THE HYPEREOSINOPHILIC SYNDROME REVISITED

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Abstract  Clinical and biological features of patients with the idiopathic hyper eosinophilic syndrome (HES) are heterogeneous. Recent evidence suggests at least two distinct underlying hematological disorders involving myeloid and lymphoid cells, respectively. We therefore suggest that the term idiopathic should be abandoned in the classification of HES. This review defines the “myeloproliferative” and “lymphocytic” variants of the HES and addresses the management of each variant, focusing on diagnosis and treatment of the newly identified lymphocytic variant.

INTRODUCTION

Hypereosinophilia is a common biological finding, arising in a number of clinical situations (1). In countries where parasitic diseases are prevalent, infestation by tissue-invasive helminths accounts for most cases of hypereosinophilia. Elsewhere, atopy or allergic drug reactions are the most frequent causes. When thorough evaluation of a patient with chronic hypereosinophilia fails to reveal an underlying disease, diagnosis of the idiopathic hypereosinophilic syndrome (HES) is considered. In this paper, we revisit management of this syndrome based on recent advances that indicate it should no longer be qualified as idiopathic.

CLINICAL DEFINITION OF THE IDIOPATHIC HYPEREOSINOPHILIC SYNDROME

Depending on the sites and severity of organ damage associated with persistent idiopathic hypereosinophilia, various disease entities have been defined, including Löeffler’s syndrome (isolated lung involvement), Löeffler’s endocarditis parietalis fibroplastica with blood eosinophilia (cardiac involvement), disseminated eosinophilic collagen disease, and eosinophilic leukemia. The frequency of overlapping disease presentations led to the concept of hypereosinophilic syndromes, encompassing the wide disease spectrum of organ damage (typically involving
the heart, lungs, and/or liver) resulting from persistent hypereosinophilia, be it idiopathic or related to an underlying disease.

In 1975, Chusid et al. established the empirical diagnostic criteria of the “idiopathic HES” that are still in use today (2):

1. Blood eosinophilia exceeding 1500/µl for more than six consecutive months.
2. Absence of an underlying cause of hypereosinophilia despite extensive diagnostic evaluation.
3. Organ damage or dysfunction as a result of local release of toxic eosinophil contents.

Major tissue targets include the skin, heart, and nervous system (3, 4). Cutaneous manifestations generally consist of either angioedematous and urticarial lesions, or erythematous, pruritic papules and nodules. Cardiac involvement generally evolves in three stages. The early necrotic stage, rarely symptomatic, is followed by a thrombotic stage in which intracavitary thrombi develop along the damaged endocardium. In the final fibrotic stage, endomyocardial fibrosis and damage of atrioventricular valves result in congestive heart failure. Neurological complications involve both the central and peripheral nervous systems. Eosinophilic infiltration of other target regions, including the lungs, liver, digestive system, articulations, and kidneys, may cause a variety of additional symptoms. A hallmark of the HES is its great clinical heterogeneity and highly variable prognosis, ranging from paucisymptomatic disease that requires no treatment and is associated with prolonged survival, to a rapidly fatal disease course due to sudden, severe heart failure or acute leukemia.

PATHOGENESIS OF HYPEREOSINOPHILIA

Accumulation of eosinophils in peripheral blood and tissues can result either from an acquired abnormality of the hematopoietic myeloid stem cell (primary eosinophilia) or from the production of eosinophilopoietic cytokines by non-myeloid cells (secondary eosinophilia) (1). In primary eosinophilia, the disorder may occur late in the process of eosinophilic differentiation, in which case the rare diagnosis of eosinophilic leukemia is appropriate. If the abnormality concerns a less advanced stage of myeloid differentiation, hypereosinophilia accompanies expansion of other members of the myeloid lineage in the setting of a given myeloproliferative disorder, and eosinophils appear to be part of the malignant clone. In secondary hypereosinophilia, the myeloid lineage is normal, and eosinophil accumulation is a cytokine-driven process.

Eosinophils are derived from myeloid progenitors in bone marrow through the action of three hematopoietic cytokines: interleukin (IL)-3, IL-5, and granulocyte-macrophage colony–stimulating factor (GM-CSF) (5). IL-5 is specifically involved in differentiation of eosinophil precursors, whereas IL-3 and GM-CSF
also favor maturation of other myeloid precursors. Mature eosinophils are released into the bloodstream and rapidly migrate to peripheral tissues, namely gut and bronchial mucosa and skin, where they soon undergo apoptosis and are cleared by macrophages, unless survival factors such as IL-3, IL-5, and/or GM-CSF are present (5). Thus, overproduction of one or more of these cytokines is sufficient to induce blood and tissue eosinophilia by stimulating bone marrow generation and inhibiting peripheral destruction.

