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REVIEW

Classification and treatment of orbital venous malformations: an updated review

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Abstract **Orbital venous malformation (OVM) is a congenital vascular disease. As a common type of vascular malformation in the orbit, OVM may result in vision deterioration and cosmetic defect. Classification of orbital vascular malformations, especially OVMs, is carried out on the basis of different categories, such as angiogenesis, hemodynamics, and locations. Management of OVM is complicated and challenging. Treatment approaches include sclerotherapy, laser therapy, embolization, surgical resection, and radiotherapy. A satisfactory outcome can be achieved only by selecting the appropriate treatment according to lesion characteristics and following the sequential multi-method treatment strategy. This article summarizes the current classification and treatment advances in OVM.**

Keywords orbit; venous malformation; treatment; sclerotherapy; laser; embolization

Introduction

Orbital venous malformation (OVM) ranks as the most common type of VM in the orbit. OVM is a congenital vascular disease due to aberrational angiogenesis during embryonic development. Abnormal, tangled, or irregular dilated vascular channels form weakened segments of the orbital venous system, in which the hemodynamics are altered. OVM usually occurs in young and middle-aged individuals with no significant difference between sexes. The common complaints of patients include cosmetic defect, intraorbital pain, exophthalmos, ptosis, and visual deterioration. Most OVMs can be managed conservatively by observation. Indications for treatment include high orbital pressure with functional defect (usually caused by acute profound hemorrhage), severe pain, and cosmetic disfigurement. The latest classification consensus has been established by the International Society for the Study of Vascular Anomalies (ISSVA) [1], which provides the basis for the treatment of vascular lesions, including those of the orbit. Several simplified classifications have been used clinically in conjunction with international classification for treatment planning. The methods used to treat OVMs include sclerotherapy, embolization, laser therapy, interventional therapy, and radiotherapy. A sequential multimodality treatment strategy, which uses two or three forms of treatment in a stepwise manner, has been proposed through the increased understanding of the pathophysiology and hemodynamics of OVMs and development of new techniques. This review focuses on the updated classification and treatment of OVMs.

Classification

Classification is the treatment foundation of different types of orbital vascular diseases. The approach is carried out in different categories according to International Society for the Study of Vascular Anomalies (ISSVA) classification and on the basis of Mulliken and Glowaki's classification based on pathologic characteristics [2]. In terms of angiogenesis, malformations may consist of arterial, venous, or lymphatic vessels. These elements may exist individually or in combination. In hemodynamic categories, congenital vascular malformations are divided into high flow [arteriovenous malformation (AVM) and congenital arteriovenous fistulas (AVF)] and low flow [venous malformation (VM), lymphatic malformation (LM), and combined lymphatic–venous malformation (LVM)]. LVMs are further divided into venous-dominant LVM

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(VD-LVM) and lymphatic-dominant LVM (LD-LVM). This classification is designed for nonorbital vascular anomalies but can also be applied to OVMs [3]. OVMs belong to the low-flow category and can be purely venous or mixed. The existence of pure LM in the orbit remains controversial because evidence suggests that lymphatic channels are absent in the post-septal or deep portion of the orbit [4]. In terms of location, these malformations can be superficial (anterior, visible lesions limited to the conjunctiva or eyelid), deep (retrobulbar or peribulbar lesions without surface manifestation), combined (superficial and deep), and complex (not only involving the orbit but also the periorbital and intracranial tissues; possibly multifocal and systemic).

Furthermore, based on hemodynamic features, OVMs can be divided into distensible and nondistensible lesions. Distensible lesions consist of VD-LVMs and some pure VMs, whereas nondistensible lesions comprise LD-LVMs and VMs. Due to their communication with venous circulation, distensible lesions show positive response to Valsalva maneuver, bending forward, or straining. Deep lesions show proptosis or globe displacement with increased pain. In certain cases, large distensible lesions may appear enophthalmic due to the enlargement of the orbital bone and atrophy of intra-orbital fat [5]. By contrast, nondistensible OVMs exhibit minimal communication with the venous system and show negative response to Valsalva maneuver; however, these OVMs are characterized by episodes of spontaneous hemorrhage or thrombosis, which leads to acute exacerbation of the syndrome. Sudden hemorrhage or thrombosis leads to severe proptosis with a marked increase in orbital pressure and to orbital compartment syndrome. Certain distensible OVMs are clinically unapparent but can be demonstrated on image examination. Therefore, distensible OVMs seem to be more prevalent than reported [3].

For clinical practice, we proposed a simplified classification, defined as stratified three-grade classification, of orbital vascular lesions. First, depending on histology, orbital vascular lesions are divided into proliferative vascular lesions (tumor) and congenital vascular malformations. Second, in terms of vascular components, congenital vascular malformations are further classified as AVM, VM, LM, LVM, and cavernous hemangioma (CH). Third, according to hemodynamic characteristics, pure VMs and LVMs are subclassified as distensible and nondistensible subtypes. CH is a special type of vascular malformation because of its arterial component (similar to AVM in the angiogenesis category) and a low blood flow (similar to VM in the hemodynamic category). The stratified three-grade classification is outlined in Fig. 1.

