Marginal Vein is Not a Simple Varicose Vein: It is a Silent Killer!: Invited Article

Marjinal Ven Basit Bir Variköz Ven Değildir: Sessiz Bir Katildir!

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ABSTRACT Marginal vein (MV) is not an ordinary varicose vein; it is an embryonic vein remnant classified as a truncular venous malformation (VM). MV is the result of defective development along the later stage of embryogenesis while the vein trunk is formed. MV exists most often with Klippel Trenaunay Syndrome (KTS), representing as its major VM component; VM is a part of combined form of congenital vascular malformation (CVM) involved with KTS together with the lymphatic malformation. MV accompanies a high risk of venous thromboembolism due to defective vessel structure with a lack of smooth muscle cell to form the media in addition to avalvulosis condition, often resulting in fatal pulmonary embolism. Early ablation of the MV is indicated whenever feasible as far as the deep vein system is normal, especially when the MV causes a vascular bone syndrome. Otherwise, prophylactic anticoagulation is strongly recommended.

Key Words: Varicose veins; Klippel-Trenaunay-Weber Syndrome

ÖZET Marjinal ven (MV) basit bir variköz ven değildir. Bu bir embriyolojik ven kalıntısıdır ve bir trunkular malformasyon olarak sınıflandırılır. MV venöz trunk oluşurken embriyogenezin geç dönemindeki defektif gelişime bağlı ortaya çıkar. MV en sık Klippel-Trenaunay Sendromu (KTS) ile birliktedir ve onun majör bir komponentidir. VM Konjenital Vasküler Malformasyonun (CVM) kombine bir formudur. KTS'de lenfatik malformasyon ile birlikte olabilir. MV, defektif damar yapısı nedeniyle yüksek bir venöz tromboembolizm riskine sahiptir. Media tabakasında düz kas hücreleri olmadığı gibi, kapakçıklardan da yoksundur. Sıklıkla ölümcül pulmoner embolilere neden olur. Uygun olduğunda, derin venöz sistem normal olduğu sürece MV'nin erken ablasyonu gereklidir. Özellikle de MV'nin bir vasküler kemik sendromuna neden olduğu durumlarda. Bunun dışında profilaktik antikoagülasyon güçlü bir şekilde önerilir.

Anahtar Kelimeler: Variköz venler; Klippel-Trenaunay-Weber Sendromu

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Marginal vein (MV)[1-5] is relatively common among various congenital vascular malformations (CVMs) affecting lower extremity;[6-10] it often mimics the ordinary varicose veins originated from saphenous/superficial vein. However the MV is NOT a varicose vein. It is an embryonic vein remnant which failed to involute as a birth defect.

Although MV often runs along the lateral aspect of the lower extremity, which is an odd/unusual location for common varicose veins, it usually locates very superficially beneath the skin with a minimum soft tissue coverage so that most of the MV looks very innocuous, confusing the phlebologists with the varicose vein (Figure 1).

