Hypereosinophilic Syndrome

TO THE EDITOR: In some patients with idiopathic hypereosinophilic syndrome, Cools et al. (March 27 issue)[1] detected a *FIP1L1-PDGFRA* fusion gene that was associated with a dramatic response to imatinib mesylate. Along with the recent description of the "lymphocytic variant" of the hypereosinophilic syndrome,[2] their observation will provide clinicians with cornerstones for tailoring the management of this heterogeneous disease according to the underlying pathogenic mechanisms.

In their discussion, Cools et al. state that the hypereosinophilic syndrome is a myeloproliferative syndrome, thereby ignoring the involvement of interleukin-5–producing T cells in the pathogenesis of hypereosinophilia in approximately one fourth of patients with the syndrome.[3] The 91 percent rate of response to imatinib in their study suggests either recruitment bias in favor of the myeloproliferative variant of the hypereosinophilic syndrome or an unexpected effect of imatinib in patients with an unsuspected lymphocytic variant. Inclusion of data concerning the T-cell phenotype and clonality would have been interesting in this regard. Incidentally, in a series of our own, one patient who had hypereosinophilia with clonal CD3–CD4+ T cells had a negative test for the *FIP1L1-PDGFRA* fusion gene (unpublished data).

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2. Roufosse F, Cogan E, Goldman M. The hypereosinophilic syndrome revisited. Annu Rev Med 2003;54:169-84.
3. Simon H-U, Plötz S, Dummer R, Blaser K. Abnormal clones of T cells producing interleukin-5 in idiopathic eosinophilia. N Engl J Med 1999;341:1112-20.

THE AUTHORS REPLY: We thank Roufosse et al. for their perspective. The phenotypic characterization of the hypereosinophilic syndrome as a myeloproliferative disease does not presuppose a primary or secondary cause. FIP1L1-PDGFRα is a primary cause of the hypereosinophilic syndrome, and the fusion gene provides a genetic tool with which to dissect involvement of the myeloid and lymphoid lineages. We agree that clonally derived T cells may cause a secondary, polyclonal expansion of eosinophils as a result of interleukin-5 production in some patients with the syndrome, as discussed by Schwartz in the Perspective article[1] accompanying our report. However, T-cell clonality associated with hypereosinophilia appears to be relatively infrequent, occurring in 8 of 60 patients (13 percent) in the series[2] cited by Roufosse et al. That study may also have overestimated the true frequency of T-cell clonality in the hypereosinophilic syndrome, because many patients had indolent disease with dermatologic manifestations.[3]

These considerations emphasize the potential for selection bias in studies of the hypereosinophilic syndrome[2,4] because of the rarity and heterogeneity of the disease. However, we reported the *FIP1L1-PDGFRA* fusion gene in four of six untreated patients (including five from Belgium), a proportion similar to that observed in treated patients. Similar frequencies have been observed by Klion et al.[5] and correlate with the high frequency of responses to imatinib reported by Gleich et al.[6]

The hypereosinophilic syndrome is indeed a heterogeneous disease, as exemplified in part by the observation that although 10 of 11 patients with the syndrome (91 percent) had a response to imatinib, only 6 of those 10 patients (60 percent) harbored the *FIP1L1-PDGFRA* fusion gene.[4] Further investigation is necessary to elucidate the molecular bases of the hypereosinophilic syndrome for diagnostic, prognostic, and therapeutic purposes.

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