OBSERVATION

Imatinib as a Treatment Option for Systemic Non-Langerhans Cell Histiocytoses

Jochen Utikal, MD; Selma Ugurel, MD; Hjalmar Kurzen, MD; Philipp Erben, MD; Andreas Reiter, MD; Andreas Hochhaus, MD; Thomas Nebe, MD; Ralf Hildenbrand, MD; Uwe Haberkorn, MD; Sergij Goerdt, MD; Dirk Schadendorf, MD

Background: Systemic non-Langerhans cell histiocytoses are disorders characterized by the accumulation of histiocytes that do not meet the criteria for Langerhans cells in various organs. So far, no causative treatment is known.

Observations: Herein, we report the case of a 41-year-old man with Rosai-Dorfman disease, a form of systemic non-Langerhans cell histiocytoses, with histiocytic infiltrations in the skin, bone marrow, liver, and spleen. Histiocytes were positive for the imatinib target proteins platelet-derived growth factor receptor β and KIT. The disease completely responded to treatment with 400 to 600 mg daily of imatinib for more than 7 months.

Conclusion: This case shows that imatinib is a powerful treatment option for patients with non-Langerhans cell histiocytoses.

Arch Dermatol. 2007;143:736-740

Author Affiliations:
Department of Dermatology, Venereology, and Allergology (Drs Utikal, Ugurel, Kurzen, Goerdt, and Schadendorf), Department of Internal Medicine III (Drs Erben, Reiter, and Hochhaus), Central Laboratory (Dr Nebe), and Department of Pathology (Dr Hildenbrand), University Medical Center Mannheim, Ruprecht-Karl-University of Heidelberg, Mannheim, Germany; Skin Cancer Unit, German Cancer Research Center, Heidelberg, Germany (Drs Ugurel and Schadendorf); and Department of Nuclear Medicine, Ruprecht-Karl-University of Heidelberg, Heidelberg (Dr Haberkorn). Dr Utikal is now also with Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, Mass.

NON-LANGERHANS CELL histiocytoses (non-LCH) are a heterogeneous group of histiocytic proliferative disorders characterized by the accumulation of histiocytes that do not meet the phenotypic, ultrastructural, and immunochemical criteria of Langerhans cells. Clinically, non-LCH can be divided into

For editorial comment see page 788

3 groups: non-LCH that predominantly affect the skin, such as juvenile xanthogranuloma; non-LCH that affect the skin but in addition show major systemic involvement, such as xanthoma disseminatum; and those that primarily involve extracutaneous sites, such as bones (Erdheim-Chester disease) or lymph nodes (Rosai-Dorfman disease [RDD]). For systemic involvement in non-LCH, various treatment modalities such as corticosteroids, high dosages of interferon alfa or of thalidomide, radiation therapy, chemotherapy, or bone marrow transplantation were reported in single patients or small series of patients, with response rates ranging from 0% to 100%.[1,2] Herein, we report the case of a patient diagnosed with RDD who showed a rapid and complete response to the tyrosine kinase inhibitor imatinib. Most patients with RDD, a systemic non-LCH affecting the skin as well as extracutaneous sites, present with an involvement of the lymph nodes; more rarely affected are organs such as the spleen and liver, the respiratory system, and the genitourinary tract.[1,3]

REPORT OF A CASE

A 41-year-old white man presented with an 18-month history of progressive, deeply infiltrated skin lesions of the trunk and upper arms (**Figure 1**A), hepatosplenomegaly, and a poor physical condition. Previous systemic treatments with corticosteroids and cyclosporine A had been ineffective. Blood test results at the time of hospital admission revealed an elevated international normalized ratio of 1.63, reduced erythrocyte counts (3.65×10^{12} cells/L), thrombocytopenia (platelet count of 36×10^3/μL), slightly elevated neutrophil count (6.43×10^9 cells/L), and a normal erythrocyte sedimentation rate. Findings from electrophoresis showed no signs of monoclonal gammopathy. The serum S100β protein level was elevated to 0.109 (reference level, <0.105 μg/L) (measured by Elecsys S100 immunoassay; Roche Diagnostics, Mannheim, Germany). Positron emission tomographic and magnetic resonance imaging scans showed

