Original Article

Clinical Profile of Overgrowth Syndromes Consistent with PROS (*PIK3CA*-Related Overgrowth Syndromes)—A Case Series

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Abstract

Context: *PIK3CA*-related overgrowth syndrome (PROS) is characterized by focal and disproportionate growth of acral body structures in a mosaic pattern with varied phenotypes. Clinical diagnostic criteria are available and testing of the mutation is recommended for diagnosis. Cutaneous features described in these conditions include epidermal nevi and vascular malformations which form part of the diagnostic criteria. **Aims:** To detail the clinical profile of patients with presumptive PROS. **Settings and Design:** We conducted a retrospective study of 15 patients with focal overgrowth of the extremities or macrocephaly who presented to the department of dermatology at a tertiary care hospital in South India. **Subjects and Methods:** Data were collected through electronic medical records from July 2012 to April 2018 over 70 months. The criterion proposed by Keppler-Noreuil *et al*. was used for classifying them as presumptive PROS in the absence of genetic studies. **Statistical Analysis Used:** Descriptive analysis. **Results:** There were nine males and six females; mean age of 12.10 years (range: 8 months to 73 years) with clinical features consistent with PROS. There was a higher frequency of vascular malformations (9/15, 60%) and of epidermal nevi (7/15, 46.6%) than that reported in the literature. Unusual features included focal acrochordons, blaschkoid hypopigmentation and linear papillomatous growths in the oral mucosa. **Conclusions:** This study provides data on the clinical features of patients with PROS from the Indian subcontinent. In resource-poor settings, clinical criteria may be adequate for diagnosis due to restricted accessibility of technically challenging diagnostic tests.

Keywords: *Cutaneous, overgrowth, PIK3CA, PIK3CA-related overgrowth syndrome*

Introduction

Focal overgrowth syndromes present with localized growth of the extremities, trunk, head, or the brain, in isolation or in various combinations in a mosaic pattern with or without epidermal and vascular nevi and variable patterns of acral bony abnormalities. With the detection of the causative mutation, they are better referred to as *PIK3CA* gene-related overgrowth spectrum (PROS). Clinical diagnostic criteria are also available.[1,2] Conditions grouped under the umbrella of PROS show phenotypic variability depending on the tissue affected (mesodermal and neuroectodermal). This includes fibroadipose overgrowth (FAO), hemi hyperplasia multiple lipomatosis (HHML), congenital lipomatous overgrowth, vascular malformations, epidermal nevi, spinal and skeletal (CLOVES) syndrome, macrodactyly syndrome, the megalencephaly syndromes such as megalencephaly capillary malformation (MCAP) and megalencephaly-polymicrogyria -polydactyly-hydrocephalus (MPPH) syndromes[1] and congenital diffuse infiltrative lipomatosis (CDIL).[3] There may be entities that cannot be categorized into these phenotypes reported in varying frequencies (4–25.8%) in a few small series.[4-6] Overgrowth may be present at birth or develop postnatally and is progressive. Activating post-zygotic mutations in the *PIK3CA* result in disproportionate but benign overgrowth with adipose tissue dysregulation. This is noteworthy since certain solid organ cancers have been associated with similar mutations.[7] Data on the clinical profile of PROS are limited to case reports and few series,[2,4-6,8-11] though there are large multicentric studies on the implicated mutation.[2,12]

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Subjects and Methods

We present a series of 15 patients with clinical features of PROS who presented to the Department of Dermatology at a tertiary care center in India from July 2012 to April 2018 (70 months) identified through a retrospective review. Ethical clearance was obtained from the Institutional Review Board. A presumptive diagnosis of PROS was made based on the diagnostic criteria proposed by Keppler- Noreuil *et al*. [Table 1].[1] Data were abstracted from electronic medical records and included demographic details, clinical features, and radiological imaging such as magnetic resonance imaging (MRI)/computed tomogram (CT)/ultrasonogram (USG)/X-ray. Histopathology of the overgrown tissue was available in two patients. Radiological images were retrieved from stored data images and analyzed again by a senior radiologist for the purpose of this study. Descriptive statistics such as frequency and mean were calculated. Genetic studies were not performed.

Results

Demography

Fifteen patients (nine males and six females) fulfilled the criteria for a presumptive diagnosis of PROS.[1] This included FAO (n = 5), CLOVES (n = 5), MCAP (n = 2), HHML (n = 1), CDIL (n = 1) and unclassifiable (n = 1). The mean age at presentation was 12.10 years (range: 8 months to 73 years). (One of the patients with CLOVES syndrome was published as a case report previously.[13])

Clinical features

Features related to overgrowth

Overgrowth was congenital in onset in 80% (12/15) and from early childhood in the rest. It was gradually progressive in all cases and was commonly observed on the left-sided limbs or face i.e., 53.3% (8/15) vs 20% (3/15) on the right.

