CLOVES SYNDROME: A CASE REPORT

Irfan Ullah[1], Zarak Khan Shiraz[1], Mehran Khan[1]

ABSTRACT
CLOVES syndrome is an extremely rare PIK3CA-related overgrowth syndrome encompassing, but not restricted to, congenital lipomatous overgrowths (CLO), vascular malformations (V), epidermal naevi (E) and spinal deformities (S). The syndrome can have features overlapping with other overgrowth syndromes resulting in a challenging diagnosis and frequent misdiagnosis. To the best of our knowledge, reports on the syndrome are lacking from Pakistan. We report a rare case of CLOVES syndrome in a previously misdiagnosed 2-year-old male child from Khyber Pakhtunkhwa, Pakistan.

Keywords: Congenital Lipomatous Overgrowth, Vascular Malformations, and Epidermal Nevi, Phosphatidylinositol 3-Kinases, Pakistan, Syndrome

INTRODUCTION

CLOVES syndrome is a recently described distinct overgrowth syndrome.[1] Like Proteus syndrome, CLOVES syndrome is also caused by somatic mutations in the PIK3CA gene.[2] The acronym CLOVES stands for congenital lipomatous overgrowths (CLO), vascular malformations (V), epidermal naevi (E) and spinal deformities (S). Combination of features present in each patient may vary and are not restricted to only those included in the acronym. CLOVES syndrome is extremely rare with an estimated prevalence of < 1 case per million individuals.[3] Data on the disease from Pakistan, with a population of over 200 million, is extremely deficient. We report here a case of CLOVES syndrome in a two-year-old male child from Khyber Pakhtunkhwa, Pakistan who remained undiagnosed since birth.

CASE PRESENTATION

A two-year-old boy was referred to the Dermatology clinic at Khyber Teaching Hospital, Peshawar, Pakistan for assessment of multiple soft tissue growths on the trunk and upper and lower limbs since birth. According to the parents, who were first degree cousins, the child was born normally after an unremarkable pregnancy. At birth a large, soft, fluctuant growth was noted on the chest (Figure 1A). Over the next few months similar growths appeared on the right upper and lower limbs, that progressed to gradually grow in size. The lesion on the chest, however, became smaller. This encouraged the parents to seek medical advice for the first time, however, no diagnosis could be reached and a wait-and-see approach was maintained until the child reached the age of two when he was referred to our department. The patient had an otherwise normal developmental history. On examination there were multiple, bilateral, asymmetrically distributed soft tissue masses of varying sizes present on the chest, abdomen, back and the right arm (Figure 1B-D).

1. Khyber Teaching Hospital, Peshawar, Pakistan

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Address for Correspondence:
Zarak Khan Shiraz
Post Graduate Resident,
Department of Dermatology, Khyber Teaching Hospital, Peshawar, Pakistan.
shiraz.zarak@gmail.com