In human pathology, dysregulated production of one or more of these cytokines either by abnormal cells or by physiological cell populations accounts for hypereosinophilia in various disorders. Hence, malignant cells producing GM-CSF, IL-3, and/or IL-5 are responsible for hypereosinophilia in some patients with non-Hodgkin’s lymphoma and Sezary syndrome (4, 6). In allergic disorders and parasitosis, the role of IL-5 in the induction of hypereosinophilia is now well established (7). Although several cellular sources of IL-5 have been identified (including mastocytes, basophils, and eosinophils), helper (CD4+) T cells that display a “type 2” cytokine profile appear to be primarily involved in these disorders (8). These so-called Th2 cells produce a variety of cytokines in addition to IL-5, including IL-4 and IL-13, which induce IgE synthesis. In clinical practice, Th2-mediated immune responses are thus characterized by the association of hypereosinophilia and high serum IgE levels. Polyclonal hypergammaglobulinemia is also a frequent finding in this setting, as a result of polyclonal B cell activation favored by the Th2 climate.

Whatever its cause, eosinophil accumulation may in itself have pathological consequences as a result of local release of toxic substances, including cationic proteins, enzymes, reactive oxygen species, pro-inflammatory cytokines, and arachidonic acid–derived factors (5).

TWO MAJOR VARIANTS OF THE HYPEREOSINOPHILIC SYNDROME

The striking clinical heterogeneity of patients with the idiopathic HES and the occasional development of malignancy involving either the myeloid or the lymphoid lineage (4) strongly suggest pathogenic diversity. Recent observations indicate that at least two distinct hematological disorders, involving the myeloid and lymphoid lineages respectively, account for hypereosinophilia in patients who meet the diagnostic criteria of the HES.

The Myeloproliferative Variant

Ever since the definition of the idiopathic HES in 1975, a set of clinical and biological features reminiscent of chronic myelogenous leukemia and other myeloproliferative (MP) syndromes has been singled out as a more aggressive disease variant,
the MP variant of the HES (3, 4). Its features include increased serum vitamin B\textsubscript{12}, an abnormal leukocyte alkaline phosphatase score, chromosomal abnormalities, anemia and/or thrombocytopenia, hepatomegaly, splenomegaly, and circulating leukocyte precursors. Prognosis is considered poor in MP variant patients because of the frequent occurrence of severe cardiac complications, resistance to glucocorticoid therapy, and the increased risk of developing myeloid malignancy. Indeed, a proportion of patients with the MP variant present “chronic myelogenous leukemia–like disease” or eventually develop blast crisis, clinically reflected either by acute (eosinophilic or myeloid) leukemia or by granulocytic sarcoma (4, 9).

Existence of a true MP disorder in some HES patients remained speculative until the recent demonstration of eosinophil clonality in two patients, using methods based on X-linked polymorphisms (10). Interestingly, these patients lacked the classical features of MP disease mentioned above, had normal karyotypes, and responded well to glucocorticoids in terms of both eosinophil levels and clinical manifestations. These observations suggest the existence of a low-grade MP disorder characterized by clonal expansion of well-differentiated eosinophils in a subgroup of HES patients, with variable outcome and prognosis. Long-term follow-up of such patients will reveal whether some eventually develop full-blown malignancy while others maintain a benign disease course.

For such patients the HES diagnosis is debatable, and the more appropriate diagnosis of (chronic) eosinophilic leukemia has been recommended for those who show eosinophil clonality, clonal cytogenetic abnormalities within cells of the eosinophil lineage, and/or increased blasts (1, 9). Modern methods such as fluorescent in situ hybridization are precious for detection of cytogenetic abnormalities at the cell level. However, without chromosomal aberrations, demonstration of eosinophil clonality may be difficult, especially in male patients. It can be hoped that further refinements in cytogenetic and molecular genetic analysis will extend the possibilities of identifying HES patients with an underlying MP disorder.

The Lymphocytic Variant

Early studies showed that T cell clones derived from peripheral blood of HES patients displayed eosinophilopoietic activity in the presence of stem cells from healthy subjects. Such findings led authors to suggest that T cells were involved in the pathogenesis of the HES through the release of soluble factor(s) (11). More recently, elaboration of the Th1/Th2 paradigm has rekindled interest in the pathogenic role of T cells in the setting of the HES, since the association of hypereosinophilia with increased IgE levels in some patients (3, 4) suggests the possibility of a Th2-mediated disorder.

