# Chapter 3
# Pediatric Orbital Tumors

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**Abstract** Though pediatric orbital tumors are rarely encountered outside referral centers, ophthalmologists must maintain a strong familiarity with these entities as efficient diagnosis and treatment are often paramount for optimal outcome. Most pediatric orbital tumors are biologically benign, but depending on their growth rate and anatomic location, benign tumors in the orbit can lead to vision loss, disfigurement, and even death. In this chapter, we review the literature on and discuss the most common benign and malignant orbital tumors in the pediatric population. We discuss tumor presentation, imaging characteristics, histopathologic appearance, treatment, and prognosis. Retinoblastoma and rhabdomyosarcoma are extensively discussed in other chapters in this book.

## 3.1 Introduction

Pediatric ophthalmic tumors are rare and differ from ophthalmic tumors seen primarily in adulthood. The majority of ophthalmic tumors in children are biologically benign, but some benign tumors can have a major impact on vision and can even result in significant mortality. In addition, a number of malignant ophthalmic tumors occur primarily in childhood. Some pediatric tumors are congenital, presenting at birth or within the first year of life, whereas others do not typically present until later in childhood or during adolescence.

Age at presentation and clinical symptoms depend largely on tumor location and rate of growth. Orbital signs such as proptosis, globe dystopia, strabismus, decreased vision, and optic nerve compression can range from subtle to alarming. Modern imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and orbital ultrasonography are essential for evaluation and management, and an ophthalmic pathologist is often critical for accurate interpretation of the surgical biopsy specimen.

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B. Esmaeli (ed.), *Ophthalmic Oncology*, M.D. Anderson Solid Tumor Oncology Series 6, DOI 10.1007/978-1-4419-0374-7_3,

Orbital lesions were previously classified by various methods. As histopathologic and immunohistochemical techniques have advanced, the lines historically drawn between seemingly distinct clinical entities have become blurred, and some lesions have crossed traditional clinical diagnostic boundaries. In Table 3.1, we have

**Table 3.1** Most common pediatric orbital tumors

| |
|---|
| *Cystic/developmental* |
| Congenital cystic eye |
| Dacryocystocele |
| Dacryops |
| Dermatolipoma |
| Dermoid cyst/epidermoid cyst |
| Encephalocele |
| Meningocele |
| Meningoencephalocele |
| Microphthalmos with cyst |
| Teratoma |
| *Vascular* |
| Arteriovenous malformation |
| Capillary hemangioma |
| Cavernous hemangioma |
| Lymphangioma |
| Orbital varix |
| *Infectious* |
| Orbital abscess |
| Subperiosteal abscess |
| *Histiocytic* |
| Juvenile xanthogranuloma |
| Langerhans cell histiocytosis (eosinophilic granuloma) |
| *Neural* |
| Neurofibroma (plexiform and solitary) |
| Optic pathway glioma |
| Schwannoma |
| *Inflammatory* |
| Idiopathic orbital inflammatory syndrome (orbital pseudotumor) |
| Thyroid orbitopathy |
| Orbital involvement of other inflammatory conditions such as Wegener's granulomatosis and sarcoidosis |
| *Mesenchymal tumors* |
| Fibrous histiocytoma |
| Rhabdomyosarcoma |
| Ewing sarcoma |
| *Other malignant tumors* |
| Granulocytic sarcoma (chloroma) |
| Leukemia |
| Neuroblastoma |
| Wilms tumor |

organized the major pediatric orbital tumors on the basis of pathophysiologic criteria. In the following pages, we briefly discuss the most common of these lesions.

## 3.2 Cystic Lesions

Collectively, cystic structures are the most commonly encountered orbital lesions in the pediatric population. Orbital cystic lesions can present as congenital or acquired lesions and are most often benign. Most orbital cystic lesions are dermoid cysts. However, other types of orbital cystic lesions are commonly reported, including neural cysts of ocular maldevelopment; neural cysts with associated central nervous system tissue; secondary cysts such as mucoceles and dentigerous cysts; parasitic cysts; and solid tumors with cystic components, such as teratomas, rhabdomyosarcomas, and adenoid cystic carcinomas.

### *3.2.1 Dermoid Cyst*

Dermoid cysts are the most common orbital cystic lesions, accounting for over 40% of all pediatric orbital tumors and up to 89% of all orbital cystic lesions of childhood [1–3]. Typically, dermoid cysts are developmental choristomas arising from ectoderm trapped in bony sutures during embryogenic migration or caused by failure of surface ectoderm to separate from the neural tube. Dermoid cysts slowly enlarge as they fill with sebum and keratin. Growth may be outward into the eyelid, in which case cysts typically present in early childhood, or inward into the orbit, in which case cysts tend to present later in life. Most dermoids arise from keratinized squamous epithelium, but occasionally dermoids can originate from nonkeratinized conjunctival epithelium with goblet cells [4, 5]. Epidermoid cysts present similarly but lack dermal adnexal elements in the cyst wall.

#### 3.2.1.1 Clinical Presentation

Orbital dermoid cysts can present at any age from infancy to old age, though they most commonly present in childhood and the teen years [6]. Fewer than 25% are clinically evident at birth. In 90% of cases, patients present with a slow-growing, painless, subcutaneous mass. Approximately 75% of dermoids are located in the superotemporal orbit associated with the frontozygomatic suture line, though they can also present medially in the frontonasal or frontoethmoid suture lines [7]. Typically, the mass is nontender, is firm to slightly fluctuant, and mimics a lacrimal gland tumor (Fig. 3.1a). Only rarely is the globe displaced or is vision decreased [8]. Deep orbital or intraconal dermoid cysts most often present in later adolescence or early adulthood with proptosis and ocular motility disturbance; this presentation is more common with dermoid cysts of conjunctival origin. Rupture of the cyst wall can result in an intense inflammatory reaction similar to orbital cellulitis. Very

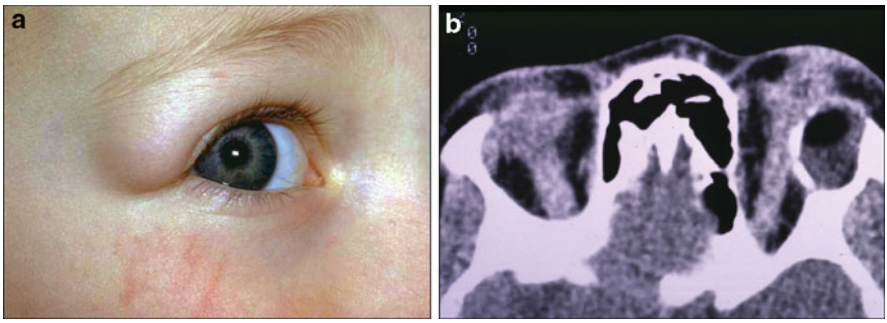


**Fig. 3.1** (**a**) Young child with a dermoid cyst at the right frontozygomatic suture line. (**b**) Dermoid cyst expanding into the superolateral orbit, showing a fluid–fat interface

rarely, a dermoid cyst can be located within an extraocular muscle [9]. Particularly for medially located dermoid cysts, differential diagnosis should include various cephaloceles and dacryocystoceles, which underscores the need for orbital imaging.

#### 3.2.1.2 Imaging

The CT appearance of orbital dermoid cysts is a round to oval, well-defined, cystic lesion, typically in the anterior superotemporal orbit (Fig. 3.1b) [10]. The lesion is almost always extraconal and has a cystic center with generally low density [11]. Denser foci within the cyst represent flecks of keratin and sebum. The cyst is surrounded by a thin rim of tissue density that may be partially calcified. Adjacent bone commonly shows remodeling, and the orbital contour can be enlarged. Occasionally, the cystic cavity extends across bones into the temporal fossa, frontal sinus, or intracranial vault [12]. Contrast administration produces enhancement of the cyst rim but not of the lumen.

On MRI with T1-weighted images, the cyst cavity produces a relatively low signal [13]. It is isointense or slightly hyperintense to vitreous and orbital muscles and hypointense to fat [14]. On T2-weighted sequences, the signal is isointense or hypointense with respect to vitreous and hyperintense to fat. Images may be homogeneous to heterogeneous depending on the cyst contents. A fat–fluid level is seen in some cases, with the upper lipid layer giving a brighter signal on T1 and a lower signal on T2 relative to the lower water–keratin layer. Newer sequencing techniques may allow improved visualization. Diffusion-weighted imaging may provide better visualization of the cystic margins and lipid component of cystic contents [15]. With gadolinium, the cyst rim shows moderate enhancement, but the lumen does not enhance.

On B-scan ultrasonography, dermoid cysts are rounded, well-outlined lesions with a smooth contour, whose internal appearance varies with the cyst's contents [16]. Orbital dermoid cysts often produce excavation of adjacent orbital bone and are occasionally associated with a small, solitary bone defect.

#### 3.2.1.3 Histopathology

Dermoid cysts are lined by keratinized, stratified squamous epithelium, identical to that of the epidermis, with adnexal structures including sebaceous and eccrine glands and hair follicles [17]. Epidermoid cysts have a similar stratified squamous epithelium lining; however, the cyst wall lacks dermal structures or other adnexal elements. The cavity of dermoid cysts may contain keratin, hair shafts, and sebaceous secretions. If the cyst ruptures, it incites an intense granulomatous inflammatory response.

#### 3.2.1.4 Treatment

Appropriate management of orbital dermoid cysts is complete surgical excision of the cyst wall and its contents [18]. More than half of cases show histologic evidence of leakage and associated inflammation. The risk of cyst wall rupture increases with cyst size and patient age [19], most likely because of thinning of the cystic wall with growth and increased risk of incidental trauma with increased age. Therefore, early removal is indicated to prevent tissue fibrosis. The lesions can often be bluntly dissected from most surrounding tissues; however, they are often firmly adherent at bony sutures. For deeper orbital cysts and very large cysts for which exposure is difficult, the cyst wall can be carefully opened and the cyst contents aspirated to allow safer complete resection of the cyst wall. Following any expression of cyst contents, the orbital site should be copiously irrigated with a dilute steroid solution to remove particles of lipid and keratin debris. When cysts extend into adjacent sinuses or intracranially, a combined approach with otolaryngology or neurosurgery may be required. For large dermoid cysts, percutaneous drainage and ablation with sclerosing agents under fluoroscopic guidance has been reported, but long-term data regarding recurrence after such treatment are lacking at this time [20].

#### 3.2.1.5 Prognosis

The prognosis of patients with orbital dermoid cysts is usually excellent. The inflammatory reaction to spontaneous cyst capsular rupture can be treated effectively with systemic steroids. In rare cases, however, spontaneous rupture can result in orbital fibrosis and permanent dysfunction.

### *3.2.2 Teratoma*

Teratoma is an extremely rare congenital solid lesion with prominent cystic components [21–23]. By definition, it contains tissue of varying maturity from all three germinal layers and may include skin, bone, cartilage, brain, bowel, lung, and glandular tissue [24]. More commonly affecting the sacrococcygeal region, head and neck, and gonads, teratoma only rarely involves the orbit, either as a primary lesion or as a secondary extension from the intracranial cavity or the paranasal sinus.

It presents unilaterally, is more common in girls, and is generally not associated with other congenital deformities or genetic syndromes [23]. Though proliferation of pluripotential stem cells is thought to contribute, the pathogenesis of teratoma remains unclear.

#### 3.2.2.1 Clinical Presentation

If abnormalities are not noted on prenatal ultrasonography, orbital teratoma generally presents at or shortly after birth with severe, rapidly progressive unilateral proptosis with significant craniofacial distortion. There is marked stretching of the eyelids, extreme chemosis, and exposure keratopathy (Fig. 3.2). Symptoms progress during the first days or weeks of life owing to retained secretions in cystic components of the tumor. Transillumination usually demonstrates the cystic nature of this lesion. The eye is usually normal in structure; however, vision loss may occur because of globe or optic nerve compression, or the globe may rupture because of marked corneal exposure and thinning. Malignant transformation is possible in some teratomas but is extremely rare [25–28]. Orbital teratoma must be differentiated from other rapidly enlarging tumors of childhood, such as rhabdomyosarcoma. Very large tumors may extend intracranially, producing secondary hydrocephalus. Though most orbital teratomas present in children younger than 2 years of age, these lesions may also progress slowly over many years.

