Perineural Spread of Head and Neck Cancer: Ophthalmic Considerations

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Abstract

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Head and neck malignancies with orbital involvement present difficult decisions to the treating physician. When the spread is perineural, the challenges are greater due to the incipient nature of the spread and the fact that the orbit can also be involved by centrifugal spread from the non-ophthalmic branches of the trigeminal nerve. The disease is often misdiagnosed and the subsequent delay in treatment results in worse outcomes. This article discusses the evaluation of the eye and the many facets of orbital involvement by perineural spread of malignancy including the treatment of complications.

Along with inflammatory (infectious) and vascular phenomena, neoplasia is one of the most common pathologies affecting the head. In particular, the orbit may be involved by direct extension of tumors from surrounding structures, especially tumors of the paranasal sinuses, mandible, and nasal cavity. Primary intracranial tumors (particularly meningiomas) also often involve the orbit.

An unusual means of tumor extension in head and neck malignancy is that of perineural spread. Although this may have been described as early as the 1830s,¹ subsequent literature has been limited (see article “Mechanisms of Perineural Invasion” in this issue).^{2–9} Cutaneous squamous cell carcinomas^{5,7,10} and adenoid cystic carcinomas^{9,11} have a propensity for perineural spread. In the former, symptoms may present several months after a lesion has been treated (► **Fig. 1**). The latter may originate in the lacrimal gland but are often seen with extension from the minor secretory glands in and around the maxillary sinus (► **Fig. 2**). It is thus not surprising that ophthalmic manifestations (particularly orbital involvement¹²) are common in patients with perineural extension. In particular, skin lesions in the distribution of the first or, less commonly, second division of the trigeminal nerve¹³ often produce orbital symptomatology via intracranial extension. Once the tumor reaches the cavernous sinus,¹⁴ there is propensity for causing additional cranial nerve palsies, including involvement of the ocular motor

nerves often associated with pain.¹⁵ Extension along the facial nerve produces dysfunction in eyelid closure, which can have marked secondary problems such as neuroparalytic keratitis from facial nerve dysfunction and lagophthalmos.

Ophthalmic findings may be the first clue to the presence of perineural neoplasia. This may occur often without a known previous history of dermatologic tumors (see article “The Natural History and Treatment Outcomes of Perineural Spread of Malignancy within the Head and Neck” in this issue). Multiple specific ophthalmic signs and symptoms are discussed in this article.

Ophthalmic Symptoms of Perineural Spread

Initial symptoms of perineural spread typically involve pain¹⁶ and numbness in and around the eye and the face,¹⁷ and the secondary loss of trigeminal function. When this involves the first division of the trigeminal nerve, normal corneal function is disrupted (indicating nasociliary involvement). Complete loss of corneal sensation often leads to neurotrophic changes including surface problems, dry eye, and corneal opacity resulting in loss of vision. Direct extension into the orbit can produce proptosis, dystopia, and secondary injection (especially if the trigeminal nerve is involved). Orbital apex involvement can result in optic nerve dysfunction producing decreased vision, visual field defects, and evidence of

Fig. 1 A 79-year-old man was referred for double vision in April 2003. Visual acuity was 20/20 and 20/80, but he had evidence of essentially complete ophthalmoplegia and marked decreased sensation over V1 and V2. MRI scan showed involvement of the cavernous sinus. In retrospect, the patient recalled having a red spot on his left temple 2 years earlier and a 6-month history of progressive numbness involving his left face followed 2 months later by pain involving his left face. He had a substantial work-up by dental surgery and neurology that diagnosed trigeminal neuralgia. He was treated with radiation therapy.

Fig. 2 A 48-year-old man was referred with a 7-month history of numbness involving his right cheek and 2 months of double vision. He had 6 mm of proptosis on the right side and decreased sensation over V2. His MRI scan clearly demonstrates a mass in the orbital apex extending from the pterygomaxillary area (A). Open biopsy showed evidence of adenoid cystic carcinoma (B), and he was treated with radiation therapy. A temporary tarsorrhaphy was used to resolve diplopia.

pupillary abnormalities. Other secondary signs include optic atrophy and optical coherence tomography thinning with loss of the ganglion cell layer.

