Dermato-Radiological Evaluation of Congenital Limb Overgrowth Vascular Syndromes

Abstract

International Society for the Study of Vascular Anomalies classification defines Congenital Limb Overgrowth Vascular Syndromes (CLOS) as a subset of vascular syndromes with other abnormalities that present with unilateral limb overgrowth. It includes Klippel–Trenaunay Syndrome, Parkes–Weber Syndrome, CLOVES (Congenital Lipomatous Overgrowth, Vascular Malformations, Epidermal Nevi, Spinal/Skeletal Anomalies/Scoliosis) Syndrome, Proteus Syndrome, PTEN Hamartomatous Syndrome, and Fibroadipose Vascular Anomaly. Due to their rare and complex nature, a multidisciplinary approach to diagnosis and treatment is required. A thorough clinical and radiological workup can go miles in reflecting on the patient's outcome. Here we report five cases of CLOS with their detailed dermato-radiological profiles.

Keywords: *CLOS (congenital limb overgrowth vascular syndromes), CLOVES syndrome, klippel–trenaunay syndrome, parkes–weber syndrome, proteus syndrome*

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Introduction

Vascular syndromes are rare disorders diagnosed based on characteristic clinical and radiological findings. These are defined by the International Society for the Study of Vascular Anomalies (ISSVA) classification as vascular malformations with other abnormalities.[1] A few of these syndromes present with congenital unilateral limb overgrowth and are also called Congenital Limb Overgrowth Vascular Syndromes. These include Klippel–Trenaunay Syndrome (KTS), Parkes Weber Syndrome, CLOVES (Congenital Lipomatous Overgrowth, Vascular Malformations, Epidermal Nevi, Spinal/Skeletal Anomalies/Scoliosis) Syndrome, Proteus Syndrome, PTEN Hamartomatous Syndrome and Fibroadipose Vascular Anomaly (FAVA).[2] Magnetic resonance imaging (MRI) and ultrasonography are modalities of choice for evaluation and non-invasive diagnosis of vascular malformations. Contrast-enhanced time-resolved magnetic resonance angiography now provides an alternative to digital subtraction angiography (DSA) for the diagnosis and treatment planning of vascular malformations and vascular syndromes.[3] Multidisciplinary management is helpful in managing congenital limb overgrowth syndromes, which includes oral medications like sirolimus, endovascular management, percutaneous sclerotherapy, and surgical resection.[2]

We describe the clinical and radiological findings in five patients with limb length discrepancies associated with vascular syndromes.

Case Series

Case 1

A 3-year-old boy presented with asymmetrically increasing swelling in the right upper limb, right chest wall, and bilateral axilla since birth. Multiple bluish nodules were noted on the anterior chest, soft to rubbery in consistency and compressible on manipulation [Figure 1a]. Some ill-defined areas of dark brown pigmentation were noted on the right antecubital region and the lower part of the upper arm. Palpable thrill, local raised temperature, or tenderness were absent in the pigmented areas. Another well to ill-defined swelling was present on the posterior neck and upper back of the patient, which was soft and compressible [Figure 1b]. Overlying skin was unremarkable.

How to cite this article: Arora S, Mehra S, Bhattacharya I, Nanda C. Dermato-radiological evaluation of congenital limb overgrowth vascular syndromes. Indian Dermatol Online J 2024;15:480-6.

Received: 27-Jun-2023. **Revised:** 02-Aug-2023. **Accepted:** 03-Aug-2023. **Published:** 29-Apr-2024.

