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Teaching Case

Malignant Mimics of Trigeminal Schwannoma

Musthafa Raswoli, MBBS,[a] Derek S. Tsang, MD, MSc,[a] Gelareh Zadeh, MD, PhD,[b] Andrew F. Gao, MD, MSc,[c] and David B. Shultz, MD, PhD[a,*]

[a]Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada; [b]Division of Neurosurgery, Toronto Western Hospital, University Health Network, Toronto, Canada; [c]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada

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Clinical Presentations

Case 1

A 67-year-old woman presented in April 2020 with a 1-month history of right facial numbness and a 1-week history of double vision. Examination revealed right-sided cranial erve (CN) IV and V palsies, and magnetic resonance imaging (MRI) showed a right cerebellopontine angle tumor involving Meckel cave (Fig. 1A). The lesion encompassed the right fifth cranial nerve with indentation of the pons and fluid-attenuated inversion recovery (FLAIR) hyperintensity changes limited to the right middle cerebellar peduncle. The mass contacted the right temporal lobe and the superior border of the right carotid artery, but there were no signs of invasion into these structures. The pituitary gland and sella were not directly involved. The tumor measured 34 mm in greatest dimension. Differential diagnoses included schwannoma or meningioma, favoring the former. She was referred to a neurosurgeon who recommended definitive radiation therapy. She was treated for presumed trigeminal (CNV) schwannoma with a single fraction of 12 Gy using Gamma Knife radiosurgery in April 2020.

In August 2020, during her first routine follow-up visit, the patient reported stable symptoms and MRI revealed a stable appearing tumor with a 2-mm reduction in the transverse diameter of the cisternal component. There were new FLAIR signal changes within the adjacent brain stem, still primarily located in the middle cerebellar peduncle adjacent to the tumor, thought to represent radiation therapy–related edema. In November 2020, the patient reported intermittent headaches and new right-sided trigeminal pain. She was prescribed a 5-day trial of dexamethasone with symptomatic improvement. However, in December 2020 she presented with recurrent headaches and ataxia. MRI demonstrated increases in both tumor size and the extent of FLAIR hyper-intensity changes within the adjacent midbrain and brain stem (Fig. 1). Her case was discussed at our multidisciplinary neuro-oncology conference, where it was concluded that her symptoms and clinical and radiographic signs were consistent with pseudoprogression.[1] Short-term follow-up with an MRI was recommended and she was prescribed a prolonged dexamethasone taper.

In January 2021, the patient presented with acute behavioral changes and steroid-induced psychosis was diagnosed. MRI revealed a stable tumor with decreased FLAIR hyperintensity changes and reduced mass effect on the surrounding midbrain and brain stem. Her dexamethasone dose was reduced, and she was prescribed risperidone. In February 2021, she reported new left-sided weakness and required a walker. By March 2021, she was restricted to a wheelchair. On examination, she had significant peripheral edema and generalized muscle wasting thought to represent the sequelae of long-term steroids. MRI of the brain showed increased FLAIR hyper-intensity changes in the brain stem, right thalamus, and internal

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*Corresponding author: David B. Shultz, MD, PhD; E-mail: david.shultz@rmp.uhn.ca

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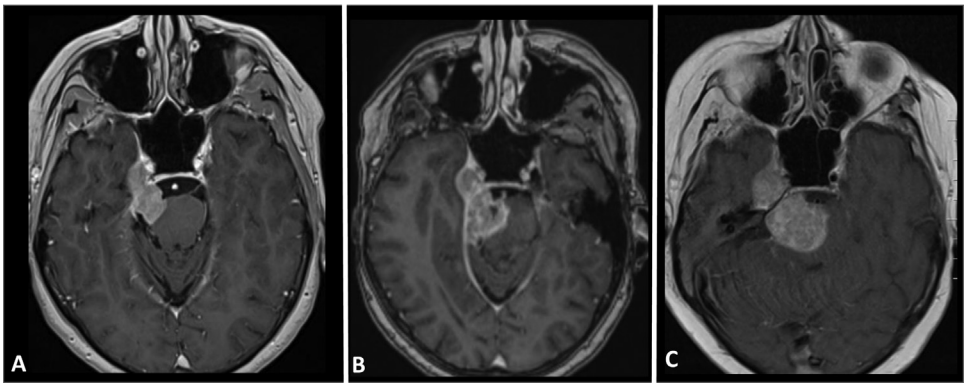

