

To the editor:

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 al¹ comment that the World Health Organization (WHO) classification for these disorders has been called into question by the identification of the *FIP1L1-PDGFR* 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 *FIP1L1-PDGFR* 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 *FIP1L1-PDGFR* 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 al¹ refer to a proposed classification of hypereosinophilia 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 *FIP1L1-PDGFR* fusion or with t(5;12)(q33;p13) and *ETV6-PDGFRB* 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.

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 (*FIP1L1-PDGFR* α) 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 “*FIP1L1-PDGFR*-positive (*F-P*⁺) HES.” Dr Bain

For example, one of the imatinib-responsive patients with rearrangements of *PDGFRB* reported by Apperley et al⁴ 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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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-PDGFR α* 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.² 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.¹ 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 *F-P*⁺ CELs. In cases where fusion testing was not available, an empiric trial of imatinib could be useful for distinguishing *F-P*⁺ CEL from idiopathic HES. However, as Dr Bain points out, some idiopathic HES (*F-P*⁻) patients may also respond to imatinib, blurring the distinction between the 2 disorders. Imatinib responsiveness in *F-P*⁻ HES patients may reflect the drug’s action against targets that remain to be elucidated, and some of these patients may ultimately be found to have CEL. Certainly, use of imatinib has raised new questions about what constitutes the entity “idiopathic HES.”

As we cite in the our review (Gotlib et al³), the classification of hypereosinophilia as reactive, clonal, and HES, advocated by Brito-Babapulle,⁴ removes the emphasis on demonstrating the clonality of eosinophils; it is sufficient to demonstrate only that eosinophils are part of a clonal bone marrow disorder, with treatment tailored to the underlying neoplasm. The classification proposed by Dr Bain surely lends more scientific rigor to the study of whether eosinophils are clonal or reactive. However, at the bedside, Brito-Babapulle’s⁴ scheme becomes more tenable: in the example of 8p11 stem cell syndrome, it is more important to know that the patient’s eosinophilic disorder has been correctly diagnosed rather than whether or when eosinophils are part of the malignant clone.

The WHO classification may place too much emphasis on the requirement that, in addition to increased blasts, clonality be proven to diagnose CEL. In the chronic myeloproliferative disorders (MPDs) essential thrombocythemia (ET), polycythemia vera, and idiopathic myelofibrosis, clonality cannot always be demon-

strated nor is it required to establish the diagnosis. For example, the diagnosis of ET is based on exclusion of reactive causes of thrombocytosis and, like the other chronic MPDs, a recognizable constellation of morphologic and clinical features. Perhaps, some of the debate regarding what constitutes “idiopathic HES” versus “CEL” may be addressed by combining these 2 entities into one chronic MPD category of “essential hypereosinophilia (EH).” After exclusion of reactive causes of eosinophilia and an abnormal T-cell population, what would remain is a common set of morphologic and clinical features that may not be capable of being divided further into idiopathic HES versus CEL. EH would have similar 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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