Neutrophilic Eccrine Hidradenitis in a Patient With Behçet's Disease

Maya Bilic, Cincinnati, Ohio
Diya F. Mutasim, MD, Cincinnati, Ohio

GOAL

To discuss a case of neutrophilic eccrine hidradenitis (NEH) in a patient with Behçet's disease

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe NEH and its associated medical conditions.
2. Identify the histologic appearance of NEH.
3. Delineate the pathogenesis of skin lesions in Behçet's disease.

CME Test on page 119.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: July 2001.

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Albert Einstein College of Medicine and Quadrant HealthCom, Inc. The Albert Einstein College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Albert Einstein College of Medicine designates this educational activity for a maximum of 1.0 hour in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

This activity has been planned and produced in accordance with ACCME Essentials.

Patients with Behçet's disease may develop multiple mucocutaneous manifestations, several of which are mediated by neutrophils. These include aphthous ulcers, pseudofolliculitis, acneform lesions, and pathergy. We report another neutrophil-mediated disorder, neutrophilic eccrine hidradenitis (NEH), in a patient with Behçet's disease. NEH should be added to the list of mucocutaneous lesions that may be seen in patients with Behçet's disease.

Ms. Bilic and Dr. Mutasim are from the University of Cincinnati College of Medicine, Ohio. Ms. Bilic is a Medical Student.
Dr. Mutasim is Professor and Chairman, Department of Dermatology.
Reprints: Diya F. Mutasim, MD, Department of Dermatology, University of Cincinnati College of Medicine, PO Box 670592, Cincinnati, OH 45267-0592.

Behçet's disease is a complex, multisystem, inflammatory disorder of unknown etiology. The diagnosis is made on the basis of the clinical criteria proposed by the International Study Group for Behçet's Disease in 1990.[1] According to the criteria, recurrent oral ulceration must be present, as well as at least two of the following: recurrent genital ulceration, eye lesions, skin lesions, and a positive pathergy test result. Cutaneous manifestations include pseudofolliculitis, acneform lesions, erythema nodosum, and pathergy.[2] Behçet's disease also may affect the gastrointestinal tract, central nervous system, and peripheral joints.

Neutrophilic eccrine hidradenitis (NEH) is a self-limited inflammatory dermatosis seen primarily in patients with hematologic malignancies who are receiving chemotherapy. Harrist et al[3] first described