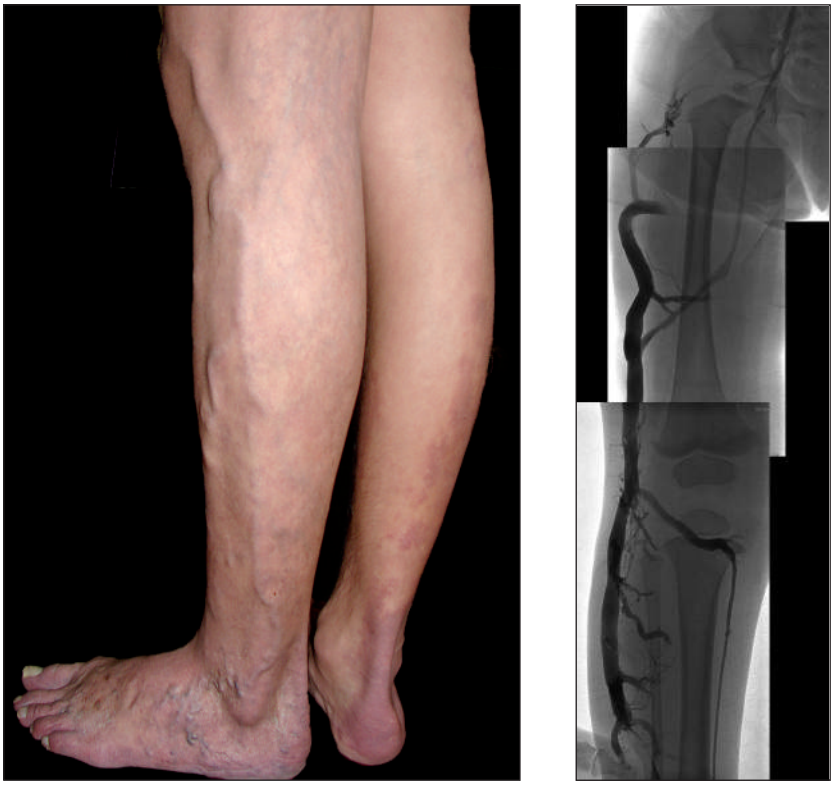

FIGURE 1: 1A depicts a clinical condition of the marginal/lateral embryonic vein along the lateral aspect of the left lower extremity. This unique vein structure is a persistent fetal remnant vessel following the failure of normal involution/regression.
1B presents an angiographic finding of this marginal vein, which remains the 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 BB. Venous embryology: the key to understanding anomalous venous conditions. Phlebolymphology. 2012;19(4):170-81).

Depending upon the stage of defective development along the last/truncular stage of embryogenesis while forming the vein trunk, the extent and severity of the MV are different so that all the MVs in different conditions as well as different locations are named together as 'lateral embryonic vein' including the 'sciatic vein'.[2,11,12]

Regardless of the location and severity, all these laterally located embryonic veins have same defective/deficient media of the vein wall with lack of smooth muscle layers (cf. varicose vein).

The MV is the most common form of venous malformation (VM) involved to Klippel-Trenaunay Syndrome (KTS)[13-17] as one of its multiple vascular malformation components.

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[1-5] is potentially most dangerous VM involved with KTS, and together with extratruncular VM, it represents the VM group of CVM components of KTS.

In addition to this VM group,[18-21] KTS has the lymphatic malformation (LM) group,[22-24] as another clinically significant CVM components, to affect the majority of clinical condition of KTS directly and indirectly besides capillary malformation (CM).[25,26] These two, VM and LM, combined form of CVMs are classified as 'hemolymphatic malformation' (HLM) by modified Hamburg Classification (Table 1).[27-30]

Nevertheless, the MV has been considered a relatively benign condition causing only chronic venous insufficiency (CVI) by its natural condition of avalvulosis- lack of venous valve- as a part of defective development of the venous wall.[1-5] However la-

TABLE 1A: Hamburg Classification* of Congenital Vascular Malformations (CVMs) - Types.

Predominantly arterial defects
Predominantly venous defects
Predominantly AV (arteriovenous) shunting defects
Predominantly lymphatic defects
Combined vascular defects

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

TABLE 1B: Hamburg Classification of CVMs*: Forms - Embryological subtypes.

1. Extratruncular forms
■ Infiltrating, diffuse
■ Limited, localized
2. Truncular forms
■ Aplasia or obstruction
Hypoplasia; Aplasia; Hyperplasia
Stenosis; Membrane; Congenital spur
■ Dilatation
Localized (aneurysm)
Diffuse (ectasia)

* 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, AV shunting, venous, hemolymphatic and/or lymphatic); and/or may exist with hemangioma.

tely, MV was found to be a much more serious condition to cause the venous thromboembolism (VTE). When this MV is combined with a unique condition of coagulopathy, which is common among the 'extratruncular' VM lesions, it becomes a source of often fatal pulmonary embolism (PE).[31-34]

Hence, a proper understanding on the MV as one of CVMs is mandated for a safe management as a whole.

