

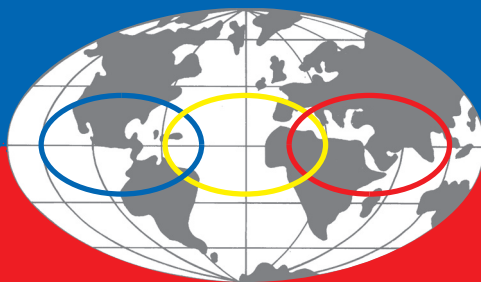
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VASCULAR FORUM**

VASCULAR ANOMALIES GUIDELINES

by the Italian Society
for the study of Vascular Anomalies (SISAV)



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General coordinator

Francesco Stillo
(President of the Scientific Committee)

Chapters' coordinators

Vittoria Baraldini, Pietro Dalmonte, Maya El Hachem,
Raul Mattassi, Francesco Stillo, Gianni Vercellio

Authors

Bruno Amato, Carlo Bellini, Mauro Bergui, Giuseppe Bianchini,
Andrea Diociaiuti, Corradino Campisi, Carlo Gandolfo, Carlo Gelmetti,
Laura Moneghini, Lidia Monti, Clara Magri, Iria Neri, Guglielmo
Paolantonio, Annalisa Patrizi, Massimo Rollo, Luigino Santecchia,
Massimo Vaghi, Nadia Vercellino

Vittoria Baraldini

Vascular Anomalies Unit, Pediatric Surgery Department
V.Buzzi Children's Hospital, ICP, Milan, Italy

Pietro Dalmonte

Director of Vascular Surgery Unit - Center for Angiomas
Cardiovascular Department
Istituto Giannina Gaslini, Genoa, Italy

Maya El Hachem

Chief of Dermatology Unit
Bambino Gesù Children's Hospital I.R.C.C.S., Rome, Italy

Raul Mattassi

Director of Vascular Surgery Unit – Center for Vascular Malformations
Humanitas Mater Domini, Castellanza, Varese, Italy

Francesco Stillo

Director Center for Vascular Malformations
Guarnieri Clinic, Rome, Italy

Gianni Vercellio

Director Center for Vascular Malformations
Italian Diagnostic Center (IDC), Milan, Italy

Bruno Amato

Associate Professor of Vascular Surgery
Department of Public Health
Federico II University of Naples, Naples, Italy

Carlo Bellini

Neonatology Unit
Istituto Giannina Gaslini, Genoa, Italy

Mauro Bergui

Director of Invasive Neuroradiology Unit
San Giovanni Battista - Molinette Hospital, Turin, Italy

Giuseppe Bianchini

Vascular Surgery Unit – Center for Vascular Malformations
I.R.C.C.S. Dermopatico dell'Immacolata, Rome, Italy

Andrea Diociaiuti

Dermatology Unit
Bambino Gesù Children's Hospital I.R.C.C.S., Rome, Italy

Corradino Campisi

University Full Professor of General Surgery, Director of Lymphatic Surgery Unit DISC/Department of General, Specialistic and Oncologic Surgery, University of Genoa, IRCCS University Hospital San Martino - IST, National Institute for Cancer Research, Genoa, Italy

Carlo Gandolfo

Director of Interventional Radiology and Neuroradiology Unit
Istituto Giannina Gaslini, Genoa, Italy

Carlo Gelmetti

Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy
Department of Dermatology, Fondazione IRCCS Ca' Granda "Ospedale Maggiore Policlinico",
Milan, Italy

Clara Magri

Center for Vascular Malformations
Italian Diagnostic Center (IDC), Milan, Italy

Laura Moneghini

Division of Pathologic Anatomy, Cytogenetic and Molecular Biology
Department of Health, University of Milan
San Paolo Hospital, Milan, Italy

Lidia Monti

Radiology Unit
Bambino Gesù Children's Hospital I.R.C.C.S., Rome, Italy

Iria Neri

Dermatology Unit
S. Orsola-Malpighi General Hospital, Bologna, Italy

Guglielmo Paolantonio

Interventional Radiology Unit
Bambino Gesù Children's Hospital I.R.C.C.S., Rome, Italy

Annalisa Patrizi

Director of Dermatology Unit, University of Bologna
S. Orsola-Malpighi General Hospital, Bologna, Italy

Massimo Rollo

Director of Invasive Radiology Unit
Chief of Interventional Radiology Unit
Bambino Gesù Children's Hospital I.R.C.C.S., Rome, Italy

Luigino Santecchia

Plastic-Reconstructive Surgery and Maxillo-facial Unit
Bambino Gesù Children's Hospital I.R.C.C.S., Rome, Italy

Massimo Vaghi

Vascular Surgery Unit
Garbagnate Milanese Hospital, Milan, Italy

Nadia Vercellino

Vascular Surgery Unit - Center for Angiomas
Cardiovascular Department
Istituto Giannina Gaslini, Genoa, Italy

LETTERS FROM THE EDITORS

Dear Colleagues and SISAV Members,

The Second National Congress of the Italian Society for the Study of Vascular Anomalies (Milan, 28-29 November 2014) was characterized by the presentation of the guidelines on the subject of vascular anomalies.

The Scientific Committee (chaired by Prof. Francesco Stillo) has completed this onerous and difficult task after over a year of work, also involving other experienced specialists who are current members of our Society.

Without going into the merits of the scientific value of this guide, and leaving the considerations to Prof. Stillo, I would rather bring to your attention the strategic importance and the practical usefulness of the effort that has been made.

The availability of a shared leadership on the diagnostic and therapeutic vascular anomalies can guarantee uniformity of language and procedures, avoiding or at least reducing the chances of improper diagnosis, inaccurate prognosis and inappropriate therapeutic treatments.

Above all, the formulation of guidelines in the context of a scientific society of national importance will be an important support and a valuable reference for both specialists and patients and at the same time a deterrent for those who still rely on outdated and obsolete tools.

Special thanks to Professor Stillo, the Scientific Committee and to all colleagues who have contributed to the successful implementation of this challenging initiative.

Pietro Dalmonte
PAST-PRESIDENT OF SISAV

Dear Colleagues,

About two years ago, when I proposed the implementation of the Guidelines on Vascular Anomalies, there was a moderate pessimism about a positive outcome, given the complexity of the work.

However, based on the experience I gained in the past 15 years in the creation of SICVE and the CIF guidelines as well as the International Consensus, I was sure that we would be able to do a good job, being comforted by the high level of the colleague members of the Scientific Committee and Board of Directors of our Society.

The guidelines are a shared benchmark on the diagnostic and therapeutic pathways to follow in such a controversial field as that of Vascular Anomalies. Therefore, they are extremely useful for colleagues who need tips and advice for an efficient framework when approaching these diseases.

The feature that I consider most important is that Dermatologists, Vascular Surgeons, Radiologists, Vascular Neuroradiologists, Plastic Surgeons, Pathologists, Pediatric Surgeons and Lymphologists have confronted one another to discuss the individual chapters in a timely and critical manner, so that the final result was a multidisciplinary synthesis. The guidelines also represent a great reference in terms of Legal Medicine.

I thank the President of the Society for the moral and material support provided in the achievement of this work.

I also thank the members of the Scientific Committee who supported and completely shared this project.

I especially thank the coordinators of the individual chapters: Maya El Hachem, Vittoria Baraldini, Pietro Dalmonte, Raul Mattassi, Gianni Vercellio and all colleagues who worked with absolute dedication to achieve the final result.

Special thanks to Giuseppe Bianchini, who shared with me all the scientific initiatives of the past 20 years, and was the prompt and precise reviewer of this important work.

Francesco Stillo
CHAIRMAN OF THE SCIENTIFIC COMMITTEE



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Guidelines for vascular anomalies: introduction

P. DALMONTE

Vascular Surgery Unit, Center for Angiomas, Cardiovascular Department, Istituto Giannina Gaslini, Genoa

Objectives

The principal objectives of the present guidelines for management of therapeutic–diagnostic vascular anomalies are:

- to indicate classification criteria for a correct medical record of such pathologies;
- to propose specific diagnostic protocols in order to optimize the use of instrumental tests;
- to define the indications and results from the different treatment methodologies in order to use the best therapeutic strategy in the various cases.

Definition

Vascular anomalies form a heterogeneous group of pathologies of the circulatory system which are characterized by morpho-structural and/or functional alterations of various natures, seriousness and extension that can affect every type of hematic and/or lymphatic vessel, of any diameter or anatomic area.¹

These anomalies represent serious medical-social problems as they are invalidating pathologies that occur in a pediatric or childhood age presenting serious functional, aesthetic and psychological alterations.

Etiology

Vascular anomalies are errors in the embryonic development of the vessels, multifactorial genetically based. In most cases they are sporadic, and manifested in sub-

jects whose family history is negative. There are, however hereditary forms that are correlated to alterations on a genetic base of various angiogenetic factors that regulate the development of the vessels during the phase of embryogenesis.²⁻⁴

Epidemiology

The global incidence of vascular anomalies in the population is not known.

The incidence of vascular tumors is estimated between 4% and 10%. In a study on 3573 children aged 3 years old the incidence of vascular malformations was 1.2%.⁵

Classification

The classification of medical records of vascular anomalies is difficult and controversial due to the heterogeneous pathologic clinical entity and by the confusion generated by medical terminology used in the past.

The need to use a universal scientific language in the last ten years has led to an international classification that allows the clinician to use a simple and pragmatic instrument in order to recognize and manage various vascular anomalies.

In 1996 the International Society for the Study of Vascular Anomalies (ISSVA) approved a classification (Table I) that represents an evolution from the previous classification of Mulliken and Glovacki of 1982. This classification is very simple and schematic. It distinguishes

TABLE I.—ISSVA Classification (1996).

VASCULAR TUMORS

- Infant hemangioma
- Congenital hemangioma
- Tufted angiomas
- Kaposiform hemangioendothelioma
- Spindle-cell hemangioendothelioma
- Other vascular tumors

VASCULAR MALFORMATIONS

SLOW FLOW VASCULAR MALFORMATIONS

- Capillary malformations
- Venous malformations
- Lymphatic malformations

FAST FLOW MALFORMATIONS

- Arterial malformations
- Arteriovenous malformations
- Arteriovenous fistulas

COMPLEX OR COMBINED VASCULAR MALFORMATIONS

TABLE II.—Modified Hamburg Classification (1993).

VASCULAR MALFORMATIONS

Predominantly arterial malformations

- Truncular (aplasia, obstruction, dilatation)
- Extratruncular (infiltrating, localized)

Predominantly venous malformations

- Truncular (aplasia, obstruction, dilatation)
- Extratruncular (infiltrating, localized)

Predominantly lymphatic malformations

- Truncular (aplasia, obstruction, dilatation)
- Extratruncular (infiltrating, localized)

Predominantly arteriovenous malformations

- Truncular (deep, superficial)
- Extratruncular (infiltrating, localized)

Combined or mixed malformations

- Arterial and Venous without fistula
- Hemolymphatic

TABLE III.—ISSVA Classification (2014).

VASCULAR ANOMOLIES

Vascular Tumors

Benign

Locally aggressive or borderline

Malignant

Simple Vascular Tumors

Capillary malformations

Lymphatic malformations

Venous malformations

Arteriovenous malformations

Arteriovenous fistula

Combined Vascular Malformations

Capillary venous malformations

Lymphatic capillary malformations

Lymphatic venous malformations

Capillary arteriovenous malformations

Capillary lymphatic arteriovenous malformations

Other combinations

*Malformation of the Major Vessels**Associated vascular malformations and other congenital anomalies*

vascular anomalies in two main groups that are radically differentiated from an anatomic-pathologic scheme: vascular tumors, that are neoplastic pathologies, and vascular malformations that are formed by disembranching alterations of various areas of the circulatory system. Furthermore, vascular malformations are distinct in relation to the hemodynamic characteristics in two main subtypes (fast flow and slow flow). There are also complex or combined forms.^{1, 6, 7}

Another classification used to diagnose vascular malformation is the Hamburg classification, modified by Belov in 1993 (Table II). It distinguishes vascular malformations in two main subtypes based on the embryogenesis stage where the defect develops: the stem/trunk forms,

that affect the main vascular axis and the extra-truncular forms that affect the peripheral vessels.⁸

The new classification adopted by ISSVA in 2014 (Table III) is an evolution, integrated and detailed than the 1996 one. Vascular tumors are divided in 3 groups in relation to their neoplastic aggressiveness. Vascular malformations are defined as simple and combined, the latter being very detailed. Malformations of the major vessels are also taken into consideration.

For both vascular tumors and each group of vascular malformations a classification of subtypes has been elaborated and will be presented separately in the following chapters of these guidelines.

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Corresponding author: P. Dalmonte, Director of Vascular Surgery Unit, Center for Angiomas, Cardiovascular Department, Istituto Giannina Gaslini, Genoa, Italy.
E-mail: MalfVasc@ospedale-gaslini.ge.it

Guidelines for vascular anomalies: vascular tumors

M. EL HACHEM ¹, I. NERI ², G. PAOLOANTONIO ¹, V. BARALDINI ³, L. MONEGHINI ⁴,
L. MONTI ¹, L. SANTECCHIA ¹, M. ROLLO ¹, A. DIOCIUTI ¹

¹Dermatology Unit, Bambino Gesù Children's Hospital I.R.C.C.S., Rome, Italy

²Dermatology Unit, S. Orsola-Malpighi General Hospital, Bologna, Italy

³Vascular Anomalies Unit, Pediatric Surgery Unit, V. Buzzi Children's Hospital, ICP, Milan, Italy

⁴Pathologic Anatomy, Cytogenetic and Molecular Biology Unit, Department of Health, University of Milan, San Paolo Hospital, Milan, Italy

Classification

The classification adopted by "ISSVA - International Society for the Study of Vascular Anomalies", and later updated and extended divides vascular tumors as shown in Table I.

INFANTILE HEMANGIOMA (IH)

Classification

The infantile hemangiomas (IH) are classified based on:

A. Clinical anatomy in:

a. Superficial IH: exophytic growth in relief compared to the skin surface

b. Deep IH: characterized by a predominant tangential development in the tegument (any outer protective layer or covering, such as a cuticle, seed coat, rind, or shell) thickness

c. Mixed IH

B. Distribution in:

a. focal

b. multifocal

c. segmental

d. eruptive

We recommend to distinguish vascular tumors from a vascular malformation in order to avoid incorrect treatment (1C).

We recommend to distinguish infantile hemangioma from other vascular tumors in order to guarantee a proper and adequate therapeutic approach (1C).

Epidemiology and Pathogenesis

IHs are very frequent, especially in the pediatric population, with an incidence of 3-10%.

Etiopathogenesis is still unknown; it seems to be multifactorial. Female gender, Caucasian race and premature birth are risk factors as also aged mother, placenta previa and pre-eclampsia condition.

Much data suggests a clonal proliferation of endothelial cells that stimulate vasculogenesis. Main hypothesized factors in literature are hypoxia, placenta embolization, pluripotent stem cells and somatic mutation.

The mediators involved in the pathogenesis of the vascular proliferation are VEGF, mTor complex, angiopoietins ANG-1 and ANG-2, E-selectin and the notch pathway.

Natural History

IHs are sometimes present at birth but more frequently appear in the first few weeks of life.

In some cases IH is preceded by a paleness that represents a precursor of the lesion. The IH life cycle is divided in three phases:

1. rapid proliferating phase (0-1 year)

2. involutive phase (1-5 years)

3. involuted phase (5-10 years)

1. IH reaches 80% of its volume in the initial phase of proliferation. It completes its growth in the first 5-6 months. Only 3% of the IH grows beyond the 9th month of life. The superficial form generally grows up to the fifth month, while the deep one manifests later and may continue to grow for some time.

2. The involutive phase is characterized by a softening of the lesion and fading starting from the central area with a progressive reduction of the volume and a decrease of vascularization of the lesion.

3. The involuted phase is characterized by a complete regression with a residual scar, which can demonstrate loose skin, atrophy, telangiectasias and/or fibroadipose tissue. The superficial IH present a higher risk of scarring compared to the deeper lesions.

We recommend closely monitoring the IH when fading appears in the first 3 months. This could be a sign of early ulceration of the lesion rather than a regression (1B).

Clinical Evaluation

Superficial IH: appears as a red or violet- red swelling, smooth or lobulated; the consistency is tight elastic. A pedunculated form is rare. Dimensions are variable from a few mm to a mass involving extended areas (whole limb, hemitrunk, etc.).

TABLE I.—Classification of vascular tumors.

Infantile Hemangioma
Congenital hemangiomas (RICH/NICH/PICH)
Tufted angioma (possible phenomena of Kasabach-Merritt)
Kaposiform Hemangioendothelioma (possible phenomena of Kasabach-Merritt)
Rare hemangioendothelioma
Angiosarcoma
Dermatological vascular tumors (e.g. pyogenic granuloma)

TABLE II.—*Histological diagnosis of vascular tumors.*

	Histological diagnosis	Immunohistochemical
Infantile Hemangiomas	Well localized lesions, lobulated arrangement with endothelial cells without atypia even if swollen and mitotically active in the proliferating phase	GLUT-1 positive CD31 and WT-1 positive
RICH	Small capillaries with prominent endothelium in the lumen and thin basal membrane. The regressive aspects consist in the thickening of the capillary basal membranes, fibrosis, outbreaks of chronic inflammation, dystrophic calcifications, thrombosis and deposits of hemosiderin	GLUT-1 negative
NICH	Large lobules with sharp margins, composed of capillaries with endothelium sometimes protruding in the lumen with thin and thick basal membrane thickened at times. Areas of fibrosis surround the lobules and contain large vessels with thickened muscle wall, mimicking arterovenous malformation and arterovenous fistulas	GLUT-1 negative
PICH	Histological aspects indistinguishable from NICH	
KHE*	Infiltrating growth pattern with features similar to capillary hemangioma and Kaposi sarcoma. Endothelial cells show little or no atypia, cytoplasmatic vasculization and very little mitotic activity. Fibrin thrombi can fill the capillary lumen	
TA°	Presence of multiple nodules in the dermis and hypodermis with a cannon ball distribution. A central vessel with small capillaries around it can be found in the nodules	Besides endothelial cells, which are positive to blood and lymphatic immunocytochemical markers (CD31, CD34 and D2-40); discrete pericytic component, positive to smooth muscle actin

*Kaposiform hemangioendothelioma; °Tufted angioma

Deep IH: appears as an elastic nodular swelling, well defined; the skin appears normal or bluish.

Mixed IH: presents both components.

IEs can appear in any part of the body. Head and neck locations are common, especially on bone prominences (center-facial area).

Segmental superficial lesions can be associated to underlying anomalies (e.g. S. PHACES in case of extended hemangioma of the face or PELVIS*, LUMBAR**, SACRAL*** in the presence of IH of the rectal-genital median line or lumbosacral). The most serious malformation frequently associated to PELVIS/SACRAL/LUMBAR is the lipomyelomeningocele.

*PELVIS: IH perineum, genital anomalies, lipomyelomeningocele, visceral anomalies, imperforate anus or skin tag.

**SACRAL: spinal dysraphism, rectal-genital anomalies, skin anomalies, kidney or urological anomalies, lumbosacral angioma

***LUMBAR: IH of the bottom part of the body, urogenital anomalies, ulceration, myelopathy, anomalies of the skeleton, rectal malformations, arterial and kidney anomalies.

A medullary and abdominopelvic magnetic resonance imaging (MRI) should be performed in all neonates, even if neurologically asymptomatic, having segmental IH, of the lumbosacral midline or of the perineum.

PHACES Syndrome

This syndrome was described by I. Frieden in 1996 as PHACE, without an "S" that corresponds to the sternal defect that was recently added. It is most frequent segmental IH associated to developmental disorders. Females are more prone to it than males (relation 9/1).

Predisposing factors are fair skin photo type familiarity for IH, advanced maternal age and neonate weight less than 1,500 g at birth. The segmental IH seems to be a consequence of suffering tissue of intrinsic origin, namely a vascular defect of the affected skin area; in fact it often manifests at birth with a wide anemic area.

PHACE is an English acronym that means: P: malformation of the posterior fossa; H: hemangioma; A: anomalies of the arteries, especially the aorta; C: heart defects; E: eye anomalies; S: sternal defects or of the supra umbilical raphe. In most cases this syndrome manifests in an incomplete way, always with the segmental hemangioma of the face. The main skin area involved of the IH is V3 (around the beard area: mandibular region, pre auricular, chin, inferior lip, neck and sometimes the breastbone).

