Diagnosis and treatment of venous malformations in China: consensus document

Vascular Malformations Panel of International Union of Angiology (IUA), China

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Abstract

Venous malformations (VMs) are the most common vascular developmental anomalies. There are many controversies over VMs in Chinese clinical medical practice. Experts on the panel from vascular-anomaly centers in China reviewed the etiology, pathophysiology, epidemiology, classification, clinical presentations, diagnosis, and treatment of VMs. The aim of this consensus document is to provide recommendations for, and assist clinicians and patients in, the diagnosis and treatment of VMs.

Keywords: venous malformations; consensus; diagnosis; treatment

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Conflict of interest: The authors declare that they have no conflict of interest.

Funding: This research was supported by grant from the National Natural Science Foundation of China, China (No. 81871458).

Ethical approval: Not applicable.

Informed consent: Not applicable.

Journal of Interventional Medicine **2018**, Vol. 1, No. 4, pp. 191–196

INTRODUCTION

Venous malformations (VMs) are one of the most common congenital vascular malformations, presenting at birth and growing proportionately with the individual. They are mainly composed of dilated and tortuous veins (1,2) surrounded by sparse, erratically distributed vascular smooth-muscle cells and a disorganized extracellular matrix (3). As slow-flow and non-proliferative vascular anomalies, VMs are most often located on skin and mucosa. They can be superficial, affecting the dermis and subcutaneous tissues, or they can be deep, involving muscle or bone. They can occur in any tissue or organ throughout the entire body, including the viscera. Their various clinical presentations range from asymptomatic birthmarks to life-threatening conditions. The term “angioma” has long been used to describe a vascular anomaly without giving a precise diagnosis, which has led to improper management. Therefore, VMs remain a most difficult and confusing diagnostic and therapeutic clinical entity, due to the wide range of clinical presentations, degree of severity, location, unpredictable clinical course, and erratic response to treatment, and high risk of recurrence due to the VM’s embryonic characteristics.

VMs Patients tend to present to different specialists, including oral and maxillofacial surgeons, head and neck surgeons, plastic surgeons, pediatricians, dermatologists, vascular surgeons, and interventional radiologists. Many clinicians therefore are not aware of this kind of disease, leading to patients not being diagnosed correctly or treated in time. In view of this, experts in China focused on VMs have written this

consensus in order to provide recommendations for VM diagnosis and treatment.

ETIOLOGY, PATHOPHYSIOLOGY, AND EPIDEMIOLOGY

The prevalence of VMs is about 1% and the incidence rate is 1–2 per 10,000. About 40% of lesions are found in the head and neck, 40% in the extremities, and 20% in the torso (1,2,4). Neither sex is predominately affected (5,6). The etiology is unknown. However, recent studies have shown that somatic mutations in *TIE2*, *PIK3CA*, and *MAP3K3* and other genes contribute to the occurrence of VMs (2,3,7-10). The pathological feature of VMs is that the sac of veins is dilated, tortuous, and covered by a thin layer of endothelial cells with flat lining. The vascular smooth-muscle cells on the wall of the vessel are abnormal and arranged irregularly (11,12). VMs progress rapidly under circumstances such as changes in hormone levels (e.g., puberty or pregnancy), infection, trauma, and inappropriate treatment (2). VMs are not restricted by anatomical level; they are not confined to the skin and mucosa but also affect muscles, nerves, joints, organs, and even bones (1,2,4,11). More than 90% of VMs are isolated and sporadic lesions. Fewer than 10% are multiple, extensive, caused by familial inheritance or complicated by certain syndromes (2,11). Clinical manifestations of VMs vary greatly, from a lack of symptoms to local-tissue swelling, deformity, pain, bleeding, and even potentially life-threatening compression of adjacent structures or organs that affects important functions, such as speech, respiration, and swallowing (1,2,4).

SIGNS AND SYMPTOMS

VMs are light-to-dark-blue lesions that can be emptied by compression or in the upright position. There is no thrill or bruit, and the affected area is not warmer than non-lesion areas on palpation. The main symptoms of VM patients are swelling, deformity, pain, and bleeding. Head and neck VMs can be seen in the skin, oral mucosa, salivary glands, face and neck muscles, jaws, respiratory tract, and other parts of the body (1,2,13). VMs in the extremities present as muscle weakness, joint dysfunction, limb atrophy, or hypertrophy of the lesion side (11). Gastrointestinal VMs often manifest as chronic anemia (11). The main clinical findings of examinations for VMs are a pale-blue mass on the body surface, normal skin temperature, compressible lesions, and palpation without pulsation. A Valsalva maneuver may enlarge the VMs, or the VMs may simply enlarge when in a dependent position. Hemodynamic changes may cause thrombosis and thrombolysis in the lesion, and thrombosis may cause local intravascular coagulation and pain (5). Persistent thrombosis may lead to local calcification and phlebitis, which can be palpated when localized in superficial sites (11).

