REVIEW

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

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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 1.5×10^9/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).

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CEL-NOS = chronic eosinophilic leukemia, not otherwise specified; FISH = fluorescence in situ hybridization; HES = hypereosinophilic syndrome; PDGFR = platelet-derived growth factor receptor; RT-PCR = reverse transcription polymerase chain reaction; WHO = World Health Organization

Eosinophilia is relatively common in the tropical and subtropical regions of the world, where the primary cause is tissue-invasive helminth infections.[1] In the West, the main causes of secondary eosinophilia are allergic or vasculitis conditions, drugs, and nonmyeloid malignancies, although parasite infections should also be considered, especially in returning travelers and recently arrived immigrants/refugees from endemic regions.[2] Drug reaction with eosinophilia and systemic symptoms is a life-threatening complication associated with use of allopurinol, carbamazepine, and other drugs, including some antibiotics.[3] Among allergic or vasculitis causes of secondary eosinophilia, eosinophilic lung diseases are noteworthy and include acute and chronic eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, and allergic angiitis and granulomatosis (Churg-Strauss syndrome–eosinophilia, asthma, systemic vasculitis, and lung infiltrates).[4] Eosinophilic gastroenteritis might not be associated with blood eosinophilia, and its pathogenesis and treatment are thought to be distinct.[5,6]

In general, exclusion of secondary eosinophilia requires careful review of travel history, medication list, physical examination, and laboratory tests, including chest radiography, multiple stool ova and parasite testing (eg, hookworm, *Schistosoma* species), and serologic tests for suspected pathogens (eg, *Strongyloides stercoralis, Schistosoma* spp, *Toxocara* species, filaria).[7,8] However, distinguishing idiopathic eosinophilia with organ involvement from eosinophilia associated with systemic vasculitis or eosinophilic gastroenteritis can be difficult; in some instances, one might be dealing with spectrums of the same disease process. Regardless, when a cause for secondary eosinophilia is not readily apparent, it is reasonable to make a working diagnosis of clonal or idiopathic eosinophilia and pursue specific diagnosis in that regard.

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).[9] 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-

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TABLE. **World Health Organization Classification of Myeloid Malignancies**

Acute myeloid leukemia and related disorders
Myeloproliferative neoplasms
Chronic myelogenous leukemia, *BCR-ABL1* positive
Chronic neutrophilic leukemia
Polycythemia vera
Primary myelofibrosis
Essential thrombocythemia
Chronic eosinophilic leukemia, not otherwise specified
Mastocytosis
Myeloproliferative neoplasms, unclassifiable
Myelodysplastic syndromes
Refractory cytopenia with unilineage dysplasia
Refractory anemia
Refractory neutropenia
Refractory thrombocytopenia
Refractory anemia with ringed sideroblasts
Refractory cytopenia with multilineage dysplasia
Refractory anemia with excess blasts
Refractory anemia with excess blasts 1
Refractory anemia with excess blasts 2
Myelodysplastic syndrome with isolated del(5q)
Myelodysplastic syndrome, unclassifiable
Myelodysplastic syndromes/myeloproliferative neoplasms
Chronic myelomonocytic leukemia
Atypical chronic myeloid leukemia, *BCR-ABL1* negative
Juvenile myelomonocytic leukemia
Myelodysplastic syndromes/myeloproliferative neoplasms, unclassifiable
Refractory anemia with ringed sideroblasts and thrombocytosis
Myeloid and lymphoid neoplasms associated with eosinophilia and genetic abnormalities
Myeloid and lymphoid neoplasms associated with *PDGFRA* rearrangement
Myeloid neoplasms associated with *PDGFRB* rearrangement
Myeloid and lymphoid neoplasms associated with *FGFR1* abnormalities

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 1.5×10^9/L or greater and eosinophil-mediated organ damage. Hypereosinophilic syndrome should be distinguished from the term *hypereosinophilia*, which simply indicates an absolute eosinophil count of 1.5×10^9/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[10,11] and progression into WHO-defined myeloid neoplasm in other cases.[12-15] Additionally, patients with *FIP1L1-PDGFRA*–positive clonal eosinophilia were often diagnosed as having HES before the mutation was discovered in 2003.[16]

