Lymphatic Mapping and Sentinel Lymph Node Biopsy in the Detection of Early Metastasis from Sweat Gland Carcinoma

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See related editorial on pages 2134–6 and accompanying article on pages 2279–84, this issue.

Presented in abstract form at the 39th Annual Meeting of The American Society of Dermatopathology, Phoenix, Arizona, October 10–13, 2002.

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Received November 15, 2002; accepted November 19, 2002.

BACKGROUND. Several subtypes of sweat gland carcinoma have been found to demonstrate a propensity to metastasize systemically and to regional lymph nodes. The predictive value and benefit of sentinel lymph node (SLN) biopsy have been established in numerous other malignancies, but to the authors' knowledge there is little literature published to date regarding the use of SLN biopsy in patients with sweat gland carcinoma. In the current study, the authors demonstrated the utility of SLN biopsy in detecting subclinical metastases of sweat gland carcinoma, which may result in early treatment.

METHODS. The authors identified five patients with malignant eccrine tumors in whom SLN biopsy was performed at the study institution. Clinical and histopathologic data were reviewed.

RESULTS. The five study cases included two cases of aggressive digital papillary adenocarcinoma (both occurring on upper extremity digits), two cases of hidradenocarcinoma (occurring on the knee and foot, respectively), and an eccrine carcinoma (occurring on the scalp). In each biopsy-established case, there was no clinical evidence of metastatic disease, and a wide local excision or amputation was performed with concurrent SLN biopsy. Four of 18 SLNs in 3 of the 5 patients (60%) were found to be positive for metastatic carcinoma, as identified in hematoxylin and eosin stains and/or cytokeratin immunohistochemical stains. All three lymph node-positive patients subsequently underwent regional lymphadenectomy and were found to have no evidence of additional metastases.

CONCLUSIONS. The results of the current study demonstrate that SLN biopsy detects subclinical metastases from sweat gland carcinomas to regional lymph nodes. SLN mapping and biopsy at the time of resection can provide useful information with which to guide early treatment. Further studies are necessary to determine whether this procedure results in a survival benefit in patients with sweat gland carcinomas. ***Cancer*** **2003;97:2285–9.**

DOI 10.1002/cncr.11328

KEYWORDS: eccrine carcinoma, sentinel lymph node (SLN) biopsy, aggressive digital papillary adenocarcinoma, hidradenocarcinoma, sweat gland carcinoma.

Sweat gland carcinomas comprise a histologically diverse and uncommon group of neoplasms of eccrine origin. Several subtypes demonstrate a general propensity for regional recurrence and metastasis. The rarity of these tumors has made clinical and pathologic study difficult. Several studies[1-4] have demonstrated that these neoplasms, especially those less differentiated, frequently spread to regional lymph nodes. Furthermore, many eventually metastasize to other organs. In one early study of 83 cases,[3] 68 patients with sweat

gland carcinoma who were followed for ≥ 5 years had a 43% rate of regional lymph node involvement and a 38% rate of visceral involvement. In the study, 31 of 83 patients (37%) died of their tumors. Although the tendency to metastasize does appear to differ somewhat between histologically distinct eccrine malignant tumors,[5] in general, metastasis is a significant clinical concern for many subtypes of sweat gland carcinoma.

Regional lymphadenectomy has long been a valuable tool with which to detect and limit the metastasis of carcinoma and melanoma. More recently, sentinel lymph node (SLN) mapping and biopsy has progressively replaced regional lymphadenectomy as the initial treatment option for many malignancies that are prone to lymphatic spread. The primary advantages of SLN biopsy over regional lymphadenectomy include reduced morbidity and fewer complications, such as chronic pain, poor wound healing, and lymphedema.[6] Another advantage is that SLN biopsy detects early metastasis and may increase clinical staging accuracy.[7] Moreover, because lymph node metastasis often requires adjuvant therapy, early detection will allow for early treatment.