VISCERAL IH

Visceral localizations are rare, but they must be investigated in case of multiple eruptive hemangiomas (miliar hemangiomatosis), in neonates having less than 6 months with 5 nodular hemangiomas and hepatomegaly with signs of congestive heart failure.

A liver ultrasound is recommended, as it is the most common involved organ. Liver hemangiomas can be focal, multifocal or diffused.

Diagnosis

The diagnosis of the IH is generally clinical. Some locations require a multidisciplinary approach. It is recommended to consult an ophthalmologist for periorbital hemangiomas and an otorhinolaryngologist (ENT) for laryngeal and auricular involvement. A cardiologist

TABLE III.—*Radiologic Diagnosis of vascular tumors.*

Vascular Tumors	Color-Doppler Ultrasound	Magnetic Resonance Imaging (MRI)
Infantile Hemangioma	PROLIFERATIVE PHASE: Lesion with a parenchymatous aspect, hypoechoic with intense vascularization and high speed flow with low resistances (RI: 0.3-0.5) INVOLUTIVE PHASE: Hyperechoic lesion with fibro-fatty aspect, and poor vascularization	- iso-hyperintensity in T1 - hyperintensity in T2 - "flow void" in T2 (arterial pedicles) - enhancement after medium contrast - absence of perilesional edema - fibroadipose content in regressive stages
Congenital hemangiomas RICH/NICH/PICH	Inhomogeneous lesion, hypo-hyperechoic, with intense vascularization at low resistance (RI: 0.3-0.5)	- iso-hyperintensity in T1 - hyperintensity in T2 - Involvement of the skin - Enhancement after contrast medium
Kaposiform hemangioendothelioma	Solid formation with uneven margins with skin involvement and extension to the soft superficial and deep tissues, inhomogeneous echo structure, infiltrative characteristics, intense vascularization with variable RI (RI: 0.5-0.7), deep coarse stems	Inhomogeneous iso-hypointensity T1 / hyperintensity T2 Widespread and inhomogeneous enhancement after contrast medium Infiltrative appearance in depth
Angiosarcoma	Solid tissue with irregular contours and feathering, widely uneven echostructure, mainly hypoechogenic, intralesional vascularization with not low resistances (RI: 0.7-1)	Inhomogeneous iso-hypointensity T1 / hyperintensity T2 Widespread and inhomogeneous enhancement after contrast medium

should be consulted to investigate cardiac anomalies in segmental IH and to check for signs of heart failure in case of liver hemangiomas. A neurosurgeon is needed for the evaluation of brain anomalies associated with PHACE syndrome.

In rare instances, especially for deep lesions, a histological exam could be necessary. Histological diagnostic for vascular tumors requires:

- Clinical-pathological correlation
- Use of immunohistochemical markers to support the hypothesis of histologic diagnostics
- Knowledge of differential diagnostics (Tables II and IV).

Instrumental diagnosis of vascular tumors is summarized in Table III; a flow chart is added at the end of this chapter (Table III).

A suspect PHACE syndrome should be studied by a cerebral magnetic resonance imaging (MRI), and an echocardiogram. In a newborn with a IH located segmentally in the face with an extension exceeding 5 cm face, an ophthalmologist should be consulted if V1 and V4 face segment is involved; in case of a location of V3 segment an ORL examination should be requested. Specific anomalies of the posterior cranial fossa, of the great vessels and of the aortic arch should be investigated.

In the presence of an IH, even of small dimensions, in the beard area (V3 trigeminal region and upper part of the neck) with scrape we recommend to investigate a subglottic implication in order to start an early treatment (1A).

The IHs that are risky for the life of the patient (subglottic IH, heart failure in very extended forms), func-

tional damage (lip, periocular and mammary gland) or permanent cosmetic damage (IH on the tip of the nose in a girl, the nose filter, the lip and the ear) require a very careful monitoring in order to start an early treatment and prevent severe complications (1A).

In selected cases, a magnetic resonance imaging (MRI) allows to explore the extension of the tumor (orbit and neck), the correlation with adjacent structures and the possible association with developmental defects (PHACE, PELVIS Syndrome, etc.).

An echocardiogram is indicated as screening of patients affected by large segmental hemangiomas of the face, neck and breastbone, in order to find out possible heart anomalies. Same investigation is required in children with liver hemangiomas and arteriovenous shunt. Furthermore, screening of liver functionality and coagulation is indicated in all patients with multifocal hemangiomas. TSH, T3 and T4 must be carried out in children with diffused or multifocal liver hemangiomas.

In most IH cases, history and accurate clinical examination are able to define diagnosis; in some cases the Color-Doppler ultrasound is helpful while in rare cases a bioptic sample is necessary (1C).

Differential diagnosis

Differential diagnosis is necessary in several cases (Table IV).

Treatment

Treatment is required in only 10-15% of IHs. Different therapeutic options are available: medical therapy (Table V), surgical therapy, laser treatment, sclerotherapy

TABLE IV.—*Differential diagnosis of IH.*

VASCULAR ANOMALIES
Congenital hemangioma (RICH / NICH)
Kaposiform hemangioendothelioma (KHE)
Tufted angioma
Vascular malformations, mainly capillary forms (for extended IHs)
Ecrrine angiomatous hamartoma
Pyogenic granuloma
Glomuvenous malformation
NON-VASCULAR PATHOLOGIES
Dermoid cysts
Encephalocele / meningocele
Leukemia (Blueberry Muffin baby)
Myofibroma
Hamartoma
Pilomatricoma, juvenile xantogranuloma, solitary reticulohistiocytoma, spitz nevus, sacral lipoma, neuroblastoma, lipoblastoma, dermatofibrosarcoma protuberans, teratoma.

or combined treatment. These different methods may overlap among themselves in order to block the proliferating phase, accelerate the spontaneous involution of the lesions and treat the residual sequelae.

The indications for treatment are:

- A. Life-threatening IH (high flow heart failure or obstruction/compression of the respiratory airways)
- B. Function-threatening IH (visus, suction, and hearing)
- C. Ulcerated IH, not responding to topical treatments
- D. IH with a risk of permanent disfigurement.

Treatment is limited to cases where there is risk of life, functional damage, relevant aesthetic damage and/or permanent ulcerated IH (1B) (Table V).

Propranolol

Oral propranolol is the first choice treatment of IH (1A).

Propranolol is a beta adrenergic non selective antagonist. The mechanism of action, not yet clear, seems to be: vasoconstriction, inhibition of VEGF and induction of apoptosis.

Contraindications

Contraindications using propranolol are asthma, hypotension, peripheral vascular disease, some heart diseases (A/V block of II and III, SSS, cardiogenic shock, la bradycardia, heart failure, and Princemetal angina) and pheochromocytoma.

We recommend that parents should be educated on the oral propranolol therapy in order to recognize possible side effects (1B) (Table VI).

Timing, dose and follow up of the treatment

Cardiological evaluation and cardiogram should be performed before the beginning of the treatment (1C).

TABLE V —*Medical therapy.*

Systemic	Propranolol, Corticosteroid, Vincristine, Interferon
Topical	Propranolol, Timolol
Intralesional	Cortison

If the treatment is recommended it should be started as soon as possible (1B).

In some cases, the treatment should be started before 5 weeks of age (e.g. closed eyes, subglottic IH) or after 5 months of age (e.g. functional damage, life-threatening conditions or children referred late).

Treatment should be carried out in a structure with adequate equipment in case of side effects, especially cardiovascular complications (1C).

Children at high risk must be inpatients (aged less than 2 months, weighing less than 2Kg, cardiovascular or respiratory comorbidity or abnormal glucose metabolism, inadequate social support). A day hospital regime is used in all other cases where vital signs (PA, FC) and fasting glucose are monitored for 2 hours (1B).

The dose of the drug is 1-3 mg/Kg/day divided generally in 2 administrations only; in case of children at high risk it could be divided in 3 (1A).

A 3 mg/Kg/day maintaining dosage must be preceded by a period of 1 or 2mg and can be increased in severe cases (laryngeal, upper eyelid) or in case of a poor response after the first month of therapy.

Children at high risk start with 1 mg/Kg/day dosage that can be increased after 4-7 days, if well tolerated, to 2 and after 4-7 days to 3 mg/Kg/day repeating the monitoring (1B).

Monthly monitoring is recommended at the hospital to see if there are side effects. Clinical evaluation, photographic documentation, weighing and measure of cardiac frequency and blood pressure is recommended (1B).

At each checkup, clinician should ask if the child manifested respiratory symptoms as cough, wheezing and scrape (1B).

In case of abnormal sweating and irritability, a glucose test should be run (1B).

If there is vomiting, diarrhea or lack of appetite, treatment should be temporarily suspended. (1B).

In case of heart rate <70bpm (<80 in neonates) or in case of signs or referred arrhythmia/cardiopathy or maternal history of connective tissue disease an ECG and cardiological evaluation should be carried out (1C).

In case of diagnostic/therapeutic procedures that require fasting, a dose of glucose by intravenous injection should be administered to avoid interruption of the therapy (1C).

Propranolol treatment do not need to be modified during vaccination schedule (1C).

The duration of treatment should be at least 6 months and preferably until the age of 1 year in order to avoid relapsing.

In some cases, the treatment should be prolonged as long as needed (e.g. intraparotid IH, persisting impairment and still improving from the therapy).

However, in case of recurrence, a new therapy cycle can be started (1C).

Suspension of the treatment should not be gradual (1C).

Side effects of oral propranolol are summarized in Table VI.

TABLE VI.—*The main side effects of propranolol.*

Bradycardia
Hypotension
Vasoconstriction
Hypoglycemia (clinically it is most relevant and frequent in neonates having less than 3 months or premature babies)
Bronchospasm
Gastrointestinal disorders: diarrhea, vomiting and constipation
Central nervous system disturbances: sleeplessness, irritability, agitation (more frequent and of yet unknown pathogenesis)
Skin rash, erythema and urticaria

The use of propranolol in PHACES is controversial because of the risk of cerebral ischemia. However, in the literature cases treated without any complication are reported. One study analyzed the cerebral perfusion of children with PHACES treated with propranolol by the SPECT (single photon emission computed tomography) technique before and after treatment, and it did not show any evidence of reduced perfusion. Therefore it seems that propranolol does not increase the risk of cerebral ischemia.

Corticosteroids

Corticosteroids at a high dose (prednisone or its equivalent) stop the proliferative phase of IH and only rarely induce regression. Corticosteroid suppresses VEGF-A in the stem cells of the hemangioma inhibiting vasculogenesis.

Corticosteroids are currently the second choice treatment if propranolol is contraindicated or causes side effects (1B).

Efficacy, tolerability and reduction of the need for surgery at the end of treatment is less than after propranolol (1B).

The dosage is 2-3 mg/kg/day administered once in the morning for a cycle of about 1-2 months (1B).

The response rate is about 35-85%. Recurrences are reported in 15-37% of cases. The side effects are those known in the high-dose systemic corticosteroids treatment. Growth retardation is common when treatment is started before 3 months of life and continued beyond 6 months. The use in premature infants appears to cause reduced growth of the brain.

The quality of life of children treated with systemic corticosteroids and their families is more compromised compared to those treated with propranolol.

Vincristine

It is a derivative of Vinca alkaloids and inhibits mitosis and angiogenesis.

The use of Vincristine is indicated in life-threatening IH resistant to oral propranolol and corticosteroid, or when these two drugs have contraindications or side effects (1B).

The usual dose is 0.05 mg/kg in patients weighing less than 10 kg and 0.75-1.5 mg/m² in those weighing more than 10 kg, administered intravenously weekly for 3-4 doses (1B).

The route of administration must provide a central access since the drug is a vesicant (1B).

The side effects are: neurotoxicity, irritability, decrease of deep reflexes, constipation, abdominal pain, paralytic ileus, cranial nerve paralysis, bone pain, alopecia and myelosuppression. Nephrotoxicity is not significant in children.

Treatment should be administered in collaboration with an onco-pediatric hematologist monitors to the neurological and hematological toxicity (1B).

Interferon-alpha

The mechanism of action is the inhibition of angiogenesis, endothelial cell migration and BFGF. A response of 90% has been described in cases resistant to steroid although with longer response times.

Interferon-alpha should be considered as a last choice in life-threatening cases due to serious neurological effects (1B).

The dose is 1M IU/m² increased to 3 M during the first month with a treatment lasting from 2 to 12 months (1B).

The reported side effects are spastic paraplegia, increase in transaminases, neutropenia, and a flu-like syndrome.

Topical Therapies

Topical therapies are advisable only for superficial and not complicated hemangiomas (IC).

Following agents are used:

- timolol
- propranolol
- high patency corticosteroid
- imiquimod.

Timolol (a non-selective beta-blocker approved for the treatment of glaucoma) and topical propranolol were used 2VV/day for 3-6 months in the proliferative phase of superficial non ulcerated hemangiomas with an efficacy in 90% of the cases.

Side effects, especially in premature infants are possible.

Topical timolol/propranolol is the topical treatment of first choice for superficial, not complicated hemangiomas (1B).

The topical beta-blockers appear to be absorbed percutaneously. Further randomized clinical trials are necessary to determine precisely the efficacy and safety (1B).

Laser treatment of vascular tumors

Laser therapy can be used with wavelengths and diversified modes. Pulsed Dye Laser with pulse emission wavelength 585-595 nm is considered since the '90s, the optimal laser for the treatment of hemangiomas.

Indications for laser therapy include:

- infantile hemangiomas in the prodromal phase (IIAC). This proposal is not accepted by all the scientific community because of the risks of ulceration
- very superficial hemangiomas limited to the thickness of the dermis (1C)
- ulcerated hemangiomas (1C)
- residual telangiectasia post-involution (1A)

Neodymium laser: YAG (wavelength 1064 nm) and diodes laser with transdermal, intralesional technique can be used for deep lesions (1C).

A more recent introduction is the sequential method that provides a double pulse

Dye-Nd:YAG provided by the same device. The sequential method is also effective for the treatment of residual telangiectasias.

The laser Nd:YAG with a mode that envisages the use of a bare fiber of 600 microns is commonly employed for the treatment of hemangiomas localized to the mucosa of the oral cavity and the epiglottic region.

The fractionated CO₂ laser, used by several authors for the treatment of certain cutaneous dystrophic post-involution results, has proven to be effective.

Laser treatment complications

Complications may be transient or sometimes permanent especially if performed incorrectly.

Most common complications are ulceration, skin discoloration and atrophy. Hyperpigmentation is particularly common in people with dark skin, as in South American and Asian populations. The use of pulses of longer duration (10 ms vs. 0.5 ms) reduces the risk of such complications.

In exceptional cases, according to some experts, injection sclerotherapy with Polidocanol 0.5-1% or Sodium tetradecyl sulfate 0.5-1% is a complementary treatment for spider veins capillaries and residual ectatic draining veins remaining after the involution of IH.

Laser photocoagulation treatment of IH with different wavelengths is indicated as part of a multimodal treatment for: ulcerated IH, deep facial IH, segmental IH of the oral cavity and upper respiratory tract, residual telangiectasias and cutaneous dystrophic post involution results (1C).

Surgical Treatment

Indications

Indications for surgical treatment of vascular tumors are similar to those of medical treatment (potential risk of life, functional damage, cosmetic damage or permanent ulcer).

Surgery is the first line of treatment, in combination or without laser treatment when:

- medical therapy is contraindicated
- medical therapy fails
- medical therapy obtains only a partial effect, especially when the IH is localized in noble seats (face and periorificial regions)
- there is exceeding or fibroadipose residual tissue after involution

Surgery is not indicated in superficial and segmental

hemangiomas because the scar would be worse than the post spontaneous involution.

The risks of surgical procedures are rare (mostly related to general anesthesia); surgery causes permanent scars.

Scars are to be positioned, if technically possible, on the natural lines of tension of the skin or in less visible areas for cosmetic reasons.

Surgery Timing

1. In the proliferative phase, the lesion is highly vascularized with difficult control of hemostasis during surgery.

2. In the involutive phase, the surgical approach is less risky, but it is appropriate to consider the intensity of vascularization.

3. In involuted phase, the hemangioma presents a reduced or absent blood flow. Often the remaining skin is redundant, discolored, translucent and inelastic, recalling an empty bag. The removal at this stage is relatively easy, since the tumor is composed by fibro adipose tissue.

A surgical treatment of IH is recommended during the phase of involution and preferably after the involuted phase (1C).

Surgery should be performed early:

- a. in exophytic pedunculated lesions
- b. when the planned surgical scar is better than expected after spontaneous regression (scalp, orbitofrontal eyelid)
- c. on an IH at the tip of the nose (Cyrano) when it may cause resorption of the alar cartilages, skin necrosis and superinfection
- d. Ulcerated IH non responder to medical therapy or laser.

Surgical treatment should be performed before school age, preventing psychological aspects related to the image of the distorted body image, particularly in case of facial hemangiomas (1C).

Surgical risks are:

- a. unmanageable bleeding
- b. lesions of noble structures (e.g. facial nerve)
- c. asymmetries or residual deformity that potentially get worse with gradual growth

CONGENITAL HEMANGIOMAS

These hemangiomas are fully developed at birth, usually they are single. They differ from the classic IH due to the absence of the proliferative phase and negativity to GLUT-1. We recognize two varieties: rapidly involuting congenital hemangioma (RICH) and not involuting congenital hemangioma (NICH). A third variety: "partially involuting congenital hemangioma" (PICH) has recently been identified.

They represent about 3% of hemangiomas and therefore are rare vascular tumors.

Epidemiology and pathogenesis

There is no gender predilection although recently it has been reported that NICH is more frequent in female. The pathogenesis is unknown.

TABLE VII.—*Kaposiform hemangioendothelioma e tufted angioma medical therapy.*

Therapeutic choice	KHE/TF without KM phenomenon	KHE/TA + KM phenomenon	Resistant cases
First Choice	Prednisolone 2 mg/kg/day Duration: 3-4 weeks (varies in relation to clinical and coagulopathy), stabilizes the tumor without allowing complete regression	● Vincristine 0.05 mg/kg iv 1/week for 20-24 weeks + prednisolone 2-3 mg/kg/day or IV methylprednisolone 1.6 mg/kg ● Duration: 20-24 weeks, in relation to the resolution of the acute phase, tumor response and to toxicity of the drug	Cyclophosphamide or vincristine and cyclophosphamide, or even triple treatment with actinomycin D (regime "VAC")
To be evaluated	Aspirin or other antiplatelet dose of 2 to 5 mg/kg/day	● Antiplatelet drugs, ticlopidine and clopidogrel variable results ● Antifibrinolytic: aminocaproic acid and tranexamic variable results	

RAPIDLY INVOLUTING CONGENITAL HEMANGIOMA (RICH)

History

The RICH is already developed at birth and quickly involutes. The regression completes spontaneously usually during the first 6-18 months of life, sometimes leaving a redundant skin similar to cutis laxa and telangiectasias.

In rare cases, the involutive phase stops and the lesion persists with an aspect similar to a NICH configuring a PICH that tends to remain stable over time.

Clinical evaluation

Three morphological variants of RICH are clinically distinguished: I) vascular lesion detected by a red-purple color, with coarse telangiectasias on the surface; II) plaque with little red-purple color and telangiectasia; III) vascular swelling detected by a grayish color with fine telangiectasias surrounded by a pale halo. Elective sites are the limbs (especially the joints), head and neck. Possible complications include bleeding, transient thrombocytopenia and self-resolving ulceration that usually appears at the center of the lesion at the beginning of the phase of involution.

Follow-up is necessary in the regression phase with periodic clinical and laboratory checkups (platelets, D-dimer, fibrinogen and fibrinogen degradation products).

Diagnosis

Diagnosis is essentially clinical. It is necessary to differentiate RICH from fibrosarcoma, rhabdomyosarcoma, kaposiform hemangioendothelioma and tufted angioma. In some cases it is necessary to perform instrumental diagnosis and/or histological study (Tables II, III).

NON INVOLUTIVE CONGENITAL HEMANGIOMA (NICH)

Clinical evaluation

NICH is already present at birth with a hyperhemic lesion, flat in 30% of the cases, nodular or as a plaque in 70% of the cases, ranging in color from red to bluish-white surrounded by peripheral whitish halo. The surface is often covered by coarse telangiectasia and ectatic veins evident in the periphery. Elective sites are trunk and lower

limbs; less frequent is the involvement of head and neck. The evolution is characterized by a progressive gradual growth together with the physiological growth of the patient till puberty. Peripheral veins may become more apparent. Few patients reported pain.

In some cases it is necessary to perform instrumental diagnosis and / or histological study (Tables II, III).

