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OCULAR ONCOLOGY

Choroidal Malignant Melanoma

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Melanoma-associated mortality: *Singh et al* — mortality did not change with increased use of radiation therapy (RT) and decreased use of enucleation between 1973 and 1997

Treatment of small tumors: Collaborative Ocular Melanoma Study (COMS) Small Tumor Observational Trial documented features predictive of growth in small tumors; *editorial by Murray et al* — made case for observational management of small suspected melanomas; *editorial by Shields* — argued for treating some small melanocytic lesions without waiting for growth; *ongoing debate* — which small tumors represent nevi and which represent small melanomas that should be treated to prevent melanoma-associated mortality; improvement in survival seen in cutaneous melanoma used as argument for treating earlier lesions

COMS Small Tumor Observational Trial: 204 patients; thickness of lesions 1 to 3 mm; largest basal diameter 5 to 16 mm; growth rate at 5 yr 31%; melanoma-specific mortality 1%; *features predictive of growth* — large tumor size; presence of orange pigment; absence of drusen or changes in retinal pigment epithelium

Case for observational management: ≥10% of population demonstrates small pigmented choroidal lesions; few represent melanomas (most nevi); mortality rate for small melanomas low; excision difficult and morbid; fine needle aspiration biopsy (FNAB) may not sample wide variation within lesions observed histopathologically; definitive therapy causes compromise of vision and globe in some patients; *University of Miami study* — 45 of 154 patients (30%) with high-risk suspected small melanoma required treatment; 0 patients in observation group and 2 patients in treatment group developed metastases

Treatment for some small lesions: *Wills Eye Institute series* — 1329 tumors ≤3 mm; 18% had documented growth; 3% developed metastases; *risk factors* — greater thickness; visual symptoms; proximity to optic disk; documented growth; *proposal* — chance for metastasis 5% with one risk factor, 10% with 2 risk factors, 15% with 3 risk factors, and 20% with 4 risk factors; treatment recommended for patients with ≥2 risk factors

Diode laser: explored due to lower morbidity, but found to be associated with development of extraocular extension (not recommended as single-modality treatment)

Diagnostic issues: *Harbour et al* — gene expression profiling in uveal melanoma reveals 2 molecular classes that predict metastatic death; however, concern raised by rare occurrence of seeding at site of FNAB (speaker does not biopsy for prognosis only); *Callejo et al (2006)* — isolated circulating malignant cells (avoids intraocular procedures)

Early genetic events: previous insights limited to late genetic alterations (*eg*, monosomy 3, 8p gain, class 1-2 expression profiles); recently, mutations in signaling protein guanine nucleotide-binding protein (G protein) q polypeptide (*GNAQ*) identified as early or initiating event in uveal melanoma; points to pathogenic mechanism common to cutaneous melanoma

Mitogen-activated protein kinase (MAPK) pathway: growth signaling pathway; driver of disease when activated constitutively (as in cutaneous melanoma); activated in ≤100% of cutaneous melanomas (by *RAS* mutation in 15%; by *RAF* mutation in 65%); activated in 86% to 100% of uveal melanomas, but *RAS* and *RAF* mutations absent

***GNAQ* mutations:** found in 46% of uveal melanomas; target codon 209 in *RAS*-like domain and convert *GNAQ* into dominant-acting oncogene; mutant *GNAQ* transformed human melanocytes (became irregular and anchorage-independent [sign of malignancy]); transformed melanocytes in nude mice (induced growth of tumors similar to uveal melanoma); in normal melanocytes, activated MAPK pathway; interfering RNA knockdown of cells harboring this mutation resulted in decreased levels of ERK; *GNAQ* mutations identified in 83% of blue nevi; suggests that *GNAQ* mutation is early or initiating event in uveal melanoma; not associated with any clinical, histopathologic, or molecular features of late progression of uveal melanoma; provides rational drug target in ≤100% of patients

***GNA11* mutations:** found in blue nevi (7%), primary uveal melanoma (32%), and uveal melanoma metastases (57%); 83% of uveal melanomas have somatic mutations in novel oncogenes *GNAQ* or *GNA11*; functional similarities between *GNAQ* and *GNA11* provide basis for developing mechanism-based therapies; MAPK/ERK kinase (MEK) inhibitors under investigation; prolongation of life seen with MEK inhibitors (unreported), but resistance to small molecule therapies develops rapidly

***BRCA*-associated protein 1 (BAP1):** inactivating somatic mutations identified in gene encoding BAP1; identified in 84% of metastasizing uveal melanomas; variety of mutations found; one mutation in germline (predisposes patients to uveal melanoma, cutaneous melanoma, adenocarcinoma of lung, meningioma, and other cancers); BAP1 pathway possible therapeutic target

Poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors: BAP1 can cause inactivation of constitutively active BAP1 pathway; drugs that inhibit PARP cause multiple double strand breaks to form; in tumors with *BRCA1* and *BRCA2* mutations, these strand breaks cannot be repaired; therefore, PARP inhibitor possible option for BAP1 mutation

Question and answer: *treatment for systemic metastases from choroidal melanoma* — currently enrolling patients in MEK inhibitor trials

Educational Objectives

The goal of this program is to improve the management of choroidal malignant melanomas, retinoblastomas, periocular tumors, and optic nerve gliomas. After hearing and assimilating this program, the clinician will be better able to:

1. Recognize risk factors for growth of small uveal melanomas.
2. Consider poly(adenosine diphosphate-ribose) polymerase inhibitors as a possible treatment option for patients with uveal melanoma.
3. Provide appropriate therapy for retinoblastoma according to the International Classification of Retinoblastoma.
4. Treat periocular tumors with topical chemotherapy.
5. Diagnose and treat optic nerve gliomas.

Faculty Disclosure

In adherence to ACCME Standards for Commercial Support, Audio-Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, the faculty and planning committee reported nothing to disclose. In his lecture, Dr. Patel presents information that is related to the off-label or investigational use of a therapy, product, or device.

Management of Retinoblastoma

Dr. O'Brien

Retinoblastoma: *traditional teaching* — results from mutation of both alleles of retinoblastoma (*RB*) gene; nonheritable form accounts for ≈60% of cases, heritable, ≈40%; *germline mutation* — occurs at single-cell stage; every cell contains mutation; inheritance ≈50%; results in bilateral multifocal tumors; *somatic mutation* — single retinal cell develops mutation; no inheritance; only 15% of children with germline mutations have unilateral disease; many children present asymmetrically; *mosaic mutation* — one cell develops mutation during development; cells derived from that cell carry *RB* mutation; inheritance based on percentage of mutation in gametes (appears somatic if not in gametes)

RB protein: functions as inhibitor of cellular proliferation; controlled by phosphorylation; member of pocket protein family (with p107 and p130); functions of RB protein occur in pocket protein region

Genetic testing: knowledge of mutation would identify *RB1* carriers and at-risk siblings, allow genetic counseling, and provide information on disease severity associated with particular mutations; *RB1* — large gene; no known hot spots for focused analysis, so all exons and adjacent introns must be sequenced; difficult to design polymers due to homopolymeric tracts

Pathogenesis: "*weak allele" hypothesis (Dryja et al [1991])* — patient with late development of RB had mutation at end of pocket protein region, with preservation of residual protein function; disease less severe; speaker found family with severe disease (high penetrance and expressivity) to have mutation at beginning of pocket region

Study: goal to determine whether particular mutations in *RB1* gene assort with different clinical presentations and distinct disease courses; correlated protein effects of *RB1* gene mutation with disease severity in 75 patients; *truncating mutations* — correlated with high severity disease, but no correlation found between predicted mean protein length and disease severity; when truncating mutations grouped by number of protein domains disrupted by mutation, degree of residual protein length did not correlate with disease severity (probably due to missense-mediated message decay); *large deletions* — majority associated with high severity disease; *nontruncating mutations* — associated with low severity disease (not significant); included 7 missense mutations, 2 exon deletions, and one amino acid deletion; missense mutations correlated exclusively with low or moderate severity disease; *conservation across species* — mutations in nonconserved regions well tolerated; those highly conserved poorly tolerated and correlate with more severe disease; *other genetic alterations* — occur on chromosomes 1q and 6p

International Classification of Retinoblastoma: *group A disease* — laser treatment only; if peripheral disease present, cryoablation performed; *group B disease* — 2-agent chemotherapy (CTX; vincristine plus low-dose carboplatin) plus laser; *group C disease* — requires monitoring of white blood count and colony-stimulating factor; monitor with audiography; *group D disease* — massive seeding or complete replacement of retina; >55% respond poorly to external-beam RT; *group E disease* — per trial, at risk for extraocular spread; requires enucleation for cure; CTX may precede enucleation, but delay may allow metastasis; rule out extraocular spread if considering intra-arterial CTX

Topical Therapy for Periocular Tumors

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Treatment for skin cancer: *surgery* — simple excision; Mohs surgery; electrodesiccation; cryosurgery; *CTX* — topical or systemic; *photodynamic therapy* — approved for actinic keratosis; involves oxygen radicals to induce cytotoxicity; option for patients with large number of basal cell carcinomas (BCCs; *eg*, basal cell nevus syndrome); *RT* — high cure rate; expensive; reserved for recurrent or advanced tumors; *biologic therapy* — stimulates natural defenses; *success rates* — high with Mohs surgery and wide local excision for basal cell carcinoma; also good with RT and cryosurgery

