

RESPONSE TO IMATINIB MESYLATE IN PATIENTS WITH CHRONIC MYELOPROLIFERATIVE DISEASES WITH REARRANGEMENTS OF THE PLATELET-DERIVED GROWTH FACTOR RECEPTOR BETA

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ABSTRACT

Background A small proportion of patients with chronic myeloproliferative diseases have constitutive activation of the gene for platelet-derived growth factor receptor beta (PDGFRB), which encodes a receptor tyrosine kinase. The gene is located on chromosome 5q33, and the activation is usually caused by a t(5;12)(q33;p13) translocation associated with an *ETV6-PDGFRB* fusion gene. The tyrosine kinase inhibitor imatinib mesylate specifically inhibits ABL, PDGFR, and KIT kinases and has impressive clinical efficacy in *BCR-ABL*-positive chronic myeloid leukemia.

Methods We treated four patients who had chronic myeloproliferative diseases and chromosomal translocations involving 5q33 with imatinib mesylate (400 mg daily). Three of the four patients presented with leukocytosis and eosinophilia; their leukemia cells carried the *ETV6-PDGFRB* fusion gene. The fourth patient had leukocytosis, eosinophilia, and a t(5;12) translocation involving *PDGFRB* and an unknown partner gene; he also had extensive raised, ulcerated skin lesions that had been present for a long time.

Results In all four patients, a normal blood count was achieved within four weeks after treatment began. In the patient with skin disease, the lesions began to resolve shortly after treatment began. The t(5;12) translocation was undetectable by 12 weeks in three patients and by 36 weeks in the fourth patient. In the three patients with the *ETV6-PDGFRB* fusion gene, the transcript level decreased, and in one patient, it became undetectable by 36 weeks. All responses were durable at 9 to 12 months of follow-up.

Conclusions Imatinib mesylate induces durable responses in patients with chronic myeloproliferative diseases associated with activation of PDGFRB. (N Engl J Med 2002;347:481-7.)

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THE association of leukemia, eosinophilia, and abnormalities of chromosome 12p13 was originally reported by Keene et al. in 1987¹; two of the four patients included in that report also had translocations involving chromosome 5q3. Subsequently, Golub et al.² showed that the previously described t(5;12)(q31-q33;p13) chromosomal abnormality, characteristic of some cases of

chronic myelomonocytic leukemia, was associated with a fusion gene linking *TEL* (now known as *ETV6*) with platelet-derived growth factor receptor beta (*PDGFRB*). At least 34 cases of chronic myeloproliferative disease associated with a t(5;12)(q31-q33;p13) translocation have now been reported,³ and the *PDGFRB* gene is known to be rearranged in some of these cases. There are also additional cases involving translocations of the *PDGFRB*-containing region of chromosome 5 — that is, 5q31-q35 — and chromosomal partners other than 12p13.⁴⁻⁶ All these leukemias, although heterogeneous, have some common features — most notably, the frequent presence of eosinophilia in peripheral blood and bone marrow.

Imatinib mesylate (formerly STI571; now Gleevec in the United States and Glivec in Europe [Novartis]) is a 2-phenylaminopyrimidine compound based on a candidate molecule designed specifically to interact with the ATP-binding site of protein tyrosine kinases. Imatinib specifically inhibits the kinase activity of ABL (including *BCR-ABL*), *PDGFRB*, and c-KIT. Recently, this compound has shown efficacy in the treatment of chronic myeloid leukemia⁷⁻⁹ and gastrointestinal stromal tumors.¹⁰

We report here the results of imatinib treatment in four patients with chronic myeloproliferative diseases characterized by leukocytosis, peripheral-blood eosinophilia, and molecular rearrangements involving the *PDGFRB* gene. Normal peripheral-blood counts and normal appearances of bone marrow were restored in all patients, and the cytogenetic abnormalities resolved.

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CASE REPORTS

Patients 1, 2, and 3

Patients 1, 2, and 3 were men 32, 50, and 68 years of age, respectively, who presented with leukocytosis, mild anemia, and eosinophilia (Table 1). Bone marrow aspirates and trephine biopsies showed hypercellularity with left-shifted myeloid series and an increase in the numbers of immature and mature eosinophils. Patient 1 was initially treated with hydroxyurea for 16 months until the disease progressed, as evidenced by a rising white-cell count and increasing splenomegaly. Pipobroman and interferon alfa failed to control the white-cell count and induced thrombocytopenia. Treatment with imatinib at a dose of 400 mg daily was begun 48 months after diagnosis. Patients 2 and 3 received no treatment until they began treatment with imatinib (400 mg daily) 9 and 12 months after diagnosis, respectively.

