A Review of Pediatric Ophthalmic Tumors

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EDUCATION GAP

Pediatric ophthalmic tumors encompass a wide range of pathologies that involve the eye, periorbital, and orbital tissue. Disease may be isolated to ocular structures or associated with broader systemic disease. The pediatrician is often the first to encounter these lesions and should have an awareness and understanding of the differential diagnosis, which will aid in prompt referral and potential vision-saving and lifesaving treatments.

OBJECTIVES *After completing this article, readers should be able to:*

1. List potentially vision- and life-threatening diseases.
2. Describe diagnostic and treatment modalities for pediatric ophthalmic tumors.

ABSTRACT

Tumors of the eye, orbit, and ocular adnexa can arise in the pediatric population. These entities can be both vision- and life-threatening and may be associated with systemic disease. Given their relative rarity, pediatricians must be aware of these conditions and understand what findings warrant immediate referral to an ophthalmologist for initiation of further testing. We aimed to review these conditions and highlight clinical features to promote awareness and expedite diagnosis. Tumors are subdivided into the following categories for review: anterior tumors of the eyelid and ocular surface, orbital tumors, and intraocular tumors.

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ABBREVIATIONS

CHRPE	congenital hypertrophy of the retinal pigment epithelium
CT	computed tomography
LAMB	lentigines, atrial myxomas, and blue nevi
MRI	magnetic resonance imaging
NAME	nevi, atrial myxoma, myxoid neurofibromas, and ephelides
NF1	neurofibromatosis type 1
TED	thyroid eye disease

INTRODUCTION

Pediatric ophthalmic tumors present at birth or are acquired during childhood and are of varied etiology. Although most are benign, malignant tumors may be life-threatening, and expedient diagnosis is imperative. (1) Both benign and malignant lesions may cause vision loss due to their effect on vital ocular structures as well as amblyogenic factors, which must be considered in young children whose visual system is developing. Certain tumors, particularly those of vascular

and neurogenic etiologies, may be associated with systemic disease, and further diagnostic evaluation may be indicated. (2)(3) The pediatrician is often the first to encounter ophthalmic tumors and should be familiar with common diagnoses and presentations of disease.

Presentation of Ophthalmic Tumors

Presentation depends on lesion location. External lesions of the eyelid and eye surface are typically self-evident, whereas intraocular and orbital lesions cannot be visualized by gross inspection alone. Rather, the patient will present with various signs that may alert the physician of an ocular pathology. Although decreased vision may be a presenting symptom in all ophthalmic tumors, it is important to note that children often do not complain of poor vision, especially if the process is unilateral.

Examination

Examination begins with evaluation of the visual acuity of each eye, tailored for patient age and developmental state; assessment of pupils for symmetry in size and red reflex, reactivity to light, and afferent pupillary defect; and examination of motility, assessing extraocular movements and evaluating for strabismus. The entire face should be inspected for asymmetry or abnormality, followed by an external eye and fundus examination. The photoscreener is a useful adjunct tool for assessing refractive error, leukocoria, and strabismus. The details of the pediatric eye examination can be found in outside references. (4)

EYELID TUMORS

Presentation

Eyelid lesions present as bumps or nodules on the eyelid. Large eyelid tumors may cause ptosis that obstructs the visual axis, and mass effect on the globe may induce astigmatism, which leads to potential deprivation or anisometropic amblyopia (unequal focus between the 2 eyes causing chronic blur on 1 retina), respectively.

Examination

Eyelid tumors are often diagnosed based on history and visualization alone. (5) Attention should be given to the eyelid margin in cases of conjunctivitis because small, inconspicuous lesions may be responsible. Focal loss of lashes at the tumor should be noted and may be a sign of malignancy, which is rare in the pediatric population. Although further testing with imaging is often not necessary, biopsy may be needed when definitive diagnosis is required. At times, deeper orbital lesions may be visualized as an eyelid lesion, representing a tip-of-the-iceberg scenario.

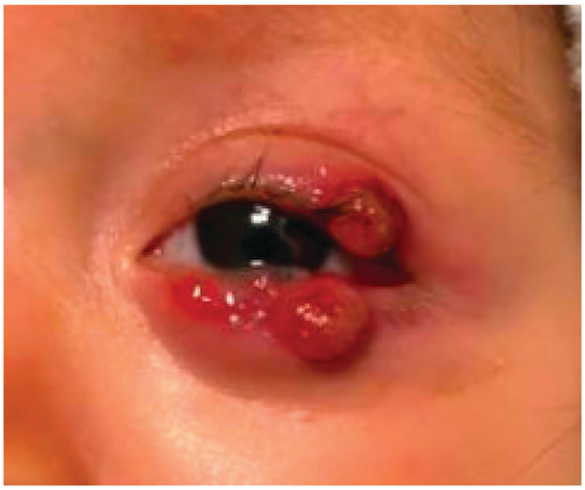

Figure 1. A 14-month-old girl with multiple severe chalazia.

Lesions Simulating Eyelid Tumors

Simulating eyelid tumors are by far the most common type of eyelid lesion and are encountered regularly in practice.

Chalazion. Chalazia, the most common eyelid lesions, are caused by blockage of eyelid sebaceous glands and present as painless, slow-growing nodules subcentimeter in size (Fig 1). (6) Most chalazia resolve with warm compresses, lid massage, and hygiene. (7) Persistent lesions may require further treatment. Options include oral macrolides or doxycycline in children older than 8 years, corticosteroid injection, and surgical excision. (8)

Hordeolum (Stye). Hordeola are acute bacterial infections of the eyelid caused by blockage of apocrine or eccrine glands. (1) Blepharitis, seborrheic dermatitis, and rosacea are risk factors. Presenting as tender pustules along the lash line, hordeola are self-limiting, lasting 1 to 2 weeks. (6) Warm compresses and lid massage are first-line therapy. Topical antibiotics or antibiotic-corticosteroid combinations are also used. Hordeola may lead to preseptal cellulitis.

Molluscum Contagiosum. Molluscum contagiosum is a benign, self-limited infection caused by a poxvirus. Spread through direct transmission, it is most common in children aged 2 to 5 years. (9) It presents as dome-shaped, pearly papules with central umbilication. Typically asymptomatic, the papules may cause irritation or secondary conjunctivitis. Molluscum contagiosum spontaneously resolves; however, this may take 6 months or longer. If secondary complications such as conjunctivitis are present, treatment is recommended. (10)

Therapies include topical antiviral agents, surgical excision, cryotherapy, and cauterization. (11)

Port-Wine Hemangioma (Facial Nevus Flammeus). Port-wine hemangiomas are capillary malformations located on the skin. They present at birth as flat, red lesions and grow with the child. They may become irregular and nodular with age. (2) Facial port-wine hemangiomas, particularly those with a distribution corresponding to embryologic vasculature development, are associated with Sturge-Weber syndrome, a phacomatosis involving hemangiomas of the skin, brain, and eyes. (12) Upper eyelid port-wine hemangiomas, especially in Sturge-Weber syndrome, are associated with congenital and juvenile glaucoma. (13)

Melanocytic Nevi. Eyelid nevi are variably pigmented, benign collections of melanocytes and are identical to those appearing on other areas of the skin. Junctional and compound nevi are acquired during puberty. (5)

Blue nevi present as well-demarcated blue to black nodules and are typically acquired and solitary in nature; those that are congenital and diffusely distributed may be associated with familial syndromes, such as LAMB (lentigines, atrial myxomas, and blue nevi) and NAME (nevi, atrial myxoma, myxoid neurofibromas, and ephelides). (14)(15)

Kissing nevi, a rare embryologic phenomenon, occur on opposing upper and lower eyelids, so named for their "kissing" appearance when the eye is closed (Fig 2). If kissing nevi are large and block the visual axis, intervention is required in childhood.

