Perineural Spread of Melanoma: Lessons Learned the Hard Way

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Abstract

Extension of tumor cells along the perineural environment is referred to as perineural spread. Amongst the head and neck malignancies, nonmelanoma cutaneous or non-cutaneous cancers such as squamous cell carcinoma, adenoid cystic carcinoma and lymphoma are the more common malignancies known to spread perineurally. Melanoma especially the rare desmoplastic subtype has a propensity to spread along cranial nerves. We present two cases of metastatic melanoma with perineural spread, in the absence of a concurrent cutaneous lesion, resulting in a delayed diagnosis. In this retrospective case series, we highlight the factors that complicate timely accurate diagnosis. Detailed medical and surgical history, clinically appropriate differential diagnosis, sensitive imaging modalities, and experience of the interpreting neuroradiologist all play crucial role in the clinical investigation and reaching a timely and accurate diagnosis.

Keywords

Melanoma, Metastatic melanoma, Perineural spread, Perineural invasion, Diagnostic delay

Abbreviations

MRI: Magnetic resonance imaging; PNI: Perineural invasion; PNS: Perineural spread

Introduction

Melanoma is a malignant tumor that arises from uncontrolled proliferation of melanocytes. Cutaneous melanoma is the fifth most common cancer in the United States [1] and accounts for 1 in 5 of all skin cancers worldwide responsible for majority of skin cancer related deaths. Melanoma cases are projected to increase by 50% by 2040 [2]. Most patients are diagnosed at an early stage; however, some patients present with metastatic disease at the time of diagnosis, an indicator of poor prognosis [3]. The most common sites of distant metastases are lymph nodes, lungs, liver, brain, and bone. Melanoma can spread to these sites via hematogenous or lymphatic route [4]. Perineural spread (PNS) of melanoma is relatively rare and results from direct extension of tumor into
the nerves [5, 6]. Desmoplastic melanoma is an uncommon subtype accounting for less than 4% of primary cutaneous melanomas that, although is known for its neurotropism but the actual PNS along cranial nerves is < 3% [7, 8]. This variant can be amelanotic making it a difficult to diagnose [9]. In this case series we highlight diagnostic challenges in two cases of perineural melanoma spread along cranial nerves.

**Case 1**

A 65-year-old male initially complained of numbness in the left aspect of the chin. Over the next two to three years numbness persisted with increased involvement of the left aspect of the chin and entire distribution of mandibular (V1) branch of the left trigeminal nerve prompting him to seek medical attention. Brain and face MR imaging was obtained at this time (discussed in detail below). Presence of a few scattered focal periventricular white matter signal changes on brain MRI lead to a suspicion of multiple sclerosis for which steroid therapy was initiated at a community clinic. Only mild clinical improvement was noted. Numbness further spread from the lower to the upper aspect of the left side of his face now involving ophthalmic (V1) and maxillary (V2) distribution of the left trigeminal nerve. No associated paresthesia or pain was reported. Over the course of next 5-6 months patient started complaining of, in addition to the above symptoms, double vision. Over the next 10 months he was diagnosed with complete left occulomotor (CN III), trochlear (IV) and abducens (VI) nerve palsies. He also had difficulty chewing and left temporal wasting. Steroid therapy was increased with mild improvement in facial numbness and ocularmotor palsy. The diagnosis of multiple sclerosis was challenged, and a cerebrospinal fluid (CSF) analysis was performed that was nonrevealing. However due to an uncertain diagnosis, high dose steroid therapy with methylprednisone 24 mg twice daily was continued. At this point patient presented to our institute. Pertinent physical exam revealed numbness of the entire left face, difficulty chewing with left-sided jaw weakness making him chew his food on the right side, inability to fully seal the lips, left sided ptosis and diplopia, and left sided hearing loss. Given multiple progressive cranial nerve involvement, a diagnosis of lymphoma was suspected. Repeat CSF analysis at this point was also nonrevealing.