In 1994, extensive characterization of circulating T cells isolated from an HES patient with high serum IgE and IgM levels revealed an underlying T cell disorder. It was characterized by clonal expansion of a T cell population able to produce IL-5 and IL-4 and by a unique CD\textsuperscript{4−}CD\textsuperscript{4+} (CD\textsuperscript{2+}TCR\textalpha/\beta) surface phenotype (12). Since then, IL-5–producing T cell subsets have been identified in the blood.
of almost 30 patients with the HES (13–18) (Table 1). The allegedly pathogenic T cells, usually CD3−CD4+ cells, display an aberrant surface phenotype in all reported cases. Whatever their surface phenotype, the aberrant lymphocyte subsets generally display an activated (HLA-DR+ and/or CD25+) memory (CD45RO+) phenotype (16). Clonality of the phenotypically aberrant T cells has been demonstrated, and chromosomal abnormalities, including 16q breakage (14) and partial 6q or 10p deletions (15), have been reported (Table 1). Extensive analysis of the cytokine profile of the aberrant T cells has led to their identification as Th2-type cells, given their simultaneous production of IL-5, IL-4, and IL-13 and their inability to produce interferon (IFN)-γ (Table 1).

CLINICAL PRESENTATION AND DEFINITION Although considerable clinical heterogeneity exists among patients who fulfill the diagnostic criteria of the HES, those in whom aberrant IL-5–producing T cells have been detected exhibit a strikingly homogenous clinical and biological profile. Cutaneous manifestations, including pruritus, eczema, erythroderma, urticaria, and angioedema, are observed in virtually all patients reported in the literature (Table 1). Although the skin is involved in many HES patients regardless of disease variant, the relative rarity of associated organ involvement in patients with an underlying T cell disorder makes cutaneous manifestations a cardinal clinical feature in such patients.

Biologically, in accordance with the type 2 cytokine profile of the aberrant T cells, serum IgE levels are often increased (Table 1) and polyclonal hyper gammaglobulinemia, principally due to increased IgM and/or IgG levels, is observed in some cases. Among 13 patients with a CD3−CD4+ T cell subset and 14 patients with other phenotypic alterations in whom IgE levels were measured, 10 (77%) and 6 (43%) presented serum hyperIgE, respectively. Glucocorticoid therapy may have contributed to underestimation of associated hyperIgE in the latter group (16). The inability of certain IL-5–producing lymphocyte subsets to produce IL-4 or IL-13 may also account for normal IgE levels in some patients, as shown in one case associated with CD3−CD4+ cells (18). However, serum hyperIgE in the setting of the HES is not restricted to patients with a Th2-mediated disorder; eosinophil clonality was formally demonstrated in two HES patients with increased IgE levels (1, 10).

Given the homogenous clinical presentation of HES patients in whom IL-5–producing T cells have been identified, it appears reasonable to define a pathogenically distinct disease. On the basis of currently available data, the lymphocytic variant of the HES is defined as a primitive lymphoid disorder characterized by nonmalignant expansion of an IL-5–producing T cell population. Approximately one quarter of HES patients have the lymphocytic variant, based on the frequency of phenotypically aberrant circulating T cell subsets detected in a large retrospective series of 60 patients with chronic idiopathic hypereosinophilia (16). However, this proportion may have been overestimated because of the predominant recruitment of patients from dermatology clinics, given the frequency of skin involvement in the lymphocytic variant.
**TABLE 1** The lymphocytic variant of the HES: major clinical and biological features

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Skin</th>
<th>Other</th>
<th>Clinical manifestations</th>
<th>Routine biology</th>
<th>T cell abnormalities</th>
<th>Cytogenetic changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>1</td>
<td>−</td>
<td>Heart</td>
<td></td>
<td>6270</td>
<td>CD3+4−8−</td>
<td>+</td>
</tr>
<tr>
<td>16</td>
<td>16</td>
<td>14/16</td>
<td>−</td>
<td>Heart</td>
<td>869–5805</td>
<td>Variable</td>
<td>8/16</td>
</tr>
<tr>
<td>17</td>
<td>1</td>
<td>+</td>
<td>−</td>
<td></td>
<td>4810</td>
<td>CD3+4−</td>
<td>+</td>
</tr>
<tr>
<td>15</td>
<td>4</td>
<td>4/4</td>
<td>−</td>
<td>Heart</td>
<td>2970–9100</td>
<td>CD3−4+</td>
<td>4/4</td>
</tr>
<tr>
<td>13</td>
<td>3</td>
<td>3/3</td>
<td>−</td>
<td>Heart</td>
<td>4800–7000</td>
<td>CD3−4+</td>
<td>3/3</td>
</tr>
<tr>
<td>U†</td>
<td>3</td>
<td>2/3</td>
<td>−</td>
<td></td>
<td>1069–9600</td>
<td>CD3−4+</td>
<td>2/2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Routine biology</th>
<th>T cell abnormalities</th>
<th>Cytogenetic changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eosino/µl</td>
<td>HyperIgE</td>
<td>Phenotype</td>
</tr>
</tbody>
</table>

