Scientific Research Publishing

Modern Plastic Surgery, 2026, 16(1), 34-50
https://www.scirp.org/journal/mps
ISSN Online: 2164-5280
ISSN Print: 2164-5213

Cloves Syndrome: A Case Series of a Rare Syndrome

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How to cite this paper: Pieterson, W., Anyigba, E., Okrah, O.A., Gbadamosi, H. and Pieterson, E. (2026) Cloves Syndrome: A Case Series of a Rare Syndrome. *Modern Plastic Surgery*, **16**, 34-50.
https://doi.org/10.4236/mps.2026.161004

Received: September 27, 2025
Accepted: January 26, 2026
Published: January 29, 2026

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Abstract

"Overgrowth" syndrome generally describes abnormal growth patterns in the milieu of a constellation of other symptoms and signs. CLOVES (Congenital Lipomatous asymmetric overgrowth of the trunk with lymphatic, capillary, venous and combined-type vascular malformations, epidermal naevi, scoliosis/ skeletal and spinal anomalies) is a segmental overgrowth syndrome with vascular anomalies. The clinical symptomatology is thus very variable and based on the involved systems. This groundbreaking series seeks to document the clinical and imaging spectrum of findings in these four children, which will be the first of its kind in Ghana, West Africa.

Keywords

Overgrowth Syndrome, CLOVES, Vascular Anomalies, Clinical Symptomatology, Imaging Spectrum

1. Introduction

CLOVES (Congenital Lipomatous asymmetric overgrowth of the trunk with lymphatic, capillary, venous and combined-type vascular malformations, epidermal naevi, scoliosis/skeletal and spinal anomalies) is a recently described rare, sporadic (non-hereditary) overgrowth syndrome. It was initially described in 2007 by Sapp *et al.* [1] and later revised in 2009 by Alomari *et al.* [2]. Cases of CLOVES syndrome reported in the literature are limited in number [3]. Although it is labelled congenital, deformities can be present prenatally, at birth or during puberty in a few and get accentuated with growth [4].

Healthy growth is an expected progression of height, weight, and head circum-

ference changes predicted to follow standardised growth curves. It reflects the overall health and nutritional status of an individual. The term "overgrowth" is generally used to describe three abnormal growth patterns: prenatal overgrowth, postnatal overgrowth, and Segmental overgrowth. CLOVES is a segmental overgrowth syndrome with vascular anomalies classified under the PIK3CA-Related overgrowth spectrum [5]. In 2007, Sapp *et al.* initially described it as a Congenital lipomatous overgrowth with vascular anomalies and epidermal nevi, and entitled it "CLOVE" syndrome [1]. It was later revised in 2009 by Alomari *et al.* as "CLOVES" upon recognising the skeletal and scoliosis-related spinal abnormalities [2]. Other segmental overgrowth syndromes include Proteus syndrome and Phosphatase and Tensin Homolog Hamartoma Tumour Syndrome. Those associated with vascular anomalies include Klippel-Trenaunay Syndrome (KTS), Arteriovenous (fast-flowing) fistulae without lymphatic malformation along an enlarged limb, as seen in Parkes-Weber syndrome (facial capillary malformation with occasional mild hypertrophy of the maxilla, closely related to Sturge-Weber syndrome [5] hogenesis of CLOVES syndrome is attributed to somatic (postzygotic) mutations in the PIK3CA gene, located on chromosome 3q26.32. The PIK3CA gene is an upstream regulator of the Akt-mTOR cell signalling pathway. Its activation mutations and Akt cell signalling axis are associated with cell proliferation and resultant lymphatic and other vascular malformation/overgrowth syndromes, grouped under the PIK3CA-related overgrowth spectrum (PROS) [6].

Overgrowth syndromes with complex vascular anomalies (OSCVA), such as CLOVES syndrome, frequently pose considerable diagnostic, nosologic, and management challenges, even for experienced clinicians. Evaluation of such patients thus requires a skilled multidisciplinary team [2]. Tissue samples, urine, or tumour cells must be evaluated for mosaic activation mutation of the PIK3CA gene to confirm a clinical diagnosis or differentiate PIK3CA gene mutation-associated lymphatic and other vascular malformation/overgrowth syndromes or PROS with many overlapping clinical features [7]-[9].

CLOVE syndrome is a rare and complex anomaly; this case series, observed at our hospital, aims to highlight its varied clinical spectrum.

2. Case Series

2.1. CASE-1

An 11-month-old boy presented at the clinic, and clinical examination revealed a larger right lower limb compared to the left. The child had been born at a government hospital, where medical professionals had identified hyperpigmented areas and red patches on the skin of the limb and trunk, suggestive of port wine naevi. The mother had had regular prenatal hospital visits, during which serial ultrasounds revealed no fetal abnormalities. The pregnancy had been uneventful. The child had a birthweight of 3.7 kg. At the time of birth, maternal and paternal ages were 31 and 32 years, respectively. Both work as nurses. The mother had only taken the prescribed medications given during the pregnancy. No history of smoking or

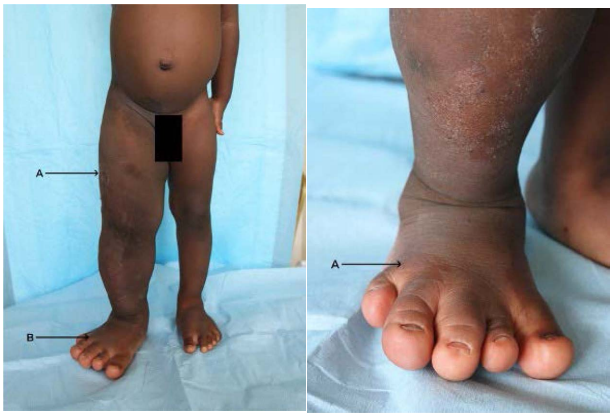
alcohol consumption during pregnancy. There was no history of consanguinity.

