Head and neck vascular anomalies. A multidisciplinary approach and diagnostic criteria

L. MONEGHINI1, V. SANGIORGIO1, D. TOSI1, G. COLLETTI3, F. MELCHIORRE1, V. BARALDINI1, D. GRAZIANI1, R.M. ALFANO1, G. VERCELLIO5, G. BULFAMANTE1
1 Unit of Human Pathology, Department of Health Sciences, San Paolo Hospital Medical School, University of Milano, Italy; 2 Maxillo-facial Surgery Department, Department of Health Sciences, San Paolo Hospital Medical School, University of Milano, Italy; 3 Department of Radiology, University of Milan, San Paolo Hospital, Milan, Italy; 4 Center for Pediatric Vascular Malformations-Pediatric Surgery Unit V. Buzzi Children’s Hospital, Milan, Italy; 5 Private Practice, Milan, Italy

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Summary

Vascular anomalies represent a heterogeneous group of pathologies of the circulatory system that can affect any type of hematic and/or lymphatic vessel of different diameter or anatomic site. The extreme variability of tissue types and districts involved by these lesions determines a wide heterogeneity of clinical manifestations, resulting in involvement of different medical expertise. In this context, a commonly agreed terminology is crucial for the appropriate evaluation and multidisciplinary management of patients. The ISSVA Classification that has its roots in the previous Classification of Mulliken and Glowacky distinguishes vascular anomalies in two main groups: vascular tumors and vascular malformations. In head and neck, where vascular anomalies are the most common benign lesions of infancy and childhood, correct diagnosis with the use of unequivocal terminology is more crucial for treatment considering the relevance of structures that can be involved. The aim of this work has been to clarify information and knowledges currently available in the field of vascular anomalies. Referring to ISSVA Classification, clinico-histopathological aspects of each entity have been elucidated.

Introduction

Vascular anomalies (VAs) represent a heterogeneous group of pathologies of the circulatory system that can affect any type of hematic and/or lymphatic vessel of different diameter and anatomic site. The global incidence of vascular anomalies in the general population is unknown, although in children under 3 years of age vascular tumors are estimated to occur in 6-8% and vascular malformations in 1.2%1. In this patient population, vascular anomalies represent the most common congenital and neonatal abnormalities2. The extreme variability of tissue types and districts involved by these lesions determines a wide heterogeneity of clinical manifestations, resulting in involvement of different medical expertise. In the vast majority of cases VAs occur individually, but sometimes can be expression of complex syndromes or rare malformative events. In these cases clinical approach, diagnosis and treatment will be more specific and may also require genetic analysis. Indeed, advances in genetics have allowed a more comprehensive understanding of the molecular mechanisms involved in development of these lesions, paving the way for the rise of novel target therapies. In this context, a commonly agreed terminology is crucial for the appropriate evaluation and patient’s management. In the last century, a wide range of terms has been used to describe these lesions, with the same classifier applied to designate different entities. In particular, many classifications utilized anatomical labels or descriptive terms, regardless of the biological behavior of the different pathologies. This approach in classification caused clinical confusion and consequently clinico-therapeutic errors3. In 2012, the Italian Society for the Study of Vascular Anomalies (SISAV) was established with the aim of bringing together in a scientific board all experts dedi-
cated to research, diagnosis and treatment of VAs. Involvement of different disciplines and competences is crucial when dealing with VAs, which for their nature must require a multidisciplinary approach.

The adopted classification currently used by SISAV to diagnose VAs is the “ISSVA Classification” that has its roots in the previous classification of Mulliken and Glowacky (1982)\(^5\). This classification is simple and schematic. It distinguishes VAs in two main groups: “vascular tumors” and “vascular malformations”. The distinctive trait of this categorization is to encompass physical findings, clinical behavior and cellular kinetics in definition of the single anomalies. The first ISSVA Classification dated 1996 distinguished VAs in relation to their hemodynamic characteristics in two main subtypes, namely “fast flow” and “slow flow”. Fast flow malformations were the artero-venous ones; slow flow were capillary, venous and lymphatic malformations. Combined forms were also possible (Tab. I). Last ISSVA Classification dated 2014 maintained the same structure of the previous edition, adding the (possible) association for some VAs with others anomalies or syndromic forms and their genetic alterations\(^6\).

The role of pathologic evaluation in the field of the VAs has to be their diagnostic confirmation and correct subclassification in the clearest way. Introduction in routine practice of a wide range of immunohistochemical endothelial markers helps pathologists to better recognize the single types of VAs as well as to identify some genetic alterations. At this purpose, besides the well known vascular markers such as CD31 and CD34, two antibodies may also be of importance. WT-1 is helpful to differentiate between vascular tumors, which are characteristically WT-1 positive, and vascular malformations which, on the contrary, are WT-1 negative\(^7\) (Tab. I). Podoplanin/ D2-40 underlines lymphatic endothelium, but does not stain hematic blood vessels\(^8\).

