# Cloves Syndrome: A Rare Disorder of Overgrowth with Unusual Features – An Uncommon Phenotype?

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## Abstract

CLOVES syndrome characterized by *C*ongenital *L*ipomatous *O*vergrowth, *V*ascular malformations, *E*pidermal nevi, and *S*keletal anomalies is a recently described sporadic syndrome from postzygotic activating mutations in *PIK3CA*. This 3-year-old boy, born to nonconsanguineous and healthy parents, had epidermal verrucous nevus, lower limb length discrepancy and bilateral genuvalgum, anterior abdominal wall lipomatous mass, central beaking of L2 and L3, and fibrous dysplasia of the left frontal bone. Ocular and dental abnormalities (ptosis, esotropia, delayed canine eruption, dental hypoplasia), ipsilateral asymmetrical deformity of skull, and large left cerebral hemisphere with mild ipsilateral ventriculomegaly were peculiar to him denoting an uncommon phenotype. The parents did not consent for magnetic resonance imaging and genetic studies because of financial constraints. The CLOVES syndrome has emerged as an uncommon yet distinct clinical entity with some phenotypic variations. Its diagnosis is usually from cutaneous, truncal, spinal, and foot anomalies in clinical and radioimaging studies. Proteus syndrome remains the major differential.

**Keywords:** *Congenital asymmetric overgrowth, congenital lipomatous hamartoma, lipoma, lymphovascular malformation, PIK3CA-related overgrowth spectrum, Proteus syndrome*

## Introduction

CLOVE (S) syndrome is a recently described overgrowth syndrome, and the acronym CLOVES includes a constellation of Congenital Lipomatous Overgrowth due to dysregulated adipose tissue, Vascular malformations (typically truncal), Epidermal nevi, and Scoliosis and/or Skeletal abnormalities such as enlarged bony structure (typically of the legs) without progressive or distorting bony overgrowth.[1,2] The venous malformations as superficial phlebectasia and capillary malformations are present in association with lipomatous masses in truncal regions and may or may not accompany skeletal overgrowth when involving extremities.[3] Central nervous system (CNS) manifestations include polymicrogyria, noncontiguous abnormalities of the gray and white matter, a four-layered cortex, ventriculomegaly, hemimegalencephaly, dysgenesis of the corpus callosum, neuronal migration defects and consequent seizures, tethered spinal cord, and neural tube defects.[4,5] Some degree of neuorologic impairment has been reported in almost 50% cases in a large series.[5] Visceral anomalies occur in the form of renal agenesis/hypoplasia, Wilms tumor, splenic lesions, and extensive deep retroperitoneal and pelvic fatty and lymphatic malformation.[3,6,7] However, no intellectual, cardiovascular, gastrointestinal, or hematopoietic abnormalities have been attributed to CLOVES syndrome.[3] The deformities are present at birth, and most acral deformities, often symmetrical, increase with growth but are not rapidly progressive. The pathogenesis of CLOVES syndrome has been attributed to somatic (postzygotic) mutations in *PIK3CA* gene mapped to chromosome 3q26.32.[8] The *PIK3CA* gene is an upstream regulator of the Akt-mTOR cell signaling pathway and its activation mutations and of Akt cell signalling axis is in the form of cell proliferation and resultant lymphatic and other vascular malformation/overgrowth syndromes clubbed under PIK3CA-related overgrowth spectrum (PROS). We report a case of extremely rare CLOVES syndrome of which only fewer than 150 cases have been reported worldwide.[9]



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## Case Report

This 3-year-old boy had pigmented skin lesions over left half of the body since birth, skull deformity, and progressive enlarging abdomen. He was the first child born after an uneventful gestation/pregnancy to otherwise healthy, nonconsanguineous parents. His family and medical history was unremarkable. The child had normal growth and mental development milestones and was immunized for his age. The child was playful and showed a linear verrucous epidermal nevus over the left side of the body extending from the neck, axilla and arm, dorsum of the hand, and anterior surface of the thigh [Figure 1a and b]. He had an asymmetrical deformity of the left side of the head, ptosis and esotropia [Figure 1c], and an ipsilateral abdominal wall mass of soft consistency [Figure 1d]. He had bilateral genu valgum, and his left lower limb was longer by 2 cm than the right one but showed no deformity of hands and feet.

