

# Cranial neuropathies as the presenting symptom of cutaneous squamous cell carcinoma



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**Key words:** cutaneous squamous cell carcinoma; cranial neuropathy; cranial neuropathies; cranial nerve; cranial nerve palsy; facial droop; facial nerve; facial nerve palsy; high-risk skin cancer; MRI; Mohs micrographic surgery; paralysis; perineural invasion; perineural protocol; perineural spread; presenting symptom; radiotherapy; skin cancer; skin malignancy; squamous cell carcinoma; trigeminal nerve; trigeminal nerve palsy; trigeminal neuralgia.

## INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) of the head and neck is a common keratinocyte carcinoma, with perineural invasion (PNI) found in approximately 2.5% to 5% of cases.<sup>1,2</sup> Head and neck cSCCs can lead to cranial neuropathies, most commonly cranial nerve V (CNV) and cranial nerve VII (CNVII).<sup>3</sup> Cranial neuropathies from tumoral PNI may be difficult to diagnose given their slow and sometimes subtle onset. Here we describe 3 cases of cranial neuropathy as the presenting symptom of cSCC. Additionally, the pathophysiology of PNI and its predilection for CNV and CNVII is discussed as well as the importance of appropriate imaging in guiding the diagnosis, workup, and treatment.

## CASE SERIES

### Case 1

A 75-year-old man with no history of skin cancer presented with a 2-year history of right facial neurologic symptoms. History of herpes zoster without neuralgia was noted more than 20 years prior. He reported eye tracking difficulty and progressive numbness that spread gradually from his temple to the right hemiface over a 1-year period. He was evaluated by 4 different neurologists, with workup including nondiagnostic lumbar puncture, computed tomography (CT), MRI, and a magnetic resonance angiogram. Gabapentin and prednisone offered mild improvement. Two years after initial

### Abbreviations used:

CNV:	cranial nerve V
CNVII:	cranial nerve VII
cSCC:	cutaneous squamous cell carcinoma
CT:	computed tomography
CVA:	cerebrovascular accident
PNI:	perineural invasion

presentation, he had shooting “electrical” pain on the right hemiface, right facial palsy, and induration over the right temple without epidermal change (Fig 1). Skin biopsy found desmoplastic and infiltrative cSCC. A repeat MRI of the brain, this time with perineural protocol, found enhancement and enlargement of all 3 branches of the right trigeminal nerve into the cavernous sinus and Meckel cave and enhancement of the pterygopalatine fossa. Additionally, multiple muscles of mastication showed enhancement and denervation. Positron emission tomography/CT found invasion of 2 level-2 lymph nodes and denervation with atrophy of the pterygoid and masticator muscles.

### Case 2

A 92-year-old man presented with right hemifacial paralysis and eye and ear pain. His neurologist determined him to have Bell palsy. On examination, ulceration at the right retroauricular sulcus was noted, and he was referred to a dermatologist (Fig 2). His only prior history of skin cancer

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**Fig 1.** Right facial palsy (A) and indurated region on the right temple (B).



**Fig 2.** Right facial palsy (A) and right retroauricular ulceration post biopsy (B).

was squamous cell carcinoma at the triangular fossa of the right ear treated with Mohs micrographic surgery 3 years prior. Results of a biopsy of the retroauricular sulcus were interpreted as fibrosing dermatitis. Six months later, a second dermatologist performed a repeat biopsy that found invasive cSCC with PNI. CT scan of the neck without contrast found abnormal soft tissue from the skin at the level of the retroauricular sulcus extending medially to the right stylomastoid foramen, bony destruction of the distal mastoid, and focal ulceration at the retroauricular sulcus. A staging positron emission

tomography/CT was negative for cervical lymph node involvement.

### Case 3

A 67-year-old man with a history of atrial fibrillation and multiple cerebrovascular accidents (CVAs) presented with a 5-year history of a slowly enlarging 2- × 2.5-cm cSCC of the left conchal bowl (Fig 3, A). A recent right middle cerebral artery CVA left him with residual left hemiparesis, expressive aphasia, and dysphagia. On examination, there was concern for tumor extension through the conchal cartilage



**Fig 3.** Left conchal bowl ulceration (A) and complete left facial droop (B).

and down the left auditory meatus. Neurologic examination was significant for left full CNVII palsy; the patient retained ability to puff cheeks symmetrically and bilaterally (Fig 3, B). This facial palsy was noted by numerous providers as sequelae of his prior CVAs. No cervical or axillary lymphadenopathy was appreciated. CT scans with and without contrast of the left temporal bone and neck was ordered to evaluate local tumor extension, bony involvement, and lymphatic invasion. Before obtaining the CT, the patient experienced a first-time generalized tonic-clonic seizure. Head and neck MRI found a soft tissue mass in the left external auditory canal, likely corresponding to recent cSCC, and left infratemporal facial nerve enhancement suspicious for perineural spread.

