Interdisciplinary Management of Vascular Anomalies in the Head and Neck

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Authors
Stefan Mattheis[1], Isabel Wanke[2]

Affiliations
1 Dept. of Oto-Rhino-Laryngology, Head and Neck Surgery, University Medicine of Essen, Germany (Professor and Chair: Prof. Dr. Stephan Lang)
2 Center of Neuroradiology, Hirslanden Hospital, Zürich, Switzerland

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Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Univ.-Prof. Dr. med. Stefan Mattheis, MHBA
Universitätsmedizin Essen
Klinik für Hals-Nasen-Ohren-Heilkunde
Kopf- und Hals-Chirurgie
Hufelandstraße 55
45122 Essen
Germany
stefan.mattheis@uk-essen.de

ABSTRACT

Vascular anomalies in the head and neck area are usually rare diseases and pose a particular diagnostic and therapeutic challenge. They are divided into vascular tumors and vascular malformations. A distinction is made between benign tumors, such as infantile hemangioma, and rare malignant tumors, such as angiosarcoma. Vascular malformations are classified as simple malformations, mixed malformations, large vessel anomalies and those associated with other anomalies. Treatment is interdisciplinary and various modalities are available. These include clinical observation, sclerotherapy, embolization, ablative and coagulating procedures, surgical resection and systemic drug therapy. Treatment is challenging, as vascular anomalies in the head and neck region practically always affect function and aesthetics. A better understanding of the genetic and molecular biological basis of vascular anomalies has recently led to clinical research into targeted drug therapies. This article provides an up-to-date overview of the diagnosis, clinic and treatment of vascular anomalies in the head and neck region.

Contents

1. Introduction

Vascular anomalies are a heterogeneous group of mostly rare diseases that differ in their clinical manifestations, anatomy, pathology, and therapeutic approaches. Since the early 1980s, vascular anomalies have been differentiated between vascular tumors and vascular malformations based on histological endothelial characteristics and clinical manifestations [1]. Vascular tumors include more common diseases such as infantile hemangioma, but also rare diseases such as aggressively growing hemangioendotheliomas or malignant angiosarcomas. Vascular tumors are true neoplasms characterized by growth and tissue proliferation. In contrast, vascular malformations are malformations in embryonic vascular development. This group includes, for example, lymphatic or venous malformations.

The treatment of vascular anomalies in the head and neck area poses a particular challenge, as functional and esthetic aspects of the disease must always be taken into account. Particularly in the functional areas, it is important to preserve the airway, important functions of sensory organs and cranial nerves, facial expressions, swallowing and voice. If the orbit is affected, maintaining eye motility and visual acuity is an important treatment goal. Bone infestation, chronic pain, bleeding and recurrent inflammation can make treatment more difficult. In addition to all these challenges, accurate diagnosis and classification are necessary for successful treatment. The current status of diagnosis and treatment of vascular anomalies in the head and neck region is explained below.

2. ISSVA classification

The classification of the International Society for the Study of Vascular Anomalies (ISSVA) divides vascular anomalies into two main groups: vascular tumors and vascular malformations [2]. In the case of tumors, a distinction is made between benign and malignant tumors. The third group in between are locally aggressive tumors or so-called “borderline” tumors. The most common benign tumor is the infantile hemangioma, locally aggressive growing is e. g. the caposiform hemangioendothelioma and the most common malignant vascular tumor is the angiosarcoma.

Vascular malformations are classified into simple and combined malformations, malformations of large vessels and malformations associated with other anomalies or syndromes. Simple malformations include capillary malformations, lymphatic malformations, venous malformations, arteriovenous malformations and arteriovenous fistulas. Combined malformations consist of two or more types of simple malformations, e. g. lymphatic-venous malformations with parts of a lymphatic and a venous malformation. These mixed forms are found more frequently in everyday clinical practice.

Another classification concerns the intravascular flow rate. A distinction is made between “low-flow” or “slow-flow” and “high-flow” malformations. Among other things, this classification is of great importance for the treatment and prognosis of malformations. “High-flow malformations tend to increase in size over time, often triggered by hormonal changes, and must be treated early and consistently, usually with a combination of embolization and resection. In the head and neck area, duplex ultrasonography generally enables a rapid assessment of malformations with regard to the flow rate. The assessment of mixed malformations is somewhat more complex, as “high-flow” and “low-flow” parts can occur side by side in one malformation. Low-flow malformations include capillary, lymphatic and venous malformations. Arteriovenous malformations and arteriovenous fistulas are high-flow malformations.

▶ **Table 1** ISSVA classification of vascular anomalies.

	Vascular anomalies			
Vascular tumors	**Vascular malformations**			
Benign	**Simple malformations**	**Combined malformations**	**Involvement of large vessels**	**Syndromes**
Locally aggressive borderline	Capillary malformations	Capillary-venous malformations		Klippel-Trenaunay syndrome
Malignant	Lymphatic malformations	Capillary lymphatic malformations		Parkes-Weber syndrome
	Venous malformations	Lymphatic-venous malformations		Servelle-Martorell syndrome
	Arteriovenous malformations	Capillary lymphatic-venous malformations		Sturge-Weber syndrome. Maffucci syndrome
	Arteriovenous fistulae	Capillary arteriovenous malformations		CLOVES. Proteus syndrome
		Capillary lymphatic arteriovenous malformations		CLAPO. Bannayan-Riley-Ruvalcaba syndrome
		Other		Other

▶ **Table 2** Vascular tumors.

Vascular tumors		
Benign vascular tumors	**Lokally aggressive tumors Borderline tumors**	**Malignant vascular tumors**
Infantile hemangiomas	Kaposiform hemangioendothelioma	Angiosarcoma
Congenital hemangiomas (RICH,PICH,NICH)		Epitheloid hemangioentotheliomas
Tufted hemangiomas		
Spindle cell hemangiomas	Other locally aggressive or borderline tumors	Other malignant tumors
Epitheloid cell hemangiomas		
Pyogenic granuloma		
Other		

In recent years, genetic testing of affected patients has become increasingly important, as it has been found that the tissues affected by vascular malformations often carry somatic mutations that lead to vascular malformation or other complications. The two central signaling pathways PI3K/Akt/mTOR and Ras/Raf/MEK are frequently affected [3, 4]. Knowledge of the underlying genetic defects has contributed to a better understanding of the biology and pathology of vascular anomalies. Different malformations can be categorized according to their genotype, e. g. lesions belonging to the PI3CA-related "tissue overgrowth spectrum". Mutations in the PI3CA gene lead to overgrowth, e. g. in the extremities. In addition to the academic interest in the underlying genetic causes of vascular malformations, genetic diagnostics is gaining a key position in the drug therapy of vascular malformations, as numerous targets for drug therapy have now been identified in the signaling pathways.

In order to make effective use of advances in imaging, surgical procedures, interventional neuroradiology and drug therapy, a clear diagnosis and uniform classification of vascular anomalies is required. This overview is based on the current classification of the International Society for the Study of Vascular Anomalies (▶ **Table 1**).

3. Vascular tumors

In vascular tumors, a distinction is made between benign tumors, locally aggressive or borderline tumors, and malignant tumors. While malignant and locally aggressive tumors are rare, infantile hemangioma is a common tumor that must be differentiated diagnostically from other vascular anomalies. Vascular anomalies in infants are very often incorrectly referred to as "hemangiomas" and may therefore be treated incorrectly (▶ **Table 2**).

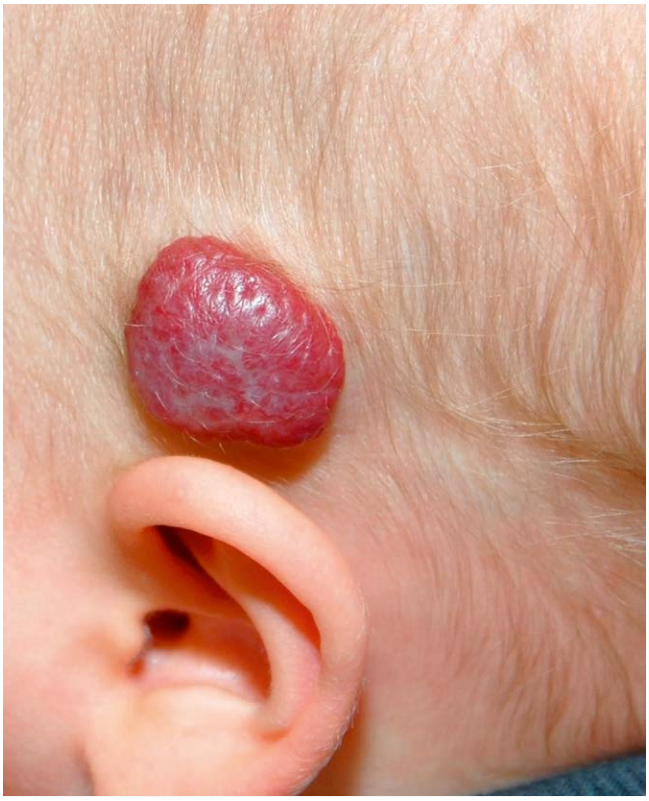
▶ **Table 3** Differentiation between infantile hemangioma and vascular malformation (modified according to [7]).

	Infantile hemangioma	Vascular malformation
Time of manifestation	Days or weeks after birth	At birth (symptoms may also develop later)
Growth	Rapidly within the first months of life, then slowly	Rarely within the first months of life, then slowly or in stages over decades
Regression	Obligat	No regression

3.1 Benign vascular tumors

3.1.1 Infantile hemangioma

Infantile hemangiomas are the most common benign neoplasm in childhood and occur in about 5 % of all infants. They are more common in females (ratio 3:1), in fair-skinned infants and in premature infants with a birth weight of less than 1000 g [5–7]. They are proliferating vascular tumors that resemble placental tissue in their structure. Local or regional tissue hypoxia is discussed as the cause [8]. The most common localization is the head and neck area, which is why the involvement of ENT specialists, ophthalmologists and pediatricians makes sense in interdisciplinary treatment.