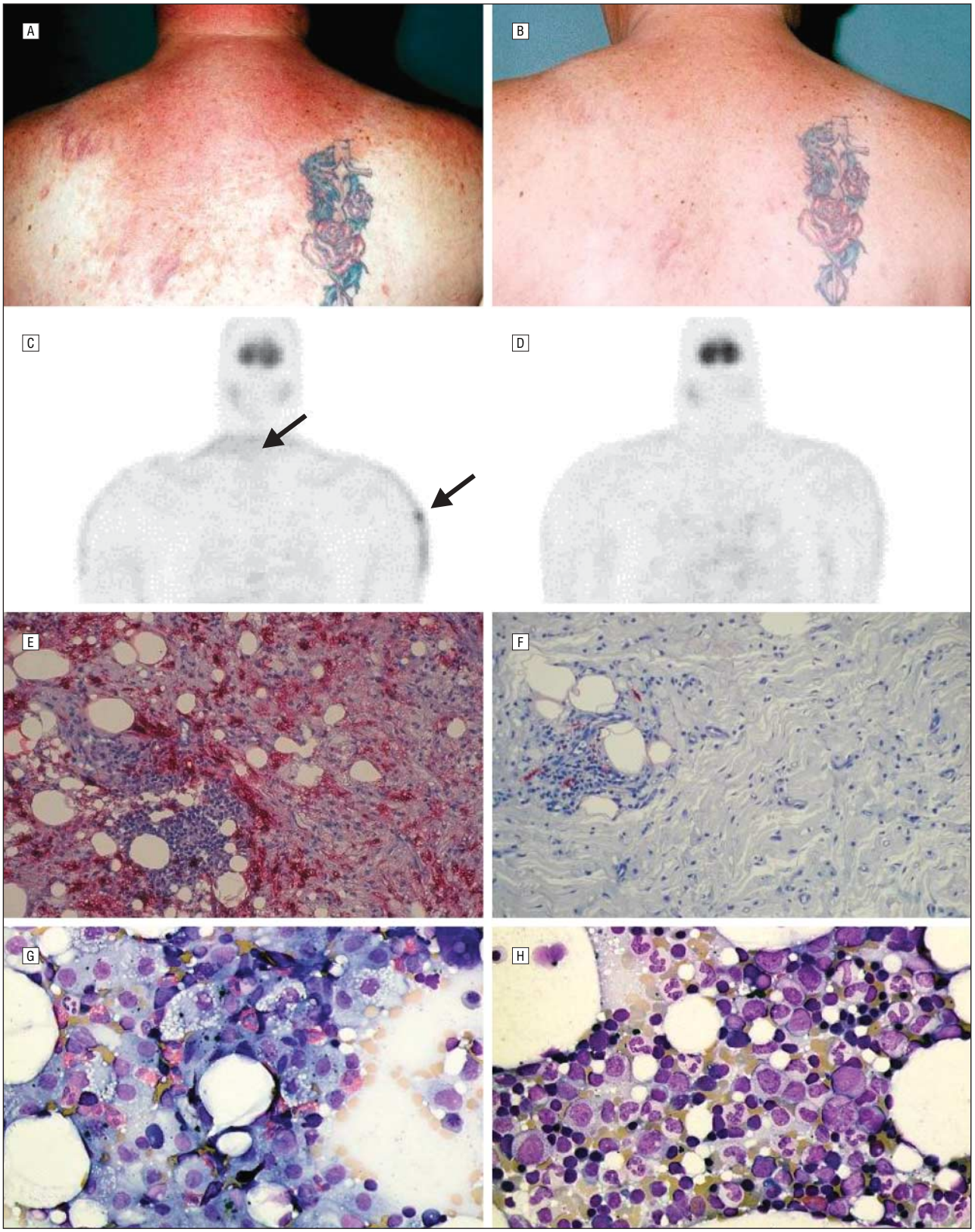

Figure 1. A 41-year-old man with Rosai-Dorfman disease. A, Erythematous patches and plaques on the patient's back, shoulders, and upper arms at his first presentation. B, After 6 weeks of treatment with imatinib, the cutaneous infiltrates had almost completely disappeared. C, Positron emission tomographic scan taken prior to treatment with imatinib shows multiple foci of pathologically increased fludeoxyglucose F 18 uptake (standardized uptake value, maximum of 5.2), predominantly within the left upper arm and chest (arrows). D, After 6 weeks of treatment with imatinib, the previous foci of increased uptake disappeared. E, Immunostaining with antibodies for S100 protein on skin biopsy samples taken prior to imatinib treatment show S100, positive histiocytic cells within the subcutis (original magnification ×40). F, After treatment, fibrosis and only single S100-positive cells remain (Immunostaining with antibodies for S100 protein; original magnification ×40). G, May-Grünwald Giemsa staining of a bone marrow smear before treatment with imatinib shows pale histiocytic cells with a dense background infiltrate of eosinophilic granulocytes and lymphocytes (original magnification ×60). H, After treatment, cytologic findings show regenerated normal bone marrow (May-Grünwald Giemsa staining, original magnification ×40).

