Orbital Vascular Anomalies

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Introduction

Vascular anomalies are a group of disorders of blood vessel growth that leads to identifiable vascular lesions and their associated deformities. For many years, understanding this group of diseases was vague due to inconsistencies in nomenclature and classification. In 2014, the ISSVA, a multispecialty interest group in diagnosis, management, and investigation of vascular anomalies, adopted a revised binary classification scheme based on the initial grouping suggested by Mulliken and Glowacki in 1982 [1]. Vascular tumors/neoplasms, like hemangiomas, that result from active cell proliferation of endothelial cells are differentiated from vascular malformations which are congenital defects in vessel morphogenesis. These two types exhibit different clinical behaviors and require different diagnostic and treatment plans (Table 8.1).

Vascular anomalies frequently occur in children, and when these lesions appear in the periocular region, they can affect visual, eyelid, and orbital development.

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C. J. Hwang et al. (eds.), *Clinical Ophthalmic Oncology*,
https://doi.org/10.1007/978-3-030-13558-4_8

Orbital Vascular Tumors

Orbital vascular tumors are actively proliferating neoplasms that are either benign, locally aggressive, or malignant (Table 8.1). The most common benign vascular tumor in children is infantile hemangioma followed by pyogenic granuloma. Congenital hemangioma is a rare vascular tumor that mimics IH but presents differently. Kaposiform hemangioendothelioma is a locally aggressive vascular tumor often associated with Kasabach-Merritt syndrome. It is rarely seen in the orbital region and will not be discussed here. Angiosarcoma is a rare malignant vascular tumor that has been reported to occur in the eyelid.

Infantile Hemangioma

Infantile hemangiomas (IH) are unique vascular neoplasms that exhibit peculiar biological behavior and more commonly appear in the head and neck. They are distinguished from vascular malformations by age at presentation, clinical behavior, histopathology, and response to treatment (Table 8.2). Incidence is higher in females, low-birthweight premature infants, and children subjected to chorionic venous sampling [2]. IH has a unique immunohistochemical profile, expressing glucose transport protein (glut-1) that is otherwise expressed only in placenta and blood-brain barrier tissues [3].

Table 8.1 Summary of ISSVA classification of vascular anomalies

Vascular anomalies		
Vascular tumors		
Benign	**Locally aggressive or borderline**	**Malignant**
Infantile hemangioma/hemangioma of infancy	Kaposiform hemangioendothelioma	Angiosarcoma
Congenital hemangioma	Retiform hemangioendothelioma	Epithelioid hemangioendothelioma
Tufted angioma	Papillary intralymphatic angioendothelioma	Others
Spindle cell hemangioma	Composite hemangioendothelioma Kaposi sarcoma	
Epithelioid hemangioma	Others	
Pyogenic granuloma		
Others		
Vascular malformations		
Simple	**Combined**	**Others**
Capillary malformations (CM) Cutaneous and/or mucosal Telangiectasia Cutis marmorata telangiectatica congenita Nevus simplex/salmon patch/"angel kiss," "stork bite" Others	Capillary-venous malformation	Vascular malformations associated with other anomalies Klippel-Trenaunay syndrome Parkes Weber syndrome Servelle-Martorell syndrome Sturge-Weber syndrome Maffucci syndrome
Lymphatic malformations (LM) Common (cystic) LM (macrocystic/microcystic/mixed cystic LM) Generalized lymphatic anomaly (GLA) LM in Gorham-Stout disease Channel type LM Primary lymphedema Others	Capillary-lymphatic malformation	Anomalies of major named vessels (aka "hannel type" or "truncal" vascular malformations)
Venous malformations (VM) Common VM Familial VM cutaneo-mucosal (VMCM) Blue rubber-bleb nevus (Bean) syndrome VM Glomuvenous malformation (GVM) Cerebral cavernous malformation (CCM) (different types) Others	Capillary-arteriovenous malformation	Others
Arteriovenous malformations (AVM)	Lymphatic-venous malformation	
Arteriovenous fistula (AVF)	Capillary-lymphatic-venous malformation	
	Capillary-lymphatic-arteriovenous malformation	
	Capillary-venous-arteriovenous malformation	
	Capillary-lymphatic-venous-arteriovenous malformation	

Table 8.2 Comparison between infantile hemangioma and vascular malformations

	Infantile hemangiomas	Malformations
Presentation	Absent at birth	Present at birth
Behavior	Independent life cycle	Relentless progression
Progression	Rapid proliferation (+ mitosis)	Slow expansion (hypertrophy)
Clinical course	Slow involution	Non-involuting
Gender predilection	Female>male	Female = male
Race predilection	Caucasians	No race predilection
Histopathology	Varies with stage	Consistent
Immunohistochemical staining	GLUT-1 positive	GLUT-1 negative

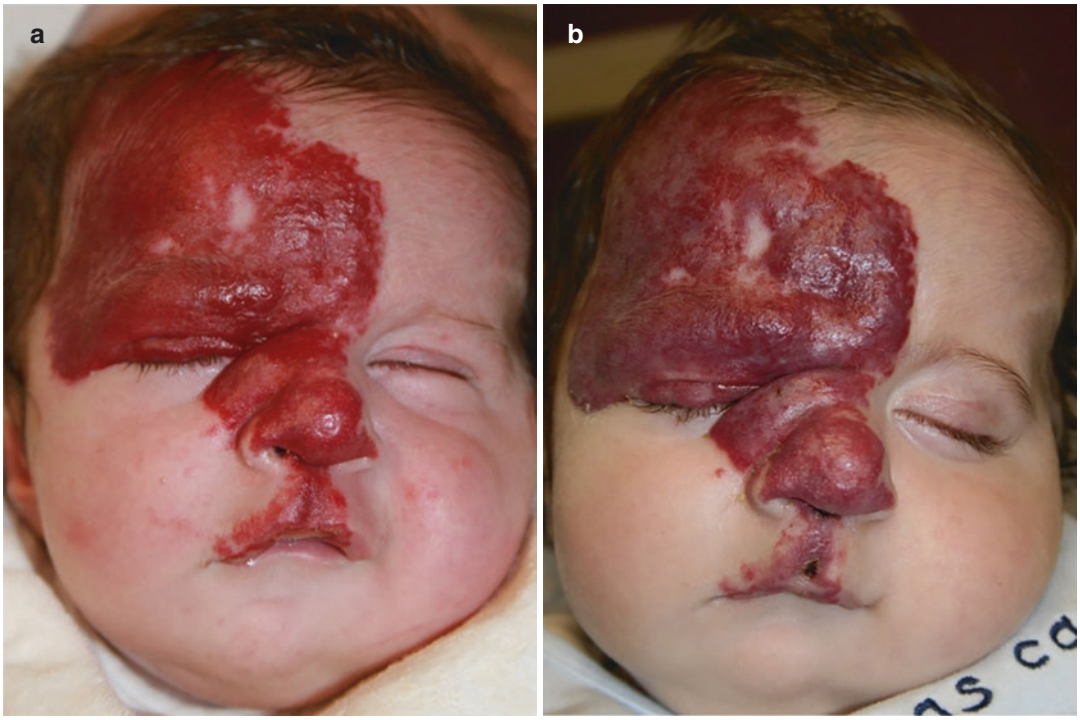

Fig. 8.1 (**a**, **b**) Demonstrating progression of hemangioma during the proliferation phase. (Courtesy of Milton Waner, MD)

Clinical Features

The unique biological behavior of IH can easily distinguish it from other vascular anomalies. They are usually absent or small at birth, generally growing rapidly in the first months of life, followed by a variable period of involution that spans months to years. Majority of these tumors are seen by the fourth week of life, while some show clinical evidence at birth, often with a paradoxically hypovascular blanch. In many cases, a pale halo, area of erythema, or cluster of telangiectatic vessels can be the initial presenting sign (Fig. 8.1).

The life cycle of IH is predictable. It starts with a proliferative phase characterized by rapid expansion and endothelial hyperplasia within the first year. This phase is often biphasic; most of the growth occurs within the first month of life, and then a second rapid growth phase happens at 6 months. The subsequent involutional phase is characterized by spontaneous, steady regression with histologic fibrosis and fat deposition. It has been observed that lesions whose involution commenced earlier tended to resolve more thoroughly [4]. However, there is no reliable method

of predicting which hemangiomas will involute, how long the regression will continue, or how completely a given hemangioma will resolve [5].

More than half of hemangiomas occur in the head-and-neck region, with clear sites of predilection within the head and neck [6]. Two subtypes of superficial IH that occur in these areas have been recognized, namely, focal IH and segmental IH. Focal IH are discrete hemangiomas that occur along lines of fusion between embryological facial placodes (Fig. 8.2) [7]. Segmental IH, on the other hand, form large plaque-like lesions overlying individual or multiple facial placodes. Each subtype varies in behavior, systemic disease association, and treatment options.

