Letter to the Editor

Unusual Presentation of a Squamous Cell Carcinoma

To the Editor:

A 57-year-old man presented with right-sided ptosis, ipsilateral headache, and facial pain of 2 months' duration. Symptoms began as numbness and tingling across the right side of the forehead; pain and pruritus later developed. These sensations subsequently involved his eye socket and he started to feel throbbing pain in the retro-orbital region. The patient noticed gradual loss of lateral motion of the right eye, which progressed to complete loss of extraocular muscle movement in all directions as well as ptosis. Subsequently he developed difficulty focusing on objects and described loss of visual acuity in the right eye. His physical examination at presentation was notable for a frank right eye photophobia with a reduced visual acuity of 20/40 OD versus 20/20 OS. There was complete ptosis and complete loss of extraocular muscle movement in the right eye. In addition, there was a sluggish direct pupillary response and loss of corneal sensations in this eye. Sensory losses were evident overlying the right side of the forehead as well as the right upper and lower eyelids. The remainder of the neurologic examination revealed no abnormalities.

The patient's medical history was remarkable for AIDS treated with a 3-drug highly active antiretroviral therapy regimen. His CD4 lymphocyte count on presentation was 121/mm^3 (reference range, 800–1050/mm^3 and human immunodeficiency virus copies were absent by serum polymerase chain reaction analysis. He had been treated for non-Hodgkin lymphoma and myelodysplastic syndrome using rituximab 3 years prior to this presentation and his disease was deemed to be in remission since then. Additionally he had a history of chronic deep vein thrombosis and an episode of remote pulmonary embolism requiring placement of an inferior venocaval filter and long-term warfarin sodium therapy. Most notably, he described a history of recurrent squamous cell carcinoma (SCC) involving his forehead. The carcinoma was originally excised 4 years prior to presentation but was recurrent and was re-excised 1 year later. Physical examination of his forehead demonstrated a local recurrence (measuring 4×3×2 mm). Furthermore, the patient vividly described casual work-related contact with a coworker diagnosed with herpes zoster; the patient subsequently developed blisterlike lesions on the right side of the scalp. The scalp lesions apparently resolved with valacyclovir hydrochloride prescribed by his local physician prior to presenting at the Cleveland Clinic, Cleveland, Ohio.

The patient was admitted and underwent extensive investigations to determine the etiology of his illness. Initial testing included lumbar puncture, which was negative for several infectious etiologies including herpes simplex virus, Epstein-Barr virus, syphilis, West Nile virus, Lyme disease, *Cryptococcus neoformans*, and other fungal causes. Magnetic resonance imaging (MRI) of the orbits demonstrated an enhancing soft tissue mass at the apex of the right orbit encompassing the right optic nerve and measuring 1.7×0.9 cm in the axial plane and 1.3 cm cephalocaudal (Figure 1). The mass extended through the superior orbital fissure and involved the right cavernous sinus. In addition, there was fusiform enlargement and enhancement of the right superior oblique muscle. Surgical biopsy of the lesion was accomplished using a transcaruncular approach through a small right orbitotomy. Pathologic review of the biopsy specimen demonstrated invasive, poorly differentiated SCC involving soft tissues of the orbit. There was evidence of perineural invasion demonstrable in the resected specimen (Figure 2).

This presentation was undoubtedly metastatic SCC of the skin extending to the right orbital apex. There was no other radiographic evidence of disease spread. The cavernous sinus involvement in this patient precluded any attempt at surgical resection. He was subsequently referred for a course of definitive radiation therapy and concurrent chemotherapy with the hope that local control could be achieved.

