Actas Dermosifiliogr. 2007;98:219-35

REVIEW ARTICLE

# Vascular malformations (II). Diagnosis, Pathology, and Treatment

**P Redondo**
Departamento de Dermatología, Clínica Universitaria de Navarra, Spain

Abstract. Diagnosis of vascular malformations is essentially clinical, based on the evolution and morphology of lesions. A biopsy is rarely needed to evaluate the nature of the vessels. Imaging examinations are necessary to assess the extension of malformations as well as the osteomuscular and visceral compromise. New techniques such as 3D angio-CT scan and angio-MRI improve the diagnosis of some vascular malformations, especially the large combined ones such as Klippel-Trénaunay syndrome, thus limiting the need for invasive procedures. On the other hand, the advances in laser technology, particularly pulsed dye laser for port-wine stains and Nd:YAG laser for superficial venous malformations constitute new alternatives for the management of these patients. Other emergent treatments include microfoam sclerotherapy for venous and combined, slow-flow malformations, and new embolizing materials associated to surgery for arteriovenous malformations. The second part of this review is focused on the complementary diagnosis (imaging exams, pathology and accessory tests) and multidisciplinary and specific treatment based on the different groups.

Key words: angio–CT scan, angio-MRI, pulsed dye laser, microfoam sclerotherapy, embolization, surgery.

## MALFORMACIONES VASCULARES (II). DIAGNÓSTICO, HISTOPATOLOGÍA Y TRATAMIENTO

Resumen. El diagnóstico de las malformaciones vasculares es fundamentalmente clínico, y está basado en la evolución y morfología de las lesiones, siendo necesaria en muy raras ocasiones la realización de una biopsia para valorar histológicamente la naturaleza de los vasos. Para delimitar la extensión de las malformaciones, así como el compromiso músculo-esquelético y visceral, son necesarias las pruebas de imagen. La incorporación de nuevas técnicas como la angio-tomografía computarizada (TC) o la angio-resonancia magnética (RM) en 3D agilizan el diagnóstico de algunas malformaciones vasculares, especialmente las combinadas extensas tipo síndrome de Klippel-Trenaunay, limitando la necesidad de procedimientos invasivos. Por otra parte, los avances en tecnología láser, concretamente el láser de colorante pulsado para la mancha en vino de Oporto y el láser de Nd:YAG para las malformaciones venosas superficiales, la escleroterapia con microespuma en las malformaciones venosas y combinadas de bajo flujo, y los nuevos materiales embolizantes asociados con la cirugía en malformaciones arteriovenosas, son terapias emergentes para el seguimiento de los pacientes. La segunda parte de esta revisión está enfocada al diagnóstico complementario (pruebas de imagen, histología y pruebas accesorias) y al tratamiento multidisciplinar y específico según los diferentes grupos.

Palabras clave: angio-TC, angio-RM, láser de colorante pulsado, esclerosante en microespuma, embolización, cirugía.

## Diagnostic Imaging

The diagnosis of cutaneous vascular malformations is based on the patient's medical history and a physical examination.[1-4] Imaging studies are used when there is doubt about the nature of the lesion and serve as a complementary tool used to clarify and confirm diagnosis. They also facilitate analysis of the extent of lesions and assessment of the nonvisible component. In certain situations, imaging techniques not only determine the optimum therapeutic approach but also form an integral part of treatment when this involves the application of embolic or sclerosing agents.

Plain radiography has today clearly been surpassed by other imaging techniques and is of only limited value even in demonstrating the degree of bone involvement and the presence of calcifications. Computed tomography (CT) is

Correspondence:
Pedro Redondo
Departamento de Dermatología. Clínica Universitaria de Navarra
Avda. Pío XII, s/n. Pamplona, Spain.
predondo@unav.es

Manuscript accepted for publication February 9, 2007.

a much more sensitive tool for these purposes and provides much more precise anatomic information.

Conventional radiography can be used to reveal the presence of phleboliths in venous malformations and to detect the rare calcifications that occasionally occur in some lymphatic malformations.[5,6] While venous and arteriovenous malformations are not visible as such on a plain radiograph, their repercussions on adjacent bone structures are visible (for example, asymmetric hypertrophy or atrophy, osteoporosis, or lytic lesions).[7-9]

In addition to anatomic information, Doppler ultrasound also provides hemodynamic data, such as the velocity and direction of flow, a contribution of considerable value in both high flow (arteriovenous) and low flow (venous) malformations.[10-12] Ultrasound is a harmless noninvasive technique that does not involve exposure to ionizing radiation. Moreover it is very accessible, economical, and particularly effective in children because it does not require a great deal of cooperation on the part of the patient.

The principal limitation of ultrasound is that it is an operator-dependent technique, making good reproducibility difficult to achieve. Venous malformations are hypoechoic and their appearance is similar to that of cysts, although a Doppler system, unlike the techniques discussed above, will demonstrate venous flow, particularly when compression maneuvers have been carried out. Lymphatic macrocystic malformations appear as hypoechoic or anechoic multiloculated masses with septa of varying thickness. In the case of arteriovenous malformations, the role of Doppler ultrasound is restricted to confirming the vascular nature of the lesion, which will present both arterial and venous waves.

The definition of soft tissues obtained with CT is better than that of conventional plain radiography but far inferior to that obtained with magnetic resonance imaging (MRI). The great advantage of MRI is its excellent demonstration of bone structures and calcifications, while one of the disadvantages of this technique is that it is based on the use of ionizing radiation and that a contrast media is nearly always necessary. These media are associated with risks because of their nephrotoxicity and the adverse reactions they may cause. In addition, sedation is necessary in pediatric patients because image quality is impaired by movement.[13-16]

MRI provides excellent tissue differentiation and this, together with its capacity to acquire images in multiple spatial planes, makes it the best radiologic technique for demonstrating anatomic relationships and studying the tissue adjacent to the vascular malformation. MRI provides both anatomic and hemodynamic data. The presence of a fast or turbulent flow decreases the intensity of the signal, and when the flow is slow or thrombosis is present, the intensity of the signal increases.[17-19] Like ultrasound, MRI does not use ionizing radiation, so that it is of great use not only in diagnosis but also for monitoring disease progression and for post-treatment follow-up. The gadolinium used as a contrast media is extremely safe and does not in general provoke any clinically significant side effects, although in patients with nephropathy a possible pathogenic relationship has been shown with fibrosing dermopathy.

The chief limitation of MRI is that it requires cooperation on the part of the patient and sedation is necessary in claustrophobic patients and children. The use of scanners with open architecture can reduce this problem, although these devices usually have a lower magnetic field strength, a characteristic that affects the quality of the image and the scan duration when multiple sequences are required.

MRI is the technique of choice for initial assessment of venous malformations because it is noninvasive and can define the complete extension of the lesion on various anatomic planes.[20,21] These malformations produce a lower signal intensity than adjacent fatty tissue in T1-weighted sequences and a higher signal intensity in T2-weighted images.

In the case of lymphatic malformations, MRI can enhance the contrast between the lesion and adjacent tissue and delineate this border anatomically.[20,21] In T1-weighted sequences, the intensity of the signal is similar or slightly lower than that produced by muscle, while in T2-weighted sequences there is a marked increase in the signal, which is of even higher intensity than that of adjacent fat and muscle.

Phlebography is indicated in the case of low-flow or venous malformations.[22] Phlebography by direct puncture of the malformation complemented by the use of tourniquets to redirect blood flow facilitates anatomical delimitation of the extension and components of the malformation as well as assessment of the volume of the venous compartments. Traditionally, phlebography has been the procedure of choice for studying the deep venous system and its patency in the limbs of patients with large venous malformations or the combined malformations of the Klippel-Trenaunay syndrome.

As mentioned earlier, in the study of arteriovenous malformations MRI images do not define afferent and efferent vessels, the nidus, patterns, or flow velocities with sufficient precision. Consequently, despite advances in 3-dimensional MRI technology, angiography remains the procedure of choice for evaluating the angioarchitecture of these lesions. It is, therefore, an indispensable prior requisite for embolization treatment and, in this context, can play a therapeutic as well as a diagnostic role.

Today, new MRI and multi-ring CT scanners can acquire images with great speed and produce high quality multiplanar reconstructions and noninvasive angiographic studies.[13,23] We recently studied 16 patients with Klippel-Trenaunay syndrome using multidetector CT venography and 3-

dimensional MRI venography by way of conventional axial images, multiplanar reconstructions, maximum intensity projections, and 3-dimensional images (Figures 1-3). The conventional axial images were useful for assessing bone and soft tissues and allowed us to locate both the deep venous system and anomalous superficial vessels and determine their relationship to adjacent structures. The axial images, multiplanar reconstructions, and maximum intensity projections were used to define the origin, trajectory, and extension of the venous malformations. Skin surface images were useful for assessing the location and extension of the port-wine stain and for demonstrating limb hypertrophy. The 3-dimensional reconstructions demonstrated varicose veins and the origin and trajectory of the anomalous vessels (Figures 4 and 5). No complementary invasive technique (conventional phlebography) was required to confirm diagnosis or facilitate therapeutic planning in any of these patients.[24]

Thus, we can conclude that CT venography—or a 3-dimensional MRI venograph in children and pregnant women to limit radiation—can be the procedure of choice for a comprehensive study of a large vascular malformation located on a limb. These techniques can pinpoint the exact location of the lesion on a 3-dimensional plane, detect muscular skeletal infiltration and thoracic or abdominopelvic involvement, characterize bone density changes (osteoporosis) and asymmetries, and verify the existence of a deep venous system while assessing its patency (Figures 6-9). They are also useful for detecting abnormalities in the superficial venous system, demonstrating the presence of sciatic or abnormal veins, and determining the extension and drainage of the malformation. Although these procedures are still not as good as conventional angiography and venography in that they do not provide as much information concerning the hemodynamics of the malformation, they nonetheless represent a very significant advance. In our experience, invasive complementary procedures are only necessary in patients with vascular hypoplasia when the hemodynamic function of the vessel is unclear.[24,25]

Specifically, an MRI of the spine should be performed in the case of vascular malformations located along the midline of the back, particularly the lumbar sacral region, in order to detect defects in neural tube closure at various levels. Likewise, in the case of facial port-wine stains and suspected Sturge-Weber syndrome, a brain MRI scan is required to assess possible neurological involvement.[26]

## Pathological Study

The diagnosis of a vascular malformation is primarily clinical, and histopathologic examination of the lesion is rarely

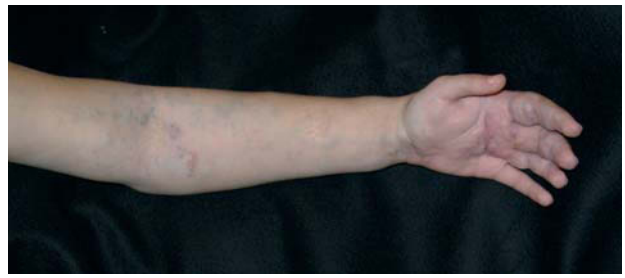

**Figure 1.** Sixteen-year-old girl with large, predominantly distal, venous malformation in the left arm.

**Figure 2.** Computed tomography angiography shows the correlation between the superficial veins and the clinical situation.