Patient 4

Patient 4 was a six-year-old boy who presented in 1987 with a generalized erythematous rash and eosinophilia. Skin biopsy showed a dermal infiltrate of eosinophils and atypical histiocytes that varied in size and nuclear morphology, with sparing of the epidermis and cutaneous appendages. There were no Birbeck granules, and a diagnosis of non-X histiocytosis was made. Over the course of the next two years, the skin condition progressed and raised, infiltrative lesions developed. The appearance of the bone marrow was consistent with a myeloproliferative disease, with hypercellularity and

an increased number of eosinophils but without the atypical histiocytes that were present in the skin. Cytogenetic analysis revealed a t(5;12)(q33;q13) translocation in 25 percent of the cells in metaphase. The skin condition and hematologic abnormalities failed to respond to corticosteroids or hydroxyurea, and two years of therapy with interferon alfa provided only minimal benefit. By October 2000, when the patient was 19 years old, 90 percent of the surface of the skin was involved, with disfiguring plaques, nodules, and tumors (Fig. 1A). Extensive areas of ulceration developed on the trunk and limbs. Hydroxyurea was recommenced in December 2000, without benefit. Repeated hospitalizations became necessary for control of pain and skin infection and for surgical débridement. Skin biopsies again showed an infiltrate of atypical histiocytes and numerous eosinophils, with surface ulceration. In March 2001 the patient began receiving imatinib at a dose of 400 mg daily.

METHODS

Study Design

The Novartis STIB2225 study was designed by the investigators and representatives of the study sponsor, Novartis. It was a phase 2 study of STI571 (now called imatinib mesylate) in patients with life-threatening diseases known to be associated with one or more STI571-sensitive tyrosine kinases. The two patients described here are the only two patients with 5q33 abnormalities. The data presented here were collected, interpreted, and analyzed by the academic investigators, who also wrote the article in collaboration with representatives of Novartis.

TABLE 1. CLINICAL AND HEMATOLOGIC CHARACTERISTICS OF FOUR PATIENTS WITH *PDGFRB*-POSITIVE LEUKEMIAS.*

| CHARACTERISTIC | PATIENT 1 | PATIENT 2 | PATIENT 3 | PATIENT 4 |
|-----------------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| Sex | Male | Male | Male | Male |
| Age at diagnosis (yr) | 32 | 50 | 68 | 6 |
| At beginning of imatinib treatment | | | | |
| Age (yr) | 36 | 51 | 69 | 20 |
| Splenomegaly | Yes | Yes | No | No |
| Hematologic characteristics | | | | |
| Hemoglobin (g/dl) | 10.1 | 12.3 | 12.5 | 9.7 |
| White-cell count (per mm ³) | 80,000 | 52,000 | 41,000 | 9,300 |
| Eosinophil count (per mm ³) | 7,820 | 4,800 | 1,640 | 4,100 |
| Platelet count (per mm ³) | 74,000 | 190,000 | 192,000 | 506,000 |
| Bone marrow cytogenetics | 100% 46,XY t(5;12)(q33;p13) | 100% 46,XY t(5;12)(q33;p13) | 100% 46,XY t(5;12)(q33;p13) | 100% 46,XY t(5;12)(q33;q13) |
| Results on RT-PCR | | | | |
| Single-step | + | + | + | NA |
| Heminested | + | + | + | NA |
| Most recent studies | | | | |
| Duration of imatinib therapy (mo) | 9 | 12 | 9 | 12 |
| Current dose of imatinib (mg/day) | 400 | 400 | 400 | 800 |
| Hematologic characteristics | | | | |
| Hemoglobin (g/dl) | 14.5 | 13.7 | 14.6 | 14.3 |
| White-cell count (per mm ³) | 5,600 | 5,000 | 5,500 | 8,500 |
| Eosinophil count (per mm ³) | 100 | 200 | 100 | 700 |
| Platelet count (per mm ³) | 176,000 | 251,000 | 245,000 | 249,000 |
| Bone marrow cytogenetics | 100% 46,XY | 100% 46,XY | 100% 46,XY | 100% 46,XY |
| Fluorescence in situ hybridization | NP | NP | NP | >95% 2 fused signals |
| Results on RT-PCR | | | | |
| Single-step | - | - | - | NA |
| Heminested | + | - | + | NA |

*RT-PCR denotes reverse-transcriptase polymerase chain reaction, NA not applicable, and NP not performed. A plus sign indicates a positive result, and a minus sign a negative result.



