Pediatric Conjunctival and Intraocular Malignancies

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Introduction

Now, nearly 15 years after the first edition of *Pediatric Oculoplastic Surgery* was published, pediatric conjunctival and ocular malignancies still are rare conditions that some ophthalmologists may never encounter in their practice. Although the rarity has changed, for some conditions, such as retinoblastoma, radical changes in the genetics, treatment, and prognosis have occurred. Still, the clinical presentation and evaluation of these lesions require a similar process as in the past with the oculoplastic physician more likely to play a secondary or tertiary role in the care of these cases requiring some basic knowledge of treatment options, prognosis, and counseling for the family when deciding on potential procedures or alternative therapies for that patients' particular condition, stage, and preference. Other chapters in this text delve in depth regarding lid and orbital processes, including benign and malignant varieties, and, therefore, these will not be covered in this chapter. What lies between these anatomic areas is the conjunctiva and globe having separate conditions that may involve oculoplastics for certain treatment options that we will attempt to elucidate.

Conjunctival Malignancies

Epibulbar tumors in children are rare and malignancies of this tissue rarer still. Several series of pediatric conjunctival lesions and their pathologic features have been reported over the last 29 years [1–3]. All series demonstrate a consistent frequency of tissue-type lesions that are grouped as being melanocytic, choristomatous, vascular, epithelial variants, xanthomatous, or reactive. These three series identified only seven malignant lesions: three non-Hodgkin's lymphomas, one botryoid rhabdomyosarcoma, two melanomas, and one squamous carcinoma that arose in a child with xeroderma pigmentosa. Melanocytic lesions accounted for over 50% of the biopsied lesions.

Clinical features may help distinguish benign from malignant lesions especially with melanocytic lesions. Called upon to evaluate, excise, or biopsy, these lesions require some forethought as to what part to biopsy and what tissue studies and stains may be needed, will immunohistochemistry be helpful in deciphering these lesions, and what additional repair or grafting may be necessary (see Chap. 16).

Ocular Melanosis

Melanosis is the presence of excessive melanocytic pigmentation. It is classified based on two considerations: whether it is congenital or acquired and whether it is intraepithelial or subepithelial. A cutaneous area of epithelial congenital melanosis is more popularly known as an ephelis or freckle. Presentation in the conjunctival epithelium shows a similar picture with a distinct area of dark pigmentation that is not adherent to the underlying Tenon's capsule or episcleral tissues. Subepithelial congenital melanosis has a distinctly different clinical picture with the abnormal melanin-containing cells situated in the sclera and episclera producing a slate blue appearance (Fig. 12.1). This external finding coupled with increased uveal melanocytes is termed ocular melanocytosis. No distinct conjunctival pigmentation is observed in this condition, but it is included here due to its frequent confusion as a pigmented conjunctival lesion.

Ocular melanocytosis is a congenital lesion often visible in the first few weeks of life as irregular areas of unilateral episcleral pigmentation, heterochromia iridis, and increased choroidal pigmentation. It may first become visible when the patient achieves puberty. Increased size and numbers of melanocytes in these areas account for this appearance. If this process carries over to the surrounding dermis with resultant patchy skin pigmentation, one can diagnose this as oculodermal melanocytosis or nevus of Ota (Fig. 12.2).

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While ocular melanocytosis is almost always unilateral, nevus of Ota can be bilateral but asymmetric. A proclivity toward Asian (especially Japanese) and Black patients is consistent; nevus of Ota occurs 50–75 times more frequently among patients of Japanese extraction compared with American Blacks [4]. The incidence of nevus of Ota in Caucasians is approximately five times less than in Blacks. Ocular melanocytosis occurs more commonly in Caucasians.

Since the conjunctiva itself has no involvement, no conjunctival pigmented malignancies arise in these forms of ocular melanosis. Due to the pigmentary abnormalities arising in the uvea, episcleral, and orbital tissues, intraocular and orbital melanomas have arisen in both ocular melanocytosis and nevus of Ota [5–8]. In the first edition of this text, a note was made of the shortage of data and studies as to the risk of developing melanoma and metastases in these individuals with oculo(dermal) melanocytosis. Newer studies, particularly retrospective evaluations in children and adolescents with melanocytosis and melanoma, give a clearer picture of these risks. Several retrospective studies mostly from the large melanoma population at the Wills' Ocular Oncology Service have revisited and recalculated incidence and metastases of intraocular melanoma in children and teenagers [9–11]. In Singh et al. 2000's review of this population of pediatric patients with intraocular melanoma, it was estimated that an iris, ciliary body, or choroidal melanoma in children under the age of 20 was nine times more common in patients with oculo(dermal) melanocytosis [9]. An additional review of this cohort was published by Shields et al. in 2013 identifying 122 children and teenagers with uveal melanoma finding 4 patients (3%) with ocular melanocytosis but no case of nevus of Ota [10]. Nevus of Ota is unusual in that uveal melanoma is unknown in the pediatric age group with the earliest reported case in a 34-year-old White female [4]. A further retrospective follow-up study of this expanding cohort of intraocular pediatric melanomas by Kaliki et al. performed a matched retrospective cohort study evaluating the influence of age on these younger patients versus adults which focused on iris, ciliary, and choroidal melanomas and the incidence of metastasis [11]. Using Kaplan-Meier analysis, this study found a significantly lower risk of metastatic disease at 3, 5, and 10 years post-diagnosis in children than adults supporting the importance of early evaluation and follow-up of children with ocular melanocytosis and oculodermal melanocytosis.

Finally, Shields et al. reported on the specific association of rate of metastases in patients with oculo(dermal) melanocytosis-related uveal melanoma in their cohort of 7282 uveal melanomas [12]. A total of 230 patients in this cohort had oculo(dermal) melanocytosis and showed a twofold greater rate of metastases at 10 years posttreatment. This led to the recommendation of twice yearly dilated exams and OCT enabling earlier diagnosis of uveal melanomas in these patients.

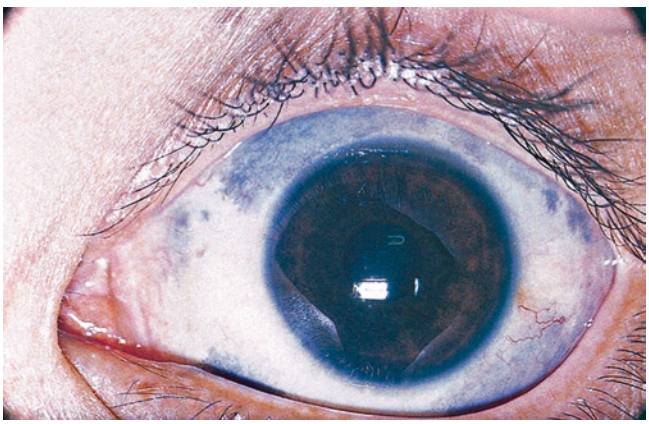

Fig. 12.1 External photograph showing bluish scleral coloration typical for ocular melanocytosis

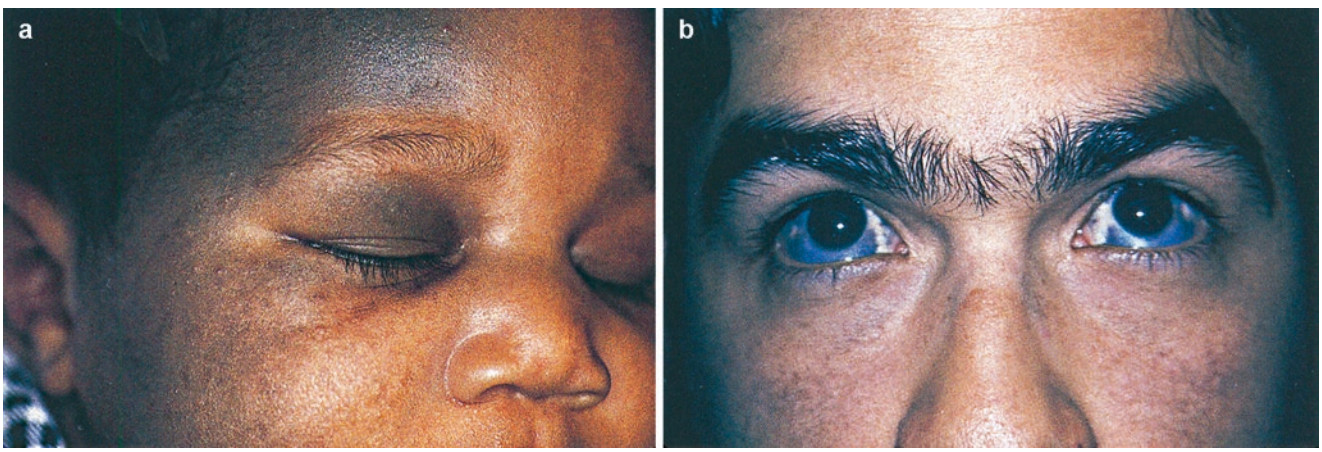

Fig. 12.2 Oculodermal melanocytosis. (**a**) Periocular facial pigmentation observed with oculodermal melanocytosis. (**b**) Unusual case of bilateral oculodermal melanocytosis

