Overgrowth Syndromes Associated With Vascular Anomalies

Frederic Bertino, MD, *† and Gulraiz Chaudry, MB, ChB, MRCP, FRCR †§

Introduction

Congenital overgrowth syndromes are characterized by excessive proliferation of an organ or region of the body. These may be focal or diffuse and symmetric or asymmetric. A subset of these syndromes is associated with vascular anomalies. The recently updated International Society for the Study of Vascular Anomalies classification of 2018 groups most of these syndromes as vascular malformations associated with other anomalies with phosphatase and tensin homolog (PTEN) hamartoma of soft tissue and fibroadipose vascular anomalies (FAVA) classified as provisionally unclassified vascular anomalies. There is frequent phenotypic overlap between different syndromes and patients often present with similar findings despite varying genetic mutations. Many of these mutations are still unknown and may occur sporadically. However, the etiology of many overgrowth syndromes can be traced to somatic mutations in the PI3K/AKT/mTOR cell regulatory pathway. Knowledge of the phenotypic, genotypic, and imaging findings help drive diagnostic and treatment decisions by multidisciplinary teams, including diagnostic and interventional radiologists, hematologist/oncologists, and vascular surgeons.

Genetic Overview and Cell Signaling for the Diagnostic and Interventional Radiologist

Most overgrowth syndromes with vascular anomalies demonstrate a somatic mutation in the affected area or tissue only (mosaicism) with a small minority showing evidence of a hereditary germline mutation. Many overgrowth syndromes are traced to mutations in the PI3K/AKT/mTOR cell signaling pathway, which is a major regulator in cell signaling and angiogenesis. Somatic mutations that occur specifically in PIK3CA (the catalytic subunit of PI3K) account for a large subset of this group and result in syndromes under the umbrella term: PIK3CA-related overgrowth spectrum (PROS). PROS disorders include hyperplasia or hypertrophy of a body part often because of lipomatous overgrowth. Additionally, slow-flow vascular malformations accompany the limb overgrowth with skin changes that serve as a hallmark of an underlying vascular malformation. Klippel-Trenaunay, congenital lipomatous overgrowth vascular malformation epidermal nevi and spine syndrome (CLOVES), and FAVA are hallmarks of PROS. Capillary malformation of the lower lip, lymphatic malformation of the face and neck, Asymmetry of the face and limbs, and Partial/generalized Overgrowth; MCAP, Megalencephaly Capillary Malformation Syndrome; PWS, Parkes Weber Syndrome; PTHS, PTEN Tumor Hamartoma Syndrome; BRR, Bannayan-Riley-Ruvalcaba syndrome.

Abbreviations: PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog; RASA1, RAS P21 protein activator 1; CM, capillary malformation; LM, lymphatic malformation; VM, venous malformation; AVM, arteriovenous malformation; AVF, arteriovenous fistula; KTS, Klippel-Trenaunay Syndrome; CLOVES, Congenital Lipomatous Overgrowth, Vascular Anomalies, Epidermal nevi, Scleroderma, FAVA, Fibroadipose Vascular Anomaly; CLAPO, Capillary malformation of the lower lip, Lymphatic malformation of the face and neck, Asymmetry of the face and limbs, and Partial/generalized Overgrowth; MCAP, Megalencephaly Capillary Malformation Syndrome; PWS, Parkes Weber Syndrome; PTHS, PTEN Tumor Hamartoma Syndrome; BRR, Bannayan-Riley-Ruvalcaba syndrome.

* Emory University, Department of Radiology and Imaging Sciences, Division of Interventional Radiology and Image Guided Medicine, Atlanta, GA.
† Children’s Healthcare of Atlanta, Division of Interventional Radiology, Atlanta, GA.
‡ Division of Vascular and Interventional Radiology and Vascular Anomalies Center, Children’s Hospital Boston and Harvard Medical School, Boston, MA.
§ Department of Radiology, Harvard Medical School, Boston, MA, USA.