Figure 1. Patient 4 at the Beginning of Imatinib Therapy (Panel A) and after Eight Months of Therapy (Panel B).

Cytogenetic Analysis and Fluorescence in Situ Hybridization

Cytogenetic analysis of bone marrow cells was performed by conventional G-banding. Two-color fluorescence in situ hybridization for the *PDGFRB* rearrangement was performed in Patients 2 and 4 with two flanking cosmid probes for chromosome 5, 9-4 and 4-1, as previously described.⁵ A total of 100 cells in interphase were scored.

Identification of *ETV6-PDGFRB* Fusion Transcript

RNA was reverse-transcribed and tested for the *ETV6-PDGFRB* fusion by single-step reverse-transcriptase polymerase chain reaction (RT-PCR) (limit of detection, 10⁻²) and hemi-nested RT-PCR (limit of detection, 10⁻⁵). Single-step PCR was performed for 30 cycles at an annealing temperature of 60°C with the use of primers ETV6-J (TTCACCATCTTCCACCCTGGA) and PD-F (TTGACGGC-CACCTTTCATCGT). For hemi-nested PCR, the products of this reaction were amplified with primers ETV6-J and PD-C (TGGCT-TCTTCTGCCAAAGCA) for 30 cycles at an annealing temperature of 64°C.

In Vitro Studies of Sensitivity to Imatinib

Peripheral-blood specimens were obtained from Patients 2 and 4; cells from leukaphereses performed in five patients with Phila-

delphia (Ph) chromosome–positive chronic myelogenous leukemia in chronic phase and cells from leukaphereses or bone marrow from three healthy donors were used as controls. All specimens were obtained with the written or oral informed consent of the donors. Mononuclear cells were cultured in RPMI 1640 medium supplemented with 10 percent fetal-calf serum, 2 percent L-glutamine, and 2 percent penicillin–streptomycin. Under these conditions (without additional cytokines), there is no proliferation or differentiation of either normal or leukemic cells. Specimens were cultured (1 million cells per milliliter) in the presence or absence of 1 μm of imatinib and were monitored by trypan blue staining for cell viability every two days.

RESULTS

Cytogenetic Analysis and Fluorescence in Situ Hybridization

All the bone marrow cells in metaphase that we examined from Patients 1, 2, and 3 contained the t(5;12)(q33;p13) translocation. Before treatment with imatinib, 5 of 10 cells in metaphase from Patient 4 (50 percent) contained t(5;12)(q33;q13). Two-color fluorescence in situ hybridization performed on cells from Patients 2 and 4 showed one fused signal and

separate red and green signals in more than 80 percent of the cells from each patient, indicating disruption of *PDGFRB* (Fig. 2). More than 95 percent of the normal control cells had two fused signals.

Identification of the *ETV6-PDGFRB* Fusion Transcript

RT-PCR to detect the *ETV6-PDGFRB* fusion gene was performed on bone marrow, blood, or both from all patients. Before treatment, products of the expected size were detected in RNA from Patients 1, 2, and 3 by both single-step (395-bp) and hemi-nested (174-bp) RT-PCR techniques (data not shown). These products were not detected in the RNA of Patient 4, in whom an unknown gene at 12q13 is presumably fused to *PDGFRB*.

Analysis of in Vitro Sensitivity to Imatinib

Mononuclear cells from Patients 2 and 4 were shown to be sensitive to in vitro treatment with imatinib. The survival of normal mononuclear cells was virtually unaffected by culture with 1 μ m of imatinib for at least 2 weeks, whereas only 40 percent of cells

from Patient 4 were viable by that time, and 100 percent of cells from Patient 2 were dead by the 12th day of culture. The average sensitivity to imatinib of cells from a patient with Ph-positive chronic myelogenous leukemia was intermediate between those of the two patients with *PDGFRB* abnormalities (Fig. 3).

