An 86-year-old woman tripped and fell on the sidewalk, hitting the front of her head. She did not lose consciousness, but diplopia developed. She presented to the emergency department where a noncontrast computed tomography (CT) scan of the head was within normal limits, and she was referred to the ophthalmology service. During ophthalmologic consultation, the patient stated she had primary hypothyroidism and osteoporosis. Her only medication was levothyroxine. Her main concern was binocular vertical diplopia that increased on downgaze, along with mild periorbital pain. The patient's uncorrected visual acuity was 20/25 in the left eye and 20/30 in the right eye. Results from an Ishihara test showed that she had normal colour vision. Her pupils were equal and reactive with no relative afferent pupillary defect. Slit lamp and dilated fundoscopic examinations were unremarkable. Intraocular pressure was within normal limits. External exam found symmetric palpebral fissures and no proptosis or enophthalmos. The patient's ocular motility was full; however, on cover testing, she had a small, right hyperdeviation in primary gaze that increased in downgaze and on right head tilt. We diagnosed post-traumatic palsy of the right fourth cranial nerve.

The patient returned for follow-up six weeks later with persistent diplopia and ongoing mild-to-moderate right periorbital pain. Upon examination, we deemed her condition to be stable with respect to the baseline ophthalmology assessment.

Three months later, the patient had worsening pain and right-sided ptosis, which prompted a visit to the emergency department, where the physician noted findings suggestive of palsy of the third cranial nerve involving the right pupil. Contrast-enhanced CT including angiography (CT-CTA) showed an incidental meningioma in the left frontal region but was otherwise normal; there was no evidence of intracranial aneurysm. The patient then returned to the ophthalmology service; we found complete ptosis and ophthalmoplegia of the right eye, suggesting involvement of the third, fourth and sixth cranial nerves. There was also numbness along the right-sided ophthalmic (V1) and maxillary (V2) distributions of the trigeminal nerve. As such, her presentation suggested a lesion in the cavernous sinus, possibly involving the orbital apex. We reviewed the CT-CTA with particular attention to these areas; we found thickening of the right cavernous sinus (Figure 1). Magnetic resonance imaging (MRI) with gadolinium showed an avidly enhancing, centrally necrotic, irregular soft tissue mass along the V1 nerve distribution in the right orbit (Figures 2 and 3) that extended to the orbital apex and cavernous sinus (Figure 3 and Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.170671/-/DC1). The radiologic appearance was suggestive of perineural spread of carcinoma.

The patient had previously reported that she did not have a history of cancer; however, when asked specifically about skin cancer, she recalled having a basal cell carcinoma excised from the right glabellar region two years earlier. We were able to obtain a copy of the original pathology, which documented the lesion as squamous cell carcinoma. She was referred to neuro-oncology and treated with radiation. Subsequent MRI showed no radiologic changes from baseline and the patient’s clinical symptoms had not improved at follow-up 1.5 years later.

**Discussion**

Perineural spread of malignant growth is the migration of tumour cells from a primary site along any of the three layers of a nerve (epineurium, perineurium, endoneurium). This unusual means of tumour extension is distinct from spread through vascular and lymphatic channels. The mechanisms underlying this phenomenon are poorly understood. It was initially postulated that neural sheaths provided planes of relatively low resistance for growth of tumour cells. More recent work has shown that complex signal interaction between tumour cells and nerve cells using neurotrophic factors probably enables migration of tumour cells.

**KEY POINTS**

- Clinicians should maintain a high index of suspicion for perineural spread when evaluating cranial neuropathy, especially if it is slowly progressive and does not improve over months.
- Clinicians should ask about skin cancer specifically when eliciting a history that suggests the possibility of perineural spread.
- Clear communication with radiology is essential when ordering neuroimaging for perineural spread (magnetic resonance imaging with gadolinium and fat suppression) to ensure close inspection of the relevant anatomy.
- Perineural spread suggests aggressive malignant growth that portends a poor prognosis for local recurrence and overall mortality.
Perineural spread occurs in a retrograde fashion from the location of the primary tumour and follows the anatomic course of the nerve; the spread can change to an anterograde direction at the site of nerve branches. Perineural spread can be diagnosed radiologically or histologically, either as an incidental finding or when a patient presents with clinical symptoms.3,4 Squamous cell carcinoma causes 90% of all head and neck cancers worldwide, with an annual incidence of more than 550 000 cases.5 Given its high prevalence, squamous cell carcinoma also accounts for the largest number of cases of perineural spread from cutaneous malignant growth.4 Findings from large, prospective, multicentre case series in regions with high incidence of skin cancer
suggest that perineural spread occurs in 2.5% to 6% of cases of cutaneous squamous cell or basal cell carcinoma of the head and neck.6

There have been conflicting reports in the literature about the prognostic significance of perineural spread; however, most studies have concluded that it is associated with poorer outcomes. Underreporting of this disease may have contributed to the historical difficulty in establishing its clinical importance. The evidence associated with perineural spread of cutaneous carcinoma of the head and neck largely stems from retrospective studies, and there is no accepted method of identifying carcinoma at high risk for perineural spread. A retrospective study involving 216 patients with perineural spread from either head and neck squamous cell carcinoma or basal cell carcinoma showed that location of the primary tumour on the temple, forehead or scalp was a risk factor.7 Patients with clinical symptoms or radiologic signs of perineural spread also had a greater likelihood of local recurrence and death at five years, despite treatment with radiotherapy or surgery/chemotherapy.7 The most devastating complication of perineural spread is leptomeningeal carcinomatosis.

