



Case Report

CLOVES Syndrome: A Rare Disorder of Growth

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ABSTRACT

Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevus and Skeletal abnormalities (CLOVES) syndrome is characterised by congenital lipomatous overgrowth, vascular malformations, epidermal nevi and skeletal anomalies without progressive or distorting bony overgrowth. A 10-month-old boy, born to non-consanguineous and healthy parents, presented with congenital lipomatosis of the left side of face and verrucous epidermal nevus extending from the left pre- and post-auricular area, neck and upper left shoulder. He also had sandal gap deformity in both feet between 1st and 2nd toe. This case is being reported on account of its rarity, as till now, <150 cases has been reported worldwide.

Keywords: CLOVES syndrome, Epidermal nevus, Vascular malformations, Bony overgrowth, Proteus syndrome

INTRODUCTION

Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevus and Skeletal abnormalities (CLOVES) syndrome, a relatively new overgrowth syndrome, is defined by the acronym CLOVES, which represents congenital lipomatous overgrowth, vascular anomalies, epidermal nevi and skeletal abnormalities.^[1] The pathogenesis is associated with somatic (postzygotic) mutations in the PIK3CA gene located on chromosome 3q26.32.^[2] CLOVES syndrome is exceptionally rare. The prevalence is fewer than one case per million individuals.^[3]

CASE REPORT

A 10-month-old boy, born to otherwise non-consanguineous and healthy parents, presented to the outpatient department of dermatology with swelling over left side of face and pigmented skin lesions over neck since birth. The child had normal developmental milestones and was immunised for his age. His family and medical history showed no notable abnormalities. On examination, we noticed an asymmetrical swelling over left side of face extending from parietal bone up to the angle of mandible [Figure 1a] and verrucous epidermal nevus extending from left pre- and post-auricular area, neck and upper left shoulder [Figure 1b]. Sandal gap deformity was present bilaterally between 1st and 2nd toe, along with bilateral hypertrophy of the second toe of the feet [Figure 1c]. No bony, visceral, ocular and dental anomalies were detected. X-rays of both feet revealed widening of web spaces between 1st and 2nd toe and enlarged metapahalenges [Figure 2]. X-ray of whole abdomen revealed no abnormality [Figure 3]. Contrast-enhanced computed tomography head showed large non-capsulated subcutaneous fat extending from the left parietal bone to angle of mandible with fatty infiltration of the left parotid gland, masseter, temporalis, buccinator, lateral and medial pterygoid muscles, intrinsic and extrinsic muscles of

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Figure 1: (a) Asymmetrical swelling over left side of face extending from parietal bone up to the angle of mandible, (b) verrucous epidermal nevus extending from left pre and post auricular area, neck and upper left shoulder and (c) sandal gap deformity between 1st and 2nd toe present bilaterally along with bilateral hypertrophy of the second toe of the feet.



Figure 2: X-rays of both feet (anteroposterior and lateral view) showing widening of web spaces between 1st and 2nd toe and enlarged metaphalanges.

left side of tongue muscle, hypertrophy of left mandible and left zygomatic arch [Figure 4]. Ultrasonography Doppler of the anterior abdominal wall mass showed no vascular malformation. Genetic workup was not done due to financial constraints and non-availability at our hospital.

DISCUSSION

CLOVES syndrome (OMIM number 612918) is a rare, sporadic and complex mosaic overgrowth syndrome. It is now classified under the umbrella of PIK3CA-Related

Overgrowth Spectrum (PROS) characterised by postzygotic activating somatic mutations in the PIK3CA gene, which is located on chromosome 3q26.32.^[4] It presents as congenital overgrowth of adipose tissue across various body regions and tissue spaces and unilateral or bilateral lipomatous masses, particularly prominent on the thoracic and abdominal walls.^[5] CLOVES syndrome is characterised by capillary malformation (including low-flow and geographic patterns), venous anomalies (such as superficial phlebectasia), lymphatic abnormalities (including macrocystic, microcystic or mixed presentations) and arteriovenous malformations.^[5]



Figure 3: X-ray of whole abdomen showing no abnormality.