Imaging

Complementary imaging examination is indispensable for the differential diagnosis and treatment of OVMs, and computed tomography (CT) and magnetic resonance imaging (MRI) are the most common techniques. CT is ideal for confirming the presence of a deep located mass and for discovering a phlebolith or an osseous abnormality, whereas MRI is excellent for revealing additional key information to distinguish between lesions with similar appearance. Under CT, OVMs show a clearly defined hyperdense mass in contrast with brain tissues, exhibiting homogenous enhancement when injected with contrast product. The mass can be round, irregular, or lobulated. The lesion border can be indistinct if hemorrhage is present. Intraconal well-defined OVM may be mimicking a cavernous hemangioma. Thus, the existence of phlebolith and absence of capsule around the lesion are key points to distinguish OVM. A dual-phase CT angiography (CTA), which introduces Valsalva maneuver during the venous phase, can effectively identify distensible lesions.

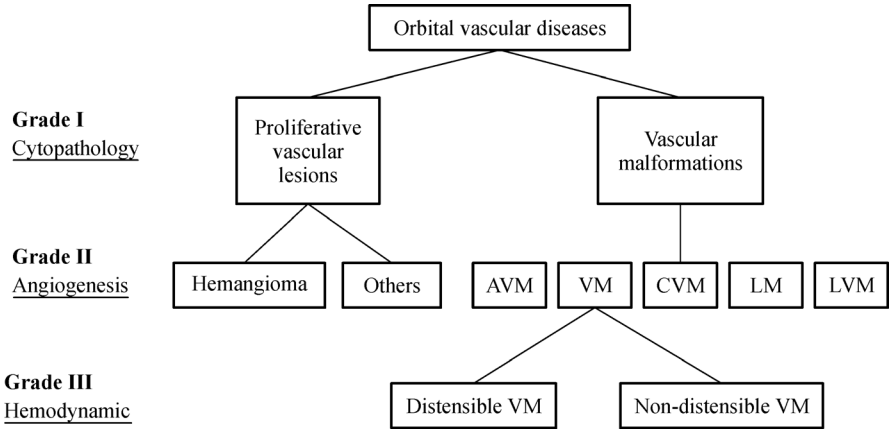

Fig. 1 Stratified three-grade classification of orbital vascular lesions.

Distensible OVM demonstrates an initial small nidus of filling in pre-Valsalva arterial phase, with progressive filling and expansion in the subsequent Valsalva venous phase. However, nondistensible OVM shows no dilatation with Valsalva maneuver. MRI appearance of OVMs shows low signal in T1 weighted image (T1WI) and medium to high signal in T2 weighted image (T2WI), with evident enhancement post contrast. The sign of flow void in MR is usually absent because OVM is a low blood flow malformation [6]. The combined lymphatic–venous malformation (LVM) shows an unencapsulated infiltrative nature on imaging.

Treatment

Management of OVMs remains challenging due to their deep or intraconal location, infiltrative nature, and tendency to bleed during operation. No definite treatment standard is available to date, but angiogenesis, phenotype, and hemodynamics are commonly considered, and OVMs are treated in a multidisciplinary manner. Small and asymptomatic lesions can be managed conservatively by periodical surveillance. Malformations with acute intralesional hemorrhage that leads to acute proptosis and compressive optical neuropathy usually require emergency decompression. Malformations that present intolerable pain, functional defect, repeated hemorrhage, and chronic cosmetic disfigurement are managed selectively [7,8]. Treatment approaches are varied, including sclerotherapy, laser therapy, embolization, surgical resection, and radiotherapy. With progress in hemodynamic studies and improvement in new therapeutic techniques, OVM treatment strategy gradually developed a sequential multimethod treatment modality. Figs. 2 and 3 show the treatment strategy of distensible and non-distensible OVM. Although various therapeutic methods are available for OVM, conventional treatment is still an option because all interventions present certain risks.

Sclerotherapy

Sclerotherapy is one of the first-line treatments for OVMs, which block abnormal vessels and cause these vessels to atrophy. This treatment is particular appropriate for nondistensible lesions, which experience low blood flow that results in increased reaction time for sclerosants. Different sclerosants include pingyangmycin, dehydrated ethanol, sodium morrhuate, ethanolamine, sodium tetradecyl sulfate, picibanil (OK-432; a sclerosant made of group A *Streptococcus pyogenes* of human origin), and polidocanol. Numerous ophthalmologists prefer pingyangmycin as their first-choice sclerosant agent [9–14]. Absolute ethanol and sodium tetradecyl sulfate are traditional sclerosants, but their intraorbital application remains controversial [3].

For retrobulbar and combined lesions, we should focus on the complications when using sclerosants. Intraocular pressure should be monitored during and after sclerotherapy because sclerosants may cause inflammatory changes that increase intraocular pressure and result in orbital compartment syndrome [15]. Intraocular pressure > 20 mmHg with afferent pupillary defects or > 40 mmHg alone is an indication for orbital decompression surgery. Lateral canthotomy and inferior cantholysis

