors and are addressed below in the section "Myeloid Neoplasms Associated With Eosinophilia and Abnormalities of *PDGFRB*."

Myeloid Neoplasms Associated With Eosinophilia and Abnormalities of *PDGFRA*.—Hypereosinophilic syndrome has historically been a clinical diagnosis applied to patients with organ damage from long-standing eosinophilia of unclear etiology.[2] Myeloproliferative HES was not appreciated as a distinct clinical entity until the early 2000s, when several groups independently discovered that some patients who meet criteria for HES respond robustly to the receptor-tyrosine kinase inhibitor imatinib mesylate (Gleevec, Novartis, Basel, Switzerland).[62–64] This observation later led to the identification of an 800-kilobase internal deletion on band 4q12 and a resultant *FIP1L1-PDGFRA* fusion transcript, which appears to be critical in the development of myeloproliferative hypereosinophilias.[65] This disorder is variably known as *chronic eosinophilic leukemia* or *myeloproliferative HES*, among other names, but is recognized in the 2008 WHO classification as *myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1*.[51]

The identification of the *FIP1L1-PDGFRA* rearrangement has led to remarkable advances in our understanding and diagnosis of clonal eosinophilias. Breakpoints in *FIP1L1* are variable, whereas those in *PDGFRA* are more restricted, occurring exclusively in exon 12.[65,66] *FIP1L1* encodes for a highly conserved protein involved in messenger RNA processing. It is unclear what function, if any, portions of FIP1L1 protein may play in development of clonal eosinophilia. Conversely, the role of *PDGFRA* has been better delineated. *PDGFRA* encodes for the receptor tyrosine kinase, platelet-derived growth factor receptor α. The 4q12 deletion removes negative regulatory motifs encoded 5′ to the exon 12 breakpoint, leading to constitutive activation of this receptor.[67] Consistent with its role in the development of eosinophilic leukemia, the activated fusion protein is capable of promoting eosinophil-lineage commitment in hematopoietic progenitor cells in vitro.[68]

The identification of the *FIP1L1-PDGFRA* rearrangement has also provided an opportunity for targeted diagnosis of this disorder. The causative deletion encompasses a gene on band 4q12 known as *CHIC2*, and many laboratories use FISH probes to this gene to identify patients harboring the *FIP1L1-PDGFRA* rearrangement.[66] Alternatively, nested reverse transcription-polymerase chain reaction tests can detect fusion transcripts.[66] These cytogenetic and molecular tools are now essential in the evaluation of many cases of eosinophilia. Reflecting the primacy of these studies, many of the established clinical criteria for HES are no longer necessary for diagnosis in the WHO framework. Instead, the presence of the *FIP1L1-PDGFRA* rearrangement is sufficient for the diagnosis of chronic eosinophilic leukemia in patients with a myeloproliferative neoplasm.[51]

In addition to the chromosome 4 deletion, there are several characteristic clinical and pathologic features of