**Figure 3.** A detailed view of the computed tomography angiogram shows the relationship between the veins and internal structures.

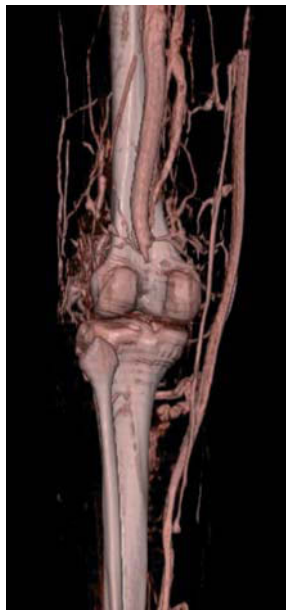

**Figure 4.** Agenesis of the popliteal vein in a patient with Klippel-Trénaunay syndrome.

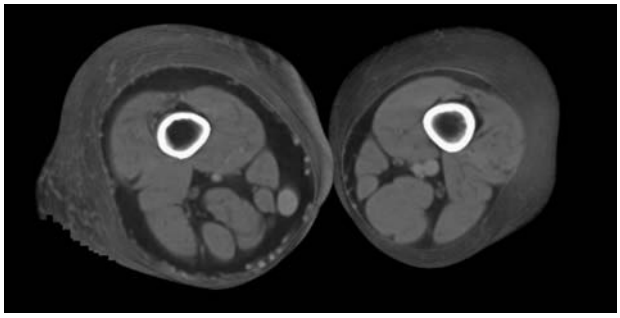

**Figure 5.** Musculoskeletal hypertrophy and hypoplasia of the superficial femoral vein in a patient with Klippel-Trénaunay syndrome.

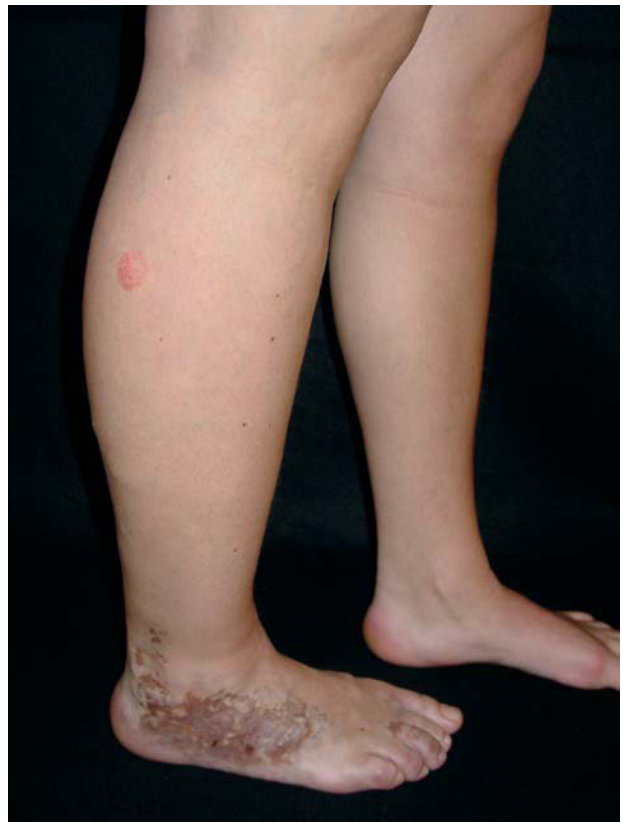

**Figure 6.** Dilation of varicose veins, particularly visible in the ankle, associated with ulcer-related pigmentary changes and hypertrophy of the limb in a patient with Klippel-Trénaunay syndrome.

needed. As mentioned above, there may be diagnostic doubt in the case of vascular tumors, such as noninvoluting congenital hemangiomas. Although extremely rare, these tumors can be confused with certain types of vascular malformations because they evolve along similar lines. Where such doubt exists, a pathological examination should be performed.

Histologically, a port-wine stain is characterized by the presence of dilated thin-walled capillaries and venules, usually located in the superficial reticular dermis although subcutaneous cellular tissue may occasionally be affected. In venular malformations, as in other vascular proliferations, high densities of mast cells have been observed,[27] but the significance of this finding is poorly understood.

Venous malformations are composed of ectatic vessels of varying sizes located in the deep dermis and subcutaneous cellular tissue. While some of these vessels are thin walled, others have a thick muscular layer.

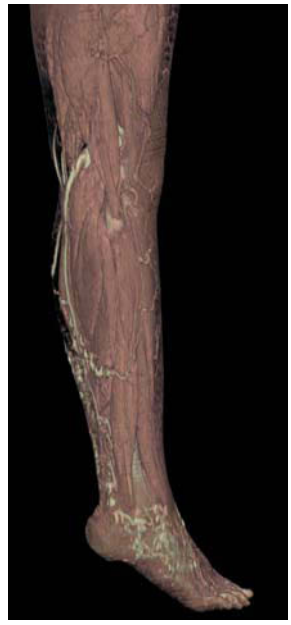

**Figure 7.** Computed tomography angiography provides a 3-dimensional view of the relationship between veins and muscle tissue.

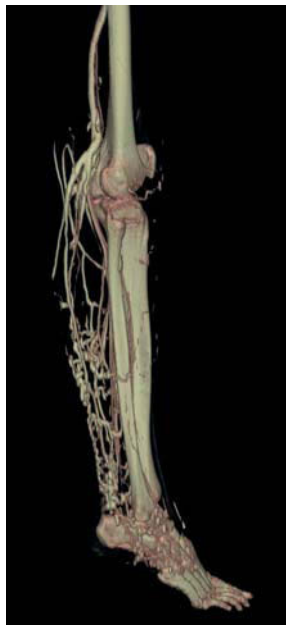

**Figure 8.** After soft tissue is removed from the computed tomography angiogram, anomalous veins in the calf and ankle area stand out on the osseous plane (side view).

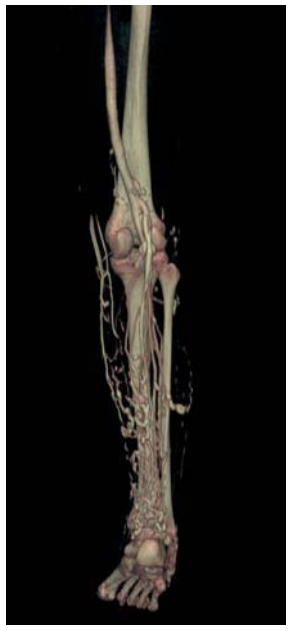

**Figure 9.** Detail of the previous figure (back view).

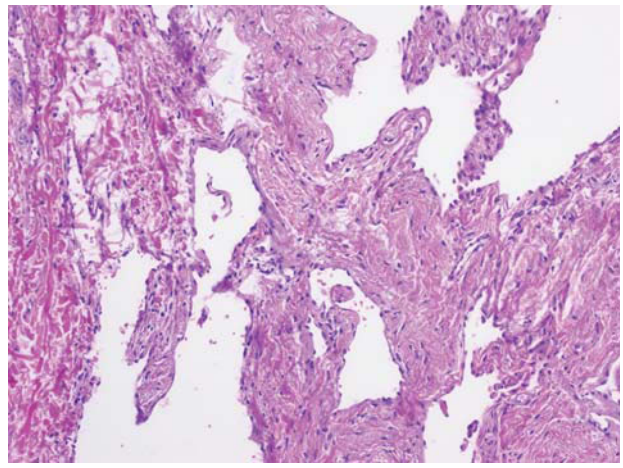

**Figure 10.** Thin-walled ectatic vessels of a venous malformation in the deep dermis. Hematoxylin-eosin, ×100.

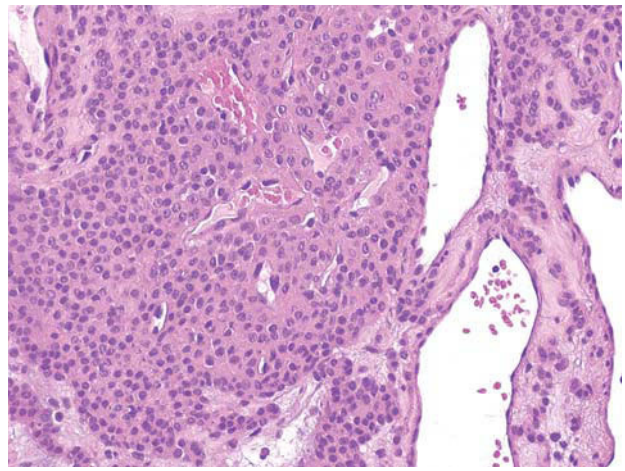

**Figure 11.** Glomuvenous malformation. Vascular lesion characterized by venous channels connected by rows of glomus cells. Hematoxylin-eosin, ×200.

Thrombosis and phleboliths are common, as are areas of hemorrhage with hemosiderin deposits and extravascular calcifications (Figure 10).