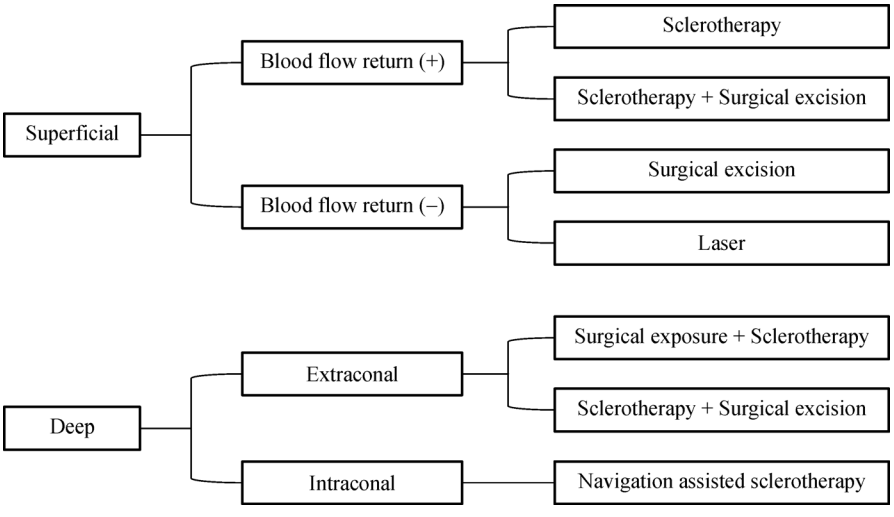

Fig. 2 Treatment strategy of non-distensible OVM. For superficial lesions, if puncture shows positive blood flow return, then sclerotherapy followed or not followed by surgical resection is the first-line treatment; if puncture shows negative blood flow return, then surgical excision or laser is an appropriate treatment. For deep extraconal lesions, sclerotherapy combined with surgical procedures is primarily considered. For deep intraconal lesions, navigation-assisted sclerotherapy is preferred.

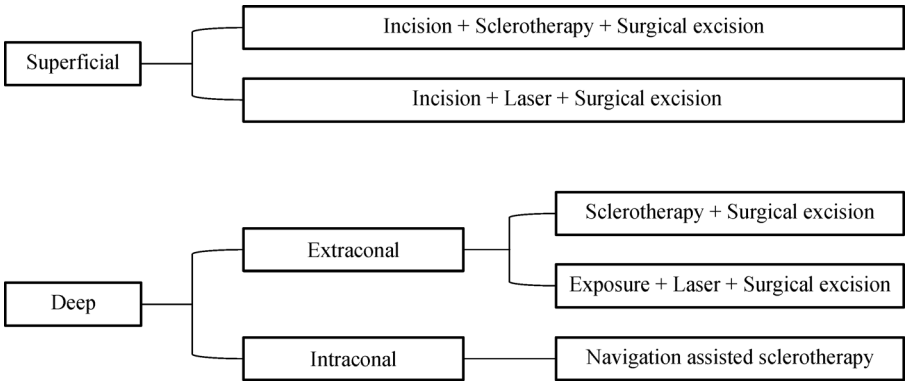

Fig. 3 Treatment strategy of distensible OVM. For superficial lesions, physicians can select surgical procedures combined with either sclerotherapy or laser. For deep extraconal lesions, sclerotherapy combined with surgical excision or surgical exposure followed by intralesional and excision is the first line treatment. For deep intraconal lesions, which are challenging in orbital surgery, navigation-assisted sclerotherapy is preferred.

are the mainstays of the management of this ophthalmic surgical emergency [16].

Pingyangmycin

Pingyangmycin, which is also referred to as bleomycin A5 [17], is isolated from *Streptomyces pingyangensis*. This sclerosant was first developed as an antitumor agent that inhibits DNA synthesis [18]. At present, it is one of the most commonly used sclerosants for treating vascular diseases. Pingyangmycin underwent its first clinical trial in China for the treatment of VMs in 1991 [19]; since then, it has been used successfully to treat a variety of lesions, including those of the head and neck [20]. Intralesional injection of pingyangmycin destroys endothelial cells by inducing apoptosis via extrinsic pathway, resulting in sclerostenosis of the lumen [21–23]. Pingyangmycin arrests endothelial cells in G2 and S phases by causing DNA strand breakage and inhibition of DNA repair by DNA ligase [24,25]. Histological studies shows that vascular intima is disrupted and vascular walls become collapsed and thickened after injection of pingyangmycin, thereby resulting in the narrowing or occlusion of vessels [26,27]. Pingyangmycin produces a dose-dependent and time-dependent devascularization effect.

Pingyangmycin is used widely for superficial and deep nondistensible OVMs. In most cases, the use of pingyangmycin as a single agent shows acceptable outcomes, and lesion volume decreases with several adverse events in treating OVMs [13]. In a recent large case series reported by Jia *et al*. [9], 33 patients with low-flow OVMs underwent intralesional injection of pingyangmycin. This study achieved a mean lesion volume decrease of 84%, as well as significant reductions in blue coloration and thickness with no recurrence. Compared with ethanol, pingyangmycin is a gentle and safe sclerosant that causes minor discomfort upon injection. In extreme cases, pingyangmycin is feasible for intraconal injection. The limitation of this sclerosant is its need for repeated and multipoint injections, which is inconvenient. The median number of pingyangmycin treatments ranges from 2 to 3.5 [9,20].

Mild complications of pingyangmycin include pain, conjunctival swelling, localized subcutaneous atrophy, skin ulceration or necrosis, and mild fever not exceeding 38.5 °C and resolved within 24 h [28]. Severe complications, such as intraorbital pressure, loss of vision, pulmonary fibrosis, and bone marrow suppression, are rare [14,29]. Risks of these complications seem to be minimal if the dose per treatment is maintained at less than 1 mg/kg per session and not more frequently than after an interval of 1 week, with the total dose limited to 5 mg/kg [30].

