Eccrine Squamous Syringometaplasia

A Cutaneous Sweat Gland Reaction in the Histologic Spectrum
of 'Chemotherapy-Associated Eccrine Hidradenitis'
and 'Neutrophilic Eccrine Hidradenitis'

Mark A. Hurt, MD; Ronald D. Halvorson, MD; F. Charles Petr, Jr, MD;
John T. Cooper, Jr, MD; David J. Friedman, MD, PhD

• A 31-year-old Hispanic man presented in the pancy-topenic phase of acute myelocytic leukemia and was treated with the chemotherapeutic agents mitoxantrone and cytarabine. After 5 days, an erythematous, blanching, papular, crusted eruption developed on his forehead, chest, and legs. Some lesions showed confluence and all were at the same developmental stage. Clinical diagnoses included necrotizing vasculitis and sepsis. A biopsy specimen revealed widespread noninflammatory syringometaplasia of eccrine ducts. Well-developed intercellular bridges and eosinophilic cytoplasm were seen within the metaplastic cells; apoptoses and occasional mitoses were present. This process is distinct and probably occurred secondary to direct toxic injury from the chemotherapeutic drugs. Because similar changes have occurred in patients with neutrophilic eccrine hidradenitis, we believe our patient represents an example of the noninflammatory end of the spectrum of chemotherapeutic eccrine gland reactions.

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I n 1982, Santa Cruz et al[1] presented clinicopathologic findings they termed *epidermal dystrophy* in 10 patients in whom eccrine squamous syringometaplasia (ESS) or eccrine gland atrophy developed subsequent to high-dose cytotoxic agents or radiation therapy for the treatment of lymphoproliferative

disorders or bone marrow malignant neoplasms. Later that year, Harrist et al[2] coined the name *neutrophilic eccrine hidradenitis* (NEH) to describe an acute inflammatory reaction occurring in eccrine lobules of a 38-year-old man who had received VAPA-10 protocol (cytarabine, doxorubicin, prednisone, and vincristine sulfate) for treatment of myelogenous leukemia. Subsequent to these reports, 10 additional patients with various malignant neoplasms, exhibiting similar cutaneous reactions to a variety of drugs,[3-9] have had their cases documented. In addition, a uremic man undergoing hemodialysis[10] and another man who was receiving acetaminophen therapy for knee trauma[11] also had similar lesions develop. The lesions have been located almost equally on the central portions of the body (neck, chest, trunk, shoulders, abdomen) as well as on the extremities; however, in most cases, when lesions occur centrally, the extremities are spared and vice versa. The pathologic findings of these lesions have ranged from entirely neutrophilic to acute inflammatory reactions mixed with squamous syringometaplasia. Greenbaum et al[12] recently described similar clinical findings in two patients with malignant neoplasms, the histologic features of which were noninflammatory and termed *eccrine necrosis* by the authors; however, we believe this is noninflammatory ESS. We detail similar findings in a patient.

REPORT OF A CASE

A 31-year-old Hispanic man presented with a chief complaint of cutaneous bruises and gingival bleeding. His medical history was significant for successfully treated acute myelogenous leukemia (M3) initially diagnosed in December 1984, almost 4 years before the present hospital admission. The initial induction therapy consisted of a combination of daunorubicin hydrochloride and cytarabine (cytosine arabinoside). His hospital course was complicated by disseminated intravascular coagulation, *Candida* sepsis, and compromised renal function secondary to aminoglycoside and amphotericin B therapy.