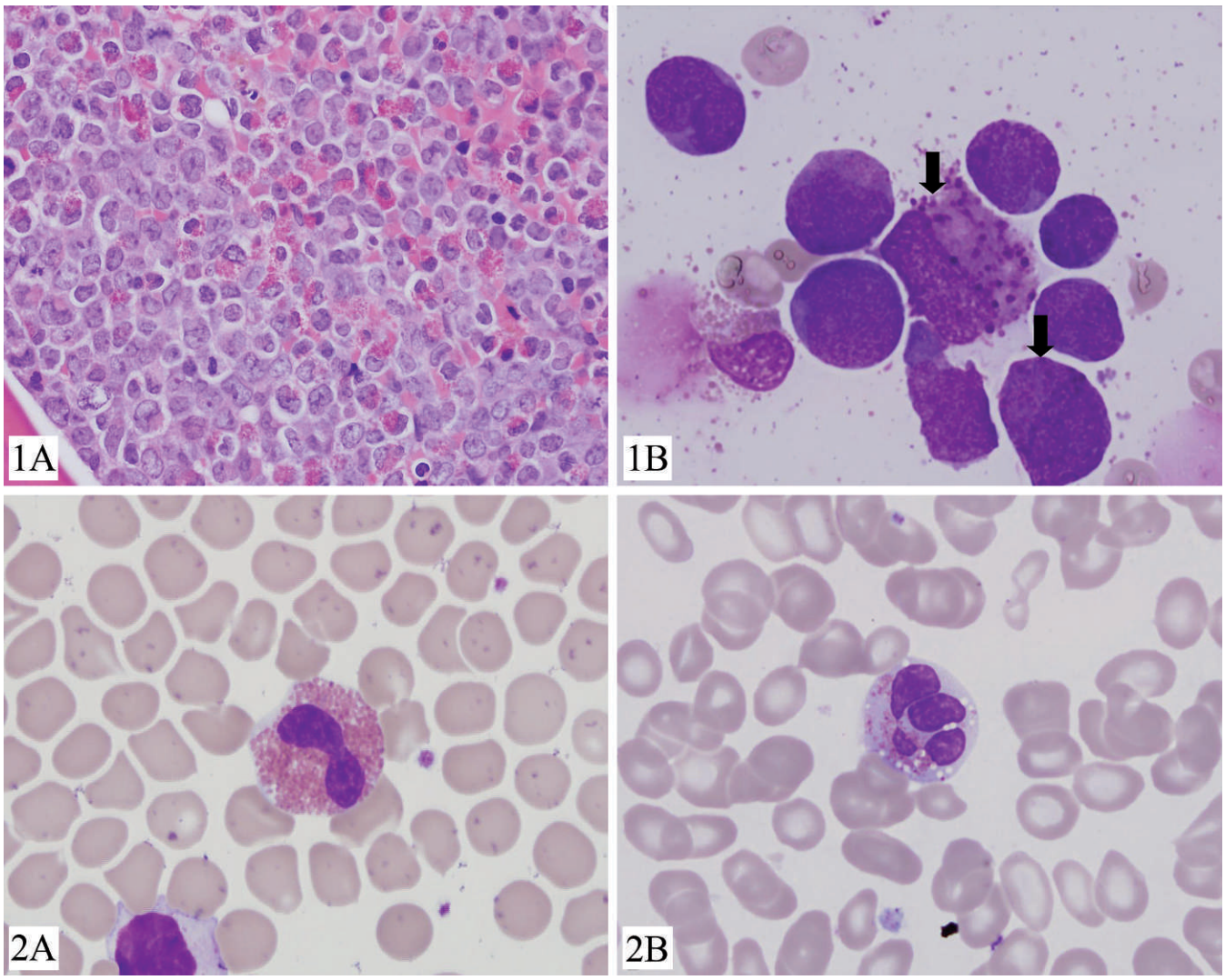

Figure 1. *Acute myeloid leukemia (AML) with abnormal eosinophils and inv(16) or t(16;16). A, Bone marrow biopsy section demonstrating near-complete replacement by myelomonocytic leukemia and an excess of eosinophils. B, Eosinophilic precursors (arrows) with scattered, large basophilic granules, characteristic of myelomonocytic leukemia with eosinophilia (AML-M4Eo)/AML with inv(16) or t(16;16) (hematoxylin-eosin, original magnification ×600 [A]; Wright-Giemsa, original magnification ×1000 [B]).*

Figure 2. *Myeloid neoplasm with eosinophilia and* FIP1L1-PDGFRA. *Comparison of peripheral blood eosinophil morphology from normal, healthy control (A), and patient with* CHIC2 *deletion identified by fluorescence in situ hybridization testing (B, case study 3). The latter shows characteristic findings including cytoplasmic vacuoles, nuclear hypersegmentation, and abnormally small eosinophilic granules (Wright-Giemsa, original magnifications ×1000).*

