Editorials, Comments & Views

The idiopathic hypereosinophilic syndrome and eosinophilic leukemias

The idiopathic hypereosinophilic syndrome (idiopathic HES) was first defined by Chusid *et al.* in 1975 as a condition in which there was unexplained eosinophilia (eosinophil count greater than 1.5×10^9/L) persisting for at least 6 months and leading to tissue damage.[1] The requirement for the eosinophilia to persist and remain unexplained for six months served to exclude examples of reactive eosinophilia in which an explanation emerged during this time. The requirement for tissue damage, such as cardiac damage, would appear to be less important since there is likely to be a phase of this disease that precedes tissue damage. Such patients can be regarded as having chronic idiopathic eosinophilia (CIE), with the recognition that they may well have the same spectrum of underlying disorders as those with idiopathic HES. Patients with eosinophilic leukemia have, by definition, a recognized cause of eosinophilia and therefore cannot be regarded as having an *idiopathic* syndrome, even if they meet the other criteria that Chusid and colleagues used to define idiopathic HES. Disease features that might lead to a patient being recognized as having eosinophilic leukemia include an increase of blast cells, *myeloproliferative* features (such as hepatomegaly, splenomegaly and a high serum vitamin B12 concentration) and evidence of clonal hematopoiesis (such as a clonal cytogenetic abnormality or very skewed expression of X chromosome genes).[2,3] In addition to patients with eosinophilic leukemia who can be distinguished from those with idiopathic HES at presentation there are others in whom a diagnosis of chronic eosinophilic leukemia becomes possible in retrospect when acute transformation (either acute myeloid leukemia or a granulocytic sarcoma) provides indirect evidence that the condition was likely to have been a clonal, neoplastic, myeloproliferative disorder from the beginning. In others with an initially normal karyotype a clonal cytogenetic abnormality subsequently appears, again suggesting a second event occurring in a neoplastic clone.[4] Acute transformation may occur many years after presentation with eosinophilia; an interval as long as 24 years has been observed.[5] Some patients with idiopathic HES survive only a short time, dying as a result of cardiac or other damage resulting from the release of eosinophil granule contents; it has always appeared likely that this group includes at least some patients who did actually have eosinophilic leukemia but in whom death occurred before a defining transformation event permitted the diagnosis to be made.

For several decades the true nature of many examples of idiopathic HES remained obscure although the striking male dominance suggested that one or more entities were there to be discovered. Recent research has revealed at least two explanations of such cases of chronic eosinophilia: (i) reactive eosinophilia as a response to cytokines secreted by aberrant T cells; (ii) chronic eosinophilic leukemia with clonal molecular genetic abnormalities but generally without cytogenetic abnormalities. With the application of appropriate diagnostic techniques, the number of patients in whom the eosinophilia remains idiopathic has been reduced considerably.

Eosinophilia as a response to cytokines secreted by aberrant T cells

Lymphoma, either Hodgkin's disease or non-Hodgkin's lymphoma, is one of the well recognized causes of reactive cytokine-driven eosinophilia. Acute lymphoblastic leukemia is a less frequent cause of reactive eosinophilia. In 1999 Simon and colleagues demonstrated that there are other patients without an overt lymphoproliferative disorder in whom hypereosinophilia results from the presence of immunophenotypically aberrant, often demonstrably clonal, interleukin (IL)-5-secreting T cells.[6] They investigated 60 patients and found 16 with aberrant T cells of whom 8 had clonal T-cell receptor (TCR) gene rearrangement. One of these 8 patients was the patient with lymphocytosis and another three patients subsequently developed overt T-cell lymphoma with the lymphoma cells having the same immunophenotype as the population initially found in the peripheral blood. Other patients with phenotypically aberrant T cells without detectable rearrangement of TCRβ or TCRγ may also have had clonal T cells since, in one such patient, clonality was demonstrable 5 years after an initially negative result. It should be noted that although these patients were described as having *idiopathic* hypereosinophilia, one patient had a lymphocyte count of 8.8×10^9/L. In addition, the patients were recruited mainly from dermatology clinics and many had pruritic erythroderma, papules, urticarial plaques or poikiloderma. In 3 of 14 patients, skin biopsies showed *some histologic features of cutaneous T-cell lymphoma* although clonal TCR rearrangement was not demonstrated in any of the six skin biopsies studied. It could be postulated that this was a selected group of hypereosinophilic patients and that the incidence of clonal T-cell disorders would be lower in unselected patients. Nevertheless, an important explanation of some previously idiopathic cases had been found. A smaller

