

Neutrophilic Eccrine Hidradenitis: A Case Report and Literature Review

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Neutrophilic eccrine hidradenitis (NEH) is a dermatitis defined by an intense infiltrate of neutrophils surrounding the eccrine gland coil.¹ Associated histologic findings include necrosis of eccrine cells, vacuolization, dyskeratosis, nuclear pyknosis, and squamous metaplasia.¹⁻⁴ Presenting as a rash and associated with fever, NEH runs a benign course lasting 1 to 3 weeks.

Initially characterized by Harrist et al,¹ NEH was found to be associated with acute myelogenous leukemia (AML) and induction chemotherapy with cytosine arabinoside. Subsequently, NEH has been reported in patients with Hodgkin's lymphoma, HIV, osteosarcoma, metastatic breast cancer, and Wilms' tumor, and in patients taking acetaminophen therapy.¹⁻¹⁶ Although diverse in associations, NEH has been linked most consistently to AML and cytarabine therapy.¹⁶ This article discusses a case of NEH in a 44-year-old woman. Pathophysiology, treatment, and a review of the literature are also presented.

CASE PRESENTATION

Initial Presentation

A 44-year-old woman presents to her primary care physician with a 1-week history of fatigue, myalgias, headache, and fever. Complete blood cell count (CBC) reveals a leukocyte count of $17 \times 10^9/L$. The patient is treated with antibiotics for a suspected bacterial infection.

Presentation 10 Days Later

Ten days after her initial presentation she returns to her physician complaining of a severe headache, low-grade temperature, worsening fatigue, nonproductive cough, swollen cheeks, and pain below her ears. A second CBC demonstrates a leukocyte count of $34 \times 10^9/L$ with 20% myeloblasts. The patient is referred to the hospital for further evaluation and management.

Hospitalization

Fourteen days after the patient's initial presentation, bone marrow biopsy confirms a diagnosis of AML. Morphology, cytochemistry, and flow cytometric analysis of the cell surface markers are consistent with the myelomonocytic subtype FAB M4 (**Figure 1**). The patient is placed on a 3-day course of idarubicin ($12 \text{ mg/m}^2/\text{day}$) and on a 7-day course of cytarabine ($100 \text{ mg/m}^2/\text{day}$).

Days five and six. On the fifth day of treatment, the patient develops a low-grade fever and a rash consisting of blanching urticarial papules and plaques, some with central pustules, primarily on her upper chest and middle and upper back. Scattered lesions are also present on her upper arms and left knee. The patient's leukocyte count is $0.964 \times 10^9/L$. Ciprofloxacin, fluconazole, and acyclovir are started. On the sixth day of treatment, the rash worsens on her trunk, arms, and neck. The patient also develops a blanching confluent macular and somewhat pruritic rash on her abdomen and flanks.

Days seven through 10. Chemotherapy is completed on the seventh day of therapy, but both rashes worsen. On the eighth day of treatment the patient develops a clustering monomorphous vesicular rash with underlying erythema on the flexor surfaces of her arms (**Figure 2**). Lesion biopsy is ordered. During the ninth day of treatment, the vesicular rash coalesces into painful plaques with superimposed vesicles spreading to both flexor and extensor surfaces of the patient's arms, chest, and back (**Figure 3**). On day 10 of therapy,

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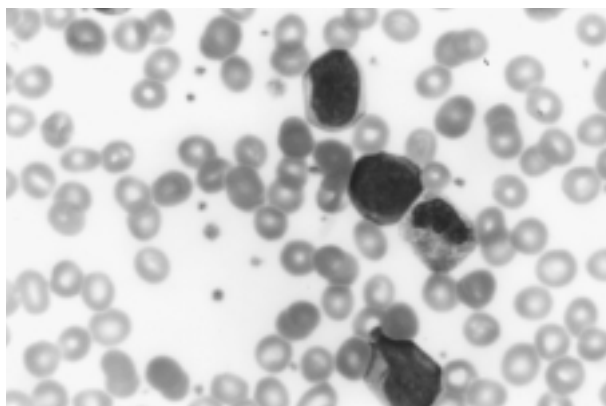


Figure 1. Peripheral blood smear showing acute myelomonocytic leukemia.

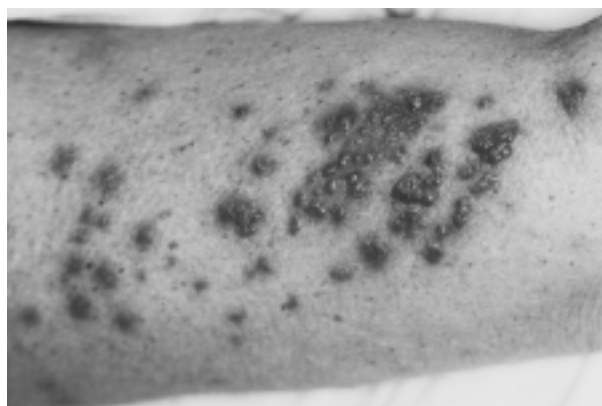


Figure 2. Photograph of monomorphous vesicular rash with underlying erythema on the flexor surface of the patient's left arm.