chronic eosinophilic leukemia with *PDGFRA* rearrangement. Clinically, there is a pronounced male predominance, and frequently, serum tryptase and B_{12} levels are increased.[36,69,70] Biopsy reveals a characteristically hypercellular marrow.[51,69] Unlike AML M4Eo, where granules are enlarged, the granules in chronic eosinophilic leukemia associated with *FIP1L1-PDGFRA* are commonly small and sparse (Figure 2, A and B). In addition, eosinophils may exhibit vacuoles, and nuclei may be either abnormally hyposegmented or hypersegmented (Figure 2, B).[51] Although these aberrant cellular features support the diagnosis, they are not entirely specific. Finally, in many cases, there is a pronounced mastocytosis. However, bone marrows with increased mast cells because of *FIP1L1-PDGFRA* rearrangements typically lack the *KIT* mutations found in other cases of systemic mastocytosis.[71] Moreover, dense mast-cell aggregates are absent in patients with *PDGFRA* rearrangements, distinguishing those cases.[71]

Myeloid Neoplasms Associated with Eosinophilia and Abnormalities of *PDGFRB* and *FGFR1*.—The 2008 WHO classification recognizes that clonal eosinophilia may also be caused by 5q33 translocations involving *PDGFRB* and 8p11 translocations involving *FGFR1*.[51] Like *PDGFRA*, these genes also encode receptor tyrosine kinases, and the mechanisms leading to eosinophilia are likely similar.

PDGFRB translocations involve rearrangements between chromosome 5 and a number of partner chromosomes.[72] Particularly relevant are cases of t(5;12)(q33;p13), in which *PDGFRB* is activated by fusion with *ETV6*.[73] Patients with this rearrangement typically have hematologic features of chronic myelomonocytic leukemia with severe eosinophilia, although the latter is not absolutely required.[72]

The band 8p11 myeloproliferative syndromes are associated with *FGFR1* translocations and also cause peripheral eosinophilia, often in the context of lymphadenopathy and lymphoblastic leukemia/lymphoma.[74] Although mechanistically similar to eosinophilic leukemias with *PDGFRA* and *PDGFRB* translocations (and grouped with these disorders in the WHO classification), neoplasms associated with *FGFR1* translocations have several distinct clinical features. Most notably, they often progress to aggressive acute myeloid leukemias or acute mixed-lineage leukemias, which are not responsive to imatinib.[74]

Both *PDGFRB* and *FGFR1* translocations may be identified by routine cytogenetic tests and, in some laboratories, by FISH for *PDGFRB* rearrangements and polymerase chain reaction for *FGFR1* translocations. Similar to eosinophilias caused by *FIP1L1-PDGFRA* fusions, neoplasms associated with *PDGFRB* rearrangement are typically sensitive to imatinib.[75] The *FGFR1* rearrangements are often associated with a worse clinical course, and early stem cell transplantation may be indicated.[66]

Chronic Eosinophilic Leukemia, Not Otherwise Specified.—Finally, a heterogenous group of clonal eosinophilias are classified by the WHO as *chronic eosinophilic leukemia, not otherwise specified*.[51] This diagnosis is reserved for patients who have evidence of clonal disease, as demonstrated by the following criteria: (1) AEC greater than 1.5×10^9, (2) no *PDGFRA*, *PDGFRB*, or *FGFR1* mutations, (3) no t(9;22) or other myeloproliferative neoplasms, (4) a blast count less than 20%, and (5) (a) more than 5% blasts in the bone, (b) more than 2% blasts in the peripheral blood, (c) clonal cytogenetic abnormalities, or (d) clonal molecular abnormalities.[51]

Familial Eosinophilia

Familial hypereosinophilia is a rare, poorly understood form of eosinophilia that is variably associated with end-organ damage.[76] Four cases of multigenerational kindred groups have been reported in the literature.[76–79] Clinical criteria include elevated AEC (with a threshold varying from 1500/μL to 4000/μL depending on the kindred), familial incidence affecting more than one generation, and exclusion of other causal factors.[76,77]