Superficial lesions are usually found at time of onset. The most common sites are the oral and maxillofacial regions, head and neck area, limbs, and trunk. Most VMs are single, although a few cases are multiple. Clinical manifestations vary significantly by location and extent of the lesions, from no clinical symptoms to lesions that involve important organs; the latter may lead to severe dysfunction or bleeding, endangering the patient's life. The main clinical symptoms are swelling, pain, bleeding, and venous stones formed after coagulation in some lesions. Lesions located in important functional areas can affect speech, swallowing, and breathing; in severe cases, bleeding and asphyxia can lead to death.

DIAGNOSIS

It is not difficult to diagnose superficial VM lesions by clinical presentation. However, diagnosing deep lesions is challenging. Congenital hemangiomas, infantile hemangiomas, lymphatic malformations, arteriovenous malformations, and many tumors should be considered as differential diagnoses for VMs (14). Ultrasound is usually the first modality used in the imaging workup of a suspected VM because it is widely available, noninvasive, low cost, and without ionizing radiation. This last point is particularly important, given the relatively young age of vascular-anomaly populations (15). Eighty percent of VMs are characterized by compressible hypoechoic lesions and 20% by isoechoic or hyperechoic lesions (4,5). Phleboliths appearing as hyperechoic masses with posterior shadowing may be present and are pathognomonic for VMs (1,2,6). Monophasic low-velocity flow is found in most lesions via color Doppler ultrasound image, although clinicians may also find biphasic low-velocity flow or no detectable flow (6).

Magnetic resonance imaging (MRI) can be used as the mainstay modality for diagnosis of VMs because it

has demonstrated 98.9% sensitivity and 90% specificity for such diagnosis in large studies (4). VMs appear hyperintense on T2-weighted images and hypointense or isointense on T1-weighted images, relative to muscle (2). If the lesions are mixed with fat, subacute hemorrhage, or calcification, bright signal areas can be found. Fat-saturated, T2-weighted images can accurately show VMs with high signals, the clear extent of lesions, and their relationship with surrounding soft tissues, making these images the best choice for VM diagnosis. Phleboliths show a low signal on MRI, while plain film shows that phleboliths are pathognomonic for VMs.

Computed tomography (CT) is not recommended as a first-line image workup for VMs unless skeletal involvement is suspected or the clinician wishes to determine the extent of intraosseous VM involvement (2,4). Venography is not a routine modality for VM diagnosis; it is used only when diagnosis is difficult or when diagnosis and treatment are performed simultaneously. Examination of D-dimer, fibrinogen, platelet count, bleeding, and coagulation time is recommended for patients with extensive or multiple VM lesions to assess coagulation during the period of peri-treatment.

CLASSIFICATION

Many clinicians have proposed classification systems for VMs (14-17). Puig et al. (17) proposed that classifying VMs by venography can significantly guide the understanding and treatment, especially sclerotherapy, of lesions. Puig et al. divides VMs into 4 types, as shown in Table 1. Sclerotherapy of types I and II can obtain better clinical outcomes, and the complications are mild. However, for types III and IV, the sclerosing agent quickly enters systemic circulation due to the high-flow velocity of the outflow veins, leading to sclerotherapy results that are often unsatisfactory. It is therefore necessary to reduce the reflux venous-flow velocity by sclerotherapy, after which satisfactory results may be obtained. In addition, the velocities of outflow veins in VM types III and IV are fast, meaning that both types pose potential risks of complications. The choice of treatment method should be carefully selected according to VM type in order to achieve satisfactory outcomes.

TREATMENT

Table 1 Classification of VMs (15-17).

Type	Anatomy and hemodynamics of VMs
I	Isolated malformation without peripheral drainage
II	Malformation that drains into normal veins
III	Malformation that drains into dysplastic veins
IV	Venous ectasia

There are many modalities of VM treatment nowadays. Since signs and symptoms of VMs may be difficult to quantify objectively, various criteria providing absolute and relative indications for therapy have evolved further to conduct management. The goal of interventional procedures should be the alleviation of signs and symptoms, especially the patient's main complaint. Individualized approaches should be selected and applied, so as to minimize the risks of interventional procedures and maximize benefit to patients.

Conservative management

For VM lesions that are asymptomatic or that pose no potential threat throughout the patient's lifetime, it is recommended that the clinician wait and see. Pressure garments, such as stockings, alone or in conjunction with other, more-active interventions, can successfully reduce symptoms and help potentiate concomitant therapies; therefore, they should be implemented early and continuously in the course of treatment (15). Elastic garments, when properly fitted, not only slow the progression of venous distention, deformity, ulceration, and pain, but they also have been shown to reduce chronic localized intravascular coagulopathy in extremities with VMs (15). During the observation period, once symptoms are aggravated or appearance and function are affected, necessary intervention measures should be taken.

