Overgrowth Syndromes Associated with Vascular Anomalies

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Abbreviations

AVF	Arteriovenous fistula
AVM	Arteriovenous malformation
BRRS	Bannayan-Riley-Ruvalcaba syndrome
CBC	Complete blood count
CLOVES	Congenital lipomatous overgrowth, vascular anomalies, epidermal nevi, and skeletal and/or spinal anomalies
CM	Capillary malformation
CM-AVM	Capillary malformation-arteriovenous malformation
CRP	C-reactive protein
CTH	Cerebellar tonsillar herniation
EKG	Electrocardiogram
IVC	Inferior vena cava
KTS	Klippel-Trenaunay syndrome
LM	Lymphatic malformation
LMWH	Low-molecular-weight heparin

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C. C. Trenor III, D. M. Adams (eds.), *Vascular Anomalies*,
https://doi.org/10.1007/978-3-030-25624-1_12

M-CM	Macrocephaly-capillary malformation syndrome
MRI	Magnetic resonance imaging
NSAIDs	Nonsteroidal anti-inflammatory drugs
PHTS	PTEN hamartoma tumor syndrome
PKWS	Parkes Weber syndrome
PS	Proteus syndrome
US	Ultrasound
VM	Venous malformation

Introduction

Overgrowth syndromes associated with vascular anomalies present special challenges to the patient and the treatment team. Proper diagnosis and management by a specialized interdisciplinary team are optimal as best outcomes require a thorough understanding of several basic principles and development of individualized treatment plans. Clinical exam remains essential although there is clinical overlap among various syndromes, with variable severity and degrees of overgrowth. In recent years there has been increasing understanding of the genetic basis of these conditions, which has provided improved understanding of the molecular pathways involved and will yield increasing treatment options in the future. It is helpful to differentiate germline from somatic mosaic genetic mutation overgrowth syndromes. Germline inheritance shows autosomal dominant transmission with whole body involvement, while somatic mutation results in limited involvement with only affected parts of the body carrying the mutated gene/overgrowth pathway. Treatment is tailored to each patient's current and potential future problems. Early treatment of lesions may be able to prevent major morbidity, so prompt diagnosis and recognition of potential associated complications are essential.

This chapter will cover major overgrowth syndromes along with diagnosis and current treatment options.

Diagnosis

History and Physical Exam

Each overgrowth syndrome has a pattern of physical findings that enables clinical diagnosis in most cases; however, overlap does occur, and occasionally additional information, such as imaging and pathology, is required to make the diagnosis.

A detailed history should be obtained, including any prenatal and postnatal findings, specifics of the timing of onset and the course of overgrowth. Additional history should focus on skin or visceral changes. Variations in lesions, including increased swelling or change in color or texture with infection, activity, growth spurts, or hormonal changes, should be noted. Associated signs and symptoms,

including pain, functional difficulties, and gait changes, are also important. A history of thrombosis, both tender superficial clots and calcified phleboliths, and any more significant clotting history including deep venous thrombosis or pulmonary embolism, are of particular interest. Any bleeding history, particularly hematuria or gastrointestinal bleeding, should also be noted. A complete history should include a developmental history and a family history as well.

Clinical exam is essential. A whole body skin exam should be performed. Skin markings should be noted and palpated for temperature, texture, tenderness, and/or thrill. Superficial capillary malformation often suggests deeper overgrowth or additional venous or lymphatic malformations in the underlying tissues. Capillary staining can also be associated with other anomalies based on its location, such as genitourinary abnormalities or spinal anomalies when located over the central lumbar/sacral area. With involvement of the limb girdle, there is a high rate of pelvic disease which may include the rectosigmoid colon, urinary bladder, and uterus.

Phlebectasia (ectatic veins) should be characterized clinically and with imaging studies. These are often found on the lateral aspect of the limbs and may be found on the seemingly less-affected limb. Abnormal veins can also be found in the chest, axilla, abdomen, and pelvis. Identification of these veins is essential as their larger caliber leads to stagnant blood flow, thereby imparting a higher risk of thromboembolism even in the absence of thrombophilia. Precise mapping of these abnormal veins is essential.

Clinical exam reliably differentiates fast-flow malformations, such as Parkes Weber syndrome (PKWS), from the slow-flow malformation typically noted in Klippel-Trenaunay syndrome (KTS). High-flow lesions are warm or even hot to touch, warmer than the surrounding tissue, and may have an audible bruit or palpable thrill in the area directly overlying the arteriovenous connection.

Any asymmetry should be noted and can include overgrowth on one side of the face or body, as in hemihypertrophy or asymmetric tissue and/or masses. The location of such tissue/masses may be helpful in differentiating between the overgrowth syndromes.

Limb overgrowth can be quantified by using a measuring tape to compare limb lengths and circumferences. Gait abnormalities are commonly seen in the setting of limb length discrepancy, so it is important to observe the patient walk. Musculoskeletal exam should document limb functionality noting contractures, masses, joint mobility, motor skills, and any limb anomalies. Particular attention should be paid to the hands and feet, as these may show unusual spacing between fingers and/or toes.

Laboratory and Additional Studies

Laboratory workup should evaluate thrombotic status whenever there is a venous component, including complete blood count, fibrinogen, and D-dimer. A renal panel should also be obtained to evaluate kidney function in case the patient will require anticoagulation for interventions or procedures in the future. Patients with poor weight gain or failure to thrive require nutritional workup and support. Testing for genetic mutations is useful to guide therapy decisions; most cases will require tissue as many of these syndromes have somatic mosaic mutations which may not be identified by genetic testing of blood.

Cardiac evaluation may be appropriate in some patients. Cardiac arrhythmias have been reported in M-CM; thus early EKG is recommended. Full evaluation, including EKG and echocardiography, should be performed regularly in patients with high-flow lesions (Parkes Weber syndrome and some vascular lesions in the setting of PTEN) to evaluate for cardiac overload or failure.