DEFINITION AND CLASSIFICATION OF THE CONGENITAL VASCULAR MALFORMATIONS (CVMs)

CVM represents a group of defective vascular structures as the outcome of developmental arrest during various stages of embryogenesis. Depending upon the embryological stage when the defective development occurs, its clinical behavior is entirely different so that a precise understanding of this embryological background of every CVM lesion is warranted.[35-39]

When the defective development occurs in its 'early' stage while the vascular structure is still in primitive condition of reticular network, this embryonic tissue will remain presenting as a cluster of malformed vessels on birth. Therefore, this inborn vascular defect exists already at birth and continues to grow at a rate that is proportional to the growth rate of the body (cf. hemangioma), and classified into the 'extratruncular' type to differentiate from 'truncular' type which represents other group of defective development originated from the 'late' stage.

This CVM group belongs to the 'vascular anomaly' together with the vascular tumor group represented by (neonatal or infantile) hemangioma.[40-43] Although both groups represent entire anomalous vascular disorders/structures as a vascular anomaly, regardless if its origin and pathogenesis, the CVMs and vascular tumor/hemangioma are totally different not only for their pathogenesis but also for their clinical behavior.

The (infantile/neonatal) hemangioma originates from the endothelial cells so that it has a distinct growth cycle characterized by a proliferation phase of early rapid growth followed by an involutional phase of slow regression. Unlike CVMs, it usually appears in the early neonatal period among perfectly normal neonates and undergo 'self-limited' growth followed by subsequent involution that usually completes before the age of 5-10 years in the majority of cases (Figure 2).

Until past three decades, there had been a significant confusion on the definition on various vascular defects based on mostly name-based eponyms; this old classification failed to provide essential information regarding the etiology, anatomy, and pathophysiology due to lack of sufficient knowledge before modern technology was available for a precise evaluation of these complex vascular conditions.[44-47]

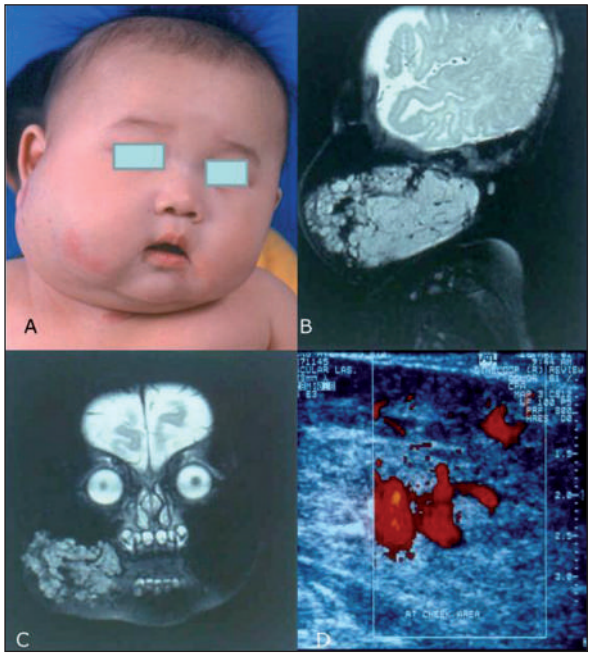

FIGURE 2: 2A depicts clinical condition of (infantile) hemangioma as a rapidly expanding lesion along the right cheek, first noted a few months after birth, which may be mistaken for a venous malformation.
2B & 2C show typical MRI findings of (infantile) hemangioma, affecting right cheek with prominent vascularity that helps differentiate it from a common VM.
2D presents Duplex ultrasonographic findings of active/high blood flow through the lesion in contrast to what would be found in a VM lesion.
(From: Lee BB, Laredo J, Lee TS, Huh S, Neville R. Terminology and classification of congenital vascular malformations. Phlebology. 2007; 22(6):249-52).

New classification was formulated for the first time through the workshop held in Hamburg, Germany in 1988 to compensate the old name-based eponyms (e.g. KTS).[27-30] Although these eponyms are still useful to describe certain conditions involved in combined forms of vascular malformations, their roles have been largely replaced by new (Hamburg) classification for the last two decades.

