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Advances in diagnosis and treatment of eosinophilia

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Abstract

Purpose of review—Hypereosinophilic syndromes (HESs) are disorders characterized by sustained blood or tissue hypereosinophilia or both with subsequent damage to various organs due to eosinophilic infiltration and release of mediators. HES are now recognized to include varied eosinophilic disorders for some of which there are recent insights into their pathogenesis and targeted treatment.

Recent findings—Studies have helped delineate two subtypes of HES: the myeloproliferative variants of HES and the lymphocytic variants of HES. Many, but not all, myeloproliferative-HES patients have interstitial deletions on chromosome 4q12 that lead to fusion of the FIP1-like 1 and platelet-derived growth factor receptor α genes, with the fusion product encoding a protein that has constitutive tyrosine kinase activity. Lymphocytic-HES is a primary lymphoid disorder characterized by nonmalignant expansion of a T-cell population able to produce eosinophilopoietic cytokines, with the T-cell population being identified by flow cytometry or reverse transcriptase-PCR for T-cell receptor usage or both. Other HES subtypes are of uncertain causes and are included in recent diagnostic algorithms for the spectrum of HES.

Summary—The contemporary definition of the hypereosinophilic syndromes encompasses a range of eosinophilic disorders characterized by chronic blood hypereosinophilia often with eosinophil-mediated damage to various organs.

Keywords

chronic eosinophilic leukemia; eosinophilia; eosinophils; hypereosinophilic syndrome; imatinib

Introduction

Eosinophilia, with elevations of blood or tissue eosinophil levels or both, can occur with atopic diseases, drug hypersensitivity reactions, certain malignancies, connective tissue disorders and helminthic parasitic infections [1–3]. When an underlying allergic, parasitic or other cause cannot be identified, the eosinophilic disorder is considered to fall into an umbrella category now known as ‘hypereosinophilic syndromes’ (HESs) [4]. Originally, HES was called the ‘*idiopathic* hypereosinophilic syndrome’ [1], reflecting the fact that little was then known about the pathophysiology of eosinophilia. With recent insights into the causes of some forms of HES and with the recognition that eosinophilic diseases include a

spectrum of disorders, an international working group has endorsed not using the term idiopathic and further recognized that HES should encompass a heterogeneous group of conditions, that is, HESs [3–5]. In addition to what was formally known as idiopathic HES, the HESs include other conditions characterized by tissue-associated eosinophilic inflammation and in most cases peripheral blood eosinophilia, such the Churg–Strauss syndrome (CSS) and the eosinophilic gastrointestinal diseases (EGIDs) [4].

History of the terms hypereosinophilic syndrome and idiopathic hypereosinophilic syndrome

Descriptions of cases of unexplained hypereosinophilia have been recorded for over 100 years [1,6]. Early cases described a variety of presentations, with peripheral eosinophilia, cardiovascular involvement, bone marrow eosinophilia, and features suggestive of collagen vascular disease being variably present, hence terms such as ‘eosinophilic leukemia,’ ‘Löffler’s syndrome,’ ‘Löffler’s fibroplastic endocarditis with eosinophilia,’ and ‘disseminated eosinophilic collagen disease’ were used [7,8]. The use of the plural term ‘hypereosinophilic syndromes’ first occurred in a 1968 review article describing three patients in comparison with previously reported cases, highlighting the heterogeneity of clinical presentations [8].

Diagnostic criteria for the HES were first proposed in 1975 by Chusid *et al.* [7] in their case series of 14 patients: peripheral blood eosinophilia with absolute eosinophil count greater than 1500 cells/ μ l sustained for greater than 6 months; no other evident cause for eosinophilia, including allergic diseases and parasitic infection, and signs or symptoms or both of organ involvement by eosinophilic infiltration. These defining criteria were used to identify patients with HES for many years. The clinical features of HES, as described in earlier case series [1,9–11], are summarized in Table 1. Throughout the years, HES has been reported to be more common in men compared with women, with a male to female ratio as high as nine to one [1]. Most cases have been described in adults, with ages at diagnosis often between 20 and 50 years [1,6,11], although pediatric cases of HES also occur [12,13].

Modern definition and classification scheme of hypereosinophilic syndromes

Contemporary experience related to the causes and management of HES patients have prompted an updating of the original diagnostic criteria proposed by Chusid *et al.* [5]. First, the need for a 6-month duration of eosinophilia [7], designed to exclude short-term episodes of eosinophilia, has been abandoned. For some patients, significant morbidity may arise if treatment is delayed until the 6-month time requirement is met. Therefore, patients can be considered to have HES without waiting for the 6-month time requirement if Chusid’s second and third criteria are also met, and diagnostic testing and especially therapeutic interventions can be initiated based on clinical needs [4,14].