Congenital giant hairy nevi present at birth or within the first weeks after birth. They can have excessive hair growth and reach a diameter greater than 20 cm, but orbital involvement is extremely rare. (16)

Malignant Eyelid Cancers

Although rare in children, periorbital skin cancers such as basal cell carcinoma can occur. Associated systemic conditions are typically present (Table 1, Fig 3). Premalignant lesions, such as giant hairy nevus and ocular melanocytosis, predispose patients to melanoma. (16) Leukemic/lymphoma lid infiltrates, Kaposi sarcoma, and histiocytoses (such as Langerhans cell histiocytosis) can also appear in the lid. (17)(18)(19) Tissue biopsy is required for diagnosis, and treatment is typically surgical. Given the location, Mohs surgery may be performed (removal of thin tissue layers until no cancer remains), and careful reconstruction is imperative to preserve lid architecture and function.

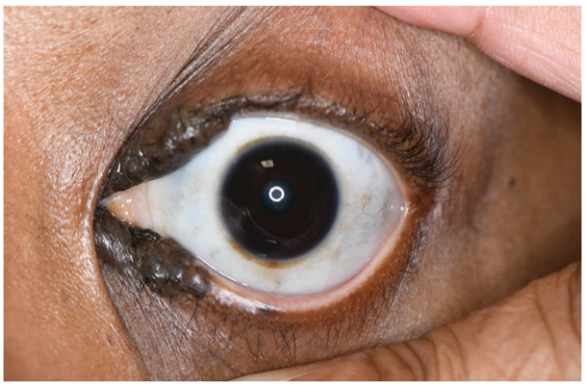

Figure 2. A kissing nevus present since birth in the left eye.

Table 1. Nonophthalmic Conditions Associated with Malignant Pediatric Eyelid Tumors

Basal cell nevus syndrome (Gorlin-Goltz syndrome)
Xeroderma pigmentosa
Linear nevus sebaceous syndrome
Epidermodysplasia verruciformis
Post radiation

OCULAR SURFACE TUMORS

Presentation

Ocular surface tumors include those of the cornea, conjunctiva, and sclera and are visualized on external examination. Patients present with a bump, abnormal pigmentation, or redness of the eye surface. They may be symptomatic, causing irritation or eye discomfort.

Examination

External examination provides details of the ocular surface, including location, pigmentation, and size of the tumor, and is easily performed with a penlight in the pediatrician's office. If available, a handheld slit lamp is useful for magnification. Lesions may hide in the culda-sacs and may not be apparent without retraction of the lid. History regarding chronicity, growth, and color change should be obtained. Clinical examination is typically sufficient for diagnosis.

Epibulbar Choristomas

Choristomas are an overgrowth of normal tissue in an aberrant location and are the most common ocular surface tumor present at birth. They may be simple, containing 1 tissue element, or complex, containing more than 1 tissue type. They appear as an opaque, yellow-white mass on the ocular surface. Usually asymptomatic, epibulbar (on the globe surface) choristomas may directly block the visual axis if located on the cornea or cause astigmatism. Amblyogenic lesions should be excised, whereas those not affecting vision can be observed. Conjunctival dermoids are

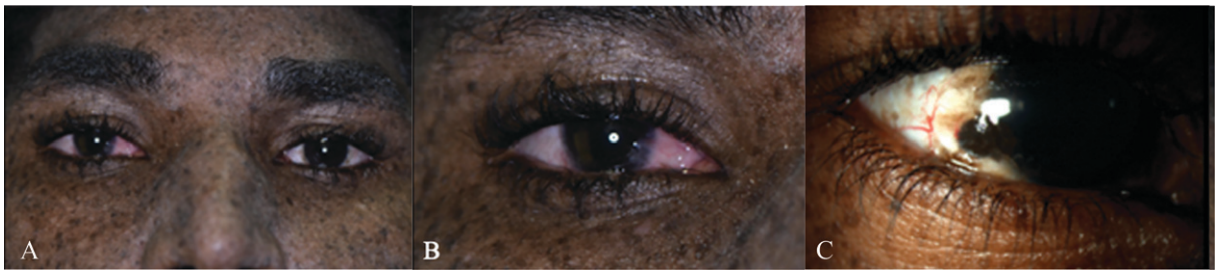

Figure 3. A 17-year-old boy with xeroderma pigmentosa. A. Facial photograph shows diffuse pigmentary changes of the skin. B. He has developed a benign pterygium growth on the nasal aspect of the right eye that is encroaching on the cornea. C. He developed a lesion suspicious for melanoma on the ocular surface that required wide surgical excision and cryotherapy treatment.

typically located at the limbus and associated with Goldenhar syndrome (Fig 4). Epibulbar complex choristomas are seen in linear nevus sebaceous syndrome. (20) Simple epibulbar osseus choristomas are composed of bone on the surface of the globe. They usually occur in females in the superotemporal quadrant and are not associated with other conditions.

Pyogenic Granuloma

A pyogenic granuloma is a collection of granulation tissue at the site of previous tissue injury. A pyogenic granuloma is caused by inflammation, surgery, or trauma and appears as an elevated, bright red mass with prominent blood (Fig 5). (21) A "teddy bear" granuloma results from synthetic fibers introduced into the conjunctival sac, typically of the lower fornix, and is particularly common in children given their use of comforting blankets and fabric toys, which often are close to the eye. (22) Treatment options include observation, topical corticosteroids, or surgical excision.

