# Cutaneous Squamous Cell Carcinoma With Perineural Invasion: A Case Report and Review of the Literature

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## Practice Points

- Patients with suspected cutaneous squamous cell carcinoma should be asked about neurological symptoms including pain, loss of motor skills, anesthesia, dysesthesia, and/or paresthesia, which may indicate perineural invasion.
- Patients with perineural invasion carry a much higher risk for local and distant recurrence and may require more aggressive treatment including Mohs micrographic surgery and adjuvant radiation.

*Perineural invasion (PNI) is an uncommon manifestation of cutaneous squamous cell carcinoma (SCC). We report a case of recurrent cutaneous SCC with PNI diagnosed both clinically and histologically. We also provide a review of the literature. Clinicians should be aware of this uncommon finding, as PNI has been associated with increased local recurrence, local and distant metastasis, and poor prognosis. Patients with clinical findings associated with perineural involvement have a poorer prognosis than those incidentally discovered on histologic examination, which emphasizes the importance of a thorough history and neurologic examination in patients with cutaneous SCC to identify those who will require more aggressive therapy.*

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## Case Report

A 74-year-old man with a history of squamous cell carcinoma (SCC) on the right side of the temple that was treated with Mohs micrographic surgery (MMS) 3 years prior presented with a burning and tingling sensation of 3 months' duration in the medial border of the repair scar. The patient denied prior anesthesia or muscle weakness of the face as well as any loss or change in vision.

Physical examination revealed a well-healed advancement flap scar with induration at the medial border (Figure 1). Biopsy results were positive for recurrent SCC. Based on anatomic location, clinical symptoms, and tumor recurrence, treatment with MMS was initiated. Mohs sections demonstrated perineural invasion (PNI)(Figures 2 and 3). Multiple treatment stages were required for tumor clearance following the retrograde course of a nerve, which resulted in a substantial defect (Figure 4). The defect was allowed to heal by second intention followed by radiation therapy.

## Comment

*Incidence and Pathogenesis*—Perineural invasion was first described by Cruveilhier[1] in a report of invasion of the facial nerve in a patient with mammary carcinoma. Neumann[2] reported the first case of a primary cutaneous lesion exhibiting PNI in a patient with a primary carcinoma of the lower lip with invasion and spread along the mental nerve. Perineural invasion is seen in approximately 5% of 200,000 total cases of cutaneous SCC reported annually in the United States.[3,4] Other malignancies exhibit PNI more frequently, such as microcystic adnexal carcinoma of the skin, which has been reported to have an 80% rate of perineural growth.[5]

Perineural invasion can involve nerves of variable thickness, but invasion of larger nerves typically portends a poorer prognosis.[6] Characteristics of cutaneous SCC that predispose the lesion to PNI include

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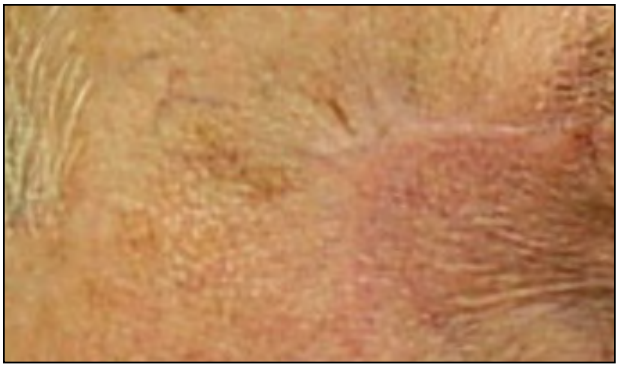

**Figure 1.** Recurrent cutaneous squamous cell carcinoma on the right side of the temple that was treated with Mohs micrographic surgery 3 years prior to presentation, which resulted in a scar.

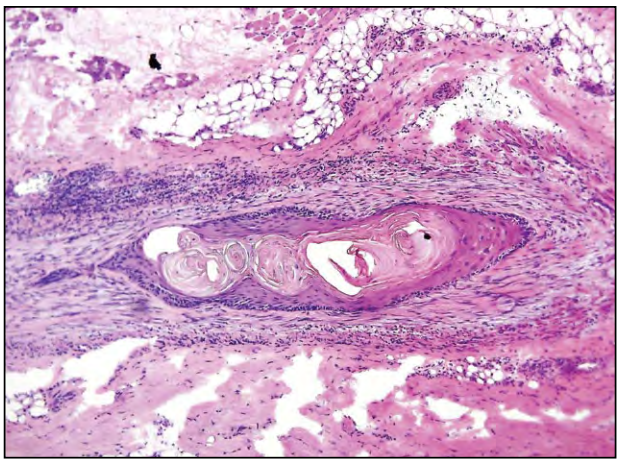

**Figure 2.** A large peripheral nerve (diameter, >0.1 mm) demonstrated an intraneural island of enlarged, atypical keratinocytes that formed keratin eddies. A lymphocytic infiltrate surrounded the perineurium (H&E, original magnification ×10).