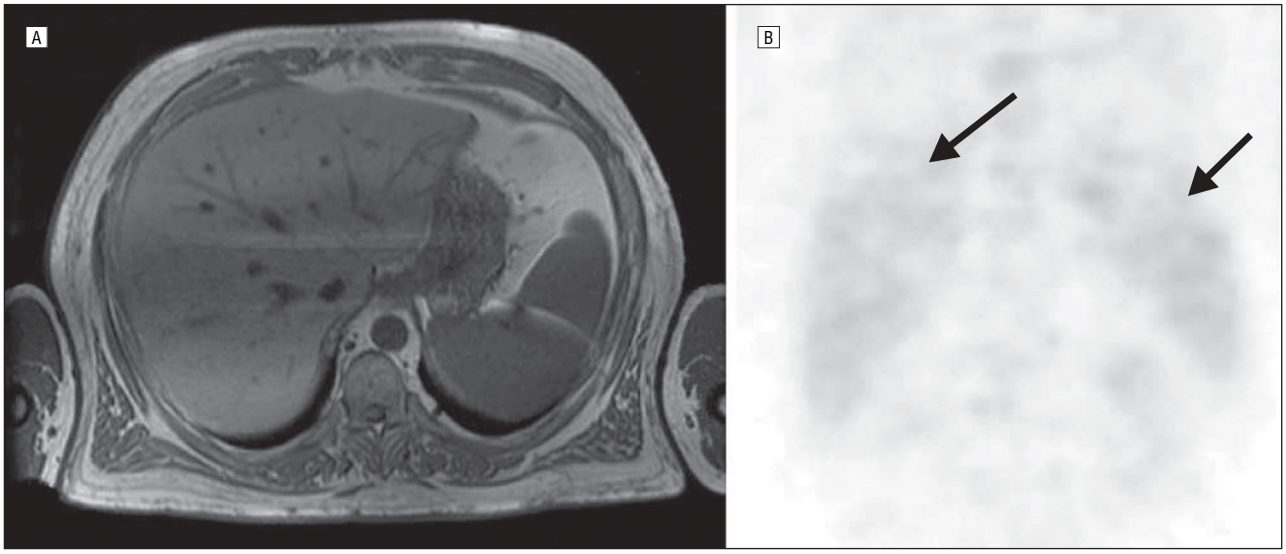

Figure 2. Magnetic resonance imaging scan (A) and positron emission tomographic (PET) scan (B) show a hepatosplenomegaly prior to treatment with imatinib. The PET scan reveals a homogeneous tracer accumulation in the liver and spleen (arrows).

superficial infiltrates within his arms, chest, and back (Figure 1C), as well as a hepatosplenomegaly (**Figure 2**).

Findings from skin biopsy samples (Figure 1E), as well as findings from bone marrow aspirates (Figure 1G), revealed infiltrates of pale histiocytic cells with a dense background infiltrate of eosinophilic granulocytes and lymphocytes. The histiocytes displayed phagocytosis of lymphocytes and eosinophils (emperipolesis) and stained positive for S100β, CD68, and stabilin-1, a marker for non-LCH,[4,5] but stained negative for CD1a. With regard to the molecular targets of imatinib, the histiocytic infiltrate stained positive for *PDGFRB* (**Figure 3**A and B) and KIT (Figure 3C and D) but was negative for *PDGFRA* and macrophage colony–stimulating factor receptor protein.