Imaging

Early imaging for CLOVES and KTS is recommended in the neonatal or early infantile period or at the time of initial presentation. MRI is the modality of choice to characterize the various components of the disorder including overgrowth, vascular malformations, and musculoskeletal, visceral, and/or neural axis anomalies. Basic sequences, including multiplanar T2-weighted imaging with fat saturation, provide the majority of findings. T1-weighted imaging, with both pre- and post-contrast sequences and MR venography, can be helpful to demonstrate ectatic or abnormal veins. Imaging should specifically evaluate for phlebectasia, particularly involving the marginal venous system and subclavian veins, as this can cause life-threatening thromboembolism and is one of the leading causes of mortality in these patients. However, MRI can be less sensitive in depicting compressed large veins or small deep veins.

MRI of the brain should be considered in any patient with macrocephaly or developmental delays. Classic imaging findings include hemimegalencephaly (in some patients with CLOVES) or megalencephaly and/or polymicrogyria (in many patients with M-CM).

Ultrasonography (US) is a practical, dynamic tool which is widely available and can provide immediate information about venous and lymphatic anomalies, as well as readily identifying acute complications such as thrombosis and intralesional bleeding. US is also a major tool for guiding minimally invasive treatment.

Cases of Wilms' tumor have now been reported in M-CM and CLOVES; thus serial renal ultrasound until the age of 7–8 years is recommended [1].

CT scan is reserved for detailed evaluation of the bony part of the limb and pelvis. CT provides quick evaluation in urgent situations such as imaging of pelviabdominal or pulmonary vessels for thromboembolism or phlebectasia.

Plain radiographs can be used to assess osseous changes including bone deformities, flexion contractures, joint degeneration, osteopenia, and leg length discrepancy. Standing leg x-rays can be used to evaluate for leg length discrepancy once patients reach walking age and should be followed serially to determine the appropriate time for intervention.

The use of diversion venography allows for the demonstration of intact deep venous system, whereas conventional venography may fail to illustrate the deep veins due to preferential flow of blood into the large anomalous veins. Angiography is not a primary imaging tool in low-flow lesions, but may be useful in high-flow lesions as in Parkes Weber syndrome or some cases of PTHS.

The Syndromes

Klippel-Trenaunay Syndrome (KTS)

Klippel-Trenaunay syndrome (KTS) (OMIM # 149000) is the prototype of uncommon overgrowth disorders associated with different types of complex vascular anomalies (Fig. 12.1).

The overgrowth in KTS is typically limited to one lower extremity and the limb girdle, although the definition of KTS has sometimes been extended to include involvement of both lower limbs. The affected limb demonstrates lymphatic overgrowth and slow-flow malformations (capillary, lymphatic, and venous) [2]. These vessel components are each associated with different potential complications, such as phlebectasia and possible thromboembolism within the ectatic veins, infection in lymphatic malformations, and leaking of lymphatic fluid from lymphatic vesicles.

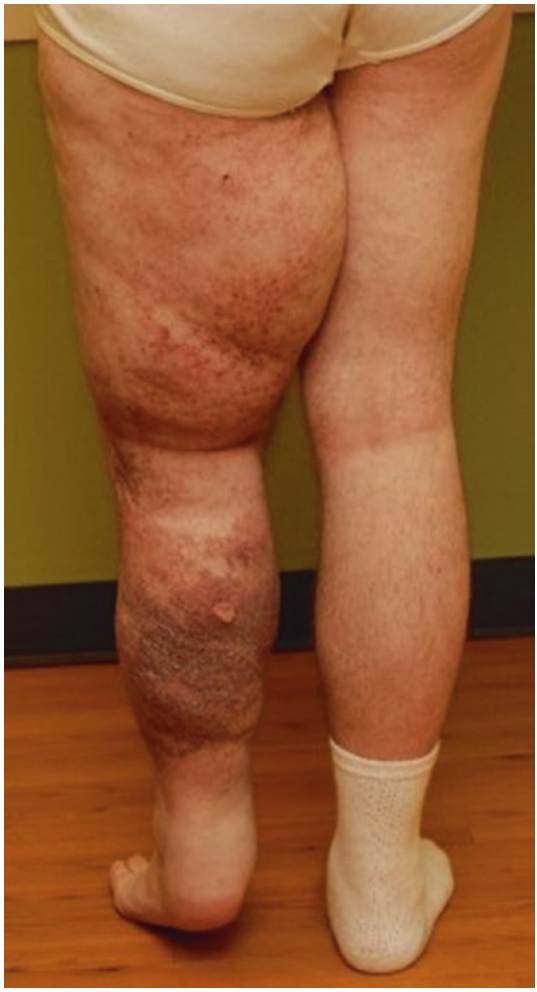

Fig. 12.1 Patient with KTS. Note the capillary lymphatic venous malformation and bulky overgrowth. This patient has previously undergone multiple surgical and interventional procedures

The anomalous venous component in KTS is composed of a complex network of enlarged dysmorphic incompetent veins distributed in the superficial and deep compartments. These dysfunctional vessels attain a considerable size, and an abnormal large communicating tributary network exists within the deep venous system. This venous network may include the marginal vein proper, small saphenous, sciatic, inferior gluteal, and internal iliac veins. Ectasias of the popliteal vein, deep femoral vein, and inferior vena cava (megacava) are common findings [3]. The deep venous system may demonstrate underdevelopment, dilatation, or duplication. Pooling and stagnation of blood in the lower limb cause distention, pain, and, in severe cases, postural hypotension. Thromboembolism remains the most significant complication.

Different forms of lymphatic malformations exist in KTS, including macrocystic and microcystic lymphatic cysts, and cause the majority of the acute symptoms such as recurrent episodes of infections, intralesional bleeds, and pain. Cutaneous manifestations of LM include vesicles and plaques usually concentrated within and around the CM on the lateral aspect of the thigh and calf. These lesions are prone to recurrent bleeding, leakage of lymph, infection, ulceration, and poor healing (Fig. 12.2).