- **Clinical manifestations**: Skin, Other
- **Routine biology**: Eosino/µl, HyperIgE
- **T cell abnormalities**: Phenotype, Clonality, IL-5
- **Cytogenetic changes**: nd

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*GL, gastrointestinal; nd, not done.

*Includes CD3−*or low* CD4+ cells (*n* = 2), CD3+ CD4+ CD8− cells (*n* = 3), and decreased or increased expression of CD2, CD5, CD6, and CD7 on CD4+ T cells.

*Clonality was likely in two additional patients whose aberrant lymphocyte population expressed a given TCRVβ chain.

*One patient of this series was previously reported in Reference 15 and is therefore not included in this table.

*Remaining patients in series not tested.

†F. Roufosse, L. Schandené, A. de Lavareille, E. Cogan, M. Goldman, unpublished observations; patient with mild eosinophilia (1069/µl) and normal serum IgE was under glucocorticoid treatment (20 mg methylprednisolone).
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PROGNOSIS  Distinguishing HES patients with the lymphocytic variant has important prognostic implications. Indeed, as Table 2 shows, identification of phenotypically aberrant T cells in peripheral blood of patients with the HES may be followed by protracted development of peripheral T cell lymphoma in some cases (13, 15, 16, 19). Importantly, the lymphomatous cells have been shown to conserve the abnormal phenotype in a few patients, indicating that the initially observed aberrant T cells may be premalignant precursors. These observations are further supported by cases of T cell lymphoma in HES patients who presented indirect evidence for a primitive lymphoid disorder (although the possibility of the lymphocytic variant was not formally investigated) (20–22), and by the occasional discovery of aberrant circulating T cell clones simultaneous with the diagnosis of peripheral T cell lymphoma (23, 24).

It could be argued that such patients present highly indolent T cell lymphoma from disease onset, and are incorrectly diagnosed with the HES. However, repeated studies of CD3^−CD4^+ cells over several years in one patient who eventually developed T cell lymphoma provide some evidence that the aberrant cells do indeed undergo progressive transformation (K. Willard-Gallo, C. Sibille, F. Roufosse, unpublished data). Over time, these cells accumulated chromosomal abnormalities and acquired surface expression of previously unexpressed activation markers, including CD25 and CD69. Morphological studies showed progression from small lymphocytes, indistinguishable from normal T cells, toward larger blast-like cells. Clinically, these events coincided with increased CD3^−CD4^+ lymphocytosis and the enlargement of lymph nodes harboring CD3^−CD4^+ lymphomatous cells (15) with important metabolic activity as assessed by fluoro-deoxyglucose positron-emission tomography.

The term “monoclonal lymphoproliferative disease of undetermined significance” has been proposed for clonal B cell disorders that are considered benign but are clearly associated with an increased risk for lymphoma (25). With the distinction of the lymphocytic variant of the HES, this concept can be extended to T cell clones. In both cases, well-differentiated and highly indolent “benign” lymphoproliferative disorders will progress to true malignancy several years later only in some patients. Such situations present clinicians with two challenges: identifying factors that predict malignancy and distinguishing aberrant clonal cells from truly malignant cells during the course of disease.

Although predictive factors for development of T cell lymphoma among patients with the lymphocytic variant remain to be determined, the literature suggests that loss of surface TCR/CD3 expression by CD4^+ cells is associated with malignant transformation. Indeed, CD3^−CD4^+ cells have been detected in patients with ataxia-telangiectasia, a congenital disease associated with an increased risk for T cell lymphoma (26), and in patients with angioimmunoblastic lymphadenopathy, a premalignant T cell disorder. In the latter and in the lymphocytic variant of the HES (Table 2), the CD3^−CD4^+ phenotype may remain a characteristic of the malignant cells in patients who develop lymphoma (15, 16, 27). It can be speculated that CD3^−CD4^+ cells are exposed to alternative TCR-independent activation...
### TABLE 2  Development of T cell lymphoma in patients with the HES