Accurate histopathological description, integrated with clinical and radiological information, is an absolute requisite for a meaningful diagnosis of VAs, both neoplastic and malformative.

In head and neck, VAs are the most common benign lesions of infancy and childhood, accounting for 14-65% of all cases. In this setting, a correct diagnosis and treatment are even more crucial considering the relevance of structures that can be involved such as eyes, ears, nose and mouth. Consequences can manifest both as loss of organ functionality and in terms of psychological impairment. Many competences are required, from radiologists, maxillo-facial and plastic surgeons, neurosurgeons, ophthalmologists, otolaryngologists, dentists and pathologists to speech therapists, psychologists and also make-up artists. This paper will investigate the most therapeutic relevant VAs that occur or at least have their preclinical stages in childhood, with a particular focus within the head and neck district. VAs affecting other districts or usually presenting in adulthood life (such as haemangioendotheliomas, Kaposi’s sarcomas and angiosarcomas) will not be treated.

### Vascular tumors

According to ISSVA classification, vascular tumors (VTs) are vascular lesions with a proliferative behavior. This classification divides VTs in benign, of intermediate and malignant grade\(^6\).

Some vascular lesions, for which is still debated the “reactive” rather than “neoplastic” nature, are grouped within benign tumors. These are “pyogenic granuloma/lobular capillary hemangioma” (PG) and the more rare “spindle cell hemangioma” and “epithelioid hemangioma”. PG is a very common vascular lesion of skin and mucosae, well known by clinicians and pathologists. It often develops in sites of previous superficial trauma and for this reason it is particularly frequent in young patients\(^9\). Excluding PG, the most common vascular tumor of infancy is “infantile hemangioma” (IH) followed at great distance by “congenital hemangioma” (CH). These two entities share a common feature, the ability to grow rapidly and then to regress partially or completely; sometimes they do not regress at all.

“Kaposiform hemangioendothelioma” (KHE) and “tufted hemangioma” (TH) are other rare forms of infantile vascular tumors. KHE is a neoplasm of intermediate-grade malignancy, TH is considered a benign vascular tumor. They have overlapping features and for some Authors represent the benign and malignant counterpart of a same vascular tumor\(^10\). They infrequently affect the head and neck district and for this reason may constitute

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Tab. I.
a diagnostic pitfall, if not evaluated in the appropriate clinico-radiological context.

**Infantile hemangioma**

Infantile hemangioma (IH), also known as “juvenile hemangioma” is a benign vascular tumor that presents early in life. IH is the most common tumor of the newborn with an incidence estimated between 3% to 10% of all infants and children. IH occurs more frequently in females than males, with a ratio of 3:1. Approximately 60% of cases occur in head and neck, with skin and subcutis being the most commonly affected sites. Caucasian race, preterm birth, weight at birth under 1000 g, old mother age, placenta previa and pre-eclampsya are recognized risk factors.

Factors as hypoxia, placental embolization, pluripotential stem cells and somatic mutations are hypothesized as responsible of the formation of His. Usually IH displays a predictable natural course: it appears after birth, within the first weeks, progressively enlarges over months and then gradually regresses spontaneously in 5 to 10 years. When fully developed, IHs can range in dimension from a few millimeters to large, mass-forming lesions.

In the vast majority of cases IHs are solitary lesions (80%), but 20% of children affected develop multiple IHs. IHs can be superficial, growing over bone prominences, or deep sited sometimes involving vital organs such as liver. Compared to IHs of other anatomical districts, IHs in head and neck can be particularly challenging and problematic lesions. Indeed, they can develop close to or directly involve structures such as eyes, ears, nose and mouth with ominous consequences especially considering the young age of patients affected. For this reasons, a multidisciplinary team made up of different expertise such ad vascular surgeons, ophthalmologists, otolaryngologists, cardiologists and neurosurgeons is required for the best management of patients, particularly when dealing with syndromic cases.

Rarely IHs are associated with other abnormalities, as it happens in syndromic forms. In head and neck the more frequent is the so called “PHACES” syndrome, characterized by posterior fossa anomalies (P), infantile hemangiomas (H), segmental anomalies of arteries, especially aorta (A), cardiovascular defects (C), eye anomalies (E) and sternal clefting and/or supraumbilical raphe (S). It is the most frequent one compared to other segmental IHs associated to developmental disorders. Females are more prone to it than males (F:M = 9/1). Recognized risk factors are fair skin photo type, a family history of IHs, advanced maternal age at birth and weight at birth less than 1,500g. In most cases this syndrome manifests in an incomplete way. Always, however, facial segmental hemangiomas are present and affect a skin area designated as “V3”. This area encompasses mandibular and pre-auricular region, chin, inferior lip, neck and sometimes the breastbone.

