Coagulation Disorders in Patients With Venous Malformation of the Limbs and Trunk

A Case Series of 118 Patients

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Objective: To investigate the clinical characteristics of venous malformation of the limbs and trunk and known but poorly appraised associated coagulation disorders. Venous malformations are ubiquitous, slow-flow vascular anomalies known to be occasionally painful because of thrombotic episodes inside the lesion.

Design: Large case series, with screening of accepted standard coagulation tests.

Setting: Ambulatory multidisciplinary clinics for vascular anomalies.

Patients: This 2-year study (2003-2005) included 118 patients with clinical, radiological, and biological features informative for better defining venous malformation and associated coagulation abnormalities.

Main Outcome Measures: The primary outcome was coagulation disorders associated with VM. Secondary measures include anatomic location, extent of lesion, localized pain, and impaired motion.

Results: The mean age of patients was 27 years, and there was a female preponderance of 64%. The venous malformation involved the upper extremity, lower extremity, and trunk in 30%, 58%, and 36% of patients, respectively; it was plurifocal in 22%. Intralesional pain (in 92% of patients) had a higher frequency in female (63%) than in male (47%) patients. Tissular involvement concerned the skin (65%), muscle (73%), bone (13%), joints (12%), and viscera (9%). According to our severity scoring system, cases of less gravity had a score of 2 or 3 (52%), cases of intermediate severity had a score of 4 or 5 (32%), and cases of major severity had a score of 6 to 9 (10%). The most frequent blood coagulation abnormality was a high plasma D-dimer level (>0.5 µg/mL) (58% of patients), which was correlated with muscle involvement and high severity score and was more frequent in women. The factor VIII–von Willebrand factor complex was documented in 84 patients, and plasma von Willebrand factor level was decreased (<60%) in 23 (27%) of them; 10 of the 84 patients (12%) had more notably decreased levels (<50%).

Conclusions: This study of a large case series of patients with pure venous malformation in the limbs and/or trunk highlights muscle involvement and frequency of pain. It validates that coagulation disorders, present in 58% of our patients, create thrombotic painful events. Under certain circumstances, these disorders entail a risk of hemorrhage because of the progression of localized intravascular coagulopathy to disseminated intravascular coagulopathy.

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Venous malformations (VMs) are slow-flow vascular anomalies, according to the classification of the International Society for the Study of Vascular Anomalies (ISSVA) (Figure 1). This congenital defect of the venous network creates distorted venous-type channels of irregularly attenuated walls, locally lacking smooth muscle cells, and dissecting the colonized tissues (Figure 2). The majority of VMs are sporadic anomalies, while 1% to 2% are familial with an autosomal dominant hereditary pattern. Inheritable cutaneous-mucosal VMs are known as venous malformations, multiple cutaneous and mucosal (VMCM) (OMIM 600195). The defective gene maps to 9p21-22 and the disease is linked to TIE2/TEK gain-of-function mutations.

See also pages 873 and 922

Venous malformation develops in superficial, deep, and visceral locations. Superficial lesions involve the skin and mucosa and are distinctively blue due to permeation of the papillary dermis by the abnormal venous network. In infancy and early childhood, they usually appear as mi-
nor bluish macular stains. As the patient ages and as the lesions swell and deflate depending on their positions and the patient’s daily activity, the VMs progressively enlarge and thicken, becoming sagging or bulky and often darker blue. However, these masses are always soft and compressible. Venous malformations are nonpulsating. The temperature of the skin overlying the VM is normal or slightly increased.

Radiological tools including ultrasonography, computed tomography, and magnetic resonance (MR) imaging are helpful in evaluating a VM. However, MR imaging is the most accurate imaging tool to demonstrate a VM because it shows a bright hyperintensity on spin-echo (SE) T2-weighted sequences with fat suppression.