The Hamburg Classification System appropriately classifies CVMs using criteria that take into account the underlying anatomical, histological, pathophysiological, and hemodynamic status of these congenital vascular defects from different embryonic stages. Modern technology and improved diagnostic studies has allowed accurate diagnosis of these lesions, which is critical for accurate classification.

The Hamburg Classification distinguished the CVMs to six clinically and hemodynamically different groups, and named them after the vascular systems involved in the predominant lesion: arterial (AM),[48,49] venous,[50-53] arterio-venous (AVM),[54-57] lymphatic LM,[58-61] capillary,[25,26] and combined vascular malformations.[62-64] When LM[65-67] is mixed/co-exists with VM or AVM[68-70] as a combined form of the CVM, they were named as Hemolymphatic Malformation (HLM) (Table 1A).[10,18]

Each CVM group is further subdivided into Extratruncular and Truncular Forms in the Hamburg classification, based on the embryological stage when developmental arrest has occurred (Table 1B).[27-30]

The "extratruncular form" of CVM lesions arise when developmental arrest occurs in the 'earlier stage' of embryonic life while the vascular system is in the reticular stage. Extratruncular lesions therefore, retain the characteristics of the mesenchymal cells (angioblasts) as embryonic tissue remnants of mesodermal origin. It retains its potential to grow and proliferate when stimulated internally (e.g. menarche, pregnancy, and hormone) or externally (e.g. trauma, surgery).[35-39]

The "truncular form" of CVM lesions arise when developmental arrest occurs during the vascular trunk formation period in the 'later stage' of the embryonic development.[35-39] Truncular lesions have lost the embryonic characteristics of the mesenchymal cells along with the potential to grow and proliferate. Thus, these truncular lesions carry minimal risk of recurrence on contrary to the extratruncular lesion. Truncular lesions however, are associated with more serious hemodynamic consequences related to the type of CVM (e.g. marginal and embryonic veins as truncular VM).

Accordingly, extreme varieties of CVM lesions with a wide range of clinical presentations, unpredictable clinical course, and erratic response to treatment with the potential for high rates of recurrence can be explained based on this embryological background; the clinical behavior of every vascular malformation is dependent on unique embryological characteristics of different stages of embryogenesis at which developmental arrest occurs.[71-74]

This new (Hamburg) classification provided the impetus for the development of a contemporary concept of CVMs based on embryological subclassification into one of two different subtypes, truncular or extratruncular, allowing clinicians to predict the clinical course, response to treatment and likelihood of recurrence. With the Hamburg classification, precise diagnosis of various CVMs became feasible based on modern technology.[10,27-30]

DEFINITION AND CLASSIFICATION OF THE VENOUS MALFORMATIONS (VMs)

VMs are developmental anomalies (birth defects) limited to the venous system only. They are the result of arrested/defective development of the venous system during the various stages of embryogenesis. VM is one of the most common CVMs, and together with arterial, capillary and lymphatic malformations, they are part of a large group of CVMs (Table 1).[75-78]

The terms "capillary or cavernous hemangioma" are still used erroneously to describe a VM lesion and should no longer be used in order to avoid confusion with a genuine hemangioma which belongs to a vascular tumor and NOT a vascular malformation.[10,18]

Numerous classifications of VMs have been proposed before the Hamburg Classification was available as a universal classification system; many were based on the appearance of the anomaly, its anatomy, pathology, or based on the velocity of blood flow in the lesion (e.g. cavernous hemangioma; cavernous angioma; phlebangioma). Many VMs are still named after the clinician who first described the lesion resulting in redundant terminology with more confusion.

EXTRATRUNCULAR VM LESIONS (TABLE 1B)

The defective development of these lesions occurs before the main vascular trunks are formed (pretruncal embryonic lesions). Therefore, the lesions never involve the main trunk of formed vein itself but remain as an independent lesion from the named/matured vein. These lesions respond to various stimuli and proliferate, carrying a high risk of recurrence following the treatment.