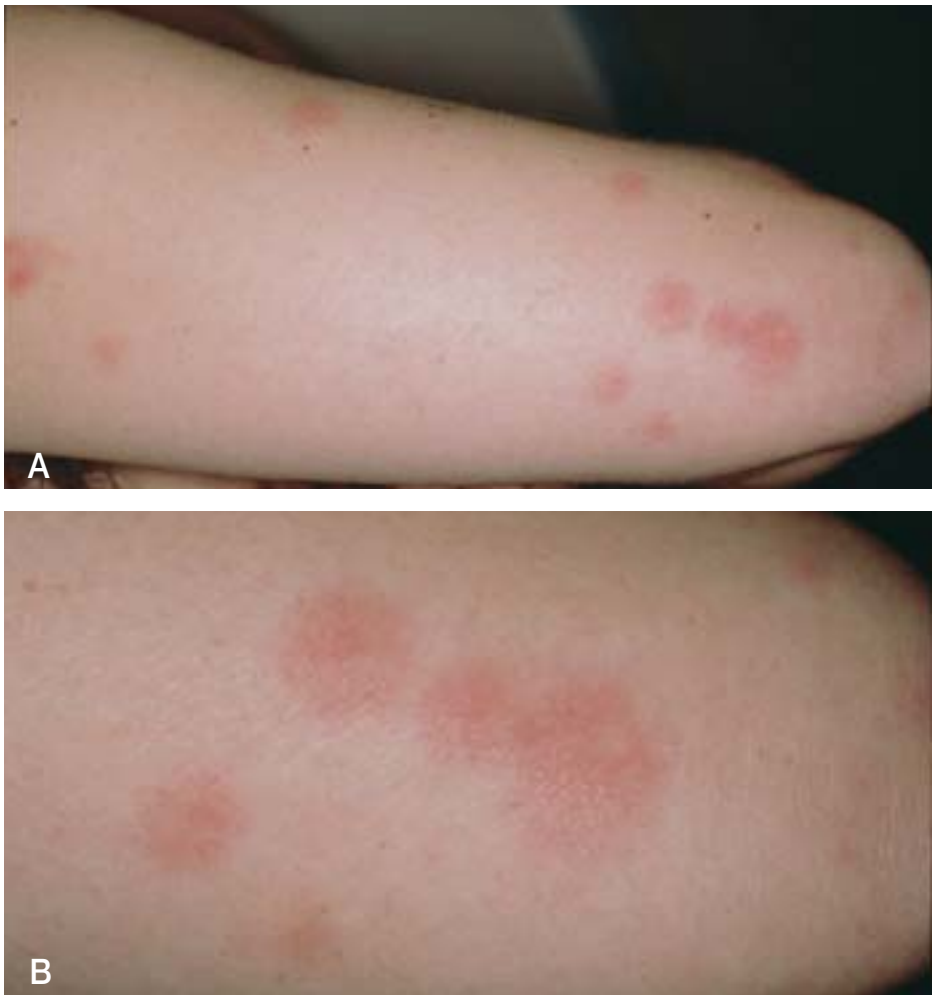

Figure 1. (A) Note multiple erythematous edematous plaques on the posterior arm. (B) Close-up view reveals vesicopustules.

this condition in a man with acute myelogenous leukemia undergoing induction chemotherapy. NEH also has been reported with many other clinical conditions and drug intake. An eruption of NEH commonly presents as solitary or grouped erythematous edematous papulopustules and plaques that are variably tender. The lesions are usually located on the proximal extremities, trunk, and periorbital region. The histopathology of NEH is characteristic and reveals a neutrophilic infiltrate around the eccrine secretory coils and ducts, with focal epithelial cell necrosis and vacuolar degeneration.[4] Diffuse dermal edema with perivascular infiltrate consisting of lymphocytes, neutrophils, macrophages, and eosinophils also may be seen.[5-7] Skin lesions spontaneously resolve in 1 to 2 weeks without scarring.

The etiology of NEH is unclear; however, there are 2 theories regarding its pathogenesis. The first suggests that NEH belongs to the spectrum of neutrophilic dermatoses, with primary involvement of the eccrine glands. The other theory postulates that the infiltrate in NEH is secondary to drug-induced eccrine gland changes. We report a case of NEH in a patient with Behçet's disease and suggest that NEH is related to the group of neutrophilic dermatoses.

Case Report

A 17-year-old white man presented with a 2-year history of lesions on the face, oral mucosa, penis, scrotum, and anterior thighs. His medical history was significant for relapsing joint pain with effusions and recurrent iritis. Antinuclear antibody test and rheumatoid factor results were negative. On physical examination, the patient had punched-out ulcers on his tongue, scrotum, and penile shaft. He had pustules and erythematous papules on his face consistent with an acneform eruption. In addition, he had several vesiculopustular lesions on the anterior thighs. Results of a biopsy of a pustule from the thigh revealed a mixed infiltrate rich in neutrophils within the superficial and deep reticular dermis. These findings are consistent with the cutaneous lesions of systemic disorders associated with

