**Case Report/Case Series**

**Generalized Eruptive Histiocytosis Associated With FIP1L1-PDGFRA–Positive Chronic Eosinophilic Leukemia**

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**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-PDGFRA–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-PDGFRA–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.

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**Report of a Case**

A male patient in his 20s presented with a 12-month history of asymptomatic red to brown macules and papules without epidermal involvement that initially appeared on his trunk and subsequently spread to the upper and proximal lower extremities (Figure 1). The lesions were symmetrically distributed and did not coalesce. His face, distal extremities, and mucous membranes were unaffected. There was no lymphadenopathy. The patient reported that some lesions had resolved spontaneously with residual hyperpigmentation. The results of a review of systems were otherwise unremarkable. His medical history was also unremarkable, and he did not take any medication on a regular basis. Skin biopsy specimens from the chest and upper extremity were taken. On hematoxylin-eosin staining, a nodular infiltration of histiocytes intermingled with a few lymphocytes and eosinophils was seen in the upper dermis. No lipid-laden foam cells or multinucleated giant cells were detected among the infiltrating histiocytes (Figure 2, A and B). No epidermotropism was present, and the histiocytic infiltration and the epidermis were separated by a Grenz zone. On immunohistochemical analysis, the histiocytes were positive for CD68 and stabilin 1, heterogeneously and weakly positive for S-100 protein, and negative for CD1a (Figure 2, C and D). Computed tomography of the chest, abdomen, and pelvis and cranial magnetic resonance imaging did not reveal any pathologic findings. On the basis of the clinical presentation and the histologic findings, a diagnosis of non-LCH with major features of GEH was made.

Because GEH has been described in association with neoplastic hematologic disorders, a respective diagnostic workup was performed. The patient’s blood cell count revealed hypereosinophilia, with an absolute cell count of 4220/μL (reference range, 50-250/μL; to convert to ×10⁹/L, multiply by 0.001). In addition, tryptase (33.7 ng/mL; reference range,
<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-PDGFRA* fusion gene positive, consistent with *FIP1L1-PDGFRA*–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-PDGFRA* 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-PDGFRA*–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, stabilin 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. 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. 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. 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. 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.

Generalized eruptive histiocytosis is rarely associated with malignant hematologic disorders of the myeloid lineages. In 2 patients, the detection of a malignant tumor preceded the GEH; in 1 patient and in our case, it occurred concomitantly with the GEH; and in 1 patient, it followed the GEH. 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. The case reports do not provide sufficient information about whether the malignant tumor and the GEH followed similar courses.

Klemke et al 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 hyp-
hothorn et al 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. 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.

REFERENCES