Topical Treatment of BCC

Imiquimod (Aldara): data on use in periocular tumors limited; available in single-use packets; *mechanism of action* — binds to toll-like receptor 7; activates cascade of activity ending with upregulation of nuclear factor-κ β from cytoplasm into cell nucleus; releases proinflammatory cytokines; unknown how drug kills cancer cells; not approved for oral, ophthalmic, or intravaginal use; *recommended dosing* — 5 times/wk for 6 wk; approved for superficial BCC (behaves differently from nodular and morpheaform BCC); causes intense inflammatory response; crust forms on skin surface, which then repopulates with healthy cells; some long-term success seen

Histopathology: *case* — patient with BC nevus syndrome (superficial BCC); biopsy after 5 days of treatment showed nests of BCC within deeper dermis; mostly inflammatory infiltrate within dermis at 8 wk; no evidence of BCC (sign of resolution); *study* — nodular BCC; no BCC in superficial area of skin after treatment, but evidence of cancer seen in deep dermis; topical treatment may not penetrate deeply enough

Cure rate: *superficial BCC* — typically, 80% to 84% in dermatologic literature; *nodular BCC* — 40% to 100%; reason unclear; *squamous cell carcinoma* — data limited

5-fluorouracil (5FU; *eg*, Carac, Efudex, Fluoroplex): *mechanisms of action* — direct DNA incorporation and blockage of thymidine synthase; data on use for superficial BCC and squamous cell carcinoma limited; some studies show good clearance of superficial BCC; no good data available on use for nodular BCC

Genetic variation: impaired ability to metabolize 5FU (dihydropyrimidine dehydrogenase deficiency) increases dose; present in 8% to 10% of population

Adverse reactions: erythema; edema; weeping; pruritus; hypertrophic or hypopigmented scar; crusting reaction; significant inflammatory response when used near eye

Potential benefits of topical therapy: *cost* — not necessarily less expensive than surgery; *improved cosmesis* — some advantage; well-performed oculoplastic surgery can provide comparable result; useful for BC nevus syndrome (*ie*, dozen tumors); *cure rate* — unknown for periocular tumors; *poor surgical candidates* — may not tolerate topical therapy

Management of Optic Nerve Glioma

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Background: generally behaves like benign entity (pilocytic astrocytoma); all children with bilateral disease have neurofibromatosis (NF); NF also seen in unilateral cases; 70% of optic nerve gliomas identified by 1 yr of age (90% by second decade of life); behavior somewhat unpredictable; generally, better outcome seen with gliomas in anterior visual pathway than those in posterior pathway (behind chiasm); management based on correct diagnosis (largely radiographic), extent of tumor at time of identification, functional deficit, and behavior over time; *anatomy* — tumor displaces fascicles; may extend into arachnoidal space; no dural invasion; can produce mucin (more common in NF cases)

Diagnosis: magnetic resonance imaging (MRI) preferable; fusiform enlargement of optic nerve seen; deformity of posterior aspect of globe possible; distinguished from meningiomas of optic nerve by absence of optic nerve shadow in midst of tumor; visual loss commonly mild; profound visual loss may occur abruptly; amblyopia nonresponsive; *other signs and symptoms* — esotropia; proptosis; afferent defects; visual field abnormalities; early optic nerve swelling uncommon

Management: careful and close observation; periodic MRI; *indications for surgical intervention* — blind proptotic eye; progressive growth encroaching on intracranial space; tumor

directly prechiasmal at time of presentation (controversial); further spread requires medical management

Surgical approach: resection using transcranial approach; combined neurosurgical and orbital surgery procedure

Abrupt visual loss: may occur in cases in which gliomatous part of optic nerve posterior; anterior part normal in diameter and flexible; as tumor grows, nerve folds over, which causes precipitous loss (compressive, not infiltrative)

Case: child with poor vision; tumor in prechiasmatic location resected; tumor removed first at chiasm; optic canal opened; nerve adherent to dura/periorbita/optic nerve sheath; caution required at ophthalmic artery to avoid hemorrhage; orbit opened from above and roof removed; full length of nerve removed

Predictor of margin: *study* — MRI defined end of tumor as intraorbital in 5 cases, intracanalicular in 2, and intracranial prechiasmatic in 6 (at highest risk for disease beyond margin); 8 of 13 (62%) had normal posterior histologic margins; in 3 of 5 cases with involved margins, MRI showed tumor in orbit only; 25% to 38% of resected margins positive (tumor *vs* reactive tumor gliosis)

Case: 5-yr-old child; blind in right eye; proptotic for 2 yr; initially, MRI showed intraorbital tumor to orbital apex (not intracranial); diagnosed as optic nerve glioma; managed with observation; 1 yr later, MRI revealed more complex cystic-appearing tumor in chiasm (*ie*, documented progression); 6 mo later, no light perception in both eyes; *referred to speaker* — 12 mm proptotic; afferent pupil defect suggested potential involvement in left eye; MRI showed larger mass; treated with steroids, RT, and CTX; achieved 20/20 vision (with field cut); *MIB-1* labeling index ≤7% focally (aggressive variant)