Wherever they are located, VMs are known to be occasionally painful when waking in the morning, when in cold weather, and during or after prolonged exercise. Some evident episodes of thrombosis and inflammatory reaction inside the lesion give localized tenderness on palpation. In the normal venous system, when thrombi develop, most are eventually destroyed by the fibrinolytic system. If not eradicated, the thrombi are inhabited by fibroblasts and capillaries and become fibrous scars. Numerous thrombi develop inside a VM. Many of them will bind to calcium deposits and form round, stonelike structures called phleboliths, which are palpable in superficial lesions and easily identifiable on plain radiography and on samples from pathologic examination (Figure 3).

To our knowledge, our team was the first to report that a localized intravascular coagulopathy (LIC) may be associated with VM, specifically VM of the limbs and trunk. This LIC is associated with painful thrombotic episodes inside the VM, resulting in the formation of multiple phleboliths. Because of the consumption of coagulation factors, the anticoagulant effect of fibrin degradation products, and the exhaustion of hyperactivated platelets, this lifelong LIC leads to hemorrhagic complication when a surgical procedure is performed on the VM area or when trauma involves this region. In these circumstances, LIC may progress to disseminated intravascular coagulopathy (DIC), with consumption of all the coagulation factors, specifically those of the prothrombin complex (factor V decreases) and very high levels of fibrin degradation products. In these settings, a major hemostatic deficiency develops when the activation and consumption of coagulation factors overwhelms the inhibitory capacities, leading to true DIC with hemorrhage and disseminated microvascular thrombosis.

This VM-associated LIC has resulted in inadequate treatment. We are aware of lethal outcomes due to therapeutic mismanagement when the LIC progresses to DIC. The locations particularly at risk for severe hemorrhages linked to LIC and DIC are visceral VM and joint intrasynovial and/or extrasynovial VM. Recurrent hemorrhage alters the joint cartilage, similar to arthropathy in individuals with hemophilia. This study of a large group of patients was specifically undertaken to better define the clinical characteristics of the VM involving the limbs and trunk and to investigate the incidence, importance, and outcomes of the VM-associated LIC in these distinctive locations.

Figure 1. Classification system of the International Society for the Study of Vascular Anomalies (1996). AVMs indicates arteriovenous malformations; CMs, capillary malformations; LMs, lymphatic malformations; and VMs, venous malformations.

Figure 2. Histological aspects of a venous malformation. The lesion is made of thin-walled tortuous venous channels, forming a complex network dissecting the affected tissue (hematein-eosin-saffron, original magnification ×25).

Figure 3. Histological aspects of a phlebolith. The phleboliths are intravascular spherical structures made of concentric aggregation of collagen fibers, due to organization of repeated minute thromboses. These phleboliths are prone to calcification, appearing with a granular blue coloration (hematein-eosin-saffron, original magnification ×10).
A 2-year study (2003-2005) included 198 consecutive patients attending the weekly clinics of our multidisciplinary center for vascular anomalies in Paris, France. All patients had limb and/or trunk pure VM including blue rubber bleb nevus syndrome (Bean syndrome). To accrue a homogeneous group, we excluded patients with other types of slow-flow vascular anomalies of the limbs and/or trunk, ie, those with complex combined venous-lymphatic malformations, patients with Klippel-Trenaunay syndrome, and patients with glomuvenous malformations (glomangiomases). Following our usual practice for patients with VM, all patients were clinically examined by 4 physicians (E.M., O.E., A.B., and J.P.) during multidisciplinary clinic visits. The patients gave their oral consent and then underwent MR imaging of their vascular anomaly and biological testing. All data were obtained on a standardized survey form.

We recorded the following measures: (1) anatomic location, extent of lesion, localized pain, and impaired motion; (2) MR imaging, focusing on the radiological features and extent, using T1- and T2-weighted sequences with fat suppression and occasionally gadolinium injection; and (3) blood cell counts and blood coagulation tests (prothrombin time and activated partial thrombin time and D-dimer, fibrinogen, factor VIII, and von Willebrand factor [vWF] plasma levels). All data were obtained on a standardized survey form.

