PHOTO ESSAY

Diagnostic Challenge: Sequential Unilateral Cranial Neuropathies Due to Perineural Spread of Carcinoma

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ABSTRACT

An 86-year old man developed sequential dysfunction of trigeminal (V1), facial, abducens, trigeminal (v2), oculomotor, and hypoglossal cranial nerves on the right over 20 months. Magnetic resonance imaging (MRI) showed a lesion in the right cavernous sinus. Although there was clinical suspicion that this was related to perineural spread of an extracranial tumour, a primary lesion was not discovered. Stereotactic biopsies of the intracranial lesion were non-diagnostic, and the patient succumbed to his tumour following a period of rapid growth. Postmortem examination showed the intracranial lesion to be a carcinoma with squamous features. This case highlights the challenges of diagnosis of intracranial perineural spread and the potential for transformation from indolent to aggressive tumour behaviour.

ARTICLE HISTORY

Received 21 February 2017
Revised 7 March 2017
Accepted 7 March 2017

KEYWORDS

Carcinoma; cranial neuropathies; perineural spread

Case

An 86-year-old man with a non-magnetic resonance imaging (MRI)-conditional pacemaker, on warfarin, developed right forehead pain. Non-contrast head computed tomography (CT) and temporal artery biopsy were unrevealing. Six months later, he complained of right forehead fullness. Ear, nose, and throat (ENT) evaluation diagnosed right seventh nerve paresis. Contrast-enhanced CT brain was unremarkable. Oral steroids and valacyclovir did not improve symptoms. Four months later (10 months after initial symptoms), he developed horizontal diplopia and was referred for neuro-ophthalmic evaluation.

Examination was remarkable for decreased right forehead sensation, right eye abduction deficit, and right frontalis more than lower facial weakness (Figure 1). There were cutaneous lesions on the right lower cheek and jawline. These were removed using Mohs technique. Pathology showed basal cell carcinomas, nodular type with clean margins, and no neural invasion. The histopathology slides were reviewed by a tertiary care dermatopathologist who agreed with the description.

Contrast-enhanced maxillofacial CT, brain CT, and chest/abdomen/pelvis CT were unrevealing. The latter were performed to identify possible source of metastases causing cranial nerve dysfunction. MRI of the brain, done 13 months after initial symptoms, at a centre that could accommodate his pacemaker, demonstrated an enhancing soft tissue mass in the right cavernous sinus, enhancement of the distal cisternal right trigeminal nerve, and thickening of the right V2 branch at the foramen rotundum (Figure 2A–C). Serum immunoglobulin G4 (IgG4) was normal. Lumbar puncture showed 48 mg/dL protein (upper limit normal: 45 mg/dL) and neither leukocytosis nor atypical cells. A course of steroids subjectively improved discomfort but did not lead to objective improvement. Biopsy was felt to be high risk.

Five months after the first MRI (18 months after symptom onset), symptoms and examination were unchanged. MRI showed stable cavernous sinus appearance of the lesion with progressive enhancement of the cisternal right trigeminal nerve and new enhancement of the right trochlear nerve (Figure 2D–E).

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Figure 1. Facial muscle function and esotropia at time of neuro-ophthalmic evaluation (10 months after initial symptoms). At rest (left), there is decreased right frontalis activation and flattening of the right nasolabial fold. With activation (right), there is no frontalis activation and moderate activation of orbicularis oris.

Figure 2. Coronal T1 precontrast (A), coronal T1 postcontrast (B), and axial T1 postcontrast (C) images, obtained 13 months after symptom onset, demonstrate infiltration of the right cavernous sinus by enhancing soft tissue (solid arrows). Note involvement of the V2 segment of the trigeminal nerve (dashed arrow). Coronal T1 postcontrast images (D, E), obtained 18 months after symptom onset showing new enhancement of the cisternal right trigeminal nerve (D, solid arrow) and new trochlear nerve enhancement (E, dashed arrow). Involvement of the cavernous sinus was otherwise stable during this period.

Twenty months after symptom onset, he developed right ptosis, altered sensation in the right mouth, and dysarthria. Examination showed new

right eye supraduction, infraduction, and adduction deficits, right ptosis with impaired levator function, and right tongue deviation. MRI showed

progression of right trigeminal nerve enhancement but was otherwise unchanged. CT-guided fine-needle aspiration through the foramen ovale was non-diagnostic. Biopsy was again discussed, but it was still felt to be high risk.

Twenty-seven months after symptom onset, he developed trouble chewing on the right and gait disturbance. MRI showed progression of the lesion, with extension into the sphenoid sinus, orbital apex, and pons, with T2 hyperintensity in midbrain, pons, and medulla (Figure 3). A stereotactic biopsy at the foramen ovale showed meningotheelial proliferation. Palliative radiation therapy was planned. Although this was being arranged, he developed increased lethargy and paraparesis and became minimally verbal. He was admitted to

hospice and passed away less than 3 weeks after the biopsy.