Imaging studies, as Magnetic Resonance Imaging (MRI), are important to analyze deep-sited IHs and/or their proximity to vital structures. Evaluation from ophthalmologists, otolaryngologists and cardiologists is requested whenever a syndromic form such as PACHE is suspected. Also, in cases of extended IHs, an echocardiogram is indicated to evaluate possible heart anomalies and for the screening of coagulopathies due to platelet consumption.

Diagnosis of IH is most of the time clinically evident. However in some cases, especially for deep-sited lesions, a histological exam is necessary for the correct definition of lesions. Typical histological appearance of IH is that of a well localized mass of capillaries, with a lobulated outline, made up of small, rounded lumina,

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**Fig. 1.**

Phase of proliferation

Phase of involution

| 0-1 years | 1-5 years | 5-10 years |
surrounded by a multilaminated basement membrane and pericytes. Endothelial cells do not show atypia, even if they may appear swollen or be mitotically active in first phase of development. Proliferating hemangioma capillaries grow interposed between normal skin structures, such as skin adnexa.

More frequently pathologists see IHs in the later stages of their natural evolution. At this time, they are characterized by more dispersed and disorganized vessels with flat, inactive endothelial cells surrounded by a thickened basement membrane and a fibrous-fatty matrix. Large arteries and draining veins, that in early phase allow lesion growth, partially regress. In this morphological setting, differential diagnosis is between the involute phase of IH and other vascular malformations and particularly helpful is for pathologists to be aware of clinical setting in which the lesions develop.

IHs are generally immunoreactive to common endothelial markers. Interestingly, they also show positive immunostain for glucose-transporter GLUT-1. In normal conditions this antigen is not expressed by endothelial cells of skin and sub-cutis, but it stains microvascular endothelia at sites of blood-tissue barriers, such as in central nervous system (CNS), retina, placenta, ciliary muscles, and endoneurium of peripheral nerves. Consequently, GLUT-1 has become extremely useful for diagnostic confirmation of IH. It has a good sensitivity, being expressed in all phases of hemangioma growth and excellent specificity, since it is not typically expressed in other vascular anomalies.

As the large majority of IHs regresses spontaneously, treatment is required only for 10-15% of IHs of head and neck. Different therapeutic options, frequently combined, are available, from medical to surgical approaches, laser treatment and sclerotherapy. In this district indications for treatment are life-threatening IHs (IHs causing high flow heart failure or obstruction/compression of respiratory airways), IHs impairing other organs functionalities (sight, nutrition, hearing), ulcerated IHs, not responsive to topic treatments and IHs with a risk of considerable relevant aesthetic imperfection (Fig. 2).

### Congenital hemangioma

Congenital hemangiomas (CHs) are a group of benign vascular tumors, first present in utero and already visible at birth, when they are fully developed as a single mass. They represent about 3% of all hemangiomas and rarely affect head and neck. Their clinical history is not as uniform as for IHs and three different evolutions are possible. In some cases, CHs regress rapidly within 1 year of age; these are called “rapidly involving congenital hemangiomas” (RICH). Sometimes CHs do not regress and a surgical treatment is necessary; these are called “non-involuting congenital hemangioma” (NICH). More rarely, CHs partially regress; these are called “partial involuting congenital hemangioma” (PICH). Usually they present in skin and underling soft tissue as red to purple plaques, superficially telangiectatic when fully developed. Eventually, they involve into a grayish color spot, with a pale peripheral halo in the least regressive form.

As it happens for infantile hemangioma, diagnosis of CH is essentially clinic. A biopsy is necessary whenever other more worrisome entities are clinically suspected, as fibrosarcoma, rhabdomyosarcoma and kaposiform hemangiomendothelioma. Histologically, CHs are characterized by large lobules with clear margins, made up of capillaries lined by endothelial cells sometimes prominent. Capillaries are surrounded by thin basal membranes, which at times become prominent. A fibrotic tissue fills the interlobular spaces where large, draining vessels, sometimes with prominent muscular walls, are present. This morphological aspect can simulate that seen in arteriovenous malformations and arteriovenous fistulas that have to be considered in differential diagnosis.

In CHs of RICH type additional regressive aspects are also observed. They consist in atrophy, loss of adnexal appendages, thickening of capillary basal membranes, outbreaks of chronic inflammatory cells, dystrophic calcifications, thrombosis and deposits of hemosiderin.

