An Isolated Trigeminal Sensory Neuropathy

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A 60-year-old woman with no significant medical history presented to her neurologist with decreased sensation of the left cheek. Magnetic resonance imaging (MRI) with gadolinium contrast of the head, including the brain and cranial nerves, and magnetic resonance angiography of the head and neck were interpreted as normal. After a 2-year period of clinical stability, the sensory deficit gradually progressed to involve the entire left lower half of her face followed by the emergence of lancinating pain and allodynia over the same region. Neurologic examination confirmed a mild sensory deficit to light touch, temperature, and pin prick in the entire distribution of the second (V2) and third (V3) divisions of the left trigeminal nerve. She was started on carbamazepine with no relief. Subsequent MRIs of the head demonstrated abnormal thickening and enhancement throughout the entire left V2 nerve segment extending through Meckel cave and involving the cisternal portion of the left trigeminal nerve. In retrospect, the initial MRI demonstrated a small enhancing focus in the same region.

The patient was referred to our facility for trigeminal nerve biopsy and concomitant microvascular decompression for symptomatic relief. Collected specimens demonstrated chronic inflammation without evidence of malignancy. A prednisone taper was started with good response. One month later, an incomitant left hypertropia with vertical diplopia (worse on right and downward gaze), along with poor activation of the left masseter and temporalis muscles, was noted on examination. The course of prednisone was extended.

Three months later, the patient was readmitted in the setting of a massive pulmonary embolism. Neurologic examination demonstrated persistent left facial numbness with a new left esotropia and left lateral rectus palsy as well as down-beating nystagmus in primary gaze.

Laboratory and Imaging Data

Magnetic resonance imaging of the brain with gadolinium prior to surgery showed prominent enhancement of the tissue within Meckel cave (Figure 1A, asterisk), which tracked distally along both V2 (extending through the left foramen rotundum into the pterygopalatine fossa and up to the infraorbital foramen) and V3 (extending distally through the left foramen ovale into the masticator space; Figure 1B, arrow). There was also enhancement within the left superior orbital fissure, but without definite

involvement of the V1 segment or frontal nerve. Atrophy of the left pterygoid, masseter, and temporalis muscles was noted, consistent with denervation. Whole-body positron emission tomography computed tomography was unremarkable. The following serum studies were negative or normal: Lyme, human immunodeficiency virus antigen/antibody, syphilis antibody screen, SS-A and SS-B antibodies, double stranded DNA antibodies, antinuclear antibodies, anti-neutrophil cytoplasmic antibody, erythrocyte sedimentation rate, and c-reactive protein. Cerebrospinal fluid studies included a normal cell count with differential, protein, glucose, cytology, flow cytometry, IgH rearrangement, and negative varicella-zoster and cytomegalovirus polymerase chain reaction and angiotensin converting enzyme (ACE). Biopsy of the trigeminal ganglion at the time of microvascular decompression showed evidence of chronic inflammation (perivascular lymphocytic infiltrate with scattered macrophages) and myelin spheroids suggestive of axonal damage. No malignant cells were present. Follow-up imaging, 3 months postoperatively, demonstrated the prior findings in addition to progressive involvement of the infraorbital nerve and expansion of the enhancing tissue in Meckel cave, which extended into the cavernous sinus (Figure 1C-F). Based on the radiological findings and clinical concern for occult malignancy with a presumed hypercoagulable state, a left infraorbital nerve biopsy was performed.

Clinical Discussion

This patient initially presented with a trigeminal sensory neuropathy. Isolated trigeminal sensory neuropathies are rare but

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Figure 1. Magnetic resonance imaging (MRI) of lesion. T1-weighted postcontrast MRIs of the brain prior to microvascular decompression (A and B) demonstrate enhancement of tissue within Meckel cave (A, asterisk) with extension along the V2 segment of the trigeminal nerve (A). Enhancement of the V3 segment is also present (B) as it passes out of Meckel cave inferiorly through the foramen ovale (B, arrow) and into the left masticator space. T1-weighted postcontrast images following microvascular decompression show persistent enhancement of the V3 segment (C, arrow). Enhancement of the V2 segment (D, arrow) clearly extends to the infraorbital nerve (D, arrow head). Persistent enhancement of tissue in Meckel cave (E, asterisk) now appears to infiltrate the cavernous sinus (F, arrow).

well-described phenomenon attributable to a number of etiologies that ultimately dictate the presentation, time course, additional signs and symptoms, and prognosis for each individual case.¹