All outside diagnostic imaging was reviewed at our institute by several neuroradiologists after the final diagnosis was made via biopsy. Initially an MRI of the face and brain was performed. Following the incorrect diagnosis of multiple sclerosis all subsequent imaging focused on brain. Crucial imaging findings consistently overlooked on several MRI were progressive thickening and enhancement of the mandibular division of the left trigeminal nerve (Figure 1a) further extending along the left inferior alveolar nerve (Figure 1b and c), denervation atrophy of the left muscles of mastication seen approximately four years after symptom onset (Figure 1c and d), and an evolving mass-like lesion in the left masticator space approximately six years after symptom onset (Figure 1e).

Enlarging enhancing nodule at the leftpons at the root entry zone of the left trigeminal nerve was noticed on the brain MRI (Figure 2b) performed three years after symptom onset and became the focus of all subsequent imaging. No lesion was identified in this location on first face MRI obtained two years after symptom onset (Figure 2a). The nodule continued to grow over the next three years (Figure 2b–e). Perineural spread along multiple additional cranial nerves (Figure 3) was also noted on retrospective review of imaging.
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Since the more accessible left mandibular/masticator space abnormality was unknown to the clinical team, patient underwent surgical biopsy of the left pontine mass. Biopsy showed a malignant neoplasm, composed of epithelioid cells with marked nuclear anaplasia, and harboring brisk mitotic activity (Figure 4a). These neoplastic cells were focally noted in intimate association with a peripheral nerve (Figure 4b). By immunohistochemistry, the malignant cells were diffusely positive for SOX-10 (Figure 4c) and showed expression of Melan-A and HMB-45 in a subset, supporting the diagnosis of melanoma. S-100 highlighted Schwann cells in the involved peripheral nerve fascicle (Figure 4d). By targeted next-generation sequencing studies, this melanoma harbored an NRAS (p. Q61K) mutation, and lacked GNA11, GNAQ and BRAF mutations, supporting origin from a systemic, rather than primary CNS, melanoma. Thorough skin exam was repeated; however, no cutaneous lesions could be identified. The patient eventually recalled a remote skin lesion over the left temple, which was never biopsied but "burned" by a dermatologist several years ago. Patient was treated with radiation therapy followed by immune checkpoint inhibitor chemotherapy with mild clinical response.

Case 2

A 36-year-old male initially complained of numbness in the right aspect of his chin when shaving. Following medical evaluation, an MRI of the face was obtained (details below) that was nonrevealing. Over the next eight months symptoms persisted with numbness extending to involve the entire distribution of the mandibular (V3) branch of the left trigeminal nerve. Approximately nine months following symptom onset, he developed right mandibular molar tooth infection that resolved with antibiotic therapy. Facial numbness persisted, and two months later patient developed a palpable nodule on the right side of the chin that was evaluated by an oral surgeon. He was initially given the diagnosis of a lipoma. The lesions from lower anterior lip associated with the mental foramen (Figures 5a-c) and right buccal anterior mucosa associated with inferior alveolar nerve (Figures 5d-f) were eventually biopsied. Both the biopsies showed nodular proliferation of malignant epithelioid cells associated with nerve bundles (Figure 5a, 2b 2d, 2e). The neoplastic cells had high-grade cytology with nuclear anaplasia and prominent nucleolus (Figure 5c, 5f) and atypical mitosis (Figure 5c). The stroma showed hyalinization with dense lymphocytic infiltrates (Figure 5e, 5f). By immunohistochemistry, the neoplastic cells were positive for S100 and SOX10 while negative for specific melanocytic markers and other lineage markers. No BRAF mutation was detected by next generation sequencing. Overall, the features were considered supportive of in transit metastatic melanoma.