Fig. 1 T1-weighted gadolinium contrasted magnetic resonance imaging axial plan images from case 1 before (A) and 8 (B) and (C) 12 months after stereotactic radiation therapy.

capsule. These changes were thought to represent severe pseudoprogression, for which continued judicious dexamethasone therapy and watchful waiting were advised. Unfortunately, she continued to decline and in May 2021 an MRI revealed further increase in tumor size (Fig. 1C). Finally, in June she experienced acute severe neurologic deterioration. Urgent head computed tomography showed a mild intratumoral bleed. Physical examination showed brief opening of the left eye only to voice. MRI revealed obstructive hydrocephalus. A neurosurgical consult was made and an external ventricular drain was placed. A debulking procedure to relieve intracranial pressure and to confirm tumor histology was considered at that time, but she was determined to be a poor surgical candidate. She was discharged to hospice care and died shortly thereafter, 15 months after her radiation therapy. Autopsy revealed a friable tan-brown mass on the right side of the brain stem in the region of CN V, with extension into Meckel cave (Fig. 2). CN III also appeared expanded and CN IV could not be identified. Axial sections of the midbrain and rostral pons revealed an intra-axial exophytic right-sided mass measuring 3.5 cm that obliterated CN V. CN III was expanded and CN IV was not readily identifiable. Microscopic analysis confirmed a World Health Organization grade IV glioblastoma centered in the midbrain and pons. The tumor was negative for IDH1 R132H, H3 K27M, and BRAF V600E. The tumor crossed the leptomeningeal space where it had apparently obliterated the Vth CN and extended into Meckel cave, infiltrating the trigeminal ganglion. CN III was also infiltrated. The mass and the surrounding brain parenchyma did not show any signs of treatment effect.

Case 2

An 80-year-old woman presented to an emergency room in April 2020 with a 1-day history of diplopia. She described a 3-year history of progressive left trigeminal neuralgia that had been previously evaluated with MRI,

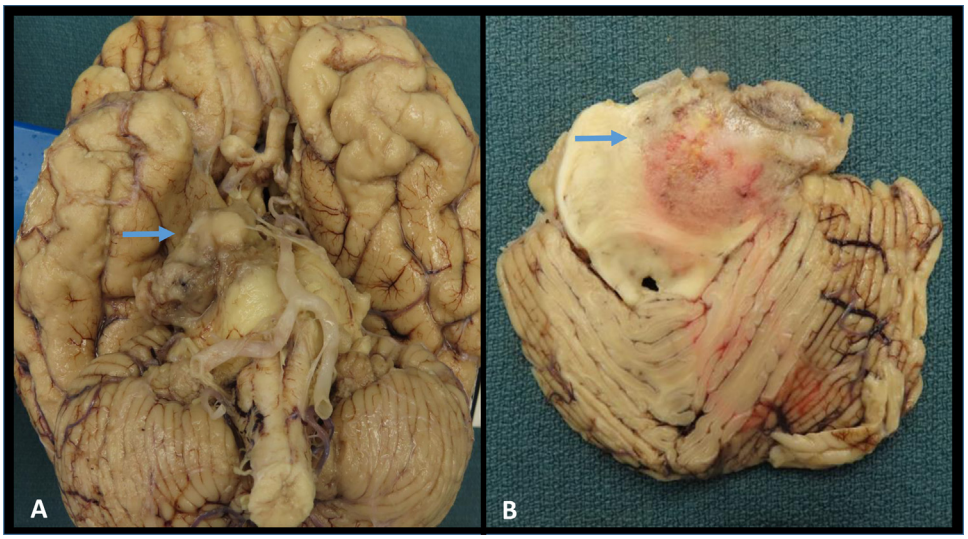

Fig. 2 Autopsy images from case 1. A, Posterior view of brain with arrow pointing to mass. B, Axial slice through pons showing right-sided infiltrating mass (glioblastoma).

showing no clear cause for her pain. She had also had a cutaneous squamous cell carcinoma (SCC), grading and perineural invasion not described, resected from her nose in 2016. Her examination revealed left-sided facial numbness and left ophthalmoplegia. MRI demonstrated an enhancing mass centered in left Meckel cave that was new in comparison to a scan from 2 years prior (Fig. 3A). The lesion extended through foramina rotundum and ovale with extension into the pterygopalatine fossa. There were FLAIR signal intensity changes in the left pterygoid muscles suggesting denervation. The cisternal component of the left trigeminal nerve was mildly atrophic. Her case was reviewed at our multidisciplinary neuro-oncology tumor board and a presumed trigeminal schwannoma was diagnosed. She was referred to radiation oncology and treated with conventionally fractionated radiation, 54 Gy in 30 fractions.