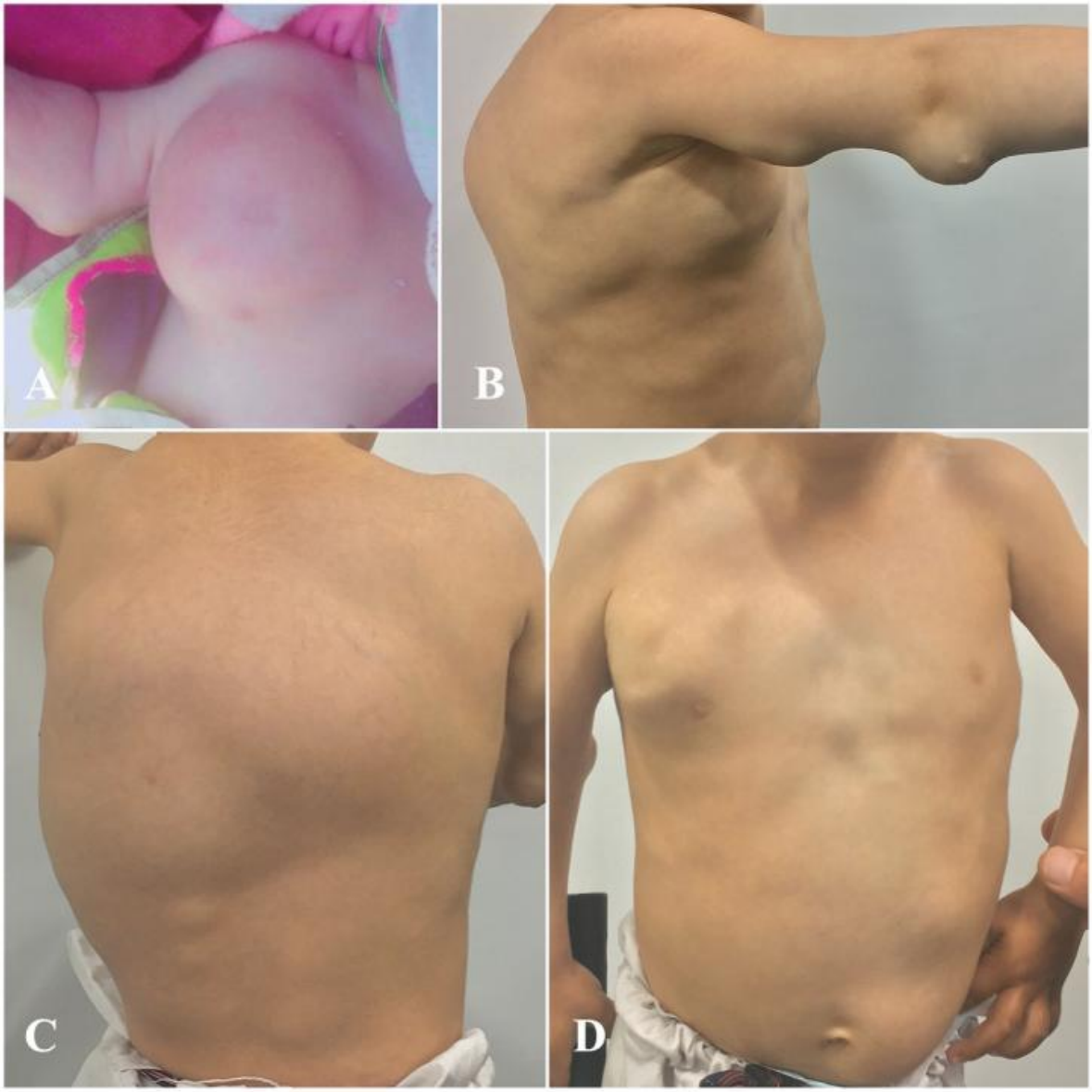

Figure 1. A. Soft tissue growth over the right side of the chest soon after birth. B-D. Multiple, bilateral, asymmetrically distributed soft tissue growths over the trunk and right arm.

Smaller masses were also noted on the left arm and legs. The right leg was bulkier than the left leg with a one-inch length discrepancy between the two (Figure 2A). A 3x2 cm erythematous, blanch-able, plaque was noted on the left side of the chest, in close proximity to an underlying soft tissue mass (Figure 2B).

The right foot was larger and triangular in comparison to the left foot and had a distinctly wide gap between the big and the second toe (Figure 2C) Additionally, the superficial veins on the chest were prominent and skeletal deformity of the chest and scoliosis was evident. The rest of the examination was unremarkable.

