Erythematous Dermal Facial Plaques in a Neutropenic Patient

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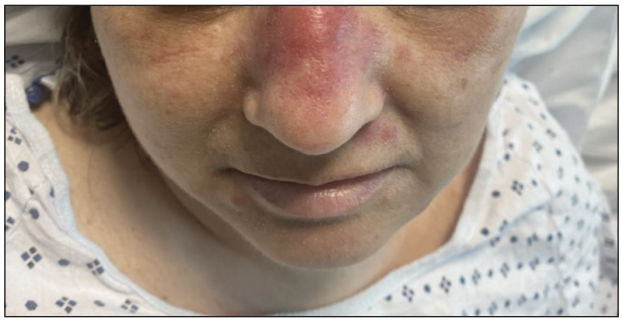

A 50-year-old woman undergoing cytarabine induction therapy for acute myeloid leukemia developed tender, erythematous, dermal plaques on the nasal dorsum, left medial eyebrow, left preauricular cheek, and right cheek. The rash erupted 7 days after receiving the cytarabine induction regimen. She had a fever (temperature, 39.9 °C [103.8 °F]) and also was neutropenic.

WHAT'S YOUR **DIAGNOSIS?**

a. bacterial cellulitis
b. leukemia cutis
c. neutrophilic eccrine hidradenitis
d. Sweet syndrome
e. Well syndrome (eosinophilic cellulitis)

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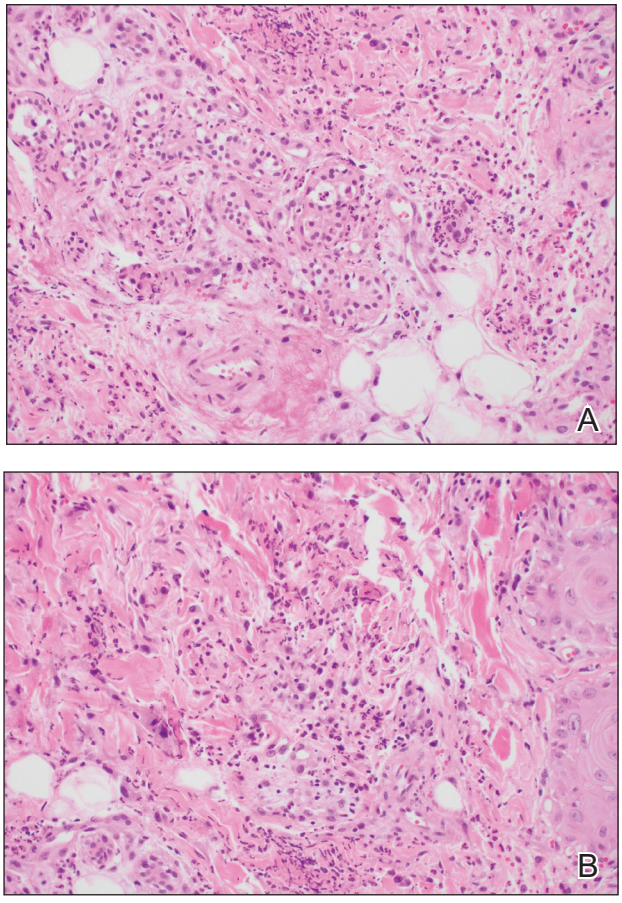
THE **DIAGNOSIS:** Neutrophilic Eccrine Hidradenitis

A biopsy from the left preauricular cheek demonstrated dermal neutrophilic inflammation around eccrine coils with focal necrosis (Figure). No notable diffuse dermal neutrophilic infiltrate was present, ruling out Sweet syndrome, and no notable interstitial neutrophilic infiltrate was present, making cellulitis and erysipelas less likely; panculture of tissue also was negative.[1,2] Atypical cells in the deep dermis were positive for CD163 and negative for CD117, CD34, CD123, and myeloperoxidase, consistent with a diagnosis of neutrophilic eccrine hidradenitis (NEH) and reactive histiocytes.[3] Treatment with oral prednisone resulted in rapid improvement of symptoms.