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex/Age</th>
<th>Delay</th>
<th>Skin</th>
<th>Others</th>
<th>Phenotype</th>
<th>Localization</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>F/36</td>
<td>5 y</td>
<td>+</td>
<td>digital vasculitis, enlarged LN</td>
<td>Leu1α⁺</td>
<td>marrow</td>
<td>immunoblastic</td>
</tr>
<tr>
<td>19</td>
<td>M/27</td>
<td>7 y</td>
<td>+</td>
<td>lung, digital vasculitis</td>
<td>CD3⁻CD4⁺</td>
<td>skin, LN</td>
<td>mixed small/large cell</td>
</tr>
<tr>
<td>23</td>
<td>M/13</td>
<td>5 y</td>
<td>+</td>
<td></td>
<td>CD3⁺CD4⁺KT⁺</td>
<td>skin, LN</td>
<td>pleomorphic, large cell</td>
</tr>
<tr>
<td>20</td>
<td>M/30</td>
<td>5 y</td>
<td>+</td>
<td>enlarged LN</td>
<td>CD3⁺CD4⁺</td>
<td>skin</td>
<td>pleomorphic, small cell</td>
</tr>
<tr>
<td>21</td>
<td>F/1 mo</td>
<td>3 y</td>
<td>+</td>
<td>lung, enlarged LN, liver, spleen</td>
<td>⟨⟨pan–T⟩⟩</td>
<td>LN, liver, lung, kidney</td>
<td>immunoblastic</td>
</tr>
<tr>
<td>15</td>
<td>M/30</td>
<td>4 y</td>
<td>+</td>
<td>lung, digital vasculitis</td>
<td>CD30/Ki–1⁺</td>
<td>LN, liver</td>
<td>anaplastic null–cell</td>
</tr>
<tr>
<td>16</td>
<td>M/45</td>
<td>20 y</td>
<td>–</td>
<td>intestine</td>
<td>CD3⁺⁺⁺⁴⁻⁻⁻⁺⁻</td>
<td>not specified</td>
<td>not specified</td>
</tr>
<tr>
<td>16</td>
<td>F/69</td>
<td>7 y</td>
<td>+</td>
<td>–</td>
<td>CD3⁺⁺⁻⁴⁻⁻⁻⁻⁻⁻</td>
<td>not specified</td>
<td>not specified</td>
</tr>
<tr>
<td>16</td>
<td>M/52</td>
<td>3 y</td>
<td>+</td>
<td>–</td>
<td>CD3⁺⁺⁻⁴⁻⁻⁻⁻⁻⁻</td>
<td>LN</td>
<td>not specified</td>
</tr>
<tr>
<td>15</td>
<td>F/16</td>
<td>5–6 y</td>
<td>+</td>
<td>tenosynovitis, parotid nodules</td>
<td>CD3⁺⁻⁻⁻⁻⁻⁻</td>
<td>LN</td>
<td>pleomorphic, small/med cell</td>
</tr>
<tr>
<td>22</td>
<td>M/36</td>
<td>14 y</td>
<td>+</td>
<td>enlarged LN, fever</td>
<td>Nd</td>
<td>skin, LN</td>
<td>CTCL</td>
</tr>
<tr>
<td>22</td>
<td>M/74</td>
<td>16 y</td>
<td>+</td>
<td>enlarged LN, fever</td>
<td>Nd</td>
<td>skin, LN</td>
<td>CTCL</td>
</tr>
</tbody>
</table>

**Footnotes:**

- **a** Age at first symptoms or discovery of hypereosinophilia.
- **b** Delay between diagnosis of the HES and development of lymphoma.
- **c** LN, lymph nodes; CTCL, cutaneous T cell lymphoma.
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pathways (28) that predispose them to malignant transformation. The development of T cell lymphoma in one patient with CD3⁺CD4⁻CD8⁻ cells indicates that other aberrant phenotypes may have premalignant potential, possibly through deficient Fas-mediated apoptosis (16).

The cytogenetic changes in aberrant T cells from HES patients may constitute an additional prognostic marker. Indeed, partial 6q deletions have been observed in CD3⁻CD4⁺ cells from two patients with the lymphocytic variant, preceding T cell lymphoma in one case (15). In patients with malignant T cell disorders, such as peripheral T cell lymphoma and adult T cell leukemia/lymphoma, 6q deletions are thought to be associated with poor prognosis due to loss of tumor suppressor genes (29, 30). In one patient with the lymphocytic variant, we observed that CD3⁻CD4⁺ cells, which displayed stable chromosomal changes (partial 6q and 10p deletions) for several years, had developed additional cytogenetic abnormalities when full-blown peripheral lymphoma was diagnosed (C. Sibille, K. Willard-Gallo, F. Roufosse, unpublished data). This observation supports the suggestion that accumulation of genomic aberrations may be a reliable sign of malignant progression (25).

