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Case Report
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Painful Trigeminal Neuropathy as a Rare but Important Presenting Complication of Metastasis of Head and Neck Cancer: A Case Report and Review

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Abstract

Neoplastic perineural involvement of cranial nerves represents an uncommon but important feature of metastatic involvement of squamous cell carcinoma of the head and neck. Tumor cells invade all nerve compartments, possibly causing ischemia and subsequent degradation of the nerve. Invasion is guided by targeted proliferation in the context of secreted neurotropins and growth factors. Patients often present insidiously with symptoms of isolated cranial neuropathies and atypical facial pain. The most frequently affected nerve is cranial nerve V (CN V), followed by cranial nerve VII (CN VII), due to the widespread anatomic connections between the skin and subcranial structures. The following case reports highlight the different presentations and the associated diagnostic challenges of perineural involvement by squamous cell carcinoma of the head and neck. We will review the proposed biology underlying perineural tumor metastasis, the anatomical basis for cranial nerve involvement, and current treatment options. Prognosis is poor in cases of extensive disease highlighting the importance of early recognition and detection.

Keywords: Cranial nerve; Trigeminal neuralgia; Paresthesia

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Introduction

Painful trigeminal neuropathy arising from dysfunction of CN V is a relatively uncommon but potentially debilitating presentation in the outpatient neurological practice. In the neurology practice, facial pain is typically caused by classic idiopathic trigeminal neuralgia or atypical painful trigeminal neuropathy. Classic trigeminal neuralgia (TN) is characterized by sudden, recurrent, brief stabbing pain, involving the distribution of one or more branches of the trigeminal nerve [1,2]. Patients report a lancinating shock like quality, often provoked by mild stimulus. Classic TN encompasses all cases without an established etiology, including idiopathic and those secondary to vascular compression of CN V; importantly, there is no clinical evidence of neurological deficit. Atypical painful trigeminal neuropathy implicates secondary structural causes, such as demyelinating plaques, trauma, infection, and skull base lesions, affecting the fifth cranial nerve.

Besides space occupying lesions, insidious infiltration of CN V by different disease processes can cause facial pain and dysfunction. Inflammatory diseases, including neurosarcoid and collagen vascular disease, and neoplastic infiltration of cranial nerves can result in pain, sensory and motor dysfunction of CN V [3,4]. Perineural spread of tumor involves extension of the tumor along the nerves and is more difficult to detect due to the lack of an obvious mass lesion. Clearly, this results in a neurological diagnostic challenge with diagnostic delays potentially limiting effective treatment.

We report 2 patients who initially presented with a typical facial pain and CN V dysfunction and then subsequently developed other cranial neuropathies due to perineural metastasis of squamous cell carcinoma of head and neck. Neoplastic involvement of cranial nerves should be an important consideration in presentation of atypical facial pain.

Case Presentation

Case 1

An 83 year old female with a remote history of basal and squamous cell facial cancer presents with a 2 year history of difficulty chewing followed by right upper lip paresthesia, radiating to the cheek and nose with occasional sharp “shock-like” pains from the cheek to lower eye. A few months later, she developed numbness to the roof of the mouth, upper gums and teeth, decreased taste