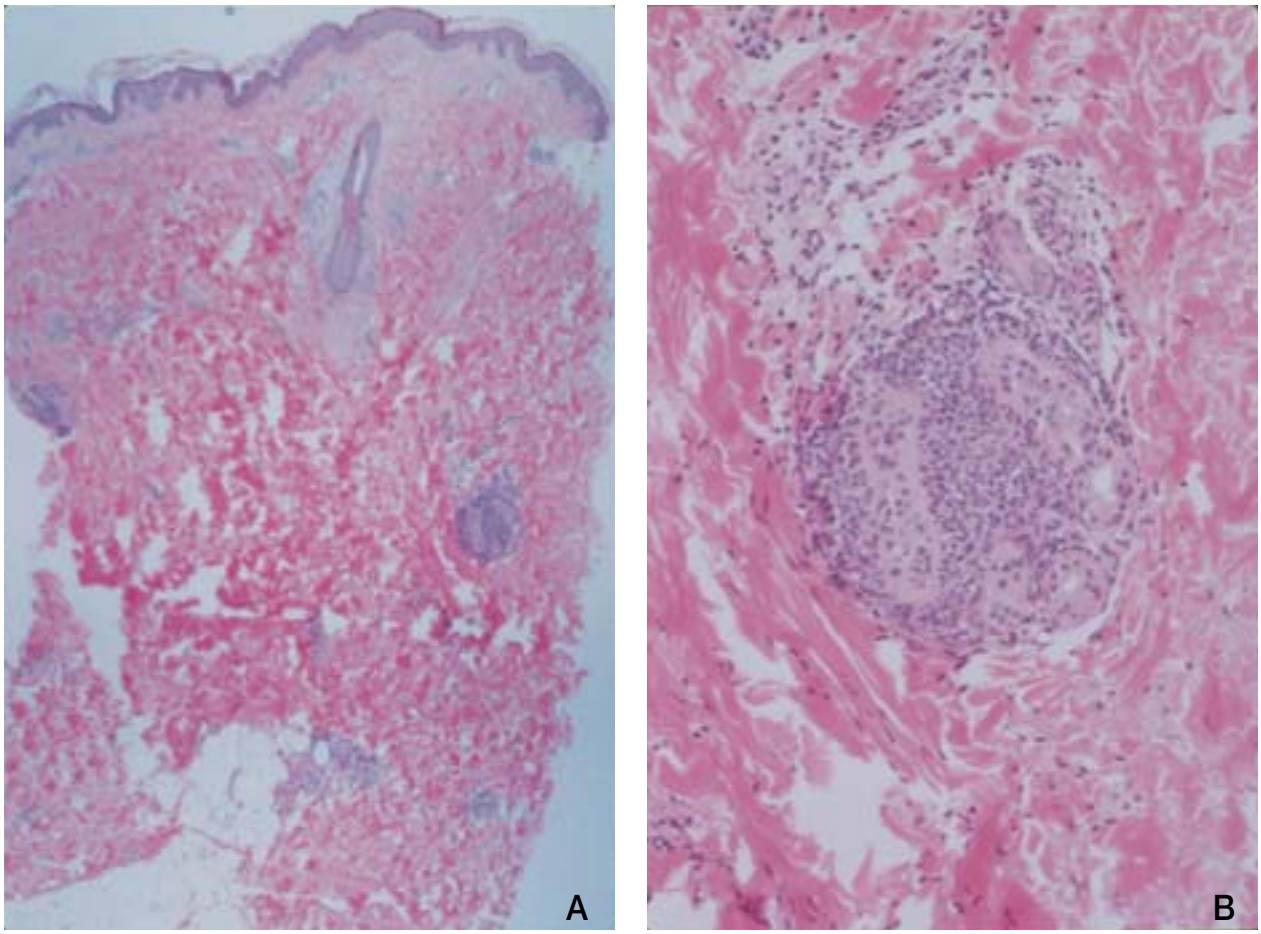

Figure 2. (A) Histologic examination of a biopsy specimen. Note a mild-to-moderate superficial and deep infiltrate (H&E, original magnification ×40). (B) Higher magnification reveals a mixed infiltrate containing lymphocytes, neutrophils, and a few eosinophils around the eccrine glands (H&E, original magnification ×200).

pathergy. Direct immunofluoroescence test results of perilesional skin were negative. A diagnosis of Behçet's disease was made, and the patient was treated with multiple systemic agents, including prednisone, dapsone, colchicine, and azathioprine, with variable success.

