A Clonal Hypereosinophilic Syndrome with Specific and Effective Therapy: A Report of Two Cases

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Hypereosinophilic syndromes are characterized by persistent eosinophilia associated with eosinophilic tissue infiltration. The intracellular contents of the eosinophil are noxious to tissues, accounting for the organ damage seen in these syndromes. Therefore, accurate diagnosis and appropriate treatment of eosinophilia is crucial. In this paper we present two cases of a newly described hypereosinophilic syndrome characterized by a specific molecular marker and demonstrating a high response rate to specific therapy.

Patient Descriptions

Patient 1

A 51 year old man was referred because of eosinophilia of 6 months duration. His general state of health was good, apart from a dry cough during the previous year. He had no fever, weight loss, diarrhea or abdominal pain. He was not taking any medications regularly.

Physical examination revealed a well-appearing man. A patchy erythematous maculopapular rash was present over the torso and legs. The heart, lungs, abdomen and nervous system were normal. Laboratory evaluation was notable for eosinophilia (absolute eosinophil count 17,500/µl, normal < 500/µl), elevated lactate dehydrogenase (745 U/L, normal 230–460 U/L) and vitamin B12 levels (1200 pg/dl, normal 180–950 ng/L).

A diagnosis of clonal or primary hypereosinophilic syndrome was suspected because of the degree (> 1500/µl) and duration (> 6 months) of eosinophilia. Bone marrow aspiration and biopsy revealed the presence of an increased number of mature normal-appearing eosinophils; the karyotype was normal. Flow cytometry demonstrated polyconal CD3+ T lymphocytes (CD4+ 18% and CD8+ 28%). No abnormal T lymphocyte clones (CD3+ CD4- CD8- or CD3-CD4+) that have been described in HES were detected. Skin biopsy demonstrated a dermal eosinophilic infiltrate, pulmonary function studies showed mild reversible small airway obstruction, and an echocardiogram was normal. These findings established a diagnosis of primary HES with skin (Wells syndrome) [1] and pulmonary involvement. Treatment was begun with prednisone, leading to a rapid amelioration in the rash but accompanied by a rapid rise in the white count with a left shift. This required a reduction in the prednisone dose and the institution of cytoreductive therapy using hydroxyurea, which in turn led to symptomatic anemia and recurrence of the skin rash [Figure 1A].

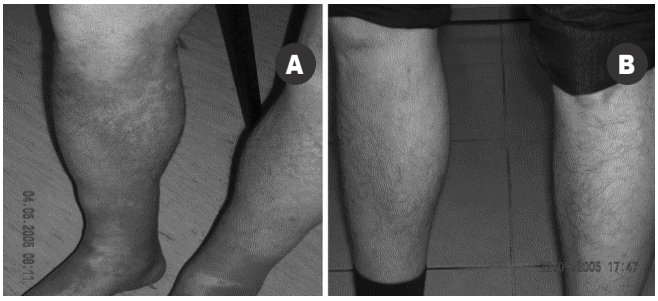

Figure 1. Patient 1: **[A]** Erythematous rash present on the patient's legs prior to treatment with imatinib mesylate. **[B]** Resolution of the rash after 3 months of treatment.

While treating the patient, initial reports appeared in the literature describing a unique deletion in the long arm of chromosome 4 that results in the approximation of the *FIP1L1* and *PDGFRα* genes present in a subgroup of patients with hypereosinophilic syndrome. Interestingly, this clonal aberration engenders exquisite sensitivity to imatinib mesylate (Gleevec®, Novartis), and its presence is thus of considerable clinical importance [2]. RNA was extracted from the patient's peripheral blood and was reverse transcribed into mRNA. Polymerase chain reaction analysis on the mRNA was performed using specific primers for the *FIP1L1-PDGFRα* mutation, and a characteristic multiple-band pattern indicating multiple *FIP1L1-PDGFRα* isoforms was obtained [Figure 2A]. Treatment with imatinib mesylate was started at a dose of 100 mg/day with rapid resolution of the eosinophilia and skin rash [Figure 1B, Figure 3]. Currently the patient is asymptomatic and has a normal blood count while receiving imatinib mesylate at a dose of 100 mg twice weekly. After 3 months of treatment, the abnormal bands seen on PCR significantly diminished in intensity [Figure 2B].