Depending on the underlying pathophysiology, the trigeminal tract may be affected diffusely or focally along its course, from its emergence proximally in the pons and distally to the Gasserian ganglion, cavernous sinus, bony foramina, sensory, and motor roots and finally terminal nerve fibers in the skin, muscles, and endocrine organs. If additional colocalizing symptoms outside of the trigeminal pathway are not apparent, clinical examination alone is often insufficient to localize the lesion as identical symptoms can arise from spatially disparate lesions along the trigeminal course and imaging becomes necessary.¹

The differential diagnosis should include (1) pontine or medullary pathology, such as a demyelinating lesion involving the primary sensory or spinal trigeminal nuclei; (2) invasive or intrinsic pathology of the trigeminal nerve, including neoplasm, autoimmune connective tissue disease (mixed connective tissue disease, systemic lupus erythematosus (SLE), Sjögren syndrome, or scleroderma), sarcoidosis, or chronic granulomatous disease (eg, syphilis); and (3) benign idiopathic trigeminal sensory neuropathy.

In the largest case series reported (2083 patients), 3.1% of patients presenting with an isolated trigeminal sensory neuropathy were eventually diagnosed with multiple sclerosis (then referred to as systemic sclerosis),² though a smaller more recent study found this diagnosis in 14%.³ In isolation, trigeminal sensory symptoms should be less commonly attributable to brain stem pathology since additional neurological deficits would be highly likely; however, a demyelinating lesion affecting the primary sensory or spinal nucleus in the pons and medulla (or the corresponding trigeminal root exit zones) may be considered.³

Collagenosis or autoimmune inflammatory conditions including mixed connective tissue disease, SLE, Sjögren syndrome, or sarcoidosis may also involve the trigeminal nerve in isolation.⁴ Systemic signs consistent with these diseases should be sought on history and examination. In these cases, the trigeminal nerve is diffusely involved and motor function is typically preserved.¹

Benign and malignant neoplastic lesions may arise along the course of the trigeminal nerve. Such processes compress or directly invade the nerve substratum. Clinical presentation does not reliably differentiate benign and malignant cases with the exception of the “numb chin” sign of a mental neuropathy, which is highly associated with malignancies from breast, lung, or lymphoproliferative diseases and associated with a mortality

as high as 75%.⁵ Frequency of tumor type varies along the course of the nerve. Near the cerebellopontine angle, schwannomas may arise from the acoustic, facial, or trigeminal nerves (acoustic being most common and trigeminal being very rare), while meningiomas and cholesteatomas can arise from adjacent tissue. Such lesions are often accompanied by hearing loss, vestibular dysfunction, or cerebellar signs, all of which assist with localization. More distally, near the trigeminal ganglion, tumors arise from the surrounding tissue in the middle cranial fossa but practically never arise from the ganglion itself. Other possibilities include meningiomas, endotheliomas, gliomas, neurofibromas, neurocytomas, carcinomas, and syphilitic gummas as well as invading sarcomas and osteochondromas arising from the mandible, antrum, nasopharynx, and internal auditory canal. Irritation of the ganglion presents with prominent hyperalgesia and is commonly mistaken for idiopathic trigeminal neuralgia; however, clinical features unique to idiopathic trigeminal neuralgia can distinguish it from mechanical irritation of the ganglion. In idiopathic trigeminal neuralgia, touching a trigger zone on the face can provoke a pain paroxysm that is spatially dissociated from the trigger zone and a refractory period exists between pain paroxysms during which a subsequent episode cannot be elicited. Accompanying sixth or third nerve deficits should make one suspicious of Meckel cave lesions with associated cavernous sinus involvement. More distal lesions affecting the roots and terminal nerves include meningiomas, neurofibromas, or invasive nasopharyngeal and mandibular malignancies.⁶

Distant metastases to the trigeminal nerve most commonly arise from breast, lung, or prostate primaries, but lymphoma may also present this way. Since malignancy accounts for about half of patients initially presenting with trigeminal neuropathy, a careful workup of isolated trigeminal neuropathy must exclude malignancy.⁷

While suspicion was raised for malignancy in this case, initial imaging studies were not diagnostic and the patient was symptomatically treated for tic douloureux. The subsequent appearance of left hypertropia with vertical diplopia (worse on right and downward gaze) suggested a left trochlear nerve palsy, while poor activation of the left masseter and temporalis muscles likely resulted from involvement of trigeminal motor efferents on the ipsilateral side. The inability to fully abduct the left eye was consistent with a partial abducens nerve palsy. The constellation of symptoms in a unilateral distribution and localizing along spatially contiguous elements of the nervous system suggested an invasive process affecting multiple cranial nerves. This was supported by the eventual emergence and progression of frank tissue enhancement on MRI. While a primary or invasive neoplasm was most likely, an inflammatory autoimmune process could mimic this appearance.