A limited autopsy of the brain was performed. Removal of the brain required transection of a mass in the posterior fossa that involved the sella turcica, was adherent to the skull base, and infiltrated the pons (Figure 4A–D). Microscopic examination of the lesion showed moderate to poorly differentiated carcinoma with squamous features including keratinisation (Figure 4E–H). Histopathologically, this could be consistent with cutaneous, mucosal, or salivary gland origin squamous cell carcinoma or salivary gland mucoepidermoid carcinoma. Careful review of pre-morbid imaging did not identify a primary lesion.

Figure 3. Follow-up examination at 27 months. Coronal T1 postcontrast image (A) showing marked progressive disease with further expansion of the right cavernous sinus as well as invasion of the sella (solid arrow) and sphenoid sinus (dashed arrow). Also note the enhancement of the muscles of mastication on the right (white and black stars), which may represent a V3 denervation effect. Sagittal (B) and axial (C) T1 postcontrast images showing new lesion growth across the cisternal right trigeminal nerve with invasion of the brainstem. Note the associated dural enhancement with extension into the right internal auditory canal (dashed arrow), as well as enhancement of the right greater superficial petrosal nerve and geniculate ganglion (white stars). Axial T2 image (D) showing marked oedema in the pons and right middle cerebellar peduncle.

Figure 4. Postmortem findings. Gross views of the skull base (A, B), demonstrating tumour adherent to the right pons, bridging to bone (A) and invading bone (B). Gross cross-sections of the pons (C) demonstrating tumour invasion. Microscopic sections, haematoxylin and eosin (H&E) stain (D–H), demonstrating carcinoma invading sphenoid bone (D); neurohypophysis (*) and adenohypophysis (**) with surrounding desmoplastic response and tumour cells (E); tumour cells infiltrating tracts in ventral right pons with partial destruction/necrosis/tumour infiltration of the right pontocerebellar fibers, middle cerebellar peduncle, corticospinal, corticobulbar, and corticopontine fibers (F); and tumour with desmoplasia (G) and keratin production (H).

Discussion

The clinical course began with initial symptoms localising to the first branch of the trigeminal nerve, followed by upper more than lower division facial nerve dysfunction localising to a peripheral origin with perineural spread. Subsequent involvement of the second branch of the trigeminal nerve, abducens nerve, and oculomotor nerve likely occurred following retrograde spread of tumour along V1 to the cavernous sinus. The origin of the tumour remains unknown despite dermatological and ENT examinations and extracranial MR imaging. This is consistent with literature suggesting that over 35% of perineural spread tumours lack a known primary lesion.¹ Theories for this phenomenon include immune or trauma-mediated regression of the primary tumour.^{2,3} The acceleration of tumour growth likely reflects transformation from a low-grade to a high-grade lesion.

MRI is the diagnostic imaging modality of choice to confirm presence and extent of

perineural spread,⁴ and in this case MRI was critical to understanding the case. There are safety concerns regarding obtaining MRI scans in patients with implantable cardiac devices pertaining both to magnetic field-induced dysfunction of the device and magnetic field-induced heating of the device and leads. These concerns, combined with widespread desire for MRI in patients with pacemakers, prompted development of MRI-conditional devices, which design features intended to make implantable devices that maximise safety in the MR scanner environment.⁵ At the time of this patient's presentation, only one such device was approved in the United States by the Federal Drug Administration and this patient did not have this device implanted. However, there is growing experience safely obtaining MRI scans in patients with non-MRI-conditional implantable cardiac devices, and this patient was able to obtain scans at a centre with appropriate cardiac electrophysiology and neuroradiology expertise, support, and staffing

to facilitate a safe study.⁶ This required extensive coordination and travel for the patient in this case given limited options for facilities that could accommodate his pacemaker. This case highlights that, through collaboration with cardiology and radiology specialists, appropriate imaging was safely obtained in a patient with an implantable electronic cardiac device.

Selection of invasive diagnostic tests for tissue diagnosis requires careful consideration of procedural risks and potential risks and benefits of resulting treatment.⁷ Risk-benefit analysis regarding invasive diagnostic procedures was challenging in this elderly patient with multiple comorbidities, including medication with warfarin. The initially slow clinical course heightened the risk-benefit ratio owing to limited perceived benefit of invasive diagnostic procedures in the setting of well-defined risks. This case highlights the challenges of diagnosis of intracranial perineural spread and the potential for tumour transformation from indolent to aggressive behaviour.

Acknowledgements

The authors thank William Porter, MD, for his assistance preparing the pathology images.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

Funding

This study was supported by grant K23 EY-024345 (to H.M.), an unrestricted grant from Research to Prevent Blindness to the University of Illinois at Chicago Department of Ophthalmology and Visual Sciences, and an unrestricted grant from Research to Prevent Blindness to the Stanford University Department of Ophthalmology.

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