PIK3CA vascular overgrowth syndromes: an update

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Purpose of review
Over the past decade many previously poorly understood vascular malformation disorders have been linked to somatic activating mutations in PIK3CA, which regulates cell survival and growth via activation of the mTOR1-AKT pathway. The goal of this article is to describe and provide an update on the clinical features, complications, and management strategies for the PIK3CA-related overgrowth spectrum (PROS).

Recent findings
PROS encompasses a heterogenous group of disorders with complications related to the tissues harboring the mutation. Vascular malformation syndromes, such as Klippel–Trenaunay syndrome and Congenital Lipomatous Overgrowth Vascular malformations Epidermal nevi and Skeletal abnormalities, have an increased risk of thromboembolic complications, which is accentuated postprocedurally. Asymmetric overgrowth, particularly of limbs, results in a high rate of orthopedic complications. Hypoglycemia screening in the neonatal period and ongoing monitoring for growth failure is recommended in megalencephaly capillary malformation due to its association with multiple endocrinopathies. Recently, sirolimus, an mTOR1 inhibitor, has shown promise in vascular anomalies and now PROS. PIK3CA direct inhibitor, Alpelisib (BYL719), was recently trialed with significant clinical benefit.

Summary
As the pathogenesis of these conditions is better elucidated and targeted treatments are developed, recognizing the clinical features, comorbidities, and evolving therapeutic landscape across the PROS spectrum becomes more crucial for optimization of care.

Keywords
mosaicism, overgrowth, PIK3CA-related overgrowth spectrum, vascular malformation syndromes

INTRODUCTION

Vascular malformations may be associated with a range of coexisting anomalies including segmental overgrowth and abnormalities of the musculoskeletal, cutaneous, and neurologic systems. Historically, various monikers were used to describe these syndromes despite overlapping clinical features. Recently, somatic activating mutations in the phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*) gene have been identified as the underlying cause of multiple syndromes involving vascular malformations and segmental overgrowth, giving rise to the umbrella term PIK3CA-related overgrowth spectrum (PROS) [1]. Diagnostic criteria for PROS were proposed by Keppler-Noreuil *et al.* [2] in 2015, highlighting the overlapping clinical features seen across multiple syndromes due to PIK3CA mutations.

Herein, we review and provide updates on the pathogenesis, clinical features, and management of syndromes belonging to the spectrum of PIK3CA-related overgrowth disorders. Recognition of these syndromes and their potential complications is vital to proper diagnosis, risk stratification, and management, thus decreasing morbidity and mortality in affected patients. Traditional management of overgrowth syndromes has been conservative and limited to addressing complications as they arise, however, the identification of the PIK3CA-mTOR pathway has opened doors for therapeutic advancement.

PATHOGENESIS

Postzygotic somatic activating mutations in PIK3CA are responsible for the PIK3CA-related overgrowth clinical spectrum. PIK3CA encodes p110a, a critical

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KEY POINTS

- The PROS encompasses a broad phenotypic spectrum of syndromes associated with vascular malformations and overgrowth.
- Vascular malformations may be associated with increased risk of infection, pain, and most notably thromboembolic complications.
- Currently there are no consensus guidelines regarding Wilms tumor screening in PROS, to date ultrasounds are still recommended for patients with overgrowth except in Klippel–Trenaunay syndrome.
- Sirolimus, an mTOR1 inhibitor, has shown therapeutic benefit in vascular anomalies and more recently in PROS.
- Alpelisib (BYL719), a direct PIK3CA inhibitor, was recently trialed in 17 patients with significant clinical improvement.

component of the PI3-kinase enzyme, which activates signaling pathways involved in cellular proliferation, survival, and growth. One of the key downstream effectors of this pathway is mTOR1 via phosphorylation of AKT. Activating hotspot mutations in PIK3CA were first identified in adult tumors [3]. More recently, a growing number of vascular malformation and overgrowth disorders have been linked to somatic PIK3CA mutations in a mosaic pattern. The majority of cases are due to oncogenic hotspot mutations; however, nonhotspot mutations have been identified and seem to correlate with a less severe but more extensive disease phenotype [4]. The wide phenotypic spectrum, ranging from an isolated digit to diffuse multisystem involvement, is likely related to the type and timing of mutation development during embryogenesis. It is speculated that germline mutations in PIK3CA are not compatible with life, highlighting the vital role this enzyme plays in cellular function [5].