Conjunctival Nevi/Melanoma

Conjunctival nevi are not uncommon in the pediatric population. An exact incidence is unknown, but when conjunctival nevi do arise, 43% are apparent by 10 years of age, and another 22% are seen by age 20 [13]. Most appear on the bulbar conjunctiva frequently near the limbus. Approximately 14% are seen on the caruncle or semilunar fold but are unusual to arise in the tarsal or lid margin conjunctiva [2]. The majority are seen in Caucasians with much less frequency in Asians and Blacks.

Three histopathological subtypes classify conjunctival nevi: junctional, compound, and subepithelial. This classification is the same as that used for cutaneous nevi. Melanocytic nevus cells derive from epithelial melanocytes or their neural crest precursors. Collections of these cells are called nevi. Junctional nevus cells are located entirely within the epithelium of the conjunctiva and account for approximately 19% of all pediatric conjunctival nevi. Subepithelial nevi are the largest group accounting for 73% of pediatric nevi [14]. Compound nevi are the least frequent (8%) and have epithelial and subepithelial rests of cells. The clinical appearance of pediatric conjunctival nevi is similar to that in adults – a variable pigmented, isolated, flat lesion usually near the limbus without significant vascularity or inflammatory signs (Fig. 12.3a).

Junctional nevi often have cysts within the pigmented portion of the lesion that purport the benign nature of the nevus (Fig. 12.3b). Clinically scattered pigmentation throughout the epibulbar tissue denotes melanosis rather than nevus. This can be racial pigmentation as seen in very dark-skinned Blacks or melanocytosis if other ocular tissues are involved as previously discussed. Gradually increasing or changing pigmentation or lesion enlargement, especially near puberty, is not unusual and does not typically denote malignant transformation.

The diagnosis of conjunctival melanoma in the pediatric age group is decidedly rare [15]. Review of a large cohort of conjunctival tumors in childhood found melanocytic lesions to have less than a 1% chance of conversion to malignancy [1]. A large study evaluating the clinical appearance of conjunctival nevi and their pathological diagnosis and therapeutic outcome found no clinical features that were consistent with malignant transformation as all specimens were benign on histopathologic examination [16]. Clinical features suspicious for melanomatous transformation in conjunctival nevi have included rapid enlargement, marked pigmentary changes, nodular enlargement within the nevus, and the development of "feeder" vessels. These features were present in multiple specimens in the previously cited reference, but no melanoma was found on pathology. What other clinical features should one use as being suspicious for melanoma resulting in the decision for surgical intervention? The largest series to date evaluating the relationship of conjunctival melanocytic lesions and melanoma did not include data regarding patent age [17]. However, the clinical information regarding the presentation of these reported melanomas features a consistent theme: a pigmented lesion noticed for several years, not evident at birth, which suddenly and rapidly began to change in size and/or pigmentation. This would insinuate that these malignant transformations occurred de novo rather than arising from melanocytic changes in the conjunctiva which is somewhat supported by histopathologic slides lacking signs of nevus cells at the base of these malignancies [17]. Two authors report conjunctival melanomas that presented with ulceration prior to excision and indicate that ulceration was an important prognosticator for local control and survival for these lesions [18, 19]. Tumor thickness was also an important prognosticator as well [18]. Presence of the lesion arising on non-bulbar conjunctiva was considered to be a risk for melanomatous transformation in one case report (Fig. 12.4) [19]. One large observational

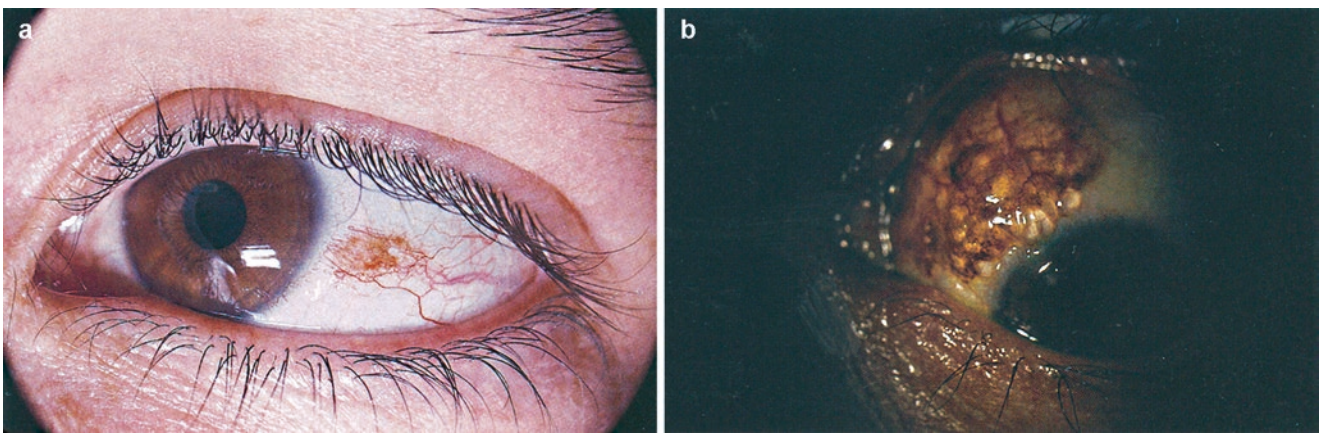

Fig. 12.3 Conjunctival nevi. (**a**) Bulbar conjunctival nevus with *brownish*, wispy conjunctival pigmentation. (**b**) Larger conjunctival nevus with multiple cysts

