Diagnosis and management of extensive vascular malformations of the lower limb

Part II. Systemic repercussions, diagnosis, and treatment

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After completing this learning activity participants should be able to delineate the underlying diseases or systemic anomalies that may be associated with vascular malformations of the lower limbs; describe the evidence-based evaluation of vascular malformations of the lower limbs; and recognize that patients with extensive vascular malformations require a multidisciplinary therapeutic approach.

Date of release: November 2011
Expiration date: November 2014

doi:10.1016/j.jaad.2011.03.009

At least nine types of vascular malformations with specific clinical and radiologic characteristics must be distinguished in the lower limbs: Klippel—Trénaunay syndrome, port-wine stain with or without hypertrophy, cutis marmorata telangiectatica congenita, macrocephaly—capillary malformation, Parkes Weber syndrome, Stewart—Bluefarb syndrome, venous malformation, glomuvenous malformation, and lymphatic malformation. Extensive vascular malformations are often more complex than they appear and require a multidisciplinary therapeutic approach. Vascular malformations may be associated with underlying disease or systemic anomalies. Part II of this two-part series on the diagnosis and management of extensive vascular malformations of the lower limb highlights the systemic repercussions (bone, articular, visceral, and hematologic involvement), diagnosis, and treatment of these lesions. (J Am Acad Dermatol 2011;65:909-23.)

Key words: cutis marmorata telangiectatica congenita; embolization; glomuvenous malformation; port-wine stain; Klippel-Trenaunay syndrome; laser; localized intravascular coagulation; lymphatic malformation; macrocephaly-capillary malformation; magnetic resonance; multi-detector computed tomography; Parkes Weber syndrome; pulmonary hypertension vascular malformations; Stewart-Bluefarb syndrome; sclerotherapy; surgery; venous malformation.

The clinical presentation of extensive vascular malformations of the limb in children includes pain, swelling, limb length discrepancy (LLD), gigantism, bruising, bleeding, and cosmetic concerns. Although the majority of vascular malformations of the lower limbs are not associated with potential complications, others can include osteoarticular involvement, hypercoagulability, visceral involvement with life-threatening hemorrhages, thrombosis, pulmonary embolism, and pulmonary hypertension. This review focuses on the systemic repercussions, diagnosis, and treatment of extensive vascular malformations of the lower limbs.

CAPSULE SUMMARY

- Multi-detector computed tomography and fast 3-D magnetic resonance image venography are extremely helpful for the global evaluation of extensive lower limb vascular malformations.
- Some extensive vascular malformations in the limbs may have bone and articular involvement.
- Localized intravacular coagulation occurs in extensive low-flow vascular malformations. D-dimer and fibrinogen levels must be measured as part of the medical evaluation.
- A significant number of patients with extensive vascular malformations of the lower limbs have pulmonary arterial hypertension presumably due to recurrent pulmonary embolism.
- Recent articles have demonstrated the efficacy and safety of ultrasound-guided sclerotherapy with microfoam in the management of slow-flow vascular malformations.

SYSTEMIC REPERCUSSIONS: QUALITY OF LIFE

Key points

- **Negative impact on patients' quality of life because of pain, functional limitations, and cosmetic effects**

Extensive vascular malformations of the lower limb have a negative impact on patients' quality of life in three main ways: pain, functional limitation, and cosmetic effects, which vary as a function of age, sex, and vascular malformation size but are always present. Although there has been little study of the health-related quality of life in patients with vascular malformations and growth disturbances, some authors have investigated their psychological impact or shown vitality impairment and elevated pain levels.[1,2] Especially in severe cases, physicians should be attentive not only to the physical aspects of extensive vascular malformations but also to the psychological and social aspects.[3]

BONE INVOLVEMENT

Key points

- **Limb length discrepancy has been reported in 66% of patients with Klippel–Trénaunay syndrome**
- **Extent of the vascular malformation is the single independent risk factor for limb length discrepancy**

Hypertrophy and atrophy

LLD has been reported as a sequela of vascular malformation in the lower limb. It can result in disfigurement, gait disturbance, pelvic tilting, scoliosis, or back pain.[4] Although LLD has been widely reported in 24.3%[5] to 46%[6] of patients with lower limb arteriovenous malformation (A-VM), other authors have observed a higher frequency of lower limb overgrowth (66%) in patients with Klippel–Trénaunay syndrome (KTS).[7]

Bone involvement is so frequent in patients with extensive vascular malformations that some authors include it under the term congenital vascular bone syndrome (CVBS; ie, a pathologic enhancement or reduction in long bone growth related to congenital abnormal circulation).[8] Arteriovenous fistulae, venous, or combined vascular malformations may be involved. The hyperemic theory posits that the flow increase in cartilaginous growth centers, high

