Ocular Tumors in Children

Consequences of misdiagnosis of 4 ocular tumors: retinoblastoma, death within 1 to 2 yr; primary hyperplastic persistent vitreous (PHPV), blindness; congenital hypertrophy of retinal pigment epithelium (CHRPE)-like lesions with familial adenomatous polyposis (FAP), colon cancer and death in 28 to 30 yr; classic CHRPE, neither death nor blindness

Eyelid tumors

Capillary hemangiomas: capillary hemangioma of infancy — occurs in ≤10% of newborns; may lead to amblyopia or strabismus; requires refraction and monitoring for amblyopia; propranolol (1 to 2 mg/kg) effective; resection preferred; topical propranolol effective on small lesions; possibly associated with Kasabach-Merritt syndrome and posterior fossa abnormalities of brain, cutaneous hemangioma, arterial lesions, cardiac abnormalities, and eye abnormalities (PHACE syndrome); Kasabach-Merritt syndrome — associated with platelet sequestration from giant hemangiomas in gut, resulting in thrombocytopenia, coagulopathy, and possibly death; PHACE — includes abnormalities of optic disc, morning glory disc, and coloboma; brain hemangioma possible; can lead to death

Other eyelid tumors: kissing nevus — seen when fused lids opened after birth; treat immediately at birth (possible to scrape off skin); more in-depth surgical resection required at later ages; pilomatrixoma — seen mostly in children <10 yr of age; usually arises from brow; treat surgically by infrabrow incision and removal of lesion with characteristic basophilic and shadow cells; little risk for malignant transformation; basal cell carcinoma (BCC) — malignant; may occur in context of BCC syndrome (autosomal dominant syndrome causing many BCCs over body throughout life); also called Gorlin-Goltz syndrome; tumors now treated medically with vismodegib (inhibits hedgehog pathway); study found resolution of multifocal BCCs in 80% of patients with basal cell nevus syndrome; vismodegib very difficult to tolerate

Conjunctival tumors

 Conjunctival benign nevus: many patients have cutaneous, introcular, and conjunctival nevus; tends to occur at limbus (3 or 9 o’clock); usually associated with cyst (cysts rare with melanoma); pigmented in ≥65% to >80%; nonpigmented in ≤5%; often misdiagnosed as allergic conjunctivitis; features and differential diagnosis — examine focal areas of conjunctivitis for cysts suggesting amelanotic nevus; anterior segment optical coherence tomography (OCT) may help document presence of cysts; other conditions producing cysts include nuchal epidermoid carcinoma; conjunctival nevus may develop more or less pigmentation with age in ≤5% of children; important to differentiate from melanoma, which can grow onto cornea, has more violaceous feeder vessels, and lacks cysts; treatment — treat either nevus or melanoma with no-touch surgery; handle only normal conjunctiva surrounding tumor, make incision, take very thin episcleral lamellar dissection, and submit for pathologic analysis; leave all margins clean

Conjunctival malignant nevus: pigmented in ≥65% to >80%; nonpigmented in ≤5%; often misdiagnosed as allergic conjunctivitis; features and differential diagnosis — examine focal areas of conjunctivitis for cysts suggesting amelanotic nevus; anterior segment optical coherence tomography (OCT) may help document presence of cysts; other conditions producing cysts include nuchal epidermoid carcinoma; conjunctival nevus may develop more or less pigmentation with age in ≤5% of children; important to differentiate from melanoma, which can grow onto cornea, has more violaceous feeder vessels, and lacks cysts; treatment — treat either nevus or melanoma with no-touch surgery; handle only normal conjunctiva surrounding tumor, make incision, take very thin episcleral lamellar dissection, and submit for pathologic analysis; leave all margins clean

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Dermolipomas: usually present at birth; congenital; found superotemporally or laterally; resembles fold of extra conjunctiva; may contain fat and hairs; not treated surgically; associated with many syndromes, eg, Goldenhar syndrome (causes ear abnormalities, preauricular skin tags, hearing loss, dysmorphism of face and skull, and systemic features including genitourinary abnormalities)

Lymphangioma: ectasia or ectatic lymphatic channel; may occur on surface of eye and extend into orbit; patient may also have hemorrhagic lymphangioma on roof of mouth in conjunction with periorcular lymphangioma; usually treated conservatively with observation; in systemic form, lymphangiomas occur in bones causing multiple fractures; surgery necessary occasionally

Capillary hemangioma: may occur in conjunctiva; treat with propranolol if large; observe if small and not affecting vision