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**Fig. 2.** Infantile hemangioma: (A) clinical presentation, (B) haematoxylin and eosin stain, (C) GLUT-1 immunostain.
CHs are positive for common endothelial markers. However, in contrast to IHs they are GLUT-1 negative. For CHs, surgical treatment is required in NICH forms (for which treatment has to be performed early in childhood) and in case PICH forms, in order to remove the non-regressing part of the tumor (Fig. 3).

**Kaposiform haemangioendothelioma**

Kaposiform haemangioendothelioma (KHE) is a rare vascular neoplasm of intermediate malignant potential. It is locally aggressive, does not regress spontaneously and has a tendency to metastasize locally, as well as to local lymph nodes.

KHE occurs almost exclusively in infancy and early childhood and typically arises from superficial or deep soft tissue of extremities, trunk and retroperitoneum without predilection of sex and race. KHE can also affect head and neck (HN- KHE), where however is rare. In this district, only 53 cases have been reported in English literature.

KHE may be associated with “Kasabach-Meritt Phenomenon” (KMP). This phenomenon is characterized by severe thrombocytopenia and coagulopathies due to platelet consumption and may result in life-threatening hemorrhages. Clinically, KHE presents as a rapidly enlarging mass, arising in cutaneous or extra-cutaneous tissues. For HN-KHE, signs and symptoms are related to site and size of tumor. Lesions arising from the external/internal auditory canal and temporo-mastoid region can present with ear symptoms such as otorrhagia, facial palsy and recurrent ear infections. Tumor forming large masses can produce symptoms due to pressure of adjacent structures, resulting in dysphagia, airway obstruction and respiratory distress. Recurrent epistaxis is a common presenting symptom if tumors arise in paranasal sinuses, sometimes accompanied by hyposmia and nasal obstruction.

KHE can be suspected on a clinico-radiological basis, but always requires histological confirmation. Histologically, KHE consists of an infiltrative, multilobular spindle cell proliferation made up of slit-like vascular channels. Endothelial cells may be small with dark nuclei, or plump with vesicular nuclei. There is minimal nuclear atypia and mitotic activity is low. Scattered throughout the tumors are epitheloid or glomeruloid cell aggregates with cytoplasmic vacuoles, deposits of haemosiderin, PAS diastase positive hyaline globules, platelet-rich fibrin microthrombi. Immunohistochemistry shows strong expression of vascular hematic and lymphatic markers, but lack of GLUT-1 expression. Due to the rarity of HN-KHE, there is no consensus regarding the optimal treatment of this disease. Surgical and medical therapeutic strategies are possible, but presence of manifestations related to KMP can represent an important limiting factor for treatment (Fig. 4).
Tufted hemagioma

Tufted hemangioma (TH) is a rare, histologically benign vascular tumor, considered a form of benign KHE. It can be congenital or acquired and has no predilection for race and sex. Originally described in young adults, it is now considered a lesion of childhood. It usually appears in the skin of upper chest, shoulders and neck as a macula or plaque with variable color from pinkish-red to purple and with variable dimensions from few millimeters to several centimeters in diameter. Areas of hyperhidrosis and more rarely hypertricosis can be observed on the surface. The lesion grows slowly and then stabilizes. Spontaneous regression is reported but can be protracted and associated with “Kasabacht Merrit phenomenon”.

THs even if clinically suspected, necessitate histological confirmation. At microscopy, they are characterized by multiple highly cellular capillary lobules, the so-called “cannon balls”, dispersed in dermis and sometimes extending into subcutis. Lobules are composed of aggregates of capillaries same of which protrude into lumina of adjacent vessels, with “crescent” or “half moon shaped” vascular spaces. Lobules are separated from each other by normal dermis. Endothelial cells of THs show positive immunostain for common endothelial markers. Endothelial cells lining the dilated vessels around capillary lobules are positive for Podoplanin/D2-40, indicating a lymphatic origin.

THs do not require necessarily a treatment. However, whenever a therapy is indicated, the same approaches used for KHEs are adopted (Fig. 5).

Vascular malformations

Vascular malformations (VaMs) are malformative events occurring during embryogenetic development of the circulatory system.

There are only few studies regarding the epidemiology of VaMs. Tasnadi and Colleagues estimated an incidence of 1.2%, but other different data exist. Indeed, especially for this type of vascular anomalies is of particular difficulty to obtain reliable epidemiologic data. First of all, at present time there is not a uniform classificative system and confusion still exists on how to define some entities. Furthermore, many studies existing on VaMs have a selection bias, since they report data related to specific, mainly age-based populations, rendering hard to estimate their incidence in the global population.

