



Recent Advances in the Diagnosis and Treatment of Hypereosinophilic Syndromes

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Hypereosinophilic syndromes (HES) are a heterogeneous group of disorders characterized by marked peripheral blood and tissue eosinophilia resulting in end organ damage. Recent advances in molecular biology and immunology have led to the identification of a number of distinct subtypes of HES with differing epidemiology, pathogenesis, and prognosis. The ability

to distinguish between these HES subtypes combined with the availability of new treatment modalities, including tyrosine kinase inhibitors and monoclonal antibodies, that target specific molecules involved in disease pathogenesis have dramatically altered the approach to the diagnosis and treatment of HES.

Hypereosinophilic syndromes (HES) are a heterogeneous group of disorders characterized by marked blood and tissue eosinophilia resulting in a wide variety of end organ manifestations.¹ In 1975, Chusid et al established the following set of diagnostic criteria for idiopathic HES: i) blood eosinophilia $> 1500/\text{mm}^3$ for at least 6 months, ii) absence of an underlying cause of eosinophilia despite extensive evaluation, and iii) presence of end organ damage or dysfunction related to the eosinophilia.² Although these criteria have been tremendously useful in the identification and characterization of patients with primary eosinophilic disorders, they have also led to a number of generalized conclusions about HES that, in fact, apply only to a subset of affected individuals. This has become increasingly apparent as a result of recent advances in molecular biology and immunology that have led to the identification of a number of distinct subtypes of HES with differing epidemiology, pathogenesis, and prognosis. The ability to distinguish between these HES subtypes combined with the availability of new treatment modalities, including tyrosine kinase inhibitors and monoclonal antibodies, that target specific molecules involved in disease pathogenesis, have revolutionized the approach to the diagnosis and treatment of HES.

Diagnosis

A first step in the diagnosis of HES is documentation of marked eosinophilia. Whereas Chusid's first criterion (>1500 eosinophils/ mm^3 for more than 6 months) provides a useful guide, it is clear that some patients with HES will

be excluded by using so precise a definition. This is of particular importance in the case of patients with serious end organ involvement who should be treated without waiting for 6 months for confirmation of the diagnosis and in patients with clear documentation of eosinophilic tissue infiltration whose peripheral eosinophil counts remain below $1500/\text{mm}^3$ because of steroid (or other immunomodulatory) treatment of concomitant conditions, such as asthma.

Regardless of the criteria used to define marked eosinophilia, however, exclusion of diagnoses associated with secondary eosinophilia is essential (Chusid's second criterion). These include hypersensitivity reactions, parasitic infections, neoplasms and a wide variety of other disorders associated with immunodysregulation (see **Table 1**). Although it is beyond the scope of this review to provide a complete list of laboratory and diagnostic tests required to exclude other diagnoses, a minimum standard for all patients should include a complete history and physical examination, a complete blood count and differential, routine chemistries, serum IgE and vitamin B₁₂ levels, HIV serology, electrocardiogram, echocardiogram, pulmonary function tests, chest and abdominal CT, and bone marrow aspirate and biopsy. Additional organ-specific evaluations should be guided by the clinical manifestations. Testing for occult parasitic infection with stool examination for ova and parasites and/or specific serologic tests is warranted in the setting of an appropriate exposure history.

End organ involvement in HES (Chusid's third criterion) is extremely variable, ranging from relatively asymptomatic disease to fatal endomyocardial fibrosis. Although large series based on Chusid's criteria have consistently shown that skin, heart and nervous system involvement are most common, any organ can be affected. Furthermore, the clinical manifestations appear to differ depending on the underlying etiology of the eosinophilia (see below).