Magnetic resonance imaging and blood tests are routine standardized examinations, which were performed at the convenience of the patient either in our hospital or close to their home location. At the end of the recruitment period, the study population comprised 118 patients with clinical, radiological, and biological features.

RESULTS

The 118 patients had a mean (SD) age of 27 (15) years (range, 3-74 years). There were 76 female patients (64%), with a mean (SD) age of 27 (13) years (range, 6-65 years), and 42 male patients (36%), with a mean (SD) age of 28 (18) years (range, 3-74 years). This unexpected female preponderance was identical in the initial group of 198 consecutive patients (68% female vs 32% male patients). All VMs were sporadic cases, including 2 patients with Bean syndrome.

CLINICALLY VISIBLE LOCATION

The following parameters were recorded: (1) anatomic location and (2) extent of lesion: localized (small and compact in 1 single anatomical location) vs extensive (extensive lesion in same anatomical location) and focal (1 single anatomical location) vs plurifocal (multiple anatomical locations or region). The blue color is a characteristic of VM involving skin or mucosal membranes (mouth or genitalia) that reach the superficial dermis (Figure 4). The VM involved the upper extremity in 36 patients (30%), 28 of whom had a focal location; the lower extremity was affected in 69 patients (58%), 59 of whom had a focal location; and the trunk was involved in 31 patients (36%), 9 of whom had a focal location. Twenty-six patients had a plurifocal location (22%).

Some orthopedic features in the lower limb were surprising. For example, muscle involvement could generate either amyotrophy or hypertrophy of the involved muscle, or it was clinically undetectable. These hidden locations were revealed by either pain and subsequent evaluation with MR imaging, or they were asymptomatic and fortuitously discovered with MR imaging.

SYMPTOMS

Intralesional VM pain was the major complaint in 109 of the 118 patients (92%). It occurred daily in 20% of them. Pain was sometimes present when waking in the morning (with suspected ill posture of the limb during sleep), or it happened after prolonged exercising or prolonged immobilization. Paresthesia and neuralgia usually indicated nerve involvement or entrapment by VM, which could be found on MR images. This was obvious in deep VM involving the buttock area (sciatic nerve) and in deep wrist locations. Female patients reported painful episodes more frequently than did male patients (63% vs 47%). We tried to correlate this high prevalence of pain in female patients with hormonal events such as puberty, pregnancy, or hormonal contraception. A link seemed possible with hormonal contraception, but this observation was limited by the low number of exposed women.

DIAGNOSTIC METHODS: RADIOLOGY

Evaluation with MR imaging disclosed 2 types of lesions. In 50% of the patients, small venous lakes (confluent, small, tortuous VM channels <1 cm) were seen. Large venous pouches (confluent, large, often lobular VM channels >1 cm) were observed as hyperintense signals on T2-weighted MR images with fat suppression in 70% of the patients, with one-fifth of them showing both features (large and small channels) simultaneously (Figure 4). The VM was stained with gadolinium on T1-weighted sequences. Venous malformation channels were either dispersed or densely packed. When thrombi were visible on MR images, they were more often seen in large VM channels (68%) than in small ones (51%). Phleboliths, the round calcifications following thrombi, were detected in 39 cases (33%) by palpation, plain radiography, and/or MR imaging.