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Access this article online

Website: https://journals.lww.com/idoj

DOI: 10.4103/idoj.idoj_500_23

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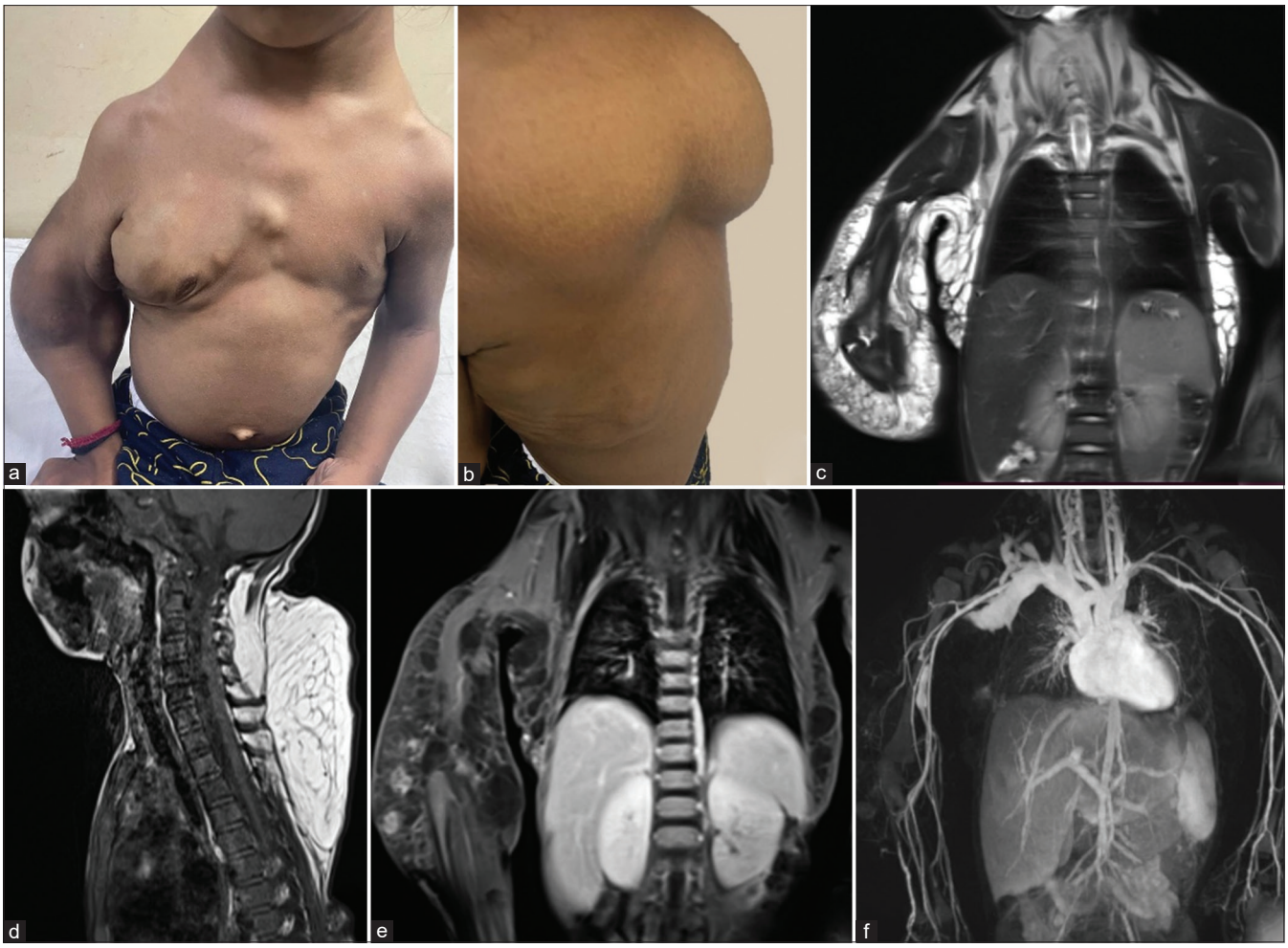

Figure 1: (a) Multiple bluish nodules on the anterior chest overlying an area of diffuse swelling extending over the right upper limb, right chest wall, and bilateral axilla. (b) Well to ill-defined soft swelling over the upper back. (c) Coronal T2 weighted image showing multiseptated, multiloculated T2 hyperintense areas in the subcutaneous plane involving the right upper limb and bilateral lateral chest wall. (d) Sagittal T1WI showing lipomatous overgrowth over the posterior aspect of the neck and chest wall, posterior to the ligamentum nuchae and trapezius muscle, extending from C2 to D7 vertebral level. (e) Post-contrast T1 weighted images (T1W1) showing enhancement of septations and patchy heterogeneous internal enhancement within the lesions. (f) Time-resolved MR angiography (TWIST) image confirming no evidence of early arteriovenous shunting, suggesting slow flow vascular malformation. Diagnosis: CLOVES Syndrome

MRI revealed multiple dilated vascular channels giving a multiseptated, multilocular appearance in the subcutaneous plane in the bilateral lateral chest wall (right > left) and right upper limb extending from the right axilla to mid-forearm involving anterior, posterior, and lateral aspects [Figure 1c]. Post-gadolinium T1-weighted fat-suppressed images revealed enhancement of septations and patchy heterogeneous internal enhancement [Figure 1d]. Asymmetric length of the bones of the upper limbs was noted with elongation of the right-side humerus, radius, and ulna compared to the left side. Hypertrophy of subcutaneous fat tissue was noted bilaterally in the posterior aspect of the neck and chest wall, showing hyperintense signal on T1, T2WI, and signal suppression on fat saturated images [Figure 1e]. MR (Magnetic Resonance) angiography was performed using the Time-resolved angiography With Interleaved Stochastic Tragectories (TWIST) sequence, which did not reveal early arteriovenous shunting [Figure 1f], thus confirming slow flow vascular malformation (venolymphatic) in the right upper limb, axilla, and bilateral chest wall. Radiological diagnosis based on MRI findings of slow flow vascular formation with bony hypertrophy and lipomatous overgrowth in the posterior neck and chest wall and correlation with dermatological findings confirmed CLOVES.