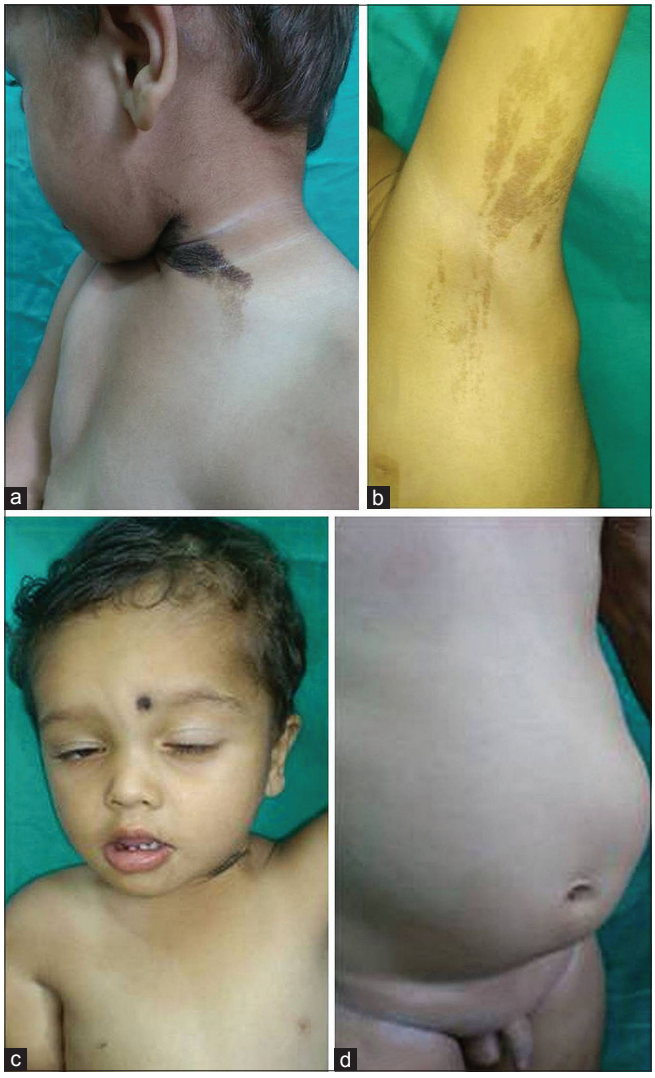


**Figure 1: (a) Verrucous epidermal nevus over left side of neck. (b) Verrucous epidermal nevus extending over left axilla and arm. Similar lesions were also present over dorsum of left hand and anterior left thigh. (c) Left ptosis and asymmetric skull. (d) Lipomatous mass of anterior abdominal wall. No overlying phlebectasia is seen**

He had delayed canine eruption and dental hypoplasia. A fine needle aspiration cytology from abdominal wall mass showed features consistent with lipoma. Spine X-rays revealed central beaking of L2 and L3 vertebrae. Ultrasonography (USG) and computed tomography (CT) of abdomen showed lipomatous mass of the anterior abdominal wall and no visceral anomaly [Figure 2a]. USG Doppler of the anterior abdominal wall mass showed no vascular malformation. CT of head showed ground glass appearance (probable fibrous dysplasia) of the left frontal bone [Figure 2b] and large volume (megalencephaly) of the left cerebral hemisphere [Figure 2c] with mild ipsilateral ventriculomegaly [Figure 2d]. However, due to affordability concerns, the parents did not consent for biopsy, magnetic resonance imaging (MRI), and genetic studies. They were counseled about the nature of disorder but did not turn up for follow-up.