## DISCUSSION

Perineural spread of cSCC can pose a diagnostic challenge, as signs and symptoms of PNI can occur in the absence of a clinically obvious lesion. The latent period between onset of symptoms and diagnosis of PNI can be long, ranging from 6 months to 5 years in the aforementioned cases. This delay results in delayed treatment and worse prognosis and limits the efficacy of treatment options. The presented series demonstrates the challenges and pitfalls associated with this condition. Two of 3 patients presented with neurologic symptoms with an occult lesion, whereas 1 patient presented with a suspicious lesion ipsilaterally to his neurologic symptoms. The last case was confounded by a history of CVA with residual neurologic deficits ipsilateral to the tumor.

*Perineural invasion* is a histologic descriptive term indicating tumor cells between the nerve and the nerve sheath along the perineurium or the endoneurial spaces.<sup>4</sup> It is not fully understood why certain tumors have a propensity for PNI while others do not. Head and neck cSCCs can involve both peripheral and cranial nerves. Multiple reports describe remarkably similar frequency of cranial nerve involvement, including CNV (69%-70%) and CNVII (30%-31%).<sup>5,6</sup> These 2 nerves may be affected individually or in combination. This finding is exemplified in case 1, with initial involvement of CNV (facial numbness and pain) followed by retrograde tumoral spread to the anastomosis with CNVII resulting in facial palsy 2 years later.

Tumors with PNI are considered high risk. They occur more in men and on the face and are less differentiated and larger preoperatively.<sup>1</sup> These tumors also are more likely to have an increased postoperative defect, increased subclinical extension, increased recurrence rate, and increased number of Mohs stages to clear the tumor.<sup>1</sup> Additional high-risk features in these tumors include larger size (>2 cm), invasion beyond the fat, and increased likelihood for lymphovascular invasion.<sup>7</sup>

For the dermatologist, a differential diagnosis for cranial nerve neuropathies includes infection, malignancy, vascular impairment, and systemic/auto-inflammatory disease.<sup>8</sup> This diagnosis is further narrowed in most clinical scenarios to Bell palsy, trigeminal neuralgia, postherpetic neuralgia, stroke, and tumoral PNI. Deficits arising from PNI are typically progressive and subacute, whereas other etiologies have a more rapid onset. With regard to

CNVII, neurologic deficits can be subdivided into upper and lower motor neuron lesions. Upper motor neuron lesions, including post-CVA, typically result in contralateral hemifacial deficits of the lower two-thirds of the face, sparing the upper one-third.<sup>9</sup> On the contrary, a lower motor neuron lesion results in either an acute or subacute/progressive complete hemifacial paralysis.<sup>9</sup> Case 3 exemplifies this important distinction. The patient's subtle progression to complete left hemifacial paralysis was falsely attributed by numerous providers to his history of CVA.

The role of imaging in the workup of skin cancers has not been clearly defined, and official guidelines are lacking. Imaging may be appropriately considered when the following items are present: bony invasion, orbital invasion, assessing soft tissue depth, tumor staging, and perineural spread or invasion.<sup>10</sup> Both MRI and CT are capable of detecting PNI, with MRI offering superior visualization of soft tissue because of the increased contrast and multiplanar capabilities.<sup>10</sup> Focused MRI of the anatomic pathways of cranial nerves is known as perineural protocol and has a sensitivity of 95% to 100%.<sup>11</sup> Typically, radiologists must be alerted ahead of time to use this protocol or risk a false-negative result. To achieve the most accurate interpretation, a re-read may be considered, notably if imaging was performed outside of the tertiary care facility. Several reviews of patients with PNI-positive head and neck malignancies have shown a false-negative imaging rate up to 84%, which can result in a change in prognosis in up to 95% of patients.<sup>12,13</sup> Thus, if clinical suspicion is high, imaging reinterpretation or periodic reimaging should be considered to achieve clinical-radiographic correlation.

Treatment often involves a multidisciplinary approach, with considerations including tumor stage, patient health, and restoration of form and function. Mohs micrographic surgery or excision can be curative for microscopic PNI; however, additional local control may be achieved with adjuvant radiotherapy.<sup>14</sup> A cohort study of 102 patients described excellent outcomes from surgery in patients with microscopic PNI (1-2 involved nerves).<sup>14</sup> Extensive PNI (>2 nerves microscopically) and/or gross PNI (on imaging or clinically) benefited from adjuvant radiotherapy.<sup>14</sup> Emerging nonsurgical options for advanced or metastatic cSCC including immunotherapy and checkpoint inhibition are being investigated, with 1 study reporting a response rate of 47% in a cohort with metastatic disease.<sup>15</sup> Although this therapeutic modality is promising for advanced disease, its specific role in the treatment of PNI remains unclear.

Ultimately, PNI from cSCC of the head and neck can lead to cranial neuropathies, most commonly CNV and CNVII. Patients may present with skin pain or vague neurologic symptoms. Suspicion for malignancy with appropriate neurologic examination and imaging should be considered as part of the workup. PNI is best confirmed by MRI with perineural protocol. Patients should be treated aggressively with surgery and/or radiotherapy for optimal outcomes. This condition may have a long latent period before diagnosis and high recurrence rates, resulting in a poor long-term prognosis. Patients should be followed up closely by their dermatologist at regular intervals for thorough examination. Periodic reimaging may be considered if symptoms warrant.

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