Hypereosinophilic Syndrome and Clonal Eosinophilia: Point-of-Care Diagnostic Algorithm and Treatment Update

Ayalew Tefferi, MD; Jason Gotlib, MD; and Animesh Pardanani, MBBS, PhD

Acquired eosinophilia is operationally categorized into secondary, clonal, and idiopathic types. Causes of secondary eosinophilia include parasite infections, allergic or vasculitis conditions, drugs, and lymphoma. Clonal eosinophilia is distinguished from idiopathic eosinophilia by the presence of histologic, cytogenetic, or molecular evidence of an underlying myeloid malignancy. The World Health Organization classification system for hematologic malignancies recognizes 2 distinct subcategories of clonal eosinophilia: chronic eosinophilic leukemia, not otherwise specified and myeloid/lymphoid neoplasms with eosinophilia and mutations involving platelet-derived growth factor receptor α/β or fibroblast growth factor receptor 1. Clonal eosinophilia might also accompany other World Health Organization–defined myeloid malignancies, including chronic myelogenous leukemia, myelodysplastic syndromes, chronic myelomonocytic leukemia, and systemic mastocytosis. Hypereosinophilic syndrome, a subcategory of idiopathic eosinophilia, is defined by the presence of a peripheral blood eosinophil count of $1.5 \times 10^9/L$ or greater for at least 6 months (a shorter duration is acceptable in the presence of symptoms that require eosinophil-lowering therapy), exclusion of both secondary and clonal eosinophilia, evidence of organ involvement, and absence of phenotypically abnormal and/or clonal T lymphocytes. The presence of the latter defines lymphocytic variant hypereosinophilia, which is best classified under secondary eosinophilia. In the current review, we provide a simplified algorithm for distinguishing the various causes of clonal and idiopathic eosinophilia and discuss current therapy, including new drugs (imatinib mesylate, alemtuzumab, and mepolizumab).

CLASSIFICATION OF CLONAL AND IDIOPATHIC EOSINOPHILIA

Clonal eosinophilia represents neoplastic proliferation of eosinophils as part of an underlying stem cell–derived myeloid malignancy. As such, clonal eosinophilia can accompany any one of the myeloid malignancies defined by the World Health Organization (WHO) classification system for hematologic malignancies (Table). Included in this classification system are 2 distinct subcategories of clonal eosinophilia: chronic eosinophilic leukemia, not otherwise specified (CEL-NOS) and myeloid/lymphoid neoplasms with eosinophilia and mutations involving platelet-derived growth factor receptor (PDGFR) α/β or fibroblast growth factor receptor 1.

Idiopathic eosinophilia implies that both secondary and clonal eosinophilia have been ruled out as possible diag-

© 2010 Mayo Foundation for Medical Education and Research

From the Division of Hematology, Mayo Clinic, Rochester, MN (A.T., A.P.); and Division of Hematology, Stanford Cancer Center, Stanford, CA (J.G.).

This article is freely available on publication, because the authors have chosen the immediate access option.

Individual reprints of this article are not available. Address correspondence to Ayalew Tefferi, MD, Division of Hematology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (tefferi.ayalew@mayo.edu).

© 2010 Mayo Foundation for Medical Education and Research

For personal use. Mass reproduce only with permission from Mayo Clinic Proceedings.
noses; rare instances of congenital eosinophilia must be considered in pediatric cases. Hypereosinophilic syndrome (HES) is a subcategory of idiopathic eosinophilia, and the diagnosis requires the presence of a peripheral blood eosinophil count of $1.5 \times 10^9$/L or greater and eosinophil-mediated organ damage. Hypereosinophilic syndrome should be distinguished from the term hyper-eosinophilia, which simply indicates an absolute eosinophil count of $1.5 \times 10^9$/L or greater. For example, the more accurate term to describe eosinophilia associated with clonal or phenotypically abnormal lymphocytes is lymphocytic variant hypereosinophilia, not lymphocytic variant HES.

The distinction between clonal and idiopathic eosinophilia is arbitrary, and evidence suggests that, in some instances, HES actually represents an underlying myeloid neoplasm. For example, eosinophil monoclonality has been demonstrated in some cases of HES, which simply indicates an absolute eosinophil count of $1.5 \times 10^9$/L or greater. For example, the more accurate term to describe eosinophilia associated with clonal or phenotypically abnormal lymphocytes is lymphocytic variant hypereosinophilia, not lymphocytic variant HES.