Although the causative mutation has not been cloned, familial eosinophilia is inherited in an autosomal-dominant fashion and, in at least one kindred group, maps to the long arm of chromosome 5, in a region where genes encoding IL-3, IL-5, and granulocyte macrophage colony-stimulating factor are all known to reside.[80] Levels of these factors do not appear to be elevated in the disease, however, and no mutations have been identified in the genes themselves.[76,80] Affected individuals have other mild hematologic abnormalities, including low red blood cell counts and leukocytosis.[76] End-organ damage, typically manifesting as cardiac or neurologic involvement, is incompletely penetrant, affecting 6 of 19 patients (32%) in the largest kindred study published to date.[76]

Idiopathic HES

In some cases, the etiology of eosinophilia remains elusive. When criteria for HES are met (see above), patients with long-standing eosinophilia of unclear cause can be classified clinically as having idiopathic HES. In fact, it is arguably most appropriate to reserve the diagnosis of HES for this subset of cases that are truly idiopathic, removing lymphocytic and myeloproliferative HESs from the classic framework. In any case, before making the diagnosis of idiopathic HES, care should be taken to rule out all alternative diagnoses, including those considered above.

TREATMENT OF EOSINOPHILIAS

Reactive Eosinophilias

Management of allergic eosinophilias involves standard allergen-avoidance measures. In cases of eosinophilia from a drug allergy, the suspected agent should be withheld. Common offenders include allopurinol, carbamazepine, and certain antibiotics.[81] However, all medications should be considered, and when there is no clear source, it may become necessary to withhold all nonessential medications.

Treatment of parasitic eosinophilia varies dependent on the implicated organism. Most important, the clinician must first recognize that the eosinophilia is, in fact, due to a parasitic infection, because steroids, which are indicated in the treatment of other reactive eosinophilias, may facilitate dissemination of *Strongyloides* species.[7] When strongyloidiasis is implicated, ivermectin is considered the first-line therapy because it is better tolerated than benzimidazoles, such as albendazole.[82,83]

Treatment of cases of eosinophilia that are secondary to a general medical condition is directed at treating the underlying disease process. In most cases, steroids are an important component of therapy.

Lymphocytic variant HES represents a special case among the reactive eosinophilias because steroid-sparing, molecularly targeted therapies are available. Mepolizumab is a monoclonal antibody against IL-5, and in some cases, it may prove effective by disrupting cytokine signals that usually promote eosinophil maturation and proliferation.[36,61,71,84] Additional medications indicated in the treatment of lymphocytic variant HES include corticosteroids and another monoclonal antibody, alemtuzumab (anti-CD52).[61]

Finally, when reactive eosinophilias are due to solid organ malignancies, Hodgkin lymphoma, or non-Hodgkin lymphomas, treatment involves chemotherapy directed at the underlying malignancy. Corticosteroids may also be indicated to directly address complications caused by hypereosinophilia.

Clonal Eosinophilias

Treatment of clonal eosinophilias involves chemotherapy selected for the underlying malignancy. Inversion (16) and t(8;21) are favorable cytogenetic abnormalities that portend a good clinical response to cytarabine and anthracycline-based chemotherapy.[85] Even more impressive is the effectiveness of imatinib in treatment of myeloid neoplasms with eosinophilia and abnormalities of *PDGFRA* and *PDGFRB* genes. Patients with the *FIP1L1-PDGFRA* rearrangement on chronic imatinib consistently achieve hematologic and cytogenetic response, and in certain series, patients have achieved major molecular responses, as well.[36,65,86] However, imatinib does not eliminate neoplastic progenitors because disease returns when therapy is interrupted.[87] Additionally, cases of imatinib resistance have been observed, with changes affecting residues homologous to those mutated in *BCR-ABL* in imatinib-resistant chronic myelogenous leukemia.[65,88,89]

Patients with eosinophilia and 8p11 translocations have poor prognosis and respond to neither tyrosine kinase inhibitors nor chemotherapy protocols developed for acute

Table 2. Review of Eosinophilia Cases at the University of North Carolina Hospitals, 2005–2010