Focal periocular IH can cause significant functional and cosmetic deformity. Visual development is affected when IH of the eyelids exert pressure on the cornea and sclera to cause astigmatism resulting in subsequent amblyopia [8]. Tumor growth within the eyelid can lead to ptosis with obstruction of the visual axis resulting in deprivational amblyopia [9].

With orbital involvement, IH can produce rapid proptosis, exposure keratopathy, compressive optic neuropathy, globe displacement, and strabismic amblyopia [10]. If left untreated, large intraorbital IH can produce orbital expansion with considerable increase in orbital volume and subsequent enophthalmos or inferior displacement of the globe.

Soft tissue ulceration can occur in segmental IH and can be extremely painful. This also increases the risk of infection and may result in cutaneous scarring. The naso-jugal and V2 distributions tend to be at highest risk for ulceration in the periocular region (Fig. 8.3).

Infants with greater than four cutaneous hemangiomas are at increased risk of visceral hemangiomatosis, most commonly involving the liver, and should undergo further screening with abdominal ultrasound. Segmental IH associates more with systemic diseases than focal IH. It is

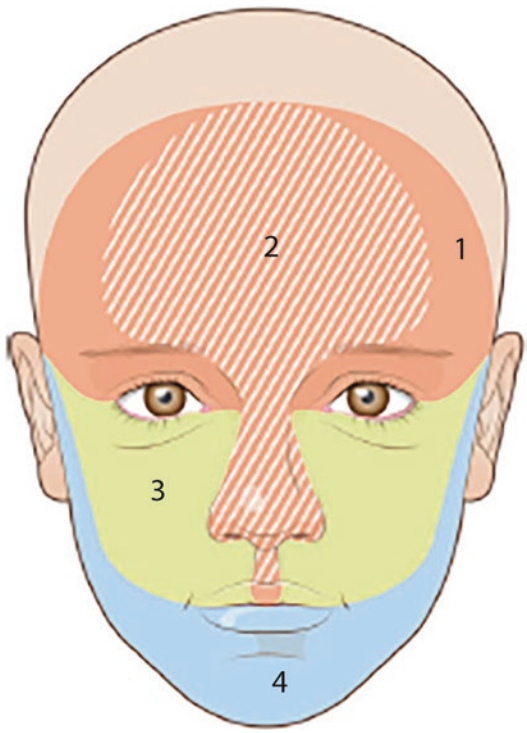

Fig. 8.2 Composition of facial placodes. Lateral optic vesicle area (1), frontonasal prominence (2), maxillary prominence (3), and mandibular prominence (4). (Modified from Zallmann et al. [7]. With permission from John Wiley & Sons]

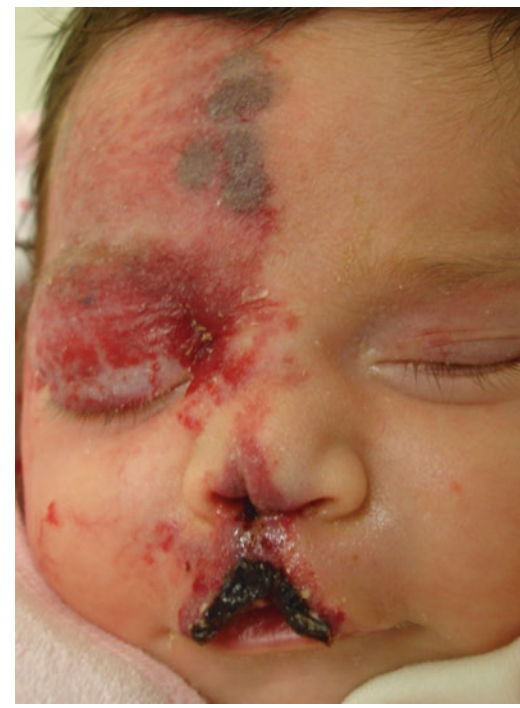

Fig. 8.3 Segmental infantile hemangioma with ulceration. (Courtesy of Milton Waner, MD)

one of the features of a neurocutaneous syndrome known as PHACE (*p*osterior fossa malformations; segmental infantile *h*emangioma of the head, neck, or face; and anomalies of cerebral *a*rteries, *c*ardiac, and *e*ye) syndrome [10].

Diagnostic Evaluation

Currently there are no laboratory investigations in clinical use for evaluation of IH. Ancillary tests that will help diagnose suspected IH are ultrasound (US), radiographic imaging, and biopsy. US can be used for screening of small, superficial periocular tumors. Grayscale and color Doppler US evaluates vascularity and type of vessels present. IH may appear as a well-defined mass with variable echogenicity on grayscale US and show high-flow vascularity on color Doppler. Computed tomography (CT) scan reveals a well-delineated, uniformly enhancing tumor. Magnetic resonance imaging (MRI) provides a detailed view of soft tissues and determines the extent of large lesions. T1-weighted contrast study shows an enhancing iso-to intermediate intensity mass that is hyperintense on T2-weighted images. Smaller lesions are more likely to be homogenous in signal and enhancement, whereas larger lesions tend to be more heterogeneous. Enhancement patterns are nonspecific in IH, and as involution occurs, gradual replacement by fibrofatty tissue causes MRI features to vary accordingly [11].

Histopathological evaluation of hemangioma tissue reveals characteristic findings in each phase of the life cycle. In the proliferative phase, the lesions appear as well-defined, nonencapsulated masses of plump, proliferating endothelial cells and attendant pericytes that focally form small, rounded red blood cell-containing lumens. Numerous mitotic figures and apoptotic bodies demonstrating nuclear fragmentation are simultaneously present in the tumor. The involution phase can be detected microscopically before the lesion begins to regress clinically. Apoptotic bodies and increased numbers of mast cells remain, while mitotic figures diminish. The endothelium begins to flatten as the lumen enlarges. As involution proceeds, loose fibrous or fibro-adipose tissue begins to separate vessels both within and between lobules as the number of proliferating vessels decrease. End-stage lesions show a fibrofatty background with a mast cell count comparable to that of normal skin, studded by a few residual vessels similar to normal capillaries or venules and scattered larger vessels with fibrotic walls. No endothelial or pericytic mitotic activity remains [12].

The most important immunohistochemical marker that is not demonstrated in other orbital vascular anomalies is the expression of GLUT-1 in IH. This important discovery has improved the accuracy of diagnosing IH. Other immunohistochemical biomarkers that are expressed by IH are CD31, CD34, Lewis Y antigen, merosin, and FC-γ RII. These markers are not specific to IH, but their presence helps provide an immunohistochemical profile that is unique to vascular tumors.

Differential Diagnosis

IH has a great variety of presentations depending on the stage and location, so differential diagnosis is extensive. Early in presentation, IH may be confused with benign venular midline malformation, also known as "nevus flammeus neonatorum," "stork bite," "angel kiss," or "salmon patch." Benign venular midline malformation occurs in up to 40% of newborns and most often disappears by the first year of life [13].

Focal IH with cutaneous components may mimic venous malformations, particularly when mucosal surfaces are involved. Deep focal lesions may resemble childhood mass lesions like rhabdomyosarcoma, metastatic neuroblastoma, hemangiopericytoma, mucocele, meningocele, etc. Small focal IH on the eyelid may look like pyogenic granulomas. Segmental hemangiomas can be easily confused with port wine stain or other cutaneous vascular malformations that also tend to follow dermatomal patterns. Lastly, the involuted cutaneous hemangioma can appear like a lipoma or may leave scarring that appears like the cicatrix of trauma, chemical injury, or thermal burns.

Treatment

Treating IH has been controversial for decades because of its high rate and unique characteristic

of spontaneous involution. Therefore, IH was popularly managed by simple "watchful waiting." The modern approach to IH was fundamentally revolutionized when the beta-blocker effect on infantile hemangiomas was discovered in 2008 [14]. Additional advances in pharmacologic treatment, laser technology, and surgical technique gave rise to the establishment of multidisciplinary clinics that are devoted to the management of vascular anomalies. These clinics offer a vast array of treatment possibilities to their patients.

Two distinct decision processes are involved in the rational approach to managing IH that must answer these questions: (1) Is treatment necessary or beneficial? (2) What is the appropriate treatment modality? [15] The first decision takes into consideration anatomic location, lesion size, and age of the child. Each of these aspects determine whether it is necessary to intervene or more prudent to postpone treatment. For instance, small lesions in the eyelid or orbit of infants that are significant enough to cause ptosis, astigmatism, and subsequent amblyopia would benefit from early treatment compared to relatively larger lesions in other locations that do not affect visual development and may be conservatively observed. Similarly, an infant may tolerate a significantly sized lesion on the face but as self-image begins to develop, an older child may start to become self-conscious even if spontaneous involution is still anticipated.

Indications for treatment of orbital and periocular IH include astigmatism, globe deformity, occlusion of visual axis, ptosis and eyelid distortion, proptosis, strabismus, corneal exposure, optic nerve compression, and orbital bone deformity. Dermatologic indications are skin and soft tissue hypertrophy and ulceration. Psychosocial implications associated with large facial deformities require treatment before self-awareness of body image develops in a child [16].