## Discussion

Except for obvious vascular and hands/feet anomalies, this child displayed characteristic features of a parietal wall lipomatous mass, linear epidermal nevus, limb length discrepancy, and CNS anomalies suggestive of CLOVES syndrome. A review of cases suggests that the deformities are present prenatally, at birth or puberty in a few and get accentuated with growth.[10] The major deformities invariably include deposition of adipose tissue in all body regions and tissue spaces including face, scrotum, paraspinal musculature, epidural spaces, mediastinum, and pleura. The prominent upper limb deformities include symmetrical overgrowth of digit(s), laxity of collateral ligaments of metacarpophalangeal and interphalangeal joints, and broad spade like hands with ulnar deviation

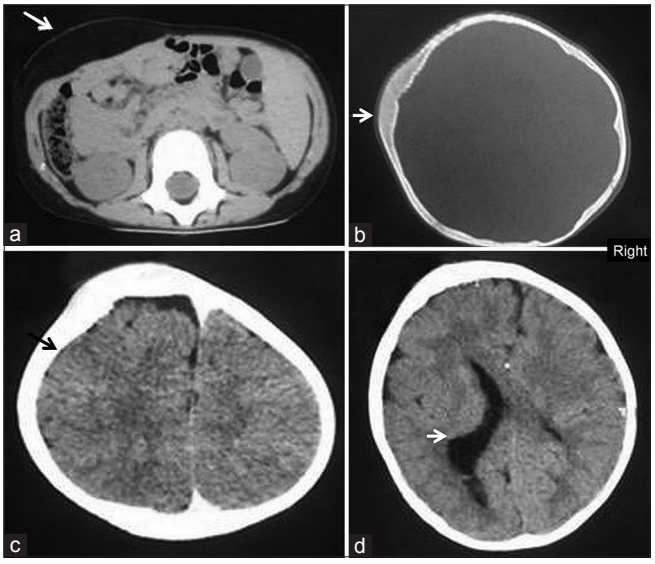


**Figure 2: (a) Anterior abdominal wall lipomatous mass in computed tomography abdomen. (b) Fibrous dysplasia (?) of left frontal bone in computed tomography head. (c) Large cerebral volume of left cerebral hemisphere in computed tomography brain. (d) Left ventriculomegaly in computed tomography brain**

of digits.[2,5] Whereas the lower limbs show soft tissue overgrowth of feet and broad forefoot, large bulbous toes, wide first toe web (sandal gap), plantar creases, lipomatous masses on plantar and dorsal feet, and wide gaps between metatarsal heads in 50% of 18 cases reviewed.[1-3,5] All patients show lymphatic, venous and capillary (low-flow), or arteriovenous malformations (port-wine stains) with or without arteriovenous fistulae (high-flow vascular anomalies) that usually become evident during childhood.[3,7] Various venous, lymphatic lymphaticovenous, and fast-flow vascular anomalies alone or adjacent to lipomatous masses or a cutaneous birthmark are most common and seen over trunk (spinal-paraspinal) and limbs, whereas lymphatic and venous malformation can involve all the affected regions. No cutaneous vascular anomaly was observed in our patient, and it is possible that deep vascular malformations in our patient remained unidentified for want of MRI studies. However, it is distinctly possible that some patients rather than all the signs have a combination of anomalies that may be subtle and do not manifest simultaneously but develop as the syndrome evolves.[5,10] Although strabismus consequent from overgrowth of face and premature growth of teeth abnormalities can occur, auditory anomalies remain unreported.[2,5,11] Interestingly, ocular and dental abnormalities (ptosis, esotropia, delayed canine eruption, dental hypoplasia), ipsilateral asymmetrical deformity of skull, and large left cerebral hemisphere with mild ipsilateral ventriculomegaly in our patient were peculiar and perhaps denote an uncommon phenotype. However, it remains conjectural for now for paucity of cases and can be resolved after long-term follow-up of such cases in view of variable and broad phenotypic spectrum of the disorder in general.[12]