study, published as a response to the paper by Simon and colleagues, investigated nine patients meeting the criteria for idiopathic HES who presented to internal medicine clinics.[7] Of these nine patients, three were found to have immunophenotypically aberrant T cells; all three had disease manifestations *almost exclusively restricted to the skin*. The phenotypically abnormal populations reported in HES by Simon and colleagues are summarized in Table 1.[6] Demonstrated abnormalities included absent, reduced or increased expression of a range of antigens and expression of activation markers. These patients were also studied with a repertoire of eight monoclonal antibodies to variable β domains (Vβ) of the TCR; in three patients this gave further evidence of clonality.

In this issue of Haematologica Bassan *et al.*[8] report a further group of patients, including four with 'idiopathic HES' and five with CIE, who have been studied with a wider repertoire (n=24) of monoclonal antibodies to Vβ domains. The assignment of one patient to the 'idiopathic HES' category could be questioned since the lymphocyte count was 6.3×10^9/L; this patient had an aberrant clone detected by standard immunophenotyping and by Vβ analysis. Of the other 8 patients, three with *idiopathic HES* and five with CIE, one had aberrant T cells on standard analysis and evidence of a clone on Vβ analysis, one had aberrant CD3-negative lymphocytes without evidence of a T-cell clone (possibly aberrant natural killer cells) and one had evidence of a T-cell clone on Vβ analysis but otherwise no immunophenotypic aberration. As expected, two patients with a myelodysplastic syndrome with eosinophilia and a clonal cytogenetic abnormality did not have any evidence of a T-cell clone. Questions are raised by the final patient with *chronic eosinophilic leukemia* of 10 years' duration and acute myeloid leukemia; this patient had both a lymphocytosis at diagnosis (lymphocyte count 6.3×10^9/L) and evidence of a T-cell clone on Vβ analysis although, by the time of study, the lymphocyte count was normal and no other immunophenotypic aberration was detected. It might be speculated that this patient had a neoplastic condition arising in a pluripotent lymphoid-myeloid stem cell. An expanded panel of monoclonal antibodies for Vβ analysis appears to be a promising tool for the detection of clonal T cells in otherwise idiopathic HES.

Mepolizumab, a humanized monoclonal antibody to IL5 is of potential benefit in patients with hypereosinophilia with predominantly skin involvement.[9]

Table 1. Phenotypic abnormalities in T lymphocytes in 16 patients with hypereosinophilia.[6]

Number of clones	*CD3, CD4, CD8*	*Phenotypic abnormalities present in some clones*
9*	$CD3^+CD4^+CD8^-$	Reduced expression of CD2, CD3, CD4, CD5 or CD6; absent expression of CD2, CD7 or CD95; expression of CD25‡ or HLA-DR‡
3	$CD3^+CD4^-CD8^+$	Reduced expression of CD2, CD3, CD5, CD6 or CD7; absent expression of CD95; increased expression of CD6 or CD8
3*	$CD3^+CD4^-CD8^-$	Absent expression of CD5 or CD95; expression of CD25 or HLA-DR
2	$CD3^-CD4^+CD8^-$	Reduced expression of CD4; increased expression of CD5; expression of CD25 or HLA-DR

**One patient had two abnormal clones; ‡Activation markers,*

Eosinophilic leukemia

It is generally accepted that a diagnosis of eosinophilic leukemia can be made when a clonal cytogenetic abnormality is demonstrated in myeloid cells in a patient with persisting, otherwise unexplained eosinophilia. Ideally, the abnormality should be demonstrated to be present in cells of eosinophil lineage. However, although clonal myeloid disorders with reactive polyclonal eosinophilia have been described, this is not common so that, in practice, efforts to demonstrate that the eosinophils belong to the abnormal clone are not often made. If a recurrent cytogenetic abnormality known to be associated with clonal eosinophils is detected then it is certainly reasonable to decide that further investigation is not needed.