DIAGNOSTIC ALGORITHM FOR CLONAL OR IDIOPATHIC EOSINOPHILIA

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 *FGR1* 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-PDGFRA*, 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-PDGFRA* 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-PDGFRA*–associated myeloid neoplasm, 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-PDGFRA* 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*, *PDGFRA*, 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-

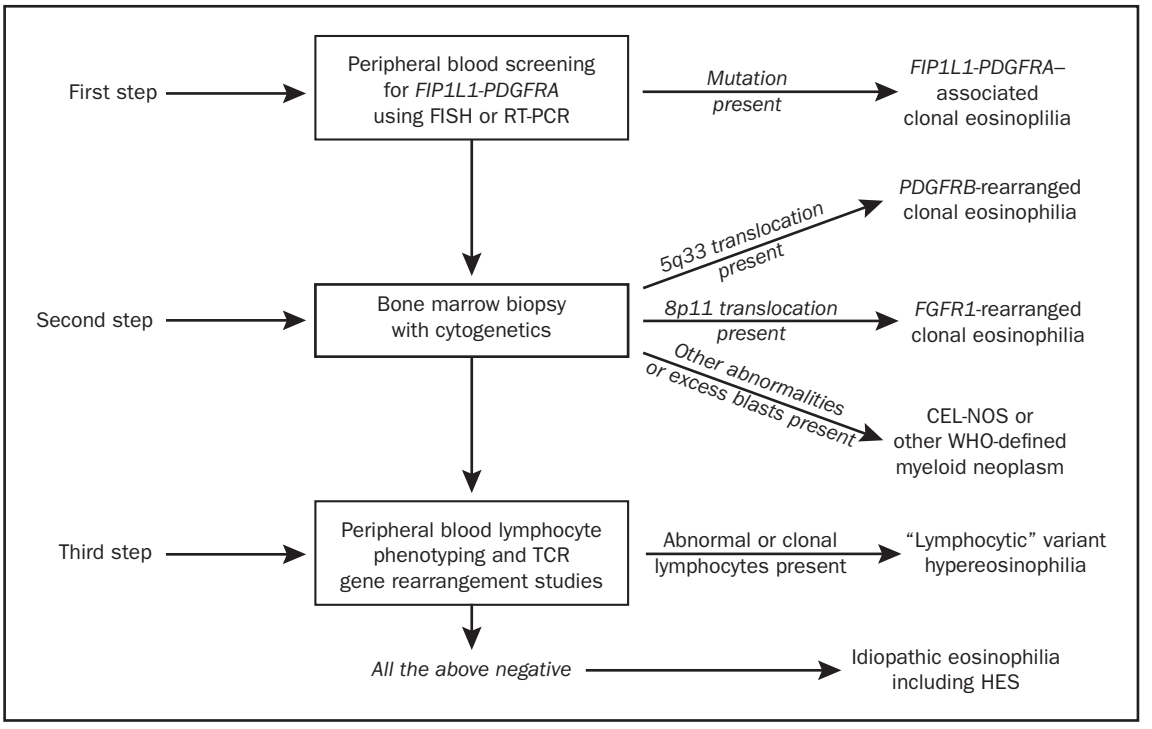

FIGURE. Diagnostic algorithm for clonal or idiopathic eosinophilia. CEL-NOS = chronic eosinophilic leukemia, not otherwise specified; FISH = fluorescence in situ hybridization; HES = hypereosinophilic syndrome; PDGFR = platelet-derived growth factor receptor; RT-PCR = reverse transcription polymerase chain reaction; TCR = T-cell receptor; WHO = World Health Organization.