Overgrowth of the extremities was noted in 86.6% (13/15). The entire limb was hypertrophied in eight patients [Figure 1a], the distal limb in five patients; three of whom had an overgrowth of only the foot/hand [Figure 1b]. The predominant pattern of limb overgrowth was of a single limb in 61.5% (8/13) with the lower limb in seven and the upper limb in one [Figure 1c]. Among the remaining five patients, three had an overgrowth of both feet, one had ipsilateral upper and lower limbs affected while the other had both upper limbs and one lower limb affected. Hemifacial hypertrophy was seen in one each of CDIL [Figure 1d] and CLOVES. Macrocephaly was noted in both patients with the MCAP syndromes and in the patient with the unclassified PROS [Table 2].

Asymmetrical truncal enlargement was seen with truncal lipomas in 46.6% (7/15) patients, that is, in all five of CLOVES syndrome [Figure 2] and in one each of FAO and HHML. Hemifacial lipoatrophy was noted in the patient with unclassified PROS.

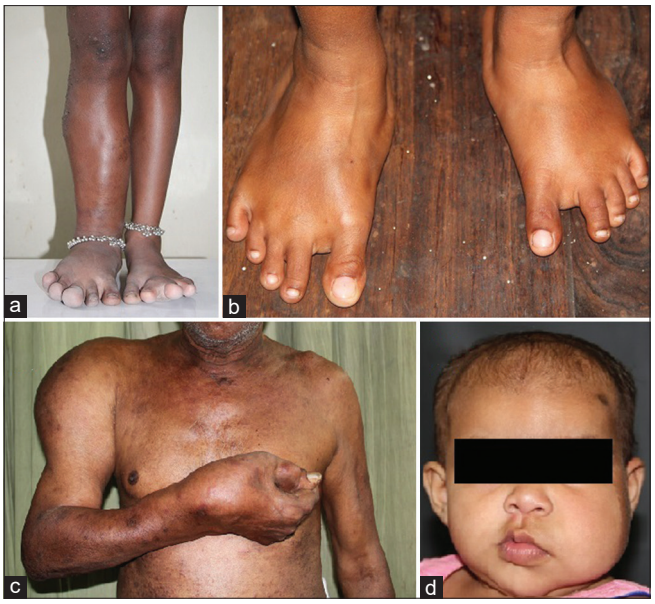

Figure 1: (a) Overgrowth of the entire right lower limb with macrodactyly of both feet and syndactyly of the left 2nd and 3rd toes in the fibroadipose overgrowth (FAO); (b) overgrowth of both feet with increased sandal gap in FAO; (c) deltoid lipoma, overgrowth of the distal one-third of the right upper limb with macrodactyly of the right thumb in FAO; (d) hemihypertrophy of the left side of face in Congenital diffuse infiltrating lipomatosis (CDIL)

Acral limb malformations

Overall, malformations of the hands or feet were found in 73.3% (11/15) which included MCAP (n = 1), CLOVES (n = 4), FAO (n = 5) and unclassified PROS (n = 1). Gross macrodactyly was noted in 40% (6/15) [Figure 1a]. Increased sandal gap was seen in 40% (6/15) patients [Figure 1b] and a similar pattern was seen in a patient with upper limb involvement who had a widened first finger web space. Other digital anomalies included syndactyly in 26.6% (4/15) [Figure 1a], polydactyly in 13.3% (2/15), clinodactyly in 13.3% (2/15) and flexion contracture of toes in 6% (1/15) which involved the normal-appearing foot as well.

Cutaneous features

Epidermal nevi were found in 46.6% (7/15) patients which included CLOVES syndrome (n = 3) [Figure 3a], FAO (n = 1), MCAP (n = 1), CDIL (n = 1), and the unclassified variant (n = 1). One patient with CLOVES had linear papillomatous growths on the tongue and upper lip mucosa [Figure 3b]. Epidermal nevi not only involved the overgrown limb but also extended beyond in 3/7 patients all being CLOVES. Epidermal nevus limited to the overgrowth was seen only in CDIL [Figure 3c].