Glomuvenous malformations are composed of irregular vascular channels covered by layers of endothelial cells and filled with red blood cells. The thick walls of these vascular structures contain glomus cells, which may clump together and form rows in the stroma of the lesion (Figure 11). A contiguous pattern of dermal nodules resembling an hourglass often appears. These glomus cells were initially thought to be pericytes, but were later found to be modified smooth muscle cells that express the markers vimentin, muscle-specific actin, and α-smooth-muscle actin.[28]

In young patients, arteriovenous malformations demonstrate only elevated numbers of capillaries, venules, and arterioles arranged loosely on fibromyxomatous tissue devoid of any large caliber vessels. However, enlarged veins and tortuous arteries develop over time. Veins become arterialized as a result of the increased pressure caused by arterial shunting. Although they occur millions of times in large lesions, these arteriovenous shunts are difficult to detect in a pathological study (Figure 12), unlike the single arteriovenous fistula caused by surgery or injury.[29]

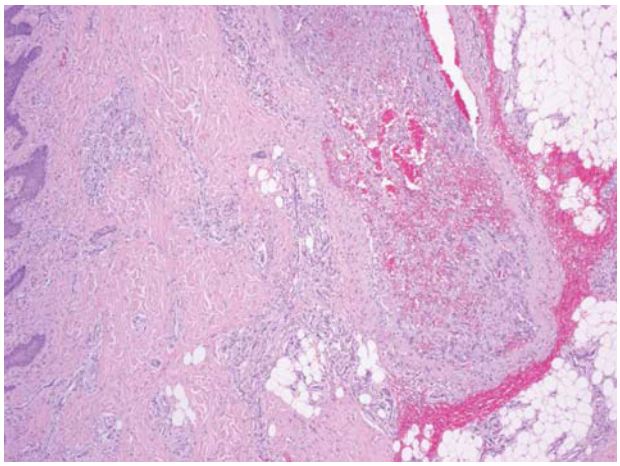

**Figure 12.** Thick-walled vessel in an arteriovenous malformation. It can be difficult to differentiate between arteries and "arterialized" veins. Hematoxylin-eosin, ×40.

From a pathological standpoint, cystic lymphatic malformations are composed of irregular and interconnected dilated vessels in the subcutaneous cell tissue. Cystic hygromas are composed of large unilocular or multilocular cavities surrounded by loose connective tissue. Finally, areas of lymphangiomatosis comprise wide, dilated and interconnected lymphatic channels lined by a row of flattened endothelial cells. Lesions usually affect the dermis and subcutaneous cell tissue, and can invade adjacent bone.[30]

## Further Testing

As has been previously documented in the literature, in cases of large venous or combined vascular malformations, a basic battery of coagulation tests should be carried out including, among others, the following measurements: prothrombin time, fibrinogen and D-dimer levels, platelet counts, and assays for soluble fibrin complexes. The presence of a procoagulant profile predisposes these patients to recurrent venous thrombosis and the risk of pulmonary embolism. These risks may be increased by sclerotherapy, surgery, bone fracture, prolonged bed rest, or pregnancy, in which cases prophylactic treatment with low-molecular-weight heparin may be required.[31,32]

In addition, bone density of the affected limb should always be assessed, by at least conventional radiography, to ensure early detection of demineralization and to forestall, as far as possible, pathological fracture.[33] A first-line treatment for localized osteoporosis in these patients is a bisphosphate such as alendronate or, in the case of severe osteoporosis and a history of stress fracture, an anabolic therapy such as teriparatide (recombinant human parathyroid hormone).[34,35]

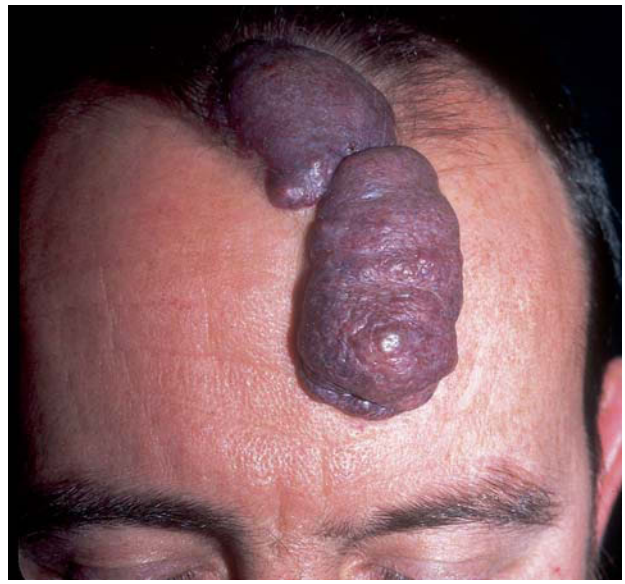

**Figure 13.** Patient with a linear hypertrophic port-wine stain on the forehead.

Serum markers of angiogenesis can be detected in patients with active and growing vascular, and in particular arteriovenous, malformations. In the not too distant future these markers may become the therapeutic target of specific antiangiogenic therapy although such therapy is still under development and more research needs to be done.[36]

## Treatment

Vascular malformations are ailments characterized by both the anatomic abnormality and the hemodynamic peculiarities of the affected vessels, which are theoretically similar but nonetheless different in every patient. The clinical presentation of the lesions varies enormously, ranging from asymptomatic stains with purely aesthetic repercussions to high-flow lesions or lesions in specific sites that may have an impact similar to that of a tumor and even be life threatening. At the same time, these anomalies are relatively rare making it difficult to acquire sufficient experience in their management and to compile evidence-based treatment guidelines.

Unlike hemangiomas, vascular malformations are radioresistant, nor do they respond to systemic or intralesional corticosteroids, interferon, or cytostatic drugs, and cryotherapy is of scant use. Surgery is indicated in clearly defined malformations of moderate size, when the possibilities of anatomic and functional restoration are excellent (Figures 13-16). The most difficult cases to treat are large diffuse malformations, intracavitary lesions, and infiltrating lesions with muscle involvement. Because venous malformations tend to invade adjacent structures, their

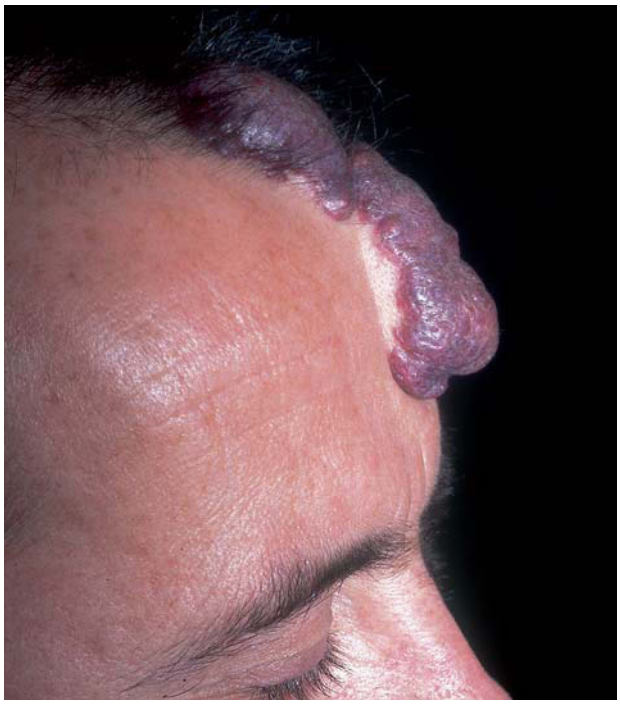

**Figure 14.** Side view of the patient shown in the previous figure.

morphology is usually complex and they are often associated with anomalies of the deep venous system in the extremities, a circumstance that limits the possibility of complete surgical excision.[37] In some cases, lesions recur even after numerous surgical interventions leaving patients in a situation very similar to where they started but with the additional burden of the negative repercussion on their emotional state.[38] Embolization, a useful although delicate procedure for the treatment of malformations with an arteriovenous component, is of little use in the treatment of large and purely venous malformations.

Symptomatic treatment is crucial in these patients. Some of the key components in the struggle to improve quality of life in these patients are analgesic therapy for painful lesions, strong tailor-made compression stockings or garments in the case of venous malformations, and the prevention of secondary infections or appropriate antibiotic treatment of infection in lymphatic malformations.

Possibly one of the most important advances in modern medicine has been the incorporation of the multidisciplinary approach into the diagnosis, treatment, and follow-up of patients. This is an approach that favors team work in that patients and their disease are seen in broader terms going beyond the individual specialty. The concept of a multidisciplinary approach to the treatment of vascular malformations was discussed and introduced for the first time at the first Samsung International Symposium for Congenital Vascular Malformations in

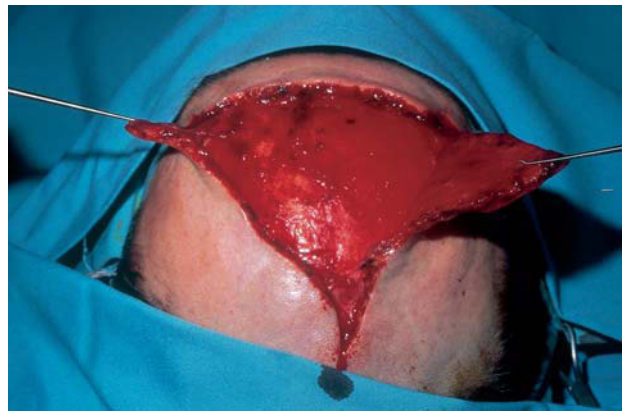

**Figure 15.** Excision of the hypertrophic port-wine stain and creation of 2 A-T advancement skin flaps.

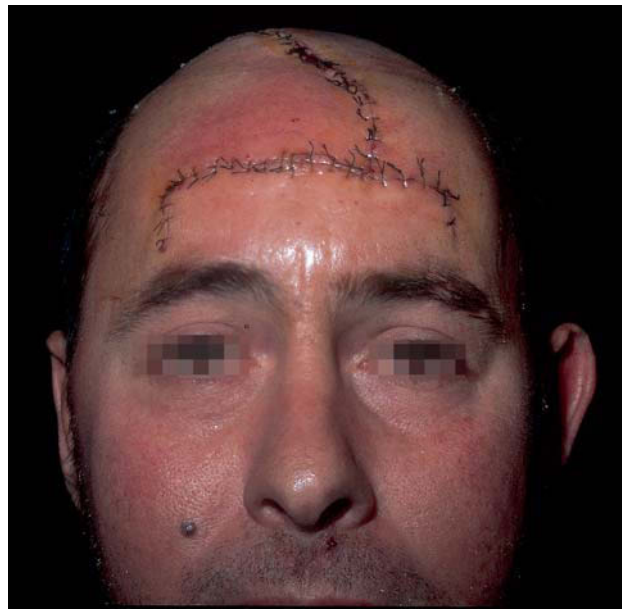

**Figure 16.** Result immediately after closure.

December 1996 in Seoul, South Korea.[39] At this conference, it was concluded that vascular malformations should be studied and treated by multidisciplinary teams bringing together the efforts of all the specialists involved in the management of these patients. This is an essential approach to the problem because the treatment of most vascular malformations requires an appropriate combination of procedures since the application of a single treatment is generally insufficient.

