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Website: www.e-tjo.org
DOI: 10.4103/tjo.tjo_62_20

# Delayed diagnosis of cranial neuropathies from perineural spread of skin cancer

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## Abstract:

Perineural spread (PNS) to cranial nerves (CNs) by cutaneous malignancies is difficult to diagnose given the indolent course and often late or absent findings on brain imaging. A 68-year-old white man with multiple cranial neuropathies secondary to PNS by squamous cell carcinoma had negative high-quality neuroimaging for 5.25 years. He first developed left facial numbness, followed 39 months later by a left CN VI palsy. Subsequent examinations over 2 years showed involvement of left seventh, right trigeminal V1–V3, and right sixth, and bilateral third nerve palsies. Repeat high-quality brain magnetic resonance imaging (MRIs) during this time showed no identifiable CNs abnormality. Full body positron emission tomography imaging and cerebrospinal fluid studies were normal. 5.25 years after initial sensory symptom onset, MRI showed new enhancement along the right mandibular branch of the trigeminal nerve with foramen ovale widening. Autopsy showed squamous cell carcinoma within both CNs sixth. A long interval to diagnosis of PNS is associated with high morbidity, emphasizing the need for earlier methods of detection when clinical suspicion is high.

## Keywords:

Cranial neuropathy, perineural invasion, perineural spread, squamous cell carcinoma

## Introduction

Perineural spread (PNS), often referred to as “clinical perineural invasion,” entails spread of cells along the perineural barrier of a nerve and causes clinical dysfunction or identifiable radiographic changes.<sup>[1]</sup> Cranial neuropathies secondary to PNS of cutaneous malignancies can be difficult to diagnose given their indolent course and often delayed or absent findings on head and neck radiography. We present a case of a man with multiple sequential cranial neuropathies secondary to PNS of squamous cell carcinoma who had normal orbital and brain magnetic resonance imaging (MRIs) imaging for 5.25 years, and review the literature with specific attention to time to diagnosis from presentation of cranial nerve (CN) dysfunction.

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## Case Report

A 68-year-old Caucasian man presented for neuro-ophthalmologic evaluation with a 3-year history of left facial numbness and a 6-week history of binocular horizontal diplopia. A small basal cell carcinoma had been removed from his forehead 1 year prior to his evaluation. Extensive prior imaging workup included a MRI from 10 months prior that was normal except for an atrophic lateral rectus muscle and mild increased signal of the left pterygoid muscle.

Examination showed normal afferent visual function, with deficits of left CN V1–V3 and VI function, and decreased left brow elevation. The patient had a partial tarsorrhaphy of the left eye for neurotrophic keratitis. Funduscopic examination was normal. Repeat MRI was unchanged.

**How to cite this article:** Nelson DG, Bidot SS, Esper GJ, Newman NJ, Biousse V. Delayed diagnosis of cranial neuropathies from perineural spread of skin cancer. Taiwan J Ophthalmol 2021;11:86-8.

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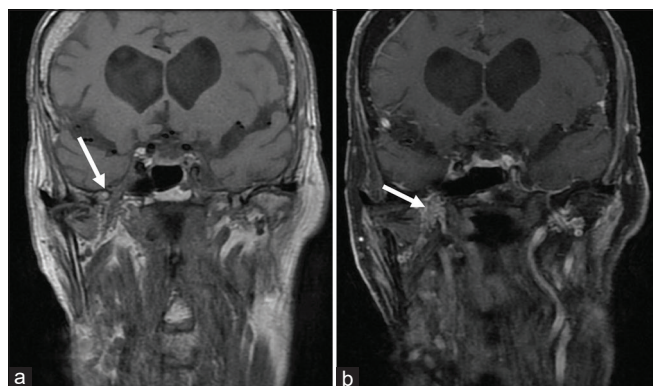
Submission: 10-08-2020  
Accepted: 13-09-2020  
Published: 19-11-2020

Subsequent examinations over 24 months showed further involvement, including left CN VII dysfunction, right CN V1–V3 decreased sensation, right CN VI deficit, and bilateral CN III deficits. This was followed by generalized swallowing and speech difficulty as well as weakness and cachexia. Subsequent high-quality MRI brain and orbits during this time again showed no further abnormalities. Full body positron emission tomography scan and three serial lumbar punctures, including cytological studies, were normal. Paraneoplastic antibodies were also negative.

Sixty-three months (5.25 years) after initial onset of CN dysfunction, repeat MRI showed new enhancement along the proximal extracranial extent of the mandibular branch of the right CN V and foramen ovale widening [Figure 1a and b]. Given the patients' poor health, no biopsy was performed and the patient died a year later. Postmortem autopsy showed squamous cell carcinoma within bilateral CNs VI [Figure 2a and b].

## Discussion

Our case has several important features. One is that CN VI was involved at the time of initial presentation to neuro-ophthalmology, and the earliest reviewed MRI from 10 months prior to examination and more than 8 months prior to the patient experiencing diplopia already showed atrophy of the left lateral rectus muscle, indicating denervation atrophy had occurred well before presentation. The involvement of CN VI at initial consultation in and of itself represents advanced disease, as PNS is thought to originate from retrograde spread along superficial nerve roots of CN V and VII,<sup>[2]</sup> not the deeper ocular motor CNs. Hence, PNS typically presents initially with facial paresthesia or dysesthesias or partial facial palsy before other CN manifestations, as in this case.