In early December 2020, 8 months after her treatment, the patient described reduction in her trigeminal neuralgia and stable diplopia. MRI showed a marked interval increase in size of her left-sided tumor with further extension into the left cavernous sinus, foramina ovale and rotundum, pterygopalatine fossa, and petrous apex (Fig. 3B). There was extension into the adjacent sphenoid sinus and increased abnormal T2 signal in the pterygoid muscles. The patient's case was discussed at our multidisciplinary tumor board where the consensus was that these MRI changes most likely represented pseudo- rather than tumor progression. Surveillance was recommended. In March 2021, she was seen in virtual follow-up where she reported worsening of her left trigeminal neuralgia, including an atypical aching component that radiated down her left jaw. However, an MRI at that time revealed no appreciable change to her tumor in comparison to the December 2020 scan.

The patient presented again in July 2021 with confusion, amnesia, fatigue, and weight loss. An MRI revealed further increase in the size of her left-sided lesion that now compressed the left temporal pole. It now had thick peripheral rim enhancement and central necrosis (Fig. 3C). There was adjacent dural enhancement edema in the frontal and temporal lobes. Taken together, these findings were favored to represent severe radiation necrosis. Urgent dexamethasone and neurosurgical consultation were requested. She underwent a left-sided craniotomy to relieve mass effect and secure a diagnosis; intraoperative pathology was consistent with a high-grade neoplasm. Postoperatively, the patient declined precipitously with delirium and died shortly after transfer to hospice care. Final pathology results revealed that her tumor's histomorphology and immunophenotype were compatible with a poorly differentiated SCC due to perineural spread.

Discussion

In contrast to other sites, intracranial tumors, especially suspected schwannomas or meningiomas of the base of skull, are often treated with radiation therapy without histologic confirmation. Herein, we report 2 cases where malignant neoplasms mimicked trigeminal schwannoma clinically and radiologically. One was a glioblastoma that originated in the pons or midbrain and invaded the Vth CN.[2] Upon autopsy, there was no evidence of schwannoma, suggesting an exophytic glioblastoma present before radiation.[3] In fact, FLAIR signal adjacent to the enhancing mass at presentation, which had been assumed to represent mass effect, likely signified parenchymal tumor. The other case was an SCC with perineural spread from a cutaneous facial lesion resected 3 years previously. In both cases, radiology posttreatment was consistent with similar to previous cases our group has seen of psuedoprogression.[4] For example, Fig. 4 shows a presumed trigeminal schwannoma treated by our group with conventional radiation therapy that expanded then eventually regressed 2 years after treatment. These cases

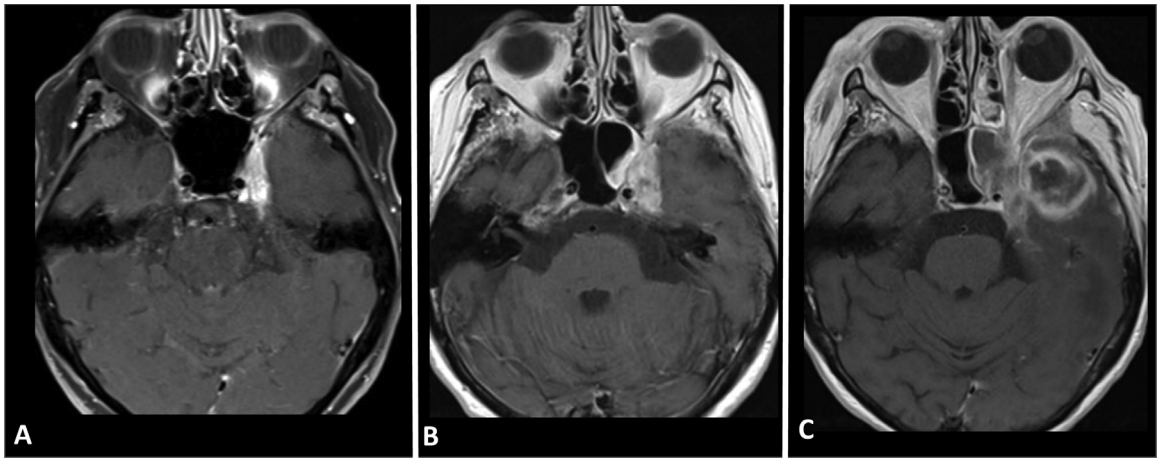

Fig. 3 T1-weighted gadolinium contrasted magnetic resonance imaging axial plan images from case 2 before (A) and 8 (B) and (C) 15 months after conventionally fractionated radiation therapy.