Vascular malformations were found in 60% (9/15) patients; capillary malformations being the commonest, that is, 80%

Table 1: Diagnostic criteria for PROS (Keppler-Noreuil *et al.*) applied to our series

Cases	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Diagnosis	CDIL	HHML	MCAP	MCAP	CLOVES	CLOVES	CLOVES	CLOVES	CLOVES	FAO	FAO	FAO	FAO	FAO	Unclassified
Required															
Presence of somatic PIK3CA mutation															
Congenital (co) or early childhood onset (ch)	co	co	co	ch	co	co	co	co	co	ch	ch	co	co	co	co
Overgrowth sporadic and mosaic	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Features of either A or B	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
A. Spectrum (two or more features)	✓		✓	✓	✓	✓	✓	✓	✓				✓	✓	✓
Overgrowth (adipose, muscle, nerve, skeletal)	✓		✓	✓	✓	✓	✓	✓	✓				✓	✓	✓
Vascular malformations (capillary, venous, arteriovenous, lymphatic)			✓	✓	✓	✓	✓	✓	✓					✓	✓
Epidermal nevus	✓		✓			✓	✓	✓					✓		✓
B. Isolated features:		✓								✓	✓	✓			
Large isolated lymphatic malformation															
Isolated macrodactyly or overgrown splayed feet/hands, overgrown limbs		✓								✓	✓	✓			
Truncal adipose overgrowth		✓								✓					
Hemimegalencephaly or dysplastic megalencephaly or focal cortical dysplasia										✓					
Epidermal nevus															
Seborrheic keratoses															
Benign lichenoid keratoses															

CDIL: Congenital diffuse infiltrative lipomatosis; HHML: Hemi hyperplasia multiple lipomatosis; MCAP: Megalencephaly capillary malformation; FAO: Fibroadenomatous overgrowth

Table 2: Pattern of overgrowth in our series

PROS (subtypes), *n*=15	Hemifacial hypertrophy	Limb hypertrophy	Macrocephaly	Hemimegalencephaly
CDIL	1	-	-	-
HHML	-	1	-	-
MCAP	-	1	2	1
CLOVES	1	5	-	1
FAO	-	5	-	1
Unclassified		1	1	-

CDIL: Congenital diffuse infiltrative lipomatosis; HHML: Hemi hyperplasia multiple lipomatosis; MCAP: Megalencephaly capillary malformation; FAO: Fibroadipose overgrowth

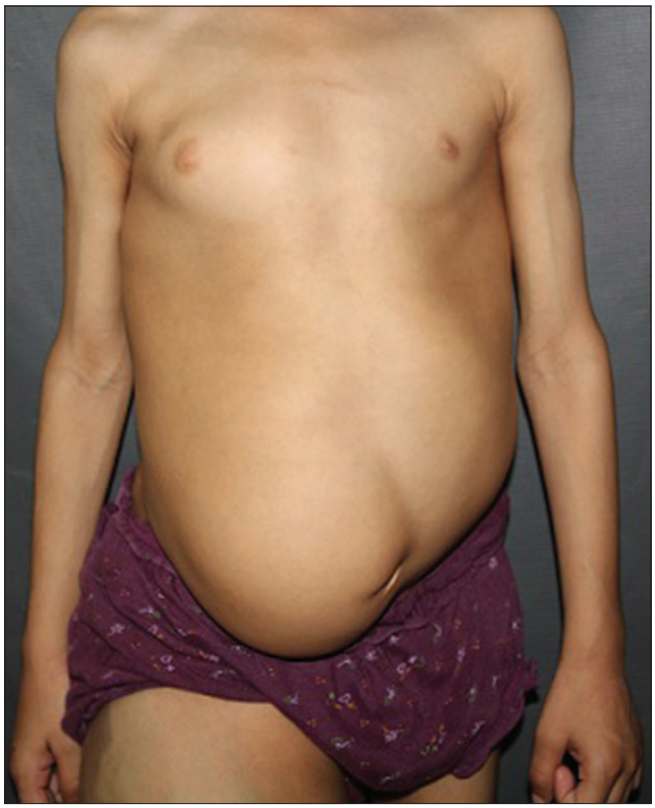

Figure 2: Lipomas on the right mammary area and the right side of the abdominal wall in CLOVES

(8/9) [Figures 4a and b]. Veno-lymphatic malformations were found in three patients, two with CLOVES syndrome and one with FAO. Two of these were present on the overgrown limb. Varicose veins of the overgrown limb were noted in two other patients. Vascular malformations involved and extended beyond the overgrowth in 5/9 patients; CLOVES (n = 3), MCAP (n = 1), and FAO (n = 1). Acrochordons were seen in 13.3% (2/15)—one adjacent to the overgrown upper limb on the anterior axillary fold [Figure 5] and in another in the gluteal cleft adjacent to the overgrown lower limb. Other cutaneous features noted were cafe au lait macules in 13.3% (2/15), hypertrichosis of the overgrown limb in 13.3% (2/15); in HHML [Figure 6a] and the FAO [Figure 6b] and blaschkoid hypopigmentation [Figure 7] which was found to be unrelated to the overgrowth in 6.6% (1/15).