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Suggested Reading

Factors predictive of growth and treatment of small choroidal melanoma: COMS Report No. 5. The Collaborative Ocular Melanoma Study Group. *Arch Ophthalmol* 1997;115:1537-44; **Attili SK et al:** Role of non-surgical therapies in the management of periocular basal cell carcinoma and squamous intra-epidermal carcinoma: a case series and review of the literature. *Photodermatol Photoimmunol Photomed* 2012;28:68-79; **Callejo SA et al:** Identification of circulating malignant cells and its correlation with prognostic factors and treatment in uveal melanoma. A prospective longitudinal study. *Eye (Lond)* 2007;21:752-9; **Caminal JM et al:** Epibulbar seeding at the site of a transvitreal fine-needle aspiration biopsy. *Arch Ophthalmol* 2006;124:587-9; **Garcia-Martin E et al:** Efficacy and tolerability of imiquimod 5% cream to treat periocular basal cell carcinomas. *J Ocul Pharmacol Ther* 2010;26:373-9; **Harbour JW et al:** Frequent mutation of BAP1 in metastasizing uveal melanomas. *Science* 2010;330:1410-3; **Murray TG, Sobrin L:** The case for observational management of suspected small choroidal melanoma. *Arch Ophthalmol* 2006;124:1342-4; **Onken MD et al:** Gene expression profiling in uveal melanoma reveals two molecular classes and predicts metastatic death. *Cancer Res* 2004;64:7205-9; **Sakai T et al:** Oncogenic germ-line mutations in Sp1 and ATF sites in the human retinoblastoma gene. *Nature* 1991;353:83-6; **Shields JA:** Treating some small melanocytic choroidal lesions without waiting for growth. *Arch Ophthalmol* 2006;124:1344-6; **Van Raamsdonk CD et al:** Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. *Nature* 2009;457:599-602; **Van Raamsdonk CD et al:** Mutations in GNA11 in uveal melanoma. *N Engl J Med* 2010;363:2191-9; **Walrath JD et al:** Magnetic resonance imaging evidence of optic nerve glioma progression into and beyond the optic chiasm. *Ophthal Plast Reconstr Surg* 2008;24:473-5; **Weber A et al:** Absence of mutations of the BRAF gene and constitutive activation of extracellular-regulated kinase in malignant melanomas of the uvea. *Lab Invest* 2003;83:1771-6.

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1. Up to _____ of the population demonstrates small pigmented choroidal lesions.
   (A) 5% (B) 10% (C) 15% (D) 25%

2. Use of a diode laser as single modality treatment has been shown to be an effective treatment for uveal melanoma.
   (A) True (B) False

3. The *GNAQ* mutation provides a rational drug target in _____ of patients with uveal melanoma.
   (A) ≤25% (B) ≤50% (C) ≤75% (D) ≤100%

4. Which of the following is a possible new therapeutic drug target for patients with uveal melanoma and *BRCA*-associated protein 1 mutation?
   (A) MAPK/ERK kinase inhibitor
   (B) Poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor
   (C) Inhibitor of mutant *RAF*
   (D) Extracellular-signal-regulated kinase inhibitor

5. In a study of the genetics of retinoblastoma, _____ were found to be associated with _____ severity disease.
   (A) Truncating mutations; moderate
   (B) Nontruncating mutations; high
   (C) Nontruncating mutations; low
   (D) Large deletions; low

6. According to the International Classification of Retinoblastoma, group B disease should be treated with:
   (A) Cryoablation only
   (B) External-beam radiation therapy
   (C) Vincristine, carboplatin, and laser treatment
   (D) Laser treatment only

7. Imiquimod is approved for treatment of:
   (A) Superficial basal cell carcinoma (BCC)
   (B) Nodular BCC
   (C) Squamous cell carcinoma
   (D) All the above

8. Which of the following are mechanisms of action of 5-fluorouracil?
   1. Binds to toll-like receptor 7, resulting in upregulation of nuclear factor-κ β
   2. Direct DNA incorporation
   3. Blockage of thymidine synthase
   (A) 1,2 (B) 2,3 (C) 1,3 (D) 1,2,3

9. Which of the following is the preferred diagnostic imaging tool for optic nerve glioma?
   (A) Computed tomography
   (B) Magnetic resonance imaging
   (C) Ultrasonography
   (D) Angiography

10. Abrupt loss of vision associated with optic nerve glioma usually occurs as a result of a(n) _____ process in patients with involvement of the _____ portion of the nerve.
    (A) Compressive; posterior
    (B) Compressive; anterior
    (C) Infiltrative; posterior
    (D) Infiltrative; anterior