

# Perineural Involvement of Squamous Cell Carcinoma Presenting With Formication

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*Perineural involvement of a cutaneous neoplasm marks an aggressive feature. Tumors with perineural involvement share an increased propensity for local invasion via perineural spread. Formication may be an indicator of perineural involvement by cutaneous neoplasms. We present a case of an 82-year-old man with perineural involvement of a squamous cell carcinoma (SCC) identified by clinical symptoms of formication. Successful resolution of these symptoms was achieved with radiation therapy.*

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Perineural invasion of cutaneous tumors marks an aggressive growth feature and has been reported in numerous malignancies, including carcinomas of the breast, prostate, uterus, and oral cavity.<sup>1</sup> It has been extensively reported in relation to cutaneous squamous cell carcinoma (SCC).<sup>1-4</sup> The sensation of bugs crawling, or formication, may be indicative of perineural involvement in the sensory distribution of the tumor. Prompt attention to and diagnosis of specific patient concerns may aid in early clinical diagnosis of perineural involvement. We present a

patient who reported formication related to perineural involvement and its subsequent management.

## Case Report

An 82-year-old man with an extensive history of skin cancer presented for routine evaluation 6 months after treatment of a poorly differentiated SCC with extension down to but not involving the outer table of the calvaria. Computed tomography (CT) of the calvaria revealed no evidence of calvarial erosion. The tumor was cleared at the time of treatment with 3 stages of Mohs micrographic surgery. Perineural involvement was histologically detected within Mohs tissue sections. Following successful surgical extirpation, the wound was allowed to heal by second intention to allow visualization of any potential recurrence. Post-operative radiation therapy was performed because of the presence of perineural involvement.

Approximately 6 months after surgery, the patient reported numbness, tingling, and formication near the prior surgical site. He stated that the sensations of “tingling” and “bugs crawling” were “driving him crazy” and he had considered suicide at one point. The patient also noted frequent headaches.

Physical examination revealed a well-healed surgical site. The treated tumor was located on the right frontal scalp in the sensory distribution of the right supraorbital nerve. There was no palpable anterior cervical, axillary, or supraclavicular lymphadenopathy. No palpable masses were noted at any neural foramina.

A clinical working diagnosis of perineural tumor involving supraorbital and possibly supratrochlear nerves was made. The patient was placed on gabapentin by a different physician without benefit. He was referred to dermatology for evaluation and subsequent radiation therapy to treat these areas. He

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received 42.6 and 44.8 Gy total dose to his frontal and parietal scalp, respectively, within one month (frontal: 6 MeV electrons, 2 Gy; parietal: 9 MeV electrons, 2 Gy). The patient had a history of radiation therapy in the area from a prior skin cancer. The supraorbital foramen was included in the treatment field. The patient experienced prompt relief of all symptoms by the completion of therapy. Overall, he tolerated radiation therapy well, with the exception of mild skin irritation. The patient subsequently died of unrelated cardiac disease.

### Comment

Perineural spread of a neoplasm was first reported by Cruveilhier<sup>5</sup> in 1835. Perineural involvement in cutaneous tumors has been reported with a variety of cutaneous neoplasms and denotes a more aggressive growth pattern with a high propensity for local recurrence, distant metastasis, and difficulty achieving complete control.<sup>1,6</sup> The incidence of tumor involvement into the perineural space by head and neck SCCs is approximately 2.4% to 16%.<sup>3</sup> Geist et al<sup>7</sup> reported perineural invasion in approximately 2.5% to 14% of cutaneous SCCs and 3% of basal cell carcinomas.

