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Approach to clinically significant vascular anomalies in children

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ABSTRACT

Vascular anomalies consist of tumours or malformations made up of abnormal growth or collections of blood vessels that can result in functional or cosmetic problems. While many vascular anomalies are present at birth, some do not appear until later in life, making diagnosis more challenging. Although many vascular anomalies are benign, some are associated with serious complications and may involve multiple organ systems. This article highlights the important features of clinically significant vascular anomalies to help physicians promptly identify and refer these cases to a specialised multidisciplinary team for evaluation and management. The discussion includes the various presenting complaints of vascular anomalies in children, namely rapidly growing birthmarks, painful lesions, seizures/neurological manifestations, bleeding diathesis, cardiac/airway abnormalities or part of an overgrowth syndrome.

Keywords: birthmarks, overgrowth syndrome, vascular anomalies, vascular malformations, vascular tumours

INTRODUCTION

Vascular anomalies (VAs) result from either disordered proliferation or development of blood vessels. They are a heterogeneous group of conditions with a wide spectrum of clinical presentations and can be classified as vascular tumours or vascular malformations. Vascular tumours are characterised by excessive endothelial cell proliferation whereas vascular malformations consist of abnormally formed channels lined by endothelial cells with normal cellular turnover.⁽¹⁾

Vascular tumours can be benign, locally aggressive or malignant. Vascular malformations can be further classified into slow-flow lesions, such as capillary, venous or

lymphatic malformations; or high-flow lesions, such as arteriovenous malformations or fistulas. Vascular malformations often consist of two or more type of vessels, such as veno-lymphatic or capillary-venous malformations. Rarely, they can occur as part of a syndrome with extracutaneous organ involvement, for instance the eye and central nervous system. Vascular malformations may also be associated with overgrowth syndromes caused by underlying somatic mutations.

HOW RELEVANT IS THIS TO MY PRACTICE?

VAs affect up to 4.5% of children.⁽²⁾ Accurate diagnosis is important as different VAs have variable prognoses and management. Some lesions, like infantile haemangiomas (IHs) can spontaneously resolve, but others may cause significant complications with systemic manifestations, resulting in morbidity and mortality. Furthermore, large and cosmetically disfiguring VAs can lead to negative socio-psychological effects on the children and their families.⁽³⁾

Up to 90% of cutaneous VAs can be diagnosed clinically without the use of radiological investigations or biopsies.⁽⁴⁾ This article aims to help physicians recognise clinically significant VAs in childhood and refer such cases to a multidisciplinary team, which includes dermatologists, oncologists, interventional radiologists and paediatric surgeons.

HOW MAY SIGNIFICANT VASCULAR ANOMALIES PRESENT IN CHILDHOOD?

Rapidly growing birthmarks

Vascular tumours grow out of proportion with the growth of the child.

The most common vascular tumour is an IH with a reported prevalence of as high as 5% in infants.⁽⁵⁾ IHs are usually absent at birth and start growing at about 2-5 weeks of life as painless, well-circumscribed, soft nodules which proliferate rapidly in 3-6 months and slowly

regress from 1 year onwards, becoming flatter and less red in appearance.⁽⁶⁾ However, it must be emphasised that when larger IHs resolve, they can leave sequelae including fibrofatty tissue, telangiectasias and atrophic scars. Superficial IHs present as bright red nodules and deep IHs present as bluish lumps (Fig. 1). There are often both deep and superficial components.

Although many IHs resolve spontaneously and do not require treatment, high risk IHs with features in Table I should be referred early for further evaluation and treatment (Fig. 2a-b). They may benefit from early administration of oral propranolol to reduce the rate of proliferation. Topical timolol may also be helpful to reduce the rate of growth and improve cosmetic outcomes in superficial IHs without the potential systemic side effects of oral propranolol.⁽⁷⁾

Congenital haemangiomas (CHs) are fully formed at birth and do not grow significantly. They are well-circumscribed and bluish with superficial telangiectasias and a pale halo at the periphery (Fig. 3). Rapidly involuting congenital haemangiomas (RICHs) usually start to involute by 4-6 months but the non-involuting variant (NICHs) or partially involuting congenital haemangiomas (PICHs) persist and may require further surgical intervention.⁽⁸⁾ Unlike IHs, CHs do not respond well to treatment with beta-blockers.