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Address reprint requests to Frederic Bertino, MD, Emory University, Department of Radiology and Imaging Sciences, Division of Interventional Radiology and Image Guided Medicine, Atlanta, GA. E-mail: fbertino@emory.edu.
Hamartoma and Banayan-Riley-Ruvalcaba syndromes are the two major PTEN syndromes that feature concomitant vascular anomalies in their phenotypes.

Mutations in AKT and RASA1 promote angiogenesis and tissue growth through the upregulation of mTOR and PI3K, respectively.\textsuperscript{10-13} AKT mutations result in the Proteus syndrome which results in an ever-changing phenotype after a normal phenotypic appearance at birth. RASA1 mutations are seen in capillary malformation-arteriovenous malformations with Parkes Weber syndrome presenting as a manifestation of this disorder.

Mutations outside the PROS spectrum or PI3K/AKT/mTOR pathway have also been discovered that result in occasional overgrowth and vascular anomalies, such as Sturge-Weber, Maffucci syndrome, and limb capillary malformation nonprogressive limb overgrowth. For purposes of this review, Sturge-Weber, Maffucci syndrome, and limb capillary malformation nonprogressive limb overgrowth will not be discussed due to their non-involvement with the PIK3CA/mTOR pathway. Table 1 provides an overview of the syndromes discussed in this review with respect to their International Society for the Study of Vascular Anomalies classification and genetic association; Table 1 summarizes the key imaging findings of the most well-known syndromes.

**Imaging of Overgrowth Syndromes**

Imaging of simple slow-flow and high-flow malformations are covered elsewhere in other chapters, so the recommendations below pertain to the evaluation of overgrowth syndromes only.

Plain radiography is often the first study pursued for patients presenting with limb overgrowth, as it can help to distinguish soft tissue and/or osseous overgrowth when present. Osseous hypertrophy represents true limb overgrowth and can be the cause of limb length discrepancy; however, this finding may be subtle and not particularly specific for an overgrowth syndrome. Radiographs with phleboliths interspersed throughout soft tissue are almost always diagnostic of a venous malformation and have value in detecting slow-flow syndromes.

Sonography is a safe, fast, and effective method of initially evaluating overgrowth syndromes. Doppler waveforms can identify the flow characteristics of a malformation while also provide information on lesion size and depth. Ultrasound is particularly useful if the anomaly in question is focal.\textsuperscript{14} Sonography can also detect superficial ectatic orthotopic or anomalous vessels, the presence of thrombus, and venous reflux.

Magnetic resonance imaging and angiography (MRI/MRA) are considered the gold standard for evaluating overgrowth syndromes as it provides excellent soft tissue resolution and specific information about soft tissue or vascular anomalies lesions.\textsuperscript{14,16} Persistent embryonic veins such as the lateral marginal vein of Servelle can be easily identified as well as ectasia of adjacent, orthotopic veins.\textsuperscript{17} The relative overgrowth of soft tissues can also be verified by using the unaffected extremity as the comparison. MRI is the best modality for evaluating the presence of vascular malformations within regions of the body affected by overgrowth, particularly in the deep soft tissues of the chest, abdomen, pelvis, and limbs. Dynamic time-resolved MRA helps to distinguish between low- and high-flow lesions and identify feeding and draining vessels.\textsuperscript{18-20} In the absence of suspected high-flow lesions, an MRA is not required for initial evaluation. In vascular anomalies syndromes, it is not uncommon to have lipomatous overgrowth, and fat may be interspersed within the lesion. The areas of lipomatous infiltration can be readily identified on MRI using sequences with and without fat suppression. As most patients present in childhood, the lack of ionizing radiation in MRI is of benefit but must be balanced against the risks of sedation or general anesthesia that is typically required to perform these studies in children.

