

Letter to the Editor

Treatment of *FIP1L1/PDGFR*A-negative hyper-eosinophilic syndrome with alemtuzumab, an anti-CD52 antibody*To the Editor:*

The criteria for the diagnosis of hypereosinophilic syndrome (HES) are blood eosinophilia equal to or exceeding $1.5 \times 10^9/L$, usually for a period of greater than 6 consecutive months; no underlying cause of eosinophilia, such as parasitic infection; and evidence of eosinophil-mediated organ damage.¹ The principal target organs are the heart, skin, and nervous system. Intracavitary thrombi might develop on damaged endocardium and disseminate throughout the circulatory system. Prognosis in HES is variable; it can be asymptomatic or progress rapidly to heart failure or acute leukemia.²

A 56-year-old woman presented with malaise and confusion, eosinophil levels up to $56.9 \times 10^9/L$, and splinter hemorrhages in her fingernails. Bone marrow aspiration and biopsy showed marked eosinophilia, an otherwise normal marrow, and no aggregates of mast cells or plasma cells. Flow cytometry failed to show T- or B-cell clones. Serum tryptase levels were in the normal range, and serum B12 values were increased (1163 ng/L; normal range, 200-650 ng/L). Karyotyping and fluorescence *in situ* hybridization did not show evidence of clonal mutations, including the *FIP1L1/PDGFR*A fusion. Imaging studies showed aortic valve vegetations and microinfarcts throughout the brain;

however, no hepatomegaly, splenomegaly, thrombocytopenia, or circulating myeloid precursors were observed. The patient had very mild anemia. Coumadin treatment was begun for anticoagulation. Administration of 200 mg/d imatinib mesylate (Gleevec) for 3 weeks was associated with increased eosinophil levels (Fig 1). Subsequently, treatment with prednisone (10-60 mg/d) and hydroxyurea (2-4 g/d) decreased eosinophilia; however, treatment was switched to IFN- α (1-7 million units every other day) and later IFN- α and hydroxyurea (0.5-3 g every other day) for nearly a year; these medications reduced eosinophils to approximately $7.0 \times 10^9/L$. Treatment with vincristine, 2 mg for 1 week, had no appreciable effect on blood eosinophil counts. Administration of 3 monthly infusions of mepolizumab (humanized anti-IL-5) at 750 mg per infusion was associated with increased eosinophil levels (Fig 1).

Because of the side effects from IFN- α and the incomplete control of eosinophilia, alemtuzumab (Campath), a humanized anti-CD52 antibody, was given biweekly (30 mg). Alemtuzumab sharply reduced eosinophil counts (0.05 - $2 \times 10^9/L$) to normal levels (Fig 1). The patient also reported a remarkable improvement in mental clarity. Lymphopenia as a result of alemtuzumab treatment was also observed (Fig 1); however, levels of other leukocytes were normal. Infusion reactions were treated successfully with Benadryl (Warren-Lambert Co, Morris Plains, NJ) and Decadron (Merck & Co, Inc, Whitehouse Station, NJ). Alemtuzumab infusions were decreased to 30 to 40 mg every 3 weeks on July 11,

