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Generalized Pruriginous Eruption on a Patient With Leukemia

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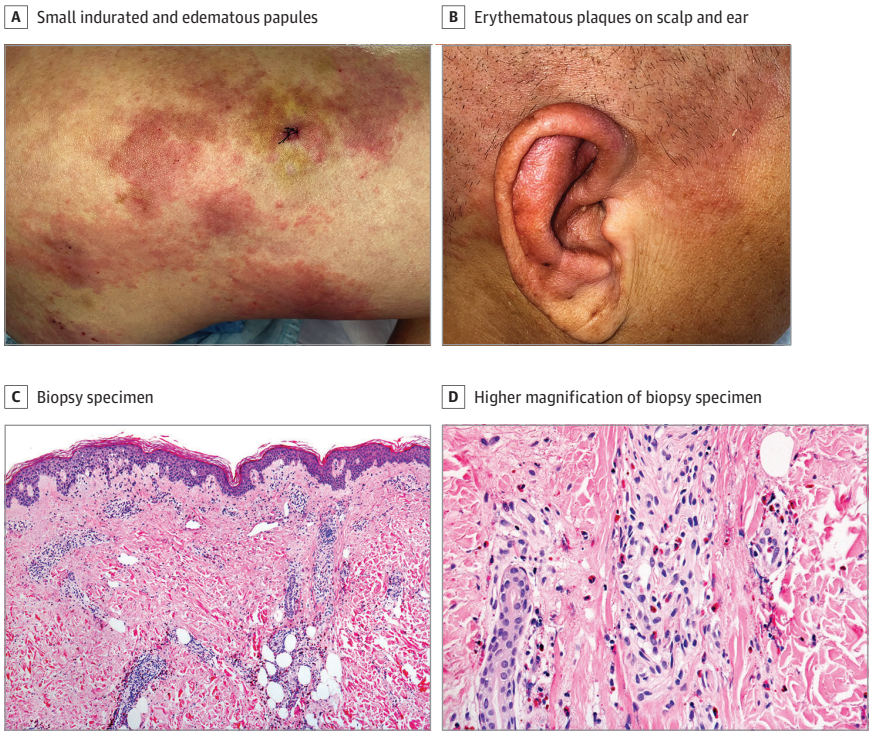

Figure. A, Erythematous indurated and edematous papules and plaques on the thighs with some residual discoloration. B, Large erythematous plaques involving the scalp and ear. C, Hematoxylin-eosin–stained histologic specimen showing a superficial and deep dermal perivascular and interstitial mononuclear infiltrate with numerous eosinophils (original magnification ×40). D, Higher magnification of C showing an abundant number of eosinophils in the infiltrate (original magnification ×400).

A woman in her 50s with a recent diagnosis of acute myeloid leukemia (subtype M5a, French-American-British classification) was admitted to the hospital for induction chemotherapy. At presentation she had a 3-week history of a striking pruritic and generalized cutaneous eruption. The patient otherwise felt well and denied fever, malaise, insect bites, or starting new drug treatments. Except for leukopenia and a slightly elevated C-reactive protein level, results of other routine blood and urine tests were unremarkable. Physical examination revealed an erythematous eruption composed of small indurated and edematous papules (**Figure**, A and B). Confluent papules leading to large urticariform plaques, some with annular configuration, were present on the flanks, lower legs, breasts, and scalp. Hyperpigmented patches and focal areas of bruiselike discoloration were seen adjacent to acute lesions. Mucous membranes, palms, and soles were spared. A biopsy specimen was obtained (Figure, C and D).

WHAT IS YOUR DIAGNOSIS?

- **A.** Drug reaction with eosinophilia and systemic symptoms
- **B.** Eosinophilic dermatosis of hematologic malignancy
- **C.** Urticarial vasculitis
- **D.** Urticarial bullous pemphigoid

Diagnosis

B. Eosinophilic dermatosis of hematologic malignancy

Microscopic Findings and Clinical Course

The biopsy revealed an intense perivascular and interstitial mononuclear infiltrate, with abundant admixed eosinophils in the superficial and deep dermis that extended to subcutaneous fat. No signs of vasculitis were seen. Results of direct immunofluorescence studies were negative for IgG, IgA, IgM, and C3. Correlation of the clinical features, histopathologic findings, and laboratory tests led to the diagnosis of eosinophilic dermatosis of hematologic malignancy (EDHM).

The patient was treated with potent topical corticosteroids twice a day with little response. Treatment with oral prednisone, 30 mg/d, was initiated with rapid improvement of the lesions and the pruritus with no relapses at last examination.