PARTIALLY INVOLUTIVE CONGENITAL HEMANGIOMA (PICH)

Described recently, it shows a clinical and radiological aspect typical of RICH, having a rapid involution in the first year of life, and regression in the following 2-3 years. However it does not regress completely and assumes NICH-like characteristics.

It is recommended to correctly define the diagnosis of the type of congenital hemangioma in order to ensure a correct and early therapeutic approach if when necessary (1C).

Congenital hemangiona therapy

RICH, generally, does not require any treatment, due to a possible rapid involution. The treatment is necessary for the residual lesions of RICH, PICH and NICH. Therapy is based on embolization and/or surgery; it is indicated in early childhood, before body awareness, or in adolescence when the child will decide to be treated. In case of excessive atrophy, autologous filling (fat, dermis) or acellular dermis can be used. The residual telangiectasias can be managed with Pulsed Dye Laser.

KAPOSIFORM HEMANGIOENDOTHELIOMA (KHE)

KHE (also called Kaposi-like hemangioendothelioma, hemangioendothelioma, Kaposi-like hemangioma and hemangioma with aspects similar to Kaposi) is a rare aggressive vascular tumor and can be associated to KM phenomenon.

Epidemiology and pathogenesis

KHE shows no predilection for sex or race. Epidemiological studies of incidence and prevalence have not been reported. In a variable percentage up to 30% to KHE can lead to exitus.

History

KHE usually appears in early childhood or in the first year of life, rarely it is already present at birth. The onset in adulthood is exceptional. The risk of association with the phenomenon Kasabach-Merrit is higher in large KHE.

KM phenomenon, reported in about half of cases, is characterized by consumption coagulopathy for entrapment of platelets in the tumor that sometimes may lead to death; it may regress in the first 2 years of life. KHE is a vascular tumor with low grade malignancy, locally aggressive with a tendency to infiltrate the surrounding tissues but with a low metastatic potential, especially to regional lymph nodes. Distant metastases are exceptional. This tumor expresses, in addition to common blood markers, also lymphatic markers, such as podoplanin.

Death is reported in 10-30% of cases due to complications related to the tumor or to the phenomenon of KM.

Clinical evaluation

We distinguish cutaneous and extra cutaneous forms especially affecting the neck, mediastinum, thyme and retroperitoneal region.

Usually the cutaneous form appears as a bluish-red vascular swelling, superficial or deep, ranging in size from a few cm to involvement of an entire limb, hard and not compressible. The lesion can affect the skin and subcutaneous tissue to the fascia, muscle and sometimes bone. The tumor is mainly located at the trunk and extremities, more rarely at the head and neck. Small tumors (<5 cm) seem to have a better prognosis due to the low risk of complications, such as KM. In all cases, platelets count, PT, PTT, D-dimer and fibrinogen must be performed.

Diagnosis

The diagnosis may be suspected clinically and supported by an Echo color ultrasound, by a magnetic resonance imaging (MRI) but requires histological confirmation (Tables II, III); a biopsy should be performed in all cases of suspected vascular lesion characterized by a rapid growth over the normal age of the proliferation of an IH.

If KM phenomenon is suspected a platelet count, dosage of D-dimer and fibrinogen must be performed.

Thrombocytopenia may be severe with values <50 x 10⁹/mL (1C).

Therapy

The treatment of KHE uncomplicated by KMP is controversial. Some authors suggest a simple follow-up. However, the risk of scarring, tissue atrophy, joint contractures or muscle fibrosis must be assessed.

Radical surgical therapy when possible is the gold standard. In many cases it is not feasible due to the risk of bleeding, and the aggressive extension of the lesion. It is suitable in small lesions, more frequently in adolescents and in adults or for symptomatic lesions that do not respond to medical therapy. During childhood, early correction of contractures secondary to the tumor may be necessary.

Medical therapy varies depending on the clinical aspect of KHE and the association to KM phenomenon (Table VII).

TUFTED ANGIOMA (TA)

The TA (also known as tufted hemangioma, progressive capillary hemangioma or angioblastoma of Nakagawa), a rare histologically benign vascular tumor, is now considered in the same clinical spectrum of the KHE and not a separate entity.

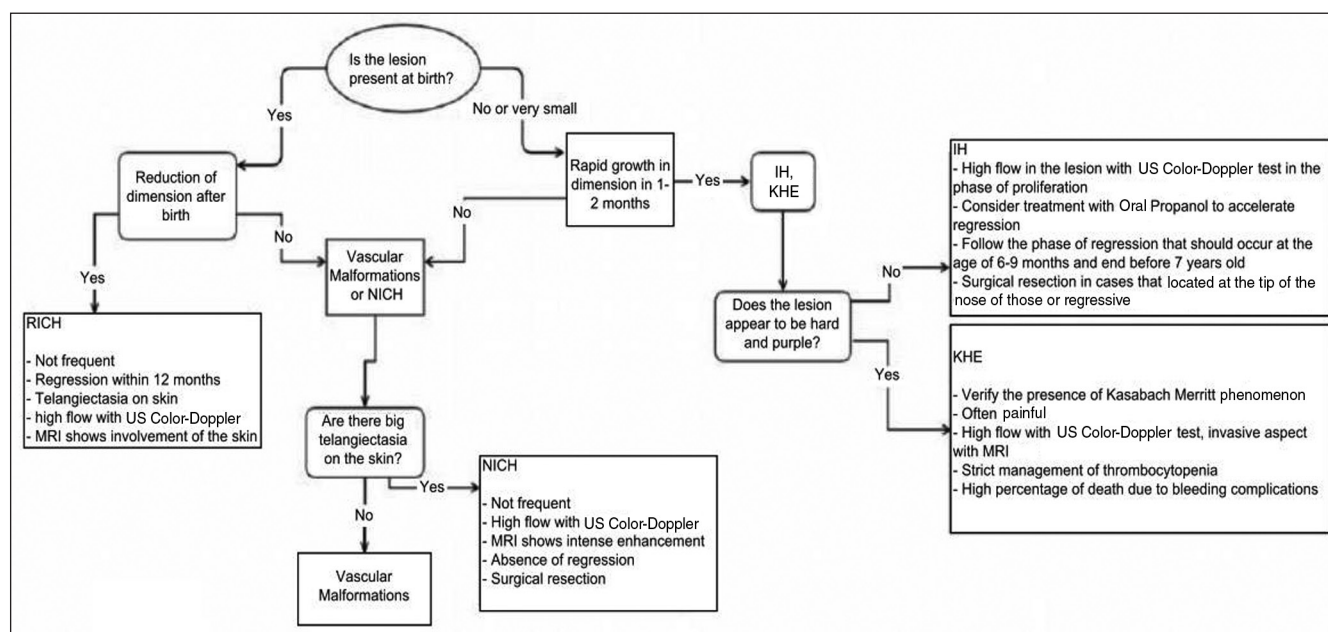


Figure 1.—Diagnostic course of vascular tumors.

Epidemiology

It shows no predilections of race or sex. It is congenital or acquired with onset usually within the first 5 years of life. Although originally described in young adults, it actually occurs more commonly in the prepubertal age.

History

The lesion tends to grow slowly and then stabilize. Spontaneous regression is possible in the first two years of life. However, in some cases regression is protracted and KM phenomenon can be associated.

Clinical Evaluation

It usually appears as a macula or plaque with papules or nodules on the skin surface, of variable color from pinkish-red to red-brown or purple. It can be a few mm to several cm in diameter, with a stretched elastic consistency, in some cases it is painful. Hyperhidrosis or, more rarely, hypertrichosis can be observed on the surface. Elective sites are the upper chest, shoulders and neck. It rarely involves the oral mucosa.

Although malignant transformation of the tumor has never been reported it requires careful follow-up especially in early childhood, due to the risk of complications such as KM phenomenon.

Diagnosis

The diagnosis is clinical, but in some cases it is necessary to perform instrumental and/or histological diagnosis (Tables II, III).

Therapy

The treatment of a tufted angioma is not always necessary. The decision and choice of therapy vary depending on the aspect of the lesion, symptoms and possible association with the KM phenomenon; when necessary, the same therapeutic scheme adopted in KHE should be applied (Table VII).

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Corresponding author: I. Neri, Dermatology, University of Bologna, Bologna, Italy.
E-mail: iria.neri@unibo.it

Guidelines for vascular anomalies: capillary malformations

V. BARALDINI ¹, A. DIOCIAIUTI ², L. MONEGHINI ³, I. NERI ⁴, C. GELMETTI ^{5, 6}

¹Vascular Anomalies Unit, Pediatric Surgery Department, V. Buzzi Children's Hospital, ICP, Milan, Italy

²Dermatology Unit, Bambino Gesù IRCCS Pediatric Hospital, Rome, Italy

³Pathologic Anatomy, Cytogenetic and Molecular Biology Unit, Department of Health, University of Milan, San Paolo Hospital, Milan, Italy

⁴Pediatric Dermatology Unit, Maggiore Hospital, Mangiagalli and Regina Elena General Hospital, Milan, Italy

⁵Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

⁶Department of Dermatology, Fondazione IRCCS Cà Granda "Ospedale Maggiore Policlinico", Milan, Italy

Definition

Capillary malformations (CM) ¹⁻³ are low-flow vascular anomalies affecting the skin and mucosal layers. They appear as congenital spots ranging in color from pink to red-purple, histologically characterized by the presence of a dense network of small vessels (proper capillaries and post capillary small veins) abnormally and permanently dilated located within the thickness of the papillary and reticular dermis of skin and mucous membranes.

CM can be isolated or associated with other congenital anomalies as part of complex polimalformative syndromes. The description of these syndromic patterns will be addressed in the section dedicated to them.

Table I below illustrates the ISSVA 2014 Classification, where different syndromic situations are included as subtypes of capillary malformations. In this paper the associations of different anomalies will be addressed in the chapter relative to Complex Pluri-Malformations Syndromes. Only isolated CM will be discussed in this chapter.

CM nomenclature is rather confusing. The term of "angioma piano", widely used in Italian language, is a source of ambiguity and should be abolished.

TABLE I.—ISSVA Classification (2014).

CAPILLARY MALFORMATIONS (CM)

- CM skin / mucosa ("port-wine" stain)
- CM associated with hypertrophy of the bone and/or soft tissue
- CM associated with abnormalities of the SNC and/or ocular system (Sturge-Weber syndrome)
- CM associated with arteriovenous malformation
- CM associated with microcephaly (MICCAP: microcephaly-capillary malformation)
- CM associated with megalencephaly polymicrogyria (MCAP: megalencephaly-capillary malformation-polymicrogyria)
- Telangiectasias
- Purple Hemorrhagic Telangiectasia (HHT: Hereditary hemorrhagic telangiectasia)
- Cutis marmorata Telangiectatica Congenita (CMTC)
- Nevus flammeus neonatorum (Nevus simplex/Salmon patches/"angel kiss"/"stork bite")
- Other

Two main subtypes of CM can be distinguished:

a) Medial congenital capillary macula

Synonyms: *nevus flammeus neonatorum*, *nevus simplex*, "salmon patch" or "fading capillary stain"

Extremely common in Caucasian babies, clinically appears as a skin macula evident at birth, of pinkish-red color vanishing to digital pressing, possibly associated with thin telangiectasias, typically characterized by a progressive spontaneous resolution within the first years of life in most cases.

The most commonly affected anatomical sites are located along the body midline:

- the neck and occipital area ("stork bite"); in this anatomical site the macula tends to persist into adulthood
- upper eyelids, mid- forehead, glabella, sometimes extending to the tip of the nose and upper lip ("Angel Kiss").

The sacral region is less frequently affected ("Butterfly Mark"): in this area the CM may affect a single area along the medial line or it can be composed by multiple spots randomly arranged on the back.

b) Lateral congenital capillary macula

Synonyms: *port wine stain (PWS)*, *nevus flammeus*

It presents at birth as a pinkish-red skin spot of variable size with sharp edges, typically vanishing to finger pressing.

The macula can manifest on any part of the body with a predilection for the face, where often takes a "mosaic" or a metamer-like distribution along the segmental distribution area of the embryonic vascularization.³⁹

The red macular stain can be single or multiple, unilateral or bilateral. Extension to the mucosal surfaces is possible.

The distribution of CM to the forehead of can be the indicator of a of Sturge-Weber syndrome, where leptomenigeal and ocular involvement are observed.

The distribution of CM to a lower limb with a "geographical contour" pattern, usually predicts the further development of venous and lymphatic abnormalities. The possible extension to external genitals and ipsilateral abdominal wall skin with a precise outline along the under umbilical midline, together with the presence of overgrowth in the affected limb, superficial dysplastic varicosities and sometimes bleeding skin angiokeratomas suggest the diagnose of complex syndromic vascular malformations (see Klippel-Trenaunay and Parkes-Weber syndromes).

Epidemiology

CM represent the most common form of vascular malformations.¹⁻³

The incidence of CM in the general population has been estimated at 0.3 % at birth, with the exclusion of "medial congenital capillary macula" forms, present in nearly half of the infantile Caucasian population.

The sex ratio is equal. CM are potentially ubiquitous, but most of them involve the head (57% the central face area) and 85% are unilateral, with segmental distribution.

Etiopathogenesis

CM are determined by an error during the embryogenesis conditioning the development of an abnormal number of capillaries in the dermis or their permanent abnormal dilation.

They are mostly sporadic forms but rare familial forms of CM have also been reported with dominant autosomal transmission with incomplete penetrance and variable expressivity.⁸

A number of different aetiopathogenetic mechanisms for CM have been hypothesized:

1 – The capillaries ectasia could be determined by a lack of neuronal vascular control. Immunohistochemical studies have demonstrated a lower number of nerve fibers associated to the dilated capillaries in capillary malformations.^{9, 10}

2 – Over-expression of VEGF and VEGF receptor, resulting increased in capillary malformations.¹¹

3 – In recent studies a somatic mutation of the GNAQ gene has been identified in patients affected by CM and by Sturge-Weber syndrome.¹² Non-syndromic CM could be the result of a late somatic mutation in vascular endothelial cells, while in Sturge-Weber syndrome an earlier mutation might involve a progenitor precursor of multiple tissues responsible for the overall syndromic neurocutaneous pattern.

4 – Various mutations of the RASA1 gene, already known for its association with some arteriovenous malformations, might also be involved in the pathogenesis of some CM. The RAS-gene family is involved in the regulation of cell proliferation and differentiation and in the organization of endothelial cells.¹³

Clinical presentation

Capillary malformations present at physical examination as persistent flat vascular skin spots vanishing to digital pressing, ranging in color from pink to red-purple.

The affected skin has normal temperature. In neonates CM can be sometimes confused with infantile hemangioma during the prodromal phase, but the misdiagnosis can be easily avoided with a simple evolutionary observation since CM are stable, while infantile haemangioma evolve with a rapid proliferation. In differential diagnosis also arterio-venous malformations in their early phase must be considered.

Natural evolution

Typically CM are already present at birth and they persist throughout life increasing in surface in proportion to body growth. At birth CM often have a bright red color secondary to the high hemoglobin content in skin capil-

laries during the neonatal period or to the phenomenon of vessel paralysis.

The color intensity naturally fades within a few months of life. Some forms may evolve over the years to a purple color due to progressive skin thickening and progressive increase in capillaries density within the dermis.

Sometimes the affected skin evolves towards a progressive nodular hypertrophy in adulthood with a progressive thickening and the development on the surface of skin nodules with a typical "cobblestone" appearance.

Furthermore lateralized forms may be associated with hypertrophy of the affected area: when localized on half side of the face, with involvement of the cheek, chin and lip they can cause hypertrophy of superficial soft tissues and of the skeleton corresponding to the maxillofacial region concerned. When localized on the limbs they may be associated with overgrowth of the affected limb.

Diagnosis

The diagnosis of CM is essentially clinical, based on clinical history and complete physical examination prior to any complementary investigation.

The instrumental evaluation must distinguish pure capillary forms from mixed capillary-venous ones and exclude the possible presence of congenital arterio-venous micro-shunts present in capillary-arterio-venous forms.

Angiokeratomas are combined capillary-lymphatic vascular malformations. In neonates differential diagnosis also arises with segmental infantile haemangiomas in their prodromal phase.

Histology

CM are histologically characterized by the presence of permanently dilated, rounded, unbranched small vessels, filled with red blood cells. Vessels density in skin affected by CM is higher than in the normal surrounding tissue.¹⁴

The vessel wall is thin, being constituted by a single layer of endothelial cells which are flat and free of abnormalities, resting on a basal membrane surrounded by occasional pericytes that increase in number going towards post-capillary venules.^{15, 16}

CM are located mostly within the skin, in the papillary and reticular dermis, more rarely they extend to the subcutaneous tissue.^{16, 17} The area affected by CM generally tends to thicken progressively with increasing age extending to the surface and in depth.¹⁷

Color Coded Duplex Sonography

Duplex Ultrasound Scan is the first level study in the diagnostic protocol for the differential diagnosis of complex capillary-venous-lymphatic or arterio-venous-capillary vascular malformations. MRI should be recommended as second level study if the clinical picture requires it.¹⁸

Duplex Ultrasound Scan allows firstly an evaluation of dermis and subcutaneous tissue thickness. It also allows to detect the presence of dysplastic veins in the subcutaneous tissue or to identify micro-arterio-venous shunts investigating their distribution and flow.¹⁸

When CM is localized at a lower limb Venous Duplex Ultrasound Scan is crucial to detect potential associated anomalies of the superficial or deep venous system in the screening of complex poli-malformative vascular syndromes.

MRI

Magnetic Resonance Imaging (MRI) with or without contrast medium can be useful to detect associated anomalies in the complex vascular syndromes.¹⁸

Arteriography

Arteriography is indicated in very rare cases, for instance when Parkes-Weber syndrome is suspected or when an arterio-venous malformation is suspected to be associated with the CM.

Other Investigations

When complex or systemic syndromes are suspected it is necessary to integrate the diagnostic protocol with instrumental targeted investigations: in particular a brain CT or MRI scan in Sturge-Weber syndrome, a lower limb venography in Klippel-Trenaunay syndrome, a peripheral arteriography in the Parkes-Weber syndrome.

Periodic monitoring during childhood by orthopedic follow-up and comparative X-rays for measurement of lower limbs length discrepancy is recommended when CM localized in a lower limb is associated with the affected limb overgrowth (see Chapter on Complex Vascular Malformations).

The diagnosis of capillary malformation is essentially clinical, based on clinical history and complete physical examination prior to any complementary investigation (Recommendation Grade 1B).

Duplex Ultrasound Scan is the first level study in the diagnostic protocol for the differential diagnosis of complex capillary-venous-lymphatic or arterio-venous-capillary vascular malformations. MRI should be recommended as second level study if the clinical picture requires it (Recommendation Grade 1C).

Treatment

Laser Photocoagulation

Laser photocoagulation by vascular lasers is the first choice treatment for pure capillary malformations, especially effective on facial localization.¹⁹⁻²⁵

Laser treatment of capillary malformations involving the face should preferably be started early in infancy for a better therapeutic response of the treated skin and for a psychosocial benefit on the quality of life of patients if treated early.^{26, 27}

Technological advances improved the specificity and selectivity of the method up to the use nowadays of Pulsed Dye Laser: it allows a selective hemoglobin photothermolysis with intra capillary red blood cells micro-agglutination, resulting in obliteration of vessels without scarring.

Pulsed Dye laser treatment efficacy was progressively increased by the introduction of devices capable of delivering longer wavelength pulses (595 nm), of longer duration, with larger diameter spot size (up to 12 mm) and by the use of skin cooling devices which allow the use of higher energy levels reducing the risk of thermal damage and the associated painful sensation.

More recently the Sequential Firing method was introduced, which employs a rapid sequence of a double pulse

Dye-Nd:YAG: the two pulses of different wavelengths (595-1064 nm, respectively) emitted in rapid sequence by the same device at a short time distance allow the processing of oxyhemoglobin into methemoglobin by the preliminary pulsed dye pulse and a secondary deeper penetration of the Nd:YAG radiation up to a depth of 7-8 mm.

The sequential firing method is indicated for the treatment of hypertrophic capillary malformations or PWS resistant to Pulsed Dye laser treatment and it is also effective for the treatment of other types of vascular anomalies such as angiokeratoma, pyogenic granuloma and spider nevus.²⁸⁻³⁰

Only a limited percentage of CM completely vanish: in most cases the skin color intensity fades significantly from treatment to treatment. Various methods have been proposed in the attempt to predict the response to laser treatment, in relation to the skin color or to the intradermal capillaries depth and size, such as spectrophotometry, video-capillaroscopy and high frequency ultrasounds.