## Surgical Treatment

The aim of surgery should, whenever possible, be complete resection because the presence of any residual tissue will

invariably give rise to recurrence of the lesion. Purely surgical treatment of vascular malformations is only possible in the case of very localized and accessible lesions,[40,41] such as venous aneurysms, some small infiltrating lesions, and rare monopedicular arteriovenous lesions of limited size that are easily accessible and can be treated by ligation and total extirpation.

The resectability of the lesion should be rigorously assessed before the patient is proposed as a candidate for surgery. The malformation ideally suited for treatment exclusively with surgery is the isolated and superficial lesion that has not spread into deep planes or infiltrated adjacent structures. Subfascial extension with involvement of the muscles, tendons or bones or invasion of structures such as the pelvis or the gluteal region are contraindications for treatment with surgery alone since, in the best of cases notwithstanding good therapeutic planning and meticulous surgery, this option represents a temporary palliative treatment[42] and involves a high risk of thromboembolic events.[43] The use of bipolar electrocautery is advised when surgery is carried out in the vicinity of neural structures. Special attention should be paid to hemostasis of the surgical field given that uncontrolled bleeding makes dissection much more difficult and increases the risk of damage to adjacent structures.

In the case of lymphatic malformations, treatment is usually conservative because these anomalies rarely affect the function of the limb or organ involved and the presenting complaint is usually an aesthetic one. The exception, although quite a common one, corresponds to lesions that can be dangerous and obstruct the airway owing to their cervical location.[44]

In practice, it is difficult in the case of arteriovenous and lymphatic malformations, particularly diffuse ones, to identify a dissection plane during excision because the margins of the lesion are almost impossible to delimit. Consequently, the resection margins should be as broad as possible. Any residual lesion, for example a residual cutaneous macular stain resembling a port-wine stain, will give rise to recurrence in the short term and this is the reason why reoperations are common. Preoperative MRI and digital angiography, particularly dynamic evaluations, are especially useful for establishing these macroscopic margins.

The aim of surgery in the case of an arteriovenous malformation is to eradicate the nidus of the malformation. In such cases, surgery is often very hemorrhagic and ineffective due to the rapid recruitment of collateral vessels to supply the nidus. Prior embolization facilitates surgery and reduces bleeding. Resection should be performed as soon as and in the most complete way possible, with excision of broad margins around the nidus.

## Laser Therapy

Pulsed dye laser treatment targeting intravascular hemoglobin with selective photothermolysis is currently the first-line treatment for port-wine stains.[45] Laser light absorbed by oxyhemoglobin generates heat and damages the vascular endothelium giving rise to thrombosis and destruction of the vessel. The most commonly reported adverse effects after pulsed dye laser treatment are the appearance of blisters, scabs, hyperpigmentation, hypopigmentation, hypertrophic or atrophic scarring, and infections. Blisters and scabs appear a few hours after treatment and rarely leave scars after healing. The most common adverse effect is hyperpigmentation, which usually resolves spontaneously within 6 to 12 months,[46] although photoprotective measures should be taken to minimize this effect. The appearance of atrophic or hypertrophic scars varies between the different case series in the literature and has been reported in up to 5% of patients.[46]

Within the large range of pulsed dye laser systems on the market, each more versatile than the last, we must limit ourselves to the following parameters and oscillation values: laser beam diameter (5-10 mm), wavelength (585-600 nm), energy or fluence density (7-15 J/cm$^2$), and pulse duration (450 µs-1500 ms). A recent study reported good results in 63% of patients with a greater than 75% clearance of the lesion after 4 sessions using the following protocol: a dynamic skin cooling system, a wavelength of 595 nm, pulses of 1.5 ms, and energy fluences between 11-12 J/cm$^2$.[47] In the same study, 75% improvement was achieved in only 40% of a second group of patients treated with 585 nm. Some of the parameters that appear to improve the final outcome are the use of longer pulse durations (1.5 ms),[48] longer wavelengths (600 nm),[49] and higher energy fluences.[47] In infants and children, treatment should be started with low fluences, which can then be increased by 0.5-1 J/cm$^2$ at each session depending on the positive response and adverse effects.

Traditionally, the standard interval between sessions has been at least 6 weeks, although a recent study produced better results with sessions at 2-week intervals.[50]

While there is still debate about the most appropriate timing for starting laser treatment, it is generally accepted that such treatment should be started as early as possible.[51] Fewer sessions are required to treat children because the response is more rapid[51]; moreover, the rate of recurrence is lower in the group treated for the first time under 10 years of age.[52] In most cases, between 4 and 8 sessions are required to obtain a satisfactory response, and complete clearance is achieved in only 10% of patients. In approximately half of the patients, at least 75% clearance is achieved, and in one third the result is considered poor (improvement under 50%).

The chief drawback of early treatment is the need for sedation (general anesthesia) because the procedure is painful and provokes uncontrollable distress and anxiety in children. The anesthetist must use low oxygen concentrations because of the potential danger of ignition caused, for example, by the combustion of a hair shaft spreading through the air.[53] This protocol has been confirmed by our experience because it facilitates longer sessions with better long term results. It also favors a perfect balance between the physician, the patient, and the family, a difficult outcome to achieve with invasive procedures in children in real life situations. The use of various systems for cooling the skin surface before irradiation with the laser beam, such as dynamic cryogen spray cooling or continuous cold air cooling,[54] can obviate the need for anesthesia in some prepubescent children and allow the use of higher energy fluences while minimizing the risk of damage to the epidermis.[55]

In venular malformations, 3 models of ectasia can be distinguished in the papillary plexus using videomicroscopy depending on whether the lesion affects the vertical vessels, the deep horizontal vessels, or both.[56] It is important to differentiate between these 3 patterns when evaluating probable response to laser therapy because the first model responds better to such treatment than the other 2.[57] As mentioned earlier, venular malformations are classified according to the degree of ectasia present, with grade I corresponding to those with the smallest vessels and grade IV to those with the largest. The deepest vessels persist after treatment, as they can dilate and even proliferate through angiogenesis and spread once again towards more superficial areas.[58] The location and color of a lesion also predicts the level of response to laser treatment. Lesions situated in V2 respond less well than those affecting V1 or V3; lesions on the face and neck respond much better than those located on the trunk and extremities.[59]

In one third of patients, lesions fail to improve even after numerous sessions partly because the limited depth of laser penetration into the tissue (1 to 1.5 mm) makes it impossible to treat vessels situated at greater depth,[60] and partly because of the presence of other, nonvascular, elements of the hamartomatous type not targeted by this technique.[61] Adult patients with deep purple port-wine stains, tuberous lesions, or hypertrophy of the affected side of the face require surgical treatment. The options are curettage and electrocoagulation, simple excision, or surgical reduction by wedge resection and vermilionectomy of lip hypertrophy. In such cases, carbon dioxide ($CO_2$) and neodymium:yttrium-aluminum-garnet (Nd:YAG) laser systems are also effective.[62] In resistant cases and areas, the administration of 2 passes per session with the pulsed dye laser improves response.[63] Overlapping of pulses is another technique shown to favor penetration without any adverse effect on the epidermis.[64]

Patients whose condition does not respond to pulsed dye laser can be treated with intense pulsed light, Nd:YAG laser light (1064 nm),[65] or potassium-titanyl-phosphate (KTP) laser light (532 nm). In a case series of patients with malformations resistant to pulsed dye laser, satisfactory results (improvement of more than 50%) were obtained in 17% of the patients treated with KTP laser light.[66] The best results were obtained with fluences in the 18 to 24 J/cm$^2$ range and pulse durations of between 9 and 14 ms. These laser systems deliver high energy fluences and afford the possibility of adjusting the pulse duration to match the thermal relaxation time of the target structure. However, although tolerance is better, when no purpura is present, they may produce a higher incidence of scars or pigmentary changes (Figures 17 and 18).[66] Although there are fewer studies in the literature on the use of intense pulsed light than on the laser systems described above, improvements of between 70% and 100% have been achieved in 70% of patients with such treatment.[67,68]

Laser treatment of venous malformations is limited to very superficial lesions, the superficial component of deeper lesions as an adjuvant to treatment with other procedures (for example sclerotherapy), or mucosal lesions. The laser system most often used is a continuous Nd:YAG laser,

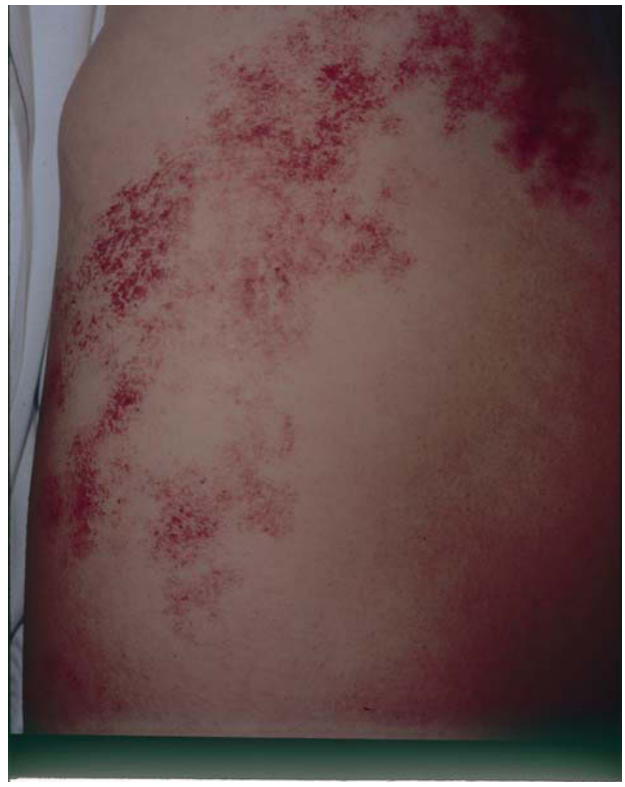

**Figure 17.** Woman with diffuse venular malformation on thigh with no other features of Klippel-Trénaunay syndrome, before treatment with neodymium:yttrium-aluminum-garnet laser.