Lymphatic mapping followed by sampling of the first lymph node draining the tumor primary site, or SLN, has proven useful in the surgical staging of a variety of malignant tumors.[8–14] However, to our knowledge there is little literature published to date describing SLN biopsy in patients with malignancies of eccrine origin. One group described SLN biopsy in a patient with an aggressive digital papillary adenocarcinoma. In this patient, the SLNs were free of metastatic tumor.[15] This appears to be the only formal report of SLN biopsy for a carcinoma of eccrine origin. Given the tendency of these tumors to metastasize, a more extensive examination of sweat gland carcinoma staging using SLN biopsy appears in order. In this report, we describe five patients with varying histologic types of sweat gland carcinoma. Each patient underwent surgical resection of the tumor with concurrent SLN biopsy.

MATERIALS AND METHODS

We searched the pathology database of the University of Michigan Medical Center from 1999 to 2002 and identified five patients with sweat gland carcinomas in whom SLN biopsy was performed. Clinical data and histopathologic material were reviewed. At the time of tumor resection and SLN biopsy, none of the patients had clinical evidence of metastatic disease.

The procedure for lymphatic mapping and SLN biopsy used in the study institution is similar to that previously described.[8,16] Briefly, 1 millicurie of unfiltered technetium 99m–sulfur colloid was injected intradermally at 4 points around the primary tumor site approximately 2–4 hours prior to surgery. Dynamic imaging was performed on the neck, axillary, and inguinal regions to localize the SLN(s). The patient then was brought to the operating room, where 1–2 mL of isosulfan blue was injected intradermally around the primary tumor site. After induction with general anesthesia, the surgical sites were prepped and sterilely draped. In vivo tracer counts of the primary tumor site and lymph node basins were measured with a handheld gamma probe. An incision was made in the lymph node basin(s) demonstrating increased radioactivity, within the confines of a putative radical lymphadenectomy incision. All blue-stained, "hot" (defined as radioactive lymph nodes with in vivo tracer counts exceeding 100 counts per minute (cpm) above background or 10% of the counts of the hottest detected lymph node, whichever was less) or palpably enlarged lymph nodes in the basin were identified and removed. After the SLNs were harvested, the primary tumor site was excised with 1–2-cm margins. All tissues were submitted in 10% buffered formalin for histopathologic evaluation.

Primary tumor specimens were processed routinely in the histology laboratory. SLNs were sectioned serially at 2–3-mm thickness and embedded in paraffin. Two serial 5-μm sections of each SLN tissue block were stained with hematoxylin and eosin (H&E) for routine histologic examination. To confirm metastatic disease identified on H&E, or to detect occult metastases, 5-μm sections of each SLN block were immunostained for pancytokeratins AE1, AE3, and Cam5.2 (1:400 final dilution for AE1 and AE3 [Boehringer-Mannheim, Indianapolis, IN] and 1:5 final dilution for Cam5.2 [Becton Dickinson, San Jose, CA]).

Patients with at least one positive SLN were offered regional lymphadenectomy. The lymphadenectomy specimens were processed routinely in the histology laboratory. This retrospective study was reviewed and approved by the University of Michigan Medical Institutional Review Board for Human Subject Research.

RESULTS

Patients ranged in age from 31–78 years (median age, 50 years). Four of the five patients were female. Three different histologic subtypes of sweat gland carcinoma were identified in these patients. Two patients had aggressive digital papillary adenocarcinoma, two patients had hidradenocarcinoma, and one patient had eccrine carcinoma (syringoid carcinoma). Four tumors were taken from the limbs and one tumor was taken from the scalp. Tumor size and depth did not appear to predict SLN involvement (Table 1). Angi-

TABLE 1
Clinical and Pathologic Data

Patient	Gender	Age (yrs)	Tumor type	Tumor size maximum dimension × depth (mm)	Tumor site	SLNs (no. pos/no. total)	Regional lymphadenectomy (no. pos/no. total)	Follow-up duration and status
1	F	78	Hidradenocarcinoma	9 × 12	Right foot	1/5	0/13	25 mos/ AW
2	F	33	Aggressive digital papillary adenoca	6 × 6	Right 5th finger	2/5	0/14	3 mos/ AW
3	F	67	Eccrine ca	5 × 4	Scalp	1/3	0/16	1 mo/AW
4	M	31	Hidradenocarcinoma	8 × 3.5	Left knee	0/3	NP	6 mos/ AW
5	F	50	Aggressive digital papillary adenoca	35 × 18	Right 1st finger	0/2	NP	6 mos/AW

SLNs: sentinel lymph nodes; F: female; AW: alive and well with no evidence of residual or metastatic disease; adenoca: adenocarcinoma; ca: carcinoma; M: male; NP: not performed.