Ophthalmic numbness and secondary neurotrophic changes may occur once the tumor reaches the cavernous sinus, due to secondary involvement of the first division. Cavernous sinus involvement is often heralded by other cranial nerve palsies, including involvement of the third, fourth, or sixth cranial nerves—usually producing diplopia and movement abnormalities on examination. Secondary pupillary involvement may occur due to involvement of the third nerve, producing mydriasis, or the sympathetics in the area of the cavernous sinus, producing miosis (apparent Horner syndrome; ▶Fig. 3). In addition to symptoms

Fig. 3 A 71-year-old man was referred to the neuro-ophthalmology unit in January 2009 second p cataract surgery with a 6-year history of numbness starting in his left cheek and a 5-year history of pain around the left eye and left side of the jaw. An MRI scan done in February 2008 was read as negative and told that it might be trigeminal neuralgia. Two months prior to referral, he started having problems with horizontal double vision. Although the patient had multiple lesions removed from his skin, he had never had any facial lesions. On examination, visual acuity was correctable to 20/30 and 20/50, and 3pt and 5pt. He did have significant decrease in sensation over V1, V2, and V3 on the left side, which was worse over V3. Motility revealed a definite left abduction deficit with an esodeviation increasing on left gaze (A). Pupils were 4.5 mm OD (oculus dexter) and 3.5 mm OS (oculus sinister) the anisocoria increased in the dark, and the left pupil dilated following iodine (B). An MRI scan demonstrated enhancing soft tissue in the left pterygopalatine fossa extending along the maxillary division of the trigeminal nerve with a widened left foramen rotundum and some extension into the vidian canal (C, D).

Fig. 4 A 60-year-old man presented with a 6-month history of tingling involving his right face and numbness, plus a 1-month history of noting decreased tearing on the right and a 3-day history of double vision. His CT scan was read as showing sinusitis (missing the cavernous sinus involvement) (A) and he had been treated on the outside with antibiotics. MRI confirmed evidence of involvement of the right cavernous sinus (B) and a transantral biopsy showed evidence of squamous cell carcinoma (C). In retrospect, the patient recalled having a lesion removed from his face 3 years earlier. Review of the pathology poorly differentiated acantholytic squamous cell carcinoma. Although the patient had some initial improvement following radiation therapy, he subsequently progressed. In spite of the radiation, he developed a mass within the orbit and neurotrophic keratitis with a melt inferiorly treated with a tarsorrhaphy (D).

produced by direct involvement of perineural spread, treatment often results in ophthalmic complications.

When the seventh nerve is affected by perineural spread, decreased blink frequency often leads to surface problems. The combination of a fifth and seventh nerve palsy is particularly severe, often resulting in corneal epithelial breakdown followed by possible infection or even corneal melt resulting in ocular perforation (► Fig. 4).

Much less commonly, decreased vision may be due to involvement in the orbital apex resulting in optic nerve pathology. This can be separated from surface abnormalities by the presence of an afferent pupillary defect (indicating asymmetric optic nerve function) or visual field changes showing focal abnormalities including central scotomas or arcuate visual field changes.

External symptomatology including redness, and chemosis can occur due to problems with blink (when the facial nerve is involved) or neurotrophic changes (when the trigeminal nerve is involved). A combination of both trigeminal and facial nerve involvement has the most dire consequences.

Less commonly, tumor spreading to the orbit may enlarge enough to displace the globe, producing dystopia or proptosis (► Fig. 8). Most complaints of double vision when related to perineural spread indicate extension to involve the cavernous sinus and to varying degrees the third, fourth, and sixth cranial nerves. Diagnosis of cranial nerve palsies in patients with perineural spread can be difficult since they are often not complete and more than one cranial nerve is involved, making pattern recognition difficult. Other symptoms include ptosis, usually associated with third nerve involvement.

When perineural spread is considered, patients need to be questioned about symptoms of visual loss and visual field defects as well as facial pain and numbness. Old records of previous ophthalmic evaluations are critical to establishing a timeline and excluding preexisting conditions.

Ophthalmic Signs

Similar to the common ophthalmic complaints of pain, numbness, decreased vision, and double vision, evidence of ophthalmic involvement includes sensory loss (usually

related to involvement of the ophthalmic division of the trigeminal nerve), decreased acuity, and visual field defects. Since the optic nerve is much less frequently involved, most patients will not demonstrate an afferent pupillary defect unless there is apex compression. While visual field changes may include diffuse depression indicating surface problems, the finding of focal abnormalities such as central scotomas and arcuate defect would be less common (possibly suggesting other pathology). Abnormalities in eye movements can theoretically be related to direct involvement of the orbit (even less commonly direct involvement of the extraocular muscles), but are much more commonly related to involvement of the third, fourth, or sixth cranial nerves in the area of the cavernous sinus or orbital apex. In the setting of painful ophthalmoplegia, cavernous sinus involvement may be mistaken for Tolosa-Hunt syndrome.¹⁸