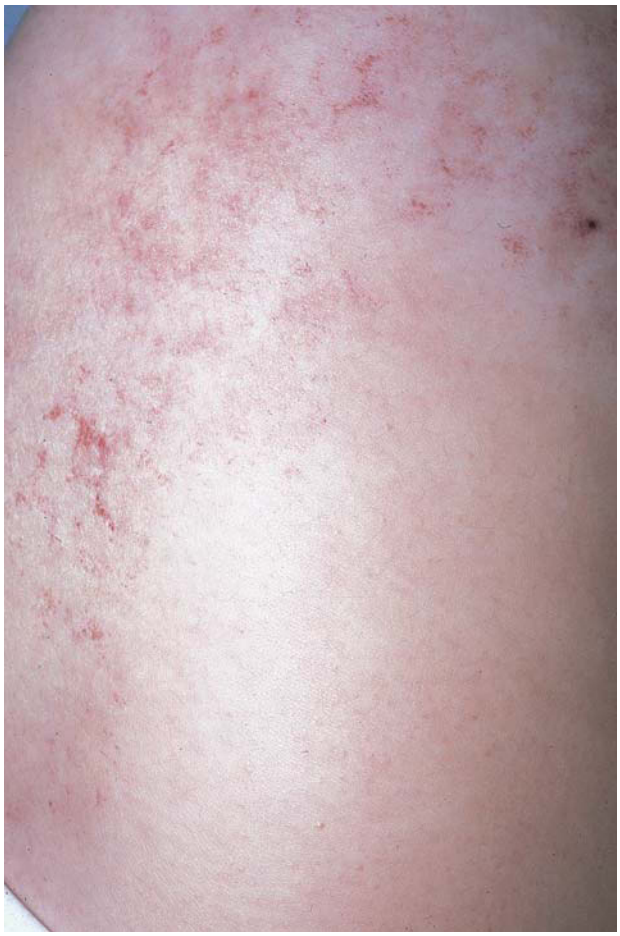

**Figure 18.** After 3 sessions of neodymium:yttrium-aluminum-garnet laser treatment an almost complete response can be seen.

which delivers infrared light at 1064 nm and has a skin penetration depth of between 5 and 7 mm. This device can deliver intralesional therapy through a catheter inserted into the lesion in a procedure controlled visually by ultrasound.[69-71]

A Nd:YAG laser system with a constant power output of 30 W, a 600 µm fiber diameter, and variable pulse duration is very useful in the treatment of mucosal lesions.[72] This procedure, which is usually performed under general anesthesia, is safe, no simultaneous surface cooling system is necessary, and the risk of fibrosis or residual scarring is negligible. When the laser beam impinges on the mucosa, the targeted spot immediately retracts and whitish spots appear in the area treated, providing a guide that helps the operator to avoid overlapping impacts. In the case of large venous malformations of the mucosa, laser treatment prior to surgery can eliminate the superficial component of the malformation and create a band of fibrosis that facilitates better excision of the lesion and reduces bleeding during the intervention. If large areas of the oral cavity are treated, especially at the back of the mouth, systemic corticosteroids should be administered to reduce inflammation and prevent airway compromise.

Ablation with $CO_2$ laser is particularly indicated in superficial lymphatic malformations of mucosal membranes, characterized clinically by the presence of multiple vesicles. These are usually diffuse lesions that reach deep planes and can permeate underlying muscle.[72] Although this treatment is not curative, it helps to control the disease and has a clearly beneficial effect on the patients' quality of life. Nonetheless, recurrence is the norm and periodic treatment is necessary. As infection can stimulate the growth of a lymphatic malformation, patients undergoing this procedure should receive appropriate prophylactic antibiotic treatment and an anti-inflammatory regimen of oral corticosteroids.

## Embolization

Embolization is a treatment particularly useful in arteriovenous malformations, and it can be used in the management of such lesions as a complete or adjuvant therapy. Despite advances in recent years, particularly in the new materials used (coils, different particles, polymers, and glues),[73-75] this technique is still a temporary solution since the blood supply in any specific anatomic area is not static and the development of collateral circulation is inevitable.[76]

As an adjuvant therapy prior to surgery, embolization is usually the most appropriate procedure for use in the case of arteriovenous malformations. Once the lesion has been mapped by angiography and the nidus and its afferents have been delineated, the lesion is embolized from distal to proximal. This reduces the vascularization of the lesion thereby minimizing the potential risk of bleeding during surgery. Because a new collateral circulation will be established very quickly, surgery should not be delayed more than 48 hours after embolization has been performed.[77]

Embolization can be use curatively or as a palliative treatment to prevent bleeding from large nonresectable lesions. The use of embolization to achieve a cure is not, however, a very realistic aim and it is preferable to envisage management of the lesion rather than a cure. In such cases, a gradual staged procedure is required, proceeding through the nidus from proximal to distal including both active and any potential arterial supply. The treatment must be repeated regularly because of revascularization of the lesion. This procedure is not risk free and should be carried out by an interventional radiologist familiar with the technique because one of the possible adverse events is the inadvertent release of embolic material leading to distant occlusion, distal necrosis, and neurological damage. Moreover, all of the embolic material used must be applied under fluoroscopic guidance.

## Sclerotherapy

Sclerotherapy is a procedure used to eliminate varicose veins through the injection of a sclerosing substance into the vein. The inflammation resulting from contact between the sclerosing agents and the endothelial cells on the inner surface of the vein leads to chemical irritation.[78] This process gives rise to the formation of a thrombus that blocks blood flow through the vein. Targeted veins gradually become fibrous sclerosed cords and are eventually reabsorbed by the body. Sclerosing agents can be classified as high potency (alcohol, iodine, and sodium tetradecyl sulfate), intermediate potency (sodium salicylate and polidocanol), or low potency (chromated glycerin). Polidocanol (aethoxysclerol), like sodium tetradecyl sulfate, is a detergent with a hydrophilic and a hydrophobic pole that acts by changing the surface tension of endothelial cells. The hydrophobic pole attaches to the cell surface while the hydrophilic portion attracts the water contained in the cell, thereby causing rapid and intense endothelial hydratation.[79] Local and general tolerance of polidocanol is excellent,[80] and this agent has been marketed in Europe for over 20 years for sclerosing varicose veins although it has not yet been approved by the American Food and Drug Administration. Its advantages contrast with the drawbacks associated with ethanol sclerotherapy, which has an aggressive impact on both the malformation and adjacent tissue. Injection of ethanol is painful and can only be carried out in hospitalized patients under general anesthesia. The use of ethanol as a sclerosing agent is not indicated in children and it can produce necrosis of the skin and mucous membranes, thrombosis of the deep venous system in the extremities, pulmonary embolism, and cardiorespiratory collapse due to pulmonary spasm. Moreover, repeated administration of ethanol is not easy, and repetition is essential in sclerotherapy because partial recanalization after initial intravascular thrombosis is common.[81]

Conventional sclerotherapy using liquid sclerosing agents, which is a palliative treatment in most types of vascular anomalies, produces good outcomes in smaller lesions.[82] In the context of surgery it is indicated as a preoperative intervention undertaken to reduce the size of the lesion, or as a postoperative complement.[83] However, conventional sclerotherapy is ineffective in the treatment of large venous malformations. This is due to a number of factors: the intrinsic limitations of the injected liquids, which are subject to dilution and progressive inactivation in large volumes of blood; the irregular distribution of the sclerosing agent on the endothelial cells of the target area; the difficulty of manipulating and controlling the sclerosing agent after injection; and the fact that the liquid agent cannot be visualized inside the blood vessels on Doppler ultrasound.

These problems have been addressed by the development of a pharmaceutical microfoam that serves as a vehicle for administering the sclerosing agent.[84] The modern use of foams in sclerotherapy started in 1944 with the work of Orbach, who used an air block technique to introduce air into the vein before injection of the sclerosing liquid. His aim was to potentiate the action of the agent by emptying the target vessel of blood.[85] Orbach later used large bubbles of sclerosant (obtained by shaking the ampule containing the liquid sclerosant) and demonstrated that the action of this foam was greater than that of the liquid form. This procedure was only shown to be of use in small veins, and the initial interest faded over the decades. In 1993, Juan Cabrera, a Spanish vascular surgeon, created a pharmaceutical form of injectable microfoam by creating microbubbles of surfactant sclerosing solutions using physiological gases that are highly soluble in body liquids.[86,87] Other authors have produced foams with such solutions using specific techniques commonly designated by the names of the researchers who have described them: Monfreux, Tessari, Frullini, etc.[88] Currently, one of the most popular techniques is the method described by Tessari in which the foam is obtained using 2 connected syringes and a 3-way stopcock. These "homemade" foams made with ambient air rich in nitrogen—a gas with low solubility in body fluids—have irregular bubble size and highly variable internal cohesion. The techniques used to apply the foams also vary,[89] although the statement issued after a consensus meeting in Tegernsee, Germany, recommended —for reasons of safety—the injection of no more than 5 mL of foam in any one treatment session.[90]

The pharmaceutical sclerosing microfoam, on the other hand, is made with physiologic gases, such as oxygen and $CO_2$, and is composed of tiny microbubbles with sufficient stability and internal cohesion to withstand injection into the vessels. The contact surface between the sclerosing agent and the vessel wall increases enormously in inverse proportion to the diameter of the bubble. Polidocanol microfoam displaces blood, thereby promoting homogeneous contact between the sclerosant and the endothelium, facilitating endothelial destruction.[86,87] Moreover, the procedure is visible in real time on ultrasound. Owing to the high solubility and lack of toxicity of $CO_2$, large amounts of the microfoam can be injected in a single session, which is not the case with foams made from ambient air.[90-94] It is sometimes necessary to inject between 20 and 100 mL of microfoam to treat large venous malformations. By contrast, the volume of "homemade" foam that can be injected in a single session cannot exceed the recommended 5 mL because of the low solubility of nitrogen, and only the concentration can be modified.

To date, we have treated congenital vascular malformations (mainly venous) in over 120 patients with sclerotherapy using polidocanol microfoam. In an initial published series, 50 patients (18 males and 32 females

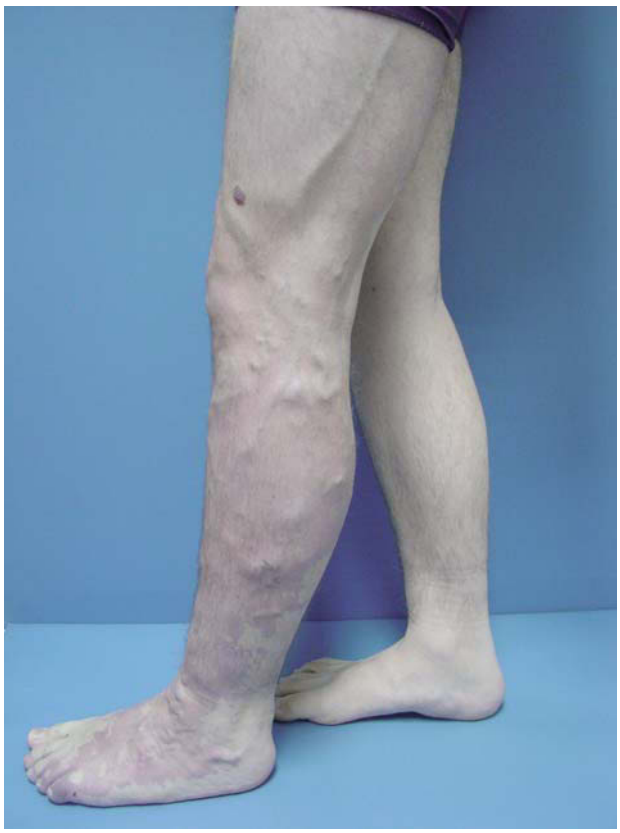

**Figure 19.** Sixteen-year-old boy with Klippel-Trénaunay syndrome. The diffuse port wine stain and lateral embryonic vein can be seen.