A cytogenetic analysis that was performed on bone marrow aspirates according to standard protocols[6] revealed a normal karyotype. For molecular analyses, total leukocyte RNA from 10 mL of peripheral blood and 5 mL of bone marrow aspirate was extracted using cesium chloride gradient ultracentrifugation (as described by Cross et al[7]) after red cell lysis. The total RNA was transcribed into complementary DNA using random hexamer primers and Moloney murine leukemia virus reverse transcriptase (Invitrogen, Karlsruhe, Germany). For mutation analysis of the *KIT* gene, exons 8 to 20 were amplified by employing a single-step reverse transcriptase–polymerase chain reaction (PCR) and analyzed by direct sequencing. A total of 3 µL of complementary DNA was amplified for 31 cycles of 1 minute at 94°C, 1 minute at 60°C, and 1 minute at 72°C. Primers were designed to amplify 4 fragments between exons 8 and 20 of c-Kit (primers for PCR are available from the authors). The *PDGFRA* gene was analyzed with 2 different PCR assays. We screened for *FIP1L1-PDGFRA* fusion using a nested PCR[8]; in addition, possible alternative *PDGFRA* fusion genes with breakpoints in exon 12 of the *PDGFRA* gene were investigated by a multiplex PCR assay.[9] Another multiplex PCR approach was used to exclude *BCR-ABL* positivity.[10] The sample quality was assessed by quantification of the number of *ABL* transcripts using real-time quantitative PCR.[11] These analyses revealed no mutations in the gene encoding for *KIT* and showed no evidence of fusion transcripts involving *PDGFRA* and *ABL*.

Because of the ineffective previous treatments and the detected KIT and *PDGFRB* positivity of the tumor cell infiltrate, we prescribed systemic treatment with 600 mg/d of imatinib (Glivec, Novartis, Switzerland) by mouth daily. A dosage of 600 mg/d was chosen because of the patient's elevated body weight of 110 kg. Within 6 weeks of therapy, cutaneous and subcutaneous infiltrates disappeared (Figure 1B, D, and F). In addition, platelet and erythrocyte counts, the international normalized ratio, and elevated S100β serum protein returned to reference range, and the cytologic characteristics of the bone marrow normalized (Figure 1H). After 10 weeks of treatment, the dosage of imatinib was reduced to 400 mg/d without relapse of the disease. Three weeks later, treatment was stopped owing to adverse effects (nausea, muscle cramps, and slight edema of both legs), and a close follow-up schedule was initiated. To date, the patient has been free of recurrence for more than 7 months.

COMMENT

This case indicates that imatinib is a new, rapid, and highly effective treatment option for patients with systemic non-LCH of the RDD type. Imatinib was shown to inhibit the tyrosine kinases BCR-ABL, *PDGFRA*, and *PDGFRB* and KIT. A strong therapeutic benefit of the drug was reported for chronic myelogenous leukemia showing expression of the BCR-ABL fusion protein and for gastrointestinal stromal tumors that commonly present mutations of *PDGFRA* and *KIT*.[12,13] As with gastrointestinal stromal tumors, a fludeoxyglucose F 18 positron emission tomographic scan could represent a sensitive indicator for early prediction of treatment response in patients with non-LCH.[14-16]

Recently, it has been shown that imatinib also targets the macrophage colony–stimulating factor receptor