KLIPPEL–TRENAUNAY SYNDROME

Klippel–Trenaunay syndrome (KTS) is traditionally defined by the presence of a capillary malformation, venous malformation, and limb overgrowth with or without a lymphatic malformation (International Society for the Study of Vascular Anomalies (ISSVA)). However, other specific clinical features are generally recognized as part of this syndrome. Classically, the findings in KTS are isolated to a lower extremity, with extension onto the lower trunk. The capillary malformation is often sharply circumscribed, violaceous in color, and localized to the lateral aspect of the affected extremity. It has been described as geographic [6], and, over time, it develops hemorrhagic and clear vesicles on its surface, the latter suggestive of an underlying lymphatic malformation [7], Fig. 1. The underlying vascular malformation is generally a complex combined venous-lymphatic malformation extending deep to muscular fascia. A characteristic venous anomaly is the presence of a persistent embryonic vein. The lateral marginal vein (LMV), also known as the vein of Servelle, is seen in up to 70% of patients [8].

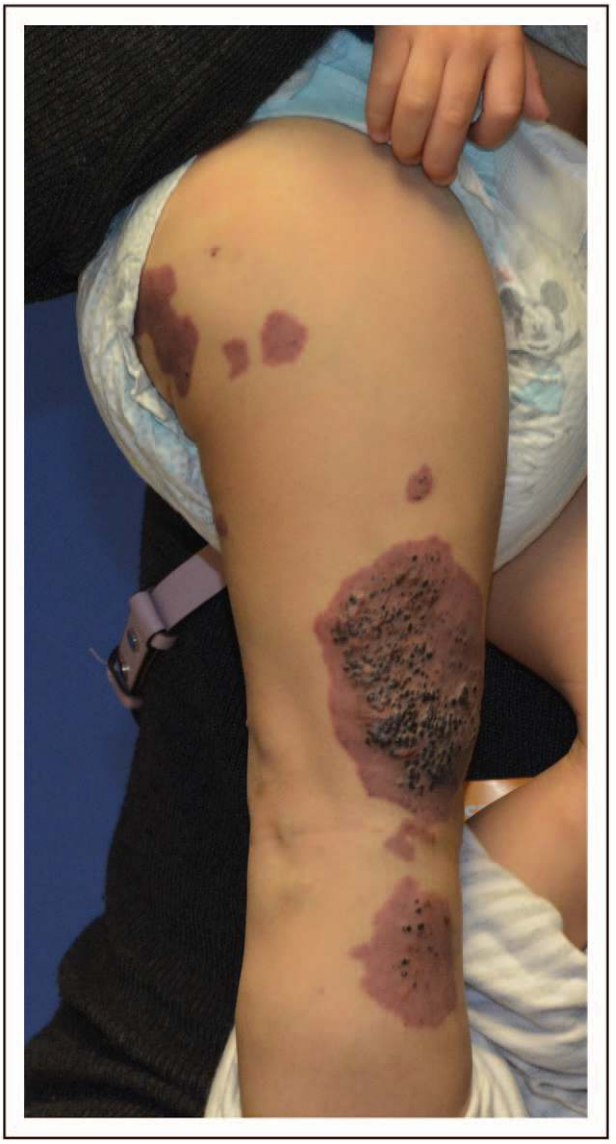

FIGURE 1. Overgrowth of the right lower extremity and buttock with an overlying violaceous geographic vascular stain studded with hemorrhagic vesicles consistent with Klippel–Trenaunay syndrome.