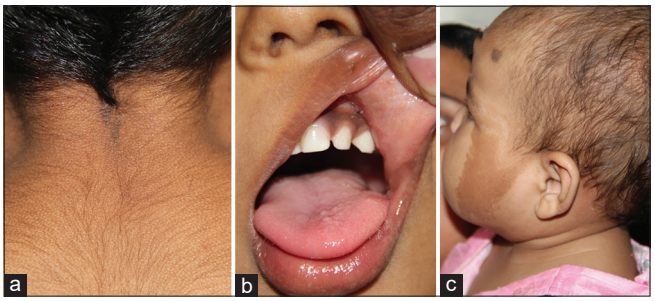

Figure 3: (a) Epidermal nevus at the nape of the neck in CLOVES; (b) linear papillomatous growths on the left side of the tongue in CLOVES; (c) epidermal nevus overlying facial overgrowth in CDIL

Skeletal involvement

One patient with CLOVES had scoliosis, recurrent patellar subluxation, bilateral genu recurvatum, and hyper-extensible joints.

Neurological involvement

The central nervous system was affected in 26.6% (4/15) which included both the MCAP and one each of CLOVES and FAO. There was a history of developmental delay in three patients, one each with MCAP, CLOVES, and FAO, seizures in one patient each with MCAP and FAO. Posterior spina bifida was also present in the patient with FAO.

Genital abnormalities

Among the nine male patients, genital abnormalities were found in 33.3% (3/9); FAO (n = 2) and CLOVES (n = 1). These included cryptorchidism in two patients, hydrocoele and hypospadias in one patient each. In the two female patients in whom imaging was available no ovarian abnormalities were found.

Ocular abnormalities

One of the patients with MCAP syndrome was detected to have congenital glaucoma and corneal clouding.

Dentition

Premature dentition with macrodontia was seen in the child with CDIL.

The clinical features of individual patients are summarized in Table 3.

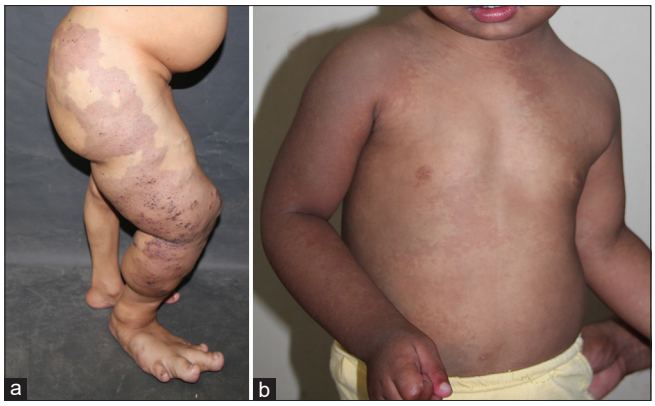

Figure 4: (a) Geographic capillary malformation overlying veno-lymphatic malformation of the overgrown right lower limb in CLOVES; (b) extensive reticulate capillary malformation in Megalencephaly-capillary malformation (MCAP) syndrome

Investigations

Radiological imaging of the hypertrophied extremity was performed in 60% (9/15) patients in whom the predominant lipomatous nature of the overgrowth was ascertained. Additionally, muscular and osseous hypertrophy was noted in 3/9, osseous hypertrophy alone in 4/9 [Figure 8a]. MRI revealed fatty infiltration of the underlying musculature in three patients [Figure 8b]. In one patient with FAO, the discrete truncal lipoma was also found to infiltrate the underlying musculature.

MRI of the brain was done for four patients with neurological symptoms. Hemimegalencephaly was detected in three patients; MCAP (n = 1) [Figure 8c], CLOVES (n = 1), and FAO (n = 1). The one other patient with MCAP had cerebral atrophy.

Visceral imaging including USG or MRI, or CT scan were available in nine patients which detected complicated pararenal cyst, small malrotated kidney and parietal peritoneal cysts in one patient each.

Histopathology of epidermal nevi done for two patients and of acrochordons done for one patient showed features consistent with the clinical diagnosis.

Discussion

PROS is a sporadic overgrowth syndrome with unknown prevalence. The estimated incidence of CLOVES is less than 1:1,000,000 with less than 200 reported cases.[14] Around 70 cases of CDIL have been reported[15] and more than 150 cases of MCAP have been reported. There is no clear data on the prevalence of the less defined FAO and the rarer HHML. These disorders have been reported across various ethnicities and do not have any gender predilection; the largest series of PROS reports a male: female ratio of 1:1.3. Keppler-Noreuil *et al*. and Kuentz *et al*. proposed clinical diagnostic and testing eligibility criteria for PROS.[1,2] All patients included in our study fulfilled the clinical criteria for a presumptive diagnosis of PROS.[1] It could not, however, be confirmed with mutation analysis.

