Neutrophilic Eccrine Hidradenitis: An Unusual Case and a Review of the Literature
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Abstract
Neutrophilic eccrine hidradenitis (NEH) is a neutrophilic dermatosis primarily affecting the eccrine sweat glands in adult patients receiving chemotherapy, notably cytarabine for acute myeloid leukemia (AML). NEH is characterized by fever and erythematous papules and plaques resolving within one to two weeks of discontinuation of the offending drug. NEH has rarely been reported to occur in other malignancies, infections, or drug reactions, or in otherwise healthy children. We present a rare case of Philadelphia-chromosome positive acute lymphoblastic leukemia (Ph+ ALL) complicated by NEH in a child receiving intensification chemotherapy with cytarabine, methotrexate, and dasatinib. The patient’s polymorphous eruption persisted for months despite discontinuation of the offending agents. We also discuss the pathogenesis, characteristics, and treatment of NEH.

Introduction
Neutrophilic eccrine hidradenitis (NEH) is an uncommon neutrophilic dermatosis of the eccrine sweat glands first described in 1982 by Harrist et al.1 NEH was initially described as a distinct disorder most often reported in adult patients receiving chemotherapy for malignancy, notably cytarabine induction chemotherapy for acute myeloid leukemia (AML), characterized by the onset of fever with erythematous papules and plaques resolving within one to two weeks of discontinuation of the offending agent.2 To date, cytarabine remains the most frequently reported cause of NEH. However, NEH has since been described in association with other malignancies, as a paraneoplastic syndrome or complication of infection, and following the ingestion of related immunomodulators or acetaminophen.

We present a rare case of Philadelphia-chromosome positive acute lymphoblastic leukemia (Ph+ ALL) complicated by NEH in a child receiving intensification chemotherapy with cytarabine, methotrexate, and dasatinib, characterized by fever and a polymorphous eruption persisting for months despite discontinuation of offending agents. The findings are important in distinguishing NEH from mimics such as Sweet’s syndrome or other neutrophilic dermatoses, drug eruptions, infection, and leukemia cutis.

Case Presentation
An 8-year-old Hispanic male with Ph+ ALL presented to the emergency department with a two-day history of fever and rash on the extensor arms that spread to involve the cheeks, lower trunk, and legs. Dermatology was consulted to evaluate for Henoch-Schönlein purpura. The patient had been administered high-dose methotrexate and cytarabine 48 hours prior to initial presentation, and leucovorin two to three hours prior to initial presentation. He denied any associated pain, pruritus, burning, or bleeding, but admitted to tenderness on the lower lip. Review of systems was otherwise negative. Additional history included sulfa-induced urticarial eruption, seizure disorder, recurrent pneumonia and otitis media, asthma, and anemia requiring multiple transfusions. Home medications included dasatinib, levetiracetam, and acetaminophen. Family history was noncontributory. There were no sick contacts, travel, or exposure to animals or UV radiation.

Physical examination revealed non-tender, blanchable, edematous, erythematous, follicular papules and nodules, some with central dusky coloration, coalescing into plaques primarily on the extensor arms, lower back, buttocks, anterolateral thighs, and lateral lower legs in a symmetric distribution (Figures 1-4). Subtle, pinpoint, skin-colored to erythematous follicular papules and papular pustules, with variable perifollicular erythema, were noted on the cheeks, extensor arms, and abdomen (Figure 5). Additional findings included superficial erosions with hemorrhagic crusting of the lower lip with smooth erythema of the dorsal aspect of the tongue. As expected, pallor and diffuse alopecia were prominent. Palms, soles, and nails were spared, and there was no appreciable palpatible lymphadenopathy. Our differential diagnosis included drug reaction, viral exanthems and other disseminated infections, erythema multiforme, Sweet’s syndrome, and leukemia cutis.

Figure 1
Figure 2
Figure 3
Figure 4
Figure 5

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Histologic examination of punch biopsies of lesions on the extensor arm and thigh revealed focal hyperkeratosis, clefting below the granular layer, and vacuolar interface dermatitis with scattered perivascular neutrophils and dyskeratotic cells within the eccrine sweat gland coils, most consistent with a drug reaction (Figures 6, 7). Follicular plugging was an incidental finding. Tissue cultures were negative. DIF was negative.

Routine laboratory tests included complete blood count (CBC) and complete metabolic panel (CMP), which revealed leukopenia with neutropenia, absolute neutrophil count (ANC) of 325/mm3, lymphocytosis, mild hypercoagulability, microscopic hematuria, elevated transaminases, hypoproteinemia, and hypoalbuminemia. Renal function and coagulation profile were within normal limits.

Serologic tests were negative for antistreptolysin O, human immunodeficiency virus (HIV)-1 and -2, hepatitis B virus (HBV), hepatitis C virus (HCV), mycoplasma pneumoniae IgM, parvovirus B19 (except for IgG), and Epstein-Barr virus (except for viral capsid IgG).

Polymerase chain reaction (PCR) targeting DNA of parvovirus B19, adenovirus, cytomegalovirus (CMV), human herpes virus (HHV)-6/-7, and herpes simplex virus (HSV)-1 and -2, together with RNA of enterovirus, were negative. Cultures taken from blood, including port line, throat, urine, lower lip, and cerebrospinal fluid (CSF), were negative. C-reactive protein (CRP) was only mildly elevated. Chest radiograph was normal. Bone marrow aspiration revealed minimal residual disease with major medical response, cellular marrow with erythroid and granulocytic hyperplasia.