▶ **Fig. 1** Exophytically growing infantile hemangioma at the temple.

Clinical appearance

Infantile hemangiomas become visible a few days after birth and subsequently grow. At the time of birth, they are practically never clinically present, at most precursor stages such as telangiectasias or livid maculae may occur. The temporal progression is an important distinguishing feature from vascular malformations, which are already present and visible at birth (▶ **Table 3**). The congenital hemangiomas, the "Rapid Involuting Congenital Hemangioma" (RICH), the "Partial Involuting Congenital Hemangioma" (PICH) and the "Non-involuting Congenital Hemangioma" (NICH) are also already present and visible at birth. The same applies to kaposiform hemangioendothelioma. In the clinical course, infantile hemangioma goes through three different phases [5]. At the beginning, days or weeks after birth, there is a sometimes rapidly progressive proliferation phase. This usually involves extensive growth with exophytic or subcutaneous spread in individual cases. After about 6 months of life, there is a transitional phase of varying length without significant growth, followed by an involution phase. By the age of 4 years, 90 % of infantile hemangiomas have completely regressed.

About 90 % of infantile hemangiomas are localized and show cutaneous and/or subcutaneous growth. Exophytic growth is possible. Rare forms are segmental and multifocal hemangiomas (five or more cutaneous hemangiomas) (▶ **Fig. 1**).

In addition to uncomplicated focal infantile hemangiomas, complicated forms also occur in 10–15 % of cases [10]. These are characterized by functional or esthetic impairments, ulceration, secondary hypothyroidism, other extracutaneous manifestations (liver, larynx, orbit, etc.), or associated syndromes with corresponding additional malformations. Especially in the head and neck area, infantile hemangiomas can lead to permanent aesthetic and functional impairment if the location is unfavorable and the growth is large. These include deformities of the skin, ears, mouth and nose, involvement of the orbit with loss of vision and motility disorders, restriction of the air and food passages and impairment of the voice with laryngeal involvement with potentially life-threatening conditions. Rarely, glottic or subglottic hemangiomas are found as part of PHACES syndrome or in segmental hemangiomas of the neck, with the risk of airway obstruction. In such cases, rapid treatment can prevent complicated progression [12]. PHACES syndrome manifests with a **p**osterior fossa malformation, an infantile **h**emangioma larger than 5 cm on the head and neck, an **a**rterial anomaly, a **c**ardiac anomaly, an aortic isthmus stenosis, **e**ye anomalies, and a **s**ternal cleft with or without supra-umbilical raphe.

Diagnosis

The most important diagnostic clues are provided by a precise medical history about the time of onset and observation of the progression over time. The most common differential diagnosis to infantile hemangiomas are vascular malformations that are already present and visible at birth. Rare differential diagnoses are congenital hemangiomas and other rare vascular tumors. In the initial diagnosis, a clinical and sonographic examination with duplex sonography should be performed. Color-coded duplex sonography provides information about the extent, in particular the depth and degree of vascularization of the hemangioma. In the growth phase, there is pronounced vascularization, which decreases in the transition phase and involution phase. Duplex sonography is therefore particularly suitable for documenting the progression and asses-

▶ **Table 4** Extended diagnostics in the context of complex infantile hemangiomas of the head and neck (modified according to [7]).

Complex infantile hemangiomas	Extended diagnostics
5 and more focal hemangiomas (multifocal hemangiomas)	Ultrasound of the scull and the liver, TSH in serum
Large (> 1 % of the body surface) infantile hemangiomas of the chin and anterior neck region	Echocardiography, TSH in serum, laryngoscopy, MRI
Segmental infantile hemangiomas of the head and neck	Echocardiography, ophthalmologic examination, MRI of the skull including orbita, contrast enhanced dynamic MR angiography of the supra-aortal and cerebral arteries (MR angiography)
Eye-near, potentially vision-threatening infantile hemangiomas	Ophthalmologic examination MRI to assess orbital involvement
Tumors of unclear classification	Biopsy (histology and immunohistochemistry), probably staging by imaging

sing the prognosis. Photographic documentation with a size scale is also necessary in order to objectively document the course of growth. If the diagnosis of an uncomplicated focal infantile hemangioma is clear from the clinical findings and progression, further diagnostic steps, such as MR imaging, which usually requires general anesthesia, are not necessary. Further examinations may be necessary in the event of a complicated course or if the diagnosis is unclear. ▶ **Table 4** provides an overview of the advanced diagnostics for complicated hemangiomas in the head and neck region.

In segmental hemangiomas of the head and neck area, MR angiography is used to detect any vascular anomalies in associated syndromes (PHACES). A biopsy with immunohistochemical examination may be useful if the differential diagnosis with other vascular tumors is unclear. In contrast to other vascular tumors, infantile hemangiomas express the glucose transporter protein 1 (Glut1-positive) as a marker [11].

Therapy

Uncomplicated focal infantile hemangiomas generally do not require treatment. In these cases, a detailed informative discussion with the parents and a follow-up with sonography and photo documentation should be carried out. Complicated infantile hemangiomas should be treated early, i. e. before a significant increase in size occurs, in order to prevent late complications. This means that treatment in such cases should begin in the 2nd-5th month of life if possible. The treatment should aim at an early growth arrest and accelerated regression.

The treatment of choice is systemic therapy with the beta-blocker propanolol [13]. The exact mechanism of action of propranolol is still unclear, but vasoconstriction, inhibition of angiogenesis, induction of apoptosis in proliferating endothelial cells and inhibition of renin release are being discussed. Before using propranolol, an ECG should also be performed on a healthy infant with an inconspicuous family history of congenital cardiovascular disease.

Treatment with propranolol is started gradually at a dose of 1 mg/kg bw/day and increased daily in the inpatient setting and weekly in the outpatient setting to the target dose of 2 (-3) mg/kg bw/day, divided into two or, in justified cases, three individual doses. The duration of propanolol treatment should be at least 6 months [14]. Side effects occur in about 30 % of cases, but are usually harmless and transient [15]. These include sleep disorders, nocturnal restlessness and gastrointestinal complaints. Bradycardia, hypoglycemia or hypotension have rarely been observed.

Alternative treatment methods should only be used if there are contraindications to propanolol therapy, in the rare event of failure of propanolol therapy or to treat residual conditions after waiting for the involution phase. Alternative treatment methods include systemic therapy with the selective beta-blockers nadolol or atenolol ("off label"), systemic corticosteroid therapy, cryotherapy for small hemangiomas, embolization, dye laser therapy, treatment with Nd:YAG laser and surgical therapy. Systemic cortisol administration should only be used as a supplement to propanolol therapy for acute respiratory distress. Laser treatment and surgical therapy are generally reserved for the treatment of residual conditions after incomplete involution. The ideal time for surgical correction of functionally and esthetically significant residual conditions is between the ages of 4 and 5, before children start school and after completion of the involution phase.

3.1.2 Congenital hemangiomas

Congenital hemangiomas are rare vascular tumors which, in contrast to infantile hemangiomas, are already present at birth and do not proliferate [16]. A distinction is made between rapidly involuting congenital hemangiomas (RICH), non-involuting congenital hemangiomas (NICH) and partially involuting congenital hemangiomas (PICH). Clinically, they sometimes resemble vascular malformations and are more bluish with a pale border compared to infantile hemangiomas. In contrast to infantile hemangiomas, congenital hemangiomas are negative for the glucose transporter GLUT1. Regression can occur within the first week of life or take many months [17]. After regression, residual conditions often remain, which must be treated surgically or with coagulation procedures in the event of esthetic or functional impairment.

3.1.3 Tufted hemangiomas

Tufted angiomas are a rare, complex vascular tumor that can show locally aggressive growth [18]. Similar to kaposiform hemangioendothelioma, the disease can lead to the Kasabach-Merritt phenomenon, a life-threatening consumption coagulopathy associated with severe thrombocytopenia, hemolytic anemia and disseminated intravascular coagulation. As a result, there is a high risk of severe bleeding. Treatment involves a combination therapy of corticosteroids, chemotherapy, transfusions and antiplatelet agents. Recent literature discusses whether tufted hemangioma and kaposiform hemangiendothelioma might belong to the same tumor group due to their similar behavior.

3.1.4 Pyogenic granuloma

Pyogenic granuloma is a common, fast-growing vascular tumor of the skin and mucous membrane that occurs preferentially in the head and neck area and on the fingers [19]. The cause is often microtrauma to the skin or mucous membrane, but spontaneous development is also possible. Clinically, a solitary red, slightly bleeding papule appears, which can also spread subcutaneously or submucosally. Histology shows lobularly arranged, proliferating capillaries. 40 % of pyogenic granulomas occur in the first 5 years of life, but they can also be present at birth or only appear in adulthood. Complications include bleeding or ulceration, which is why pyogenic granulomas are usually removed surgically or treated with a laser.

3.1.5 Spindle cell hemangiomas

It is a benign tumor with proliferating spindle cells and cavernous vessels that occurs preferentially on the extremities but also in the head and neck region [20]. Children of both sexes are affected, with a peak age in infancy. Treatment is usually surgical.

3.1.6 Epithelioid hemangioma

Epithelioid hemangiomas occur particularly on the head and distal extremities. After resection, they have a high recurrence rate [21].

3.1.7 Other benign vascular tumors

In addition to the tumors mentioned above, there are a number of very rare other benign vascular tumors for which the diagnosis must be confirmed by a biopsy in case of doubt.

3.2 Locally aggressive tumors or semi-malignant tumors

3.2.1 Kaposiform hemangioendothelioma

Similar to tufted hemangiomas, the locally aggressively growing kaposiform hemangioendothelioma can be accompanied by the life-threatening Kasbach-Meritt phenomenon. The tumors usually occur on the extremities, rarely in the head and neck area and can reach a considerable size. Treatment is performed individually; clinical studies have shown that sirolimus is an effective agent [18, 22].