Kaposiform haemangioendothelioma (KHE) or tufted angioma (TA) should be suspected if the lesion is indurated, violaceous and occasionally tender (Fig. 4). KHE and TA are thought to be on a spectrum and can be locally aggressive. Systemic bleeding may ensue due to consumptive coagulopathy and thrombocytopenia (Kasabach-Merritt phenomenon (KMP)) (see below). Some treatment options include mTOR (mechanistic target of rapamycin) inhibitors, such as sirolimus or everolimus, corticosteroids and chemotherapy agents, such as vincristine.⁽⁹⁾

Painful lesions

Pain may occur in invasive vascular tumours like KHE due to superficial ulceration and infiltration of underlying tissues.

In venous malformations (VMs), thrombosis due to venostasis, trauma, superimposed infection or venous congestion results in pain and sometimes acute swelling. VMs initially appear as soft, irregular, bluish lumps which grow proportionately with the child until puberty, when they may rapidly increase in size (Fig. 5). They are compressible and predisposed to the formation of hard calcifications called phleboliths, which are pathognomonic for VMs.⁽¹⁰⁾

Lymphatic malformations (LMs) are also low-flow vascular malformations and they commonly occur together with VMs. 60% of LMs present at birth in the lymphatic rich areas, such as the cervical, axillary and inguinal areas.⁽¹¹⁾ Microcystic LMs commonly present as irregular clusters of skin coloured to brownish vesicles, each less than 2 cm in diameter (frog spawn appearance) that may have recurrent discharge of clear to pink fluid (Fig. 6).⁽¹²⁾ In contrast, macrocystic LMs are more than 2 cm in diameter and appear as flesh coloured cystic nodules which can enlarge and leak lymphatic fluid, causing distortion of the underlying soft tissue and bone (Fig. 7).⁽¹³⁾ During an acute infection or after vaccination, the size of LMs can increase considerably and become tender, red and warm.

Treatment should be considered for symptomatic or complicated VMs and LMs. Single or combination treatment with injection sclerotherapy, mTOR inhibitors and surgical excision may be considered in the treatment of these malformations.⁽¹⁴⁾

Seizures and other neurological manifestations

A port wine stain is a form of capillary malformation (CM) which presents at birth as a homogenous, erythematous patch which grows proportionately and may darken overtime especially during adulthood. Sturge Weber syndrome (SWS) needs to be considered in children

presenting with a segmental port wine stain over the forehead and upper eyelid, corresponding to the distribution of the ophthalmic branch of the trigeminal nerve (V1) (Fig. 8).⁽¹⁵⁾ The distribution of the port wine stain may be bilateral in up to 15% of patients with SWS.⁽¹⁶⁾ Patients with SWS can present with seizures caused by the presence of an ipsilateral leptomeningeal angioma and/or microgyria, causing cortical irritation and ischemia. Further neurological and ophthalmological assessments are necessary as other manifestations, such as developmental delay, stroke-like episodes and acute glaucoma can occur. The treatment of SWS may include anticonvulsants to control the seizures, low-dose aspirin to prevent stroke episodes and reduction of intraocular pressure for glaucoma.

Segmental facial IH may be associated with PHACES syndrome, which presents with arterial abnormalities in the head and neck region, posterior fossa abnormalities, cardiac defects and eye abnormalities. The brain abnormalities can result in acute ischemic stroke and cerebellar dysfunction, with the sudden onset of neurological deficit and ataxia.⁽¹⁷⁾ Segmental IH affecting the lower body, especially the groin, lumbar and sacral regions may be a part of PELVIS/LUMBAR syndrome with associated myelomeningocele and spinal dysraphism, which manifests as worsening lower limb weakness, urinary and bowel incontinence.⁽¹⁸⁾ Structural abnormalities in the vesico-urinary system may also be present.

