

Marginal vein is *not* a varicose vein; it is a venous malformation

Byung-Boong Lee

Center for the Lymphedema and Vascular Malformations, George Washington University, Washington DC; Uniformed Services University of the Health Sciences, Bethesda, MD, USA

Abstract

Marginal vein (MV) is one form of venous malformation (VM); MV is *not* a varicose vein. MV is the outcome of defective development during the later stage of embryogenesis while the vein trunk is formed. It is an embryonic vein tissue remnant remaining on birth following the failure of normal involutonal process. MV is the most common VM involved to Klippel-Trenaunay syndrome (KTS); together with the lymphatic malformation, MV is one of two clinically most important congenital vascular malformation components among KTS. MV causes chronic venous insufficiency (CVI) due to a unique condition of *avalvulosis* (lack of venous valve development) it accompanies with. Besides, it accompanies a high risk of venous thromboembolism (VTE) due to its structural defect with a lack of smooth muscle cell to form the media properly as a *truncular* VM infrequently causing fatal pulmonary embolism. Therefore, the MV is indicated for the surgical excision whenever feasible not only for the prevention of VTE and CVI but also for abnormal long bone growth known as vascular bone syndrome as well as lymphatic complication precipitated by MV.

Introduction

Marginal vein (MV)¹⁻⁴ is often mistakenly considered as a varicose vein since most of MV locates very superficially beneath the skin with a minimum soft tissue coverage although it runs on the lateral aspect of the lower extremity, which is odd/unusual location for common varicose veins. MV is *not* a matured vein like varicose veins (of superficial vein system); vein; it is an embryonic vein remnant following the failure of normal involutonal process through the maturation period of vein trunk formation and remains after the birth. Although MV looks like ordinary varicose vein of saphenous/superficial vein especially when it is located in superficially, MV is a lot more clinically serious not only to cause severe

chronic venous insufficiency (CVI) but also constant source of intravascular coagulation resulting in venous thrombo-embolism (VTE) (Figure 1). MV is one of venous malformations (VMs);⁵⁻⁸ VM is a common form of congenital vascular malformations (CVMs)⁹⁻¹² and the MV is one form of *truncular* VMs as the outcome of defective development during the *later* stage of embryogenesis while the vascular/venous trunk is formed. The extent and severity of the MV are variable depending upon the degree of defective development along the last/truncular stage of embryogenesis while forming the vein trunk so that all the MVs present in different lengths as well as different locations; they are also named differently from *lateral embryonic vein* to *sciatic vein*.^{3,13-15} However, all these laterally located embryonic veins have same defective condition of the vein wall with insufficient smooth muscle layers development (cf. varicose vein). Besides, as a part of defective development of the venous wall, they accompany a unique condition of the lack of normal venous valves development known as *avalvulosis*. The MV has a unique clinical significance as the most common form of VM involved to Klippel-Trenaunay syndrome (KTS).¹⁶⁻¹⁹ KTS is a well known name-based eponym representing a clinical condition of various congenital anomalies affecting not only the vascular system but also the soft tissue as well as the skeletal system. The MV/lateral embryonic vein as a truncular VM lesion^{1-4,20,21} is potentially most dangerous CVM lesion among various vascular malformation components involved to the KTS; together with less common extratruncular VM, MV as a truncular VM belongs to the CVM components of KTS.

Together with this VM group,²²⁻²⁵ the lymphatic malformation (LM) group²⁶⁻²⁹ affects the clinical condition of the KTS as second most serious CVM components, directly and indirectly in various degrees together with capillary malformation (CM);^{30,31} LM presents in the majority as a truncular lesion known as primary lymphedema and/or extratruncular lesion known as lymphangioma among KTS. These two, VM and LM, combined form of CVMs are classified as *hemolymphatic malformation* (HLM) by modified Hamburg Classification in view of inseparable impact on overall hemodynamic status³²⁻³⁵ (Tables 1 and 2). Nevertheless, such complicated condition of the MV, often combined with other CVMs (e.g. deep vein aplasia/hypoplasia) has been often neglected as a relatively benign condition although the chronic venous hypertension generated by the unique condition of *avalvulosis* - lack of venous valve - will give a profound impact on the CVI.