3.3 Malignant tumors

3.3.1 Angiosarcoma

The rare angiosarcoma is one of the most aggressive soft tissue sarcomas with a poor prognosis [23]. The tumor usually affects older patients and grows from blood and lymph vessels. Risk factors include previous radiotherapy or chronic lymphoedema. Despite multimodal and interdisciplinary treatment, recurrences are frequent and the 5-year survival rate is around 35 %.

3.3.2 Epithelioid hemangioendothelioma

It is a very rare sarcoma with early metastasis. In the head and neck area, epithelioid hemangioendotheliomas occur more frequently in the oral cavity on the tongue and gingiva. The aim of treatment is complete resection. In a recently published large multicenter study, the two-year survival rate of epithelioid hemangioendothelioma after multi-modality therapy was approximately 82 % [24].

▶ **Table 5** Classification of simple vascular malformations based on the flow rate.

Simple vascular malformations	Slow-flow	High-flow
	Capillary malformations	Arteriovenous malformations
	Lymphatic malformations	Arteriovenous fistulas
	Venous malformations	

4. Vascular malformations

Vascular malformations are divided into simple malformations, combined malformations, malformations involving large vessels and malformations that occur as part of syndromes (▶ **Table 5**).

4.1 Simple vascular malformations

In the case of simple malformations, a distinction is made between "low-flow" or "slow-flow" and "high-flow" malformations based on the blood flow and the associated flow rate. High-flow malformations have an arterial component and this group includes arteriovenous malformations (AVM) and arteriovenous fistulas. Duplex ultrasonography can be used to quickly assess the perfusion of malformations in the head and neck region. Simple "low-flow" malformations include capillary, lymphatic and venous malformations.

4.1.1 Capillary malformations

Capillary malformations are the most common congenital vascular malformations in the head and neck region. They are characterized by an expansion of the capillaries at the skin level. A distinction is made between nevus simplex (stork bite), capillary cutaneous or mucosal malformations ("port wine stain"), reticular capillary malformations, cutis marmorata and the group of telangiectasias. Capillary malformations can be associated with an arteriovenous malformation (AVM). In Sturge-Weber syndrome, capillary malformations occur on the forehead and face together with CNS and ocular anomalies.

4.1.1.1 Nevus simplex (stork bite)

Nevus simplex is a common capillary malformation of the skin that occurs in about 40 % of all newborns with light skin color in the neck, forehead or eyelid area [26, 27]. Infants with dark skin are affected less frequently. The lesions are usually located in the midline, but can also occur on both sides. Single or multiple reddish patches with irregular, blurred edges appear, which fade when pressure is applied. The diagnosis is made on the basis of the typical clinical appearance. In most cases, the nevus fades during the first two years of life and disappears after the second year of life. In the case of persistent lesions with esthetic impairment, these can be treated with a pulsed dye laser.

4.1.1.2 Cutanous or mucosal capillary malformations (port wine stain)

Capillary malformations of the skin and mucosa are already present at birth and often occur in the head and neck area. They are characterized by blotchy, smooth reddening of the skin, caused by

congenital dilation of the capillaries of the skin and mucosa [28]. In infancy, these skin changes have a reddish appearance, which is why they are also known as nevus flammeus. In the course of life, some malformations fade, while others become darker, leading to the term port-wine stain. The term "port-wine stain" is widely used for capillary malformations. Over time, some malformations lead to hypertrophy of the connective tissue in the affected areas. There may also be increased growth of neighboring bone or a nodular transformation of the tissue. Apart from the esthetic impairment, which is particularly important in the facial area, isolated capillary malformations do not cause any symptoms. The diagnosis is usually made on the basis of the classic clinical appearance, so that additional imaging is not necessary. Further diagnostics are only required if capillary malformations occur in the context of syndromes. In the head and neck area, the presence of a capillary malformation in the area of the forehead, glabella and upper eyelid may indicate the presence of Sturge-Weber syndrome.

4.1.1.3 Reticular capillary malformationes

According to the ISSVA classification, reticular capillary malformations include two rare syndromes in which capillary malformations are associated with microcephaly or megalencephaly. In microcephaly-capillary malformation syndrome, affected patients suffer from multiple capillary malformations, microcephaly, seizures, neurological impairment and general developmental delay [29]. The even rarer megalencephaly-capillary malformation-polymicrogyria syndrome is characterized by multiple capillary malformations, megalencephaly, focal seizures and mental retardation [30].

4.1.1.4 Capillary malformations and AVM

Capillary malformation-arteriovenous malformation syndrome is an autosomal dominant inherited disorder caused by a mutation in the RASA1 gene (type I) or in the EPHB4 gene (type II) and is characterized by multiple, small, oval capillary malformations [31, 32]. In about one third of cases, arteriovenous malformations also occur, which can affect the spinal cord or brain. Type II forms also show telangiectasia more frequently and patients suffer from nosebleeds. A differential diagnosis in such cases is hereditary hemorrhagic telangiectasia (HHT, Osler's disease).

4.1.1.5 Cutis marmorata teleangiectatica congenita

Cutis marmorata teleangiectatica congenita (CMTC) is a rare congenital vascular malformation characterized by a reticular vascular pattern with telangiectasias [33]. The extremities on one side are often affected, but there are also generalized forms. In about 50 % of cases, CMTC is associated with syndromes. In some cases, ulceration may occur in the area of the affected skin. Tissue hypoplasia is rarely seen on the affected extremity. In most cases, the skin changes regress during the first two years of life. Residues can possibly be treated with dye pump lasers.

4.1.1.6 Telangiectasias

Various rare diseases associated with telangiectasias are subsumed in this category in the ISSVA classification. Some of these diseases are currently being discussed as belonging to the group of capillary malformations and may be reclassified [2]. The most common disease in this group is hereditary hemorrhagic telangiectasia.

4.1.1.7 Hereditary hemorrhagic telangiectasia

HHT, also known as Osler's disease or Rendu-Osler-Weber disease, is an autosomal dominant disease caused by mutations in the ENG, ACVRL1, SMAD4 or GDF2 genes and characterized by multiple lesions with dilation of the capillaries [34]. These telangiectasias can affect the entire skin and mucosa. The lips, oral cavity and nasal mucosa are frequently affected in the head and neck area. Telangiectasias on the fingers are also characteristic. However, other organ systems such as the gastrointestinal tract, lungs, liver or CNS are also frequently affected. In later stages, some patients show arteriovenous fistulas in the area of the pulmonary or hepatic lesions, rarely also in the CNS, which can reach considerable shunt volumes [35–36].

Diagnosis

In 2000, Shovlin et al [37] defined clinical criteria for the diagnosis of HHT, the so-called "Curaçao criteria" (▶ **Table 6**). These include nosebleeds, telangiectasia of the skin and mucosa, organ involvement and a positive family history. If three or more of these criteria are observed, the diagnosis is considered certain. If two criteria are present, the diagnosis is probable or possible; if only one criterion is present, the diagnosis of M. Osler is unlikely.

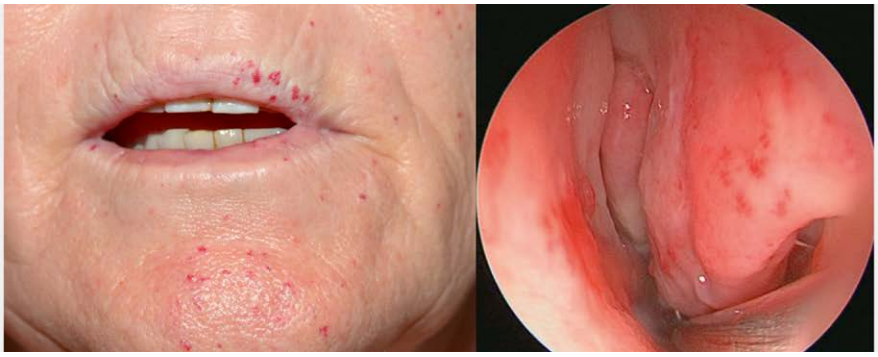
Diagnostics in the area of the nose and oral cavity are carried out by an ENT specialist using endoscopy. If bleeding from the gastrointestinal tract is suspected, endoscopies are also necessary. Imaging is required to visualize lesions in the lungs, liver, gastrointestinal tract and spinal cord. A combination of CT scan, MRI and sonography provides reliable results. If AV shunts are suspected, particularly in the lungs and liver or CNS, angiography may be indicated (▶ **Table 6**).

Clinical appearance

The leading symptom of HHT is recurrent nosebleeds, beginning in childhood and adolescence. In the course of the disease, particularly in the third decade of life, the telangiectasias and the associated symptoms increase. Recurrent epistaxis and sometimes occult bleeding from the gastrointestinal tract often lead to chronic anemic conditions during the course of the disease. The arteriovenous malformations in the lungs and liver can have a hemodynamic effect when they are large enough and must therefore be treated if necessary (▶ **Fig. 2**).

▶ **Table 6** Curaçao criteria for clinical diagnosis of hereditary hemorrhagic telangiectasia (HHT) [37].

Criterion	Description
Epistaxis	Spontaneous recurrent nosebleeds
Telangiectasia	Multiple telangiectasias in typical sites: lips, oral cavity, fingers, nose
Visceral lesions	Telangiectasias in the gastrointestinal tract, lung, liver, cerebral or spinal
Family history	One relative of first degree suffers from the above-mentioned criteria



▶ **Fig. 2** Telangiectasias of the perioral skin and nasal mucosal in Osler's disease.

Therapy

The treatment of Osler's disease is individualized and primarily includes the treatment of nasal and gastrointestinal bleeding, with the associated management of anemia and any coagulation disorders [38]. Nasal measures include moistening, application of ointments and, if necessary, coagulation of the bleeding telangiectasias with radiofrequency, laser and other procedures. In individual cases, surgical closure of the nose may be necessary. If necessary, arteriovenous fistulas of the lungs, liver and CNS must be treated in specialized centers.