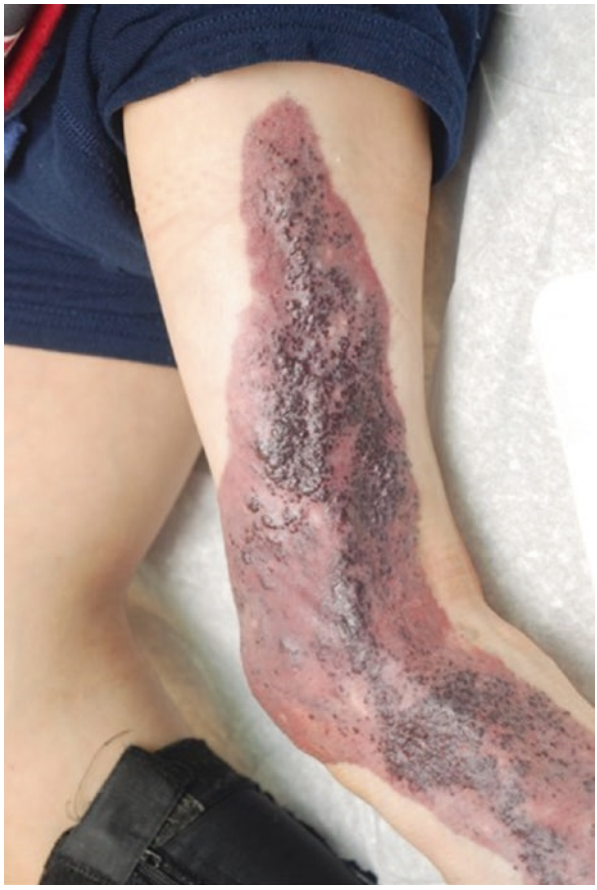

Fig. 12.2 Lymphatic blebs in a KTS patient. They are raised and crusting. Also visible is the dilated marginal vein

Lymphatic macrocysts are often found in the thigh, limb girdle, and pelvis, but are generally less symptomatic than the microcystic type. The latter are typically extensive and affect the fatty extrafascial and intrafascial compartments of the limb. In the pelvis, microcystic LM and fatty overgrowth commonly present as concentric encasement of a thickened anorectum and sigmoid and are often associated with rectal bleeding. The urinary bladder may be elongated with anteroventral displacement. The presence of abnormal superficial venous channels in bladder or urethral mucosa frequently presents as bleeding per urethra.

Clinical Findings

The affected limb is usually diffusely enlarged, both in girth and length. The capillary malformation (CM) is characteristically large and located on the lateral aspect of the thigh and calf. Smaller stains can also be seen in the foot and limb girdle. The CM typically contains lymphatic vesicles and overlies the course of the marginal venous system. Mosaic PIK3CA mutations have been identified in some but not all KTS patients.

CLOVES Syndrome

CLOVES is an acronym for *c*ongenital *l*ipomatous *o*vergrowth, *v*ascular malformations, *e*pidermal nevi, and *s*coliosis/spinal/skeletal anomalies [4]. This syndrome is highly variable as it results from a mosaic *PIK3CA* mutation that occurs early in embryonic development [5]. Thus, parts of the body carry the mutation with variable abnormalities, while unaffected parts of the body do not carry the mutation. Presentation of CLOVES is highly variable depending on where the mutated cells are located.

CLOVES patients have findings similar to that in KTS as discussed above, generally including at least one limb but with more extensive involvement extending into the trunk. Truncal involvement includes fatty lipomatous overgrowth and risk of spinal involvement (Fig. 12.3).

Associated vascular malformations are usually combined capillary venous lymphatic malformations, although high-flow arteriovenous malformations have been reported particularly in the spine. Capillary staining is usually visible overlying affected areas, often patchy and discontiguous. As in KTS, lymphatic blebs impart risk of infection as well as bleeding if overlying a capillary malformation. Venous abnormalities are particularly prominent in these patients, with anomalous veins that can enlarge and lead to thromboses, both deep venous thromboses (DVT) and pulmonary embolism (PE), particularly periprocedurally. Like in KTS, an enlarged lateral marginal leg vein (vein of Servelle) is common; in addition, anomalous truncal and upper extremity systems can be seen in CLOVES.

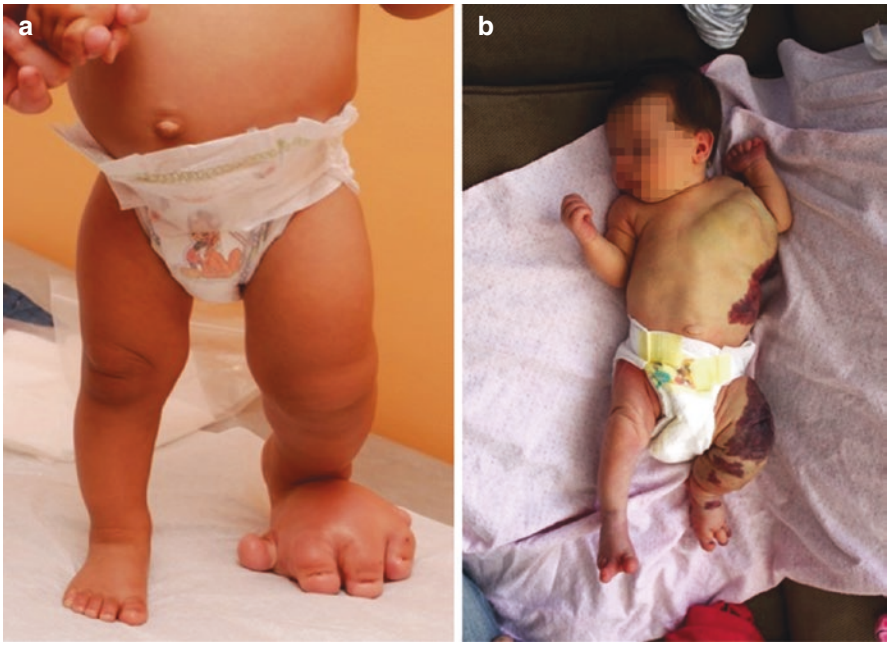

Fig. 12.3 Two patients with CLOVES. Both demonstrate classic foot abnormalities. Patient A has evidence of lipomatous overgrowth of the left leg. Patient B has truncal and leg overgrowth with lipomatosis and capillary venous malformation

Clinical Findings

Large areas of overgrowth consisting of fat, lymphatic malformation, or lymphaticovenous malformation are typical, particularly on the trunk. This growth tends to be progressive and may not cease with skeletal maturity.

Epidermal nevi are often present and can be extensive or more limited in area.

Limb overgrowth, often severe, is frequently present and may affect more than one extremity. As in KTS, this includes both girth and length overgrowth, with significant leg length discrepancy possible. Patients are also noted to have relative wasting (lipoatrophy) of "unaffected" limbs, with frequent concerns for malnutrition without metabolic evidence of calorie deprivation.