Sclerotherapy

Sclerotherapy is a widely used mainstay treatment method for VMs. For patients who cannot be completely cured by sclerotherapy alone, it can be used as a major adjuvant therapy before surgery. In this modality, sclerosant is applied to induce thrombosis, inflammation, and fibrosis of the channels. At present, sclerosants used in clinical practice include absolute ethanol, polidocanol, bleomycin or pingyangmycin, sodium tetradecyl sulfate, and urea.

Of all of the sclerosing agents, absolute ethanol has the most effective therapeutic outcomes with the lowest recurrence rate, but also a relatively higher risk

of serious local and systemic side effects (11). If it is used improperly, serious complications may occur. Absolute ethanol may be the only sclerosant for treating VMs with extensive oropharyngeal involvement in the head and neck (18). Due to the potential complications, it is critical for clinicians using absolute ethanol to grasp the indications for and techniques of VM sclerotherapy. Other sclerosants are relatively mild in terms of sclerosing property. The use of foamed sclerosants, such as polidocanol, improves sclerosing efficiency while lowering dosage, thereby reducing possible systemic side effects.

The consensus on the details of sclerotherapy of VMs includes but is not limited to the following: General anesthesia is recommended because of the severe pain and potential risk when absolute ethanol is applied. Venous access is necessary because some sclerosing agents may cause allergic reactions. In addition, intravenous infusion of twice the maintenance dose should be administrated before, during, and after sclerotherapy. If the dosage of ethanol exceeds 0.5 mL/kg in a single session, arterial pressure and urine volume should be monitored during the procedure. To reduce the incidence of potential acute renal injury and systemic effects of sclerosing agents, balanced fluid and sodium bicarbonate should be administrated intravenously to alkalize urine and prevent hemoglobinuria causing acute renal failure.

Clinicians who are experienced or who are familiar with the anatomy of the lesion site do not need to perform venogram-guided sclerotherapy. For patients with dominant outflow veins, the use of digital pressure, tourniquet, or embolization of the reflux vein may be considered to avoid rapid entry of the sclerosing agent into the outflow vein, which could reduce sclerosing efficiency and thus increase the risk of systemic adverse reactions to the sclerosing agent. It is recommended that clinicians use the "double-needle" technique to avoid filling the lesion with excess sclerosing agent and thus maintain the stability of lesion content. Moreover, it is further confirmed that the needle tip is located in the lesion through the second needle return sclerosing agent during the injection and the risk of nontarget sclerosis can be reduced. In patients with lesions located at the base of the tongue or in the parapharynx, soft palate, or oropharynx, potential obstruction of the airway should be fully evaluated before treatment. Awake tracheal intubation guided by nasopharyngeal fibroscope, preventive tracheotomy if necessary, or tracheal intubation 24–48 hours after surgery is required to prevent post-operative asphyxia due to upper respiratory-tract obstruction caused by swelling (18). Moderate local pressure can be exerted after puncture needle extraction to avoid leakage of the sclerosing agent resulting in local skin pigmentation, especially in the face and neck. Analgesic and anti-edema drugs should be used after sclerotherapy, and limb elevation can alleviate swelling after treatment. When bleomycin or pingyangmycin is used as a sclerosing agent, total dosage should be controlled to avoid pulmonary fibrosis. For patients with extensive or multiple VM lesions or with localized intravascular coagulation before treatment, 100 U/kg low-molecular-weight heparin can be administrated 2 weeks before treatment to prevent the occurrence of coagulation disorders (2,4-6).

When the venous-reflux velocity of the lesion is fast, the effect of sclerotherapy alone is often poor. At the same time, sclerosant accompanied by rapid venous reflux into systemic circulation can easily lead to systemic complications, such as increased pulmonary-artery pressure or acute liver/kidney injury. Therefore, embolizing the reflux veins of VM lesion types III and IV with embolic agents, such as coils or absolute ethanol, can improve the effectiveness of sclerotherapy and reduce the incidence of complications.

Surgical treatment

For small, localized VM lesions with well-defined borders and no significant functional structures, surgical excision alone can achieve a cure (6,19). In addition, surgery is often used as a stage of comprehensive treatment, mainly to improve appearance, restore function, and reduce or eliminate pain. In larger and/or infiltrative lesions, pre-operative sclerotherapy is often recommended to decrease the volume of the VM and to induce local thrombosis, which will reduce blood loss during surgery and recurrence of the malformation. For intramuscular VMs with painful symptoms, it is difficult to achieve complete remission of symptoms with sclerotherapy alone; surgical treatment is necessary to control the lesion and alleviate symptoms. Surgery is indicated only if it will not affect function within certain limits. For lesions located in joints, only surgery can relieve or eliminate pain and improve function.