4.1.2 Lymphatic malformations

Lymphatic malformations are congenital developmental anomalies of lymphatic vessels that clinically present as "low flow" malformations with dilated lymphatic vessels. They occur with a frequency of 1:2,000 - 1:3,000 and both sexes are affected about equally often. About half of all lymphatic malformations are already apparent at birth. Another part becomes visible during the first two years of life. Rarely do lymphatic malformations only manifest themselves in adulthood. Frequent localizations are the head and neck area and the extremities. Pronounced findings can be diagnosed by intrauterine diagnostics even before birth, so that measures can be taken to secure the airways, for example. Clinically, lymphatic malformations appear as soft, painless masses, with cutaneous involvement and livid discoloration of the skin. Acute viral infections can lead to considerable swelling and bleeding. The exact cause of the development of lymphatic malformations has not yet been clarified. However, mutations associated with activating variants in the PIK3/Akt/mTOR signaling pathway and in the Ras/Raf/MEK signaling pathway are partly responsible [3, 4, 39, 40].

4.1.2.1 Simple (cystic) lymphatic malformations

In simple malformations, a clinical distinction is made between macrocystic and microcystic malformations and mixed malformations with macrocystic and microcystic components. Macrocystic lesions show large, smooth cysts surrounded by a small amount of lymphocytic stroma. Microcystic lesions are characterized by multiple small cysts surrounded by broad connective tissue strands in a sponge-like manner. This classification is also important for therapy, as macrocystic malformations are easier to treat both surgically and with sclerotherapy. Frequent localizations are cervical in the area of the soft tissues of the neck, as well as in the angle of the jaw with involvement of the parotid gland. The respiratory tract and swallowing tract can also be affected. The oral cavity is frequently affected, with involvement of the tongue muscles and the base of the tongue. The larynx and trachea are less frequently affected. When the larynx is involved, lymphatic malformations are often found in the supraglottic region, with transition of the lesion to the base of the tongue [41].

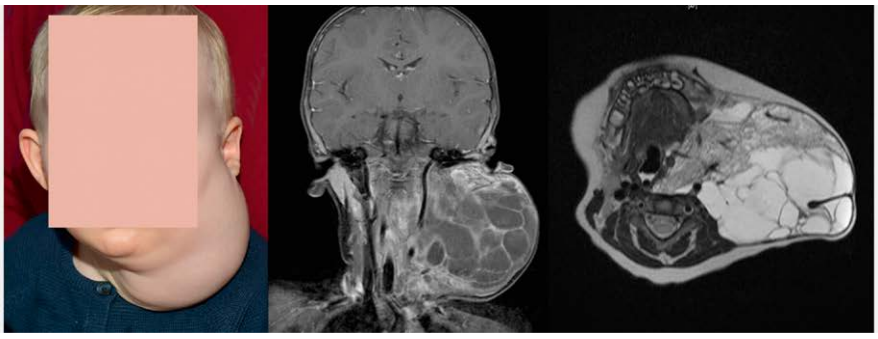
Diagnostics

In addition to the medical history and clinical examination, ultrasound and imaging play an important role in the diagnosis of lymphatic malformations. On ultrasound, lymphatic malformations appear smoothly bordered, hypoechoic to echoless and filled with fluid, with sedimentation in the case of hemorrhagic complications. Duplex sonography shows no flow. In magnetic resonance imaging, lymphatic malformations are hyperintense in the fat-saturated T2 weighting. In the case of large cervical lymphatic malformations, magnetic resonance imaging precisely shows the depth of extension, in particular the involvement of the pharynx, larynx, trachea and mediastinum. If the orbit is involved, MRI provides information about the extent in the orbital apex and the positional relationship of the malformation to the optic nerve. Various proposals for staging have been made to improve comparability of the very different manifestations of lymphatic malformations. The most commonly used classification is that of de Serres et al [42], which classifies lymphatic malformations according to their positional relationship to the midline and the hyoid (▶ **Table 7**).

The Cologne Disease Score (CDS) for children records the functional and esthetic impairments caused by lymphatic malformations [43]. It assesses breathing, swallowing, voice, the extent of esthetic impairment and the progression of the disease. The joint classification of the American Society of Pediatric Otolaryngology Vascular Anomalies Task Force and the American Academy of Otolaryngology, Head and Neck Surgery Workgroup for Evidence in Vascular Anomalies from 2015 [44], which takes elements from both of the above classifications into account, is very complex. Wiegand et al. were able to show that functional limitations after CDS due to lymphatic malformations in children are most pronounced in stages IV and V according to de Serres and in macrocystic malformations [45] (▶ **Fig. 3**).

▶ **Table 7** Classification of lymphatic malformations according to de Serres et al. [39].

	Stage I	Stage II	Stage III	Stage IV	Stage V
Location of the lymphatic malformation	Unilateral infrahyoidal	Unilateral suprahyoidal	Unilateral infrahyoidal and suprahyoidal	Bilateral suprahyoidal	Bilateral infrahyoidal and suprahyoidal



▶ **Fig. 3** Large cervical lymphatic malformation with macrocystic and microcystic parts.

▶ **Table 8** Clinical stages of lymph edema [78].

Clinical stages of lymph edema	Symptoms
Stage 0	No visible edema, subclinical disease with pathological lymph node scintigraphy
Stage 1	Compressible edema, fluid accumulation that disappears on elevation
Stage 2	Edema can no longer be compressed, fluid accumulation does not disappear on elevation, accumulation of fatty and connective tissue
Stage 3	Non-compressible hard edema, fibrosis, skin changes, “elephantiasis”

Therapy

Treatment of lymphatic malformations is not always necessary, as in some cases the patient is only slightly affected and consistent findings can be observed over a long period of time. In infants, the benefits and risks of treatment must be carefully weighed against each other, as diagnosis and treatment can often only be carried out under general anesthesia and with intensive medical monitoring. The controlled delay of treatment for lymphatic malformations in stages I-III according to de Serres can improve the long-term prognosis under certain circumstances [46]. On the other hand, however, acute inflammation or hemorrhages in particular can lead to an acute increase and permanent enlargement of lymphatic malformations, so that a therapeutic action is required in the event of functional limitation or possible danger. Lymphatic malformations can be treated by surgical procedures, sclerotherapy or systemic drug therapy. In recent years, percutaneous sclerotherapy has become the standard treatment method for superficial as well as deeper lymphatic malformations [47]. Surgical resection or ablation procedures are used for very large malformations or in cases of recurrence. In addition, prospective studies have shown that systemic administration of the mTOR inhibitor rapamycin (sirolimus) leads to a significant reduction in the size of the malformation in around 80–90 % of lymphatic malformations and other low-flow malformations [48, 49]. A closer look shows that malformations with large growths, mixed malformations and syndromic forms in particular respond to this systemic therapy. A high vascular density of lymphatic microvessels and thus a higher proliferation tendency of the malformations also appears to result in a better response to sirolimus [50].

Sclerotherapy

In most cases, percutaneous sclerotherapy is the first treatment method used. Various sclerosing agents are applied. These include doxycycline [51], sodium tetradecyl sulphate (STS) [52], bleomycin [53], ethanol, pingyangmycin or OK-432. All procedures act via local tissue damage or inhibit local growth. Doxycycline inhibits matrix metalloproteins and VEGF and thus angiogenesis. STS damages the lipids in the vascular wall and leads to an inflammatory reaction, bleomycin causes DNA damage to the vascular wall cells and leads to local inflammation via peroxidation, ethanol causes direct damage to the endothelium and pingyangmycin, like bleomycin, damages the cell wall via peroxidation and damage to the DNA, but has a stronger effect. OK-432 contains a killed Streptococcus pyogenes strain and leads to a strong immune reaction and local inflammation via activation of natural killer cells, T lymphocytes, granulocytes and macrophages. ▶ **Table 9** provides an overview. All sclerosing agents lead to local inflammation, sometimes with significant swelling. If localized in the airway, this can lead to obstruction, so that post-interventional ventilation or a temporary tracheostomy may have to be planned (▶ **Fig. 4**).

▶ **Table 9** Effect mechanism and side effects of the different sclerosing agents, modified according to [86].

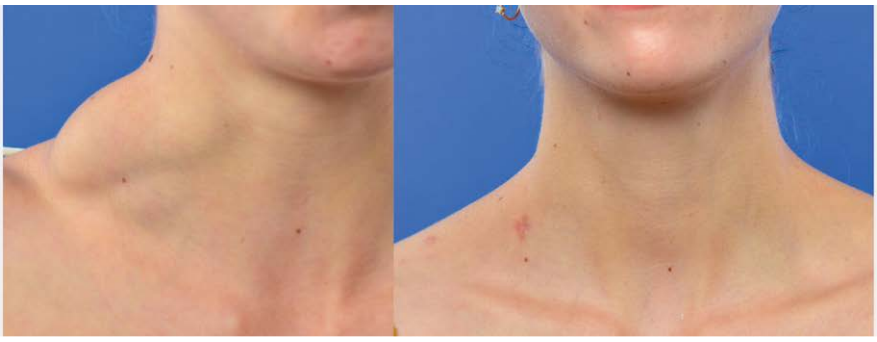
Sclerosing agent	Effect	Dosage	Side effects
Ethanol	Endothelial damage and thrombosis	1ml/kg body weight Overall dose of 10-20-ml	Skin necroses, tachycardia, deep vein thromboses, pulmonary embolism, pain, nerve lesion
Bleomycin	DNA damage, lipid peroxidation, unspecific inflammation	0,5-1mg/kg body weight Overall dose of up to 15mg	Skin pigmentation, fever, mucositis, pulmonary toxicity (rare, dose-depending)
STS Sodium Tetradecyl Sulfate	Lipid damage of the vascular wall, unspecific inflammatory reaction	0,5-2ml 3 % solution, in adults overall dose of up to 5ml	Pain, edema, local ecchymosis, rarely nerve lesion
Ethanolamin oleate	Fat-acid emulsion leading to endothelial damage and thrombosis	2ml of a 50mg/ml solution	Skin ulceration and necroses
Pingyangmycin	DNA damage, lipid peroxidation, unspecific inflammatory reaction	4ml of a 2mg/ml solution Overall dose of 8 mg	Atrophy of the subcutaneous tissue, fever, swellings, anaphylactic shock
OK-432, Picibanil	Proliferation of NK cells, granulocytes, lymphocytes, macrophages, leading to inflammation and endothelial damage	0,2 KE streptococci to 10ml NaCl	Fever, pain, edema, inflammatory reaction, tachycardia
Doxycycline	Inhibition of matrix metalloproteins and VEGF, inhibition of angiogenesis	10-20mg/kg body weight	Severe pain in the area of injection

▶ **Fig. 4** Large cystic lymphatic malformation in a typical submandibular site before and after single sclerotherapy with STS 3 %.