#### 3.2.2.2 Imaging

On CT, teratomas appear as irregular, heterogeneous masses with both solid and multilobulated, cystic components. Cystic areas of low-attenuation fat density are seen, and a fat–fluid level may be demonstrated in some of the cyst cavities. Focal spots of internal calcification, representing formed bone elements and even teeth, are common. The orbital contour is usually enlarged, and the lesion may extend into

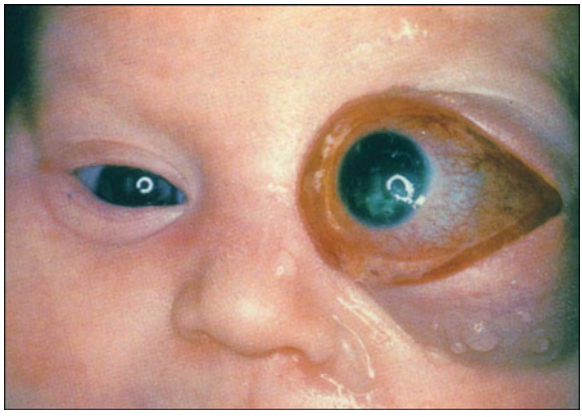

**Fig. 3.2** Orbital teratoma of the left orbit displacing the globe forward. From Dutton JJ, Byrne SF, Proia AD, eds. Diagnostic Atlas of Orbital Diseases. Saunders; 2000. Reprinted with permission

adjacent sinuses or intracranially. With contrast administration, the more solid areas show moderate enhancement.

MRI of orbital teratomas shows an orbital mass with heterogeneous signal intensity representing solid and cystic elements. Regions of tissue inflammation show increased signal intensity, especially on T1-weighted images. Fat within cystic cavities, or less commonly within the cyst walls, produces a high signal intensity that is hyperintense to vitreous on T1-weighted images and hypointense to vitreous on T2-weighted images. A fat–fluid level may be seen in some cases, with the upper lipid layer giving a brighter signal on T1 and a lower signal on T2 relative to the lower water–keratin layer. With gadolinium, the solid regions and rim show moderate enhancement, but the cyst cavities do not enhance.

#### 3.2.2.3 Histopathology

Teratomas display well-differentiated structures arising from varying proportions of ectodermal (keratinized squamous epithelium and adnexal structures), mesodermal (bone, cartilage, fat, and fibrous tissue), and endodermal germ layers (gastrointestinal or respiratory mucosa). Retained secretions from mucosal tissue form the cystic component of these lesions.

#### 3.2.2.4 Treatment

For definitive diagnosis of orbital teratoma, fine-needle aspiration is not sufficient. For diagnosis and treatment, surgical excision with preservation of the eye is preferred if at all possible [29, 30]. In some cases, vision may be preserved. Aspiration of the cyst contents can facilitate removal of large lesions through a lateral orbitotomy incision. Advanced cases with a deformed blind eye may require enucleation or a limited exenteration for adequate removal; involvement of surrounding structures may require a combined approach with neurosurgery or otolaryngology.

#### 3.2.2.5 Prognosis

The cosmetic result in patients with orbital teratoma following prompt surgical treatment can be good. Vision is usually decreased but may be preserved in some cases. When a teratoma is advanced or neglected, the prognosis for vision is poor owing to compression and/or exposure of ocular structures. Incompletely resected lesions may recur. Though extremely rare, tumors containing immature cells are associated with malignant degeneration; in these cases, wide surgical excision has been successfully employed. Currently, data regarding adjuvant therapies are insufficient [27].

## 3.3 Vascular Tumors

Vascular lesions are the second most common type of orbital tumor in the pediatric population. This group of tumors is better understood as a spectrum of disease, as lesions often have multiple components with a predominant morphology and velocity of blood flow. Capillary hemangiomas and lymphangiomas comprise the majority of pediatric orbital vascular tumors and are the focus of this section. Other vascular tumors rarely encountered in the pediatric population include cavernous hemangiomas, arteriovenous malformations, and orbital varices [31].

### *3.3.1 Capillary Hemangioma*

Capillary hemangiomas are congenital hamartomas of vascular channels. In the orbit, they represent the most common vascular tumors of childhood. They may involve the eyelid skin or deep orbit but nearly always include an anterior component. Typically, there is a proliferative phase characterized by a period of rapid growth during the first 6–12 months of life, which is thought to be due to rapid division of immature, incompletely differentiated vascular endothelium and pericytes [32]. This is usually followed by a general involutional phase of slow regression, clinically evident in 75% of cases by 7 years of age. There is a slight female preponderance; the female:male ratio is 3:2.

#### 3.3.1.1 Clinical Presentation

Capillary hemangiomas of the orbit usually present at birth or, less commonly, within the first year of life [33, 34]. The most common location is in the upper eyelid and superior orbit. Lesions vary from small, isolated, and clinically insignificant masses to large and disfiguring masses causing visual impairment (Fig. 3.3). Lesions with eyelid and dermal involvement most often have a nonblanching red color, while anterior lesions are fluctuant to palpation and bluish. About half of cases show tumor enlargement on crying or Valsalva maneuver. Close clinical observation is indicated as more than half of affected patients will develop amblyopia, primarily due to asymmetric astigmatism or visual deprivation because of upper eyelid ptosis.

#### 3.3.1.2 Imaging

On CT, orbital capillary hemangiomas appear as well-defined to infiltrating masses. They may be intraconal or extraconal in location and can extend forward into the eyelids. Rarely, these lesions occur as intraosseous lesions, forming an expansile mass with intact tables. With contrast administration, enhancement is moderate to marked.

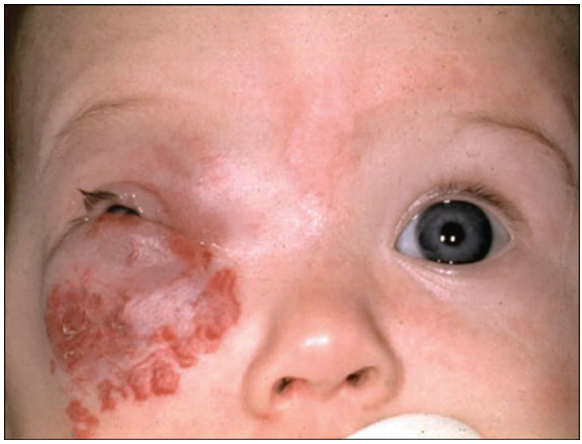

**Fig. 3.3** Capillary hemangioma of the right lower eyelid occluding the pupillary axis

On T1-weighted images, capillary hemangiomas give a heterogeneous signal, hyperintense to muscle and hypointense to fat. On T2-weighted sequences, the signal remains heterogeneous with areas of both high and low intensity. Stagnant blood appears as hyperintense to fat, whereas blood with a high flow rate produces a signal void that is hypointense to other orbital tissues. With gadolinium, there is diffuse heterogeneous enhancement, best demonstrated with fat suppression algorithms.

On B-scan ultrasonography, capillary hemangiomas are typically irregular orbital masses with heterogeneous internal echoes [35]. These tumors can be quite poorly outlined, or they may display a relatively distinct posterior border. Kinetic findings include a soft, compressible consistency.

#### 3.3.1.3 Histopathology

Capillary hemangiomas are composed of closely packed, thin-walled capillaries forming lobules. Lobules are separated by thin fibrous septa. The capillaries may be lined by flattened endothelium and contain erythrocytes, or they may have plump endothelial cells, making the vascular lumen inconspicuous [36]. The tumors are usually well circumscribed, though not encapsulated, by fibrous connective tissue.

#### 3.3.1.4 Treatment

In most cases, the appropriate treatment of capillary hemangioma is observation. Glucocorticoid receptor expression is high in these lesions [37]. Therefore, when lesions are large, causing amblyopia, globe exposure, or optic nerve compromise, intralesional or systemic steroids are most commonly used and generally result in dramatic regression [38]. The treatment regimen must be tailored to tumor location and treatment responsiveness as well as to the patient's age and the inherent risks of each modality. For small, localized, noninfiltrative lesions, surgical excision

can be effective [39, 40]. For larger lesions not responsive to steroids, recombinant interferon alpha-2a has been used as an alternative treatment with good results [39]. Various types of intralesional laser photocoagulation have also been found to reduce lesion size significantly [40, 41]. After a serendipitous discovery of its effectiveness, propranolol has recently been reported to be highly effective in the treatment of severe, disfiguring lesions; a multicenter trial is currently being organized to study optimal treatment paradigms [42].

#### 3.3.1.5 Prognosis

Most capillary hemangiomas regress spontaneously by the age of 7 years, leaving a remnant of fibrofatty tissue [43, 44]. Intralesional steroid injections are generally safe and effective [45–47] but can be associated with serious complications such as central retinal artery occlusion from intravascular placement and hemodynamic continuity between the hemangioma and systemic circulation. Local steroids have also been associated with skin depigmentation, fat atrophy, eyelid necrosis, and even adrenal suppression [48–51]. Surgery can result in significant bleeding and cosmetic deformity and is often reserved for cosmetically objectionable tumor remnant.

### *3.3.2 Lymphangioma*

Lymphangiomas are congenital lesions of abortive vascular elements that arborize among normal structures in the orbit [52]. They arise from venous anlage with variable proportions of venous and lymphatic components. Although lymphangiomas are hemodynamically isolated from large-flow vessels of the arteriovenous system, they are prone to intralesional hemorrhage from intrinsic capillaries. Such events expand portions of the vascular network into large “chocolate” cysts, leading to clinical urgency. Orbital lesions may be deep or combined with a superficial component. Approximately 65% of lymphangiomas present in the first decade of life, and 92% present by the end of the third decade [53].

#### 3.3.2.1 Clinical Presentation

Generally, deep lesions may not be clinically apparent until there is a sudden hemorrhage, which may be associated with upper respiratory infections. Such events can be associated with motility impairment, compressive optic neuropathy, or exposure keratopathy; in such cases, the lesion must be differentiated from orbital cellulitis or rhabdomyosarcoma. Increased intraocular pressure can cause nausea and vomiting, and excessive vagal stimulation can result in bradycardia and somnolence through the oculocardiac reflex. The eyelids may be infiltrated, and more superficial components in the conjunctiva may appear as clear fluid-filled channels and cysts (Fig. 3.4a). Periorbital and facial cellulitis is sometimes associated with upper respiratory infections [54]. Recurrent hemorrhages are seen in about half of cases, and the interval between events may be weeks to decades. Hemorrhagic cysts

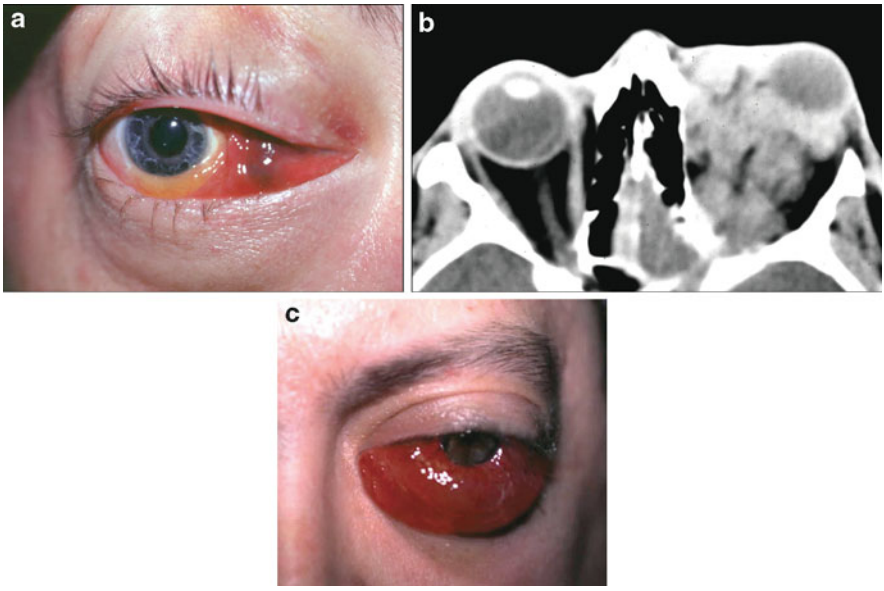


**Fig. 3.4** (**a**) Orbital lymphangioma with proptosis and hemorrhagic chemosis. (**b**) CT scan of orbital lymphangioma diffusely infiltrating orbital tissues. (**c**) Massive, acute proptosis and chemosis after acute hemorrhage associated with lymphangioma

usually resolve spontaneously but in some cases require surgical drainage. Large lesions can extend intracranially; in addition, a high proportion of patients with orbital lymphangiomas have associated noncontiguous intracranial vascular anomalies, necessitating concurrent brain imaging [55, 56]. Less commonly, children and some adults present with slowly progressive, painless proptosis.

#### 3.3.2.2 Imaging

CT in a patient with orbital lymphangioma typically shows an irregular, heterogeneous, poorly defined density that infiltrates among normal orbital structures and crosses anatomic boundaries such as the orbital septum and fascial layers (Fig. 3.4b). Low-density cystic areas are present, and occasionally calcified phleboliths may be seen [57]. With contrast administration, enhancement varies from patchy to diffuse. Larger lesions may extend into adjacent sinuses, the middle cranial fossa, or through the inferior orbital fissure into the infratemporal fossa.