It has been shown that skin areas with a lower response to laser treatment are characterized by increased dermis thickness, reduced innervation, higher capillaries density rate and higher capillaries average caliber size.³¹⁻³⁴

Laser photocoagulation by vascular lasers is the first choice treatment for pure capillary malformations, especially recommended for facial localization.

Laser treatment of capillary malformations involving the face should preferably be started early in infancy (Recommendation Grade 1C).

Sclerotherapy

Sclerotherapy is not indicated in pure CM.

Combined capillary-venous malformations may benefit from a multimodal treatment, combining sclerotherapy of subcutaneous veins and telangiectasias by percutaneous sclerosants injection and laser photocoagulation of the small capillaries net.

In mixed capillary-venous or arteriolar-capillary forms and in telangiectatic forms percutaneous injective sclerotherapy can be useful. Different sclerosing agents can be employed, such as for instance Polidocanol or Sodium tetradecyl sulphate (STS) at different concentrations (Recommendation Grade 1C).

Surgery

The role of surgery in pure capillary malformations is very restricted, especially in the craniofacial area. The required large incisions do not produce satisfactory cosmetic results since they produce extremely disfiguring scars.

Surgery should only be considered in selected cases as follows:

— In case of skin-mucosa and skeletal hypertrophy of the face associated with the presence of CM: in particular when it is necessary to reduce labial or mandibular hypertrophy to correct contour deformities;

— In hypertrophic CM, especially in adulthood when large cobblestones and pedunculated vegetations are present, if laser therapy is ineffective due to the marked skin hypertrophy;

— Surgical removal of angiokeratomas is indicated

only in selected cases, especially in the localized hypertrophic forms that can be radically removed, since high risk of postoperative wound dehiscence and high rate of local recurrence on the surgical scar are associated with partial removals.

The surgical technique can take advantage from the use of skin expanders or rotational flaps for reconstructive purposes.³⁵⁻³⁸

Surgery should be taken into consideration only in selected cases: for the correction of contour deformities of the face secondary to labial or skeletal hypertrophy associated with CM; for removal of large "cobblestone" vegetations in hypertrophic CM in adulthood; for radical removal of hypertrophic localized angiokeratomas (Recommendation Grade 1C).

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Corresponding author: I. Neri, Dermatology, University of Bologna, Bologna, Italy.
E-mail: iria.neri@unibo.it

Guidelines for vascular anomalies: venous malformations

F. STILLO ¹, B. AMATO ², R. MATTASSI ³, L. MONEGHINI ⁴, M. VAGHI ⁵, G. BIANCHINI ⁶

¹Center for Vascular Malformations, Guarnieri Clinic, Rome, Italy

²Vascular Surgery Unit, Department of Public Health, Federico II University of Naples, Naples, Italy

³Vascular Surgery Unit, Center for Vascular Malformations, Humanitas Mater Domini, Castellanza, Varese, Italy

⁴Pathologic Anatomy, Cytogenetic and Molecular Biology Unit, Department of Health, University of Milan, San Paolo Hospital, Milan, Italy

⁵I Vascular Surgery Unit, Garbagnate Milanese Hospital, Milan, Italy

⁶Vascular Surgery Unit, Center for Vascular Malformations, IRCCS Dermopatico dell'Immacolata, Rome, Italy

Definition

Venous malformations (VM) are congenital anomalies in the development of the venous system caused by errors in different developmental stages of embryogenesis, characterized by pathological alterations and clinical pictures of variable severity.¹⁻³

Classification

The ISSVA Classification 2014 (Table I) distinguishes common VM from rare forms and that will not be discussed in this paper (Table I).

The Hamburg classification is very useful in the establishment of common VM, which are divided in two radically different groups. They differ in embryogenetic, anatomical, functional and clinical characteristics: malformations of major veins (truncular forms) and malformations of dysplastic veins localized in the tissues, at a variable distance from the main venous axes (extra-truncular forms).^{4, 5}

Extra-truncular Forms

Extra truncular forms are the most frequent VM. They can be localized or infiltrating, extended into the tissue. They are dysplastic veins deriving from an error that occurs in the early phase of the embryogenetic development of the vascular bed. They consist of undifferentiated vessels of mesenchymal origin with a high proliferative potential and are characterized by a worsening evolution and by a high rate of recurrence after treatment. They often produce compressive effects or infiltrate the surrounding anatomical structures.

Truncular Forms

Truncular forms are less frequent. They consist of anatomical and functional alterations of variable sever-

ity that affect the main venous axes and are caused by developmental anomalies of the more advanced stages of vascular embryogenesis.

They have a low potential to proliferate and therefore limited post treatment recurrences. They induce major hemodynamic pathological effects on the involved vascular district because of obstruction and/or reflux in the main veins.

There are many types of truncular VM: valvular anomalies (avalvulia or dysplasia), obstructive lesions (atresia, aplasia, hypoplasia, intraluminal membranous sept), dilatations (venous aneurysms), persistence of avalvulated embryonic veins (marginal vein, ischiatic vein).⁶⁻⁸

Recommendation grade 1A: In the clinical and nosological establishment of VM, it is preferable to refer to the Hamburg Classification, avoiding old eponym based classifications.

Recommendation grade 1B: The identification of the embryological subtype (truncular or extra-truncular) of a VM is essential in order to determine the therapeutic strategy.

Epidemiology

VM are the most frequent variety among congenital vascular malformations (CVM) which represent about 2/3 of the total. Their incidence among the general population has been estimated to be approximately between 0.8% and 1%.⁹

Etiology

Most VM are rare. However, hereditary autosomal dominant forms have been reported.

The endothelial receptor TIE2/TEK for angiopoietin, whose gene is located on chromosome 9, has been identified as a cause of mucocutaneous forms of venous malformations.

A variety of VM is the glomuvenous form. It is hereditary and associated to anomalies of the glomulin gene which is located on the short arm of chromosome 1.¹⁰

Clinical history

A detailed personal and family history is very important in order to determine the necessary diagnostics.

Most VM are rare, however other forms that are similar can be observed.

TABLE I.—ISSVA 2014 Classification of venous malformations.

Common venous malformations
Familial cutaneous-mucous venous malformations
Bean Syndrome
Glomus venous malformations
Cerebral cavernous malformations
Other forms

Generally they are evident from birth although sometimes they manifest late. They do not undergo any spontaneous regression but persist lifelong and tend to grow in a progressive manner. Increase in size of the lesions is usually slow and proportional to the somatic development. Worsening during puberty or pregnancy can be observed.

Clinical evaluation

VM occur in most cases in an isolated form, but can also be multifocal. Size and extension are extremely variable, as well as the type and severity of the anatomical and functional alteration.

These malformations can appear on any part of the body, preferring the limbs and the cranio-facial area. They are mostly superficial, on skin and mucous membranes, but some are deep, intramuscular, intraosseous or visceral.

VM may be associated with other CVM: lymphatic malformations, capillary malformations and arteriovenous malformations. Mixed forms with a lymphatic component are defined hemo-lymphatic malformations (HLM).

Klippel-Trenaunay syndrome (KTS) is the combination of a VM with a capillary and lymphatic one. Parkes-Weber syndrome contains all the above defects including an arteriovenous malformation.

Superficial extra-truncular VM are clinically very evident and typically occur as a bluish or purple swelling, soft-elastic consistency, not throbbing, expandable and collapsible to compression. Deep forms may be difficult to recognize and to diagnose by a simple physical examination: the most frequent clinical signs are swelling and local pain. Infiltrating forms may cause signs and symptoms of compression on the surrounding anatomical structures (nerves, muscles and tendons, bone and joint, visceral structures).

In extra-truncular VM a coagulopathy is often present (40% of cases). This is caused by venous stasis and activation of the coagulation cascade with a tendency to form endoluminal clots in dysplastic vessels. This clinical picture is called "localized intravascular coagulation" (LIC) and is characterized by high levels of D-dimer and FDP associated with normal platelet count and sometimes a reduced level of fibrinogen.^{11, 12} Calcification of intravascular clots can lead to the formation of solid nodules known as "phleboliths".

Local thrombotic complications are observed more frequently in very extensive and infiltrating forms. They are also favored by trauma and by the interventions of surgical resection or scleroembolization.

Truncular VM produce hemodynamic alterations with clinical pictures of chronic venous insufficiency (varicose veins, edema and stasis dermatitis, skin ulceration). In some cases, especially on the limbs, you can see angio-osteo-hypotrophy or regional angio-osteo-hypotrophy, caused by abnormalities of bone vascularization affecting skeletal development. These lesions define the so-called "vascular bone syndrome" and typically occur with a dysmetria at the extremities.¹³

In the truncular forms a significantly high incidence of deep vein thrombosis and pulmonary embolism is documented.¹⁴

Recommendation grade 1C: Clinical examination is essential in the diagnosis of VM and should include a full evaluation (inspection, palpation, auscultation) of the anatomical area under observation and of the entire circulatory system.

Recommendation grade 1B: In VM it is always advisable to investigate for the coexistence of other vascular malformations (capillary, lymphatic, arteriovenous) in order to achieve a complete diagnostic picture.

Recommendation grade 1C: In VM, a complete coagulation screening including the dosage of D-dimer to assess the risk of thrombosis and the presence of LIC is recommended.

Diagnosis

Ultrasonography

Ultrasonography (US) is the test of choice for a non-invasive assessment of the first level of VM. It provides information on the morphological and hemodynamic characteristics of the malformation.¹⁵

A morphological evaluation is carried out in the "B-mode": VM typically appear ashypo- or hyper-echogenic compressible vascular gaps which are compressible by local pressure with the probe and are located subcutaneously in the soft tissues or deeper.

A hemodynamic study is carried out in the "Duplex" mode: dysplastic gaps with characteristic venous low flow speed, evoked by compression maneuvers, can be detected. US consent to study the hemodynamic characteristics of the malformation and the entire venous system.

The entire limb should be evaluated and not only the locations of major vascular bundles, as VM may have a typical localization. Ultrasonography should be carried out by an experienced operator to obtain reliable diagnostic information.

Recommendation grade 1A: Ultrasonography examination is recommended as a non-invasive diagnostic first level in all patients with a VM.

Standard X-ray

Standard X-ray examination is useful to recognize phleboliths in soft tissues, and to study any associated skeletal anomalies, by performing measurements of the length of the extremities.

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) allow to establish the type of VM, to assess the extent and the infiltration of the tissues in the extra-truncular forms and to point out drainage of venous pathways.¹⁶

Dysplastic veins typically occur as lacunar are as isohypointense on T1-weighted sequences and hyperintense on T2-weighted sequences and after signal suppression of adipose tissue. After intravenous injection of paramagnetic contrast a characteristic enhancement with possible presence of fluid-fluid levels in ectatic vessels with stagnant flow is observed. Edoluminal calcifications appear as hypointense focal areas.

The “dynamic contrast” method provides information on the hemodynamic flow velocity within the malformation.¹⁷

Recommendation grade 1B: Magnetic resonance imaging (MRI) is recommended for the preoperative assessment of the extent and anatomical relationships of venous extra-truncular malformations.

Computed Tomography (CT)

Computed tomography (CT) is not as reliable as MRI for evaluation of extra-truncular VM. However, if a contrast medium is used, MR can be useful in the study of extra-truncular venous malformations, both central and peripheral, pointing out stenosis, aplasia, venous aneurysms and embryonic venous circles.¹⁸

CT exam is very effective in craniofacial venous malformations to study the relations with the skull and to find out any extra-intracranial venous communications.

Recommendation grade 1B: Computed tomography with contrast medium is recommended for pre-operative assessment of the anatomy of truncular VM.

Recommendation grade 1B: Computed tomography with contrast medium is recommended in extra-intracranial VM to find out any draining veins with extra-intracranial communication.

Angioscintigraphy

Total body angioscintigraphy with radio-labeled red blood cells is a useful complementary examination for the screening of VM, particularly in multifocal forms.

This test provides qualitative and quantitative parameters on VM, useful for monitoring both the natural evolution and the response to sequential scleroembolization treatments. It also allows the differential diagnosis among venous and lymphatic malformations.¹⁹

Venography

Venography is an invasive examination whose role in the diagnosis of VM has been significantly reduced because data provided by doppler ultrasound and MRI, possibly supplemented by angio-CT, are usually sufficient to obtain a complete picture.²⁰

However, venography is still useful in preoperative planning of complex truncular venous malformations, when diagnostic details are needed that cannot be obtained with non-invasive tests.

Furthermore, it is used in intra-operating monitoring of percutaneous scleroembolization treatments.

Ascending venography allows to evaluate the patency and hemodynamics of deep venous circulation. The descending venography is useful in the study of congenital deep vein incontinence. Direct puncture venography allows to evaluate the course of the embryonic venous trunks or drainage veins of the extra-truncular VM.

Recommendation grade 1B: Venography should be used for the study of pre-operative complex VM or monitoring intra-operative treatments of scleroembolization. Arteriography is of no use and should therefore be avoided.

Endoscopic exams

In cases of cervical VM with involvement of the pharyngolaryngeal area, diagnosed by MRI, it is essential to perform a preoperative laryngoscopy to assess the risks of intubation and post-scleroembolization edema.

In pelvic VM with colorectal mucous involvement a proctoscopy is needed to evaluate the extent of intra-mucous venous dysplasias.

Recommendation grade 1C: Before treatment of a cervical VM with potential involvement of the airways, it is essential to perform a laryngoscopy.

Recommendation grade 1C: In pelvic VM a rectoscopy is recommended.

Specialist advice

For VM located in critical areas a multidisciplinary team approach should be utilized involved. For example, advice from a neurosurgeon for cerebral localization, ENT for cervical localizations, ophthalmologist for ophthalmic forms and gynecologist for pelvic forms should be consulted.

Histology

A biopsy is indicated if there is a reasonable doubt of the differential diagnosis with a malignant form.

VM are characterized histologically by vascular dysplastic lacunae having a thin wall with a flat monostratified endothelium, in the absence of a significant endothelial mitotic activity.²¹

Dysplastic vessels typically show venous features and may present different aspects in relation to the anatomical site.

In VM localized in the soft tissues and skin, vessels are often large with a muscular wall, sometimes rich in elastic fibers, but always without internal elastic lamina; in the nervous system the vessel wall can be thin or thick but always fibrous while in the intra-osseous area it is thin with rare smooth muscular fibers.²²⁻²⁴ The endothelial lining is flat and single-wire, immunoreactive with endothelial markers as CD31 and CD34, while it is negative to WT-1 and GLUT-1.²⁵⁻²⁷

Some dysplastic vessels may present dilation with wall thinning and development of intraluminal blood clots that, with time, undergo fibrous organization, until the formation of phleboliths by precipitation of calcium salts.

Some VM are accompanied by the proliferation of perivascular cells normally present in the vascular glomus, similar to smooth muscle cells, and are diagnosed as glomuvenous or glomangioma malformations.²²

Conservative treatment

Elastic Compression

Compression therapy with bandages or elastic stockings can be effective in venous malformations of the lower limbs, particularly in truncular forms with chronic venous insufficiency.

Topic Medications

Treatment with topic medications is necessary in complicated superficial VM having skin ulcers or bleeding.

Physiotherapy

Physiotherapy can be useful in selected cases.

Manual lymph drainage (MLD) is indicated in combined hemolymphatic malformations.

The use of braces is useful to improve the functionality and quality of life in the forms associated with skeletal abnormalities (e.g. corrective orthotics in VM with dysmetria of the lower limbs).

Psychotherapy

It is always advisable to evaluate the need for psychological support, both for patients and for family members, in VM that cause deformities or severe disability.

Drug therapy

The treatment with low molecular weight heparin is indicated in VM with clinical signs of LIC, especially in case of low levels of fibrinogen, to control both the pain caused by thrombotic phenomena and to prevent the progression to disseminated intravascular coagulation (DIC).²⁸

Recommendation grade 1C: Treatment with prophylactic doses of fractionated heparin is recommended in all patients with VM that present with: considerable size, presence of embryonic veins, clinical signs of LIC or severe venous stasis, thrombophylic alterations.

Invasive treatment

Invasive treatment of VM is indicated in the presence of clinical abnormalities or severe complications: bleeding, chronic venous insufficiency, disabling pain, functional deficits, aesthetic deformity, osteo-angiodystrophic syndrome, (especially during growth), impairment of vital organs and thromboembolism.²⁹

Sclero-embolization

Sclero-embolization is the most commonly used treatment for VM. Good results are obtained with low morbidity.

Sclero-embolization consists of the injection of various sclerosing agents in order to obtain occlusion of dysplastic vessels and the destruction of their endothelium.

Sclero-embolization can be performed with fluoroscopic or ultrasound guidance. Ultrasound is useful during percutaneous puncture to locate the malformation and check the position of the needle. Fluoroscopy allows to monitor the spread of the sclerosing agent, suitably mixed with a contrast agent, within the malformation in the drainage vessels.

Ethanol is the most powerful and effective sclerosing agent in the treatment of VM, and is considered the gold standard.³⁰

However, ethanol may cause a high rate of morbidity. The most common complications are: skin ulceration, neuropathy and thromboembolism. The risk is greater in venous malformations localized in the mucus-cutaneous

area, near peripheral nerves or acral regions. It is recommended to not exceed the dose of 1-2 ml/kg.

Sclerosis with ethanol should be carried out by experienced personnel, preferably under phlebographic guidance. Since the injection of ethanol is very painful, loco-regional or general anesthesia is necessary.

Recently, a gel-ethanol was produced, with the addition of ethyl-cellulose, which has the advantage of increasing local effectiveness reducing the dose of ethanol and consequently morbidity.^{31, 32}

Polidocanol (1-3%) and sodium tetradecyl sulfate (0.2 to 3%) are alternative sclerosing agents in the treatment of VM, mainly used for their low morbidity.

Polidocanol and sodium tetradecyl sulfate are mainly administered as foam, preferably under ultrasound control.³³⁻³⁵ They are especially indicated for superficial skin or mucous VM.

These sclerosing agents allow to obtain satisfactory clinical results, reducing the risk of cutaneous or neurological side effects. The main limit of these sclerosing products is the high incidence of recurrences, compared to ethanol. There is also a high risk of neurological complications of embolism in patients with patent of the oval foramen or other right-left shunts.

Laser therapy

Laser therapy can play a complementary role in the ablative treatment of VM. It can be performed with the use of different methods depending upon the location and extent of the venous malformation.

Different wave lengths can be used (laser diode with a wave length between 1310 and 1470 nm or Nd:YAG laser with a wave length of 1064 nm). The methods of application are described as follows:

- transdermal in skin or mucous membranes malformations (especially the oral cavity)
- interstitial in the subcutaneous or deep forms
- endoscopic in the visceral forms
- endovascular in the treatment of truncular VM, especially for the occlusion of embryonic veins as the marginal vein.^{36, 37}

The procedure of endovascular laserphotocoagulation is performed percutaneously by the endoluminal insertion of a bare fiber. The most commonly used laser with this technique is the diode laser. The recommended maximum power is variable from 10 to 15 W according to the caliber of the cannulated vessel. We recommend to perform the procedure under ultrasound monitoring due to the high risk of perforation of the vein wall and subsequent spillage of the fiber with fotodermal damage of the adjacent tissues.

Non-vascular surgery

Orthopedic surgery or plastic surgery interventions are used to correct skeletal or cosmetic abnormalities that are side effects of a VM.³⁸ Sometimes they are performed simultaneously with vascular interventions in one session.

Severe limb length discrepancy (more than 3 cm), due to an overgrowth or a growth reduction of the affected limb caused by the malformation can be corrected in the pediatric age with epiphysiodesis surgery. In adulthood, after the consolidation of the epiphysis, aosteotomy for

bone shortening or bone lengthening according to Ilizarov can be performed.

Vascular Surgery

Vascular surgery aims to correct the hemodynamic defects in patients with VM and is classified as ablative and reconstructive.

Surgical ablation

Surgical resection, either as an isolated or combined procedure with sclerotherapy, is the most effective method for treatment of extra-truncular VM in all cases where it is possible to remove the lesion in a radical manner.³⁹ The main indication is represented by the focal and circumscribed malformations, in both the cutaneo-mucous surface and subfascial forms engaging a single muscle or in the intra-articular forms, particularly of the knee.

However, surgical excision is burdened with a high morbidity, especially in very extensive and infiltrating VM, with a significant risk of bleeding, neurological lesions and relapses. In the complex forms the risk of complications can be reduced, if possible, with a surgical approach in multiple sessions.

