Generalized Eruptive Histiocytosis Associated With
FIP1L1-PDGFRα-Positive Chronic Eosinophilic Leukemia

Birgit Ziegler, MD; Wiebke K. Peitsch, MD; Andreas Reiter, MD; Alexander Marx, MD; Sergij Goerdt, MD; Cyril Géraud, MD

Generalized eruptive histiocytosis (GEH) is a rare non-Langerhans cell histiocytosis with a benign, self-healing course. Neoplastic hematologic disorders of the myeloid lineage have been reported in association with GEH in 4 patients. A clonal association between GEH and the underlying leukemia was suspected in these patients but could only be confirmed in one patient.

Report of a Case

A male patient in his 20s presented with a 12-month history of asymptomatic red to brown macules and papules. A skin biopsy confirmed a diagnosis of GEH. His blood cell count revealed hypereosinophilia. Morphologic and molecular analyses from bone marrow and blood samples revealed FIP1L1-PDGFRα-positive chronic eosinophilic leukemia. The patient was treated with imatinib and achieved complete clinical remission of his leukemia and the GEH.

OBSERVATIONS

A male patient in his 20s presented with asymptomatic red to brown macules and papules. A skin biopsy confirmed a diagnosis of GEH. His blood cell count revealed hypereosinophilia. Morphologic and molecular analyses from bone marrow and blood samples revealed FIP1L1-PDGFRα-positive chronic eosinophilic leukemia. The patient was treated with imatinib and achieved complete clinical remission of his leukemia and the GEH.

CONCLUSIONS AND RELEVANCE

To our knowledge, this is the first report of a patient with GEH associated with FIP1L1-PDGFRα-positive chronic eosinophilic leukemia. Generalized eruptive histiocytosis in association with a myeloid neoplasm may occur in 2 variants: a reactive condition or a clonal derivative of the underlying leukemia. In this case, both diseases responded well after initiation of treatment with imatinib.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Birgit Ziegler, MD, Department of Dermatology, Venereology, and Allergology, University Medical Center, Medical Faculty Mannheim, University of Heidelberg, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany (birgit.ziegler@umm.de).

Published online April 29, 2015.

IMPORTANCE Generalized eruptive histiocytosis (GEH) is a rare non–Langerhans cell histiocytosis with a benign, self-healing course. Neoplastic hematologic disorders of the myeloid lineage have been reported in association with GEH in 4 patients. A clonal association between GEH and the underlying leukemia was suspected in these patients but could only be confirmed in one patient.

OBSERVATIONS A male patient in his 20s presented with asymptomatic red to brown macules and papules. A skin biopsy confirmed a diagnosis of GEH. His blood cell count revealed hypereosinophilia. Morphologic and molecular analyses from bone marrow and blood samples revealed FIP1L1-PDGFRα-positive chronic eosinophilic leukemia. The patient was treated with imatinib and achieved complete clinical remission of his leukemia and the GEH.

CONCLUSIONS AND RELEVANCE To our knowledge, this is the first report of a patient with GEH associated with FIP1L1-PDGFRα-positive chronic eosinophilic leukemia. Generalized eruptive histiocytosis in association with a myeloid neoplasm may occur in 2 variants: a reactive condition or a clonal derivative of the underlying leukemia. In this case, both diseases responded well after initiation of treatment with imatinib.
<11.5 ng/mL) and vitamin B₁₂ levels were elevated (>6000 pg/mL; reference range, 211-911 pg/mL; to convert to picomoles per liter, multiply by 0.7378). Serologic test results for human immunodeficiency virus and hepatitis A, B, and C as well as stool specimen and serologic test results for parasitic infections (Toxoplasma gondii and Echinococcus species) were negative.

Bone marrow morphologic analysis revealed hypercellularity with myeloid hyperplasia (especially eosinophils, eosinophilic promyelocytes, and myelocytes). Eosinophils were estimated to account for 20% of the cells (reference range, <5%). Reverse transcription–polymerase chain reaction analysis from RNA and complementary DNA extracted from peripheral blood nucleated cells was FIP1L1-PDGFRα fusion gene positive, consistent with FIP1L1-PDGFRα–positive chronic eosinophilic leukemia (CEL). To analyze whether GEH and CEL were clonally related, fluorescence in situ hybridization and reverse transcription–polymerase chain reaction for a FIP1L1-PDGFRα fusion gene were also performed on the formalin-fixed, paraffin-embedded tissues of bone marrow and skin biopsy specimens. However, because of the technical limitations of these techniques on formalin-fixed, paraffin-embedded tissue, it was not possible to evaluate the presence and cellular distribution of the fusion gene in these biopsy specimens with certainty. Therefore, it was not possible to assess whether the GEH and CEL were clonally related.