Solid dermoid: tends to occur inferotemporally at limbus; unifocal or multifocal; may occur in center of cornea and require grafting; often has feeder vessels, hair coming through surface, and develops lipid ring in cornea over time; treat with observation or resection (especially if lipid ring, multifocal cosmetic deformity, or astigmatism present); complex dermoids — often associated with syndromes, eg, complex choristoma found with nevus sebaceous of Jadassohn or organoid nevus syndrome; nevus sebaceous carries risk for BCC; examine skin for related defects

Conjunctival papilloma: seen in <1% of pediatric population; may occur anywhere in eye; often in fornix or caruncle in children; multiple or bilateral; usually self-limited; caused by human papilloma virus; may proliferate on surface of eye; generally treated with resection; may present as solitary bulbar lesion, with classic fibrovascular frond of tarsal lesion, or large multifocal lesion; case example — treated with oral cimetidine Tagamet (to boost immune system) and injection of interferon after resections performed elsewhere

Educational Objectives

The goal of this program is to improve the diagnosis and treatment of ocular tumors. After hearing and assimilating this program, the clinician will be better able to:

1. Diagnose common tumors of the eyelid and conjunctiva in children.
2. Differentiate common intraocular tumors from melanoma.
3. Diagnose and treat retinoblastoma.
4. Examine patients with nevus to determine the presence of factors that increase the risk for transformation to melanoma.
5. Treat patients with uveal melanoma.

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, Dr. Shields and the planning committee reported nothing to disclose.
Iris nevus and melanoma: iris melanoma can occur in children; (Shields CL et al, 2012); prognosis better when melanoma located in iris than when more posterior

Choroidal nevus and choroidal melanoma: melanoma generally >3 mm in thickness; nevus generally <2 mm thick; “To Find Small Ocular Melanoma” (TF SOM; mnemonic to identify ocular melanoma); risk factors that suggest melanoma include subretinal fluid, orange pigment, and location near optic disc; treat promptly; children more often show melanocytosis with ocular melanoma; examine sclera; melanocytosis in fundus indicates higher risk for melanoma (1 in 400); melanoma in children often smaller with less extracellular extension, located in iris, and has better prognosis; 9% of 10-yr-olds with melanoma, show metastatic disease vs 28% of adults with uveal melanoma at 10 yr

Medulloepithelioma: arises in ciliary body, pushes lens, and causes lens coloboma (Kaliki S et al, 2013); presents with neovascularization of iris, subluxed lens, mass in iris, cystic ciliary body mass on ultrasound biomicroscopy, retrolental fibrous proliferation, and membrane on back of lens; hyaloid canal often present; variant of PHPV seen in 30% of cases

Retinal pigment epithelium (RPE) tumors: solitary congenital hypertrophy of RPE (CHRPE) — presents with halo and lacunae; lesion remains flat or possibly multifocal (called bear tracks); FAP — systemic cancer with CHRPE-like flat lesions with pisciform tail; very difficult to see; FAP produces colonic cancer in 100% of patients by 30 yr of age; defects in RPE visualized better with fluorescein angiography; retinoblastoma — class A, smallest tumors; B, larger tumors or tumors with fluid; C, localized seeds; D, more diffuse seeds; E, most extensive; management includes enucleation, chemoreduction, plaque radiotherapy, intra-arterial chemotherapy, or injection (vitreous chemotherapy); enucleation — obtain long section of nerve and harvest fresh tissue for DNA analysis in all cases; invasion of optic nerve indicates need for systemic chemotherapy because of risk for metastatic disease; high-risk eyes include those with invasion of optic nerve or choroid; survival rate 100% after treatment; chemotherapy — intravenous chemoreduction to shrink tumor and consolidation with thermotherapy can produce good regression, even in bilateral high-risk eyes; survival rates >90% in classes A through C; rates poorer in class D; intra-arterial chemotherapy — feed catheter through femoral artery to ophthalmic artery; deliver chemotherapeutic agents directly to eye; 3 consecutive sessions gives dramatic regression (2 doses sufficient for smaller tumors); may boost with subconjunctival thermotherapy or inject into eye with advanced disease

Uveal Melanoma

Nevus: most common tumor of eye; seen in 7% to 10% of population; features — pigmented in 90%, thickness <2 mm, overlying drusen, and RPE atrophy

Features: change according to age at presentation; study of patients <20 yr of age with choroidal nevi showed pigmented lesions but few drusen and little change in RPE; middle-aged adults showed fibrous metaplasia and atrophy of RPE, drusen, and trough of subretinal fluid overlying choroidal nevi; patients >60 yr of age showed fibrous metaplasia and turbid RPE detachments