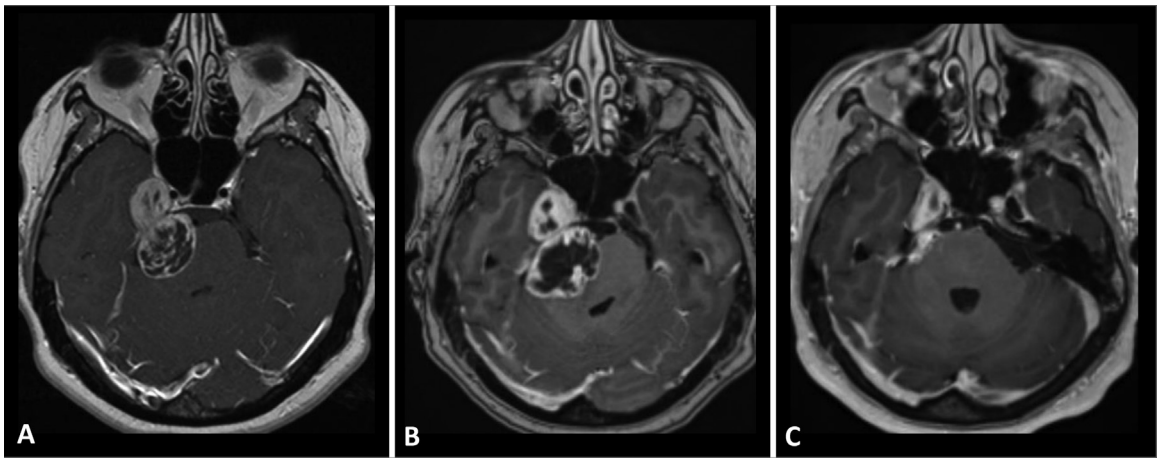

Fig. 4 T1-weighted gadolinium contrasted magnetic resonance imaging axial plan images of a presumed trigeminal schwannoma before (A) and 12 (B) and (C) 24 months after conventionally fractionated radiation therapy.

showcase a diverse set of lesions that can appear radiologically similar before and after treatment.

Advanced imaging modalities may be useful for distinguishing between tumor progression and pseudoprogression,[5] including perfusion MRI and magnetic resonance spectroscopic imaging.[6] Nuclear imaging such as [^{18}F]fluorothymidine positron emission tomography may also have a role in differentiating active tumor from radionecrosis.[7] Finally, traditional MRI sequences may be insufficient to distinguish between common and uncommon entities arising from cranial nerves. For example, a combination of features from diffusion-weighted imaging, diffusion tensor imaging, susceptibility-weighted imaging, perfusion MRI and magnetic resonance spectroscopic imaging, perfusion MRI, and diffusion tension imaging has been proposed to be uniquely associated with ganglioneuromas.[8]

Although it is not conceivable to perform a biopsy on every patient with suspected trigeminal schwannoma, neurosurgical consultation and advanced imaging techniques should be considered early in cases of suspected pseudoprogression. A careful history and physical examination are also essential, with particular emphasis of prior history of head and neck neoplasms, for cases of suspected benign intracranial tumors that have not undergone biopsy. There have been several prior reports of malignant and nonmalignant tumors misdiagnosed for vestibular schwannoma, including hemangioblastoma,[9] lipoma, epidermoid tumor,[10] glioblastoma,[11] leptomeningeal carcinomatosis,[12] and primary central nervous system melanoma.[13] There is also a reported case of solitary fibrous tumor misdiagnosed as a trigeminal schwannoma.[14] Common themes among these reports include rapid growth before surgery, discordant symptoms, and incomplete pretreatment imaging (eg, both fat-suppressed and nonsuppressed imaging noncontrasted T1-weighted MRI). The prior report of glioblastoma mimicking vestibular schwannoma shared a critical feature with our first case: multiple CN deficits appearing in a relatively short duration. The authors of that paper suggest that gliomas be considered in the differential diagnosis of cerebellar pontine angle lesions when they have imaging features that include "heterogeneous signal intensity and ringlike enhancement with poorly defined margins."[11] Ultimately, although both cases presented in our report were likely incurable at the outset, more histologically directed therapy may have led to extended survival and improved quality of-life after treatment.