Complications in KTS frequently include infection, which may present as cellulitis, abscess, or bacteremia. Patients are also prone to hemorrhage into their lymphatic cysts, which leads to erythema,

swelling, and pain mimicking infection. Chronic pain can be debilitating and is found at higher rates in patients with a history of cellulitis, superficial thrombophlebitis, and thrombotic events [9].

One of the more significant complications seen in KTS and other PROS syndromes, most notably Congenital Lipomatous Overgrowth Vascular malformations Epidermal nevi and Skeletal abnormalities (CLOVES), is the increased risk of thromboembolic complications, including deep vein thromboses (DVT) and pulmonary embolism. Risk factors are multifactorial. Disorganized channels within venous malformations result in stasis and localized intravascular coagulation with consumption of coagulation factors. Patients with pain or asymmetric overgrowth may have limited mobility, which is accentuated postprocedurally. In fact, a recent study looking at thromboembolic events in PROS patients, including those with KTS, reported that 64% of pulmonary embolisms occurred after surgery or sclerotherapy [10]. Endothelial activation is an additional risk factor for thrombosis. Soluble markers of endothelial cell activation such as thrombomodulin and E-selectin are known to be significantly elevated in PROS patients when compared with controls, possibly secondary to chronic inflammation though activation of endothelial cells and abnormal vascular morphogenesis due to PIK3CA mutation may confer an additional biologic predisposition to endothelial activation [11]. To date, no clinical or laboratory markers have been found to correlate with risk for thrombosis in PROS patients [11].

Pulmonary embolisms have been reported in 12.5 and 9% of patients studied with KTS and CLOVES, respectively [10]. In KTS, connection of persistent embryonic veins to the deep venous system creates a direct conduit for clots to the lungs. Chronic thromboembolic pulmonary hypertension, which is a severe complication of recurrent pulmonary embolism, was reported in five patients with KTS [12].

Given elevated risk for DVT and pulmonary embolism, Keppler-Noreuil *et al.* suggest that PROS patients with a vascular anomaly may benefit from baseline coagulation laboratory studies including D-dimer level, thus allowing comparison when DVT/pulmonary embolism is suspected or when vigilance is heightened, that is postoperatively. To reduce postoperative DVT risk the authors recommend 0.5 mg/kg enoxaparin, sequential compression devices, and early mobilization following surgery [11]. Traditionally, the management of persistent embryonic veins in the setting of KTS has been conservative with compression stockings and pain control, however, closure of the LMV results in improvement in symptoms and decreased risk of thrombosis [8]. There have been 17 cases to date reporting endovenous laser ablation of a persistent embryonic vein with good results [13,14]. Two additional cases were successfully treated with *n*-butyl cyanoacrylate for small marginal veins [13]. Due to risk of thrombosis and pulmonary embolism, some are advocating early closure of persistent embryonic veins [8].

The presence of limb overgrowth, one of the diagnostic features of KTS, predisposes patients to orthopedic complications. In a recent review, 84% of patients had documented leg length discrepancy, the most common orthopedic finding [15]. Orthopedic evaluation was required in 64% of patients, with 50% of patients requiring surgical intervention. Surgical intervention in affected limbs has traditionally drawn hesitance due to the associated vascular malformation. However, 12 patients who underwent total knee arthroplasty were reported to have clinical improvement and tolerable adverse effects [16].