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Table 1. Causes of secondary eosinophilia.*

- Allergic disorders
 - asthma and/or atopic disease (rare)
 - allergic bronchopulmonary aspergillosis
- Drug hypersensitivity reactions
- Infectious diseases
 - helminth infection
 - ectoparasite infestations (scabies, myiasis)
 - protozoal infection (rarely in isosporiasis and sarcocystis)
 - fungal infection (especially coccidiomycosis)
 - human immunodeficiency virus infection
- Neoplasms
 - leukemia
 - lymphoma
 - adenocarcinoma
- Hypoadrenalism
- Diseases associated with immunodysregulation
 - sarcoid
 - inflammatory bowel disease
 - connective tissue disorders
- Other
 - cholesterol embolization
 - radiation exposure

*lists are not exhaustive

HES Subtypes

Although the striking clinical heterogeneity of HES had been recognized since the original description of the syndrome, it is only recently that etiologically distinct syndromes have begun to be identified. The best described of these to date are the myeloproliferative variant caused by an interstitial deletion in chromosome 4q12³ and the lymphoproliferative variant associated with clonal proliferation of phenotypically abnormal T cells.⁴ A number of less common, but clinically distinct, variants of HES have also been described, including an autosomal dominant familial form that has been mapped to chromosome 5q31,⁵ an episodic form (Gleich's syndrome),⁶ and a clinically silent or benign form. However, all of these taken together account for approximately 50% of the cases of HES in most large series, suggesting that additional subtypes are likely to be identified in the future.

The importance of subtype identification in the diagnostic evaluation of HES cannot be overemphasized. Not only is knowledge of the HES subtype useful in predicting treatment response, but it has profound implications with respect to likely end organ manifestations and prognosis.⁷ Although not all of the specialized testing necessary to definitively distinguish between subtypes is routinely available, presumptive classification is usually possible (Table 2).

Myeloproliferative variant

Unresponsiveness to steroid therapy and poor prognosis had long been recognized in a subset of patients with a more aggressive form of HES associated with features of

Table 2. Subtype classification of hypereosinophilic syndromes (HES).

Myeloproliferative variant

Definitive Evidence
FIP1L1-PDGFR α fusion by RT-PCR or FISH
Eosinophil clonality by HUMARA analysis, karyotype or other modality

Supportive Evidence
≥ 4 of the following:
increased serum tryptase level
increased serum B₁₂ level
splenomegaly
anemia, thrombocytopenia
increased circulating myeloid precursors
dysplastic eosinophils
myelofibrosis
increased spindle-shaped mast cells in the bone marrow

Lymphoproliferative variant

Definitive Evidence
Phenotypically aberrant T cell population*
Clonal T cell rearrangement pattern by PCR
Increased T cell production of eosinophilopoietic cytokines

Supportive Evidence
Increased serum TARC \ddagger
Increased serum IgE
Predominantly cutaneous manifestations
History of atopy
Steroid-responsive

*antibodies specific for the following additional markers should be included if routine phenotyping is normal and the lymphoproliferative variant is suspected: CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD25, CD27, CD45RO, TCR $\alpha\beta$, TCR $\gamma\delta$, HLA-DR and CD95

\ddagger TARC-CC thymus and activation related chemokine (CCL17)

myeloproliferative disorders. It was the observation that imatinib therapy had a dramatic effect in these patients, however, that led to the identification of FIP1L1/PDGFR α (F/P), a fusion tyrosine kinase associated with most cases of imatinib-responsive HES.³ Although patients with PDGFR α -associated HES occasionally have cytogenetic abnormalities, the vast majority of cases are due to a small interstitial deletion in chromosome 4, del(4)(q12q12), that is undetectable by standard cytogenetics. The breakpoints in *FIP1L1* are variable but are typically located in a 40-kb region spanning introns 7–10 of *FIP1L1*. In contrast, the breakpoints in *PDGFR α* appear to be restricted to a region of exon 12 that contains the WW-like region of the juxtamembrane domain. Definitive diagnosis of PDGFR α -associated HES requires demonstration of the fusion gene by reverse-transcriptase polymerase chain reaction (RT-PCR) or fluorescence in situ hybridization (FISH). Presumptive diagnosis is possible based on the characteristic constellation of clinical and laboratory features (see below).