Patient 2

A 40 year old man was seen because of an incidental finding of eosinophilia. He was generally well and had no chronic illnesses. He complained of a dry cough of 4 months duration and an unexplained nodular erythematous rash over his legs during

HES = hypereosinophilic syndrome

PCR = polymerase chain reaction

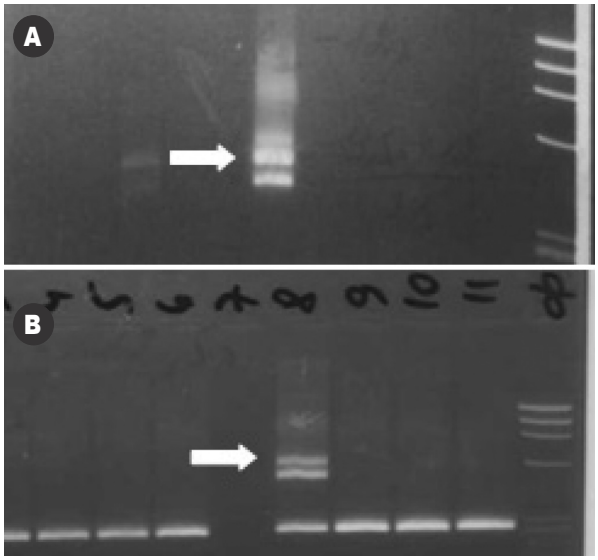

Figure 2. Patient 1: PCR gel **[A]** at the time of diagnosis: the arrow designates the two isoforms of the abnormal *FIP1L1-PRGFRα*, and **[B]** after 3 months of treatment with imatinib mesylate: only a faint band remains, indicating significant molecular response.

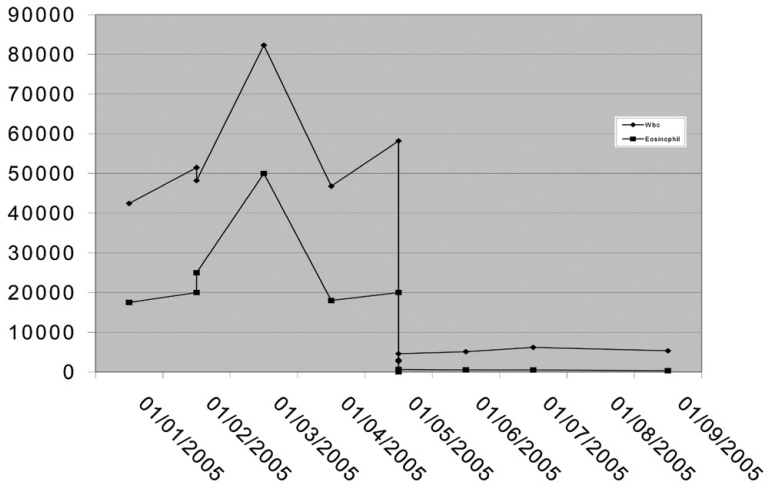

Figure 3. Representative values for total white blood cell and absolute eosinophil counts in patient 1. The arrow denotes the time at which imatinib mesylate treatment was begun.

the same period. He had no history of allergy, diarrhea or drug ingestion. His absolute eosinophil count on presentation was 8500/μl and his lactate dehydrogenase 764 IU/dl. The rest of his blood count and serum chemistry was normal. Chest X-ray and pulmonary function studies were normal. Biopsy of a skin lesion revealed dermal and epidermal eosinophilic infiltration. PCR analysis of RNA obtained from a peripheral blood sample revealed the *FIP1L1-PDGFRα* fusion gene. On the basis of the clinical and laboratory findings, the patient is a candidate for treatment with imatinib mesylate.

Comment

The classification of eosinophilia has typically differentiated among patients with an obvious exogenous cause for eosinophilia, such as parasitic infection or allergy, patients with an underlying clonal disorder, such as acute myeloid leukemia, in which case the eosinophilia does not arise from the malignant clone, and finally, patients with clonal eosinophilia typified by acute eosinophilic leukemia and the myeloproliferative disorders.

Among the hypereosinophilic syndromes that were not easily classifiable previously is primary hypereosinophilic syndrome. An abnormal monoclonal T cell population (CD3+CD4-CD8-) that is thought to drive the eosinophilia via production of interleukin-5 is demonstrable in a variable percentage of patients (5–50%) with primary HES [3]. These patients typically have marked dermatologic involvement and may occasionally develop T cell lymphoma. Recently, another form of clonal HES was demonstrated, a so-called myeloproliferative variant of HES. In this subset of patients, a 40 kilobase deletion in chromosome 4 results in the fusion of the *FIP1L1* and the *PDGFRα* genes. This fusion gene is found in 10–50% of patients with HES and may be detected using PCR or fluorescent *in situ* hybridization [4]. The apposition of the two genes results in the constitutive activation of PDGFRα, a receptor tyrosine kinase that transforms hematopoietic cells. Serendipitously, patients bearing the *FIP1L1-PDGFRα* fusion gene were found to respond rapidly and completely to a low dose (100 mg/day) of imatinib mesylate, a tyrosine kinase inhibitor used to treat chronic myeloid leukemia where its target is the abl kinase molecule [5].

We report here what we believe to be the first documented cases of FIP1L1-PDGFRα-positive HES diagnosed in Israel, and in one of the cases confirm the dramatic clinical and molecular responses to treatment with imatinib mesylate. These cases demonstrate both the importance of molecular diagnostic testing in patients with hypereosinophilic syndromes and one of the most impressive paradigms in modern medicine – namely, the power of specific molecularly targeted therapy.

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