Pathologic Discussion

Given the progression of clinical symptoms in conjunction with the neuroimaging findings, a biopsy of the left infraorbital

Figure 2. Hematoxylin and eosin (H&E) stain of left infraorbital nerve biopsy (×400).

nerve was performed. Histologic evaluation of the nerve biopsy showed a population of malignant cells within and surrounding the nerve (Figure 2, hematoxylin and eosin stain, ×400). The malignant cells were dispersed as single cells and present as loosely cohesive cords with a surrounding dense fibrotic response. Individual neoplastic cells varied from polygonal to stellate while some were spindled. Nuclei were oval and pleomorphic. Chromatin was variably hyperchromatic. Occasional intranuclear inclusions were present. The tumor cells had moderate amounts of clear-to-eosinophilic cytoplasm. A panel of immunohistochemical stains showed that the tumor was positive for p63, calponin, smooth muscle actin, and cytokeratin 5/6; weakly positive for S-100; and negative for cytokeratin 7 and 20. This immunohistochemical profile together with the histomorphologic features supported myoepithelial differentiation, compatible with a myoepithelial carcinoma.

Clinical Outcome

Following diagnosis, the patient underwent proton beam radiation with concurrent weekly cisplatin over an 8-week period. She had marked improvement in sensory symptoms. Follow-up neurologic examination showed improvement in left sixth nerve palsy but with persistent diplopia. Repeat MRI after completion of radiation and chemotherapy demonstrated persistent trigeminal nerve enhancement with a decrease in the bulk of enhancing tissue within Meckel cave. No new areas of enhancement were identified. Notably, no definitive “primary” tumor has been identified over the last 2 years, despite repeat imaging and endoscopic exploration of the nasal cavities. The malignancy was assumed to have originated in a salivary gland of the left maxillary or posterior nasal sinus.

Conclusions

In this case, a rare malignant myoepithelial carcinoma presented with an isolated trigeminal sensory neuropathy.

The indolent course of symptoms over a 3-year period, during which time imaging and biopsy were not initially diagnostic, confounded the diagnosis, which later became clear with secondary, relentless disease progression, new imaging findings, and a second and diagnostic biopsy. The initial symptoms likely represented the primary emergence of a low-grade malignancy with subsequent transformation into a more aggressive neoplasm, as has been previously suggested in similar cases of myoepithelial lesions.⁸ Although a primary tumor has not been identified, a minor salivary gland is likely the site or origin given the known natural history of this type of malignancy.

Myoepithelial carcinomas are composed of a mix of epithelial and smooth muscle components. Mean age of presentation is 50 years, with males and females equally affected. They may arise in the setting of a benign pleomorphic adenoma or myoepithelioma or arise de novo. Malignant lesions involving the head and neck typically originate in the parotid gland, hard palate, retromolar space, or larynx. Because of their infrequent occurrence or identification, information on the natural history of these tumors is scarce. Time between initial presentation and diagnosis is usually protracted (1-3 years), which is consistent with the current case. Lesions tend to be locally invasive and destructive with a propensity for nerve infiltration. Metastases to the liver, lungs, skin, vertebrae, and peritoneum have also been reported.

On pathological examination, myoepithelial carcinoma can be highly pleomorphic in appearance as with other tumors of an epithelioid origin. Tumor cells appear as spindle-shaped, plasmacytoid, epithelioid, or clear cells, but typically with 1 cell type predominating. In some areas, tumors are densely cellular, while other areas contain stroma of myxoid or hyaline appearance. Grading and staging are based on the American Joint Committee on Cancer (7th edition) staging system for malignant tumors of the major salivary glands. Due to a limited understanding, myoepithelial carcinoma is best considered a tumor with high-grade potential and unpredictable biologic behavior. Optimal treatment is uncertain and clear prognostic factors have not been established, though perineural invasion has been associated with an aggressive phenotype resulting in 100% fatality in 1 small case series.⁸ Close follow-up and restaging is therefore prudent.

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