Effect on vision: Kaplan-Meier analysis of visual acuity (VA) in 3000 patients over 20 yr showed eyes with nevi under foveola had 26% chance of 3-line loss

Enlargement: Collaborative Ocular Melanoma Study (COMS) stated growth of pigmented lesion represents presumed but not unequivocal indicator of melanoma

Rate of transformation: estimated risk for transformation of choroidal nevi into melanoma 1 in 8800 (Singh AD et al, 2005); others estimated 1 in 4500; lifetime cumulative risk estimated at 1 in 100; genetic analysis can help determine transformation potential of nevus; clinical factors — nevi in fundus with overlying drusen and RPE atrophy probably low-risk; nevi with orange pigment and subretinal fluid considered high-risk; TF SOM risk factors — thickness >2 mm, fluid, symptoms, orange pigment, and margin near disc (Shields CL and Shields JA, 2002); additional factors (mnemonic, “Helpful Hints Daily”) include hollowness on ultrasoundography, absence of halo, and absence of drusen (Shields CL et al, 2009a)

Imaging: OCT — choroidal nevus shows overlying RPE detachment and shadowing at side of nevus; small choroidal melanomas show shaggy photoreceptors on enhanced depth imaging spectral-domain (EDI-OCT) (nevis does not), swollen elongated photoreceptors, or macrophages clinging to back of detached retina (Shields CL et al, 2012a); autofluorescence — speaker uses in all cases of fundus lesion; choroidal nevus shows little change in overlying RPE; atrophy of RPE sometimes seen; with melanoma, orange pigment and subretinal fluid show hyperautofluorescence (Almeida A et al, 2013)

Melanocytosis: study found melanocytosis carried lifetime risk for development of melanoma of 1 in 400 (Singh AD et al, 1998); sector melanocytosis increases risk for melanoma within that sector

Features: average thickness at time of detection 5.5 mm (high risk for metastatic disease); most melanoma in fundus pigmented; mean thickness in fovea, 2.6 mm; mean thickness at equator, ≤4 mm; near ora serrata, ≤7 mm

Therapy: depends on tumor size, location, vision in fellow eye, and patient’s age and wishes; small tumors treated with laser, thermotherapy, or radiotherapy; mid-sized tumors (ie, 3-8 mm) treated with radiotherapy (plaque), resection, or enucleation; large tumors, custom fitted plaque radiotherapy or enucleation Plaque radiotherapy: same dose used regardless of tumor thickness; melanoma requires large apex dose, ie, 8,000 centigray; manipulations performed with dummy plaque to limit exposure to live plaque to 30 sec; all devices sterilized; accurate seed count needed to ensure complete removal of seeds from eye; close with interrupted vicryl 7-0 sutures; perform temporary tarsorrhaphy; residual flat scar of melanophages with dead pigment common

Collaborative Ocular Melanoma Study (COMS): prospective study showed plaque radiotherapy gave same prognosis as enucleation for medium-sized melanoma (tumors 2.5-10 mm thick); for large tumors (>10 mm), irradiation not necessary before enucleation; neither radiation nor enucleation proven to prevent metastatic disease

Prognostic factors: study found ≤50% of patients with uveal melanoma died within 20 yr, most of these died within 10 to 15 yr (Kujala E et al, 2003)

Thickness: each millimeter of thickness adds ≤5% risk for metastasis in 10 yr

American Joint Committee on Cancer (AJCC) classification: category 1, 10 mm in base and <3 mm thick; category 2, 10 mm in base and 3 to 6 mm thick; category 3, 12.5 mm thick; prognosis for category 1 better than those for categories 2 through 4; risk for metastatic disease doubled with each higher category

Age: prognosis better in children than adults

Melanocytosis: patients who have oculodermal melanocytosis include subretinal fluid, orange pigment, and location near disc for category 1 better than those for categories 2 through 4; risk for metastatic disease doubled with each higher category

Genetic testing: microarray analysis — monosomy 3 associated with increasing thickness and peripheral location of tumor; seen in 25% of small and 50% of large melanomas; patients with monosomy 3 have ≤70% risk for metastatic disease at 10 yr; melanoma without monosomy 3 does not cause death; RNA
testing or gene expression profiling — class 1 associated with 95% survival, class 2, with 30% survival.