Capillary malformation-arteriovenous malformation (CM-AVM) syndrome is characterized by the presence of progressive and increasing numbers of small CMs (1-2cm) which are commonly localized to the face and limbs. It may also have associated arteriovenous malformations (AVMs) and/or arteriovenous fistulas (AFVs) in the spine and brain that could result in life-threatening complications such as intracranial bleeding.⁽¹⁹⁾ Some patients with CM-AVM may also present with excessive soft-tissue and skeletal overgrowth of the affected limb called Parkes-Weber syndrome (see below).

Bleeding diathesis

Coagulopathy

KMP usually occurs secondary to KHE or TA. In these tumours, intravascular coagulation and platelet trapping cause consumptive thrombocytopenia and depletion of clotting factors, leading to disseminated intravascular coagulation (DIC). Patients present with generalized petechiae, bruising, anaemia and haemodynamic instability. KMP is associated with a high degree of mortality and morbidity, if not recognised and treated promptly.⁽²⁰⁾

The risk factors of developing KMP in KHE are an early presentation of less than 6 months of age, trunk location, a diameter of more than 5 cm and mixed lesions (superficial with deep infiltration).⁽²¹⁾ While KMP occurs in up to 70% of KHE, the prevalence is lower at 10% for TA.⁽²²⁾

A localised intravascular coagulation may also occur in VMs, LMs and RICHs. The thrombosis triggers a fibrinolytic cascade which in turn causes DIC, shown by high D-dimer and low fibrinogen levels.⁽²³⁾

Gastrointestinal and mucosal bleeding

In the blue rubber bleb nevus syndrome (BRBNS), patients may experience gastrointestinal bleeding due to multiple VMs along the digestive tract. Multiple cutaneous VMs may occur and appear as bluish, rubbery and at times tender lesions, due to thrombosis (Fig. 9). VMs in BRBNS can also be found in muscles, joints, central nervous system, eyes, parotid gland, spine, kidneys and lungs.⁽²⁴⁾

Klippel-Trenaunay syndrome (KTS) is a rare congenital syndrome presenting with various vascular malformations, anomalous marginal venous systems and soft tissue/bone hypertrophy of unilateral limb, most commonly the lower limb (Fig. 10). Involvement of the

gastrointestinal tract is uncommon in KTS, but it can be a source of life-threatening bleeding when the VMs extend upwards to affect the rectal veins.

Hereditary haemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease is a rare condition which may present with gastrointestinal bleeding, epistaxis and iron deficiency anaemia due to multiple AVMs and associated cutaneous and mucosal telangiectasias.⁽²⁵⁾ This is an autosomal dominant disease so other family members may be affected. AVMs also occur in the lungs, brain and liver.

Cardiac and airway abnormalities

Some VAs are associated with various cardiac abnormalities. Children with large CHs, large AVMs or high-flow syndromic VAs, such as CM-AVM and Parkes-Weber syndrome may suffer from high output cardiac failure and present with tachypnoea, pulmonary oedema and a displaced apex beat. These lesions may require urgent embolization to alleviate the symptoms, in addition to intensive supportive measures.

In PHACES syndrome, the most common cardiac abnormality is aberrant subclavian artery origin found in 21% of patients, followed by coarctation of aorta in 19% of patients.⁽²⁶⁾ Patients with aberrant subclavian artery are usually asymptomatic although they may rarely present with stridor or dysphagia if the abnormal vessel forms a vascular ring around the trachea or the oesophagus respectively.

Chylopericardium is also reported in macrocystic LMs affecting the mediastinum, causing cardiac tamponade.⁽²⁷⁾

In PHACES syndrome and IHs presenting in the beard area, a rapidly growing subglottic haemangioma causing airway obstruction presents with progressive stridor and dyspnea due to extraluminal compression of the trachea.⁽²⁸⁾ Cervical macrocystic LMs compressing on the airway may also compromise airway function.