A second issue not treated in the earlier criteria of Chusid *et al.* was how to consider nominally organ specific eosinophilic diseases such as the acute and chronic eosinophilic pneumonias and EGIDs. Many of these diseases satisfied the early criteria of Chusid *et al.* for HES but often did not have the systemic complications seen in many with HES. At times, the organ specific eosinophilic diseases, often idiopathic, were difficult to exclude as premonitory presentations of more systemic eosinophilic disorders (e.g., HES or CSS).

These issues were discussed at an international workshop on eosinophilic diseases convened in May 2005 in Bern, Switzerland, and consensus opinions from the workshop were published in 2006 [4]. The more encompassing plural term of HESs was used with the intent

of capturing all of the heterogeneous presentations of HES. The criteria for HESs presented in the workshop report differed from the original Chusid's criteria in that the 6-month time requirement was eliminated: eosinophils more than 1500/ μ l; persistent eosinophilia or end-organ damage/dysfunction or both; and exclusion of secondary causes of eosinophilia. The breadth of HES was then subcategorized into the following categories: 'myeloproliferative variants (M-HES)', 'lymphocytic variants (L-HES)', 'familial eosinophilia', 'undefined forms of HES', 'overlap eosinophilic diseases', and 'eosinophil-associated diseases.'

Recognition of the myeloproliferative and lymphocytic variants of HES (considered below) provides an etiologic understanding for the nature of the hypereosinophilia. The relative frequencies of these variants as causes of HES are not yet clear and differ among referral centers [5]. As yet, most patients with HES lack etiologic understanding for their hypereosinophilia and fall in the subcategory of 'complex undefined HES'. This subcategory includes those with symptomatic organ involvement associated with eosinophilia and represents the majority of HES patients seen in many referral centers. Another subcategory of 'benign undefined HES' includes patients in whom elevated blood eosinophilia is not associated with evidence of organ involvement. Such patients would not satisfy the early HES criteria requiring signs and symptoms of organ involvement; but neither the causes for the eosinophilia nor the natural history of such patients are as yet known. Individuals with eosinophilia associated with single organ system involvement (e.g. eosinophilic pneumonias, EGIDs) would be categorized within 'overlap eosinophilic diseases.' Other diseases at times associated with eosinophilia, including Churg–Strauss vasculitis, mastocytosis and others, would be encompassed in 'eosinophil-associated diseases.'

It is realized that such classification schemes of the HESs remain a work in progress, and changes and refinements will occur as more is learned about the biological mechanisms underlying the various heterogeneous HES subtypes. [4,5].

Chronic eosinophilic leukemia and the myeloproliferative variants of hypereosinophilic syndrome

Early in the history of eosinophilic disorders, some HES patients appeared to have an eosinophilic form of leukemia, with cytogenetic or molecular evidence of eosinophil clonality [15]. However, such clonality was not often seen using available diagnostic techniques in early HES case series [1,5,9,11]. Reports in the 1970s and 1980s noted that some HES patients presented with clinical and hematologic features suggestive of a myeloproliferative-type process. Such features including very high peripheral blood eosinophil counts (more than 100 000/ μ l), hepatosplenomegaly, presence of chromosomal abnormalities or circulating immature precursor cells, increased serum vitamin B12, elevated leukocyte alkaline phosphatase, anemia or thrombocytopenia or both predicted a worse outcome [5,7,16,17]. Chromosomal karyotyping of such patients rarely demonstrated a gross defect. However, a major breakthrough in diagnostics for HES occurred in 2003 with the recognition of an interstitial deletion on chromosome 4q12 that leads to fusion of the FIP1-like 1 (FIP1L1) and platelet-derived growth factor receptor (PDGFR) α genes, with the fusion product encoding for a protein that has constitutive tyrosine kinase activity [18]. Such patients have very pronounced peripheral blood eosinophilia as well as the myeloproliferative features discussed above, and are now included in the subcategory of M-HES [4,19,20**]. M-HES disease with the FIP1L1-PDGFR α fusion mutation is a form of chronic eosinophilic leukemia (CEL), as WHO criteria identify eosinophil clonality as the defining feature of CEL, and identification of the FIP1L1-PDGFR α fusion mutation establishes clonality [19,20**]. Analogous chromosomal mutations involving the fibroblast growth factor receptor or PDGFR β can also be associated less commonly with

hypereosinophilia [3]. Common clinical and hematologic features [5] of M-HES are as follows:

1. often FIP1L1-PDGFR α fusion gene mutation positive,
2. usually male,
3. dysplastic peripheral eosinophils,
4. elevated serum B12,
5. elevated serum tryptase,
6. anemia or thrombocytopenia or both,
7. hepatosplenomegaly,
8. increased bone marrow cellularity,
9. atypical/spindle-shaped mast cells in bone marrow,
10. myelofibrosis,
11. frequent imatinib response (known with FIP1L1-PDGFR α fusion),
12. often get cardiac involvement.