When evaluating a patient with eosinophilia that is not thought to be secondary, 5 diagnostic possibilities should be considered: (1) myeloid or lymphoid neoplasms associated with eosinophilia and PDGFR or FGFR1 rearrangements, (2) clonal eosinophilia associated with an otherwise WHO-defined myeloid malignancy, (3) CEL-NOS, (4) lymphocytic variant hypereosinophilia, and (5) idiopathic eosinophilia including HES. The stepwise approach to specific diagnosis (Figure) requires careful assessment of the peripheral blood smear, bone marrow morphologic features, cytogenetic analysis, molecular studies including screening for FIP1L1-PDGFR and peripheral blood lymphocyte phenotyping and T-cell receptor gene rearrangement studies.

After examining the peripheral blood smear and blood test results for clues regarding an underlying myeloid malignancy (eg, circulating blasts, dysplastic cells, monocytosis, elevated serum tryptase level), which, if present, dictates immediate bone marrow examination for specific diagnosis, it is reasonable to start with peripheral blood mutation screening for FIP1L1-PDGFR using fluorescence in situ hybridization (FISH) or reverse transcription polymerase chain reaction (RT-PCR) (Figure). If the particular mutation is present, one could forego bone marrow examination, make a working diagnosis of FIP1L1-PDGFR-positive clonal eosinophilia, and initiate treatment with imatinib mesylate (see subsequent section on treatment). However, we prefer to include bone marrow examination in the diagnostic work-up to exclude the presence of prognostically relevant morphologic or cytogenetic markers of clonal evolution.

If peripheral blood screening for FIP1L1-PDGFR is negative, the next step is to perform bone marrow examination and cytogenetic studies to look for other evidence of clonal eosinophilia. With this approach, one must first pay attention to the presence or absence of 5q33, 4q12, or 8p11.2 translocations, which, if present, suggest PDGFRB, PDGFR, or FGFR1-rearranged clonal eosinophilia, respectively (Figure). This step is of immense therapeutic relevance because the presence of 5q33 or 4q12 translocations predicts favorable response to treatment with imatinib mesylate, whereas 8p11.2 translocations are associated with aggressive myeloid malignancies that are refractory to current drug therapy (see subsequent section on treatment). Furthermore, in patients with 5q33 or 8p11.2 translocations, FISH or RT-PCR should be used to confirm the respective involvement of PDGFRB or FGFR1.

Bone marrow morphologic examination also helps to exclude the possibility of an otherwise well-defined my-
Hypereosinophilic syndrome and clonal eosinophilia

For personal use. Mass reproduce only with permission from Mayo Clinic Proceedings.
Asymptomatic Patient

In the absence of symptoms, the best approach is to postpone treatment until the diagnostic work-up is completed and the specific diagnosis made. In clonal eosinophilia associated with imatinib mesylate–sensitive molecular markers (eg, FIP1L1-PDGFRα, PDGFRB rearrangement, BCR-ABL), early initiation of therapy is reasonable because (1) development of symptoms or evolution into aggressive disease is inevitable, and (2) targeted therapy results in complete clinical and molecular remission and can prevent complications, including leukemic transformation.24-26

In contrast, no evidence supports early drug therapy for asymptomatic patients with idiopathic eosinophilia, regardless of eosinophil count. We realize that simply observing a markedly elevated eosinophil count is unnerving. If the decision is made to follow up such patients without initiating treatment, it is important to monitor serum troponin levels and perform echocardiography periodically. Additionally, it is equally reasonable to initiate eosinophil-lowering therapy if the patient or the treating physician is uncomfortable with observation alone, keeping in mind the lack of evidence to support such an approach. Our personal preference, again not supported by evidence, is to avoid drug therapy in asymptomatic patients with idiopathic eosinophilia unless the absolute eosinophil count is considered too high (eg, >30 × 10⁹/L). Even then, an individualized approach is recommended, paying special attention to anticipated adverse drug effects.