Epidermal nevi is either congenital or develop in childhood and is usually found on the neck, abdomen, flank or limbs. Skeletal malformations in CLOVES syndrome often present as scoliosis and asymmetric enlargement of skeletal structures in the extremities. Scoliosis may be congenital or develop during childhood, possibly due to lower limb asymmetry.^[6] Other musculoskeletal manifestations include leg length discrepancy, genu recurvatum, polydactyly, syndactyly, splayed feet and sandal gap (widened first toe web).^[7]

The diagnosis of CLOVES syndrome remains clinical, but it must be differentiated from other PROS disorders, particularly from Proteus syndrome and Klippel-Trenaunay syndrome, as mentioned in Table 1.^[8,9]

We made the diagnosis of CLOVES syndrome in our patient based on diagnostic criteria by Keppler-Noreuil *et al.*, as mentioned in Table 2.^[8,9]

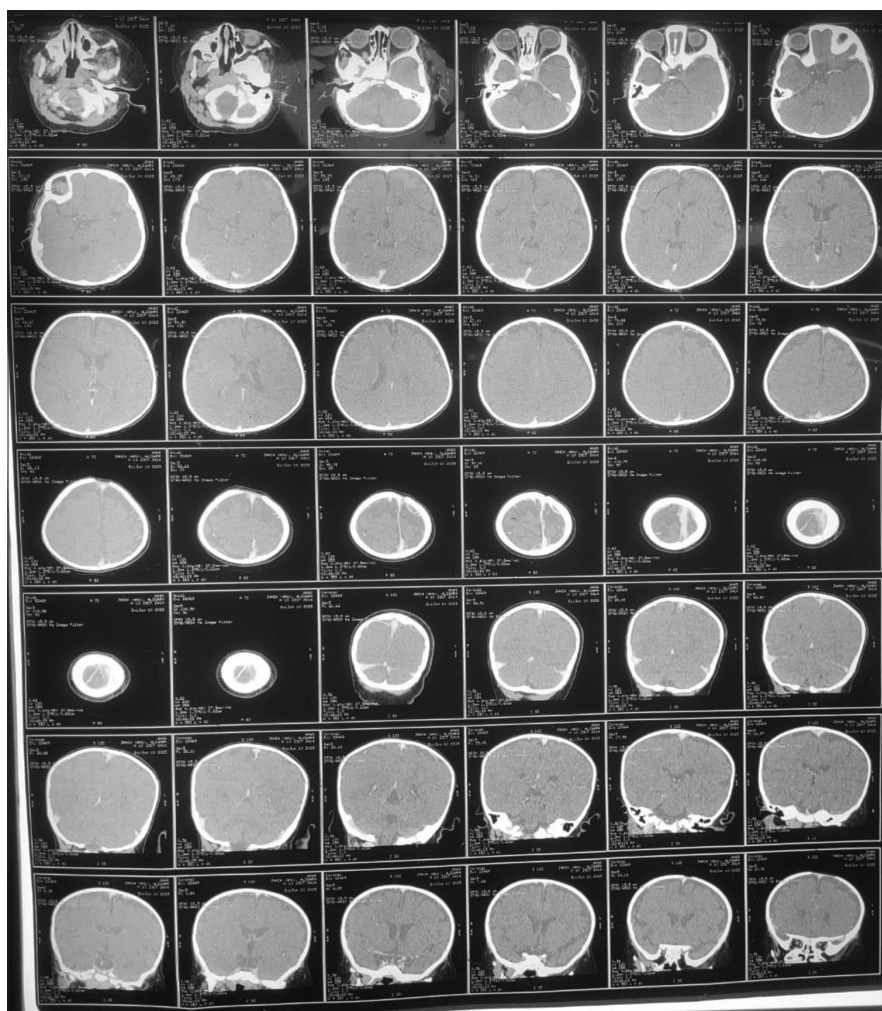


Figure 4: Contrast-enhanced computed tomography head showing large non-capsulated subcutaneous fat extending from left parietal bone to angle of mandible with fatty infiltration of left parotid gland, masseter, temporalis, buccinator, lateral and medial pterygoid muscles, intrinsic and extrinsic muscles of the left side of tongue muscle, hypertrophied condylar process, hypertrophy of left mandible and left zygomatic arch.

Table 1: Differential diagnosis of PROS disorders.