The patient went into remission and remained in reasonably good health until his relapse in October 1988, when he
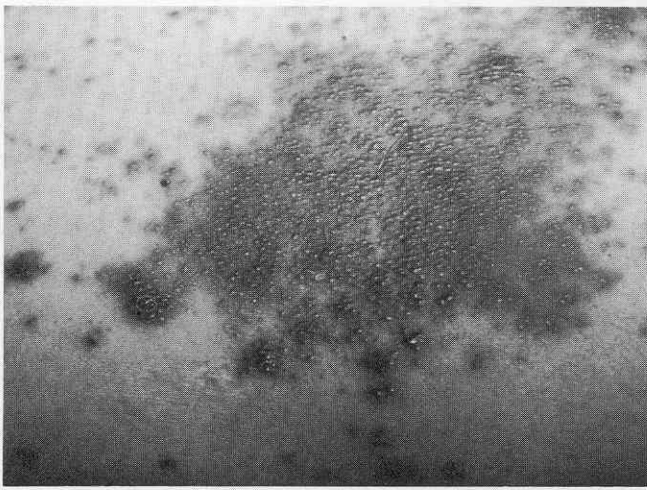
Fig 1.—This maculopapular eruption was located principally on the chest, neck, and face. It was purpuric and blanched slightly when palpated. All lesions appeared to be at the same stage of development.
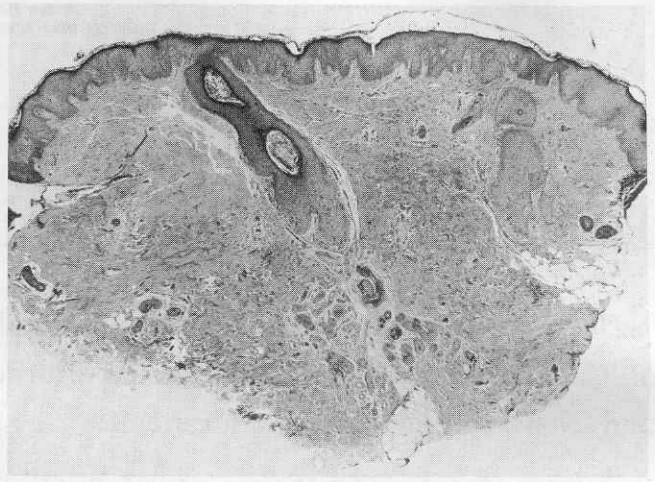

Fig 2.—The whole-mount section reveals normal epidermis, two hair follicles, and several expanded eccrine lobules with squamous syringometaplasia of the interlobular ducts. Horny metaplasia was also seen in the straight ducts (hematoxylin-eosin, ×17).

presented with fever, pallor, shortness of breath, gingival bleeding, and labial herpes. Ecchymoses on the trunk, flank, and extremities were noted. A complete blood cell count revealed the following: hematocrit, 0.179; white blood cell count, $0.9 \times 10^9/L$; and platelet count, $0.019 \times 10^{12}/L$. The bone marrow was hypercellular with 0.60 myeloblasts and promyeloblasts containing Auer rods, consistent with acute myelogenous leukemia (M3). His antimicrobial therapy consisted of piperacillin sodium, gentamicin sulfate, vancomycin hydrochloride, acyclovir sodium, and, subsequently, amphotericin B for persistent fever. All initial blood cultures were consistently negative for bacteria and fungi. Viral studies were negative for human immunodeficiency virus and hepatitis B, but positive for cytomegalovirus (1:128) and herpes simplex virus (1:256). The leukemic relapse was treated with two agents: high-dose cytarabine ($3 g/m^2$) every 12 hours for eight doses on days 1 through 4 and mitoxantrone ($10 mg/m^2$ per day) on days 2 through 5.

Five days after administration of a combination of cytarabine and mitoxantrone (day 10), an erythematous, violaceous papular rash developed that extended from the chest and left shoulder to include an area on the patient's back (Fig 1). Subsequent involvement of the face and neck was noted; the inguinal regions and legs had minor involvement. Biopsy specimens of the skin were obtained to evaluate for fungal sepsis, but the initial biopsy specimen showed only edema. Two days later, a second biopsy specimen of the papular eruption of the chest was obtained. The findings from the biopsy specimens are discussed below.

The patient's condition continued to decline and he subsequently had Escherichia coli sepsis develop that was associated with progressive hepatic and renal dysfunction. During this time, the rash progressively diminished but never completely disappeared. After several days, renal failure developed; he ultimately lapsed into a coma, and he died on hospital day 42. No autopsy was performed.

PATHOLOGY
Methods

The 4-mm punch biopsy specimen was fixed in 10% neutral buffered formaldehyde solution (Lyne Pathology solution, Lyne Laboratories Inc, Stoughton, Mass), embedded in paraffin, serially sectioned at 4 µm, and stained with hematoxylin-eosin and Gomori methenamine silver according to standard techniques.

