The hypereosinophilic syndrome: idiopathic or not, that is the question

The (idiopathic) hypereosinophilic syndrome (HES) comprises a heterogeneous group of hematologic disorders characterized by unexplained sustained eosinophilia (>1500 eosinophils/μL for more than 6 months). The diagnosis of HES is not uncomplicated, and requires a detailed analysis to exclude all other known causes of eosinophilia, such as infection, allergy, and neoplasia known to be associated with eosinophilia (either reactive eosinophilia or eosinophils that are part of the neoplastic clone). Organ involvement, as a consequence of infiltrating eosinophils, is a frequent observation in HES, but is not present in all patients. Several studies have indicated that at least two subgroups of HES patients can be distinguished: those with the lymphocytic variant of HES and those with the myeloproliferative variant of HES, in addition to the remaining *HES* patients that cannot be classified into these two subgroups.[1-3] *HES* is also closely related to chronic eosinophilic leukemia (CEL) and it is in fact in many cases difficult to make the distinction reliably.

Chronic eosinophilic leukemia

The diagnosis of CEL is made when there is evidence of a clonal myeloid disorder, or when blast cell numbers are elevated. We now know, however, that many HES cases without obvious chromosomal abnormalities are clonal in origin, further illustrating the difficulty in distinguishing *HES* and CEL and the need for new molecular markers to establish clonality. Not only is the difference between *HES* and CEL sometimes difficult to determine, but also the subclassification of the different subgroups of *HES* is not trivial. Recent studies have refined our insights into the molecular causes of *HES* and CEL, but it may still take a long time before the word *idiopathic* can definitively be removed.

The distinction between *HES* and CEL is easy to make when there is a clonal chromosomal abnormality present. Important examples include chromosomal translocations involving the regions 5q33 and 8p11, associated with rearrangements of the PDGFRB and FGFR1 kinase genes. Recently, a novel *PCM1-JAK2* fusion gene, generated by the t(8;9)(p22;p24) has also been described in different hematological malignancies, including one CEL.[4] Other chromosomal abnormalities such as the presence of an extra chromosome 8 are also indicative of the clonal origin of the myeloid cells. These results clearly show that CEL is similar to chronic myeloid leukemia (CML) in that activated tyrosine kinases seem to play a central role in the cause of CEL. Besides the importance for the diagnosis of CEL, the presence of these fusion kinases also indicates that patients are likely to respond to treatment with the appropriate kinase inhibitor. This has been nicely illustrated for the treatment of *ETV6-PDGFRB* positive leukemias with imatinib.[5]

The myeloproliferative variant of HES

A subgroup of HES shares a lot of characteristics with the myeloproliferative diseases, and is sometimes referred to as the myeloproliferative variant of HES. Patients with these HES are characterized by increased serum vitamin B_{12} levels, splenomegaly, increased myeloid precursor cells, and show a more aggressive course of the disease.[6,7] In addition, these patients were recently shown to have higher serum tryptase levels, which may become an important test to classify HES patients into this subgroup.[6] The close relationship between CEL and the myeloproliferative variant of HES was also the basis for testing imatinib for the treatment of HES. The remarkable response of a significant fraction of HES patients to this kinase inhibitor finally led to the identification of the FIP1L1-PDGFRα fusion kinase as the cause of the disease in these patients.[8] We know now that most of the patients with the myeloproliferative variant of HES express the *FIP1L1-PDGFRA* fusion gene, which confirms that this subgroup do indeed have a clonal myeloproliferative disease.[6]

In contrast to other fusion genes, which are generated by chromosomal translocations or inversions, the *FIP1L1-PDGFRA* fusion gene is generated by a relatively small deletion on chromosome 4q12 that is not detectable by standard cytogenetic analysis.[8] This is the reason why the *FIP1L1-PDGFRA* fusion gene remained undiscovered for such a long time. The identification of the *FIP1L1-PDGFRA* fusion gene and the corresponding deletion on the long arm of chromosome 4 provide new markers that can be used to demonstrate the clonality of the eosinophils. The diagnosis of *FIP1L1-PDGFRA* positive CEL can now be made by reverse transcriptase-polymerase chain (RT-PCR) analysis for the detection of the *FIP1L1-PDGFRA* fusion transcript, or by fluorescence in situ hybridization (FISH).[7,8] As a consequence, *FIP1L1-PDGFRA* positive *HES* should be reclassified as *FIP1L1-PDGFRA* positive CEL.

Most importantly, *FIP1L1-PDGFRA* positive CEL patients respond very well to imatinib therapy, even to lower doses than do CML patients (100 mg per day is common for the treatment of CEL).[6-8] Most patients achieve a complete hematologic and molecular remission, but in some patients the FIP1L1-PDGFRA fusion transcript remains detectable even after more than one year of imatinib treatment.[7] The question remains whether these patients are at increased risk of relapse; in other words, whether these patients are at risk of developing resistance to imatinib. To date, the development of resistance to imatinib in FIP1L1-PDGFRA positive CEL patients has been rare. Only two patients have been described who relapsed during imatinib therapy, and in both cases this was as a consequence of an acquired T674I mutation in the kinase domain of PDGFRα.[8,9] However, despite the low incidence of resistance, we should be prepared for the future, since these patients need life-long treatment with low dose imatinib, and our current follow-up is relatively short (1-2 years). The development of *in vitro* and *in vivo* models of *FIP1L1-PDGFRA* positive disease provides us with the right tools to test novel kinase inhibitors, which has already led to the identification of PKC412 as a potent inhibitor of FIP1L1-PDGFRα and the imatinib-resistant mutant (T674I).[10,11] So there is hope that we will be able to treat imatinib resistant CEL patients in the future. Several studies have pointed out that some HES patients, who are negative for the *FIP1L1-PDGFRA* fusion, do respond to imatinib treatment.[7,8,12] This has two important consequences. First, it suggests that these cases are likely to be