Classically, patients have notable foot abnormalities, including sandal gap deformity and other unusual spacing of the digits (Fig. 12.3).

Spinal anomalies along with scoliosis are common, including spinal arterial venous malformations.

Imaging

As for KTS, MRI with contrast is the preferred imaging modality to assess for extent of internal and soft tissue involvement in CLOVES.

Early whole spine MRI is indicated to evaluate for intrathecal anomalies such as tethered cord or vascular malformation.

Unlike KTS patients, CLOVES patients do have increased risk of Wilms' tumor of the kidney (approximately 3%). Children should be screened according to a protocol of serial abdominal ultrasounds every 3 months until age 8.

Macrocephaly-Capillary Malformation (M-CM)

Macrocephaly-capillary malformation (M-CM) is a rare syndrome involving macrocephaly, capillary malformation often with a distinct pattern reminiscent of CMTC, somatic overgrowth, brain abnormalities, and varying degrees of developmental delay (OMIM # 602501). It has been previously called macrocephaly-cutis marmorata telangiectatica congenita (M-CMTC), megalencephaly-cutis marmorata telangiectatica congenita, and megalencephaly-capillary malformation-polymicrogyria (MCAP). Recently, many patients with this syndrome have been found to carry PIK3CA mutations in affected tissues [6].

The syndrome was first described in 1997 as consisting of vascular birthmark, macrocephaly, and early overgrowth (including prenatally, manifested by high birthweight and very large head circumference), resulting in developmental delays and localized skeletal defects including asymmetric overgrowth and toe syndactyly [7, 8]. Neurologic issues include hypotonia and cognitive impairments and nonobstructive hydrocephalus. Clinical diagnostic criteria have been proposed independently by two groups, but neither has been widely adopted as definitive [9, 10].

Physical Findings

Craniofacial findings are often most striking including occipito-frontal head circumference several standard deviations above the mean. This measurement is often increased at birth, but increases markedly during infancy. Frontal bossing may be present. Capillary malformation is often present on the face, most commonly involving the philtrum and/or nose.

A more reticulated pattern of capillary malformation may be seen on the body, and asymmetric overgrowth may be visible (Fig. 12.4). Skeletal abnormalities include syndactyly and polydactyly, as well as sandal gap deformity.

Neuroimaging and Neuropathology

Neuroimaging is usually abnormal [11]. Patients commonly show ventriculomegaly (obstructive or nonobstructive). Patients often show evidence of cortical dysgenesis, including focal cortical dysplasia and polymicrogyria, often in a perisylvian distribution. White matter abnormalities are frequently observed, attributed to delayed myelination or dysmyelination. Brain asymmetry is also common and tends to correlate with ipsilateral facial hemihyperplasia. Posterior fossa crowding is seen in a

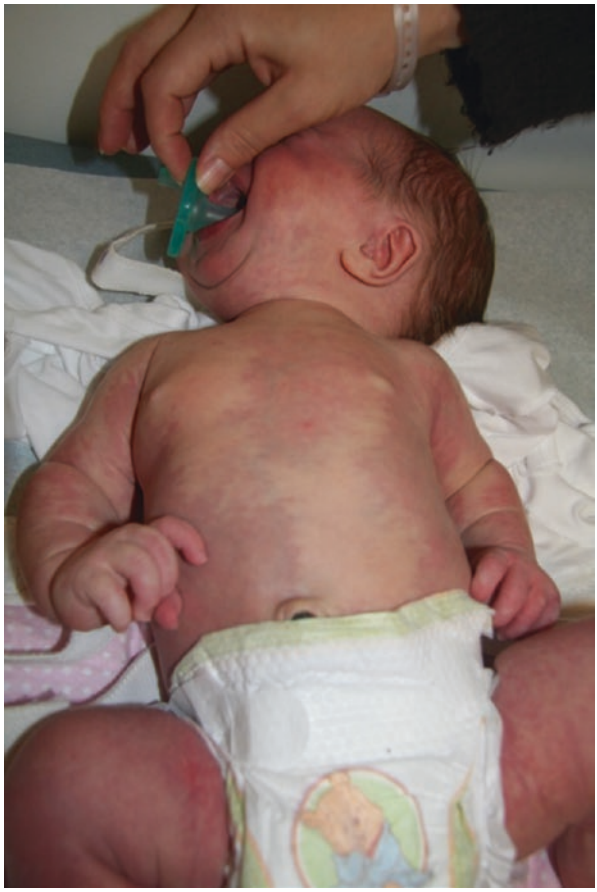

Fig. 12.4 Patient with M-CM and macrocephaly. Notice the faint capillary malformation and overgrowth

majority of cases. Cerebellar tonsillar herniation (CTH) occurs frequently in M-CM, in up to 70% of patients in two studies, often developing during infancy rather than as a congenital process [11, 12]. The postnatal development of herniation suggests that rapid excessive brain growth in the first few months to year of life may be responsible for the CTH. CTH, with potential for brainstem compression, has been implicated in several sudden deaths, and posterior fossa decompression should be considered in patients with evidence of CTH. While many patients have ventriculomegaly, ventricular shunting has not been shown to improve macrocephaly in M-CM patients, so may not be sufficient alone to decrease the risk of CTH and brainstem compression.

Given the progressive brain changes that can occur during infancy and early childhood, MRI of the brain is recommended at the time of diagnosis and every 6 months until the age of 2 years, with a follow-up at 3 years of age. Brain growth is generally complete by age 3, and it is expected that imaging should become stable at that time.

Neuropathology has not been studied extensively to date. Microscopic evaluation of brains from two affected individuals revealed extensive neuromigration defects – including polymicrogyria and heterotopia [11].

Parkes Weber Syndrome (PKWS)

Parkes Weber syndrome (PKWS), first described in 1907, is characterized by bone and soft tissue hypertrophy of an extremity in association with capillary malformation and high-flow vascular lesion(s), generally multiple arteriovenous fistulas (AVFs) or microfistulas (OMIM #608355). The affected limbs show increasing overgrowth over time, with both increased girth and length, resulting in limb length discrepancy. Skin changes are also progressive over time, with increasing color change and even ischemia leading to ulceration and pain in the distal extremity. Venous dilatation gradually occurs as a result of high pressure in the venous system through communication with the arterial system and tends to extend proximally over time. Long-term, the high flow through the AVM/AVFs and the extensive network of ectatic draining veins can lead to high output heart failure and cardiac dysfunction.