We also believe that an appreciation for cognitive biases is important for avoiding misdiagnosis as described here.[15] A particularly severe case of pseudoprogression after radiation for trigeminal schwannoma that occurred immediately before these events likely affected our decision making, causing us to misidentify unexpected postradiation changes for severe pseudoprogression, instead of the alternate and serious possibility of misdiagnosis of the tumor before treatment. Of note, our department was recently referred a 60-year-old man with a history of trigeminal paresthesia and a suspected trigeminal schwannoma based on MRI (Fig. 5A). Upon further history, the patient was noted to have had a well-differentiated superficially invasive SCC resected from his forehead 3 years prior. An updated MRI was ordered protocoled for head and neck as opposed to brain sequences that revealed progression of the mass as well as enhancement of V1 within the orbit tracking back to the orbital apex (Fig. 5B). In addition to more extensive perineural spread, the tumor extended into the parenchyma of the right side of the pons and mid- brain. There was also leptomeningeal enhancement over the surface right side of the pons and the right mid-brain and along the floor of the right IAC. Finally, there was perineural tracking along the right greater superficial petrosal nerve to the right facial nerve (Fig. 5C). A neurosurgical consult was requested, upon which endoscopic biopsy of the pterygopalatine fossa revealed SCC with perineural invasion.

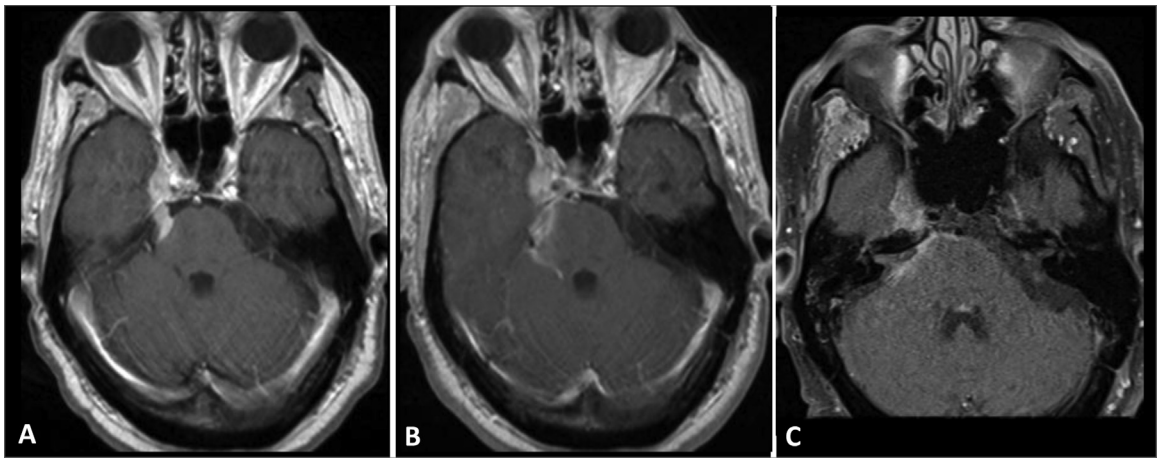

Fig. 5 T1-weighted gadolinium contrasted magnetic resonance imaging axial plan images of cutaneous squamous cell carcinoma with perineural invasion at initial presentation (A) and 5 months later (B, C). Panel (C) shows fat suppression and demonstrates perineural invasion within the internal auditory canal.

To decrease the likelihood of misdiagnosis of malignant tumors for schwannomas and treatment with radiation therapy, we suggest that all cases with atypical symptoms, which may include multiple cranial nerve involvement, a rapidly progressive clinical course, or atypical radiologic features, be carefully reviewed. In those cases, neurosurgical intervention should be strongly considered to obtain a lesional biopsy. A full medical history should always be undertaken and all patients with a history of head and neck skin cancers, even remote, should undergo an MRI protocoled for head and neck (as opposed to brain) cancers. After radiation, lesions that change atypically should be considered as potentially misdiagnosed and followed closely (at least every 3 months) with appropriate imaging and referral to a neurosurgeon.

Conclusion

These cases highlight the risks of treating without a biopsy and the need to consider alternative diagnoses at all phases of care, including when a patient develops unexpected treatment sequelae. They also highlight the importance of a multidisciplinary approach to the treatment of presumed schwannomas and other benign tumors.

Acknowledgments

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