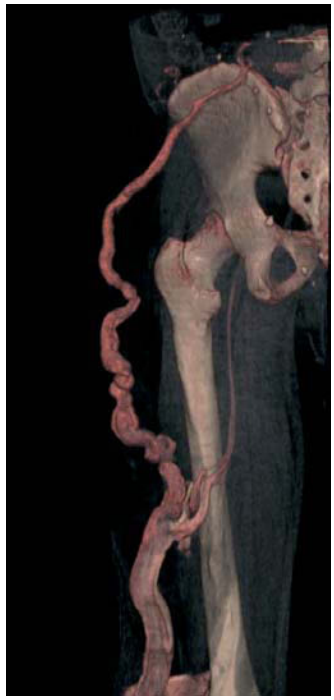

**Figure 20.** Persistent sciatic vein in a patient with Klippel-Trénaunay syndrome.

aged between 8 and 62 years) were divided into 3 groups according to the Hamburg classification: Group 1 (n=16) had infiltrating venous malformations; Group 2 (n=19) had limited venous malformations; and Group 3 (n=15) had combined vascular malformations of the Klippel-Trénaunay syndrome.[95] In some cases, besides ultrasound, other complementary imaging techniques were used. All the patients were treated with polidocanol microfoam administered by injection under Doppler ultrasound guidance. Between 20 and 80 mL of microfoam was administered in each session, which corresponds to 3 to 6 mL of 2% polidocanol. The polidocanol concentration injected varied from 0.25% to 3% depending on the size of the malformation and the hemodynamic characteristics of the area being treated. Infiltrating malformations required higher concentrations (2%-3%), while the anomalous lateral veins of the patients with Klippel-Trénaunay syndrome were treated with lower concentrations (0.25%-0.5%). The procedure was performed without anesthesia and the number of sessions varied between 1 and 46 (mean=12). Only 21 patients required more than 10 sessions. Sessions were repeated every 2 to 4 weeks. In 46 patients (92%), there was clinical and radiographic improvement, and only 4 patients did not respond to treatment. Of the 46 who responded to treatment, in 18 cases (39%) the malformation treated disappeared completely, in 15 (33%) a reduction of 50% or more was achieved, and in 13 (28%) the reduction of the malformation was less than 50%. Of the 39 patients who presented with pain, this disappeared in 25 and was reduced in the other 14. The 5 patients who presented with chronic ulcers reported complete healing, and in all 9 patients who had a history of episodes of hemorrhage these were reduced or disappeared completely. With respect to adverse effects, 4 patients developed skin pigmentation that resolved spontaneously, and 2 developed a small area of skin necrosis after superficial sclerosis with 0.5% polidocanol microfoam. One patient developed a larger area of skin necrosis caused by inadvertent injection of a distal artery. There were no cases of deep vein thrombosis, pulmonary embolism, or neurological lesions. The patients with Klippel-Trénaunay syndrome had the best response to the sclerotherapy, with total elimination of the pathological areas in 80% of the patients and recurrence of small varicosities (less than 20% of the original lesion) in only 10 of these (Figures 19-21).[95]

Vascular malformations of the head should be treated with restraint since veins in the head and neck region have no valves and those situated in the upper two-thirds of the facial region are directly connected to the cavernous sinus through the upper and lower ophthalmic veins.

The therapeutic efficacy of polidocanol microfoam depends on its mechanical action—the displacement of blood from the treated veins. In the presence of increased blood flow, the injected microfoam is diluted and the effect

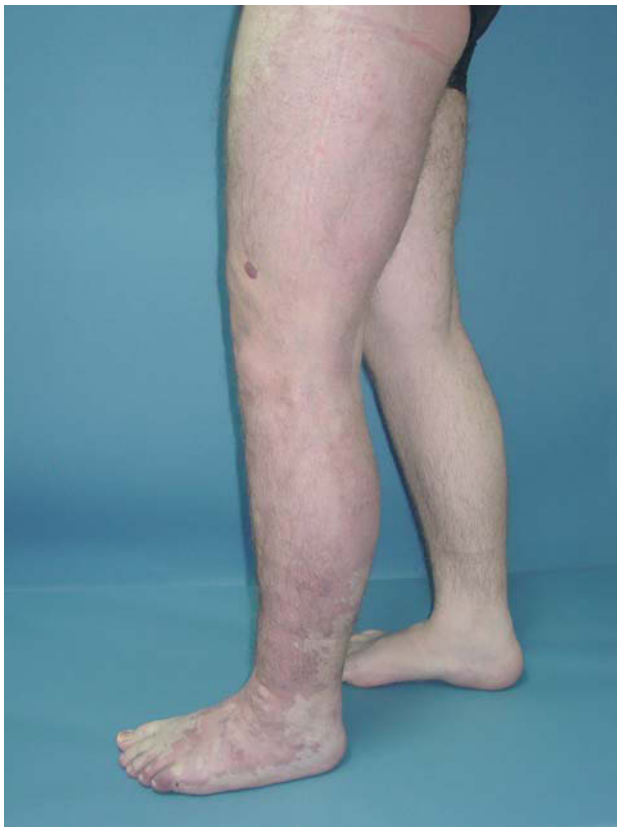

**Figure 21.** Patient shown in Figure 19 after 7 sessions of sclerotherapy with polidocanol microfoam. Note the absence of lateral veins and the persistence of the port-wine stain.

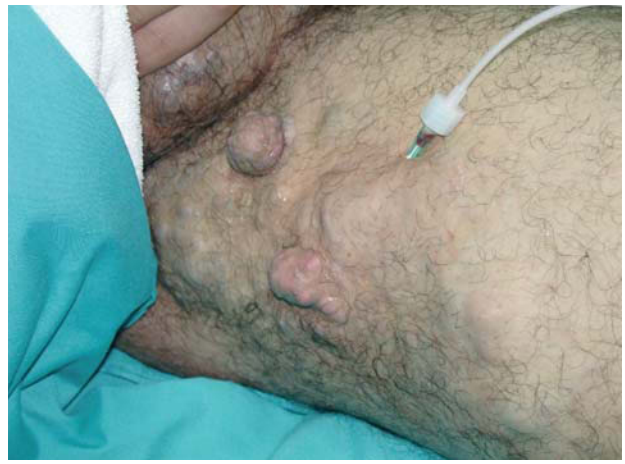

**Figure 22.** Prominent venous dilatations with exophytic elements on the upper thigh during a sclerotherapy session with polidocanol microfoam.

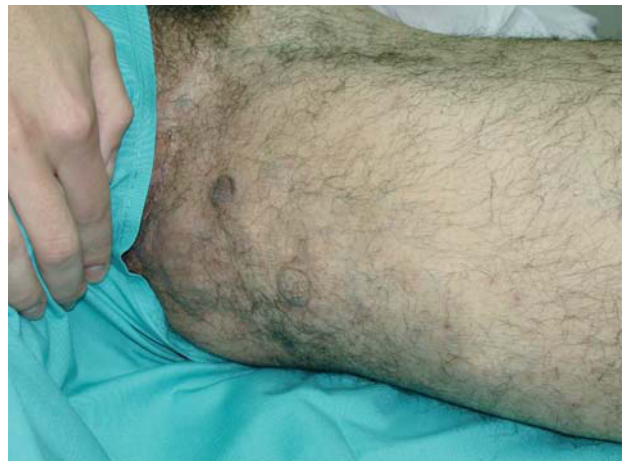

**Figure 23.** Patient shown in previous figure. Result at 3 months after 3 treatment sessions.

reduced. In routine practice, small arteriovenous fistulas are commonly found in some venous malformations. These tend to reduce the effectiveness of sclerotherapy as they reduce the area initially thrombosed after injection and favor early partial recanalization.

Sclerotherapy with polidocanol microfoam is well tolerated and produces no important adverse effects. The treatment is safe, simple, reproducible, inexpensive, and can be administered to outpatients, making it the procedure of choice for the functional and anatomical elimination of a pathologic venous region (Figures 22 and 23).[96]

## *Sclerotherapy of Lymphatic Malformations*

Lymphatic malformations can be sclerosed with dextrose, tetracyclines, bleomycin, and OK-432. The mechanism of action of all these substances is the same: their diffusion into the stroma causes irritation and inflammation that leads to shrinkage and scar contracture of the lesion. Before injection of the sclerosant, as much lymph as possible should be aspirated thereby "emptying" the malformation.

OK-432 (picibanil; Chugai Pharmaceutical Co. Ltd., Tokyo, Japan) is a preparation of dead bacteria produced by incubating the culture of *Streptococcus pyogenes* (group A, type III) isolated from human samples with penicillin G benzathine. The preparation is not infectious and has no systemic repercussions.

In addition to being a sclerosing agent, OK-432 has also been reported to have various immunopharmacological properties in that it promotes an increase in the cytotoxicity of natural killer cells, cytotoxic T-cells, lymphokine-activated killer cells, and macrophages, and stimulates the synthesis of cytokines such as tumor necrosis factor and interferons, thereby increasing endothelial permeability and accelerating lymph drainage, which in turn promotes shrinkage of the cystic cavity.[97] The first clinical application of this substance

was reported in 1987 when 9 patients with cystic hygroma were treated, and the outcome was complete regression in 8 cases.[98] In later publications on series of 23 and 64 patients, the same team demonstrated excellent or good results in 93% of cystic lymphangiomas and 47% of cavernous lymphangiomas.[99,100] Over the years, the published results of various studies by other authors have confirmed the efficacy of this procedure and proposed sclerotherapy with OK-432 as the first-line treatment for lymphatic malformations, and in particular for macrocystic lesions.[101,102] Although most of the malformations treated have been located in the head and neck region because this is the most common site for these lesions, the response to treatment has been satisfactory in all sites, including large retroperitoneal lesions[103] and lesions in complex sites, such as the periorbital region.[104] There is no limitation on the age of the patient. The only contraindication for this therapy is allergy to penicillin.