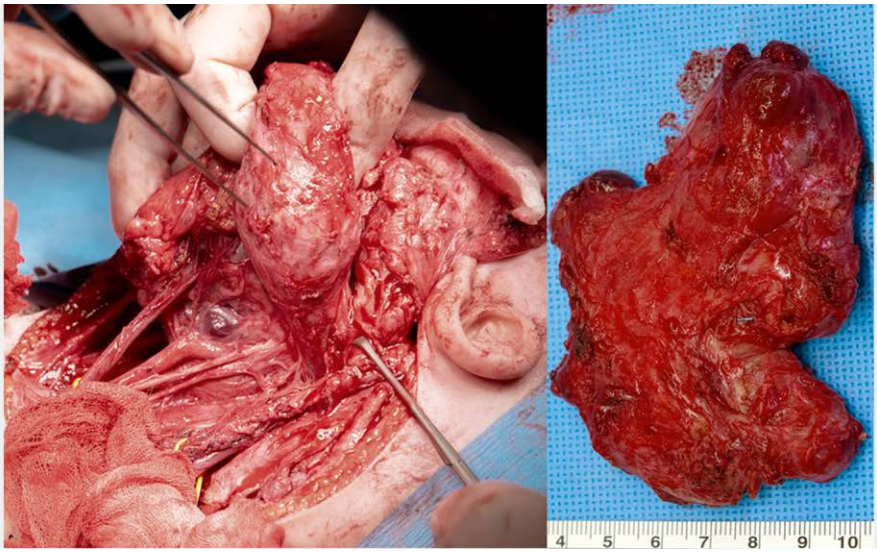
The medication is applied by ultrasound-guided, transcutaneous or endoscopic transmucosal puncture and injection. The distribution of the drug in the lesion can be controlled by mixing it with contrast medium using fluoroscopy. Large cystic lesions respond better to treatment, partly because a better distribution of the medication in the lesion is possible. The response rates of lymphatic malformations to sclerotherapy are good, ranging from 70 to 100 %, with no clear evidence of superiority of any single drug [54, 55]. Post-interventional drainage should be considered in order to optimize the efficacy of the injected drugs. However, there are differences in the frequency and severity of side effects. Here, ethanol and OK 432 show the most side effects, including local ulceration, necrosis and severe general reactions. In individual cases, paresis of the facial nerve occurred when it was adjacent to the lesions. In the case of aggressive drugs, such as ethanol, there is also a risk of diffusion into the neighboring extravascular tissue. The combination of different drugs could further improve treatment [56] (▶ **Fig. 5**).

Surgical and ablative procedures

In recent years, advances in drug therapy and sclerotherapy have pushed surgical treatment of lymphatic malformations into the background. However, surgical procedures, as well as sclerotherapy, show better results in macrocystic lesions, especially in unilateral lesions that are localized infrahyoidally [57]. If the parotid gland is involved and medial parts reach the pharynx or larynx, there is a significantly greater risk of nerve lesion as a result of surgery. The caudal cranial nerves of the facial, hypoglossal, accessory and glossopharyngeal nerves are particularly affected. The nerve branches may be displaced by the malformation and are often surrounded on all sides by pathological tissue, which makes dissection difficult. Suprahyoidal lesions should therefore be operated on under neuromonitoring [58, 59]. However, despite microsurgery under neuromonitoring, transient nerve lesions after surgery occur in up to 25 % of operated cases [60] and represent a significant complication. When the tongue is involved, the resulting macroglossia often presents a functional problem in breathing and swallowing. In lymphatic malformations of the tongue, the muscle tissue is permeated by pathological lymphatic vessels, which can lead to a significant increase in volume. In addition to reducing the size of the vascular malformation, functional muscle tissue is always lost during surgical treatment, resulting in functional losses and scars [61]. On the tongue, superficial parts of lymphatic malformations can lead to ulceration and recurrent bleeding. In such cases, the affected area can be coagulated or ablated using radiofrequency or laser



▶ **Fig. 5** Large cystic lymphatic malformation above the clavicula (left). On the right: S/P single sclerotherapy with a total of 5 ml STS 3 % four weeks after therapy.



▶ **Fig. 6** Resection of a large cervical lymphatic malformation with exposure of the neck vessel sheath under neuromonitoring of the brain nerves.

surgery [62, 63]. In complex cases and with more severe malformations, a combination therapy of surgery and sclerotherapy may be indicated and successful [64] (▶ **Fig. 6**).

Sirolimus for therapy of lymphatic malformations

For more than 10 years, the mTOR inhibitor sirolimus has also been used to treat vascular malformations [65]. Sirolimus (rapamycin) directly inhibits mTOR, a central regulatory protein that is also responsible for cell growth, proliferation and also angiogenesis and lymphangiogenesis. In a prospective study of 57 patients with complicated malformations, Adams et al. observed a reduction in the size of the malformations in 85 % of the treated patients after one year [66]. However, there was no complete regression. About 30 % of patients experienced side effects due to bone marrow toxicity and gastrointestinal complaints. In a systematic review with 73 articles and 373 included patients, 94 % of patients with lymphatic malformations showed clinical improvement with sirolimus therapy [67]. Venous malformations also improved with sirolimus in 89 % of cases. Sirolimus therapy achieved the best results in vascular tumors associated with the Kasabach-Meritt phenomenon. Patients improved clinically in 96 % of cases and coagulopathy normalized in 93 % of cases. Arteriovenous malformations did not respond to treatment. However, the majority of studies are retrospective observational studies or case reports, so that the demand for prospective studies is repeatedly voiced. One problem, for example, is that very different dosages and target levels of sirolimus make comparability difficult. Maruani et al. [68] were able to show in a prospective randomized study of 59 children aged 6-18 years with slow-flow malformations that the volume of the malformation was not significantly reduced in children with lymphatic malformations treated with sirolimus. However, there was a significant improvement in symptoms and quality of life. With sirolimus, patients suffered less pain, less bleeding and less swelling. The target serum level in the study was 10–5 ng/ml. The most common side effect was mucosal ulceration in about half of the patients. In summary, treatment with sirolimus appears to have a positive effect on a larger proportion of patients with lymphatic malformations, but complete remissions are not to be expected.

4.1.2.2 Complex lymphatic anomalies

Complex lymphatic malformations include the generalized lymphatic anomaly (GLA), lymphatic malformations in Gorham-Stout syn-

drome (GSD), kaposiform lymphangiomatosis (KLA), and the lymphatic anomaly of the central collecting lymphatic vessels (central conducting lymphatic anomaly-CCLA), also known as "channel type" lymphatic malformation [69]. Complex lymphatic malformations are rare and cannot always be reliably distinguished from one another on the basis of their clinical manifestations. Treatment is difficult and there is hope in the development of targeted therapies.

4.1.2.2.1 Generalized lymphatic anomalies

It is a disease with multifocal lymphatic malformations with manifestations in different organs. The disease is probably caused by somatically activating PIK3CA mutations with hyperactivation in the PI3K-AKT-mTOR signaling pathway [70]. Bone involvement is frequently found and pulmonary and gastrointestinal lymphatic fistulas may occur. Treatment with sirolimus reduces symptoms, e. g. there is a significant reduction in pain.

4.1.2.2.2 Kaposiform lymphangiomatosis (KLA)

Kaposiform lymphangiomatosis is a life-threatening disease of childhood and adolescence characterized by multifocal dysplasia of the lymphatic vessels [71]. It is a rare disease and the correct diagnosis is often only made very late. Spindle cell-shaped cell nests are found in the vessels, which justify the term kaposiform. The disease often affects the lungs, mediastinum, skin, fatty tissue and spleen. Clinically, it is similar to Gourham-Stout syndrome and the lymphatic anomaly of the central collecting vessels. Treatment is with sirolimus.

4.1.2.2.3 Lymphatic malformation in Gorham-Stout syndrome

Gorham-Stout syndrome is also a rare lymphatic vascular malformation characterized by progressive osteolysis [72]. A generalized lymphatic anomaly with bone involvement must be differentiated in the differential diagnosis. Radiologically, there is progressive osteolysis with cortical bone loss. The ribs and cranial bones are most frequently affected. Treatment consists of surgical measures, radiotherapy and drug therapy with biphosphonates. Sirolimus has shown efficacy in individual cases of Gorham-Stout syndrome [73].

4.1.2.2.4 Lymphatic anomaly of the central collecting lymphatic vessels

The disease is characterized by dilation and dysplasia of the large central lymphatic vessels, such as the thoracic duct, which leads to insufficient lymphatic drainage. This results in pericardial effusions, pleural effusions and central and peripheral lymph congestion. Treatment is difficult, but there are promising new surgical approaches [74]. Lymphangiography is used to visualize the affected dysplastic vessels. Surgical treatment methods include anastomoses between the thoracic duct and large veins, ligation of aberrant vessels, pleurectomies to reduce effusions, creation of lymphocutaneous fistulas or sclerotherapy.