There are several rare but well recognized cytogenetic/molecular genetic entities that can present as eosinophilic leukemia, although some patients with identical molecular abnormalities may be better characterized as having chronic myelomonocytic leukemia with eosinophilia or atypical chronic myeloid leukemia with eosinophilia. These entities are summarized in Table 2 and further details are given in references.[10–12] These clusters of conditions differ in their clinical and hematologic characteristics. The hematologic neoplasms associated with t(5;12)(q33;p13) and variants, these having *PDGFRB* rearrangement, are specifically myeloid disorders. This is also true of other neoplasms associated with rearrangement of the *ETV6 (TEL)* gene. Neither of these groups have a high rate of transformation to acute leukemia. The 8p11 syndrome with *FGFR1* rearrangement is, however, a neoplasm resulting from a mutation in a pluripotent lymphoid-myeloid stem cell with a high rate of acute transformation.

Table 2. Cytogenetic/molecular genetic entities that can present hematologically as chronic eosinophilic leukemia (more details, including original references, can be found in references #10-12).

Group	*Cytogenetic abnormality*	*Molecular abnormality*
PDGFRB rearranged	t(5;12)(q33;p13)	*ETV6-PDGFRB**
	t(1;5)(q23;q33)	*PDE4DIP-PDGFRB**
	t(5;7)(q33;q11.2)†	*HIP1-PDGFRB*
	t(5;10)(q33;q21)‡	*H4/D10S170-PDGFRB*
	t(5;17)(q33;p13)†	*RAB5-PDGFRB**
ETV6 rearranged	t(5;12)(q33;p13) (as above)	*ETV6-PDGFRB* (as above)
	t(9;12)(q22;p12)†	*ETV6-SYK*
	t(9;15;12)(p21;q15;p13)†	*ETV6-MDS/EVI1*
	t(9;15;12)(p24;q15;p13)†	*ETV6-JAK2*
	t(12;14)(p12;q11-13) or cryptic or uncharacterized chromosomal rearrangement	*ETV6-ABL*
FGFR1 rearranged,	t(8;13)(p12;q12)	*ZNF198-FGFR1*
t(8;13 and variants -	t(6;8)(q27;p12)	*FOP-FGFR1*
the 8p11 syndrome	t(8;9)(p12;q33)	*CEP110-FGFR1*
	t(8;17)(p11;q25)	*TIAF1-FGFR1*†
	t(8;19)(p12;q13.3)	*HERVK-FGFR1*†
	t(8;22)(p11;q11)	*BCR-FGFR1*
	ins(12;8)(p11;?p11p22)	*GEMS-FGFR1*†
PDGFRA rearranged;	Usually normal	*FIP1L1-PDGFRA**
cryptic deletion at 4q12		*Rhe-PDGFRA*

**imatinib responsiveness has been demonstrated; †single cases; ‡two cases.*

Patients with the 8p11 syndrome can present with chronic eosinophilic leukemia, acute lymphoblastic leukemia (usually of T lineage but sometimes of B lineage) or acute myeloid leukemia. In those presenting with chronic eosinophilic leukemia, the disease often transforms into acute lymphoblastic or acute myeloid leukemia within a short time. A case of this aggressive condition is described by Invernizzi *et al.*[13] in this issue.

Identification of these rare entities is important because of the therapeutic implications. Patients with rearrangement of the *PDGFRB* gene have been found to be responsive to imatinib and use of this drug is clearly indicated.[14,15] Imatinib is known to inhibit PDGFRB and its clinical efficacy is likely to result from inhibition of the product of the fusion gene, *ETV6-PDGFRB*. Specific therapy has not yet been identified in the 8p11 syndrome, which has such a poor prognosis that, in the absence of such specific therapy, stem cell transplantation should be considered at diagnosis.