Ophthalmic Evaluation in a Patient with Suspected Perineural Spread

Recognition of cranial nerve abnormalities is critical in a patient with suspected perineural spread. Acuity measurements and visual fields are an essential part of every ophthalmic evaluation. An additional critical feature is the assessment for a subtle afferent pupillary defect that would indicate asymmetric optic nerve pathology. More importantly, assessment of the efferent system includes evaluation of ductions (movements of each eye separately). This can usually be seen grossly on examination, but may be quantitated using a Goldmann perimeter. Versions, or movements of the two eyes together, may be subtly affected when there is mild involvement of the ocular motor or abducens nerve and less commonly trochlear. A Maddox rod is particularly helpful here,^{19,20} as it will show subtle abnormalities in motility that may not be obvious with direct examination. Versions may be quantitated by the use of a Hess¹¹ or Lancaster screen and may be particularly useful in following patients for progression or response to treatment.

Adnexal evaluation is also important in these patients. Since most tumors affect the trigeminal nerve, careful assessment for sensory changes, particular in the cornea, is critical. This may be done grossly using a cotton wisp or quantitatively using an esthesiometer. Quantitative assessment could also be performed for evidence of globe position abnormalities, including measuring dystopia or proptosis through the use of a Hertel ophthalmometer. Measurement of tear production (Schirmer strips) or tear abnormality (osmolarity) may indicate pathology affecting the parasympathetic innervation to the lacrimal gland (most commonly in the pterygomaxillary area).

Ophthalmic Considerations and Diagnosis

The ophthalmologist can also diagnose by recognizing the spread of these tumors.²¹ As discussed in other articles, imaging²²⁻²⁵ is critical, especially with magnetic resonance imaging (MRI) (see article "The Imaging of Large Nerve Perineural Spread" in this issue). In particular, loss of the normal fat signal around branches of the trigeminal nerve can

be extremely useful (►Fig. 5) and is best recognized comparing images both with and without fat suppression. Cranial nerves themselves often enhance with gadolinium, and the bony canals transmitting the cranial nerves may be enlarged.²⁶ Needless to say, the most important issue in terms of imaging is to alert the radiologist about the suspicion of perineural spread and cranial nerve involvement. Often, MRI scans that have been read as negative clearly demonstrate extension of tumor (►Fig. 6) on review.

In addition to direct imaging, the involved nerves may be biopsied and may result in a definitive diagnosis²⁷ (see article "Pathology of Perineural Spread" in this issue). Obvious masses, such as those in the orbit, may be definitively identified by fine needle aspiration (►Fig. 7). The frontal nerve²⁷ and its distal branches, the supraorbital²⁸ and supra-trochlear, may be biopsied with a mini-anterior orbitotomy (often through a lid crease incision). The infraorbital nerve can be approached transantrally (►Fig. 6) or even more easily through a cul de sac incision in the floor of the orbit. Since these nerves are usually already substantially involved, the biopsy will not add to morbidity. Once the cavernous sinus is involved, it is theoretically possible to obtain evidence via a fine needle aspiration through the superior orbital fissure or the foramen ovale²⁹ when there is extension to the posterior aspect of the cavernous sinus (►Fig. 8). This may be particularly helpful in lymphoproliferative disorders.

Ophthalmic Therapeutic Concerns

With involvement of the facial nerve and failure of lid closure, short-term improvement may be obtained with a temporary tarsorrhaphy. This may be extended to a period of weeks by placing the sutures through bolsters. It is also possible to make this last longer by tarsal approximation (made more permanent by tarsal two-layer closure) (►Fig. 7). This can easily be reversed if necessary.

Complete fifth nerve involvement often leads to neurotrophic corneal changes, resulting in nonhealing epithelial defects, corneal infection, ulcer, abscess, and even perforation. This may be made less likely with tarsorrhaphy. In a one-eyed patient, narrowing of the palpebral fissure with a partial lateral tarsorrhaphy may be helpful. The use of autologous serum can also be beneficial³⁰ in treating neurotrophic changes. Artificial tears may be helpful if there is an additional component of drying (occasionally seen with lacrimal gland involvement), but is usually far less effective than autologous serum.