**Clinical signs and symptoms**

Perineural spread can affect any cranial nerve, but it most commonly involves branches of the trigeminal and facial nerves (the fifth and seventh cranial nerves).2–4 In one retrospective case series of patients with cutaneous squamous cell carcinoma of the head and neck, involvement of both the fifth and seventh cranial nerves was present in 11 of the 12 cases.8 The extensive facial innervation patterns of these nerves, as well as the many communications between their terminal branches, make the fifth and seventh cranial nerves especially vulnerable to perineural spread of cutaneous malignant growth.9

Symptoms of perineural spread are subtle at first, such as paresthesias or a crawling sensation beneath the skin (formication), but eventually progress to pain, numbness or muscle weakness.10,11 Once the patient has begun to show symptoms, the median time to diagnosis is six months.9 In the case of an occult primary tumour, perineural spread is often misdiagnosed as benign cranial neuropathy, such as trigeminal neuralgia or Bell palsy.10,12 Onset of Bell palsy tends to be acute, but perineural spread has an insidious presentation over weeks to months.

The anatomic proximity of cranial nerves and communications between their peripheral branches can lead to involvement of multiple cranial nerves, especially if perineural spread reaches the level of the orbital apex or cavernous sinus. Decreased vision, visual field defects and a relative afferent pupillary defect are signs of compression of the optic nerve (second cranial nerve). Perineural spread involving the cavernous sinus can cause diplopia and painful ophthalmoplegia, which may be misdiagnosed as Tolosa–Hunt syndrome (idiopathic inflammation of the cavernous sinus) — a diagnosis of exclusion.

**Diagnosis of perineural spread**

Perineural spread should always be considered in patients with a history of cancer of the head and neck that presented with sensory symptoms or diplopia. It can be easily missed on imaging if an adequate clinical history is not provided to the radiologist. Conversely, neuroimaging can suggest this process if there is no known primary malignant growth or, as in our case, when the patient’s medical history is incomplete. A high index of suspicion is necessary, and patients should be specifically asked about history of skin cancer. If clinical findings suggest a clear anatomic localization (i.e., multiple cranial neuropathies indicating involvement of the cavernous sinus or orbital apex, as in our patient), imaging studies should be obtained or repeated, even if initial neuroimaging does not show a clear structural abnormality (Figure 4).12,13

Gadolinium-enhanced MRI is the imaging test of choice because of its high resolution of soft tissue. Examination of the entire course of the nerves and their branches innervating the region of the primary tumour is essential to making the diagnosis. Radiologic evidence of perineural spread includes enlargement or

[| 1. Maintain a high index of suspicion |
|---|
| Always inquire about history of head and neck cancer, asking about skin cancer specifically. |

| 2. Understand the most commonly affected nerves |
|---|
| Knowing the anatomy of the cranial nerves helps predict the probable path of perineural spread. The fifth and seventh cranial nerves are most likely to be affected because of extensive innervation of the facial skin/musculature. |

| Trigeminal nerve (fifth cranial nerve): |
| Facial sensation, paresthesias, numbness, pain, masticatory muscle weakness |

| Facial nerve (seventh cranial nerve): |
| Facial weakness, lagophthalmos |

| Third, fourth and sixth cranial nerves: |
| Diplopia (indicates involvement of the cavernous sinus/orbital apex) |

| 3. Choose appropriate neuroimaging |
|---|
| Magnetic resonance imaging with gadolinium, thin sections and fat suppression Communication with the radiologist is extremely important. |

**Figure 4:** Approach to diagnosis of perineural spread of cancer of the head and neck.12,13
abnormal enhancement of the nerve, obliteration of the fat plane surrounding the nerve and/or erosion or enlargement of the related foramen.\(^{12}\)

Perineural spread also presents a challenge for histological diagnosis, because of the presence of skip lesions and its resemblance to peritumoural fibrosis, which presents as concentric layers of fibrous tissue that surround the tumour.\(^1\) Its prevalence may be underestimated on histology, as a retrospective review involving 120 patients showed that evidence of perineural invasion was not reported in the evaluation of the primary tumour for one-third of patients with perineural spread.\(^3\)

**Conclusion**

Perineural spread of cutaneous malignant growth can be an evasive diagnosis, because patients and health care providers frequently assume that resection of the primary lesion is curative. With the exception of malignant melanoma, most skin cancers are often considered to be benign entities and irrelevant to the medical history following excision. Additionally, challenges on diagnostic imaging and histology make this entity one that requires attention by primary care physicians, surgeons, radiologists and pathologists alike. Increasing our awareness and understanding of perineural spread may improve the likelihood of diagnosis and patient survival.

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