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

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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.

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ON-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 immunohistochemical criteria of Langerhans cells. Clinically, non-LCH can be divided into 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 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

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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 1A), 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).
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 S100/H9252, 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 3A and B) and KIT (Figure 3C and D) but was negative for PDGFRα and macrophage colony-stimulating factor receptor protein.

A cytogenetic analysis that was performed on bone marrow aspirates according to standard protocols6 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 al7) 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 PDGFRα gene was analyzed with 2 different PCR assays. We screened for FIP1LI-PDGFRα fusion using a nested PCR8, in addition, possible alternative PDGFRα fusion genes with breakpoints in exon 12 of the PDGFRα 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 PDGFRα 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 S100/H9252 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.

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, PDGFRα, 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 PDGFRα 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.14,15

Recently, it has been shown that imatinib also targets the macrophage colony–stimulating factor receptor protein.
(c-fms), inhibiting the development of the monocyte/macrophage lineage and reverting the transformed phenotype of hemopoietic cell lines expressing the oncogene v-fms. A recent case report 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.

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REFERENCES