CONGENITAL LIPOMATOUS OVERGROWTH VASCULAR MALFORMATIONS EPIDERMAL NEVI AND SKELETAL ABNORMALITIES

CLOVES represent a severe phenotype in the PIK3CA spectrum characterized by progressive asymmetric overgrowth, combined vascular anomalies, musculoskeletal abnormalities, and cutaneous lesions. A defining feature of CLOVES syndrome is the complex lipomatous overgrowth involving the trunk. Infiltration into adjacent tissue leads to progressive scoliosis, and, if paraspinal or intraspinal spaces are involved, subsequent compression of the cord, thecal sac, or nerve roots can occur [17]. Vascular malformations are usually combined, slow-flow (lymphatic-venous-capillary) that may infiltrate the lipomatous overgrowth, Fig. 2a [18]. Although fast-flow lesions are less common, spinal and paraspinal arteriovenous malformations have been described in CLOVES and are a cause of myelopathy [19].

Skeletal anomalies, the most common being scoliosis, can be progressive and deforming. The severity of scoliosis varies from mild to severe and is related to the extent and progression of the adjacent lipomatous mass. Acral deformities include broad, spade-like hands with ulnar deviation of the digits, Fig. 2b, and furrowing of the palms and soles secondary to fatty deposition, which is distinct from the characteristic connective tissue nevus seen in Proteus syndrome [17]. Skeletal anomalies often manifest distally and become more pronounced proximally with time [1]. Epidermal nevi can be present and are usually in a blaschkoid pattern.

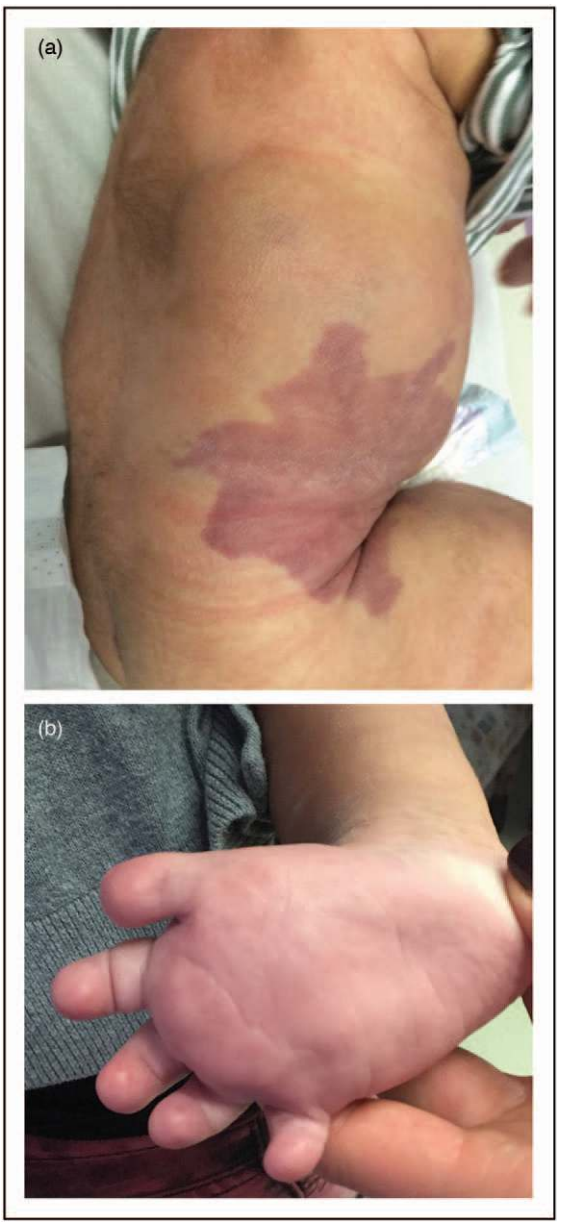

FIGURE 2. Characteristic clinical findings seen in Congenital Lipomatous Overgrowth Vascular malformations Epidermal nevi and Skeletal abnormalities syndrome: (a) lipomatous overgrowth of the low back with an overlying capillary malformation, (b) overgrowth of the right foot with wide spacing between digits.