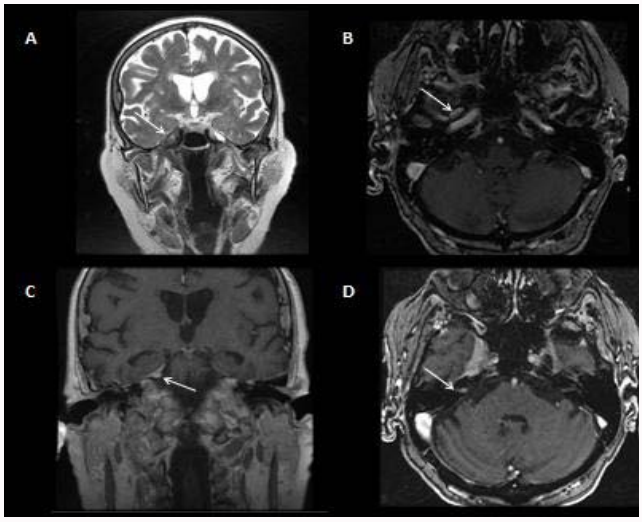

Figure 1: A) MRI coronal T2 sequence showing the obliteration of Meckel's cave (white arrow) by tumor. B) MRI axial T2 sequence highlighting infiltration of foramen rotundum (white arrow) by tumor. C) MRI coronal gadolinium sequence highlight enhancement of CN V (white arrow) as it exits the pons. D) MRI axial gadolinium sequence depicting the small nodular mass (white arrow) arising from CN VII.

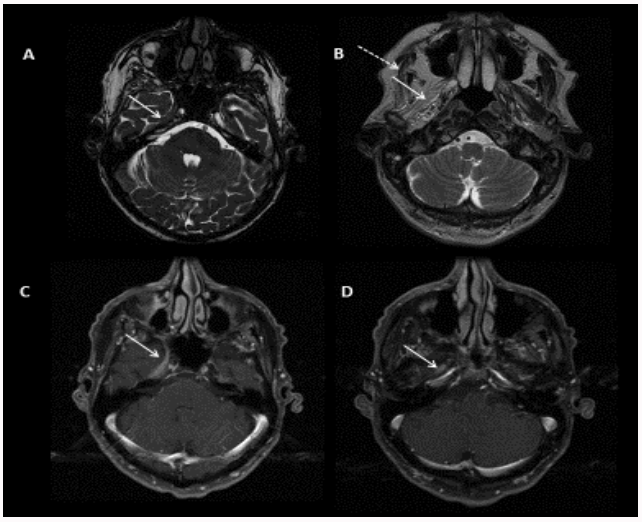

Figure 2: A) MRI axial T2 demonstrates obliteration of Meckel's cave (white arrow) by tumor. B) MRI axial T2 depicts the replacement normal pterygoid muscles by fat (white arrow) secondary to denervation of muscle by perineural involvement of CN V3. There has been atrophy of the masseter muscle (dashed arrow) when compared to the contralateral side. C) MRI axial T2 sequence highlights the infiltration of foramen ovale (white arrow) by perineural involvement of CN V2. D) MRI axial T2 sequence inferior to that shown in C shows the infiltration of foramen rotundum by tumor involvement (white arrow) of CN V3.

in the right tongue, and tearing of the right eye. Exam was notable for decreased sensation to the right V2-3 distributions. Initial non-contrast brain MRI reported nonspecific ischemic T2 changes in the subcortical white matter of the cerebral hemispheres. Labs, including TSH, B12, SPEP and HgA1c, were all normal. Lyme titers were positive, and she was treated with antibiotics.

2.5 months later, her symptoms progressed to constant paresthesia of the entire right face, right facial edema, buccal mucosa burning, and further difficulties with jaw opening. Exam was notable for right facial swelling, enlargement of the palpebral fissure on the right, and numbness in the right face. Repeat brain MRI with contrast revealed an enhancing right intracanicular nodule with enhancement of the preganglionic segments of the facial nerve and geniculate ganglion (Figure 1). There was also a fusiform process within the right cavernous sinus, extending into the foramina rotundum and ovale with involvement of the sphenopalatine foramen and masticator space. Cerebrospinal fluid (CSF) analysis was negative for leukocytosis, malignant cells, or inflammatory disease. CSF Lyme titers were inconclusive.

Over the next 6 weeks, the patient continued to develop worsening symptoms suggestive of additional cranial nerve involvement with refractory facial pain. Repeat contrast MRI revealed an enlarging soft tissue density with enhancement of the right cavernous sinus, right Meckel's cave and right foramen ovale. The patient eventually underwent a tissue biopsy, which revealed invasive squamous cell carcinoma. Ultimately, the patient refused oncologic treatment and went home on hospice.