Lately, MV was found to generate much more serious condition to cause the VTE. When this MV is combined with a unique condition of coagulopathy, which is common

Correspondence: Byung-Boong (B.B.) Lee, Center for Vein, Lymphatics and Vascular Malformation, George Washington University School of Medicine, Washington, DC, USA. Division of Vascular Surgery, Department of Surgery, George Washington University Medical Center, 22nd and I Street, NW, 6th Floor, Washington, DC 20037 USA. E-mail: bblee38@comcast.net

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among the *extratruncular* VM lesions, it infrequently becomes a source of serious, even fatal, pulmonary embolism (PE) as well.³⁶⁻³⁹

Therefore, proper understanding on the MV is warranted for all the phlebologists who will have more chance to encounter such unique condition mimicking innocuous varicose veins than other clinical specialists.

Definition

The MV is one of the VMs, and VM is one of the CVMs affecting the venous system alone.⁹⁻¹²

CVM represents a whole group of birth defects caused by the developmental arrest during the embryogenesis to form the vascular system: artery, vein, and lymphatics. Depending upon the embryological stage when the defective development occurs, its clinical behavior is affected profoundly by unique embryological characteristics originated from the mesenchymal cells/angioblasts.⁴⁰⁻⁴³

Therefore, all these inborn vascular defects exist already at birth and the embryonic tissue remnant originated from the defective development in its *early* stage continues to grow at a rate that is proportional to the growth rate of the body (cf. hemangioma); this unique group originated from the early stage is further defined/sub-classified to the *extratruncular* type to differentiate from *truncular* type which represents other group of defective development originated from the *late* stage. The extratruncular lesions remain as a cluster of malformed vessels since defective development

Table 1. Hamburg Classification of congenital vascular malformations.

Malformations types according to Hamburg Classification*

Predominantly arterial defects

Predominantly venous defects

Predominantly arteriovenous shunting defects

Predominantly lymphatic defects

Combined vascular defects

*Based on the consensus on congenital vascular malformation through the international workshop in Hamburg, Germany, 1988, and subsequently modified. Capillary malformation was not included.

occurred while the vascular structure is still in primitive reticular network.

This CVM group is classified together with the vascular tumor group under the category of the *vascular anomaly*; the most of vascular tumor is represented by (neonatal or infantile) hemangioma.⁴⁴⁻⁴⁷ CVM and vascular tumor/hemangioma represent entire anomalous vascular structures together but both groups are totally different not only its etio-pathogenesis but also its clinical behavior.⁴⁸

The Hamburg Classification³²⁻³⁵ has a unique value to provide not only different embryological characteristics of the CVMs from different embryonic stages but also its anatomical, histological, patho-physiological, and hemodynamic status for accurate diagnosis to improve its clinical management. The Hamburg Classification defined the CVMs to six groups based on the vascular systems involved: arterial,^{49,50} venous,⁵¹⁻⁵⁴ arteriovenous (AVM),⁵⁵⁻⁵⁸ LM,⁵⁹⁻⁶² capillary,^{30,31} and combined vascular malformations.⁶³⁻⁶⁵ When LM⁶⁶⁻⁶⁸ is mixed/co-exists with VM or AVM⁶⁹⁻⁷¹ as a combined form of the CVM, they were named to HLM^{21,65,72} (Table 1).

Based on Hamburg Classification, each CVM is further sub-classified to two different groups in order to verify unique embryological characteristics certain CVM groups possess: *Extratruncular* and *Truncular* lesions based on the embryological stage when developmental arrest has occurred³²⁻³⁵ (Table 2).

The extratruncular lesions represent the defective development occurred in the *earlier stage* of embryonic life retaining the mesenchymal cells (angioblasts) characteristics of mesodermal origin. Therefore, they possess evolutionary potential to grow when stimulated internally (e.g. menarche, pregnancy, and hormone) or externally (e.g. trauma, surgery).⁴⁰⁻⁴³

On contrary, the truncular lesions no longer possess this embryonic characteristics of the mesenchymal cells since they represent the defective development during the *later stage* of the embryonic development during the vascular trunk formation period.⁴⁰⁻⁴³ However, truncular lesions cause more serious hemodynamic consequences related to the type of CVM (e.g. marginal veins) despite minimal risk of recurrence

Table 2. Hamburg Classification of congenital vascular malformations: forms and embryological subtypes.**Extratruncular forms***

Infiltrating, diffuse

Limited, localized

Truncular forms*

Aplasia or obstruction

Hypoplasia; aplasia; hyperplasia

Stenosis; membrane; congenital spur

Dilatation

Localized (aneurysm)

Diffuse (ectasia)

*Congenital vascular malformation represents developmental arrest at the different stages of embryonic life: Earlier stage - Extratruncular form; Later stage - Truncular form. Both forms may exist together; may be combined with other various malformations (e.g. capillary, arterial, arteriovenous shunting, venous, hemolymphatic and/or lymphatic); and/or may exist with hemangioma.