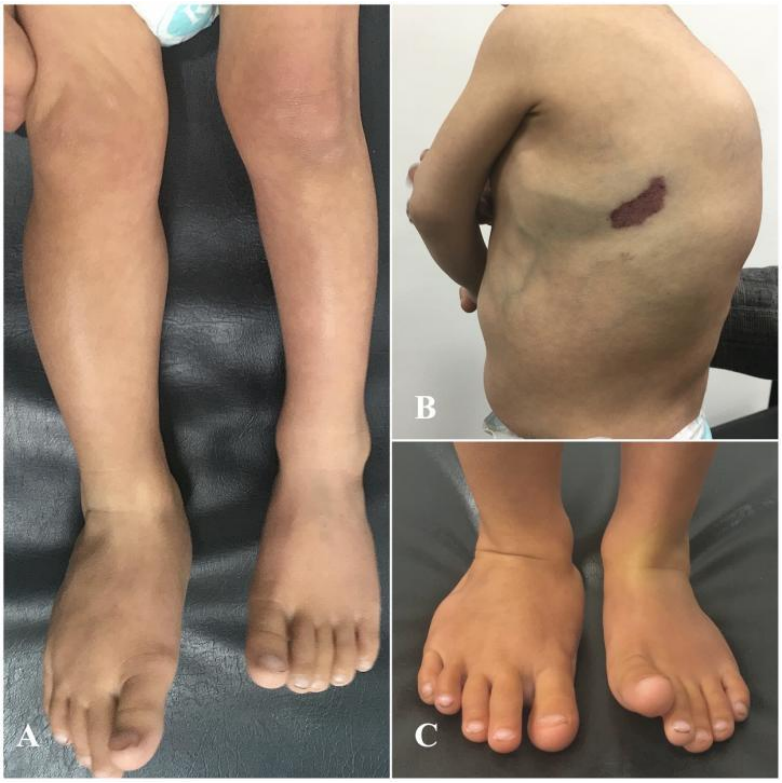

Figure 2. A. Hypertrophy of the right leg and foot with length discrepancy. B. Enlarged veins, soft tissue growths and a capillary malformation on the left side of the chest. C. Enlarged, triangular right foot with an exaggerated "sandal gap".

INVESTIGATIONS

Upon radiological work-up, most of the soft tissue masses were identified as lipomatous growths except a few on the chest that were identified as lymphangiomas.

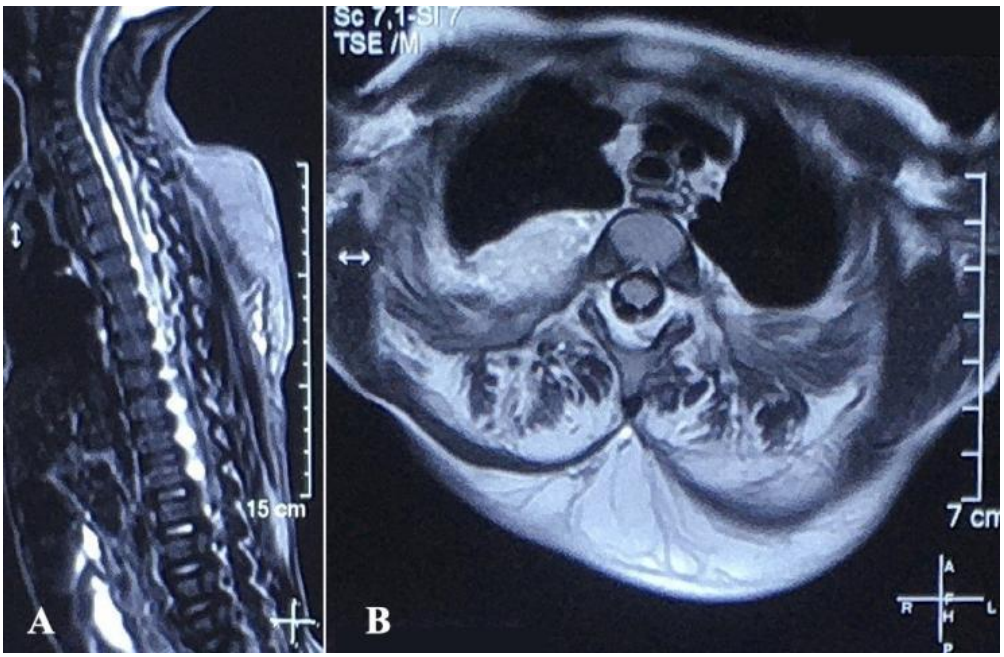

Figure 3. A. An MRI scan showing diffuse lipomatous infiltration in subcutaneous region of posterior trunk and paraspinal muscles. B. Paravertebral changes suggestive of vascular malformation

DIAGNOSIS

Based on the history, examination and radiological findings, a diagnosis of CLOVES syndrome was made.