Due to inferior soft tissue contrast resolution of computed tomography (CT) (compared to MRI) and ionizing radiation, CT is typically reserved for improving classification of osseous lesions.

**PROS Disorders**

Sporadic somatic mutations (mutations that occur after conception) involving PIK3CA result in phenotypically similar syndromes that fall under the PROS umbrella.\textsuperscript{7,9,21} The phenotypic similarities between these syndromes can make clinical diagnosis challenging, and specific clinical diagnostic criteria are used to supplement genetic testing when a PROS disorder is suspected. A clinical diagnosis of PROS is made when two or more of the following features are present on physical examination of a patient: limb overgrowth, vascular malformation, epidermal nevi, or hemimegalencephaly; as well as isolated findings of lymphatic malformations, limb abnormalities, truncal overgrowth, focal cortical dysplasia, and skin abnormalities. If PROS is suspected on clinical assessment, confirmatory genetic testing is then pursued.\textsuperscript{6}

**Klippel-Trenaunay Syndrome**

Klippel-Trenaunay syndrome (KTS) is characterized by unilateral limb overgrowth, a cutaneous “port-wine stain,” and slow-flow vascular malformations.\textsuperscript{22-25} The term “port-wine stain” refers to cutaneous capillary malformations that appear as pink unreared patches over the skin and are often limited to the affected limb. Vascular malformations in KTS are limited to only slow-flow subtypes (venous and lymphatic); if high-flow arteriovenous malformations or fistulas are discovered, another diagnosis should be pursued.\textsuperscript{11} The limb overgrowth is primarily extrinsic and is most commonly due to microcystic lymphatic malformation and fatty hypertrophy.\textsuperscript{22} The lymphatic malformation may be associated with vessels that leak lymphatic fluid or blood. There may be associated osseous overgrowth and leg-length discrepancy.\textsuperscript{22}