Pingyangmycin-combined lipiodol emulsion

Pingyangmycin-combined lipiodol emulsion causes the sclerosant to stay longer in lesions with extensive communication with the surrounding venous system and high blood flow, such as distensible OVMs. Lipiodol (iodized oil) is a drug-carrying agent with high viscosity, which may accumulate in malformed veins and lead to slow release of pingyangmycin. Lipiodol is radiopaque and generally administered by percutaneous puncture under fluoroscopic guidance. This condition allows the administration of adequate pingyangmycin lipiodol emulsion (PLE) into the lesion and decreases the risk of PLE leakage. This approach is widely used to treat numerous types of VMs [31], and is a safe and effective treatment [32]. Adverse effects of PLE include swelling and mild intraorbital or periorbital pain. A drawback of this therapy includes radiation, which may harm the patients and the operators.

Sodium morrhuate

Sodium morrhuate presents a long history as a sclerosant in the treatment of vascular diseases, including VMs, hemangiomas, and esophageal varices. The sclerosant, destroys endothelial and red blood cells, triggers platelets, and aggregates granulocytes at the vascular walls without affecting plasma coagulation [33]. Similar to pingyangmycinn, sodium morrhuate is administered by intralesional injection. Sodium morrhuate and pingyangmycin can cause vessel occlusion, but their mechanisms are different. Pingyangmycin acts in abnormal vessels by causing vessel wall thickening and luminal narrowing, and then total vessel occlusion within ~3 weeks. Sodium morrhuate acts similarly to phlebosclerosis, which leads to hematopexis and thrombogenesis, and causes vessel occlusion within approximately 2 weeks [34]. Although sodium morrhuate has long been used to treat VMs effectively and within a short time, the adverse effects are frequent and severe, and the recurrence rate is higher than that with pingyangmycin [35]. Recurrence after sodium morrhuate treatment occurs mainly because of thrombosis dissolution and absorption. Therefore, the application of sodium morrhuate has decreased.

Ethanol

Ethanol is a highly effective sclerosing agent, which causes degeneration of hemoglobin via dehydration, destroys vascular endothelial cells, and causes tissue necrosis and thrombogenesis at a concentration of 95%. Percutaneous ethanol therapy of VMs is successful and safe in various anatomical sites [36], and exhibits a lower risk of recurrence than other sclerosants. However, its use for treatment of OVMs is limited because the orbit is a confined space; thus, swelling of tissues after ethanol therapy induced by intense inflammation, and the possibility of ethanol leaking from the lesions are risky in optic nerve injury [37]. Therefore, ethanol can only be used periorbitally for superficial OVMs, but definitely not within the orbit. Periorbital injection of ethanol by experienced surgeons may obtain acceptable outcomes [38].

Ethanolamine oleate

Ethanolamine oleate is a fatty acid emulsion with an established role in treating VMs of the head and neck. Its mechanism is to induce thrombosis and damage the endothelium. The overall response rate ranged from 88% to 100% [17,39–41], but to our best knowledge, ethanolamine oleate has not been reported in managing OVMs. Complications of this sclerosant include skin ulceration and necrosis.

Embolization

Gentle sclerosants, such as pingyangmycin, require a long onset time to become effective. For distensible OVMs, application of sclerosants may be poorly effective due to rapid washout. Thus, numerous physicians prefer embolization for distensible OVMs. Embolization aims to reduce or block the vascularity of lesions. The approach includes embolizing glues, such as cyanoacrylate glue, fibrin glue, polyvinyl alcohol copolymer, microfibrillar collagen, gelatin sponge, and detachable coils (such as platinum Guglielmi detachable coils) and thermoelectric desiccation.

Cyanoacrylate glue

Cyanoacrylate glue, an acrylic polymer, is usually administered as a mixture of *n*-butyl-2-cyanoacrylate, lipiodal, and a radiopaque medium (tantalum powder) to treat distensible OVMs. Histopathology shows that cyanoacrylate glue causes local acute vasculitis, chronic inflammation, and granulomatous lesions in ~1 month after injection [42]. Therefore, resection is often performed immediately after glue injection to prevent further inflammatory reactions. After injection, the glue polymerizes and forms a glue cast that results in solid and well demarcated lesion from the surrounding unaffected tissues, thereby allowing easy identification of the lesion and assists with excision. Concomitant administration of contrast agents can prolong the polymerization time of the glue (~5 min). Thus, the lesions can be completely filled before solidification, and the surgeons can surveil any changes in the lesions under venography. Numerous studies have reported that therapy with cyanoacrylate glue followed by surgical excision of the embolized lesion with minimal blood loss [43,44] exhibits good outcomes with no or mild complications and infrequent recurrence. Sometimes, the entire lesion is difficult to remove because it is adjacent to vital orbital structures. Such situations may lead to postoperative thrombosis or hemorrhage [37]. Moreover, remnant lesions are the main cause of recurrence [45].

