Successful Treatment of Corticosteroid-Refractory Hypereosinophilia With Reslizumab

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Hypereosinophilia, defined as a persistent absolute eosinophil count (AEC) of >1500/µL, has a broad differential diagnosis, with conditions ranging from benign to life-threatening. Causes of hypereosinophilia may be primary or secondary, such as infection, atopy, or drug reactions [1]. Hypereosinophilic syndrome (HES) is hypereosinophilia associated with end-organ damage and includes myeloproliferative, lymphoproliferative, and idiopathic variants. Corticosteroids are the first-line treatment for HES, although the response may be variable [2]. Alternative therapies include hydroxyurea, interferon α, imatinib, and monoclonal antibodies to IL-5, specifically mepolizumab [3,4]. We report on a patient with marked hypereosinophilia and respiratory failure that were refractory to high-dose corticosteroids. The patient was successfully treated with reslizumab, an intravenous IL-5 antagonist.

A 72-year-old Vietnam veteran with a history of relapsing polychondritis, myasthenia gravis, and hypertension and a remote history of seizure disorder presented to the emergency department with a 1-week history of dyspnea. He had been admitted 8 weeks previously with dizziness, left-sided hearing loss, and fatigue; at that time, his white blood cell count (WBC) was slightly elevated at 12.3 × 10^9/L, with no eosinophils. Following discharge, his long-term prednisone dose for myasthenia gravis (40 mg) was increased to 60 mg because of presumed peripheral vestibulopathy. Mycophenolate was changed to azathioprine 2 weeks prior to the current presentation because of dizziness. The patient saw his rheumatologist on the day of admission for progressive weakness, fatigue, weight loss (10 kg), and dyspnea. He was referred to the emergency department for respiratory distress and possible myasthenic crisis. He had an elevated WBC of 25.6 × 10^9/L with an AEC of 2.3 × 10^9/L (9% of differential) (Figure). A chest radiograph showed multifocal opacities, and within hours he developed respiratory failure requiring intubation and mechanical ventilation. Chest CT demonstrated patchy bilateral consolidations, ground-glass opacities, and scattered nodules.

He was treated with a single dose of intravenous methylprednisolone (125 mg) and subsequently maintained on prednisone 80 mg daily. He received multiple antibiotics for presumed infectious pneumonia. Testing for *Histoplasma, Cryptococcus, Legionella*, and *Cytomegalovirus* was negative. WBC trends showed rising eosinophilia, peaking at an AEC of 12.68 × 10^9/L (40% of WBC) despite high-dose prednisone. Therefore, bronchoscopy was performed and demonstrated 22% eosinophils in the bronchoalveolar lavage fluid. Cultures and cytology data from bronchoscopy were negative. The patient was treated empirically with ivermectin while awaiting the result of testing for *Strongyloides* antibodies (subsequently negative). The antineutrophil cytoplasmic antibody panel, rheumatoid factor, antinuclear antibody, and anti–cyclic citrullinated peptide studies were all negative. Tryptase was normal at 8 ng/mL, and vitamin B12 was slightly elevated at 1074 pg/mL. Cardiac studies were unremarkable, with no elevation in troponin and a normal ejection fraction on the echocardiogram. Preliminary histopathology of a bone marrow biopsy showed mild hypercellularity, with no evidence of lymphoma, leukemia, or increased blasts. There were varying stages of eosinophilic maturation and mild dyspoiesis. Peripheral blood flow cytometry showed no $CD34^+$ myeloblasts, although it did reveal many granulocytes including eosinophils.

Hypereosinophilia persisted despite treatment with high-dose prednisone and discontinuation of phenytoin, azathioprine, and all antibiotics (Figure). After 2 weeks of 80 mg prednisone daily and persistent eosinophilia, the patient received anti-IL5 treatment with reslizumab (3 mg/kg, 300 mg IV). His AEC prior to the reslizumab infusion was 8.73 × 10^9/L (43%); 6 hours after the infusion it fell to 4.53 × 10^9/L (25%) and 25 hours later it was 1000 cells/µL (6%) (Figure). He was transferred out of the intensive care unit the following day, and his oxygen requirement decreased from 10 L/min to 2 L/min. His WBC showed no detectable eosinophils 6 days after starting reslizumab, and he was discharged to a rehabilitation facility after 1 week. Following a brief stay in rehabilitation, he returned home with no residual oxygen requirement.