Case 2

A 25-year-old male patient presented with left leg swelling and elongation since birth. An ill-defined area of dark-brown discoloration was noted in the left popliteal fossa [Figures 2a and 2b]. No nodules, varicosities, or palpable thrills were noted along the swelling.

An MRI of bilateral legs revealed soft tissue hypertrophy in the left leg. Multiple dilated vascular channels were visualized in muscular planes in the left leg [Figure 2c]. MR angiography (TWIST) images demonstrated venous phase

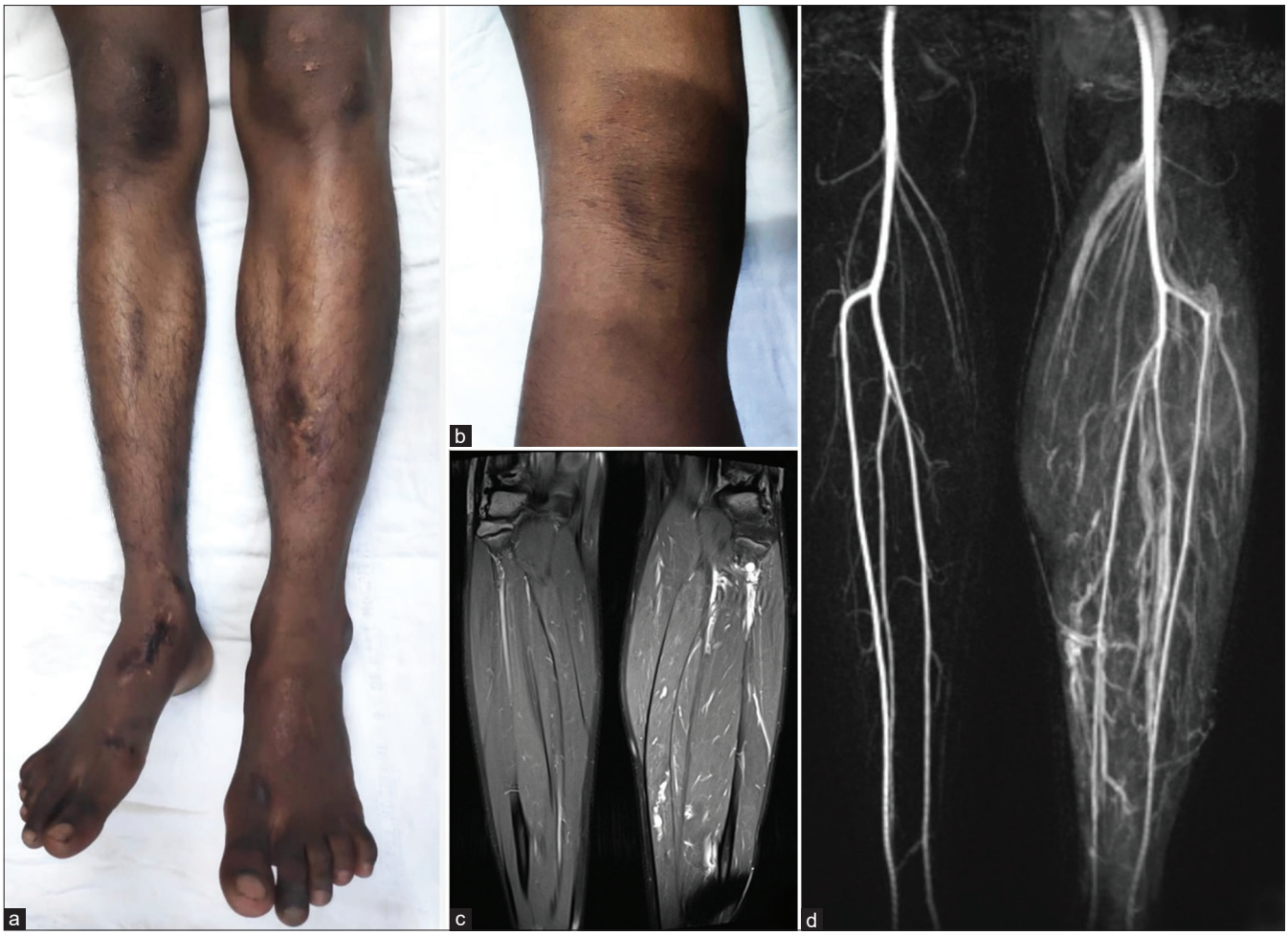

Figure 2: (a and b) Left lower limb swelling and elongation since birth with hyperpigmented areas noted in the popliteal fossa. (c) Coronal T2-weighted image of bilateral lower legs showing multiple dilated vascular channels and hyperintense signal in the muscular plane in the left leg. (d) Time-resolved MR angiography (TWIST) image showing dilated vascular channels and widespread venous malformation within the left leg with no evidence of arteriovenous malformation. Diagnosis: Klippel–Trenaunay Syndrome

filling in vascular channels without any early arteriovenous shunting [Figure 2d], confirming a slow flow (venous) vascular malformation. The findings of slow flow vascular malformations, along with soft tissue hypertrophy and skin changes in the left lower limb were diagnostic of KTS.

Case 3

A 19-year-old female patient presented with irregular, diffuse swelling since 1 year involving the right upper limb and axilla, which was soft in consistency and compressible, along with elongation of the right upper limb. Patchy areas of skin discoloration showing a reddish-pink hue were noted on the palmar aspect of the right hand and right extensor forearm, suggesting capillary malformations [Figure 3a].

A plain radiograph of the right upper limb showed soft tissue thickening involving upper arm and hand, as well as a few radiodense foci in soft tissue indicating phleboliths [Figure 3b]. MRI of the right upper limb revealed multiple dilated vascular channels in the subcutaneous and muscular planes in the right upper limb and right axilla, with soft tissue [Figure 3c] showing venous phase enhancement on post-contrast images [Figure 3d]. A nidus was identified in the lateral aspect of the right arm on MR angiography (TWIST) images, supplied by the brachial artery. The axillary and subclavian veins were seen dilated and draining the malformation [Figure 3e and f]. The rest of the dilated vascular channels in the right forearm and hand did not show early arteriovenous shunting.

MRI findings showed diagnostic arterio-venous malformations in the right arm and slow flow vascular malformations in the right forearm and hand. A diagnosis of Parkes–Weber Syndrome was made based on these characteristic dermatological and radiological findings.

Case 4

A 21-year-old male patient presented with disproportionate enlargement of the left lower limb along with focal swelling involving the left knee and upper lateral aspect of the left leg [Figures 4a and b]. Minimal swelling was present at birth and gradually progressed over time to the present size. Multiple soft-to-rubbery, bluish, compressible cutaneous nodules were