A subset of patients with Parkes Weber syndrome develop PKWS as a part of a familial syndrome, called capillary malformation-arteriovenous malformation (CM-AVM). Many families with CM-AVM have been shown to have a mutation in RASA1 [13, 14], with additional families recently shown to have mutation in EPHB4 [15]. These patients have multiple capillary malformations, often with a small surrounding halo suggesting steal, on their skin. Some will have associated AVMs of the brain and spinal cord.

Physical Findings

On exam, the affected limb is larger and longer than the unaffected side. The overlying capillary malformations are warm or even hot to touch and often have palpable thrill or audible bruit. Distended draining veins are usually prominent and may be traced proximally toward the heart. There may be ulceration of the digits or proximal extremity (Fig. 12.5). Lymphedema is often present within the affected limb.

Imaging and Other Studies

MRI is useful in characterizing the soft tissue changes, but angiography is necessary to map the abnormal connections between arteries and veins in order to consider intervention.

Echocardiogram and EKG are recommended to follow cardiac function at regular intervals.

PTEN Hamartoma Tumor Syndrome (PHTS)

PTEN is an important tumor suppressor gene located on chromosome 10q22–23, responsible for downregulation of the PI3K/Akt/mTOR pathway via its phosphatase activity (OMIM #601728). Loss of negative regulation allows for increased growth and inappropriate cell survival and has been implicated in multiple cancers.

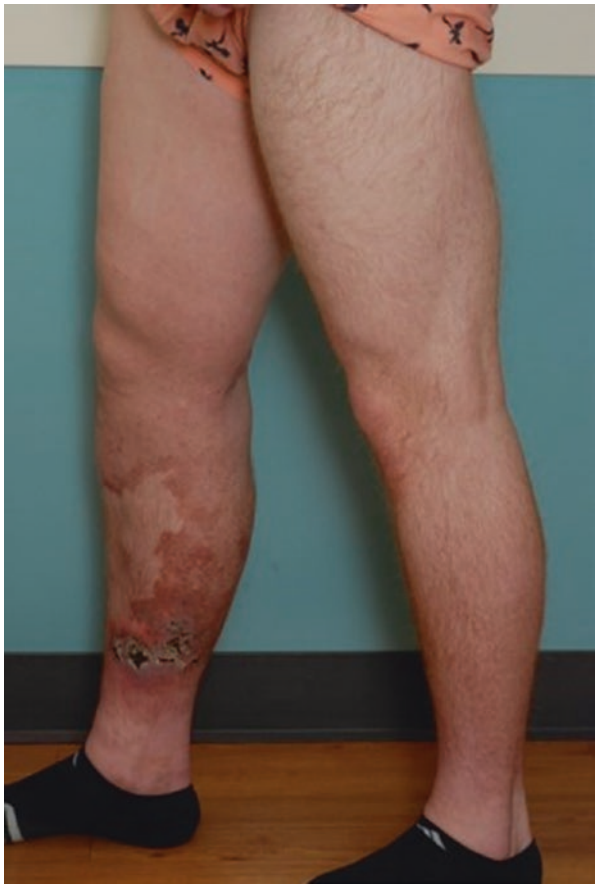

Fig. 12.5 Patient with PKWS in the setting of familial CM-AVM. Notice the faint capillary malformation, warm to touch. This lesion was complicated by a non-healing ulcer

Inheritance is autosomal dominant in fashion, although the majority of germline mutations occur *de novo*. Patients with PTEN hamartoma tumor syndromes (PHTS) are at significantly increased lifetime risk for multiple neoplasms both benign and malignant, particularly in breast, thyroid, renal, and endometrial tissues.

The PTEN hamartoma tumor syndrome encompasses Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome [16]. While initially only Cowden syndrome was identified as having an increased risk of cancer, all of these "PTENopathy" phenotypes are now considered to carry the same increased risks for cancer development and are recommended for the same screening on the basis of their genetics [17].

The PI-3-kinase:AKT:PTEN pathway has been implicated in cell growth and proliferation phenotypes, including a number of vascular anomalies [18], and not surprisingly patients with PHTS may have vascular malformations as part of their phenotype. In fact, this was added as a minor diagnostic criterion for PTENopathies in 2013 [19]. The vascular malformations in patients with PTEN vary widely and include high-flow AVM type lesions as well as mixed- and low-flow lesions, often with ectopic fat [20]. A subset of these lesions, collectively designated PTEN

hamartoma of soft tissue (PHOST), tend to be intramuscular and painful and have a distinctive microscopic appearance [21]. Histopathology reveals increased fat and myxoid fibrous tissue, intermixed with abnormal vascular channels.

However, clinically there is overlap with PIK3CA and AKT mutations. In one study of patients meeting criteria for PTEN based on Cleveland Clinic's risk calculator (http://www.lerner.ccf.org/gmi/ccscore) but without an identifiable mutation, 11% of patients were found to have germline PIK3CA or AKT mutations [22].

Clinical Exam

Classic findings typically noted in patients with PTEN hamartoma tumor syndrome (PHTS) include macrocephaly and penile freckling. Patients with PTEN mutations frequently have benign overgrowth, including lipomas, papillomas, and tricholemmomas. Vascular masses are often fatty, may be warm, and may have overlying vascular discoloration or internal vascularity (Fig. 12.6). In addition, patients frequently have some developmental delays and have an increased risk of autism.