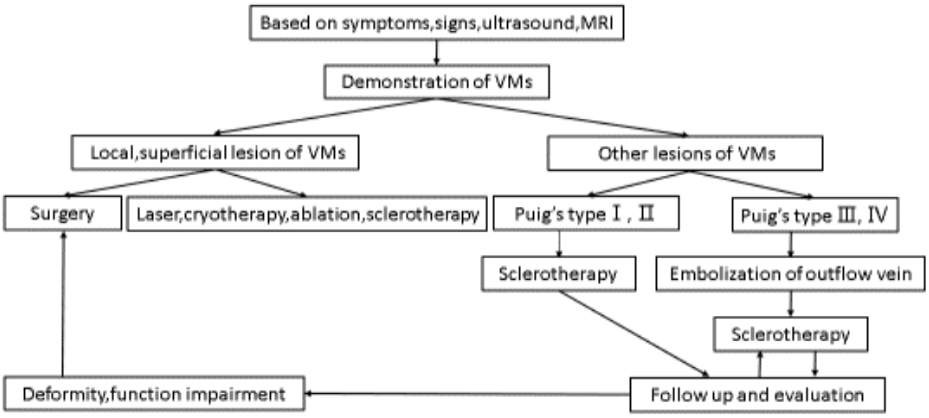

Figure 1. Flowchart of VM treatment.

Laser therapy

Laser therapy is one of the main modalities for skin and mucosal VMs, especially in areas with limited and superficial lesions, and it can achieve good results (6). This mode of therapy has advantages that are unmatched by others, especially for VMs located in the airway mucosa (2). Compared with other treatment methods, laser therapy has no adverse effects on adjacent structures or the whole body because of the limitation of the action site (2). Although clinically different types and parameters of lasers, including endoluminal lasers, are used to treat VMs, the general recommendation is that if smaller vessels like capillaries are involved, a shorter wavelength and pulse duration should be used; the larger the vessel diameter, the longer the wavelength and exposure time (5).

Other

Cryoablation and radiofrequency ablation are also options for treating VMs (4). When using these methods, clinicians should take particular care to protect adjacent tissue structures, especially important nerves, such as facial nerves, to avoid accidental injuries.

Although there are many effective methods for treating VMs, there are still a wide range of patients with complicated VMs whose symptoms cannot be controlled or relieved to a satisfactory degree by the above treatment methods. Recent studies have shown that phase II clinical trials of targeted rapamycin therapy for VMs have achieved satisfactory clinical results. Multiple multicenter, prospective phase III clinical trials are underway to further evaluate the safety and efficacy of rapamycin in the treatment of VMs (2,12,20), and rapamycin is expected to be the first possible target drug for future VM treatment (12,20,21).

The process of VM treatment is summarized in Figure 1.

COMPLICATIONS

Complications related to VM treatment can be local or systemic. Local complications include swelling, pain, pigmentation, ulcer, tissue necrosis, temporary or permanent nerve injury, thrombophlebitis, deep-vein thrombosis, muscle contracture, septal syndrome, deformity from post-treatment complications, and dysfunction (15). Systemic complications include hemolysis, kidney injury, pulmonary embolism, allergy, hypotension, arrhythmia, and cardiopulmonary accidents. The key to reducing the risk of complications is to comprehensively grasp the indications of VM treatment and the characteristics of different treatment methods and sclerosing agents, and especially to avoid injecting sclerosing agents into the arteries during sclerotherapy if possible. If necessary, such injection can be performed with the guidance of ultrasound or venography, which can minimize the occurrence of complications.

SUMMARY

In conclusion, given the diversity in presentation, symptomatology, location, and extent of VMs, an

individualized treatment plan should be devised using a multidisciplinary approach. Even though superficial and small VMs can be successfully treated by single-treatment modalities, curing deep, infiltrative VMs presents a medical challenge and requires a multidisciplinary approach with individualized treatment modalities. The goal of VM treatment is not to obliterate the lesion completely but to improve quality of life while restoring appearance and function.

ACKNOWLEDGEMENTS

The authors would like to thank the following professors for their contributions to this work: Jiawei Zheng, MD, Jing Zhang, MD, Gang Shen, MD, Zhongping Qin, MD, Yaowu Yang, MD, Changxian Dong, MD, Dekai Zhou, MD, Pingfan Guo, MD, Lei Guo, MD, Xukai Wang, MD, and Zhengyin Liao, MD.

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