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Bilateral Renal Anomalies and Macrocephaly in CLOVES Syndrome: A Rare Case Report with PIK3CA Hotspot Mutation

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Abstract

Background: CLOVES syndrome (Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi, Scoliosis/Skeletal anomalies) is a rare, sporadic disorder categorized within the PIK3CA-Related Overgrowth Spectrum (PROS). Recent evidence underscores the clinical relevance of identifying systemic manifestations and novel genetic mutations in optimizing diagnosis and targeted treatment. Case Presentation: We report a three-year-old male presenting with progressive, asymmetric lipomatous overgrowth beginning at six months of age, complicated by veno-lymphatic malformations, profound growth failure, relative macrocephaly, and persistently bilateral renal anomalies. Pathogenic mosaicism for PIK3CA (c.1624G>A; p.Glu542Lys) was discovered by high-depth sequencing of the afflicted tissue, with a variant allele frequency of 23%. Clinical management included multidisciplinary care and initiation of alpelisib, resulting in clinical stabilization at follow-up.

Conclusion: This case enriches the phenotypic understanding of CLOVES syndrome, highlights the importance of renal surveillance, and supports the emerging efficacy of PIK3CA-targeted therapy in pediatric overgrowth syndromes.

Keywords: CLOVES syndrome; PIK3CA-related overgrowth spectrum; vascular malformations; lipomatous overgrowth; renal anomalies; macrocephaly; alpelisib

Introduction

CLOVES syndrome represents the most severe phenotype within the PIK3CA-Related Overgrowth Spectrum (PROS), a group of rare mosaic disorders characterized by tissue-specific overgrowth resulting from postzygotic activating mutations in the PIK3CA gene. The syndrome was first delineated by Sapp et al. defining diagnostic standards in 2007 based on the combination of vascular malformations, epidermal nevi, congenital lipomatous overgrowth, and scoliosis/skeletal abnormalities. Recent epidemiological studies indicate a prevalence of approximately 1 in 50,000 live births, with fewer than 300 cases reported in the medical literature to date .[1]

The underlying pathophysiology involves somatic mosaicism for gain-of-function mutations in PIK3CA, which encodes the p110α catalytic subunit of phosphoinositide 3-kinase (PI3K) . These mutations lead to hyperactivation of the PI3K/AKT/mTOR signaling pathway, resulting in dysregulated cellular proliferation, survival, and metabolism within affected tissue compartments. One of the most commonly found hotspot variants in PROS is the c.1624G>A (p.Glu542Lys) mutation, which accounts for about 20% of all pathogenic PIK3CA changes in overgrowth disorders.

The therapeutic landscape for PROS has been revolutionized by the development of alpelisib, a selective PI3Kα inhibitor that received accelerated FDA approval in April 2022 for severe manifestations of PROS in patients aged ≥2 years. Clinical trials have demonstrated significant efficacy in reducing lesion volume and improving quality of life, with response rates of 37.5% achieving ≥20% volume reduction at 24 weeks . The recommended pediatric dosing ranges from 50–125 mg daily based on body surface area, with excellent tolerability profiles in long-term studies .[2][3]

Despite extensive clinical characterization, certain phenotypic associations within CLOVES syndrome remain inadequately described. Renal manifestations, in particular, have been reported in fewer than ten cases in the literature, with most descriptions limited to single case reports . Similarly, the pattern of relative macrocephaly in the context of somatic growth failure has received minimal attention in the PROS literature, despite its potential diagnostic significance .

This case report describes a patient with classical CLOVES syndrome features accompanied by bilateral renal anomalies and distinctive growth patterns, contributing novel phenotypic data to the expanding PROS spectrum and demonstrating therapeutic response to targeted PI3K inhibition in the pediatric population.

Case Presentation

A three-year-old male, born to non-consanguineous parents, was referred due to progressive multiple soft-tissue masses and failure to thrive. The patient was delivered at term (38 weeks gestation) via uncomplicated vaginal delivery, with a birth weight of 3,500 g and normal Apgar scores. His early development was appropriate, with no neurological deficits documented.

At six months, a soft frontal swelling was first observed, which gradually increased in size. Over the next two years, new masses appeared in the neck, mastoid region, thorax, abdomen, axilla, back, thighs, and perineum. Chest masses became intermittently painful during rapid growth phases. At eighteen months, the patient developed a painless scrotal mass. At two and a half years, he required intensive care for respiratory distress due to mediastinal compression.