Tissue involvement was evaluated with MR imaging. Multiple tissue type involvement was present in the majority of the patients. Venous malformation involved the skin in 76 patients (65%), muscle in 93 (79%), bone in 16 (13%), and joint (elbow, knee, or ankle) in 14 (12%). Visceral extent was observed in 11 patients (9%) and genital extent in 5 (4%). Single intramuscular VM was observed in 26 cases and purely cutaneous involvement in 19. Visceral involvement was a fortuitous finding in 9 patients: abdominal or pelvic extent was found in 5 patients (4 female and 1 male patient); pleural involvement was found in 2 female patients; a thoracic VM infiltrated the mediastinum reaching pleura and pericardium in 1 female patient; and liver, spleen, and pararenal VM was discovered in 1 female patient clinically affected with a thoracic superficial VM (Figure 4). In 2 other patients, visceral involvement was already clinically diagnosed (because of preceding intestinal hemorrhages)
Figure 4. Various clinical aspects and magnetic resonance (MR) image patterns of our patients. 
A-G, Clinical patterns: the blue color characterizes skin involvement. H-J, Spin-echo, T2-weighted sequences of MR images showing, in various locations, the venous malformation (VM) as a hyperintense signal. K, A recent spontaneous thrombotic event inside a lesion in 1 patient modified the signal on this MR image. L and M, In these 2 patients, skin VM is associated with visceral VM, reaching the kidney and affecting the liver and spleen (L) or reaching the pleura (M).
and confirmed by endoscopy; both had sporadic Bean syndrome with tiny dark blue papules scattered on the skin. In 1 of them, congenital thoracic skin and muscular VM created a bump, which was excised early in life but partially recurred.

SEVERITY SCORING SYSTEM

To our knowledge, no gold standard to assess the gravity of a VM exists in the literature. To appreciate the extent and seriousness of the VM, we used a severity scoring system derived from the first 2002 scoring system. It combines sites involved and tissue types concerned: the more there are, the higher the score and the more problematic the VM course (Table). Graded for 10 items and based on both clinically visible locations and tissue involvement seen on MR images, the score provides a relatively precise assessment of the superficial and deep spreading of the vascular malformation. According to this system, the scores of our patients ranged from 2 to 9. The less severe cases had a score of 2 (28%) or 3 (24%); more severe cases had a score of 4 (20%) and 5 (18%); and the most severe cases (12 patients [10%]) had scores of 6 (8 patients), 7 (1 patient), 8 (2 patients), and 9 (1 patient) (Figure 5).

BIOLOGICAL PARAMETERS

Blood cell counts were normal in these patients. Platelet counts were normal (>161 × 10^9/L) in all but 1 patient (94 × 10^9/L). The various coagulation parameters revealed a specific profile associated with VM. In these patients, who were exclusively affected with VM of the limbs and/or trunk, the most frequent blood coagulation test abnormality was an increase in plasma D-dimer levels. Only severe cases had a more complete profile of consumptive coagulopathy (prolonged prothrombin time and activated partial prothrombin time). A moderate decrease in platelet count affected some of the most severe cases. Results from the general clinical examination of the patients, the MR imaging and general biological testing (mainly liver and kidney), and the assessment of individual coagulation factors ruled out another cause of coagulopathy and increased D-dimer level. Results of laboratory investigations of the patients with VM were compared with accepted standard values as well as with the normal values obtained from the Lariboisière Hematology Laboratory, a reference center in Paris, France. These values included the 95th percentile of distribution of values obtained from normal subjects of the same age and sex.

Of 118 patients, 58% had a plasma D-dimer level higher than 0.5 µg/mL, the “normal” limit for exclusion of venous thrombotic event (range, 0.5-11.2 µg/mL; mean [SD], 2.3 [2.2] µg/mL; and median, 1.5 µg/mL); 70% of these patients were female, 90% of whom had muscle involvement, with severity scores ranging from 2 to 9. Also, 39% of the 118 patients had plasma D-dimer levels higher than 1.0 µg/mL (range, 1.0-11.2 µg/mL; mean [SD], 2.9 [2.3] µg/mL; and median, 2.0 µg/mL); 67% of these patients were female, 93% of whom had muscle involvement, with severity scores ranging from 2 to 9. However, a comparison between the severity score and the mean plasma D-dimer level demonstrated a relationship with the vascular anomaly extension and seriousness (Figure 6). Increased plasma D-dimer levels were correlated with muscle involvement as well as increased severity score; it was more frequent in women. Yet, a small number of patients (n=6) with a severity score of 2 had plasma D-dimer levels of 1.0 µg/mL or higher, but all 6 patients had muscle VM involvement.