The 2005 workshop consensus [4] was that a patient with HES, in the absence of detectable FIP1L1-PDGFR α (or related) chromosomal mutation or other evidence of eosinophil clonality, could be considered to fall under M-HES if four or more of the following eight features are present: presence of dysplastic eosinophils on peripheral blood smear, serum B12 level more than 1000 pg/ml; serum tryptase at least 12 ng/ml; anemia or thrombocytopenia or both; hepatosplenomegaly; bone marrow biopsy cellularity greater than 80%; presence of dysplastic mast cells in the bone marrow (defined as > 25% of mast cells being spindle-shaped [21]); and myelofibrosis (presence of antireticulin antibody staining on bone marrow biopsy [21]).

Recent studies [20²²] have looked at the presence of elevated serum tryptase and atypical bone marrow mast cells in M-HES, as well as the clinical overlap between M-HES and systemic mastocytosis. Although there can be overlap between HES and mastocytosis, HES patients are differentiated from mastocytosis by the fact that they do not have the somatic *c-kit* mutations that can be seen in mastocytosis [21]. The most common *c-kit* mutation seen in mastocytosis, the 'D816V' mutation, is unresponsive to treatment with imatinib [19,20²²,23].

Lymphocytic variants of hypereosinophilic syndrome

CD4⁺ T cells, especially of the Th2 subtype, are major sources of the eosinophilopoietic and eosinophil-activating cytokine, interleukin (IL)-5, as well as cytokines stimulating IgE production. Individuals with L-HES have an underlying T-cell disorder [14,24,25]. Since 1994, patients have been recognized who have T-cell clones capable of secreting elevated amounts of IL-5 [26–28]. The abnormal T-cell subpopulations often have aberrant surface phenotypes, often being CD3⁺CD4⁺ and less commonly being CD3⁺CD4⁺CD8⁺ [3]. Further investigation of the CD3⁺CD4⁺ aberrant T-cell sub-populations revealed high expression of CD5 and loss of CD7 or CD27 expression on the T-cell populations in many cases [29]. The abnormal subsets also often demonstrate an activated (CD25 or HLA-DR⁺) memory (CD45RO⁺) phenotype [28,29]. Accordingly, L-HES was defined as 'a primitive lymphoid disorder characterized by nonmalignant expansion of a T-cell population able to produce eosinophilopoietic cytokines (generally IL-5)' [3,14], with the T-cell population being identified by flow cytometry or reverse transcriptase (RT)-PCR for altered T-cell receptor usage or both [4]. Elevated IgE, IgM, and IgG can often be seen in L-HES, but these

findings are not specific for L-HES [27–30]. Other common features of L-HES [5] are outlined as follows:

1. could be male or female with equal frequency,
2. FIP1L1-PDGFR α fusion gene mutation negative,
3. often increased serum IgE,
4. may have increased serum IgG, IgM,
5. may have increased serum IL-5,
6. may have increased serum TARC (thymus and activation-regulated chemokine),
7. abnormal or clonal T-cell populations may be detected or both,
8. rarely have cardiac involvement,
9. frequent cutaneous involvement,
10. frequent history of atopy,
11. usually good response to glucocorticoids.

Contemporary diagnosis and treatment of categories of hypereosinophilic syndrome

The following paragraphs highlight the major issues that have been covered in the literature on HES over the past 1–2 years.

Cardiovascular complications of hypereosinophilic syndrome

In eosinophilic disorders, including those secondary to parasitic infections and to cytokine therapies, eosinophil-mediated damage to the endocardium and myocardium may occur. The cardiac manifestations of HES are more likely to occur with M-HES (particularly when FIP1L1-PDGFR α positive) compared with the other HES subtypes [4,20^{**},31^{*}], for reasons that remain unknown [5]. In potential M-HES and other forms of HES, assays of serum troponins are now recognized to provide sensitive, early indications of eosinophil-mediated endomyocardial damage in forms of HES and secondary hypereosinophilia [32^{**}]. Elevated troponins in concert with hypereosinophilia should prompt consideration of therapies for the hypereosinophilia.