Case 2

A 72 year old man presented with five months of diplopia, intermittent dysphagia, paresthesia and lancinating pain in the right V2 distribution. Exam was notable for inability to depress the right eye, decreased sensation in the right V1-V3 distribution, and decreased hearing. Initial non-contrast brain MRI revealed small vessel disease though retrospective review indicates that there may have been asymmetry in Meckel's cave. Infectious and inflammatory laboratories (ESR, CRP, Lyme titers, RPR, ANA, RF, Sjogren's antibodies, ACE) were negative. CSF was negative for leukocytes are, HSV PCR, gram stain and culture, oligoclonal bands, and malignant cells.

Over the next 2 years, the patient's facial pain worsened, and he started to note intermittent swelling and facial spasm over the right cheek. Exam showed new right ptosis. A repeat MRI with contrast at this time revealed abnormal enhancement along the course of the right trigeminal nerve with enlargement of the gasserian ganglion and enhancement in the foramen ovale and rotundum (Figure 2).CSF signal within Meckel's cave was obliterated. Malignancy was suspected. The patient underwent a CT guided biopsy of the trigeminal nerve which confirmed the diagnosis of squamous cell carcinoma. The patient was treated with cetuximab and radiotherapy with improvement of his facial pain.

Discussion

The two cases presented above reveal the diagnostic difficulties when facing progressive isolated painful trigeminal neuropathy with or without other cranial neuropathies. The 1st patient presented initially with symptoms (difficulties opening and closing jaw) attributable to the motor division of CN V3. After a few years, she developed neuralgic pain and facial numbness (implicating the sensory fibers of CN V), taste alteration (involvement of lingual nerve from CN V and chorda tympani from CN VII), and lacrimation (occurring via the parasympathetic nerves that travel with CN VII). Familiarity with neuroanatomy would localize symptoms predominantly to CN V and possibly CN VII. Despite progression over years, initial MRI was not revealing and positive Lyme titers were suggestive of peripheral cranial nerve involvement by the B. burgdorferi. The follow up MRI demonstrated enhancement that could be consistent with peripheral involvement of the cranial nerves by Lyme though the presence of the nodular mass is atypical for infection. Only with further

progression of symptoms to involve other cranial nerves including the extraocular nerves, did MRI finally reveal findings consistent with perineural invasion along multiple nerves concerning for neoplastic involvement. Unfortunately, the nonspecific nature of symptoms, unrelated abnormal labs, and initial nonspecific MRI findings resulted in considerable delay to diagnosis. This delay limited effective treatment options due to the extensive involvement of the tumor by the time of diagnosis. Interestingly, squamous cell carcinoma was not initially entertained due to the remote history of her facial cancer and lack of any obvious skin findings. This highlights the long asymptomatic period between treatment of a cutaneous malignancy and metastatic presentation via perineural invasion. In the 2nd case, the patient did not have any prior history of malignancy involving the head and neck. Again, presenting symptoms were nonspecific, and he was treated initially as idiopathic classic TN. Over course of 2.5 years, symptoms progressed to involve other cranial nerves, and eventually neuroimaging revealed enhancement and expansion of CN V.

Perineural involvement of squamous cell carcinoma of the head and neck is an unusual metastatic pathway. It is thought to occur via invasion of the perineural space with spread of tumor cells in all nerve compartments [3,5,6]. While the exact biological mechanism for the spread is unknown, proposed theories have included axonal and myelin degeneration, segmental infarction of the neural bundle, as well as ischemic compromise causing hypoxia and subsequent degeneration of the nerve [5,7]. This may be the pathological mechanism underlying the refractory pain often associated with tumor involvement of CN V. Perineural invasion has been defined as the movement of cancer cells into the neural space, usually with smaller nerves, and diagnosed by histological evaluation as it is undetectable on imaging [8]. Perineural spread describes the gross extension of tumor along a nerve and is generally detectable via imaging studies [8-10].Metastatic invasion and spread are guided by a targeted proliferation process involving neurotrophins, growth factors, axonal guidance receptors, and specific interactions between cell adhesion molecules and the stroma [3,11,12]. Changes of p53 regulation, such as gain of function mutations, have been proposed as a pathway leading to perineural invasion and spread [13].