MRI delineates lymphangiomas better than does CT and is more definitive in imaging of the cystic components [52, 58]. On MRI, a diffuse infiltrative mass is seen that may have one or more distinct cystic cavities [58, 59]. T1-weighted imaging produces a heterogeneous signal that is mildly hyperintense to muscle and hypointense to fat. The T2-weighted images are highly variable; blood cysts generally show a high signal intensity that is hyperintense to fat. Serpentine zones of signal voids in the orbit represent vessels containing rapidly flowing blood. Within

cysts, acute hemorrhage is hypointense to muscle on T1-weighted images; older blood is hyperintense on both T1- and T2-weighted sequences because of the presence of paramagnetic methemoglobin. With further degradation of the blood to ferritin and hemosiderin, low signal intensity is seen on the T1- and T2-weighted images.

Lymphangiomas are typically composed of numerous channels that contain lymph and/or blood and thus produce heterogeneous echoes on B-scan ultrasonography [60]. Hemorrhage produces weak internal echoes, but lymph is echolucent. Endothelial-lined walls of the cystic spaces present dense acoustic interfaces. Lymph-filled channels are more easily compressible on kinetic examination than are blood-filled channels.

#### 3.3.2.3 Histopathology

Orbital lymphangiomas are infiltrative lesions having wide variation in the size of the lymphatic channels. The channels in a given lesion vary from the size of capillaries to cavernous spaces. Attenuated endothelium resembling normal lymphatic endothelium lines the channels. The adventitial coat of the lymphatic spaces is inconspicuous in most orbital lymphangiomas. The lymphatic spaces contain proteinaceous (eosinophilic) fluid with lymphocytes, and erythrocytes may be seen after spontaneous hemorrhage into the tumor. The stroma between lymphatic channels begins as loose fibrous connective tissue with lymphoid aggregates. Older lesions and lesions previously partially resected have a fibrotic stroma, often with hemosiderin deposits from prior bleeding. Platelet-derived growth factor receptors alpha and beta and epidermal growth factor receptor tyrosine kinase are expressed on endothelial and smooth muscle cells of vascular channels [61].

#### 3.3.2.4 Treatment

For most cases, observation is the best course of action as spontaneous hemorrhages most often spontaneously resolve [62, 63]. Close monitoring of relative afferent pupillary defects and extraocular motility is essential. Because of the highly infiltrative nature of orbital lymphangiomas, surgery is hazardous and may lead to significant damage to normal ocular and orbital structures. However, acute hemorrhagic cysts sometimes require urgent surgical evacuation because of visual compromise or corneal exposure (Fig. 3.4c). Drainage with partial resection of the cyst or ligation of feeding vessels should be the goal, rather than complete resection. Parenteral steroids have been reported to expedite resolution of signs and symptoms but are not always effective [64, 65]. Recent alternative interventions with described success include intralesional administration of sclerosing agents [66] and use of tissue adhesives to augment cystic dissection [67]. The role of platelet-derived growth factor receptor inhibitors such as imatinib mesylate is also being studied [61].

#### 3.3.2.5 Prognosis

Except in rare cases, complete resection of orbital lymphangiomas is not possible. Recurrent hemorrhages occur in over half of cases over many years. Severe amblyopia unresponsive to therapy and disfiguring cosmesis are common sequelae. Relentless orbital bleeding with severe pain may require orbital exenteration for palliation. Poor visual outcome and sequelae of orbital scarring are associated with multiple surgeries.

## 3.4 Histiocytic Lesions

Though much less common than cystic or vascular lesions, histiocytic orbital tumors are also commonly reported in the pediatric population. Histiocytic proliferation in bone and soft tissues can affect any location in the body; however, the pediatric entities of most significance for the ophthalmologist are Langerhans cell histiocytosis (eosinophilic granuloma) and juvenile xanthogranuloma. Juvenile xanthogranuloma, which is caused by macrophage-derived non-Langerhans-cell histiocytes, is rarely encountered in the orbit and most commonly presents as iris lesions or cutaneous nodules. On the other hand, the dendritic histiocytic proliferation of the Langerhans cell histiocytosis spectrum of disease ranges from solitary orbital lesions to disseminated fatal disease. The most common form, eosinophilic granuloma, is the focus of this section.

### *3.4.1 Eosinophilic Granuloma*

Langerhans cell histiocytosis is a spectrum of disease, ranging from solitary bone lesions to acute systemic, life-threatening involvement [68, 69]. It involves the pathologic proliferation of Langerhans cells, which is thought to result from a cytokine-mediated immune dysregulation [70]. Eosinophilic granuloma accounts for up to 70% of cases of Langerhans cell histiocytosis and is unifocal, primarily involving the skull [71, 72]. Orbital involvement is common, predominantly in children and teens. The peak incidence is at 5–10 years of age, and males are affected more than females in a ratio of 2:1.

#### 3.4.1.1 Clinical Presentation

Symptoms of eosinophilic granuloma usually develop rapidly over weeks to months. The most common orbital site of involvement is superotemporal in the zygomatic and frontal bones, the marrow of which is a potential site for Langerhans cell proliferation. Patients typically present with an expanding painful mass, upper eyelid swelling, ptosis, and displacement of the globe (Fig. 3.5a). Local tenderness and erythema of the overlying skin are usually prominent features. In patients with this

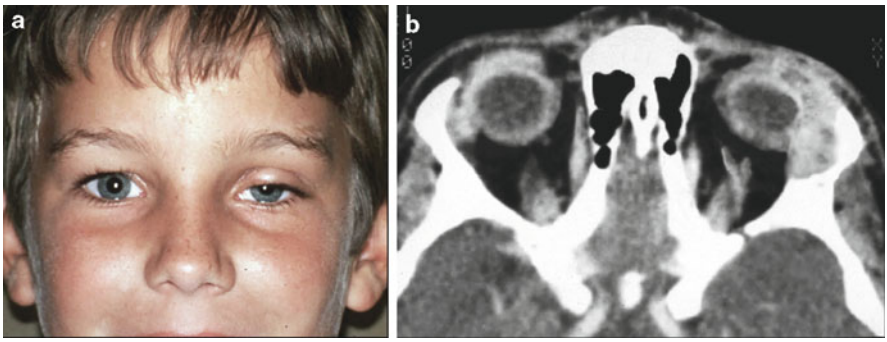


**Fig. 3.5** (**a**) Eosinophilic granuloma at the left superotemporal orbital rim, causing ptosis of the upper eyelid. (**b**) CT scan showing the lesion originating in the zygomatic bone

presentation and with bony destruction noted on imaging, dermoid cysts, neuroblastoma, Ewing sarcoma, Wilms tumor, and lacrimal gland malignancies must be considered in the differential diagnosis.

#### 3.4.1.2 Imaging

On CT, a soft-tissue mass of moderate density is characteristically seen near the superotemporal bony orbital rim [73]. The mass occurs within a well-defined osteolytic defect with irregular "punched-out" borders that may extend into the intracranial fossa (Fig. 3.5b). The inner and outer tables are unevenly involved, producing a "beveled edge" appearance. Marginal sclerosis and variable periosteal reaction may be present. With contrast administration, there is mild enhancement.

On MRI, bone destruction appears as an irregular signal void. The soft-tissue component produces a well-circumscribed heterogeneous signal that is hyperintense to muscle and hypointense to fat on T1-weighted images. T2-weighted images demonstrate high-signal areas that are hyperintense to fat. Enhancement with gadolinium is marked and slightly heterogeneous. Intracranial extension is sometimes demonstrated on MRI when it is not seen on CT.

#### 3.4.1.3 Histopathology

Langerhans cells are large histiocytes with grooved or folded nuclei. In eosinophilic granuloma, the Langerhans cells are mixed with mononuclear and multinucleated histiocytes, lymphocytes, plasma cells, and neutrophils. The eosinophilic component of the infiltrate varies from scattered cells to sheets of eosinophils. Classically, intracytoplasmic Birbeck granules can be demonstrated in the Langerhans cells by electron microscopy. However, this diagnostic confirmation has largely been replaced with positive immunohistochemical staining for S100 protein and CD1a [74].

#### 3.4.1.4 Treatment

After diagnostic confirmation with biopsy, management with subtotal surgical curettage has yielded good results with lesion involution and reossification [75]. Intralesional corticosteroids can provide additional benefit [76], likely by inhibition of the cytokine inflammatory mediators interleukin-1 and prostaglandin E2 [68]. Historically, low-dose radiotherapy at 900–1500 cGy has also yielded good results; however, it probably should be reserved for lesions not responsive or not amenable to surgical intervention or intralesional steroids. For patients with multifocal or systemic involvement, a multidisciplinary approach with pediatric oncology is recommended because, particularly in children younger than 1 year of age, these findings significantly raise the risk of recurrence, reactivation, and death [77]. Some studies suggest that administration of systemic chemotherapy may help prevent future onset of diabetes insipidus, orthopedic problems, and hearing and other neurologic sequelae [78]. More aggressive attempts at complete resection and various combinations of chemotherapeutic protocols have been reported [79].

#### 3.4.1.5 Prognosis

In children with eosinophilic granuloma, the prognosis for vision and for life is excellent. Spontaneous resolution with healing of the bony defects has been reported. Treatment with surgery or radiotherapy generally results in a cure. However, these children should be followed with serial examinations and CT in a concerted effort with pediatric oncology.

## 3.5 Neural Tumors

Pediatric orbital tumors of neural origin may arise from the optic nerve or any of the peripheral nerves in the orbit. Of neuroectodermal origin, these tumors typically present with acquired, progressive proptosis or vision loss in childhood and are most often benign. The most commonly encountered neural orbital tumors, optic nerve gliomas and plexiform neurofibromas, are highly associated with neurofibromatosis type 1 and are described below. Others neural orbital tumors include solitary neurofibroma, schwannoma (neurilemoma), medulloblastoma, and neuroblastoma (usually metastatic to the orbit and discussed later in this chapter).

### *3.5.1 Optic Nerve Glioma*

Optic nerve gliomas are uncommon neoplasms of astrocytic glia located along the visual pathways [80]. They represent 1.5–3.5% of all orbital tumors and 66% of primary optic nerve tumors [81]. Gliomas are seen most commonly in children, with a mean age at presentation of approximately 9 years [82]. Males and females are equally affected. The optic nerve alone is involved in 24% of cases; the chiasm is

involved with or without at least one contiguous optic nerve in the remaining 76% of cases. In 46% of patients, invasion of the midbrain or the third ventricle is present. About 29% of optic gliomas are seen in patients with neurofibromatosis type 1, and 15% of patients with neurofibromatosis develop optic gliomas [83]. In patients with neurofibromatosis, the mean age at diagnosis of optic glioma is younger [84], and the tumor tends to involve the chiasm less frequently. The presence of bilateral optic nerve gliomas is virtually diagnostic of neurofibromatosis.

#### 3.5.1.1 Clinical Presentation

Most children with optic nerve glioma present with slowly progressive decreased vision [84]. More than 55% have visual acuity of 20/300 or worse in the affected eye at diagnosis [81]. Proptosis is frequent with gliomas involving the orbital portion of the optic nerve but is uncommon when the lesion primarily involves the chiasm (Fig. 3.6a). Motility disturbance or nystagmus occurs in 25% of cases. Optic atrophy is a typical finding, but one-third of cases present with disc edema. Chiasmal tumors can be associated with increased intracranial pressure and with hypothalamic signs, including precocious puberty, diabetes insipidus, and panhypopituitarism. Sudden enlargement of the tumor can result from mucodegeneration and arachnoid hyperplasia rather than from tumor growth. Normal orbital imaging findings in children with neurofibromatosis do not preclude the future development of optic nerve glioma [85].

#### 3.5.1.2 Imaging

On CT, orbital glioma appears as a well-outlined enlargement of the optic nerve that is usually fusiform but may be more rounded or even multilobulated (Fig. 3.6b). Increased tortuosity or kinking of the nerve is a common finding. The tumor is isodense to brain but typically has a heterogeneous structure. Less dense cystic spaces

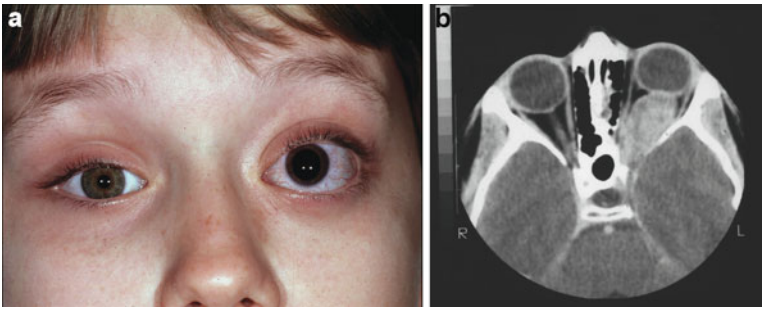


**Fig. 3.6** (**a**) Left optic nerve glioma in a child with neurofibromatosis type 1. (**b**) CT scan showing a fusiform lesion of the optic nerve extending from the globe to the orbital apex

correspond to areas of mucinous accumulation. Small high-attenuation foci of calcification are rare. Following contrast administration, enhancement is heterogeneous and varies from imperceptible to moderate.