VaMs have a peculiar characteristic: they are congenital anomalies already present at birth. At this time, however, they may be unapparent but then, due to their limited but persistent endothelial mitotic activity, grow throughout life in a slow albeit continuous manner. They are often sporadic and only less than 1% hereditary. They may be isolated or occur in syndromic forms. Head and neck is the most commonly involved sites.

VaMs may contain exclusively one type of vessel, namely venous, capillary or lymphatic vessels, or may be composed of any combination. An exception is represented by arterial malformations. These forms originate by an embryogenetic error in the arterial system, but always contain venous structures.

Diagnosis of VaMs requires clinical and radiological information. At this purpose, Magnetic Resonance Imaging (MRI) is the best technique to study VaMs arising in soft tissues, whether Computer Tomography (CT) is preferable for intraosseous forms.

In the setting of VaMs, histopathologic diagnosis is first of all useful to recognize and correctly classify the lesions. Pathologists may also recognize pattern of growth suggestive of specific subtypes. This is particularly important since some entities are associated with known genetic alterations, suggesting the necessity to perform more specific laboratory and/or genetic tests. Pathologic evaluation can also give clinicians information regarding the presence of alterations due to hematic stasis, high flow, or arteriovenous shunting. Last but not least, histology is essential to rule out other possible differential diagnosis.

Arterovenous malformation

Arterovenous malformations (AVMs) are malformations made of arteries and veins variably connected to each other. They may have direct arteriovenous communications named “arteriovenous fistulae” or may be separated by groups of “anastomosing” vessels, residual of the primitive embryonic vascular network, denominated “nests”.

The few data available about AMVs come from USA, where about 250,000 people are estimated to be affected by these lesions. AVMs become clinically evident in adulthood. In children they may not be fully developed and can be con-
fused with capillary malformations and infantile hemangiomas, with possible underestimation of their consequences.

AVMs appear as hyperemic, pulsating and warm skin areas. With time, tissues involved become hypertrophic and asymmetric. Events as trauma, puberty, pregnancy and estroprogestinic drugs can accelerate their evolution.

Clinical diagnosis is supported by imaging, and specifically by Doppler US, angio-CT and selective angiography scans.

AVMs are potentially the most aggressive type of vascular malformations and may cause problems in involved areas: minor defects, swelling, pain, local ischemia with ulcerations, hemorrhage and in diffuse infiltrating forms, hemodynamic complications with cardiac overloading.

In head and neck, AVMs can affect soft tissue, bone or both. Maxillary and mandibular bones are the most commonly affected. In bones, AVMs can be misdiagnosed as “cysts” and for this is important to be aware of the clinical scenario. For example, presence of spontaneous bleeding, gingival dislocation and tooth mobility is a hallmark of AVMs of jaw.

AVMs at advanced stage are life-threatening lesions especially in head and neck and require preoperative embolization followed by surgical resection.

At a microscopic level, AVMs present typically an arterious and venous component, the last often with secondary “arterialized aspects” of the wall, as thickened fibro-muscular wall with multilayered elastic fibers and a variable number of accessory vessels.

There is no evidence of intravascular thrombosis, fibrinolysis or papillary endothelial hyperplasia due to abnormal high flow.

Histologic differential diagnosis between capillary malformations and AVMs in children can be difficult. Vascular density, different length, distribution and thickness of vascular walls are parameters useful for this distinction.

WT1 staining, which is negative in most vascular malformations, may be positive in AVMs. For some AVMs genetic alterations have been identified. In “Hereditary Hemorrhagic Telangiectasia”, an autosomal dominant hereditary disease, mutations of genes ACVRL1 and ENG seem to be responsible of formations of arteriovenous fistulae.

“En bloc” surgical resection of AVMs has been for years the only treatment option. This, however, may be sometimes extremely destructive and at risk of causing conspicuous bleeding. Embolization can be used as palliative treatment to stabilize or slow down progression of symptoms. In this context, interdisciplinary collaboration is essential even more than in other vascular malformations, with a special regard to possible complementary roles of surgeons and the radiologists (Fig. 6).

### Venous malformation

Venous malformations (VMs) are localized developmental defects of venous district. Among congenital vascular malformations, VMs are some of the most frequent.

VMs generally occur as isolated lesions, but can also be multifocal. They may involve any part of the body, but limbs and cranio-facial surfaces are the most frequently affected sites. They may grow superficially on skin or mucous membranes or be deeply located, being intramuscular, intraosseous or visceral.

Usually, VMs are already evident at birth, but they may also become evident later in life and sometimes may appear during pregnancy. These lesions do not undergo spontaneous regression; instead, they persist and tend to grow in a progressive manner. For this reason the time of onset is relevant, since their growth, albeit slow, may be more imperious in young patients.