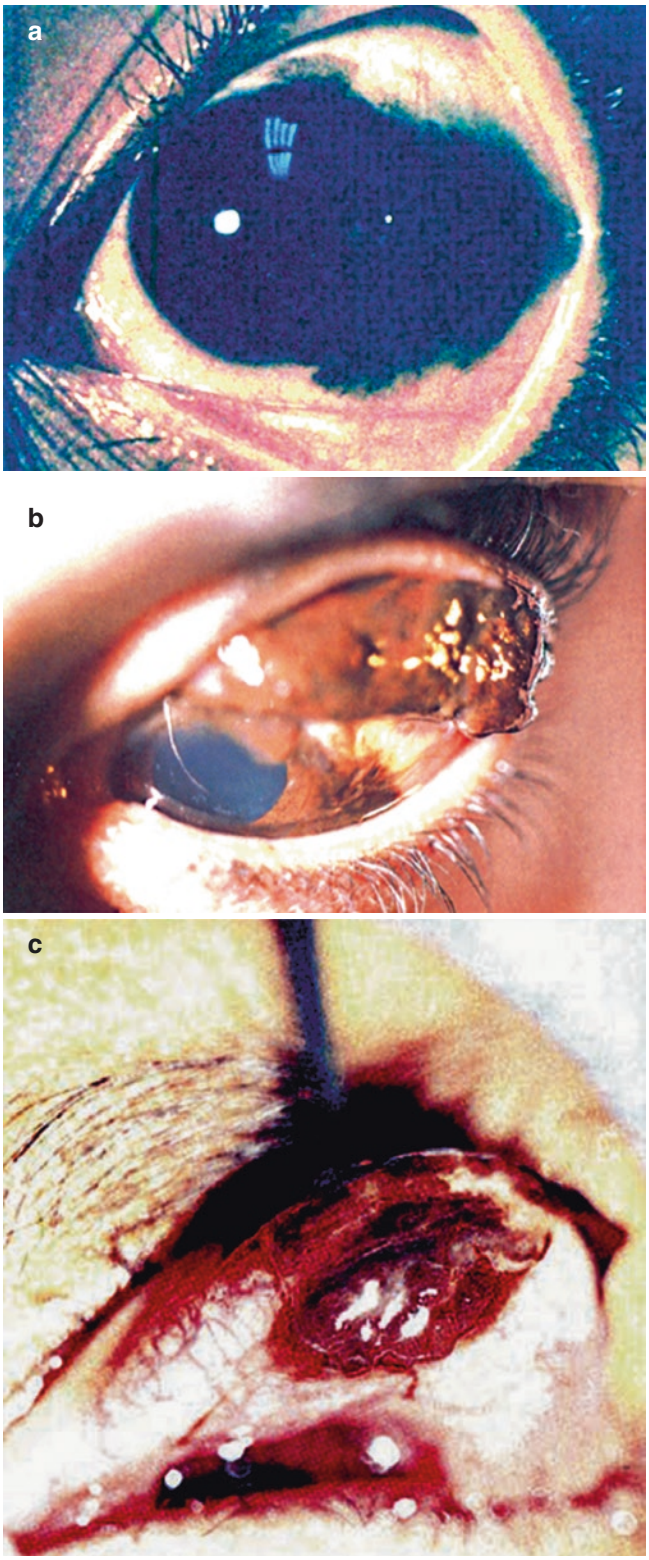

Fig. 12.4 (**a**) Polaroid photograph of large, congenital bulbar conjunctival pigmented lesion in a 12-year-old female. Surgical excision was performed and the pathology report indicated a nevus. (**b**) Clinical appearance 1 year later demonstrating bulbar and palpebral recurrence of pigmented masses that on biopsy are malignant melanoma. (**c**) Double eversion of the upper lid shows supra-tarsal tumor

study of 410 patients with conjunctival nevi found three patients transforming to melanoma (two compound nevi and one blue nevus), but all of these three were adults [20].

It is difficult to arrive at any solid clinical criteria that signal malignant transformation of childhood nevi primarily because so few cases have been reported. A pigmented lesion present for several years, not present at birth, with sudden change in size, pigmentation, thickness, and ulceration or arising from palpebral conjunctiva should alert the clinician to possible transformation.

What should be the next step: biopsy or excision? In children, strong consideration should be given to complete excision with 3 mm margins and submission for fixation and evaluation for tumor type and tumor thickness and whether the margins are free of tumor [13]. Frozen section analysis is fraught with difficulties including obscuration of cells by pigment and distortion of cell morphology. Pathology is very important in establishing the tumor type, marginal involvement, and grade for staging purposes. General agreement among pathologists has emerged regarding the features of atypia in grading conjunctival melanocytic lesions [21, 22].

Still, some lesions defy easy classification resulting in the pursuit of immunohistochemical markers to achieve more definitive diagnostic certainty for the classification of benign, carcinoma in situ and melanomatous lesions of the conjunctiva [23–25]. Here again, the vast majority of these conjunctival melanomas occur in adults, most of which arise from primary acquired melanosis which are exceedingly rare in children and which dominate this research in immunohistochemical analysis as an avenue of better identification for differentiating equivocal melanotic specimens as benign or malignant. Despite the adult predilection, the expression of certain cell antigens could possibly be expected from any melanocytic lesion with the potential of malignant transformation. Jakobiec et al., in a study of immunohistochemical analysis of atypical conjunctival melanocytic lesions (blue nevus, granular cell nevus, epithelioid nevus, and balloon cell nevus), demonstrated that Ki-67 expression was very low (<1%) in these benign variants, whereas this same expression in conjunctival melanomas is usually greater than 10% in nuclear positivity among all cells counted in these specimens [23, 24]. The consideration of immunohistochemical analysis should be utilized in any atypical melanocytic conjunctival lesion where clinical features do not reveal a clear-cut diagnosis.

Faced with these limitations, one must still consider the rate of recurrence after resection and the potential for metastatic spread. Adjuvant treatment with topical mitomycin C, interferon alpha-2b, or 5-fluorouracil may control future recurrence with positive margins seen on pathologic specimens as a secondary treatment based on final pathology findings [18]. As with adult conjunctival melanoma, clinical

recurrence may be difficult to assess if pigmentation is not present. Consideration of conjunctival biopsies for any suspicious area of conjunctival erosion, hypervascularity, spotty pigmentation, or amelanotic thickening is warranted. The potential role of topical adjuvant treatment in superficial recurrence or de novo melanomatous change would seem advantageous in these circumstances. It warrants reinforcement that palpebral conjunctiva needs to be adequately visualized in the follow-up of these patients.

Finally, with clear marginal resection, what should be done to monitor for future systemic disease? Only two case reports of metastatic disease in children with conjunctival malignant melanoma have found their way into the literature [15, 26]. Both cases had a history of rapid recurrence after initial and subsequent surgical resection. Folberg et al., with their clinicopathologic review of conjunctival melanosis and melanoma in adults, reported both pathologic and clinical entities that indicate the likelihood of future metastatic or local recurrence: tumor extending to the margin or base of the specimen, orbital extension, a common pagetoid growth pattern, involvement of the caruncle, the full thickness of the epithelium simulating an in situ carcinoma, the absence of an inflammatory response to the invasive component of the lesion, tumor thickness greater than 0.8 mm, and the presence of five or more mitotic figures per ten high-power fields [17]. One could certainly add rapid recurrence after resection to this list which, individually or in multiples, would be a good reason for the involvement of a pediatric oncologist for short-term metastatic assessment and long-term monitoring. The role of the oculoplastic physician will undoubtedly be integral to the original surgical resection and repair of postsurgical defects as well as the possible role of exenteration as a life-sparing technique in hopes of surgical tumor control. The above reference of orbital extension harboring worsening prognosis for survival is based on the clinical findings that approximately 90% of patients at the time of exenteration are already manifesting systemic metastases making exenteration of little use except for pain or mass effect control.

Other Conjunctival Malignancies

A variety of rare conjunctival tumors have been described in the pediatric population. While most practitioners are unlikely to encounter these entities, an awareness of their presentation is essential when evaluating a suspicious conjunctival mass.

Conjunctival Rhabdomyosarcoma

Periocular rhabdomyosarcoma typically not only arises as an intraorbital tumor but can also originate in other sites (lids, iris, and periorbital subcutaneous tissues) and as a conjunctival mass [27]. The conjunctival clinical features are typically

Fig. 12.5 Conjunctival embryonal rhabdomyosarcoma in a 9-year-old female

a pinkish multilobulated/papillary epibulbar lesion with prominent feeder vessels with rapid growth (Fig. 12.5) [28].

Other pediatric conjunctival lesions have similar appearances and include juvenile xanthogranuloma, squamous papilloma, leukemia, lymphoma, and neurofibroma [29]. The clustering multilobulated appearance is the origin of its name, botryoid rhabdomyosarcoma. While the tumor appears to arise from the conjunctiva, it is a subconjunctival mass that can have the episcleral, lid, or anterior orbital tissues as its site of origin.

Clinical series reporting on primary ocular rhabdomyosarcoma place the conjunctiva as the least likely site of origin in the periocular region. One series found only one case in the 33 patients with primary ocular rhabdomyosarcoma [30]. Single case reports along with their review references bring the total of conjunctival rhabdomyosarcoma cases to 14 [28–35]. No sex predilection or specific age range has been identified. Embryonal, alveolar, and botryoid patterns have been reported. No intraocular invasion has been reported, but one case of subconjunctival extension as the presenting sign of an intraocular rhabdomyosarcoma has been reported.