Surgical excision is the gold standard in the treatment of truncular VM with persistence of embryonic veins, as the marginal vein.⁴⁰ Generally a pluri-segmental excision through micro-incisions along the anomalous vein is carried out. Stripping is feasible but is burdened by a high risk of bleeding.

The removal of embryonic veins should be performed early in childhood, in order to avoid development of an osteo-angiodystrophy syndrome. The surgical removal of embryonic trunks is contraindicated in cases where atresia of the deep venous circulation coexists. It should be thoroughly investigated to avoid the risk of phlebostatic gangrene from loss of vicarious circulation.

Recommendation grade 1C: Surgical removal of embryonic veins should be performed early in order to prevent the osteo-angiodystrophy syndrome.

Recommendation grade 1B: Surgical removal of embryonic veins is contraindicated in the presence of atresia of the deep venous axis. A pre-operative study of the entire venous circulation is recommended.

Reconstructive surgery

Reconstructive surgery is indicated in various forms of truncular VM.

Surgical excision is the most simple and effective method in the treatment of congenital venous intraluminal septal or membranes.

Total surgical resection followed by grafting/venous transposition or partial surgical resection followed by a reducing suture are indicated in congenital aneurysms of the deep veins (such as the popliteal or femoral surface) to prevent possible thromboembolic complications.

Various internal or external valvuloplasty interventions have been described for the treatment of valvular hypoplasia.

The transposition of venous segments with valves or percutaneous implantation of prosthetic valves has been proposed for the correction of valve agenesis.⁴¹

The percutaneous transluminal angioplasty, which may be supplemented by the implant of an endovascular stent, has proven effective in the treatment of stenotic congenital obstruction of the deep veins (such as the iliac vein or inferior vena cava).⁴²

Recommendation grade 1B: The indication for invasive treatment of a VM requires a careful analysis of the expected benefits (cosmetic, functional, psychological) and potential risks related to the operation.

Recommendation grade 1C: The choice of the therapeutic strategy must be based on a multidisciplinary approach and on a careful assessment of the clinical case.

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Corresponding author: F. Stillo, Director Center for Vascular Malformations, Guarnieri Clinic, Rome, Italy.
E-mail: f.stillo47@gmail.com

Guidelines for vascular anomalies: lymphatic malformations

P. DALMONTE ¹, C. CAMPISI ², N. VERCELLINO ¹, C. BELLINI ³, L. MONEGHINI ⁴, B. AMATO ⁵, F. STILLO ⁶

¹Center for Angiomas, Cardiovascular Department, Istituto Giannina Gaslini, Genoa, Italy

²Operative Unit of Lymphatic Surgery, DISC/Department of General, Specialistic and Oncologic Surgery - IRCCS University Hospital San Martino - IST National Institute for Cancer Research, Genoa, Italy

³Neonatology Unit, Pediatric Department, Istituto Giannina Gaslini, Genoa, Italy

⁴Pathologic Anatomy, Cytogenetic and Molecular Biology Unit, Department of Health, University of Milan, San Paolo Hospital, Milan, Italy

⁵Vascular Surgery Unit, Department of Public Health, Federico II University of Naples, Naples, Italy

⁶Center for Vascular Malformations, Guarnieri Clinic, Rome, Italy

1. DEFINITION AND CLASSIFICATION (ISSVA Hamburg, 1988 - Rome, 1996)

Lymphatic malformations (LM) are embryogenetic errors of the lymphangiogenesis which are further divided into two subgroups (Hamburg Classification) according to both an anatomical and embryological criteria: extra-truncular and truncular forms.

Extra-truncular LM are embryonic residues due to the block of development in the early stages of embryogenesis. It is an "immature" vascular tissue of mesenchymal type that preserves the potential for growth if stimulated (menarche, pregnancy, hormone therapy, trauma, infection, surgery).

Truncular LM are errors of the later stages of angiogenesis. It is a "mature" vascular tissue which has lost the growth potential when stimulated.

Different types of lymphatic malformations:

— **extra-truncular LM:**

a) *macrocystic (synonym old classification: cystic hygroma)*

b) *microcystic (synonym in old classification: lymphangioma)*

c) *combined (micro and macro-cystic)*

— **truncular LM: primary lymphedema**

— **syndromic LM:**

a) *Hennekam S.*

b) *Gorham Stout S.*

c) *Lymphedema cholestasis S.*

d) *Generalized lymphatic anomaly (GLA)*

1.1. New ISSVA Classification (Melbourne, April 2014)

a) Common cystic LM

- *macrocystic*

- *microcystic*

- *mixed*

b) Generalized lymphatic anomaly (GLA)

c) LM of the Gorham-Stout Syndrome

d) Truncular LM: primary lymphedema

- *Nonne-Milroy disease*

- *Hereditary primary lymphedema*

- *Lymphedema-distichiasis syndrome*

- *Hypotrichosis-lymphedema-telangectasia*

- *Primary lymphedema with myelodysplasia*

- *Generalized primary lymphatic anomaly (Hennekam Syndrome)*

- *Microcephaly with or without chorioretinopathy and lymphedema*

- *Lymphedema and choanal atresia*

e) **Other forms**

2. ETIOLOGY

Etiology of LM is still unknown. Presently a genetic approach is not possible, yet with the exception of the primary lymphedema. LM occasionally appears without a hereditary transmission. Only in the primary lymphedema has an aberrant gene been identified for all forms (see new classification).

3. EXTRATRUNCULAR (OR SIMPLE) LYMPHATIC MALFORMATIONS OF A MACROCYSTIC TYPE (MLET-MC)

3.1 Clinical Evaluation

It is related to volume, site of the lesion and hemorrhagic, inflammatory and infectious complications. The most common sites are the neck, axilla, face and chest. There is a tendency to gradual increase in volume over the years.

3.2 Diagnosis

The first diagnosis (or diagnostic suspect) is always clinical: certainty of the diagnosis is obtained by doppler ultrasound and magnetic resonance imaging (MRI) or TC.¹⁻⁵

Doppler Ultrasound: excludes the presence of arterial and / or venous vascular anomalies and solid lesions. The appearance is that of cystic cavities, uniform multi-chamber, bounded by fibrous septa with hyper-echogenic and echogenic signal type fluid inside; absence of vascularity within the lesion and present only with Doppler examination. There is the possibility of prenatal diagnosis (ultrasound) from the second trimester of pregnancy (**Recommendation Class I; Level of Evidence A**).

Magnetic resonance imaging (MRI): it confirms the clinical-ultrasound diagnosis, evaluates the extension, the dimensions and anatomical relations of the malformation. It must be carried out with mdc for a differential diagnosis for venous malformations, and more rarely with proliferating soft tissue. The MRI should always be carried out

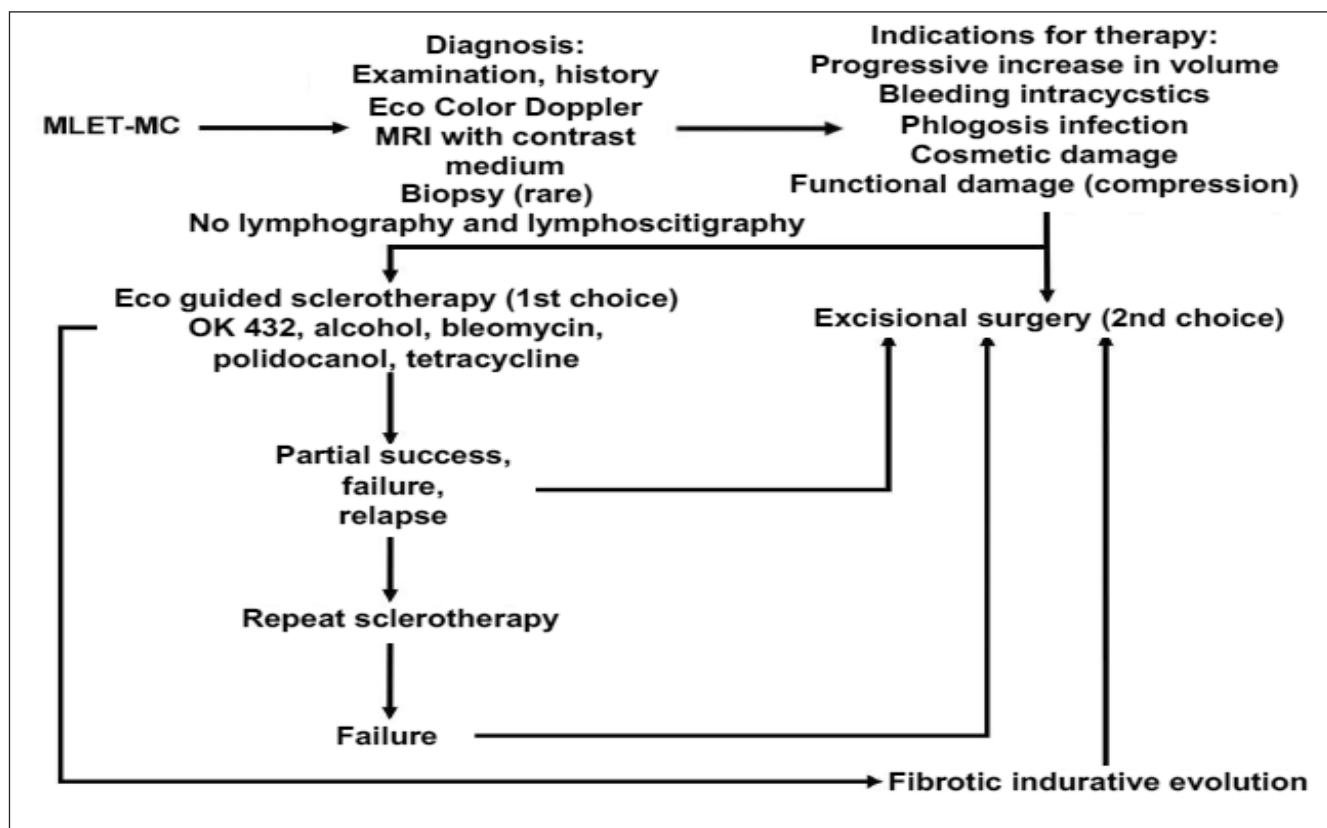


Figure 1.—Algorithm for the therapeutic approach to MLET-MC.

before therapeutic procedures with the exception of small and superficial areas where a Doppler ultrasound is sufficient (**Recommendation Class I; Level of Evidence A**).

CT with contrast: it allows to confirm the diagnosis but does not provide all the information of the MRI (survey alternative to MRI, but second choice) (**Recommendation Class II A; Level of Evidence B**).

Invasive imaging techniques: traditional lymphography, lymphography with direct puncture, lymphoscintigraphy and angiography are unsuitable (**Recommendation Class III; Level of Evidence C**).

Biopsy: it is rarely indicated for diagnosis, but must be carried out every time instrumental techniques (ECO, MRI, CT) do not give a definite diagnosis.

3.3 Therapy

In the absence of symptoms, evolutionary and functional problems, therapeutic treatment can be deferred after two years of age.

The therapeutic approach of choice is sclerotherapy with direct puncture eco guided under general anesthesia. Usually phlebography is not needed. In cystic malformations of small size and in the adult the sclerotherapy procedure can be performed with the patient awake.¹⁰⁻¹³

The single-chamber forms are those that best take advantage of sclerotherapy. The sclerosing agents used are: OK 432 (picibanil), alcohol, bleomycin, tetracycline doxycycline, polidocanol, sodium tetradecyl-sulfate: these last two also in the form of “foam” (or “mousse”, through a preparation which provides for their mixing with O₂ and

CO₂, with the possibility of obtaining better therapeutic effects, with lower amounts and concentrations of the sclerosing agent.

The type of sclerosing agent must be chosen based on the experience of the operator or medical clinic (the choice is strictly operator-dependent) (**Recommendation Class I; Level of Evidence A**).

The most severe complications are caused by the use of alcohol as sclerosing agent; the most damage affecting the skin, mucous membranes and peripheral nerves; a special training for use of alcohol is recommended in order to minimize morbidity.

Recurrence or the partial result constitutes the major problem of sclerotherapy in the long term, while in the short and medium term results are generally favorable. The procedure can be repeated.

The second treatment of choice is surgical excision. It is indicated for malformations that do not respond favorably to sclerotherapy (**Recommendation Class I; Level of Evidence A**).

Sclerotherapy and surgery can be used together or sequentially in the treatment of lymphatic malformations in relation to personal experience.

3.4 Follow-up

Post-procedural clinical checkup is recommended after one to three weeks, ultrasound checkup 6-12 weeks after the procedure. Based on the outcome of the ultrasound, the need for additional therapeutic intervention is evaluated which can be preceded by MRI reevaluation (Figure 1).

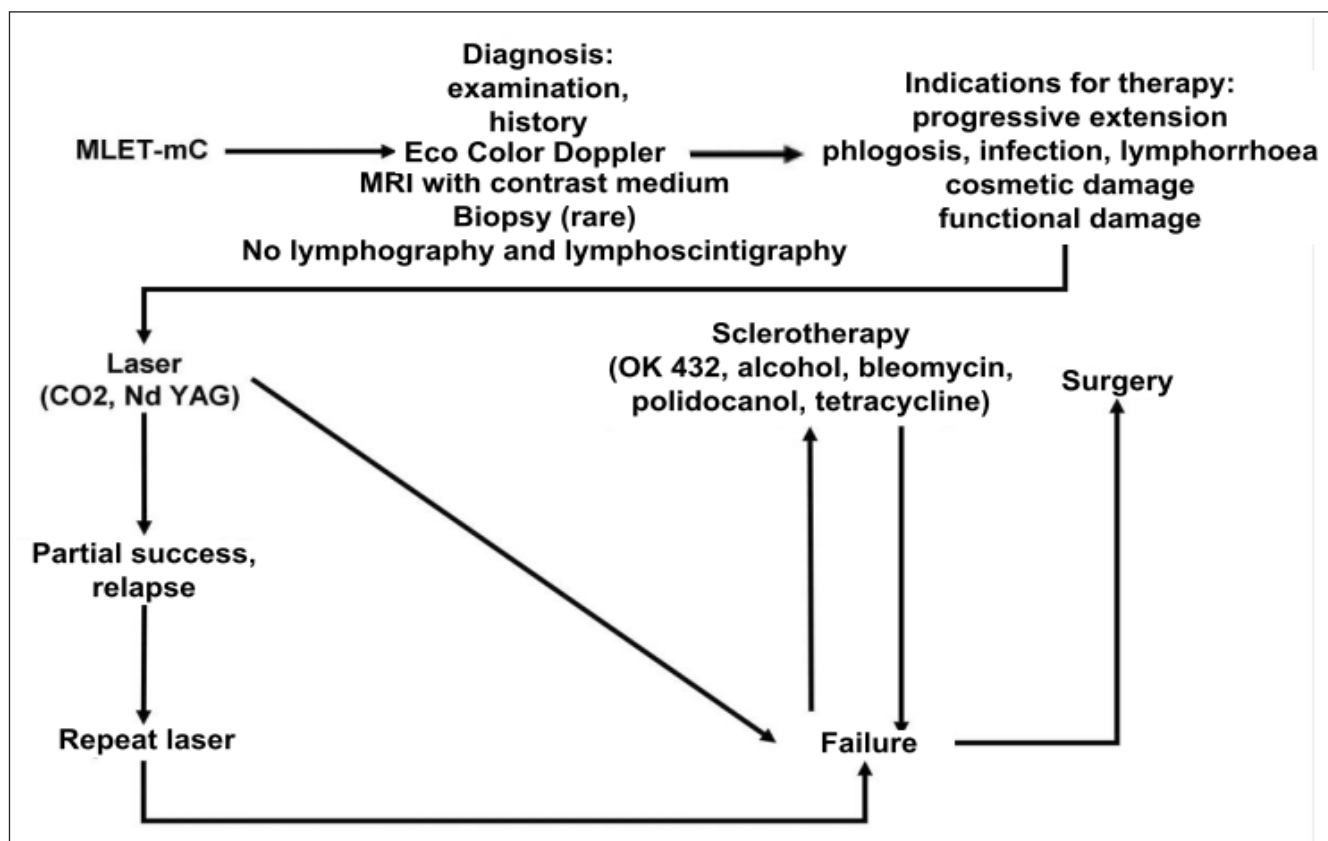


Figure 2.—Algorithm for the therapeutic approach to MLET-mC.

4. EXTRATRUNCULAR (OR SIMPLE) LYMPHATIC MALFORMATIONS OF A MICROCYSTIS TYPE (MLET-mC)

4.1 Clinical Evaluation and Diagnosis

Clinically appear as superficial multiple lesions of vesicular type of the skin, subcutaneous tissue, tongue and mucous membranes of the oral cavity, the genital region, conjunctive; are evolutionary, infiltrating the superficial tissues, symptomatic (pain, itching, minor bleeding) and are often associated with components of capillary malformation and/or venous.

More rarely they have deep localizations (mediastinum, retroperitoneum) and even more rarely the bones.

No possibility of prenatal diagnosis.

The ultrasound is used for different diagnosis and to point out macrosystic malformation components that are associated or deep. The MRI confirms the diagnosis, allows to estimate the extension of the lesion and points out the the deepest and bone malformation components.⁶⁻⁸ (**Recommendation Class I; Level of Evidence A**).

The invasive imaging techniques (angiography and lymphography) find no indication (**Recommendation Class III; Level of Evidence C**).

4.2 Therapy

The therapeutic strategies are based on use of laser, surface sclerotherapy, through the use of radiofrequency ablation and surgical excision. All of these therapeutic op-

tions generally give partial or temporary results, except for modest malformations where a final result can be obtained.

- **Sclerotherapy**: the results are generally unfavorable. Complications are immediate ulcers and scarring in the long run.⁹⁻²⁸ (**Recommendation Class II B; Level of Evidence C**).

- **Surgery**: it provides for the removal of portions of skin and subcutaneous tissue infiltrated by the malformation, which may require the use of skin grafts, rotation flap and skin expanders. In less frequent cases of tissue hypertrophy (of subcutaneous fat), surgical excision is indicated for the reduction of the volume of the lesion.

The major complications of surgery are lymphorrhoea, the difficulty of wound healing from surgery with keloid formation and recurrence.²⁹⁻³⁴ (**Recommendation Class II A; Level of Evidence B**).

- **Laser**: the CO₂ laser and the neodymium YAG laser surface or interstitial allow the best results. The more frequent unfavorable outcomes are the scar and local recurrence (**Recommendation Class II A; Level of Evidence B**) (Figure 2).

4.3 Follow-up

Follow up in the majority of the cases is clinical. MRI (or in alternative contrast CT) in the cervical-mediastinal and retroperitoneal localizations is used.

5. EXTRATRUNCULAR (OR SIMPLE) LYMPHATIC MALFORMATIONS OF MIXED MACRO-MICRO-CYSTIC TYPE (MLET-MmC)

5.1 Diagnosis

The association is very common, and is manifested clinically by both superficial and deep localizations. The same considerations reported in the two previous chapters apply.

5.2 Sclerotherapy

See the previous two chapters.

5.3 Surgical Therapy

Major surgical indications and relative difficulty depend on the location.

We distinguish among:

- LM of cervical mediastinal deviation/airway compression: excisional surgery preceded by sclerotherapy or in combination with sclerotherapy. Provision should be made for preoperative tracheotomy. The surgical access may be cervical anterior-lateral (along the anterior margin of the sternocleidomastoid) or sternotomy or combined.

- Giant and evolutionary LM of the newborn, usually localized in the cervical or axillary extending to the homolateral hemithorax: excisional surgery sometimes preceded by sclerotherapy or in combination with sclerotherapy. Provision should be made for preoperative tracheotomy.

- Lingual, labial and intraoral LM: Laser Therapy (CO₂ laser) for labial mucosa and intraoral, in preparation or associated with surgery; excisional-reductive surgery, combined or after sclerotherapy. Provision should be made for preoperative tracheotomy

- Fronto-temporo-orbital LM: excisional surgery (followed or not by sclerotherapy) through coronal incisions.

- LM of upper eyelid / brow at ophthalmologic risk: excisional surgery; preferably incision along the upper tarsal groove

- LM of the cheek: Sclerotherapy in stages; any subsequent excisional surgery through engravings pre-ear or along the naso labial groove or by intraoral; Intraoperative mapping of the facial nerve and / or use of electrostimulation

- Bone locations: osteotomic and orthognathic procedures should be performed preferably after puberty. The Gorham Syndrome should be excluded (**Recommendation Class II A; Level of Evidence C**).