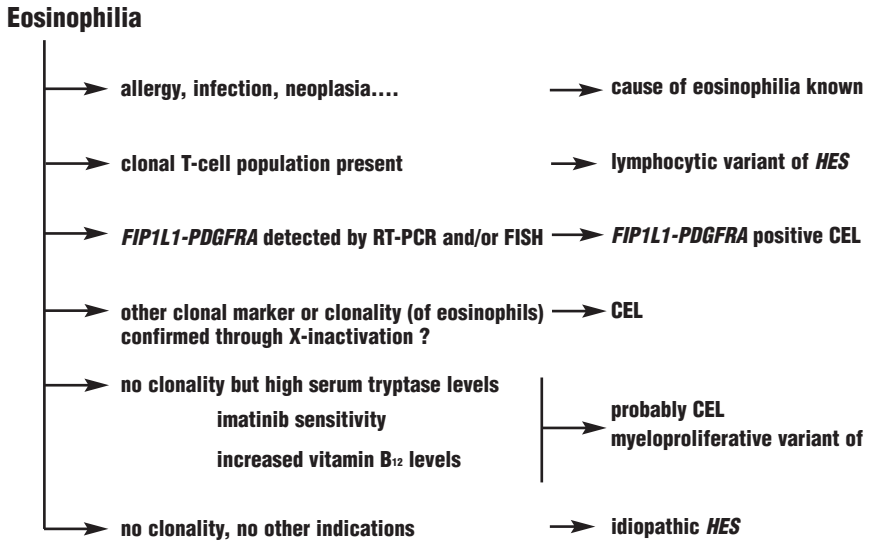

Figure 1. Different subgroups of *HES/CEL* and their specific characteristics.

clonal leukemias caused by an activated tyrosine kinase that is sensitive to imatinib. Second, this observation indicates that screening HES/CEL patients for the FIP1L1-PDGFRA fusion will not identify all patients who can benefit from imatinib treatment. In this issue of the journal, La Starza *et al*.[13] describe 2 HES patients who were negative for the *FIP1L1-PDGFRA* fusion, both by FISH and RT-PCR analysis, but who had complete hematologic responses to imatinib treatment. They went on with further molecular FISH studies and investigated whether the reason for the imatinib response could have been a rearrangement of *PDGFRB* or ABL, two known targets of imatinib. Since FISH did not reveal any rearrangements of these genes, the cause of HES in these patients, as well as the reason for their response to imatinib remains unknown. It is still possible that activating mutations in *PDGFRB* or *ABL* are the cause of HES in these patients, but that they could not be detected by FISH. These could be point mutations or other subtle nucleotide changes, small deletions or duplications within *PDGFRB* or ABL, or cryptic rearrangements of these genes that could not be detected with the current FISH probes. Alternatively, it is possible that the defect is not in *PDGFRB* or ABL, but rather in *PDGFRA*, KIT, ARG or another (maybe even unknown) imatinib target. In addition, the current study by La Starza *et al*. rules out that *FIP1L1-PDGFRA* negative patients in general have rearrangements of *PDGFRB*, *ABL*, *FGFR1* – three kinase genes frequently implicated in the pathogenesis of myeloproliferative diseases – or *ETV6*, a gene involved in the generation of various kinase fusions. They had previously found similar results in a HES patient with the myeoproliferative variant.[14] More molecular work needs to be done, and currently these cases remain idiopathic.

The lymphocytic variant of HES

A second subgroup of HES patients is characterized by the presence of a clonal T-cell population in the blood, and is referred to as the lymphocytic variant.[1] The underlying molecular cause of the T-cell clonal expansion remains unknown. Although the T cells may show chromosomal abnormalities, no recurrent aberrations have been described.[15] In contrast to myeloid cells, however, clonality of T-cells can be demonstrated by T-cell receptor rearrangement, and thus no chromosomal aberrations are needed to diagnose this variant of *HES*. It is believed that the T cells produce a number of cytokines (including interleukin-5) that stimulate the proliferation and survival of eosinophils and their precursors. The eosinophilia in this subgroup of *HES* is thus likely to be the consequence of the T-cell defect, and our molecular studies should focus on a better understanding of the molecular cause of the T-cell defect. Based on the known cause of the eosinophilia in this subgroup of *HES*, one could argue that this subgroup is not a true *HES* subgroup, and should be classified separately.[3]

Conclusions

In a recent study of French HES patients, approximately 30% of the patients showed clear evidence of T-cell clonality, and 17% of the patients were positive for *FIP1L1-PDGFRA*.[12] This still leaves ~50% of HES patients having an *idiopathic* disease. The recent discovery of the cryptic chromosomal deletion associated with the *FIP1L1-PDGFRA* fusion gene in HES patients,[8] the identification of the cryptic extra-chromosomal amplification associated with the *NUP214-ABL1* fusion gene in T-cell acute lymphoblastic leukemia,[16] and the identification of the remarkable *JAK2* mutation in polycythemia vera, essential thrombocythemia and myeloid metaplasia with myelofibrosis,[17,18] clearly indicates that there are many more tyrosine kinase mutations than the ones we see in the karyotype of the patients. Molecular characterization of HES cases using genome-wide approaches such as micro-array comparative genomic hybridization, combined with sequencing and FISH analysis, may reveal additional defects that can explain the cause of eosinophilia. This will not only further decrease the number of diagnoses of idiopathic HES, but may also provide new therapeutic options for a better treatment of HES.

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