Features	CLOVES syndrome	Proteus syndrome	Klippel-Trenaunay syndrome
Mutations	<i>PIK3CA</i> gene	<i>AKT-1</i> gene	<i>PIK3CA</i> gene
Presentation	Overgrowth features present at birth, asymmetric, disproportionate and less progressive	Overgrowth features seen at 6–18 months of life, become severe with advancing age	Capillary hemangioma or port-wine stain presents at birth, during early infancy, or childhood. Limb hypertrophy may be observed at birth, typically progressing further during the first years of life
Cutaneous	Phlebectasia, epidermal nevi	Soft-tissue overgrowth, cerebriiform overgrowth over palms and soles	Vascular malformation, port-wine stain
Fat malformations	Congenital fat hamartoma can affect the trunk, face, limbs and scrotum, and may extend into the retroperitoneum, epidural space, thoracic cavity, or mediastinum	Acquired fat hypertrophy	Acquired extrafascial/subcutaneous fat overgrowth
Vascular malformations	Phlebectasia, low-flow and high-flow vascular anomalies, CM, VM, LM and spinal AVM	CM, VM and LM	CM (port-wine stain), VM (marginal venous system), LM affecting lower limb in most cases and no high-flow component
Skeletal anomalies	Asymmetric lower limb, scoliosis and pectum excavatum	Scoliosis, lower limb asymmetry, soft and bone tissue hypertrophy	Soft and bone tissue hypertrophy, lower limb asymmetry
Acral anomalies	Macrodactyly, polydactyly, syndactyly and sandal gap . Present at birth and slowly increase with growth	Asymmetric and disproportionate acral overgrowth, Macrodactyly	Macrodactyly, polydactyly and syndactyly
Neural anomalies	Hemi-megalencephaly, seizures and corpus callosum dysgenesis	Hemi-megalencephaly, developmental delay	Hemi-megalencephaly, seizures, developmental delay and spina bifida
Complications	Scoliosis, haemoptysis, cardiac failure from AVM, pulmonary embolism, gastrointestinal bleeding/obstruction	Hyperostosis, developmental delay, benign and malignant tumours, restrictive lung functions, pulmonary embolism, DVT	Developmental delay, DIC, pulmonary thromboembolism, Kassabach–Merritt syndrome and superficial thrombophlebitis

CM: Capillary malformation, VM: Venous malformation, LM: Lymphatic malformation, AVM: Arteriovenous malformation, DIC: Disseminated intravascular coagulopathy, DVT: Deep venous thrombosis. Modified after Martinez-Lopez A, et al.^[9] CLOVES: Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevus and Skeletal abnormalities. The clinical feature of CLOVES syndrome noted here in bold were present in the index case.

Table 2: Clinical diagnostic criteria for PROS.

Criteria	Features	Remarks
Required	Presence of somatic <i>PIK3CA</i> mutation Congenital or early childhood onset Overgrowth sporadic and mosaic	If no mutation identified, then consider a presumptive diagnosis of PROS - -
Spectrum (require two or more features)	Overgrowth: Adipose, muscle, nerve and skeletal Vascular malformations: capillary, venous, lymphatic, arteriovenous malformations Epidermal nevus Hemi-megalencephaly	Typically progressive. 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 tumour/ovarian cystadenoma
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 lichenoides keratoses	- - - - - -

PROS: *PIK3CA*-related overgrowth spectrum, CNS: Central nervous system

Managing CLOVES syndrome requires a comprehensive, multidisciplinary approach personalised to each patient's specific needs. Treatment strategies include surgical debulking for lipomatous overgrowths, sclerotherapy and embolisation for vascular malformations, pulse-dye lasers for capillary malformations and epiphysiodesis for limb length discrepancies.^[10] The Food and Drug Administration granted accelerated approval to Alpelisib (Vijoice, Novartis Pharmaceuticals) on 5 April 2022, for treating severe manifestations of PROS in adult and paediatric patients aged 2 years and older who need systemic therapy.^[11]

CONCLUSION

CLOVES syndrome is exceptionally rare, and research in this area is predominantly limited to a scant body of published literature. Herein, we report a case of a 10-month-old baby with CLOVES syndrome. We are presenting this case to contribute to medical literature by providing a comprehensive account on CLOVES syndrome.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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