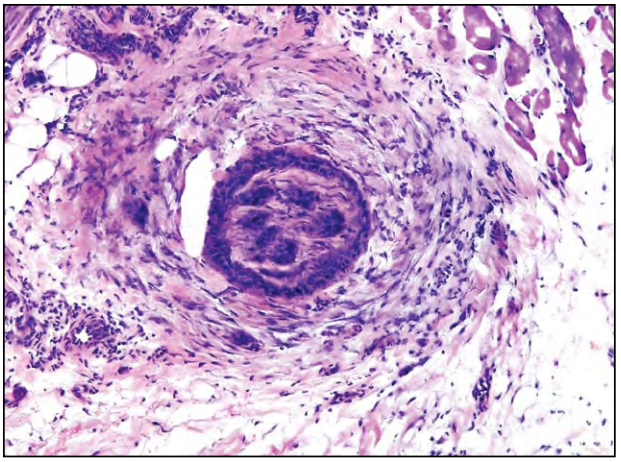

**Figure 3.** A large peripheral nerve (diameter, >0.1 mm) in cross-section with perineural and intraneural carcinoma was evident. An associated lymphocytic inflammatory infiltrate was present around the nerve bundle (H&E, original magnification ×10).

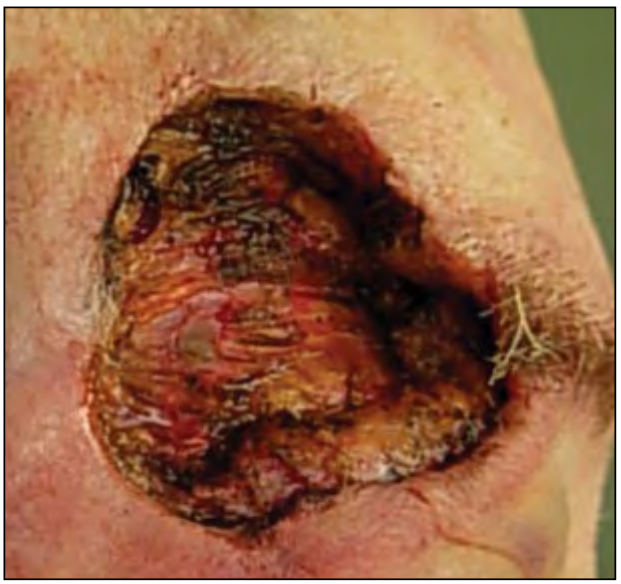

**Figure 4.** Multiple stages of Mohs micrographic surgery resulted in a substantial defect.

size greater than 2 cm, male gender, location on the face, and prior treatment of the lesion.[6,7] In a study of cutaneous SCC, Leibovitch et al[7] found PNI in 4.7% (36/772) of primary lesions and 6.9% (34/491) of recurrent lesions. In another study of 180 SCC tumors of the head and neck with PNI, Carter et al[8] found that PNI was most commonly seen in tumors that were greater than 2.5 cm, suggesting that larger lesions have an increased predisposition for PNI.

The mechanism(s) by which PNI develops from these malignancies has not been fully elucidated, but some clues have been found. Vural et al[9] showed a statistically significant difference ($P<.01$) in expression of neural cell adhesion molecules with 93% (38/41) of SCCs with PNI showing evidence of expression versus 36% (9/25) of SCCs without PNI. Chen-Tsai et al[10] also suggested that levels of neural cell adhesion molecules may be a factor in determining the metastatic potential of cutaneous SCCs and that levels of neurotrophic tyrosine kinase receptor type 1 (TrkA) may predict PNI, but their study results lacked statistical power to form a firm conclusion.

*Diagnosis and Prognosis*—Perineural invasion can be diagnosed clinically, radiologically, or microscopically. On clinical examination, PNI is suggested by findings of neuropathy most frequently in cranial nerves V and/or VII, likely due to their extensive subcutaneous distribution.[11] Common symptoms include pain, loss of motor skills, anesthesia, dysesthesia, and/or paresthesia

(ie, tingling, burning, pricking, numbness).[12,13] In a study of 72 cases, Goepfert et al[14] found that only 40% (29/72) of patients with pathologically confirmed PNI presented with clinical symptoms and these patients had a poorer prognosis.