Papilloma

A conjunctival papilloma is a benign fibrovascular tumor with a pink cauliflowerlike appearance, most often occurring in the inferior fornix and associated with human papilloma virus. (23) It may cause foreign body sensation, incomplete eyelid closure, or hemorrhagic tears. Large or symptomatic papillomas may be excised or treated with cryotherapy. (23) Oral cimetidine may also be effective. (24)

Conjunctival Nevi

Conjunctival nevi are the most common melanocytic tumors of the ocular surface. They are variably pigmented, often with clear, cystic changes, and typically occur near the limbus. Growth and increased pigmentation may occur in the adolescent years and do not necessarily signify malignant transformation. Nevi should be monitored with photographic comparison; less than 1% undergo malignant transformation (Fig 6). (25)

Congenital Oculodermal Melanocytosis

Congenital oculodermal melanocytosis is a benign melanocytosis following the distribution of the V1 or V2 branch of the trigeminal nerve. Congenital oculodermal melanocytosis results in a grey-blue pigmentation of the conjunctiva and sclera. When involving the periocular skin, it is termed nevus of Ota (Fig 7). It typically presents at birth

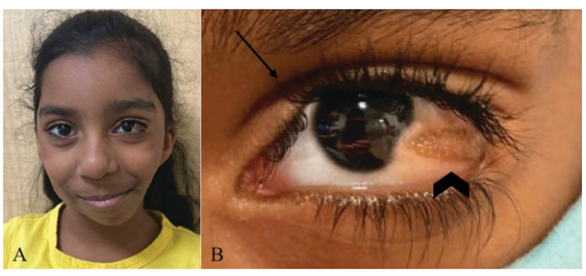

Figure 4. An 8-year-old girl with Goldenhar syndrome. A. A full facial photograph demonstrates hemifacial microsomia and left macrostomia. The patient had bilateral preauricular scars from previous surgery not visualized here. B. There is a coloboma of the left eyelid (arrow) and an epibulbar dermoid cyst (arrowhead).

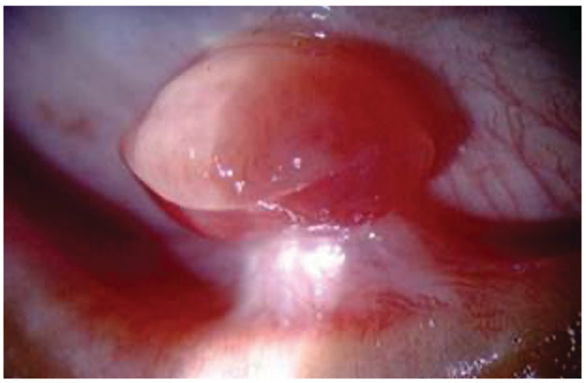

Figure 5. Benign pyogenic granuloma of the conjunctiva.

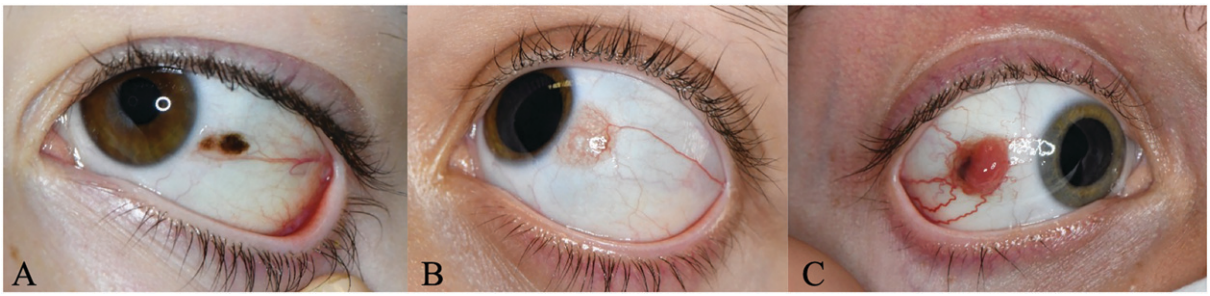

Figure 6. A. A 15-year-old boy with a conjunctival nevus. Recent increase in pigmentation seen in the setting of puberty without signs of malignant transformation. B. A benign, amelanotic conjunctival nevus in an 8-year-old girl. C. Conjunctival melanoma arising from a known conjunctival nevus in a 20-year-old male.

and in patients of Asian and African descent. (26) There is an increased risk of glaucoma as well as a significant increase in the risk of uveal melanoma formation to 1 in 400, thus requiring yearly monitoring. (26)

ORBITAL TUMORS

Orbital tumors in children are rare; 95% of those biopsied are benign, with cystic and vascular lesions being the most common. (27)

Presentation

An orbital tumor presents with nonspecific findings. Superficial lesions involving the anterior orbit may be visualized subcutaneously as a palpable nodule. Deeper orbital lesions are often more challenging to diagnose. Signs of space-occupying lesions in the orbit include proptosis, or protrusion of the globe, globe displacement, strabismus, eyelid ptosis, and swelling and discoloration of the eyelids. Decreased vision may occur with optic nerve compression from mass effect of posterior lesions. Orbital signs can occur acutely in hours to days or slowly over time, depending on the etiology. Occasionally, a malignancy may mimic orbital cellulitis and should be suspected when a patient presents with proptosis and edema and no other signs of inflammation. Periorbital hematoma and ecchymosis without trauma should also raise concern for potential malignancy. Characteristic findings of orbital diseases are presented in Table 2.

Examination

In addition to vision and pupillary assessment, evaluation of orbital tumors should include monitoring for extraocular movement deficit, strabismus, and proptosis or displacement of the eye. Proptosis can easily be identified by a "worm's-eye view," tilting the patient's head upward and looking from below (Fig 8). True proptosis should be differentiated from pseudo-proptosis, which can be caused from lid drooping or retraction, asymmetrical orbital size, congenital deformity, or enlarged globe or cornea. The direction of globe displacement and characteristics of the periorbital changes are useful to narrow the differential diagnosis (Table 3). Color vision and confrontational visual fields are additive tests to assess optic nerve function. High-quality imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is often needed and can help differentiate masses. Ultrasonography may be

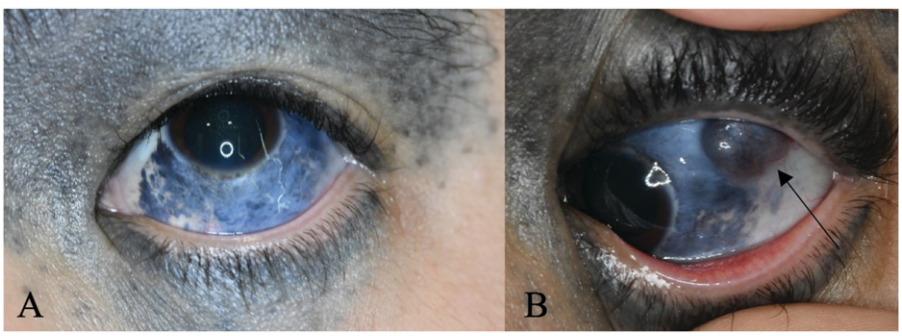

Figure 7. A. Nevus of Ota involving the periocular skin and eye. B. At age 33 years, the patient developed an ocular melanoma (arrow).