Current data suggest that 10%-50% of HES cases that meet Chusid's classic definition have PDGFR α -associated

disease.^{8,9} Most of these cases belong to a distinct clinical subgroup characterized by extreme male predominance, pathologic evidence of eosinophil-related tissue damage and tissue fibrosis, elevated serum tryptase levels, splenomegaly, anemia, thrombocytopenia, and bone marrow hypercellularity with reticulin fibrosis and an increase of atypical mast cells.⁹ Interestingly, some clinical manifestations, such as endomyocardial fibrosis, restrictive lung disease and mucosal ulcerations, appear to occur predominantly in patients with PDGFRA-associated disease. Although rare cases of PDGFRA-associated HES have been described in women, to date there have been no reports in children. Prior to the availability of imatinib, mortality in this group was extremely high (> 50%). Leukemic transformation is rare, but does occur.^{3,10}

The F/P mutation has also been described in a subset of eosinophilic patients presenting with clinical features of systemic mastocytosis that are indistinguishable from *c-kit* mutation-driven systemic mast cell disease.¹¹ It is extremely important to distinguish these patients from those with *c-kit* mutation-driven disease, as 816V, the most common *c-kit* mutation associated with systemic mastocytosis, is resistant to imatinib. Conversely, some cases of HES with features of myeloproliferative disorders (up to 20% in our experience) are not associated with the F/P mutation. Although occult leukemias have been described in a few instances,¹² the etiology of most of these cases remains unknown, and the response to imatinib is variable.

Lymphoproliferative variant

Since the initial description of a patient with clinical features of HES and the presence of a phenotypically distinct clonal T cell population in the peripheral blood by Cogan et al in 1994, it has become increasingly apparent that the lymphoproliferative variant of HES (L-HES) represents a distinct clinical syndrome.⁷ Hypereosinophilia in these patients appears to occur in response to the production of eosinophilopoietic cytokines, particularly interleukin 5 (IL-5), by clonal populations of phenotypically abnormal, activated T lymphocytes. Diagnosis is based on the identification of a population of T cells with an aberrant phenotype, most often CD3⁺CD4⁺CD8⁻, in the peripheral blood by flow cytometry. Demonstration of T cell clonality by T cell receptor rearrangement analysis is not essential, but strongly supports the diagnosis. Other evidence of Th2 activation in patients with this variant that may be helpful in making the diagnosis includes serum elevations of IgE and thymus and activation-regulated chemokine (TARC).¹³

L-HES occurs with equal frequency in men and women. Although the clinical manifestations can be extremely varied, dermatologic involvement is present in a majority of patients. Gastrointestinal symptoms and obstructive lung disease are also common; whereas tissue fibrosis, including endomyocardial fibrosis and myelofibrosis, are rarely seen. The prevalence of this subtype is unknown at the present time, since estimates vary considerably (< 5%-50%)

depending on the study population and diagnostic methods employed.

Despite the relatively low mortality in patients with L-HES, morbidity, due both to the underlying disease and secondary effects of treatment, is significant. Furthermore, progression to T cell lymphoma appears to be most common in this subgroup of patients and should be suspected in the setting of increasing numbers of aberrant T cells and/or the development of lymphadenopathy. Two features that appear to be associated with an increased likelihood of progression to lymphoma are the CD3⁺CD4⁺CD8⁻ surface phenotype and the presence of cytogenetic abnormalities (6q deletions).¹⁴

Other clinically distinct syndromes

Approximately 50% of HES patients in most series remain unclassified despite careful evaluation for the F/P mutation and evidence of an aberrant lymphocyte population. Some of these patients have hypereosinophilic syndromes with distinctive clinical features that appear to set them apart. One of the most intriguing of these is Gleich's syndrome,⁶ a rare disorder characterized by monthly episodes of pronounced eosinophilia and angioedema preceded by cyclical increases in eosinophilopoietic cytokines, most often IL-5. In patients whose primary complaint is swelling and/or weight gain, it is useful to measure eosinophil counts every three days for several weeks off therapy in order to identify episodic angioedema and eosinophilia. Oftentimes, the periodicity is missed because of intermittent steroid use and measurement of eosinophil counts only when symptoms are present. Although some patients with this syndrome ultimately progress to HES and/or develop clonal populations of lymphocytes, the unique clinical presentation is suggestive of a common and distinct etiology in this clinical subgroup of patients.