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0190-9622/$36.00

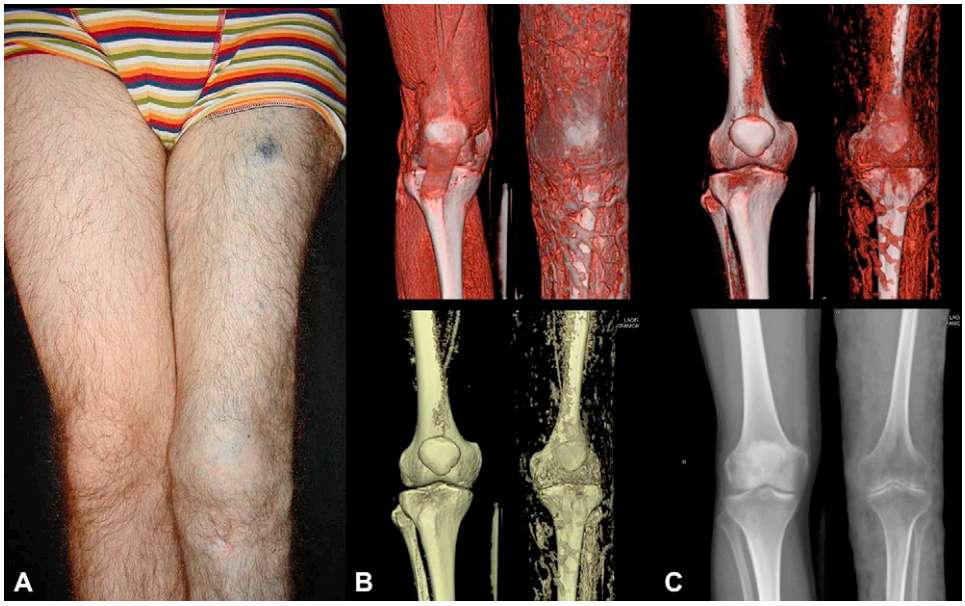

Fig 1. **A**, A 24-year-old man with extensive venous malformation of the lower limb. **B** and **C**, Indirect multidetector computed tomography venography clearly shows severe unilateral osteoporosis involving the affected extremity and significant muscular infiltration by the venous malformation. Note involvement of the knee.

temperature, and augmented oxygenation in the bone caused by arteriovenous fistulae may stimulate the osteoblasts to produce bone overgrowth.[9] However, some authors concluded that the cause of CVBS is venostasis rather than hyperemia after obtaining elongation of long bones in animals by ligation of deep veins,[10] while bone hypotrophy has been related to a mechanical compression on bones by dilated vascular malformations.[11] A recent review found that the extent of the vascular malformation lesion was the single independent risk factor for LLD, regardless of the type or depth of the vascular malformation lesion; data also suggested that the cause of LLD (overgrowth or undergrowth) of the affected limb might be related to gender.[12]

Osteoporosis and pathologic fractures

Key points

- **Some extensive vascular malformations of the limbs may have knee involvement with bone thinning and demineralization**
- **Possible osteoporosis must be studied to prevent pathologic fractures**

It has also been reported that extensive vascular malformations, especially those situated deeply in the soft tissue, may cause reactive changes in the adjacent bones, such as periosteal reaction, cortical erosion, trabecular change, demineralization, or lytic changes[13,14] (Fig 1). These bony anomalies differ from Gorham syndrome, which is characterized by extensive osteolysis. Other authors detected bone demineralization in 71% of these patients, sometimes associated with pathologic fractures.[15] It is not known whether this demineralization is the consequence of prolonged immobilization or the extensive vascular malformations. It has been hypothesized that transient osteoporosis may result from bone marrow edema secondary to regional arterial hyperflow.[16] Some studies have reported pathologic fractures and subsequent therapeutic complications caused by excessive perioperative bleeding and the difficulty of bony union.[17,18] Although many of these authors refer to hemangiomas, they are in fact vascular malformations—generally venous, but also KTS- or Parkes Weber—type combined malformations.[19-21]

ARTICULAR INVOLVEMENT

Key points

- **Knee artropathy is irreversible and similar to that seen in hemophilic syndromes with frequent hemarthroses**

A large number of patients with extensive vascular malformations of the lower limb have knee intra-articular vascular malformation and knee arthropathy (Fig 2).[22-24] Knee arthropathy is irreversible, and its presentation is similar to that in hemophilic syndromes with frequent hemarthroses. The pathogenesis results from recurrent bleeding in the subsynovial vascular plexus within the knee joint. This

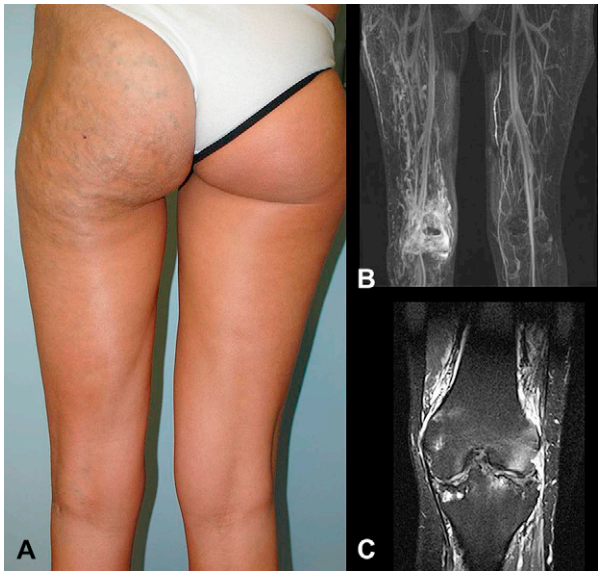

Fig 2. A, A 21-year-old woman with extensive venous malformation of the lower limb. **B**, Three-dimensional magnetic resonance venography revealing the extent of the venous malformation. **C**, Coronal view of a magnetic resonance imaging scan of the knee with fat saturation, demonstrating severe arthrosis with loss of articular cartilage, subchondral cysts, bone edema, and disruption of the tibial plateau.

leads to a chronic synovial inflammatory response and to the erosion of local tissues, including articular cartilage and periarticular bone. The most common surgical pathologies encountered are extensive proliferative synovitis, hemosiderin staining, pannus formation, and destruction of the femoral, patellar, and tibial articular surfaces. Loss of knee motion, swelling, morning stiffness, and especially the development of a knee flexion contracture are an urgent indication for magnetic resonance imaging (MRI) scans, even in young children. These symptoms improve after synovectomy with excision of the venous mass embedded in the synovial membrane, and they do not recur unless severe arthritic changes were already present at the time of the surgery. Synovectomy protects articular cartilage from erosion but is not beneficial once the joint surfaces have been lost.