Table 2. Characteristic Findings of Orbital Eye Diseases

CLINICAL FINDING	ORBITAL DISEASE
Eyelid retraction	TED
Vascular anomaly of eyelid skin	Vascular anomaly (lymphatic malformation, varix, or hemangioma)
S-shaped eyelid	Plexiform neurofibroma, lacrimal gland mass
Ecchymoses of eyelid skin	Metastatic neuroblastoma, leukemia
Bilateral proptosis	Myeloid sarcoma, TED, histiocytoses, IOI, metastatic neuroblastoma
Prominent temple	Sphenoid wing meningioma, metastatic neuroblastoma
Facial asymmetry	Craniosynostoses, fibrous dysplasia, neurofibromatosis
Blue discoloration of skin	Vascular lesion, lymphangioma, dacryocystocele

IOI=idiopathic orbital inflammation, TED=thyroid eye disease.

useful and can be done quickly in an uncooperative child without sedation. Definitive diagnosis often requires biopsy.

Dermoid and Epidermoid Cysts

Dermoid cysts are the most common orbital lesion of childhood. (5) They present as a painless, slow-growing, well-circumscribed, mobile growth at the superolateral orbital rim near the zygomaticofrontal suture. (5)(28) Clinical examination is typically sufficient for diagnosis. Cyst rupture can lead to a robust inflammatory response; lesions are typically excised to avoid this complication. (5)(28)

Infantile Hemangioma (Capillary Hemangioma)

An infantile hemangioma is the most common childhood vascular tumor of the orbit. (28)(29) Infantile hemangiomas typically present in the first weeks of life with an initial phase of rapid growth followed by stability and involution in the following years. Superficial tumors have a bright red, bumpy appearance, and deeper hemangiomas appear bluish (Fig 9). (1) Diagnosis is based on clinical appearance, but in ambiguous scenarios, imaging is useful. (29) Large facial lesions should raise suspicion for PHACE syndrome, which includes posterior fossa malformations, facial hemangiomas, arterial lesions, cardiac anomalies, and eye abnormalities. Observation is reasonable if there is no effect on vision. Visual compromise or threat to vision requires treatment. Topical timolol maleate (0.5% gel-forming solution 4–5 times daily for 6–9 months) or pulsed dye laser therapy has shown efficacy for superficial lesions, and oral propranolol (2–3 mg/kg daily) is preferred for larger and deeper lesions. (30)

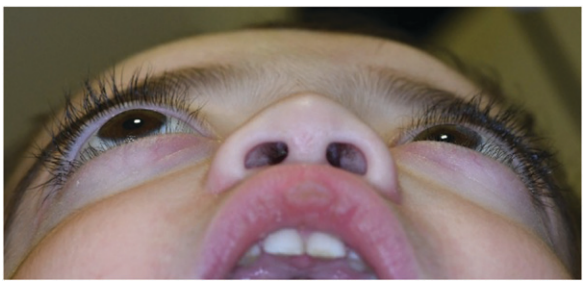

Figure 8. A worm's-eye view can help visualize proptosis.

Vascular Malformations

Vascular malformations include venous malformation, arteriovenous malformations, and lymphangiomas. History, physical examination, and imaging are useful to distinguish the lesions and aid in diagnosis. Vascular malformations that are in the anterior orbit present as soft, bluish masses. Those that are posterior may present as proptosis.

Orbital veins that dilate through a weakness in the vascular wall are termed orbital varices. These low-flow lesions occur throughout childhood, most often in the teenage years. (31) Changes in venous pressure (ie, Valsalva) may cause filling of the lesion and proptosis. (32) Complications include thrombosis leading to pain, proptosis, and decreased vision; acute orbital hemorrhage; and decreased vision from optic nerve compromise. (33) Imaging aids in diagnosis, and Valsalva during imaging may be useful. Risk of noncontiguous intracranial vascular malformations exists; brain evaluation is required. (33)

Lymphatic malformations usually present in the first decade of life. (28) They contain both venous and lymphatic components and are thought to be a variant of the orbital varix. (33) Lymphatic malformations may enlarge during acute viral illness or in the setting of spontaneous hemorrhage, which can cause an acute, painful proptosis. Recurrent orbital cellulitis precipitated by viral illness should raise suspicion for occult lymphangioma (Fig 10). (28)(34) Treatment options are observation, systemic treatment with sildenafil or sirolimus, (34) complete or partial excision, and sclerotherapy. (34)

Rhabdomyosarcoma

A rhabdomyosarcoma is the most common childhood sarcoma and the most common primary pediatric orbital malignancy. Ten percent of rhabdomyosarcoma cases originate in

Table 3. Differential Diagnosis for Proptosis

DIFFERENTIAL DIAGNOSIS	PRESENTATION
Congenital	
1. Teratoma	1. Healthy newborn with rapidly enlarging mass with severe proptosis and damage to the adjacent globe.
2. Microphthalmia with cyst	2. Unilateral, blue, cystic lower eyelid mass in a child with poor vision since birth.
Autoinflammatory/infectious	
1. Dacryoadenitis	1. Superotemporal orbital inflammation with an "S"-shaped eyelid. May be infectious or autoinflammatory as below.
2. Orbital cellulitis	2. Periorbital inflammation with or without visual changes, pain, and/or restriction with extraocular movement.
3. Tuberculosis	3. Exposed child with proptosis, chemosis, and headache. Visual loss may occur. May involve multiple ocular or periocular structures.
4. Mucormycosis	4. Immunocompromised child with rapid-onset cellulitis, chemosis, proptosis, and facial swelling. Epistaxis and eschar may be seen.
5. Idiopathic orbital inflammation	5. Variable presentation based on site of inflammation (ie, EOMs, lacrimal gland, periocular soft tissue).
6. Sarcoidosis and IgG4-related disease	6. Typically presents as a dacryoadenitis but may involve multiple ocular or periocular structures.
7. Thyroid eye disease	7. Proptosis, increased scleral visibility, high lid position (retraction), conjunctival injection, chemosis, restriction of EOMs, and vision loss.
Solid tumors	
1. Rhabdomyosarcoma	1. Rapid-onset proptosis in a child with or without chemosis, eyelid swelling, palpable mass, ptosis, and globe displacement.
2. Neuroblastoma	2. A young child (<2 years old) most commonly with periorbital ecchymosis ("raccoon eyes").
3. Retinoblastoma	3. RB commonly presents with leukocoria, strabismus, and "pseudo-inflammation," but proptosis can occur in advanced cases.
4. Ewing sarcoma	4. Painful, progressive proptosis with or without visual changes or motility deficits.
5. Wilms tumor	5. The most common pediatric renal tumor. Can rarely metastasize to the orbit with painful, progressive proptosis.
6. Optic nerve glioma and meningioma	6. Often presents with vision loss or less commonly with proptosis and headache. ONG may or may not occur in a child with NF1.
7. Schwannoma	7. Slowly progressive proptosis, often with downward displacement of the eye.
8. Solitary fibrous tumor	8. Progressive proptosis with or without ptosis and motility deficits.
Hematologic disorders	
1. Leukemia and lymphoma	1. Periorbital swelling and proptosis with or without symptoms. An orbital mass may be present in leukemia (ie, granulocytic sarcoma).
2. Histiocytosis	2. Orbital swelling and proptosis due to histiocytic infiltration of orbital bones or soft tissues. Usually involves multiple organ systems.
Vascular lesions	
1. Hemangioma	1. Progressive proptosis with a palpable, well-circumscribed orbital mass.
2. Orbital varix	2. Proptosis that is positional (head down) and intermittent (occurring with coughing, straining, or Valsalva).
3. Arteriovenous malformation	3. Proptosis that can be associated with a bruit and dilated episcleral "corkscrew" vessels.
4. Lymphangioma	4. Onset of proptosis and ptosis triggered by trauma or a URI.