Detachable coils

Detachable coils are used to treat distensible OVMs. Their clinical application was first reported by Gugilemi to treat aneurysm in 1991 [46,47]. The coil is a soft device with satisfactory compliance. The structure is fabricated from platinum and connected with a stainless steel guide wire for direct feed into the vessel. The coils are used in a percutaneous or endovascular approach after catheterization. When direct current is applied, the coil attracts the blood components with a negative charge and leads to

electrocoagulation and thrombosis. The connecting part of the coil and the stainless steel wire are fused due to electrolysis, leaving the coil within the malformed vessel. However, the electrothrombotic effect alone cannot cure VM because of its possible association with acute and significant swelling, which may affect the normal outflow of ocular structures, and the possibility of recanalization [3]. Case reports of the application of detachable coils in treating OVMs have been mainly discussed in the past decades [48–50]. Coils are more useful for segmental or saccular channels compared with tangled plexus vascular lesions. At present, coils have been largely replaced by less-aggressive embolization techniques, such as glue embolization. A new type of coil, namely, the microfilament nexus coil has recently appeared. However, such as coil has yet to be used in treating OVMs [51].

Laser therapy

Laser therapy is another method with a long history to treat VMs. The mechanism of laser therapy is called selective photothermolysis, which indicates that suitable brief pulses of selectively absorbed optical radiation can cause selective damage to different tissues [52]. Oxyhemoglobin, the main chromophore in blood vessels, exhibits a specific absorption spectrum [53]. At these specific wavelengths, the laser can selectively cause coagulation necrosis and vessel closure without damaging the surrounding tissues. Light absorption by hemoglobin increases the temperature of vascular lesions and results in vessel coagulation [54]; thus, the patients experience size reduction of the lesions. The types of laser with different wavelengths are as follows: Nd:YAG, flashlamp-pumped pulsed dye laser (PDL), CO_2, argon, potassium titanium phosphate, and diode.

Adverse effects include edema, orbital congestion, necrosis, scarring, hyperpigmentation, or hypopigmentation [55]. These effects, most of which are transient, are mainly caused by heat damage. Wavelength, pulse duration, spot size, and total energy dose are the most important factors when deciding on the therapeutic and adverse effects, and intra- and postoperative cooling aids in reducing these adverse effects.

Nd:YAG laser

Nd:YAG laser produces continuous-wave infrared light at 1064 nm, penetrating to a depth of 4–7 mm into the dermis [56,57] and oftentimes 8 mm for soft tissues [58]. The two different methods for application of Nd:YAG laser include transcutaneous for superficial lesions and intralesional for deep or combined lesions. The outcomes of Nd:YAG laser therapy may be unsatisfactory in certain high-flow lesions mainly due to the circulating blood that acts as a cooling circuit, which probably prevents effective coagulation of the lesions [57]. Therefore, deep and superficial VM with low blood flow are indicated for Nd:YAG laser. Surgical exposure combined with laser therapy is frequently performed with acceptable outcomes [59,60]. This operative approach is usually preferred by the authors.

Flashlamp-pumped PDL

Flashlamp-pumped PDL exhibits a wavelength of 585 nm and pulse duration of 0.45 ms. This approach was first used to treat cutaneous vascular diseases, such as wine stains because of its short penetration distance of ~1 mm. Thus, its application in OVM treatment is limited to those of superficial lesions. However, Bagazgoitia reported a case of eyelid VM treated with combined PDL–Nd:YAG laser, which can penetrate deeper than PDL alone and uses lower fluencies than Nd:YAG alone [61]. Therefore, it can reach deep lesions and reduce the risk of adverse effects.

Surgical resection

Surgical resection used to be a common and primary method to treat OVMs. For small and superficial lesions, the approach usually exhibits good outcomes. However, for distensible lesions with abundant communications with the drainage veins, especially for those that are large and located deep in the orbit, surgical removal may not be sufficient or may even be risky. These lesions do not exhibit clear anatomical relationships with the surrounding tissues. Simple resection can potentially cause bleeding and extraorbital muscle and optic nerve damage. If serious bleeding increases the intraorbital pressure, then surgical exposure with subtotal removal and drainage are often required to save vision [8]. A second operation may be required to remove coagulated blood. At present, surgery remains a major option to manage superficial nondistensible OVMs. Moreover, removal of remnant lesions after other therapeutic treatment has become an accessory or secondary method for treating other types of OVMs.

VM associated with osseous hypertrophy is rare, accounting for $< 1\%$ of all osseous lesions [62]. Some researchers believe that this type of VM results from increased blood flow to the adjacent tissues, whereas others think that these particular VMs may be related to pressure stimulation of the growing periosteum [63]. Sclerotherapy and embolization can only manage abnormal soft tissues, but these procedures cannot treat expanded bone or restore the orbital skeleton. Thus, surgical removal of excess bone or osseous reconstruction is the key to achieve satisfactory correction of ocular dystopia caused by VM.

Surgical options include lateral orbitotomy, anterior orbitotomy, medial orbitotomy, combined lateral and medial orbitotomy, coronal incision, and transfrontal

orbitotomy. The option of surgical approach to achieve improved visualization and minimal manipulation of orbital tissues mainly depends on lesion location.

Navigation-assisted surgery

Navigation-assisted surgery is a combination of computer technology and medical imaging with the aim of improving the accuracy and safety of surgery by preoperative planning, intraoperative navigation, and postoperative evaluation [64]. A case of navigation-assisted sclerotherapy of OVM by using a 20-G cannula placed on a needle holder and integrated with the navigation system was reported [65]. Follow-up evaluation showed improvement of proptosis with no nerve damage or visual deterioration. Our group also treated several patients by using navigation-assisted sclerotherapy or laser therapy. All patients showed good outcomes without severe neural or vascular damage. The navigation-assisted surgical system can locate osseous structures and soft tissues, such as VMs.