Definite treatment should involve an ophthalmologist.³¹ So-called stage 1 tumors that have not extended beyond the orbit can be excised (potentially endoscopically³²), but as these tumors often involve small nerves, this may not always be successful. Exenteration has been advocated for treatment in the past,^{33,34} although there is fairly good evidence that this does not prevent systemic spread in adenoid cystic carcinoma. Even with exenteration, evidence of perineural involvement has a worse prognosis.³⁵

In most cases, radiation therapy will become an essential part of treatment once perineural spread has reached the cavernous

Fig. 5 In 1996, a 43-year-old man had noticed problems opening his mouth and numbness involving his left upper lip. Biopsy demonstrated adenoid cystic carcinoma originating in the left soft palate. He underwent craniofacial resection followed by radiation therapy. In November 1997, he developed evidence of metastatic lesion in the left lung, which was excised followed by additional radiation therapy. In 2005, he underwent a left radical neck dissection after fine needle biopsy showed recurrence of adenoid cystic carcinoma. Two and a half years prior to referral, he began to develop some numbness involving V2 and V3 on the left side. In 2012, visual acuity was 20/40 and 20/25 and 4pt at near with nonspecific visual field changes. There was absence of sensation over V2 and V3 on the left side and moderate decrease over V1, and 10 diopters of esodeviation increasing on left gaze. He was treated initially with prism glasses. When motility appeared stable, he was straightened with a medial rectus recession and Faden procedure on the opposite eye. In spite of this, the esotropia increased to 25 diopters and by October 2013 (10 months after original referral) he had lost all abduction on the left side (A). Because of a combination of trigeminal loss of sensation and VII nerve dysfunction with lagophthalmos, a tarsorrhaphy was done to protect the left eye. Imaging studies were particularly revealing, showing loss of the normal fat signal at the petrous apex (B, C) with subsequent enhancement with gadolinium (D, E). In spite of evidence of continued slowed growth, 20 years after original presentation, the patient is still functionally productive.

sinus, pontine brain stem (—Fig. 9), or other parts of the skull base. This radiation may have potential deleterious effects on visual function. The pericytes lining the vessels in the retina are particularly sensitive to radiation, although evidence of damage to the retina may not appear for months or years following radiation. Patients often present with decreased central vision, evidence of central scotoma, microvascular changes seen on funduscopic examination, and evidence of microinfarcts includ-

ing cotton wool spots and perfusion abnormalities seen on fluorescein angiography. Moderately high doses of radiation therapy will often cause radiation retinopathy if the posterior aspect of the globe is included or even radiation optic neuropathy, which may occur anywhere along the course of the optic nerve through the chiasm. These complications are particularly true if more than 50 Gy are administered and even more likely in diabetic and vascular patients.

Fig. 6 A 63-year-old man was referred for a 13-month history of progressive left facial numbness and 2 months of double vision (A). His history began 15 months earlier when during dental work he was noted to have a left cheek lesion, which on punch biopsy showed squamous cell carcinoma. Subsequent Mohs surgery, however, showed negative pathology. He then proceeded to have progressive numbness over the next 13 months and had four MRI scans that were read as negative and was treated for “atypical facial pain.” Review of his last MRI scan, however, showed clear involvement of the second division of the trigeminal nerve (B) and transcranial biopsy showed squamous cell carcinoma (C).

While posterior segment pathology (radiation retinopathy or optic neuropathy) is usually seen only with high-dose treatment, even relatively low doses of radiation therapy will cause abnormalities in the goblet cells, resulting in abnormal wetting and corneal surface problems. It is also possible to have decreased tear production from involvement of the parasympathetic innervation to the lacrimal gland when the sphenopalatine ganglion or the vidian nerve is involved. Radiation will also accelerate

Fig. 7 A 78-year-old man was referred for “an eye infection” and seventh nerve palsy (A). He had a history of multiple skin cancers removed from his left brow and forehead. He seems to recall being told that the pathology was a basal cell. One year ago, he developed facial droop on the left side and was told he had Bell palsy. Following excision of a temporal lesion, the eye became significantly red. On examination, visual acuity was 20/30 OD (oculus dexter) and light perception OS (oculus sinister) but without an afferent pupillary defect. There was mild limitation in depression OS. He did have evidence of macular degeneration causing a relative central scotoma on the right and had marked decrease sensation over V2 on the left. Review of his MRI showed atrophy of the muscles innervated by V3 (B). Because of severe exposure problems, he was treated with a tarsorrhaphy and radiation therapy. He did develop crusting related to the radiation, but the tarsorrhaphy protected the cornea (C).

cataract formation, although this can be treated with extraction.