A physical examination revealed a noticeable difference in the size of his lower limbs. Specifically, his right lower limb, from the buttock to the foot, appeared to be significantly larger than his left (Image 1(a) and Image 1(c)). The right foot also showed signs of enlargement (Image 1(b)). Furthermore, there were large, flat, hyperpigmented patches on the skin of his right lower limb and trunk (Image 1(c)). These patches were reportedly red at birth.

Additionally, a raised, hyperpigmented macular naevus was present that extended across his inguinal region, from the suprapubic region to the right hip (Image 1(d)). A few naevi were also observed on his pubic and groin area. No murmur was detected during the auscultation of the heart, and heart sounds were normal. The abdominal examination was unremarkable.

To investigate further, the hospital of birth requested a Doppler ultrasound of the right lower limb, which returned normal results.

Further evaluation, when referred to the Teaching hospital, led to a CT scan of the chest, abdomen and pelvis as well as of both lower limbs, done based on the clinical suspicion of CLOVE syndrome.



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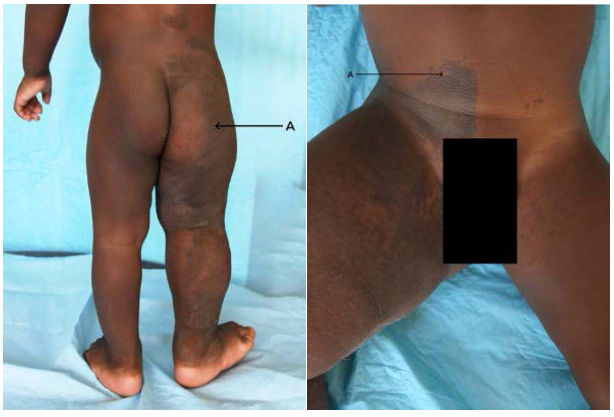


(c) (d)

Image 1. (a), (b), (c): A -Shows a grossly enlarged right lower limb with hyperpigmented patches suggestive of previous port wine stains. (d): A- Shows a naevus over the right pubic and groin area.

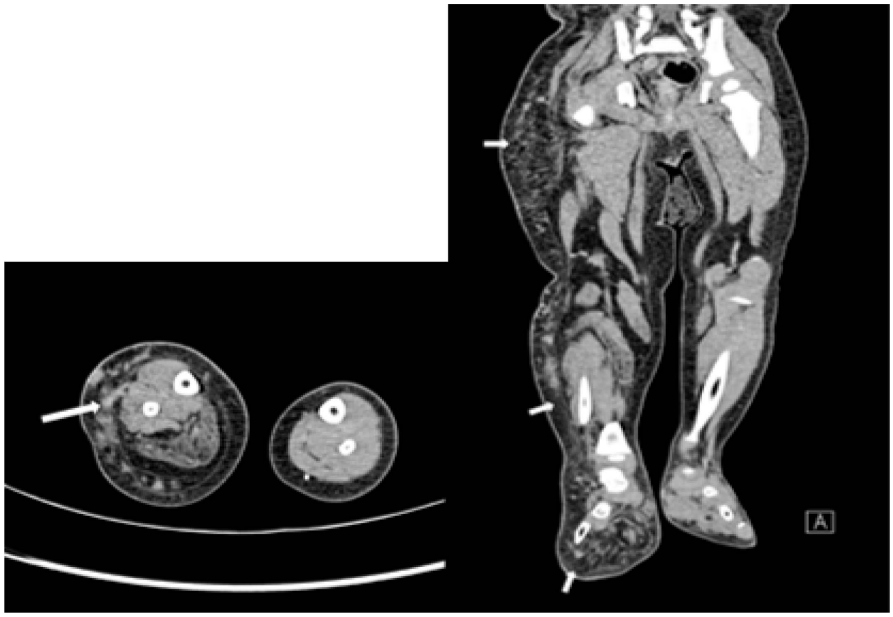


Figure 1. Contrast-enhanced Axial and coronal reformatted CT of the lower limbs shows overgrowth of the right lower limb with fatty infiltration of the subcutaneous tissues (short arrows). The right lower limb is consequently considerably larger than the left. Tortuous venous collateral seen within the subcutaneous tissues (long arrow).