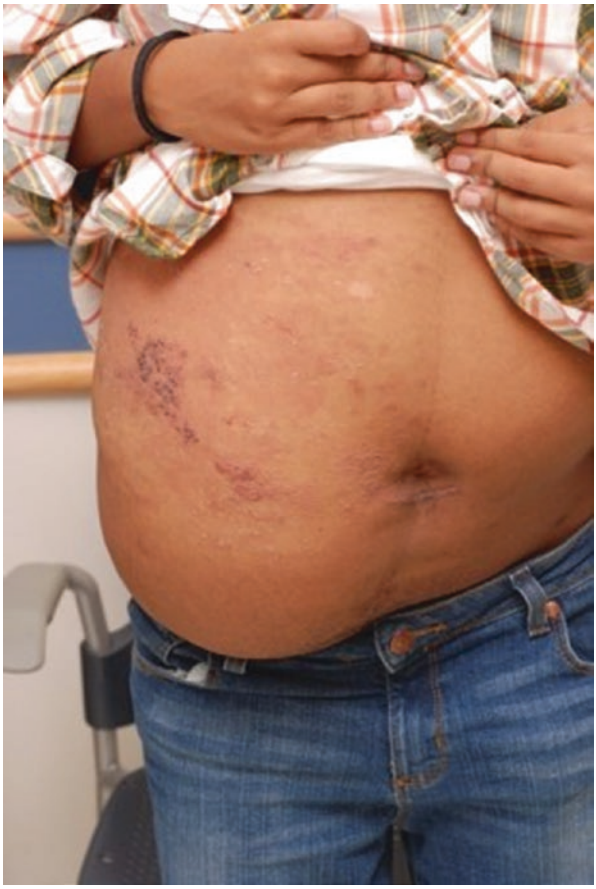

Fig. 12.6 Patient with PHTS and large abdominal wall hamartoma with lymphatic component and visible superficial lymphatic vessels

Imaging

In addition to imaging of the affected areas, patients with PHTS may require imaging of the CNS and tumor surveillance of the thyroid, breast, and kidneys. This can be best done in a Cancer Predisposition Clinic or by a geneticist as part of a comprehensive screening program [15].

Summary (Table 12.1)

Treatment Principles

General

For each of these overgrowth syndromes, it is important to understand the natural history of the condition in order to anticipate problems relevant to the patient. For example, in M-CM developmental delays with low muscle tone and fatigue are prevalent, while in PTEN autism spectrum disorder is often seen concomitantly. These are lifelong and not progressive and have established treatments, which should be applied as they are in the general population affected by the same problems. In contrast, limb length discrepancy and overgrowth generally progress and should be treated if the discrepancy is over 2 cm/1 inch.

Another issue is the rapid pace of changing knowledge in the field. The patient and family should be counseled about the variety of treatment options at present and advised that these will likely change in the coming years. Thus, any treatment plan must weigh risks and benefits now against the possibility that a better treatment will exist in the near future. For disorders with aberrant veins (KTS/CLOVES), these must be closed prior to invasive surgical procedures due to risk of thromboembolism with immobility. A hematology consult for evaluation of thrombosis risk and anticoagulation planning should also be completed prior to any treatment. High-risk patients may need perioperative anticoagulation (usually with Lovenox) as well as an IVC filter in certain cases.

Symptoms caused by the vascular components can be acute (such as pain, thromboembolism, or infection) or chronic (such as bleeding from intestinal, genitourinary, or cutaneous lesions or venous hypertension). Limb overgrowth may lead to various degrees of dysfunction, chronic disability, and lowered quality of life.

Early diagnosis and timely approach are paramount to treat symptoms and prevent high-risk morbidity. Coordinated management by a specialized interdisciplinary team prevents fragmentation or delay of care. The major therapeutic options for these overgrowth syndromes include the combination of conservative, medical, minimally invasive, and surgical.

Table 12.1 Summary table of characteristics of each overgrowth syndrome

Overgrowth syndrome	Gene(s)	Inheritance pattern	Overgrowth pattern	Vascular malformation	Other findings
Klippel-Trenaunay syndrome (KTS)	PIK3CA	Somatic mosaic	Usually limited to the limb girdle and one lower extremity – Girth and length	Capillary Lymphatic Venous	Phlebectasia Risk of thromboembolism Leaking of lymphatic fluid from vesicles/blebs Recurrent infections in lymphatic malformation
Congenital Lipomatous overgrowth, vascular anomalies, epidermal nevi, and skeletal/spinal anomalies (CLOVES)	PIK3CA	Somatic mosaic	Lipomatous overgrowth of trunk often with wasting of unaffected limbs	Capillary venous ectasias Lymphatic Rarely high-flow spinal lesion	KTS findings, above Sandal-gap deformity and/or syndactyly of toes Spinal anomalies, including tethered cord
Macrocephaly-capillary malformation (M-CM)	PIK3CA	Somatic mosaic	Somatic overgrowth usually involving brain and face and may involve body as well	Capillary malformation (usually face), often in a reticular pattern reminiscent of CMTC	Brain overgrowth-megalencephaly Frequent cortical dysplasia – polymicrogyria High risk of cerebellar tonsillar herniation
Parkes Weber syndrome (PKWS)	RASA-1 EPHB4	Germline	Limited to single limb, secondary to high flow	Capillary + arteriovenous malformations or (micro) fistulas	Frequently progressive risk of heart failure
PTEN hamartoma tumor syndrome (PTHS)	PTEN	Autosomal dominant	Lipomatous masses (PHOST histology)	Capillary or venous or lymphatic or combined May even be high-flow (AVM) though usually atypical	Macrocephaly Penile freckling Autism Family history cancers (thyroid, breast, renal, endometrial)

Conservative Management

Conservative management of patients with these overgrowth syndromes may include elastic compression stockings, physical therapy, proper skin care and hygiene practices, pain management, and psychosocial support. Shoe lifts may help patients with mild leg length discrepancy or even more severe discrepancies until definitive surgical intervention can be performed.

Education of the patients and their families and regular follow-up with an interdisciplinary team are crucial for proper care of these patients.

Interventional (Minimally Invasive) Management

Closure of dilated veins reduces the risk of thromboembolism and venous distension. This should be performed early in childhood if possible and particularly prior to surgical procedures. We recommend closing specific dilated veins (lower limb and truncal marginal veins, axillary-subclavian, sciatic, and short saphenous veins) early in life. Later in life, these enlarged veins must be identified prior to any procedures and treated if possible.

Diversion and selective venography are used to demonstrate the small deep venous system of the affected limb. Ectatic anomalous veins are disconnected from the normal veins to prevent migration of clots caudally. Minimally invasive techniques such as embolization and endovenous laser treatment can be safely used to permanently close these veins. In addition, phlebectomy and ligation of the superficial segments of the anomalous veins can be performed through small incision(s) along the course of the vein.