Overgrowth syndromes

Some vascular malformations are associated with overgrowth of parts of the body caused by an underlying somatic mutation which are not inherited and occur sporadically. They have varied and overlapping clinical presentations which can affect adipose, muscle, nerve and skeletal tissues as shown in Table II. Many conditions in the overgrowth syndromes are caused by mutation in the *PIK3CA* gene and they are called *PIK3CA*-related overgrowth spectrum (PROS).

The AVMs and AVFs in Parkes-Weber syndrome can potentially cause high output cardiac failure, arterial ischemia and intracranial bleeding. Patients with Proteus syndrome have higher risk of developing fatal pulmonary embolism from the underlying venous thrombosis and malformations.⁽²⁹⁾

The management of children with overgrowth disorders is challenging and requires a multidisciplinary approach. Sirolimus has shown promising results although patients may rarely suffer from side effects which include mucositis, neutropenia, interstitial pneumonitis and hypersensitivity syndrome.⁽³⁰⁾ Other treatments include sclerotherapy, embolisation, lasers and surgical resection. Some lesions may require more than one modality for optimal results.

MAIN FEATURES AND MANAGEMENT OF VASCULAR ANOMALIES

Fig. 12 shows a simplified clinical approach to diagnose the more common VAs. Investigations are needed when the diagnosis is uncertain or to determine the extent of the VAs and their relation to other anatomical structures. Imaging modalities include ultrasound with Doppler, MRI and angiography. Tissue biopsy and genetic testing are also done to evaluate more complicated VAs. The main characteristics of different VAs and their management are summarised in Table III.

CONCLUSION

Understanding the various clinical presentations of VAs is important for the identification of high-risk VAs. A timely referral to a multidisciplinary team reduces the risks of associated complications. A delay in escalating care can adversely impact the prognosis and the quality of life of these patients.

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Table I. High risk features of IHs. (17,28,31-33)

Location/Features of IH	Complications/Associations	Investigations
Nose, lips, genital areas	Ulceration, bleeding, deformation	Bedside doppler, ultrasound of the lesion if the diagnosis is uncertain
Prominent on the face	Disfigurement	
Periorbital, obstructing visual field	Amblyopia, astigmatism, proptosis	Magnetic Resonance Imaging (MRI) of the orbit if there is concern of a deep component
Beard area	Airway haemangioma	Laryngoscopy/bronchoscopy
Segmental (>5 cm) on the face or scalp	Posterior fossa malformations, arterial anomalies, cardiac defects, eye abnormalities and sternal cleft (PHACES)	MRI with angiography (MRI/MRA) of the head and neck, echocardiography, detailed eye examination
Segmental on perineal/lumbosacral area	Urogenital abnormalities, myelopathy, renal anomalies (PELVIS/LUMBAR)	Spinal ultrasound (for infant < 6 months), MRI of the lumbosacral spine, abdominal ultrasound
Multiple (>5 lesions)	Liver haemangiomas, hypothyroidism	Hepatobiliary ultrasound, thyroid function test

Table II. Clinical manifestations of overgrowth syndromes. (34-38)

	Conditions	Affected Genes	Clinical Presentations
PIK3CA-related overgrowth spectrum (PROS)	Klippel-Trenaunay syndrome (KTS)	<i>PIK3CA</i>	CMs/VMs/LMs + unilateral limb overgrowth. May have recurrent per-rectal bleeding if rectal veins are affected
	CLOVES		CMs/VMs/LMs + congenital lipomatous overgrowth + epidermal naevi + scoliosis/skeletal anomalies + spinal anomalies (Figure 11a-b)
	Megalencephaly-capillary malformation syndrome (MCAP)		CMs + progressive megalencephaly + distal limb anomalies, e.g. syndactyly
	Hemihyperplasia-multiple lipomatosis syndrome (HHML)		Vascular malformations + unilateral limb overgrowth + subcutaneous lipomas
	Parkes-Weber syndrome (PWS)	<i>RASA1</i>	AVMs + AVFs + asymmetric limb growth
	Proteus syndrome	<i>AKT1</i>	Vascular malformations + segmental somatic overgrowth + cerebriiform plantar hyperplasia (thickened gyrate pattern of the plantar surface of the feet resembling appearance of the brain)