Figure 3. Photograph of plaques with superimposed vesicles on the patient's chest.

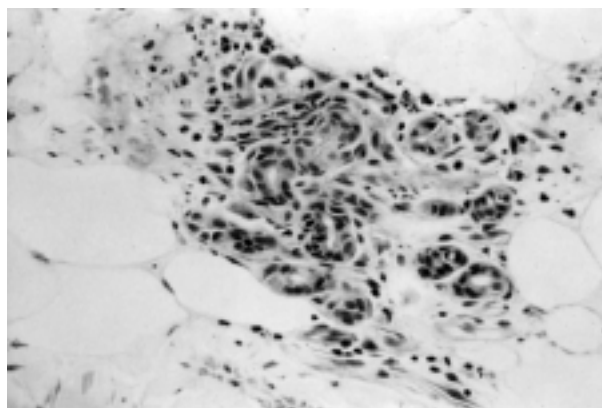


Figure 4. Skin biopsy demonstrating mixed infiltrate consisting of lymphocytes, histiocytes, eosinophils, and neutrophils.

the rash appears more severe. Domeboro soaks (aluminum subacetate) are started.

Days 11 through 13. On day 11 of treatment, the rash decreases in severity for the first time, and on day 12 of treatment the patient's fever reduces as the rash continues to regress. The patient's leukocyte count is $0.335 \times 10^9/L$. Bone marrow biopsy on day 13 demonstrates no evidence of leukemic cells. Blood, skin, urine, and fecal pathogen cultures remain negative, despite multiple specimens on consecutive days.

Results of lesion biopsy and clinical appearance. Punch biopsy of the clustering monomorphous vesicular rash from the flexor surface of the patient's left arm (obtained on treatment day eight) is reviewed by a dermatopathologist and shows evidence of NEH. A basket-weave orthokeratosis with moderate epidermal hyperplasia and a neutrophilic infiltrate around the coils of the eccrine glands are demonstrated. Focal areas of

spongiosis with exocytosis of lymphocytes, eosinophils, and neutrophils are evident.

Evidence of microabscess formation is demonstrated within the epidermis, in the papillary dermis, and around both acrosyringia and follicular units. Necrotic keratinocytes are evident within the epidermis, and the dermal-epidermal junction is intact. Prominent interstitial edema of the papillary dermis is present. The remaining dermis demonstrates a moderate superficial, deep perivascular, and interstitial mixed infiltrate consisting of lymphocytes, histiocytes, eosinophils, and neutrophils (**Figure 4**).

DISCUSSION

NEH is a self-limiting dermatosis commonly associated with chemotherapy. A wide variety of clinical lesions (ie, plaques, nodules, papules, and pustules) have been reported in association with NEH.⁷ Most lesions have an