4.1.2.3 Primary lymph edema

Primary lymph edema is a congenital disease with dysplasia of the lymphatic vessels, which leads to lymph congestion with edema and swelling due to drainage disorders [75, 76]. The affected lymphatic vessels can be aplastic or hypoplastic, or in 10 % of cases, hyperplastic. The lower extremities are most frequently affected, followed by the upper extremities and the genitals. The majority of cases are spontaneous diseases with unknown mutations. In more than a third of cases, especially in cases of familial clustering, the mutation is known. To date, mutations in more than 20 genes have been identified as the cause of primary lymph edema.

Primary lymph edema must be distinguished from the much more common secondary lymph edema, which is caused by injury or damage to the lymph channels, e. g. due to infections, surgery or radiation.

Clinical appearance

In pediatric patients, primary lymph edema manifests itself in about 50 % of cases in infancy, in about 10 % of cases in primary school age and in about 40 % of cases in adolescence [77]. Boys are affected earlier than girls. The International Society of Lymphology differentiates primary lymph edema from stage 0 without symptoms to stage 4 with irreversible hard swelling with skin symptoms (▶ **Table 8**).

Lymph edema is diagnosed clinically and by imaging. Clinically, there is an increasing doughy swelling, usually on the lower extremities. The upper extremities and genitals are less frequently affected. Lymphoscintigraphy has a sensitivity of 96 % and a specificity of 100 % in the diagnosis of lymph edema [79]. Other specific diagnostic procedures are lymphangiography and near-infrared fluorescein angiography of the lymph vessels.

Therapy

Primary lymph edema is treated with physical therapy (complex physical decongestive therapy), with a combination of lymph drainage, compression bandages and gymnastics [78]. In individual cases, surgical procedures are also used. These include lymph vessel anastomoses, reduction of congested tissue and lymph node transplants.

4.1.3 Venous malformations

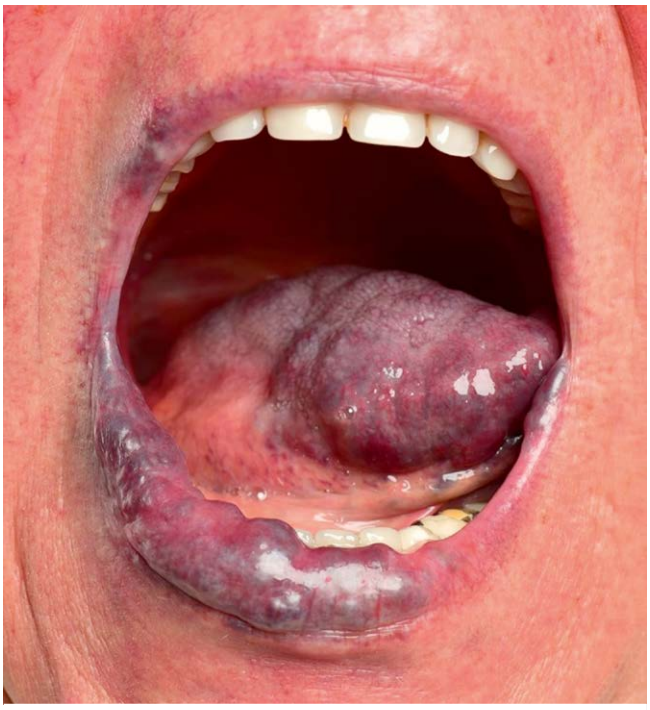
Venous malformations are a network of dysplastic venous vessels filled with blood. About 40 % of venous malformations are found in the head and neck region [80]. In addition to simple venous malformations, which occur sporadically and are circumscribed (about 90 % of all venous malformations), a distinction is made between familial venous malformations, which occur multifocally or as part of syndromes. Defects in the TEK and PIK3CA genes have been detected in simple unifocal venous malformations.

4.1.3.1 Simple venous malformations

The most common localization of venous malformations in the head and neck region are the masticatory muscles, the tongue muscles and the lip. The mucous membrane of the pharynx or larynx may also be involved, which can potentially pose a risk to the airway [82, 83].

Clinical appearance

Inspection and endoscopy reveal smooth, purple-bluish lesions of the skin or mucosa. The malformations are soft, can be compressed and show no pulsations. The volume may change with changes in position or fluctuations in blood pressure. Typically, venous malformations in the head and neck area swell when the head is in a



▶ **Fig. 7** Venous malformation of the tongue and the lips.

low position due to increased blood filling. Superficial mucosal lesions can lead to bleeding, which is usually less serious. Venous malformations are constant in size over long periods of time, but can increase in size due to increasing ectasia of the caverns. As with other vascular malformations, infections or trauma can lead to a permanent increase in the size of venous malformations. Infections can lead to painful swelling. Over 60 % of venous malformations in childhood increase in volume during adolescence, so that the right time for treatment must be discussed [84]. Over time, coagulation and partial thrombosis often lead to calcifications with the formation of so-called pathognomonic phleboliths, which can be detected diagnostically by ultrasound and imaging.

Diagnostics

Most venous malformations can be diagnosed on the basis of their characteristic clinical appearance by looking at the patient's medical history. In addition, duplex ultrasonography is helpful. This shows smoothly defined, low-echo vascular dilatations with low flow ("slow-flow" malformation). In some lesions, especially in older patients, typical calcifications can be detected. In magnetic resonance imaging, venous malformations appear hyperintense in the T2 weighting. Magnetic resonance imaging is important in assessing the depth of the lesions. If the diagnosis is unclear and to assess the risk of bleeding, MR angiography or angiography may be useful (▶ **Fig. 7**).

Therapy

In principle, venous malformations can be treated surgically, with or without prior embolization, with the help of sclerotherapy or with medication. Small, operable lesions can directly be completely resected. For larger and possibly not completely resectable lesions, the focus is on local therapy with the use of intralesional sclerotherapy. As with lymphatic malformations, incomplete resections may trigger a growth impulse in the malformation. In the area of the oral cavity and oropharynx, sclerotherapy, surgical procedures and coagulation procedures such as laser treatment can be combined. This can be particularly helpful for bleeding malformations. Superficial coagulation with closure of the mucosal vessels can reduce the tendency to bleed.

As with lymphatic malformations, various drugs are available as sclerosing agents. These include bleomycin, ethanol, sodium tetradecyl sulphate (STS), ethanolamine, pingamycin or OK-432 (picibanil).

In a systematic meta-analysis, de Maria et al. compared these agents with regard to efficacy and side effect profile in the treatment of venous malformations [86]. A total of 37 studies with 2,067 patients were included. It was found that sclerosing agents that cause direct damage to the vein wall, such as ethanol, ethanolamide or pingyangmycin, cause a higher rate of complete or incomplete regression. However, milder sclerosing agents, such as bleomycin or STS, which trigger a non-specific inflammation in the malformation, have fewer side effects. ▶ **Table 9** provides an overview of the effects and side effects. Overall, complete remission was achieved in around 65 % of patients with the help of sclerotherapy. Further 28 % showed partial remission. Patient satisfaction after treatment was over 90 %. Mild complications due to local, temporary reactions occurred in almost half of the cases. Severe complications such as skin necrosis, permanent damage or pulmonary complications occurred in about 1 % of cases.

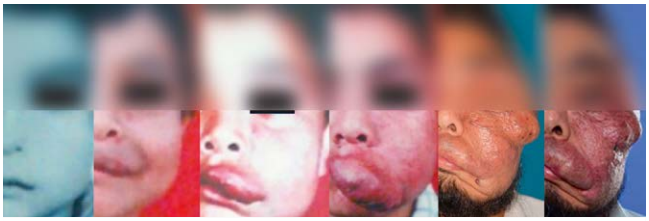
Overall, the sclerotherapy of venous malformations appears to be successful and has few side effects, but in some cases several applications are required; in young children, these are performed under general anesthesia. In contrast to sclerotherapy and surgery, there is little experience to date of drug therapy with sirolimus for venous malformations. Systemic administration of sirolimus led to a significant reduction in venous malformations with TIE-2 gene and PIK3CA gene mutations [48]. TIE-2 mutations, which can be detected in half of all venous malformations, are partly responsible for the pathological growth behavior of lymphatic vessels and veins. In half of the cases of TIE-2 negative venous malformations, activating mutations are found in the PIK3CA gene. A systematic review of previous studies on sirolimus in venous malformations showed a response in about 67 % of simple venous malformations. Side effects were frequent, but were usually mild [87].

4.1.3.2 Hereditary mucocutaneous venous malformations

It is a very rare, autosomal-dominantly inherited disease characterized by multifocal, bluish venous lesions on the skin and mucous membrane [88]. It is caused by mutations in the TIE-2/TEK gene. The lesions increase in size over the course of a lifetime, but the prognosis is good. They are treated with sclerotherapy.

4.1.3.3 Blue rubber bleb nevus (Bean) syndrome VM

This rare syndrome is characterized by recurrent bluish venous lesions on the skin and mucous membranes as well as on internal organs [89]. The disease is caused by a mutation in the TEK gene. The disease can lead to sometimes life-threatening bleeding. Treatment is endoscopic surgery, including coagulation procedures. Under treatment with sirolimus, a significant reduction in the lesions and the tendency to bleed is observed [90].



▶ **Fig. 8** Development of a large arteriovenous malformation of the left face over a period of around 40 years. Right: Situation after re-embolization and surgery.

▶ **Table 10** Classification of Schobinger, modified according to Houdart [99].

Stage	Description of AVM
1	Quiescence: The AVM does not cause clinical symptoms
2	Expansion of arteriovenous malformation lesion
3	Destructive tissue changes; symptomatic malformation: pain, bleedings, esthetic and functional impairment
4	Decompensation: cardiac failure

4.1.3.4 Glomuvenous malformation (GVM)

It is a familial form of venous malformation that usually affects the skin and subcutis in a plaque-like manner. Histologically, glomus cells are found in the vessel walls. The disease is triggered by a mutation in the glomulin gene [91]. Treatment is usually surgical resection, if possible complete. Successful laser treatments with the diode laser or Nd:Yag laser have also been described [92]. These are used in particular for very extensive flat lesions.