In general, MRI is regarded as superior to CT in imaging of optic gliomas, and particularly in identifying intracranial extension [86, 87]. On T1-weighted images, gliomas are isointense or slightly hypointense with respect to cortical gray matter. A dilated subarachnoid space filled with cerebrospinal fluid may appear on MRI as a hypointense zone surrounding the tumor. Low-signal hypointense areas within the lesion represent cysts of mucinous degeneration and necrosis. On T2-weighted images, the signal may be more variable. Small fusiform tumors can be homogeneously hyperintense owing to the proton-rich water component and prolonged relaxation time. Larger lesions are usually heterogeneous, with a peripheral zone of hyperintense arachnoidal hyperplasia and cerebrospinal fluid and a hypointense inner zone of optic nerve and glial cells. There is moderate to marked enhancement with gadolinium, but less than with meningiomas. Chiasmal or optic tract enhancement is a sign of intracranial involvement.

#### 3.5.1.3 Histopathology

The histologic picture is that of a low-grade pilocytic ("hair-like") astrocytoma. Elongated spindle-shaped astrocytes with uniform oval nuclei form intersecting bundles that distend the fibrous pial septa of the optic nerve. The astrocytes are cytologically benign, and mitotic figures are not apparent. In most tumors, there are some astrocytes with spherical or cylindrical, swollen cell processes that stain brightly eosinophilic ("Rosenthal fibers"). There are usually pale cystic areas scattered among the astrocytes; these contain mucin (glycosaminoglycans) that can be highlighted using immunohistochemical stains. Mucin may be particularly prominent in long-standing tumors. If the tumor infiltrates the surrounding meninges, the astrocytes are accompanied by fibroblasts and meningothelial cells. Though confirmation is not usually necessary for diagnosis, the astrocytic nature of the neoplasm can be immunohistochemically confirmed in paraffin sections using antibodies against glial fibrillary acidic protein.

#### 3.5.1.4 Treatment

The goal of treatment of optic gliomas is to halt vision loss or tumor growth.

The natural history and the clinical course of optic gliomas are highly variable. As a result, therapeutic options are controversial and must be individualized.

For lesions confined to the orbit in patients with good vision, minimal proptosis, and no signs of progression, observation with serial examination and MRI is appropriate. Advances in therapeutic regimens and the negative sequelae of alternative treatments have brought many authors to recommend chemotherapy as first-line treatment for all children [88]. While chemotherapy may shrink tumors and delay progression, visual acuity typically does not improve, and a high progression rate persists [82, 89]. Traditionally, use of radiotherapy had been limited to advanced

cases in older children owing to the risk of neurocognitive effects, secondary malignancies, endocrinopathies, and cerebrovascular disease, such as moyamoya disease; however, newer techniques that limit damage to normal tissues, such as fractionated stereotactic radiotherapy and proton beam radiotherapy, have been reported to be effective in preventing progression and are less likely to cause damage to normal tissues [90]. Surgical debulking is now typically limited to hypothalamic debulking combined with adjuvant therapy and shunting in cases of secondary hydrocephalus. In addition, because of certain loss of vision, resection of orbital optic nerve gliomas is currently limited to scenarios in which proptosis is of cosmetic concern or causing severe exposure.

#### 3.5.1.5 Prognosis

Tumor location determines prognosis for vision and for life. More posterior tumors tend to cause more visual loss [91]. After the initial visual deterioration seen in 80% of patients, vision tends to stabilize. In 26% of cases, vision remains better than 20/40, and in 45% of cases, vision remains better than 20/200. For lesions confined to the orbit, prognosis for life is excellent, and the mortality rate is less than 5%. With chiasmal involvement, the mortality rate remains less than 10% [92]. Tumors associated with midbrain invasion are associated with a 55% mortality rate over 10 years. There is some evidence that sporadic lesions are associated with higher morbidity than neurofibromatosis-associated gliomata [93].

### *3.5.2 Plexiform Neurofibroma*

Plexiform neurofibroma represents 1–2% of all orbital tumors. It is the most common benign peripheral nerve tumor occurring in the eyelid and orbit and is considered pathognomonic for neurofibromatosis. The lesion can arise from and grow along any peripheral nerve, but in the orbit, it most often involves sensory nerves.

A hamartoma of neuroectodermal origin, plexiform neurofibroma typically presents in children during the first decade of life, and one-third of tumors involve the eyelids. Plexiform neurofibroma may be associated with widening of the superior orbital fissure or defects in the greater sphenoid wing. It should be differentiated from solitary neurofibromas, which are isolated, well demarcated on imaging, and typically completely resectable.

#### 3.5.2.1 Clinical Presentation

When the eyelid is involved, plexiform neurofibroma has a characteristic S shape due to thickening, fat deposition, and horizontal redundancy [94]. On palpation, the individual thickened nerve bundles have been described as feeling like a “bag of worms.” Mechanical ptosis can be profound and in younger children may result in deprivation amblyopia (Fig. 3.7). With orbital involvement, the globe can be proptotic or enophthalmic, depending on the degree of bony expansion of the

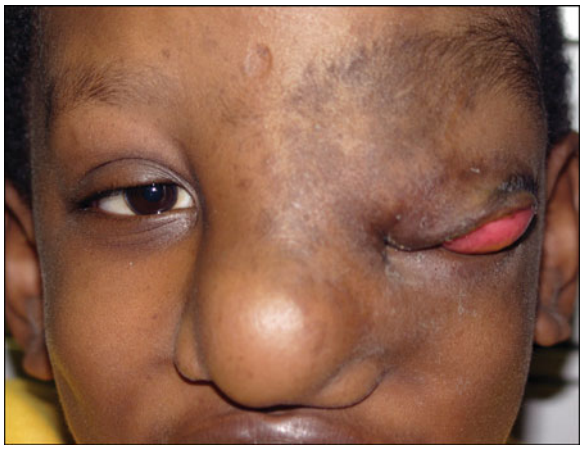

**Fig. 3.7** Plexiform neurofibromatosis of the left eyelids and face with typical S-shaped contour of the upper lid

orbit and the degree of greater sphenoid wing dysplasia [95]. With large defects in the sphenoid bone, the temporal lobe may herniate into the orbit, causing pulsatile exophthalmos. The orbital lesion may be associated with uveal neurofibromas (50%), iris nodules (77%), prominent corneal nerves (25%), or optic nerve gliomas (15%). There may also be extensive temporal and facial involvement and intracranial extension [96].

#### 3.5.2.2 Imaging

On CT, plexiform neurofibroma appears as a moderately dense, irregular, diffuse mass that crosses multiple tissue planes. There is thickening of eyelids and periorbital soft tissues. Abnormalities may include increased density of intraconal fat due to involvement of small intraconal nerves; irregular nodular thickening of optic nerve sheath from tumor involvement of posterior ciliary nerves; or thickening of sclera/choroid from tumor within these structures. Plexiform neurofibroma surrounds normal orbital structures and may be inseparable from extraocular muscles. The orbital contour and superior orbital fissure are frequently enlarged. When large regions of the sphenoid bone are absent, a meningoencephalocele may prolapse into the orbit. With contrast administration, the tumor shows moderate enhancement.

The MRI appearance is of an ill-defined and irregular mass in the orbit or the eyelid. On T1-weighted images, the tumor produces a heterogeneous, hypointense signal with respect to muscle. Signal intensity is increased on T2-weighted sequences, where the tumor is hyperintense to muscle and isointense or slightly hyperintense to fat. Tumor is best demonstrated using fat suppression techniques. With gadolinium, enhancement is variably mild to moderate.

#### 3.5.2.3 Histopathology

In plexiform neurofibromas, large segments of peripheral nerve become convoluted and appear like a “bag of worms” macroscopically. Microscopically, there

is an unencapsulated tortuous mass of expanded nerve branches, each surrounded by a perineurium. In early lesions, the nerve is swollen by endoneurial accumulation of myxoid (glycosaminoglycan-rich) matrix. As the lesions age, Schwann cells proliferate, and collagen accumulates within the nerves.

#### 3.5.2.4 Treatment

Management is usually frustrating and disappointing for the patient and surgeon because of the infiltrative nature and vascularity of this tumor. Typically, complete resection is uncommon, and recurrences are expected. When the lesion is stable or its enlargement does not cause visual loss or psychosocial concern, observation is prudent [97]. Repeated surgical debulking may be necessary to maintain visual function and for some cosmetic improvement. Concurrent conservative levator resection can aid in ptosis repair. Advances in custom alloplastic implants and computer-aided stereolithography have been described to address pulsatile exophthalmos [98]. In cases of poor vision, severe proptosis, and orbital pain, exenteration may be considered, followed by appropriate reconstruction [99]. There is no role for radiotherapy, and it may increase the risk of secondary malignancies [100].

#### 3.5.2.5 Prognosis

The overall prognosis for life is good. Rarely, the tumor can erode into the cranial cavity with fatal results, and patients with neurofibromatosis have a significant risk of secondary malignant tumors. The prognosis for vision depends on the extent of tumor invasion as well as the potential complications of surgical intervention. Rarely, rhabdomyosarcoma has been reported in association with neurofibromatosis type 1 and should be considered by the clinician if initial presentation or clinical course is atypical [101]. Malignant transformation of neurofibromas into myxoid sarcomas and development of malignant peripheral nerve sheath tumors have also been reported in a small proportion of patients with neurofibromatosis [100, 102]. Please also see Chapter 2 and Fig. 2.6.

## 3.6 Malignant Lesions

Orbital malignancies comprise a very important minority of pediatric orbital tumors. They may be primary, secondary, or metastatic and more commonly present later in infancy and childhood. Acquired proptosis, motility disturbances, and visual compromise can range from insidious to disquieting. Combinations of therapeutic advances have improved prognosis for patients with many but not all pediatric orbital malignancies. Appropriate diagnosis and treatment requires the cooperative efforts of the orbital surgeon, pediatric oncologist, and radiotherapist. Rhabdomyosarcoma is the most commonly encountered malignant pediatric orbital tumor and is discussed elsewhere in this book (Chapter 4). We focus here on three

other less commonly encountered primary malignant tumors of the orbit—Ewing sarcoma, neuroblastoma, and granulocytic sarcoma—and on retinoblastoma with orbital extension.

## *3.6.1 Ewing Sarcoma*

Ewing sarcoma is part of a family of neoplasms characterized by undifferentiated small round cells arising in bone. Though the cell of origin is still controversial, most believe the cell of origin is a mesenchymal cell reprogrammed to a neuroectodermal phenotype [103]. The tumor classically involves the long bones of the limbs, ribs, and pelvis; when the orbit is involved, the tumor usually has arisen as a metastasis from a distant site, though primary osseous and extraosseous orbital lesions have been reported [104–106]. Seventy-five percent of patients are aged 20 years or younger, and 90% are less than 30 years old. Males are more frequently affected than females in a ratio of 1.6:1, and Ewing sarcoma primarily affects Caucasians.

### 3.6.1.1 Clinical Presentation

Tumor growth is typically insidious. Although the patient often comes to medical attention following an episode of trauma, ophthalmic symptoms usually have been present for months [107]. Ophthalmoplegia and ptosis are followed by proptosis, displacement of the globe, and possibly diplopia (Fig. 3.8). There may also be intermittent pain [108]. A soft nontender mass may be palpable beneath the orbital rim. Hemorrhagic necrosis may cause erythema and local warmth, simulating osteomyelitis. Systemic symptoms of fever, fatigue, anorexia, and weight loss are associated with disseminated metastases, seen in 10–30% of patients at initial diagnosis.

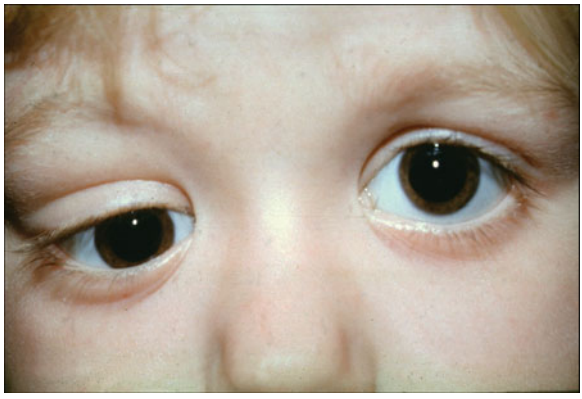

**Fig. 3.8** A young child with Ewing sarcoma of the right superior orbital rim displacing the globe downward. From Dutton JJ, Byrne SF, Proia AD, eds. Diagnostic Atlas of Orbital Diseases. Saunders; 2000. Reprinted with permission

#### 3.6.1.2 Imaging

The CT scan reveals an irregular heterogeneous cystic mass [109]. Adjacent bone shows mottled destruction, and the mass frequently extends from the maxillary sinus or mandible. Patchy hypodense areas correlate with old hemorrhage and necrosis. Enhancement with contrast administration is variable.