Myeloproliferative variants of hypereosinophilic syndrome: diagnosis and treatment

Patients with HES, especially those with clinical and hematologic features compatible with M-HES, should be evaluated with RT-PCR or fluorescence in-situ hybridization (FISH) for the presence of the FIP1L1-PDGFR α mutation. If FIP1L1-PDGFR α mutations are demonstrable or patients present with other features of M-HES, therapy with imatinib is indicated. Most M-HES patients are unresponsive to glucocorticosteroid therapy. Based on the high rate of response of FIP1L1-PDGFR α M-HES to imatinib, this drug is the first-line agent for FIP1L1-PDGFR α M-HES [33,34]. Dosing of imatinib is best based not on levels of eosinophilia or clinical symptoms, but on RT-PCR-based evaluations of suppression of FIP1L1-PDGFR α transcripts [35^{**},36]. There may be reversal of hematological features of M-HES in patients who are responsive to imatinib, including reduction of serum tryptase, molecular remission of FIP1L1-PDGFR α positivity, disappearance of the bone marrow atypical spindle-shaped mast cells, and improvement of myelofibrosis [33,37]. Trials of imatinib therapy are warranted on M-HES patients without the FIP1L1-PDGFR α mutation [33,34]. Newer tyrosine-receptor kinase inhibitors and allogeneic bone marrow transplantation may be considered for those unresponsive to imatinib.

Lymphocytic variants of hypereosinophilic syndrome, complex undefined hypereosinophilic syndrome, and other forms of hypereosinophilic syndrome

To ascertain a diagnosis of a L-HES variant of HES, T-cell immunophenotyping by multicolor flow cytometry or assays of T-cell receptor (TCR) clonality or both should be performed on HES patients. L-HES patients are at risk of developing T-cell lymphomas [3]. For L-HES, complex undefined HES and other forms of HES, the principal therapeutic has been glucocorticosteroids.

For L-HES, though it has been speculated that interferon (IFN) α may have benefit in L-HES by reducing the activity and cytokine production of abnormal T-cell clones [38], IFN α may inhibit the spontaneous apoptosis of CD3⁺CD4⁺ T cells [39], so it is theoretically possible that monotherapy with IFN α could enhance the transformation of L-HES to lymphoma [3,14]. In conjunction with glucocorticosteroids, IFN α may be used as a steroid-sparing agent [40].

For undefined complex subcategories of HES, steroids, perhaps in conjunction with hydroxyurea and IFN α (as steroid-sparing agents) may be used, but specific data are lacking.

Candidate future therapies for nonmyeloproliferative variants of hypereosinophilic syndrome

The most prominently studied anti-cytokine therapy for HES has been with monoclonal antibodies to IL-5. One such antibody, mepolizumab, was recently reported to be both safe and highly effective as a corticosteroid-sparing therapy for non-FIP1L1-PDGFR α HES patients [41^{**},42^{*}].

In theory, other therapies might be able to modulate the abnormal activity of aberrant T-cell populations, such as alemtuzumab (monoclonal antibody to CD52) [43,44], cyclosporine A, and monoclonal antibodies to IL-2R- α , but have not undergone significant study for this purpose [14,43,44].

Conclusion

A contemporary consideration has expanded the range of eosinophilic disorders that are included within the spectrum of HESs. Based on recent advances in molecular and genetic diagnostic techniques and increasing experience with differences in clinical features and prognosis, subtypes have been defined, including M-HES and L-HES. Other HES subtypes, including the likely most common type of 'complex undefined HES', await future insights into their underlying pathophysiology.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 61).

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Table 1

Traditionally described clinical features of hypereosinophilic syndrome

Organ system involvement (frequency)	Specific features that may be seen
Hematologic (100%)	Eosinophilia (by definition) Anemia Thrombocytosis Thrombocytopenia Lymphadenopathy
Cardiovascular (58%)	Endomyocardial damage or necrosis or both Intramural thrombi Endomyocardial fibrosis Congestive heart failure
Cutaneous (56%)	Urticaria Angioedema Pruritic papules or nodules or both
Neurologic (54%)	Generalized CNS symptoms Peripheral neuropathies (variable patterns described) Thromboembolic neurologic phenomena
Pulmonary (49%)	Dry cough Nonspecific infiltrates Pulmonary fibrosis
Spleen (43%)	Splenomegaly Hypersplenism
Liver (30%)	Chronic active hepatitis Budd–Chiari syndrome
Gastrointestinal (23%)	Eosinophilic inflammatory esophagitis Eosinophilic gastroenteritis Eosinophilic colitis
Ocular (23%)	Choroidal abnormalities Nonspecific vision changes

The left column includes the percentage of patients who have involvement of each organ system. Adapted from [1,9–11].