Compliance with ethics guidelines

Tianyuan Li, Renbing Jia, and Xianqun Fan declared no conflict of interests. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

References

1. ISSVA classifiaction for vascular anomalies. www.issva.org. 2014
2. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg 1982; 69(3): 412–420
3. Rootman J, Heran MKS, Graeb DA. Vascular malformations of the orbit: classification and the role of imaging in diagnosis and treatment strategies. Ophthal Plast Reconstr Surg 2014; 30(2): 91–104
4. Rootman J. Venous malformation. In: Rootman J, Marrota TR, Graeb DA. Diseases of the Orbit: A Multidisciplinary Approach. 2nd ed. Philadelphia: Lippincott Williams and wilkins, 2003: 517–522
5. Chung CF, Lai JS. Enophthalmos caused by an orbital venous malformation. Hong Kong Med J 2009; 15(4): 299–300
6. Yen MT. Imaging vascular lesions of the orbit and face. In: Poll J, Yen MT, Mukerji SK. Vascular Lesions of Orbit and Face. Springer, 2016: 11–17
7. Yen MT. Low-flow vascular malformations of the orbit: evaluation and management. In: Pimpalwar S, Chinnadurai P, Marx DP. Vascular Lesions of Orbit and Face. Springer, 2016: 89–99
8. Arat YO, Mawad ME, Boniuk M. Orbital venous malformations—current multidisciplinary treatment approach. Arch Ophthalmol 2004; 122(8): 1151–1158
9. Jia R, Xu S, Huang X, Song X, Pan H, Zhang L, He F, Lin M, Ge S, Fan X. Pingyangmycin as first-line treatment for low-flow orbital or periorbital venous malformations: evaluation of 33 consecutive patients. JAMA Ophthalmol 2014; 132(8): 942–948
10. Dai W, Li L, Lin G. Clinical observation of pingyangmycin in treatment of 18 orbital neoplasm. J North China Coal Med Univ (Hua Bei Mei Tan Yi Xue Yuan Bao) 2011; 13: 665–666 (in Chinese)
11. Li J, Lin M, Jia R. Histopathological and immunohistochemical studies of orbital venous malformations after pingyangmycin and Nd:YAG laser local treatment. Ophthalmol CHN (Yan Ke) 2011; 20: 274–278 (in Chinese)
12. Lin M, Li J, Jia R. The combined effects of pingyangmycin and Nd: YAG laser in treatment of nondistensible orbital venous malformations. Chin J Pract Ophthalmol (Zhongguo Shi Yong Yan Ke Za Zhi) 2011; 29: 962–965 (in Chinese)
13. Yue H, Qian J, Elner VM, Guo J, Yuan YF, Zhang R, Ge Q. Treatment of orbital vascular malformations with intralesional injection of pingyangmycin. Br J Ophthalmol 2013; 97(6): 739–745
14. Shen CY, Wu MC, Tyan YS, Ou CH, Chen TY, Wong HF. Preliminary experience of percutaneous intralesional bleomycin injection for the treatment of orbital lymphatic-venous malformation refractory to surgery. Clin Radiol 2012; 67(2): 182–184
15. Chiramel GK, Keshava SN, Moses V, Mammen S, David S, Sen S. Percutaneous sclerotherapy of congenital slow-flow vascular malformations of the orbit. Cardiovasc Intervent Radiol 2015; 38 (2): 270–279
16. Lima V, Burt B, Leibovitch I, Prabhakaran V, Goldberg RA, Selva D. Orbital compartment syndrome: the ophthalmic surgical emergency. Surv Ophthalmol 2009; 54(4): 441–449
17. Horbach SE, Lokhorst MM, Saeed P, de Goüyon Matignon de Pontouraude CM, Rothavá A, van der Host CM. Sclerotherapy for low-flow vascular malformations of the head and neck: a systematic review of sclerosing agents. J Plast Reconstr Aesthet Surg 2016; 69 (3): 295–304
18. Blum RH, Carter SK, Arge K. A clinical review of bleomycin—a new antineoplastic agent. Cancer 1973; 31(4): 903–914
19. Zhang Q. Local injection of bleomycin A 5 in chilrdren with hemangiomas: analysis of 210 cases. Chin J Surg (Zhonghua Wai Ke Za Zhi) 1991; 29: 290–291 (in Chinese)
20. Zheng JW, Yang XJ, Wang YA, He Z, Ye WM, Zhang ZY. Intralesional injection of pingyangmycin for vascular malformations in oral and maxillofacial regions: an evaluation of 297 consecutive patients. Oral Oncol 2009; 45(10): 872–876
21. Mungunsukh O, Griffin AJ, Lee YH, Day RM. Bleomycin induces the extrinsic apoptotic pathway in pulmonary endothelial cells. Am J Physiol Lung Cell Mol Physiol 2010; 298(5): L696–L703
22. Wang C, Liu J, Pan W, Wang X, Gao Q, Hou S. Pingyangmycin loaded bovine serum albumin microspheres for chemoembolization therapy—*in vitro* and *in vivo* studies. Int J Pharm 2008; 351(1–2): 219–226
23. Lin M, Fan X. Advances in treatment of orbital venous malformations. J Clin Oph (Lin Chuang Yan Ke Za Zhi) 2011; 19: 368–371 (in Chinese)
24. Burger RM, Peisach J, Horwitz SB. Activated bleomycin. A transient complex of drug, iron, and oxygen that degrades DNA. J Biol Chem 1981; 25;256(22): 11636–11644
25. Tai KW, Chang YC, Chou LS, Chou MY. Cytotoxic effect of