The occurrence of marked eosinophilia in multiple members of the same family is rare, with only a few reports in the literature to date. Autosomal dominant transmission appears to be most common. In one such family, the gene responsible for the eosinophilia has been mapped to chromosome 5q31-33.⁵ Despite marked eosinophilia (2000–6000/mm³) from birth, a minority of family members appear to develop clinical manifestations consistent with the relative lack of evidence of eosinophil activation in these patients as compared to patients with non-familial HES. When clinical disease does occur, it resembles F/P-associated HES with endomyocardial fibrosis and neurologic complications. Whether the sudden disease progression in a small number of these patients after a lifetime of asymptomatic eosinophilia represents a second mutation remains unknown.

A number of other examples of clinically distinct, primary eosinophilic disorders exist, including organ-specific eosinophilic syndromes, a Churg-Strauss-like syndrome in which vasculitis cannot be demonstrated despite appropriate biopsies, and an autoimmune variant characterized

by eosinophilia, elevated levels of autoantibodies, Raynaud's syndrome, and stroke. The relationship of these syndromes to HES awaits elucidation of the underlying molecular and immunologic mechanisms of pathogenesis.

Controversies

A number of controversies exist with respect to the diagnosis of HES. These include i) the appropriate classification of well-defined, organ-specific eosinophilic disorders of unknown etiology, such as eosinophilic gastroenteritis, eosinophilic cystitis, and chronic eosinophilic pneumonia, ii) the most correct nomenclature for the myeloproliferative subtypes of HES (chronic eosinophilic leukemia vs HES vs systemic mastocytosis with eosinophilia¹⁵), and iii) the relationship between HES and "overlap syndromes," a wide variety of idiopathic multisystem disorders that are associated with marked peripheral eosinophilia in a subset of patients. It is important to note as well that some patients with marked eosinophilia ($> 1500/\text{mm}^3$) of many years' duration do not develop any evidence of end organ damage in the absence of specific treatment. Whether these patients represent one end of the spectrum of HES or a normal variant is unclear at this time. As the number of chemotherapeutic agents with specific molecular and immunologic targets continues to grow, resolution of these issues will become increasingly important for the appropriate management of patients with primary eosinophilic disorders.

Treatment

Steroids

Steroids have been and continue to be a mainstay of treatment in HES. With the exception of F/P-associated HES, steroids remain the first-line treatment for most patients. Steroids should also be used in addition to imatinib in patients with F/P-associated HES and evidence of myocarditis, as suggested by EKG or echocardiographic assessment or the presence of an elevated serum troponin level.¹⁶ Although the most appropriate initial steroid dose and the duration of steroid therapy have not been studied, it seems prudent to start with moderate to high doses (≥ 40 mg prednisone equivalent daily) and to taper very slowly following the eosinophil count closely. Using this approach, most, but not all, patients will respond initially to steroid therapy, and some will be able to be maintained on low doses for long periods. Over time, however, the toxicities of steroid therapy become limiting and alternative therapies must be used.

Cytotoxic agents

A number of cytotoxic therapies, including hydroxyurea,¹⁷ vincristine, and cytarabine,¹⁸ have been used for the management of steroid-refractory HES. Of these, hydroxyurea has been the most extensively studied and, at doses of up to 2 g/day, is associated with few side effects.¹⁷ Although

some patients will respond to low-dose hydroxyurea therapy, many require higher doses to adequately control the eosinophil count. As the dose increases, hematologic and gastrointestinal side effects become common, limiting the utility of hydroxyurea in the treatment of HES. Furthermore, hydroxyurea cannot be used to acutely lower the eosinophil count since a therapeutic effect is generally not achieved for up to 2 weeks.

Immunomodulatory therapies

In patients with steroid-refractory disease or who are intolerant of the side effects of steroid treatment, a number of immunomodulatory agents with effects on Th2 cytokine production and T cell proliferation, including interferon- α , cyclosporine and intravenous immunoglobulin, have been shown to have a therapeutic effect. Of these, interferon- α has been the most successful with stable responses achieved with relatively low doses (1-2 mU/day) over prolonged periods of time.¹⁹ Rarely, patients have remained in remission for extended periods of time following cessation of interferon therapy, suggesting that interferon may be curative in a small subset of individuals.