On MRI, an extraosseous mass is seen contiguous with bone destruction. The T1-weighted signal is low and hypointense to both fat and muscle. On T2-weighted sequences, the signal is high and is isointense to fat and hyperintense to muscle. Heterogeneity is due to areas of necrosis that produce lower signal intensity. There is generally no significant periosteal reaction. With gadolinium, only the cellular areas enhance.

#### 3.6.1.3 Histopathology

The most common pattern of Ewing sarcoma, referred to as diffuse or cohesive, has broad sheets of uniform, small, round cells mixed with dark cells; other malignancies with similar microscopic presentation include rhabdomyosarcoma, neuroblastoma, and lymphoma. Round tumor cells are slightly larger than lymphocytes and have round nuclei (often with indentations), finely dispersed chromatin, one or two small nucleoli, and scant cytoplasm that is pale or vacuolated owing to the presence of glycogen. The cytoplasmic borders are indistinct. The dark cells have denser and more elongated nuclei and tend to form aggregates. Positive immunohistochemical staining for CD99, a cell surface glycoprotein, or for O13, a monoclonal antibody against the *MIC2* gene product, supports the diagnosis of Ewing sarcoma, though neither is specific for this entity [103, 110]. In addition, virtually all Ewing tumor cells demonstrate a translocation involving chromosome 22.

#### 3.6.1.4 Treatment

Ewing sarcoma is typically regarded as a systemic disease until a metastatic evaluation reveals no other lesions. After initial biopsy for diagnosis, aggressive multiagent chemotherapy is initiated, using one of various combinations of vincristine, doxorubicin, cyclophosphamide, and dactinomycin [111]. After initial chemotherapeutic cytoreduction, definitive surgical excision or radiotherapy is performed, followed by consolidation chemotherapy. Regular surveillance is critical. Multiple biological therapies are under investigation [112].

#### 3.6.1.5 Prognosis

Until recently, treatment with surgery and radiotherapy alone yielded a 5-year survival rate of only 10%. Advances in therapy, primarily in adjunctive chemotherapy, have reduced the recurrence rate to about 5% and improved the 5-year survival

rate to approximately 65% [112]. However, patients with metastasis at presentation continue to have a poor prognosis, with a 25% survival rate at 5 years, though a concerted effort is under way to advance the understanding and therapeutic options for this subset of the population [113].

### *3.6.2 Neuroblastoma*

Representing 8–10% of pediatric cancers, neuroblastoma is the most frequent extracranial solid tumor and the most common tumor metastatic to the orbit in children. It is a malignant neoplasm of primitive neuroblasts—progenitor cells of the sympathetic nervous system. The tumor usually arises during the first 2 years of life, and the primary tumor is usually located in the adrenal medulla or the sympathetic or parasympathetic tissues of the pelvis, chest, or cervical region. The vast majority of orbital involvement is from metastatic disease, and in 90% of these cases, the primary tumor is in the abdomen. In 92–97% of cases involving the orbit, the presence of a primary tumor in the chest or abdomen is known prior to onset of orbital symptoms, and 40% of metastatic neuroblastomas to the orbit are bilateral [114, 115]. Very rarely, neuroblastoma arises as a primary tumor in the orbit [116].

#### 3.6.2.1 Clinical Presentation

Ophthalmic involvement develops in 20% of children with neuroblastoma. These children are often systemically ill-appearing, with fever, weight loss, and irritability. The child typically presents with rapid progression of proptosis and periorbital ecchymosis (due to rapid necrosis of tumor cells) over several weeks (Fig. 3.9). Eyelid edema, ptosis, and displacement of the globe are also common findings. In

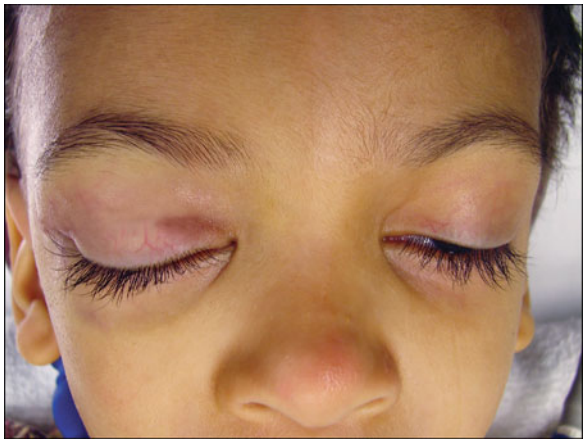

**Fig. 3.9** Metastatic neuroblastoma of the right orbit with ecchymosis of the upper eyelid

5% of children, blindness is seen, either as an early finding or as a result of treatment [117]. On funduscopic examination, optic disc edema, choroidal folds, retinal striae, and dilated retinal vessels may be seen. Horner syndrome together with ipsilateral iris heterochromia, secondary to tumor in the cervical sympathetic chain, is the presenting sign in rare cases. Opsoclonus is a paraneoplastic finding that has been reported with systemic as well as localized disease [118]. Increased intracranial pressure and separation of bony sutures can be associated with intracranial metastases. In very rare instances, neuroblastoma can occur as a primary tumor in the orbit of adults.

#### 3.6.2.2 Imaging

On CT, neuroblastoma appears as a large, irregular, poorly defined orbital mass. It may be unilateral or bilateral. Lower-attenuating, more lucent areas within the lesion represent sites of tumor necrosis and hemorrhage. Destruction of adjacent bone may be seen on bone window settings.

The MRI appearance of neuroblastoma is of a mass with ill-defined margins from infiltration into adjacent orbital structures. On T1-weighted images, the resonance signal is heterogeneous or homogeneous and hypointense to cortical gray matter and muscle. On T2-weighted images, the signal is isointense or slightly hyperintense to gray matter and muscle. With gadolinium, enhancement varies from mild to marked.

In addition to CT and MRI, scintigraphic imaging can help with staging and with evaluation of response to treatment. A norepinephrine analog, metaiodobenzylguanidine, with an attached iodine radioisotope can show bony and soft-tissue involvement due to preferential uptake by adrenergic secretory vesicles [119]. In addition, technetium 99 bone scans can further decrease the risk of false-negative imaging findings [120].

#### 3.6.2.3 Histopathology

In neuroblastoma, small regular cells with round deeply staining nuclei, scant cytoplasm, and indistinct cell borders form sheets or vague nodules. One-fourth to one-third of cases have Homer-Wright rosettes with tumor cells around a central area containing fibrillar material. Most tumors exhibit necrosis, which may be extensive, leaving viable tumor cells only around blood vessels. Neuroblastoma cells express neuron-specific enolase, neurofilament protein, peripherin, chromogranin, synaptophysin, and other neural-related antigens. Immunohistochemical staining for neuron-specific enolase and protein gene product 9.5 [117] is often necessary to differentiate neuroblastoma from other small cell tumors such as Ewing sarcoma/primitive neuroectodermal tumor, rhabdomyosarcoma, lymphoma, and retinoblastoma.

#### 3.6.2.4 Treatment

If orbital findings are the presenting signs, then urgent referral to pediatric oncology for systemic evaluation is critical. Systemic evaluation includes measurement of urine catecholamines, various imaging modalities for staging, and possibly bone marrow biopsy. Biopsy of orbital lesions may occasionally be necessary for diagnosis; however, resection is not indicated initially as staging will determine the most appropriate treatment. The principal treatment is chemotherapy, often including vincristine, doxorubicin, carboplatin, dacarbazine, and etoposide. After induction chemotherapy, surgical resection of primary tumors and bulky metastatic disease may be indicated. In cases of low-risk disease, surgical resection without chemotherapy may be recommended. Radiotherapy has been shown to decrease local recurrence but is typically not recommended for early-stage tumors because of the risk of secondary tumors. Autologous bone marrow transplantation is often necessary because of marrow ablation by chemotherapy. Current efforts to advance therapy include immunotherapy and targeting of biological markers of the disease [121].

#### 3.6.2.5 Prognosis

One-third of children with orbital neuroblastoma develop visual loss either as a direct consequence of tumor or secondary to treatment. Prognosis is primarily dependent on risk stratum as determined on the basis of the initial presentation. Age at presentation, stage, histopathologic characteristics, DNA index (ploidy), and N-*myc* amplification status allow disease to be characterized and treated. Recent data reveal 95 and 90% 10-year survival rates for patients with low- and intermediate-risk disease, respectively; however, the 10-year survival rate for patients with high-risk or metastatic disease remains low, at 30–40% [119, 122]. Seventy percent of patients present to the ophthalmologist with metastatic disease, and therefore orbital disease typically portends a poor prognosis. Palliative fractional external-beam radiotherapy ($\geq$2,000 cGy) has been reported to produce good results for symptomatic metastatic lesions [123]. Once orbital metastases develop, the overall prognosis is generally poor. Despite aggressive therapy, recurrence rates of 90% may be seen at 1–2 years. The 3-year survival rate in patients with recurrence is 11%.

### *3.6.3 Retinoblastoma*

Retinoblastoma is the most common intraocular malignancy in childhood. Chapter 14 describes its evaluation and treatment. In this section, primary consideration is given to orbital extension of retinoblastoma and the risk of secondary tumors associated with retinoblastoma.

Orbital involvement by retinoblastoma occurs via extraocular extension along the optic nerve or through scleral emissary canals. The risk of metastasis is greatly

increased by orbital disease. Tumor can spread to the central nervous system via the subarachnoid space, to regional lymph nodes via the lymphatics, or hematogenously to bones or viscera.

#### 3.6.3.1 Clinical Presentation

In developed nations, at primary presentation of retinoblastoma, extraocular extension is usually absent or only microscopic, and therefore orbital symptoms are usually absent. However, in developing nations, extraocular extension of tumor and orbital symptoms are much more common at primary presentation [124, 125]. With significant orbital involvement, proptosis or globe displacement may be seen (Fig. 3.10) [126]. Periocular inflammation similar to orbital cellulitis has also been reported [126, 127]. In developed nations, most cases of orbital retinoblastoma present as a recurrence following primary enucleation for ocular tumor. Displacement of the orbital implant, inability to wear an ocular prosthesis, ecchymosis, chemosis, bleeding from the socket, signs of cellulitis, or nondescript constitutional symptoms may be present. Tumor can spread intracranially via the paranasal sinuses or neural foramina.

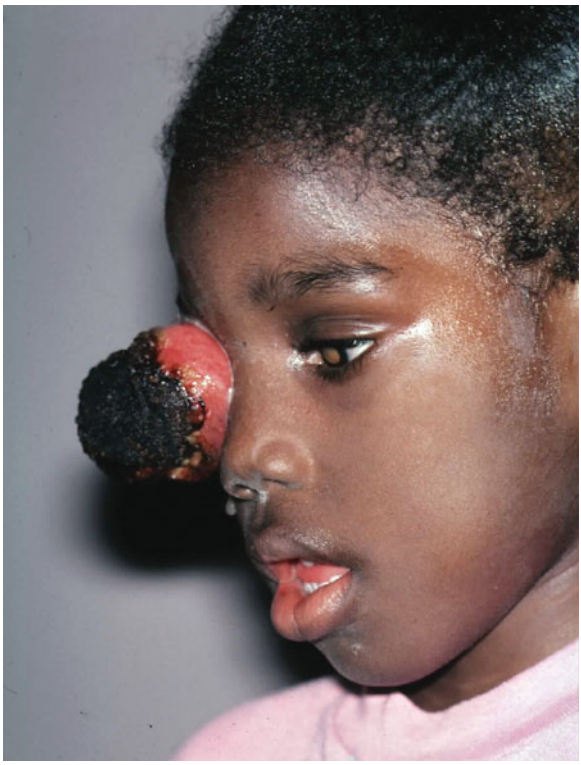

**Fig. 3.10** Massive orbital extension of retinoblastoma with surface necrosis. Photograph used with permission courtesy of Dr. Ted Wojno

#### 3.6.3.2 Imaging

On CT, orbital extension of retinoblastoma appears as a contiguous, high-density intraconal mass that may be localized along the optic nerve. Intralesional calcification is present in 90% of tumors. Mild to moderate enhancement is seen with contrast administration.