TREATMENT, OUTCOME AND FOLLOW UP

A multidisciplinary team comprising the Paediatric, Surgery, Dermatology and Orthopaedics departments was formulated for further management and follow-up of the patient. A detailed surgical review concluded that debulking or embolization procedures at the current stage of the disease process where not needed and hence a collective decision to follow the patient at 3-monthly visits was made. The parents of the patient were counselled in detail regarding the chronic nature of the patient's condition and the need for strict adherence to follow-up visits.

DISCUSSION

Previously, patients with features of CLOVES syndrome were grouped with other similar syndromes, most frequently Proteus syndrome. Studies on a cohort by Sapp et. al in 2007 followed by a descriptive study of 18 cases by Alomari in 2009 led to distinct categorisation of the syndrome.[1,4] Most common features identified by these studies included asymmetric lipomatous overgrowths, low-flow vascular malformations, leg length discrepancy and scoliosis, wide hands and feet and a wide sandal gap, renal agenesis and hypoplasia. Occasionally, fast-flow malformations, linear epidermal naevi, hemi-hypertrophy were also reported.[1] In our patient no cutaneous naevi, renal abnormalities or fast-flow malformations were identified. Other studies also report a low incidence of naevi in patients of CLOVES syndrome, emphasising how the patients may not have all the features entailed by the acronym. [5,7] The syndrome is part of the PIK3CA-related overgrowth syndromes (PROS) known to be caused by somatic mutations in the PIK3CA gene.[2] Variations in phenotypes depend on the developmental stage at which the mutation happened.[2] Most cases in literature have been reported in patients born to non-consanguineous parents. A relationship between consanguinity, as in our case, and CLOVES syndrome has not been documented, indicating room for further investigation. However, the lack of case reports on the syndrome from Pakistan, a country with high prevalence of consanguineous marriages,[6] may further strengthen the somatic nature of the causative mutations. Management of patients with CLOVES syndrome is complex and requires a multidisciplinary approach that is fine-tuned to the patient's condition. Treatment options include surgical de-bulking for lipomatous overgrowths, sclerotherapy and embolization for vascular malformations, pulse-dye lasers for capillary malformations, and epiphysiodesis for discrepancies of limb length.[7] Role of targeted therapies against the PI3k/AKT kinase signalling pathway remain under study.[8] Wilms tumour is a noted complication in some patients and requires serial ultrasounds over the course of time, especially in the early years of age.[9] Timely diagnosis can delay morbidity in the patient and prevent complications. Despite multiple medical visits before presenting to our hospital, a diagnosis in our patient was missed, necessitating the need to report this case.

LEARNING POINTS

CLOVES syndrome is an exceedingly rare disorder caused by somatic mutations in the PIK3CA gene. Early diagnosis and multidisciplinary care can decrease the morbidity associated with the disease and identify life-threatening complications. Similar cases from Pakistan should be reported to allow further assessment of variations of the syndrome in our population and to encourage initiation of greater multidisciplinary care protocols.

DECLARATIONS

Patients consent for use of data for publication: Consent taken in writing.

Authors contributions: The authors confirm contribution to the paper as follows: Report conception, literature research, draft manuscript: Dr. Irfan Ullah, Dr. Zarak Khan Shiraz. Draft manuscript, and review: Dr. Mehran Khan.

Conflicts of Interests: None.

Funding: None.

Acknowledgements: Dr. Fahad Faiz Ullah.

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