Once treatment is deemed necessary, the second decision is to determine which of the many treatment modalities is most advantageous: pharmacologic treatment, laser, surgery, or any combination of the three. Additional factors that weigh in this decision are subtype, depth, and stage of the tumor.

Pharmacologic Treatment

Localized intralesional corticosteroid injection has been popularly used in the past to promote involution of IH. It aims to deliver a high concentration of medication directly to the tumor while minimizing systemic absorption and potential side effects of systemic corticosteroids. A variety of formulations use a mixture of triamcinolone and betamethasone with great success. Although effective, serious ocular complications have been reported including ophthalmic artery occlusion, retinal embolization, and central retinal artery occlusion. These occur as a result of high pressure during intralesional injection that promotes particle embolization [9, 17–19]. Therefore, slow injection under low pressure may prevent retrograde arterial flow and minimize these potential problems. Other complications are eyelid hypopigmentation, subcutaneous fat atrophy, sclerodermiform linear atrophy, eyelid necrosis, periocular calcification, retrobulbar hemorrhage, and inadvertent ocular penetration [20, 21]. In light of newer, safer treatment options, and the risks mentioned above, periocular steroid injection should be avoided in hemangioma patients.

Steroid-resistant IH have reportedly been treated effectively with immunosuppressants like interferon-alpha, vincristine, cyclophosphamide, and imiquimod. Use of these agents are now extremely limited after the discovery of safer alternatives.

Propranolol, a nonselective beta-blocker, was serendipitously found to inhibit hemangioma proliferation in pediatric patients that were concomitantly being treated for congenital cardiac disorders [14]. Leaute-Labreze observed that severe hemangiomas in these patients stabilized or regressed after being treated with systemic propranolol of 2 milligrams per kilogram body weight per day (mg/kg/day) for up to 9 months with no systemic side effects reported. Subsequent case reports and case series validated the dramatic efficacy of propranolol in treating primarily segmental hemangiomas [22, 23]. The effect on focal hemangiomas has been less dramatic. Rare complications of systemic propranolol are transient hypoglycemia, bradycardia, and hypoten-

sion; bronchospasm can be seen in patients with underlying reactive airway. These risks can be managed anticipatorily by obtaining a pediatric pretherapy evaluation, by monitoring vital signs and blood glucose levels at initiation and throughout therapy, and by maintaining frequent pediatric follow-ups. Doses of propranolol can be administered intravenously or orally. Propranolol has also clearly emerged as the preferred medical treatment for deep orbital and other inaccessible infantile hemangiomas.

The best protocol for administering propranolol to infants as young as 1 week of age has not been clearly determined. Several protocols have been suggested. A recent randomized clinical trial recommended a safe and effective regimen of 3 mg/kg/day in two or three divided doses [24]. Some authors recommend pretreatment cardiac workup for infants younger than 6 weeks of age, while others believe there is no indication for additional evaluation in otherwise healthy infants; the latter starts the medication on an outpatient basis.

Laser Photocoagulation

Laser treatment is utilized for cutaneous IH [24]. Pulsed dye laser (PDL) has become the standard for treating superficial proliferative hemangiomas, reaching up to a depth of 1.2 mm. Adjunctive treatment with propranolol, intralesional steroid injection, or surgery may be used for deeper lesions. A typical treatment regimen consists of PDL, 585–595 μm, with fluences of 5–12 J/cm^2, pulse duration 300–450 μs, spot size 5–7 mm, and concomitant surface cooling device. The desired purpuric response is produced by two to three passes with overlapping spots over the lesion. Up to eight treatments may be necessary to produce the desired endpoint, with 6–8 weeks interval between treatments, depending on response. Complications include minor temporary blistering, ulceration, crusting, textural changes, scarring, and skin pigmentary changes.

CO2 laser resurfacing CO_2 and non-ablative fractional photothermolysis are now used to improve the skin texture of atrophic scars from involuted IH and to revise surgical scars.

Surgery

The effect of surgical excision of IH is rapid and definitive. Furthermore, proliferating subcutaneous IH has a tissue-expanding effect that is advantageous during early surgery, making skin closure and reconstruction easier and minimizing surgical scars. Unfortunately, surgery is still only considered by many centers for vision- and life-threatening cases, and end-stage reconstruction, emphasizing the higher risk compared to medical management. Current advances in pediatric anesthesia and new surgical technologies and techniques have narrowed the gap between these risks, allowing for a more balanced treatment planning.

Hemorrhage is the most significant risk factor that limits surgery and requires strategies to manage intraoperative and postoperative bleeding. Bloodless dissection techniques continue to improve with the use of fine electrocautery dissecting needles. Adjunctive use of chemical and mechanical hemostatic agents such as topical thrombin, gelatin and cellulose coagulants, fibrin tissue adhesives, etc., during surgery, have allowed better control of intraoperative bleeding especially in previously inaccessible areas like the deep orbit. As more options for controlling intraoperative hemorrhage become available, surgeons have been able to dissect in hard to reach areas with relative safety. Surgical excision has been recommended as primary treatment for periocular IH and for lesions refractory to medical treatment.

Prognosis

Correct timing and proper mode and execution of treatment can prevent the plausible periocular complications that may otherwise cause visual impairment, physical deformity, and psychological damage to children with IH.

Congenital Hemangioma (CH)

Congenital hemangioma is a benign vascular neoplasm that grossly resembles IH but appears fully developed at birth and does not express the

GLUT-1 protein. Since CH undergoes the proliferative phase in utero, some can be identified during prenatal screening [11, 25]. It is further classified into rapidly involuting congenital hemangioma (RICH), when it spontaneously regresses from a few weeks after birth up to 2 years of age, and non-involuting congenital hemangioma (NICH), when it does not undergo involution but, instead, grows proportionately with the child.

Clinical Features

The presentation of CH greatly varies and can grossly appear just like IH. It could present as elevated, violaceous lesions with ectatic veins, raised grayish tumors with multiple telangiectasias surrounded by a pale halo, or flat infiltrative tumor with violaceous overlying skin (Fig. 8.4). They can also occur as variable shades of pink to purple, round to ovoid lesions with telangiectasia, and central or peripheral pallor. NICH are generally larger that RICH, and some lesions demonstrate high flow on Doppler ultrasonography.

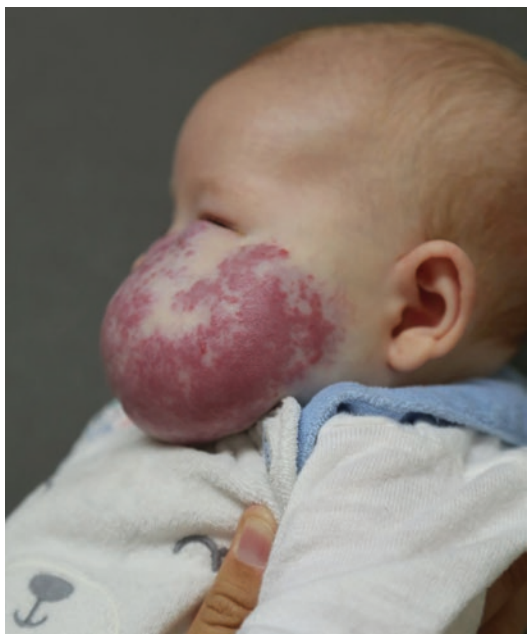

Fig. 8.4 Congenital hemangioma present at birth

Diagnostic Evaluation

Imaging features of CH overlap with IH in terms of heterogeneity, visible vessels, and calcifications. Therefore, the radiologist must be aware of the age at presentation and clinical findings, in order to suggest a congenital hemangioma.

Histopathological examination of congenital hemangiomas reveals lobular collections of capillaries with prominent endothelial cells. Dilated dysplastic veins within interlobular areas and increased mast cells may be seen in NICH. The main differentiating feature between CH and IH is the absence of GLUT-1 in immunohistochemical staining of CH. Additionally, D2-40 and Wilms' tumor 1 can be expressed in lobular areas of NICH.

Differential Diagnosis

CH can mimic the same lesions that resemble IH in the proliferative and involutional phases, respectively.

Treatment

RICH behaves almost similarly to IH in terms of its ability to spontaneously resolve while also potentially causing visual, physical, and psychological complications. Therefore, the same principles in decision-making process apply when managing these cases. On the other hand, NICH often needs to be excised with or without selective embolization [26].

Pyogenic Granuloma

Pyogenic granuloma (PG) or lobular capillary hemangioma is the second most common benign vascular tumor. It also resembles infantile hemangioma. PG can appear at any age, with a predilection for females. It has been postulated that female sex hormones may play a role in the pathogenesis of this tumor. In the periocular region, it may arise in response to various stimuli such as minor trauma or surgery and has been reported as a complication of pterygium surgery, chalazia, anophthalmic sockets, and punctal plug use in dry eye treatment.