MRI is the gold-standard for noninvasive imaging of KTS as the modality can include the entire affected limb in the field of view and capture the presence of a large embryonic
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>ISSVA Classification</th>
<th>Mutation</th>
<th>Clinical Features</th>
<th>Summary of Key Imaging Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klippel-Trenaunay (KTS)*</td>
<td>CM + VM ± LM + limb</td>
<td>PIK3CA</td>
<td>• Pink cutaneous “port-wine nevus” CM</td>
<td>• Soft tissue and osseous overgrowth on radiography and MRI</td>
</tr>
<tr>
<td></td>
<td>overgrowth</td>
<td></td>
<td>• Unilateral osseous and soft tissue overgrowth</td>
<td>• Slow-flow malformations (venous and lymphatic)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Slow-flow VM and LM</td>
<td>• Large lateral embryonic vein (classically “vein of Servelle”) is pathognomonic of KTS</td>
</tr>
<tr>
<td>CLOVES*</td>
<td>LM + VM + CM ± AVM +</td>
<td>PIK3CA</td>
<td>• Congenital lipomatous overgrowth</td>
<td>• MRI demonstrates clear lipomatous overgrowth</td>
</tr>
<tr>
<td></td>
<td>Limb overgrowth</td>
<td></td>
<td>• Slow-flow malformations (CM, VM)</td>
<td>• VM, LM often within areas of lipomatous overgrowth</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Fast-flow spinal/paraspinal AVM is a typical entity of CLOVES syndrome</td>
<td>• Spinal/Paraspinal AVM common, and detected on MRI</td>
</tr>
<tr>
<td>Fibroadipose vascular</td>
<td>Provisionally unclassified</td>
<td>PIK3CA</td>
<td>• Painful lump, typically in the calf</td>
<td>• Intralosomal VM and LM.</td>
</tr>
<tr>
<td>anomaly (FAVA)*</td>
<td>vascular anomaly</td>
<td></td>
<td>• Gastrocnemius most commonly affected &gt; wrist, foot, thigh, and trunk</td>
<td>• Rarely, fast flow or mixed-variants may be appreciated on imaging if present</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Associated joint contractures, may present with toe-walking</td>
<td>• Fibrofatty signal mass lesion on MRI with postcontrast enhancement</td>
</tr>
<tr>
<td>CLAPO*</td>
<td>lower lip CM + face and neck</td>
<td>PIK3CA</td>
<td>• Lip and face/neck overgrowth due to underlying slow-flow malformations</td>
<td>• Enlargement of the affected muscle but no associated limb overgrowth</td>
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<td></td>
<td>LM + asymmetry and partial/</td>
<td></td>
<td>• Generalized or partial body overgrowth</td>
<td>• CM limited to the vermilion border of the lower lip (classic appearance)</td>
</tr>
<tr>
<td></td>
<td>generalized overgrowth</td>
<td></td>
<td>• Findings classically limited to the head/neck in most cases</td>
<td>• Head and neck VM and LM with associated overgrowth.</td>
</tr>
<tr>
<td>MCAP*</td>
<td>Megalencephaly + CM</td>
<td>PIK3CA</td>
<td>• Megalencephaly</td>
<td>• MRI Brain typically shows megalencephaly, hydrocephalus/ventriculomegaly, cerebellar tonsillar ectopia/Chiari malformation, and cortical irregularities/polymicrogyria</td>
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<td></td>
<td></td>
<td></td>
<td>• CM of the face, which may appear as cutaneous staining</td>
<td>• CM of the face and cutis marmorata</td>
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<td></td>
<td></td>
<td></td>
<td>• Syndactyly, polydactyly</td>
<td>• AVM/AVF with unilateral limb overgrowth</td>
</tr>
<tr>
<td>Parkes Weber (PWS)</td>
<td>CM + AVF + limb</td>
<td>RASA1</td>
<td>• Similar clinical appearance to KTS</td>
<td>• Imaging necessary to prove high-flow lesion as true distinction from KTS</td>
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<tr>
<td></td>
<td>overgrowth</td>
<td></td>
<td>• Cutaneous AVM/CM</td>
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<td></td>
<td></td>
<td></td>
<td>• High-output cardiac failure related to low-resistance high-flow malformations</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Cutaneous ulceration related to steal syndromes</td>
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</table>
KTS has been shown to have many eponymous embryonic veins; the most characteristic is a large, lateral marginal vein of Serville (Fig. 1a). The marginal system extends superiorly from the dorsum of the foot to the thigh, most commonly draining into the internal iliac vein.22 (Fig. 1b and c). This vein can be readily identified on axial MRI sequences, obviating the need for MR venography. Less commonly appreciated on MRI is a persistent sciatic vein, which typically extends superiorly from the short saphenous vein and also terminates in the internal iliac veins (Fig. 1b and c). These anomalous veins demonstrate stagnant flow, with an increased risk of superficial thrombophlebitis and thromboembolic phenomena.17 Lower extremity thrombi can be diagnosed by sonography alone, but clinical concern for pulmonary embolus may necessitate a CT pulmonary angiogram. The deep veins within the affected limb are often hypoplastic due to underuse. Characterizing a deep venous system within the overgrown limb is critical when planning for potential embolization of the ectatic embryonic veins. Endovascular therapy/embolization is contraindicated if the deep venous system of the affected limb is absent.23,26

Venous malformation may be seen in the pelvis, most commonly in the anorectal region, and patients may present with rectal bleeding. Involvement of the bladder and urethra may also result in hematuria and frank bleeding per urethra.22 Multidisciplinary management is essential for these patients. Treatment is primarily aimed at alleviating symptoms and prevention of life-threatening complication. This may include endovascular closure of persistent embryonic veins, use of compression stockings, sclerotherapy of venous and lymphatic malformations, and CO2 laser of lymphatic vesicles. Patients with rectal bleeding may benefit from an endorectal pull through, and orthopedic follow-up is necessary for treatment of leg-length discrepancy. Hematology specialists assist with management of associated coagulation abnormalities, sirolimus dosing and monitoring, as well as prophylactic antibiotics for infection. Oral sirolimus (an oral mTOR inhibitor) has shown efficacy in the treatment of both PROS and non-PROS disorders.27,28