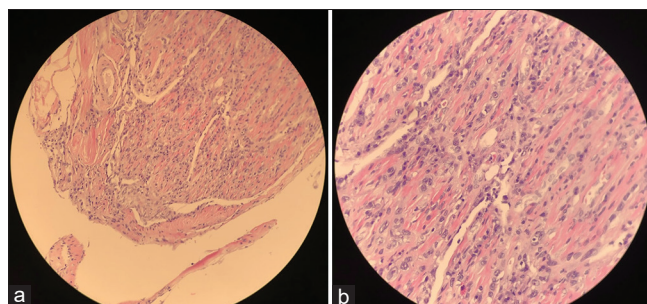


**Figure 1:** (a) Coronal T1 magnetic resonance imaging precontrast shows enlargement of the right foramen ovale (b) Coronal T1 magnetic resonance imaging postcontrast shows mandibular branch of the right choroidal neovascularization enlargement and enhancement

Perhaps the most important aspect of our case is that although index of suspicion was high for PNS, dedicated neuroimaging remained negative for 63 months, which represents a substantially longer time course than the majority of other reported times to diagnosis. In the largest published case series of PNS, a median time to diagnosis of 6 months was reported in a cohort of 120 patients.<sup>[3]</sup> This number may be skewed to a shorter time frame because the study was performed at a tertiary referral center in Australia (which has the highest prevalence of skin cancer and therefore PNS from skin cancer), and because of this high prevalence, new imaging modalities have been adopted to target the radiographic diagnosis of PNS in Australia.<sup>[4]</sup>

In traditional MRI brain and orbital imaging, some of the first identifiable changes are seen on axial and coronal T1 images evaluating the juxta foraminal fat pads in the skull base, as was the case in our patient. Later changes include gross CN enlargement or enhancement seen on postcontrast images.<sup>[5]</sup> Earlier radiographic detection is reported with dedicated “magnetic resonance (MR) neurography,” a high-resolution MRI protocol ideally performed on a 3T magnet. Critical sequences include fat suppressed gadolinium pictures comprised of 2D T1 sequences and 3D isotropic T1 sequences with reformatting, which help best demonstrate asymmetrical nerve enhancement.<sup>[4]</sup> In a study of 3T MR neurography in PNS cases, the modality was found to have a 95% sensitivity and an 84% specificity for detecting PNS in the head and neck.<sup>[6]</sup> While MR neurography promises high sensitivity and specificity, the preferred 3T magnet, detailed protocoling, and specialized reading capability precludes it from being widely available at this time.

In light of these shortcomings of imaging diagnosis, CN biopsies of branches of CN V or VII are often proposed. In our review, the majority of reported biopsies have accompanied known radiographic changes of the infraorbital or supraorbital CN V.<sup>[7–10]</sup> There have been no dedicated reports on the diagnostic sensitivity of CN biopsies in the absence of imaging changes.<sup>[11]</sup> However,



**Figure 2:** (a) Cranial nerve VI (H and E, ×100) sections demonstrate infiltration of the peripheral nerve tissue by dysplastic cells (b) Cranial nerve VI (H and E, ×400) Cells demonstrate abundant cytoplasm, large, and pleomorphic nuclei. Immunohistochemistry was positive for CK5 and p63, strongly suggesting squamous cell carcinoma

a series of four cases of PNS described one patient with a high suspicion of PNS and V1 paresthesias with negative MRI findings, who underwent a supraorbital nerve biopsy that confirmed PNS from squamous cell carcinoma.<sup>[12]</sup> In this case, the onset of symptoms to time of diagnosis was only 10 months.

Despite recent advances in neuroimaging and advocating for earlier CN biopsies, there are clinical reasons that further contribute to the delay in diagnosis of PNS. Often in clinical practice, cranial neuropathies are simply observed as part of their management because of a presumed benign pathophysiology. Such is the case with most CN VII palsies designated as Bell's palsy with negative neuroimaging, or with CN V paresthesias or dyesthesias, often initially mislabeled as essential trigeminal neuralgia. Even with ocular motor CN dysfunction, such as a CN VI palsy, many patients have their findings attributed to ischemic microvascular pathology before further investigations are pursued. In addition, patients often may not remember minor dermatologic procedures or may not volunteer them as relevant medical history. Furthermore, in as many as, 20% of patients with PNS, there is no identifiable primary tumor or history of one.<sup>[3]</sup>

Given the myriad reasons for delay in diagnosis and the high morbidity of PNS, the clinician should have a high index of suspicion for PNS in elderly individuals with multiple cranial neuropathies regardless of history of skin cancer. As awareness of PNS grows, we hope diagnostic tools such enhanced neuroimaging or earlier nerve biopsies are adopted to decrease the interval time to diagnosis and promote earlier treatment for these patients.

### Ethical Consideration

The patient had passed away, so there was no consent form obtained from the patient. No family member was contacted because the patient is not pictured and all provided information is completely de-identified. The IRB at Emory University waives review for case reports with de-identified information. So, IRB was not necessary to be obtained.

### Financial support and sponsorship

VB and NJN have received research support from NIH/NEI core grant P30-EY006360 (Department of Ophthalmology) and from NIH/PHS (UL1-RR025008).

### Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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