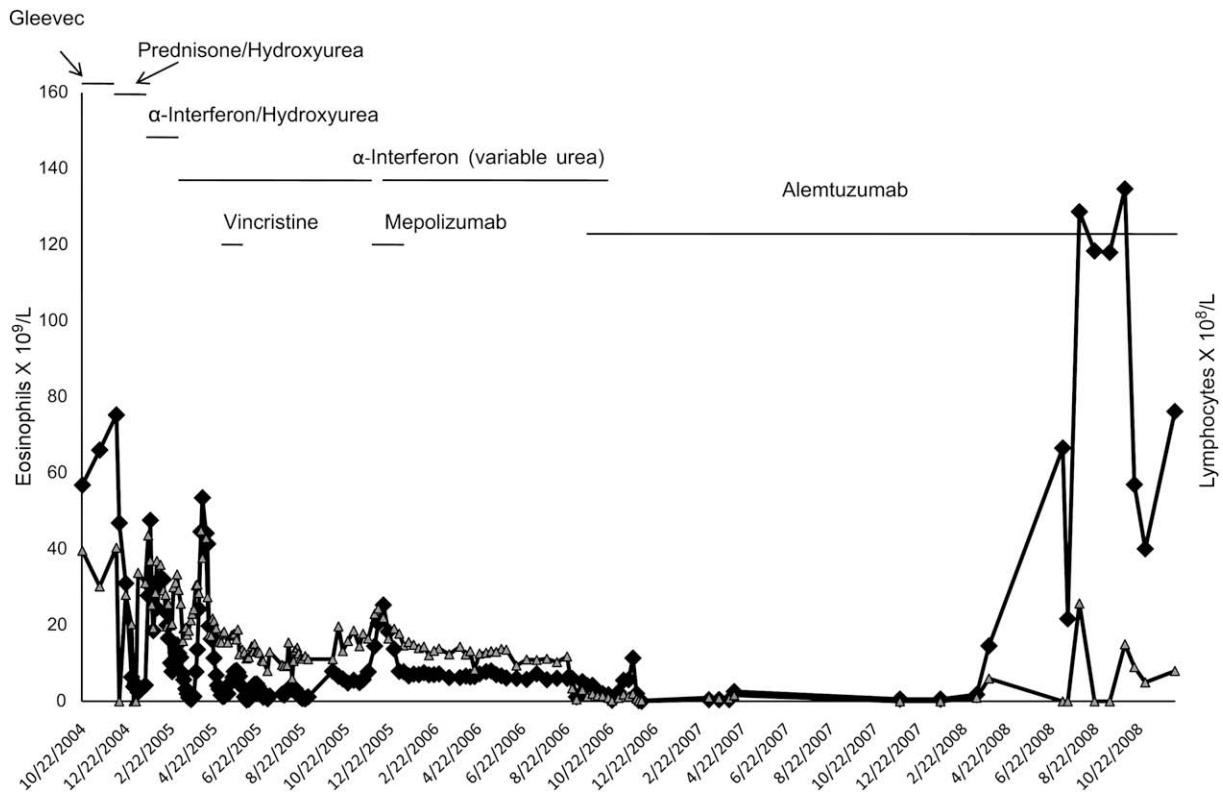


FIG. 1. Blood eosinophil and T-lymphocyte levels. Black diamonds, Eosinophils; gray triangles, T lymphocytes.

2007, at the patient's request. After approximately 1½ years of normal eosinophil levels, the patient's eosinophilia worsened during late 2008 (Fig 1). A single osseous plasmacytoma was found and irradiated but progressed to multiple lytic lesions and multiple myelomas confirmed by means of bone marrow biopsy. The patient died in December 2008 as a result of this disease.

HES can occur as a myeloproliferative, lymphoproliferative, or, most frequently, idiopathic variant. Some myeloproliferative patients respond to imatinib mesylate³ and possess a mutant gene on chromosome 4.⁴ Deletion of approximately 800 kB on chromosome 4 results in a *FIP1L1/PDGFR* fusion gene and formation of a kinase potentially inhibited by imatinib mesylate. In our patient the *FIP1L1/PDGFR* fusion gene was not detected, and imatinib mesylate failed to control eosinophilia. In the lymphoproliferative HES variant, T-lymphocyte clones produce cytokines, especially IL-5, that stimulate eosinophil production in the bone marrow. Mepolizumab, an anti-IL-5 drug, is used to inhibit eosinophil proliferation stimulated by IL-5; however, for unknown reasons, 16% of patients do not respond to mepolizumab.⁵ In this case mepolizumab had no effect, suggesting that eosinophilia was not IL-5 dependent or that other cytokines, such as IL-3 or GM-CSF, were supporting eosinophil growth. Alternatively, the patient might have been producing so much IL-5 that the levels might have outpaced mepolizumab injections. IFN- α treatment is often effective because of a shift in the cytokine milieu from T_H2, which is supportive of eosinophil growth, to a T_H1-type response. In this case IFN- α caused a decrease in eosinophil counts, although not to normal levels, and the patient experienced the side effects of IFN- α .

Alemtuzumab is an anti-CD52 antibody that can bind to both eosinophils and T cells, potentially inhibiting either the myeloproliferative, lymphoproliferative, or idiopathic variant.⁶ CD52 is a glycosylphosphatidylinositol-anchored molecule expressed on human eosinophils, lymphocytes, macrophages, and monocytes but not on neutrophils.⁷ Alemtuzumab is approved for the treatment of B-cell chronic lymphocytic leukemia and is also used to treat small lymphocytic lymphoma and mantle cell lymphoma in conjunction with other treatments. Side effects include infusion reactions (often severe), lymphopenia, anemia, thrombocytopenia, and infections. Alemtuzumab was used successfully as a treatment for HES in 2 prior cases, 1 lymphoproliferative and 1 myeloproliferative, both of which did not respond to imatinib mesylate or IFN- α and that were not tested for the *FIP1L1/PDGFR* fusion.^{8,9} Alemtuzumab controlled our patient's

eosinophilia for 1½ years, and the patient's quality of life appeared improved. Our patient most likely had the idiopathic HES variant. However, the occurrence of thromboembolism and an increased B12 level point to a possible myeloproliferative HES variant. The patient had a plasmacytoma and then multiple lytic lesions and multiple myelomas, suggesting involvement of 2 cell lineages by a single mutation or possibly independent mutations. Overall, the results in our patient and the previously reported cases suggest that alemtuzumab might be an effective treatment for the myeloproliferative, idiopathic, and lymphoproliferative HES variants.

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