The treatment of conjunctival rhabdomyosarcoma is no different than the presentation in other body sites; attempts at complete excision with follow-up chemotherapy and/or radiation therapy based on systemic staging work-up yield the greatest long-term survival [31]. Inability to completely excise the tumor increases the death rate with greater short-term findings of increased regional and systemic metastasis. One must weigh the morbidity of surgical resection against the side effects of radiation therapy especially around the eye and orbit which is increased in still developing sockets. Oculoplastic surgeons will be called upon for their expertise in the surgical management of these patients due to their periocular origin. Imaging studies are a must in guiding surgical decision-making. If the conjunctival lesion fits the profile of a suspected rhabdomyosarcoma, one should assume that it is arising from orbital or peribulbar tissue rather than conjunctiva alone just based on the infrequency of pure conjunctival rhabdomyosarcoma.

Leukemia/Lymphoma

Conjunctival involvement in pediatric leukemias and lymphomas as a presenting sign is rare. With leukemias, especially the acute forms, eye signs in general and conjunctival forms specifically are not unusual. Several large series have looked at the incidence of ocular abnormalities associated with pediatric leukemias [36–38]. A very recent series found 24% of all children diagnosed with acute myelogenous leukemia, and acute lymphoblastic leukemia had ocular signs [36]. Of this group with ocular signs, 12% had conjunctival signs of venous stasis, conjunctival hemorrhage, or conjunctival mass (Fig. 12.6). The venous stasis is thought to arise from leukemic hyperviscosity of these small vessels and is visible in the retina as well, while the conjunctival hemorrhages are thought to be from decreased platelet levels. Interestingly, in this series, low systemic platelet levels were significantly lower in children with ocular changes from their leukemia [36]. Only one third of the patients with eye signs had symptoms from their ocular changes.

Postmortem studies reveal that 27% of children with leukemia have ocular, orbital, and /or conjunctival changes [38]. Clinically, these present as either infiltration of tissues by leukemic cells or the manifestations of some systemic hemodynamic abnormality, usually hypercoagulation, with attendant physical signs. Proptosis, hypopyon, reduced visual acuity, and cranial nerve palsy can signal leukemic infiltration in the orbit, anterior chamber, optic nerve, and cavernous sinus, respectively. Conjunctival hemorrhages and tortuous vessels mark the presentation of hyperviscosity complicating leukemias [39]. Conjunctival mass formation from leukemia has been reported but carries no specific clinical features that allow accurate diagnosis of leukemic infiltration without biopsy [40]. Anterior orbital involvement can "spill" into the subconjunctival area and appear as an isolated conjunctival mass or hemorrhage.

There is a major change in the association of ocular findings in childhood leukemia and its association with increased mortality. Ridgway et al. and Ohkoshi and Tsiams both reported a greatly increased mortality risk with ocular findings in children with leukemia [37, 41]. The very recent publication by Bitirgen et al. found no increased risk of mortality in their large cohort of children followed long term with leukemia [36]. This may be due to advances in treatment that have led to increased survival rates in these acute pediatric leukemias.

With this increased survival, recurrences are predictably more commonly seen. A few case reports have been published describing eye findings as the first presentation of the recurrence [42, 43]. Three of the four cases in these two reports of eye findings heralding the recurrence of acute leukemia in previously treated children were initially diagnosed as acute iritis. These cases were initially treated with topical corticosteroids with a poor response to the treatment resulting in suspicion of a potential recurrence of the leukemia as a masquerade syndrome. These three cases underwent anterior chamber paracentesis and aqueous aspirates that showed leukemic recurrence. The fourth case presented as a hemorrhagic conjunctival mass that was biopsied showing leukemic cellular collections. These recurrences are a reminder of the protean features of recurrence in childhood leukemias and the importance of history taking regarding other systemic conditions with pediatric uveitis [43].

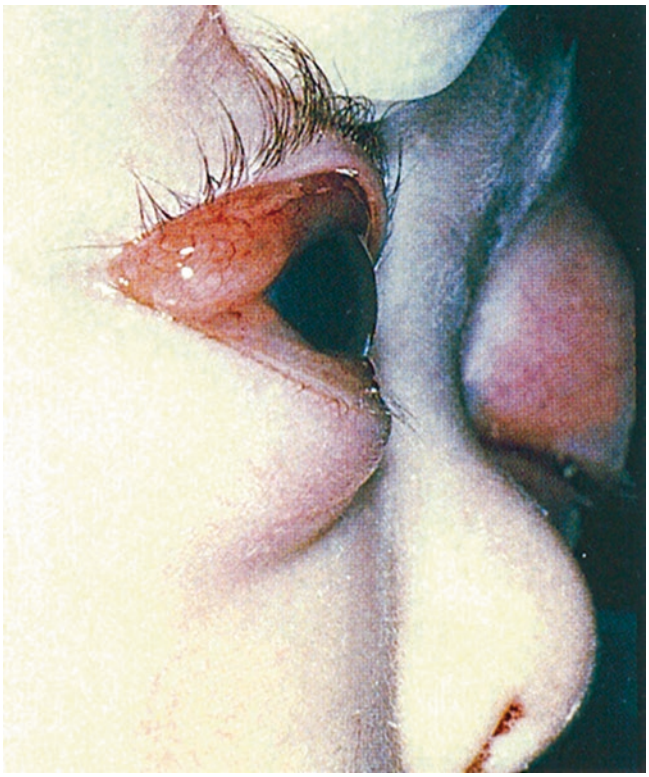

Fig. 12.6 Conjunctival extension of AML in a 3-month-old child

Pediatric ocular lymphoproliferative disorders continue to be rare with most large series of pediatric conjunctival lesions reporting no lymphomatous processes [3]. Several case reports of a single pediatric patient have been published identifying unilateral or bilateral conjunctival lymphomas of the anaplastic large cell, follicular, MALT, and extranodal marginal B-cell variants [44–48]. Several case reports have been published of benign reactive lymphoid hyperplasia with both unilateral and bilateral presentations [49, 50]. The clinical features are similar in appearance to adults with a salmon pink-colored, smooth, noninflamed, solid-appearing conjunctival lesion presenting on the bulbar conjunctiva or fornices (Fig. 12.7).

It is much more common for ocular adnexal lymphomas in any age group to arise in the orbit presenting with proptosis, but if the lymphoma is in the anterior orbit, a conjunctival