The clinical phenotype of CLOVES continues to expand. Recently, a pediatric CLOVES patient with pancreatic steatosis complicated by elevated HgbA1c was reported. The authors postulate that PIK3CA mutation predisposes patients to fatty overgrowth of the pancreas, and they suggest that PROS patients should be assessed for pancreatic abnormalities given association of pancreatic steatosis with diabetes and pancreatic cancer [20].

Overgrowth disorders, most characteristically hemihyperplasia and Beckwith–Wiedemann syndrome, have been associated with an increased risk of Wilms tumor, a malignant embryonal renal neoplasm. Precursor lesions, such as nephrogenic rests or early tumors, may be detected by screening ultrasounds; thus surveillance recommendations, including abdominal ultrasound every 3 months through age 7, were implemented [21]. The applicability of these screening recommendations to PROS patients continues to come into question. A recent retrospective review of CLOVES patients demonstrated a 3.3% risk of Wilms tumor, significantly greater than the 0.0001% risk of the general population, therefore, continued surveillance has been recommended in CLOVES [22]. Separate evaluations of KTS have been performed showing either no risk or a modestly increased risk for Wilms tumor, thus routine screenings are not currently advised for KTS [23,24]. The utility of Wilms tumor screening for other phenotypes within the PROS spectrum remains unclear.

PIK3CA has now been identified as one of the most common oncogenes in human cancer; however, there has been no evidence of increased risk of PIK3CA-associated cancers in PROS [4]. Although there was not an overall increased risk of skin cancer, skin cancers were found in capillary malformations and chronic ulcers in patients with PROS, thus cutaneous monitoring is recommended [23].

MEGALENCEPHALY CAPILLARY MALFORMATION

Brain overgrowth, or megalencephaly, with associated neurologic manifestations has been identified as part of the PROS spectrum, which may present as part of a syndrome, as in megalencephaly capillary malformation (MCAP), or as a more isolated finding, as in dysplastic megalencephaly (DMEG). Patients with MCAP, also known as macrocephaly capillary malformation (M-CM), present with congenital or early postnatal megalencephaly, segmental overgrowth, and reticulated or confluent capillary malformations [25]. Other neurologic manifestations include ventriculomegaly and cerebellar tonsillar ectopia, which may be complicated by hydrocephalus and Chiari malformation, respectively [26,27].

Several endocrinopathies are now recognized to be potential complications in PROS. Severe hypoglycemia was reported in six patients with MCAP [28]. Insulin activates PI3K-AKT signaling, leading to further insulin secretion. The authors postulate that activating mutations in PIK3CA lead to hypersecretion of insulin [28]. Thus, screening for hypoglycemia during childhood is recommended for

patients with PROS. In addition, growth hormone (GH) deficiency has been described in a series of 11 patients with MCAP. Hypoglycemia and other pituitary deficiencies were also identified in the majority of these patients [29]. Central gain-of-function PIK3CA mutations may mimic negative feedback on the hypothalamus and pituitary. Conservative doses of GH showed reversal of hypoglycemia and normalization of linear growth velocities without an increase in overgrowth [29]. Consequently, Davis *et al.* recommend evaluation for GH deficiency in MCAP patients presenting with hypoglycemia and/or growth failure. Furthermore, the possibility of comorbid endocrinopathies should be considered [28,29].

DYSPLASTIC MEGALENCEPHALY

DMEG is characterized by bilateral brain overgrowth that may occur in isolation or as part of a megalencephaly syndrome. DMEG and other brain overgrowth disorders, namely hemimegalencephaly and focal cortical dysplasia (FCD), are thought to represent a phenotypic spectrum [26]. Intractable epilepsy, global development delay, and complex neurologic deficits are linked to these brain malformation syndromes. Everolimus, an mTOR inhibitor, is FDA-approved for partial-onset seizures in patients with tuberous sclerosis complex. Two clinical trials (NCT02451696, NCT03198949) assessing everolimus in patients with FCD are underway.