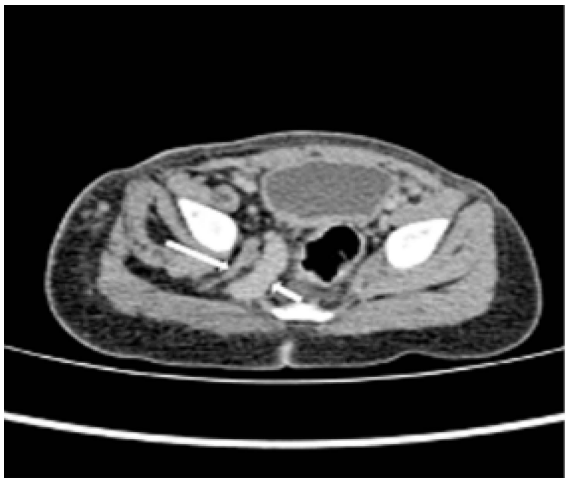


Figure 2. Axial CT scan of the pelvis showing infiltration of the enhancing right superior gluteal vein (short arrow). The linear structure anterior to it represents an enlarged right superior gluteal vein (long arrows).

Contrast-enhanced computed tomography (CT) of the pelvis and lower limbs, acquired in the venous phase, demonstrated overgrowth and enlargement of the entire right lower limb and foot due to circumferential fatty infiltration of the subcutaneous tissues extending up into the gluteal region (**Figure 1**). Numerous dilated torturous venous channels were present within the subcutis of the thigh and leg (**Figure 1**). Note was made of a significantly dilated right superior gluteal vein, right up to the internal iliac vein, with dilatation of its distal tributaries in the

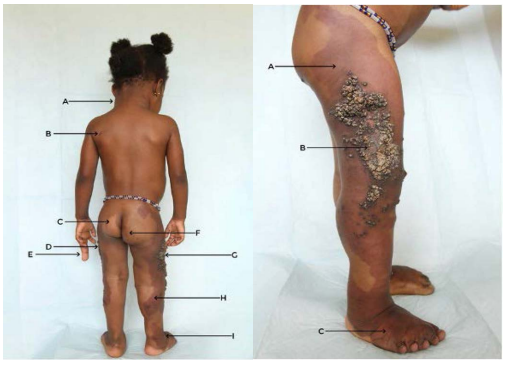
lower limb. A tubular structure lying anterior to the dilated superior gluteal vein and exiting via the superior sciatic foramen is indicative of an enlarged superior gluteal nerve, as shown in Figure 1 and Figure 2. Atrophy and resultant fatty replacement were observed involving the distal psoas muscle, gluteal muscles, anterior and posterior thigh muscle groups, and soleus muscles on the right. Initial abdominal ultrasound findings done at birth were unremarkable. There were no bony malformations documented.

2.2. CASE-2

A female child of 24 months presented with a right lower limb larger than the left. The child was born at a government hospital. She was first seen at our facility at age two months. The child was born by caesarean section on account of 2 previous caesarean sections. The mother was an antenatal clinic attendant and took only routine drugs. The antenatal period and pregnancy were uneventful.

Serial ultrasounds performed during her hospital antenatal visits did not reveal any fetal abnormalities. The baby was born weighing 3.2 kg, and both parents were 29 years old at the time of birth. The father works as an accountant and is also a pastor, while the mother is a caterer. There is no history of consanguinity, and the mother did not consume alcohol or tobacco during pregnancy. The baby did not experience any delayed milestones during growth.

During the physical examination, it was observed that the patient had a visibly swollen right lower limb, extending from the thigh to the foot (Image 2(a)). The toes on the right foot were also enlarged compared to the left (Image 2(e)). Additionally, there were large, flat red patches on the right lower limb and trunk (Images 2(a)-(c)). The patient also had a raised, hyperpigmented macular nevus that extended from the suprapubic region to the right hip, across the inguinal region (Images 2(a)-(c)). Furthermore, there were large naevi on both lower limbs, which occasionally bled (Images 2(a)-(c)). The left middle finger was significantly larger than the right (Image 2(d)), involving both skeletal and soft tissue. She also had a left-sided soft tissue neck swelling (Image 2(a)). No murmur was detected during auscultation of the heart, and heart sounds were normal. The abdominal examination was unremarkable.



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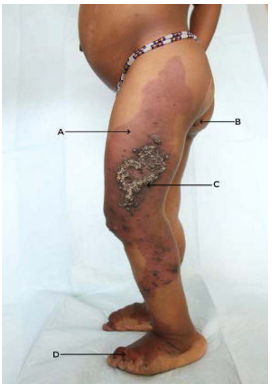

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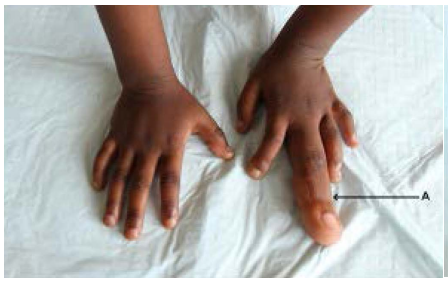
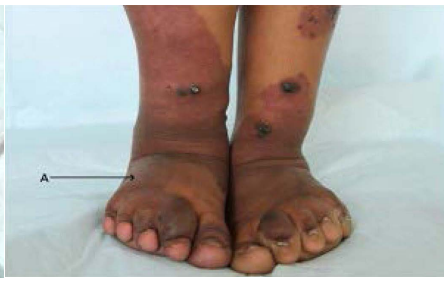




(d) (e)

Image 2. (a): A: Left-sided soft tissue neck swelling. B: hyperpigmented patches suggestive of naevi. C: Enlarged left middle finger. D and G: Raised skin naevi on the left and right thighs, respectively. F: Enlarged right buttock. H and I: port wine stain on the right lower limb; (b) and (c): A: Port wine stain on both lower limbs. B: Raised naevi. C: Port wine stains on both feet; (d): A: Enlarged Left middle finger; (e): A: Enlarged right foot.