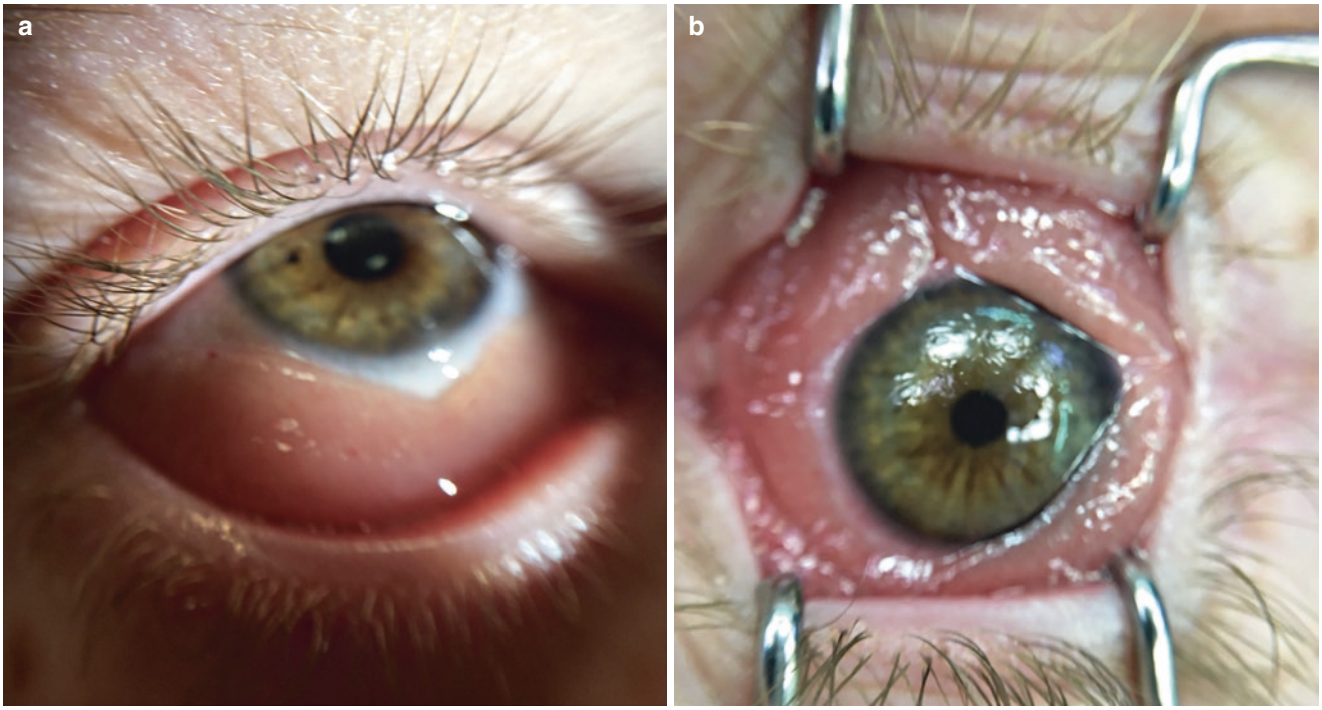

Fig. 12.7 (**a**, **b**) Conjunctival MALT lymphoma in a 6-year-old child

portion may be the visible component announcing the presence of this condition. With purely conjunctival onset, no other clinical findings such as proptosis, ptosis, motility disorders, or globe dystopia would be expected which should draw one's attention from the conjunctival component and the investigation of additional areas of involvement. MR imaging should be strongly considered with conjunctival lesions suspicious for lymphoma due to their rarity as an isolated presenting position. Conjunctival biopsy, if large, or resection, if small, with histopathologic and histoimmunologic analysis will be able to identify the lesion and direct appropriate workup and eventual treatments. Oculoplastic surgeons may be the primary referral for this intervention or for orbital biopsy to obtain adequate tissue.

Burkitt's lymphoma has been reported as an entity that can present with conjunctival involvement [51]. Although typically presenting in the orbit or extending from paranasal sinuses to involve the orbit, associated cranial neuropathy, proptosis, optic neuropathy, African descent, and an immunocompromised status such as positive HIV status or immunosuppressants for organ transplantation should alert one to this diagnosis. A report of three non-African non-immunocompromised patients with Burkitt's lymphoma along with a literature review accumulating 16 cases found the average age of presentation was 12 years old with 50% having coexisting sinus involvement [52]. This reminds us that lymphoma is always a systemic disease likely not arising from a single abnormality but a variety of cofactors such as genetic abnormalities and mutations and various viral and bacterial agents creating a treatment environment that currently includes chemotherapeutic agents, radiation therapy, and even antibiotics [44, 53–58]. The care of this condition always resides in the hands of pediatric oncologists.

Langerhans Cell Histiocytosis

Formerly known as a triad of conditions, eosinophilic granuloma, histiocytosis X, and Letterer-Siwe disease, Langerhans cell histiocytosis comprises a set of clinical presentations related to the tissue infiltration of the Langerhans cell, a type of histiocyte. Localized and systemic forms of this condition have varying prognoses, with fulminant malignant histiocytosis being uniformly fatal [59]. Approximately 20% of cases demonstrate orbital involvement with infiltration of these histiocytes in the temporal or sphenoid bones presenting with lid edema and proptosis. The uveal tract, sclera, extraocular muscles, optic nerve, and conjunctiva have rarely shown involvement [60, 61].

The conjunctival presentation is usually in the disseminated form with multisystem disease [62]. Most cases have periorbital bone involvement that extends into the lid soft tissue with attendant lid edema, chemosis, episcleral vessel dilation, and the appearance of a subconjunctival soft tissue mass. Imaging studies quickly define this not as an isolated conjunctival lesion but part of a multifocal systemic disease. However, a single case of an isolated conjunctival histiocytic lesion in a newborn with pathology similar to that of

Langerhans cell histiocytosis has been reported, but without other systemic involvements, it is difficult to classify this as part of this condition [63]. It is unlikely that oculoplastic surgeons will be involved in the management of this condition, but they may present urgently with these periocular findings without a firm diagnosis warranting this inclusion.

Squamous Cell Carcinoma

All ophthalmologists are likely to be familiar with the adult forms of ocular surface squamous cell neoplasia ranging from dysplasia, carcinoma in situ, and squamous cell carcinoma (SCCA). Many reports have established that this condition has several cofactors that increase the risk of onset of this malignant disorder: chronic ultraviolet exposure, certain viral infestations, smoking, exposure to coal tar, and chronic immunosuppression [64–66]. Most children have not been exposed to the environmental factors long enough for these tumors to form which is likely to be the reason these are rare under 20 years of age, but as with most rare conditions, significant assessment of epidemiologic factors is difficult simply due to low numbers of cases.

Conjunctival SCCA has been reported in a child as young as 3 or 4 years of age [67, 68]. Two conditions are known to predispose children to the development of conjunctival SCCA: xeroderma pigmentosa and acquired human immunodeficiency syndrome (AIDS) [69, 70]. Xeroderma pigmentosum is a rare autosomal recessive disorder creating a defect in one of eight genes responsible for the repair of ultraviolet-damaged DNA in epithelial cells resulting in early-onset skin cancers (basal cell carcinoma, squamous cell carcinoma, and melanoma) [71]. When accompanied by progressive neurological abnormalities such as ataxia, deafness, and mental retardation, it is named De Sanctis-Cacchione syndrome [72].

The conjunctival and lid skin changes that occur with xeroderma pigmentosa include scarring, symblepharon formation, cicatricial ectropion with corneal exposure, xerosis, melanosis, and the development of lid and conjunctival SCCA [69, 72]. Basal cell carcinoma and melanoma have been reported on facial skin and the scalp but do not appear to arise in childhood [72]. It is projected that 50% of children will develop a periocular malignancy by 20 years of age [69]. Siblings with this syndrome have developed conjunctival malignancies (Fig. 12.8) [73].

Unlike the adult form of conjunctival SCCA, these lesions occur as localized, reddish masses in sun-exposed conjunctiva with telangiectatic vessels. Multiple areas can be involved and the limbus is not the most common site [69, 72]. Invasion into the orbit or globe may occur, as these are rapidly progressive lesions, if not identified early on and may require more aggressive treatments. Regarding AIDS, conjunctival squamous cell carcinoma arising at a young age was once regarded as a marker for this condition. With ever-advancing therapies for AIDS, conjunctival SCCA and other secondary malignancies have greatly declined where these therapies have been available [74].

Therapy for squamous cell carcinoma of the conjunctiva has changed dramatically over the last 15 years changing from wide margin "no-touch" resection with adjuvant cryotherapy to topical antitumor medications such as mitomycin C, 5-fluorouracil, and interferon alpha-2b (also given as subconjunctival injection). These are frequently the mainstay either alone with smaller lesions or coupled with surgical resection and topical medications to "sterilize" the surface of any remaining cancerous or not yet identifiable dysplastic cells. Much more experience exists with the adult forms to potentially make practitioners comfortable with pediatric use with these medi-