VISCERAL (DIGESTIVE/GENITOURINARY) INVOLVEMENT

Key points

- **Bleeding is the most common symtom reported in extensive vascular malformations of the limb with gastrointestinal and genitourinary involvement**

Extensive vascular malformations of the lower limb frequently extend to the trunk, with visceral involvement of the pelvis and abdominal cavity. Patients with cutaneous vascular abnormalities on the trunk or perineum are around three times more likely to have a visceral vascular anomaly than those without, although the absence of skin lesions does not preclude the presence of abdominal or pelvic involvement.[25]

Although most studies have addressed KTS, this visceral involvement is not exclusive to combined malformations and has been reported in other vascular malformations.[26,27] Involvement of the gastrointestinal tract is detected in >20% of KTS patients, especially involvement of the distal colon and rectum, and may go unrecognized in patients without overt symptoms. Bleeding is the most common symptom reported in KTS patients with gastrointestinal involvement, with life-threatening hemorrhages and consumptive coagulopathy.[28,29] In these patients, defecation is frequently associated with rectal bleeding.

Around 30% of patients with KTS have genitourinary involvement, manifesting as intrapelvic and retroperitoneal vascular malformations that can affect the bladder, penis, scrotum, vagina, or vulva.[30] The most common cutaneous manifestations are progressive genital lymphedema, lymphatic weeping, recurrent cellulitis, and recurrent bleeding. Women with KTS and perineal, vaginal, and/or perirectal vascular malformations may have menorrhagia, which can be controlled by hormonal therapy. Bladder lesions in KTS are mostly found at the dome and anterior wall, whereas the trigone and neck are rarely involved. The presence of gross hematuria in KTS patients should alert pediatricians and urologists to the possibility of urinary tract vascular malformations.

Multidetector computed tomography (MDCT) or MRI of the abdomen and pelvis provides a simple noninvasive means of assessing visceral vascular malformations.[31]

HEMATOLOGIC INVOLVEMENT: PROCOAGULANT PROFILE

Key points

- **Localized intravascular coagulation has been reported in up to 85% of patients with venous malformations with a segmental pattern, as in KTS-type malformations**

The association between extensive vascular malformations and hypercoagulability is well established. Localized intravascular coagulation (LIC) has been reported in up to 85% of patients with pure venous malformations (VMs) with a segmental pattern, as in KTS-type combined malformations.[13]

In LIC, there is a local consumption of coagulation factors within the malformation secondary to venous stasis, resulting in the formation of microthrombi. Numerous microthrombi will bind to calcium deposits and form round, stone-like structures called phleboliths, which are palpable in superficial lesions and easily identifiable on plain radiography. This local coagulation is distinct from the disseminated intravascular coagulation (DIC) found in Kasabach–Merritt syndrome, with profound thrombocytopenia related to platelet trapping in a vascular tumor (Kaposiform hemangioendothelioma or tufted angioma).[32,33] Coagulation abnormalities associated with limb vascular malformations should not be reported as Kasabach–Merritt syndrome, although this inappropriate usage is frequently found in the literature.[34] A recent study revealed that LIC is frequently associated with VMs and that a large surface area, muscle involvement, and palpable phleboliths are strong predictable criteria for a coagulation anomaly.[35]

Although LIC is well tolerated in everyday life, systemic activation of coagulation (DIC) can occur during surgical resection, bone fracture, prolonged immobilization, pregnancy, traumatism, or ethanol sclerotherapy. Some patients with extensive vascular malformations also have a prolonged prothrombin time as the result of an elevated consumption of fibrinogen and factor V. Together with a mild thrombopenia, this can favor bleeding with painful hematomas, hemarthrosis, and hemorrhages in the digestive system or other sites, which may be life-threatening.[36] It is important to determine fibrinogen and D-dimer baseline levels, because treatment with low molecular weight heparin (LMWH), independent of these risk factors, has beneficial effects on blood test disturbances, pain, and bleeding tendency.[35]

PULMONARY ARTERIAL HYPERTENSION

Key points

- **Many patients with extensive vascular malformations of the limb may present with pulmonary hypertension caused by recurrent pulmonary embolism**

Cardiac compromise is well documented in large active A-VMs that grow without control and can produce congestive heart failure, but has been rarely reported in low-flow venous or KTS-type combined malformations. The main complication of Parkes Weber syndrome and Stewart–Bluefarb syndrome (SBS) is an increase in cardiac output secondary to the A-VM, which can cause ischemia-induced skin ulceration and heart failure in the most severe cases.[37] Whether or not the vascular malformation involves the trunk, many patients with extensive vascular malformations in the limb present with pulmonary hypertension caused by recurrent pulmonary embolisms[38,39] or a proliferation of new vessels, possibly related to neoangiogenesis.

Patients with KTS and extensive venous malformations, including children, are known to be at significantly increased risk of pulmonary embolism.[38-40]

It has been suggested that recurrent or unresolved pulmonary embolism from vascular malformation related to hypercoagulability can lead to the development of chronic thromboembolic pulmonary hypertension (CTEPH) in patients with KTS[40] and extensive pure VMs.[38] Pulmonary hemodynamic progression is thought to be the consequence of a secondary arteriopathy in nonobstructed precapillary pulmonary vessels.

Pulmonary hypertension in KTS patients with no evidence of pulmonary thromboembolism has been attributed to hemodynamic changes from small vessel abnormalities, whereas CTEPH affects a large vessel. Although the pathogenetic mechanisms of pulmonary arterial hypertension (PAH) are unknown, pulmonary vascular changes of distinct origins lead to endothelial dysfunction and activation, producing an imbalance in vasoconstriction and smooth muscle cell proliferation, the main culprit of PAH.[41]

A preliminary study revealed that statistically significant PAH correlated with levels of D-dimer in patients with extensive VMs and KTS as compared to the respective healthy control populations.[42]

DIAGNOSIS: RADIOLOGY

Key points

- **The diagnosis of extensive vascular malformations is based on the patient's medical history and physical examination**
- **The work-up for patients who have extensive vascular malformations of the lower limbs should include echo Doppler and magnetic resonance imaging**
- **Multidetector computed tomography and 3-dimentional magnetic resonance venography are helpful in assessing the extent of the vascular malformation and verify the presence and patency of the deep venous system**
- **Indirect multidetector computed tomography provides better spatial resolution and shows bone density changes; indirect magnetic resonance is useful to evaluate and**

follow-up on the extent of the vascular malformation without ionizing radiation

- **Arteriography is the technique of choice to evaluate arteriovenous malformations**

The diagnosis of extensive vascular malformations is based on the patient's medical history and a physical examination, and biopsy speciemens are not routinely taken. Imaging studies are used when there is doubt about the nature of the lesion and serve as a complementary tool to clarify and confirm the diagnosis. They also facilitate analysis of the extent of lesions and assessment of the nonvisible component.