CN V and CN VII are attractive targets for perineural invasion and spread due to their rich network of branches that covers a wide anatomic distribution along the skin and within subcranial structures. A study of 135 patients with perineural invasion of skin cancer found that in clinically symptomatic patients, the trigeminal nerve was most frequently involved, followed by the facial nerve [14]. In addition, there are anatomic connections (sphenopalatine ganglion, junction of chorda tympani and lingual nerve, and at the parotid gland along the auriculotemporal branch of the mandibular branch of CN V) between CN V and CN VII which may be why these two nerves are frequently involved together. These pathways may also serve as another conduit for the tumor cells to spread from one nerve to another.

While we focused on squamous cell carcinoma, other head and neck cancers can be associated with neoplastic perineural involvement including basal cell carcinoma of the skin, adenoid cystic carcinoma of the parotid gland, sarcoma, melanoma, and lymphoma [15]. The incidence of perineural involvement by tumor range from 14%-63.2% depending on the study cited [16]. Perineural metastasis is associated with decreased rate of disease free survival, decreased quality of life due to symptoms, and increase rate of local tumor recurrence [17-20]. Overall, it is reported as a poor prognostic factor for head and neck cancer, especially in advanced cases, highlighting the need for early detection and recognition.

Clinically, patients present with dysfunction of the involved nerves. Most common clinical symptoms include pain, paresthesia, numbness, and facial weakness. The pain can be quite disabling and persistent. It may present as classic neuropathic pain with paroxysmal burning, deep aching discomfort, allodynia, hyperesthesia, or itching [15]. Patients often complain of burning pain or formication affecting the distal branches which eventually extend to more proximal branches [21]. A careful history and exam should be able to discern between classic trigeminal neuralgia and secondary atypical facial pain. In the setting of progressive trigeminal neuropathy with or without other cranial neuropathy, we recommend a careful skin examination to evaluate for potential perineural involvement of tumor as cause of symptoms. Often the pain can be difficult to treat despite trials of numerous neuropathic agents. This may be related to the segmental nerve infarction and axonal injury associated with perineural invasion of tumor cells.

Typically, MRI focusing on the skull base with fat saturation may help discern the extent of nerve involvement. There may be obliteration of the fat planes around the nerve branches especially at the level of the foramina. Enhancement of the nerve and/ or enlargement of the nerve may also be seen. Attention should be focused at the level of Meckel's cave, cavernous sinus, sphenopalatine fossa, and the bony foramina and fissures involved throughout the course of CN V and CN VII [15]. Denervation of muscles innervated by motor branches of cranial nerves may be marked by contrast enhancement, T2 hyper-intensity (seen in the early stages of denervation), and eventually T1 hyper-intensity (indicating chronic changes from denervation) [10,22]. CT with contrast may highlight the widening or erosion of bony foramina through which CN V may exit. Sensitivity for these imaging modalities vary with one retrospective study of 39 cases reporting a sensitivity of 56% for CN V and 40% for CN VII when combining MRI and CT [23]. However, other studies have reported higher sensitivities with MRI approaching 95% [8,24].

Unfortunately, the difficulties in diagnosing perineural invasion and spread often lead to delay in diagnosis. Treatment of invasive cutaneous squamous cell carcinoma of the head and neck often involves surgery and/or radiation in the hopes of achieving local control [25]. While the data surrounding the use of multimodal treatment is scarce, a few studies have suggested there may be an added benefit of surgical resection in selected patients [26,27]. For instance, a retrospective study of 24 patients with advanced nonmelanoma cutaneous cancers with skull based involvement demonstrated improvement in local regional control with the inclusion of surgery [26]. Another study of 25 patients with cutaneous squamous cell carcinoma of head and neck showed an increase in 5 year local control with surgery and radiation compared to radiation alone (38% versus 20%) [27]. Achieving wide margins through resection of the involved tumor along the cranial nerves clearly remains a challenge for many neurosurgeons. Adjuvant radiotherapy has been increasingly used to manage advanced cutaneous squamous cell carcinoma. Multiple retrospective studies have reported the beneficial impact of adjuvant radiotherapy on local control and survival in squamous cell carcinoma with perineural invasion [26,28]. It is thought that radiation may reduce tumor cell viability and disruption of the tumor microenvironment [29].