Case No.[a]	Age, y/Sex	Peak AEC, $\times 10^9$/L	Bone Marrow Eosinophils, %	Test Results			Diagnosis
				CHIC2	Routine Karyotype	Other	
1	69/M	12.9	38	Normal	45,X,−Y[4] /46,XY[20]	O&P$^-$, *Strongyloides* IgG$^+$	Parasitic eosinophilia
2	14/M	38.9	35	Normal	Complex	9p21$^{-/-}$	BLL with eosinophilia
3	63/M	8.0	21	*FIP1L1-PDGFRA*	Normal	NA	Chronic eosinophilic leukemia
4	69/M	1.7	6	Normal	Normal	High IgE	Idiopathic
5	53/M	1.0	3	Normal	Normal	History of eosinophilic dermatitis	Allergic
6	75/F	2.2	11	Normal	Normal	High IgE	Allergic
7	59/F	3.5	29	NA	Normal	NA	Allergic
8	48/M	1.7	19	Normal	Normal	NA	Allergic
9	17/F	12.1	4	Normal	Normal	NA	Allergic
10	36/M	1.8	11	Normal	Normal	NA	Allergic
11	33/M	2.8	19	Normal	Normal	NA	Idiopathic
12	65/M	6.8	14	Normal	Normal	NA	Idiopathic
13	58/F	5.3	8	Normal	Normal	High IgE	Idiopathic
14	44/F	NA	2 (on steroids)	Normal	Normal	NA	Idiopathic
15	72/M	3.4	13	NA	NA	High tryptase, High IgE	Idiopathic
16	69/M	1.7	6	Normal	Normal	High IgE	Idiopathic
17	58/M	4.5	21	Normal	Normal		Idiopathic vs. allergic
18	31/M	7.0	34	Normal	Normal	O&P$^-$, *Strongyloides* IgG$^-$	Parasitic, unclear etiology. Responded to albendazole
19	40/M	28.1	49	FIP1L1-*PDGFRA*	Normal	NA	Chronic eosinophilic leukemia
20	50	2.1	26	NA	Inv(16)	NA	AML M4Eo
21	66	2.6	0	Normal	Normal	Peripheral monocyte count 11.5 $\times 10^9$/L	CMML
22	27	4.5	15	NA	Normal	NA	Familial eosinophilia
23	23	8.8	49	Normal	Normal	NA	ITP

Abbreviations: AEC, absolute eosinophil count; AML M4Eo, acute myeloid leukemia with abnormal eosinophils and inv(16) or t(16;16); BLL, B-cell lymphoblastic leukemia; CHIC2, cysteine-rich hydrophobic domain 2 (probe for *FIP1L1-PDGFRA* fusion); *FIP1L1-PDGFRA*, fusion gene of FIP1-like 1 and platelet-derived growth factor receptor, α polypeptide; CMML, chronic myelomonocytic leukemia; IgE, Immunoglobulin E; IgG, immunoglobulin G; ITP, idiopathic thrombocytopenic purpura; O&P, ova and parasite.
[a] Cases 1–4 correspond to the cases 1–4 in the text, otherwise presented in chronological order.

leukemias. Given such poor outcomes, early stem cell transplant is indicated.[75]

Idiopathic Eosinophilias

When the etiology of eosinophilia is not apparent, corticosteroids are appropriate therapy.[36] A smaller percentage of these patients may respond to empiric treatment with targeted therapies like imatinib, mepolizumab, and alemtuzumab.[61,90]

INSTITUTIONAL SERIES AND CASES

To evaluate the spectrum of cases of eosinophilia at our own institution, we reviewed clinical and pathologic information on all patients with bone marrow biopsies evaluated primarily for eosinophilia between January 2005 and August 2009 at the University of North Carolina (Chapel Hill) Hospitals. We restricted our search to patients receiving diagnostic bone marrow biopsies, excluding bone marrow biopsies performed for evaluation after induction or consolidation chemotherapy; 23 cases were reviewed, and results are shown in Table 2. A FISH test for CHIC2 was performed in 19 cases (83%), and results were abnormal in 2 of 19 patients (11%). This incidence is consistent with other recent studies in which the prevalence of *FIP1L1-PDGFRA* has been 10% to 14% in patients meeting criteria for HES.[36,91] However, our series is distinct in that patients were not required to meet all criteria for HES and because the search was restricted to cases in which bone marrow biopsies were performed; therefore, patients with clearly reactive etiologies or peripheral eosinophilia that did not merit bone marrow biopsies were excluded.