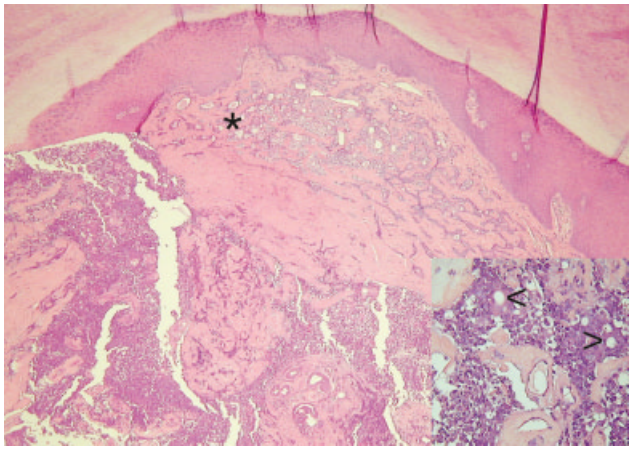

FIGURE 1. Hidradenocarcinoma from the right foot of Patient 1 demonstrated infiltrative islands and cords of clear cells with round lumens in the superficial dermis (*). *Inset*: Solid areas of tumor were observed in the deeper dermis. At a higher magnification tumor cells formed duct-like structures (arrowheads) and were surrounded by hyalinized stroma.

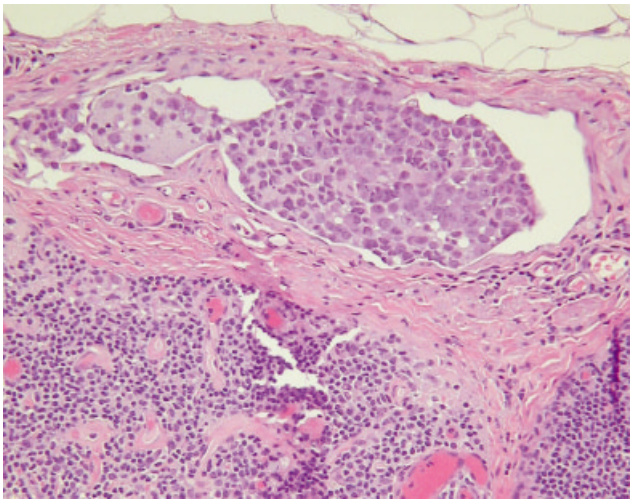

FIGURE 2. Tumor cells lodged in the capsular lymphatics of a sentinel lymph node from Patient 1 demonstrated focal cytoplasmic vacuolation reflecting intracytoplasmic lumen formation.

olymphatic invasion was not detected in any of the cases.

Although histopathologic findings varied somewhat for each carcinoma, histomorphologic evidence of eccrine differentiation was noted in all five tumors. Hidradenocarcinomas were comprised of islands and sheets of cells, many with clear cytoplasm and distinct cell membranes (indicated by the asterisk in Fig. 1), separated by hyalinized collagen (Fig. 1, *inset*). Both round ductal lumens (Fig. 1, arrowheads and *inset*) and cytoplasmic vacuoles representing intracellular lumen formation were evident in both well differentiated and less differentiated areas of the primary tumor and the SLN metastasis (Fig. 2). Aggressive digital papillary adenocarcinoma demonstrated tubuloalveolar and ductal structures with intralumenal papillary projections infiltrating the dermis (Fig. 3). Tumor cells displaying similar tubuloductal structures were identified in the SLN (Fig. 4). Eccrine carcinoma (syringoid carcinoma) was comprised of comma-shaped tubular tumor islands with well defined, round lumens (Figs. 5, 6). Tumor cells appeared basaloid and strikingly uniform, with few mitoses noted.