The evaluation of any therapeutic procedure in the lower limb requires the meticulous study of the deep venous system (DVS) by echo Doppler, angio-CT, angio-MRI, or phlebography.[43] Echo Doppler is usually the technique of choice and is often the only one needed. Ultrasound is a harmless noninvasive technique that does not involve exposure to ionizing radiation. In addition to anatomic information, echo Doppler also provides hemodynamic data, such as the velocity and direction of flow, which are of considerable value in both high-flow (arteriovenous) and low-flow (venous) malformations. In addition, it is an accessible and economical technique that is especially effective in children because patient cooperation is not a major issue. Nevertheless, aside from being an operator-dependent examination, it is sometimes difficult to obtain a clear evaluation of the lower half of the leg, and phlebography is then required.

Although invasive, venous angiography (phlebography) and arterial angiography (arteriography) are the methods of choice to study changed vascular dynamics. In ascending phlebography, radiographs are taken of the lower limb after iodine contrast is injected into a superficial vein on the dorsal surface of a foot. Different compression maneuvers enable examination of the presence and patency of the DVS. The technique is also useful to determine the anatomy of superficial veins, the state of the valves, the presence of embryonic veins, connections between superficial venous system and DVS, and the degree of venous incompetence. The disadvantages of phlebography include the possibility of allergic reactions and venous thrombosis caused by the use of iodine contrast. Arteriography, usually performed via the femoral artery, serves not only as a diagnostic test but also as the pathway for the embolization of malformations and arteriovenous fistulas.

MRI is the technique of choice to evaluate soft tissue, detect the extent and infiltration of VMs and lymphatic malformations, and determine the nature of hypertrophy (subcutaneous tissue, muscle, and/or bone), and it also yields information on the presence and extent of intraabdominal and pelvic vascular involvement.[44] MRI is a useful tool for delineating the extent of intraarticular lesions and predicting arthropathy. The main limitation of MRI is that it requires cooperation on the part of the patient, and sedation is necessary for claustrophobic patients and children. MRI is the most accurate imaging tool to show a VM because it shows a bright hyperintensity on spin-echo T2-weighted sequences with fat suppression.[45,46] MR images do not define afferent and efferent vessels, the nidus, patterns, or flow velocities with adequate precision. In two recent publications, our group showed that MDCT and 3-dimensional magnetic resonance (3D-MR) venography are extremely helpful to assess the musculoskeletal extent of the malformation, characterize bone density changes, study limb dissymmetry and thoracic or abdominopelvic involvement, and verify the presence and patency of the DVS.[26,47] Radiation exposure is the main drawback of MDCT venography. A further limitation of direct MDCT and 3D-MR venography is that the contrast administered during the procedure may not be sufficient to fill the entire DVS.[48] Indirect magnetic resonance venography provides precise volumetric delineation of the extent of vascular malformations and drainage pathways while depicting the anatomy and patency of DVS, thereby enabling appropriate therapeutic planning, as with indirect MDCT venography. Considering the young age of patients with extensive vascular malformations and the need for sequential follow-up studies, we firmly believe that indirect magnetic resonance venography is now the most suitable imaging technique, although the spatial resolution is lower in comparison to indirect MDCT venography (Fig 1).[49]

Lymphoscintigraphy with Tc-99–labeled antimony sulfur and conventional direct lymphography have been the preferred imaging modalities to assess the lymphatic system in patients with vascular malformations, specifically KTS.[50] Magnetic resonance lymphangiography now represents a safe noninvasive imaging modality for assessing the involvement of the lymphatic system in these patients.[51]

DIAGNOSIS: MISCELLANEOUS

Key points

- **In order to predict a future limb length discrepancy, a Doppler examination of arterial blood flow should be conducted in children >1 year of age with extensive vascular malformations of the lower limb**

- **Annual plain radiography of the limbs is recommended after 2 years of age**
- **A scoring system is useful to avoid misdiagnosis of Klippel–Trénaunay syndrome with Proteus syndrome**
- **Young patients with localized kaposiform lesions in the lower limbs should be examined for underlying arteriovenous malformations**
- **All patients with extensive slow-flow vascular malformations should be referred for a echocardiogram study to exclude the presence of pulmonary arterial hypertension**
- **D-dimer and fibrinogen levels must be measured as part of the medical evaluation of vascular malformations**

Future pelvic tilting and scoliosis could be observed in a few patients with extensive vascular malformations of the lower limb. In order to prevent it, a Doppler examination should be included in the management of children >1 year of age with KTS, even when no LLD is present at first examination. A significant arterial blood flow difference ($\geq 50\%$) between the limbs may predict a future LLD, and indicates a close follow-up of the child.[52] Plain radiography (scanograms) allows us to measure the length of the limb and detect any discrepancy with its collateral limb. It is not usually necessary to perform radiographs before 2 to 3 years of age or after skeletal maturity is reached, because LLDs do not progress after physeal cartilage closure. Annual clinical and radiologic measurements are recommended after 2 years of age.

In patients with combined malformations, other syndromic anomalies should be discounted. The scoring system of Hotamisligil[53] is useful to avoid misdiagnosis of KTS with Proteus syndrome. The Hotamisligil rating scale assesses macrodactyly and/or hemihypertrophy (5 points); plantar or palmar cerebriform hyperplasia (4 points); lipoma/subcutaneous tumor (4 points); epidermal nevus (3 points); macrocephaly and/or skull exostoses (2.5 points); and other minor abnormalities (1 point). The maximum score is 19.5 points, and scores <10 are considered to rule out a diagnosis of Proteus syndrome.