5.4 Lasertherapy

The laser (CO₂ or Nd: YAG) is preferably used to treat the mucosal and skin in general malformation localizations ³⁵⁻⁴⁰ (**Recommendation Class II A; Level of Evidence B**).

6. SYNDROMIC LYMPHATIC MALFORMATIONS

6.1 Hennekam Syndrome

Rare inherited autosomal recessive disorder, characterized by the lymphedema of the lower limbs, intestinal lymphangiectasia, cognitive impairment and facial dysmorphism. The disease gene is CCBE1, which encodes a protein that binds collagen and calcium; however, not all phenotypes of Hennekam Syndrome present mutations in CCBE1.

Clinical onset occurs during early childhood. Facial symptoms are characterized by a flat face, broad nasal bridge, hypertelorism, epicanthal folds, low-set ears.

Cognitive impairment is highly variable, even within the same family. The intestinal lymphangiectasia may involve protein-losing enteropathy, peripheral edema and ascites. Pulmonary lymphangiectasia can be associated.

Lymphatic impairment can be evaluated by radionuclide lymphoscintigraphy, but diagnostic confirmation requires duodenal biopsy. Laboratory tests show hypogammaglobulinemia, hypoalbuminemia, lymphopenia, fecal alpha-1 antitrypsin hypersecretion.

Treatment is symptomatic; many patients requiring parenteral feeding and albumin infusions. Pulmonary lymphangiectasia is difficult to treat and can be relentlessly progressive in adulthood. Lymphedema can be evolutionary and disabling.⁴¹⁻⁴⁶

6.2 Gorham Stout Syndrome

This syndrome is a rare vascular malformation, sporadic and unknown etiology. It is manifested by spontaneous and sometimes massive osteolysis associated with intraosseous vascular proliferation of small blood vessels predominantly lymphocytic, with secondary progressive destruction and bone resorption. This syndrome preferably affects children and adolescents, with no difference between the sexes. Less than 300 cases have been described in the literature.

The syndrome can affect one or more bones, usually contiguous, with a more frequent involvement of the pelvis, shoulder girdle, spine, ribs and skull bones. There is an involvement of varying amounts of soft tissue, which can be infiltrated by vascular malformation (capillary-lymphatic). Chylothorax is associated in 40% of cases.

The clinical presentation is characterized by pain, spontaneous fractures and chylothorax. The progression of osteolysis can stop at any time, but often evolves with the complete loss of bone tissue, which is replaced by a fibrous band; this framework has suggested the term "ghost bone syndrome".

The diagnosis is often difficult and can be reached by exclusion (differential diagnosis with osteolysis secondary to infection, inflammation, endocrine disorders, neoplastic processes). The diagnostic confirmation requires bone biopsy.

At the moment there is no effective therapy available. Taking care of these patients is multidisciplinary and includes surgery, radiation therapy and medical pharmacology; the latter is based on the variable use of interferon alpha-2b, rapamycin, bisphosphonates (pamidronate, zoledronic acid), cortisone, vitamin D and calcium.⁴⁷⁻⁶¹

6.3 Lymphedema-Cholestasis Syndrome

Lymphedema-cholestasis syndrome (LCS) is an autosomal recessive genetic syndrome described for the first time in 1968 in children of Norwegian families. Also known as Aagaenæs Syndrome, it is characterized by lymphedema of the lower limbs and neonatal cholestasis, which generally become episodic and less severe during or after infancy. The cause of lymphedema is a hypoplasia of the lymphatic manifold system, while the cause of cholestasis is not yet known.

The disease leads to growth retardation, cholestatic liver disease, and evolution to cirrhosis with portal hypertension, rickets and peripheral neuropathies.

Therapy is based on special diets based on short-chain fatty acids (MCT), derivatives of fat-soluble vitamins, vitamin K prophylaxis, symptomatic treatment of itching in periods of acute cases.

The prognosis is variable and depends on the extent of cholestasis: some patients die in early childhood due to liver failure (mainly because of bleeding from vitamin K deficiency), while others die of cirrhosis in later childhood. In less severe cases, recurrent episodes of cholestasis can lead to death from cirrhosis in the third and fourth decade of life. Some cases have undergone liver transplantation with a good result.⁶²⁻⁶⁸

6.4 Generalized Lymphatic Anomaly (GLA)

Generalized Lymphatic Anomaly is a malformation of lymphatic nature to somatic extension, also referred to as "generalized cystic lymphangiomatosis" or more simply "Lymphangiomatosis". It is characterized by the presence of dilated lymphatics that infiltrate the bone, and soft tissue, with clinical pictures characterized by skeletal pain and spontaneous fractures. It is progressive and disabling.

Compared to the Gorham-Stout Syndrome, the intraosseous malformation component is confined only to the cancellous bone and there is cortical osteolysis; the malformation component of the soft tissues adjacent to bone localization is not constant. Pleural effusions (chylothorax) and hepato-splenic and superficial macrocystic lymph localizations can be associated.

The diagnosis is difficult, and similarly to the Gorham-Stout Syndrome, it is reached by exclusion. The diagnostic confirmation requires biopsy.

There is no available effective therapy. Taking care of these patients is multidisciplinary and includes surgery, radiation therapy, drug therapy (rapamycin, bisphosphonates, interferon alpha-2b, cortisone, vitamin D, calcium).⁶⁹⁻⁷⁰

Appendix I.—PRIMARY CHYLOTHORAX

i. Definition and etiology

The chylous spilling in the pleural space is defined as the primary chylothorax (PC). This is due to an abnormal development of the lymphatic chest collectors, which is configured as a visceral vascular malformation of a truncular type. Agenesis/hypoplasia of the lymphatic collectors is guilty of a dilation of the more peripheral lymphatic circle (lymphangiectasia lung pleurodesis). Similar is the etiology of the much rarer chylopericardium, usually coexisting to chylothorax.

ii. Diagnosis

The fetal ultrasound can demonstrate the presence of unilateral or bilateral pleural effusion in utero; if the pleural effusion is isolated in the uterus, most probably of chylous nature.

After birth the diagnosis is by an ultrasound and x-rays.

The next step is diagnostic thoracentesis, which allows the diagnosis of chylous nature of the spilling, in addition to encouraging the re-expansion of the lung with improvement of respiratory mechanics.

CT and MRI are complementary investigations, which become necessary later in the clinical picture, in anticipation of invasive therapeutic procedures.

Lymphography and lymphoscintigraphy investigations are useful (but not required) to be used only in anticipation of surgical procedures (**Recommendation Class II A; Level of Evidence C**).

iii. Therapy

Therapy is controversial and not standard.

In chylothorax at birth, resuscitation in the delivery

room should be possible. The first objective is to reduce the production of lymph and encourage spontaneous resolution of lymphatic endopleural "leakage". The initial approach is therefore always conservative.

In cases of severe respiratory distress at birth tracheal intubation with mechanical ventilation should be used, thoracentesis and chest tube placement, placement of central venous catheter, start of total parenteral nutrition for a minimum of 2-4 weeks.

In cases of mild to moderate respiratory distress maintaining autonomous respiration, placement of chest drainage and the initiation of parenteral nutrition should be practiced.

In newborns and infants with chylothorax not responsible for respiratory problems and which allows a normal breathing autonomy, the first therapeutic approach consists in thoracentesis associated with total parenteral nutrition (or, alternatively, an alipidic diet) for a minimum period of 2-4 weeks (**Recommendation Class II A; Level of Evidence C**).

The total parenteral nutrition should be associated with infusion of splanchnic vasoconstrictors (somatostatin or octreotide in drip) for an average of 4-6 days (but no more than two weeks): Currently octreotide is preferred at a mean dose of 4-6 mg/kg/hour (**Recommendation Class II B; Level of Evidence C**).

After 4 weeks of total parenteral nutrition and re-expanded lung, an oral diet is started with short chain fatty acids (MCT), bypassing the lymphatic system, thus reducing the production of lymph.

It is not recommended to start feeding again in the absence of evidence (clinical, ultrasound and radiological) of complete emptying of the pleural cavity and before the suspension of drug therapy.

The diet with MCT must be continued for a minimum period of two months. In the case of early recurrence of chylous effusion, a second attempt of conservative therapy is indicated (**Recommendation Class II B; Level of Evidence C**).

Surgery or, alternatively, thoracoscopy procedures that must be reserved for selected cases refractory to medical therapy, and are therefore always second choice options (**Recommendation Class II B; Level of Evidence C**).

In thoracotomy or video-thoracoscopy the following procedures can be performed: pleurectomy, pleurodesis, electrocoagulation and suture of the points of greatest lymphatic draining, ligation of the thoracic duct just above the diaphragm (with access from the right hemithorax).

For a better localization of the leakage points, lymphatic imaging may be useful (lymphography or lymphoscintigraphy). Chemotherapy and radiation are to be proscribed.

iv. Prognosis

The prognosis of congenital chylothorax is good in most cases with conservative therapy treatment; rare but possible spontaneous resolution.⁷¹⁻⁸⁷

Appendix II.—CHYLOUS ASCITES

i. Definition and etiology

Chylous ascites is defined as the intraperitoneal abdominal chylous effusion.

The etiology is unknown, but is thought to be an abnormal development of the abdominal lymphatic collectors,

with secondary development of linfangiectasie groaning in the intra-peritoneal area. This situation allows to enter the chylous ascites in the group of visceral truncular lymphatic malformations.

ii. Diagnosis

The fetal ultrasound shows the presence of fetal ascites already in utero; if ascites are isolated in the uterus (and not associated with craniofacial edema, pericardial effusion, pleural effusion or placentomegalia), they most probably are of chylous nature.

The clinical onset is almost always at birth; the diagnosis of ascites requires ultrasound confirmation. The next step is diagnostic paracentesis, which allows the diagnosis of chylous nature of the effusion and promotes the detension of the abdomen with improvement by mechanical breathing.

CT provides better detail of the root of the mesentery and excludes masses compressing lymphatic and / or venous drainage.

MRI is useful for the confirmation of chylous ascites and to rule out other diseases. Lymphography and lymphoscintigraphy investigations are to be used only in anticipation of surgery (**Recommendation Class II A; Level of Evidence C**).

iii. Therapy

Therapy is controversial and not standard.

It is always necessary to foresee assisted childbirth (with possible resuscitation in the delivery room), in addition to positioning peritoneal drainage. The first therapeutic objective, once the optimum ventilation is insured, is to reduce the production of lymph and favor the spontaneous resolution of the "leakage". The initial approach is therefore always conservative.

In newborns and infants with chylous ascites in the absence of respiratory problems at least initially, the placement of peritoneal drainage is avoided and a alipidic diet or a total parenteral nutrition for a minimum period of 2-4 weeks is started. In cases of total parenteral nutrition, an infusion of octreotide in drip (or somatostatin) can be associated for an average of 4-6 days (but no more than two weeks). After 4 weeks and with an emptied abdomen, an oral diet with short chain fatty acids (MCT) is started, to be continued for a minimum period of two months. In the case of early recurrence of chylous effusion, a second attempt of conservative therapy is indicated (**Recommendation Class II A; Level of Evidence C**).

Surgery is reserved for cases refractory to medical therapy; may be ineffective due to the difficulty of identifying and closing lymphatic drainage points. For a better localization of the points of leakage, lymphatic imaging (lymphography or lymphoscintigraphy) and preoperative administration of lipophilic dyes (e.g. Sudan black) can be useful (**Recommendation Class II A; Level of Evidence C**).

You can have post-surgical recurrence even after years.

Peritoneal-venous shunts are used very rarely, because the chylous fluid often is rich in protein and occludes them quickly, so they have a limited lifespan. They are indicated in the very rare cases of refractory and evolutionary chylous ascites with secondary refractory respiratory distress.

A long-term follow-up with the use of such devices is not available.

Chemotherapy and radiation are to be proscribed.

TABLE I.—Classification of lymphedema of the limbs.

Primary lymphedema:

- a) connatal(already present at birth)
- b) Precoce (manifest from 2 to 35 years of age)
 - I. Sporadic
 - II. Hereditary(hereditary-family transmission: see syndromic LM)
- c) Tardive (manifest after 35 years)

Secondary lymphedema:

- a) post-surgical
- b) post-actinic
- c) post-lymphangitic
- d) parasitic

iv. Prognosis

Good in most cases, with spontaneous resolution, even in the first month of life and only with conservative treatment.

v. Follow-up

Follow-up is clinical and with an ultrasound.⁸⁸⁻⁹⁴

Appendix III) TRUNCULAR LYMPHATIC MALFORMATIONS OF THE LOWER LIMBS: PRIMARY LYMPHEDEMA

i. Definition and Classification

Truncular lymphatic malformations of the limbs include primary lymphedemas (PL) of the upper limbs (rarer) and lower limbs (in most cases), sometimes also localized (or exclusive) to the external genitalia, which develop in the final stages of lymphangiogenesis, when the lymphatics and lymph nodes are formed.

These malformations can be due to a condition of aplasia, hypoplasia or hyperplasia of the lymphatic vessels and lymph nodes. They manifest clinically as a state of obstruction or dilation, or with the absence of, or defect to, intraluminal valves where gravitational reflux of lymph represents the primary clinical manifestation.

These conditions of altered development or lymphatic dysplasias, if restricted to lymphatic collectors can also be defined lymphangiodysplasias (LADI), to distinguish them from those limited to the lymph nodes, also called lymphadenodysplasias (LADII), and the mixed forms, described as lymphangio-adenodysplasias (LAAD). The LADII form is most frequently encountered.

Depending on whether they manifest at birth or later, before or after age 35, primary lymphedemas are classified as connatal, precocious, or tardive. Precocious lymphedema as are distinguished as sporadic or hereditary (hereditary-familial transmission). Recently the genes responsible for primary lymphedema, as in the new ISSVA Classification, have been identified.

In this way, primary lymphedemas are more easily and properly differentiated from the so-called secondary or acquired lymphedema, in turn divided into post-surgical, post-actinic, postlymphangitic, and parasitic (Table I) (**Recommendation Class I; Level of Evidence A**).

ii. Clinical Evaluation and Staging

The more modern staging integrates clinical and instrumental criteria (lymphoscintigraphy). For the best comprehension of the evolution of the pathology and an appropriate prognostic evaluation, immuno-histopatho-

TABLE II.—*Lymphedema staging.*

STAGE I

- IA - "Latent" Lymphedema: without clinical evidence of edema, but with impaired lymphatic transport capacity (demonstrated by lymphoscintigraphy) and with initial alterations of immuno-histochemical lymph nodes, lymph vessels, and extracellular matrix
- IB - "Initial" Lymphedema: totally or partially decreasing with rest and draining position, with worsening impairment of lymph transport capacity and of immuno-histochemical alterations of the lymph collectors, nodes, and extracellular matrix

STAGE II

- IIA - "Increasing" Lymphedema: with vanishing lymph transport capacity, relapsing lymphangitic attacks, fibroindurative skin changes and developing disability
- IIB - Column-shaped Limb Fibrolymphedema: with lymphostatic skin changes, suppressed lymph transport capacity, and worsening disability

STAGE III

- IIIA - Properly-called Elephantiasis: with scleroindurative pachydermitis, papillomatosis lymphostatic verrucosis, no lymph transport capacity and life-threatening disability
- IIIB - Extreme Elephantiasis: with total disability

Recommendation Class I; Level of Evidence A

logical criteria and degrees of disability due to the worsening of the clinical picture should be included.

This staging refers to the official Consensus Document of the International Society of Lymphology (ISL), more recently partially modified (Table II), to distinguish Latent Lymphedema (Stage IA), Initial (Stage IB), Worsening (Stage IIA), Fibro-Lipo-Lymphedema (Stage IIB, with "column" limb), properly called 'Elephantiasis' (Stage IIIA), and Extreme Elephantiasis (Stage IIIB) (Table II).

iii. Diagnosis

The instrumental investigations of Levels I, II and III are summarized in Table III, which represents the diagnostic algorithm most often agreed on by the international literature.

Diagnosis is always based on history, physical examination, and the imaging studies of level I; lymphoscintigraphy, ultrasound, and today also with Lymphangio-MRI.

Lymphoscintigraphy is currently the "gold standard" diagnostic instrument and must be carried out for the comparative study of both the superficial and deep lymphatic circulation, adding a quantitative assessment, by measuring the Lymphatic Transport Index (LTI, normal 1 to 9, pathological if > 10).

Ultrasound is essential to verify the coexistence of a venous pathology which is necessary to distinguish pure Lymphedema from that with a venous component; Phlebo-Lymphedema or Lympho-Phlebedema, depending on the predominance of one of the two components; lymphatic or venous, and can also highlight the coexistence of an arterial component associated with the first two conditions (Arterio-Venous Fistula).

Lymphangio-MRI today is especially useful for the diagnosis of gravitational chylolymphatic reflux on a base of malformation or dysplasia. Among the instrumental in-

vestigations of level II, Fluorescent Microlymphography and direct Lymphography are of particular importance today.

Fluorescent Microlymphography using indocyanine green (Photo-Dynamic-Eye: PDE Test) surpasses the traditional lymphangioscopy or lymphochromic test of Blue Patent Violet (BPV), and allows the mapping of the subcutaneous superficial lymphatic network with the possibility to distinguish different patterns of alterations (linear, starburst, and diffuse), deriving from different pathological entities.

Lymphography, director conventional, consists of the evaluation of the lymphatic pathways by direct injection of soluble iodinated contrast (Lipiodol ultrafluid) in the bipedal lymphatic collectors previously prepared by a microsurgical technique under the Operating Microscope. It is advantageously combined with computed tomography (Lymphangio-CT) for the diagnostic definition of primary lymphedema (or chylolymphedema), resulting from gravitational lymphatic (or chylous) reflux based on malformation. These selected instruments, since they are minimally invasive, retain today an essential role in differential diagnosis.

Finally, for the level III instrumental investigation, especially considering the possible venous and arterial malformations in combination with lymphatic malformations, phleboscintigraphy, phlebography, and arteriography may be indicated (Table III).

iv. Therapy

Therapy for Primary Lymphedema consists of 2 types of treatment: Non-Surgical Treatment and Surgical Treatment (Table IV).

Non-Surgical Treatment is based on Multimodal Combined Physical Therapy (CPT: Combined Physio-Therapy) and Drug-Phyto-Therapy.

Multimodal Combined Physical Therapy consists of:

- "Skin Care" (careful skin hygiene, particularly of the digits and external genitalia);
- Manual and Mechanical Lymph Drainage (with uniform pressure devices, intermittent and decreasing pressure gradients (distal to proximal); peristaltic-sequential pumps; negative intermittent pressure therapy; and non-invasive mechanical body massage);
- Multilayer Functional Bandages;
- Isotonic Muscular Exercises and appropriate Physical Activity;
- "Life Style" (healthy life style habits and appropriate diet).

Drug-Phytotherapy involves Nutritional Supplements, natural extracts of Benzopyrones (Melilotus Officinalis and Coumarin), associated with Antibiotics/Antimycotics (for the treatment and prevention of acute lymphangitis; bacterial and or fungal).

Surgical Treatment consists of Functional Surgery and Reductive or Excisional Surgery. Functional Surgery includes one of two types of Microsurgery:

- Derivative Microsurgery (Multiple Lymphatic Venous Anastomoses; MLVA)
- Reconstructive Microsurgery (Lymphatic-Venous Lymphatic-Plasty; LVLA), by the interposition of autologous venous valve grafts between the lymphatics, above and below the functional obstacle to lymph flow. Veins are taken from healthy sites, such as the volar surface of the forearm (segments of cephalic or basilic vein of vari-

TABLE III.—Diagnostic algorithm for lymphedema.