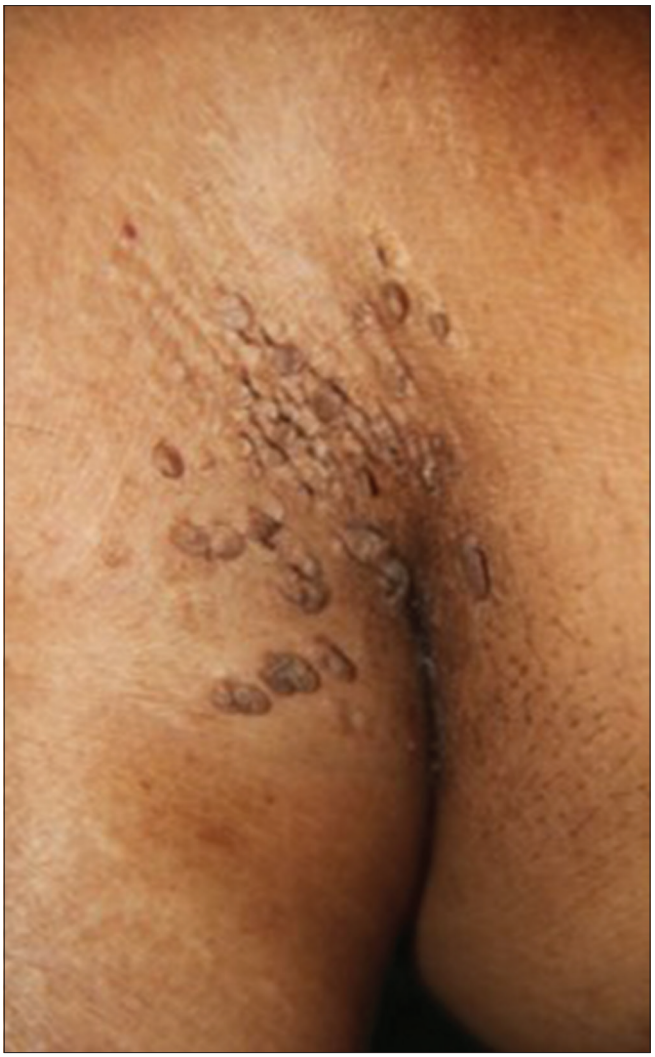

Figure 5: Acrochordons on the anterior axillary fold adjacent the overgrown right upper limb in FAO

In our case series of 15 patients with PROS, all except one patient could be assigned a phenotypic diagnosis. Among our patients, CLOVES and FAO were the most common subtypes, seen in five patients each. Keppler *et al*. had reported a frequency of 45.7% of FAO and 25.7% of CLOVES in their series.[9] Distal limb malformations were found in all series described thus far.[4,6,8-11] The largest series reported a frequency of 22.8% (8/35)[9] whereas our series had 73.3% (11/15). The infiltrative nature of the fatty overgrowth was also noted in some of our patients as has been documented.[16]

The description of cutaneous features was sparse across the literature. Epidermal nevi, seborrheic keratosis, and lichenoid keratosis are the cutaneous features listed under PROS.[1] We report a higher frequency of epidermal nevi as compared to the largest descriptive series reported in literature (46.6% vs 11.4% in Keppler-Noreuil *et al*.'s series)