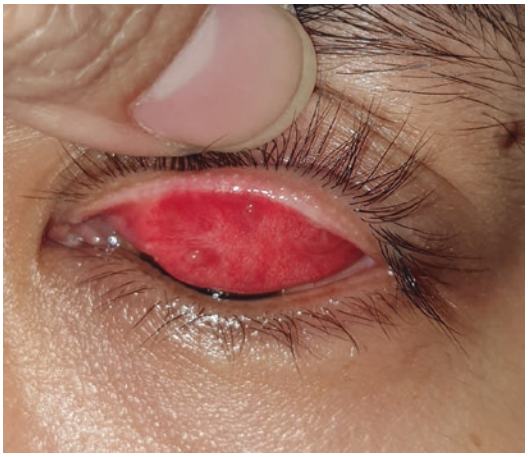

Fig. 8.5 Pyogenic granuloma of the eyelid

Clinical Features

PG presents as a pink, red, or purple lesion that is often pedunculated and may bleed recurrently (Fig. 8.5). It usually grows in mucosal tissue and is more common in the oral and nasal cavities. Periocular tumors involve conjunctiva, eyelids and, rarely, the cornea.

Diagnostic Evaluation

Laboratory and ancillary testing are often not necessary to diagnose this lesion. Surgical biopsy best confirms diagnosis.

The term pyogenic granuloma is a misnomer because it suggests a pus-forming lesion that contains epithelioid giant cells that are universally seen in granulomatous inflammation.

Histopathologically, however, PG is composed of acute and chronic inflammatory cells interspersed between fibroblasts, fibrocytes, and lobules of proliferating capillaries. Lobular capillary hemangioma is, therefore, a more apt descriptive term.

Treatment

Management of PG includes surgical excision and removal of the known inciting agent or irritant. Electrocautery, laser photocoagulation, and medical management with topical or oral beta-blockers have also been reported as effective for managing PG. Further studies are necessary to establish their advantages.

Prognosis

Prognosis is good after proper surgical resection and removal of known inciting agent.

Angiosarcoma

Angiosarcoma is a rare malignant vascular tumor that occurs in the head and neck. It accounts for less than 0.1% of malignancies in this area [27]. It rarely grows in the periocular region. There are a few case reports and series in literature of angiosarcoma developing in the eyelid, either as an isolated tumor or as part of a more diffuse malignant process [28].

Clinical Features

Eyelid angiosarcoma is a painless mass that may appear like any of the following: erythematous nodule, erythematous-to-violaceous maculopapular lesion, red-to-violaceous plaque or infiltrative lesion, yellow plaque or infiltrative lesion, or yellow nodule. Many occur with diffuse eyelid swelling.

Diagnostic Evaluation

The main modality for the diagnosis of angiosarcoma is surgical biopsy. Its histological features range from well- to poorly differentiated lesions, but the hallmark finding is abnormal pleomorphic malignant endothelial cells [29]. Atypical endothelial cells line anastomosing dissecting sinusoids with either diffuse epithelioid or spindle cell proliferation [30]. Immunohistochemical staining may show expression of factor VIII-related antigen, CD31, and CD34 in angiosarcoma cells [29].

Differential Diagnosis

Eyelid angiosarcoma may resemble a chalazion and malignancies of the eyelid such as squamous cell carcinoma, basal cell carcinoma, and sebaceous gland carcinoma.

Treatment

Due to its rarity, there is no generally accepted treatment guideline for angiosarcomas. The popular standard of care is wide excision surgery followed by external beam radiotherapy (EBRT). The invasiveness and multifocal nature of angiosarcoma make complete resections difficult. Therefore, adjuvant treatment with doxorubicin or paclitaxel and docetaxel has been utilized.

Prognosis

Prognosis is poor in spite of aggressive treatment of angiosarcoma. In Dermici and Christanson's review of 22 patients, those who underwent excisional biopsy with EBRT or chemotherapy had the best outcome, but the reported treatment successes were all within less than 5 years [28]. In angiosarcoma of the head and neck, tumor size, depth of invasion, and completeness of surgical resection are more reliable prognostic indicators than histologic grading. These are aggressive tumors that can recur locally and metastasize in spite of multimodal treatment. Angiosarcoma can spread to the lungs, liver, cervical lymph nodes, spleen, heart, and brain with a mean survival time of 4 months after metastasis. Death can occur from 15 to 24 months of presentation, either from local extension or metastasis.

Orbital Vascular Malformations

Vascular malformations are lesions that result from inborn morphogenesis defects of various vessels. Vascular development occurs during the retiform stage of embryogenesis, beginning at approximately day 48 of development, and vascular malformations, therefore, result from errors beginning at this stage. Examples include isolated lesions as well as numerous congenital syndromes: Sturge-Weber, Osler-Weber-Rendu, Wyburn-Mason, Klippel-Trénaunay, and blue rubber-bleb nevus (BLEB) syndrome. Vascular malformations grow with age and never involute. They are comprised of ectatic venules, veins, arterioles, arteries, and lymphatic vessels, all with flat (normal appearing) endothelial cells. The most common malformations that present in the orbit are venous and lymphatic malformations or a combination of the two (Table 8.1).

In 1999 the Orbital Society published a classification concept unique to orbital lesions and based entirely on clinical and radiographic hemodynamics. Lesions were classified by flow characteristics: no flow, slow flow, and rapid flow [31]. The emphasis on flow, rather than tissue type, was felt to help guide treatment planning (Table 8.3).

Unlike vascular neoplasms, vascular malformations usually grow in proportion with the child and can be exaggerated by hormonal changes during puberty or pregnancy or as a result of thrombosis or infection.

Lymphatic Malformations

Lymphatic malformations (LM), formerly called lymphangiomas, are benign malformations of the lymphatic system representing up to 8% of all orbital masses. Since these are not proliferative lesions, the "-oma" nomenclature is inap-

Table 8.3 Diagnostic features of orbital vascular lesions

Type	Flow	Imaging		Treatment
		Doppler US angiography	CT MRI	
Lymphangioma (type I)	No flow	No flow	No enhancement Fluid levels	Debulking
Varix (type II)	Venous flow	Venous flow	Contrast enhancement Flow voids	Sclerotherapy, ligation, and excision
AV malformation (type III)	Arterial flow	Arterial flow	Contrast enhancement Flow voids	Embolization then debulking

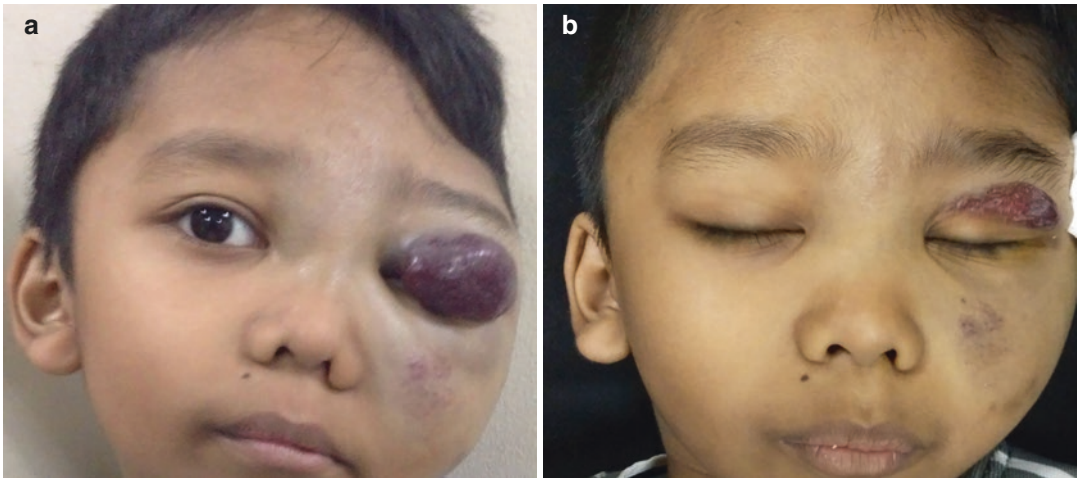

Fig. 8.6 Venous malformation on the eyelid, midface, and scalp of a 7-year-old boy (**a**) distention of the upper eyelid and cheek on upright position, (**b**) swelling subsides in supine position, and distention moves to the scalp

propriate. The specific etiology has not been fully elucidated. It has no gender predilection and typically involves subconjunctival and periocular tissues. LM contain tissue pockets that can range from microscopic to greater than 1 cm in diameter [32]. Lymphatic malformations would be classified as "no-flow" lesions in the flow-based scheme.

Clinical Features

Patients with LM may present with swelling, sudden proptosis, intraorbital hemorrhage, and ptosis. Unilateral proptosis or swelling is the primary symptom in 76% of patients [33]. When lymphatic malformations are combined with venous components, known as venolymphatic malformations, they present with soft, compressible bluish masses that may swell in dependent positions or with Valsalva (Fig. 8.6).

Orbital LM has the tendency to slip through extraconal and intraconal spaces, violating normal anatomic boundaries. Deep orbital LM that do not have superficial subconjunctival or eyelid extensions may be asymptomatic until there is an infection and sudden swelling ensues. Fluctuations in size are a typical feature of LM with upper respiratory tract infections. The lesion suddenly expands after intralesional hemorrhage. This sudden increase in size poses a risk for optic nerve compression that can lead to permanent visual impairment. In such cases, the need for treatment becomes urgent.