The evidence for increased risk of lymphoid malignancy in patients with the recently defined lymphocytic variant of the HES challenges the long-held notion that isolated cutaneous manifestations associated with serum hyperIgE and/or polyclonal hypergammaglobulinemia, in the setting of the HES, are markers of good prognosis (3, 4). Moreover, identification of clonal CD3⁻CD4⁺ cells in the blood of two patients whose clinical presentations were compatible with Gleich's disease (episodic angioedema with eosinophilia) (15, 17) indicates that this reputedly benign idiopathic hypereosinophilic disorder is not pathogenically distinct from the lymphocytic variant of the HES and may also be associated with an increased risk of malignant transformation.

MANAGEMENT OF CHRONIC HYPEREOSINOPHILIA

Classical therapeutic algorithms for the HES have been designed on the basis of similarities with MP disorders and are therefore not adapted to patients with a primary lymphocytic disorder. Before considering therapies for a patient who fulfills the diagnostic criteria of the HES, it is critical to identify which clinical variant the patient has.

Diagnosis of HES Variants

Predominant cutaneous manifestations, serum hyperIgE, and/or polyclonal hypergammaglobulinemia should arouse suspicion of the lymphocytic variant of the HES. However, proper identification of patients with this variant requires thorough analysis of circulating T cells. Current literature indicates that lymphocyte phenotyping in search of a phenotypically aberrant T cell subset, and analysis of TCR
gene rearrangement patterns in search of T cell clonality, are generally sufficient to
detect patients with an underlying T cell disorder in the setting of routine clinical inves-
tigations, and should therefore systematically be performed on peripheral blood
and bone marrow samples of all patients who meet HES diagnostic criteria. How-
ever, both methods have limitations, and results should be interpreted with caution.

Although lymphocyte phenotyping may indeed reveal a grossly aberrant
CD3^-CD4^+ or CD3^+CD4^-CD8^- population, phenotypic abnormalities of IL-5-
producing T cells are occasionally very discrete, consisting of slight alterations of
staining intensity for surface antigens that are not always included in routine phe-
notyping panels, such as CD5, CD6, CD7, and CD27. Furthermore, aberrant
T cells may represent only a minor proportion of circulating lymphocytes. Identifi-
cation of abnormal subsets in such cases depends on the ability to test a large panel
of surface antigens and to recognize slight modifications in their distribution.

When flow cytometry fails to reveal a phenotypically aberrant lymphocyte sub-
set, a search for T cell clonality using both Southern blot and PCR amplification is
indicated, since detection of a clonal T cell population may suggest the presence
of a pathogenic IL-5--producing T cell subset. On the other hand, the search for
T cell clonality by these methods may be negative in patients with a demonstrated
aberrant lymphocyte subset, as illustrated by one series showing clonality in only
50% (8/16) of cases. Negative findings may reflect true absence of clonality,
or clonality may go undetected because of clonal deletion of TCR chain genes,
choice of primers in PCRs, or lack of sensitivity when aberrant cells represent a
small proportion of total lymphocytes.

Although many patients with the lymphocytic variant can be identified using
this strategy, recent observations indicate that, even in experienced hands, phe-
notyping may be normal and the search for clonality may be negative in some
patients who have highly suggestive clinical presentations and whose peripheral
blood mononuclear cells (PBMC) produce increased levels of IL-5 in vitro. The
gold standard for identification of patients with the lymphocytic variant is
therefore demonstration of increased IL-5 production by T cells. This can be done
either by measuring IL-5 concentrations by enzyme-linked immunosorbant assay
in supernatants of cultured PBMC or aberrant lymphocyte subsets, with or without
T cell stimulating agents, or by determining the proportion of IL-5-positive cells
within a given lymphocyte subset by flow cytometry. Both methods require
cell purification and culture currently available from specialty labs.

Diagnostic markers for the lymphocytic variant that would be both reliable and
easily detectable remain to be identified. Serum levels of IL-5 and soluble CD25
(sCD25), both thought to reflect the presence of activated IL-5--producing T cells
in vivo, appear to lack sensitivity and also theoretically lack specificity in distin-
guishing patients with the lymphocytic variant, since activated eosinophils
themselves are now recognized as a potential source of both molecules.