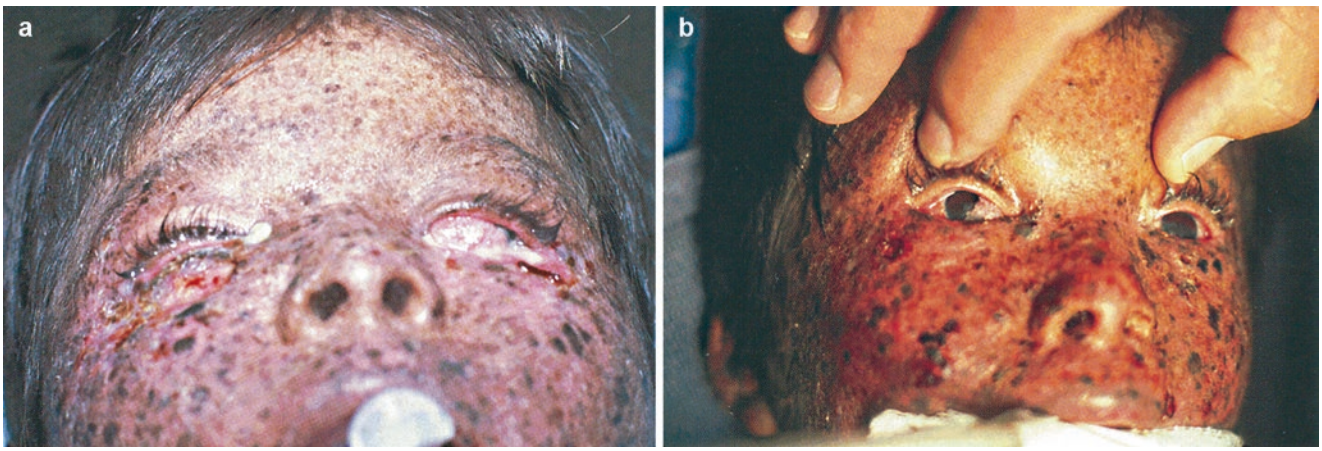

Fig. 12.8 Xeroderma pigmentosa. (**a**) Intraoperative photograph showing facial features typical of xeroderma pigmentosa in a 6-year-old patient. Note the epibulbar mass almost filling the interpalpebral space in the left eye and severe ulcerative changes of the right lower lid. (**b**) Intraoperative photograph of the 5-year-old brother of the patient in (**a**), showing facial skin changes typical of xeroderma pigmentosa. A translucent medial epibulbar mass is present in the right eye. Inferior corneal opacification is present in the left eye (From Hertle et al. [73]. Reprinted with permission from Slack Incorporated)

cations. Cidofovir, approved for human papilloma viral therapy topically or as an injection, has been used on conjunctival and eyelid SCCA but would appear to play no role in the treatment of pediatric conjunctival SCCA due to its different causation. Oculoplastic surgeons could be involved in the care of these patients if intraocular or intraorbital extension occurs, requiring anterior or complete exenteration for tumor control.

Pediatric Intraocular Malignancies

Faced with a child harboring an intraocular mass, the ophthalmologist is obligated to rapidly diagnose the condition such that effective treatment can be undertaken. The diagnosis may require secondary studies such as ultrasonography, CT and/or MR imaging, systemic evaluations by consulting physicians in ophthalmology or pediatrics, and eventual surgical procedures for tissue diagnosis or curative resection. Most ophthalmologists refer these patients to centers in proximity of their practice whom are experienced in the diagnosis and treatments of potentially malignant intraocular lesions.

After establishment of the diagnosis of an intraocular malignancy in a child, oculoplastic surgeons may be called upon to surgically manage this child by performing an enucleation. Many questions will come from the parents regarding the condition, the procedure, the expected healing, prosthesis fitting once healed, and, most importantly, will this save the child's life. This section reviews the malignant ocular tumors of childhood with emphasis on the oculoplastic surgeon's role in the care of these special individuals.

Retinoblastoma

Perhaps no other ophthalmic condition has had as much change in its management than retinoblastoma over the last 20 years. At the time of publication of the first edition of this text, systemic chemoreduction was just beginning to be embraced as a replacement for direct retinal tumor treatment alone or combined with external beam radiotherapy for both unilateral and bilateral retinoblastoma. The need for improved visual outcomes and survival rates along with reduced induction of secondary malignancies drove these therapeutic migrations. Now, intravenous chemoreduction is largely supplanted by intra-arterial delivery of chemotherapeutic agents, via interventional radiographic ophthalmic artery cannulation, giving better targeting of the tumor load and hopefully less systemic and ocular side effects [75–79]. These changes along with earlier detection of the condition have led to a 5-year survival rate of approximately 96.5% but continued the risk of retaining useful vision from new tumor damage, especially in heritable bilateral retinoblastoma cases [80]. More eyes and patients are surviving these treatments.

Where does that leave the oculoplastic/orbital surgeon in the management of retinoblastoma? For the most part, it has not changed very much at all over the last 20 years. The clinical presentation of retinoblastoma is certainly well known to ophthalmologists: leukocoria, strabismus, and ocular inflammation are the initial signs in over 80% of retinoblastomas (Fig. 12.9). Other presenting signs include heterochromia, hyphema, increased intraocular pressure, decreased vision, rubeosis iridis, and phthisis bulbi. Anterior chamber involvement with iris nodules or free-floating tumor is rare and traditionally difficult to treat short of enucleation. With indirect ophthalmoscopy, the presence of multiple pink or white retinal tumors in one or both eyes is highly suggestive of retinoblastoma. A large unilateral tumor with a white-pink mulberry implant-like appearance is the classic retinal lesion and is virtually diagnostic of retinoblastoma (Fig. 12.10).

The dilation and examination of parents and siblings are important because the presence of a retinocytoma or regressed, calcified lesion in the retina nearly completely establishes the possibility of genetic inheritance. When examining children, it is important to keep in mind the lengthy differential diagnosis of retinoblastoma to help direct ancillary investigations (Table 1).

Once the possibility of retinoblastoma is established, at this point, the patient should be referred to an ocular oncologist who will pursue a careful systemic work-up to rule out metastatic disease. Thin-section, 1.5 mm non-contrasted and contrasted computer tomography (CT) of the orbit and head is used to look for calcification within the intraocular lesion

Table 12.1 Differential diagnosis of retinoblastoma

Persistent hyperplastic primary vitreous
Retinopathy of prematurity
Congenital cataract
Coats' disease
Optic nerve coloboma
Nematode endophthalmitis
Retinal dysplasia
Congenital toxoplasmosis
Retinal astrocytoma
Retinal detachment
Norrie disease
Uveitis
Metastatic endophthalmitis
Congenital retinoschisis
Congenital retinal fold
Familial exudative retinopathy
Medulloepithelioma
Persistent tunica vasculosa lentis
Tapetoretinal degeneration
Myelinated nerve fibers

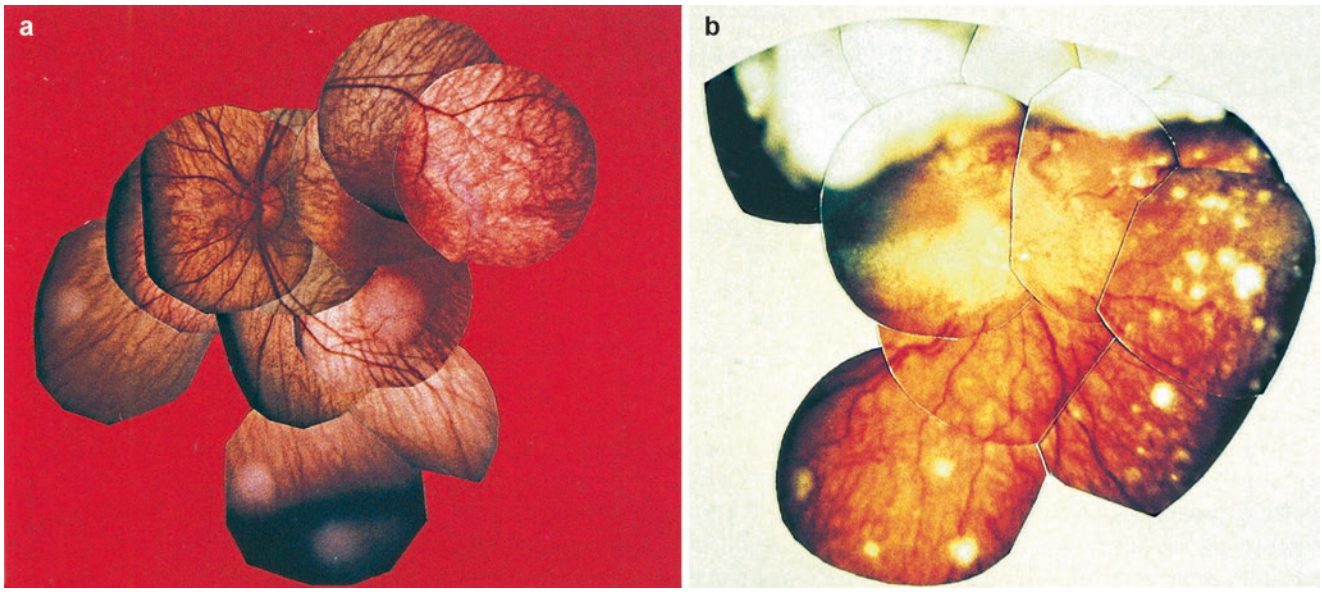

Fig. 12.9 Retinoblastomas. (**a**) Montage photograph of a child with hereditary retinoblastoma with multiple small tumor sites in one eye. (**b**) Montage photograph of child with a presumed somatic retinoblastoma with vitreous seeding and retinal implantation of retinoblastoma seeds. No tumors were in the opposite eye and long-term follow-up will be needed to determine if no other tumors will occur

