Eosinophilic leukemia and idiopathic hypereosinophilic syndrome are mutually exclusive diagnoses

In a recent review of the idiopathic hypereosinophilic syndrome (HES) and chronic eosinophilic leukemia (CEL), Gotlib et al\(^1\) comment that the World Health Organization (WHO) classification for these disorders has been called into question by the identification of the \(FIP1LI-PDGFRA\) fusion gene. This is by no means true. The WHO classification specifies that if patients who would otherwise be classified as having idiopathic HES have myeloid cells that “demonstrate a clonal chromosomal abnormality or are shown to be clonal by other means,” the diagnosis is chronic eosinophilic leukemia.\(^2\) Clearly, the WHO criteria for CEL are satisfied by the demonstration of the \(FIP1LI-PDGFRA\) fusion gene in myeloid cells (including eosinophils).

Idiopathic HES is a diagnosis of exclusion, whereas CEL requires positive identification of features indicative of leukemia, such as increased blast cells or evidence of clonality. The 2 groups of disorders are mutually exclusive. It is possible that some patients who can currently only be classified as having idiopathic HES do actually have CEL, but if no evidence to support this suspicion can be found, a diagnosis of idiopathic HES is appropriate. Conversely, when eosinophilia is a feature of a myeloid leukemia, it is not idiopathic and the diagnosis is not idiopathic HES.

The discovery of the \(FIP1LI-PDGFRA\) fusion gene in a significant proportion of patients who would have previously been regarded as having idiopathic HES was very important in advancing our understanding of this group of disorders. Because of the marked sensitivity of this condition to imatinib therapy, identifying these patients is also now of considerable clinical importance. However, since some patients who lack the fusion gene also respond to imatinib, a trial of this drug is also justified in patients with idiopathic HES.

Gotlib et al\(^3\) refer to a proposed classification of hypereosinophilias as reactive, clonal, and HES.\(^3\) One may well question the wisdom of lumping together all hypereosinophilias resulting from clonal hematologic malignancies. The eosinophilia is reactive in Hodgkin disease and T-cell lymphoma just as it is reactive in drug allergy and parasitic disease, whereas in patients with \(FIP1LI-PDGFRA\) fusion or with t(5;12)(q33;p13) and \(ETV6-PDGFBR\) fusion, the eosinophils are part of the neoplastic clone. The situation is highly complex since even myeloid neoplasms may have an eosinophil population that is reactive rather than clonal.

For example, one of the imatinib-responsive patients with rearrangements of \(PDGFBR\) reported by Apperley et al\(^4\) had previously been shown to have nonclonal eosinophils.\(^5\) Furthermore, the 8p11 pluripotent stem cell syndrome is often a biphasic or triphasic disease, with both eosinophils in the CEL phase and T lymphoblasts in the T-lymphoblastic lymphoma phase belonging to the clonal population with t(8;13)(p12;q12) and \(ZNF198-FGFR1\) (or related abnormalities).\(^6\) A more appropriate classification of hypereosinophilias might be (i) reactive, (ii) clonal myeloid or biphenotypic neoplastic disorders, and (iii) idiopathic HES. Hematologic neoplasms with reactive eosinophilia would be assigned to group i, not group ii.

With advances in knowledge, the term “idiopathic hypereosinophilic syndrome” should only be used for a disorder in which the nature or underlying cause of the eosinophilia remains unknown after appropriate thorough investigation.

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References


Response:

Practical caveats to the classification of chronic eosinophilic leukemia and idiopathic hypereosinophilic syndrome as mutually exclusive diagnoses

The identification of the FIP1-like–1–platelet-derived growth factor receptor-α (FIP1LI-PDGFRA) fusion tyrosine kinase in patients who have carried the diagnosis of idiopathic hypereosinophilic syndrome (HES) has, in some cases, led to persistent use of the term “FIP1LI-PDGFRA–positive (F-P+) HES.” Dr Bain correctly states that identification of this clonal abnormality would define individuals as having a chronic eosinophilic leukemia (CEL) according to the World Health Organization (WHO) classification.\(^1\)

Dr Bain asserts that idiopathic HES and CEL are “mutually exclusive” diagnoses based on the latter exhibiting increased blasts.
or evidence of clonality (eg, F-P). However, in our experience, cases of HES that ultimately were found to be FIP1L1-PDGFRA negative (F-P−) and cases of HES that were ultimately found to be F-P+ (CEL, by definition) may, in some instances, be phenotypically identical with regard to morphologic and clinical features. In the absence of increased blasts and widespread clinical availability of F-P testing, it may be quite difficult to distinguish these 2 diagnoses that are considered “mutually exclusive” by the WHO.

The WHO’s use of morphologic, immunophenotypic, clinical, and genetic features has been useful for categorizing myeloid and lymphoid diseases. However, the current WHO classification of eosinophilic disorders provides limited clinical utility in distinguishing HES versus CEL. In fact, it took the empiric use of imatinib to unmask the identity of a proportion of idiopathic HES cases as CE

![Image](https://via.placeholder.com/150)

The classification requirements to the aforementioned chronic MPDs, in that evidence of clonality may or may not be able to be demonstrated, and no current molecular or biologic marker would be specific to the disease.

With the discovery of the F-P fusion and other recurrent molecular abnormalities associated with hypereosinophilia, the collaborative team of WHO hematopathologists and clinical advisors is best suited to tackle whether this new information will necessitate revisions to the current classification of eosinophilic disorders.

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We thank Dr Bain for her discussion and appreciate the opportunity to reply.

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