Seven patients (30%) in our series were ultimately classified as having idiopathic hypereosinophilia, and in an eighth patient, idiopathic hypereosinophilia was favored, but allergy could not be entirely excluded. Before the advent of CHIC2 testing, the 2 patients (9%) with *FIP1L1-PDGFRA* rearrangements would likely have been classified as having idiopathic hypereosinophilia as well. Hence, in this small series, modern diagnostic modalities reclassified 2 of 10 patients (20%), providing a more-specific diagnosis than would have been available historically. Larger studies will be necessary before accurate estimates can be made regarding what percentage of cases formerly classified as idiopathic HES can now be reclassified, as well as what percentage of cases of hypereosinophilia remain idiopathic.

Several cases within the series are particularly notable because they demonstrate the wide spectrum of etiologies that the hematopathologist must consider when evaluating a bone marrow biopsy performed on a patient with eosinophilia. Details of these informative cases are included below.

REPORT OF CASES

Case 1

Case 1 (Table 2) was a 69-year-old, Puerto Rican man with a history of B-cell lymphoblastic leukemia, who presented with skin rash, dyspnea, and peripheral eosinophilia (12 900/μL; reference range, 0–400/μL). Skin biopsy revealed a dense, perivascular dermal eosinophilic infiltrate. His serum IgE was also markedly elevated.

The onset of the patient's symptoms coincided with initiation of lisinopril, and initially, his eosinophilia was thought to be drug related. However, despite drug cessation, his AEC count continued to rise. A subsequent bone marrow biopsy demonstrated hypercellular marrow with less than 5% blasts and florid eosinophilia (38% of marrow cells by aspirate differential). Routine cytogenetic test results were normal, with only rare loss of the Y chromosome, not uncommon in a patient this age. Additionally, FISH studies failed to detect evidence of *PDGFRA-FIP1L1* fusion. Although the patient's stool was negative for ova and parasites, serologic studies demonstrated positive *Strongyloides* species IgG results, suggesting chronic infection by this helminth. Given the absence of other documented causes of eosinophilia, he was treated empirically with ivermectin; after which, his AEC gradually returned to within reference range.

Case 2

Case 2 (Table 2) was a previously healthy, 14-year-old, adolescent boy who presented to an outside hospital with acute onset of dyspnea, cough, low-grade fever, and myalgias. At the time of his presentation, he was noted to have a profound leukocytosis (62 100/μL) with marked eosinophilia (38 900/μL), as well as respiratory failure from pulmonary hemorrhage. He was referred to our institution for evaluation and treatment.

Given the patient's underlying hematologic abnormalities, a bone marrow biopsy was performed, which revealed hypercellular marrow (98%) with eosinophilia (35% of nucleated marrow cells by aspirate differential) and an increase in blasts (38%). Flow cytometry confirmed precursor B-lymphoblast immunophenotype results (CD19 bright, CD10 bright, CD20 heterogenous, CD34 dim/partial), and DNA studies demonstrated clonal IgH (immunoglobulin heavy chain) rearrangement. Conventional cytogenetics identified a complex karyotype, and targeted FISH studies revealed a homozygous deletion of p16/p15 on band 9p21. *FIP1L1-PDGFRA* FISH testing was also performed, and results were negative.

Based on these findings, the patient was diagnosed with precursor B-cell lymphoblastic leukemia, suggesting a clonal malignancy with a reactive eosinophilia. His elevated AEC rapidly normalized after the initiation of corticosteroids. Induction chemotherapy was initiated with vincristine, daunorubicin, PEG-asparaginase, prednisone, and intrathecal methotrexate and cytarabine. After a robust response to induction, he continues on maintenance chemotherapy, and his AEC has remained within reference range.