According to Hamburg Classification, VMs can be divided into two main groups, which differ in embryo-
genetic, anatomical, functional and clinical characteristics. Malformations arising from major veins are classified as “truncular forms” (TVMs), whilst malformations of dysplastic veins localized at a variable distance from the main venous axes are defined “extra-truncular forms” (ETVMs).

ETVMs are the most frequent forms. They can be localized or deeply infiltrative, with consequent compression of adjacent tissues and structures. They are made of dysplastic veins deriving from an error that occurs early in the embryogenetic development of vascular system. They are made of undifferentiated vessels of mesenchymal origin with a high proliferative potential. For this reason, they show high rates of recurrences after surgical treatment.

TVMs are less frequent than ETVMs. They affect the main venous axes and are caused by developmental anomalies of more advanced stages of vascular embryogenesis. Consequently, they have a low proliferative potential and thus rarely recur.

Identification of the specific type (TVMs vs ETVMs) of VM is essential, since therapeutic approaches differ for each single entity.

Clinical presentation of VMs is extremely variable, depending on site, size, type (ETVMs vs TVMs) and dimension of lesions. Superficial ETVMs are in general well evident at first glance. They typically occur as a bluish or purple swelling of soft-elastic consistency, expandable and collapsible to compression when not complicated by endoluminal clots. On the contrary, deep forms may be difficult to recognize just with physical examination. Their most frequent clinical signs are swelling and local pain. Particularly problematic may be the infiltrative forms of ETVMs, which may cause signs and symptoms due to compression of surrounding anatomical structures such as nerves, muscles, tendons, bones, joints and visceral structures. In a relevant percentage of cases (around 40%), ETVMs may cause coagulopathies. These are caused by venous stasis and activation of the coagulation cascade, which can consequently lead to formations of endoluminal clots. This clinical situation is called “localized intravascular coagulation” and is characterized by high levels of D-dimer and of Platelet Derived Growth Factor (PDGF), associated with normal platelet count and sometimes reduced level of fibrinogen. The calcification of endoluminal clots can lead to formation of nodules of hard consistency, known as “phleboliths”. Such complication is observed more frequently in very extensive and infiltrating forms and it is also observed after trauma, surgical resection or scleroembolization of lesions.

Head and neck VMs usually affect skin and subcutaneous tissues, but also bones can be interested often as indolent masses, sometimes causing deformity and functional impairment.

In the setting of VMs, histopathologic evaluation is indicated whenever there is a reasonable problem in differential diagnosis with other (malignant) forms. VMs are composed of vascular dysplastic lacunae with a thin wall lined by flat, monostratified endothelium. Endothelial cells are bland, without a significant mitotic activity. Dysplastic vessels show venous features and present different aspects in relation to the anatomical site involved. VMs localized in soft tissues and skin have large vessels with a muscular wall, sometimes rich in elastic fibers, but always without internal elastic lamina. In central nervous system, vascular walls can be thin or thick but always fibrous, while intrasosseous lesion show thin vascular walls, with rare smooth muscular fibers. In ETVMs, endoluminal phleboliths may be observed. Endothelial cells in VMs are immunoreactive for classical endothelial markers. Characteristically, staining for WT-1 and GLUT-1 are negative.

VMs are sporadic lesions, but hereditary autosomal dominant forms have been reported. Activating mutations in “TEK” gene, encoding for the Endothelial Cell Tyrosine Kinase Receptor “TIE2”, are responsible for familiar forms, but may also be observed in sporadic VMs. Downstream alterations of PI3K/AKT signaling pathway represent a major effector mechanism in lesion formation. Scleroembolization is the most commonly used treatment. Laser therapy can play a complementary role in the ablative treatment. Finally, vascular surgery aims to correct the hemodynamic defects in patients with VMs; they are classified as ablative and reconstructive (Fig. 7).
Capillary malformation

Capillary malformations (CMs) are slow flow vascular anomalies, typically affecting capillaries and/or venulocapillary components of skin and mucosae.

“Capillary malformation” is a definition used to refer to any clinically evident cutaneous vascular discoloration, with or without a true capillary malformative component, ranging from telangiectasias to arteriovenous, venous, and lymphatic malformations.

For this reason, true incidence of CMs is unclear. They are considered among the most common vascular malformations. If taken together, they affect nearly half of all infantile caucasian population, while excluding the most common form (“Medial congenital capillary macula”); see below), they go down to 0.3% at birth.