Recent studies demonstrating increased serum levels of thymus and activation-
regulated chemokine (TARC) in patients with atopic dermatitis, an established
Th2-mediated disorder, have prompted us to measure these chemokines in serum
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from HES patients. Increased serum TARC levels (consistently 10-to 100-fold higher than in healthy control subjects) appear to be highly discriminative for the lymphocytic variant (31, 33), since patients with no evidence of an underlying lymphoid disorder have strictly normal levels. These preliminary observations suggest that serum TARC levels in patients who fulfill the diagnostic criteria of the HES may represent a reliable diagnostic marker for the lymphocytic variant, provided that patients are free of glucocorticoid therapy at time of sampling (32).

Cytogenetic analysis of T cells will probably prove to be an important step in determining the prognosis of patients with the lymphocytic variant. Although abnormal karyotypes are still considered a hallmark of the MP variant of the HES, it is now clear that T cells from some patients with the lymphocytic variant also harbor various chromosomal abnormalities, some of which may be indicators of an increased risk for malignant lymphoma. Demonstration of these abnormalities may be delicate, since CD3−CD4+ (18) and CD3+CD4−CD8− cells (14) respond poorly to phytohemagglutinin (PHA) stimulation in terms of mitosis compared with conventional T cells. In one patient with the lymphocytic variant, chromosome 16 abnormalities were detected in a large proportion of CD3+CD4−CD8− cells only after addition of IL-2 to PHA cultures (14). Hence, as previously recommended for Sezary cells (30), growth-promoting cytokines such as IL-2 and IL-7 should be added to cultures prior to cytogenetic analysis of aberrant T cells associated with the HES.

In the years to come, it is likely that parallel revelations concerning pathogenesis of the MP variant of the HES will lead to development of diagnostic tools for this variant, providing clinicians with complementary methods for exploring the entire disease spectrum of the HES.

Therapeutic Approaches

Therapeutic strategies to control eosinophil levels in HES patients have changed little since they were defined in 1975 (3, 4). Glucocorticoids and hydroxyurea are the classical cornerstones for management of hypereosinophilia, and IFN-α has been suggested more recently on the basis of several encouraging studies reported in the early 1990s. The rationale for the use of hydroxyurea and IFN-α was based on similarities between the HES and chronic myelogenous leukemia in some patients and thus still applies to patients with the MP variant of the HES. Along the same line, a recent report suggests that imatinib mesilate (formerly STI-571) might be of great benefit in patients with the MP variant (33a). However, therapeutic measures should be adapted for the lymphocytic variant of the HES. Therapeutic aims should include abrogating production of eosinophilopoietic cytokines by the aberrant T cells and controlling their expansion in hopes of preventing malignant transformation. Below, we discuss the ability of current strategies to achieve these aims, and we propose future strategies based on recent studies concerning the activation pathways that operate in CD3−CD4+ clones isolated from HES patients (28).
Glucocorticoids could theoretically meet both therapeutic aims, since they inhibit production of type 2 cytokines by CD4+ T cells and interfere with clonal IL-2–dependent expansion of T cells by reducing IL-2 production and CD25 expression in vitro (34). Although methylprednisolone (mPDN) displays a potent pro-apoptotic effect on CD3−CD4+ cells in vitro (L. Schandené, unpublished data), its effects on survival of the aberrant T cell subset in vivo appear less clear-cut. Indeed, although mPDN does not affect the proportion of CD3−CD4+ cells in most cases, a significant decline of the clonal CD3−CD4+ subset was reported in two cases (15, 18), and cytogenetic remission was observed in one patient with partial 6q and 10p deletions (15). Despite persistence of CD3−CD4+ cells in most patients, clinical manifestations are generally well controlled by glucocorticoids. This may be related both to the direct inhibitory effects of glucocorticoids on eosinophils themselves (4) and to interference with cytokine-chemokine amplification loops between pathogenic T cells and resident cells in affected tissues. Glucocorticoid administration to patients with the lymphocytic variant is rapidly followed by normalization of serum TARC levels in most cases, possibly explaining one patient’s complete regression of enlarged lymph nodes infiltrated by lymphomatous cells within hours after a single dose of mPDN (F. Roufosse, unpublished data).

Hydroxyurea, a chemotherapeutic agent used in the management of indolent MP disorders, has been proposed as second-line therapy for HES patients refractory to glucocorticoids (4). In the absence of data indicating that hydroxyurea could be useful in other lymphoproliferative disorders, this molecule is not recommended in the management of the lymphocytic variant of the HES. Its effects on IL-5 production and expansion of pathogenic T cells in this setting remain to be assessed in vitro.