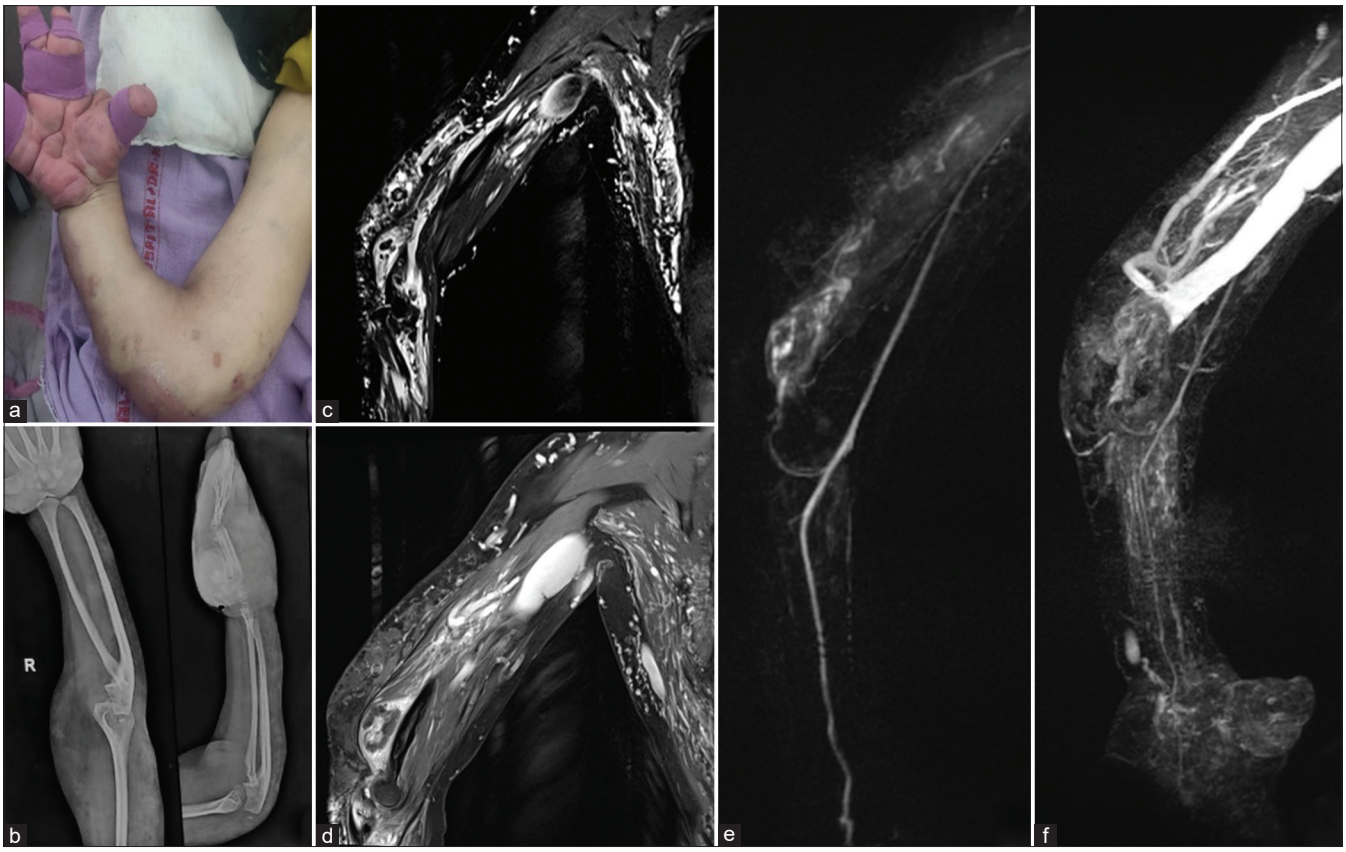

Figure 3: (a) Irregular, diffuse swelling and elongation of the right upper limb with overlying well defined reddish-pink patches on the palmar aspect of the right hand and right extensor forearm. (b) Plain radiograph of right upper limb showing soft tissue thickening involving upper arm and hand, with few radiodense foci in soft tissue-phleboliths. (c and d) Coronal T2WI and coronal post-contrast T1WI showing multiple dilated tortuous vascular channels diffusely involving subcutaneous and muscular planes in the right upper arm and right axilla, and soft tissue showing venous phase enhancement, respectively. (e) Time-resolved MR angiography image at 25s (early arterial phase) showing a nidus in the lateral aspect of the right arm with arterial supply from the brachial artery and early arteriovenous shunting suggesting an arteriovenous malformation. (f) Time-resolved MR angiography in the venous phase showing an extensive slow flow vascular malformations in the right upper limb. Diagnosis: Parkes–Weber Syndrome

present overlying the swelling [Figure 4b]. MRI of bilateral lower limbs detected tubular elongated channels in the subcutaneous plane insinuating into the muscle compartment in the left lower limb, the gluteal region extending into the left iliopsoas muscle, and the pelvis [Figures 4c and d], demonstrating hypointense signal on T1WI and hyperintense signal on T2WI/STIR (short TI inversion recovery) images with multiple hypointense septations. A few T2 hypointense foci were noted within the lesions, suggesting phleboliths. MR angiography confirmed the presence of slow flow vascular malformations with absent arteriovenous shunting and the presence of venous phase enhancement of these tubular structures [Figure 4e]. There was hypertrophy of muscles in the left thigh and elongation of the left lower limb (femur, tibia, and fibula). The diagnosis of KTS was made based on MR findings and the cutaneous changes in the left lower limb.

Case 5

A five-year-old female patient presented with diffuse swelling and bluish discoloration of the left lower limb [Figure 5a] with multiple well-defined dark-red patches on the skin. The child also had enlarged head size, frontal bossing, and hypertelorism. A large, ill-defined swelling was also noted in the left dorsolumbar region with hyperpigmented skin [Figure 5b]. These changes were not present at birth, started developing at one year of age and gradually progressed to the present size. Doppler USG (Ultrasonography) and MR angiography of the left lower limb confirmed slow flow vascular malformations in the subcutaneous plane in the left lower limb, along with muscular hypertrophy. A diagnosis of proteus syndrome was made based on the combination of findings of facial dysmorphism, the presence of unilateral limb hypertrophy and associated slow flow vascular malformation, and asymmetric somatic overgrowth in the left dorsolumbar region.

Clinical and radiological findings of all five cases has been summarised in Table 1.