Orbital cancers may occur via direct spread, vascular or lymphatic spread, or perineural spread (PNS) from head and neck cancers. Orbital metastases most commonly occur because of SCC in addition to other rare etiologies, namely basal cell carcinomas, adnexal carcinomas, and melanomas. This cancer has almost always been described in association with skin cancer involving the face or scalp; in some instances, the patient is unaware of its presence in these areas.[1] Our patient presented a perplexing case scenario with

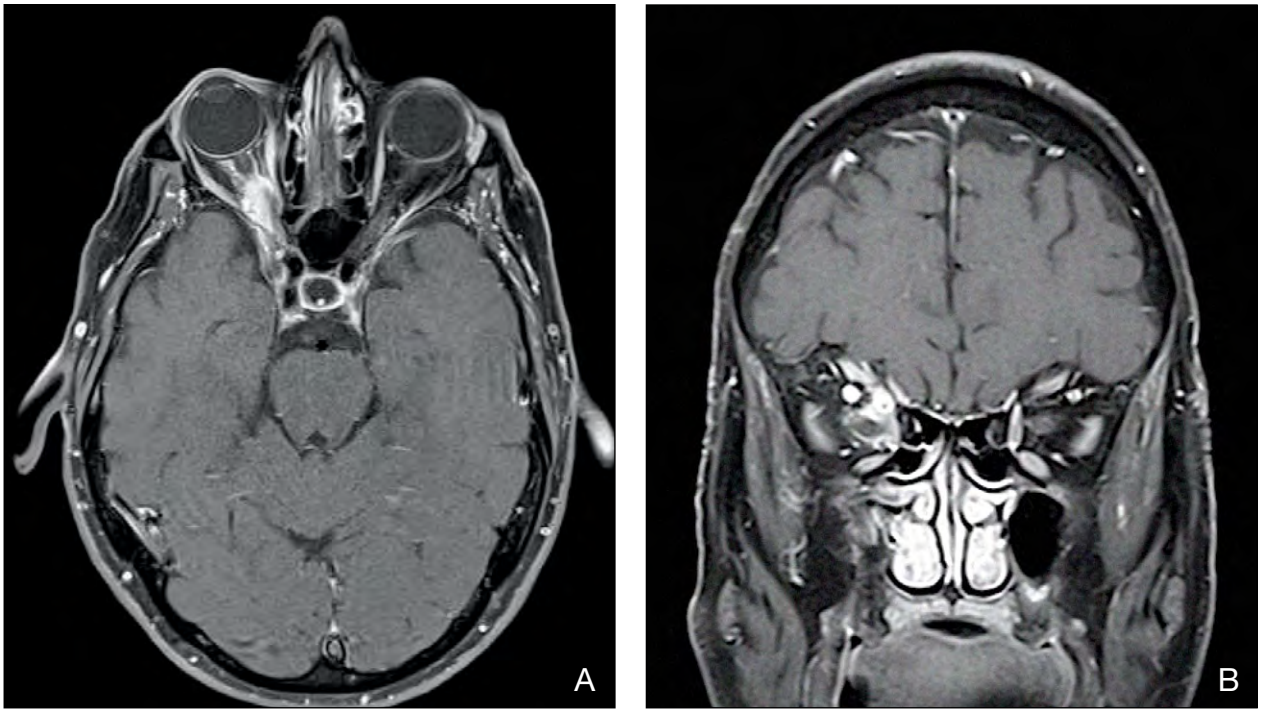

Figure 1. T1-weighted magnetic resonance imaging of the orbits (axial view) demonstrated an avidly enhancing mass at the right orbital apex with extension into the right cavernous sinus (A). The coronal view demonstrated the presence of an enhancing mass present in the right retrobulbar space (B). There was evidence of involvement of the right superior oblique muscle and right orbital nerve as indicated by hyperintense signals in these locations.

a medical history of both lymphoma and SCC; the etiology of both likely causes orbital masses. His human immunodeficiency virus status raised the concern for other opportunistic infections or conditions.