These lesions are further subdivided into diffuse, infiltrating lesions and localized, limited lesions. Diffuse, infiltrating extratruncular VM lesions may cause symptoms due to compression of the surrounding structures (muscles, nerves). They may produce significant hemodynamic impact on the involved venous system that is dependent on lesion size and location including the risk of coagulopathy. Growth is usually slow and proportionate to the person's growth like other extratruncular CVM lesions throughout the rest of the person's life and there is no spontaneous regression like a hemangioma.

TRUNCULAR VM LESIONS (TABLE 1B)

The defective development of these lesions occur long after the primitive reticular stage of vascular development. These lesions are also known as "post-truncal fetal lesions" since the defective development occurs along the late stage while the vascular trunk is formed. Truncular lesions therefore, no longer carry the risk of recurrence after treatment. However, these lesions have varying degrees of hemodynamic consequences due to congenital valvular incompetence, obstruction (atresia, hypoplasia) or dilatation/aneurysm formation with associated risk of VTE especially when the condition is combined with a consumptive coaguloathy, common phenomenon among the extratruncular VM lesions.

The truncular lesions are further subdivided into obstructive[79-82] or dilated[83-86] lesion types. All truncular lesions involve often 'named' vein trunk (e.g. femoral, popliteal, iliac veins); they present as a deformed vein with various degrees of developmental defect (e.g. agenesis/rudimentary deep vein), ranging from incomplete or immature lesions (aplasia or hypoplasia) to overdeveloped lesions (hyperplasia) directly affecting the main axial veins (cf. extratruncular lesion).

Therefore, these truncular VM lesions clinically manifest as a defective vessel either as an obstruction (e.g. vein web, spur, annulus, or septum)[87-90] or dilatation (e.g. popliteal or iliac vein ectasia/aneurysm).[91-94] Avalvulia/avalvulosis, or absence of valves is another form of hypoplasia that

produces venous reflux which is a hallmark of the MV. Together with atresia of the lumen of venous trunks and venous aneurysms, these are relatively common VM lesions.[95]

Another unique form of truncular VM lesions is a persistent fetal remnant (truncal) vessel as persistent, large, embryonic veins such as the MV or the sciatic vein when a fetal (truncal) vessel fails to undergo normal involution.[1-5]

DEFINITION-MARGINAL VEIN (MV)

The truncal venous development of the lower extremity goes through three stages to form matured veins along the later stage of embryogenesis and the MV/lateral embryonic vein is the result of defective development of vein trunk formation through these three stages as following;[11,12]

Early venous outflow from the primitive lower limb is established through a lateral/posterior fibular (peroneal) vein draining into the posterior cardinal vein, which is *the FIRST embryonic vein* of the limb. This first stage of the primitive fibular /peroneal vein formation is soon followed by the second stage of the sciatic vein formation; when 'primitive fibular vein' develops two branches, 'anterior/medial tibial vein' and 'connecting branch', anterior (medial) tibial vein becomes/evolute to the main deep draining vein of the calf. Anterior tibial vein and primitive fibular veins together now constitute the "sciatic vein", which is *the SECOND embryonic vein* (Figure 3A).

Through the third stage, 'a connecting branch' growing medially from the middle of the sciatic vein connects with a new proximal medial vessel that will become the femoral vein to establish the definitive deep venous system later, and the sciatic vein would regress. Another words, *a THIRD embryonic vein* of the leg which evolutes to become the femoral vein later, grows toward the connecting branch of the lateral fibular/sciatic vein, now a part of the sciatic vein; it is further evoluted with the anastomoses to sciatic veins and pass down the leg as the 'posterior tibial' vein to finish the evolution of the deep femoral vein system of the lower extremity (Figure 3B).

However, when the anterior/medial tibial vein fails to form the sciatic vein to become the main draining vein of the lower limb in the second phase of limb vessel development, subsequently a 'connecting' branch growing medially from the middle of the sciatic vein will not be able to connect with a new proximal medial vessel, the femoral vein, to become the definitive deep venous system in the third phase.