GENERALIZED LYMPHATIC ANOMALY

Previously referred to as lymphangiomatosis, generalized lymphatic anomaly (GLA) was recently added to the PIK3CA spectrum. GLA presents in infancy or early childhood and is characterized by diffuse or multifocal lymphatic malformations. Skin, soft tissue, abdominal, and thoracic viscera are the most common sites of involvement [30]. Disease severity is usually dictated by presence of visceral involvement. Recurrent effusions, particularly if pericardial, pleural, or peritoneal, can cause significant morbidity and mortality. Multifocal lytic bone lesions, more frequently affecting the appendicular skeleton, are complicated by pain, increased risk of fracture, and immobility [31].

DIFFUSE CAPILLARY MALFORMATION WITH OVERGROWTH

Diffuse capillary malformation with overgrowth (DCMO) is characterized by extensive capillary malformations, usually pale pink, reticulate, and involving contiguous anatomic locations, Fig. 3. Overgrowth, typically of an extremity, can involve the soft tissue or bone, and does not necessarily correlate with the location or severity of the capillary malformations. Variable prominent draining veins in DCMO should be distinguished from deep venous anomalies and complex vascular malformations, the latter two of which are characteristic of KTS but lacking in DCMO. Therefore, MRI is not required in DCMO if there is no obvious clinical sign of a deeper vascular malformation [32]. Apart from leg length discrepancy secondary to overgrowth, complications seen in KTS are not seen in DCMO.

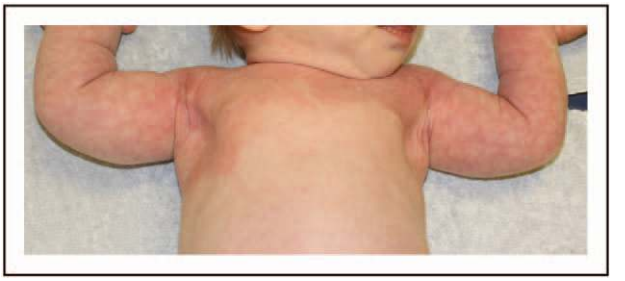

FIGURE 3. Reticulate capillary malformation characteristic of diffuse capillary malformation with overgrowth.

Similar to other PROS phenotypes, the association with Wilms tumor continues to be under investigation. A recent retrospective review of 89 patients with DCMO or M-CM did not identify any cases of Wilms tumor [33].

OTHER

As genetic testing improves and clinical features associated with PIK3CA become more defined, the number of syndromes being identified within this spectrum continues to expand. Lipomatosis or diffuse fatty deposits has been implicated in multiple PROS syndromes including CLOVES as described above, as well as hemihyperplasia multiple lipomatosis, fibroadipose infiltrating lipomatosis, and macrodactyly/lipomatosis of nerve. These are described further in Table 1 along with other newly recognized syndromes associated with PIK3CA [34–43].

DIAGNOSIS

Challenges continue to exist when confirming a diagnosis of PROS. Mutations are usually undetectable in blood and observed only in the affected tissue, which carry variable mutational burdens ranging from 33 to 67% [44]. Traditional Sanger sequencing misses up to 65% of mutations due to low-level mosaicism [45]. More sensitive techniques such as digital droplet PCR and targeted ultradeep sequencing have increased diagnostic yield [45,46]; however,