Case 3

Case 3 (Table 2) was a 63-year-old man with an unremarkable previous medical history, who was incidentally noted to have eosinophilia (4200/μL) during an unrelated emergency department visit. During the following 4 months, the patient's white blood cell and eosinophil counts trended upward, eventually reaching 40 100/μL and 5200/μL, respectively. Accompanying these findings was a mild microcytic anemia. Despite laboratory abnormalities, the patient remained largely asymptomatic, without any constitutional symptoms.

Because of his hematologic findings, the patient eventually presented to our institution, and a bone marrow biopsy revealed dramatic hypercellularity (100%) with marked eosinophilia (49% of nucleated bone marrow cells). Cytogenetic test results revealed a normal 46,XY karyotype. Additionally, FISH study results were negative for the t(9;22) translocation, and molecular studies failed to identify a *JAK2* mutation. However, interphase FISH study results did reveal that 93.5% of nuclei were positive for the *FIP1L1-PDGFRA* fusion, consistent with a diagnosis of chronic eosinophilic leukemia (WHO classification, *myeloid neoplasms with eosinophilia and abnormalities of* PDGFRA). The patient was started on imatinib, and 5 months after initiation of targeted therapy, he has no hematologic or cytogenetic evidence of disease.

Case 4

Case 4 (patient 7; Table 1) was a 69-year-old man with restrictive lung disease and chronic bronchitis, who presented with a 3-year history of increasing dyspnea and worsening allergy symptoms. During the previous 7 months, test results showed he had chronically elevated absolute eosinophil counts greater than 1500/μL. Additionally, his serum IgE was markedly elevated. Biopsy revealed a normocellular bone marrow (40%) with only a modest increase in eosinophils (6% of nucleated bone marrow cells). He had a normal 46,XY karyotype, *FIP1L1-PDGFRA* FISH failed to identify a chromosome 4 deletion, and molecular study results were negative for the *KIT* Asp816Val mutation, which has been implicated in systemic mastocytosis. After definable etiologies were excluded, the patient was treated empirically with prednisone, with improvement, but not normalization, of his AEC. No definitive cause of the patient's hypereosinophilia was identified, and he now carries a diagnosis of idiopathic HES.

APPROACH TO EOSINOPHILIA

With the advent of powerful molecular tools capable of diagnosing rare causes of eosinophilia, it is tempting for the practicing hematopathologist to take a "shot-gun" approach to elucidating the cause of eosinophilia. However, such a strategy is neither efficient nor cost effective. Instead, the first step should always be to rule out the most common causes of eosinophilia (Figure 3). Nonessential medications should be discontinued and parasitic illnesses ruled out. Although the need for stool studies is generally appreciated by clinical teams, the need for serologic studies should not be overlooked (see case 1). The initial workup should also seek to exclude eosinophilia due to a general medical condition, and at a minimum, this evaluation should include serum chemistries and serum immunoglobulin levels. Morning cortisol level, antineutrophil cytoplasmic antibodies titer, thymus and activation-related chemokine level, and referral to a dermatologist for evaluation of skin lesions may also be appropriate, depending on clinical suspicion. After common reactive causes have been excluded, it becomes appropriate to consider the comparatively rare, other reactive, clonal, and idiopathic eosinophilias (Figure 3). In such cases, bone marrow biopsy, flow cytometry, and routine karyotyping studies are clearly indicated to identify reactive or clonal eosinophilias associated with hematologic malignancies (see patient 2). When initial bone marrow evaluation is not definitive, tools to identify specific rearrangements, such as CHIC2 FISH, may be helpful in distinguishing molecularly defined eosinophilias, as in patient 3, from cases still defined as *idiopathic hypereosinophilias*, as with patient 4. Despite this utility, as demonstrated in previous series and by our institution's experience (Table 2), CHIC2 FISH is not a high-yield study when applied to all cases and could conceivably be reserved for those situations where other explanations are not present and where clinical suspicion is high for chronic eosinophilic leukemia (Figure 3). Finally, chronic eosinophilic leukemia not otherwise specified, the lymphocytic and idiopathic hypereosinophilic syndromes, and paraneoplastic