With a defect in the second stage, the lateral fibular vein will persist and become the 'marginal vein'. However, if the defect occurs in the passage

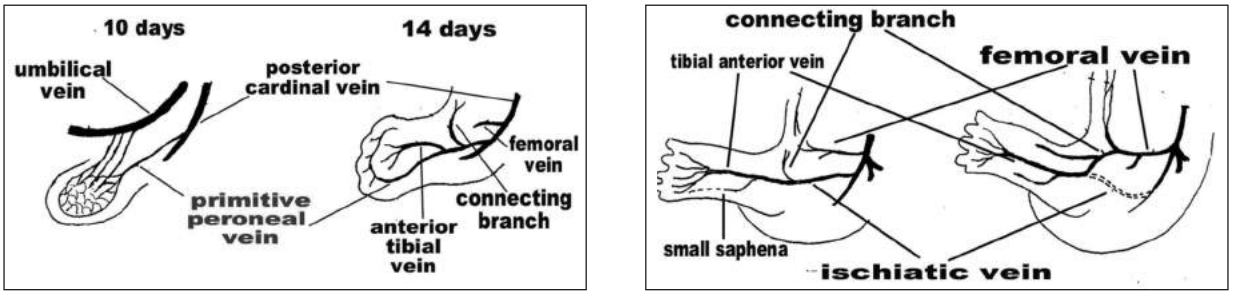

FIGURE 3: A (left photo) depicts the first stage of truncal vein development along the lower limb through the evolution of the primitive fibular (peroneal) vein as the FIRST embryonic vein of the lower limb. Through the second stage (right photo), 'primitive fibular vein' develops into two branches; 'anterior tibial vein' and 'connecting branch' to newly forming femoral vein. Anterior tibial vein and primitive fibular veins together now constitute the "sciatic vein", which is the SECOND embryonic vein.

B (left photo) illustrates the final/third stage to form the femoral vein by 'a connecting branch' from the middle of the sciatic vein, to establish new definitive deep venous system. The sciatic vein (right photo) regresses, and femoral vein is further evoluted, following the anastomoses to sciatic veins, and passes down the leg as the 'posterior tibial' vein to finish the evolution of the veins along the lower limb. This third embryonic vein is also known as the precursor of long/greater saphenous vein.

(From: Lee BB. Venous embryology: the key to understanding anomalous venous conditions. Phlebolymphology. 2012;19(4):170-81).

to the third stage, a 'sciatic vein' will remain as the main draining vein of the limb.

As an embryonic vein, a persisting marginal vein is always 'valveless', as the outcome of an abnormally developed vein devoid of valves and causes a severe reflux resulting in chronic venous hypertension/stasis. This abnormal vessel structure with a defective vessel wall that is deficient in smooth muscle also carries a high risk of thrombo-embolic events and infrequently lead to fatal PE,[1-5] especially among Klippel-Trenaunay Syndrome patients.[13-17]

The MV occurs in many different conditions with varying extent and severity (e.g. limited sciatic vein), and belongs to one group of 'lateral embryonic vein'. In addition, more than one third of patients with the MV have a defective deep venous system (e.g. hypoplasia of femoral vein, aplasia of iliac vein). Therefore, assessment of the MV is required along with precise evaluation of the deep venous system.

DIAGNOSIS-MARGINAL VEIN

The MV can be easily confirmed through the physical examination since the majority are quite visible as a protruding vein along the lateral aspect of the extremity. However, when it is located within thick subcutaneous fat along the swollen limb, it is not quite visible. On the other hand, they are invariably detected by a light palpation and frequently run beneath the coexisting CM known as a port wine stain.

Laboratory evaluation of the MV with Duplex ultrasonography (DUS) should include full evaluation of hemodynamic status of the MV and the deep vein system at the same time (e.g. extent and severity of the reflux and outflow resistance). Entire length/course of MV, located supra- and subfascially, should be visualized together with the perforators.