An extensive vascular malformation may have cardiac compromise, especially those with high flow. All patients with localized kaposiform lesions, especially those <30 years of age, should be examined for underlying A-VM (SBS) in order to avoid future amputation.[54]

The prevention or at least early detection of CTEPH in patients with VMs appears to be mandatory. PAH is a serious process that leads to right ventricular insufficiency and can cause death. All patients with extensive slow-flow vascular malformations should be referred for an echocardiogram study to exclude the presence of PAH.

Endoscopic study of the entire gastrointestinal tract should be routine clinical practice in blue rubber bleb nevus syndrome and KTS patients for the accurate localization and effective management of gastrointestinal bleeding. Cystoscopy is also indicated in case of urethral bleeding.

Elevated D-dimer levels are highly specific for VMs. An elevated D-dimer level can help diagnose the presence of a venous component in combined and syndromic malformations.[55] In these patients, fibrinogen levels are usually low (<0.5 g/L), D-dimer levels are high, a soluble fibrin complex is detected, and platelet counts are normal or slightly reduced. D-dimer and fibrinogen levels must be measured as part of the medical evaluation of vascular malformations.

TREATMENT

The management of vascular malformations is complex and involves prediction of the disease based on genetic evaluation; diagnostic studies tailored to the planned therapy; prevention of vascular, orthopedic, hematologic, and systemic complications; and the treatment of clinical manifestations to improve the quality of life and, as far as possible, the appearance of patients. Because of the complex nature of extensive vascular malformations of the lower limb, patients are best initially treated in a center with an experienced multidisciplinary team (Fig 3).

Venous disease is a major source of morbidity in patients with KTS.[56] A recent article described the nine most frequent causes of pain in patients with KTS,[57] pointing out that chronic venous insufficiency accentuates and predisposes to other causes of pain. Therefore, controlling venous insufficiency and improving venous drainage may reduce pain from a variety of causes.

Compression and physical measures

Key points

- **The day-to-day management of low-flow vascular malformations requires the use of compression stockings**

The day-to-day nonsurgical management of low-flow vascular malformations requires elevation of the affected limb, the use of compression stockings, and the cure of ulcers to prevent infections. Patients with extensive slow-flow VMs of the limb should be instructed from childhood in the proper use of

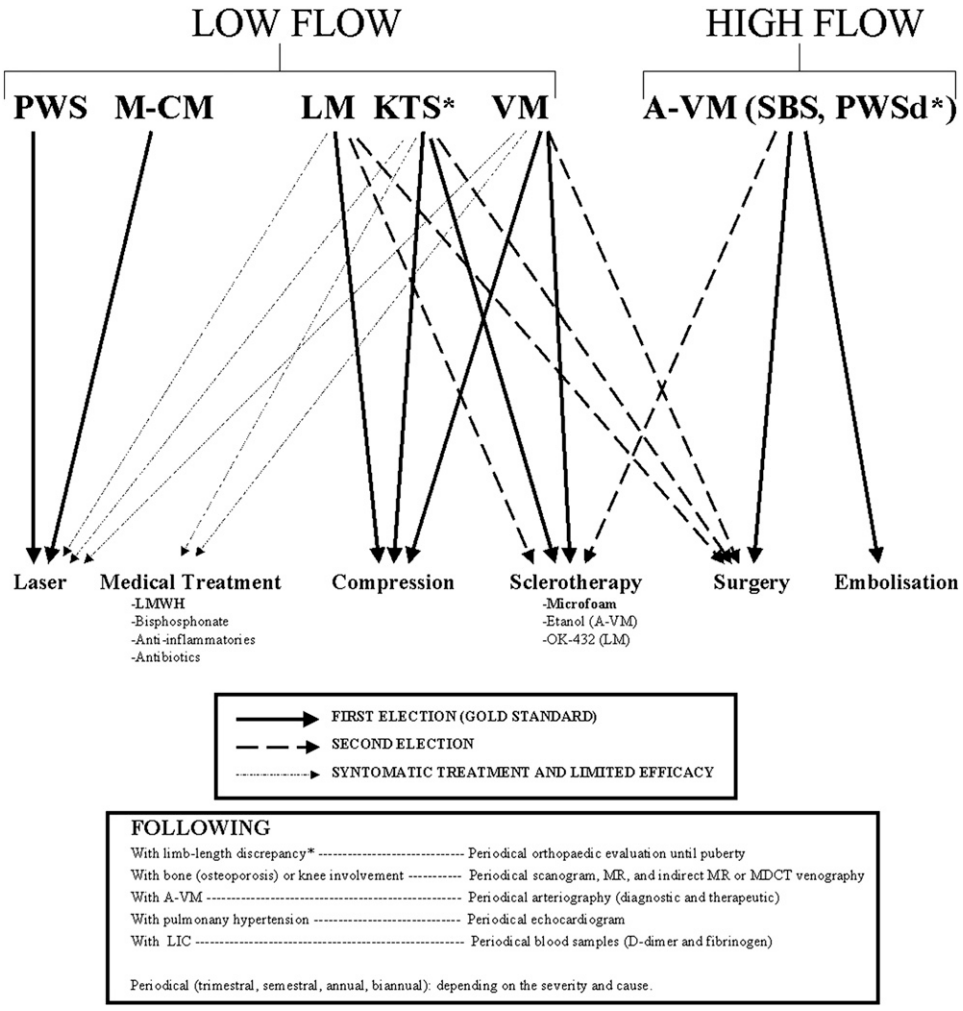

Fig 3. Algorithm for management of established patients with extensive vascular malformations in the lower limb. *A-VM*, Arteriovenous malformation; *CMTC*, cutis marmorata telangiectasica congenita; *DVS*, deep venous system; *G-VM*, glomuvenous malformation; *KTS*: Klippel–Trénaunay syndrome; *LIC*, localized intravascular coagulation; *LM*, lymphatic malformation; *M-CM*, macrocephaly-capillary malformation; *MDCT*, multidetector computed tomography; *MR*, magnetic resonance; *PWS*, port-wine stain; *PWSd*, Parkes Weber syndrome; *SBS*, Stewart–Bluefarb syndrome; *VM*, venous malformation.