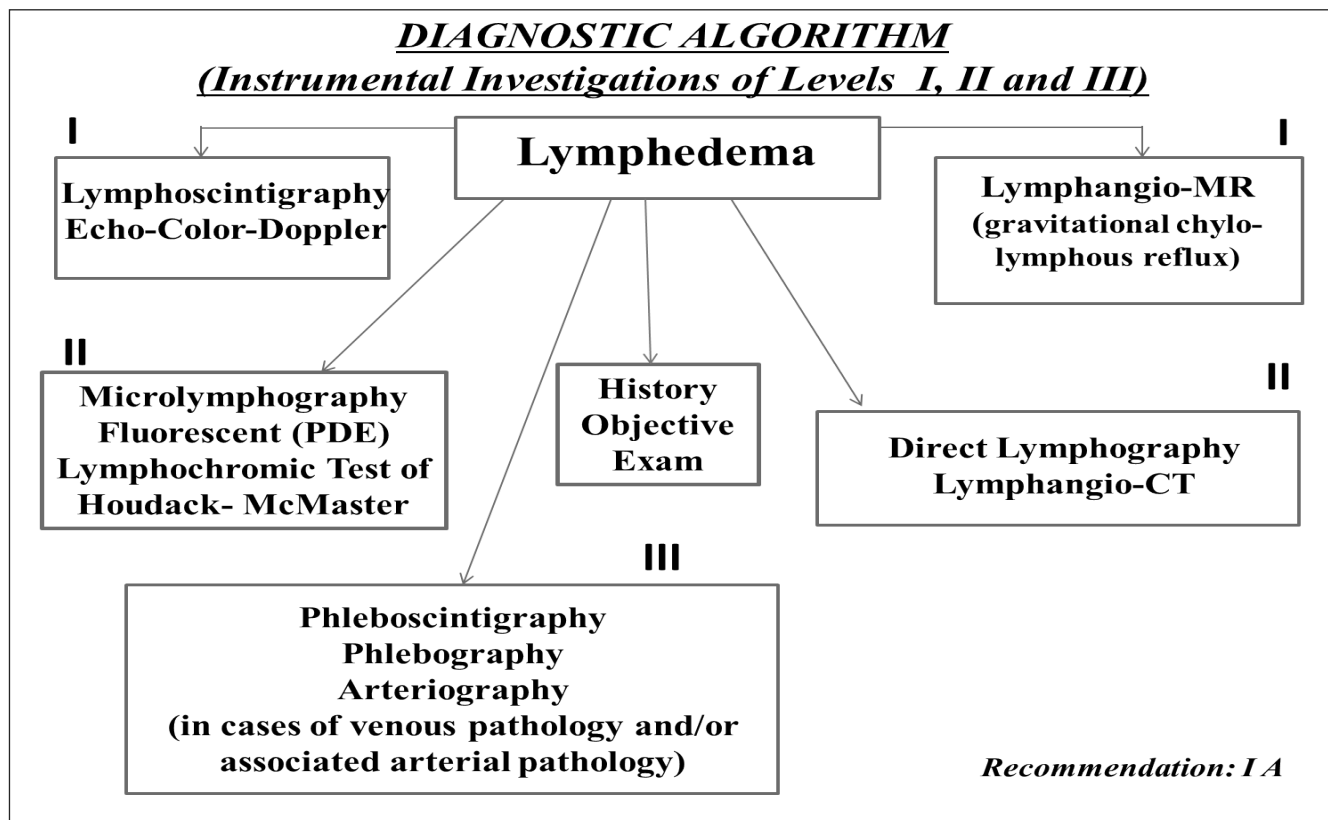


TABLE IV.—Therapeutic options for primary lymphedema.

<u>LYMPHEDEMA THERAPY</u>	
Non Surgical Treatment:	
A) Multimodal Combined Physical Therapy (CPT: Combined Physiotherapy) • Skin care • Mechanical and manual lymphatic drainage • Multilayer functional bandages • Isotonic exercises – physical activity • Healthy life style	B) Drug-Phyto-Therapy • Benzopyrones • Antibiotics • Antifungals • Diuretics • Diethylcarbamazine
Surgical Treatment:	
I) Functional Surgery • Derivative Microsurgery (Multiple Lymphatic-Venous Anastomoses) • Reconstructive Microsurgery (Lymphatic-Venous-Lymphatic-Plasty) II) Excisional Surgery • Fibro-Lipo-Lympho-Aspiration (Lymph Vessel Sparing Procedure, Eco-Color-Doppler and PDE guided) • Reductive Plasty	
Recommendation: I B	

able lengths from 7 to 21cm). This method is indicated, especially, in the treatment of primary lymphedema of the lower limbs associated with venous pathology that is not correctable by appropriate surgery (such as external valvoplasty for valvular incontinence with significant venous reflux) at the same time as the lymphatic surgery. Uncorrectable venous pathology is an absolute contraindication for derivative lymphatic techniques.

The autograft or transposition of one or more lymphatic collectors, as well as lymph node transplantation, are still rarely used methods and represent little more than experimental value, given the real risk of donor site secondary lymphedema.

The Excisional or Reductive Surgery involves the application of plastic surgery methodologies in order to eliminate, as much as possible, excess fibrotic-adipose tissue, remaining after the reduction in lymphatic stasis induced by the Microsurgery intervention. The most satisfying results from tissue removal surgeries can be obtained with the application of a method similar to Liposuction, tumescent (prior infiltration of Klein's Solution), guided by ultrasound mapping of the main superficial venous branches and the mapping of the superficial lymphatic network obtained by Fluorescent Microlymphography with indocyanine green, creating a "Lymph Vessel Sparing" procedure, able to prevent injury to the lymphatic collectors, especially those commencing close to the veins. This method is called Fibro-Lipo-Lympho-Aspiration (FLLA).

Surgical treatment must only be carried out in cases where non-surgical treatment was ineffective. The interval of time generally agreed upon for the "timing" of surgical treatment is 6-12 months after a correct, but ineffective application of non-surgical conservative treatment, always evaluated by the degree of reduction of the edema and the consequent improvement in the quality of life of the patient (Table IV).⁹⁴⁻¹³⁰

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Corresponding author: P. Dalmonte, Director of the Center for Vascular Malformations, Cardiovascular Department, Istituto Giannina Gaslini, Genoa, Italy.
E-mail: MalfVasc@ospedale-gaslini.ge.it

Guidelines for vascular anomalies: arteriovenous malformations

R. MATTASSI ¹, C. GANDOLFO ², L. MONEGHINI ³, M. BERGUI ⁴, G. VERCELLIO ⁵

¹Vascular Surgery Unit, Center for Vascular Malformations, Humanitas Mater Domini, Castellanza, Varese, Italy

²Center for Angiomas, Cardiovascular Department, Istituto Giannina Gaslini, Genoa, Italy

³Pathologic Anatomy, Cytogenetic and Molecular Biology Unit, Department of Health, University of Milan, San Paolo Hospital, Milan, Italy

⁴Invasive Neuroradiology Unit, San Giovanni Battista, Molinette Hospital, Turin, Italy

⁵Center for Vascular Malformations, Italian Diagnostic Center (IDC), Milan, Italy

Definition and classification

Arteriovenous malformations (AVM) are defined as *anomalous connections between arteries and veins, directly or through a network of vessels denominated “nidus”*. Regardless of the presence or absence of a “nidus” and of the size of the anomalous connections (micro or macro), AVM are classifiable as “high flow” malformations. This type of vascular anomaly may create in the involved area different problems, from minor defects, to swelling, pain, local ischemia with ulcer, hemorrhage, and in diffuse infiltrating forms, hemodynamic complications with cardiac overloading.

The abbreviation AVM is sometimes improperly attributed also to the low-flow vascular malformations (VM).

AVM are divided in two forms: *truncular* and *extratruncular*.¹ In the rare truncular type, there is a direct and unique arteriovenous communication with no “nidus” which corresponds to the “arteriovenous fistula” (AVF) of the ISSVA classification (1996), updated in 2014. Patent ductus arteriosus (defect of Botalli), some lung and other located direct a-v fistulas can be included in this category. The great majority of AVMs are of the extratruncular type, infiltrative and with the presence of a “nidus”. Existence of a nidus is the result of a failure in the regression of the primitive embryonic network. The nidus has been recently classified according to an angiographic criteria into three subgroups (Cho *et al.* 2006). That classification is useful as it offers indication about treatment procedures (embolization and others) and their possibilities of success (Figure 1).²

Another classification of AVM, based on the clinical condition and the necessity of treatment, has been pro-

posed by Schobinger (1977) and distinguish four stages of the disease (Table I).³

Epidemiology

To date no environmental, geographical, racial or gender factors have been identified that could determine the prevalence of these malformations. The little data available comes from the United States where 250,000 people are affected by AVM.⁴ Compared with other congenital vascular defects in all the case studies the percentage of AVMs would not exceed 10-20%.

Etiopathogenesis

Recent advances in genetics have led to the identification of type and location of some gene mutations responsible for the clinical picture of many simple and complex vascular malformations.

In AVMs these mechanisms have been identified only for some diseases having a syndromic type.

For example, in hereditary hemorrhagic telangiectasia (HHT), an autosomal dominant hereditary disease, the presence of high-flow malformations (FAV specifically) is only one aspect of the clinical picture that is characterized by diffuse cutaneous and mucosal telangiectasia (genes involved ACVRL1 and ENG).

A gene mutation RASA1 has been recognized some years ago in two other diseases characterized by AVMs, one being hereditary dominant (CM-AVM) and one being sporadic (Parkes Weber Syndrome).⁵

Pathophysiology

The abnormal connections between the arterial high pressure and venous low pressure system influence important evolving loco-regional effects (ischemia, venous hypertension, degenerative changing of the vessel wall with rupture and bleeding) and in some cases heart failure, especially in the diffuse type and in the rare cases of arteriovenous truncular malformations. The tendency to worsen requires continuous clinical-instrumental monitoring and a therapeutic strategy of great flexibility.

TABLE I.—AVM Shobinger Staging (1977).

Stage I	Cosmetic Impact
Stage II	Functional Impact
Stage III	Bleeding/Ulceration
Stage IV	Heart Failure

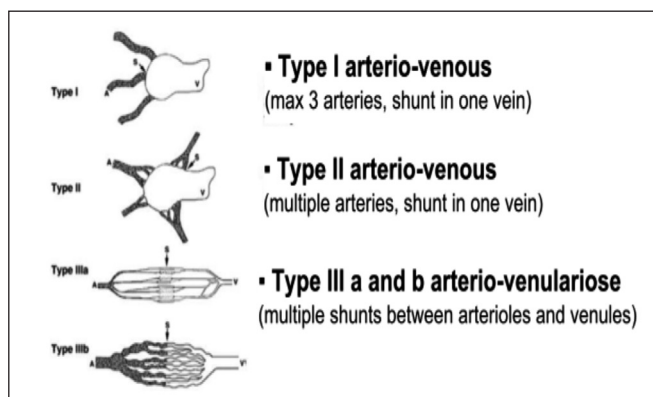


Figure 1.—Angiographic classification of the AVM “nidus” (Cho *et al.*).

Clinical evaluation

Typically an AVM appears as a hyperemic area with abnormal pulsation and/or thrill, with a probable evolution characterized by swelling and hypertrophy of the tissue and bone segments involved. Hypertrophy manifest, like in venous and in syndromic complex malformations, by lengthening of the involved limb resulting in limb length discrepancy.

In case of a localization in the lower limbs, a particular skin alteration, known as *acroangiokeratosis* (or *Pseudo-Kaposi sarcoma*) may be evident in form of papules and/or discromic violet/purple defects.⁶

In children, an AVM can initially manifest as a flat skin lesion, pinkish or purplish and easily confused with a capillary malformation (PWS).⁷ The clinical evolution is accelerated by trauma or biological events (puberty, pregnancy) and also by estrogen-progestin drugs.

Diagnosis

The instrumental and imaging diagnostics of AVMs include following:

- Continuous Wave Doppler (CWD)
 - Ultrasonography Doppler (USD)
 - MRI
 - Angio-CT
 - Selective Angiography
- Other optional diagnostic methods are:
- Whole Body Blood Pool Scintigraphy (WBBPS)
 - Transarterial Lung Perfusion Scintigraphy (TLPS)

CW Doppler

CW (Continuous Wave) Doppler, also in pocket size, allows instant recognition of the characteristics of high turbulent flow in a-v vascular lesion by emphasis of the diastolic component.

Ultrasonography Doppler (Duplex scan)

More information can be obtained by using the Ultrasonography Doppler (USD): typically, a pulsating flow in a multichannel structure (honeycomb conformation) can be recognized. The vascular mass is not easy compressible like VM. Characteristics of flow speed, amplitude and volume can be recognized. Limits of the exam are that it is operator dependent and not able to allow a complete tridimensional evaluation of the lesions (especially in case of infiltration of the deep tissues and bones).⁸

Magnetic Resonance Imaging

As for lymphatic and venous malformations, MRI gives a good spatial evaluation of the AVM; however, the first ones show low flow and a clear signal in the T2 sequences, while AVM has a dark signal called *flow void*.⁹ There are *quantitative* methods to determine the volume of shunt and *dynamic* methods of new generation which are able to analyze flow characteristics (dynamic contrast-enhanced MRI).^{10, 11}

Angio-CT

The nidus of the AVM, its anatomy and the distribution of afferent and efferent vessels, especially those involving bone, are better investigated with CT angiography, espe-

TABLE II.—*Diagnostic recommendations.*

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- Instrumental investigations of level I (CW Doppler, USD) are sufficient for the diagnosis of AVMs (Class I, level C) (Class I, level C)
 - MRI is recommended in case of unclear cases (Class I, level C)
 - MRI and/or CT are recommended if there is a treatment intention (Class I, level C)
 - Diagnostic angiography is recommended only in extreme complex cases (Class I, level C)
-

cially if implemented with 3D images.¹² Angio CT with high-resolution equipment (64-slice) should be used with extreme caution in fertile age women and in children for the non-negligible risk of radiation exposure.

Scintigraphy

The scintigraphic methodologies (whole-body blood pool scintigraphy [WBBPS] and transarterial lung perfusion scintigraphy [TLPS]), are not essential for a correct diagnosis and are performed rarely. They can however be useful for research, to give a general overview of the extension of the defect (WBBPS) and for the evaluation of the percentage of shunts pre and post treatment (TLPS).^{13, 14}

Arteriography

Selective and super selective arteriography is no longer used for diagnostic purposes, except in selected cases. Angiography as an intention to treat procedure (catheter embolization) is preferred.

Histology

A histologic differential diagnosis between capillary and potential AVM in children can be difficult. Some authors have proposed to differentiate both by some data as vascular density in intraluminal content of red blood cells, different length and distribution of vessels and thickness of vascular walls. The WT1 antibody present in Wilms' tumors, which is absent in most vascular malformations, can be found in AVM (Table II).¹⁶

Treatment

Treatment of a-v malformations, compared to other types of vascular defects, is considered particularly difficult and controversial in terms of timing and methodology, due to the frequent recurrences and high risk of worsening of the clinical conditions in case of incomplete procedures.¹⁷⁻¹⁹ The indication for treatment is mandatory in stage 3 and 4 of Schobinger classification (Table I), but can also be extended to cases of stage 2 (Table III).

Surgery

"En bloc" surgical resection of the malformation was for years the only treatment option. Chances of success of surgery depends from the radicality of the resection. However, radical surgical excision may be sometimes (especially in diffuse infiltrating forms) extremely destructive and, in severe cases, risky for catastrophic bleeding.

Chance of success is greater in cases of circumscribed

TABLE III.—Treatment recommendations.

- For extratruncular forms, goal of treatment is the occlusion of the “nidus” that can be obtained with embolization, surgical or combined procedures (Class I, level C)
- Simple occlusion or ligation of afferent and efferent vessels to the AVMs is wrong and should be avoided (Class III, level C)

AVM, especially in the more frequent intramuscular cases. In peripheral AVM, blood loss can be minimized by application of a pneumatic tourniquet. To perform a more radical removal of the defect and improves success rate, some specific surgical techniques, like transplant of vascularized grafts including muscles and skin or skin alone (with or without previous implant of skin expanders) are available.

Partial removal, especially in childhood or adolescence, may worsen the clinical situation, as recurrence is common.

Embolization

Transarterial catheter embolization and/or percutaneous occlusion are alternative, well established, treatments for AVM. They are considered the first choice for the extended or surgically inaccessible AVMs. By partial occlusion of AVM, embolisation may have the same limits of surgery regarding recurrence. However, it can be used as palliative treatment to stabilize or slow down the progression of symptoms. The chance of success with endovascular treatment is best in type I and II AVM (arteriovenous and arteriovenous) and less in type III (arteriovenularis) of the Cho classification.²

The main materials of embolization currently in use are:

- Coils
- N-Butyl-Cyanoacrylate (NBCA)
- Onyx
- Ethanol.

Particles of polyvinyl-alcohol (PVA) are now rarely used because of the difficulty to find out the optimal size for “nast” occlusion without embolizing the afferent vessels or passing through the defect into the lungs.

Coils as the only embolizing material are also less frequently used than before because closure of the afferent vessels without occlusion of the “nidus”, as coils mainly do, brings only to a temporary improvement with a quick recurrence by opening of collaterals towards the “nidus” itself. However, coils are effective for occlusion of venous efferent vessels on type II (arteriovenous) AVM, mainly combined with ethanol embolization.²⁰ A contemporary retrograde venous catheterization is necessary.

N-Butyl-Cyanoacrylate (NBCA) is glue, able to penetrate and occlude the “nidus” by polymerization when it gets in contact with blood. Preparation of the product ready for use is done by mixing it with an oily contrast. Precise concentration of glue is crucial to get an optimal occlusion of the “nidus” itself, avoiding passage of the material into the veins and to the lungs if too diluted, or occlusion of the only afferent vessel if too concentrated.

The effect of the inflammatory reaction due to polymerization on recurrence and the possibility of resorption of the material at distance is material of discussion.

Onyx, widely used in interventional neuroradiology, is less adhesive than NBCA and is able to determine, by

TABLE IV.—Recommendations on the roles of the surgeon and the radiologist.

- The interventional radiologist should share with the surgeon not only the choice of the best therapeutic strategy, but also the outcome and follow-up of each patient treated (Class I, Level C)
- The surgeon should assist at the interventional procedure. (Class I, level C)

polymerizing, a strong “mould” of the “nidus”. Its use in extended AVMs is controversial because of the risk of inducing neoangiogenesis; therefore it is recommended in the pre-surgical procedures.^{21, 22}

Ethanol (absolute alcohol 96%) has been considered the most effective embolic agent for its ability to destroy the endothelium (incomplete destruction induces neoangiogenesis, responsible for recurrence). Risks of ethanol are related to neurotoxicity (nerve damage in case of contiguity of AVM with a peripheral nerve), to the possibility of cutaneous necrosis and the risk of pulmonary hypertension. The last can be minimized by limiting the total injected volume (1 ml/kg), and by fractioning of the boluses (max. 0:14 ml/ethanol/Kg every 10').^{23, 24} Quick outflow of the injected ethanol in veins can be avoided by manual compression of the efferent veins, by reduction of inflow with a balloon catheter and by occlusion of the outflow veins with coils or by a pneumatic tourniquet. In case of superficial AVM (especially type III, arteriovenous) a percutaneous injection in the “nidus” may be indicated.

Finally, we mention other procedures indicated only in selected cases: the use of covered stents (in diffuse malformations, in case of bleeding, in cardiac complications and in arteriovenous fistulas in large vessels) and the use of interstitial or intraluminal laser techniques (for limited superficial AVM).^{25, 26}

It is emphasized that a close interdisciplinary collaboration is recommended, especially between surgeon and interventional radiologist, due to their complementary roles especially in the treatment of AVM, rather than in other types of CVM (Table IV).

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Corresponding author: R. Mattassi, Director of the Vascular Surgery Unit, Center for Vascular Malformations, Humanitas Mater Domini, Castellanza, Varese, Italy.
E-mail: raulmattassi@gmail.com

Guidelines for vascular anomalies: complex malformations (syndromes)

G. VERCELLIO ¹, F. STILLO ², A. PATRIZI ³, L. MONEGHINI ⁴, C. MAGRI ¹, R. MATTASSI ⁵

¹Center for Vascular Malformations, Italian Diagnostic Center (IDC), Milan, Italy

²Center for Vascular Malformations, Guarnieri Clinic, Rome, Italy

³Dermatology Unit, University of Bologna, S. Orsola-Malpighi General Hospital, Bologna, Italy

⁴Pathologic Anatomy, Cytogenetic and Molecular Biology Unit, Department of Health, University of Milan, San Paolo Hospital, Milan, Italy

⁵Vascular Surgery Unit, Center for Vascular Malformations, Humanitas Mater Domini, Castellanza, Varese, Italy

Definition

In the wide spectrum of vascular malformations, traditionally classified according to histological criteria integrated with hemodynamic data (1996 ISSVA XI Workshop, Rome), a group of malformations defined as *Complex Malformations or Syndromic Malformations* deserve a special mention in a recent classification review (2014 ISSVA XX Workshop, Melbourne).

They are characterized by:

- coexistence of 2 or more different histological components (combined malformations)
- multiple locations, with cutaneous and visceral components
- coexistence of non vascular anomalies
- recognized or in definition genetic mutations. Sporadic onset for somatic mutation or inheritance.

Some complex malformations are traditionally classified as *syndromes*. In some cases they are defined with *eponyms* (prototype is the Kippel-Trenaunay Syndrome), while others more recently, with *acronyms* (the latter's prototype is CLOVES Syndrome).