Non- to less- invasive tests based on the DUS, magnetic resonance imaging (MRI), and/or computerized tomography (CT) evaluation is generally sufficient for the MV assessment, but occasionally, direct puncture phlebography together with ascending phlebography would be needed as a road map for the surgical intervention (Figure 4).[18,95]

The deep vein system should be assessed both in lying and standing positions to differentiate among normal, aplastic and hypoplastic venous segments. If there is any suspicion of pulsating flow, the arteriography may be added to rule out the AVM involved.

Another important findings along the MV among KTS patients is 'limb-length discrepancy' either as an elongation or shortening of the affected limb. A significant numbers of the MV accompany this angio-osteohypertrophy/hypotrophy known as vascular bone syndrome.[96-99]

They are the response/outcome of stimulation to the epiphyseal plate during the bone growth age by the nearby VM, either intraosseous or extraosseous/soft tissue lesions. These patients often have an ache or pain along the limb by the venous stasis, especially while standing.

TREATMENT-MARGINAL VEIN

Prophylactic anticoagulation with the weight adjusted low molecular weight heparin (LMWH) is generally recommended in all patients with the MV.[100-103] This is especially important when the MV presents with an aplastic or hypoplastic iliac-femoral venous system. Anticoagulation is critical in this setting as the MV remains the major outflow vein of the lower extremity where the normal deep venous system is absent. In this subgroup of MV patients, thrombus within the vein would cause serious and often fatal PE.[104-107]

MV is invariably an indication for surgical excision since it causes various extents of acute as well as chronic complications including potentially fatal PE as explained in previous section. In patients with normal or even mildly hypoplastic deep veins, surgical excision- rarely endoluminal thermal ablation-of the MV should be considered to eliminate altered/abnormal hemodynamics as a possible source of thrombosis without compromising lower extremity blood return. Compression stockings are seldom beneficial and should not be used as a permanent regimen regardless of its symptoms.

Symptomatic MV to causing a limb-length discrepancy in childhood should be treated as soon as