Microscopic Pathology

The epidermis was surfaced by basket-weave orthokeratosis and was of normal thickness. Two hair follicles were present. Below the center follicle were portions of three eccrine lobules. The peripheral part of the biopsy specimen showed portions of two eccrine lobules (Fig 2). No cellular infiltrate was present. All eccrine lobules showed similar changes (Fig 3). The lobules were expanded by edema of the lobular stroma. The lumens of the secretory glands were prominent and all lobules showed prominent squamous metaplasia of the intralobular ducts. Apoptotic squamous cells were seen in the interlobular and coiled ducts (Fig 4). The straight ducts, near the epidermis, were also filled with apoptotic cells and keratinous debris (Fig 5). Slight dilatation of the superficial venular plexus was noted, but no vasculitis was seen. Focal red blood cell extravasation was present. No fungi were seen on the Gomori methenamine stain.

COMMENT

Eccrine squamous syringometaplasia has been an uncommonly documented or reported lesion that has usually been experimentally produced[13,14] or described in association with surface tumors[15,16] or skin trauma. Although it was not mentioned in a review of eccrine sweat gland reactions,[17] it has been recently reported in deep locations, associated with lobular panniculitis and pyoderma gangrenosum,[18] with toxic reactions to 2,3,7,8-tetrachlorodibenzo-p-dioxin[19] and as a reaction to benoxaprofen, a nonsteroidal anti-inflammatory drug.[20] Eccrine squamous syringometaplasia bears some architectural resemblance to necrotizing (squamous) sialometaplasia of the salivary gland[21] and lobular squamous metaplasia of the breast,[22] both lesions that are probably traumatic-ischemic in origin. King and Barr[23] emphasized that isolated lesions
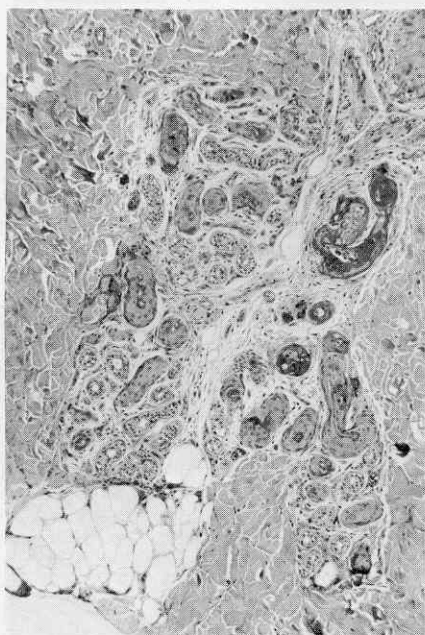
Fig 3.—There are portions of three eccrine lobules expanded by edema of the lobular interstitial cells. Interlobular squamous syringometaplasia is prominent (hematoxylin-eosin, ×70).
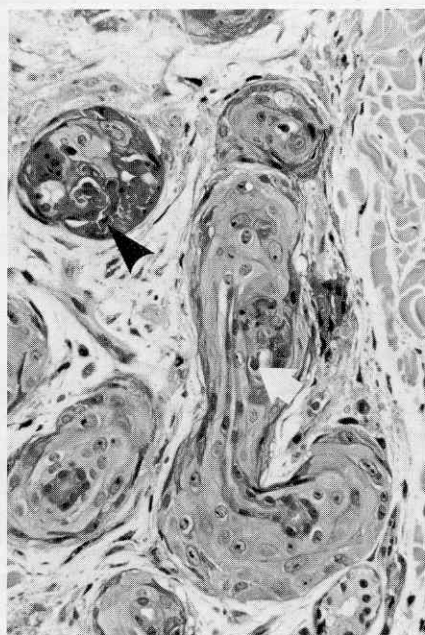
Fig 4.—There is an elongated interlobular eccrine duct with several layers of metaplastic cells joined by intercellular bridges. Apoptotic cells (arrow and arrowhead) are noted in the ducts. Note the interstitial lobular edema with myxoid fibroblastic stroma (hematoxylin-eosin, ×270).
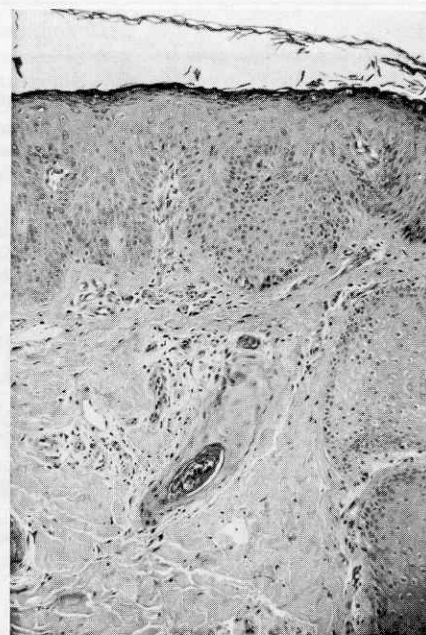
Fig 5.—The straight duct exhibits several layers of glassy squamous cells and the lumen is filled with keratin. Note the slight perivascular edema and vascular dilatation but no vasculitis (hematoxylin-eosin, ×100).