Treatment of Complications of Therapy

In exacerbations of surface disorders, whether due to lid position abnormalities preventing closure, facial nerve palsies decreasing blink frequency, or sensory changes resulting in neurotrophic problems, intervention may improve the situation. This includes the use of temporary or even permanent tarsorrhaphy. Lubrication may play a role, as may autologous serum. Sensory changes and lagophthalmos require much more attention than simply closing the lid. Lens pathology may respond to cataract surgery, although it is imperative not to neglect the surface. Corneal limbal stem cells may be transplanted from the opposite eye in

Fig. 8 This 57-year-old patient was referred for lid retraction. His medical history was remarkable for an account of “aneurysm” presenting with a VII nerve palsy, hypertension, and cigarette abuse. Fifteen months earlier, he bit his tongue in which he presumed with secondary to VII nerve palsy, but subsequent evaluation revealed a squamous cell cancer treated with radical neck dissection and radiation therapy. His post-op course was complicated by cryptococcal meningitis; 1 month before he was referred, he developed redness involving his left eye followed by double vision. He was referred for a possible “lid tuck.” When evaluated, his visual acuity was 20/30 and 2/200. He had lower-lid retraction with 3+ inferior injection on the left side (A), and marked decreased sensation over V1-3 on the left. He had 6 mm of proptosis with resistance to retropulsion. He had almost complete ophthalmoplegia on the left with only minimal residual depression. A CT scan showed a mass involving the peripharyngeal space extending through the floor of the medial cranial fossa (B, C). He underwent a fine-needle aspiration biopsy that showed evidence of squamous cell carcinoma (D) and was treated with a tarsorrhaphy for globe protection.

the case of unilateral loss. Bilateral involvement becomes much more problematic. Donor stem cells may be transplanted but require systemic therapy to prevent rejection. There are unfortunately no good options for treating radiation optic neuropathy, although some have experimented with hyperbaric oxygen and Trental. Neovascular complications of radiation retinopathy can possibly be treated with the use of anti-vascular endothelial growth factor agents³⁶ and even laser photocoagulation. The loss of capillary perfusion at this point, however, remains untreatable.

Case Series

We reviewed 23 patients evaluated and treated at the University of Virginia Neuro-Ophthalmology clinic from 1994 to 2012 with orbital complications of perineural spread. Included in our series were patients diagnosed with perineural spread involving extension into the orbit confirmed by pathological analysis and/or diagnosed on the basis of history, clinical exam, and imaging. Similar to previous series, the primary malignancies consisted of squamous cell carcinoma (39%), adenoid cystic carcinoma (39%), melanoma (13%), and undefined malignancy (8%). All patients referred developed some form of orbital complication involving function of the afferent or efferent visual systems. Trigeminal nerve involvement with sensory changes was found in 16 patients (69%), while atypical facial pain was encountered in 3 patients (13%). Corneal problems as a result

of exposure or sensory loss occurred in seven patients (30% of all cases, 43% of those with trigeminal nerve involvement). All patients with corneal exposure problems required treatment with topical lubricants or tarsorrhaphy. Ocular motility disturbances producing diplopia were also common (60%), with the abducens and oculomotor nerves most often affected. Three patients developed complete ophthalmoplegia with ptosis. Seventy-three percent of patients received treatment: with surgery alone (4), radiation alone (3), or both (10). Of the 13 patients who were treated with radiation, 4 developed cataracts as a result of radiation treatment, leading to decreased visual acuity, although no other ocular complications of radiation were encountered in this series. Eyelid malposition (retraction and cicatricial ectropion as a result of surgical therapy) occurred in three patients. Orbital apex and/or cavernous sinus involvement was present in 11 cases overall (5 out of 9 of squamous cell cases). Extension beyond the cavernous sinus to the brainstem was fortunately uncommon (—Fig. 9).

Future Horizons

Surgery will continue to play an important role in diagnosis (often directed by imaging). At this time, no specific chemotherapeutic regimens exist for most of these tumors, but understanding the biologies of perineural spread may allow us to design specific therapies to prevent this type of spread in the future. Stereotactic fractionated radiation therapy

Fig. 9 A 77-year-old man presented with a 2-year history of left facial numbness followed by a 1-year history of left lid droop and 4 months of right-sided weakness. On examination, visual acuity was 20/25 and 20/60 but he had ophthalmoplegia on the left side (A) and numbness involving V1 and V2. MRI scan showed involvement of the cavernous sinus and extension into the pontine brainstem (B, C). Transantral biopsy of the infraorbital nerve showed evidence of squamous cell carcinoma (D), and he was treated with radiation therapy.

can deliver more treatment to the tumor and less to surrounding tissues, but it is still limited by our ability to define the extent of involvement. Proton beam and other forms of fractionated radiation therapy may also play a role,^{37,38} with some suggesting that adenoid cystic carcinoma is particularly sensitive to proton therapy.³⁹ As Harvey Cushing pointed out in 1912 in discussing pituitary tumors, it is likely that surgery will come to play a less, not more important, role in future management of these extremely difficult clinical problems.

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