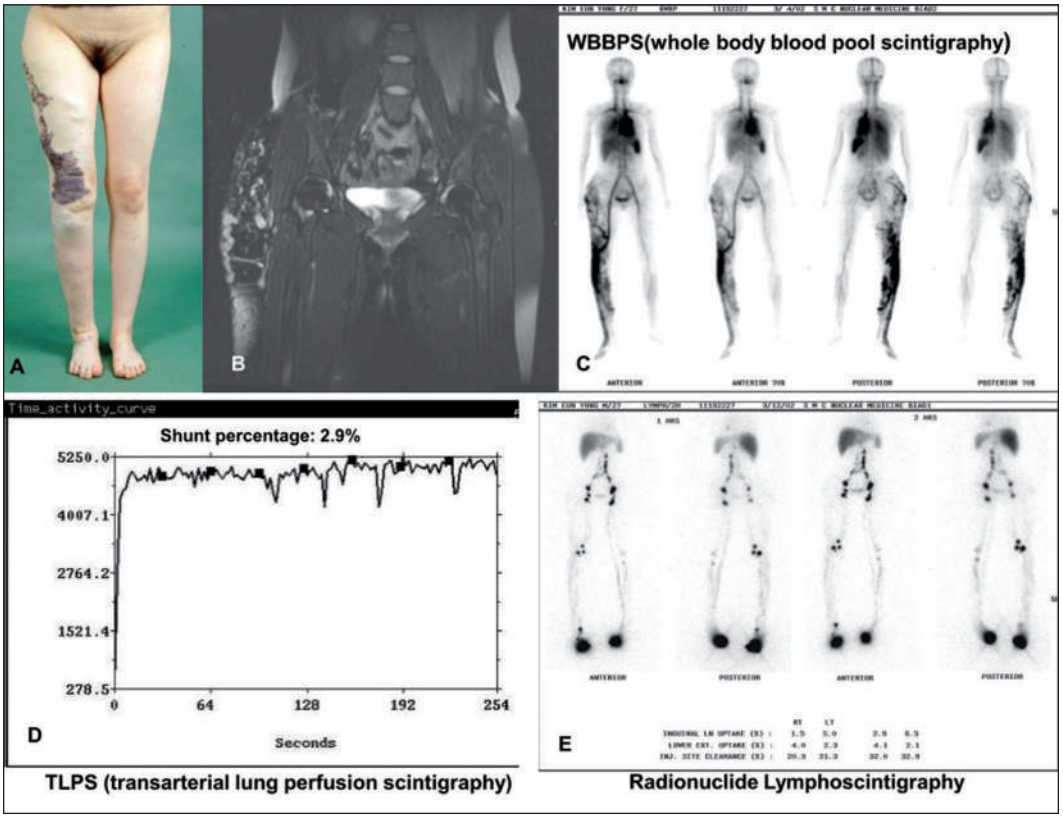

FIGURE 4: A presents clinical appearance of VM (venous malformation) lesion affecting the right lower extremity as a hemolymphatic malformation (HLM), mixed with LM (lymphatic malformation) and CM (capillary malformation), often known as Klippel-Trenaunay Syndrome.
B depicts magnetic resonance imaging finding of extratruncular VM lesion diffusely infiltrating in the soft tissue and muscles of right lower extremity.
C shows WBBPS (whole body blood pool scintigraphy) findings of massive abnormal blood pool throughout entire right lower extremity; this WBBPS effectively ruled out any additional lesions throughout the body.
D illustrates TLPS (transarterial lung perfusion scintigraphy) study that is negative for abnormal AV shunting - 2.9% is within normal range.
E delineates 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 BB, Laredo J, Lee TS, Huh S, Neville R. Terminology and classification of congenital vascular malformations. Phlebology. 2007; 22(6):249-52).

possible to achieve length discrepancy correction. In cases with normal deep veins, complete surgical resection of the MV remains the best and most ideal treatment for the vascular bone syndrome to control the angio-osteodystrophy.[96-99,108,109]

Due to its extremely superficial location beneath the skin, the endovascular obliteration using the laser or radiofrequency is seldom technically applicable. The foam therapy is also very difficult due to extremely large amount and relatively fast venous flow through the MV. Perforators in particular may be difficult to close and risky with this foam therapy because of potential extension of thrombosis to the deep vein system with no barriers.

However the surgical excision is also extremely difficult with high risk of bleeding. The MV often accompanies very large perforators to the deep vein so that closed stripping is almost impossible due to high risk of excessive bleeding and hematomas. Routine use of the tourniquet is strongly recommended during the surgical procedure whenever applicable. Occasionally, subfascial endoscopic perforator surgery (SEPS) is indicated for large incompetent perforating veins. MV patients who are candidates for surgical removal, should receive perioperative anticoagulation with LMWH.[110]

Nevertheless, the ablation of the MV is totally depends on the status of deep vein system; it

can be done safely only when the deep system is in normal condition to tolerate sudden increase of the venous influx following the obliteration of the MV. Otherwise, it would accompany a high risk of acute venous stasis and subsequent venous hypertension to precipitate acute venous gangrene.

However, when the deep vein system is in minimally hypoplastic condition rather than as an aplasia, the MV can be resected through multistage approach for 'rerouting of venous flow' since hypoplastic vein can dilate spontaneously to almost normal size following the resection of the MV.[109,110] 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 not possible.

When the indolent venous ulcers is caused by the CVI of 'limited venous anomaly' origin, deep venous reconstructions can be considered for the selected case.

CONCLUSION

Marginal vein (MV) is NOT an ordinary varicose vein; it is an embryonic vein remnant with a defective vessel structure accompanying high risk of VTE. Early ablation is indicated whenever feasible especially when the MV causes a vascular bone syndrome as far as the deep vein system is normal. Otherwise, prophylactic anticoagulation is strongly recommended.

Conflict of Interest

The author declared no conflict of interest or financial support.

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