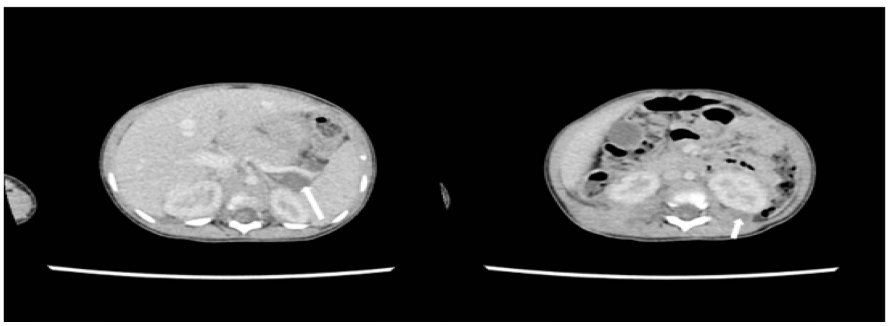


Figure 3. Axial contrast enhanced CT scans of the abdomen; shows a cystic lesions in the splenic hilum (long arrow) and another posterior to the left kidney (short arrow).

Computed tomography (CT) imaging of the trunk and lower limbs revealed several findings, including a (2.9 × 2.2) cm non-enhancing cystic lesion in the splenic hilum, a smaller (1.2 × 0.7) cm one in the left posterior pararenal space, and a third in the right hemipelvis; these were presumed to be lymphatic malformations. There was fatty overgrowth of the inferior right preperitoneal fat and ectasia of the superior gluteal veins bilaterally.

Also noted was a fatty overgrowth of the subcutaneous tissues of the right gluteal region and thigh; noticeable within this space are multiple venous collaterals

and a solitary phlebolith, the latter indicative of the underlying venous origin of the vascular lesions. An avidly enhancing (1.6 × 1.2) cm, poorly defined lesion in the left vastus lateralis was concerning for a venous malformation.

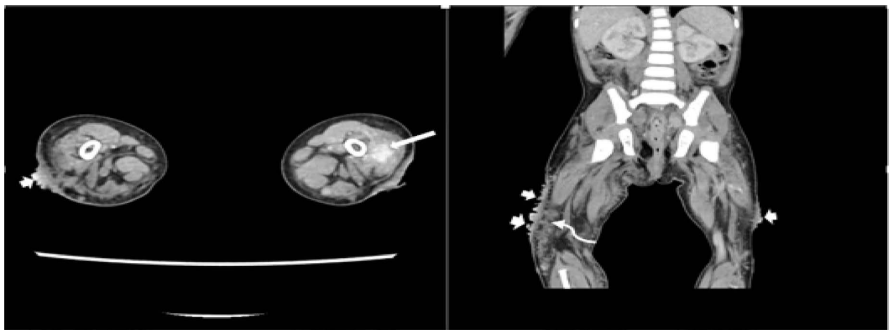


Figure 4. Axial CT and Coronal reformatted CT of the trunk and both thighs showing lipomatous infiltration of the subcutaneous fat of the right thigh with similar venous collaterals within it (wriggly arrow). An intensely enhancing left quadriceps muscle lesion concerning for a vascular malformation (long arrow) is seen. Epidermal overgrowth of the skin in the lateral aspects of both distal thighs—epidermal naevi (short arrows).

An additional finding of fatty infiltration and atrophy of the right hamstring muscles was present, as well as macrodactyly of the third digit of the left hand. Vascular findings, including trifurcation of the portal vein and a left-sided Superior Vena Cava, were also documented.

Finally, there was epithelial overgrowth with a lobular, irregular outer surface affecting the lateral skin of both distal thighs, consistent with epidermal naevi, as shown in **Figure 3** and **Figure 4**. Once again, no skeletal malformations were demonstrable.

2.3. CASE-3

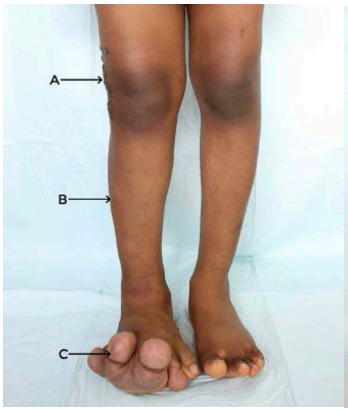
A male child of 9 years presented with a right lower limb larger than the left. The child was born at a government hospital. She was first seen at our facility at the age of nine years. The child was born by vaginal delivery. The mother was an antenatal clinic attendant and took only routine drugs. The antenatal period and pregnancy were uneventful.