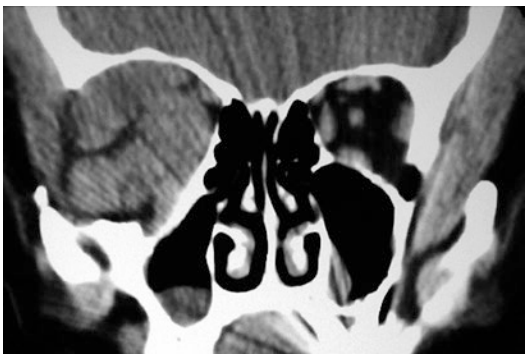

Fig. 8.7 Coronal CT imaging study shows lobulated appearance of lymphangioma (type 1 vascular lesion). Note surgical absence of lateral wall

Diagnostic Evaluation

The extent of orbital LM is best demonstrated by MR or CT imaging (Fig. 8.7). (CT scanning is typically avoided in young children.) LM appear as multilobulated, septated masses with intermediate to hypointensity on T1-weighted studies and hyperinsity on T2-weighted images. Internal fluid-fluid levels are commonly seen when intralesional hemorrhage is present manifesting as hyperintensity on T1-weighted studies in contrast to the intermediately intense cystic fluid.

Differential Diagnosis

Lymphatic malformations can present like other orbital masses depending on its extent and location of tumors. Differentials include other orbital vascular malformations, and hemangiomas, and orbital mass lesions like rhabdomyosarcoma, lymphoma, meningioma, and neurofibroma.

Treatment

The standard of care for LM is total resection of the lesion because of its high recurrence rate. However, involvement of deeper orbit and extension around major neurovascular structures make complete removal challenging. Ablative treatment with sclerosing agents have been utilized to decrease the impact and complications of surgery. Sclerosing agents induce collapse of these channels by destroying the endothelial lining and inciting an inflammatory reaction and fibrosis that occurs over several weeks. Doxycycline and bleomycin have been effectively used as sclerotherapeutic agents but can cause perilesional fibrosis that makes subsequent surgical excision more difficult. Other sclerosing agents such as alcohols and OK-432 that are useful in most anatomic regions should be avoided in the orbit due to intense inflammation and iatrogenic compartment syndrome [34]. OK-432 is a lyophilized biologic product that contains a mixture of a low virulence strain of *Staphylococcus pyogenes* that has been inactivated with penicillin G [34]. Intralesional pingyangmycin (a close analog of bleomycin) is another effective agent with sequelae of only mild inflammation and fibrosis [35].

Acute enlargement and swelling of LM often results from upper respiratory infection, hormonal shifts surrounding puberty, as well as other systemic stressors. These patients, who often present to unsuspecting emergency room staff, should receive systemic corticosteroids.

When complete surgical resection seems implausible, the goal of partial resection surgery or tumor debulking is to remove sight-threatening and cosmetically disfiguring lesions. Alternatively, patients with very large, recurrent, and incompletely resectable LM may benefit from orbital decompression. However, medial wall decompression can potentially cause spread of the lesion into the nasal cavity and sinuses, causing sinus-related complications. Other alternative, yet less effective and limited, options are aspiration, radiofrequency ablation, and laser treatment. Sirolimus, a systemic immunosuppressant used to prevent transplant rejection, is another alternative treatment that shows promising effects for treating unresectable, life-threatening lymphatic malformations. Efficacy of sildenafil for the treatment of LM remains to be assessed in large series of patients [36, 37].

Prognosis

Prognosis is excellent when complete surgical excision of LM is possible. However, when it is located in the deep orbit adjacent to vital orbital structures, complete resection becomes unlikely, and a high recurrence rate is expected.

Venous Malformations

Venous malformations (VM), formerly called cavernous hemangioma, consist of venous channels that are connected, albeit unpredictably, to normal veins and sinuses. Histopathology reveals large, thin-walled vessels within fibrous stroma. These channels are endothelial lined and contain smooth muscle. According to the flow-based scheme, lesions that behave this way are defined in the "slow-flow" category. Venous and lymphatic malformations can occasionally contain substantial proportions of both tissue types. This is generally where the flow classification and the tissue classification diverge.

Clinical Features

Venous malformations, like all malformations, are present at birth. A blue hue may be seen subcutaneously when the eyelids, temple, nose, or cheek are involved. Hemifacial VM involving the orbit is not uncommon. Purely orbital lesions may remain clinically dormant for some years but tend to come to attention during puberty. Symptoms include positional pain or exercise intolerance. Symptoms are sometimes worse in the morning,

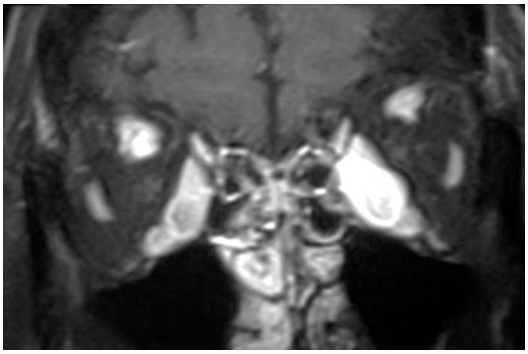

Fig. 8.8 Coronal Gd-DTPA-enhanced MRI shows bilateral contrast-enhancing lesions consistent with type 2 vascular lesions

presumably due to nocturnal distension in the recumbent position. Later in life, patients may complain of pain when upright that correlates with impressive enophthalmos. The long-standing lesion evidently compresses and eventually replaces normal orbital fat. Increased venous pressure will cause VMs to distend, producing pathognomonic positional exophthalmos when located in the orbit.

Diagnostic Evaluation

Color Doppler and directional ultrasound detect venous flow in venous malformations that are not thrombosed. CT and MRI reveal diffuse contrast enhancement (Fig. 8.8). CT scans may reveal pathognomonic calcified phleboliths, bony hypertrophy, or intraosseous extension. MR imaging best delineates these lesions and may reveal thrombosed areas. MR taken without raised intravenous pressure may miss the lesion entirely. MR angiography often detects the venous flow through distensible lesions. Percutaneous or remote access angiography remains the most comprehensive imaging method, allowing precise evaluation of drainage routes and rates.

Treatment

Surgery

Surgical management for orbital venous malformations is notoriously difficult. Surgical excision of venous malformations carries a high risk of complications, including hemorrhage, orbital compartment syndrome, and vision loss. Complete excision is difficult because these lesions often encase critical neuromuscular structures. Certain precautions can minimize intraoperative bleeding. Both preoperative thrombotherapy and fibrin sealant intraoperative injection (prior to excision) may significantly reduce flow. Maintaining normothermia and regional venous hypotension further reduces risk. Matched blood and platelet donor products may be needed when operating on small infants.

Sclerotherapy

Intralesional sclerotherapy that has revolutionized treatment of lymphatic malformations has been less useful for venous malformations. The flow found in VMs can recanalize these lesions 2–3 years or more after seemingly successful sclerotherapy. Furthermore, sclerotherapy for venous malformations requires careful assessment of the lesion's outflow so as to avoid inadvertent damage in the cavernous sinus. This assessment can be done with percutaneous or endovascular fluoroscopy. Newer methods include CT image fusion and frameless stereotactic guidance in combination with x-ray fluoroscopic monitoring of the injection [38].

Sclerotherapy of venous malformations not only may produce transient effects but also may induce catastrophic visual loss. Needle puncture of the delicate vessel wall may lead to intraoperative or delayed rupture resulting in orbital hemorrhage, compartment syndrome, and compressive optic neuropathy. For these reasons, many venous malformations ultimately require surgical treatment [39].

Other Methods

Venous malformations respond well to Nd:YAG laser, delivered percutaneously or by optical fiber, but have not been used extensively in the orbit where collateral heat and fibrosis cannot be well controlled [40]. Other treatment options include electrocoagulation and cryotherapy. These techniques may be used alone or preoperatively in order to reduce hemorrhagic complications.

Arteriovenous Malformations

Orbital arteriovenous malformations (AVM), like all AVMs, shunt blood from the high-pressure arterial vasculature, across an absent or defective capillary network, to the venous circulation. These are "high-flow" vascular malformations that are present at birth but may not manifest until childhood or adulthood. Like other vascular malformations, these lesions generally grow proportionately with the child and may be influenced by hormonal changes, thrombosis, infection, or trauma. In contrast to venous and lymphatic malformations, AVMs may enlarge very rapidly over months or years and destroy large regions or previously normal tissue. Congenital AVM is embryologically derived from the arterial or venous systems or both. These are characterized by progressively enlarging communications between arteries and veins that bypass normal capillary beds usually with numerous feeder arteries, a central low-resistance nidus, and multiple draining veins. Often, both internal and external carotid branches act as feeder vessels. Histologically, the muscularis layer of the involved arteries and veins appears abnormal.