Metastatic carcinoma was identified in 4 of 18 SLNs in 3 of the 5 patients. Tumor cells were found to lodge primarily in the lymph node capsular lymphatics (Figs. 2, 6) and occasionally in the subcapsular sinuses and parenchyma (Fig. 4). Patient 2 had two positive SLNs. Both the metastases in this patient were identified definitively only in pancytokeratin-stained SLNs. Metastases in Patients 1 and 3 were obvious in H&E sections and confirmed by pancytokeratin stains. There was a moderate degree of lymph node involvement by metastatic carcinoma in the SLN from Patient

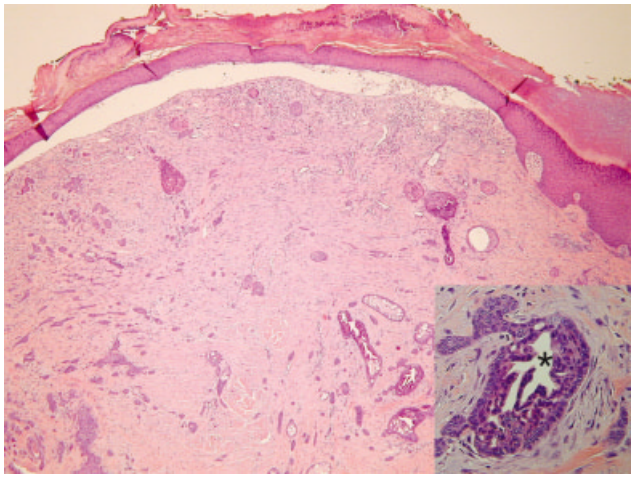

FIGURE 3. An aggressive papillary digital adenocarcinoma from the right fifth finger of Patient 2 demonstrated infiltrative tubular ducts with intralumenal papillary projections in the dermis (*inset**).

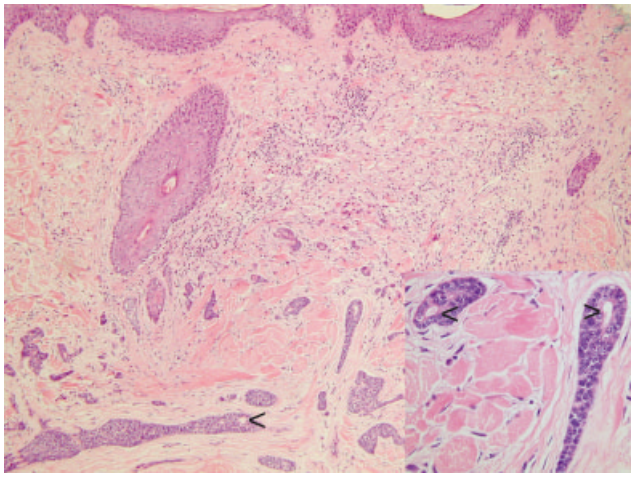

FIGURE 5. Eccrine carcinoma from the scalp of Patient 3 was found to invade the surrounding dermis as bland-appearing, comma-shaped tubular ducts with well defined lumens (*inset* and arrowheads).

1 (estimated to be 20% of the sectioned lymph node surface area), with prominent extracapsular extension. There was less involvement in the SLNs of Patients 2 and 3 (< 5% of the sectioned lymph node surface area).

All three patients with positive SLNs subsequently elected to undergo regional lymphadenectomy. Metastatic tumor was not identified in additional regional lymph nodes from these patients. Only Patient 3 received additional therapy (local radiation therapy to the primary tumor site). All patients were alive and well without evidence of recurrent or metastatic disease after 1–25 months of follow-up. Clinical and pathologic data are summarized in Table 1.

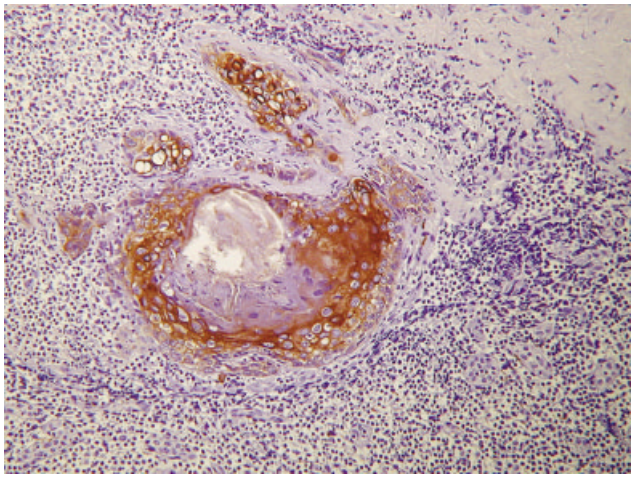

FIGURE 4. Pancytokeratin-positive tumor cells were present in the parenchyma of a sentinel lymph node from Patient 2.