CMs: capillary malformations, VMs: venous malformations, LMs: lymphatic malformations, AVMs: arteriovenous malformations, AVFs: arteriovenous fistulas

Table III. Main features and management of different vascular anomalies. (2,4,8)

	Vascular Anomalies	Onset and Progression	Associated Conditions	Physical Examinations	Management
Vascular Tumour	Infantile haemangiomas (IHs)	Present at 2-5 weeks, rapid proliferation at 3-6 months, plateau then slow regression from 1 year	PHACES, PELVIS/LUMBAR, internal haemangiomas in multiple IHs	Usually soft, well circumscribed, bright red nodule in superficial IHs, bluish in deep IHs	Non-selective beta blockers (i.e. oral propranolol, topical timolol)
	Congenital haemangiomas (CHs)	Fully formed at birth. Some might start resolving by 4-6 months	High output cardiac failure, disseminated intravascular coagulation (DIC) in big CHs	Circumscribed, blue nodules with superficial telangiectasia and a pale halo at the periphery	Embolization, surgical resection for big symptomatic CHs
	Kaposiform haemangioendothelioma (KHE)	Prominent before 5 years old. Disproportionate growth, locally aggressive	Kasabach-Merritt phenomenon (KMP)	Indurated/ill defined, violaceous, locally invasive plaque	mTOR inhibitor (sirolimus), corticosteroids, chemotherapy (i.e. vincristine)
Vascular Malformations	Sturge Weber syndrome (SWS)	Present at birth. Grow proportionately, darkening with age	Ipsilateral leptomeningeal angioma causing seizures, acute glaucoma	Homogenous, erythematous patch over the forehead and eyelid	Anticonvulsants, low dose aspirin, glaucoma control, pulsed dye laser for CMs
	Venous malformations (VMs)	May be noticed at birth. Grow proportionately, increase in size during puberty	Blue rubber bleb nevus syndrome (BRBNS), DIC	Irregular border, compressible, soft, bluish plaques. Occasional small hard nodules on palpation	Compression therapy, sirolimus, sclerotherapy, surgical resection
	Lymphatic malformations (LMs) - microcystic (< 2 cm) - macrocystic (> 2cm)	60% noticed at birth, 90% at 2 years old. Can increase in size during infection/trauma	Cellulitis. Large mass can cause airway obstruction and deformity	Microcystic: irregular cluster of brownish vesicles Macrocystic: large cystic swelling, pseudotumor	Ablative (e.g. carbon dioxide) or vascular (e.g. pulsed dye) lasers for microcystic lesion. Sclerotherapy, surgical resection, sirolimus for macrocystic lesion
	Arteriovenous malformations (AVMs)	Present at birth. Some may grow rapidly during puberty	High output cardiac failure in late stage	Compressible, presence of thrill or bruit	Embolization
	Overgrowth syndromes	Present at birth or early childhood. Increase in size with the overgrowth area	Overgrowth of adipose, muscle, nerve and/or skeletal tissues	Combination of vascular malformations with overgrowth of underlying tissue	Sirolimus, embolization, surgical resection, orthopaedic management for significant leg length discrepancies



Fig 1. Superficial infantile haemangioma (IH)



Fig 2a. Segmental infantile haemangioma (IH) on the face in PHACES syndrome

Fig 2b. Segmental infantile haemangioma (IH) on the perineum in PELVIS syndrome



Fig 3. Congenital haemangioma (CH) over the popliteal region



Fig 4. Kaposiform haemangioendothelioma (KHE)



Fig 5. Venous malformations (VMs)



Fig 6. Microcystic lymphatic malformations (LMs)



Fig 7. Macrocystic lymphatic malformations (LMs)



Fig 8. Sturge-Weber syndrome (SWS)



Fig 9. Venous malformations (VMs) in blue rubber bleb nevus syndrome (BRBNS)



Fig 10. Klippel-Trenaunay syndrome (KTS)