EOM=extraocular muscle, NF1=neurofibromatosis type 1, ONG=optic nerve glioma, RB=retinoblastoma, URI=upper respiratory infection.

the orbit. (35) Secondary orbital rhabdomyosarcoma may also occur. (36) Age distribution is bimodal (peaks at 4 years and 14 years), and the younger age group is more likely to present with orbital tumors. (35)(37) Classic presentation is rapid-onset, progressive, unilateral proptosis (Fig 11). Globe displacement, eyelid edema, and ptosis occur in most patients. Few patients will have palpable mass and pain at presentation. (38) It is imperative to differentiate a suspected case of aggressive orbital cellulitis from rhabdomyosarcoma because these diagnoses may share extensive clinical overlap. (39) Treatment may involve chemotherapy and radiation in conjunction with surgery. (37) Prognosis depends on morphology; embryonal is the most common orbital subtype with the best prognosis, whereas the alveolar subtype portends a worse prognosis. (38)

Lymphoma

Orbital lymphomas are rare in pediatrics. (40) Burkitt lymphoma is the most common orbital type and is typically unilateral, but bilateral disease can occur. Children may present with constitutional symptoms along with ocular signs. (40) Imaging and complete eye examination followed by biopsy is required for diagnosis. Treatment regimens include systemic chemotherapy with or without adjuvant radiotherapy. There is a good prognosis if promptly treated. (40)

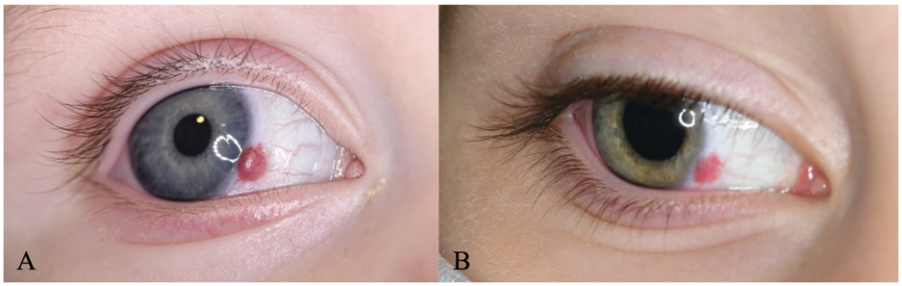

Figure 9. A. A 4-month-old boy with a capillary hemangioma of the conjunctiva, a rare location for the lesion. B. At age 4 years, the lesion has decreased in size and thickness with observation alone.

Leukemia and Granulocytic Sarcoma

Acute myeloid leukemia is the most common type of leukemia to affect the orbit and is the most common etiology of bilateral proptosis in children. (41) The orbit may be the first sign of disease. Orbital acute myeloid leukemia typically presents with bilateral periorbital swelling and proptosis, although unilateral presentations are seen in 40% of children. (41) Proliferation of extramedullary granulocytic cells can lead to a discrete mass, termed granulocytic (myeloid) sarcoma, and is a harbinger for acute myeloid leukemia. (42) Other extraocular findings include subconjunctival hemorrhage, conjunctival chemosis, lid edema, and extraocular restriction. (43) Constitutional manifestations, lymphadenopathy, hepatosplenomegaly and bony pain may be present. Orbital involvement has been associated with worse prognosis, making prompt diagnosis imperative for good outcomes. (44)

Optic Nerve Sheath Meningioma

Optic nerve sheath meningiomas are rare in the pediatric population but can be associated with neurofibromatosis type 2. (45)(46) They cause painless, gradually progressive monocular vision loss. Imaging with MRI or CT is crucial to diagnosis; CT classically shows diffusely thickened optic nerve sheath with areas of thickening parallel to the optic nerve known as "tram tracking." Pediatric optic nerve sheath meningiomas are thought to behave more aggressively than in adults, with higher malignant potential. Intracranial extension is more common in children than in adults. (45) Thus, lesions are usually excised as the first treatment modality in children. In some cases, disease is nonprogressive and can be observed. (47)

Optic Nerve Glioma (Optic Pathway Glioma, Juvenile Pilocytic Astrocytoma)

Pediatric optic nerve gliomas are typically low-grade pilocytic astrocytomas and are the most common central nervous system tumor in childhood. They often occur in children with neurofibromatosis type 1 (NF1) but may occur sporadically. Mean age at presentation is 9 years. (48) Children present with ipsilateral vision loss and slowly enlarging proptosis. MRI demonstrates well-circumscribed enlargement of the optic nerve. Lesion growth is unpredictable, and management is challenging. Observation is appropriate; however, if vision is threatened, management with chemotherapy or molecular targeted therapy is indicated. In rare cases of rapid vision loss or progressive proptosis, surgical debulking may be required.

Neurofibromas

A neurofibroma can occur on the eyelid as a plexiform neurofibroma, which is suggestive of neurofibromatosis.

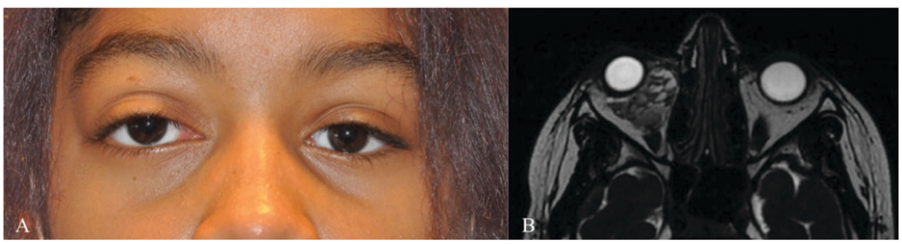

Figure 10. A. 12-year-old girl with right-sided, painless proptosis that worsens during illness. B. Axial magnetic resonance image shows a T2 hyperintense mass involving the intraconal and extraconal space of the right orbit with multiple internal septae and fluid-fluid levels consistent with a lymphangioma of the orbit.

Plexiform neurofibromas are described as having a "bag of worms" consistency and produce an S-shaped curve of the upper lid. (49) Rarely, neurofibromas can undergo malignant transformation. Management is observation or, in cases of vision loss or cosmetic deformity, surgical debulking.

