Title
What's in a name? a new nomenclature has been proposed For eosinophilic dermatosis of hematologic malignancy (EDHM): hematologic-related malignancy-induced eosinophilic dermatosis (He Remained)

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Author
Cohen, Philip R

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What's in a name? a new nomenclature has been proposed For *e*osinophilic *d*ermatosis of *h*ematologic *m*alignancy (EDHM): *he*matologic-*re*lated *ma*lignancy-*in*duced *e*osinophilic *d*ermatosis (*He Remained*)

Philip R Cohen MD[1-4]

Affiliations: [1]San Diego Family Dermatology, National City, California, USA, [2]Touro University California College of Osteopathic Medicine, Vallejo, California, USA, [3]Scripps Family Medicine Residency, Scripps Mercy Hospital Chula Vista, Chula Vista, California, USA, [4]Family Medicine Residency, Family Health Centers of San Diego, San Diego, California, USA

Corresponding Author: Philip R Cohen MD, 10991 Twinleaf Court, San Diego, CA 92131-3643, Email: mitehead@gmail.com

Abstract

*He*matologic-*re*lated *ma*lignancy-*in*duced *e*osinophilic *d*ermatosis (*He Remained*) has recently been introduced as a new nomenclature to describe the eosinophilic dermatosis that has previously been observed in patients with hematologic malignancies. The condition has been reported in 208 patients; the ratio of men to women is 1.3:1. It is most commonly observed in chronic lymphocytic leukemia patients (77%, 160/208 patients). The chronic and relapsing eosinophilic dermatosis typically presents with pruritic lesions that are pleomorphic in morphology and mimic other conditions. The definitive pathogenesis of *He Remained* is still being established. However, neoplastic leukemia B cells — directly or indirectly (by stimulating a reactive polyclonal T cell response) — likely have an etiologic role in the pathogenesis of this condition in chronic lymphocytic leukemia patients. In addition, recruitment of eosinophils to the skin may occur secondary to an immune shift toward a T helper 2 type response, possibly caused by the neoplastic cells, that results in these T cells producing interleukin 4. Clinical observations, currently based on the prompt (within four weeks) and sustained (at least 12 weeks to 6 months) resolution of *He Remained* in two elderly men with *He Remained*, suggests that dupilumab may be the treatment of choice in chronic lymphocytic leukemia patients with this condition.

Keywords: chronic, dermatosis, dupilumab, eosinophil, eosinophilic, he, hematologic, leukemia, lymphocytic, malignancy, remained

To the Editor:

I read with interest the excellent report by Almeida et al. [1] that described a 71-year-old man with a prior history of chronic lymphocytic leukemia — without need of treatment for approximately 13 years. He then presented with the new onset of both pancytopenia (indicating the progression of his leukemia to myelodysplastic syndrome) and a pruritic eruption consisting of multiple, erythematous and violaceous, papules and nodules on his face, ear helices, and neck. Correlation of his clinical history (neither medications nor insect bites), cutaneous lesion morphology, and pathology results (dilated capillaries with a superficial perivascular and interstitial mixed inflammatory infiltrate of neutrophils and numerous eosinophils) suggested the correct diagnosis. In addition, he had negative studies (including serologic testing for human immunodeficiency virus, syphilis, and hepatitis, skin biopsy for direct immunofluorescence and bullous pemphigoid antigen-1 and enzyme-linked immunosorbent assays for bullous pemphigoid antigen-2) that established a diagnosis of eosinophilic dermatosis of hematologic malignancy. He received symptomatic treatment for his skin condition with oral antihistamines; however, his condition rapidly deteriorated and he died. The authors emphasize that more effective treatment modalities for this condition need to be investigated [1].

The term *e*osinophilic *d*ermatosis of *h*ematologic *m*alignancy (EDHM) was proposed by Farber et al. [2] in 2012. However, the condition was originally

Table 1. *Nomenclature of the condition observed in patients with a hematologic malignancy whose cutaneous lesions had eosinophils in the dermis.*

Author (Year of publication)	Nomenclature	Reference
Weed (1965)	Exaggerated delayed hypersensitivity to mosquito bite in chronic lymphocytic leukemia	[3]
Barzilai et al. (1994)	Insect bite-like reaction in patients with hematologic malignant neoplasm	[4]
Byrd et al. (2001)	Eosinophilic dermatosis of myeloproliferative disease	[5]
Farber et al. (2012)	Eosinophilic dermatosis of hematologic malignancy	[2]
Visseaux et al. (2018)	T-cell papulosis associated with B-cell malignancy: TCP-BCM	[6]
Cohen (2020)	Hematologic-related malignancy-induced eosinophilic dermatosis: He Remained	[7]

reported in 1965 by Weed [3] as an exaggerated delayed hypersensitivity reaction to mosquito bites in eight patients with chronic lymphocytic leukemia. Subsequently, the condition has been referred to by other designations (**Table 1**), [2-7].