Discussion

According to the updated International Society for the Study of Vascular Anomalies (ISSVA) classification, combinations of vascular malformations with other anomalies like soft tissue or skeletal hypertrophy or atrophy, microcephaly, or macrocephaly are essential for the diagnosis of vascular syndromes. The vascular malformations in these syndromes may be high

Table 1: Clinical and Radiological findings

Age (years)/Sex	Limb hypertrophy	Clinical and radiological findings	Diagnosis
3/M	Right upper limb: Soft tissue and bony hypertrophy	Slow flow vascular malformation (venolymphatic) in the right upper limb and chest wall Lipomatous hypertrophy in the upper back	CLOVES syndrome
25/M	Left lower limb: Soft tissue hypertrophy	Slow flow vascular malformation (venous) in the left lower limb	Klippel Trenaunay Syndrome
19/F	Right upper limb: Soft tissue hypertrophy	Capillary malformation in the hand and forearm Arteriovenous malformation in the right arm; Venous malformation in the right upper limb and right axilla	Parkes-Weber Syndrome
21/M	Left lower limb: Soft tissue and bony hypertrophy	Slow flow vascular malformation (venolymphatic) in the left lower limb and left gluteal region	Klippel Trenaunay Syndrome
5/F	Left lower limb, left Dorsolumbar region: Soft tissue hypertrophy	Enlarged head size, hypertelorism, and frontal bossing. Capillary malformation in the left dorsolumar region and left lower limb Slow flow vascular malformation (venous) in the left lower limb.	Proteus Syndrome

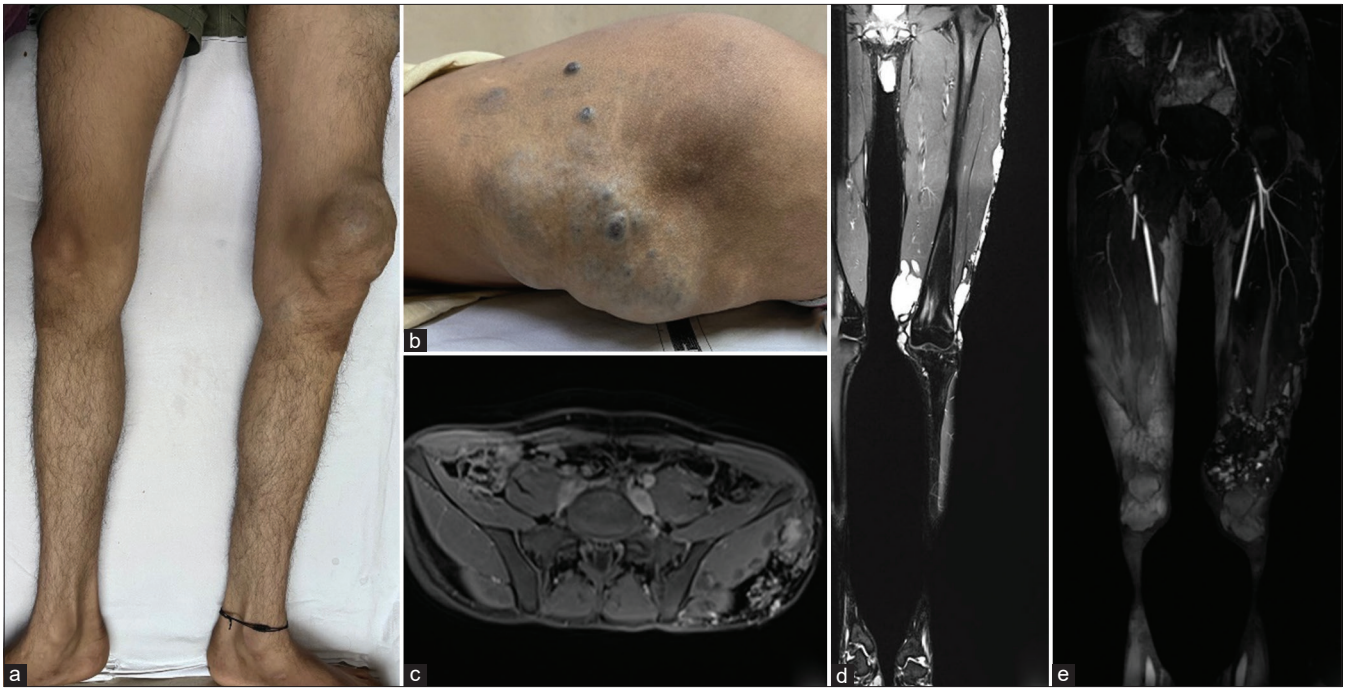

Figure 4: (a) Disproportionate enlargement of the left lower limb along with swelling around the left knee and upper lateral aspect of the left leg (b) Multiple soft to rubbery, bluish, compressible nodules overlying the swelling in the lateral aspect of the knee. (c and d) Axial and Coronal T2WI showing tubular, elongated channels in the subcutaneous and muscular planes in the left gluteal region and left lower limb. (e) MR angiography image in venous phase showing heterogeneous enhancement of vascular malformation with no evidence of early arteriovenous shunting suggesting venolymphatic malformation. Diagnosis: Klippel–Trenaunay Syndrome