Two weeks after starting reslizumab, final cytogenetic studies showed no clonal abnormalities, with negative results in *FIP1L1-PDGFRA, JAK2*, and *BCR-ABL* testing. However, next-generation targeted sequencing revealed a missense mutation in *SRSF2* and a frameshift mutation in *TET2*. These results supported the diagnosis of chronic eosinophilic

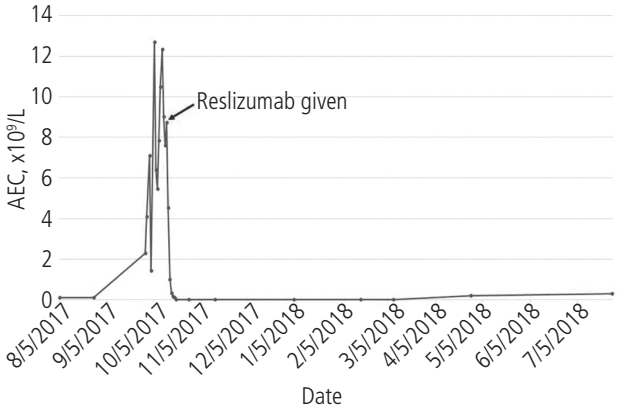

Figure. Absolute eosinophil count (AEC) over time.

leukemia, not otherwise specified (CEL-NOS), as *TET2* mutations have previously been associated with CEL-NOS [5]. However, idiopathic HES (I-HES) was considered as an alternative diagnosis, given the lack of increased blasts and chromosomal abnormality in bone marrow histopathology. Six months after starting reslizumab, the patient's AEC remains suppressed (Figure). Prednisone for treatment of myasthenia gravis was tapered to 10 mg/d.

This case illustrates a clinical dilemma involving the classification of primary hypereosinophilia. Next-generation targeted sequencing identified a mutation in *TET2* that has been seen in CEL-NOS [5]. On the other hand, the lack of blasts in peripheral blood and bone marrow would argue against an underlying neoplasm and favor a classification of I-HES with a mutation. Although inferior to the survival rate for I-HES without a mutation, the survival of patients with I-HES and a mutation is similar to that of patients with CEL-NOS [5].

Reslizumab was selected because it could be administered intravenously and dosed based on body weight. At the time of this patient's treatment, mepolizumab was only available for subcutaneous dosing at a significantly lower dose (100 mg) than that used in clinical trials for HES (700 mg IV) [4]. More recently, higher subcutaneous dosing (300 mg) of mepolizumab was approved for eosinophilic granulomatosis and polyangiitis [6], although there are no data on this dose in HES. There is scant literature regarding the use of reslizumab in HES. In a small study of 4 patients with HES who were treated with reslizumab (1 mg/kg), 2 of the 4 patients presented an initially favorable clinical response. However, the AEC and symptoms rebounded within 8 weeks in these 2 patients, who required 5 additional monthly doses, with transient and diminished subsequent responses [7]. In another study [8], a patient with eosinophilic dermatitis received reslizumab 3 mg/kg monthly, with a significant improvement in symptoms, although the response to AEC was not reported. In the case we present, the improvement in symptoms and suppression of eosinophils lasted at least 9 months without relapse after a single reslizumab infusion at 3 mg/kg, although the exact mechanism of this lasting remission remains unknown. To our knowledge, this is the first report of reslizumab being used to induce a successful and sustained treatment response in symptomatic I-HES with a mutation/CEL-NOS. Additional studies are required to further explore the efficacy of higher-dose reslizumab for treatment of hypereosinophilic disorders.

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Conflicts of Interest

Mark Gladwin is a shareholder, advisor, and director of Globin Solutions, Inc. He has had research funded by Bayer. He has been a consultant for Actelion, Epizyme, and Jenesis.

Andrej Petrov has participated on advisory boards for Genentech and CSL Behring.

The remaining authors declare that they have no conflicts of interest.

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