During her pregnancy, the mother attended the antenatal clinic at the hospital, and no abnormalities were detected during her serial ultrasound examinations. At birth, the baby weighed 2.9 kg, and the father was 48 years old while the mother was 30. The father works as a mason, and the mother works as a seamstress. There is no history of consanguinity. The mother did not consume alcohol or tobacco during her pregnancy. The baby did not experience any delayed milestones during growth.

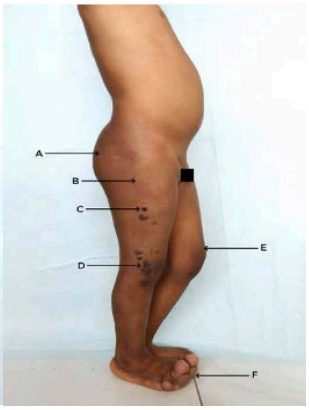
During the physical examination, it was observed that the patient had an enlarged right lower limb, extending from the thigh to the foot (**Image 3(a)** and **Image 3(b)**). All toes on the right foot were also enlarged compared to the left (**Image 3(a)**, **Image 3(d)**, and **Image 3(e)**). Clinically, the foot swelling involved

both skeletal and soft tissue components. In addition, there were large, hyperpigmented, flat patches on the right thigh and back of the neck (Image 3(b)). According to the patient's mother, these patches appeared red at birth. A raised, hyperpigmented macular naevus was also observed on the thigh (Image 3(b)). The left limb was visibly longer than the right as seen in Image 3(c).

Additionally, a large red patch extended from the hip to the leg (Image 3(b)). The patient exhibited dilated and tortuous superficial veins in the right lower limb. Auscultation of the heart did not reveal any murmurs; heart sounds were normal, and abdominal examination was unremarkable.



(a)



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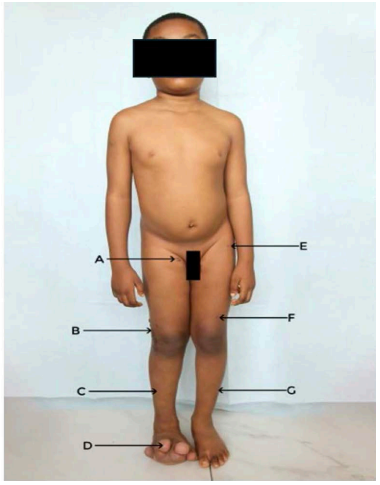

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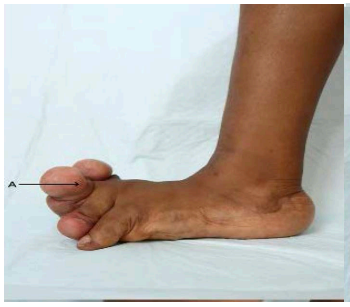

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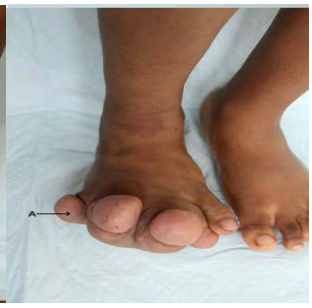


(e)

(f)

Image 3. (a): Raised naevi on the right lower limb. B: Port wine stain on the right lower limb. C: Grossly enlarged right foot; (b): A: Enlarged right buttock. B: Port wine stain. C and D: Naevi. F: Enlarged right foot; (c): A and B: naevi. C: Port wine stain. D: Enlarged right foot; (d) and (e): A: Enlarged right foot; (f): Postoperative picture after a ray amputation of the 2nd and third toes.

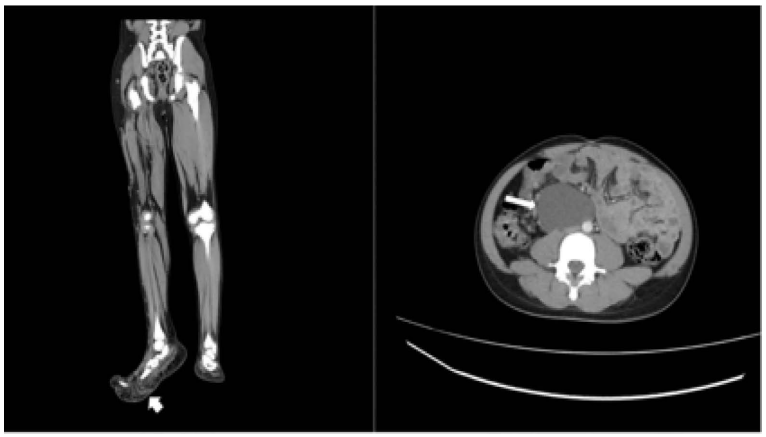


Figure 5. Coronal reformatted computed tomography of the lower limbs and axial image of the abdomen demonstrated fatty overgrowth of the subcutaneous tissues of the right foot (short arrow). A well circumscribed cystic retroperitoneal lesion is seen in the lower abdominal region (long arrow).