There were 26 children (age range, 2-15 years) among our 118 patients. Of the 26 children, 23 recorded pain episodes (often a disabling situation); 10 had D-dimer levels of 0.5 µg/mL or lower, and 16 (including 2 children with Bean syndrome) had D-dimer levels higher than 1.0 µg/mL (mean [SD], 3.0 [2.8] µg/mL; median [range], 1.9 [1.1-11.2] µg/mL) (2 of these 16 children were without pain).

Mean (SD) plasma fibrinogen level was 286 (88) mg/dL (range, 62-541 mg/dL). Increased plasma D-dimer level was associated with a decrease in plasma fibrinogen level in 6 patients (range, 62-190 mg/dL); a decrease of the prothrombin time and of the plasma factor V level was observed in only 2 patients.

The factor VIII–vWF complex was measured in 84 patients (71%). Among them, 10 (12%) had a decrease in plasma vWF level (activity) between 28% and 50% (1 of

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Table. Severity Scoring System for Superficial and Deep Venous Malformations of the Limbs and Trunk

<table>
<thead>
<tr>
<th>Scoring Method</th>
<th>Criteria</th>
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</thead>
<tbody>
<tr>
<td>Each anatomic location is scored as involved based on clinical observation. One point is awarded for each location.</td>
<td>Upper extremity, lower extremity, trunk, genitalia, visceral location</td>
</tr>
<tr>
<td>Each type of tissue is scored as involved based on clinical and magnetic resonance imaging evaluation. One point is awarded for each type of tissue.</td>
<td>Skin, subcutis, muscle, bone, joint</td>
</tr>
<tr>
<td>Total points</td>
<td>10</td>
</tr>
<tr>
<td>Minimum severity score</td>
<td>2 (1 location + 1 tissue type involved)</td>
</tr>
</tbody>
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Figure 5. Extent of severity of venous malformation (N=118). Repartition of the “severity extension scoring system” in our population. “Scores are based on clinically visible location and tissue involvement evaluated by magnetic resonance imaging (skin, subcutis, muscle, joint, bone, genital, visceral trunk, and limb [superior and inferior]). The scores ranged from 2 to 9.
these patients had an abdominal VM location), and in 13 patients (15%), the plasma vWF level was between 50% and 60% (1 patient had an abdominal VM location). The observed values are characteristic of a particular patient (the values remain stable over time in the patients who have been repetitively examined). To our knowledge, the observed 27% prevalence of a plasma vWF level below 60% (10 times that observed in the normal control population of the Lariboisière Hematology Laboratory) and 12% prevalence of vWF deficiency in our VM population has not been reported previously. Hemoglobin level was normal in all patients when measured in usual stable conditions.

**COMMENT**

Two unexpected clinical findings were noted in this study: (1) lower extremities were involved by a VM twice as frequently as the upper extremity (58% vs 30%) and (2) although no sex preponderance for VM has been recognized in the literature, to our knowledge, we observed a higher prevalence of female patients (64%) affected with VM of the limbs and/or trunk.

Magnetic resonance imaging is considered the most informative imaging modality for VM, which is consistent with our observations. In our study, we additionally observed that evaluation with MR imaging of clinically superficial trunk VM is mandatory before offering any type of treatment (surgical excision or sclerotherapy) because some patients had asymptomatic deep visceral locations, reaching the pleura, pericardium, or kidney (Figure 4), a potential risk for therapeutic complications (eg, pneumothorax or unwanted diffusion of ethanol during a sclerosing procedure).