Sixteen months later, the patient presented with a 1-week history of a pruritic, burning eruption on his arms (Figure 1A), hands, and face. Examination revealed multiple discrete and confluent erythematous papules and plaques, with a few minute vesicopustules on the upper extremities (Figure 1B) and crusted erosions on the face. Histopathologic examination of an upper extremity lesion revealed an unremarkable epidermis. There was an infiltrate around the eccrine glands and blood vessels, consisting of neutrophils and lymphocytes characteristic of NEH (Figure 2). The lesions resolved after 2 weeks of prednisone therapy. Similar lesions recurred 2 years later. A biopsy specimen revealed similar findings. Treatment with thalidomide was initiated. The skin lesions and oral and genital ulcers resolved and remained clear during 18 months of thalidomide therapy.

Comment

NEH is associated with numerous conditions. Bachmeyer and Aractingi[4] reviewed 51 reports of NEH and found that 90% of cases developed in patients with malignancies. Furthermore, 84% of patients had recently received antineoplastic chemotherapy before the onset of skin lesions. The main cytotoxic agents used were cytarabine and anthracyclines. Acute myelogenous leukemia was the most frequently associated malignancy. Chronic lymphocytic leukemia,[8] Hodgkin's disease,[9] and non-Hodgkin's lymphoma[6] also have been reported. Occasional cases with solid tumors, including testicular carcinoma,[10] Wilms' tumor,[11] osteosarcoma,[12] breast cancer,[13] and lung[14] cancer, have been described. Attempts to link a specific cytotoxic drug to NEH have been unsuccessful

because most patients receiving chemotherapy for the treatment of cancer receive multiple drugs. Several studies have suggested that NEH belongs to the spectrum of drug-induced eccrine gland changes that include syringosquamous metaplasia and eccrine necrosis. There are several reports of chemotherapy-related eruptions in which histologic examination showed isolated necrosis or syringometaplasia of the eccrine coils without neutrophilic infiltration.[11,15,16] In 1997, Brehler et al[17] reported a case of a patient with acute myelogenous leukemia receiving cytarabine, daunorubicin, and thioguanine who developed NEH on the third day of treatment. The lesions healed spontaneously and reappeared with the administration of chemotherapy. Histologic examination and immunohistochemical staining revealed necrosis of the eccrine and apocrine glands with a mixed infiltrate of neutrophils, histiocytes, and lymphocytes (T- and B-cell types). Based on these findings, they suggested that NEH occurs secondary to the cytotoxic effect of chemotherapeutic agents on eccrine glands.[17] The theory that NEH is a drug side effect is supported by a study that demonstrates the presence of NEH after intradermal injections of bleomycin into normal human skin.[18] NEH also has been observed in HIV-infected patients, two of whom were treated with zidovudine[19] and one with stavudine.[20]

To our knowledge, there are 2 reported cases of NEH heralding the onset of acute myelogenous leukemia.[21-22] In addition, NEH has been reported in 2 patients receiving granulocyte colony-stimulating factor[23-24] and in a healthy adult taking acetaminophen.[25] Furthermore, there are rare case reports of NEH attributed to bacterial infections including *Serratia marcescens*, *Enterobacter cloacae*, and *Staphylococcus aureus*.[26-29] The diversity of the presentations suggests that there are various etiologies of NEH, including drug toxicity, paraneoplastic, infectious, and idiopathic. As such, NEH represents a cutaneous reaction pattern to a broad spectrum of clinical conditions.

