Malignant Mimics of Trigeminal Schwannoma

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Abstract
Background: Trigeminal schwannomas are benign tumors arising from the Vth cranial nerve that can be definitively treated with surgery, conventional radiation, or radiosurgery. Suspected schwannomas and other benign tumors of the base of skull are usually diagnosed without histologic confirmation prior to treatment with radiotherapy. Here we report 2 cases of malignant tumors with trigeminal nerve invasion that were misdiagnosed and treated as schwannomas.

Clinical Presentations:

Case #1: A 67-year-old woman presented with new right facial numbness and double vision. MRI showed an enhancing lesion centered in Meckel’s cave and she was treated with radiosurgery for a suspected trigeminal schwannoma. Subsequent MRI scans showed lesion growth; this was presumed to be pseudoprogression. She died 15 months later after a prolonged clinical deterioration. Her autopsy revealed a glioblastoma of the mid-brain and pons with CN V invasion.

Case #2: An 80-year-old woman presented with acute diplopia in the background of trigeminal neuralgia. MRI revealed a suspected trigeminal schwannoma that extended through foramina rotundum and ovale and into the cavernous sinus. She was treated with 54 Gy in 30 fractions followed by suspected pseudoprogression characterized by interval tumor expansion and clinical deterioration; 15 months after radiation she underwent surgery followed shortly thereafter by her death. Pathology confirmed perineural invasion from poorly-differentiated squamous cell carcinoma.

Conclusion: High grade malignancies with CN invasion can mimic schwannomas. In addition to a careful history and physical exam, advanced imaging modalities and timely neurosurgical
intervention should be considered when there is diagnostic uncertainty about suspected CN schwannomas before or following radiotherapy.

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 CN IV and V palsies and MRI showed a right cerebellopontine angle (CPA) tumour involving Meckel’s 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 radiotherapy. 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 2mm reduction in the transverse diameter of the cisternal component. There were new FLAIR signal changes within the adjacent brainstem, still primarily located in the middle cerebellar peduncle adjacent to the tumour, thought to represent radiotherapy-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 brainstem (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 was diagnosed with steroid-induced psychosis. MRI revealed a stable tumor with decreased FLAIR hyperintensity changes and reduced mass effect on the surrounding midbrain and brainstem. 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 exam she had significant peripheral edema and generalized muscle wasting thought to represent the sequelae of long-term steroids. MRI brain showed increased FLAIR hyper-intensity changes in the brainstem, right thalamus, and internal capsule. These changes were thought to represent severe pseudoproggression 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 CT head 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 following her radiotherapy. Autopsy revealed a friable tan-brown mass on the right side of the brainstem in the region of CN V, with extension into Meckel’s 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 WHO grade IV glioblastoma centred 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’s 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 one-day history of diplopia. She described a 3-year history of progressive left trigeminal neuralgia that had been previously evaluated with MRI 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 exam revealed left sided facial numbness and left ophthalmoplegia. MRI demonstrated an enhancing mass centered in left Meckel’s 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 in the left pterygoid muscles suggesting denervation. The cisternal component of the left trigeminal nerve was mildly atrophic. Her case was reviewed at our multi-disciplinary neuro-oncology tumor board and the patient was diagnosed with a presumed
trigeminal schwannoma. She was referred to radiation oncology and treated with conventionally fractionated radiation, 54 Gy in 30 fractions.

In early December 2020, 8 months following her treatment, the patient described reduction in her trigeminal neuralgия 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 multi-disciplinary 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 consistent with a high-grade neoplasm. Post-operatively, the patient declined precipitously with delirium and died shortly after transfer to hospice care. Final pathology results revealed that her tumor’s histomorphology
and immunephenotype were compatible with a poorly differentiated squamous cell carcinoma 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 radiotherapy 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 prior to radiation[3]. In fact, FLAIR signal adjacent to the enhancing mass at presentation, which had ben assumed to represent mass effect, likely signified parenchymal tumor. The other case was a SCC with perineural spread from a cutaneous facial lesion resected 3 years previously. In both cases, radiology post-treatment 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 radiotherapy that expanded then eventually regressed 2 years after treatment. These cases showcase a diverse set of lesions that can appear radiologically similar before and after treatment.

Advanced imaging modalities may be useful for distinguishing between tumour progression and pseudoprogression [5], including perfusion MRI, andmagnetic resonance spectroscopic imaging (PMRSI) [6]. Nuclear imaging such as FLT PET 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, PMRSI, perfusion MRI, and diffusion tension imaging has been proposed to be uniquely associated with ganglioneuromas [8].

While 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 exam 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 non-malignant tumors misdiagnosed for vestibular schwannoma, including hemangioblastoma [9], lipoma, epidermoid tumor [10], glioblastoma [11], leptomeningeal carcinomatosis [12], and primary CNS melanoma [13]. There is also a reported case of solitary fibrous tumour misdiagnosed as a trigeminal schwannoma [14]. Common themes among these reports include rapid growth prior to surgery, discordant symptomatology, and incomplete pre-treatment imaging (e.g. both fat-suppressed and non-suppressed imaging non-contrasted T1-weighted MRI). The prior report of glioblastoma mimicking vestibular shared a critical feature with our case 1: multiple CN deficits appearing in a relatively short duration. They 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 following treatment.

We also believe that an appreciation for cognitive biases is important for avoiding misdiagnosis as described here [15]. A particularly severe case of pseudo-progression following
radiation for trigeminal schwannoma that occurred immediately prior to these events likely affected our decision making, causing us to misidentify unexpected post-radiation changes for severe pseudo-progression, instead of the alternate and serious possibility of misdiagnosis of the tumor prior to 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 protocoded 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 pterygopalantine fossa revealed SCC with perineural invasion.

In order to decrease the likelihood of misdiagnosis and treatment with radiotherapy of malignant tumors for schwannomas, we suggest that all cases with atypical symptomatology, which may include multiple cranial nerve involvement or a rapidly progressive clinical course, or atypical radiologic features, be carefully reviewed. In those cases neurosurgical intervention should be strongly considered in order 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 protocoded for head and neck (as opposed to brain) cancers. Following 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.

**Figures**

1. T1-weighted gadolinium contrasted MRI axial plans images from Case #1 prior to (A) and 8 (B) and (C) 12 months following stereotactic radiotherapy.

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).

3. T1-weighted gadolinium contrasted MRI axial plans images from Case #2 prior to (A) and 8 (B) and (C) 15 months following conventionally fractionated radiotherapy.

4. T1-weighted gadolinium contrasted MRI axial plans images of a presumed trigeminal schwannoma prior to (A) and 12 (B), and (C) 24 months following conventionally fractionated radiotherapy.

5. T1-weighted gadolinium contrasted MRI axial plans images of cutaneous squamous cell carcinoma with perineural invasion at initial presentation (A) 5 months later (B and C). Panel C
is performed with fat suppression and demonstrates perineural invasion within the internal auditory canal.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.


Figure 1

![Figure 1](image1)

Figure 2

![Figure 2](image2)
Figure 3

Fig 3
Figure 4

Figure 5