Therefore, an extreme variety of the clinical behavior of the CVM lesions is heavily influenced by unique embryological characteristics of different stages of embryogenesis. Accordingly, CVM lesions are known as an enigma of modern medicine with a wide range of clinical presentations, unpredictable clinical course, and erratic response to treatment with the potential for high rates of recurrence.⁷³⁻⁷⁶

Extratruncular VM lesions never involve the main trunk of formed vein itself but remain as an independent lesion from the named/matured vein since they are pre-truncular embryonic lesions occurred before the main vascular trunks are formed. Therefore, they represent clinically either as diffuse, infiltrating lesions or localized, limited lesions.

But the majority of truncular lesions are directly involved to the vein trunks since the defective development occurs along the late stage while the vascular trunk is formed as post-truncular fetal lesions. Therefore, they present as a deformed vein with various degrees of developmental defect (e.g. agenesis/rudimentary deep vein), often as incomplete or immature development (aplasia or hypoplasia) directly affecting the main axial veins.

Therefore, the truncular lesions no longer possess the evolutionary potential with the risk of



Figure 1. A) Clinical condition of the marginal/lateral embryonic vein along the lateral aspect of the left lower extremity. This unique vein structure is a persistent foetal remnant vessel following the failure of normal involution/regression; B) Angiographic finding of this marginal vein, which remains only major venous drainage route for this patient with a lack of normal development of deep venous system. Therefore, surgical excision to control the venous hypertension is contraindicated. From: Lee, 2012.³

recurrence but have varying degrees of hemodynamic consequences due to defective vein trunk either as obstructive⁷⁷⁻⁸⁰ or dilated⁸¹⁻⁸⁴ lesion often affecting *named* vein trunk (e.g. femoral, popliteal, iliac veins).

In addition to such defective vessel condition presented either as an obstruction (e.g. vein web, spur, annulus, or septum)⁸⁵⁻⁸⁸ or dilatation (e.g. popliteal or iliac vein ectasia/aneurysm)⁸⁹⁻⁹² to cause flow disturbance, another form of hypoplasia causes venous reflux with the absence of valves known as *avalvulia/avalvulosis*. This unique condition is a hallmark of the MV. Together with atresia of the lumen of venous trunks and venous aneurysms, *avalvulosis* is relatively common VM lesion.⁹³ MV itself is a different form of truncular VM lesion as the outcome of defective maturation; it is an embryonic truncal vein remnant, which failed to undergo normal involutional process and persists/remains as the MV or the sciatic vein.¹⁻⁴

Maturation and development of the main venous system in the primitive lower limb goes through three different stages: the first phase to form lateral peroneal/fibular vein draining into the cardinal vein; second phase to progress to form sciatic vein as a main vessel while medial draining vessel develop; and third/last phase to complete the evolutionary process, in which the early lateral veins regress.^{3,14} Failure of regression of the lateral peroneal vein will result in the existence of the MV at birth.

The MV occurs in varying extent and severity (e.g. limited sciatic vein), and they are grouped together as *lateral embryonic vein*. Extension of the MV therefore, may be variable depending upon the limb development stage involved; in mild case it is limited within calf level before it is connected/drain into the proximal deep venous system but its entirety might remain with an extension to the thigh and even to the buttock draining into internal iliac vein.

The MV persistence might have a close relationship with a failure of normal development of the deep venous system; more than one third of patients with the MV are known to have a defective deep venous system (e.g. hypoplasia of femoral vein, aplasia of iliac vein). In such case, MV remains as the main draining vein of the limb although it may exist together with normal deep veins. Therefore, precise evaluation of the deep venous system is mandated for the assessment of the MV.

But in general, MV has a numerous connection with the perforators, sometimes huge in caliber and fragile in consistence to make its management risky. Mild/micro AV fistula has been described in cases of extensive aplasia of deep veins.^{78,94,95}

Valveless condition of MV as an embryonic vein causes a severe reflux resulting in chronic venous hypertension/stasis accompanying various degree of CVI. Besides, a defective ves-

sel wall that is deficient in smooth muscle also carries a high risk of thrombo-embolic events and infrequently leads to fatal PE, especially among KTS patients.³⁶⁻³⁹

Clinical assessment

Correct assessment of MV together with the deep venous system is crucial for the treatment planning. Clinical examination is often easy to demonstrate the MV. However, collaterals or even the MV itself may not be easy to remain visible by increased subcutaneous fat or combined with extratruncular LM in which thickening of subcutis by lymphatic abnormal tissue may hide the vein.^{4,93}

But in general, the MV can be easily confirmed through the physical examination as an abnormal superficial draining vein of the lower limb which is sited on the lateral edge of the extremity frequently running beneath the coexisting CM known as a port wine stain.¹⁻⁴ Unless it is located within thick subcutaneous

fat along the swollen limb, the majority is quite visible as a protruding vein along the lateral aspect of the extremity invariably detected by a light palpation.