of ESS could sometimes be confused with squamous carcinoma, as the extracutaneous lesions have been.

Flynn et al[3] first illustrated focal ESS in a patient with NEH; the case of another patient with similar findings was recently reported.[8] Additionally, it has been shown that NEH can occur in patients receiving a variety of chemotherapeutic drugs. Most patients who had these reactions develop, regardless of their type of malignant neoplasm, usually had NEH develop *without* ESS. In almost all cases, the lesions were culture negative and special stains were negative for organisms. Most patients healed without scarring in 5 to 7 days, rarely longer. To our knowledge, only one other patient, besides ours, has died subsequent to the diagnosis of a sweat-gland reaction.[6] The clinicopathologic features of these patients are given in the Table.

Our patient was similar to those of Greenbaum et al[12] because the sweat-gland coils and ducts of our patient were also free of any kind of inflammation, suggesting that a neutrophilic infiltrate was not a major factor in the development of the cutaneous lesions. Our patient was also similar to theirs with regard to the severe clinical leukocytopenia. While these similarities may be speculatively attributed to the fact that there was marked leukocytopenia and absolute neutropenia at the onset of the clinical rash in all three patients, it does not necessarily provide a clear-cut answer. This is borne out by the fact that a previously documented patient with morphologically classic NEH was also profoundly neutropenic.[6] In this patient, an 11-year-old white girl with acute myelomonocytic leukemia, the total leukocyte count was less than 0.2×10^9/L when a biopsy was performed. Most reports, however, do not give the details of the patient's peripheral white blood cell count at the time of the biopsy. Thus, we have no way to adequately assess the findings based on these few cases in which the peripheral counts are known.

The absence of an inflammatory infiltrate in our patient, as well as those of Greenbaum et al,[12] suggests that a direct toxic effect of the chemotherapeutic drugs on the sweat gland apparatus may have been responsible for the secondary changes of ESS, although the toxic effect of a cross-reacting antibody or other drug reactions cannot be completely excluded. Mitoxantrone, an anthraquinone, binds directly to keratins 8, 18, and 19 in vitro with persistence of binding of a small percentage of the drug.[24] Thus, the papular rash developing in our patient may have been secondary to the drug binding to the sweat-duct keratin proteins in vivo, but no hard data directly support this despite the knowledge that small concentrations of the drug have been detected in the skin in one autopsy study.[25] Likewise, no information exists on the sweat gland concentration of cytarabine in patients receiving high doses or that the drug may be eliminated in the sweat (George Royer, MD, Upjohn Co, Kalamazoo, Mich, oral communication, July 14, 1989). However, in light of recent knowledge that thiotepa, another chemotherapeutic alkylating agent, has been detected in the sweat of patients receiving