compression garments. Compression helps decrease discomfort associated with the lesions, protects the overlying skin, limits swelling, and improves LIC (by reducing transmural pressure, minimizing blood stasis, and local coagulation activation).[58,59] Moreover, if a compression bandage or stocking is not used, some patients develop orthostatic hypotension secondary to the local accumulation of blood in the affected limb. Any type of stocking or compressive dressing is contraindicated in patients with glomuvenous malformations.[60] Most patients with extensive high-flow vascular malformations of the limb (Parkes Weber syndrome and SBS) are managed by nonoperative means, including the use of external compression garments and wound dressing.

The first treatment for patients with lymphedema is symptomatic, using decongestive physiotherapy, which includes manual lymphatic drainage and compression bandage combined with a physical exercise protocol and pneumatic compression garments (50-60 mm Hg),[61] although these procedures are not recommended in children because of their low tolerance. Other essential measures include skin care to prevent infections and a dietary regimen to control weight.

Medical treatment

Key points

- **The administration of low molecular weight heparin in patients with localized intravascular coagulation and the clinical presence**

of phleboliths improves their symptoms and their analytical parameters (D-dimer and fibrinogen), reducing the risk of thrombosis

The sporadic use of analgesics and nonsteroidal antiinflammatory drugs is effective to control malformation-related muscle pain or discomfort related to articular involvement, although the treatment of these patients should be directed against the cause of the pain rather than being merely symptomatic, as noted below.

Prophylactic antibiotherapy is necessary for patients with repeated cellulitis before surgery or for those with persistent ulcers after bacteriologic culture and antibiogram. The hemostatic control of coagulation activation within a VM has two objectives: (1) to relieve local pain and (2) to prevent hemorrhagic complications. The continuous or periodic subcutaneous administration of LMWH in patients with LIC and clinical presence of phleboliths can improve their symptoms (pain relief) and their analytic parameters (a reduction in D-dimer and normalization of fibrinogen levels), reducing the risk of thrombosis.[35,62] Antiplatelet agents, such as aspirin or ticlopidine, have proven to be of little or no clinical benefit in patients with VM-associated LIC.

With regard to osteoporosis, it is highly unlikely that a sufficient number of patients with extensive vascular malformations of the limb could be enrolled to perform a randomized clinical trial. However, based on the available clinical evidence, the treatment of choice for preventing or treating regional osteoporosis is oral bisphosphonate alendronate (70 mg/wk) or risedronate sodium (35 mg/wk).[63] In patients with severe osteoporosis or pathologic fracture, a course of teriparatide (recombinant parathyroid hormone fragment) is recommended for at least 2 years.[64]

Laser

Key points

- **Pulsed dye laser treatment is currently the first-line treatment for port-wine stain**

Pulsed dye laser treatment targeting intravascular hemoglobin with selective photothermolysis is currently the first-line treatment for port-wine stain (PWS). Pulsed dye (at 585-600 nm), KTP (532 nm), long-pulsed Alexandrite (755 nm), diode (800-930 nm), and long-pulsed neodymium-doped yttrium aluminium garnet (Nd:YAG; 1064 nm) lasers are effective to eliminate the lesions in some patients, generally after several treatment sessions.[65,66] When the lesions are asymptomatic (no hypertrophy or bleeding) and only have cosmetic impact, treatment is sometimes unnecessary. At any rate, the response to laser treatment is usually worse in lesions of acral localization than in facial lesions, possibly because of the effect of gravity on capillary pressure. As at the cephalic pole, it is difficult to achieve the complete disappearance of the PWS, which requires multiple sessions for the treatment and will then need follow-up sessions, given the natural tendency to recur over time.

Laser treatment of vascular malformations is limited to very superficial lesions or the superficial component of deeper lesions as an adjuvant to treatment with other techniques (eg, sclerotherapy). The laser system most often used is a continuous Nd:YAG laser, which delivers infrared light at 1064 nm and has a skin penetration depth of between 5 and 7 mm. The superficial component of a lymphatic malformation can be treated with continuous-wave and ultrapulse CO_2 and Nd:YAG lasers.[67]

Orthopedic surgery

Key points

- **Stapling epiphysiodesis of the knee cartilages is indicated to delay growth of the lower limb**
- **Synovectomy is protective in the initial phases of the knee arthropathy**

Patients with LLD require traumatologic assessment before their correction, avoiding repercussions on the vertebral column cord. Orthopedic procedures are applied to halt abnormal limb growth (by the implantation of staples or other minimally invasive procedures to temporarily block specific cartilage growth) or to elongate (the Ilizarov technique) or shorten (osteotomy) the bone.[68] In KTS patients, endoscopic epiphysiodesis at distal femoral level is indicated to detain growth of the longer limb when the LLD is >2 cm. Generally, the most suitable age for this intervention is around 11 years. Although epiphysiodesis of the cartilages can correct the discrepancy, it can also worsen the progression of the A-VM; therefore, a more conservative approach is recommended in some cases.[69] Feet with severe hypertrophy or highly deformed toes may require partial resection or Syme amputation. It is rarely necessary to perform a complete amputation of a limb.