Symptomatic Patient With Clonal Eosinophilia

Therapeutically relevant mutations in clonal eosinophilia include PDGFRα, PDGFRB, and FGFR1 rearrangements. In a Mayo Clinic study of prevalence and clinicopathologic correlation, FIP1L1-PDGFRα was detected by FISH in approximately 14% of patients with primary eosinophilia,27 whereas PDGFRB and FGFR1 translocations were extremely rare.28,29 Interestingly, with the exception of rare instances,30 all reported cases of FIP1L1-PDGFRα–associated clonal eosinophilia have been in male patients.30 PDGFRB (5q33 translocations), FGFR1 (8p11.2 translocations), and PDGFRα (4q12 translocations)29 fusion genes are often apparent by cytogenetic analysis of the bone marrow, whereas FIP1L1-PDGFRα is karyotypically occult and requires FISH or RT-PCR studies for detection.31

The first drug to consider in the presence of clonal eosinophilia is imatinib mesylate, but only in the presence of FIP1L1-PDGFRα or PDGFRα/PDGFRB translocations.29,32 Ample evidence supports the use of low-dose imatinib mesylate (100 mg/d) for inducing molecular and histologic remission in FIP1L1-PDGFRα–positive clonal eosinophilia and even lower doses (eg, 100 mg/wk) might be effective for remission maintenance.27,32-36 However, dose reduction might be associated with clinically occult molecular relapses,37 and dose discontinuation with overt relapse; therefore, we currently prefer to maintain the dosage at 100 mg/d in the absence of adverse effects.

Rare cases of mutant FIP1L1-PDGFRα that are resistant to imatinib mesylate (eg, T674I, D842V) have been reported.16,38 In vitro, the T674I, but not the D842V, mutant was shown to be sensitive to other kinase inhibitors, including nilotinib, sorafenib, and PKC412.28 Also, there are reported instances of interferon alfa–induced complete remissions in FIP1L1-PDGFRα–positive clonal eosinophilia.27,39 Therefore, in patients with imatinib mesylate–resistant FIP1L1-PDGFRα–positive clonal eosinophilia, it is reasonable to institute interferon alfa therapy first. If such treatment fails, mutation information should be obtained (available only in research laboratories at this time), and in the presence of the T674I mutation, nilotinib or sorafenib therapy should be initiated (both are currently approved by the Food and Drug Administration, although not for this indication). In such refractory cases, allogeneic hematopoietic cell transplant needs to be considered.

Imatinib therapy is also effective for clonal eosinophilia associated with PDGFRB mutations.40,41 These mutations occur largely from translocations involving chromosome 5q33 and multiple other partner chromosomes/genes.42,43 Drug doses in this instance have usually been higher (400 mg/d), and currently it is unknown if lower doses would have the same effect. As was the case with FIP1L1-PDGFRα–positive clonal eosinophilia,27,39 patients with PDGFRB rearrangements, possibly due to 5q31-33 cytogenetic abnormalities, might achieve clinical and cytogenetic remissions with interferon alfa therapy,44-46 an observation that supports the use of interferon in imatinib mesylate–resistant or – intolerant cases.

All other cases of clonal eosinophilia should be managed as dictated by the diagnosis of their underlying myeloid malignancy. FGFR1-rearranged clonal eosinophilia presents with an aggressive disease course (myeloproliferation with eosinophilia, lymphadenopathy, and a high incidence of T cell lymphoblastic lymphoma with progression to acute myeloid leukemia)47 and requires early aggressive combination chemotherapy (eg, Hyper-CVAD [fractionated cyclophosphamide, vincristine, Adriamycin (doxorubicin), and dexamethasone]) followed by allogeneic hematopoietic cell transplant.

Imatinib therapy for FIP1L1-PDGFRα–positive clonal eosinophilia has occasionally been associated with drug-
induced cardiogenic shock that is reversible with systemic corticosteroid therapy. Therefore, it is prudent to measure serum troponin levels and perform echocardiography before initiating treatment with imatinib mesylate; if cardiac involvement is evident, concomitant oral prednisone therapy (1 mg/kg/d) should be considered during the initial 1 to 2 weeks of imatinib therapy.22,48 Pretreatment sperm banking (ie, making deposits of sperm for later use) might be considered because of the possible association of oligospermia (ie, making deposits of sperm for later use) might be considered because of the possible association of oligospermia with imatinib therapy.49 The drug has also been associated with fetal abnormalities (eg, hypospadias, exomphalos, renal agenesis) when used during pregnancy,50 but this might not be relevant in the current context because imatinib-sensitive clonal eosinophilias rarely affect women.

**Management of HES**

Tissue injury in patients with HES is mediated by material released from eosinophilic granules, including major basic protein, eosinophil cationic protein, and eosinophil-derived neurotoxin.51 Such eosinophil-derived substances, either directly or indirectly, could conceivably contribute to thromboembolic complications associated with HES. Therefore, the major goal of therapy for symptomatic HES is to debulk the blood and tissue eosinophil burden.