The molecular basis of several different subtypes of eosinophilic leukemia was initially established following the detection of recurrent cytogenetic abnormalities. The most recently recognized subtype was also discovered following investigation of a patient with a cytogenetic abnormality, specifically t(1;4)(q44;q12), who was found to have a *FIP1L1-PDGFRA* fusion gene.[15] Subsequently it was discovered that this was a common molecular genetic abnormality in patients who would previously have been categorized as having idiopathic HES but, in the majority of patients, there was no cytogenetic abnormality and the formation of the fusion gene was the result of a cryptic deletion at 4q12.[15] The striking responsiveness of these patients to imatinib provided an explanation of the responsiveness to imatinib reported in a number of patients with idiopathic HES in the preceding year. Imatinib was shown to inhibit tyrosine phosphorylation of FIP1L1-PDGFRA and its downstream target, STAT5.[15] Interestingly, however, responses were also found in several patients in whom the fusion gene was not detected suggesting the possibility of some other molecular genetic event that is activating a tyrosine kinase in other patients with so far unexplained hypereosinophilia. A notable male preponderance was found in patients with *FIP1L1-PDGFRA*, providing an explanation for the male preponderance previously noted in patients categorized as idiopathic HES. In this issue of Haematologica Martinelli and colleagues report on a further patient with *FIP1L1-PDGFRA*-positive HES who had a complete molecular response to imatinib;[16] although the long-term results of imatinib therapy are not yet established, this is a very encouraging result. As for *BCR-ABL*-positive chronic myeloid leukemia, a hematologic response occurred well in advance of a complete molecular response. Although imatinib therapy is a major advance in the treatment of eosinophilic leukemia, it should be noted that there have been three reports of acute cardiac failure in patients with

hypereosinophilia shortly after starting on imatinib; all three responded to corticosteroid therapy.[17,18] It has been suggested that serum cardiac troponin T should be monitored prior to and during the early stages of therapy to predict and detect this adverse effect.[17]

More than half of the patients previously categorized as having idiopathic HES who were studied by Cools and colleagues[15] were found to have chronic eosinophilic leukemia associated with the *FIP1L1-PDGFRA* fusion. Others have found this abnormality in about one fifth of unselected patients (*Professor NCP Cross, personal communication*). The fusion gene can be detected by reverse transcription polymerase chain reaction (RT-PCR) or by fluorescence *in situ* hybridization (FISH), using a probe for the *CHIC2* gene that is deleted as a result of the causative interstitial deletion.[19]

Recently, a fusion gene involving *PDGFRA* was detected in blood cells from two patients with a condition that would otherwise have been interpreted as idiopathic HES.[20] There was an apparent interstitial deletion leading to fusion of a newly recognized gene at 4q12 to *PDGFRA*. The authors named the oncogenic partner of *PDGFRA Rhe* for *rearranged in hypereosinophilia*. While this paper was in press information on the *FIP1L1-PDGFRA* fusion gene was published and it became clear that *Rhe* and *FIP1L1* were the same.*

The relationship of eosinophilic leukemia with a *FIP1L1-PDGFRA* fusion gene to hypereosinophilic syndrome with high serum tryptase and *FIP1L1-PDGFRA* fusion[21,22] and to *systemic mastocytosis* with *FIP1L1-PDGFRA* fusion[19,23] remains to be established. Klion and colleagues considered that their patients differed from patients with typical systemic mastocytosis[20,21] whereas the patients described by Pardanani and colleagues met the WHO criteria for systemic mastocytosis and were considered to have this condition.[18,22] What is clear at this stage is that systemic mastocytosis with the most frequently observed KIT mutation, Asp816Val, is different from *systemic mastocytosis* with *FIP1L1-PDGFRA* fusion; the former condition is refractory to imatinib[23,24] whereas the latter is responsive.[19,22]

Classification of eosinophilic leukemia

The WHO classification of eosinophilic leukemia[24] remains valid since clonality of myeloid cells shown by any means leads to classification as eosinophilic leukemia rather than idiopathic HES. Patients with *FIP1L1-PDGFRA* fusion therefore meet the WHO criteria for chronic eosinophilic leukemia. Consideration should, however, be given to recognizing this and other cytogenetic/molecular genetic entities as specific diseases since, although they are all rare, there are likely to be an increasing number of specific therapeutic modalities applicable to specific entities.