The maximum recommended dose is 0.3 mg of OK-432 per session.[99,105] In general, the lesion shrinks without scarring or alteration of the local anatomy and no recurrence has been reported after follow-up over a number of years in the published series.

**Conflict of Interests**

The author declares no conflicts of interest.

## References


1. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg. 1982;69:412.
2. Hand JL, Frieden IJ. Vascular Birthmarks of infancy: resolving nosologic confusion. Am J Med Genet. 2002; 108:257-64.
3. Finn MC, Glowacki J, Mulliken JB. Congenital vascular lesions: clinical application of a new classification. J Pediatr Surg. 1983;18:894.
4. Belov S. Classification of congenital vascular defects. Int Angiol. 1990;9:141-6.
5. Burrows PE, Mulliken JB, Fellows KE, Strand RD. Childhood hemangiomas and vascular malformations: angiographic differentiation. Am J Roentgenol. 1983;141: 483-8.
6. Bliznak J, Staple TW. Radiology of angiodysplasias of the limb. Radiology 1974;110:35-44.
7. Schmidt GH. Hemangioma in the zygoma. Ann Plast Surg. 1982;3:330-6.
8. Hein KD, Mulliken JB, Kozakewich HP, Upton J, Burrows PE. Venous malformations of skeletal muscle. Plast Reconstr Surg. 2002;110:1625-35.
9. DesPrez JD, Kiehn CL, Vlastou C, Bonstelle C. Congenital arteriovenous malformation of the head and neck. Am J Surg. 1978;136:424-9.
10. Yoshida H, Yusa H, Ueno E. Use of Doppler color for imaging for differential diagnosis of vascular malformations: a preliminary report. J Oral Maxillofac Surg. 1995;53:369-74.
11. Yang WT, Ahuja A, Metreweli C. Sonographic features of head and neck hemangiomas and vascular malformations: review of 23 patients. J Ultrasound Med. 1997;16:39-44.
12. Sheth S, Nussbaum AR, Hutchins GM, Sanders RC. Cystic hygromas in children: sonographic-pathologic correlation. Radiology. 1987;162:821-4.
13. Foley WD, Karcaaltincaba M. Computed tomography angiography: principles and clinical applications. J Comput Assist Tomogr. 2003;27 Suppl 1:S23-30.
14. Levine E, Wetzel LH, Neff JR. MR imaging and CT of extrahepatic cavernous hemangiomas. Am J Roentgenol. 1986;147:1299-304.
15. Davidson AJ, Hartman DS. Lymphangioma of the retroperitoneum: CT and sonographic characteristic. Radiology. 1990;175:507-10.
16. Fan X, Qiu W, Zhang Z, Mao Q. Comparative study of clinical manifestation, plain-film radiography, and computed tomographic scan in arteriovenous malformations of the jaws. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;94:503-9.
17. Remonda L, Schroth G, Ozdoba C, Lovblad K, Ladrach K, Huber P. Facial intraosseous arteriovenous malformations: CT and MR features. J Comput Assist Tomogr. 1995;19:277-81.
18. Herborn CU, Goyen M, Lauenstein TC, Debatin JF, Ruehm SG, Kroger K. Comprehensive time-resolved MRI of peripheral vascular malformations. Am J Roentgenol. 2003;181:729-35.
19. Caseiro-Alves F, Gil-Agostinho P, Ramalheiro G, Gil-Agostinho P. Contrast-enhanced MR angiography of thoracic vascular malformations in a pediatric population. Am J Roentgenol. 2003;181:861-6.
20. Konez O, Burrows PE. Magnetic resonance of vascular anomalies. Magn Reson Imaging Clin N Am. 2002;10:363-88.
21. Kern S, Niemeyer C, Darge K, Merz C, Laubenberger J, Uhl M. Differentiation of vascular birthmarks by MR imaging. An investigation of hemangiomas, venous and lymphatic malformations. Acta Radiol. 2000;41:453-7.
22. Dubois J, Soulez G, Oliva VL, Berthiaume MJ, Lapierre C, Therasse E. Soft-tissue venous malformations in adult patients: imaging and therapeutic issues. Radiographics. 2001;21:1519-31.
23. Sunagawa T, Ikuta Y, Ishida O, Ishiburo M, Yasunaga Y, Ochi M. Arteriovenous malformation of the ring finger. Pre- and postoperative evaluation using three-dimensional computed tomography angiography. J Comput Assist Tomogr. 2003;27:820-3.
24. Bastarrika G, Redondo P, Sierra, Cano D, Martínez-Cuesta A, López-Gutierrez JC, et al. New techniques for the evaluation and therapeutic planning of patients with Klippel-Trenaunay syndrome. J Am Acad Dermatol. 2007;56:242-9.
25. Pretel M, Bastarrika G, Redondo P. Nuevas técnicas diagnósticas en pacientes con síndrome de Klippel-Trenaunay. Piel. 2007. In press.

26. Vilela PF. Sturge-Weber syndrome revisited. Evaluation of encephalic morphological changes with computerized tomography and magnetic resonance. Acta Med Port. 2003;16:141-8.
27. Hagiwara K, Khaskhely NM, Uezato H, Nonaka S. Mast cell "densities" in vascular proliferations: a preliminary study of pyogenic granuloma, port wine stain, cavernous hemangioma, cherry angioma, Kaposi's sarcoma, and malignant hemangioendothelioma. J Dermatol. 1999;26:577-86.
28. Nuovo MA, Grimes MM, Knowless DM. Glomus tumors: clinicopathologic and immunohistochemical analysis of forty cases. Surg Pathol. 1990;3:31-40.
29. Lawton RC, Tidrick RT, Brintnall ES. A clinicopathological study of multiple congenital arteriovenous fistulae of the lower extremities. Angiology. 1957;8:161-9.
30. Peachey RDG, Lim CC, Whimster JW. Lymphangioma of the skin: a review of 65 cases. Br J Dermatol. 1970;83:519-27.
31. Enjolras O, Ciabrini D, Mazoyer E, Laurian C, Herbreteau D. Extensive pure venous malformations in the upper or lower limb, a review of 27 cases. J Am Acad Dermatol. 1997;36:219-25.
32. Mazoyer E, Enjolras O, Laurian C, Houdart E, Drouet L. Coagulation abnormalities associated with extensive venous malformations of the limbs: differentiation from Kasabach-Merrit syndrome. Clin Lab Haem. 2002;24:243-51.
33. Benchakroun M, Ouadghiri M, Berrada S, Hermas F, Wahbi S, El Yaacoubi M, et al. Pathological fracture of the femur in a patient with a venous malformation. Rev Chir Orthop Reparatrice Appar Mot. 2004;90:280-4.
34. Plotkin LI, Weinstein TS, Parfitt AM, Roberson PK, Manolagas SC, Bellido T. Prevention of osteocyte and osteoblast apoptosis by bisphosphonates and calcitonin. J Clin Invest. 1999;104:1363-74.
35. Hodsman AB, Bauer DC, Dempster D, Dian L, Hanley DA, Harris ST, et al. Parathyroid hormone and teriparatide for the treatment of osteoporosis: a review of the evidence and suggested guidelines for its use. Endocr Rev. 2005;26:688-703.
36. Ferrara N, Kerbel RS. Angiogenesis as a therapeutic target. Nature. 2005;438:967-74.
37. Enjolras O, Mulliken JB. Vascular tumors and vascular malformations (new issues). Adv Dermatol. 1998;13:375-422.
38. Jacob AG, Driscoll DJ, Shaughnessy WJ, Stanson AW, Clay RP, Gloviczki P. Klippel-Trenaunay syndrome: spectrum and management. Mayo Clin Proc. 1998;73:28-36.
39. Lee BB. What is new in venous disease: new approach to old problem of venous disease: congenital vascular malformation. In: Angelides NS, editor. Advances in Phlebology. Limassol: Hadjigeogiou Printing & Co; 1998. p. 59-64.
40. Szilagyi DE, Smith RF, Elliott JP, Hageman JH. Congenital arteriovenous anomalies of the limbs. Arch Surg 1976;111:423-9.
41. Rutherford RB. Congenital vascular defects or malformations (CVMs). Semin Vasc Surg. 1993;6:197-8.
42. Hartman M, Spauwen M, Rieu A. Surgical treatment of hemangiomas and vascular malformations in functional areas. Pediatr Surg Int. 1996;11:308-11.
43. Noel AA, Glovizcki P, Cherry KJ Jr, Rooke TW, Stanson AW, Driscoll DJ. Surgical treatment of venous malformations in Klippel-Trénaunay syndrome. J Vasc Surg. 2000;32:840-7.
44. Lee BB, Bergan JJ. Advanced management of congenital vascular malformations: a multidisciplinary approach. Cardiovasc Surg. 2002;10:523-33.
45. Poetke M, Philipp C, Berlien HP. Flashlamp-pumped pulsed dye laser for hemangiomas in infancy. Treatment of superficial vs. mixed hemangiomas. Arch Dermatol. 2000;136:628-32.
46. Seukeran DC, Collins P, Sheehan-Dare RA. Adverse reactions following pulsed tunable dye laser treatment of port wine stains in 701 patients. Br J Dermatol. 1997; 136:725-9.
47. Geronemus RG, Quintana AT, Lou WW, Kauvar ANB. High-fluence modified pulsed dye laser photocoagulation with dynamic cooling of Port-wine stain in infancy. Arch Dermatol. 2000;136:942-3.
48. Scherer K, Lorenz S, Wimmershoff M, Landthaler M, Hohenleutner U. Both the flashlamp-pumped dye laser and the long-pulsed tunable dye laser can improve results in port-wine stain therapy. Br J Dermatol. 2001;145:79-84.
49. Edstrom DW, Ros AM. The treatment of port-wine stains with the pulsed dye laser at 600 nm. Br J Dermatol. 1997; 136:360-3.
50. Tomson N, Lim SPR, Abdullah A, Lanigan SW. The treatment of port-wine stains with the pulsed-dye laser at 2-week and 6-week intervals: a comparative study. Br J Dermatol. 2006;154:676-9.
51. Ashinoff R, Geronemus RG. Flashlamp-pumped dye laser for port wine stains in infancy: earlier versus later treatment. J Am Acad Dermatol. 1991;24:467-72.
52. Tevar E, Calvo M, Moratinos M, Boixeda P. Láser y otras fuentes de luz en el tratamiento de manchas en vino de Oporto. Actas Dermosifiliogr. 2006;97:419-27.
53. Molin L, Hallgren S. Hair ignition by dye laser for portwine stain: risk factors evaluated. J Cutan Laser Ther. 1999;1:121-4.
54. Greve B, Hammes S, Raulin C. The effect of cold air cooling on 585 nm pulsed dye laser treatment of port-wine stains. Dermatol Surg. 2001;27:633-6.
55. Chang CJ, Nelson JS. Cryogen spray cooling and higher fluence pulsed dye laser treatment improve port-wine stain clearance while minimizing epidermal damage. Dermatol Surg. 1999;25:767-72.
56. Eubanks LE, McBurney EI. Videomicroscopy of port-wine stains: correlation of location and depth of lesion. J Am Acad Dermatol. 2001;44:948-51.
57. Fiskerstrand EJ, Svaasand LO, Kopstad G, Dalaker M, Norvang LT, Volden G, et al. Laser treatment of port-wine stains: therapeutic outcome in relation to morphological parameters. Br J Dermatol. 1996;134:1039-43.
58. Michel S, Landthaler M, Hohenleutner U. Recurrence of Port-wine stains after treatment with the flashlamp-pumped pulsed dye laser. Br J Dermatol. 2000;143:1230-4.
59. Renfro L, Geronemus RG. Anatomical differences of Port-wine stains in response to treatment with the pulse dye laser. Arch Dermatol. 1993;129:182-8.
60. Lanigan SW. Port-wine stain unresponsive to pulsed dye laser: explanations and solutions. Br J Dermatol. 1998; 139:173-7.