Arteriovenous fistulae usually occur within the brain, a phenomenon in which arteries and veinous sinuses communicate directly [41]. The arteriovenous fistula known to ophthalmologists is the carotid artery-cavernous sinus communication in which carotid blood enters the venous sinus and superior ophthalmic vein causing orbital and ocular congestion. These lesions, typically seen in older adults, can occur spontaneously or as a result of trauma.

Clinical Features

AVM may manifest as a red pulsatile, warm mass that may cause proptosis, periorbital pain, increased intraocular pressure, pulsation, and bruit. Prolonged ocular ischemia may cause glaucoma and vision loss via progressive venous hypertension or diminished peak retinal arterial pressure from shunting. Venous hypertension may cause arterialization of conjunctival vessels reminiscent of changes seen with carotid-cavernous fistula (Fig. 8.9). A combination of cutaneous angiomas and retinal, orbital, and cerebral AVMs is known as Wyburn-Mason syndrome.

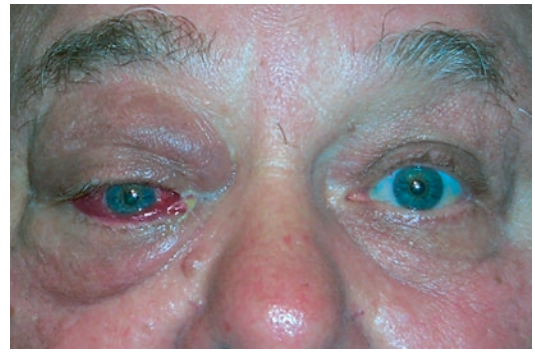

Fig. 8.9 External photograph demonstrates severe arterialization and proptosis of the right eye in a patient with type 3 orbital vascular lesion

Although these malformations typically display slow growth, acute aggravation of symptoms may occur after spontaneous orbital hemorrhage, and this presentation may mimic an acquired AV shunt. The older demographic and certain angiographic characteristics may help to distinguish acquired shunts from congenital malformations.

Diagnostic Evaluation

Noninvasive tests that can help diagnose high-flow malformations are ultrasonography and radiographic imaging to delineate the extent of the malformation. They are often multispacial and hypervascular on color Doppler US. MRI of the orbit may not show a discrete mass lesion but can reveal a dilated superior orbital vein and signs of congestion of intraocular soft tissue. Angiography is the main basis for diagnosis AVM, showing an engorged rapidly filling proximal arterial system, malformation, and distal venous drainage (Fig. 8.10). Histologically, the affected vessels show irregularities in the thickness of the muscularis layer and a partial elastica in some vessels.

Differential Diagnosis

Orbital lesions that have similar characteristics as orbital AVM are carotid-cavernous fistulas, dural cavernous fistulas, and cerebral AVM.

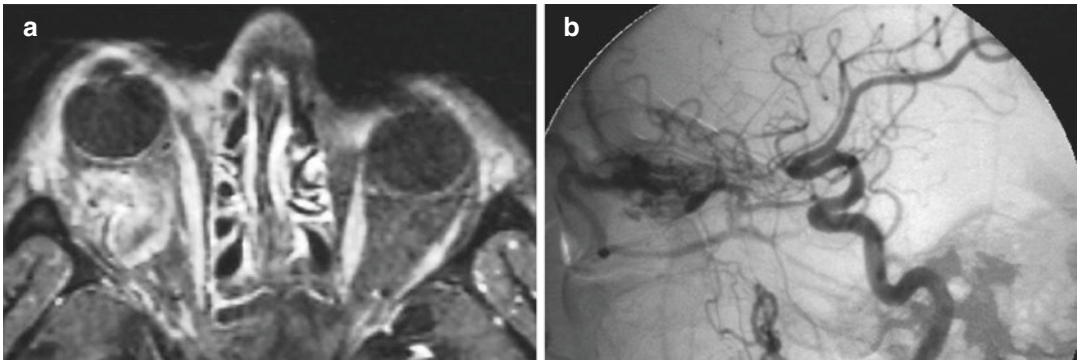

Fig. 8.10 MRI of orbital AVM shows enhancing lesion with flow voids (**a**). Angiography of orbital AVM demonstrates communication to the internal and external carotid arteries (**b**)

Treatment

Management of AVM follows a multidisciplinary approach, involving the orbit specialist, interventional radiologist, and other relevant specialists [39, 42, 43]. Asymptomatic lesions may be observed. Treatment is indicated when there is visual compromise, lesion-related patient discomfort, and/or deformity.

The main mode of treatment is surgery usually requiring preoperative embolization.

Surgical excision of any arterial-flow lesion risks intraoperative bleeding. Preoperative endovascular embolization of the lesion significantly reduces the risks incurred during surgical debulking. Surgery should be planned within 24 h after embolization. Incomplete excision may result in rapid recurrence through recruitment of collateral vessels.

Prognosis

The risk of recurrence is high when incomplete resection and only partial embolization is done. These lesions have a tendency to recruit new feeder vessels when their supply is partially reduced. Outcomes after a multidisciplinary approach can be surprisingly good.

Orbital Cavernous Venous Malformations

Orbital cavernous venous malformation (CVM) is the most common benign vascular tumor in adults [44]. It used to be called cavernous hemangioma. However, further understanding of the composition and behavior of this lesion makes the use of "hemangioma" in its name obsolete [45]. The term, "hemangioma," is reserved for neoplastic lesions that undergo active proliferation and mitosis with increased endothelial cell turnover. CVM exhibits normal endothelial turnover and is formed merely as a result of structural abnormalities of the venous system. Lesions previously described as "intraosseous hemangiomas" are also now pathologically known as venous malformations due to their histopathologic presentation and lack of GLUT-1 expression [46].

Clinical Features

CVMs present an etiologic conundrum because while they show low proliferative tendencies, they are not generally seen in children. They contradict theories of both neoplasm and malformation! Nevertheless, tissue studies and clinical behavior favor the classification into malformations. It is more common in women between the 2nd and 6th decades of life, presenting as slow painless, progressive proptosis [47]. Often they are detected incidentally when imaging studies are performed for unrelated headache or trauma (Fig. 8.11). Vision may be diminished due to compressive optic neuropathy or an induced hyperopic shift. Some patients complain of diplopia or pain.

Previously quiescent lesions may grow significantly during pregnancy as a result of hormonal shifts. When large enough, it may induce

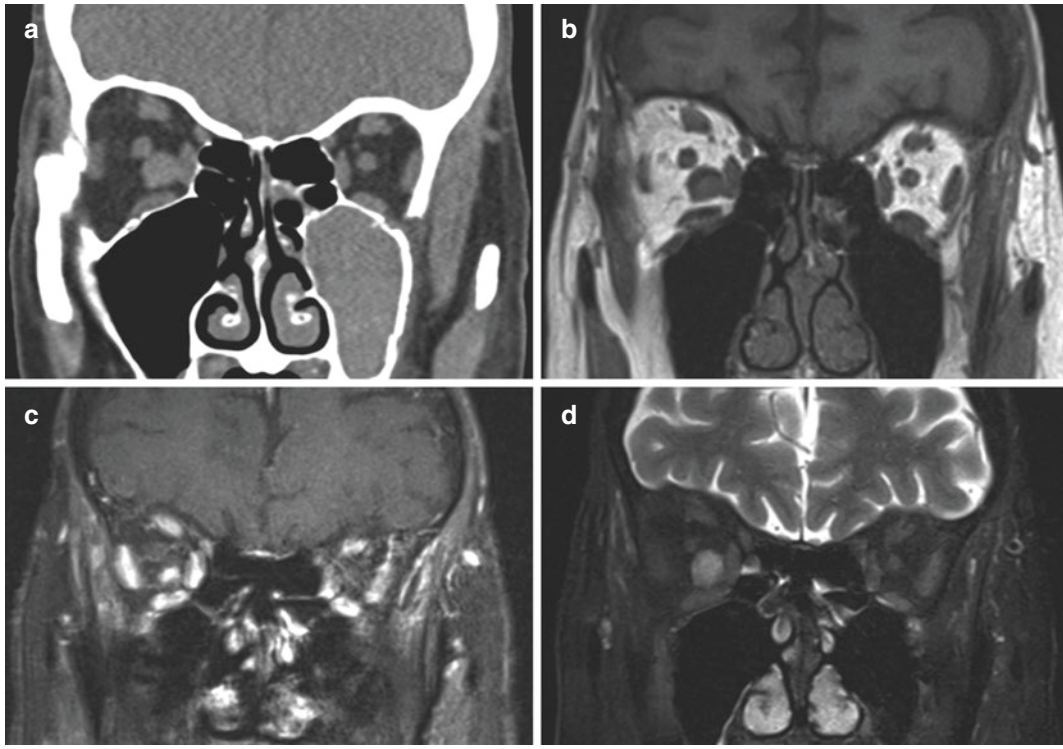

Fig. 8.11 Cavernous hemangioma. A 69-year-old woman underwent CT of the head following a bicycle accident. Incidental intraconal orbital mass was identified (**a**) in addition to opacified left maxillary sinus. Patient had no orbital signs on examination with visual acuity of 20/20. MRI revealed an intraconal circumscribed mass inferonasal to the optic nerve without signs of compression (**b**, T1). The lesion enhanced following administration of contrast (**c**, T1 fat suppressed and **d**, T2 fast suppressed)

hyperopia or optic nerve compression leading to decreased vision. Other clinical findings may include axial proptosis, elevated intraocular pressure, extraocular muscle (EOM) motility defects + diplopia, relative afferent pupillary defect, and other signs of optic nerve compression.