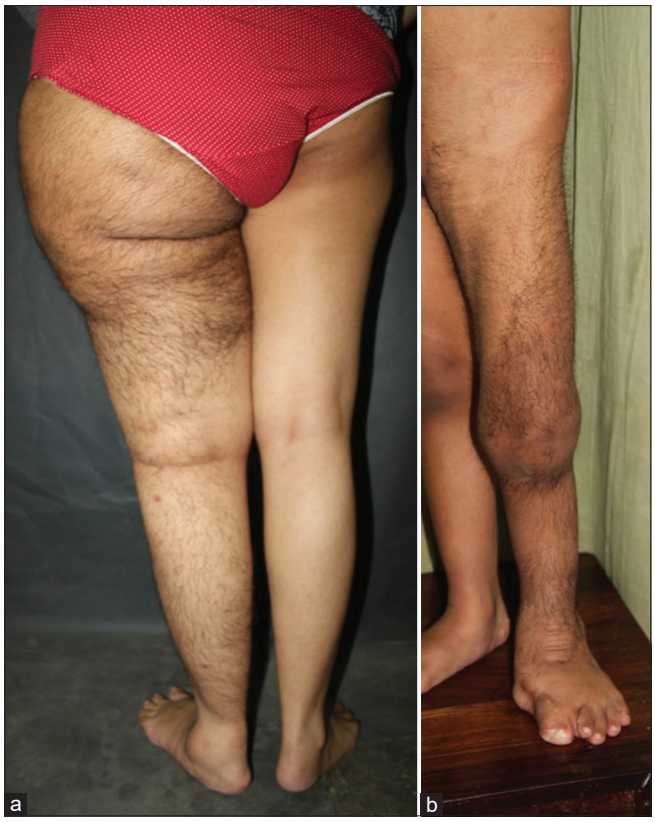

Figure 6: Hypertrichosis of the overgrown left lower limb in (a) hemi hyperplasia multiple lipomatosis (HHML); (b) in FAO

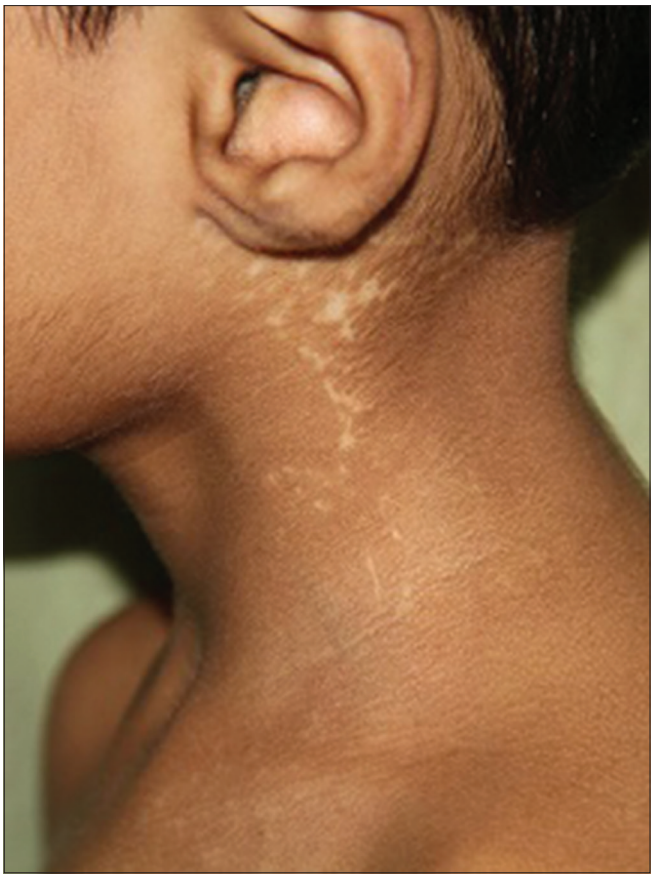

Figure 7: Blaschkoid hypopigmentation on the neck in FAO

and a higher frequency of vascular malformations as well (60% vs 57.1% in Hucthagowder *et al.*'s series and 42% in Keppler-Noreuil *et al.*'s series). Capillary malformations were the commonest type of vascular malformation as noted in previous studies.[9] These cutaneous features were not limited to the overgrown tissues but extended beyond and sometimes were unrelated to the overgrowth. Epidermal nevi have been found overlying the lipomatous overgrowth in CLOVES.[17] The unusual findings in our series were acrochordons adjacent to the overgrown extremity in two patients with FAO, blaschkoid hypopigmentation in one patient with FAO and linear papillomatous growths in the oral mucosa on the same side as the hemifacial hypertrophy in one patient with CLOVES. Focal or segmental acrochordons have not been reported in association with PROS whereas multiple acrochordons occur in inherited conditions such as Birt-Hogg-Dube syndrome, tuberous sclerosis, and *PTEN* hamartoma syndrome.

Regional lipoatrophy was noted in 25.7% (9/35) patients by Keppler-Noreuil *et al*. We had one patient with hemifacial atrophy. Other reported cutaneous features such as hypotrichosis, dermal melanocytosis, and haemangiomas were not seen in our series.

Neurological involvement in CLOVES syndrome is a relatively rare occurrence[18] which we found in one of our patients in the form of delayed developmental milestones and megalencephaly. Of the two patients with MCAP, one had typical features whereas the other had features that overlapped with CLOVES syndromes such as the presence of epidermal nevus and distal limb malformations with overgrowth This overlap has been termed as MCAP-plus in literature.[17] The patients with CDIL, HHML were not found to have any unusual features than those reported in the literature.