Neutrophilic eccrine hidradenitis is a rare reactive neutrophilic dermatosis characterized by eccrine gland involvement. This benign and self-limited condition presents as asymmetric erythematous papules and plaques.[2] Among 8 granulocytopenic patients with neutrophilic dermatoses, 5 were diagnosed with NEH.[4] Although first identified in 1982, NEH remains poorly understood.[2] Initial theories suggested that NEH developed due to cytotoxic substances secreted in sweat glands causing necrosis and neutrophil chemotaxis; however, chemotherapy exposure cannot be linked to every case of NEH. Neutrophilic eccrine hidradenitis can be extremely difficult to differentiate clinically from conditions such as cellulitis and Sweet syndrome.

A patient history can be helpful in identifying triggering factors. Neutrophilic eccrine hidradenitis most commonly is associated with malignant, drug-induced, or infectious triggers, while Sweet syndrome has a broad range of associations including infections, vaccines, inflammatory bowel disease, pregnancy, malignancy, and drug-induced etiologies (Table).[1] On average, NEH presents 10 days after chemotherapy induction, with 70% of cases presenting after the first chemotherapy cycle.[5] Bacterial cellulitis or erysipelas have an infectious etiology, and patients may report symptoms such as fever, chills, or malaise. Immunosuppressed patients are at greater risk for infection; therefore, clinical signs of infection in a granulocytopenic patient should be addressed urgently.

Physical examination may have limited value in differentiating between these diagnoses, as neutrophilic dermatoses notoriously mimic infection. Cutaneous lesions can appear as pruritic or tender erythematous plaques, papules, or nodules in these conditions, though cellulitis and erysipelas tend to be unilateral and may have associated purulence or inflamed skin lymphatics. Given the potential for misdiagnosis, approaching patients with a broad differential can be helpful. In our patient, the differential diagnosis included Sweet syndrome, NEH, bacterial cellulitis, erysipelas, leukemia cutis, sarcoid, and eosinophilic cellulitis.



A, Histopathology showed a neutrophilic infiltrate surrounding and extending into intact eccrine coils. B, Within the same specimen, other areas demonstrated destruction of the eccrine coils in areas of dense neutrophilic inflammation (H&E, original magnifications ×20).

Leukemia cutis refers to the infiltration of neoplastic leukocytes in the skin and often occurs in patients with peripheral leukemia, most often acute myeloid leukemia or chronic lymphocytic leukemia. Patients with leukemia cutis often have a worse prognosis, as this finding signifies extramedullary spread of disease.[6] Clinically, lesions can appear similar to those seen in our patient, though they typically are not symptomatic, can be nodular, tend to exhibit a violaceous hue, and occasionally may be hemorrhagic. Wells syndrome (also known as eosinophilic cellulitis) is an inflammatory dermatosis that presents as painful or pruritic, edematous and erythematous plaques.[7,8] A green hue on resolution is present in some

Differences Between NEH, Bacterial Cellulitis, and Sweet Syndrome

Characteristic	NEH	Bacterial cellulitis	Sweet syndrome
Histopathology	Neutrophilic infiltrate around eccrine glands and coils with necrosis; occasional intraductal abscesses; syringosquamous metaplasia of sweat glands and fibrosis of adjacent dermis	Nonspecific histologic features such as dermal edema, lymphatic dilation, and diffuse neutrophilic infiltrate around blood vessels	Dermal infiltrate of mature neutrophils with marked dermal edema without leukocytoclastic vasculitis
Laboratory findings (cases, %)	Low WBC (80%)	Elevated WBC (34%–50%); ESR >20 mm/h (59%–91%); elevated CRP (77%–97%); blood cultures positive (<10%)	Elevated WBC >8000/μL; ESR >20 mm/h; elevated CRP >70%; neutrophils (47%–60%)
Physical examination	Asymmetric erythematous and edematous plaques that may be pruritic or tender; systemic symptoms are rare	Poorly defined areas of erythema with warmth and tenderness with or without purulence or dilated inflamed skin lymphatics; typically unilateral; systemic symptoms: fever, chills, malaise	Tender erythematous plaques or nodules in an asymmetric distribution on the upper extremities, head, neck, legs; systemic symptoms: fever and arthralgia
Resolution	Few days to weeks	Few days to weeks	6–12 wk
Treatment	Systemic corticosteroids; NSAIDs; recurrences: oral dapsone	Antibiotics	Systemic corticosteroids for 4–6 wk; dapsone, colchicine, potassium iodide; topical or intralesional corticosteroids for localized lesions
Triggering factors	Malignancy: AML, CML; drug induced: chemotherapeutic agents, G-CSF, acetaminophen, antiretroviral agents; infectious: HIV, *Staphylococcus*, *Enterobacter*, *Serratia*, *Streptococcus*, *Nocardia*	Common infections: β-hemolytic *Streptococcus*, *Staphylococcus aureus*, gram-negative aerobic bacilli; uncommon infections: *Haemophilus influenzae* type b (buccal cellulitis), *Clostridia* and non–spore-forming cellulitis (crepitant), *Streptococcus pneumoniae*, *Neisseria meningitidis*	Classic infections: URI, GI; vaccines: PCV, BCG; IBD; pregnancy; idiopathic; malignancy: hematologic (AML), solid tumors (GU, GI, breast); drug induced: G-CSF, TMX, minocycline, nitrofurantoin, antiepileptics, antihypertensives, oral contraceptives, retinoids