61. Sánchez-Carpintero I, Mihm MC, Mizeracki A, Waner M, North PE. Epithelial and mesenchymal hamartomatous changes in a mature port-wine stain: morphologic evidence for a multiple germ layer field defect. J Am Acad Dermatol. 2004;50:608-12.
62. del Pozo J, Fonseca E. Port-wine stain nodules in the adult: report of 20 cases treated by $CO_2$ laser vaporization. Dermatol Surg. 2001;27:699-702.
63. Bencini PL. The multilayer technique: a new and fast approach for flashlamp-pumped pulsed (FLPP) dye laser treatment of port-wine stains (preliminary reports). Dermatology Surg. 1999;25:786-9.
64. Koster PH, van der Horst CM, van Gemert MJ, van der Wal AC. Histologic evaluation of skin damage after overlapping and nonoverlapping flashlamp pumped pulsed dye laser pulses: A study on normal human skin as a model for Port wine stains. Lasers Surg Med. 2001;28:176-81.
65. Groot D, Rao J, Johnston P, Nakatsui T. Algorithm for using a long-pulsed Nd:YAG laser in the treatment of deep cutaneous vascular lesions. Dermatol Surg. 2003;29:35-42.
66. Chowdhury MM, Harris S, LAnigan SW. Potassium titanyl phosphate laser treatment of resistant port-wine stains. Br J Dermatol. 2001;144:814-7.
67. Raulin C, Schroeter CA, Weiss RA, Keiner M, Werner S. Treatment of port-wine stain with a noncoherent pulsed light source. Arch Dermatol. 1999;135:679-83.
68. Cliff S, Misch K. Treatment of mature port wine stains with the PhotoDerm VL. J Cutan Laser Ther. 1999;1:101-4.
69. Werner JA, Lippert BM, Hoffmann P, Rudert H. Nd:Yag laser therapy of voluminous hemangiomas and vascular malformations. Adv Otorhinolaryngol. 1995;49:75-80.
70. Glaessl A, Schreyer AG, Wimmershoff MB, Landthaler M, Feuerbach S, Hohenleutner U. Laser surgical planning with magnetic resonance imaging-based 3-dimensional reconstructions of intralesional Nd:Yag laser therapy of a venous malformation of the Neck. Arch Dermatol. 2001; 137:1331-5.
71. Derby LD, Low DW. Laser treatment of facial venous vascular malformations. Ann Plast Surg. 1997;38:371-8.
72. Waner M, Suen JY. Treatment options for the management of vascular malformations. In: Waner M, Suen JY, editors. Hemangiomas and vascular malformations of the head and neck. Chapter 10. New York: Wiley-Liss; 1999. p. 315-50.
73. Fujii Y, Keene BW, Mathews KG, Atkins CE, Defrancesco TC, Hardie EM, et al. Coil occlusion of residual shunts after surgical closure of patent ductus arteriosus. Vet Surg. 2006;35:781-5.
74. Cekirge HS, Saatci I, Geyik S, Yayuz K, Ozturk H, Pamuk G. Intrasaccular combination of metallic coils and onyx liquid embolic agent for the endovascular treatment of cerebral aneurysms. J Neurosurg. 2006;105:706-12.
75. Sánchez MJ, Ananian CL, Berkmen T. Embolization of an aortic arch pseudoaneurysm with coils and N-butyl-cyanoacrylate. J Vasc Interv Radiol. 2006;17:1677-9.
76. Gomes AS. Embolization therapy of congenital arteriovenous malformations: use of alternate approaches. Radiology. 1994;190:191-5.
77. Latchaw RE, Gold LHA. Polyvinyl foam embolization of vascular and neoplastic lesions of the head, neck, and spine. Radiology. 1979;131:669-74.
78. Weiss RA, Goldman MP. Advances in sclerotherapy. Dermatologic Clin. 1995;13:431-45.
79. Van der Stricht J. The sclerosing therapy in congenital vascular defects. Int Angiol. 1990;9:224-7.
80. Cadere T. Treatment of varices with ethoxysclerol. Phebologie. 1980;33:377-8.
81. Villavicencio JL. Primum non nocere: Is it always true? The use of absolute ethanol in the management of congenital vascular malformations. J Vasc Surg. 2001;33:904-6.
82. Goldman MP, Bennet RG. Treatment of telangiectasia: a review. J Am Acad Dermatol. 1987;17:167-82.
83. de Lorimier AA. Sclerotherapy for venous malformations. J Pediatr Surg. 1995;30:188-94.
84. Bikerman JJ. Foams. New York: Springer-Verlag; 1973.
85. Orbach EJ. Sclerotherapy of varicose veins: utilization of intravenous air block. Am J Surg. 1994;66:362-6.
86. Cabrera J, Cabrera J Jr, García-Olmedo MA. Elargissement des limites de la sclerotherapie: Nouveaux produits sclerosants. Phlebologie. 1997;2:181-8.
87. Cabrera J, Cabrera J Jr, García-Olmedo MA. Treatment of varicose long saphenous veins with sclerosant in microfoam form: long-term outcomes. Phebology. 2000;15:19-23.
88. Wollmann J-CGR. The history of sclerosing foams. Dermatol Surg. 2004;30:694-703.
89. Redondo P, Cabrera J. Microfoam sclerotherapy. Semen Cutan Med Surg. 2005;24:175-83.
90. European consensus meeting on foam sclerotherapy. April 4-6, 2003, Tegernsee, Germany. Dermatol Surg. 2004;30: 709-17.
91. Paul RE, Durant TM, Oppenheimer MJ, Stauffer HM. Intravenous carbon dioxide for intracardiac gas contrast in the roentgen diagnosis of pericardial effusion and thickening. Am J Roentgenol Radium Ther Nucl Med. 1957;78:224-5.
92. Meltzer RS, Serruys PW, Hugenholtz PG, Roelandt J. Intravenous carbon dioxide as an echocardiographic contrast agent. J Clin Ultrasound. 1981;9:127-31.
93. Martínez-Cuesta A, Elduayen B, Vivas I, Delgado C, González-Crespo I, Bilbao JI. $CO_2$ wedged hepatic venography technical considerations and comparison with direct and indirect portography with iodinated contrast. Abdom Imaging. 2000;25:576-82.
94. Bendib M, Toumi M, Boudjellab A. $CO_2$ angiography and enlarged $CO_2$ angiography in cardiology. Ann Radiol (Paris). 1977;20:673-86.
95. Cabrera J, Cabrera J Jr, García-Olmedo MA, Redondo P. Treatment of venous malformations with sclerosant in microfoam form. Arch Dermatol. 2003;139:1409-16.
96. Hsu TS, Weiss RA. Foam sclerotherapy: a new era. Arch Dermatol. 2003;139:1494-6.
97. Ogita S, Tsuto T, Nakamura K, Deguchi E, Tokiwa K, Iwai N. OK-432 therapy for lymphangiomas in children: why and how does it work? J Pediatr Surg. 1996;31:477-80.
98. Ogita S, Tsuto T, Tokiwa K, Takahashi T. Intracystic injection of OK-432: a new sclerosing therapy for cystic hygroma in children. Br J Surg. 1987;74:690-1.
99. Ogita S, Tsuto T, Deguchi E, Tokiwa K, Nagashima M, Iwai N. OK-432 therapy for unresectable lymphangiomas in children. J Pediatr Surg. 1991;26:263-70. 100. Ogita S, Tsuto T, Nakamura K, Deguchi E, Iwai N. OK-432 therapy

in 64 patients with lymphangioma. J Pediatr Surg. 1994;29:784-5.
100. Ogita S, Tsuto T, Nakamura K, Deguchi E, Iwai N. OK-432 therapy in 64 patients with lymphangioma. J Pediatr Surg. 1994;29:784-5.
101. Luzzatto C, Midrio P, Tchaprassian Z, Guglielmi M. Sclerosing treatment of lymphangiomas with OK-432. Arch Dis Child. 2000;82:316-8.
102. Claesson G, Kuyelenstierna R. OK-432 therapy for lymphatic malformation in 32 patients (28 children). Int J Pediatr Otorhinolaryngol. 2002;65:1-6.
103. Uchida K, Inoue M, Araki T, Miki C, Kusunoki M. Huge scrotal, flank and retroperitoneal lymphangioma successfully treated by OK-432 sclerotherapy. Urology. 2002;60:1112xxiv-1112xxvi.
104. Suzuki Y, Obana A, Gohto Y, Miki T, Otuka H, Inoue Y. Management of orbital lymphamgioma using intralesional injection of OK-432. Br J Ophtalmol. 2000;84:614-7.
105. Banieghlbal B, Davies MR. Guidelines for the successful treatment of lymphangioma with OK-432. Eur J Pediatr Surg. 2003;13:103-7.