Table 1. Hypothetical Mechanisms of Neutrophilic Eccrine Hidradenitis

Neutrophil attraction secondary to local chemotactic factors or abnormal neutrophil function and response; the subsequent release of neutrophil hydrolytic enzymes causes eccrine coil epithelial necrosis (Harrist TJ, Fine JD, Berman, et al. Arch Dermatol 1982;118:263–266)	Primary necrosis of eccrine apparatus with a secondary infiltration of neutrophils; a high concentration of the chemotherapeutic agent in the sweat could account for necrosis, but authors are unaware of documentation of the concentration of chemotherapeutic agents in sweat (Scallan PJ, Kettler AH, Levy ML, Tschen JA. Cancer 1988;62:2532–2536)
Secretion and concentration of drug (cytarabine) by eccrine gland manifestation of acute leukemia (Flynn TC, Harrist TJ, Murphy GF, et al. J Am Acad Dermatol 1984;11:584–590)	Absence of inflammatory infiltrate in patients suggests direct toxic effect of chemotherapeutic drugs on sweat gland apparatus; toxic effect of a cross-reacting antibody or other drug reactions cannot be completely ruled out (Hurt MA, Halvorson RD, Petr FC Jr, et al. Arch Dermatol 1990;126:73–77)
Cellular damage caused by chemotherapeutic drugs and release of mediators, such as prostaglandins or leukotrienes, secondary to neutrophil attraction (Fitzpatrick JE, Bennion SID, Reed OM, et al. J Cutan Pathol 1987;14:272–278)	Localization in the epidermis after transfer through the eccrine duct may again concentrate the toxic substance and lead to focal epidermal changes in the acrosyringium as have been observed in NEH (Smith KJ, Skelton HG, James WD, et al. J Am Acad Dermatol 1990;23:945–947)
General reaction pattern to chemotherapy (Beutner KR, Packman CH, Markowitch W. Arch Dermatol 1986;122:809–811)	More than one factor may be required to initiate NEH (Margolis DJ, Gross PR. Cutis 1991;48:198–200)
NEH is a point on the spectrum of neutrophilic dermatosis (Beutner KR, Packman CH, Markowitch W. Arch Dermatol 1986;122:809–811)	Because chemotherapy, like transretinoic acid, is able to induce the differentiation of leukemic blast cells, it is possible that such maturation occurred in some patients and that the enhanced chemotaxis to the skin was carried out on clonal neutrophils derived from leukemic precursors, leading to clinical picture of neutrophilic dermatosis (Aractingi S, Mallet V, Pinquier L, et al. Arch Dermatol 1995;131:1141–1145)
Doxorubicin exerts toxic effect on eccrine epithelial cells with subsequent local release of chemotactic factors and secondary neutrophilic infiltration (Katsanis E, Luke KH, Hsu E, et al. Am J Pediatr Hematol Oncol 1987;9:204–208)	
Neutrophil infiltrate is secondary to direct tissue injury from chemotherapy and may or may not be associated with neutrophilic infiltrate (Greenbaum BH, Heymann WR, Reid CS, et al. Med Pediatr Oncol 1988;16:351–355)	
Chemotherapeutic agents and/or one of their metabolites are excreted and possibly concentrated in eccrine ducts with neutrophilic accumulation secondary to local release of chemotactic factors after degeneration of epithelium (Bailey DL, Barron D, Lucky AW. Pediatr Dermatol 1989;6:33–38)	

NEH = neutrophilic eccrine hidradenitis.

erythematous component; some lesions are tender, edematous, or hemorrhagic.⁷ The differential diagnosis for such lesions includes leukemia cutis, bullous pyoderma, pyoderma gangrenosum, erythema multiforme, Sweet's syndrome, drug hypersensitivity, and vasculitis.^{1,2,8} Histologically, only NEH has a pronounced neutrophilic infiltration of the lower dermis around the eccrine glands.¹

Etiology and Pathophysiology

Many authors have speculated about the etiology of NEH. Harrist et al¹ initially hypothesized that the neutrophilic accumulation around the eccrine cells was either caused by local chemotactic factors or developed secondary to abnormal neutrophil function and response. Harrist et al¹ further suggested that both of these mechanisms could be caused by an unusual toxic

chemotherapeutic reaction. The most popular etiologic theory is that the chemotherapeutic agent is concentrated in the eccrine sweat gland and directly damages the gland, leading to the release of chemotactic factors and the accumulation of neutrophils.^{1–3,5,8,9,11,12,16} Some authors hypothesize that NEH may represent a neutrophilic dermatosis associated with an underlying malignancy (Table 1).^{1,4,5,7,8}

The development of rash after antineoplastic therapy and the histologic appearance of the neutrophil infiltrate at a time of absolute neutropenia in the patient's circulation are curious features of NEH associated with AML. Aractingi et al¹⁷ recently suggested that NEH is actually a unique subtype of neutrophilic dermatosis in which antineoplastic chemotherapy induces the differentiation of myeloid leukemia blast cells into neutrophils. In this hypothesis, the leukemia blasts

disappear from circulation because they develop mature morphology and differentiated functional characteristics, which allows margination, diapedesis, and accumulation in tissues. In the skin, these clonal neutrophils are presumably attracted to the eccrine gland coils either by an undescribed chemotactic signal or by the presence of necrotic cellular debris from direct chemical injury.

Treatment

There is no generally accepted treatment for NEH; therefore, many different approaches have been attempted. Fever is commonly present, and empiric antibiotic therapy is often started secondary to neutropenia. Intravenous corticosteroids were administered in a total of five reported cases.^{15,17,18} Intravenous corticosteroids in one patient resulted in resolution of both fever and rash-associated pain within 24 hours.¹⁵ Another patient experienced resolution of symptoms with oral naproxen (375 mg three times daily).³ Ibuprofen prescribed for fever in a patient resulted in resolution of the rash.¹⁹ Dapsone was successfully used in one instance of recurrent NEH.¹⁹

SUMMARY

A rare condition initially described in association with patients given chemotherapy for AML, NEH is a self-limiting dermatosis. More recently NEH has been associated with chronic renal failure, trauma, HIV, and granulocyte colony-stimulating factor. Although many authors have theorized about the pathological mechanism, no etiology is widely accepted mainly because of the lack of direct clinical and experimental evidence. No clearly superior treatment exists.

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