**CLOVES Syndrome**

CLOVES syndrome serves as an acronym for the classic phenotype, which is characterized by congenital lipomatous overgrowth (CLO), vascular anomalies (V), epidermal nevi (E), and spinal abnormalities/scoliosis (S). The CLOVES phenotype is often misdiagnosed as other PROS disorders, PTEN, or Proteus syndrome; thus confirmatory genetic testing is paramount for an accurate diagnosis and treatment planning.6,29,30 CLOVES syndrome typically presents with highly specific signs and symptoms that include truncal/thoracic lipomatous hyperplasia, skin nevus, and high-flow spinal and paraspinal vascular malformations (Fig. 2).6,29-32 These high-flow malformations frequently result in cardiac failure and neurologic deficits from perfusion shunting from the spinal cord.31,33 Overgrowth associated with CLOVES is present and apparent at birth and grows with the child. In contradistinction, Proteus syndrome appears phenotypically normal at birth but becomes progressively...
5.34 In addition to superficial phlebectasia in the lower extremities, CLOVES patients often have an ectatic, anomalous vein in the lateral thoracic wall.22 As with KTS, these patients are at increased risk of thromboembolic disease.17

MRI/MRA can definitively characterize lipomatous overgrowth (high T1 signal) and underlying slow- or high-flow malformations within areas of soft tissue hyperplasia. Spinal imaging, specifically with arterial phase angiographic sequences is necessary to identify high-flow AVMs.31,32 Patients with CLOVES syndrome have an increased likelihood to develop Wilms’ tumor, for which screening ultrasound is recommended at minimum every 3 months until age 7.35-38 Treatment options are similar for KTS (as well as all PROS disorders) and include embolization, sclerotherapy, and surgical resection with combination therapy for spinal and para-spinal AVMs. Sirolimus use in CLOVES syndrome is increasing in use in those patients with micro and macrocystic lymphatic malformations.27,28,39 There have been promising early results with the use of BYL719, a PIK3CA inhibitor, with decrease in overgrowth and improvement in scoliosis and congestive cardiac failure.40

**Fibroadipose Vascular Anomaly**

FAVA is a recently recognized condition that results in fibro-fatty replacement of the affected muscle and is associated with a low-flow vascular anomaly.38,39 While limb or regional overgrowth has not been clearly described, FAVA is considered a provisionally unclassified vascular anomaly that results from the same somatic mutations in the PIK3CA mutation spectrum as KTS and CLOVES and features focal hypertrophy and mass-like enlargement of affected tissue. The classic clinical presentation of FAVA is that of an adolescent with an asymmetric painful lump involving the calf disfiguring as the child ages.5,34

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muscle. Less common regions affected are the wrist, thigh, foot, and trunk, but the lesion is classically local. The FAVA lesion is typically a slow-flow anomaly characterized by phlebectasia without discrete cutaneous findings.41,42 Doppler ultrasound allows for a noninvasive, initial interrogation of the mass because of the focality of the lesion. Ultrasound appearance is typically an echogenic, solid, fibro-fatty mass with phlebectasia (Figure Se). The solid, mass-like component allows for the differentiation from simple, intramuscular venous malformations on both ultrasound and MRI (Fig. 3b). FAVA lesions are classically intramuscular and will disrupt the normal striated muscle on imaging. MRI/MRA will show characteristics of a fibro-fatty lesion with T1 and T2 hyperintense and heterogeneous signal relative to muscle, with avid postcontrast enhancement. High-flow variants of FAVA are atypical but may rarely occur. Endovascular and sclerotherapy treatment of FAVA can control symptoms, but chance of recurrence of the lesion is high. Surgery is therefore indicated for resection if sarcoma is not excluded. Endovascular and sclerotherapy treatment of FAVA can control symptoms, but chance of recurrence of the lesion is high. Surgical resection is indicated for large or recurrent lesions and can result in cure. Cryoablation may also serve as a viable therapeutic option in the treatment of FAVA lesions.41-43