Fig 11a. Vascular malformations with congenital lipomatous overgrowth in CLOVES
Fig 11b. Epidermal naevi on the nape in CLOVES

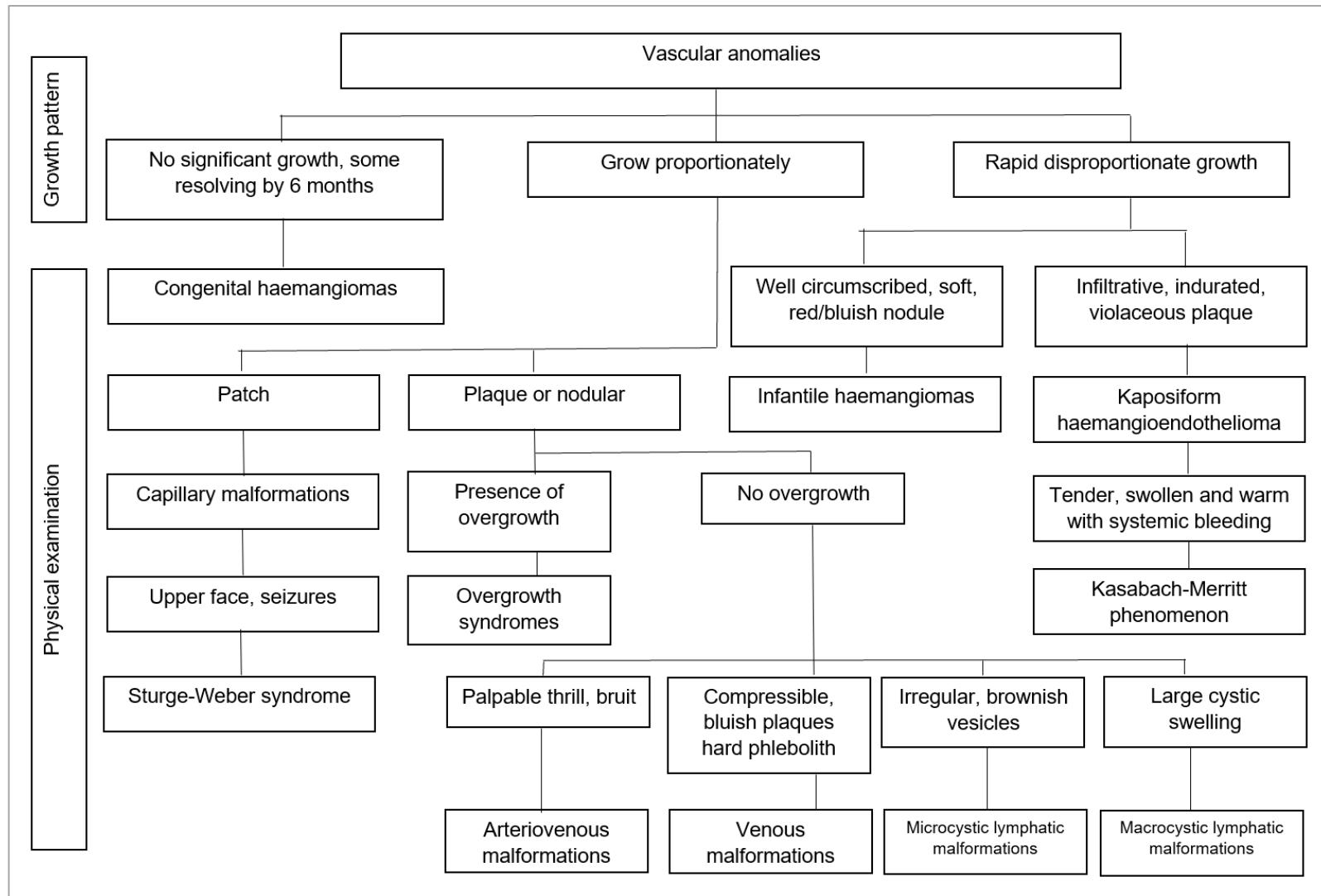


Fig 12. Clinical algorithm for vascular anomalies