There is a need for a unifying nomenclature for cutaneous eruptions associated with hematologic malignancies. Visseaux et al. [8] recommended that a descriptive denomination, that does not predict any hypothesized mechanism of pathophysiology, be used to name the condition. In contrast, Maglie et al. [9] suggested that introducing a new definition for the disease should incorporate not only its polymorphic clinical morphology but also its relapsing and chronic course.

More recently, a new nomenclature for this condition (*he*matologic-*re*lated *ma*lignancy-*in*duced *e*osinophilic *d*ermatosis: *He Remained*) was introduced [7]. The terminology emphasizes not only the relationship with hematology disorders but also that the pathogenesis is induced by the associated malignancy. The proposed acronym, *He Remained*, has already been acknowledged by other investigators [10].

He Remained has been reported, to the best of my knowledge, in 208 patients. This includes 109 men (56% of 195 individuals) and 86 women (44% of 195 individuals). The gender was not described in 13 of the patients [1, 7, 11].

The most common hematologic malignancy associated, observed in 77% (160 of 208 patients) with *He Remained* is chronic lymphocytic leukemia. Lymphomas (17%, 34 of 208 patients), other leukemias (3.5%, 7 of 208 patients) and other hematologic disorders (2.5%, 5 of 208 patients) were also other hematologic malignancies in individuals with disease-associated eosinophilic dermatosis (**Table 2**), [1, 7, 11]. Oncology patients with solid tumors have not been observed to develop this condition.

There are multiple clinical morphologies for the typically pruritic *He Remained* skin lesions including papules, nodules, urticarial plaques, vesicles, and bullae [7, 12, 13]. Indeed, the cutaneous manifestations of *He Remained* can masquerade as other eosinophilic dermatoses such as arthropod assault reaction, bullous pemphigoid, cellulitis

Table 2. *Hematologic malignancies in patients with disease-related eosinophilic dermatosis.*

Malignancy	Number of patients	Percent of patients
Chronic lymphocytic leukemia	160	77.0
Lymphomas[a]	34	17.0
Other leukemias[b]	7	3.5
Other hematologic disorders[c]	5	2.5
Total	208	100.0

[a]These include non-hodgkin lymphoma (14 patients), mantle cell lymphoma (9 patients), mucosa-associated lymphoid tissue lymphoma (3 patients), diffuse large B-cell lymphoma (1 patient), follicular lymphoma (1 patient), large cell lymphoma (1 patient), lymphocytic B-cell lymphoma (1 patient), lymphoplasmacytic lymphoma (1 patient), mycosis fungoides (1 patient), nodal marginal cell lymphoma (1 patient) and T-cell lymphoma (aggressive, 1 patient).

[b]These include acute leukemia (4 patients), acute lymphoblastic leukemia (1 patient), acute monocytic leukemia (1 patient) and acute myeloid leukemia (1 patient).

[c]These include multiple myeloma and monoclonal gammopathy of undetermined significance (3 patients), myelodysplastic syndrome (1 patient) and myelofibrosis (1 patient).

Box 1. *Clinical differential diagnosis of hematologic-related malignancy-induced eosinophilic dermatosis (He Remained).*

Acute febrile neutrophilic dermatosis (Sweet syndrome)
Arthropod assault reaction
Bacterial infection
Bullous pemphigoid
Drug eruption
Dermatitis herpetiformis
Eosinophilic cellulitis (Wells syndrome)
Eosinophilic folliculitis
Leukemia cutis
Mycosis fungoides
Pemphigus vulgaris
Scabies
Varicella zoster virus infection

(eosinophilic, also referred to as Wells syndrome), and folliculitis (eosinophilic). In addition, there are several conditions that can mimic the appearance of *He Remained*. These include autoimmune disorders, infections, exogenous conditions, neoplasm, and reactive dermatoses (**Box 1**), [7, 9-12, 14].

The pathogenesis of *He Remained* is yet to be definitively established. Earlier researchers speculated that the condition was caused by insect bite hypersensitivity [3, 4]. However, neither insect bites nor exposure to insects were experienced by several of the *He Remained* patients [12].

Currently there are various, potentially complementary and not necessarily mutually exclusive, hypotheses. One group of investigators demonstrated that in patients with chronic lymphocytic leukemia, up to 20% of the lymphocytes in the *He Remained* dermal infiltrate are neoplastic B cells. Hence, the leukemic B cells — directly or indirectly (by stimulating a reactive polyclonal T cell response) — have an etiologic role in the pathogenesis of this condition [6, 10, 15]. Indeed, the neoplastic cells may cause an immune shift toward a T helper 2 type response which could result in the production of cytokines, such as interleukin 4, from these T cells and the subsequent recruitment of eosinophils to the skin [8-10].