The diagnosis of CLOVES syndrome remains clinical from cutaneous, vascular, truncal, spinal, and limb anomalies and needs differentiation particularly from Proteus syndrome. However, the differentiation made on the basis of lack of visceral involvement and skeletal overgrowth being gradual in increasing volume of the affected soft tissues in CLOVES syndrome referred as "ballooning" overgrowth compared with involvement and rapidly deforming and "distorting" bony overgrowth that is relentlessly progressive and out of proportion to somatic growth in Proteus syndrome remains contested.[3,7] While demonstrating mosaic activation mutation of *PIK3CA* gene in affected tissue samples, urine, or tumor cells is essential for confirmation of clinical diagnosis or differentiating *PIK3CA* gene mutation-associated lymphatic and other vascular malformation/overgrowth syndromes or PROS with many overlapping clinical features [Table 1],[13-15] we considered the diagnosis of CLOVES syndrome in our patient based on diagnostic criteria by Keppler-Noreuil *et al.* [Table 2].[15]

**Table 1: Common differentials of overgrowth syndromes with overlapping features**

| Features | CLOVES syndrome* | Proteus syndrome | Klippel-Trenaunay syndrome | McCune-Albright syndrome |
|---|---|---|---|---|
| Presentation | **Overgrowth features** mostly present at birth and are asymmetric, disproportionate, and less progressive | Overgrowth features mostly present at 6-18 months of life and become severe with advancing age | Capillary hemangioma or port-wine stain presents at birth, during early infancy, or childhood. Hypertrophy of limb may be appreciated at birth, but usually progresses during the first years of life | Gonadotropin-independent precocious puberty (breast development, genital maturation with or without pubic hair, macroorchidism, increased height) |
| Cutaneous | Lesions of phlebectasia, lymphatic vesicles, **epidermal nevi** | Soft tissue overgrowth, cerebriform overgrowth over palms and soles | Lesions of vascular malformation port-wine stain, marginal venous system. | Café-au-lait macules (often segmental without crossing midline) |
| Acral anomalies | Macrodactyly, polydactyly, syndactyly, bulbous toes, and sandal gap. Present at birth and slowly increase with growth | Asymmetric and disproportionate acral overgrowth, macrodactyly | Macrodactyly, polydactyly, syndactyly | Large hands and feet of acromegaly |
| Skeletal anomalies | **Asymmetric lower limb**, scoliosis, pectum excavatum, laxity of collateral ligaments of MCP and IP joints | Scoliosis lower limb asymmetry, soft and bone tissue hypertrophy | Soft and bone tissue hypertrophy, lower limb asymmetry | Polyostotic fibrous dysplasia (as pathologic fractures), gait anomalies, visible bony deformities (including abnormal skull bone growths), bone pains, painful joint stiffness |

*Contd...*

**Table 1: Contd...**

| Features | CLOVES syndrome* | Proteus syndrome | Klippel-Trenaunay syndrome | McCune-Albright syndrome |
|---|---|---|---|---|
| Fat malformations | **Congenital fat hamartoma of the trunk (main)**, face, limbs, and scrotum. This may extend to retroperitoneum, epidural space, thoracic cavity. or mediastinum | Acquired fat hypertrophy | Acquired extrafascial/ subcutaneous fat overgrowth | Not reported |
| Vascular malformations | Phlebectasia, low-flow and high-flow vascular anomalies, CM, VM, LM, spinal AVM | CM, VM, LM | CM (port-wine stain), VM (marginal venous system), LM affecting lower limb in most cases, no high-flow component | Not reported |
| Neural anomalies | **Hemi-megalencephaly,** seizures, corpus callosum dysgenesis, tethered spinal cord, neural tube defects, syringomelia, and neuorologic impairment | Hemi-megalencephaly, developmental delay | Hemi-megalencephaly, seizures, developmental delay, spina bifida | Pituitary tumors |
| Visceral/ endocrine anomalies | Renal agenesis/hypoplasia, Wilms tumor, spleen lesions, **ocular and dental anomalies (rare)** | Hypertrophy of liver, spleen, thymus, ptosis | Lymph node hyper-/ hypoplasia | Thyroid tumors, gigantism and acromegaly, Cushing syndrome |
| Complications | Scoliosis, hemoptysis, cardiac failure from AVM, pulmonary embolism, gastrointestinal bleeding/obstruction | Hyperostosis, developmental delay, benign and malignant tumors, restrictive lung functions, pulmonary embolism, DVT | Developmental delay, DIC, pulmonary thromboembolism, Kassabach-Merrit syndrome, superficial thrombophlebitis | Hyperthyroidism (tachycardia, arrythemias, hypertension, hyperthermia, tremors, sleeplessness, weight loss, failure to thrive), hypophosphatemia (hypophosphatemic rickets), hypogonadotropic hypogonadism |
| Mutations | Mosaic activation mutation in *PIK3CA* gene | Mosaic activation mutation in *AKT-1* gene | Mosaic activation mutation in *PIK3CA* gene | Mutation in the *GNAS* gene encoding guanine nucleotide-binding protein or G-protein resulting in constitutively activated adenylate cyclase enzyme leading to overproduction of several hormones resulting in abnormal bone growth and other signs and symptoms of the syndrome |