Treatment options for fractures related to a vascular malformation are complex. Internal fixation is possible when bleeding can be controlled. When internal fixation is hindered by extensive or diffuse vascular malformations, or when the general

condition of the patient is poor, a cast or external fixation offers an alternative. Bony union is slow but may be accelerated by the injection of bone marrow.[17,70]

The current approach for knee arthropathy is to perform a synovectomy when patients develop symptoms and have a demonstrable intraarticular VM on MRI, although some authors have proposed its prophylactic application in patients with asymptomatic intraarticular VM.[71] Indications for total knee arthroplasty with a cemented, posterior stabilized implant in extensive vascular malformations are intrusive pain, limitation of activity, and lifestyle impairment.[72,73]

Vascular surgery

Key points

- **Drawback of a high recurrence rate after surgery of slow-flow vascular malformations**
- **Surgery may play an essential role in the treatment of patients with high-flow vascular malformations immediately after embolization**

Classic surgical excision of the varicose veins has been indicated in the treatment of large VMs or combined malformations of lower limb after testing the patency of the DVS, although several much less invasive techniques have emerged as effective and frequently durable alternatives over the past 2 decades. Some patients can benefit from the partial excision of VMs or lymphatic malformations, although the invasive growth of proximal structures limits the possibility of complete excision.[74,75] Lesions occasionally recur after several surgical interventions leaving patients close to their original condition, which can have a major negative impact on their state of mind.[68] Glomuvenous malformations are more superficial and theoretically easier to treat with surgery, while sclerotherapy appears to be less effective in these patients than in those with VMs.[60]

An additional surgical option in lymphedema is partial ablative excision of all tissue between the skin and fascia[76] to remove areas of dermatofibroliposclerosis that form folds of difficult access and hygiene, favoring local overinfection and cellulitis episodes. A more natural shape of the limb is achieved by this procedure, permitting decongestive physiotherapy. Reconstructive microsurgery can be performed in some cases of lymphedema by means of venolymphatic anastomosis[77] or the autotransplantation of lymph nodes.[78]

The aim of surgery in A-VM is to eradicate their nidus. Surgery is often very hemorrhagic and ineffective in these cases because of the rapid recruitment of collateral vessels to supply the nidus. Previous embolization facilitates surgery and reduces bleeding. Surgery may therefore play an essential role in the treatment of patients with high-flow vascular malformations, in some cases immediately after embolizations and in others in a direct manner with the skeletonization of the normal vein and the meticulous ligation of all arteriovenous fistulae.[79,80] When intense hemorrhage, refractory pain, recurrent infection, necrosis, physical deformity, and cardiac decompensation are present, partial amputation of the affected limb may be necessary.

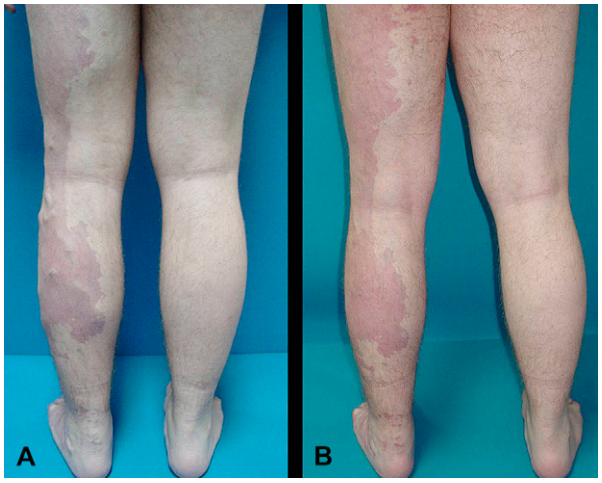

Fig 4. A, A 16-year-old boy with simple Klippel–Trénaunay syndrome. The diffuse port-wine stain and marginal embryonic vein can be seen. **B**, After 7 sessions of sclerotherapy with polidocanol microfoam. Note the absence of marginal vein and the persistence of the port-wine stain.

KTS patients with life-threatening bleeding episodes require resection of the diseased bowel, performing preoperative angiography to define the anatomy and extent of intestinal involvement.[81] When hematuria in these patients is recurrent and potentially life-threatening, subtotal cystectomy and enterocystplasty appears to be the treatment of choice.[82]

Sclerotherapy

Key points

- **Polidocanol microfoam sclerotherapy may be the treatment of choice for low-flow venous malformations and Klippel–Trénaunay syndrome**

Sclerosants produce chemical irritation on vascular endotelial cells with subsequent occlusion of treated veins by fibrosis. Conventional liquid sclerotherapy offers good outcomes in small VMs but is

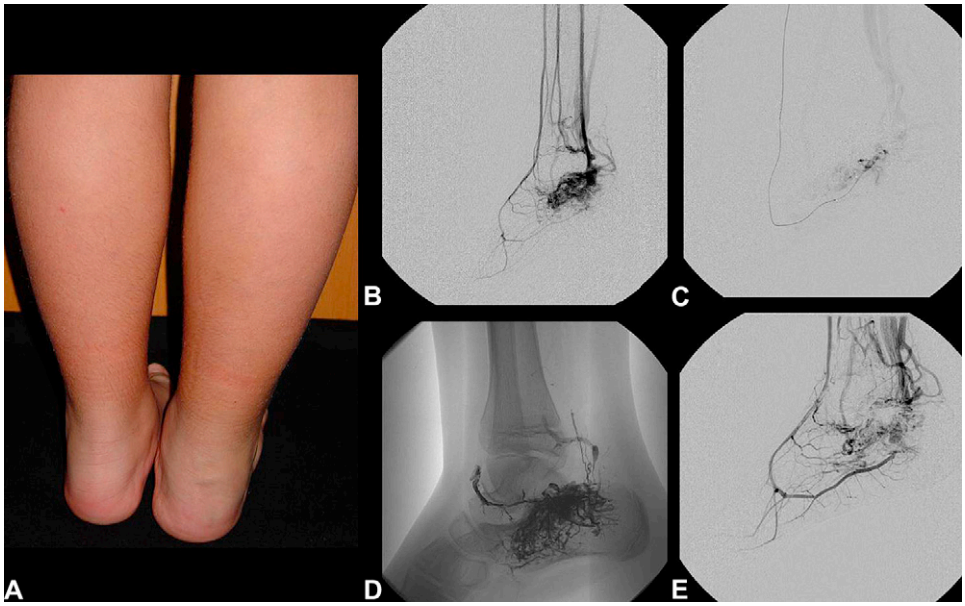

Fig 5. **A**, A 13-year-old girl with an arteriovenous malformation of the left leg. Angiography of the intraosseus arteriovenous malformation (**B**) treated by superselective embolization with onyx (**C**) forming a cast (**D**) resulting in significant decrease of the lesion (**E**) with significant clinical improvement.