Examination revealed multiple, non-fluctuant, lobulated masses (range 3×4 cm to 8×12 cm) distributed asymmetrically: frontal (8×12 cm), bilateral mastoid, chest (tender, 6×8 cm), abdomen, back, axillae, thighs (predominance on left), and scrotum (4×5 cm). Anthropometry showed weight of 11.8 kg (3rd–10th percentile), height 84 cm (<3rd percentile, Z-score –2.8), and head circumference 53.5 cm (>97th percentile, Z-score +2.1), consistent with marked growth failure and relative macrocephaly. Two linear epidermal nevi were present on the left thorax, and mild thoracic scoliosis (Cobb angle 15°) was noted. Cardiorespiratory and neurological evaluation was otherwise unremarkable.

Laboratory evaluation revealed mild anemia (hemoglobin 9.7 g/dL) but preserved renal (creatinine 0.23 mg/dL, eGFR 98 mL/min/1.73 m²) and hepatic function. Ultrasound revealed bilateral renal anomalies with a right kidney of 7.8 cm (poor corticomedullary differentiation) and a left kidney of 6.9 cm (relatively small with maintained echogenicity). MRI of the brain was normal except for benign macrocephaly. Contrast-enhanced MRI of the thorax, abdomen, and pelvis showed widespread, T1-hyperintense lipomatous masses interspersed with slow-flow veno-lymphatic malformations. Renal DMSA scintigraphy demonstrated a right:left split function of 58%:42%, without cortical defects.

Somatic mutational analysis (high-depth next-generation sequencing) of affected tissue detected a pathogenic PIK3CA c.1624G>A (p.Glu542Lys) variant in exon 9 with a 23% mosaic allele frequency. Parental studies were negative, confirming a de novo event. The diagnosis of CLOVES syndrome was established by clinical and genetic criteria.

The patient's management involved a multidisciplinary team: pediatric genetics, vascular anomalies, nephrology, orthopedics, and nutrition. Initial care focused on pain management, nutritional optimization (130 kcal/kg/day), and supportive physiotherapy. After institutional review and informed parental consent, low-dose alpelisib (50 mg daily) was initiated at age three. Ongoing monitoring included clinical, laboratory, and imaging assessments for efficacy and potential adverse events.

Discussion

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This case contributes several significant observations to the evolving understanding of CLOVES syndrome phenotypic diversity and therapeutic management. The bilateral renal anomalies documented in this patient represent a rarely described but potentially important systemic manifestation of PIK3CA-mediated overgrowth. A comprehensive literature review reveals fewer than twelve prior reports of renal involvement in CLOVES syndrome, suggesting either genuine rarity or systematic under-recognition of urogenital complications in PROS evaluation protocols.

The functional significance of these renal anomalies, as demonstrated by differential DMSA scanning (58:42% split function), supports the recommendation for routine nephrological assessment in CLOVES syndrome management guidelines. Recent studies have identified an increased risk of Wilms tumor development in PROS patients, with an estimated prevalence of 2–3% across the spectrum, further emphasizing the importance of ongoing renal surveillance.[4]

The distinctive anthropometric pattern observed in this patient—relative macrocephaly (>97th percentile) concurrent with significant somatic growth failure (<3rd percentile for height)—has received limited attention in the PROS literature. This phenotype may reflect differential tissue sensitivity to PIK3CA pathway activation, with neural tissue demonstrating enhanced growth response compared to somatic tissues . Recent advances in understanding PIK3CA's role in neuronal proliferation and brain development provide mechanistic support for this observation .

The molecular characterization of this case confirms the pathogenic significance of the c.1624G>A (p.Glu542Lys) mutation, which represents one of the most thoroughly validated hotspot alterations in PIK3CA-related disorders. Located within the helical domain of the p110α subunit, this mutation disrupts autoinhibitory interactions and results in constitutive kinase activation. The 23% variant allele frequency detected in affected tissue demonstrates the characteristic mosaic distribution pattern and underscores the critical importance of tissue-based molecular testing rather than conventional blood-based analysis for PROS diagnosis.[5]

The therapeutic response to alpelisib therapy in this patient aligns with emerging real-world evidence supporting the efficacy of PI3K pathway inhibition in pediatric PROS management. The EPIK-P1 retrospective study, which formed the basis for FDA approval, demonstrated clinical benefit in 74% of patients, with sustained response rates of 60% at 12 months. Pediatric-specific data indicate excellent tolerability at the standard 50 mg daily dosing, with the most common treatment-related adverse events being hyperglycemia (12.3%) and aphthous ulceration (10.5%).[6][7][2]

Long-term management considerations for patients with CLOVES syndrome extend beyond symptom control to encompass comprehensive surveillance for potential complications. Recent evidence suggests increased risks for thromboembolic events, particularly in patients with extensive vascular malformations, necessitating prophylactic anticoagulation in high-risk scenarios. Additionally, emerging data indicate elevated cancer predisposition in PROS patients, with particular attention required for Wilms tumor surveillance in those with renal involvement.[3][4]

The multidisciplinary care approach exemplified in this case reflects current best practices for PROS management, involving collaboration between genetics, vascular anomalies, nephrology, orthopedics, and allied health services.[8]

Future research priorities in CLOVES syndrome should focus on comprehensive phenotypic characterization across larger patient cohorts, long-term outcome studies following alpelisib therapy, and investigation of combination therapeutic strategies for patients with incomplete responses to PI3K inhibition monotherapy. The development of validated outcome measures for pediatric PROS patients remains a critical need for future clinical trial design and regulatory approval processes.