Figure 3: Additional multiple cranial nerve involvement. Coronal T1 postcontrast brain MRI (a.) showing abnormal enhancement of the maxillary division (V2) of the left trigeminal nerve in the foramen rotundum, observed retrospectively. Coronal (Axial T1 postcontrast fat suppressed images (b-e) show abnormal enhancement along the supraorbital nerve (b.), a branch of the ophthalmic division (V1) of the left trigeminal nerve, left abducens (CN VI) nerve (c, yellow arrow), facial (CN VII) nerve (d.) and vestibulocochlear (CN VIII) nerve (c, white arrow). Coronal T1 postcontrast fat suppressed image shows enhancing enlarged left oculomotor (CN III) nerve (e.).

Figure 4: Biopsy showed a malignant neoplasm, composed of epithelioid cells with marked nuclear anaplasia, and harboring brisk mitotic activity (Figure 4a). These neoplastic cells were focally noted in intimate association with a peripheral nerve (Figure 4b). By immunohistochemistry, the malignant cells were diffusely positive for SOX-10 (Figure 4c) and showed expression of Melan-A and HMB-45 in a subset, supporting the diagnosis of melanoma. S-100 highlights Schwann cells in the involved peripheral nerve fascicle (Figure 4d). All images at 200x magnification.
Outside imaging was reviewed at our institute after the patient presented for a second opinion. The first available MRI of the face (Figure 6) one year after symptoms onset was read as negative. In retrospect, a subcutaneous small nodule was potentially present on the right aspect of the chin on axial T1-postcontrast image (Figure 6). CT soft tissue neck with IV contrast at the time of tooth infection (Figure 7), demonstrated developing phlegmon involving right masticator space (Figure 7a-b), effacing right parapharyngeal fat and right visceral mucosal space with trans-spatial edema (Figure 7a-b) and reactive lymphadenopathy. Findings that were overlooked at the time of initial reporting included an enhancing mildly thickened subcutaneous nodule adjacent to the right mental foramen (Figure 7c) with associated mental (Figure 7d) and mandibular foraminal (Figure 7e) widening. Six months following resolution of infection, due to persistent facial numbness, a positron emission tomography/computed tomography (PET/CT) with 2-[fluorine 18]fluoro-2-deoxy-D-glucose (FDG) was performed (Figure 8a) and demonstrated a hypometabolic nodule adjacent to the right mental foramen. Subsequent iodinated contrast enhanced face CT (Figure 8b) demonstrated a colocalizing enhancing lesion. Face MRI with and without intravenous gadolinium (Figure 9a-c) confirmed an avidly enhancing, T1 hypointense, T2 hyperintense nodule. Additionally, enhancement along the right inferior alveolar nerve (Figure 9d) now extending proximally along the mandibular division of the trigeminal nerve (CN V) was also noted (Figure 9e). Patient was started with immune checkpoint inhibitors ipilimumab and nivolumab chemotherapy with excellent clinical response with neurologic improvement.

Discussion

Melanoma constitutes up to only 5% of all skin cancers, yet remains the most lethal, accounting for about two-thirds of all skin cancer-related deaths [10]. It is the fifth most common cancer in the United States [1]. Melanomas in the head and neck account for about 20% of all melanoma cases and portend a poor prognosis [11, 12]. Most patients are diagnosed at an early stage; however, some patients present with metastatic disease at the time of diagnosis, an indicator of poor prognosis.
Its presence is not only linked to the Gasserian ganglion or cavernous sinus, it may spread along other cranial nerves [5]. PNS is a major poor prognostic factor bearing crucial implications for therapeutic strategies making early detection critical [23, 24]. Its presence is not only linked to a high rate of recurrence and metastases, but also alters the surgical approach often deeming the tumor unresectable [20].

Factors leading to delay in diagnosis

Delay in seeking care due to insignificant symptoms and lack of a visible cutaneous lesion

The absence of a recognized cutaneous lesion, as in our cases, is a known diagnostic challenge with PNS leading to clinical underdiagnosis [13, 25]. In our cases numbness about the chin, the first clinical symptom, was not perceived as significant enough by the patient likely due to lack of interference with daily activities. Only after symptoms persisted and progressed, medical attention was sought.