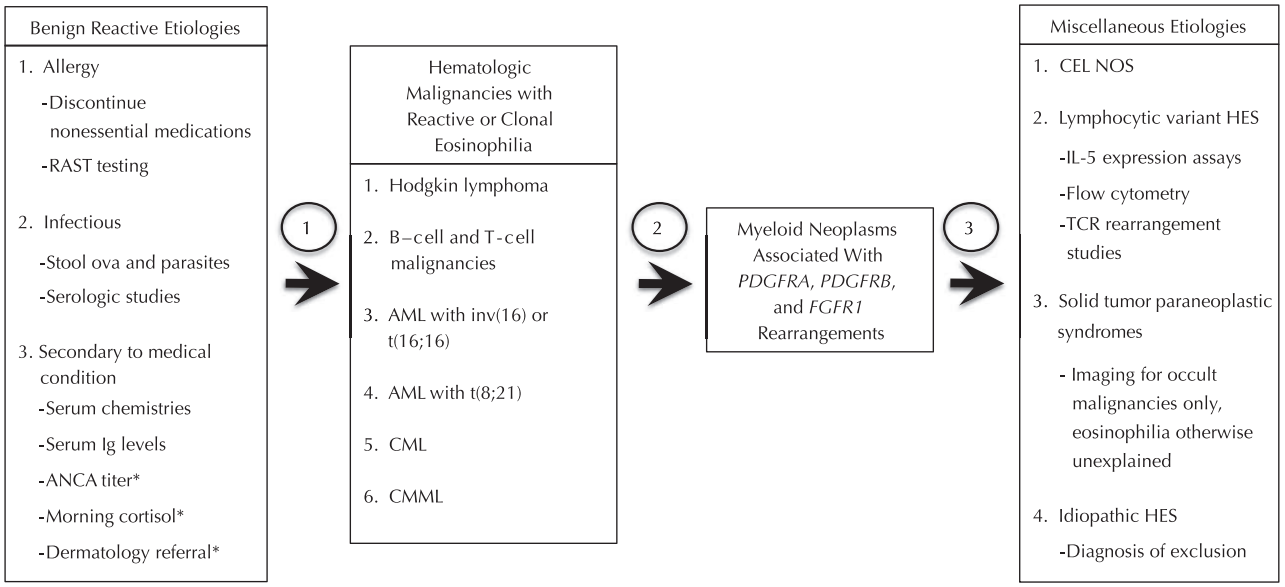

Figure 3. *Diagnostic approach to eosinophilia. A stepwise approach for evaluating cases of eosinophilia is provided. Benign, reactive etiologies should be ruled out first. Asterisks indicate diagnostic tests appropriate only when indicated by clinical suspicion. A, Once reactive causes have been excluded, the next diagnostic step is a standard hematologic-malignancy evaluation, consisting of bone marrow biopsy, flow cytometry, and karyotyping. B, If the diagnosis remains elusive, proceed to CHIC2 fluorescence in situ hybridization testing (FISH). If not identified by routine karyotyping, at this step, PDGFRB and FGFR1 translocations can also be evaluated by FISH and polymerase chain reaction. C, Chronic eosinophilic leukemia not otherwise specified (CEL NOS), lymphocytic variant hypereosinophilic syndrome (HES) paraneoplastic syndromes associated with occult tumors, and idiopathic HES should only be considered if the previous studies do not explain the observed eosinophilia.*
Abbreviations: AML, acute myeloid leukemia; ANCA, antineutrophil cytoplasmic antibody; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; HES, hypereosinophilic syndrome; Ig, immunoglobulin; IL-5, interleukin 5; RAST, radioallergosorbent test; TCR, T-cell receptor.

eosinophilia from occult solid organ tumors should only be considered when other etiologies have been excluded.

CONCLUSIONS

The finding of eosinophilia carries a broad differential diagnosis. Although reactive etiologies remain most common, the approach to eosinophilia is evolving. The increasing availability of molecular tools has transformed diagnosis and therapy, and as reflected in the revised WHO classification, these changes have dramatically influenced the clinical approach to eosinophilia.

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