This case is a classic presentation of orbital tumors beginning as paresthesia and pain in the V1 (ophthalmic) distribution of the trigeminal nerve and progressing to profound ptosis and ophthalmoplegia. The terminal ophthalmologic symptoms in our patient were indicative of involvement of several nerve roots simultaneously from disease at the orbital apex and cavernous sinus. This constellation of symptoms has been referred to as orbital apex syndrome or superior orbital fissure syndrome.[1]

The diagnosis of an orbital tumor is evident with clinical presentation of the patient. Perineural spread was suspected in our patient because of involvement of multiple contiguous nerve roots prior to biopsy findings. Nerve cell adhesion molecules have been shown to play a key role in PNS of SCC arising in the head and neck regions.[2,3] Spread between contiguous branches of trigeminal or facial nerves leading to multiple cranial neuropathies, as well as involvement of supraorbital, supratrochlear, and infraorbital nerves leading to rapid progression of the tumor, has been vividly described in the literature.[4] Simultaneous involvement of multiple nerve roots allows spread through the superior or inferior orbital fissures into the cavernous sinus where the third, fourth, fifth, and sixth cranial nerves along with the sympathetic fibers are closely related to each other.

The detection of PNS caused by SCC often may be difficult, especially in the early stages of disease. Computed tomography and MRI often are unable to pick up early disease and may only help with macroscopic disease. Magnetic resonance imaging has been considered the imaging modality of choice, as it possesses multiplanar capabilities and helps in accurate soft tissue delineation. The sensitivity of MRI for detection of PNS in orbital tumors is 95%[5] with typical findings such as nerve enlargement or enhancement, foraminal enlargement or destruction, obliteration of fat planes, and convexity of the lateral cavernous sinus wall.[1] Computed tomography complements MRI by clearly defining the foramina of the skull base to help delineate the extent of the tumor.[1,4] Obtaining tissue diagnosis remains a challenge primarily because of the location of the tumor. Despite this difficulty and requirement of full-fledged orbital surgery for biopsy, this step is of utmost importance, as therapy for SCC often is associated with substantial morbidity.

There is no standard treatment of orbital SCC with PNS. With early presentation, curative intent