Misleading diagnosis and incomplete imaging investigation

It is vital to remember that PNS can be asymptomatic [23, 26]. When present, symptoms can be nonspecific such as paraesthesias, numbness and pain leading to incorrect and often benign/less ominous diagnoses such as trigeminal neuralgia or, as in our case, multiple sclerosis [26-28]. The type of imaging modality and subsequent protocoling is led by the initial working diagnosis [29]. Although the initial imaging in both cases was appropriately MRI of the face, a working diagnosis of multiple sclerosis in the first case and none in the second may have led to a biased and incomplete radiologic search. This highlights the crucial issue of appropriate tailored protocoling and scrutinizing images based on symptom distribution [23, 29]. With progressively increasing numbness along the face and development of sequential ipsilateral cranial neuropathies in the first case, a more central cause was sought. When the left pre-pontine nodule in the first case was recognized, it led to subsequent brain (not face) MRIs, which inadequately evaluate abnormalities along the mandible, usually only partially covered on a typical brain MRI field of view. The persistent facial numbness and development of an ipsilateral palpable nodule along the right side of the chin in the second case, was appropriately investigated with F18 FDG PET/CT that has an established role in imaging of head and neck malignancies and has been successfully shown to draw attention to PNS of tumors [13, 30]. This led to reevaluation of previous imaging and recognition of a slow growing mass. Additionally, expansion of the right mental and mandibular foramina on the prior imaging confirmed PNS even before the palpable lesion developed in the second case.

PNS can have an antegrade or a retrograde spread with retrograde route being more common [16]. A retrograde spread toward the brainstem poses a diagnostic challenge due to difficult tissue sampling [31]. In cases of known perineural involvement and uncertain diagnosis, a transcutaneous biopsy...
of the involved accessible nerve is an established minimally invasive and cost effective diagnostic procedure often done without sedation [32]. In our first case, with the more peripheral abnormality remaining undetected and clinical suspicion of a benign process, surveillance imaging was conducted for the pre-pontine lesion for about four years. This led to a more invasive diagnostic approach with a surgical biopsy via craniotomy under general anesthesia. The presence of a more accessible target only recognized after reevaluation of the imaging added time and cost to the diagnostic work-up.

Experience of the interpreting radiologist and ‘satisfaction of search’

The key role of a radiologist in diagnosing PNS is well established [23, 25]. PNS on imaging can present with subtle findings requiring detailed anatomic understanding of the involved neural pathways [25]. Experience and sub-speciality training of the interpreting radiologist are, therefore, crucial. Importance of satisfaction of search cannot be undermined in this scenario either. Successful recognition of the more obvious lateral preptitone abnormality in the first case, and changes related to tooth infection in the second case were classic errors of satisfaction of search [33]. Prevalence of an abnormality [34] and the amount of searchable visual data available [35] are also well-known factors that contribute to accurate target detection. Reported variability in incidence of PNS [15], and gravitation towards more brain imaging than face (as in the first case) can potentially explain why even experienced radiologists may not perceive subtle PNS findings.

Conclusion

Careful comparison of prior serial imaging (not just most recent exam), thorough clinical history, and high suspicion, regardless of the provided initial diagnosis, are a radiologist’s best resources to appropriately detect subtle, but often crucial abnormality.

Even in the absence of a known cutaneous or mucosal malignancy, when perineural spread on imaging is suspected, especially with progressive deficits in a single cranial nerve distribution, metastatic melanoma (or other malignancy) should be mentioned in the differential diagnoses, even if clinical suspicion is that of a benign process.

Satisfaction of search remains a major cause of diagnostic error and should be minimized by a thorough search pattern covering all the available imaging data.

Conflict of Interest

The author(s) declare that they have no competing interests.

References