MRI is the most sensitive method for detection of orbital extension of retinoblastoma. On T1-weighted images, retinoblastoma produces a homogeneous to heterogeneous signal that is hyperintense to vitreous and muscle and hypointense to fat. On T2-weighted images, retinoblastoma is hypointense to vitreous and isointense to fat. Small foci of calcification may not be visible, but larger calcifications appear as dark signal voids on T1- and T2-weighted images. With gadolinium, the tumor shows moderate to marked heterogeneous enhancement, with areas of calcification remaining markedly hypointense [128].

#### 3.6.3.3 Histopathology

Typically associated with an exophytic growth pattern, orbital extension of retinoblastoma or recurrent orbital tumor tends to be much less differentiated than that of the intraocular primary tumor. The tumor cells are small and round with large, deeply staining nuclei of variable size and shape and scant cytoplasm. Rosettes are uncommon and are poorly formed if present in the orbit. It is difficult, and sometimes impossible, to conclusively distinguish a recurrent retinoblastoma from a second primary tumor. Foci of calcification are noted in areas of necrosis.

#### 3.6.3.4 Treatment

Management of orbital retinoblastoma depends on the extent of orbital involvement. For large orbital tumors, excision combined with chemotherapy and radiotherapy offers the best chances for long-term survival [129]. Exenteration should be reserved for massive orbital involvement [130]. Overall, use of external-beam radiotherapy is limited because of the risks of secondary malignancies. When radiotherapy is used in cases of positive surgical margins or massive orbital or metastatic disease, it is combined with chemotherapy to help minimize the radiation dosage [131–133]. Metastatic disease is currently being approached with various combinations of induction chemotherapy; surgery and irradiation to treat bulky disease; high-dose chemotherapy; and autologous stem cell rescue [134, 135].

#### 3.6.3.5 Prognosis

Extraocular extension is one of the most prominent risk factors for metastatic retinoblastoma [136]. With gross orbital invasion, the likelihood of central nervous system extension, systemic metastases, and death is increased considerably, though current therapeutic regimens have resulted in a vast improvement in mortality [137–139]. The risk of secondary malignancies is well described in survivors of

hereditary retinoblastomas and necessitates lifelong clinical follow-up; this risk is considerably amplified if initial treatment included irradiation [140]. In one series, rates of second malignancies were reported to be as high as 30% in the radiation field (especially in patients treated before 1 year of age) and 8% in untreated areas [141]. The most common of these secondary tumors are osteosarcoma, soft-tissue sarcomas, melanoma, and extraorbital cancers, including cancers of the brain and nasal cavities, sarcomas, and epithelial carcinomas, particularly of the lung and bladder [134, 142, 143]. Irradiation also carries the risk of cataract, keratopathy, radiation retinopathy, and retarded orbital growth in young children.

### *3.6.4 Granulocytic Sarcoma*

The term "granulocytic sarcoma" is a misnomer—granulocytic sarcoma is an extramedullary solid tumor commonly associated with acute myelogenous leukemia (AML) in children. In adults this tumor is more commonly associated with acute lymphoblastic leukemia, chronic myelogenous leukemia, or myelodysplastic disorders [144–146]. Also referred to as chloroma or myeloid sarcoma, granulocytic sarcoma is the most common form of leukemic infiltrate involving the orbit and affects 30% of patients with AML [147]. In up to 88% of cases, orbital tumor presentation precedes the blast phase of AML by months to years, though it can also occur concurrently with the blast phase, or even during periods of remission [148].

#### 3.6.4.1 Clinical Presentation

The mean age of presentation of granulocytic sarcoma is typically 8–9 years. The disease is unilateral in 90% of cases and presents as a rapidly enlarging orbital mass with diplopia and proptosis (Fig. 3.11a). The lateral orbital wall is most commonly involved, causing medial displacement of the globe. Pain, retinal striae, or optic disk edema may also be present [149]. Myeloperoxidase within the mass often imparts a green hue on examination, which is why granulocytic sarcoma is also referred to as chloroma. Orbital involvement can also be bilateral [150, 151].

#### 3.6.4.2 Imaging

On CT, granulocytic sarcomas typically are irregular, are moderately defined, and have a homogeneous density (Fig. 3.11b). Often lateral in location, they may also encase or invade the lacrimal gland, extraocular muscles, or orbital fat [152]. Bony erosion and subperiosteal reaction have been noted, and contrast enhancement is uniformly minimal to moderate [153]. Brain lesions demonstrate more variability in appearance [154].

On T1-weighted images, the irregular mass is isointense to cortical gray matter and to muscle. On T2-weighted sequences, the lesion is isointense to white matter and muscle. Enhancement is homogeneous and moderate with gadolinium [155].

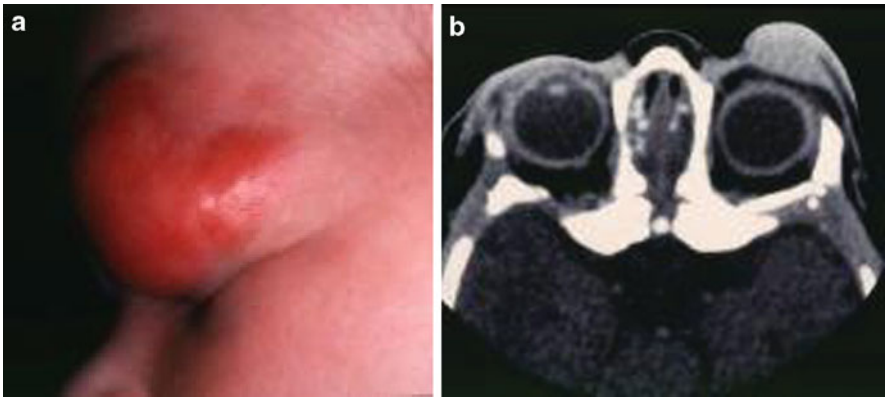


**Fig. 3.11** (**a**) Rapidly enlarging granulocytic sarcoma of the superotemporal orbit causing mechanical ptosis. (**b**) CT scan showing an infiltrative, homogeneous lesion in the anterior orbit and subcutaneous eyelid soft tissue. From Dutton JJ, Byrne SF, Proia AD, eds. Diagnostic Atlas of Orbital Diseases. Saunders; 2000. Reprinted with permission

#### 3.6.4.3 Histopathology

Granulocytic sarcomas range from being composed entirely of myeloblasts to demonstrating variable evidence of granulocytic differentiation. Myeloblasts are large cells with ovoid, vesicular nuclei, multiple nucleoli, and scant cytoplasm. With granulocytic differentiation, eosinophilic granules appear in the cytoplasm, cytoplasm increases, and the nuclei are more progressively folded. In highly differentiated tumors, eosinophils are often present. Special staining for myeloperoxidase, lysozyme, and chloracetate esterase (Leder stain) can be used to confirm the granulocytic origin of the cells [150, 156]. However, immunohistochemistry, particularly staining for CD68, is essential to confirm the diagnosis as poorly differentiated tumors are often misdiagnosed as medium- to large-cell lymphoma [157]. Cytogenetic studies demonstrate a high incidence of translocations, particularly *t*(8:21) [158].

#### 3.6.4.4 Treatment

Granulocytic sarcoma in the setting of known systemic AML is treated primarily with chemotherapy, though surgery and radiotherapy can be used in an adjunct role [159, 160]. Bone marrow transplantation may be necessary in aggressive cases [158, 161]. In patients with localized orbital lesions and no evidence of systemic disease, radiotherapy was previously used. However, these lesions are also responsive to intensive induction chemotherapy protocols for AML.

#### 3.6.4.5 Prognosis

The prognosis of patients with AML and granulocytic sarcoma or other forms of extramedullary infiltration was previously described to be poorer than the prognosis

of patients with AML only [158, 161, 162]. However, more recently, the prognosis of patients with AML with and without extramedullary infiltration is controversial and under close study [163]. The 5-year event-free survival rates are typically between 30 and 40%, though higher white blood cell counts and central nervous system involvement are reportedly poor prognostic indicators [164, 165]. There may be a role for positron emission tomography in the evaluation of response and relapse [166].

### *3.6.5 Rhabdomyosarcoma*

Rhabdomyosarcoma is the most common soft-tissue mesenchymal tumor and the most common malignancy of the orbit in children, representing about 4% of all childhood orbital mass lesions and 1% of orbital tumors. This topic is addressed extensively in Chapter 4.

## References

1. Ohtsuka K, Hashimoto M, Suzuki Y. A review of 244 orbital tumors in Japanese patient during a 21-year period: origins and locations. Jpn J Ophthalmol 2005;49(1):49–55.
2. Shields JA, Augsburger JJ, Donoso LA. Orbital dermoid cyst of conjunctival origin. Am J Ophthalmol 1986;101:726–9.
3. Shields JA, Shields CL. Orbital cysts of childhood—classification, clinical features, and management. Surv Ophthalmol 2004;49(3):281–99.
4. Dutton JJ, Fowler AM, Proia AD. Dermoid cyst of conjunctival origin. Ophthal Plast Reconstr Surg 2006;22(2):137–9.
5. McCollough ML, Glover AT, Grabski WJ, et al. Orbital dermoid cysts showing conjunctival epithelium. Am J Dermatopathol 1991;13:611–15.
6. Sherman RP, Rootman J, LaPointe JS. Orbital dermoids: clinical presentation and management. Br J Ophthalmol 1984;68:642–52.
7. Bonavolonta G, Tranfa F, de Conciliis C, et al. Dermoid cysts: 16-year survey. Ophthal Plast Reconstr Surg 1995;11:187–92.
8. Emerick GT, Shields CL, Shields JA, et al. Chewing-induced visual impairment from a dumbbell dermoid cyst. Ophthal Plast Reconstr Surg 1997;13:57–61.
9. Howard GR, Nerad JA, Bonavolonta G, et al. Orbital dermoid cysts located within the lateral rectus muscle. Ophthalmology 1994;101:767–71.
10. Blei L, Chambers JT, Liotta LA, et al. Orbital dermoid diagnosed by computed tomographic scanning. Am J Ophthalmol 1978;85:58–61.
11. Nugent RA, Lapointe JS, Rootman J, et al. Orbital dermoids: features on CT. Radiology 1987;165:475–8.
12. Sathananthan N, Moseley IF, Rose GE, et al. The frequency and clinical significance of bone involvement in outer canthus dermoid cysts. Br J Ophthalmol 1993;77:789–94.
13. De Potter P, Flanders AE, Shields CL, et al. Magnetic resonance imaging of orbital tumors. Int Ophthalmol Clin 1993;33:163–73.
14. Hakyemez B, Aksoy U, Yildiz H, et al. Intracranial epidermoid cysts: diffusion-weighted, FLAIR, and conventional MR findings. Eur J Radiol 2005;54:214–20.
15. Grove AS Jr. Giant dermoid cysts of the orbit. Ophthalmology 1979;86:1513–20.
16. Traboulsi EI, Azar DT, Khattar J, et al. A-scan ultrasonography in the diagnosis of orbital dermoid cysts. Ann Ophthalmol 1988;20:229–32.