CM=Capillary malformation; VM=Venous malformation; LM=Lymphatic malformation; AVM=Arteriovenous malformation; MCP=Metacarpophalangeal; IP=Interphalangeal; GI=Gastrointestinal; DIC=Disseminated intravascular coagulopathy; DVT=Deep venous thrombosis. Modified after Martinez-Lopez A, *et al*.[12], *The clinical feature of CLOVES syndrome noted here in bold were present in the index case

A detailed clinical examination and radioimaging studies such as skeletal X-rays, USG abdomen, Doppler USG, cranial and spinal X-rays, CT, and MRI are imperative for delineating the extent of deformities, their management, and assessing long-term prognosis.[13,16,17] However, severe scoliosis, large truncal mass, paraspinal high-flow lesions with spinal cord ischemia, lymphatic malformations, cutaneous vascular malformations, orthopedic problems of feet and hands, and central phlebectasia/thromboembolism in CLOVES syndrome need active or prophylactic surgical/ medical interventions to improve quality of life. This will also prevent cutaneous and visceral morbidities, neurological deficit, pain, breathing difficulties, and possible complications such as hemoptysis, gastrointestinal bleeding or obstruction, and pulmonary embolism arising from vascular anomalies.[7,9,11,18] mTOR inhibitors (sirolimus), PI3K inhibitors (copanlisib and other isoforms), and BYL719 in the treatment of complicated vascular or other overgrowth anomalies in experimental and early clinical trials appear attractive therapeutic possibilities.[19-21] However, excessive scarring after surgery in these individuals remains a concern.[22] This syndrome can also be detected during the prenatal period from the presence of truncal mass and other body and acral anomalies and mosaic PIK3CA mutation in cultured amniocytes.[23] Overall, the nonprogressive distorting nature

**Table 2: Clinical diagnostic criteria for PROS[13,15]**

| Criteria | Features* | Remarks |
|---|---|---|
| Required | Presence of somatic PIK3CA mutation | If no mutation identified, then consider a presumptive diagnosis of PROS |
| | **Congenital or early childhood onset** | - |
| | Overgrowth sporadic and mosaic | - |
| Spectrum (require two or more features) | **Overgrowth: adipose,** muscle, nerve, skeletal | Typically progressive. |
| | Vascular malformations: capillary, venous, lymphatic, arteriovenous malformations | Can manifest as scoliosis, limb overgrowth, CNS anomalies (hydrocephalus, cerebellar tonsillar ectopia, Chiari, megalencephaly, mega corpus callosum), regional lipomatous undergrowth with overgrowth, infiltrating lipomatosis, Wilms tumor/ovarian cystadenoma. |
| | **Epidermal nevus** | |
| | **Hemi-megalencephaly** | |
| Isolated features | Large isolated lymphatic malformation | - |
| | Isolated macrodactyly or overgrown splayed feet/hands, **overgrown limbs** | - |
| | **Truncal adipose overgrowth** | - |
| | Dysplastic megalencephaly/focal cortical | - |
| | **Epidermal nevus** | - |
| | Seborrheic keratoses | - |
| | Benign lichenoids keratoses | - |

PROS=PIK3CA-related overgrowth spectrum. *The clinical feature of CLOVES syndrome noted here in bold were present in the index case

of CLOVES syndrome can be explained while counseling the parents.

## *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.

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## *Conflicts of interest*

There are no conflicts of interest.

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