eloid malignancy (Table). Of special importance in the differential diagnosis is the diagnostic consideration of systemic mastocytosis, chronic myelomonocytic leukemia, and CEL-NOS.[17] Diagnosis of systemic mastocytosis requires the presence of aggregates of morphologically abnormal mast cells, demonstration of abnormal mast cell expression of CD25, or presence of *KIT*D816V.[18] The diagnosis of chronic myelomonocytic leukemia requires the presence of peripheral blood monocytes of more than 1×10^9/L. CEL-NOS is considered when the peripheral blood eosinophil count is 1.5×10^9/L or greater and is accompanied by cytogenetic or morphologic evidence of a myeloid malignancy that is otherwise not classifiable. Specifically, CEL-NOS is distinguished from HES by the presence of either a cytogenetic abnormality or greater than 2% peripheral blood blasts or greater than 5% bone marrow blasts.[19]

Diagnosis of idiopathic eosinophilia, including the HES subcategory, requires exclusion of both secondary and clonal eosinophilia and absence of phenotypically abnormal and/or clonal T lymphocytes. In addition, diagnosis of HES (a subcategory of idiopathic eosinophilia) requires presence of a peripheral blood eosinophil count of 1.5×10^9/L or greater for at least 6 months (although a shorter period is acceptable in the presence of symptoms requiring eosinophil-lowering therapy) and evidence of organ involvement. All suspected HES cases should undergo peripheral blood lymphocyte phenotyping and T-cell receptor gene rearrangement studies to rule out lymphocytic variant hypereosinophilia, which is defined by the presence of clonal or phenotypically abnormal (eg, $CD3^-CD4^+$) T cells.[20]

TREATMENT

Both clonal eosinophilia and HES might be accompanied by eosinophil-mediated tissue injury in the form of cardiomyopathy, pneumonitis, dermatitis, sinusitis, central nervous system or peripheral neuropathy, gastrointestinal inflammation, thromboembolic complications, and other manifestations.[20] In addition, clonal eosinophilia is usually associated with cytopenia and hepatosplenomegaly. The decision to use drug therapy for hypereosinophilia depends partly on the presence or absence of such organ involvement. As such, initial evaluation of the patient with eosinophilia should include tests that facilitate assessment of target organ damage: complete blood cell count, chest radiography, echocardiography, and serum troponin level. An increased level of serum cardiac troponin has been shown to correlate with the presence of cardiomyopathy in patients with HES.[21,22] Typical echocardiographic findings in such patients include ventricular apical thrombus, posterior mitral leaflet or tricus-

pid valve abnormality, endocardial thickening, dilated left ventricle, and pericardial effusion.[23] Other tests indicated in the presence of organ-specific symptoms include pulmonary function tests, gastrointestinal endoscopy, skin biopsy, sinus radiography, and neuroimaging studies.

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-PDGFRA, 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, $>30 \times 10^9$/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 *PDGFRA*, *PDGFRB*, and *FGFR1* rearrangements. In a Mayo Clinic study of prevalence and clinicopathologic correlation, *FIP1L1-PDGFRA* 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-PDGFRA*–associated clonal eosinophilia have been in male patients.[30] *PDGFRB* (5q33 translocations), *FGFR1* (8p11.2 translocations), and *PDGFRA* (4q12 translocations)[29] fusion genes are often apparent by cytogenetic analysis of the bone marrow, whereas *FIP1L1-PDGFRA* 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-PDGFRA* or *PDGFRA/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-PDGFRA*–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[36]; therefore, we currently prefer to maintain the dosage at 100 mg/d in the absence of adverse effects.

Rare cases of mutant *FIP1L1-PDGFRA* 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.[38] Also, there are reported instances of interferon alfa–induced complete clinical remissions in *FIP1L1-PDGFRA*–positive clonal eosinophilia.[27,39] Therefore, in patients with imatinib mesylate–resistant *FIP1L1-PDGFRA*–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-PDGFRA*–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-PDGFRA*–positive clonal eosinophilia has occasionally been associated with drug-

induced cardiogenic shock that is reversible with systemic corticosteroid therapy.[48] 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 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.[20] 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-PDGFRA*–negative patients, usually at higher drug dosage levels (400-800 mg/d).[16,34,56,57] 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.[58] 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-PDGFRA*–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-PDGFRA*[74] 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]

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