Radiologically, PNI can be identified via computed tomography or magnetic resonance imaging through findings of enlargement or abnormal enhancement of the nerve, obliteration of the normal fat plane surrounding the nerve, or erosion or enlargement of its related foramen.[15] Magnetic resonance imaging is the preferred method for assessing enhancement of the nerve, while computed tomography is preferred to assess involvement of bone.[16,17] Microscopically, there is some debate as to what defines PNI. Suggested findings include the presence of cells inside the epineurium, involvement of nerves outside the main bulk of the tumor, or presence of tumor cells surrounding a nerve.[18]

These definitions have prognostic significance. Mendenhall et al[16] found that patients with radiologic evidence of PNI without clinical symptoms had a higher cure rate using surgery and postoperative irradiation compared to patients with clinical symptoms (80% vs 45%). Although prognosis generally is good in patients with cutaneous SCC without PNI, prognosis is notably poorer when PNI is present due to the association of this finding with increased tumor recurrence and both local and distant metastasis.[13] Most frequently, cutaneous SCC with PNI spreads proximally, which can lead to invasion into the base of the brain, but also can extend distally, leading to increased local burden.[12,19] In a study of 64 patients with mucosal SCC, Soo et al[20] found that patients with lesions that exhibited PNI had a 5-year survival of 16% versus 44% in those without PNI. In their study of SCC of the head and neck, Goepfert et al[14] reported that 46% (33/72) of patients with PNI had died or were alive with recurrence at 2 years' follow-up versus 9.1% (41/448) of patients without PNI. In a systematic review of outcomes, Jambusaria-Pahlajani et al[21] reported a disease-specific death rate of 16% for cutaneous SCC with PNI compared to 4% for SCC without PNI.

Perineural invasion can be further classified as clinical or microscopic (incidental) for prognostic purposes. A study by Garcia-Serra et al[13] found that patients with clinical PNI had a notably poorer prognosis than those with microscopic (incidental) PNI. The clinical group achieved a local control rate of 55% at 5 years' follow-up versus 87% in the microscopic group. McCord et al[22] found a 5-year local control rate of 78% for microscopic (incidental) PNI versus 50% for clinical PNI; they also found that patients with radiologic evidence of PNI had a worse prognosis, noting that patients with radiologic evidence of PNI were nearly all clinically symptomatic.

Prognosis also is altered by the diameter of the nerve involved. In a study of 48 patients, Ross et al[23] found that patients with cutaneous SCC involving small-caliber nerves (diameter, ≤0.1 mm) had a 0% disease-specific death rate versus 32% in those with large-caliber nerves (>0.1 mm). Perineural involvement of small-caliber nerves (<0.1 mm) was a positive prognostic indicator in that it was associated with smaller tumor diameter, more shallow invasion, and increased likelihood to be primary tumors.[23] In a recent study, Jambusaria-Pahlajani et al[24] investigated tumor staging for cutaneous SCC and reported that PNI is a statistically independent prognostic risk factor for nodal metastasis (subhazard ratio, 2.2 [95% confidence interval, 0.9-5.1]) and disease-specific death (subhazard ratio, 3.4 [95% confidence interval, 0.9-13.3]). Of interest, this increased risk applied only to PNI in nerves that were greater than 0.1 mm.[24]

*Treatment Options*—Management of confirmed cases of cutaneous SCC with PNI is difficult because of the nature of the lesions, including their increased propensity for metastasis, increased frequency of poorly differentiated cell types, highly aggressive nature, and the unique challenge of skip lesions.[4,16] Skip lesions are found microscopically and show (or appear to show) neoplastic cells invading a nerve in a discontinuous fashion. This phenomenon has been suggested as one explanation for the relatively higher postsurgical recurrence rate of SCC with PNI compared to lesions without PNI.[7] They are of particular interest when removing cutaneous SCC with PNI using MMS and attempting to define clear margins. Despite this limitation, MMS generally is accepted as the primary mode of excision of cutaneous SCCs with PNI, as it has the highest known cure rate.[7] Cottel[4] did not report any cases of local recurrence over 1 to 42 months in 17 patients who were treated with MMS, in contrast to Rowe et al[25] who demonstrated that traditional surgical excision had a 47% (34/72) local recurrence rate; however, it bears noting that the varying follow-up periods in the Cottel[4] study may underestimate recurrence rate. Leibovitch et al[7] had similar findings in their prospective case series study of 70 patients, which revealed an 8% recurrence rate within 5 years in patients treated with MMS, a rate lower than other non-MMS modalities. In this same study, the authors noted that some researchers believe an additional level should be taken with MMS beyond the appearance of free margins in cases with PNI.[7]

Jambusaria-Pahlajani et al[21] reported that PNI is one of the most common reasons cited for using adjuvant radiation therapy for cases of cutaneous SCC because of the known propensity of local recurrence; however, in 74 reviewed cases, there was no statistically significant difference in outcomes in cases of

surgery alone versus surgery and adjuvant irradiation. Radiation therapy is a possible alternative primary treatment of cutaneous SCC with PNI, especially in cases of perineural involvement that is extensive or affects proximal portions of cranial nerves when surgery is a less viable option.[17] Mendenhall et al[16] suggested that patients with positive margins after excision who display extensive PNI should be treated with adjuvant irradiation locally and along the course of the involved nerve to the skull base.

## Conclusion

Physicians should recognize the importance of early detection of PNI in cases of cutaneous SCC. A thorough history with good neurologic examination of the head and neck in patients with cutaneous SCC is imperative so patients can be treated earlier in the course of the lesion, increasing the likelihood of local control, minimizing the risk for future recurrence, and decreasing mortality.

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