flow (arteriovenous), slow flow (capillary, venous, lymphatic), or more commonly, a combination of these. Vascular malformations with limb overgrowth are characteristically seen in KTS and Parkes–Weber Syndrome; lipomatous overgrowth is characteristic of CLOVES and Bannayan-Riley-Ruvalcaba; asymmetric somatic overgrowth is seen in Proteus Syndrome; and bone undergrowth is typical of Servelle-Martorell Syndrome. A few of the described syndromes affect the craniofacial region, like Sturge–Weber syndrome or capillary malformation of the lower lip, lymphatic malformation predominant on the face and neck, asymmetry, and partial/generalized overgrowth (CLAPO) syndrome.[1]

Clinical and radiological evaluation establish the diagnosis and treatment plan in congenital limb overgrowth syndromes, with the need for genetic evaluation arising in only a few cases. A genetic link has been described in each of these syndromes, and mutations in the *PIK3CA* gene are linked to multiple syndromes, including KTS, CLOVES, and FAVA. These disorders have been grouped together as PROS (PIK3CA-related overgrowth syndromes).

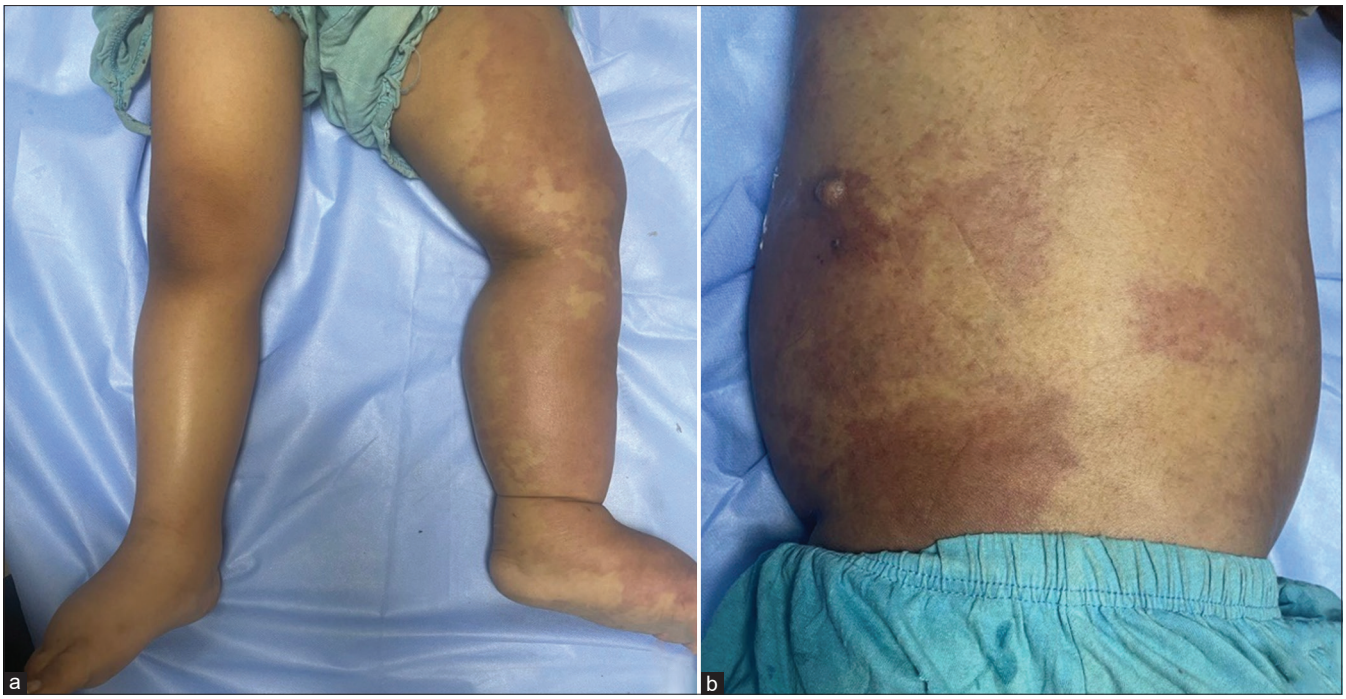

Figure 5: (a and b) Diffuse swelling and bluish discoloration of the left lower limb and left side of the trunk with overlying well to ill-defined reddish patches