4.1.3.5 Cerebral cavernous malformation (CCM)

Cerebral cavernomas are venous vascular malformations that can occur sporadically or familial [93]. About 20 % of all cases are inherited autosomal-dominantly and show mutations in the CCM1-3 genes. In these cases, multiple intracerebral lesions are found in the majority of cases. 80 % of cases occur sporadically and usually show unifocal lesions. The most common localization is supratentorial, less frequently cavernomas are found in the cerebellum or spinal cord.

Clinical appearance

The clinical appearance of cerebral cavernomas is wide-ranging. Most cavernomas are clinically asymptomatic and are discovered as an incidental finding during imaging. Seizures are a possible symptom of cavernomas. Localization in the cerebellum or brainstem may result in focal neurological symptoms due to intralesional thrombosis or hemorrhage. After resorption of the intralesional hemorrhage or thrombosis, the prognosis is good with regression of symptoms. In the event of acute bleeding from cavernomas, patients may show severe neurological deficits.

Diagnostics

Diagnostic measures at initial diagnosis and during the course of the disease are carried out using magnetic resonance imaging, which requires both T1 and T2 weighted images. Computed tomography plays a role in emergency diagnostics.

Therapy

A wait-and-see approach is adopted for asymptomatic cavernomas. Symptomatic solitary cavernomas can be operated on if they are favorably localized, the affected patients suffer from clear symptoms, future bleeding is not unlikely or the patients require treatment with coagulation inhibitors. This also applies to patients who suffer from seizures that cannot be controlled with medication due to a cavernoma. Necessary treatment with coagulation inhibitors is not contraindicated for cavernomas, but tends to show a lower rate of symptoms due to bleeding or thrombosis.

4.1.3.6 Familial intraosseous vascular malformation (VMOS)

It is a rare venous malformation that occurs in bones, particularly craniofacial bones [94]. The mandible, cranial calvaria, skull base and clavicle are frequently affected. The ribs and spine can also be involved. Initially there is swelling in the affected regions, in later stages there may be bleeding, which can be life-threatening. The disease is caused by a mutation in the ELMO-2 gene. Treatment consists of resection as early as possible.

4.1.3.7 Verrucous venous malformation (formerly verrucous hemangioma)

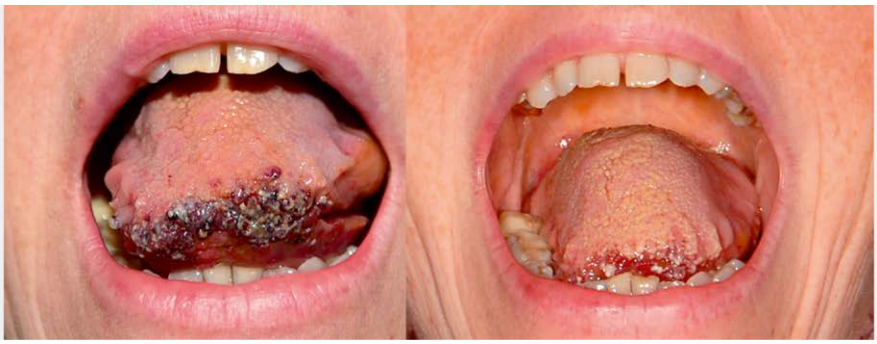
This cutaneous malformation is often found at birth and is characterized by bluish-livid, hyperkeratotic skin changes [95, 96]. The extremities are usually affected, but lesions on the trunk or in the head and neck region have been described. There are dilated capillaries and veins in the skin and subcutis. A somatic mutation in the MAP3K3 gene has been detected in affected patients.

4.1.4 Arteriovenous malformations

Arteriovenous malformations are rare "high-flow" malformations with abnormal, pathological vascular connections between dysplastic arteries and veins [39]. There is a shunt connection between the arterial and venous branches, bypassing the capillary flow area. Nest-like ("nidus") vascular clusters with an arteriovenous connection are also common. AVMs can occur sporadically in isolation or as part of syndromes, such as Osler's disease or in capillary malformations. They are caused by somatic mutations in the MAP2K1, KRAS and BRAF genes [97].

4.1.4.1 Sporadic AVM

More than half of extracranial AVMs affect the head and neck region, particularly the midface and oral cavity, including the lips. As with other malformations, the head and neck region and the face pose a particular challenge in the treatment of arteriovenous malformations, as functional and esthetic impairment quickly occurs. The complex vascular anatomy also makes treatment more difficult [98]. There are a number of symptom-oriented classifications of arteriovenous malformations. The most common clinical classification is Schobinger's classification, which was modified by Houdart [99] (▶ **Table 10**).



▶ **Fig. 9** Lymphatic venous malformation of the tongue. The mucous lymph vessels at the tip of the tongue are seen with secretion and recurrent bleedings. Left: before treatment, right: after sclerotherapy and laser treatment.

Classification of AVM according to angiographic criteria and angiographic morphology is also helpful. The most common classification is that according to Cho [99], see ▶ **Fig. 9**; an even more detailed classification is that of Yakes and Baumgartner [100].

a. Type I: up to three arteries flow over a shunt into a vein
b. Type II: many arterioles have a shunt into a vein
c. Type IIIa: several small shunts are seen between arterioles and venoles with blush in angiography
d. Type IIIb: many shunts are seen between arterioles and venoles with complex mesh in angiography and large shunt volume

Clinical appearance

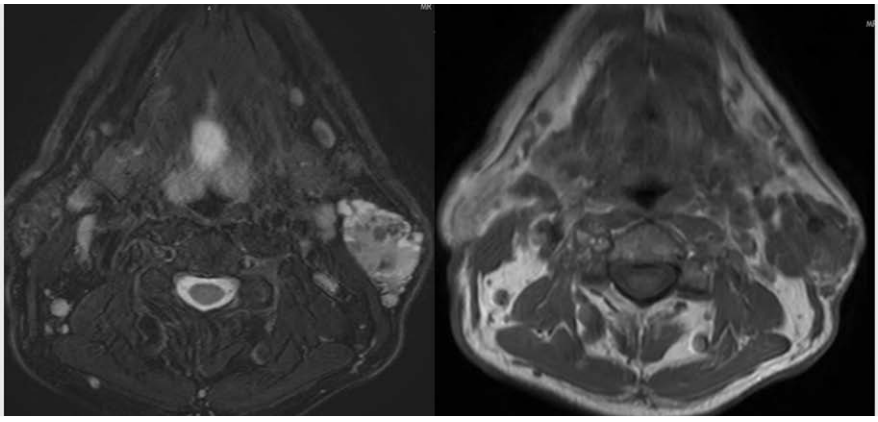
The clinical symptoms of AVMs range from minor complaints to life-threatening complications such as heart failure and bleeding. In stage I according to Schobinger, AVMs show no progression. In cutaneous or subcutaneous AVMs, a skin pattern may be present and there is often a circumscribed overheating of the affected area with palpable pulsation, which is also perceived by the patient. Most AVMs increase in size over time. If the AVM occurs in childhood, an increase in size is very often seen during puberty under the influence of hormones. With increasing size, the malformations recruit vessels from the surrounding area, so-called “feeders” and “drainers”, which also pathologically increase in size. As the disease progresses, the symptoms and complaints also increase. There is often pain and swelling, as well as increasing functional and aesthetic impairment, with dystrophy of the surrounding tissue. In later stages, sometimes grotesque swellings with ulceration of the overlying skin appear. Bleeding can also occur with dangerous blood loss. Ultimately, pronounced shunt volume leads to the onset and later decompensated heart failure. The aim of treatment is to prevent these symptoms and slow down the progression of the disease.

Diagnostics

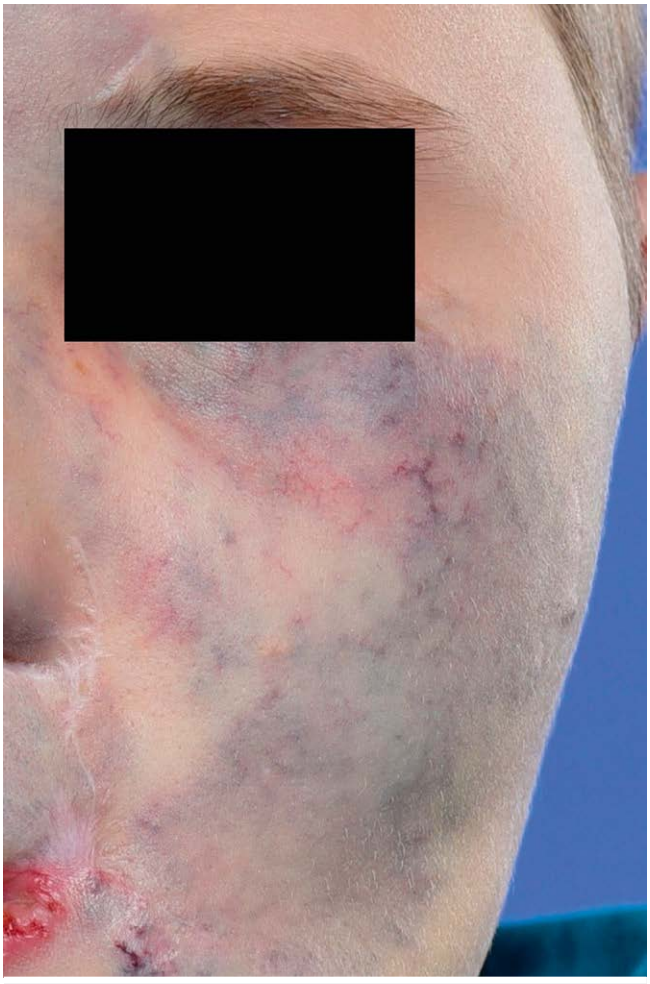
As with other vascular anomalies, the medical history and course of arteriovenous malformations are crucial. In the head and neck area, duplex sonography is almost always possible and very helpful as a non-invasive, informative and cost-effective diagnostic measure. Duplex sonography reveals dilated vessels with "high-flow" and “fast-flow” and the pulsatile character can be detected. The next step is CT scan and MRI imaging, ideally with CT and/or MRI angiography. Both procedures can confirm the diagnosis. Despite its invasiveness, the gold standard in the diagnosis of AVM is still arterial angiography, usually in the form of digital subtraction angiography (DSA) [100, 101]. It provides all the necessary information about the vascular supply and architecture of the AVM in order to plan and carry out subsequent treatment if necessary. The catheters are inserted via the femoral artery, brachial artery or radial artery. As part of the diagnostic procedure, it is important to visualize all the “feeders” of the AVM and the collateral situation in order to obtain an overview of the overall architecture of the malformation. Selective angiography of the external and internal carotid arteries and catheterization of smaller end branches is often necessary. Novel time-resolved, so-called 4D angiographies [102] have shown very good results in the visualization of all supplying vessels and draining veins.