A diagnostic process for hypereosinophilia

Recent advances in this field permit a more logical approach to diagnosis of patients with hypereosinophilia. Assessment should start with a detailed history, including a drug and travel history, physical examination and a blood count and film, followed by any other tests specifically indicated as a result of the clinical assessment (e.g. tests for parasites). If the eosinophilia remains unexplained after these initial steps, further investigation is indicated. Skin abnormalities, lymphocytosis or cytologically abnormal lymphocytes are an indication for immunophenotyping of peripheral blood lymphocytes and TCR gene rearrangement analysis.

The presence of monocytosis, basophilia, immature granulocytes in the peripheral blood or hepatosplenomegaly is an indication for a bone marrow aspirate and trephine biopsy, cytogenetic analysis and molecular analysis for *FIP1L1-PDGFRA*. Whether immunophenotyping or molecular analysis for *FIP1L1-PDGFRA* is performed first in patients in whom there are no clues as to the probably nature of the underlying condition is likely to depend on how readily tests are available. However, because of the therapeutic implications, patients with idiopathic hypereosinophilia now require extensive investigation. In patients whose condition remains idiopathic, despite full testing, a trial of imatinib therapy may still be justified since response can occur and may ultimately give superior results to treatment with hydroxyurea.

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**During the editing process a misleading reference to an apparently new gene, Rhe (rearranged in eosinophilia), contributing to a fusion gene underlying hypereosinophilia, was added. It should be pointed out that, as noted by the authors in an addendum, this was an independent observation of the presence of a FIP1L1-PDGFRA fusion gene in hypereosinophilia. The designation FIP1L1 takes priority since the paper of Cools et al. was published while the paper of Griffin et al. was in press.*

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Towards a rational treatment of essential thrombocythemia, despite limited evidence and old prejudices

This issue of Haematologica reports recommendations for the therapy of essential thrombocythemia, produced by a group of experts on behalf of the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation.[1] The methodology employed for development of these recommendations is a classical one and has been previously employed for the preparation of evidence- and consensus-based practice guidelines for the therapy of primary myelodysplastic syndromes.[2]

As underlined by Barbui and co-workers,[1] essential thrombocythemia is the chronic myeloproliferative disorder with the most favorable outcome. In fact, in large cohort studies patients with this condition showed equal or only slightly shorter survival than an age- and sex-matched healthy population. By contrast, life expectancy of patients with polycythemia vera (especially if younger than 50 years) is shorter tthat that of the reference population.[3,4] The two major problems with essential thrombocythemia are thromboembolic complications, which may markedly impair quality of life, and the increased risk of developing acute leukemia.

Based on the current diagnostic criteria, essential thrombocythemia very likely includes heterogeneous conditions. While most patients have evidence of clonal hematopoiesis[5] some patients unequivocally show polyclonal patterns of X chromosome inactivation and are very unlikely to have a stem cell disorder.[6] Clearly there is a need for biological[7,8] and molecular studies that may allow clinicians to identify the very different nosological entities currently grouped under a single definition, and to treat patients according risk-adapted strategies.

There is no question that clinicians need practice guidelines for the therapy of essential thrombocythemia. One way of realizing this is to spend some time in an Outpatient Department of a referral center for patients with myeloproliferative disorder. It can be seen how patients with very similar features and risk factors receive totally different treatments, ranging from aspirin to interferon-α.

However, scientific evidence is required in order to develop rational guidelines. In the case of essential thrombocythemia, as emphasized by one of the four reviewers of the paper by Barbui and co-workers,[1] the lamentable absence of rigorous scientific evidence necessary to support such guidelines had so far prevented their formulation. According to this reviewer, rather than *practice guidelines* based on scientific evidence, the recommendations in this paper actually represent the opinion of *expert* clinicians.