Clinical Outcome

Patients 1, 2, and 3 began treatment with imatinib at a dose of 400 mg daily; Patient 2 was treated within the Novartis STIB2225 study. In Patients 2 and 3, the blood count normalized (with resolution of eosinophilia) within one week. After 12 weeks, 30 of 30 cells in metaphase from Patient 2 and 50 of 50 cells in metaphase from Patient 3 were cytogenetically normal. As of this writing, and after 15 months of therapy in Patient 2 and 12 months of therapy in Patient 3, the appearance of bone marrow aspirate is normal, with eosinophils and their precursors comprising less than 5 percent of nucleated cells. Fluorescence in situ hybridization of bone marrow cells obtained from Patient 2 after nine months of therapy showed that 27

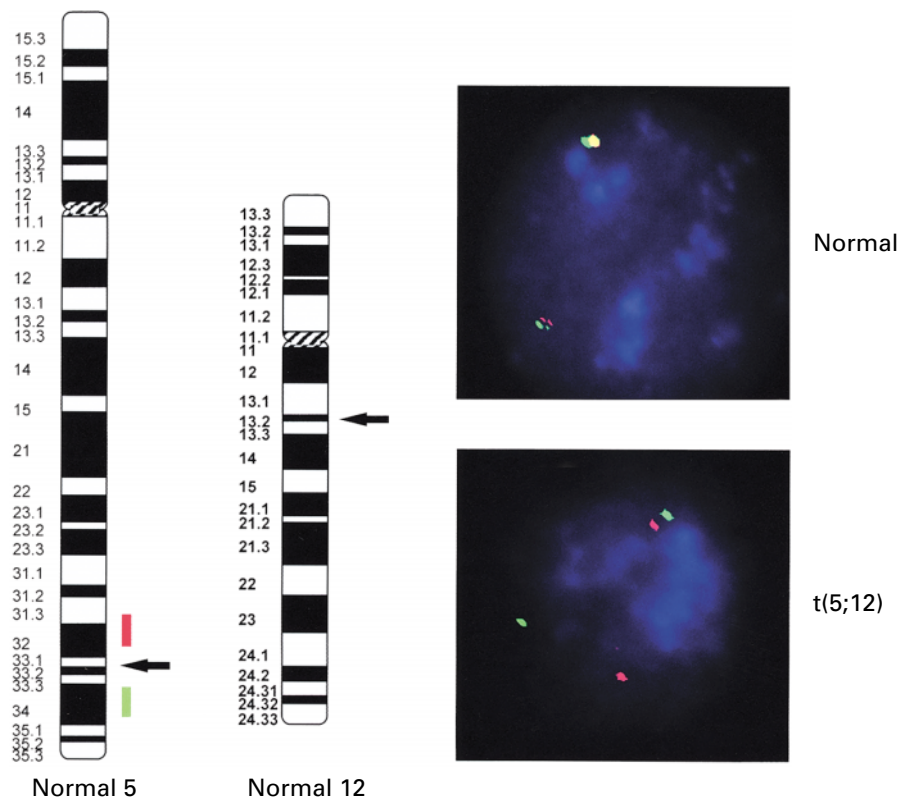


Figure 2. Two-Color Fluorescence in Situ Hybridization of Cells from Patient 2, with Schematic Representation of Chromosomes 5 and 12 Indicating the Break Points of t(5;12)(q33;p13).

Cells in interphase were probed with two flanking cosmid probes for chromosome 5, 9-4 and 4-1.⁵ More than 80 percent of cells showed one fused signal and separate red and green signals, indicating disruption of the *PDGFRB* gene. Arrows indicate break points.

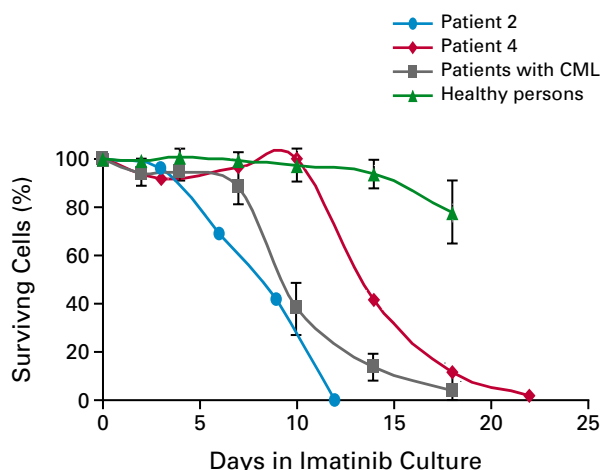


Figure 3. Viability of Mononuclear Cells on Exposure to Imatinib. The viability of cells from Patients 2 and 4 and from five patients with chronic myelogenous leukemia (CML) and three healthy persons on exposure to 1 mM of imatinib was compared with viability in paired, nonexposed control cultures.

of 200 cells (14 percent) had one fused signal. Peripheral-blood cells obtained after six months of therapy (from both patients) and after nine months of therapy (from Patient 2) tested negative by single-step RT-PCR and positive by the heminested technique. Cells from Patient 2 were negative by both techniques at 12 months.