Therapy

Treatment is carried out by a multidisciplinary team using interventional and/or surgical methods. Small superficial AVMs can be resected primarily. However, treatment often results in esthetic and functional losses, which is why treatment should be started as early as possible. Incomplete resection often leads to increased growth and should be avoided if possible. With larger AVMs, intraoperative bleeding is more severe, which often makes controlled resection impossible. In most cases, endovascular treatment is therefore recommended as primary therapy. Possible procedures include endovascular and/or percutaneous techniques [85, 98]. Complete embolization of the entire vascular architecture should be aimed for. If a nidus or AV fistula is identified, it should be completely occluded. The sole closure of larger proximal feeding vessels must be avoided, as this does not achieve healing and also because subsequent access to the malformation is no longer possible or more difficult. Particles, platinum coils and liquid embolizates are available as embolization agents. The liquid embolizates are the adhesive n-butyl-2-cyanoacrylate (Glubran) [85] and the copolymer ethylene-vinyl alcohol (Onyx) [103]. The differences lie primarily in the application and flow properties of the liquid embolizates, as well as in the different precipitation methods. Furthermore, sclerotherapy with ethanol is possible and successful, especially for smaller AVMs. Complications of both embolization and sclerotherapy include swelling, inflammation and pain. In individual cases, necrosis of the tissue or skin adjacent to the AVM can occur. This mainly affects embolization with Glubran and sclerotherapy with ethanol. Emboli remaining in the tissue often lead to



▶ **Fig. 10** T2 fatsat and T1 native, mixed venous-lymphatic malformation. Phleboliths are well displayed as well as the blood level.



▶ **Fig. 11** Capillary lymphatic-venous malformation of the left side of the face. S/P partial resection in childhood.

a disturbing mass with foreign body reactions, which can become inflamed even weeks and months after the intervention. A combination treatment of embolization and subsequent resection of the AVM including the embolized material is therefore recommended for more superficial lesions.

Despite all the advances in interventional and surgical therapy, recurrences and progression of the disease are common. Liu et al. were able to show that the recurrence rate of AVM is up to 98 % after embolization alone [104]. However, it should be borne in mind that complete embolization can rarely be achieved initially in the case of extensive findings and more frequent applications are necessary. The recurrence rate is significantly lower with surgical resection (with or without preoperative embolization), but is still very high at 81 % over a follow-up period of more than 10 years. Patients with a Schobinger stage greater than I at the start of treatment fared significantly worse (▶ **Fig. 8**).

The aim is to treat the AVM as early as possible in order to prevent or slow down the progression of the disease. If possible, resection preceded by embolization should be attempted, possibly in combination with systemic drug therapy.

4.1.4.2 AVM im HHT

Approximately 50 % of all Osler's disease patients develop pulmonary AVMs in adulthood, which is why screening for pulmonary AVMs is recommended [105]. In the head and neck region, AVMs play a subordinate role in the context of HHT. Intracranial AV fistulas occur only rarely.

4.1.4.3 AVM in capillary malformations

Capillary malformation-arteriovenous malformation syndrome (CM-AVM) is an autosomal dominant disease with mutations in the RASA1 and EPHB4 genes. There are smooth, oval, bluish or reddish-brown patches of skin with localized hyperthermia. The syndrome can be associated with limb growth, lymphatic malformations and retinal changes [106].

4.1.5 Arteriovenous fistulas

Arteriovenous fistulas (AVF) are a direct connection between an artery and a vein, bypassing the capillary flow area. AVFs can occur sporadically or as part of other diseases.

4.1.5.1 Sporadic AVF

Sporadic AVFs can be acquired or congenital. In the majority of cases, they are acquired and the result of injuries or operations. After a traumatic or iatrogenic vascular injury, a pathological connection between

an artery and a vein occurs during the healing process [107]. The most common localization is the groin area, where AVFs can occur as a result of previous catheter examinations. In the context of dialysis, AVFs are created as shunts, e. g. on the forearm between the radial artery and the cephalic or brachial vein. A congenital arteriovenous fistula is rare and can, in principle, develop anywhere in the body. However, it often affects the lower extremity, the dura (dural AV fistula), the spinal cord (spinal AV fistula) or the lungs (pulmonary AV fistula). The cause of congenital AV fistulas is still unclear; a mutation in the MAP2K1 gene has been detected in individual AVFs. They may be associated with fibromuscular diseases or neurofibromatosis.

▶ **Table 11** Classification of anomalies of large vessels (modified according to [2]).

Description based on affected vessels	Classification based on the appearance of the malformation
	Origin of the vessel
Venes	Course of the vessel
	Number of affected vessels
Arteries	Lenth of affected vessels
	Luminal changes of the affected vessels (aplasia, hypoplasia, stenosis, ectasia, aneurysm)
Lymph vessels	Heart valve involvement
	Communication (arteriovenous fistula)
	Persisting embryonic vessels

4.1.5.2 AVF in HHT

Hereditary hemorrhagic telangiectasia can lead to AVF in the lungs and liver during the course of the disease. This is caused by autosomal dominant mutations in the ENG, ACVRL1, SMAD4 or GDF2 genes.

4.2 Mixed malformations

Mixed malformations are defined as two or more malformations in one lesion and account for about 10 % of all vascular malformations [108]. The majority are "low-flow" malformations, such as lymphatic venous malformations or capillary malformations with venous and/or lymphatic components.

4.2.1 Lymphatic venous malformations

Lymphatic venous malformations are often found in the head and neck region in the oral cavity, e. g. on the tongue (▶ **Fig. 11**) or in the orbita [109]. The treatment corresponds to the treatment of simple malformations, both components are addressed. Sclerotherapy is usually performed, possibly combined with surgical resection. The superficial lymphatic part of the tongue can be coagulated with a laser to reduce secretion and bleeding (▶ **Fig. 9**).

Lymphatic venous malformations also respond positively to systemic drug therapy with sirolimus [48] (▶ **Fig. 10**).

4.2.2 Mixed malformations with capillary component

For mixed malformations with a capillary component, the ISSVA classification distinguishes between capillary-lymphatic malformations, capillary-venous malformations, capillary-arteriovenous malformations, capillary-lymphatic-venous malformations, capillary-lymphatic-arteriovenous malformations, capillary-venous-arteriovenous malformations and capillary-lymphatic-venous-arteriovenous malformations. The treatment of these complex malformations is even more difficult than the one of simple malforma-

▶ **Table 12** Vascular malformations in the context of syndroms and other anomalies (modified according to [2]). CM = capillary malformation, VM = venous malformation, LM = lymphatic malformation, AVM = arteriovenous malformation, AVF = arteriovenous fistula.

Syndrome	Clinical appearance	Triggering genes
Klippel-Trenaunay syndrome	CM, VM, LM, extremities, venous anomalies	PIK3CA
Macrocephaly-capillary malformation	CM, macrocephaly, cerebral malformations	
CLAPO syndrome	CM of the lower lip, LM of the face and neck, asymmetry, partial overgrowth	
CLOVES syndrome	LM, CM, VM, AVM, lipomatous overgrowth, skeletal and acral anomalies	
Proteus syndroms	CM, LM, VM, asymmetric overgrowth	AKT1
Parkes Weber syndrome	CM, AVM, overgrowth of extremities	RASA1
CM-AVM	CM, AVM, AVF, overgrowth of soft parts	
Sturge-Weber syndrome	Facial CM, leptomeningeal angiomas, choroidea angiomas, overgrowth of bones and soft parts	GNAQ
Microcephaly-capillary malformation	CM, microcephaly	STAMBP
Bannayan-Riley-Ruvalcaba syndrome	VM, AVM, macrocephaly, lipomatous overgrowth	PTEN
SOLAMEN	AVM, segmental overgrowth, lipomatosis, skin nevus	
Maffucci syndrome	VM, spindle cell hemangioma, enchondroma	IDH1, IDH2
CM of the extremities with congenital overgrowth		GNA11
Servelle-Martorell syndrome	Extremities, VM and bone atrophy	–

tions, as each individual part of the malformation must be addressed. Low-flow and high-flow parts are often found simultaneously, as well as involvement of the skin. Treatment therefore involves a combination of embolization, sclerotherapy, surgical resection and laser therapy (▶ **Fig. 11**).

4.3 Anomalies of large vessels

This rare group of congenital anomalies affects large central vessels with their own names. They are also referred to as truncus malformations or "channel-type" malformations. They can be named according to the ISSVA classification in ▶ **Table 11**, but are often clinically independent clinical pictures. Veins, arteries and lymphatic vessels can be affected and very different manifestations are possible.

4.4 Anomalies in the context of other malformations

In addition to solitary malformations, there are also a number of complex syndromes that are associated with vascular anomalies. ▶ **Table 12** provides an overview of the syndromes with vascular involvement. As with the syndromes from the so-called PIK3CA large growth spectrum, an activating PIK3CA mutation can also be detected in venous and lymphatic malformations.

Conflict of Interest

S.M. declares: Firma Medtronic GmbH, Meerbusch - Dozenten und Beratertätigkeit; Firma Olympus, Hamburg - Dozenten und Beratertätigkeit
I.W. declares, that she has no conflict of interest.

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