ineffective in large VMs because of the intrinsic limitations of injected liquids. Sclerotherapy with ethanol, the most widely used agent for these lesions, is highly aggressive and is associated with major complications.[83-85]

In contrast, sclerosants in microfoam form do not mix with the blood but rather physically displace it, minimizing dilution of the sclerosant and obtaining a higher intravenous concentration. The foam also distributes the sclerosant more homogeneously on the endothelial surface and prolongs the contact between sclerosant and endothelium, while the echogenicity of the microbubbles means that they can be visualized.[86,87] Foamed sclerosants are typically produced by cyclical mechanical agitation of the liquid agent in the presence of a gas to generate the froth used for intravascular injection. This is commonly achieved by hand using room air as the gas and rapid manual displacement of the mixture between two syringes joined by a stopcock (or between a syringe and a drug vial) to manufacture "home made" foam.[87] The microfoam is made with CO_2, a physiologic gas whose intravenous injection is used as a contrast for radiographic diagnosis.[88,89] In particular, the bubble size is appreciably smaller than that resulting from manual foam production techniques, and the absence of nitrogen facilitates more rapid absorption of bubbles within the body. Both these considerations are important to safety profile, given the potential for gas embolism to occur with any type of foam sclerosant therapy.[90-92]

Based on our previous results and subsequent reports, we consider polidocanol microfoam sclerotherapy to be the treatment of choice for the low-flow vascular malformations present in KTS (Fig 4).[93-98]

In the treatment of the lymphatic component of some combined malformations, some macrocystic lesions benefit from lymph aspiration and the injection of sclerosants, including OK-432, ethanol, or the above-described microfoam sclerosants, which may be of great value before surgery. OK-432 (picibanil; Chugay Pharmaceutical, Tokyo, Japan) is a preparation of dead bacteria obtained by culture of *Streptococcus pyogenes* (group A, type III) of human origin with penicillin G benzathine. Different published studies reported the complete resolution of cystic hygroma in almost 90% of patients treated with OK-432.[99,100]

Interventionist radiology

Key points

- **The most common combinations in high-flow vascular malformations includes surgery, catheter embolization, and ethanol sclerotherapy**

There have been anecdotal reports on interventional radiologic treatment using embolization with coils and endovascular radiofrequency ablation of venous insufficiency in some low-flow vascular malformations.[101,102] Angiographic supraselective

embolization and local clips can also control active rectal bleeding in KTS patients.[103] Recalcitrant gross hematuria from urethral, bladder, and upper tract can be safely managed by endoscopic and angiographic techniques, saving the patient from the more aggressive and moribund open surgical approach.

Progress in the management of A-VM has been significant because of developments of microcatheters and embolic agents. The most important materials for embolization include mechanical agents (stainles steel or platinum coils), particulate agents (gelfoam, polyvinyl alcohol particles 100-500 μm in size, spherical embolics, or absorbable gelatin pledgets), and liquid agents (cyanoacrylate or onyx). Coils occlude medium to small arteries; liquid agents and the smaller-diameter particles occlude at the arteriolar level or the capillary bed.

Treatment of arteriovenous shunts by superselective embolization[104,105] or surgical ligation can have a successful long-term outcome (Fig 5). However, both approaches carry a high risk of necrosis or ischemia, and there is a relatively high risk of developing new arteriovenous fistulas. Embolization is not risk-free and should be carried out by an interventional radiologist who is familiar with the technique. All embolic materials used must be applied under fluoroscopic guidance.

THE FUTURE

Key points

- **Antiangiogenic drugs could have specific targets in some vascular malformations, especially in those with high flow and aggressive growth**

The pathogenesis of vascular malformations has not been fully elucidated, but their formation and progression are closely related to angiogenesis.[106-108] Angiogenesis is a highly complex network closely regulated by numerous angiogenic factors. Various pathways control integral events that contribute to the formation of a functional vasculature, including endothelial and mural cell differentiation, cell proliferation and migration, and the specification of arterial, venous, and lymphatic fate. Angiopoietin-1 (Ang-1) and Ang-2 are reported to be the most potent regulators of neovascularization. Ang-2 is a ligand of the endothelial receptor tyrosine kinase Tie-2, which acts as a critical regulator of vessel stabilization and maturation. Our group observed elevated levels of Ang-2, Tie-2, and other angiogenic factors in 31 patients with extensive vascular malformations.[109]

Future hopes for the treatment of extensive vascular malformations, especially in active malformations in growth phase, lie in antiangiogenic and specifically antilymphangiogenic drugs.[110] More frequently used in oncology, these drugs could have specific targets in some vascular malformations, especially in those with high flow and aggressive growth.

Extensive vascular malformations are often more complex than they appear, and they require a multidisciplinary therapeutic approach. A comprehensive examination and ancillary studies should be considered in patients with extensive vascular malformations of the lower limb. Advances in diagnosis (MDCT venography and magnetic resonance venography) and treatment (microfoam sclerotherapy) are extremely helpful. One should also be cognizant of the suggested relationship of systemic repercussions associated with these vascular malformations.

We thank Alejandro Sierra and Juan Cabrera for their invaluable help in the evaluation and treatment of the patients.

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Answers to CME examination

Identification No. JB1111

November 2011 issue of the Journal of the American Academy of Dermatology.

Questions 1 and 2, Redondo P, Aguado L, Martínez-Cuesta A. J Am Acad Dermatol 2011;65:909-23.

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