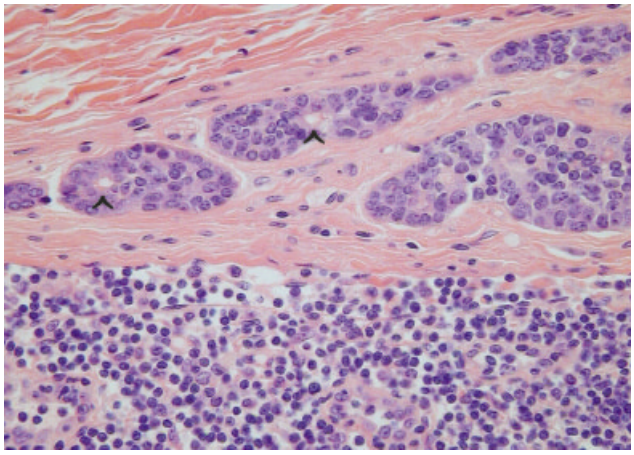

FIGURE 6. Capsular lymphatics of a sentinel lymph node from Patient 3 was found to contain tumor resembling eccrine ducts (arrowheads).

DISCUSSION

Aggressive digital papillary adenocarcinoma and hidradenocarcinoma reportedly behave as aggressive tumors and commonly metastasize. Aggressive digital papillary adenocarcinoma usually occurs as a painless solitary mass almost exclusively on the distal limbs. In 1 study, 7 of 17 patients (41%) with aggressive papillary digital adenocarcinomas developed metastases. Three of 17 patients (18%) developed regional lymph node metastasis. Five of 17 patients (29%) had metastatic lung disease. Three of the 17 patients (18%) died of metastases at a range of 5–20 years after undergoing surgical resection of the primary tumor.[17] Hidradenocarcinoma, also known as malignant eccrine acrospiroma, usually presents as an ulcerated reddish nodule on the face or limbs of the elderly and may have a slightly higher rate of metastasis. A literature review of 16 cases of recurrent hidradeno-

carcinoma reported metastasis in 10 patients (63%). Seven of 16 patients (44%) had lymph node involvement. Ten of 16 patients (63%) died of disease 6 months to 7 years after diagnosis.[18] Although these results may be biased somewhat by the authors' selective and retrospective analysis of recurrent tumors, it appears clear that even nonrecurrent primary hidradenocarcinoma has a high rate of metastatic spread.[19] Eccrine carcinoma (also known as syringoid carcinoma) typically presents as a slowly growing indurated plaque on the scalp or nodule on the limbs and trunk. Eccrine carcinoma is reported to metastasize only infrequently.[20] However, there are a few reported cases with metastasis,[20–22] occasionally with wide dissemination resulting in death.[20] Hence, the high rate of metastasis (60%) observed in the current study appears to be consistent with that previously reported for sweat gland carcinoma patients as a group.

The use of SLN biopsy for aggressive papillary digital adenocarcinoma has been reported in one case,[15] but to our knowledge no formal examination of multiple patient cases has been documented in the literature. In the current study, we presented a group of five patients in whom SLN biopsy was performed for three histologic subtypes of sweat gland carcinoma. Our data confirm the propensity of eccrine malignant tumors to metastasize. The results also demonstrate the utility of SLN biopsy in detecting subclinical or early regional lymph node metastasis. In principle, this sensitivity is attributable to the selection of lymph nodes first to receive lymphatic drainage from the tumor site, and the careful and focused histopathologic examination these SLN receive from the pathologist. All three patients with positive SLNs had negative completion lymphadenectomies, a factor that also supports the principle of lymphatic mapping by which tumor metastasizes first to the draining SLN. The early detection of metastatic eccrine carcinoma is important because tumor recurrence at the draining lymph node basin can be prevented. However, whether the early detection and treatment of lymph node metastasis improves overall survival is not clear at this time, and long-term follow-up of these and subsequent patients will be required to make this determination.

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