17. Shields JA, Kaden IH, Eagle RC Jr, et al. Orbital dermoid cysts: clinicopathologic correlations, classification, and management. The 1997 Josephine E. Schuleler lecture. Ophthal Plast Reconstr Surg 1997;13:265–76.
18. Kersten RC. The eyelid crease approach to superficial lateral dermoid cysts. J Pediatr Ophthalmol Strabismus 1988;25:48–51.
19. Columbo, F, Holbach LM, Naumann GO. Chronic inflammation in dermoid cysts: a clinicopathologic study of 115 patients. Orbit 2000;19(2):97–107.
20. Golden RP, Shields WE 2nd, Cahill KV, et al. Percutaneous drainage and ablation of orbital dermoid cysts. J AAPOS 2007;11(5):438–42.
21. Appalanarasayya K, Dev OB. Teratoma of the orbit. Int Surg 1970;54:301–3.
22. Berlin AJ, Rich LS, Hahn JF. Congenital orbital teratoma. Child's Brain 1983;10:208–16.
23. Bilgic S, Dayanir V, Kiratli H, et al. Congenital orbital teratoma: a clinicopathologic case report. Ophthal Plast Reconstr Surg 1997;13:142–6.
24. Ferry AP. Teratoma of the orbit: a report of two cases. Surv Ophthalmol 1965;10:434–42.
25. Garden JW, McManis JC. Congenital orbital–intracranial teratoma with subsequent malignancy. Case report. Br J Ophthalmol 1986;70:111–13.
26. Lee GA, Sullivan TJ, Tsikleas GP, et al. Congenital orbital teratoma. Aust N Z J Ophthalmol 1997;25:63–6.
27. Mahesh L, Krishnakumar S, Subramanian N, et al. Malignant teratoma of the orbit: a clinicopathological study of a case. Orbit 2003;22(4):305–9.
28. Soares EJC, Lopes KDS, Andrafe JDS, et al. Orbital malignant teratoma. A case report. Orbit 1983;2:235–42.
29. Chang DF, Dallow RL, Walton DS. Congenital orbital teratoma: report of a case with visual preservation. J Pediatr Ophthalmol 1980;17:88–95.
30. Itami K, Traboulsi EI, Karim FWA, et al. Conservative surgery in orbital teratoma. Orbit 1986;5:61–5.
31. Gundalp I, Gunduz K. Vascular tumors of the orbit. Doc Ophthalmol 1995;89:337–45.
32. Dadras SS, North PE, Bertoncini J, et al. Infantile hemangiomas are arrested in an early developmental vascular differentiation state. Mod Pathol 2004;17(9):1068–79.
33. Haik BG, Jakobiec FA, Ellsworth RM, et al. Capillary hemangioma of the lids and orbit: an analysis of the clinical features and therapeutic results in 101 cases. Ophthalmology 1979;86:760–92.
34. Haik BG, Karcioglu ZA, Goson RA, et al. Capillary hemangioma (infantile periocular hemangioma). Surv Ophthalmol 1994;38:399–426.
35. Byrne SF, Green RL. Ultrasound of the Eye and Orbit. St. Louis, MO: Mosby-Yearbook, 1992:332.
36. Balchunas ER, Quencer RM, Byrne SF, et al. Correlative of the computed tomographic, ultrasonographic, and pathological characteristics of cavernous versus capillary hemangiomas of the orbit. J Clin Neuroophthalmol 1983;6:14.
37. Jiang XW, Wang GH, Li JH, et al. Expression of glucocorticoid receptor isoforms in cutaneous hemangiomas and vascular malformations. Chin Med J 2005;118(12): 977–81.
38. Cogen MS, Elsas FJ. Eyelid depigmentation following corticosteroid injection for infantile ocular adnexal hemangioma. J Pediatr Ophthalmol Strabismus 1989;26:35–8.
39. Wilson MW, Hoehn ME, Haik BG, et al. Low-dose cyclophosphamide and interferon alpha 2a for the treatment of capillary hemangioma of the orbit. Ophthalmology 2007;114(5):1007–11.
40. Deans RM, Harris GJ, Kivlin JD. Surgical dissection of capillary hemangiomas. An alternative to intralesional corticosteroids. Arch Ophthalmol 1992;110:1743–7.
41. Burstein FD, Simms C, Cohen SR, et al. Intralesional laser therapy of extensive hemangiomas in 100 consecutive pediatric patients. Ann Plast Surg 2000;44(2):188–94.
42. Léauté-Labrèze CE, Hubiche T, Boralevi F, et al. Propranolol for severe hemangiomas of infancy. N Engl J Med 2008;358(24):2649–51.

43. Verity DH, Rose GE, Restori M. The effect of intralesional steroid injections on the volume and blood flow in periocular capillary haemangiomas. Orbit 2008;27(1):41–7.
44. Kavanagh EC, Heran MK, Peleg A, et al. Imaging of the natural history of an orbital capillary hemangioma. Orbit 2006;25(1):69–72.
45. Egbert JE, Paul S, Engel WK, et al. High injection pressure during intralesional injection of corticosteroids into capillary hemangiomas. Arch Ophthalmol 2001;119(5):677–83.
46. O'Keefe M, Lanigan B, Byrne SA. Capillary haemangioma of the eyelids and orbit: a clinical review of the safety and efficacy of intralesional steroid. Acta Ophthalmol Scand 2003;81(3):294–8.
47. Schwartz SR, Kodsi SR, Blei F, et al. Treatment of capillary hemangiomas causing refractive and occlusional amblyopia. J AAPOS 2007;11(6):577–83.
48. Sutula FC, Glover AT. Eyelid necrosis following intralesional corticosteroid injection for capillary hemangioma. Ophthalmic Surg 1987;18(2):103–5.
49. Ruttum MS, Abrams GW, Harris GJ, et al. Bilateral retinal embolization associated with intralesional corticosteroid injection for capillary hemangioma of infancy. J Pediatr Ophthalmol Strabismus 1993;30(1):4–7.
50. Goyal R, Watts P, Lane CM, et al. Adrenal suppression and failure to thrive after steroid injections for periocular hemangioma. Ophthalmology 2004;111(2):389–95.
51. Weiss AH, Kelly JP. Reappraisal of astigmatism induced by periocular capillary hemangioma and treatment with intralesional corticosteroid injection. Ophthalmology 2008;115(2):390–7.
52. Bilaniuk LT. Vascular lesions of the orbit in children. Neuroimag Clin N Am 2005;15(1):107–20.
53. Selva D, Strianese D, Bonavolonta G, et al. Orbital venous-lymphatic malformations (lymphangiomas) mimicking cavernous hemangiomas. Am J Ophthalmol 2001;131(3):364–70.
54. Brooks SE, Pillai JJ, Bains H. Orbital cellulitis due to occult orbital lymphangioma. South Med J 2001;94(5):532–5.
55. Bisdorff A, Mulliken JB, Carrico J, et al. Intracranial vascular anomalies in patients with periorbital lymphatic and lymphaticovenous malformations. AJNR Am J Neuroradiol 2007;28(2):335–41.
56. Vachharajani A, Paes B. Orbital lymphangioma with non-contiguous cerebral arteriovenous malformation, manifesting with thrombocytopenia (Kasabach–Merritt syndrome) and intracerebral hemorrhage. Acta Paediatr 2002;91(1):98–9.
57. Huckabee RE, Raila FA. MRI and CT comparison of an orbital cavernous lymphangioma. J Miss State Med Assoc 1991;32:371–3.
58. Bond JB, Haik BG, Taveras JL, et al. Magnetic resonance imaging of orbital lymphangioma with and without gadolinium contrast enhancement. Ophthalmology 1992;99: 1318–24.
59. Gelbert F, Riche MC, Reizine D, et al. MR imaging of head and neck vascular malformations. J Magn Reson Imaging 1991;1:579–84.
60. Byrne SF, Green RL. Orbital ultrasound. In: Tasman W, Jaeger EA, editors. Duane's Clinical Ophthalmology. Vol 1. Philadelphia, PA: JB Lippincott, 1991:24.
61. Esmaeli B, Prieto VG, Gonnering R, et al. Growth factor receptor expression in orbital lymphangioma: possible therapeutic implications. Orbit 2004;23(4):263–9.
62. Harris GJ, Sakol PJ, Bonavolonta GT, et al. An analysis of thirty cases of orbital lymphangioma. Pathophysiologic considerations and management recommendations. Ophthalmology 1990;97:1583–92.
63. Wilson ME, Parker PL, Chavis RM. Conservative management of childhood orbital lymphangioma. Ophthalmology 1989;96:484–9.
64. Sires BS, Goins CR, Anderson RL, et al. Systemic corticosteroid use in orbital lymphangioma. Ophthal Plast Reconstr Surg 2001;17(2):85–90.
65. Tawfik HA, Budin H, Dutton JJ. Lack of response to systemic corticosteroids in patients with lymphangioma. Ophthal Plast Reconstr Surg 2005;21(4):302–5.

66. Schwarcz RM, Ben Simon GJ, Cook T, Goldberg RA. Sclerosing therapy as first line treatment for low flow vascular lesions of the orbit. Am J Ophthalmol 2006;141(2):333–9.
67. Boulos PR, Harissi-Dagher M, Kavalec C, et al. Intralesional injection of Tisseel fibrin glue for resection of lymphangiomas and other thin-walled orbital cysts. Ophthal Plast Reconstr Surg 2005;21(3):171–6.
68. de Graaf JH, Egeler RM. New insights into the pathogenesis of Langerhans cell histiocytosis. Curr Opin Pediatr 1997;9(1):46–50.
69. Shields JA, Shields CL. Clinical spectrum of histiocytic tumors of the orbit. Trans Pa Acad Ophthalmol Otolaryngol 1990;42:931–7.
70. Harris GJ. Langerhans cell histiocytosis of the orbit: a need for interdisciplinary dialogue. Am J Ophthalmol 2006;141(2):374–8.
71. Egeler RM, Annels NE, Hogendoorn PC. Langerhans cell histiocytosis: a pathologic combination of oncogenesis and immune dysregulation. Pediatr Blood Cancer 2004;42(5): 401–3.
72. Konrad H, Clark BJ, Rose GE. Lymphocytic, plasmacytic, histiocytic, and hematopoietic tumors of the orbit. In: Tasman W, Jaeger EA, editors. Duane's Clinical Ophthalmology. Philadelphia, PA: Lippincott Williams & Wilkins, 2000:30–2.
73. Banna M, Oltuola PS. Orbital histiocytosis on computed tomography. J Comput Tomogr 1983;7:167–70.
74. Leonidas JC, Guelfguat M, Valderrama E. Langerhans cell histiocytosis. Lancet 2003;361(9365):1293–5.
75. Gündüz K, Palamar M, Parmak N, et al. Eosinophilic granuloma of the orbit: report of two cases. J AAPOS 2007;11(5):506–8.
76. Kindy-Degnan NA, Laflamme P, Duprat G, et al. Intralesional steroid in the treatment of an orbital eosinophilic granuloma. Arch Ophthalmol 1991;109:617–8.
77. Jubran RF, Marachelian A, Dorey F, et al. Predictors of outcome in children with Langerhans cell histiocytosis. Pediatr Blood Cancer 2005;45(1):37–42.
78. Haupt R, Nanduri V, Calevo MG, et al. Permanent consequences in Langerhans cell histiocytosis patients: a pilot study from the Histiocyte Society Late Effects Study Group. Pediatr Blood Cancer 2004;42(5):438–44.
79. Binning MJ, Brockmeyer DL. Novel multidisciplinary approach for treatment of Langerhans cell histiocytosis of the skull base. Skull Base 2008;18(1):53–8.
80. Thompson CR, Lessell S. Anterior visual pathway gliomas. Int Ophthalmol Clin 1997;37:261–79.
81. Dutton JJ. Gliomas of the anterior visual pathway. Surv Ophthalmol 1994;38:427–52.
82. Lee AG. Neuro-ophthalmological management of optic pathway gliomas. Neurosurg Focus 2007;23(5):E1.
83. North KN. Neurofibromatosis 1 in childhood. Semin Pediatr Neurol 1998;5(4):231–42.
84. Astrup J. Natural history and clinical management of optic pathway glioma. Br J Neurosurg 2003;17(4):327–35.
85. Zeid JL, Charrow J, Sandu M, et al. Orbital optic nerve gliomas in children with neurofibromatosis type 1. J AAPOS 2006;10(6):534–9.
86. Es SV, North KN, McHugh K, et al. MRI findings in children with neurofibromatosis type 1: a prospective study. Pediatr Radiol 1996;26:478–87.
87. Pungavkar SA, Lawande MA, Patkar DP, et al. Bilateral optic pathway glioma with intracranial calcification: magnetic resonance imaging and magnetic resonance spectroscopy findings. Australas Radiol 2005;49(6):489–92.
88. Liu GT. Optic gliomas of the anterior visual pathway. Curr Opin Ophthalmol 2006;17(5):427–31.
89. Jahraus CD, Tarbell NJ. Optic pathway gliomas. Pediatr Blood Cancer 2006;46(5):586–96.
90. Combs SE, Schulz-Ertner D, Moschos D, et al. Fractionated stereotactic radiotherapy of optic pathway gliomas: tolerance and long-term outcome. Int J Radiat Oncol Biol Phys 2005;62(3):814–9.