In Patient 1, the white-cell count normalized within four weeks after the start of treatment, although the platelet count was low, at 68,000 per cubic millimeter. The blood count and bone marrow morphology were normal by 12 weeks. The proportion of cells in metaphase containing a $t(5;12)(q31-q33;p13)$ translocation gradually decreased, and cells from Patient 1 became cytogenetically normal at nine months. He continues to receive imatinib at a dose of 400 mg daily without side effects 13 months after the start of therapy.

Within five days after imatinib treatment began in Patient 4 in the Novartis STIB2225 study, the white-cell count and the eosinophil count had normalized. The skin lesions became flatter and less erythematous, and the ulcerated areas began to granulate; autologous and cadaveric skin grafts were applied to the right wrist, right lower leg, anterior chest wall, and back in order to speed recovery. After four weeks of treatment, cytogenetic analysis of 50 cells in metaphase showed that 100 percent had the 46,XY karyotype, with no evidence of the $t(5;12)$ abnormality. However, the thrombocytosis persisted, and bone marrow aspirate obtained after eight weeks of therapy remained hypercellular, although the eosinophilic component had de-

creased to 6 percent. The dose of imatinib was therefore gradually increased to 800 mg daily, and the appearance of the bone marrow at 20 weeks was normal. Skin biopsies after 20 weeks of treatment showed xanthomatized cells within the middle dermis. There were no atypical histiocytes or eosinophils. After 15 months of imatinib treatment, the patient is well and free of side effects (Fig. 1B). Fluorescence in situ hybridization analysis of bone marrow cells obtained at 12 months showed two fused signals in more than 95 percent of cells — equivalent to the proportion in normal control cells.

DISCUSSION

We have used imatinib mesylate to treat four patients with chromosomal rearrangements involving *PDGFRB*. All had prompt responses, with normalization of the blood count, disappearance of eosinophilia, resolution of cytogenetic abnormalities, a decrease in or disappearance of fusion transcripts, and in one case, healing of long-standing skin lesions.

The platelet-derived growth factor (PDGF) family includes at least five dimeric forms (PDGF AA, PDGF AB, PDGF BB, PDGF CC, and PDGF DD).¹¹⁻¹⁴ The PDGF dimers activate the receptors specific for PDGF- α (PDGFRA) and PDGF- β (PDGFRB), thereby stimulating the proliferation and migration of mesenchymal cells. PDGFRA and PDGFRB belong to type III-receptor tyrosine kinase families and are characterized by five immunoglobulin-like domains in the extracellular region, a transmembrane domain, an ATP-binding site, and a hydrophilic kinase insert domain in the intracellular portion.^{15,16} Ligand binding to these receptors results in dimerization of the subunits of the receptor, followed by the activation of the tyrosine kinase domain and autophosphorylation. The resulting phosphotyrosines act as docking sites for intracellular signaling proteins,^{11,17} and signaling through PDGFRB plays an important part in mitogenesis, cytoskeletal rearrangements, and chemotaxis.

The PDGFRB fusion proteins that result from the various chromosomal translocations can no longer be activated by PDGF, since they do not contain the ligand-binding domain. Instead, the fusion proteins are constitutively active and can transform interleukin-3-dependent cell lines into growth factor-independent cell lines. Furthermore, the ETV6-PDGFRB and RAB5-PDGFRB fusion proteins induce myeloproliferative diseases in mice.^{6,18,19} It is likely that the partner genes encode a specific dimerization motif that enables the fusion protein to self-associate, mimicking the normal process of receptor activation after ligand binding.