pingyangmycin on cultured KB cells. Oral Oncol 1998; 34(3): 219–223
26. Zeng Q, Li Y, Chen Y, Xu X, Lu E, Wang J. The experimental study of intra-arterial infusion of pingyangmycinlipiodol emulsion in rabbits. J Clin Radiol (Lin Chuang Fang She Xue Za Zhi) 2000; 19 (6): 376–379 (in Chinese)
27. Kong W, Li Y, Zeng Q, Chen Y, He XF. Effect of pingyangmycin on the growth and cell cycle of human vascular endothelial cells. J First Mil Med Univ (Di Yi Jun Yi Da Xue Xue Bao) 2003; 2003(23): 830–832 (in Chinese)
28. Zhao JH, Zhang WF, Zhao YF. Sclerotherapy of oral and facial venous malformations with use of pingyangmycin and/or sodium morrhuate. Int J Oral Maxillofac Surg 2004; 33(5): 463–466
29. Chiramel GK, Keshava SN, Moses V, Mammen S, David S, Sen S. Percutaneous sclerotherapy of congenital slow-flow vascular malformations of the orbit. Cardiovasc Intervent Radiol 2015; 38 (2): 270–279
30. Sung MW, Chang SO, Choi JH, Kim JY. Bleomycin sclerotherapy in patients with congenital lymphatic malformation in the head and neck. Am J Otolaryngol 1995; 16(4): 236–241
31. Zeng Q, Li Y, Zhu Q. Pingyangmycin lipiodol emulsion intracavitary injection in the treatment of superficial venous malformations. J Intervent Radiol (Jie Ru Fang She Xue Za Zhi) 2001; 10: 274–276 (in Chinese)
32. Chen Y, Li Y, Zhu Q, Zeng Q, Zhao J, He X, Mei Q. Fluoroscopic intralesional injection with pingyangmycin lipiodol emulsion for the treatment of orbital venous malformations. AJR Am J Roentgenol 2008; 190(4): 966–971
33. Stroncek DF, Hutton SW, Silvis SE, Vercellotti GM, Jacob HS, Hammerschmidt DE. Sodium morrhuate stimulates granulocytes and damages erythrocytes and endothelial cells: probable mechanism of an adverse reaction during sclerotherapy. J Lab Clin Med 1985; 106(5): 498–504
34. Zhao J, Zhao Y, Chen X. A comparative study on the blood vessel sclerosing effect of pingyungmycin and Natrii morrhuates. West Chin J Stomatol (Hua Xi Kou Qiang Yi Xue Za Zhi) 1997; 15(2): 97–98 (in Chinese)
35. He W, Gu AL, Shang JL. Comparison of the clinical therapeutic effects between local injection of pingyangmycin and sodium morrhuate on oral and maxillofacial venous malformation. Chin J Stomatol (Zhong Hua Kou Qiang Yi Xue Za Zhi) 2007; 42(5): 308–309 (in Chinese)
36. Orlando JL, Caldas JG, Campos HG, Nishinari K, Krutman M, Wolosker N. Ethanol sclerotherapy of head and neck venous malformations. Einstein (Sao Paulo) 2014; 12(2): 181–186
37. Lacey B, Rootman J, Marotta TR. Distensible venous malformations of the orbit: clinical and hemodynamic features and a new technique of management. Ophthalmology 1999; 106(6): 1197–1209
38. Chen H, Lin X, Jin Y. Treatment of localized upper eyelid venous malformations by double-needle absolute ethanol sclerotherapy. Chin J Aesth Plast Surg (Zhongguo Mei Rong Zheng Xing Wai Ke Za Zhi) 2011; 22: 535–537 (in Chinese)
39. Alexander MD, McTggart RA, Choudhri OA, Marcellus ML, Do HM. Percutaneous sclerotherapy with ethanolamine oleate for venous malformations of the head and neck. J Neurointerv Surg 2014; 6(9): 695–698
40. Costa JR, Torriani MA, Hosni ES, D'Avila OP, de Figueiredo PJ. Sclerotherapy for vascular malformations in the oral and maxillofacial region: treatment and follow-up of 66 lesions. J Oral Maxillofac Surg 2011; 69(6): e88–e92
41. Hoque S, Das BK. Treatment of venous malformations with ethanolamine oleate: a descirptive study of 83 cases. Pediatr Surg Int 2011; 27(5): 527–531
42. Brothers MF, Kaufmann JC, Fox AJ, Deveikis JP. n-Butyl 2-cyanoacrylate–substitute for IBCA in interventional neuroradiology: histopathologic and polymerization time studies. Am J Neuroradiol 1989; 10(4): 777–786
43. Garcia DD, Heran MK, Amadi AJ, Rootman J. Low outflow distensible venous malformations of the anterior orbit: presentation, hemodynamic factors and management. Ophthal Plast Reconstr Surg 2011; 27(1): 38–43
44. Couch SM, Garrity JA, Cameron JD, Rootman J. Embolization of orbital varices with N-butyl cyanoacrylate as an aid in surgical excision: results of 4 cases with histopathologic examination. Am J Ophthalmol 2009; 148(4): 614–618.e1
45. Mokhtarzadeh A, Garrity JA, Cloft HJ. Recurrent orbital varices after surgical excision with and without prior embolization with n-butyl cyanoacrylate. Am J Ophthalmol 2014; 157(2): 447–450.e1
46. Guglielmi G, Vinuela F, Sepetka I, Macellari V. Electrothrombosis of saccular aneurysms via endovascular approach. Part 1: Electrochemical basis, technique, and experimental results. J Neurosurg 1991; 75(1): 1–7
47. Guglielmi G, Vinuela F, Sepetka I, Macellari V. Electrothrombosis of saccular aneurysms via endovascular approach. Part 2: Preliminary clinical experience. J Neurosurg 1991; 75(1): 8–14
48. Diolaiuti S, Iizuka T, Schroth G, Remonda L, Laedrach K, El-Koussy M, Frueh BE, Goldblum D. Orbital venous malformation: percutaneous treatment using an electrolytically detachable fibred coil. Acta Ophthalmologica 2009; 87(2): 229–232
49. Takechi A, Uozumi T, Kiya K, Yano T, Sumida M, Yoshikawa S, Pant B. Embolisation of orbital varix. Neuroradiology 1994; 36(6): 487–489
50. Weill A, Cognard C, Castaings L, Robert G, Moret J. Embolization of an orbital varix after surgical exposure. AJNR Am J Neuroradiol 1998; 19(5): 921–923
51. Van Rooij WJ, DeGast AN, Sluzewski M. Results of 101 aneurysms treated with polyglycolic/polylactic acid microfilament nexus coils compared with historical controls treated with standard coils. Am J Neuroradiol 2008; 29(5): 991–996
52. Anderson RR, Parrish JA. Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation. Science 1983; 220(4596): 524–527
53. Liu G, Liu X, Li W, Shi H, Ye K, Yin M, Huang Y, Lu X, Huang X, Lu M, Jiang M. Ultrasound-guided intralesional diode laser treatment of congenital extratruncular venous malformations: mid-term results. Eur J Vasc Endovasc Surg 2014; 47(5): 558–564
54. Proebstle TM, Lehr HA, Kargl A, Espinola-Klein C, Rother W, Bethge S, Knop J. Endovenous treatment of the greater saphenous vein with a 940-nm diode laser: thrombotic occlusion after endoluminal thermal damage by laser-generated steam bubbles. J Vasc Surg 2002; 35(4): 729–736
55. Levine VJ, Geronemus RG. Adverse effects associated with the 577- and 585-nanometer pulsed dye laser in the treatment of