IFN-α has induced clinical, biological, and even cytogenetic remission in some patients with the HES, whose case histories are generally highly suggestive of the MP variant (4, 35). However, on theoretical grounds, IFN-α may also have a place in the management of the lymphocytic variant, since it antagonizes Th2 responses, both in vitro and in vivo. In accordance with these studies, IFN-α decreases in vitro production of IL-5 by CD3−CD4+ cells isolated from HES patients in a dose-dependent manner and inhibits their proliferation (36). In vivo, administration of IFN-α to two patients in our series was rapidly followed by clinical improvement and regression of hypereosinophilia. However, these encouraging results have recently been challenged by the observation that IFN-α prolongs survival of clonal CD3−CD4+ cells in vitro by inhibiting spontaneous apoptosis (37) and may therefore provide these cells with a selective advantage. Given the malignant potential of aberrant T cells associated with the lymphocytic variant of the HES, monotherapy with IFN-α should be avoided in this setting.

The data obtained in vitro with IFN-α and clonal CD3−CD4+ cells isolated from HES patients illustrate that effects of candidate therapeutic molecules on IL-5 production by pathogenic T cells and on the growth of these T cells should not be dissociated. Recent studies investigating activation and survival requirements of CD3−CD4+ cells suggest that several immunomodulatory molecules, including cyclosporin A, anti-interleukin 2 receptorα mAb, and CTLA-4-Ig, may achieve therapeutic response in patients with this particular lymphocyte subset. Indeed,
IL-2/IL-2 receptor interactions were shown to be critical not only for survival and proliferation of these cells but also for their production of Th2 cytokines, and costimulatory signaling through CD28 was a prerequisite to initiation of their autocrine IL-2-dependent activation (28).

Another potential therapeutic approach for patients with the lymphocytic variant is extracorporeal photopheresis. Its suppressive effects on the pathogenic T cell clones that mediate diseases such as cutaneous T cell lymphoma, atopic dermatitis, and graft-versus-host disease are the result of several distinct mechanisms, including induction of T cell apoptosis and modulation of cytokine profiles in favor of type 1 responses (38). Since pathogenic T cell clones responsible for the lymphocytic variant are largely sequestered in the intravascular compartment, they could be an ideal target for extracorporeal irradiation.

Once full-blown peripheral T cell lymphoma has developed in patients who initially fulfilled the diagnostic criteria of the HES, classical chemotherapeutic regimens directed against lymphoid malignancy are generally administered (19, 23). In our experience (limited to one patient), chemotherapy associating cyclophosphamide, doxorubicin, vincristine, prednisone, teniposide, and bleomycin (CHVmP-BV) failed to eradicate the CD3\(^-\)CD4\(^+\) T cell clone (F. Roufosse, unpublished data). Interestingly, although the aberrant T cells reappeared as soon as she emerged from aplasia after each cycle of chemotherapy, we observed partial cytogenetic remission; most chromosomal abnormalities disappeared, leaving only the initial 6q deletions. This may reflect the existence of several subclones within the CD3\(^-\)CD4\(^+\) population, one of which accumulates genomic aberrations and ultimately becomes malignant. Although this subclone may respond to chemotherapy, its premalignant precursors appear to be more resistant because of their indolent growth characteristics.

Purine nucleoside analogues such as fludarabine and 2-chlorodeoxyadenosine have shown promising clinical activity in several indolent lymphoid malignancies (39) and are therefore theoretically interesting in this context. Indeed, these molecules can induce apoptosis of nondividing lymphocytes, in addition to their cytotoxic effects on proliferating cells. Their potent and prolonged suppression of CD4\(^+\) T cells could be advantageous in patients with aberrant IL-5--producing CD4\(^+\) T cells.

Finally, complete eradication of aberrant clones associated with the lymphocytic variant could be obtained by intensification of chemotherapy followed by allogeneic stem cell transplantation, as recently observed in one patient in our series who developed T cell lymphoma resistant to standard chemotherapy (F. Roufosse, D. Bron, M. Goldman, E. Cogan, unpublished data).

CONCLUDING REMARKS

The so-called myeloproliferative and lymphocytic variants of the HES are each characterized by specific clinical and biological presentations and are associated with increased risk for development of specific hematological malignancies. Most
efforts have focused on characterizing the T cells implicated in the lymphocytic variant of the HES. This work has led to important prognostic and therapeutic considerations. The observation of nonrandom cytogenetic abnormalities within these cells, and the occurrence of T cell lymphoma in some patients with the lymphocytic variant, challenge the long-held notion that isolated cutaneous involvement and serum hyperIgE are markers of good prognosis for HES patients. Future progress in unveiling variants of the syndrome is likely to consign to history the term “idiopathic” hypereosinophilic syndrome, replacing it with an array of well-defined hematological disorders.

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LITERATURE CITED
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