The role of chemotherapy and targeted therapy is less clear with supporting data limited to case reports. Cisplatin and cetuximab

(Erbitux®), a monoclonal antibody against epidermal growth factor receptor, have been used with radiotherapy for locally advanced head and neck cancer [30,31]. Whether these beneficial results translate to positive outcomes in tumors with perineural invasion remains less clear. Unfortunately, the deficits caused by the cranial neuropathies are often irreversible with only 7% of patients reporting some alleviation of symptoms with treatment [15]. Consideration of perineural invasion and growth as a cause of painful trigeminal neuropathy and other cranial neuropathy is not only important to affect survival, but also to affect the morbidity associated with cranial nerve deficits and dysfunction.

Conclusion

Neoplastic perineural involvement of cranial nerves often serves as a diagnostic dilemma for the clinician. The presentation of isolated painful trigeminal neuropathy can be misleading especially if the original cancer source remains occult or is overlooked and often leads to a delay in diagnosis. Findings on neuroimaging may be quite subtle, thus attention should be focused on obliteration of fat planes, enhancement and expansion of nerves rather than the typical findings of mass tumor bulk. Therapies often include surgery and radiation with the possibility of the addition of chemotherapy and/or target therapy. Traditionally, perineural involvement has been reported as a poor prognostic factor, especially for advanced disease though the increasing use of adjuvant radiation with the possible incorporation of systemic therapy may provide benefit to these patients.

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References

1. Gronseth G, Cruccu G, Alksne J, Argoff C, Brainin M, Burchiel K, et al. Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies. Neurology. 2008; 71:1183-1190.

2. Headache Classification Committee of the International Headache S. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013; 33: 629-808.

3. Liebig C, Ayala G, Wilks JA, Berger DH, Albo D. Perineural invasion in cancer: a review of the literature. Cancer. 2009; 115: 3379-3391.

4. Braksick S, Shah-Haque S, El-Haddad B, Moussa R. Neurosarcoidosis presenting as trigeminal nevralgia: a case report and review of the literature. Sarcoidosis Vasc Diffuse Lung Dis. 2013; 30: 153-156.

5. Carter RL, Foster CS, Dinsdale EA, Pittam MR. Perineural spread by squamous carcinomas of the head and neck: a morphological study using antiaxonal and antimyelin monoclonal antibodies. J Clin Pathol. 1983; 36: 269-275.

6. Veness MJ. Perineural spread in head and neck skin cancer. Australas J Dermatol. 2000; 41: 117-119.

7. Goepfert H, Dichtel WJ, Medina JE, Lindberg RD, Luna MD. Perineural invasion in squamous cell skin carcinoma of the head and neck. Am J Surg. 1984; 148: 542-547.

8. Nemzek WR, Hecht S, Gandour-Edwards R, Donald P, McKennan K. Perineural spread of head and neck tumors: how accurate is MR imaging? AJNR Am J Neuroradiol. 1998; 19: 701-706.

9. Panizza B, Warren TA, Solares CA, Boyle GM, Lambie D, Brown I. Histopathological features of clinical perineural invasion of cutaneous squamous cell carcinoma of the head and neck and the potential implications for treatment. Head Neck. 2014; 36: 1611-1618.

10. Ginsberg LE. Imaging of perineural tumor spread in head and neck cancer. Semin Ultrasound CT MR. 1999; 20:175-186.

11. Kowalski PJ, Paulino AF. Perineural invasion in adenoid cystic carcinoma: Its causation/promotion by brain-derived neurotrophic factor. Hum Pathol. 2002; 33: 933-936.

12. Vural E, Hutcheson J, Korourian S, Kechelava S, Hanna E. Correlation of neural cell adhesion molecules with perineural spread of squamous cell carcinoma of the head and neck. Otolaryngol Head Neck Surg. 2000; 122: 717-720.