cutaneous vascular lesions: a study of 500 patients. J Am Acad Dermatol 1995; 32(4): 613–617

56. Buainian H, Verhaeghe E, Dierckxsens L, Naeyaert JM. Early treatment of hemangiomas with lasers. A review. Dermatology 2003; 206(4): 370–373
57. Glaessl A, Schreyer AG, Wimmershoff MB, Landthaler M, Feuerbach S, Hohenleutner U. Laser surgical planning with magnetic resonance imaging-based 3-dimensional reconstructions for intralesional Nd:YAG laser therapy of a venous malformation of the neck. Arch Dermatol 2001; 137(10): 1331–1335
58. Vlachakis I, Gardikis S, Michailoudi E, Charissis G. Treatment of hemangiomas in children using a Nd:YAG laser in conjunction with ice cooling of the epidermis: techniques and results. BMC Pediatr 2003; 3:2
59. Lin M, Li J, Jia RB, Fu Y, Fan XQ. Surgical flap and Nd:YAG lasers coagulation in the treatment of nondistensible orbital venous malformations. Ophthalmol CHN (Yan Ke) 2009; 8: 395–398 (in Chinese)
60. Fan XQ, Xiao CW, Zhou GY, Jia RB, Fu Y, Zhou HF. Treatment of orbital venous malformation using surgical procedure combined with Nd:YAG laser. Chin J Ophthalmol (Zhonghua Yan Ke Za Zhi) 2008; 44(8): 681–686 (in Chinese)
61. Bagazgoitia L, Boixeda P, Lopez-Caballero C, Beà S, Santiago JL, Jaén P. Venous malformation of the eyelid treated with pulsed-dye-1064-nm neodymium yttrium aluminum garnet sequential laser: an effective and safe treatment. Ophthal Plast Reconstr Surg 2008; 24 (6): 488–490
62. Burke RM, Morin RJ, Perlyn CA, Laure B, Wolfe SA. Special considerations in vascular anomalies: operative management of craniofacial osseous lesions. Clin Plast Surg 2011; 38(1): 133–142
63. Tan ST, Bialostocki A, Brasch H, Fitzjohn T. Venous malformation of the orbit. J Oral Maxillofac Surg 2004; 62(10): 1308–1311
64. Li Y, Fan X. Application of computer-aided surgical navigation system in orbital surgery. Chin J Ophthalmol (Zhonghua Yan Ke Za Zhi) 2011; 47(8): 759–761 (in Chinese)
65. Ernemann U, Westendorff C, Troitzsch D, Hoffmann J. Navigation-assisted sclerotherapy of orbital venolymphatic malformation: a new guidance technique for percutaneous treatment of low-flow vascular malformations. Am J Neuroradiol 2004; 25(10): 1792–1795