91. Balcer LJ, Liu GT, Heller G, et al. Visual loss in children with neurofibromatosis type 1 and optic pathway gliomas: relation to tumor location by magnetic resonance imaging. Am J Ophthalmol 2001;131(4):442–5.
92. Tow SL, Chandela S, Miller NR, et al. Long-term outcome in children with gliomas of the anterior visual pathway. Pediatr Neurol 2003;28:262–70.
93. Czyzyk E, Jóźwiak S, Roszkowski M, et al. Optic pathway gliomas in children with and without neurofibromatosis 1. J Child Neurol 2003;18(7):471–8.
94. Farris SR, Grove AS Jr. Orbital and eyelid manifestations of neurofibromatosis: a clinical study and literature review. Ophthal Plast Reconstr Surg 1996;12:245–59.
95. Jackson IT, Carbonnel A, Potparic Z, et al. Orbitotemporal neurofibromatosis: classification and treatment. Plast Reconstr Surg 1993;92(1):1–11.
96. Tada M, Sawamura Y, Ishii N, et al. Massive plexiform neurofibroma in the orbit in a child with von Recklinghausen's disease. Childs Nerv Syst 1998;14:210–2.
97. Erb MH, Uzcategui N, See RF, et al. Orbitotemporal neurofibromatosis: classification and treatment. Orbit 2007;26(4):223–8.
98. Wu CT, Lee ST, Chen JF, et al. Computer-aided design for three-dimensional titanium mesh used for repairing skull base bone defect in pediatric neurofibromatosis type 1. A novel approach combining biomodeling and neuronavigation. Pediatr Neurosurg 2008;44(2): 133–9.
99. Kwiat DM, Bersani TA, Hodge C, et al. Surgical technique: two-step orbital reconstruction in neurofibromatosis type 1 with a matched implant and exenteration. Ophthal Plast Reconstr Surg 2004;20(2):158–61.
100. Dutton JJ, Tawfik HA, DeBacker CM, et al. Multiple recurrences in malignant peripheral nerve sheath tumor of the orbit: a case report and a review of the literature. Ophthal Plast Reconstr Surg 2001;17(4):293–9.
101. Shome D, Honavar SG, Reddy VA, et al. Orbital embryonal rhabdomyosarcoma in association with neurofibromatosis type 1. Ophthal Plast Reconstr Surg 2007;23(2): 147–8.
102. Schatz H. Benign orbital neurilemoma: sarcomatous transformation in von Recklinghausen's disease. Arch Ophthalmol 1971;86:268–73.
103. Zagar TM, Triche TJ, Kinsella TJ. Extraosseous Ewing's sarcoma: 25 years later. J Clin Oncol 2008;26(26):4230–2.
104. Choi RY, Lucarelli MJ, Imesch PD, et al. Primary orbital Ewing sarcoma in a middle-aged woman. Arch Ophthalmol 1999;117(4):535–7.
105. Guzowski M, Tumuluri K, Walker DM, et al. Primary orbital Ewing sarcoma in a middle-aged man. Ophthal Plast Reconstr Surg 2005;21(6):449–51.
106. Li T, Goldberg RA, Becker B, et al. Primary orbital extraskeletal Ewing sarcoma. Arch Ophthalmol 2003;121(7):1049–52.
107. Dutton JJ, Rose JG Jr, DeBacker CM, et al. Orbital Ewing's sarcoma of the orbit. Ophthal Plast Reconstr Surg 2000;16(4):292–300.
108. Sharma A, Garg A, Mishra NK, et al. Primary Ewing's sarcoma of the sphenoid bone with unusual imaging features: a case report. Clin Neurol Neurosurg 2005;107(6):528–31.
109. Henk CB, Grampp S, Wiesbauer P, et al. Ewing sarcoma. Diagnostic imaging. Radiologe 1998;38:509–22.
110. Wilson DJ, Dailey RA, Griffeth MT, et al. Primary Ewing sarcoma of the orbit. Ophthal Plast Reconstr Surg 2001;17(4):300–3.
111. Frandsen E. Ewing's sarcoma of the orbit. Nord Med 1952;48:1673.
112. Ludwig JA. Ewing sarcoma: historical perspectives, current state-of-the-art, and opportunities for targeted therapy in the future. Curr Opin Oncol 2008;20(4):412–8.
113. Leavey PJ, Collier AB. Ewing's sarcoma: prognostic criteria, outcomes, and future treatments. Expert Rev Anticancer Ther 2008;8:617–24.
114. Belgaumi AF, Kauffman WM, Jenkins JJ, et al. Blindness in children with neuroblastoma. Cancer 1997;80:1997–2004.

115. Musarella M, Chan HSL, DeBoer G, et al. Ocular involvement in neuroblastoma: prognostic implications. Ophthalmology 1984;91:936–40.
116. Mirzai H, Baser EF, Tansug N, et al. Primary orbital neuroblastoma in a neonate. Indian J Ophthalmol 2006;54:206–8.
117. Lau JJ, Trobe JD, Ruiz RE, et al. Metastatic neuroblastoma presenting with binocular blindness from intracranial compression of the optic nerves. J Neuroophthalmol 2004;24(2):119–24.
118. Mortada A. Clinical characteristics of early orbital neuroblastoma. Am J Ophthalmol 1967;63:1787–93.
119. Messina JA, Cheng SC, Franc BL, et al. Evaluation of semi-quantitative scoring system for metaiodobenzylguanidine (mIBG) scans in patients with relapsed neuroblastoma. Pediatr Blood Cancer 2006;47(7):865–74.
120. Park JR, Eggert A, Caron H. Neuroblastoma: biology, prognosis, and treatment. Pediatr Clin North Am 2008;55(1):97–120.
121. Ishola TA, Chung DH. Neuroblastoma. Surg Oncol 2007;16:149–56.
122. Friedman GK, Castleberry RP. Changing trends of research and treatment in infant neuroblastoma. Pediatr Blood Cancer 2007;49(7 Suppl):1060–5.
123. Paulino AC. Palliative radiotherapy in children with neuroblastoma. Pediatr Hematol Oncol 2003;20(2):111–7.
124. Bakhshi S, Singh P, Chawla N. Malignant childhood proptosis: study of 104 cases. J Pediatr Hematol Oncol 2008;30(1):73–6.
125. Menon BS, Alagaratnam J, Juraida E, et al. Late presentation of retinoblastoma in Malaysia. Pediatr Blood Cancer 2009;52(2):215–7.
126. Rootman J, Ellsworth RM, Hofbauer J, et al. Orbital extension of retinoblastoma: a clinicopathologic study. Can J Ophthalmol 1978;13:72–80.
127. Agarwal M, Biswas J, S K, Shanmugam MP. Retinoblastoma presenting as orbital cellulitis: report of four cases with a review of the literature. Orbit 2004;23(2):93–8.
128. Foster BS, Mukai S. Intraocular retinoblastoma presenting as ocular and orbital inflammation. Int Ophthalmol Clin 1996;36:153–60.
129. Antoneli CB, Steinhorst F, de Cassia Braga Ribeiro K, et al. Extraocular retinoblastoma: a 13 year experience. Cancer 2003;98:1292–8.
130. Kiratli H, Bigic S, Ozerdem U. Management of massive orbital involvement of intraocular retinoblastoma. Ophthalmology 1998;105:322–6.
131. Chantada G, Fandiño A, Casak S, et al. Treatment of overt extraocular retinoblastoma. Med Pediatr Oncol 2003;40(3):158–61.
132. Eng C, Li FP, Abramson DH, et al. Mortality from second tumors among long-term survivors of retinoblastoma. J Natl Cancer Inst 1993;85(14):1121–8.
133. Moll AC, Imhof SM, Bouter LM, et al. Second primary tumors in patients with hereditary retinoblastoma: a register-based follow-up study, 1945–1994. Int J Cancer 1996;67(4):515–9.
134. Chung EM, Specht CS, Schroeder JW. From the archives of the AFIP. Pediatric orbit tumors and tumorlike lesions: neuroepithelial lesions of the ocular globe and optic nerve. Radiographics 2007;27(4):1159–86.
135. Dunkel IJ, Aledo A, Kernan NA, et al. Successful treatment of metastatic retinoblastoma. Cancer 2000;89(10):2117–21.
136. Finger PT, Harbour JW, Karcioglu ZA. Risk factors for metastasis in retinoblastoma. Surv Ophthalmol 2002;47(1):1–16.
137. Bowman RJ, Mafwiri M, Luthert P, et al. Outcome of retinoblastoma in east Africa. Pediatr Blood Cancer 2008;50(1):160–2.
138. Gündüz K, Müftüoglu O, Günalp I, et al. Metastatic retinoblastoma clinical features, treatment, and prognosis. Ophthalmology 2006;113(9):1558–66.
139. Kim JW, Kathpalia V, Dunkel I, et al. Orbital recurrence of retinoblastoma following enucleation. Br J Ophthalmol 2008;115(8):1398–1404.

140. Kleinerman RA, Tucker MA, Tarone RE, et al. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. J Clin Oncol 2005;23(10):2272–9.
141. Abramson DH, Melson MR, Dunkel IJ, et al. Third (fourth and fifth) non-ocular tumors in survivors of retinoblastoma. Ophthalmology 2001;108(10):1868–76.
142. Wong FL, Boice JD Jr, Abramson DH, et al. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. JAMA 1997;278(15):1262–7.
143. Fletcher O, Easton D, Anderson K, et al. Lifetime risks of common cancers among retinoblastoma survivors. J Natl Cancer Inst 2004;96(5):357–63.
144. Porto L, Kieslich M, Schwabe D, et al. Granulocytic sarcoma in children. Neuroradiology 2004;46(5):374–7.
145. Esmaeli B, Medeiros LJ, Myers J, et al. Orbital mass secondary to precursor T-cell acute lymphoblastic leukemia: a rare presentation. Arch Ophthalmol 2001;119(3):443–6.
146. Padillo D, Mencía E, Gutiérrez E, et al. Orbital granulocytic sarcoma in a myelodysplastic syndrome. Orbit 1999;18(4):287–90.
147. Jakobiec FA. Granulocytic sarcoma. AJNR Am J Neuroradiol 1991;12(2):263–4.
148. Watkins LM, Remulla HD, Rubin PA. Orbital granulocytic sarcoma in an elderly patient. Am J Ophthalmol 1997;123(6):854–6.
149. Davis JL, Parke DW 2nd, Font RL. Granulocytic sarcoma of the orbit. A clinicopathologic study. Ophthalmology 1985;92(12):1758–62.
150. Zimmerman LE, Font RL. Ophthalmologic manifestations of granulocytic sarcoma (myeloid sarcoma or chloroma). The third Pan American Association of Ophthalmology and American Journal of Ophthalmology Lecture. Am J Ophthalmol 1975;80(6):975–90.
151. Banna M, Aur R, Akkad S. Orbital granulocytic sarcoma. AJNR Am J Neuroradiol 1991;12:255–8.
152. Chung EM, Murphey MD, Specht CS, et al. From the archives of the AFIP. Pediatric orbit tumors and tumorlike lesions: osseous lesions of the orbit. Radiographics 2008;28(4): 1193–214.
153. Bulas RB, Laine FJ, Das Narla L. Bilateral orbital granulocytic sarcoma (chloroma) preceding the blast phase of acute myelogenous leukemia: CT findings. Pediatr Radiol 1995;25(6):488–9.
154. Pomeranz SJ, Hawkins HH, Towbin R, et al. Granulocytic sarcoma (chloroma): CT manifestations. Radiology 1985;155(1):167–70.
155. Pui MH, Fletcher BD, Langston JW. Granulocytic sarcoma in childhood leukemia: imaging features. Radiology 1994;190(3):698–702.
156. Stockl FA, Dolmetsch AM, Saornil MA, et al. Orbital granulocytic sarcoma. Br J Ophthalmol 1997;81(12):1084–8.
157. Audouin J, Comperat E, Le Tourneau A, et al. Myeloid sarcoma: clinical and morphologic criteria useful for diagnosis. Int J Surg Pathol 2003;11(4):271–82.
158. Tallman MS, Hakimian D, Shaw JM, et al. Granulocytic sarcoma is associated with the 8;21 translocation in acute myeloid leukemia. J Clin Oncol 1993;11(4):690–7.
159. Ohta K, Kondoh T, Yasuo K, et al. Primary granulocytic sarcoma in the sphenoidal bone and orbit. Childs Nerv Syst 2003;19(9):674–9.
160. Lee SG, Park TS, Cheong JW, et al. Preceding orbital granulocytic sarcoma in an adult patient with acute myelogenous leukemia with t(8;21): a case study and review of the literature. Cancer Genet Cytogenet 2008;185(1):51–4.
161. Cavdar AO, Babacan E, Gözdaşoğlu S, et al. High risk subgroup of acute myelomonocytic leukemia (AMML) with orbito-ocular granulocytic sarcoma (OOGS) in Turkish children. Retrospective analysis of clinical, hematological, ultrastructural, and therapeutical findings of thirty-three OOGS. Acta Haematol 1989;81(2):80–5.
162. Byrd JC, Weiss RB, Arthur DC, et al. Extramedullary leukemia adversely affects hematologic complete remission rate and overall survival in patients with t(8;21)(q22;q22): results from Cancer and Leukemia Group B 8461. J Clin Oncol 1997;15(2):466–75.

163. Schwyzer R, Sherman GG, Cohn RJ, et al. Granulocytic sarcoma in children with acute myeloblastic leukemia and t(8;21). Med Pediatr Oncol 1998;31(3):144–9.
164. Bisschop MM, Révész T, Bierings M, et al. Extramedullary infiltrates at diagnosis have no prognostic significance in children with acute myeloid leukaemia. Leukemia 2001;15:46–9.
165. Kobayashi R, Tawa A, Hanada R, et al. Japanese childhood AML cooperative study group. Extramedullary infiltration at diagnosis and prognosis in children with acute myelogenous leukemia. Pediatr Blood Cancer 2007;48(4):393–8.
166. Kumar J, Seith A, Bakhshi S, et al. Isolated granulocytic sarcoma of the orbit. Eur J Haematol 2007;78(5):456.