	Chemotherapy-Associated Eccrine Reactions: Literature Review*				
Source, y	Sex/Age, y/Race	Underlying Disease	Skin Lesion Location	Drugs Involved	Reaction
Santa Cruz et al,[1] 1982	Ten patients with lymphoproliferative and bone marrow malignant neoplasms; no specific details		Palms, soles	Cytarabine, cyclophosphamide (Cytoxan), daunorubicin hydrochloride (various combinations); irradiation in some patients	ESS
Harrist et al,[2] 1982	M/38/...	Acute myelogenous leukemia	Neck, shoulder	Cytarabine, doxorubicin, prednisone, vincristine sulfate (VAPA-10 protocol)	NEH
Flynn et al,[3] 1984					
Case 1	M/63/...	Acute myelogenous leukemia	Finger	Cytarabine, doxorubicin	NEH
Case 2	M/55/W	Acute myelogenous leukemia	Shoulder	Cytarabine, doxorubicin, prednisone, vincristine (VAPA-10 protocol)	ESS, NEH
Moreno et al,[10] 1985	M/48/...	Chronic renal failure	Upper and lower extremity	None (possible *Serratia* infection)	NEH
Beutner et al,[4] 1986	M/44/W	Hodgkin's disease	Face, chest	Bleomycin sulfate, dacarbazine, doxorubicin, vinblastine sulfate	HEH, NEH
Fitzpatrick et al,[5] 1987					
Case 1	M/22/W	Testicular embryonal cancer	Hand, finger	Bleomycin, cisplatin, hydrocortisone, vincristine	NEH
Case 2	M/22/W	Testicular teratoma	Lower anterior legs	Bleomycin, cisplatin, hydrocortisone, vincristine	NEH, NEC
Case 3	F/51/W	Acute myelocytic leukemia	Neck, back, shoulder, chest, abdomen	Cytarabine, daunorubicin, methotrexate (intrathecal), thioguanine	NEH
Katsanis et al,[6] 1987	F/11/W	Acute myelomonocytic leukemia	Upper and lower extremity	Cytarabine, doxorubicin, prednisone, vincristine	NEH
Burg et al,[7] 1988	F/59/...	Breast cancer	R arm	Cyclophosphamide, mitoxantrone (fourth cycle)	NEH
Greenbaum et al,[12] 1988					
Case 1	F/3/W	Bilateral Wilms' tumor	Trunk, axilla, chest, abdomen, buttock	Cyclophosphamide, dactinomycin, vincristine	ESS
Case 2	F/66/W	Acute promyelocytic leukemia	Wrist	Cytarabine, doxorubicin	ESS
Kuttner and Kurban,[11] 1988	M/59/W	Knee trauma	Trunk, extremities	Acetaminophen (other drugs denied)	NEH
Scallan et al,[8] 1988	F/15/H	Osteosarcoma, R thigh	Neck, axilla	Bleomycin, cyclophosphamide, dactinomycin (fourth course)	ESS, NEH
Bailey et al,[9] 1989	M/9/W	Non-Hodgkin's lymphoma	Neck, upper and lower extremity	Cytarabine	NEH
Present study	M/31/H	Acute myelocytic leukemia (M3)	Face, neck, chest, extremities	Cytarabine, mitoxantrone	ESS

*W indicates white; H, Hispanic; ESS, eccrine squamous syringometaplasia; HEH, "histiocytic" eccrine hidradenitis; NEC, eccrine gland necrosis (large areas); and NEH, neutrophilic eccrine hidradenitis.

high doses,[26] it would seem possible that a similar phenomenon may have occurred in our patient. Finally, although mitoxantrone combined with cytarabine has been associated with "skin toxicity" in a small number of patients,[27] the pathologic spectrum of the toxic reaction in the skin has not previously been reported.

We agree with Greenbaum et al[12] that there should be a more appropriate name for the sweat gland reactions associated with toxic chemotherapy, one that embraces both the inflammatory and noninflammatory spectra of syringotropic changes. Because the reactions seem to range morphologically from principally neutrophilic, to mixed, to noninflammatory (with or without ESS), we suggest that these changes be termed *chemotherapy-associated eccrine reactions*.

Since the acceptance of this article, we have learned of two additional cases of NEH, reported recently by Fernández Cogolludo et al.[28] These patients both had leukemias (acute myelocytic leukemia and chronic lymphocytic leukemia), both were treated with cytoxic agents, and both developed classic NEH. Neither patient had ESS. Additionally, we have learned of cases of ESS occurring subsequent to extravasation of doxorubicin into the skin, causing a severe toxic effect.[29]

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