Laboratory evaluation for the diagnosis of the MV is sufficient only with non- to less-invasive tests based on the Duplex ultrasonography (DUS), magnetic resonance imaging, and/or computerized tomography. DUS is the test of choice to assess the hemodynamic status of the MV and the deep vein system simultaneously (e.g. extent and severity of the reflux and outflow resistance). The deep vein system should be assessed both in lying and standing position to differentiate among normal, aplastic and hypoplastic venous segments.

DUS is also excellent for the mapping of the MV course to delineate entire length of MV, located supra- and sub-fascially, and site and size of perforators besides the extension of reflux.^{8,22} Further evaluation with invasive tests (e.g. direct puncture phlebography together with ascending phlebography) can be deferred till needed as a road map for the surgical intervention^{8,22,93} (Figure 2).

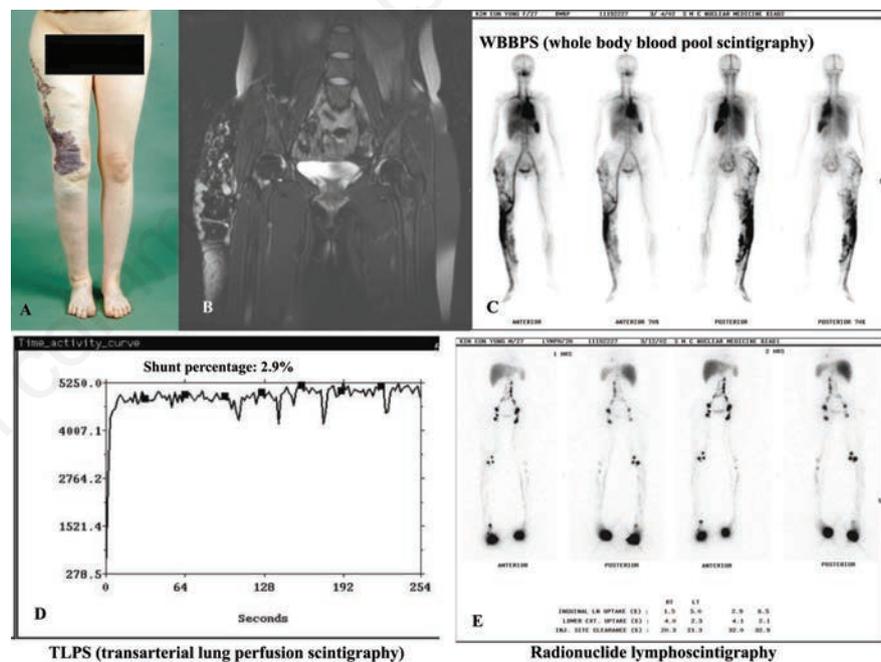


Figure 2. A) Clinical appearance of venous malformation (VM) lesion affecting the right lower extremity as a hemolymphatic malformation, mixed with lymphatic malformation and capillary malformation, often known as Klippel-Trenaunay syndrome. B) Magnetic resonance imaging finding of extratruncular VM lesion diffusely infiltrating in the soft tissue and muscles of right lower extremity. C) Whole body blood pool scintigraphy (WBBPS) findings of massive abnormal blood pool throughout entire right lower extremity; this WBBPS effectively ruled out any additional lesions throughout the body. D) Transarterial lung perfusion scintigraphy (TLPS) study that is negative for abnormal arteriovenous shunting - 2.9% is within normal range. E) Radionuclide lymphoscintigraphy findings of anatomically normal, but functionally abnormal double (deep and superficial) lymphatic transporting vessel, visualized along right lower extremity. This finding is consistent with a clinical finding of chronic lymphedema secondary to hypoplasia of the superficial lymphatic system, which is well compensated by deep system. From: Lee *et al.*, 2007.²¹

Arteriography seldom needed unless needed to rule out the AVM involved.