Abbreviations: AML, acute myeloid leukemia; CML, chronic myelogenous leukemia; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; G-CSF, granulocyte colony-stimulating factor; GI, gastrointestinal; GU, genitourinary; IBD, inflammatory bowel disease; NEH, neutrophilic eccrine hidradenitis; NSAID, nonsteroidal anti-inflammatory drug; PCV, pneumococcal conjugate vaccine; TMX, tamoxifen; URI, upper respiratory infection; WBC, white blood cell count.

cases and may help clinicians differentiate this disease from mimickers.[7] Often, eosinophilic cellulitis is misdiagnosed as bacterial cellulitis and treated with antibiotics. The presence of systemic symptoms such as fever or arthralgia is more typical of bacterial cellulitis, erysipelas, eosinophilic cellulitis, or Sweet syndrome than of NEH.[1] Additionally, inflammatory markers (ie, C-reactive protein) and white blood cell counts tend to be elevated in bacterial cellulitis and Sweet syndrome, while leukopenia often is seen in NEH.

Histopathology is crucial in distinguishing these disease etiologies. Neutrophilic eccrine hidradenitis is diagnosed by the characteristic neutrophilic infiltrate and necrosis surrounding eccrine glands and coils. There also may be occasional intraductal abscesses and syringosquamous metaplasia of the sweat glands along with fibrosis of the adjacent dermis. In contrast, histologic sections of Sweet syndrome show numerous mature neutrophils infiltrating the dermis with marked papillary dermal edema. The histopathology of bacterial cellulitis and erysipelas is less specific, but common features include dermal edema, lymphatic dilation, and a diffuse neutrophilic infiltrate surrounding blood vessels. Pathogenic organisms may be seen on histopathology but are not required for the diagnosis of bacterial cellulitis or erysipelas.[2] Additionally, blood and tissue culture can assist in identification of both the source of infection and the causative organism, but cultures may not always be positive.

Comparatively, the histopathologic features of eosinophilic cellulitis include dermal edema, eosinophilic infiltration, and flame figures that form when eosinophils degranulate and coat collagen fibers with major basic protein. Flame figures are characteristic but not pathognomonic for eosinophilic cellulitis.[7] The histopathology of leukemia cutis varies based on the leukemia classification; generally, in acute myeloid leukemia the infiltrate is composed of neoplastic cells in the early stages of development that are positive for myeloid markers such as myeloperoxidase. Atypical and immature granulocytes within the leukocytic infiltrate differentiate this condition from the other diagnoses. Treatment may entail chemotherapy or radiotherapy, and this diagnosis generally carries the worst prognosis of all the conditions in the differential.[6]

Differentiating between these conditions is important in guiding treatment, especially in patients with febrile neutropenia. Unnecessary steroids in immunosuppressed patients can be dangerous, especially if the patient has an infection such as bacterial cellulitis. Furthermore, unwarranted antibiotic use for noninfectious conditions may expose patients to substantial side effects and not improve the condition. Neutrophilic eccrine hidradenitis typically is self-limited and treated symptomatically with systemic corticosteroids and nonsteroidal anti-inflammatory drugs.[3] Sweet syndrome often requires a longer course of oral steroids. Leukemia cutis worsens as the leukemia advances, and treatment of the underlying malignancy is the most effective treatment.[9]

Early and accurate recognition of the diagnosis can prevent harmful diagnostic delay, unnecessary antibiotic use, or extended steroid taper in neutropenic patients. Appreciating the differences between these diagnoses can assist clinicians in investigating and tailoring a broad differential to specific patient presentations, which is especially critical when considering common mimickers for life-threatening conditions.

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