The clinical course of *He Remained* is chronic and relapsing. Patients often initially respond to either systemic corticosteroids or antineoplastic therapy or both. However, the condition usually recurs [7, 12].

Numerous other treatments have been utilized, with variable degrees of short-term success, to manage patients with *He Remained*. These include antibiotics, antihistamines, dapsone, interferon alpha, intravenous immunoglobulin, nicotinamide, phototherapy, radiation, and topical corticosteroids [12, 13]. Omalizumab, a recombinant humanized monoclonal antibody against human immunoglobulin E, which only binds to free immunoglobulin E, has been suggested as a

Table 3. *Characteristics of He Remained patients successfully treated with dupilumab*[a].

C	A R S	HM	CLL Tx	OF	Prior Th	Comments	Ref
1	81 Hs M	CLL	Rtxmb Chlor	LC	OCs	The chest, face and scalp He Remained lesions had resolved by the 4-week follow-up visit (after 2 injections). The complete response was sustained for more than 6 months with continued CLL and dupilumab treatment.	[11]
2	82 NS M	CLL	Chemo	Pru	OCs TCI TCs	He had chronic pruritus and a NRSII of 6/10 prior to treatment; it decreased to 0/10 at the 4-week follow-up visit. The complete response was sustained; at 12-weeks of follow-up, the NRSII was still 0/10 and there had been no adverse events.	[17]

Abbreviations: A, age (years); C, case; Chemo, chemotherapy, not otherwise specified; Chlor, chlorambucil; CLL, chronic lymphocytic leukemia; He Remained, hematologic-related malignancy-induced eosinophilic dermatosis; HM, hematologic malignancy; Hs, Hispanic; LC, leukemia cutis; M, man; NRSII, numeric rating scale itch intensity; NS, not stated; OCs, oral corticosteroids; OF, Other features; Pru, pruritus; R, race; Ref, reference; Rtxmb, rituximab; S, sex, TCI, topical calcineurin inhibitors; TCs, topical corticosteroids; Th, therapy (for He Remained); Tx, treatment

[a]The patients received the standard subcutaneous dosing regimen of dupilumab used for atopic dermatitis: induction dose of 600 milligrams, followed every 2 weeks thereafter by 300 milligrams.

potential therapy based upon its successful use in patients with eosinophilic cellulitis — a condition that has a clinical and pathologic presentation similar to *He Remained* [9, 10, 16].

Recent reports have described prompt and persisting resolution of *He Remained* with dupilumab (**Table 3**), [11, 17]. Two octogenarian men with chronic lymphocytic leukemia had *He Remained* that had not only failed systemic corticosteroids but also persisted during leukemia-directed therapy. Both patients achieved a rapid response with complete clearing of their leukemia-associated cutaneous eosinophilic dermatosis within four weeks after initiating treatment with subcutaneously administered dupilumab. The dramatic resolution of symptoms and clinical lesions was sustained without relapse at the 12-week [17] and 6-month [11] follow-up visits.

Dupilimab is currently approved for the management of patients with asthma, atopic dermatitis, and chronic rhinosinusitis with nasal polyposis. It is a fully human immunoglobulin G4 monoclonal antibody that inhibits both interleukin 4 and interleukin 13 signaling pathways by recognizing the alpha subunit receptor site for interleukin 4. Hence, dupilimab may exert its beneficial action in chronic lymphocytic leukemia patients with *He Remained* by attenuating excess interleukin 4 levels or interfering with the downstream effects of interleukin 4, or both, in these individuals [7, 10, 11, 17, 18].

In conclusion, *He Remained* is a simple acronym that is not only easy-to-remember but also relevant to the patient's history of a blood dyscrasia, the etiology of the condition, and the unifying pathology of the diverse clinical lesions associated with the condition. The first word and initial two letters of the second word (He Re) represent the first two letters of the following words: 'hematologic-related;' this is to emphasize the condition's relationship to hematologic cancers such as chronic lymphocytic leukemia. The third, fourth, fifth and sixth letters of the second word (main) refer to the first two letters of the following words: 'malignancy-induced;' this is to emphasize the mechanism of pathogenesis for the condition. The final two letters of the second word (ed) represent the first letter of the following words: 'eosinophilic dermatosis;' this is to emphasize the associated pathology for the pleomorphic cutaneous lesions. A direct or indirect effect of the neoplastic B cells in patients with chronic lymphocytic leukemia, with or without an associated immune shift toward a T helper 2 type response, likely has a role in the etiology of the condition. Clinical observations suggest that dupilumab may be the treatment of choice for *He Remained* in chronic lymphocytic leukemia patients.

Potential conflicts of interest

Dr. Cohen is a paid consultant for ParaPRO; however, this activity has no influence as a potential conflict of interest with regards to the manuscript.

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