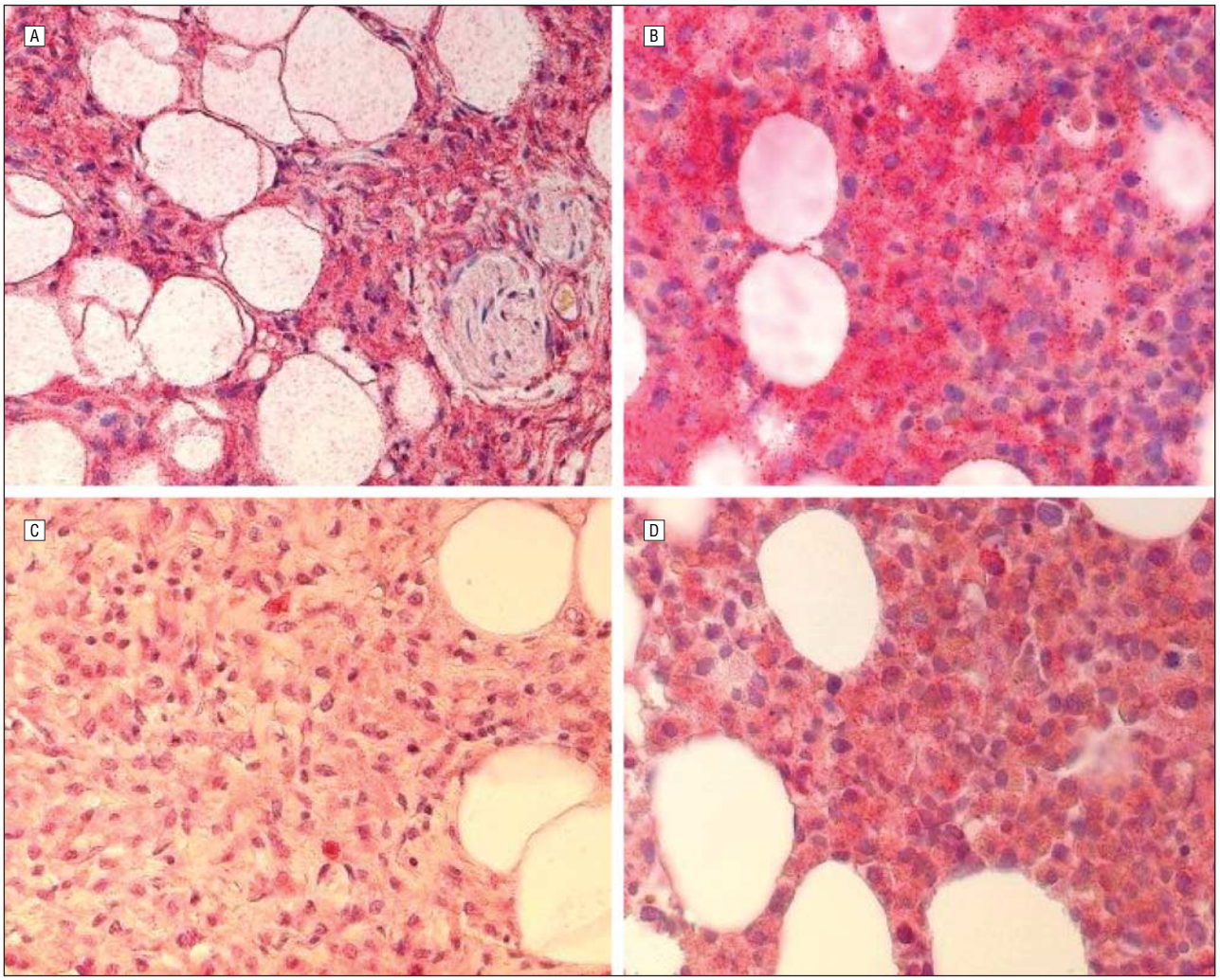

Figure 3. Molecular targets of imatinib. The histiocytic infiltrate stained positive for *PDGFRB* in the subcutaneous tissue (A) and the bone marrow (B). KIT staining was detected as well in the subcutaneous tissue (C) and in the bone marrow (D). (Immunostaining with antibodies for platelet-derived growth factor receptor β protein [A and B] and antibodies for Kit protein [C and D]; original magnification ×60.)

(c-*fms*), inhibiting the development of the monocyte/macrophage lineage and reverting the transformed phenotype of hemopoietic cell lines expressing the oncogene v-*fms*.[17-19] A recent case report[20] described a patient with LCH and cerebral involvement whose good clinical response to imatinib was attributed to a strong expression of *PDGFRB*. In contrast to that case, we could detect not only *PDGFRB* positivity but also KIT protein in the histiocytic infiltrate of our patient. Thus, we suggest that direct activity against histiocytes, modulation of cytokine expression within tissue and bone marrow infiltrates of non-LCH, or both, probably through the inhibition of *PDGFRB* and KIT, account for the strong activity of imatinib we observed in non-LCH.

Accepted for Publication: November 21, 2006.
Correspondence: Jochen Utikal, MD, Massachusetts General Hospital Cancer Center and Harvard Stem Cell Institute, 185 Cambridge St, Boston, MA 02114 (jutikal@mgh.harvard.edu).
Author Contributions: *Study concept and design:* Utikal, Ugurel, Hochhaus, Goerdt, and Schadendorf. *Acquisition of data:* Utikal, Kurzen, Erben, Reiter, Hochhaus, Nebe, Hildenbrand, Haberkorn, Goerdt, and Schadendorf. *Analysis and interpretation of data:* Utikal, Ugurel, Hochhaus, Haberkorn, Goerdt, and Schadendorf. *Drafting of the manuscript:* Utikal, Erben, and Schadendorf. *Critical revision of the manuscript for important intellectual content:* Utikal, Ugurel, Kurzen, Reiter, Hochhaus, Nebe, Hildenbrand, Haberkorn, Goerdt, and Schadendorf. *Obtained funding:* Hochhaus. *Administrative, technical, and material support:* Utikal, Kurzen, Reiter, Hochhaus, Nebe, Hildenbrand, Haberkorn, Goerdt, and Schadendorf. *Study supervision:* Utikal, Ugurel, Hochhaus, Goerdt, and Schadendorf.
Financial Disclosure: None reported.
Acknowledgment: We thank Jan Hastka, MD, and Georgia Metzgeroth, MD, for help with the molecular analysis.