An LIC disorder was present in more than half of our patients with VM. From our experience, we know that this biological anomaly is underrated or overlooked. It is often inappropriately labeled as Kasabach-Merritt syndrome. In the literature, the appellation Kasabach-Merritt syndrome is erroneously used for adults affected with vascular disorders associated with slow-flow vascular malformations or malignant disease such as angiosarcoma. Kasabach-Merritt syndrome is a distinct phenomenon with profound thrombocytopenia related to platelet trapping in a vascular tumor, Kaposiform hemangioendothelioma, or tufted angioma. Thrombocytopenia was minor or absent in our patients with VM-associated coagulation disorders. Kasabach-Merritt syndrome is a purely infantile disease with a different course and, moreover, a fully different therapeutic management.

Patients with LIC complained of more significant and prolonged episodes of pain. The LIC was mainly associated with muscle involvement and diffuse tissue involvement by VMs. The higher the severity score, the higher the plasma D-dimer level during the acute painful phase of thrombosis and inflammation. A higher prevalence of painful episodes was observed in female than in male patients with VM (63% vs 47%). To explain this, it could be hypothesized either that the presence of estrogen receptors on endothelial cells could influence the development of the VM itself or that the estrogen prothrombotic effect could stimulate the occurrence of painful thromboinflammatory events inside the VM of female patients, which would allow the physician to more easily recognize and diagnose asymptomatic VM in female patients.

An abnormality in vWF level was observed in 23 (27%) of our 84 patients with VM in whom factor VIII–vWF complex was documented, and a more notable decrease (vWF level <50%) was observed in 10 (12%) of them, whereas the literature gives an estimated prevalence of 3 per 100 000 to 1.3% of the general population—an estimation complicated by variable penetrance of the disease phenotype. Von Willebrand factor is a protein synthesized by the endothelial cell and megacaryocytes from the bone marrow. Venous malformation is a pathologic condition involving the vessel wall, and thus the higher prevalence of vWF disease observed in our patients may be explained either by an increased consumption or by an abnormal synthesis.

From our experience, it is possible to reduce the burden of pain linked to thrombotic events occurring inside the patient’s VM using low-molecular-weight heparin (LMWH) treatment. It has proven to be the most effective treatment that is able to reduce the symptoms while decreasing D-dimer levels and restoring normal fibrinogen levels. In children, as in adults, the acute painful events were also related to thromboinflammatory phenomenon within their VM. Children could get very high D-dimer levels (>10.0 µg/mL), and they also benefited from LMWH treatment. Some of these patients necessitate protracted and even continuous care. Further studies are required to define which type of LMWH is the best therapeutic option.
This study of a large series of patients with purely VM in the limbs and/or trunk confirms our previous findings concerning the existence of a frequent (>50% of patients), chronic LIC in VM of the limbs and/or trunk. This LIC is responsible for thrombotic painful events inside the lesions. Determining D-dimer level allows us to correctly follow the variations of the LIC episodes. Localized intravascular coagulopathy was prominent in patients with large VMs and VMs with muscle involvement and in the female population. The age of the patient did not influence the LIC. This LIC occasionally progresses to DIC with life-threatening hemorrhage, especially when local trauma or various therapeutic procedures affects the VM area. A D-dimer test should be ordered for all patients with VM of the limbs and/or trunk at (1) baseline to know the current coagulation status of the patient; (2) when an acute painful episode expands the vascular malformation, a phenomenon usually linked to exacerbation of the LIC; and (3) as soon as a therapeutic procedure is planned to decide if a treatment preventing the progression of LIC to DIC is necessary. Low-molecular-weight heparin proved to be the best therapeutic method for VM-LIC. We advise prescribing an LMWH treatment in (1) prophylactic doses when protracted painful thrombotic events occur; (2) prophylactic or curative doses—depending on the severity of the exacerbation of the LIC—when local complications arise, such as hemarthrosis or intramuscular VM thrombosis impairing function; and (3) prophylactic doses when sclerotherapy and/or excision are planned in a patient with a large VM (in this case, the LMWH treatment should be given before and after the therapeutic procedures to avoid complications such as extensive thrombosis or difficult to control intraoperative hemorrhage).

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Author Contributions: Dr Mazoyer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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