**Charged particle radiotherapy:** helmet ion or proton beam used; both equally effective; comparisons of proton beam or helmet ion methods with plaque radiotherapy found equal efficacy but higher rates of complications and neovascular glaucoma with proton beam and helium ions; all methods associated with radiation papillopathy and maculopathy.

**Follow-up of patients with nevus:** check nevus with overlying druse or RPE atrophy in 3 to 6 mo after initial diagnosis to confirm absence of growth; photograph at least once per year to document lack of enlargement; OCT and autofluorescence not required; development of orange pigment, accumulation of fluid, or change in margins indicates need for consultation with specialist.

**Dysplastic nevus syndrome (DNS):** monitor eyes in patients with melanoma or DNS at risk for skin melanoma; patients at slightly higher risk for choroidal and conjunctival nevi but no higher incidence of melanoma.

**Environmental exposure:** risk higher for arc welders (Shah CP, 2005); speaker recommends examining arc welders twice per year for uveal melanoma.

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### Acknowledgements

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### Suggested Reading

TUMORS IN CHILDREN/UVEAL MELANOMA

To test online, go to www.audiodigest.org and sign in to online services.
To submit a test form by mail or fax, complete Pretest section before listening and Posttest section after listening.

1. All the following conditions can lead to death or blindness, except:
   (A) Retinoblastoma
   (B) Primary hyperplastic persistent vitreous (PHPV)
   (C) Congenital hypertrophy of retinal pigment epithelium (CHRPE)
   (D) CHRPE-like lesions of familial adenomatous polyposis (FAP)

2. Which of the following conditions may be associated with Kasabach-Merritt syndrome?
   (A) Kissing nevus
   (B) Pilomatrixoma
   (C) Basal cell carcinoma
   (D) Capillary hemangioma of infancy

3. Which of the following conditions is treated with vismodegib?
   (A) Pilomatrixoma
   (B) Basal cell carcinoma
   (C) Capillary hemangioma of infancy
   (D) Kissing nevus

4. Which of the following conjunctival tumors is treated with propranolol?
   (A) Capillary hemangioma
   (B) Dermolipoma
   (C) Lymphangioma
   (D) Solid dermoid

5. Which of the following factors suggest(s) that a lesion is melanoma, rather than a choroidal nevus?
   (A) Thickness >3 mm
   (B) Presence of subretinal fluid
   (C) Location near the optic disc
   (D) A, B, and C

6. Choose the correct statements about retinoblastoma.
   1. Management may include vitreal injection of chemotherapeutic agents
   2. The survival rate for patients with retinoblastoma classes A through C after chemotherapy is <80%
   3. Invasion of the optic nerve indicates systemic chemotherapy is needed
   4. The survival rate for patients with retinoblastoma after enucleation is generally 100%
   5. Intra-arterial chemotherapy can provide dramatic regression after 3 sessions
      (A) 1,2,3,4
      (B) 2,3,4,5
      (C) 1,3,4,5
      (D) 1,2,4,5

7. All the following statements about choroidal nevi are correct, except:
   (A) Patients <20 yr of age with choroidal nevi showed pigmented lesions but few drusen
   (B) Nevi under the foveola do not affect vision
   (C) Growth of a pigmented lesion represents a presumed but not unequivocal indicator of melanoma
   (D) The lifetime cumulative risk that a nevus will transform into melanoma has been estimated to be 1 in 100

8. Which of the following findings is typical of a choroidal nevus?
   (A) Overlying RPE detachment and shadowing at the side of the lesion on optical coherence tomography (OCT)
   (B) Shaggy photoreceptors on enhanced depth imaging spectral-domain-OCT
   (C) Hyperautofluorescence
   (D) Hollowness on ultrasonography

9. Choose the correct statement about treatment of melanoma.
   (A) For large tumors (>10 mm), irradiation is necessary before enucleation
   (B) Plaque radiotherapy is delivered at a dose of <4000 centigray
   (C) Enucleation is the only treatment that has been proven to prevent metastatic disease
   (D) A study found plaque radiotherapy gave the same prognosis as enucleation for medium-sized melanoma (2.5-10 mm in thickness)

10. Choose the correct statement about the prognosis of uveal melanoma.
    (A) The prognosis is poorer in children than adults
    (B) Patients with category 4 disease according to the American Joint Committee on Cancer (AJCC) classification have a 2-fold higher risk for metastatic disease than those with category 1 disease
    (C) Most patients who die from uveal melanoma do so between 15 to 20 yr after diagnosis
    (D) Uveal melanoma that is not associated with monosomy 3 does not cause death

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