The identification of NEH in a patient with Behçet's disease supports the theory that it belongs to the spectrum of neutrophilic dermatoses including Sweet's syndrome. Sweet's syndrome and NEH have similar clinical findings, such as erythematous edematous plaques, and are differentiated on the basis of histology. Sweet's syndrome demonstrates a neutrophilic infiltrate of the dermis sparing the glandular apparatus. In NEH, the neutrophilic infiltrate is concentrated around the eccrine coils and ducts. Both disease processes may be paraneoplastic to hematologic malignancies. Pathergy, a feature seen in Behçet's disease and Sweet's syndrome, also is present in NEH.[30]

The pathogenesis of skin lesions in Behçet's disease, including those of NEH, is unclear. Previous studies have demonstrated that active lesions in Behçet's disease, including those induced by the pathergy test, are infiltrated by neutrophils.[2] Neutrophilic vasculitis is believed to contribute to various organ pathology in Behçet's disease. To our knowledge, this is the first case that documents a neutrophilic infiltrate involving the eccrine glands in a patient with Behçet's disease. The predominance of neutrophils in spontaneous and induced lesions of Behçet's disease is interesting. Neutrophils from patients with Behçet's disease have increased superoxide production, enhanced chemotaxis, and excessive production of lysosomal enzymes that are believed to result in tissue injury.[31-32] Levels of circulating tumor necrosis factor α, interleukin 1β, and interleukin 8 are elevated; these cytokines may be involved in the activation of neutrophils.[32] Neutrophil hyperfunction is only one aspect of the complex immunopathology of Behçet's disease. Antibodies, endothelial cells, autoreactive T cells, and circulating immune complexes also have been implicated in the pathogenesis of Behçet's disease.[2,33,34]

Conclusion

We report a case of Behçet's disease with an unusual eruption that revealed the histologic findings of NEH. NEH should be added to the list of skin lesions that may be seen in Behçet's disease.

REFERENCES

1. International Study Group for Behçet's disease. Criteria for diagnosis of Behçet's disease. *Lancet*. 1990;335:1078-1080.
2. Sakane T, Takeno M, Suzuki N, et al. Behçet's disease. *N Engl J Med*. 1999;341:1284-1290.
3. Harrist TJ, Fine JD, Mihm MC Jr, et al. Neutrophilic eccrine hidradenitis: a distinctive dermatosis associated with myelogenous leukemia and chemotherapy. *Arch Dermatol*. 1982;118:263-266.
4. Bachmeyer C, Aractingi S. Neutrophilic eccrine hidradenitis. *Clin Dermatol*. 2000;18:319-330.
5. Flynn TC, Harrist TJ, Murphy GF, et al. Neutrophilic eccrine hidradenitis: a distinctive rash associated with cytarabine induction chemotherapy and acute leukemia. *J Am Acad Dermatol*. 1984;11:584-590.
6. Baily DL, Barron D, Lucky AW. Neutrophilic eccrine hidradenitis: a case report and review of literature. *Pediatr Dermatol*. 1989;6:33-38.
7. Bernsterin EF, Spielvogel RL, Topolsky DL. Recurrent neutrophilic eccrine hidradenitis. *Br J Dermatol*. 1992;127:529-533.