There is no sex predilection. CMs are potentially ubiquitous, but most of them involve the head (57% of all cases), mainly central portions of face. CMs are mostly sporadic and rarely familiar with an autosomal dominant transmission; however, penetrance is incomplete with consequent variable phenotypic expression.

Different aetiopathogenetic mechanisms are considered responsible of CMs development such as capillaries ectasia determined by a lack of neuronal vascular control, over-expression of vascular endothelial growth factor (VEGF) and its receptor (VEGFR), somatic mutation of GNAQ gene, and RASA1 gene.

Clinically, CMs appear as pink to red macules, vanishing to digital pressure. They are present at birth and can disappear or persist throughout life. The most common form of CMs is represented by “Medial congenital capillary macula”. This variant, common in caucasian babies, is characterized in many cases by a progressive, spontaneous resolution within the first years of age. They frequently involve the body midline, in particular neck, occipital area, upper eyelids, mid-forehead, glabella, sometimes extending to the tip of the nose and upper lip. Another variant of CM, the least frequent, is “Lateral congenital capillary macula”. This can manifest on any part of the body with a predilection for the face, where often takes a “mosaic” or “metameric-like” distribution along the segmental areas of the embryonic vascularization.

The distribution of CMs to forehead, specifically in the ophthalmic division of trigeminal nerve, can be suggestive of “Sturge-Weber syndrome”, in which CMs can also involve leptomeningeal, ocular districts and brain. When CMs persist, they may become thicker and darker so involve leptomeningeal, ocular districts and brain. In newborn, CMs may pose a problem of differential diagnosis with IHs in their prodromal phase. In this setting, simple observation of the clinical evolution of lesions can solve the question. Indeed, CMs are stable, not regressing lesions, whilst IHs rapidly change their clinical aspect. Another possible diagnosis to be excluded is that of AVMs in their early phase. This distinction is achieved mostly with imaging.

When clinico-radiological evaluation is inconclusive, a biopsy of the lesion may be resolving. On microscopic ground, CMs consist of a dense network of dilated, rounded, unbranched capillaries and/or post-capillary venules, filled with red blood cells. These vascular proliferations grow within the thickness of papillary and reticular dermis of skin and mucous membranes, determining a vascular density higher than that in normal surrounding tissue. More rarely they extend to subcutaneous tissue. Vessel walls are thin, lined by a single layer of endothelial flat cells, resting on a basal membrane. Areas affected by CMs tend to become thicker with time and when associated with overgrowth can develop aggregates of venous like vessels.

Somatic mutations in GNAQ gene, an activating non-synonymous single nucleotide variant, have been found in cases of Sturge-Weber Syndrome and in patients with “Port-wine-stains” (which is synonymous with CMs). Timing of occurrence of these mutations during development likely impacts clinical phenotype, ranging from uncomplicated “port-wine-stains” to much severe Sturge-Weber Syndrome.

Treatment of CMs is mandatory when anomalies do not regress and laser photoagulation represent the first choice, especially for facial lesions. Better results are obtained when treatment is performed very early. Surgery is considered in isolated cases, as for skin-mucosae of face or for CMs in adulthood when cobblestones are formed (Fig. 8).

Lymphatic malformation

Lymphatic malformations (LMs) are embryogenetic errors of lymphangiogenesis. They occur most commonly in infants, with an incidence of 1/20 000 in children admitted to hospital, as compared to 1/100 000 of hospitalized adults. Two-thirds of all reported cases involve the head and neck, usually before 2 years of age. There is no sex predilection. They can be ubiquitous, but most frequently involve lymphatic-rich areas, such as head and neck (where they represent 45-52% of all cases), axilla, mediastinum, groin, and retroperitoneum.

The genesis of LM is related to a failure of lymphatic vessels in connecting to venous system during embryogenesis. Sabin in 1902 proposed that lymphatic system was derived from primordial endothelial buds, sprouting from the developing venous system and coalescing to form plexi. He postulated this process started in neck. This concept is still maintained today and LMs are believed to originate from aberrant primordial buds that fail to reestablish communication with the venous plexus from which they originate. See comment in PubMed Commons below. Later on these lymphatic tissues become ectatic, giving a cystic appearance to lesions.

As VMs, LMs can be divided in two groups according to Hamburg Classification: “truncular” and “extratrunc-
colar” forms. Extratruncular LMs result from errors occurring in early stages of vascular embryogenesis, whilst truncular LMs result from errors in later stages. According to ISSVA classification, LMs are categorized in “cystic or common” forms (further subdivided in microcystic, macrocystic and mixed), generalized lymphatic anomalies and lymphedema. Cystic LMs of ISSVA classification correspond to extratruncular LMs of Hamburg classification.