CLAPO Syndrome
CLAPO Syndrome is a rare and infrequently described overgrowth syndrome associated with vascular anomalies, characterized by the phenotype of capillary malformation of the lower lip (C), lymphatic malformation of the face and neck (L), asymmetry of the face and limbs (A), and partial/generalized overgrowth. The first description of this syndrome was in 2008 in 6 unrelated patients, but subsequently found to possess similar somatic activating mutations in PIK3CA, inaugurating it as a member of the PROS disorders.44 In the original cohort, patients displayed a variety of lymphatic and venous malformations of the neck and/or mouth with asymmetric faces and partial or generalized overgrowth. Subsequent case reports describe the malformation limited to the vermilion border.45,46 Differentiation of the specific type of slow-flow malformation is easily made on postcontrast T1-weighted images, with venous malformations demonstrating enhancement and lymphatic malformations showing minimal to no enhancement. Overgrowth is classically limited to a limb or face, without visceral involvement; however, the overgrowth can be generalized and symmetric and grow in proportion to the patient. Developmental delay associated with CLAPO syndrome is not reported.44 Sclerotherapy and surgical resection is used for vascular anomaly treatment in CLAPO syndrome however longitudinal studies in efficacy are not available at the time of this publication.

MCAP Syndrome
MCAP and its sister syndrome, megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome share a similar phenotype of brain overgrowth including megalencephaly, ventriculomegaly with progression to hydrocephalus, cerebellar tonsillar ectopia with progression to Chiari malformation, and polymicrogyria (or other cortical abnormalities). The patients may demonstrate significant developmental delay. MCAP syndrome possesses cutaneous vascular malformations, specifically capillary malformations of the face and cutis marmorata. Somatic activating mutations in PIK3CA, PIK3R2, and AKT3 have been identified.1 Additional features of MCAP syndrome include syndactyly and polydactyly, and focal or segmental overgrowth.47,48

Non-PROS Syndromes Associated With Mutations in PI3K/AKT/mTOR

Parkes-Weber Syndrome
Parkes-Weber syndrome (PWS) results from mutations in RASA1 and represents a specific manifestation of capillary-arteriovenous malformation. Although often confused, PWS
and KTS are distinct conditions. The difference is due to the type of primary underlying vascular malformation: PWS is associated with high-flow, arteriovenous malformation, while KTS is associated with slow-flow, venous, and lymphatic malformations. PWS patients usually present with overgrowth and a capillary stain that is warm to palpation. In contrast to KTS, the overgrowth is primarily due muscular and osseous hyperplasia, rather than the subcutaneous fat. In a small proportion of PWS patients, there is an associated lymphatic component. Patients may develop cutaneous ulceration of the skin related to the high-flow anomalies causing to a cutaneous steal-phenomenon.

MRI/MRA findings of PWS include increase in size of the muscles (when compared to the unaffected extremity), increase in size of the arteries of the affected extremity, and early filling as well as ectasia of the draining veins (Fig. 4). Digital subtraction angiography typically demonstrates enlargement of the arteries, a diffuse vascular blush within the affected area and early filling of the draining veins. PWS phenotype is known to worsen over time and serial imaging is required to monitor progression. Embolic treatment of PWS is limited by the small vessels involved; therefore, embolization treatment is often withheld until the patient’s quality of life is affected. Limb amputation is warranted for refractory cases.