Discussion

EDHM is a rare condition characterized by tissue eosinophilia arising in the context of hematologic disease. It was originally interpreted as an exaggerated and specific hypersensitivity reaction to mosquito bites in patients with chronic leukemia.[1] Although some of the reported dermatoses in the setting of hematologic disease may indeed represent an actual exaggerated response to insect bites,[2] it is now considered a distinct entity.[3-5]

EDHM usually presents as a widespread eruption involving mostly the lower and upper limbs.[4] The spectrum of clinical manifestations varies from erythema, papules, plaques, and nodules, most with a smooth or indurated surface, to vesicles or tense blisters and color ranging from slightly pink to bright red or cyanotic hues.[3,4]

The pathogenesis of EDHM is poorly understood. An altered immunologic response has been ascribed to underlying malignancy, resulting in an eosinophil-rich eruption in which interleukin 5 probably plays an important role.[6] Neoplastic B cells have been found in the skin infiltrate, which supports the hypothesis that leukemic cells may also play a pathogenetic role.[7]

EDHM has been reported in the setting of multiple hematologic malignancies; the majority of affected patients had chronic lymphocytic leukemia. It has also been associated with acute lymphoblastic and monocytic leukemia and B-cell non-Hodgkin lymphomas, among many others.[3,4,6] The eruption often occurs concurrently with or years after the hematologic diagnosis, but it can also precede it. Although a rapidly progressive course of the associated malignancy has been observed,[8] there is no evidence to suggest that EDHM adversely affects its prognosis.[4]

Histopathologically, lesions typically display a superficial and deep dense perivascular infiltrate of lymphocytes accompanied by numerous eosinophils, arranged both perivascularly and interstitially. Eosinophils may be present both within the epidermis associated with spongiosis and in the subcutis.[5]

Although standardized treatment protocols are lacking, systemic corticosteroids usually prompt responses. Several other options have been reported, including chemotherapy, antibiotics, antihistamines, dapsone, interferon alfa, phototherapy, and dupilumab, with some providing good responses.[2-5,8,9]

Histopathologic study is crucial for differential diagnosis. In the urticarial stage of bullous pemphigoid—the most common autoimmune blistering skin disease—edema is usually seen in the superficial dermis and eosinophils are founded at the upper dermis as well as aligning at the dermal-epidermal junction and in a spongiotic epidermis. Direct immunofluorescence microscopy shows linear IgG and C3 fluorescence along the epidermal basement membrane. Drug reaction with eosinophilia and systemic symptoms is an uncommon multiorgan adverse drug reaction. Fever, morbilliform eruption, and a prominent peripheral blood eosinophilia are common manifestations. Although there are no specific histopathologic findings, they consist mainly of lymphocyte exocytosis; spongiosis; scattered keratinocyte necrosis; vacuolization of the basal layer; superficial perivascular or junctional lymphocytic infiltration, often with eosinophils and extravasated erythrocytes; swollen endothelial cells; and intravascular neutrophils but no vasculitis. Urticarial vasculitis is a clinicopathologic entity consisting of persistent urticarial lesions that regress, leaving residual purpuric macules with histopathologic features of leukocytoclastic vasculitis—namely, neutrophilic infiltrate with leukocytoclasia, red blood cell extravasation, and fibrinoid necrosis of small blood vessel walls.

In conclusion, EDHM is a disease that could be underdiagnosed and may mimic many other entities. A specific diagnosis of this entity is important as it could lead to the diagnosis of an unknown hematologic neoplasm or point out a recurrence in a patient with a personal history of it.[8]

ARTICLE INFORMATION

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REFERENCES

1. Weed RI. Exaggerated delayed hypersensitivity to mosquito bites in chronic lymphocytic leukemia. *Blood*. 1965;26:257-268. doi:10.1182/blood.V26.3.257.257

2. Davis MD, Perniciaro C, Dahl PR, Randle HW, McEvoy MT, Leiferman KM. Exaggerated arthropod-bite lesions in patients with chronic lymphocytic leukemia. *J Am Acad Dermatol*. 1998;39(1):27-35. doi:10.1016/S0190-9622(98)70398-6

3. Byrd JA, Scherschun L, Chaffins ML, Fivenson DP. Eosinophilic dermatosis of myeloproliferative disease. *Arch Dermatol*. 2001;137(10):1378-1380.

4. Grandi V, Maglie R, Antiga E, et al. Eosinophilic dermatosis of hematologic malignancy. *J Am Acad Dermatol*. 2019;81(1):246-249. doi:10.1016/j.jaad.2018.11.048

5. Farber MJ, La Forgia S, Sahu J, Lee JB. Eosinophilic dermatosis of hematologic malignancy. *J Cutan Pathol*. 2012;39(7):690-695. doi:10.1111/j.1600-0560.2012.01906.x

6. Agnew KL, Ruchlemer R, Catovsky D, Matutes E, Bunker CB. Cutaneous findings in chronic lymphocytic leukaemia. *Br J Dermatol*. 2004;150(6):1129-1135. doi:10.1111/j.1365-2133.2004.05982.x

7. Meiss F, Technau-Hafsi K, Kern JS, May AM. Eosinophilic dermatosis of hematologic malignancy. *J Cutan Pathol*. 2019;46(3):175-181. doi:10.1111/cup.13389

8. Lucas-Truyols S, Rodrigo-Nicolás B, Lloret-Ruiz C, Quecedo-Estébanez E. Eosinophilic dermatosis of hematologic malignancy. Article in Spanish. *Actas Dermosifiliogr*. 2017;108(6):e39-e44. doi:10.1016/j.ad.2016.10.021

9. Jin A, Pousti BT, Savage KT, Mollanazar NK, Lee JB, Hsu S. Eosinophilic dermatosis of hematologic malignancy responding to dupilumab in a patient with chronic lymphocytic leukemia. *JAAD Case Rep*. 2019;5(9):815-817. doi:10.1016/j.jdcr.2019.07.026