Table 1. Additional phenotypes associated with mutations in PIK3CA

Condition	Clinical features	Complications
Fibroadipose hyperplasia [34]	Fibroadipose overgrowth (SC, muscular, visceral) ±Skeletal overgrowth Frequently progressive	Lipoatrophy Skeletal complications such as leg length discrepancy
HHML [35–37]	Congenital asymmetry and overgrowth Cutaneous vascular anomalies Recurrent subcutaneous lipomata Static or slowly progressive	Lipomatous compression of the spinal cord Nonlipomatous hydrocephalus
Facial infiltrating lipomatosis [38,39]	Mature adipose tissue infiltrating hemifacial soft tissues Facial asymmetry and adjacent skeletal overgrowth Precocious dental development Macrodontia Hemimacroglossia Mucosal neuromas	Cerebral abnormalities
LON [40,41]	Fibroadipose proliferation within a peripheral nerve, more rarely an axial nerve ±Territory overgrowth (i.e., macrodactyly)	Compressive neuropathies
CLAPO [42]	Capillary malformation of the lower lip Lymphatic malformation of the face and neck Asymmetry with partial/generalized overgrowth	
Upper limb muscle overgrowth with hypoplasia of the index finger [43]	Unilateral isolated upper limb muscle overgrowth Hypoplasia ± ulnar drift of index finger	Orthopedic complications

HHML, hemihyperplasia multiple lipomatosis; LON, lipomatosis of nerve; SC, subcutaneous.

a negative result does not exclude a diagnosis of PROS in individuals with suggestive features [3].

Mutation confirmation is important as the therapeutic landscape shifts to targeted therapy. The highest diagnostic yield is from involved tissue, and blood testing is not recommended. Both affected and unaffected tissue samples should ideally be tested to increase the confidence in pathogenicity when a genetic variant is identified [44]. There are rare cases of mutation identification from uninvolved sites including blood in megalencephaly syndromes [44], urine in a set of patients with CLOVES [47], and cultured amniotic cells from embryos with overgrowth enabling prenatal diagnosis [44,48].

TREATMENT

Over the past decade, the paradigm shift toward molecular classification of vascular anomalies has opened the door for targeted therapeutics. Sirolimus emerged as a therapeutic option for complex vascular anomalies in 2011 [49]. Since then, sirolimus has been described as an effective treatment for KTS [50], GLA [51], CLAPO [52], and has been shown to stabilize disease severity and diminish symptoms in PROS [53]. A recent open-label trial supports sirolimus' ability to modestly reduce tissue growth at overgrown sites. However, this study also reported a significant adverse effect profile with 72% reporting an adverse effect, 37% grade 3 or 4, and 18% withdrawing from treatment [53]. These studies show that sirolimus targets growing tissue instead of promoting regression of prior overgrowth, suggesting that long-term continuation and early initiation of therapy would result in maximum benefit [53]. Low-dose sirolimus therapy should be considered in PROS on a case-by-case basis after weighing the risks and benefits.

Several direct PIK3CA inhibitors are FDA-approved for lymphoma/leukemia, and, in May 2019, Alpelisib (BYL719) – an alpha-specific PIK3CA inhibitor – was approved for breast cancer. BYL719 was recently trialed in seventeen patients with various different phenotypic expressions across the PIK3CA spectrum, including six CLOVES, two MCAP, and nine localized overgrowth patients. All patients had notable improvements, including reduction in capillary malformations and epidermal nevi, discontinuation of chronic gastrointestinal (GI) bleeding, improvement in scoliosis, and improved cognitive function in the two patients with MCAP [54]. In this cohort, Alpelisib was well tolerated without organ toxicity. Reported adverse effects included grade 1 oral ulcerations and mild hyperglycemia. Recently, a patient with severe external genital involvement was started on BYL719, enabling surgical reconstruction [55].

Due to the large range of potential comorbidities seen across the PROS spectrum, a multidisciplinary team, such as in a vascular anomalies clinic, would be optimal for the management of PROS patients. Subspecialties that may be involved in their care may include dermatology, interventional radiology,

hematology–oncology, orthopedics, neurology, surgery, and endocrinology. Baseline coagulation studies including D-dimer may be considered for patients with an underlying vascular anomaly. Further evaluation and work-up should be determined by the individual phenotype and complications as outlined above.

CONCLUSION

Recognizing the broad clinical features, complications and diagnostic strategies for vascular overgrowth syndromes associated with mosaic mutations in PIK3CA is important in preventing morbidity, particularly as the therapeutic landscape evolves to more targeted therapy.

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Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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