Microcystic LMs appear as superficial multiple clear, tiny vesicles on skin and mucosae, extending deeply in tissue causing pain, itching and bleeding. Macrocytic LMs determine large, compressible or non-compressible, smooth, translucent masses under normal or bluish skin. Mixed LMs contain a mixture of micro- and macro-cysts.

Microcystic and mixed LMs are most commonly seen above the level of the mylohyoid muscle and involve the oral cavity, oropharynx, tongue, parotid gland, submandibular gland, and pre-epiglottic space. Macrocytic LMs are typically located between neck and lower part of the face, below the level of the mylohyoid muscle and involve the anterior and posterior cervical triangles, often interesting vital structures in these areas.

Large LMs can compress upper aero/digestive tract, can cause macroglossia, determining difficulty in eating and breathing. LMs can induce, like CMs, soft tissue overgrowth with consequent asymmetrical deformity. LMs may also affect soft tissues and bones, often sparing the bone cortical boundaries. Very rarely, however, bones are involved by an intrasosseous vascular proliferation, predominantly lymphatic, with progressive cortical bone osteolysis and bone consumption. This condition, named “Disappearing- Vanishing bone disease” or “Gorham-Stout disease”, can cause spontaneous fractures. The most frequently involved bones are those of pelvis, shoulder girdle, spine, ribs but also cranio-facial bones. Identification of these lesions is often difficult and several differential diagnosis with infectious osteolysis, inflammations, endocrine disorders and neoplastic diseases have to be taken into account. Therefore, a diagnostic confirmation may require a histopathologic evaluation.

LMs are generally recognized at birth and the vast majority become evident by 2 years of age. Sometimes, however, LMs are diagnosed before birth. Indeed, some large cystic LMs can be evidenced in utero with ultrasound as early as at the beginning of second trimester. Histologically, LMs are distinguished in “macrocystic”, “microcystic” and “mixed” forms. Macrocyctic LMs contain cysts equal or more than 5 mm in greatest dimension; microcystic contain cysts less than 5 mm in diameter; “mixed” forms have a combination of micro and macrocysts. Lymphatic vessels are composed of vascular spaces filled with eosinophilic, protein-rich fluid with a single layer of flattened typical endothelium. In macrocystic forms, lymphatic walls are of variable thickness and in more invertebrate lesions with fibrous bands of different thickness. Perivascular tissues may contain lymphocytes, isolated or in aggregates. Hemorrhage within cystic spaces is common, following trauma or spontaneous intralesional bleeding. Endothelial cells of lymphatic malformed vessels are positive for common endothelial cell markers and more specifically for lymphatic markers.

Somatic PIK3CA mutations have been found in isolated LMs and in combined forms. Management of this heterogeneous group of lesions is complex and strictly dependent on clinical presentation, size of lesion, anatomic location, and possible complications. Advanced LMs of head and neck are even more challenging, especially when they cause function impairment such as aerodigestive tract obstruction, severe dysgestia or visual loss. Some LMs may regress spontaneously and for this reason treatment should ideally be delayed in young children. Therapeutic strategies range from observation...
to pharmacotherapy, surgery and sclerotherapy and each patient needs to be evaluated singly. When performed, the mainstay of surgical management is to eradicate lesions causing minimal damage to adjacent structures (Fig. 9).

**Combined vascular malformations**

Vascular malformations (VaMs) can combine each other in a same lesion or may be present separately in the same patient. The most frequent associations are VMs combined with CMs, CMs with LMs, VMs with CMs and LMs; less frequently AVMs associate with other VaMs. Capillary-lymphatico-venous malformations (CLVMs) are the most common complex combined VaMs. Their occurrence in head and neck is exceptional. An example is represented by “angiokeratoma” which is characterized by a combination of capillary and lymphatic. In newborns angiokeratoma may be confused with the more frequent “segmental infantile haemangioma” in its prodromal phase. AVMs can also combine with other VaMs arising separately in different part of the body. For head and neck this is the case of combined CMs-AVMs. This association is characterized by multiple, small cutaneous CMs located mainly on the face and extremities and increasing in number with age. At the same time, AVMs and arterovenous fistulae develop in superficial and deep tissues, also intracranially and intraspinaly. It has been demonstrated that combined CMs-AVMs are inherited condition caused by RASA1 mutations. Histological identification of all the different vascular components combined in a same lesion or vascular anomalies occurring in a single patient is not just a classificative matter. Indeed, it gives clinicians crucial indications for planning any further treatment for each single lesion and patient (Fig. 10).
Data and information reported in this work derive from a collaboration between clinicians, pathologists, geneticists, radiologists and surgeons. Constant discussion and confrontation on each single case have allowed us to understand and learn something more about these rare, but not that rare, lesions.

References