Computed Tomography demonstrated a well-defined cystic para-aortic mass measuring (6.0 × 5.4 × 4.0) cm (**Figure 5**). Also noted is enlargement of the right foot due to expansion of the subcutaneous tissues in the right leg and foot, with several ectatic veins in the subcutis of the right leg (**Figure 5**). Again, several foci of epidermal overgrowth in the lateral aspects of the leg in keeping with epidermal naevi.

The patient had debulking surgery of the right foot with amputation of the 3rd and 4th toes with satisfactory results (**Image 3(f)**). He was able to wear similarly sized shoes on both feet after the surgery, and his parents were happy with the result.

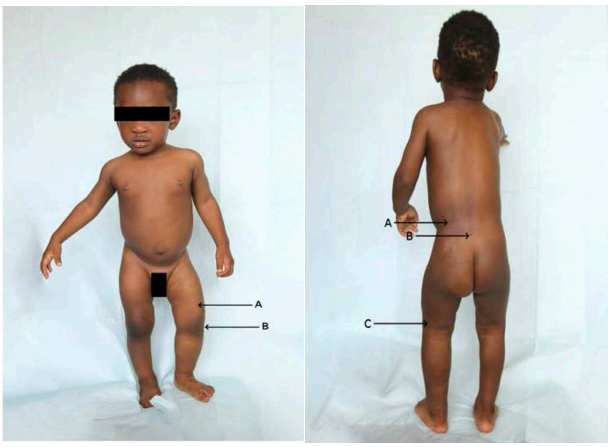
2.4. CASE-4

A male child of 14 months presented with a left lower limb larger than the right. The child was born at a government hospital. She was first seen at our facility at age 13 months.

The child was born through spontaneous vaginal delivery (SVD). The mother attended the antenatal clinic and took only routine medication. The mother did not consume alcohol or tobacco during pregnancy, and there were no developmental delays during growth. The antenatal period and pregnancy were uneventful, and the baby's birth weight was 3.3 kg. At birth, the father was 33 years old, and the mother was 32 years old. The father is a teacher, and the mother is a beauty therapist. There is no history of consanguinity between the parents. Additionally, the mother received a dose of the COVID-19 vaccination during the fourth or fifth month of pregnancy.

The mother attended an antenatal clinic, and serial ultrasounds showed no abnormalities. At three days of age, an ultrasound was performed, and no issues were found.

During the physical examination, it was noticed that the left lower limb was larger than the left with some naevi and some red patches on the limb and trunk suggestive of port wine stains (**Image 4(a)**, **Image 4(b)** and **Image 4(d)**). There were epidermal naevi on the lateral aspect of the left lower limb and lower back as seen in **Image 4(c)** and **Image 4(e)**. The left buttock was also larger than the right. Auscultation of the heart did not reveal any murmur, and the heart sounds were normal. Abdominal examination was unremarkable.



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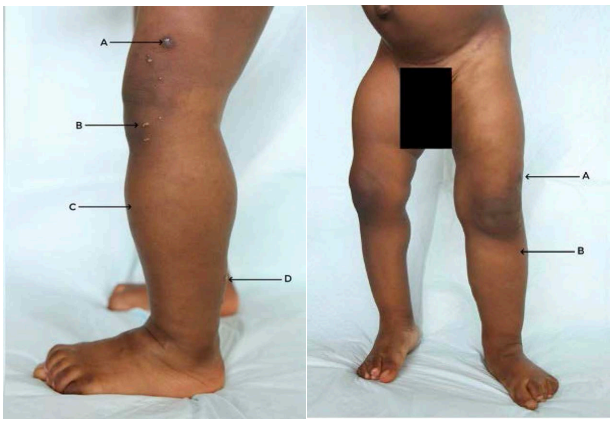

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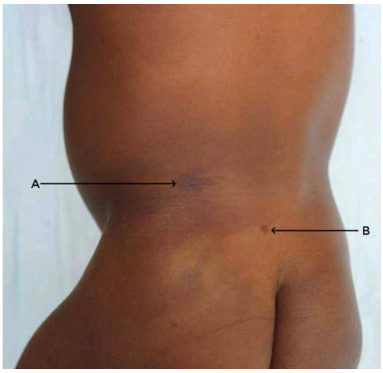

(e)

Image 4. (a) (b) and (c): A and D Naevi. B Port wine stain. C Enlarged left lower limb; (d) and (e): A and B naevi.

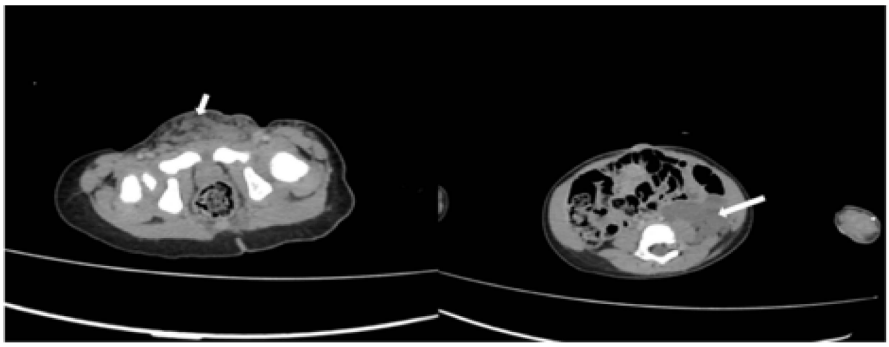

Figure 6. Contrast enhanced axial CT scans of the abdomen and pelvis showing fatty overgrowth of the mons pubis (short arrow) with numerous vessels within. A septated cystic left retroperitoneal mass is seen in the left iliac fossa displacing the descending colon anteriorly (long arrow).