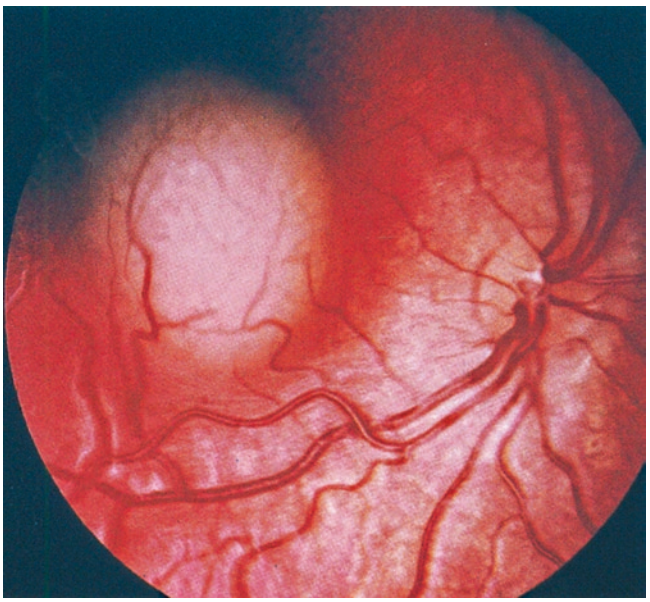

Fig. 12.10 Clinical appearance of retinoblastoma. Common clinical appearance of retinoblastoma with pinkish-white appearance, dilated feeder vessels, and specks of calcium visible in tumor

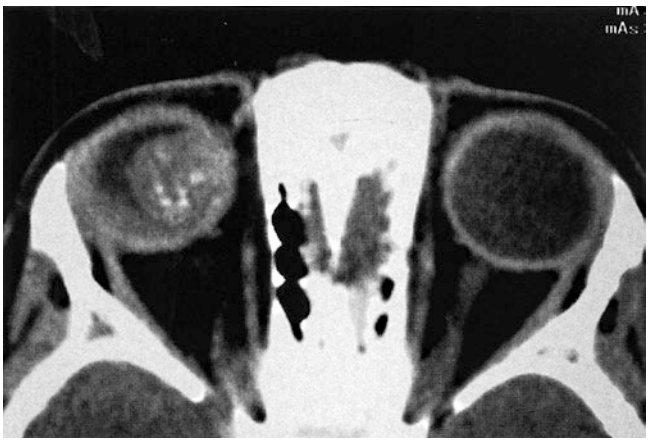

Fig. 12.11 CT of the orbits. Non-contrast CT of the orbits demonstrating intraocular with calcium consistent with retinoblastoma

and when found is virtually diagnostic of retinoblastoma (Fig. 12.11). Rare cases of calcification in *Toxocara* infection and intraocular abscess have been reported and require careful evaluation of the clinical aspects of the disease to differentiate their presentation from retinoblastoma [81, 82].

The non-contrast study shows calcifications better, while the contrasted study better identifies any secondary tumors. Any questionable findings should be pursued with magnetic resonance imaging, which is capable of detecting optic nerve extension better than other imaging techniques [83]. It is important to include the head during the imaging study to rule out the presence of a pinealoma or other midline intracranial primitive neuroectodermal tumors that can occur in children with germline mutations at the retinoblastoma locus (trilateral retinoblastoma).

Spiral CT scanning allows these imaging studies to be performed without anesthesia due to rapid scanning times [84]. Ultrasonography can also be used as a quick evaluation tool for the differentiation of retinoblastoma when high internal reflectivity and acoustic shadowing from calcifications are found [85]. Serology, to include a complete blood count, liver function tests, plasma carcinoembryonic antigen,

and ELISA for *Toxocara* (if clinically appropriate), is used to rule out metastatic disease or to rule in nematode endophthalmitis.

After a rapid review of these tests, the child is then examined under anesthesia at which time the following tasks are performed: a complete ocular examination with emphasis on a 360° scleral depressed retinal examination with retinal drawing to detect any tumor foci, performance of a technetium-99 injection for bone scan, lumbar puncture for cerebrospinal fluid cytology, two-site bone marrow biopsy, and possible treatment of selected tumors with targeted chemo- and/or radiation modalities. If intra-arterial delivery of chemotherapeutic agents has been ruled out, eyes more than 50% filled with tumor, eyes with anterior chamber extension, and eyes with glaucoma due to tumor invasion or neovascularization, or those tumors that have failed local treatment and/or radiation therapy, are typically enucleated.

No treatment has yet been found that eliminates the need for enucleation in some patients with retinoblastoma. The current chemoreduction therapies seem to delay the eventual need for enucleation in some patients, but, as yet, this does not seem to worsen their prognosis [86].

Additionally, a study comparing high-risk histopathologic features of eyes treated primarily with enucleation for retinoblastoma or following chemoreduction with a secondary enucleation for retinoblastoma found no significant difference in metastatic or survival rates [87].

Oculoplastics typically becomes involved in the treatment of retinoblastoma when either intraocular tumor load is no longer responsive to treatment or the eye is irreparably damaged with little hope for any useful vision due to this tumor load or side effects from the attempts to eradicate the tumor. Oculoplastic enucleation skills come into play to provide removal of the involved eye with an adequate specimen for the ophthalmic oncologist to determine if any high-risk pathology features (e.g., tumor through the lamina cribrosa of the optic nerve, tumor at the cut end of the optic nerve, extraocular extension through emissary canals, extensive choroidal invasion) are present and to replenish the orbital volume with an appropriate implant for best long-term orbital stability. Direct communication with the treating ophthalmologist for the patient being referred for enucleation is a must due to heritable retinoblastoma usually being bilateral, and, therefore, both eyes may be responding poorly to ongoing or past treatment. What the family thinks should be done might be different than what their treating physician considers of primary importance.

Once the decision for enucleation has been made, the surgeon must make a choice of an implant if one is to be primarily placed. Most surgeons would agree that primary placement is strongly indicated. Unsuspected extraocular extension can be dealt with by excision of contiguous orbital tissue but would warrant postoperative chemotherapy or radiation therapy as well. With radiotherapy waning in its usage with retinoblastoma, fewer implant problems after enucleation occur than in the past, but periocular chemotherapy with carboplatin and topotecan or past brachytherapy as treatments for intraocular retinoblastoma create a new set of potential issues for both postoperative healing, possible scleral thinning of the enucleated eye, and orbital tissue scarring that can complicate enucleation [88–91]. Despite this, a long-term follow-up (mean, 60 months) of 531 children with coated or wrapped hydroxyapatite implants with four or six extraocular muscles attached developed very few problems (0% extrusion, 1% implant infection, 3% implant exposure) [92]. Another study did not report this same success but did not limit their treatment to a single orbital implant. A 23-year study of 224 enucleations that utilized several different implants (acrylic, Allen, and scleral-wrapped hydroxyapatite) found a 4.6% exposure rate, a 2.7% extrusion rate, and a tripling of these events if the patient had undergone chemoreduction or external beam radiotherapy [93]. This relatively greater risk of implant complications was mirrored in a study of 135 children at St Jude's Research Hospital with 20.7% implant exposure, 11.9% socket contracture, 2.2% extrusion rate, and a 6.7% pyogenic granuloma formation rate [94]. Nearly 80% of the exposures resolved without treatment in this study, but chemotherapy and, especially, radiotherapy before or after the enucleation significantly raised the complication rate. Porous polyethylene orbital implants were used in 44 patients followed over a mean of 5 years after unilateral primary enucleation for retinoblastoma with no implant exposures, extrusions, or infections [95]. Another study looked at dermis fat grafts as a primary procedure in unilateral enucleations of retinoblastoma patients looking specifically at orbital volume compared to the nonoperated side over a median follow-up of 38.5 months [96]. Equal orbital volumes as measured on MRI scans were found, but patients who had undergone radiation or chemotherapy were excluded from the study leaving questions as how dermis fat would fare with concomitant chemotherapy or radiation therapy. One can conclude that any orbit with any implant will have some chance of healing post-enucleation with proximal perioperative need for chemotherapy and/or radiation therapy. Often, this therapy cannot wait an adequate time for orbital healing without increased risk for orbital recurrence or metastatic spread if high-risk pathology features are found. A case can be made for muscle attachment to a pervious implant that can be well covered by orbital and conjunctival tissue as the best approach to prevent implant complications.