Visceral abnormalities in PROS involve mesodermal structures such as the renal and the reproductive system. An abnormal PIK3/mTor/AKT1 pathway is responsible for cellular proliferation forming renal cysts in polycystic kidney disease. Whether the same defect is responsible for the increased frequency of renal and genital abnormalities in the absence of involvement of other mesodermal structures needs to be further explored and is limited by the difficulty in obtaining the necessary tissue to analyze mutations.[19] Renal abnormalities were noted only in one of our patients (11.1%, 1/9) whereas Keppler *et al*. had observed the same in 42% (11/26) of patients in whom it was assessed.[9] Sapp *et al*. and Alomari *et al*. have made similar observations in their series of CLOVES.[16,20] Male genital abnormalities have been reported by Keppler-Noreuil *et al*. with a frequency of 26.6% (4/15)[9] and by Sapp *et al*. in two patients in whom it was looked for in the original series of CLOVES.[14] Male genital abnormalities were noted at a higher frequency of 33.3% (3/9) in our study.

Table 3: Demographic and clinical features of individual patients (*n*=15)

Diagnosis	Age (years)	Sex	Onset	Cutaneous features	Extra-cutaneous features
CDIL	0.66 (8 months)	F	Congenital	Epidermal nevus	Macrodontia
HHML	17	F	Congenital	Truncal lipomatous overgrowths, regional hypertrichosis	-
MCAP	4	F	Congenital	Epidermal nevus, extensive capillary malformation, varicose veins of the overgrown limb	Macrocephaly (HC=53 cm), developmental delay, clinodactyly, increased sandal gap, macrodactyly
MCAP	2.5	F	5 months of age	Extensive capillary malformation	Macrocephaly (HC=53 cm), seizures, bilateral congenital glaucoma, unilateral corneal clouding
CLOVES	16	M	Congenital	Veno-lymphatic malformation, truncal lipomas, single café au lait macule	Increased sandal gap, basal syndactyly of 2nd, 3rd, 4th toes bilaterally, recurrent patellar subluxation, bilateral genu recurvatum, hyperextensible joints, scoliosis, surgery for unilateral hip deformity, cryptorchidism
CLOVES	21	M	Congenital	Epidermal nevus, capillary malformation, varicose veins of the overgrown limb, truncal lipomas	Increased sandal gap, flexion contracture of bilateral 2nd toe, peritoneal cysts
CLOVES	0.91 (11 months)	M	Congenital	Epidermal nevus, extensive capillary malformation, truncal lipoma	Increased sandal gap, macrodactyly
CLOVES	5	M	Congenital	Epidermal nevus including linear papillomatous growths on the tongue and upper lip mucosa, capillary malformation, truncal lipoma	Developmental delay, small malrotated left kidney
CLOVES	5	M	Congenital	Extensive capillary malformation, veno-lymphatic malformation of the overgrown limb, truncal lipoma	Macrodactyly
FAO	4.5	M	Childhood (age <4 years)	Truncal lipoma, café au lait macules	Increased sandal gap, unilateral syndactyly of 1st and 2nd toes, bilateral clinodactyly, posterior spina bifida, hypospadias, unilateral encysted hydrocoele, complicated pararenal cyst, developmental delay, seizures
FAO	73	M	Childhood (age <5 years)	Acrochordons in the anterior axillary fold adjacent the overgrown upper limb	Macrodactyly, increased 1st finger web space
FAO	3	F	Congenital	-	Macrodactyly
FAO	5	M	Congenital	Epidermal nevus, blaschkoid hypopigmentation, single acrochordon in the gluteal cleft adjacent the overgrown lower limb, regional hypertrichosis	Syndactyly of the 1st and 2nd toes and polydactyly of the overgrown foot, unilateral nipple hypoplasia, surgery for cryptorchidism
FAO	7	F	Congenital	Capillary malformation, veno-lymphatic malformation	Increased sandal gap, macrodactyly bilateral feet, unilateral syndactyly
Unclassified	17	M	congenital	Epidermal nevus, capillary malformation, hemifacial atrophy, high arched palate	Polydactyly, macrocephaly (HC=63 cm)

CDIL: Congenital diffuse infiltrative lipomatosis; HHML: Hemi hyperplasia multiple lipomatosis; MCAP: Megalencephaly capillary malformation; FAO: Fibroadipose overgrowth