PTEN Hamartoma Syndrome

PTEN serves as a regulator of PI3K, inhibiting signals that promote cellular growth and angiogenesis; mutations in this system result in unregulated overgrowth (Fig. 5a). Syndromes associated with PTEN mutations include Bannayan-Riley-Ruvalcalba and Cowden syndromes. These are now collectively referred to as PTEN hamartoma syndrome (PTHS) due to their phenotypic overlap. Diagnostic criteria for PTHS include macrocephaly, thyroid disorders, and macular pigmentation of the glans penis.

Vascular anomalies are identified in over half of the patients with PTHS. Characteristically these are multifocal, intramuscular, high-flow lesions with ectopic fat disrupting the structure of the muscles (Fig. 5b). Detection of large arteriovenous malformations on MRA should prompt genetic testing for PTEN mutations. Sclerotherapy and embolization continue to be a mainstay of treatment with surgical resection as definitive treatment for tumoral/hamartoma growth control. However, there is early data reporting sirolimus and specific tyrosine kinase inhibitor efficacy in treating vascular anomalies associated with PTEN mutations. PTEN mutation disorders carry increased risk of tumor growth, especially in the gastrointestinal tract. The detection of a PTEN mutation should prompt further imaging workup for hamartomas or colon cancers/polyps. Screening programs for cancers associated with PTHS/PTEN mutations should be initiated upon genetic diagnosis.

Proteus Syndrome

Proteus syndrome is characterized by a unique phenotype that gradually changes over time. Patients are often normal at birth and develop overgrowth and dysmorphisms as they age. The name of the syndrome originates from the shape-shifting Greek God. Somatic mutations of the AKT1 gene
result in the characteristic finding of Proteus syndrome: the cerebriform connective tissue nevus, particularly in the plantar aspects of the feet. There are some overlapping features with PROS, including asymmetric limb overgrowth, epidermal nevi, dysregulated adiposity, and slow-flow vascular malformations. Therefore, the progressive nature of the phenotypic features that are otherwise not present at birth is a hallmark finding of the syndrome and can be confirmed with genetic testing. The clinical diagnostic criteria for Proteus syndrome are listed in Table 2.

Table 2 Diagnostic Criteria for the Clinical and Imaging Diagnosis of Proteus Syndrome, Adapted From Cohen

| General Criteria | – Lesions with mosaic distribution
|                  | – Sporadic occurrence of symptoms/features
|                  | – Progressive course, worsening with time
| And Category A   | – Cerebriform connective tissue
| Or Category B (at least 2 features) | – Epidermal nevi
|                   | – Asymmetric and disproportionate overgrowth of:
|                   |   ○ Limbs
|                   |   ○ Skull or external auditory meatus
|                   |   ○ Megaspodylodyplasia
|                   |   ○ Abdominal viscera, including spleen or thymus
|                   | – Tumor growth before the second decade of life
|                   |   ○ Ovarian cystadenoma
|                   |   ○ Parotid monomorphic adenoma
| Or Category C (at least 3 features) | – Dysregulated adiposity
|                                      |   ○ Lipomas or
|                                      |   ○ Lymphoedema
|                                      | – Vascular malformations
|                                      |   ○ CM
|                                      |   ○ VM
|                                      |   ○ LM
|                                      | – Cystic lung disease
|                                      | – Classic facial phenotype (usually seen with severe intellectual disability or seizure)
|                                      |   ○ Dolichocephaly
|                                      |   ○ Long face
|                                      |   ○ Downslanting palpebral fissures/ptosis
|                                      |   ○ Low nasal bridge
|                                      |   ○ Wide, antverted nostrils
|                                      |   ○ Resting open mouth

Conclusions

Overgrowth syndromes with vascular anomalies are associated with somatic mutations, particularly of PIK3CA.
Diagnosis can be readily established by clinical examination and imaging and confirmed by genetic testing. For optimal treatment and follow-up these patients should be cared for by a multidisciplinary group with special interest and expertise in the field of vascular anomalies.

References