Metastatic Disease to the Orbit

The orbit is the most common site of ocular metastases in children, whereas in adults the uvea is primarily affected. (1)

Neuroblastoma, a childhood malignancy of neural crest origin, is the most common extracranial solid tumor in children. (50) It metastasizes to the orbit via hematogenous spread in 15% of cases, and it is the most common type of metastatic orbital tumor in pediatric patients. (51)(52) Orbital presentation commonly involves bilateral eyelid ecchymoses and proptosis. (3) Commonly referred to as "raccoon eyes," the findings result from obstruction of palpebral blood vessels by orbital metastases. (52) Most patients have a primary adrenal tumor at the time of orbital presentation; however, 3% present with the orbital metastases as the first sign of disease. (5) Other ocular findings of neuroblastoma may include Horner syndrome resulting from interruption of the sympathetic pathway and opsoclonus, a paraneoplastic syndrome presenting with "dancing" eyes.

Ewing sarcoma and Wilms tumor less commonly metastasize to the orbit in children.

Lesions Simulating Orbital Tumors

Thyroid Eye Disease. Thyroid eye disease (TED) is rare in the pediatric population. It is more common in females and occurs at a median age of 12 years. (53) Most patients develop TED in a hyperthyroid state at the same time as disease onset. (54) The most common presentation for pediatric TED is proptosis followed by eyelid retraction (Fig 12). Pediatric patients with TED have milder symptoms than adults. (53)(55) Strict management of thyroid levels is crucial, but disease does not always correlate with hormone levels. In rare cases, use of corticosteroids or surgical decompression of the orbit is required in cases of impending vision loss. (53) Tocilizumab, an interleukin-6 receptor antagonist, has been used successfully in a case of progressive pediatric TED. (56)

Orbital Cellulitis. Orbital cellulitis is a vision- and potentially life-threatening infection posterior to the orbital septum. It is typically secondary to sinusitis but can occur in the setting of odontogenic disease, hematogenous infection, or eyelid/facial infection. (57) In advanced cases, subperiosteal abscesses can be seen. Dedicated orbital imaging may be required, especially if visual loss, reduced extraocular motility, proptosis, loss of color vision, afferent pupillary defect, bilateral disease, or lack of response to antibiotics is noted. (57) Rapid initiation of broad-spectrum intravenous antibiotics is crucial, and intravenous corticosteroids may be of benefit in the pediatric population. (58) Source control with sinus surgery may also be required. Malignancies such as rhabdomyosarcoma and retinoblastoma may masquerade as orbital cellulitis.

Idiopathic Orbital Inflammation (Orbital Pseudotumor, Nonspecific Orbital Inflammation). Idiopathic orbital inflammation describes a space-occupying orbital lesion without infectious etiology or histopathologic features consistent with a known inflammatory disorder. Although common in adults, it is rare in pediatrics. (59) Idiopathic orbital inflammation typically presents with orbital signs; children are more likely to have bilateral disease and concomitant constitutional symptoms. (59)(60) A diagnosis of exclusion, MRI and serologic evaluation are useful to eliminate alternate diagnoses. (61) Most cases are successfully treated with high-dose corticosteroids, followed by an extended taper, although recurrence is reported in up to 75% of pediatric cases. (59) Immunomodulatory agents are considered early to avoid prolonged corticosteroid use in children. (60)

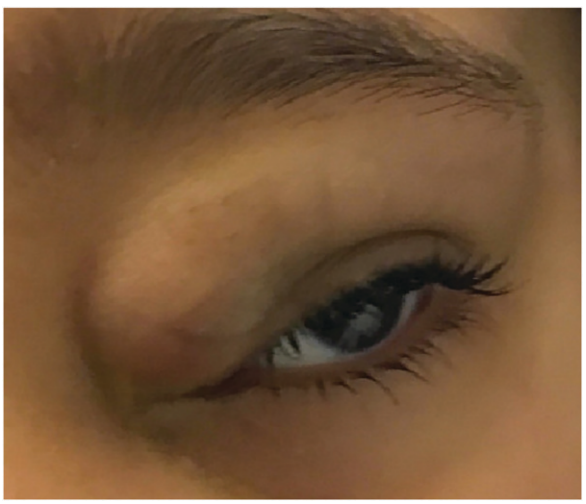

Figure 11. A 4-year-old girl with rhabdomyosarcoma.

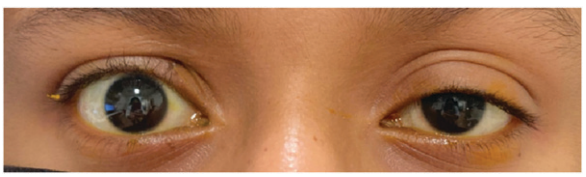

Figure 12. A 15-year-old girl with thyroid eye disease; photograph shows proptosis of the right eye with resultant superior lid retraction and relative ptosis of the left eye.

INTRAOCULAR TUMORS

Presentation

Presentation of intraocular tumors depends on tumor size and location in the eye. Small or peripheral tumors may be asymptomatic and found only on routine fundus examination. Larger tumors or those affecting vision may cause leukocoria, strabismus, and decreased vision; the differential diagnosis for leukocoria is presented in Table 4. Patients with an intraocular tumor and poor vision since early infancy may present with nystagmus.

Examination

Intraocular tumors of the anterior segment, such as those involving the iris, can be visualized on inspection but often require magnification with a slit lamp. Posterior tumors of the ciliary body, retina, and choroid require fundus examination. Ophthalmic testing with ultrasonography, optical coherence tomography, and fluorescein angiography can be useful.

Iris Hamartoma (Lisch nodule)

Lisch nodules are 1- to 2-mm, tan or brown melanocytic hamartomas of the iris surface. Typically asymptomatic, they do not cause visual disturbances or require treatment. They are pathognomonic markers for NF1. The lesions are rarely present during infancy but appear during the childhood years, and 100% of patients with NF have Lisch nodules by young adulthood. (62) They usually occur earlier than neurofibromas and so can be helpful in clinching the diagnosis. Other characteristic ophthalmic findings of NF1 include optic nerve gliomas and sphenoid wing dysplasia.