Even at low doses, systemic toxicity is common with interferon therapy and can be dose-limiting. Low-dose hydroxyurea (500 mg daily) appears to potentiate the effect of interferon- α on eosinophils without increasing toxicity and can be used in these situations. The use of a second agent in combination with interferon- α is recommended in L-HES on the basis of *in vitro* data demonstrating inhibition of apoptosis of clonal CD3⁺CD4⁺ T cells by interferon.²⁰ In this instance, steroids are the preferred second agent because of their pro-apoptotic effect.

Tyrosine kinase inhibitors

Although few experts would disagree with the initial use of the tyrosine kinase inhibitor, imatinib, in patients in whom the fusion gene has been demonstrated or in selected patients with the characteristic clinical and laboratory features of this HES subtype, a number of controversies remain with respect to the appropriate dose and duration of imatinib therapy and the use of imatinib in other subgroups of patients with HES.

Imatinib response rates in F/P-positive patients approach 100%,²¹ with only 2 reported cases of acquired drug resistance, both associated with a T6741 substitution in the ATP-binding domain of PDGFRA that is analogous to the T3151 mutation in ABL seen in imatinib-resistant CML.^{3,10} Clinical responses in F/P⁺ patients are rapid, with normalization of eosinophil counts generally occurring within 1 week of initiation of treatment and reversal of signs and symptoms within 1 month. The exception is cardiac involvement, which is irreversible unless treatment is begun before fibrosis leads to permanent anatomic alterations.^{21,22} Although side effects of imatinib therapy are generally mild and rarely lead to discontinuation of therapy, cardiac decompensation has been observed in at least one

patient treated with imatinib, and has led to the recommendation that patients be screened for elevated troponin levels prior to therapy and pre-treated with steroids if levels are elevated.¹⁶

Clinical remission and normalization of eosinophil counts has been reported in patients treated with imatinib at doses as low as 100 mg daily; however, some patients will continue to have molecular evidence of the mutation at this dose. Our experience suggests that all F/P⁺ patients treated with 400 mg daily achieve durable clinical, hematologic and molecular remission.²¹ In view of the data from CML, which suggest that clinical relapse is more common in patients with detectable residual disease, it seems prudent to begin imatinib treatment at 400 mg to achieve molecular remission and to then decrease the dose slowly following closely for evidence of molecular relapse.

The utility of imatinib therapy in patients without the F/P mutation remains to be determined, although some patients have demonstrated a response.³ In general, these responses have been slower and have required higher imatinib doses than those in patients with F/P-associated disease. Imatinib does not appear to be useful in treating patients with the L-HES and should not be used as first-line therapy in these patients.⁷

Although imatinib is the only tyrosine kinase inhibitor with activity against PDGFRA that is commercially available at this time, additional agents currently in development are likely to be effective in PDGFRA-associated HES. One of these, PKC412, has already been demonstrated to be effective against the T6741 resistance mutation *in vitro*.³

Monoclonal antibody therapy

Monoclonal anti-IL-5 antibody therapy for HES has a number of unique advantages related to the specificity of IL-5 for the eosinophil lineage. Preliminary studies using two different anti-IL-5 antibodies, SCH55700 and mepolizumab, demonstrated a dramatic and prolonged lowering of the peripheral eosinophil count in response to a single dose of antibody in a majority of HES patients regardless of the underlying etiology or baseline IL-5 level.²³ The therapy was extremely well tolerated, although a rebound in symptoms and eosinophilia associated with an increase in serum IL-5 levels was noted in one study as antibody levels decreased.²⁴ The safety and efficacy of anti-IL-5 therapy as a steroid-sparing agent in HES is currently being assessed in a large, double-blind, placebo-controlled study of mepolizumab.

Bone marrow transplantation

Nonmyeloablative allogeneic bone marrow transplantation has been used successfully in the treatment of HES²⁵ and should be considered in patients with F/P⁺ disease who become resistant to or are unable to tolerate imatinib therapy and in F/P⁻ patients with severe progressive end organ damage once standard therapies have been exhausted.

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