Enucleation technique is well covered in this text in Chap. 42. Two points need to be emphasized in securing the removal of a globe with retinoblastoma. First, the length of optic nerve

segment is still an important consideration as tumor at the cut edge of the optic nerve is a very poor prognosticator for orbital recurrence and mortality [97]. Most studies suggest a length of 8 mm would be desirable. The pediatric orbit does not offer the posterior or periocular space that an adult has, making the approach to nerve transection more difficult. The temptation to try and gain more room to achieve a longer nerve segment is to push the globe more temporal or nasal to improve seeing the nerve. It is best to think of giving the enucleation scissors more room which means placing the globe on gentle anterior traction by securing clamps to the small stumps of the medial and lateral rectus muscles after they are disinserted from the globe. I personally do not like to pass sutures into the muscle insertions or sclera for fear of penetration or passage through a tumor laden emissary canal. Gentle forward traction yields 6 or 7 mm of anterior globe displacement and considerably improves the space for scissors. Blunt straight Stevens scissors or a slightly curved small Mayo scissors works well when inserted in the medial orbit straight posterior toward the optic canal.

Once successful transection of the optic nerve has been accomplished and any Tenon's has been separated freeing the globe, the second step is inspection of the sclera and the cut end of the optic nerve for any signs of gross tumor extension. If a short portion of the optic nerve is found (<5 mm), strong consideration should be given to obtaining several more millimeters of the intraorbital portion marking the true margin and placing this in a separate specimen cup. Careful inspection of the perioptic nerve sclera with all the short posterior ciliary vessels and nerves should be performed especially if intraocular tumor covers and hides the optic nerve on preoperative examination. Noting the exact position for the pathologist is important, but also resection of approximately 1 cm of surrounding orbital tissue should be performed to potentially reduce any orbital tumor load. Pathology is very important in deciding on staging but also high-risk features not only for postoperative adjunctive treatment decisions but also for long-term follow-up for local recurrence [98, 99]. Besides the implant, other considerations of tumor therapy also need to be followed (Table 2).

The research originally identifying the first tumor suppressor gene, RB1, to the 13q14.2 locus and the subsequent identification of what that gene produces, pRb, a chemical protein which functions as a regulator of gene expression, has shifted to studying ways to influence the loss of gene suppression utilizing the multitude of chemical pathways controlled by the pRb gene in oncogenesis [100]. The clinical importance of the retinoblastoma gene, RB1, rests not only with the importance in discovering its functions and how these may be manipulated into a treatment algorithm but also in its prediction of the aggressiveness of the patient's retinoblastoma and its predictive value for its transmission to future offspring [101–103]. Genetic counseling should not only be an important part of the care of all children with retinoblastoma but also their family. Determination of heritable versus somatic forms of retinoblastoma greatly affects their short-term prognosis (development of new tumors in the same eye or the other eye) and their long-term prognosis (risk of primitive neuroectodermal tumors and other nonocular malignant neoplasms). Examination of siblings and parents for signs of regressed retinoblastoma and the negative findings of intraocular pathology augment the counseling from genetics specialists and prepare the family for what is ongoing and what may be down the road. A regular ophthalmic follow-up schedule to monitor for new tumor growth or recurrence is essential.

Genetic testing will undoubtedly advance rapidly in the future, and these changes can be researched via the National Institute of Health Genetic Testing Registry (www.ncbi.nlm.nih.gov/gtr/).

Table 12.2 Post-enucleation follow-up points

Risk of genetic causation in unilateral presentation
Risk of second nonocular malignancies
Postradiation tumor risk
Follow-up examination schedule and metastatic evaluation
Genetic testing for the patient and siblings
Sibling examinations

Uveal Melanoma

Intraocular uveal melanoma is rare in children. A recent survey of the European Ophthalmic Oncology Group reported on the frequency of choroidal and ciliary body melanomas in children under 18 years of age reporting on the long-term prognosis of their collective 114 patients [104]. This represented less than 1% of their database cohort which mirrors other ocular oncologists reported incidence of uveal melanomas across all age groups [10]. Reports of uveal melanoma in children in the last 15 years have focused primarily on ciliary body and choroidal melanomas [9–11, 98]. Older series indicate initial clinical misdiagnosis with 20% of children having no suspicion of the presenting lesion being a melanoma but rather were diagnosed initially as glaucoma, vitreous hemorrhage, or Coats' disease [105].

Virtually all recent studies rely on the same methods for diagnosis as one would use for adults: dilated fundus exam, ocular ultrasonography, and a similar metastatic work-up including head, chest, and abdominal thin cut imaging studies looking for other potential malignancies. Faced with this diagnosis, several predisposing clinical conditions need to be

evaluated. First, ocular melanosis and oculodermal melanocytosis have a marked predisposition for uveal melanoma as discussed in the first section of this chapter. In one recent study, 11% of the study cohort was found to have oculo(dermal) melanocytosis [9]. In this same study, dysplastic nevus syndrome was diagnosed in 3% which is known to have increased uveal nevi and a lifetime 100% risk of early onset cutaneous melanoma [106, 107]. Neurofibromatosis has been reported in older literature to harbor an increased propensity over the general population of uveal melanomas, but this has largely been disproven [108]. Familial uveal melanoma syndrome is a very rare condition with the youngest reported onset at age 20 years [109].

The treatment for childhood uveal melanoma is the same as for adults with brachytherapy and enucleation being the primary considerations based on tumor size and location. The decision is reached after systemic work-up is negative for metastases. Children have better survival rates than adults: 10 year survival is 80% after treatment versus 64% in adults [9].

Other Intraocular Tumors

Metastatic lesions and other primary intraocular malignancies are exceedingly rare in children. Typically reported as single cases, these must be kept in mind if an intraocular mass does not have classic features of retinoblastoma or melanoma. The most common malignancy to show ocular involvement in children is leukemia [36, 37, 42]. As many as 9% of children with acute leukemia will have ocular involvement with the choroid being the most frequent site of involvement [41]. Clinically, a thickened, occasionally nodular appearance is seen in the choroid, while iris nodules, hypopyon, hyphema, and optic nerve head mass can be presenting signs as well. Diffuse histiocytosis can involve the choroid but not as frequent as orbital soft tissue or periorbital bone involvement [110]. Neuroblastoma usually displays orbital involvement with metastases but has been demonstrated at autopsy with choroidal invasion [111]. Other single case reports of mass-like choroidal metastases have been found in children with testicular carcinoma, fibrosarcoma, colon carcinoma, bronchial carcinoma, thyroid carcinoma, and soft tissue extraosseous sarcoma [112–114]. Some of these case reports were diagnosed by pathologic examination rather than by clinic appearance indicating that these would likely be very late findings in a disease course and not necessarily a presenting sign. Knowing this list gives one a starting place to look when the appearance of the intraocular condition fits no clear example of other primary intraocular malignancies in children.

Medulloepithelioma finishes the list of pediatric intraocular malignancies. Usually reported as individual case reports in the past, a recent retrospective study describes the clinical features, histopathology, treatments, and outcomes for 41 cases of ciliary body medulloepithelioma [114]. Thirty-five of the 41 cases were in children presenting at a mean age of 5 years. Unilateral in presentation, whitish in color, these are solid or cystic congenital rests of embryonic retina in the nonpigmented epithelium of the ciliary body. Once they have grown large enough to displace or erode through the iris, they are visible in the anterior chamber causing variable leukocoria, pupillary ectopia, glaucoma, and hyphema. Some cases have presented as extrascleral extension which is most commonly the time one finds metastatic disease. Not all medulloblastomas are malignant but all have that potential. Local resection has a high rate of recurrence leaving enucleation, plaque radiation, and external beam radiation as the remaining potential treatments [114].

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