Imatinib is a tyrosine kinase inhibitor that shows specificity at the submicromolar level for ABL, PDGFR, and KIT kinases. It inhibits ligand-stimu-

lated PDGFR tyrosine phosphorylation at a 50 percent inhibitory concentration (IC_{50}) of $0.3 \mu\text{mol}$ per liter, which is similar to the IC_{50} for ABL.²⁰ The IC_{50} of imatinib for the proliferation of cell lines expressing *ETV6-ABL* is $0.35 \mu\text{mol}$ per liter, and the IC_{50} for the proliferation of cell lines expressing *ETV6-PDGFRB* is $0.15 \mu\text{mol}$ per liter, indicating that the potency of the drug against ABL and PDGFRB is equivalent.²¹ Furthermore, the ability of imatinib to inhibit the growth of cell lines transformed by *RAB5-PDGFRB* and to reverse the leukemic phenotype in a mouse model of *ETV6-PDGFRB* transformation suggested that this agent might be effective in the treatment of patients with *PDGFRB* rearrangements.^{22,23}

The four patients with myeloproliferative diseases described here all had a t(5;12) translocation and involvement of the *PDGFRB* gene. The phenotypes of their diseases were similar in some ways but also had important differences. Patients 1, 2, and 3 presented with peripheral-blood leukocytosis, eosinophilia, an appearance of bone marrow compatible with myeloproliferative diseases, and the well-described *ETV6-PDGFRB* fusion gene. Patient 4 was more unusual, in that he presented at the age of six years with cutaneous involvement, peripheral-blood eosinophilia, myelodysplasia, and myeloproliferation. This patient was described previously, when the eosinophilia was thought to be reactive because the eosinophils apparently lacked the t(5;12) translocation.²⁴ Over the course of the next 14 years, disfiguring skin disease that was unresponsive to hydroxyurea and interferon alfa was the predominant feature in Patient 4. We remain uncertain whether the cutaneous infiltrates were reactive or were in fact a manifestation of the myeloproliferative disease. However, the strong and rapid response to imatinib suggests a direct relation between the PDGFRB oncoprotein and the mechanism responsible for the cutaneous infiltration. Although Patient 4 has no *ETV6* rearrangement and the *PDGFRB* partner gene has not been identified, it is likely that an activated PDGFRB oncoprotein is responsible for the clinical phenotype.

We have recently reviewed the clinical features of Ph-negative myeloproliferative diseases with translocations of 5q31–35.³ The literature includes 34 patients with the classic t(5;12)(q31–33;p13) translocation, although in some cases, involvement of *PDGFRB*, *ETV6* (*TEL*), or both was not demonstrated. The majority of patients were male and had peripheral-blood eosinophilia, monocytosis, and splenomegaly. A number of patients had progression to blastic transformation, and the two-year survival rate among the 18 patients who could be evaluated was only 55 percent. An additional 20 patients with reciprocal translocations involving 5q31–q35 but not 12p13 were also described. The phenotypes in this group were more di-

verse, but certain similarities persisted; all 11 patients who could be evaluated had peripheral-blood eosinophilia. In our series, Patients 1, 2, and 3 had the typical features of the t(5;12) myeloproliferative diseases.

Eosinophilia is a prominent but not invariable feature of transformation induced by the PDGFRB oncoprotein. A number of genes that are important in the proliferation and differentiation of eosinophils are found in the same 5q31–q35 chromosomal region, including interleukin-3, interleukin-4, interleukin-5, and interleukin-13 and granulocyte–macrophage colony-stimulating factor. It is possible that these genes are dysregulated in the translocation process. Furthermore, studies of linkage disequilibrium in a family with familial eosinophilia confirmed the importance of 5q31–q35 in this rare condition²⁵; there were no mutations in the genes for interleukin-3, interleukin-5, and granulocyte–macrophage colony-stimulating factor, but the *PDGFRB* gene was not studied. Thus, activation of PDGFRB could underlie the eosinophilia in the patients described here, but the precise mechanism remains unknown. Recently, Gleich et al. reported that four of five patients with hypereosinophilic syndrome and normal findings on cytogenetic analysis had a prompt response to imatinib with resolution of peripheral-blood eosinophilia.²⁶ The *PDGFRB* gene was not studied. The absence of a response in the fifth patient was associated with an elevated interleukin-5 level, perhaps suggesting an alternative mechanism of eosinophilia in this patient. Interleukin-5 levels were considerably elevated in Patient 4 in our series (data not shown), but this elevation did not interfere with the response to imatinib.

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