Computed Tomography (CT) scan of his abdomen and lower limbs demonstrated a well-defined (5.7 × 3.4 × 2.6) cm cystic mass in the retroperitoneal region of the left iliac fossa, as shown in **Figure 6**. A similar but smaller lesion is observed in the popliteal fossa, both indicative of lymphatic malformation. Additionally, fatty overgrowth with tortuous veins was noted in the child's mon pubis, left gluteal fat, and subcutaneous tissues of the left leg (**Figure 6**).

3. Discussion

CLOVES syndrome is a recently identified rare condition, with fewer than 200 cases reported worldwide [1] [2] [10]. The estimated incidence is less than 1 in 1,000,000. There is no gender preference, and the syndrome has been observed across all races and ethnic groups. It is a congenital disorder with prenatal onset; therefore, it manifests either at birth or in early childhood [11]-[13]. The diagnosis of CLOVES syndrome remains primarily clinical, based on the presence of cutaneous, vascular, truncal, spinal, and limb anomalies, and requires differentiation, especially from Proteus syndrome [10]. Some also argue that diagnosis should not rely solely on clinical examination but should include radiologic imaging studies

and genetic analysis, because, due to the rarity, complexity, and significant overlap among PROS disorders, a definitive diagnosis of CLOVES syndrome may only be confirmed through the detection of the specific PIK3CA mutation [11]. Diagnostic criteria for PIK3CA-related overgrowth spectrum (PROS) disorders include the presence of somatic PIK3CA mutations, congenital or early disease onset, overgrowth of tissue that appears sporadic and mosaic (patchy, irregular), and features of ≥2 of the following: overgrowth of adipose, muscle, nerve, or skeletal tissue; vascular malformations (capillary, venous, arteriovenous malformation, lymphatic); and epidermal nevi. Some argue that, in the context where a PIK3CA mutation is not identified, the diagnosis should be considered presumptive [14]-[16]. The features presented in the cases align with the diagnostic criteria above.

Genetic analysis for the patients in this case series was difficult because, at the time of publication, there was no laboratory in that country capable of performing such highly specialised genetic tests. This is especially true since the PIK3CA gene is not solely responsible for CLOVES syndrome but also for other PIK3CA-related overgrowth spectrum (PROS) disorders. More specialised tests will be necessary to distinguish between these disorders. Blood samples from the patients and their parents were collected and sent abroad for genetic testing with assistance from a charitable organisation. However, after several months, they requested tissue samples to precisely identify CLOVES syndrome, which was no longer feasible due to factors like patient consent and the patients' geographical locations. Nevertheless, the clinical features of all patients strongly fulfilled the criteria for CLOVES syndrome as the primary diagnosis. These patients were distinguished from other overgrowth syndromes by the characteristic presence of epidermal naevi and skeletal involvement, which are not seen in other PIK3CA-related overgrowth spectrum disorders.

The differential diagnoses of overgrowth syndromes are numerous, including fibroadipose overgrowth (FAO), Proteus syndrome, Klippel-Trenaunay syndrome, and Sturge-Weber syndrome. A definitive diagnosis is therefore established through genetic testing. For example, both CLOVES syndrome and FAO harbour mutations in the PIK3CA gene; however, a mutation in the C2 domain of the PIK3CA gene can, to a greater extent, differentiate CLOVES syndrome from FAO. Conversely, Proteus syndrome and lipodystrophy syndrome-hypoglycaemia are characterised by activating somatic mutations of the AKT1 and AKT2 genes, respectively [13] [15].

The frequency of vascular malformations in PROS disorders varies between 42% and 60%. Vascular malformations tend to overlie the lipomatous masses on the trunk, but they may extend to areas of skeletal overgrowth on the extremities as well [11] [12]. The frequency of epidermal nevi in PROS disorders ranges from 11.4% to 46.6%. Epidermal nevus (particularly linear keratinocytic nevus) is a common, albeit not universal, feature in CLOVES syndrome [11] [12].

Skeletal malformations encompass varying degrees of scoliosis and asymmetric enlargement of skeletal structures in the extremities. Scoliosis may be congenital

or develop during childhood, sometimes due to lower limb asymmetry. Bony overgrowth most commonly affects the lower extremities, with the distal segment involved more frequently than the proximal segment [11] [13] [17].

All our patients had progressive, complex, and mixed primarily truncal vascular malformations, which are characteristic of CLOVES syndrome [3]. The most commonly described musculoskeletal anomaly is congenital overgrowth of the hands and feet that grows proportionately with the patient [1] [2] [18]. This was also present in all of our patients. In our patients, the right lower limb was always involved along with the left hand. Dysregulated adipose tissue growth, presenting as a truncal mass, is another key feature of CLOVES [3] and was also observed in our patients. Macrodactyly, typically affecting the third digit [1] [17] [19], was seen in one patient.