Because the tyrosine kinase inhibitor imatinib is approved by the US Food and Drug Administration as first-line treatment for FIP1L1-PDGFRα–positive CEL, treatment was initiated with 100 mg/d of imatinib. The CEL achieved complete hematologic and complete molecular remission on continued treatment of the patient with 100 mg/d of imatinib. Under this regimen, most of the skin lesions had resolved within 6 months, leaving behind some residual hyperpigmentation. No new lesions occurred during a follow-up period of 24 months.

**Discussion**

Although LCHs are a group of related diseases of clonally proliferative, neoplastic Langerhans cells, non-LCHs are a group of heterogeneous diseases usually characterized by a reactive infiltration of monocytes and macrophages. Among the non-LCHs, GEH was first described by Winkelmann and Müller in 1963 as a rare entity characterized by multiple self-healing, noncoalescing, symmetrical, red to brown papules distributed on the trunk and extremities and sparing the flexures. On histologic analysis, GEH lacks the lipid-laden foam cells and multinucleated giant cells that constitute hallmarks of the other multilesional non-LCH syndromes, such as xanthoma dis-
seminatum or multicentric reticulohistiocytosis. Usually, GEH tests CD68 positive, stablin 1 positive, CD1a negative, and S-100 protein negative. However, atypical expression of S-100 protein, as in our case, is described in some cases of non-LCHs, including GEH.6,7 Some authors regard each type of non-LCHs as a different stage of the same disease instead of a discrete entity. With this concept, GEH is seen as an initial stage of more mature non-LCHs.8 Usually, GEH is self-healing and therefore does not necessarily require treatment. If remission does not occur spontaneously, successful treatment has been reported with carbon dioxide laser therapy of localized lesions, cryotherapy, systemic psoralen–UV-A, hydroxychloroquine, oral isotretinoin, or systemic corticosteroids.9 With respect to our case, treatment with imatinib for patients with sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease), a variant of non-LCH, was successful in one patient but not in another.10,11 These conflicting findings may be explained by the reported differences in imatinib target gene expression. PDGFRB expression is found in histiocytes in the imatinib-responsive patients, whereas immunohistochemical analysis of the nonresponsive tumor is only weakly positive for PDGFRA. Likewise, imatinib responses in patients with cutaneous adult LCH are variable, indicating that imatinib responses are unsteady in LCH and non-LCH.12,13

Generalized eruptive histiocytosis is rarely associated with malignant hematologic disorders of the myeloid lineages.1-4 In 2 patients, the detection of a malignant tumor preceded the GEH1,2; in 1 patient and in our case, it occurred concomitantly with the GEH3; and in 1 patient, it followed the GEH.4 Two patients with GEH associated with hematologic malignant tumors had unusual features of the GEH, such as multiple lipid-laden histiocytes and numerous foreign-body giant cells seen histopathologically or a tendency of the lesions to coalesce without spontaneous resolution.4 The case reports do not provide sufficient information about whether the malignant tumor and the GEH followed similar courses.

Klemke et al5 speculated that atypical GEH and acute myeloid leukemia in their patient might have originated from the same neoplastic CD34+ stem cell. Indeed, a previous case report is the only other report that searched for a clonal association by molecular studies and provided evidence of this hy-
hypothesis by detecting the same deletion of the Y chromosome in chronic myelomonocytic leukemia and the associated GEH.1

For the first time, to our knowledge, our case report describes an association of GEH and CEL. Because of technical limitations, our molecular studies were not able to identify or exclude a clonal association between the 2 entities. Nevertheless, it can be hypothesized that there is either a clonal association between the 2 entities or an indirect, reactive, pathogenetic association between the CEL and GEH in our patient. The FIP1L1-PDGFRα fusion gene translates into a constitutively activate tyrosine kinase and causes the expansion of leukemic eosinophils. The activated eosinophils may also stimulate the development of skin-directed histiocyte precursors as bystander cells that evolve into full-blown non-LCH histiocytes in the skin. This process may be caused by an altered cytokine milieu in the bone marrow, circulation, and skin. In support of this notion, Hoermann et al34 reported that the FIP1L1-PDGFRα fusion protein induces expression of the cytokine oncostatin M in leukemic eosinophils. Of interest, oncostatin M drives macrophage differentiation toward M2 polarization, with M2 macrophages being the polarized macrophage phenotype also represented by stabilin 1-positive non-LCH histiocytes.15 Additional reports and molecular studies are necessary to improve our understanding of the molecular mechanisms that underlie the rare association of non-LCH with hematologic malignant tumors.

Conclusions
It is important to recognize that GEH, a generally benign disease, can be associated with leukemia. Therefore, patients with GEH should be screened thoroughly for associated hematologic disorders.

Conflict of Interest Disclosures: None reported.

REFERENCES