Conclusion

This case broadens the recognized phenotypic spectrum of CLOVES syndrome by documenting persistent, bilateral renal anomalies and a pronounced pattern of relative macrocephaly in the setting of severe somatic growth failure. The findings reinforce the importance of systematic renal surveillance and anthropometric assessment in all patients with PROS disorders. Targeted PIK3CA inhibition with alpelisib represents a promising therapeutic strategy with

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potential to alter the disease trajectory in pediatric overgrowth syndromes. Comprehensive, multidisciplinary evaluation and follow-up remain cornerstones for optimizing clinical outcomes in this rare and heterogeneous condition.

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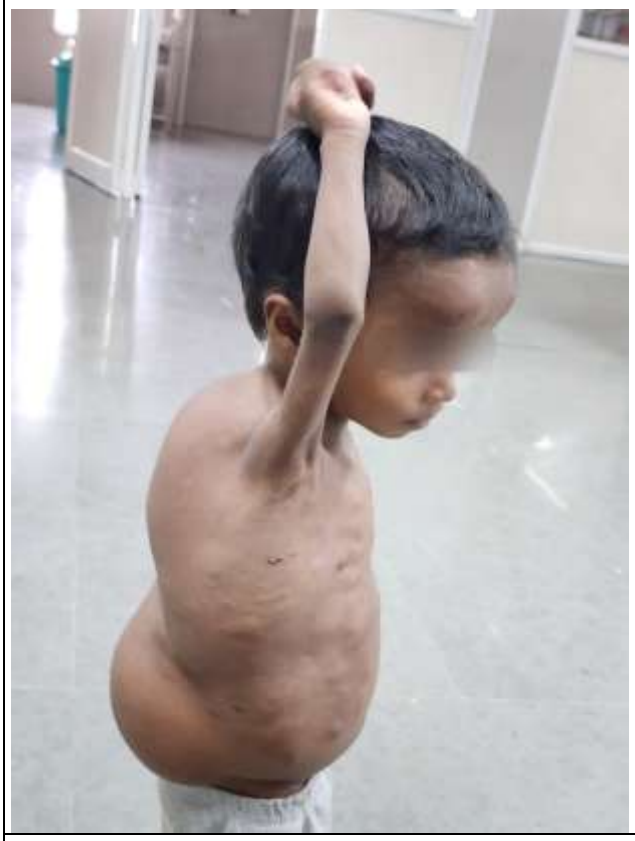
Figures

Figure No. 1



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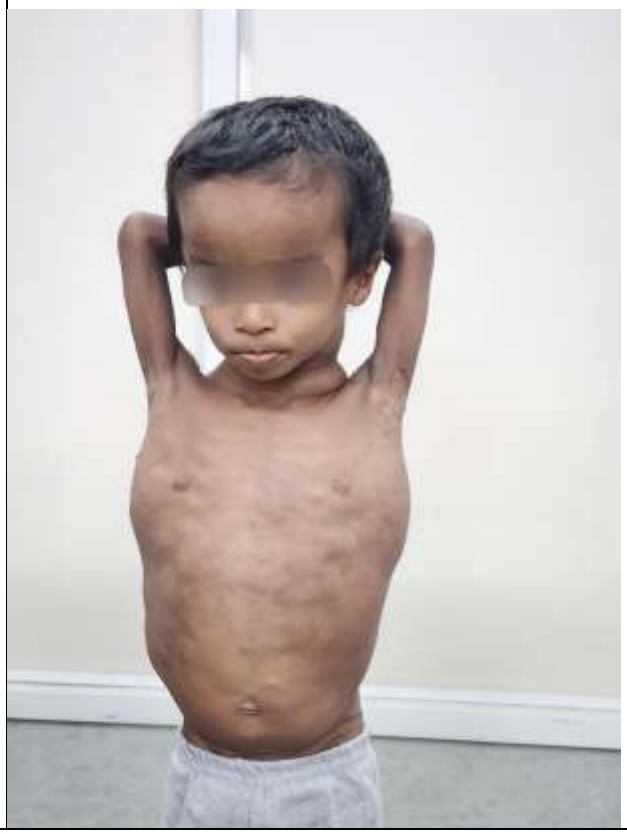

Figure No. 3

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