8. Fernandez CE, Ambrojo AP, Anguilar MA, et al. Neutrophilic eccrine hidradenitis: a report of two additional cases. *Clin Exp Dermatol*. 1989;14:341-346.
9. Beutner KR, Packman CH, Markowitch W. Neutrophilic eccrine hidradenitis associated with Hodgkin's disease and chemotherapy: a case report. *Arch Dermatol*. 1986;122:809-811.
10. Fitzpatrick JE, Bennion SD, Reed OM, et al. Neutrophilic eccrine hidradenitis associated with induction chemotherapy. *J Cutan Pathol*. 1987;14:272-278.
11. Greenbaum BH, Heymann WR, Reid CS, et al. Chemotherapy-associated eccrine hidradenitis, neutrophilic eccrine hidradenitis reevaluated: the role of neutrophilic infiltration. *Med Pediatr Oncol*. 1988;16:351-355.
12. Scallan PJ, Kettler AH, Levy ML, et al. Neutrophilic eccrine hidradenitis: evidence implicating bleomycin as a causative agent. *Cancer*. 1988;62:2532-2536.
13. Burg G, Bieber T, Langecker P. Localized neutrophilic eccrine hidradenitis in mitoxantrone therapy: a typical side-effect of cytostatic drugs [in German]. *Hautarzt*. 1988;39:233-236.
14. Bhawan J, Malhotra R, Syringometaplasia: a distinctive eruption in patients receiving chemotherapy. *Am J Dermatopathol*. 1990;12:1-6.
15. Allegue F, Soria C, Rocamora A, et al. Neutrophilic eccrine hidradenitis in two neutropenic patients. *J Am Acad Dermatol*. 1990;23:1110-1113.
16. Hurt MA, Halvorson RD, Petr FC Jr, et al. Eccrine squamous syringometaplasia: a cutaneous sweat gland reaction in the histological spectrum of chemotherapy-associated eccrine hidradenitis and neutrophilic eccrine hidradenitis. *Arch Dermatol*. 1990;126:73-77.
17. Brehler R, Reimann S, Bonsmann G, et al. Neutrophilic eccrine hidradenitis induced by chemotherapy involves eccrine and apocrine glands. *Am J Dermatopathol*. 1997;19:73-78.
18. Templeton SF, Solomon AR, Swerlick RA. Intradermal bleomycin injections into normal human skin: a histopathologic and immunopathologic study. *Arch Dermatol*. 1994;130:577-583.
19. Smith KJ, Skelton HG, Angritt P, et al. Neutrophilic eccrine hidradenitis in HIV-infected patients. *J Am Acad Dermatol*. 1990;23:945-947.
20. Krischer J, Rutschmann O, Roten SV, et al. Neutrophilic eccrine hidradenitis in a patient with AIDS. *J Dermatol*. 1998;25:199-200.
21. Pierson JC, Helm TN, Taylor JS, et al. Neutrophilic eccrine hidradenitis heralding the onset of acute myelogenous leukemia. *Arch Dermatol*. 1993;129:791-792.
22. Saada V, Aractingi S, Leblond V, et al. Neutrophilic eccrine hidradenitis developing concomitantly with acute myelogenous leukemia relapse [in French]. *Annals Dermatologie Venereologie*. 1998;125:420-422.
23. Okcu A, Soyer HP, Kaddu S, et al. Eccrine hidradenitis: case report and review of the literature [in German]. *Hautarzt*. 1997;48:743-748.
24. Bachmeyer C, Chaibi P, Aractingi S. Neutrophilic eccrine hidradenitis induced by granulocyte colony-stimulating factor. *Br J Dermatol*. 1998;139:354-355.
25. Kuttner BJ, Kurban RS. Neutrophilic eccrine hidradenitis in the absence of an underlying malignancy. *Cutis*. 1988;41:403-405.
26. Combemale P, Faisant M, Azoulay-Petit C, et al. Neutrophilic eccrine hidradenitis secondary to infection with *Serratia marcescens*. *Br J Dermatol*. 2000;142:784-788.
27. Moreno A, Barnadas MA, Ravella A, et al. Infectious eccrine hidradenitis in a patient undergoing hemodialysis. *Arch Dermatol*. 1985;121:1106-1107.
28. Taira JW, Gerber HB. Eccrine hidradenitis. *Int J Dermatol*. 1992;31:433-434.
29. Allegue F, Rocamora A, Martin-Gonzalez M, et al. Infectious eccrine hidradenitis. *J Am Acad Dermatol*. 1990;22:1119-1120.
30. Aractingi S, Mallet V, Dombret H, et al. Neutrophilic dermatoses during granulocytopenia. *Arch Dermatol*. 1995;131:1141-1145.
31. Sakane T. New perspective on Behçet's disease. *Int Rev Immunol*. 1997;14:89-96.
32. Ehrlich GE. Vasculitis in Behçet's disease. *Int Rev Immunol*. 1997;14:81-88.
33. Aydintug AO, Tokgoz G, Cruz DP, et al. Antibodies to endothelial cells in patients with Behçet's disease. *Clin Immunopathol*. 1993;67:157-162.
34. Gupta RG, O'Duffy JD, McGuffie FC. Circulating immune complexes in active Behçet's disease. *Arthritis Rheum*. 1977;20:209-213.