13. Warren TA, Broit N, Simmons JL, Pierce CJ, Chawla S, Lambie DL, et al. Expression profiling of cutaneous squamous cell carcinoma with perineural invasion implicates the p53 pathway in the process. Sci Rep. 2016; 6: 34081.

14. Garcia-Serra A, Hinerman RW, Mendenhall WM, Amdur RJ, Morris CG, Williams LS, et al. Carcinoma of the skin with perineural invasion. Head Neck. 2003; 25: 1027-1033.

15. Bourque PR, Bourque G, Miller W, Woulfe J, Warman Chardon J. Combined isolated trigeminal and facial neuropathies from perineural invasion by squamous cell carcinoma: A case series and review of the literature. J Clin Neurosci. 2017; 35: 5-12.

16. Roh J, Muelleman T, Tawfik O, Thomas SM. Perineural growth in head and neck squamous cell carcinoma: a review. Oral Oncol. 2015; 51: 16-23.

17. Boerman RH, Maassen EM, Joosten J, Kaanders HA, Marres HA, van Overbeeke J, et al. Trigeminal neuropathy secondary to perineural invasion of head and neck carcinomas. Neurology. 1999; 53: 213-216.

18. Fagan JJ, Collins B, Barnes L, D'Amico F, Myers EN, Johnson JT. Perineural invasion in squamous cell carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg. 1998; 124: 637-640.

19. Pinto FR, de Matos LL, Palermo FC, Kulcsar MA, Cavalheiro BG, de Mello ES, et al. Tumor thickness as an independent risk factor of early recurrence in oral cavity squamous cell carcinoma. Eur Arch Otorhinolaryngol. 2014; 271: 1747-1754.

20. Ju J, Li Y, Chai J, Ma C, Ni Q, Shen Z, et al. The role of perineural invasion on head and neck adenoid cystic carcinoma prognosis: a systematic review and meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016; 122: 691-701.

21. Reddy GD, Wagner K, Phan J, DeMonte F, Raza SM. Management of Skull Base Tumor-Associated Facial Pain. Neurosurg Clin N Am. 2016; 27: 337-344.

22. Russo CP, Smoker WR, Weissman JL. MR appearance of trigeminal and hypoglossal motor denervation. AJNR Am J Neuroradiol. 1997; 18: 1375-1383.

23. Lee KJ, Abemayor E, Sayre J, Bhuta S, Kirsch C. Determination of perineural invasion preoperatively on radiographic images. Otolaryngol Head Neck Surg. 2008; 139: 275-280.

24. Hanna E, Vural E, Prokopakis E, Carrau R, Snyderman C, Weissman J. The sensitivity and specificity of high-resolution imaging in evaluating perineural spread of adenoid cystic carcinoma to the skull base. Arch Otolaryngol Head Neck Surg. 2007; 133: 541-545.

25. Redmond MJ, Panizza BJ. Intracranial Management of Perineural Spread in the Trigeminal Nerve. J Neurol Surg B Skull Base. 2016; 77: 150-160.

26. Raza SM, Ramakrishna R, Weber RS, Kupferman ME, Gidley PW, Hanna EY, et al. Nonmelanoma cutaneous cancers involving the skull base: outcomes of aggressive multimodal management. J Neurosurg. 2015; 123: 781-788.

27. Mendenhall WM, Parsons JT, Mendenhall NP, Brant TA, Stringer SP,

Cassisi NJ, et al. Carcinoma of the skin of the head and neck with perineural invasion. Head Neck. 1989; 11: 301-308.

28. Kropp L, Balamucki CJ, Morris CG, Kirwan J, Cognetta AB, Stoer CB, et al. Mohs resection and postoperative radiotherapy for head and neck cancers with incidental perineural invasion. Am J Otolaryngol. 2013; 34: 373-377.

29. Bakst RL, Lee N, He S, Chernichenko N, Chen CH, Linkov G, et al. Radiation impairs perineural invasion by modulating the nerve microenvironment. PLoS One. 2012; 7: e39925.

30. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006; 354: 567-578.

31. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med. 2004; 350: 1945-1952.