Proper technique should be known to perform the phlebography correctly in case of a large MV, because standard phlebography may show only the MV itself with poor demonstration of the deep venous system even if this is normal, bringing to a wrong conclusion of aplasia of deep veins. Therefore, phlebography should be combined with DUS, and phlebography alone should be avoided.^{1,96}

A significant numbers of the MV accompany *limb-length discrepancy* either as an elongation or shortening of the affected limb. Hence, the assessment of the MV among KTS patients should be extended to possible involvement of angio-osteohypertrophy/hypotrophy known as vascular bone syndrome.⁹⁷⁻¹⁰⁰

Inconsistent terminology that characterizes the MV with the terms *superficial*, *embryonic* etc. has brought significant confusion. From the anatomical stand point the term *superficial* is a misnomer; although the MV remains in the superficial compartment of the lower extremity, it frequently penetrates the deep fascia and involves muscles of the deep compartment and remains with the high risk of potentially fatal thromboembolic events associated with the MV thrombosis like other major deep vein thrombosis (DVT).

From a therapeutic standpoint, evaluation for the MV deserves a special consideration on the hemodynamic alterations associated with blood stasis in these frequently valveless, truncal VM, carrying a high risk for thromboembolic events: DVT and PE.

Management

Anticoagulation is critical to the management of the MV due to its natural thrombosis prone condition; prophylactic anticoagulation with the weight adjusted low molecular weight heparin (LMWH) is generally recommended in all patients with the MV whenever possible.¹⁰¹⁻¹⁰⁴ Especially when the MV is further combined with an aplastic or hypoplastic iliac-femoral venous system and the MV remains the major venous outflow of the lower extremity where the normal deep venous system is absent, the anticoagulation is essential. In this subgroup, thrombus within the vein would cause serious and often fatal PE.¹⁰⁵⁻¹⁰⁸

Nevertheless, MV is generally indicated for the removal whenever feasible to prevent if not control various acute as well as chronic complications: CVI, VTE, and vascular bone syndrome, as explained in previous section. But the feasibility of the surgical ablation of the MV will depend solely on the deep vein system status; only when the deep system is in normal condition, sudden increase of the venous

influx following the removal of the MV can be tolerated by the deep system. If not tolerate, it would precipitate acute venous stasis and subsequent venous hypertension to cause acute venous gangrene.

The MV among the children in particular with evidence to cause a limb-length discrepancy should be removed as soon as possible in order to give a sufficient time for natural compensation to correct leg length discrepancy.^{13,109} In cases with normal deep veins, complete surgical resection of the MV either in a single stage or multiple stages remains the best and most ideal treatment to control the angio-osteodystrophy.^{97-100,110,111}

When the deep vein system is in minimally hypoplastic condition, the MV can be removed in multistages to give a sufficient time for hypoplastic vein to be dilated spontaneously to tolerate new hemodynamic status following the resection of the MV to insure *rerouting of venous flow*.^{110,111} In cases of aplasia of the deep veins, the embryonal vein becomes a part of the main draining vessel of the limb and resection is no possible.

Therefore, surgical excision of the MV remains the treatment of choice in general and should be carried on to correct abnormal hemodynamic condition to cause various morbidities although endoluminal thermal ablation is occasionally technically feasible. Even for the patients with mildly hypoplastic deep veins it would be worthy for a trial as long as it would not compromise lower extremity blood return. In this subgroup of patients perioperative anticoagulation with LMWH should be considered.

The endovascular obliteration using the laser or radiofrequency is seldom technically applicable for the MV management due to extremely superficial location of the MV right beneath the skin, which makes sufficient tumescent anesthesia difficult. Therefore, currently available endovascular ablation by laser or radiofrequency is generally unsuitable for the MV under thin skin because of high risk of skin damage.^{4,8,22}

Foam sclerotherapy is also less effective and often difficult due to extremely large venous volume and relatively fast venous flow through the MV. Further, it is risky for DVT especially when large perforators are involved with potential extension of thrombosis to the deep vein system without barrier.

But the surgical excision is also often technically difficult due to extreme fragility of the defective vein with lack of media, huge and fragile perforators, and/or dense dysplastic lymphatic tissue surrounding the vein to dissect. Due to high risk of bleeding, the tourniquet is strongly recommended during the surgical procedure whenever applicable and closed stripping is often contraindicated. MV patients who are candidates for surgical

removal, should receive perioperative anticoagulation with LMWH.¹¹² Nevertheless, the results of surgical excision are good; recurrence has not been reported.¹¹³

Conclusions

Marginal vein is one of venous malformations due to defective development of venous trunk formation during the later stage of embryogenesis. MV is *not* an ordinary varicose vein but an embryonic vein with defective vessel structure; it therefore, accompanies high risk of venous thromboembolism in addition to chronic venous insufficiency caused by lack of venous valves (avalvulosis). As far as the deep vein system is normal, early ablation should be done whenever feasible especially when complicated with leg length discrepancy.

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