A functioning PI3K-AKT-mTOR pathway is required for the development of vascular, limb and brain structures[21] which is also regulated by extrinsic mechanisms.[22] To date, 41 variants of PIK3CA mutations have been reported in PROS.[12] Many authors surmise that the phenotypic variation in PROS may be dependent on the timing and the coding sequence affected during embryogenesis.[8,23] Diagnostic molecular studies are hampered by several factors including the best tissue to sample, prevalent low levels of mosaicism (<5%) and the low sensitivity and specificity of conventional techniques. Mutations have been identified in lesional skin fibroblasts, keratinocytes, fatty tissue, neural elements, muscles, bone, vascular malformations, brain hemispherectomy samples[9] and even a few saliva and peripheral blood lymphocyte samples in MCAP,[24] often requiring tissue cultures. Highly sensitive techniques such as targeted deep sequencing of genes coupled with high depth next-generation sequencing, droplet digital polymerase chain reaction, restriction fragment length polymorphism (RFLP) and others are preferred over Sanger sequencing and standard depth next-generation sequencing.[5,9] Targeted deep sequencing methods have reported a diagnostic yield of up to 71%.[5]

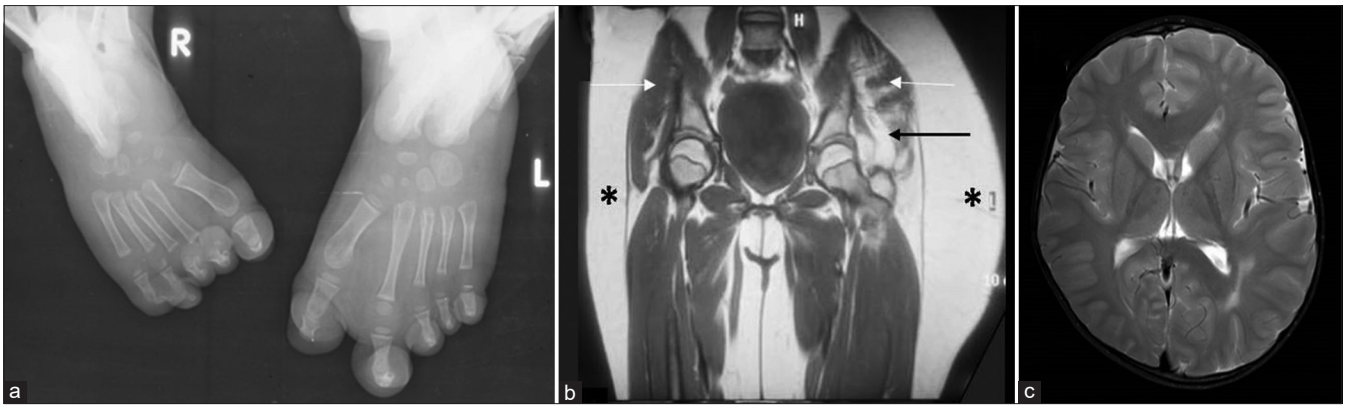

Figure 8: (a) Soft tissue and bony hypertrophy of the left foot with macrodactyly, increased sandal gap on X-ray in MCAP; (b) MRI T1 coronal images showing left lower limb hemi hyperplasia with increased unencapsulated fat in subcutaneous plane (asterix), intermuscular fascial planes (black arrows), and intramuscular plane (white arrows) in HHML; (c) MRI brain T2W showing left hemimegalencephaly in MCAP

The current treatment strategy for PROS is primarily medical using m-Tor inhibitors whose optimum therapeutic potential remains to be ascertained over time.[22] Lipomatous overgrowth seems to relapse despite liposuction and surgical debulking is often complicated by lipomatous infiltration into the underlying tissues.[10] Seizures associated with hemimegalencephaly have required hemispherectomy of the affected side in addition to medical management in some cases.[25] Veno-lymphatic malformations in these syndromes may be managed with sclerotherapy following or prior to medical therapy. Alpelisib (BYL719), a specific PIK3CA inhibitor that is currently undergoing clinical trials holds promise with successful short term outcomes to date.[26]

Limitation

Mutation analysis was not performed to substantiate the diagnosis.

Conclusions

Our case series has clinical features in keeping with the PROS with few unreported mucocutaneous features such as acrochordons, blaschkoid hypopigmentation, and linear papillomatous growth in the oral mucosa. Atypical clinical features found in certain phenotypes and the overlap of features between the various phenotypes in PROS as noted in our series suggest that a genotypic categorization would be superior to phenotypic categorization. However, in resource-poor settings, clinical criteria may be adequate for the diagnosis of these mosaic conditions considering the limited accessibility of expensive molecular tests to detect mutations that are present only at low levels. Besides being a functionally and socially debilitating condition, identifying PROS is important so that patients are screened for genitourinary complications and for tumor surveillance. In addition, there is a possibility of treatment based on emerging data on the development of specific PIK3CA inhibitors.[26] A multidisciplinary team of specialists is required for accurate clinical evaluation and optimum management. The clinical features of this series of patients from the Indian subcontinent add to the phenotypic profile of PROS.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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