Corticosteroids are the cornerstone of therapy for HES, and the lack of glucocorticoid receptor expression by eosinophils has been associated with treatment resistance.51 Treatment with oral prednisone is usually started at 1 mg/kg per day and continued for 1 to 2 weeks before the dose is tapered slowly during the ensuing 2 to 3 months. If symptoms recur with a prednisone dosage level of greater than 10 mg/d, either hydroxyurea (starting dosage, 500 mg twice daily) or interferon alfa (starting dosage, 1 million units subcutaneously 3 times a week) is used as a corticosteroid-sparing agent.52

For patients in whom usual therapy fails (as outlined previously), several cytotoxic (eg, cladribine) and noncytotoxic (eg, cyclosporine) drugs have been used as salvage therapy, but current attention is focused on imatinib mesylate and 2 humanized monoclonal antibody drugs: mepolizumab and alemtuzumab. Mepolizumab targets interleukin 5, which is a well-recognized survival factor for eosinophils.53 Alemtuzumab targets the CD52 antigen, which has been shown to be expressed, at both the protein and the transcript level, by eosinophils but not by neutrophils.54

Imatinib mesylate is usually ineffective for the treatment of WHO-defined HES.55 However, occasional reports have described successful results with imatinib mesylate therapy for FIP1L1-PDGFRα-negative patients, usually at higher drug dosage levels (400-800 mg/d).16,34,36,57 Therefore, initiation of a therapeutic trial of high-dosage (800 mg/d) imatinib mesylate for 2 to 4 weeks could be tried before alemtuzumab or mepolizumab treatment is considered in patients with refractory HES.

In a large randomized study, intravenous mepolizumab (750 mg) was administered monthly to corticosteroid-dependent patients with HES and resulted in successful reduction of their corticosteroid dose and lowering of blood eosinophil count.55 The drug was well tolerated, and adverse event rates and pattern were not significantly different than those seen with placebo. However, mepolizumab-induced remissions were not durable, and relapse occurred 1 to 3 months after discontinuation of therapy. Additional studies are needed to evaluate the feasibility, safety, and efficacy of maintenance mepolizumab infusions.59 Mepolizumab is currently available in a compassionate-use program (http://clinicaltrials.gov) sponsored by GlaxoSmithKline, for patients with life-threatening HES that is not responding to usual therapy.

In a recently published study, 11 patients with refractory HES received intravenous alemtuzumab (5-30 mg) 1 to 3 times a week, and 10 (91%) achieved normalization of their eosinophil count and alleviation of symptoms and signs of disease.60 Response was quick (median, 2 weeks), but remission was not sustained in the absence of continued therapy. Adverse events included infusion-related symptoms, reactivation of cytomegalovirus infection, and development of orbital lymphoma in 1 patient. Subcutaneous alemtuzumab is also effective at 30 mg weekly or at longer intervals and has shown activity in lymphocytic variant hypereosinophilia.61 Alemtuzumab is currently approved by the Food and Drug Administration for use in B-cell chronic lymphocytic leukemia. We recommend prophylactic use of oral valganciclovir (450 mg twice daily, 3 times a week) and trimethoprim/sulfamethoxazole (80/400 mg twice daily, 3 times a week) while the patient is receiving alemtuzumab therapy.62,63

Finally, few case reports have shown successful treatment of HES or clonal eosinophilia, including a FIP1L1-PDGFRα–positive case, with either conventional or reduced-intensity conditioning allogeneic hematopoietic cell transplant.64,66 We think that such therapy should be considered for drug-refractory HES or clonal eosinophilia.

**Conclusion**

Accurate diagnosis is critical for effective management of eosinophilia. Several mutations have recently been described in myeloproliferative neoplasms,67-73 including those associated with clonal eosinophilia,74,75 and this has greatly simplified our current diagnostic approach to these diseases.9,76 In particular, the discovery of FIP1L1-PDGFRα74 has opened our eyes to the possibilities of not only deciphering the molecular pathogenesis of what we currently consider HES but also the prospect of effective molecularly targeted therapy.77
REFERENCES
Hypereosinophilic Syndrome and Clonal Eosinophilia


75. Cross NC, Reiter A. Tyrosine kinase fusion genes in chronic myeloproliferative diseases. Leukemia. 2002;16(7):1207-1212.