Diagnostics

Ancillary tests than can support a clinical diagnosis of CVM are ultrasonography and CT or MRI imaging. B-scan can show a well-delineated round retrobulbar mass with iso- to hyper-echogenicity. CT scan typically reveals a well-circumscribed, moderately enhancing intraconal lesion that is hyperdense to EOM. Coronal views are helpful in assessing the position of the tumor in relation to the optic nerve. MRI may show a mass that is isointense to muscle on T1-weighted study and hyperintense on T2-weighted study, exhibiting contrast enhancement that is patchy in the early phase and then later becomes homogenous [48]. Phleboliths are also characteristically seen in radiographic images of venous malformations.

Histologically, CVM contains abnormally formed and dilated deep and superficial veins with thin walls that lack smooth muscle. The pseudocapsule is formed by progressively condensed collagen as the lesion slowly enlarges.

Differential Diagnosis

CVM may clinically resemble other well-circumscribed solid orbital tumors such as schwannoma, neurofibroma, solitary fibrous tumor, hemangiopericytoma, and melanoma.

Treatment

The decision to treat CVM depends on the presence or absence of symptoms. Small, asymptomatic lesions may be found incidentally in patients who undergo radiographic imaging for other indications. These lesions may be observed. Large lesions that cause visual impairment and diplopia are surgically removed. Careful dissection is done especially in large intraconal lesions to prevent damage to the optic nerve, EOMs, and surrounding adnexa. However, attempts to resect a tumor at or near orbital apex can be associated with visual morbidity. Therefore, use of stereotactic radiation therapy has been explored. Gamma Knife radiation (GKR) used in multiple treatment sessions is reported to show promising results (Fig. 8.12) [49, 50]. In a study of five patients, use of multisession GKR with a marginal dose of 5 Gy and 50% isodose in four sessions seems to be an effective management strategy for circumscribed tumors at orbital apex tumors [50]. Outcome in larger series of patients is expected to be published soon [51]. Alternatively, orbital apex CVM respond well to sclerotherapy, orbital apex decompression, or, when medially or inferiorly located, endonasal resection [52].

Prognosis

Complete resection of CVM results in cure for symptomatic lesions [53, 54].

Orbital Hemangiopericytoma

Hemangiopericytomas are characterized by a spectrum of pericyte proliferation. Histopathology often shows a mixed pattern of ovoid cells and sinusoidal space formations creating the classic "staghorn" vascular pattern (Fig. 8.13) [55]. Varying levels of cellular atypia underlie the less benign nature of this lesion, which may malignantly transform or metastasize. In 2002, controversy in its classification arose when the WHO considered solitary fibrous tumor, giant cell angiofibromas, and hemangiopericytoma as part of a spectrum of spindle cell neoplasms, rather than unique diagnostic entities. The 2013 WHO Classification of Tumors of Soft Tissue and Bone, Fourth Edition no longer recognizes hemangiopericytoma as a distinct pathologic diagnosis [56].

Clinical Features

Hemangiopericytoma typically presents in middle-aged adults as slowly progressing unilateral proptosis, often with pain and vision loss [57, 58]. Other signs and symptoms depend on tumor location (Fig. 8.13). Frequent intracranial extension and invasion into sinus cavities may produce additional associated symptoms.

Hemangiopericytomas are characterized by a spectrum of pericyte proliferation. Histopathology often shows a mixed pattern of ovoid cells and sinusoidal space formations creating the classic "staghorn" vascular pattern. Varying levels of cellular atypia underlie the less benign nature of this lesion, which may malignantly transform or metastasize [55, 59].

Diagnostic Evaluation

Ultrasound reveals an encapsulated and well-defined solid mass with low internal reflectivity. Orbital hemangiopericytoma has been reported to undergo cystic changes within necrotic zones and may resemble the echographic appearance of lymphangiomas. On MRI, T1-weighted images reveal a well-defined hypointense mass to fat. T2-weighted studies show less lesion definition. CT imaging often detects bony changes around these contrast-enhancing lesions. Angiography typically reveals early tumor blush with rapid washout of contrast. Diagnosis of this lesion requires histologic confirmation.

Differential Diagnosis

The differential diagnosis for hemangiopericytoma includes meningiomas, lymphangioma, orbital venous malformation, and schwannoma.

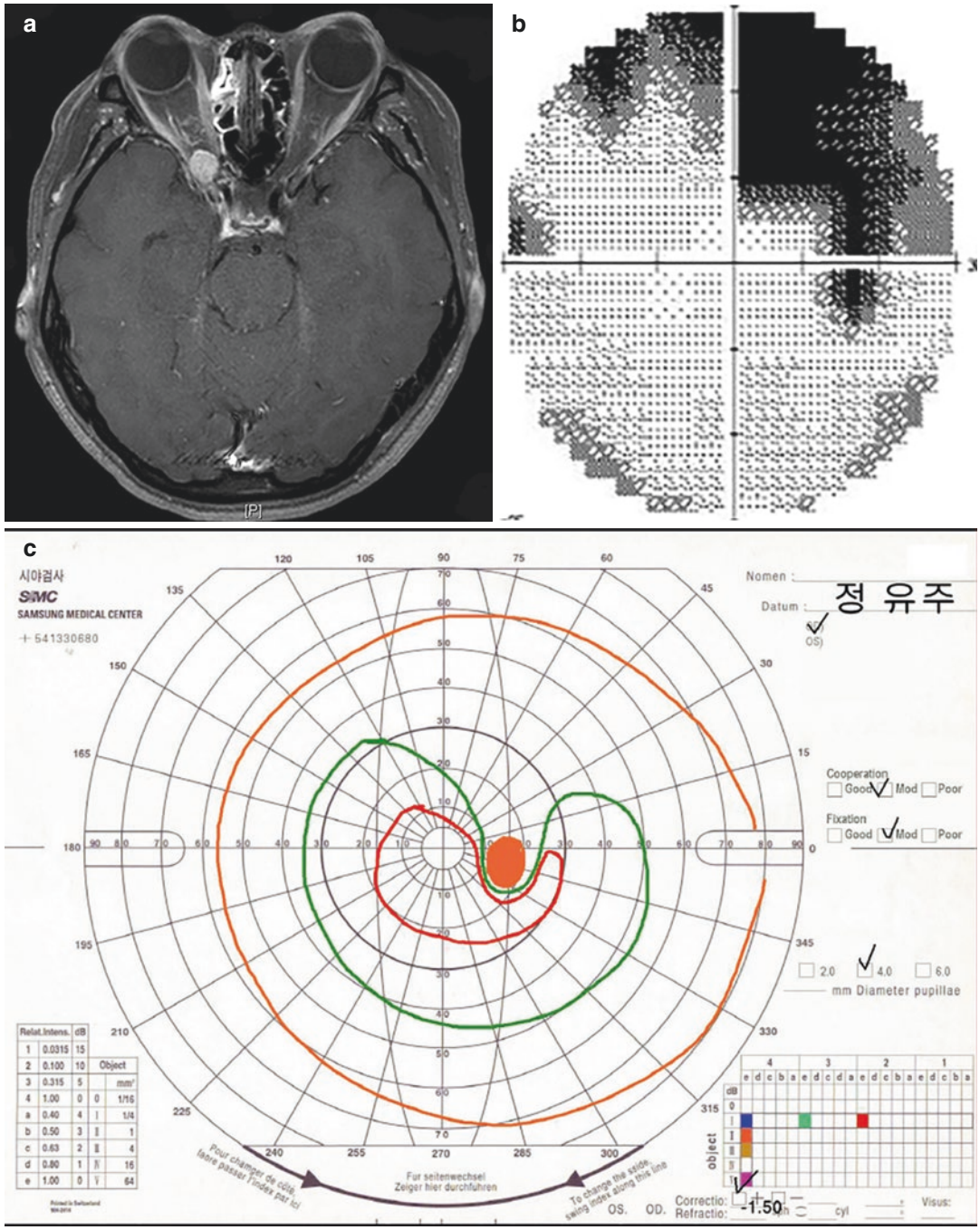

Fig. 8.12 A 34-year-old woman presented with headache and eye pain. Enhancing circumscribed mass was observed at orbital apex (**a**, MR Gd-enhanced). Visual field deficit was observed on visual field testing (**b**, Humphey; **c** Goldmann). Following fractionated Gamma Knife radiosurgery, the mass has become smaller (**d**), and visual fields have become normalized (**e**, Humphey; **f**, Goldmann). (Courtesy of Yoon-Duck Kim, MD)