REFERENCES

1. McClain KL, Natkunam Y, Swerdlow SH. Atypical cellular disorders. *Hematology Am Soc Hematol Educ Program.* 2004;1:283-296.

2. Weitzman S, Jaffe R. Uncommon histiocytic disorders: the non-Langerhans cell histiocytoses. *Pediatr Blood Cancer*. 2005;45:256-264.
3. Foucar E, Rosai J, Dorfman R. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): review of the entity. *Semin Diagn Pathol*. 1990; 7:19-73.
4. Goerdt S, Kolde G, Bonsmann G, et al. Immunohistochemical comparison of cutaneous histiocytoses and related skin disorders: diagnostic and histogenetic relevance of MS-1 high molecular weight protein expression. *J Pathol*. 1993; 170:421-427.
5. Utikal J, Klemke CD, Gratchev A, Goerdt S. Cutaneous non-Langerhans' cell histiocytoses. *J Dtsch Dermatol Ges*. 2003;1:471-491.
6. Schoch C, Schnittger S, Bursch S, et al. Comparison of chromosome banding analysis, interphase- and hypermetaphase-FISH, qualitative and quantitative PCR for diagnosis and for follow-up in chronic myeloid leukemia: a study on 350 cases. *Leukemia*. 2002;16:53-59.
7. Cross NC, Feng L, Bungey J, Goldman JM. Minimal residual disease after bone marrow transplant for chronic myeloid leukaemia detected by the polymerase chain reaction. *Leuk Lymphoma*. 1993;11:39-43.
8. Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med*. 2003;348:1201-1214.
9. Score J, Curtis C, Waghorn K, et al. Identification of a novel imatinib responsive KIF5B-PDGFRA fusion gene following screening for PDGFRA overexpression in patients with hypereosinophilia. *Leukemia*. 2006;20:827-832.
10. Cross NC, Melo JV, Feng L, Goldman JM. An optimized multiplex polymerase chain reaction (PCR) for detection of BCR-ABL fusion mRNAs in haematological disorders. *Leukemia*. 1994;8:186-189.
11. Emig M, Saussele S, Wittor H, et al. Accurate and rapid analysis of residual disease in patients with CML using specific fluorescent hybridization probes for real time quantitative RT-PCR. *Leukemia*. 1999;13:1825-1832.
12. Jones RL, Judson IR. The development and application of imatinib. *Expert Opin Drug Saf*. 2005;4:183-191.
13. van Oosterom AT, Judson I, Verweij J, et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. *Lancet*. 2001; 358:1421-1423.
14. Gayed I, Vu T, Iyer R, et al. The role of 18F-FDG PET in staging and early prediction of response to therapy of recurrent gastrointestinal stromal tumors. *J Nucl Med*. 2004;45:17-21.
15. Menzel C, Hamscho N, Dobert N, et al. PET imaging of Rosai-Dorfman disease: correlation with histopathology and ex-vivo beta-imaging. *Arch Dermatol Res*. 2003;295:280-283.
16. Harik L, Nassar A. Extranodal Rosai-Dorfman disease of the kidney and coexistent poorly differentiated prostatic adenocarcinoma. *Arch Pathol Lab Med*. 2006; 130:1223-1226.
17. Dewar AL, Domaschenz RM, Doherty KV, et al. Imatinib inhibits the in vitro development of the monocyte/macrophage lineage from normal human bone marrow progenitors. *Leukemia*. 2003;17:1713-1721.
18. Dewar AL, Cambareri AC, Zannettino AC, et al. Macrophage colony-stimulating factor receptor c-fms is a novel target of imatinib. *Blood*. 2005;105:3127-3132.
19. Taylor JR, Brownlow N, Domin J, Dibb NJ. FMS receptor for M-CSF (CSF-1) is sensitive to the kinase inhibitor imatinib and mutation of Asp-802 to Val confers resistance. *Oncogene*. 2006;25:147-151.
20. Montella L, Insabato L, Palmieri G. Imatinib mesylate for cerebral Langerhans'-cell histiocytosis. *N Engl J Med*. 2004;351:1034-1035.