Medulloepithelioma

Intraocular medulloepitheliomas are rare congenital tumors of the ciliary body epithelium. (63) They present as a fleshy or cystic mass in the ciliary body and may lead to complications such as lens subluxation, cataract formation, or neovascular glaucoma. (63)(64) They generally become apparent between the first and second decades of life, and adults who are newly diagnosed are presumed to have slow-growing tumors or malignant transformation of a congenital tumor. (63) Fifty percent of medulloepitheliomas are malignant, but extraocular extension and metastasis are rare. (63)(65) They can rarely be associated with the hereditary cancer predisposition syndrome DICER-1. Treatment includes local resection, plaque brachytherapy, and enucleation. (63)(64)(66)(67)

Astrocytic Hamartoma

Astrocytic hamartomas are benign proliferations of glial cells arising from the retinal nerve fiber layer. (68)(69) They can arise sporadically but are associated with tuberous sclerosis and are a criterion for establishing the diagnosis. (64) Astrocytic hamartomas have also been reported in NF1. (70) Most cases present in adolescence or early adulthood. (68)(71) The tumors can have several different forms,

Table 4. Differential Diagnosis for Leukocoria

DIFFERENTIAL DIAGNOSIS	PRESENTATION
Tumors	
1. Retinoblastoma	1. Often leukocoria but can present as strabismus or mimic orbital cellulitis. May endorse family history but can be sporadic. White or cream-colored mass with calcifications, may have vitreous involvement.
2. Astrocytic hamartoma of the retina	2. Typically asymptomatic, occurring in a child with tuberous sclerosis. Flat, grey-white lesions or "mulberry" lesions with calcification.
Congenital malformations	
1. Persistent fetal vasculature	1. Remnants of fetal vasculature. Often associated with small eye (microphthalmos) and cataract
Vascular diseases	
1. Coats disease	1. Retinal exudates (often temporal) from telangiectasias. Typically presents unilaterally in male children aged <8 y.
2. ROP	2. Failure of complete retinal vascularization in preterm, low birthweight infants, leading to neovascularization, fibrotic membranes, exudation, and/or retinal detachment.
3. FEVR	3. Similar in presentation to ROP, FEVR represents an inherited form of incomplete retinal vascularization in term infants.
Cataract	Clouding of the crystalline lens often with a white appearance. May be congenital (with or without systemic associations) or acquired (secondary to trauma, inflammation, infection, etc)
Infectious or inflammatory disease	A variety of congenital or acquired diseases (ie, toxoplasmosis, toxocariasis, herpes viruses) can cause inflammation in any layer of the eye, giving a white appearance.
Pseudoleukocoria	High and/or asymmetrical refractive error (anisometropia) can give an asymmetrical appearance to the red reflex, simulating leukocoria.

FEVR=familial exudative vitreoretinopathy, ROP=retinopathy of prematurity.

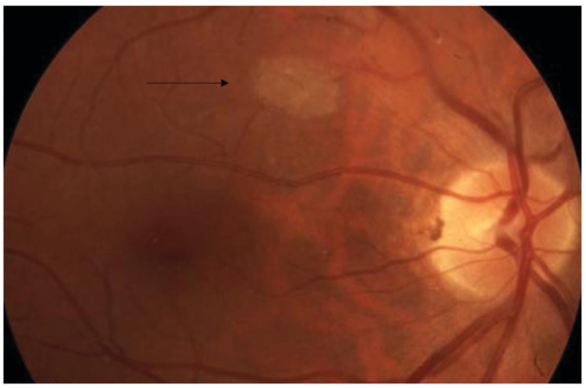

Figure 13. Astrocytic hamartoma in a patient with known tuberous sclerosis.

from flat, sessile, translucent masses to nodular "mulberry"-type tumors with calcifications (Fig 13). (68)(69) Patients with tuberous sclerosis and astrocytic hamartomas are more likely to have intracranial and extracranial tumors, such as subependymal giant cell hamartomas and renal angiomyolipomas. (72) Astrocytic hamartomas are often asymptomatic but have the potential to exert traction on the retina and cause visually significant accumulation of subretinal fluid depending on size and proximity to the macula. (68) In vision-threatening cases, the mTOR inhibitors sirolimus and everolimus have been shown to reduce lesion exudation and size. (73)

Intraocular Melanocytic Lesions

Uveal Nevi. Uveal nevi are benign proliferations of melanocytes of the iris and posterior choroid (Fig 14). (74) They are asymptomatic and remain stable in size over time. (75)(76)

Congenital Hypertrophy of the Retinal Pigment Epithelium. Congenital hypertrophy of the retinal pigment epithelium (CHRPE) are benign, flat, darkly pigmented lesions of the retina present from birth. (77) They have characteristic nonpigmented lacunae with surrounding halo and are

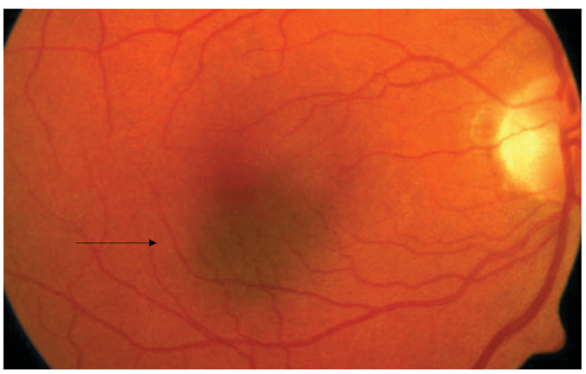

Figure 14. Benign choroidal nevus (arrow) in the macula diagnosed on routine fundus examination.

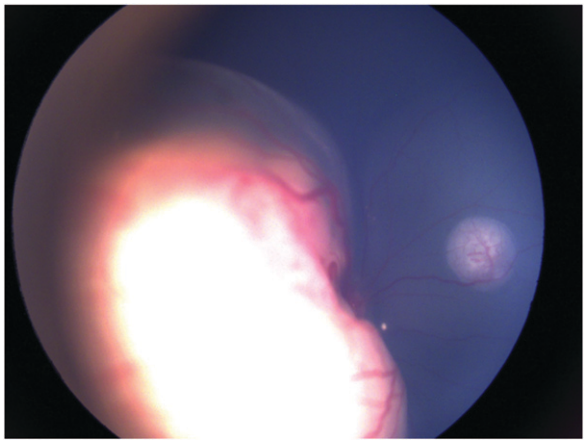

Figure 15. A 5-year-old boy with leukocoria found to have retinoblastoma.

diagnosed incidentally on fundus examination. (78) The presence of bilateral or multiple small, pisciform CHRPEs is associated with familial adenomatous polyposis, and patients are at high risk for colon cancer. (79)(80)

Melanocytoma. Melanocytomas are benign lesions typically at the optic disc where they appear deeply pigmented and are easily diagnosed on fundus examination. Although most are diagnosed in adulthood, children as young as infancy have presented with these benign lesions. (81) Growth and complications, including glaucoma and vision loss, may rarely occur. Malignant transformation occurs in 1% to 2% of lesions. (82)

Melanoma. Uveal melanoma is rare in children and composes less than 1% of all uveal melanomas. (83) Ocular melanocytosis, described previously herein, increases the risk of uveal melanoma, and patients with this condition should be followed regularly for life.