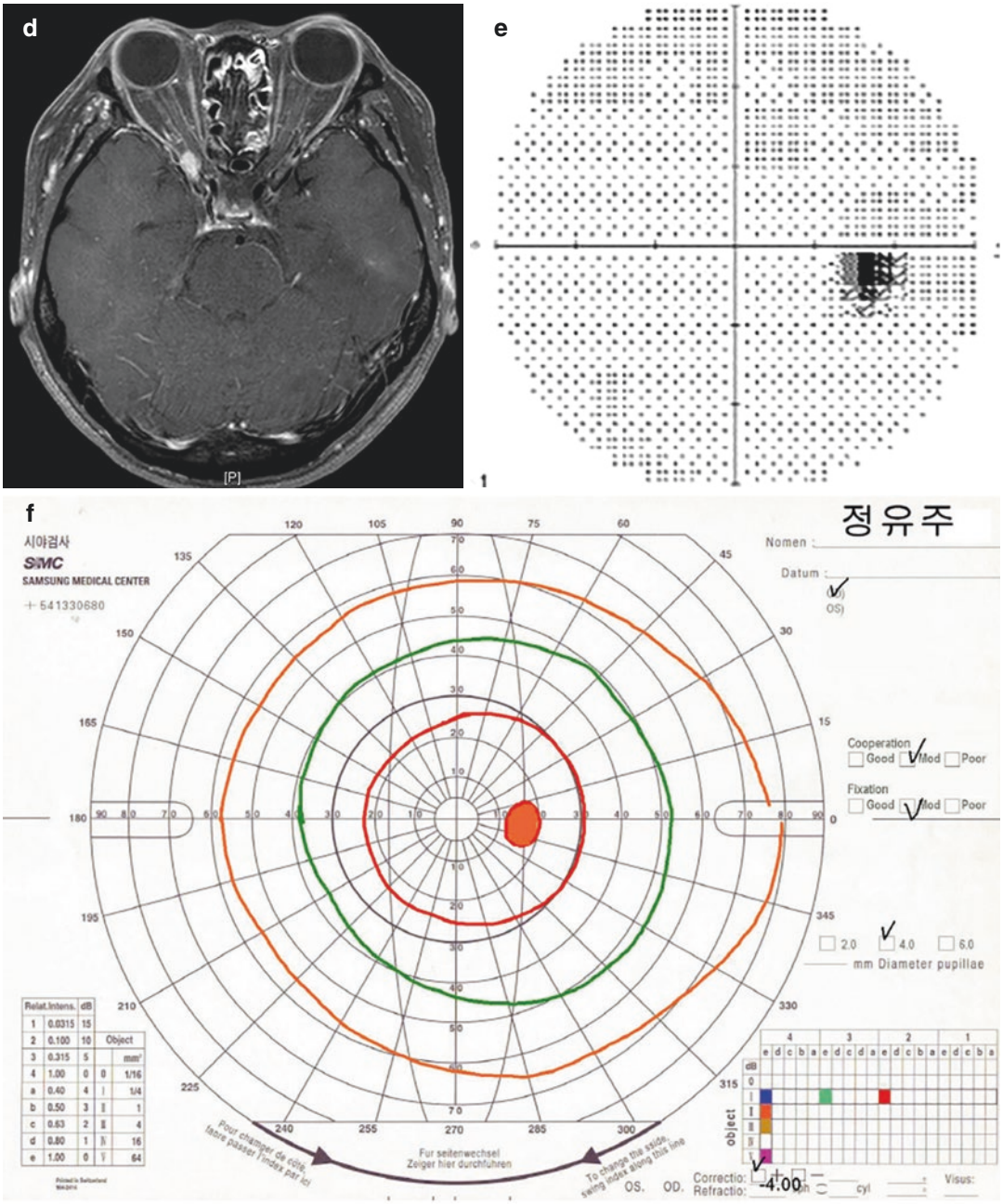

Fig. 8.12 (continued)

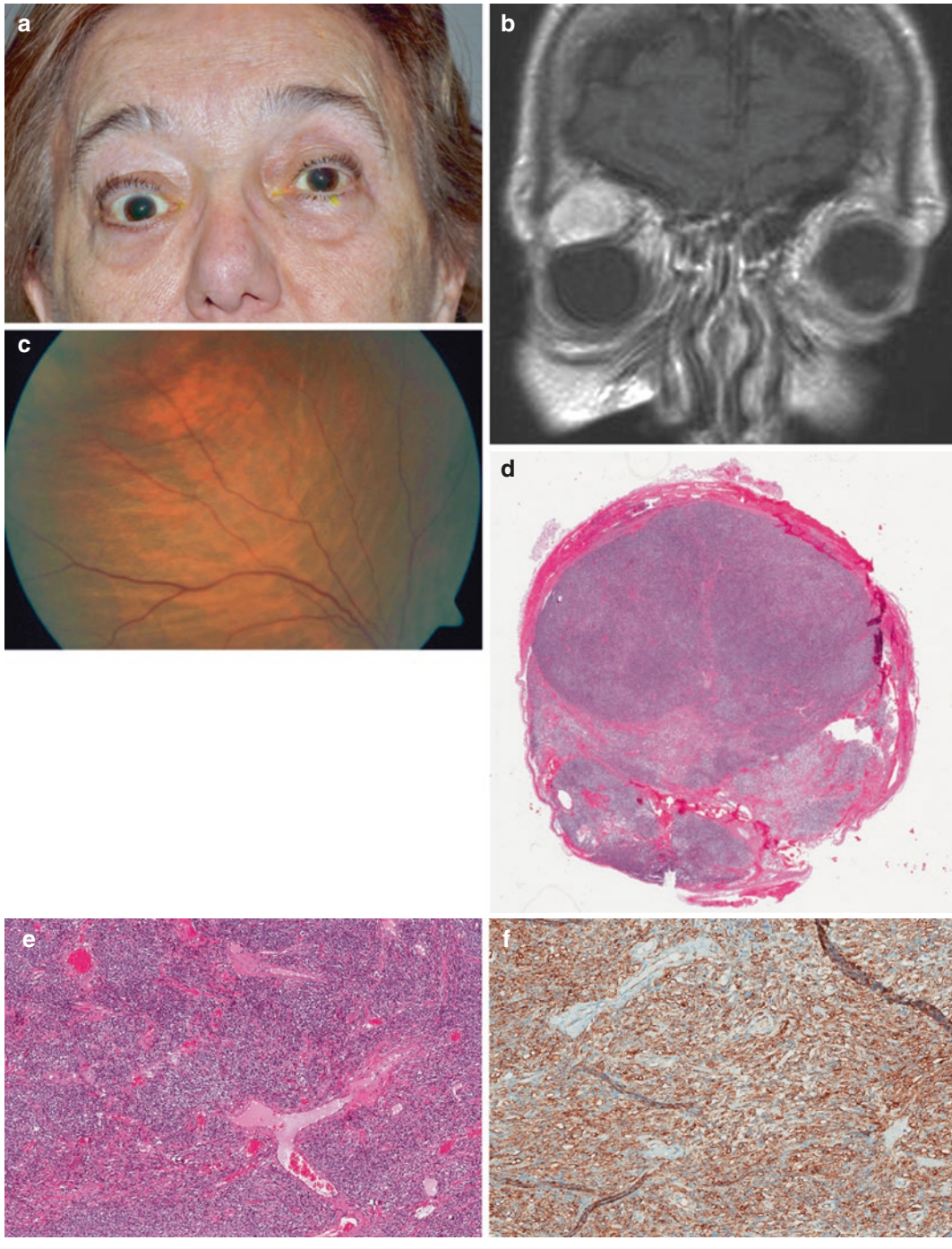

Fig. 8.13 Hemangiopericytoma. Clinical appearance of proptosis and hypoglobus (**a**). Coronal (**b**) MRI showing a circumscribed enhancing mass. Funduscopic examination revealed choroidal folds (**c**). Low-power photomicrograph demonstrating a well-circumscribed cellular lesion (**d**). Medium-power photomicrograph revealing relatively uniform spindle cells without a recognizable growth pattern. Small areas of densely pink "ropey" collagen are seen, as is a branched "staghorn" blood vessel (**e**). CD34 stain is diffusely and strongly positive in the spindle cells (**f**). (**d**–**f** Courtesy of Thomas Plesec, MD, Cleveland, Ohio, USA)

Treatment

Although the majority of these lesions are benign, the high rate of malignant transformation and recurrent disease mandates aggressive en bloc excision with wide margins. Adjunctive radiation therapy may be of benefit although conclusive studies are difficult due to the rarity of this tumor [55, 57].

Prognosis

The spectrum of aggressiveness of a particular lesion is difficult to predict as even more histologically benign lesions may result in clinically invasive disease or malignant transformation. The elusive nature of this entity warrants aggressive surgery and often adjuvant therapy.

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