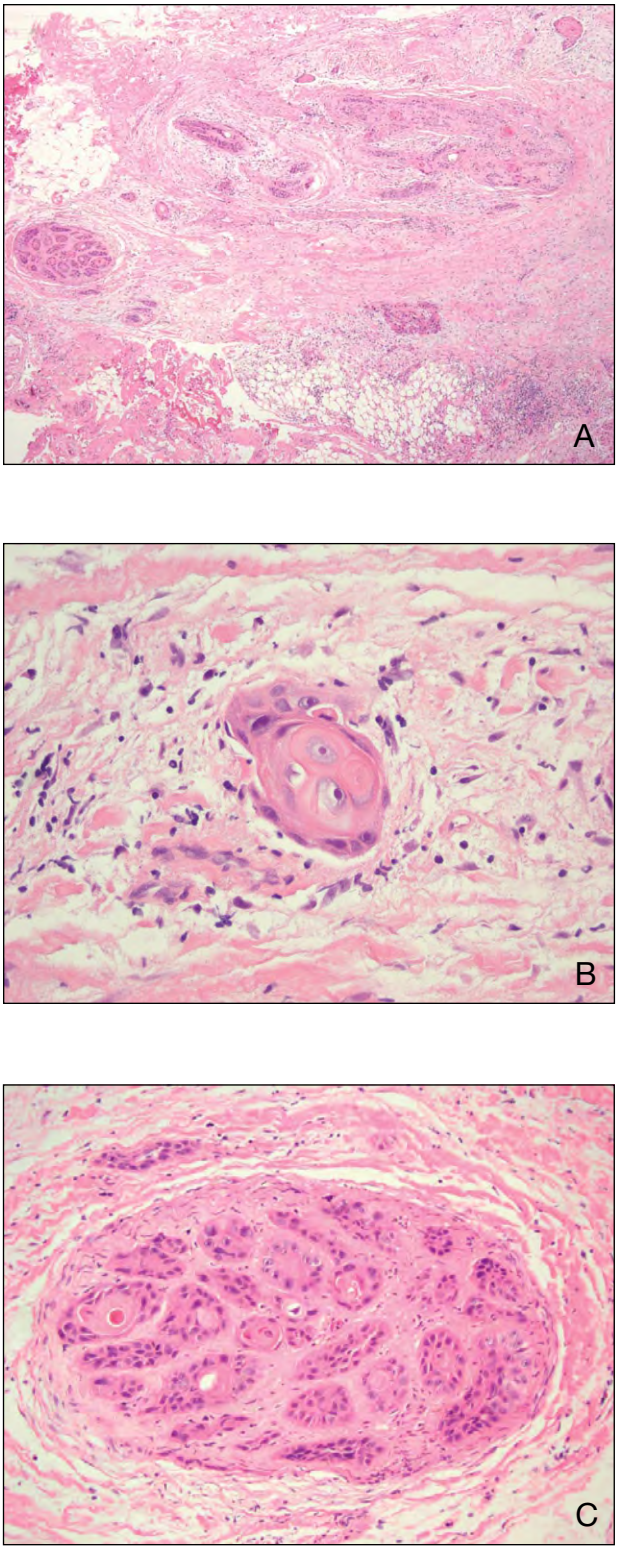

Figure 2. Fibroadipose tissue and nerves involved in invasive squamous cell carcinoma (A)(H&E, original magnification ×40). Large, polygonal, keratinized cells consistent with squamous differentiation (B)(H&E, original magnification ×400). Segment of nerve invaded by squamous cell carcinoma (C)(H&E, original magnification ×200).

may be presumed; however, with advanced disease, the primary objective is tumor burden reduction and growth restraint to palliate symptoms. Surgical treatment is precluded by cavernous sinus involvement. Radiotherapy has been shown to have a possible role in palliation of pain-related symptoms. Treatment using radiation has been limited by lack of definition of target volume for radiation to the orbital area. Target volumes ought to include any skin lesions; neural pathways within the orbit; the cavernous sinus; and, in some instances, the middle cranial fossa and brain stem. Substantial treatment-related mortality including soft tissue necrosis, bone exposure, radiation-induced encephalopathy, and irreversible loss of vision have been described.[6] Synchronous chemoradiation has been described with good results, especially in aggressive tumors and large tumor burden.[7,8] Despite aggressive treatment, this disease portends a poor prognosis. The mortality rate in patients with PNS from a cutaneous SCC has been reported to be 62% by 3 years of follow-up after diagnosis.[9]

Sincerely,
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The authors report no conflict of interest.

REFERENCES

1. Veness MJ, Biankin S. Perineural spread leading to orbital invasion from skin cancer. *Australas Radiol*. 2000;44:296-302.
2. McLaughlin RB Jr, Montone KT, Wall SJ, et al. Nerve cell adhesion molecule expression in squamous cell carcinoma of the head and neck: a predictor of propensity toward perineural spread. *Laryngoscope*. 1999;109:821-826.
3. Vural E, Hutcheson J, Korourian S, et al. 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.
4. Bowyer JD, Sullivan TJ, Whitehead KJ, et al. The management of perineural spread of squamous cell carcinoma to the ocular adnexae. *Ophthal Plast Reconstr Surg*. 2003;19:275-281.
5. Nemzek WR, Hecht S, Gandour-Edwards R, et al. Perineural spread of head and neck tumors: how accurate is MR imaging? *AJNR Am J Neuroradiol*. 1998;19:701-706.
6. Mendenhall WM, Parsons JT, Mendenhall NP, et al. Carcinoma of the skin of the head and neck with perineural invasion. *Head Neck*. 1989;11:301-308.

7. Munro AJ. An overview of randomised controlled trials of adjuvant chemotherapy in head and neck cancer. *Br J Cancer*. 1995;71:83-91.
8. Adelstein DJ, Saxton JP, Lavertu P, et al. Maximizing local control and organ preservation in stage IV squamous cell head and neck cancer with hyperfractionated radiation and concurrent chemotherapy. *J Clin Oncol*. 2002;20:1405-1410.
9. McNab AA, Francis IC, Benger R, et al. Perineural spread of cutaneous squamous cell carcinoma via the orbit. clinical features and outcome in 21 cases. *Ophthalmology*. 1997;104:1457-1462.