Lymphatic macrocysts are amenable to percutaneous aspiration and sclerotherapy. Carbon dioxide laser can be used to evaporate lymphatic vesicles and plaques.

Embolization may be used in high-flow lesions, including those in Parkes Weber, a subset of PTHS lesions, and small number of CLOVES patients.

The color of CM can be diminished with the use of pulsed dye laser, although is generally less effective on extremities than on the face.

Surgical Management

Patients who are seriously disabled by the massive size of the affected limb, as with significant bulky circumferential limb overgrowth, may benefit from surgical debulking. This lightens the load on the limb but carries significant morbidity. This can be extrafascial lymphaticovenous debulking in Klippel-Trenaunay or removal of large fatty growths in CLOVES. Liposuction can only be used for isolated fatty overgrowth in selected cases and is not appropriate for areas with vascular malformations.

Preoperative imaging and closure of anomalous veins should be completed prior to any surgical procedures in order to reduce the morbidity from perioperative thromboembolism.

Endorectal pull-through procedure should be considered for patients who are transfusion-dependent due to severe chronic gastrointestinal hemorrhage.

Orthopedic Treatments

The goal of orthopedic management is to maintain a balanced pelvis and spine with functional limbs and plantigrade shoeable feet that allow independent ambulation. With multidisciplinary management, this can be accomplished in most patients.

Leg length discrepancy is common in Klippel-Trenaunay and CLOVES. This should be assessed clinically and shoe lift prescribed for any limp with definitive limb length equalization planned for discrepancies that imbalance the pelvis by more than 2 cm/1 inch at maturity. Equalization is usually accomplished by selective physeal ablation of the proximal tibia and/or distal femur (epiphysiodesis) around the age of puberty (10–11 in girls, 13–14 in boys in most cases). Epiphysiodesis is a minor procedure which takes approximately 1 hour, with the physis closed either by percutaneous drilling/curettage or transphyseal screw placement. Excellent predictive growth charts and models exist to determine appropriate timing. This method is best for discrepancies in the range of 2–6 cm/1–3 inches. Guided growth can be used for angular deformities and is minimally invasive. A small tethering device or partial physeal closure is implanted on the side of deformity, and correction is obtained with further physeal growth gradually correcting the deformity (Fig. 12.7).

Intra-articular disease can lead to limb contractures. Early contracture can be managed with physical therapy and night extension bracing but will likely progress. In some cases, tendon lengthening is possible. Intra-articular venous malformation can be managed with combined sclerotherapy followed by synovectomy. However, there is a high rate of recurrence, so multiple procedures may be needed to avoid end-stage arthritis. Few patients with end-stage arthritis and severe vascular

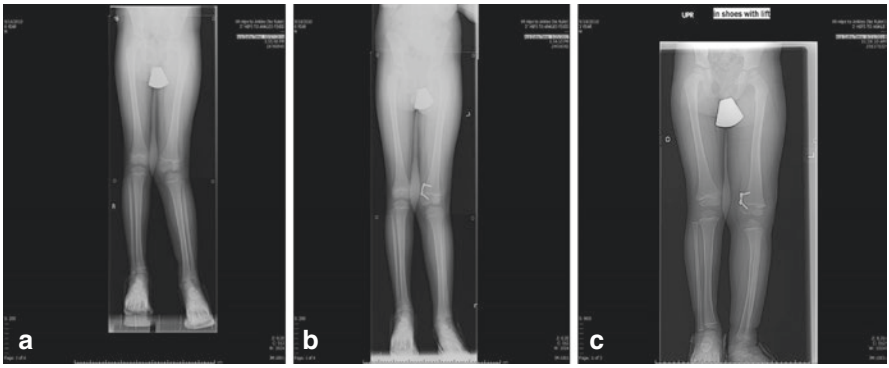

Fig. 12.7 Guided growth can also be used for angular deformities and is minimally invasive. A small tethering device or partial physeal closure is implanted on the side of deformity and correction is obtained with further physeal growth gradually correcting the deformity

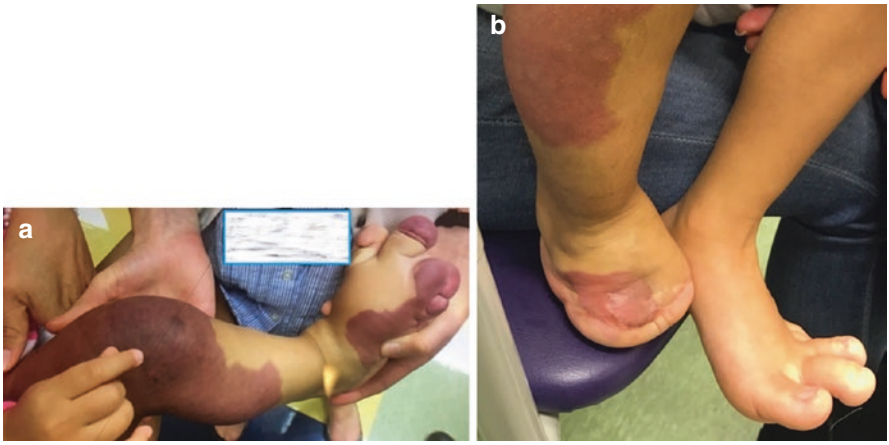

Fig 12.8 (**a**) A patient pre and post surgical amputation of the forefoot. (**b**) A patient pre and post surgical amputation with improvment in the functionality of the foot

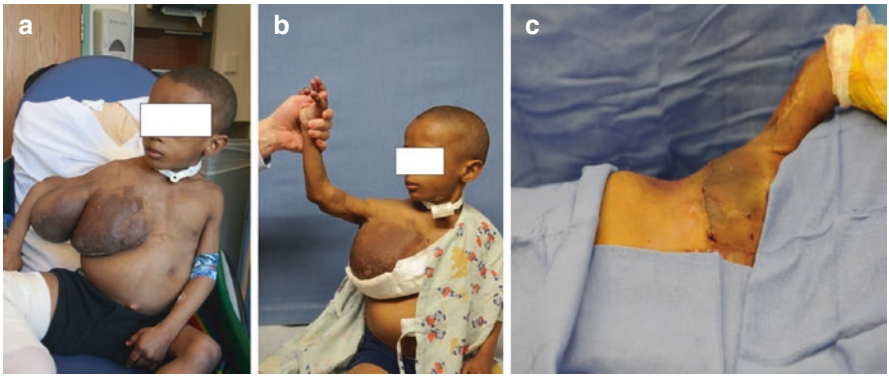

Fig. 12.9 Staged debulking procedures with the final result improving the funtionality of the upper extremity

malformation involving the limb are eligible for joint replacements due to the poor soft tissue and/or bone quality and the resulting high-risk of bleeding, wound complication, and infection.