Although magnetic resonance imaging (MRI) would be ideal for soft tissue and vascular assessment, computed tomography was chosen due to the reduced financial burden on patients, as MRI is more expensive and includes the cost of anaesthesia required for children, despite its inherent radiation exposure risk.

Prenatal imaging by high-resolution ultrasound complemented with fetal MRI can help characterise CLOVE syndrome in utero, although its distinguishing feature may be difficult to recognise. Further mutation analysis on genomic DNA using amniotic fluid can also detect any known mutations in the PIK3CA gene. This was explored in a study done by Emrick *et al.* [20]. An uneventful antenatal period and a normal ultrasound scan preceded the birth of all our patients. This could be due to the use of low-resolution ultrasound scans, no use of fetal MRI and the absence of a team of maternal-fetal medicine specialists, neonatologists, fetal surgeons, geneticists and other pediatric subspecialists.

Abnormality was detected at birth for all our patients; however, most were reported late for clinical evaluation and management. The earliest presentation to the unit was at 11 months of age. This is attributable to the extremely rare nature of the syndrome. However, it is generally accepted that the earlier a child with CLOVES syndrome is diagnosed and treatment is started, the better the general outcome.

The management of CLOVES syndrome is quite challenging, and consensus management guidelines for CLOVES syndrome are poorly described in the literature. Conventional therapeutic approaches, such as sclero-embolisation or surgical debulking procedures, are rarely curative and are not devoid of risks of complications and recurrence. They, however, can help reduce the size or prevent further asymmetric growth of the affected limb. Large hands and feet can be surgically debulked and, in some cases, digits amputated. The available options can be grouped into procedures that limit ongoing growth, reduce the size of affected digits or limbs, correct deviation or amputation.

Epiphysiodesis can be used to control the growth of individual digits. This can be achieved by burring or drilling, epiphyseal plate resection, or physeal stapling in larger bones. This procedure is usually performed when the digit reaches the length of the corresponding digit in the parent of the same gender as the child

[21].

The third patient in the series underwent a ray amputation of the 2nd and 3rd toes and surgical debulking of the foot to create some foot symmetry and enable him to wear the same-sized shoes. Both the patient and his parents are happy with the results, and he currently wears the same shoe size on both feet.

The second patient is being evaluated for a growth plate ablation (epiphysiodesis) of her enlarged digit when it reaches approximately the same size as her mother's. The goal is to halt the growth of the digit once it attains its full adult size, which is determined by the size of the same digit in the same-sex parent.

For now, the other patients do not require any urgent surgical procedures, but they are monitored regularly. They may be offered surgical debulking or sclerosis-embolic procedures when necessary.

Recently, Alpelisib has shown promise as a targeted therapy in patients with overgrowth syndromes, with or without vascular malformations, caused by overactivity of PI3K. Research published in 2018 by Canaud's research group demonstrated impressive results in a group of 19 patients with CLOVES and other PROS conditions. Alpelisib is a direct and specific inhibitor of the p110α subunit of PI3K, which is strongly and permanently activated due to a gain-of-function mutation in PIK3CA. Using a selective inhibitor of p110α, located at the top of the PI3K/AKT/mTOR signalling pathway, provides a direct effect on affected tissues while reducing the risk of off-target effects. In both children and adult patients, Alpelisib was not associated with severe adverse events. So far, Alpelisib has proven to be a safe drug; however, further studies are needed to optimise treatment outcomes without adverse effects [22]-[24]. The main goal of management remains improving the quality of life [13].

A detailed clinical examination and radiological imaging studies, such as skeletal X-rays, abdominal ultrasound (USG), Doppler USG, cranial and spinal X-rays, Computed Tomography (CT), and Magnetic Resonance Imaging (MRI), are imperative for delineating the extent of deformities and their management, as well as assessing long-term prognosis. However, severe scoliosis, large truncal mass, paraspinal high-flow lesions with spinal cord ischemia, lymphatic malformations, cutaneous vascular malformations, orthopaedic problems of feet and hands, and central phlebectasia/thromboembolism in CLOVES syndrome need active or prophylactic surgical/ medical interventions to improve quality of life. These interventions prevent worsened morbidity and complications arising from vascular anomalies [8] [10] [11]. The mTOR inhibitors (sirolimus), PI3K inhibitors (copanlisib and other isoforms), and BYL719 appear to be attractive therapeutic possibilities for treating complicated vascular or other overgrowth anomalies in experimental and early clinical trials. However, excessive scarring after surgery in these individuals remains a concern.

4. Conclusion

CLOVES syndrome is a rare disease; however, it has certain distinct features which should arouse clinical curiosity. Management remains quite challenging

due to the paucity of guidelines in the literature. Alpelisib is a safe drug, but further studies are still needed. Largely, decisions concerning management are multidisciplinary and focus on the improvement of the quality of life.

Informed Consent

Informed consent was obtained from the parents of these patients to publish this case report.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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