CASE REPORT

A rare case of acral cutaneous squamous cell carcinoma with multiple late cutaneous metastases and extensive neurotropic spread

Erin Lowe, BA,a Timothy Brown, MD,b and William A. Geary, MD, PhDc
Erie, Pennsylvania and Jamestown, New York

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INTRODUCTION
Perineural invasion (PNI) is seen in approximately 5% of cutaneous squamous cell carcinomas (cSCC).1 The trigeminal and facial nerves are most commonly involved, and few cases of cSCC with clinical PNI outside of the head and neck are reported.2,3 We present a patient with a history of an excised left wrist cSCC and subsequent motor neuropathy of the left arm. He then had 2 additional proximal tumors of the left arm. These subsequent malignancies were associated with extreme perineural invasion with histologic features consistent with perineural spread and cutaneous metastases.

CASE REPORT
An 88-year-old man presented to the general surgeon with a lesion of the left posterior wrist. Medical history was negative for previous skin cancers or other malignant neoplasms, radiation exposure, or immunodeficiency (although old age alone may be an independent determinant of immune function). Physical examination did not find lymph node involvement or other cutaneous malignancies. Biopsy yielded a well-differentiated cSCC, American Joint Committee on Cancer stage I (T1Nxm) with no high-risk features. The tumor was removed by conventional excision with clear margins and no perineural or angiolymphatic invasion. The patient did not follow-up with a dermatologist.

One year later, the patient had progressive left arm weakness followed by several episodes of twitching of the left upper extremity, head, and neck. He was evaluated by a neurologist. Standard computed tomography scans and contrast-enhanced magnetic resonance imaging of the brain were unremarkable. Electroencephalogram results suggested seizure activity involving the right hemisphere. Electromyography and nerve conduction studies had findings suggestive of significant involvement of the median, ulnar, and left radial nerve proximal to innervation of the left triceps muscle. There was complete loss of extension and weakness in flexion at the left elbow, wrist, and 5 digits. Sensation remained intact. Focal seizures were diagnosed, and the patient was placed on anticonvulsant drugs. His weakness was explained as multiple nerve palsy.

Three years after the original excision, the patient presented to the same general surgeon for evaluation of 2 new growths, grossly characterized as a 4-cm lesion in the left posterior forearm and a 3-cm lesion in the left antecubital fossa. They were ulcerated, tender, and suspicious for skin malignancy. The surgeon promptly scheduled conventional excision. During surgery, it was obvious that the lesions were adherent to underlying tissue. There was gross invasion of skeletal muscle, vessels, and nerves. All visible and palpable tumor was removed. Histology of the cutaneous components yielded well- to moderately differentiated cSCC. Deep and peripheral margins of both wide excisions were positive. There was an extensive neurotropic component with
multifocal perineural invasion and satellite tumor deposits throughout the cutaneous soft tissue.

Comparison of these malignancies with the prior cSCC of the left wrist yielded histologic similarities. The original tumor biopsy, first excision, and subsequent tumor excisions all share a highly reproducible pattern of giant cell reaction and granulomalike inflammation associated with the keratinizing component, occurring as “skip” areas laterally and deep in relation to the surface (Fig 1). The giant cell reactive clusters persist even in the later deep tumor masses associated with large nerves involved by otherwise moderately to poorly differentiated squamous cell carcinoma (Fig 2).

There is evidence of heterogeneity of differentiation within the original tumor that is replicated in the subsequent tumor sites with a continuous progression from well-differentiated elements (superficially in the first biopsy) to moderately differentiated in the first excision, to moderately to poorly differentiated carcinoma in the deeper and perineural foci in the later resections. Finally, the later tumor sites are predominantly dermal and subcutaneous with growth architecture most consistent with subepidermal origin and subsequent growth up to and through the overlying skin. This condition represents a continuous process of a cSCC initially diagnosed in a superficial biopsy that yielded no evidence of high-grade attributes but most likely had undetected deep or otherwise discontinuous areas of persistence, which eventually manifested as relatively large deep tumors in a short time interval.

**DISCUSSION**

PNI is a high-risk feature for cSCC tumor recurrence and both local and distant metastasis according to the current America Joint Committee on Cancer Staging Manual. Other high-risk markers include poor differentiation, tumor diameter ≥ 2 cm, tumor thickness greater than 2 mm, and Clark’s level ≥ 4. Host factors, such as immunosuppression or radiation exposure, also play a role in assessing prognosis. Approximately 30% to 40% of cSCC with PNI display clinical symptoms such as pain, paresthesia,
or weakness, whereas most PNI are histologically incidental findings. Clinical PNI is indicative of advanced disease and is associated with poorer prognosis. Skin malignancies that show an affinity for nerve sheaths are well described in the head and neck but are rarely described in the periphery.

Clinical examination, electromyography, and nerve conduction studies provided evidence that at least 4 major nerves are involved in this patient’s motor neuropathy: the radial, musculocutaneous, median, and ulnar nerves. It is possible that the initial cSCC on the left posterior wrist invaded the radial nerve with neurotropic propagation retrograde and throughout small, unnamed communicating branches, creating distal deficits of the musculocutaneous, median, and ulnar nerves as well as cutaneous metastases. Neurologic, surgical, and histologic findings support this pattern of spread. It is unclear if the new-onset seizure disorder is related to neural dysfunction secondary to perineural cSCC or an independent finding.

Because of the aggressive nature of clinical PNI, it is recommended to treat with Mohs resection to clear nerve margins and postoperative salvage radiotherapy. Our patient was offered referral to a regional cancer center for Mohs micrographic surgery but declined because of geographic limitations. He also declined further dissection by the general surgeon, magnetic resonance imaging of the left arm and shoulder to assess nerve involvement, and a positron emission tomography—computed tomography scan to rule out metastasis. He initially avoided adjuvant radiotherapy because of the labor-intensive time commitment; however, at 6-week surgical follow-up the patient had recurrent tumors arising in the setting of healing fibrous tissue. At this point, he accepted referral to a radiation oncologist to discuss palliative options and will undergo treatment with 6000 cGy in 30 fractions delivered over 6 weeks to cease further perineural spread.

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