Severely enlarged hands and feet with macrodactyly may be best served by ray resection or amputation of the forefoot (Fig. 12.8). Focal overgrowth can be debulked with significant improvement (Fig. 12.9). Thus, this is used in severe overgrowth to facilitate the ability to wear clothes and shoes off the shelf. In cases of truly massive parasitic limbs that have little to no function, amputation may be the best option. In cases of high-flow lesions that show signs of impending heart failure, amputation can be considered on a case-by-case basis.

Scoliosis is often atypical and does not respond well to bracing. Progressive curves >50 degrees may require neurosurgical intervention.

Neurosurgical Treatments

Spinal deformity and involvement is commonly seen in CLOVES. MRI is essential to facilitate appropriate neurosurgical treatment of tethered spinal cord or compressive lesions. Preoperative sclerotherapy may be needed for paraspinal malformations to minimize bleeding risk. Progressive scoliosis rarely responds to bracing and is treated with instrumented spinal fusion.

Patients with M-CM may experience ventriculomegaly (+/− increased pressure) and cerebellar tonsillar herniation. Such patients may require posterior decompression and/or ventricular shunting to prevent brain stem herniation.

Medical Therapies

Patients with a lymphatic component, particularly with leaking or bleeding blebs, may experience infections within their lesions. This can be a local cellulitis or a more complicated infection with bacteremia and sepsis. Education of families is crucial to help distinguish signs of cellulitis (erythema, swelling, warmth, pain, and fever) from those of superficial phlebitis. Patients should not delay treatment and should be evaluated promptly by a medical provider. If cellulitis is suspected, antibiotics should be started immediately after blood work is obtained, which should include a complete blood count (CBC) with differential, markers of inflammation such as C-reactive protein (CRP), and blood culture given the rapid rate at which these can progress from localized to systemic. Antibiotics may need to be administered intravenously and for a longer course than is usual for patients without underlying syndromes. Documentation of the number and severity of infections can be helpful in determining if prophylactic antibiotics should be implemented for individual patients. A care plan that includes a personalized problem list and suggestions for treatment options in case of acute illness can be a valuable tool for patients.

Patients with a significant venous component, particularly patients with KTS, are likely to have a coagulopathy (elevated D-dimer +/− low fibrinogen). The coagulopathy may need to be treated with anticoagulation prior to procedures to prevent bleeding and following procedures to prevent thrombosis. Low-molecular-weight heparin (LMWH) has been the treatment of choice, as new oral Xa inhibitors have not yet been evaluated for this indication. Once a patient has had a deep venous thrombosis, a chronic course of anticoagulation may be needed. Inferior vena cava (IVC) filter placement should also be considered with the interdisciplinary team on an individual patient basis.

Some patients have reported improvement in pain during perioperative courses of LMWH. For some with very significant clotting (frequent tender clots or phleboliths), LMWH may be used to manage this clotting and pain. NSAIDs are frequently recommended in short courses (scheduled dosing for 3–7 days) to decrease the inflammation associated with occasional clots. Some patients may benefit from chronic anti-inflammatory medications, such as celecoxib.

Until fairly recently, there was little medical intervention available for patients with these overgrowth syndromes. However, with the identification of more genes causing vascular anomalies, it has become clear that the PI-3-kinase/AKT/mTOR pathway is crucial to regulate growth. Loss of negative regulation, as in inactivating mutations of PTEN or TSC1/TSC2, or upregulation of pro-growth proteins through activating mutations, as in PIK3CA or AKT, result in loss of homeostasis and overgrowth of affected tissues. mTOR serves to integrate all of these incoming signals, and inhibition of mTOR using rapamycin (sirolimus) and its rapalogs has proven to be a valuable tool in the treatment of these patients [23].

A recent Phase II study investigated the use of sirolimus for the treatment of patients with complicated vascular malformations, including several with overgrowth syndromes [24]. The study included 13 patients with capillary venous lymphatic malformations (including many meeting criteria for Klippel-Trenaunay and CLOVES), as well as 6 patients with known PTEN mutations and vascular anomaly. At the end of the study, of the 11 evaluable patients with CLVM and the 4 evaluable patients with PTEN-related vascular malformations, all 15 experienced a partial response to sirolimus therapy. These partial responses included improved quality of life, decreased pain, and improvement in function. In addition, none of these 15 patients experienced further growth of their malformations while on sirolimus. Much more remains to be learned about the use of mTOR inhibition for these patients, including length of treatment required, trough levels of drug required for efficacy, and potential long-term complications. Monitoring is ongoing in the Phase II study, with patients being monitored for 5 years following their completion of the study.

Newer options, also related to the PIK3CA/AKT/mTOR and RAS/MAPK/MEK pathways, are now becoming available (see Chap. 4). Venot et al. recently treated 19 patients having a diagnosis of PROS (4 adults and 15 children) with a PIK3CA inhibitor under a compassionate use protocol, with all patients noting improvement (radiologically and clinically) with minimal side effects [25]. In addition, there is an open AKT inhibitor study for patients with PIK3CA-related overgrowth syndromes (ClinicalTrials.gov Identifier: NCT03094832).

Conclusions

Proper diagnosis is critical and should involve a careful history, complete physical exam, laboratory studies, and pathology and imaging as appropriate. Correct diagnosis will inform potential complications and drive follow-up and interventions necessary to optimize function and quality of life for the patient. Genetic causes have recently been identified in many of these overgrowth syndromes, but may be somatic and are therefore not necessarily detected by genetic testing of blood, though should be present in affected tissues.

Optimal treatment plans will include a multidisciplinary team providing coordinated care, as most patients will require surgical interventions, interventional procedures, and/or medical therapies at some point in their lives for maximal function and quality of life.

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