Traditional terminology is still today applied wrongly and

is a source of confusion and ambiguity also because several syndromes may show overlapping clinical pictures.

Therefore, proper redefinition and interpretation of the criteria to differentiate these diseases are essential not only for prognosis, clinical practice, therapeutic strategy and timing of treatment, but also for proper counseling to family members of the patients.

Recent studies have in fact emphasized the unreliability of cases in which the distinguishing criteria between the various syndromes were not properly applied.^{1, 2}

Besides the frequent overlap of the constitutive features of some complex congenital vascular diseases, recent advances in genetics seem to indicate the presence of common etiopathogenic elements such as gene mosaicism, which manifests phenotypically with alterations of some parts of the body affected by the mutation (otherwise lethal), sparing the other parts.³

The vascular anomaly of these malformations may not be the main characteristic.

A common element in many syndromes is bone and other tissues hypertrophy with gigantism, defined as *overgrowth*.

Therefore, complex malformations may be divided in 2 groups (Table I).

TABLE I.—Classification of complex malformations.

Group A: syndromes Associated with hypertrophy and/or gigantism	Group B: syndromes Not associated with hypertrophy and/or gigantism
1. Klippel-Trenaunay Syndrome (KTS)	1. Blue Rubber Bleb Nevus Syndrome (BRBNS)
2. Parkes Weber Syndrome (PWS)	2. Osler-Weber-Rendu Syndrome (OWR) or Hereditary Hemorrhagic Telangiectasia (HHT)
3. CLOVES Syndrome	3. Cobb Syndrome
4. Proteus Syndrome (PS)	4. Bonnet-Dechaume-Blanc Syndrome or Wiburn-Mason Syndrome
5. Diffused Capillary Malformation with Overgrowth (DCMO)	5. Sturge-Weber Syndrome (SWS)
6. Cutis Marmorata Telangiectatica Congenita (CMTC)	6. Maffucci Syndrome
7. Macrocephaly-Capillary Malformation (M-CM)	7. Fibro-Adipose Vascular Anomaly (FAVA)
8. Hemihypertrophy-lipomatosis or Beckwith-Wiedemann Syndrome (BWS)	8. Capillary Malformations - ArterioVenous Malformation syndrome (CM-AVM)
9. Stewart-Bluefarb Syndrome (SBS) or Pseudo-Kaposi Sarcoma (PKS)	
10. Capillary malformation of the lower limb, Lymphatic malformation of the face and neck, Asymmetry and Partial/generalized Overgrowth (CLAPO)	

Summary of distinctive clinical, epidemiological, diagnostic and therapeutic data of the group A syndromes

1.A Klippel-Trenaunay Syndrome (KTS)

Clinical Evaluation: involvement of a lower and/or upper limb, venous anomalies (superficial and/or deep), capillary malformations, lymphatic malformations, skeletal and soft tissue hypertrophy.

Epidemiology: unknown. It is included in the list of Rare Diseases (exemption code RN1510).

Etiopathogenesis: sporadic mutations have been identified in the genes *VG5Q* and *RASA1*^{4,5} in some subjects.

Diagnostics: deep venous ultrasound evaluation, angio MRI, orthopedic monitoring.

Therapy: varicectomy, removal of anomalous veins (*i.e.* marginal vein) and/or dysplastic lymphatic masses, sclerotherapy, laser (superficial and/or interstitial), epiphysiodesis.

2.A Parkes Weber Syndrome (PKWS) Often erroneously included in the previous syndrome.

Clinical Evaluation: lower or upper limb, capillary malformations, a-v shunts, skeletal and soft tissue hypertrophy.

Epidemiology: unknown.

Etiopathogenesis: in a high percentage of cases related to a mutation of the *RASA1*⁶ gene.

Diagnostics: ultrasound, angio MRI or angio CT with 3D images, orthopedic monitoring.

Therapy: conservative, embolization in selected cases, removal of fistulous areas, laser (superficial and/or interstitial), epiphysiodesis.

3.A CLOVES Syndrome Acronym of Congenital Lipomatous Overgrowth Vascular anomalies, Epidermal nevi, spinal anomalies.

Clinical Evaluation: mosaic distribution of lesions, proliferating lipomas on the dorsum, epidermal nevi and capillary malformations, lymphangioma and/or a-v malformation (spinal or paraspinal), abnormal hands or feet with hypertrophy of skeletal and soft tissue.^{7,8}

Epidemiology: unknown. Less than 100 cases described. Not included in the ministerial list of rare diseases.

Etiopathogenesis: recent studies have shown a correlation of the mutation of the *PIK3CA* gene, in an early phase of the embryonic development that would cause the increase in the activity of the 3-kinase phosphoinositide. In the etiopathogenetic hypothesis of this syndrome the concept of mutated genes seems compatible only with survival in mosaicism.⁹

Diagnostics: angio MRI.

Therapy: surgical removal of lipomas and/or lymphangiomas (possible sclerotherapy), surgical correction of hands and feet hypertrophy (minimal amputation), embolization of spinal AVMs.

4.A Proteus Syndrome (PS) Often confused with the previous one.

Clinical Evaluation: skeletal anomalies of the limbs and at the extremities, hyperostosis, dimorphism of the face, mental retardation, vascular malformations of various types, lipomas, epidermal nevi with cerebriform appearance (collagenomas?), rarely associated with cancers, limited survival.

Epidemiology: Extremely rare (< 1 case per million of inhabitants). It is included in the list of Rare Diseases (exemption code RN1170).

Etiopathogenesis: correlated to the mutation of the *AKT1c.49G* gene, found, like the previous one in the affected tissues.¹⁰

Diagnostics: angio MRI, cerebral and orthopedic monitoring, abdominal ultrasound monitoring (rare tumors).

Therapy: conservative surgical excision.

5.A Diffuse Capillary Malformation with Overgrowth (DCMO) Recently identified.¹¹

Clinical Evaluation: diffuse or localized reticular capillary malformations limited to a hemisoma associated with hypertrophy of a limb or of the entire side of the body.

Epidemiology: unknown.

Diagnostics: venous Duplex ultrasound, orthopedic monitoring.

Therapy: conservative, laser on capillary malformation.

6.A Cutis Marmorata Telangiectatica Congenita (CMTC)

Clinical Evaluation: diffuse or localized reticular capillary malformations, atrophic skin (sometimes ulcerated) associated with hypotrophy or hypertrophy of a limb or of the hemisoma. Tendency to attenuation.¹²

Epidemiology: unknown. It is included in the list of Rare Diseases (exemption code RN0540).

Diagnostics: ultrasound evaluation of the venous system.

Therapy: conservative.

7.A Macrocephaly-Capillary Malformation (M-CM)

Clinical Evaluation: diffused capillary malformations (and in the center of the face), hypertrophy of a limb and anomalies of the hands and feet, severe cranio-facial dimorphism with macrocephaly (possible mental retardation with onset within 2 years of life).

Epidemiology: unknown.

Etiopathogenesis: mutation of the *PIK3CA*¹³ gene.

Diagnostics: MRI/CT cerebral and cranio-facial.

Therapy: conservative.

8.A Beckwith-Wiedemann Syndrome (BWS)

Clinical Evaluation: hemihypertrophy, lipoma, macroglossia, omphalocele, visceromegaly, center facial capillary malformation.¹⁴

Epidemiology and etiopathogenesis: unknown. It is included in the list of Rare Diseases (exemption code RN0820).

Diagnostics: cerebral and abdominal MRI.

Therapy: conservative.

9.A Stewart-Bluefarb Syndrome (SBS) or Pseudo-Kaposi Sarcoma (PKS) Also defined as *acroangiodermatitis*.

Clinical Evaluation: characterized by well defined "plaque" capillary malformation, located on the lower limb in the arteriovenous shunts site, associated with bone and soft tissue hypertrophy.^{15,16}

Epidemiology: unknown.

Etiopathogenesis: one hypothesis is that there is a local increase of the venous pressure, determined by the presence of shunts that would stimulate the endothelial proliferation.

Diagnostics: ultrasound, angio MRI.

Therapy: conservative, laser and embolization in selected cases.

10.A CLAPO Acronym of Capillary malformation of the lower lip, Lymphatic malformation of the face and neck, Asymmetry and Partial/generalized Overgrowth.¹⁷

Clinical Evaluation: characterized by capillary malformation limited to the lower lip and associated with

TABLE II.—Group A: Diagnostic Recommendations Class I level C.

- By recognizing the main clinical signs of each syndrome, proper nosology may be found out in most cases
- By first level instrumental examination (ultrasound) a differential diagnosis between some syndromes may be possible (KTS, PWS, PKS)
- (MRI) imaging is recommended to evaluation and monitoring of the deep vascular components (CLOVES, PS, M-CM, BWS) also for therapeutic perspective (KTS, CLOVES)
- Orthopedic monitoring is recommended in case of hypertrophy and/or gigantism of the lower limbs

progressive hypertrophy (macrocheilia), lymphatic malformations (sometimes venous) on the face or tongue, asymmetry and partial or total hypertrophy of a body segment not correlated with vascular malformation. It is not associated with mental retardation.

Epidemiology: unknown.

Etiopathogenesis: unknown.

Diagnostics: angio MRI.

Therapy: plastic surgery of the lips, surgical and/or sclerosing of the lymphatic component.

A different syndrome, which present not an overgrowth of a limb but, conversely, a growth reduction, is the **Servelle-Martorell Syndrome (SMS)**. This disease is characterized by venous diffuse infiltrative malformations and limbs length difference due to an inhibition of long bone growth because of the venous malformations.

Clinical evaluation: diffuse infiltration of skin and muscles by venous malformations that may involve the majority of even the whole limb, including buttock. In some cases the limb may be swollen while in others a diffuse hypotrophy may be evident. The involved limb is shorter than the contralateral one.

Epidemiology: unknown.

Etiopathogenesis: unknown. Diagnostics: Duplex scan for evaluation of main venous system. MR effective to demonstrate the involved areas and infiltrated tissues. Plain RX to study bone altered structure and to recognize phlebolithes.

Therapy: elastic compression, sclerotherapy, interstitial laser (Tables II, III).

Summary of distinctive clinical, epidemiological, diagnostic and therapeutic data of the group B syndromes

1.B Blue Rubber Bleb Nevus Syndrome (BRBNS) or Bean Syndrome

Clinical Evaluation: circumscribed venous lesions spread over the skin, mucous membranes and gastrointestinal tract (mainly small bowel), anemia, iron deficiency.

Epidemiology: extremely rare, not more than 200 cases documented in literature. It is included in the list of Rare Disease (exemption code RN0150).

Etiopathogenesis: sporadic, but in some families there was an autosomal dominant inheritance. The mutated gene was identified in chromosome 9p, tyrosine kinase receptor, TIE2.¹⁸

Diagnostics: abdominal angio MRI, gastro-colonos-

TABLE III.—Group A: Therapeutic Recommendations Class I level C.

- The correction of the vascular defect must be taken into account for both functional and major aesthetic improvement (dysmorphia)
- A therapeutic proposal must consider single or combined available options: surgery, laser (transdermal or intralesional), sclerotherapy (echo or drip assisted)
- Orthopedic treatment (even preventive) should be proposed in case of limb overgrowth and/or gigantism

copy, wireless capsule endoscopy, blood count monitoring.

Therapy: surgical in occlusive bowel complications, photo thermocoagulation laser or endoscopic argon plasma, medical therapy with somatostatin or rapamycin in selected cases.¹⁹

2.B Osler-Weber-Rendu Syndrome (OWR) or Hereditary Hemorrhagic Telangiectasia (HHT)

Clinical Evaluation: autosomal dominant inheritance, scattered cutaneous-mucosal telangiectasia, a-v shunts (lungs in the first place), epistaxis/hemoptysis.

Epidemiology: prevalence in the population of 1-8 cases on 5-8.000 individuals. It is included in the list of Rare Disease (exemption code RG0100).

Etiopathogenesis: due to the mutation of two genes, involved in the development of the circulatory system and tissue repair: endoglin located on chromosome 9 and activin receptor-like kinase-1 (ALK-1) on chromosome 12.²⁰

Diagnostics: angio MRI/lung²¹ CT.

Therapy: epistaxis treatment with laser photocoagulation, embolization of lung AVMs, thalidomide and bevacizumab in selected cases.²²

3.B Cobb Syndrome

Clinical Evaluation: metamerical association of cutaneous capillary malformation with spinal or paraspinal a-v malformation, neurological symptoms of various types.²³

Epidemiology: extremely rare with less than 50 cases reported in literature (probably not recognized in many cases).

Etiopathogenesis: unknown.

Diagnostics: angio MRI/spinal CT.

Therapy: conservative (corticosteroids), embolization/surgery in selected cases.²⁴

4.B Bonnet-Dechaume-Blanc Syndrome or Wyburn Mason Syndrome or Congenital Retino-Encephalofacial Syndrome (CRC)

Clinical Evaluation: triad characterized by the combination of superficial and deep vascular malformations, in this case skin-retinal-brain type, exclusively arterovenous. Variable ocular and neurological symptoms.

Epidemiology: very rare (less than 50 cases described in the literature).²⁵

Etiopathogenesis: unknown.

Diagnostics: angio MRI/CT, oculistic monitoring.

Therapy: conservative, embolization/ stereotactic techniques in selected cases of cerebral AVMs.

5.B Sturge-Weber Syndrome (SWS)

Clinical Evaluation: capillary malformation (PWS) front-eye, glaucoma, leptomeningeal capillary-venous malformation (calcifications, hemisphere hypotrophy) epileptic seizures.

TABLE IV.—Group B: Diagnostic Recommendations Class I level C.

- By recognizing the main clinical signs of each syndrome, proper nosology should be used in most cases
- MRI imaging is recommended for diagnostic confirmation (FAVA, HHT, SWS, CRC, Cobb, CM-AVM) and for prognostic monitoring (Maffucci). Endoscopic investigation and/or video capsule is recommended when there is suspect of BRBNS
- Neurological Monitoring (SWS, CRC, Cobb, CM-AVM)

TABLE V.—Group B: Therapeutic Recommendations Class I level C (in close relationship with the peculiarities and the severity of the disease).

- Laser / Sclerotherapy / Embolization / Medical Therapy (BRBNS)
- Embolization (HHT on lung, FAVA, Cobb, CRC)
- Laser therapy / Medial Therapy (HHT, SWS)
- Surgery (Maffucci, FAVA)

Epidemiology: a prevalence of not less than 1: 20-50,000 is credited within the population. It is included in the list of Rare Disease (exemption code RN0770).

Etiopathogenesis: sporadic, linked to somatic mutations detected recently of the GNAQ gene on chromosome 9q21.^{26, 27}

Diagnostics: cerebral angio MRI, oculistic and neurological monitoring.

Therapy: antiepileptic, aspirin at a low dosage, therapy for glaucoma, laser for the skin manifestations, surgery for the epileptic foci in selected cases.

6.B Maffucci Syndrome

Clinical Evaluation: venous malformation associated to enchondromas, mainly localized in the hands, frequent malignant transformation (chondrosarcoma).

Epidemiology: extremely rare, not more than 200 cases have been reported in literature. It is included in the list of Rare Diseases (exemption code RN0960).

Etiopathogenesis: mutation of the IDH1 and IDH2 genes in somatic mosaicism.^{28, 29}

Diagnostics: X-ray (phleboliths), orthopedic monitor-

SUMMARY TABLE I.

	LOCATION			CLINICAL EVALUATION					DIAGNOSTICS		
	TRUNK	LIMBS	HEAD/NECK	PWS	AVM	MV	ML	ANOMALIES	DOPPLER	MRI/CT	ANGIO
KTS		X		X		X	X	X	X	X	
PWS		X		X	X			X	X	X	X
CLOVES	X	X	X	X	X		X	X		X	X
PS	X	X	X	X		X	X	X		X	
DCMO	X	X		X				X	X		
CMTC	X	X		X				X	X		
M-CM		X	X	X				X		X	
BWS		X	X	X				X		X	
SBS-PKS		X		X	X			X	X	X	X
CLAPO	X	X	X	X		X	X			X	

KTS: Klippel-Trenaunay Syndrome; PSW: Parkes-Weber Syndrome; CLOVES: Congenital Lipomatous Overgrowth Vascular Anomalies, Epidermal Nevi, Spinal Anomalies; PS: Proteus Syndrome; DCMO: Diffuse Capillary Malformation with Overgrowth; CMTC: Cutis Marmorata Telangiectatica Congenita; M-CM: Macrocephaly-Capillary Malformation; BWS: Beckwith-Wiedemann Syndrome or Hemitrophy-Lipomatosis; SBS-PKS: Stewart-Bluefarb Syndrome or Pseudo-Kaposi Sarcoma; CLAPO: Capillary malformation Lymphatic malformation Asymmetry Partial/generalized Overgrowth; SMS: Servelle-Martorell Syndrome.

ANOMALIES: hypertrophy/gigantism of bone and soft tissue; skeletal anomalies of hands, feet and brain

SUMMARY TABLE II.

	LOCATION			CLINICAL EVALUATION					DIAGNOSTICS		
	TRUNK	LIMBS	HEAD/NECK	PWS	AVM	MV	ML	ANOMALIES	DOPPLER	MRI/CT	ANGIO
BRBNS	X	X	X			X				X	
OWR	X	X	X		X	X				X	X
S.COBB	X	X		X	X			X		X	X
CRC	X	X	X	X	X			X		X	X
SW			X	X				X		X	
S.MAFFUCCI		X				X		X		X	
FAVA	X	X				X		X		X	
CM-AVM	X	X	X	X	X					X	

BRBNS: Blue Rubber Bleb Nevus Syndrome; OWR: Osler-Weber-Rendu Syndrome or Hereditary Hemorrhagic Telangiectasia; S. COBB: Cobb Syndrome; RC: Bonnet-Dechaume-Blanc Syndrome or Wyburn-Mason Syndrome or Congenital Retino-Cephalo-Facial Syndrome; SWS: Sturge-Weber Syndrome; S.MAFFUCCI: Maffucci Syndrome; FAVA: Fibro-Adipose Venous Anomalies.

ANOMALIES: hypertrophy/gigantism of bone and soft tissue; skeletal anomalies of the hands, feet and brain

ing (malignant evolution: chondrosarcoma), supervision of possible rare malignant tumors.

Therapy: targeted osteotomies, courretage and packing with bone grafts, minimum amputations. Sclerotherapy and laser photocoagulation of the vascular component.

7.B Fibro-adipose vascular anomaly (FAVA)

Clinical Evaluation: extra-fascial and intramuscular venous malformation associated to prevalent fibro-adipose dysplasia.³⁰

Epidemiology: unknown (recently identified syndrome).

Etiopathogenesis: unknown.

Diagnostics: angio MRI.

Therapy: Surgical resection of the involved muscles (sclerotherapy is inefficient due to poor vascular component).

8.B Syndrome with capillary malformations-arteriovenous malformations (CM-AVM)

Clinical Evaluation: multiple capillary malformations (usually more than 3, and rarely more than 15) appearing as red-pink, round and oval, 1-3 cm in diameter; vascular macules. The vascular macules sometimes have a white halo. AVMs are associated, especially at the intracranial and spinal level.

Epidemiology: autosomal dominant extremely rare syndrome with a prevalence of 1/10.000 patients.

Diagnostics: cerebral-spinal MRI and in cases where there is a doubt a genetic test for RASA1 should be carried out. It belongs to the group of RAS- pathies.

Therapy: endovascular surgery.

Conclusions

This nosologic summary includes pathological complex malformations and syndromes according to a review of the most recent bibliography (only the key items are reported).

We believe that the situations described above give a well-defined nosological picture in relation to the recent acquisitions in the etiopathogenetic field (mentioned in the new recent ISSVA classification in April 2014).

For their significant clinical, prognostic and therapeutic impact these complex malformations must be recognized in their differential constituent characteristics.

Notice: Some not-well-classified malformations were not included in the proposed list (multifocal lymphangiomas) as well as other congenital and/or hereditary anomalies of the lymphatic system, those exclusively neurological (brain cavernomas CCM), familial glomovenous malformations and the Bannayan-Riley-Ruvalcaba Syndrome, as the vascular component is irrelevant. PHACES Syndrome is not included because the hemangiomatous component is prevalent compared to the associated vascular anomalies and therefore it is included in the group of vascular tumors.

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Corresponding author: A. Patrizi, Director of Dermatology Unit, S. Orsola-Malpighi General Hospital, University of Bologna, Bologna, Italy. E-mail: annalisa.patrizi@unibo.it