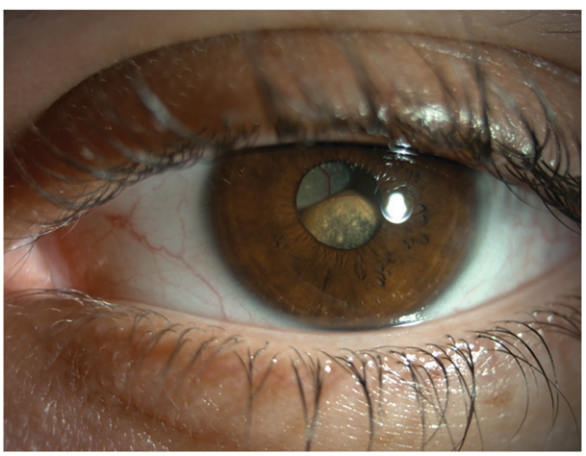

Figure 16. Tumor visualization in the pupil causing leukocoria.

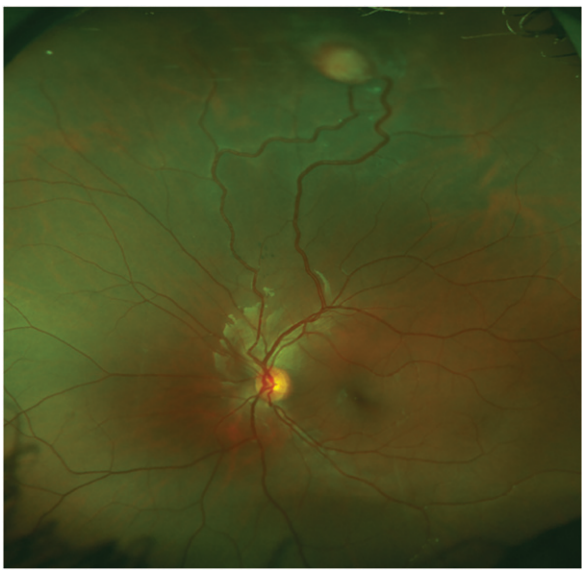

Figure 17. A 16-year-old girl with von Hippel–Lindau disease and retinal hemangioblastoma. Note the classic feeder and drainage vessels from the tumor.

Retinoblastoma. Retinoblastoma is the most common intraocular malignancy of childhood (Fig 15). (84)(85) It is caused by a loss-of-function mutation in the *RB1* gene on chromosome 13. (86) Sporadic mutations lead to unilateral disease, and hereditary, germline mutations typically cause bilateral disease. Patients with germline mutations are at risk for other tumors, including pineoblastomas and secondary sarcomas. Retinoblastoma typically presents in children before 4 years of age. (84) Approximately 30% of cases are due to germline mutations. It is crucial that these patients and their families receive appropriate genetic counseling. All first-degree relatives of a patient with germline retinoblastoma should be screened as soon as able after a diagnosis and then receive dilated fundus examinations every 1 to 2 years, indefinitely. (87)

The most common presenting sign is leukocoria, followed by strabismus and orbital inflammation, or pseudocellulitis (Fig 16). (84)(88) Standard of care for advanced tumors is enucleation. Smaller tumors can be treated with globe-salvaging methods, including intravitreal chemotherapy, intravenous chemotherapy, and intra-arterial chemotherapy, a newer technique that delivers chemotherapy via a microcatheter directly into the ophthalmic artery. Other focal treatment types, such as laser, cryotherapy, and plaque radiotherapy may also be used. (89)(90) In developed countries, death from retinoblastoma is rare. (91)

Choroidal Hemangioma. Choroidal hemangiomas are benign, congenital, vascular tumors that occur in 2 forms, circumscribed and diffuse, the latter being associated with Sturge-Weber syndrome. (92) When asymptomatic, they can be monitored. If visual complications occur, such as retinal detachment, treatment options include lasers, radiation, and/or anti–vascular endothelial growth factor injections. (93)(94)

Retinal hemangioblastoma. Retinal hemangioblastoma is a rare, benign, vascular tumor with a characteristic dilated feeder artery and a tortuous draining vein (Fig 17). (95) Retinal hemangioblastoma is highly associated with von Hippel–Lindau disease, an autosomal disease resulting in a range of benign and malignant tumors. Patients with retinal hemangioblastoma should undergo evaluation for von Hippel–Lindau. (96) Macular involvement, leakage of subretinal fluid and exudates, and bleeding may result in vision loss; treatment options include laser therapy and radiation. (96)(97) Early studies have shown that belzutifan, an HIF-2a inhibitor recently approved for treatment of von Hippel–Lindau–associated tumors in patients older than 18 years, leads to regression of retinal hemangioblastomas. (98)

Summary

Tumors of the eye, orbit, and ocular adnexa can arise in the pediatric population. These entities can be vision- and life-threatening and may be associated with systemic disease. Given their relative rarity, pediatricians must be aware of these conditions and understand what findings warrant immediate referral to an ophthalmologist for initiation of further testing. (Based on strong clinical evidence and consensus)

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PIR QUIZ

1. A 14-month-old child is brought to the clinic by his parents because of a 0.5-cm-diameter lesion on the left lower eyelid along the lash line. The parents report that the lesion has been slowly growing during the past few weeks. On physical examination the lesion appears nontender. You suspect a chalazion. Which one of the following mechanisms represents the etiology of this eyelid lesion?

   A. Bacterial infection of the eyelid eccrine glands.
   B. Blockage of the eyelid sebaceous glands.
   C. Capillary malformation of the eyelid.
   D. Melanocytic proliferation.
   E. Poxvirus infection.

2. You are examining a newborn infant and find an opaque yellow-white mass on the right eye just lateral to the cornea. You suspect that this represents a choristoma. Which one of the following is the most appropriate management at this time in this patient?

   A. Antibiotic ophthalmic solution.
   B. Corticosteroid ophthalmic drops.
   C. Excision of the lesion.
   D. Observation.
   E. Referral to pediatric oncology.

3. A 3-month-old infant is being followed for an enlarging blueish, bumpy lesion of the upper eyelid. The lesion is now causing ptosis, obstructing the visual axis. Which one of the following is the most appropriate initial treatment in this patient?

   A. Observation.
   B. Systemic antibiotics.
   C. Topical antibiotic ointment.
   D. Topical antiviral therapy.
   E. Topical timolol.

4. A 10-year-old boy presents with the rapid onset of proptosis of the left eye, associated with eyelid edema, redness, and ptosis. A mass is palpable in the lateral aspect of the orbit. A computed tomographic scan shows a solid mass displacing the globe. Which one of the following steps in management is most likely to inform the prognosis of this condition in this patient?

   A. Biopsy of the lesion.
   B. Chemotherapy.
   C. Genetic testing for neurofibromatosis type 1.
   D. Intravenous antibiotics.
   E. Observation.

5. A 2.5-year-old child with neurofibromatosis type 1 presents with decreased vision in the left eye and slowly progressive proptosis. A magnetic resonance image of the brain and orbits shows a well-circumscribed enlargement of the optic nerve on that side. Which one of the following is the most likely diagnosis in this patient?

   A. Acute myelogenous leukemia.
   B. Ependymoma.
   C. Low-grade pilocytic astrocytoma.
   D. Meningioma.
   E. Metastatic neuroblastoma.

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