Diagnostic criteria for PROS include two of the following four features: limb overgrowth, vascular malformation, epidermal nevi, and hemimegalencephaly.[2]

The aim of imaging in vascular syndromes is to diagnose the type of malformation, that is, slow flow (venous/lymphatic/venolymphatic) or high flow (arteriovenous) malformations and delineate the anatomic extent of the malformation while simultaneously detecting bone hypertrophy/atrophy, hamartomatous tumors, or other anomalies.[4] Ultrasonography with color doppler is a useful screening modality for detecting vascular malformations. Vascular syndromes can affect large areas of the limb or torso or be multifocal, which can prove challenging for evaluation with ultrasonography.[5] Cross sectional imaging can delineate the anatomic extent of the malformations and other associated anomalies. MRI is superior to CT due to better soft tissue and contrast resolution. T2 weighted MR images can help in the identification of the type of malformation without contrast administration in some cases, with high flow malformations showing flow voids and low flow malformations depicting high signal on T2WI.[6]

MR angiography with or without time-resolved angiography is the investigation of choice in the evaluation of these disorders. CT and conventional MR angiography have the limitation of limited spatial and temporal resolution, cannot demonstrate in real-time the contrast flow in vascular malformations, and thus cannot reliably distinguish slow flow and high flow malformations.

Time-resolved contrast-enhanced MR angiography is an advanced MR technique that enables the acquisition of multiple images during the passage of contrast using view sharing and k-space undersampling and can reliably distinguish between high flow and low-flow lesions and provide information about feeding arteries and draining veins. The limitation of this MR technique is its lower spatial resolution and limited field of view (FOV) compared to conventional MR angiography.[7] Conventional angiography and venography with digital subtraction are not used in the current era for the diagnosis of vascular malformations. Catheter angiography provides a selective assessment of arteriovenous malformations before embolization is carried out. Similarly, direct percutaneous phlebography is carried out to find out the detailed flow patterns in the venous system just before sclerotherapy.[8]

In our study, the TWIST sequence was used, which enabled the identification of a small arteriovenous malformation in case 3, which had been missed on doppler imaging. To overcome the limited FOV of TWIST angiography, we used conventional MR angiography in case 4 for the evaluation of the entire left lower limb and gluteal region.

KTS is characterized by unilateral limb overgrowth with low flow (capillary, venous, and lymphatic) malformations. Though it has been present since infancy, it may become clinically apparent in later stages of life. It is commonly associated with a persistent embryonic vein in the affected lower limb called the lateral marginal vein. Management of KTS includes oral sirolimus and sclerotherapy for vascular malformations.[9,10]

MR Angiography is essential to differentiate Parkes Weber Syndrome from KTS by eliciting a high flow malformation (arteriovenous malformation or arteriovenous fistula) as other radiological and clinical

findings overlap. Parkes–Weber Syndrome is not linked to the *PIK3CA* gene, and thus oral sirolimus is not indicated for its management; the crux of treatment is surgical excision or embolization of arteriovenous malformations.[11]

CLOVES syndrome is characterized by lipomatous overgrowth, with slow flow malformations, limb or torso overgrowth, epidermal nevi, and spinal deformities. The changes are usually apparent before birth, distinguishing them from proteus syndrome.[2,12] CLOVES syndrome is associated with an increased risk of Wilm's tumor, and ultrasonography screening has proven to be beneficial in children with CLOVES.[13] *PTEN* mutation syndromes presenting with lipomatous overgrowth need to be differentiated from CLOVES and demonstrate macrocephaly and multiple visceral hamartomas.[2]

Proteus syndrome is associated with mutations in the *AKT1* gene and is characterized by asymmetric somatic or limb overgrowth not seen at birth but presenting/developing later in life. Mosaic distribution of lesions, progressive course, and sporadic occurrence are mandatory for the diagnosis of proteus syndrome. Along with these, specific criteria include cerebriform connective tissue nevus, epidermal nevus, asymmetric disproportionate limb overgrowth, vascular malformations, cystic lung disease, characteristic facial phenotype, and specific tumors like parotid monomorphic adenoma and ovarian cystadenoma.[14,15]

Conclusions

MRI with MR angiography is the investigation of choice for diagnosis, evaluation of extent of involvement, and identification of the type of vascular malformation. Time-resolved contrast-enhanced MR angiography is of great value in the non-invasive differentiation of slow flow and high flow malformations. This is essential for appropriate treatment, planning, and management of these syndromes.

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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