Multiple factors are associated with perineural invasion, including tumor size, site, type, histologic subtype, and recurrence.<sup>8,9</sup> In an evaluation of 180 study participants, perineural invasion occurred in 64% of cutaneous SCCs measuring more than 2.5 cm and in 11% of those less than 2.5 cm.<sup>2,10</sup> Among SCC variants, spindle cell, adenosquamous, and poorly differentiated subtypes were the most likely to have perineural involvement.<sup>9</sup> Perineural involvement of larger nerves carries a prognosis that is worse than involvement of smaller nerves.<sup>11</sup>

Perineural involvement often is clinically asymptomatic. Tumor bulk that subsequently impinges on a nerve is believed to be the reason for symptoms.<sup>1</sup> Histologic examination characteristically reveals perineural invasion seen incompletely to completely encircling the nerve axis.<sup>8</sup> Symptoms are similar to those expected with neurotropic involvement, including local pain, neuropathic pain, pruritus, and burning.<sup>3</sup> Patients often report sensations of ants, bugs, or worms crawling in the skin, which may progress to pain and/or numbness.<sup>12,13</sup> McNab et al<sup>14</sup> surveyed 21 patients with perineural SCC and found that decreased/altered sensation, ophthalmoplegia/ptosis, facial weakness, and pain were common clinical symptoms.<sup>14</sup> However, the absence of clinical symptoms does not eliminate perineural involvement and must be considered in the presence of other suggestive features. In a study involving 72 patients with perineural SCC, Goepfert et al<sup>9</sup> noted that 60% (n=43) of patients were asymptomatic. Additionally, involvement of the facial nerve

was common.<sup>9</sup> Neurotropic involvement has been associated with metastases to local and regional lymph node basins.<sup>4,15,16</sup>

Carter et al<sup>10</sup> reported tumor cell invasion in the perineural space with subsequent spread. The perineural space is a virtual space that communicates with the subarachnoid lining.<sup>17</sup> Tumor extension typically is contiguous; however, the presence of skip lesions is documented.<sup>3,12,18,19</sup> Perineural skip lesions are rare, but this phenomenon has been reported.<sup>20</sup>

The pathophysiology of perineural spread is not completely understood. Multiple theories exist, including growth in the plane of least resistance along the nerve sheath. Chen-Tsai et al<sup>8</sup> proposed the relation of perineural invasion to expression of the neural cell adhesion molecule and the protein p75 nerve growth factor and its receptor, p75<sup>NGFR</sup>, as well as the high-affinity receptor tyrosine kinases A, B, and C. The p75<sup>NGFR</sup> and tyrosine kinase expression was demonstrated in perineural invasion in bile duct carcinoma, rectal carcinoma, and both basal cell carcinomas and SCCs. Chen-Tsai et al<sup>8</sup> demonstrated that 4 of 5 SCCs with perineural invasion stained positive with p75<sup>NGFR</sup>.

The presence of formication in patients with cutaneous neoplasms is suggestive of perineural involvement. Histologic confirmation of perineural involvement may be difficult because of sampling error. Physical examination in these patients should include palpation of the foramina where the sensory nerves enter the calvaria and possibly radiographic imaging to assess for in-transit spread. The preferred treatment of cutaneous SCC with perineural involvement is Mohs micrographic surgery followed by radiation.<sup>1,3,4,16</sup> The method of choice for the investigation of suspected perineural involvement is magnetic resonance imaging.<sup>13-15,21,22</sup> The use of CT may demonstrate enlarged nerves but not as effectively as magnetic resonance imaging.<sup>14</sup> Hybrid positron emission tomography-CT also has been used for investigation of perineural involvement.<sup>23</sup> Ginsberg and Eicher<sup>24</sup> presented a case of perineural SCC involving the great auricular nerve. This nerve typically is not visible with standard CT, but the enlargement secondary to perineural involvement allowed visualization on CT.<sup>23</sup> However, radiologic imaging in these patients often results in a low yield of positive findings without involvement of large nerves and bony involvement. Erosion of foramina is one useful clue to perineural involvement that may be seen with radiography.

### Conclusion

Formication may be suggestive of perineural involvement. The presence of formication and a history of

skin cancer warrants further examination to rule out perineural involvement. Histologic and radiologic confirmation may be used to help identify perineural involvement.

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