Clinical and histologic findings were consistent with NEH, likely the result of cytarabine, although methotrexate could not be excluded as the offending agent. Further, dasatinib has been reported to cause follicular papular and pustular eruptions, similar to the acneiform or keratosis pilaris-like eruption of our patient, with follicular plugging noted on histology as well.

Infectious disease was consulted by the pediatric hospitalist for empiric cefepime and micafungin, rather than fluconazole due to possible drug interaction with dasatinib, pending negative cultures. Due to the severity of the eruption, topical class I corticosteroid was incorporated into the regimen.

The patient was discharged when cultures were negative and he had been afebrile for 24 hours, with instructions to follow up with outpatient Dermatology. One month later, he presented to our dermatology clinic with only mild improvement of the lesions and was started on oral prednisolone with instructions to return in two weeks for re-evaluation.

Discussion
Neutrophilic eccrine hidradenitis (NEH) is an uncommon neutrophilic dermatosis primarily directed against the eccrine sweat glands. First described in 1982, the exact etiology is unknown, although NEH tends to occur in patients receiving cytarabine, as a complication of chemotherapy for acute myeloid leukemia (AML). Since then, other agents have been implicated, including bleomycin, methotrexate, anthracyclines, 5-fluorouracil, taxanes, cyclophosphamide, vinca alkaloids, and imatinib mesylate. In patients with chemotherapy-induced neutropenia, neutrophils may be absent from biopsy specimens, hence the suggested name “chemotherapy-induced eccrine hidradenitis.” NEH has also been reported after zidovudine treatment in HIV patients. Granulocyte-colony stimulating factor (G-CSF) and acetyaminophen also may induce lesions of NEH.

Clinically, NEH usually presents with erythematous papules and plaques, and less frequently as a polymorphous eruption of erythematous papules, small nodules, plaques, pustules, purpura, and urticaria. Areas most commonly include the face, trunk, and extremities. NEH presenting in the periorbital region of the face may mimic orbital cellulitis. Lesions may be asymptomatic or tender. Fever often accompanies the cutaneous eruption, as seen in our patient. Because of these highly variable clinical presentations, it can be difficult to differentiate NEH from other neutrophilic dermatoses such as Sweet’s syndrome and pyoderma gangrenosum, which may also be associated with leukemia.

When NEH is drug-induced, most commonly a result of chemotherapy agents, it takes an average of 9.7 days for cutaneous signs and symptoms to appear following initial drug exposure. However, some cases have reported NEH in patients with no previous treatment. Previous studies have also shown an association of NEH with other hematological malignancies, Behçet disease, hemodialysis, and solid tumors such as osteosarcoma. Infectious causes include HIV, Streptococcus, Serratia, Nocardia, Enterobacter, and Staphylococcus aureus.

Historically, NEH has been a condition most often affecting adults, and children with NEH have presented with lesions limited to the palms and soles, referred to as palmoplantar eccrine hidradenitis, an idiopathic variant of NEH. In contrast to NEH, palmoplantar eccrine hidradenitis is not associated with underlying disease, but is thought to occur as the result of mechanical and/or thermal trauma in otherwise healthy children. Regardless of etiology, the eccrine glands and coils serve as the ultimate target of destruction.

The pathophysiology of NEH is poorly understood. It is postulated that NEH is the result of a direct drug-induced effect mediated by neutrophilic chemotaxis. In this view, neutrophils are attracted to the site by cytokines C5a, interleukin-8, tumor necrosis factor alpha, and granulocyte colony-stimulating factor. Induction of an inflammatory response leads to cellular damage and eventual necrosis of the eccrine epithelium. Toxic byproducts of cytarabine may play a role in altering vessel walls, leading to leukocytoclastic vasculitis, which may also be seen in association with NEH. Alternatively, NEH has been placed on the neutrophilic dermatoses spectrum, seen as a paraneoplastic condition similar to Sweet’s syndrome. Also, NEH has been reported in healthy individuals, suggesting the possibility of underlying sweat gland abnormalities.

Diagnosis is confirmed by skin biopsy. Histologically, NEH usually demonstrates a perivascular and periductal infiltration of neutrophils around and within the eccrine glands. The upper dermis commonly shows edema and extravasation of red blood cells. Necrosis of the eccrine coils and glands may result from the neutrophilic inflammatory infiltrate. Infection as the cause of NEH must be excluded by tissue culture to avoid unnecessary use of antibiotics or changes in chemotherapy regimens.

NEH tends to be a self-limited disease, although some cases indicate the possibility of relapse upon future exposure to the same or a different chemotherapy agent. Topical or systemic corticosteroids may aid in the healing of skin lesions, as seen in our patient. Analgesics may be used for painful lesions. Of note, initiating dapsone prior to the administration of chemotherapy and continued daily for 14 days has been reported to help prevent relapse of NEH.

Conclusion
NEH is an uncommon neutrophilic dermatosis affecting the eccrine glands, most often seen in adults receiving chemotherapy for AML. In contrast, our patient was a child with Ph+ ALL, an extremely rare malignancy seen in children. Drug eruptions are often polymorphous and may have the potential to be life threatening, so clinicians must broaden their differential diagnosis to include other neutrophilic dermatoses or opportunistic infections with systemic features that mimic NEH. Our case emphasizes the fact that NEH can mimic many cutaneous eruptions, and biopsy is key in making a definitive diagnosis. NEH should be considered in the diagnosis of any eruption presenting with erythematous papules and plaques associated with fever, especially in the setting of chemotherapy.
References


