CLOVES Syndrome: Lower Extremity Management in a Young Child

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Statement of Purpose

CLOVES Syndrome, also known as congenital lipomatous overgrowth (CLO), vascular malformations (V), epidermal nevi (E) and scoliosis and spinal deformities (S) presents a unique and challenging problem to podiatric surgeons. CLOVES syndrome was first recognized as a diagnostic entity in 2007, with diagnosis originally based on clinical examination, not histopathological analysis.[1,2,3] This rare congenital disorder was found in a group of seven patients with physical attributes including gigantism of extremities, epidermal nevi, hemihypertrophy, macrocephaly, and lipomatosis.[1] Phenotypic data show some of the cardinal features in CLOVES syndrome may overlap with Proteus syndrome (spontaneous, mosaic, and progressive).[4] We present this case to underscore proper diagnostic technique and offer suggestions for surgical and medical management. Fewer than 200 cases have been reported worldwide.

Literature Review

To date, no literature exists for the medical or surgical management of lower extremity in CLOVES syndrome patients. The musculoskeletal presentation can include lipomatous masses, leg-length discrepancy, dislocated knees, scoliosis, enlarged hands and feet, sandal gap toe, and hemihypertrophy.[5] Many of these skeletal abnormalities may be apparent on ultrasound in late pregnancy.[6] Research suggests that a post-zygotic somatic mutation in PIK3CA, a gene involved in the receptor tyrosine kinase phophatidylinositol-3-kinase (PI3)-AKT growth signaling pathway, leads to this progressive disorder.[6,7]

There are limited literature regarding surgical treatment of CLOVES, but the existing literature includes benefits of utilizing interventional radiograph procedure, highlights the risks of treating tissue overgrowth in hazardous areas such as the paravertebral or epidural spaces and describes the complications of these surgeries, such as wound dehiscence, and venous thromboembolism secondary to phlebectasis and stasis.[8,9,10] Bracing for scoliosis can be problematic in growing children since the contact pressure needed for curvature correction is unattainable due to large truncal overgrowth with cutaneous vascular lesions.[9]

Medical management of this disorder remains experimental. However, the use of Sirolimus has been entertained. One study on the efficacy and safety of oral Sirolimus in sixty-one patients with complicated vascular anomalies showed this drug to be efficacious and well tolerated.[13] Sirolimus is a mammalian target of rapamycin (mTOR), which combines signals from the PI3K/AKT pathway to coordinate proper cell growth and proliferation by regulating ribosomal synthesis.[13,14] According to Lee et al., enhanced mTOR signaling increases expression of the vascular endothelial growth factor, a key regulator of angiogenesis and lymphangiogenesis.[15] Improper activation of the PI3K/AKT/mTOR pathway in disorders such as CLOVES has been shown to result in tissue overgrowth with vascular anomalies.[13,14,15] Our review of the literature suggests the treatment of this disorder requires both medical and surgical approach.

Procedures

The child presented at age 2 years, 7 months with lipodystrophy of his arms, mosaic overgrowth of both feet (figure 1 and 2), severe genu valgum left (figure 4), and a large tense abdominal mass (figure 3). The lower extremity examination was also remarkable for limb length discrepancy, right greater than left, pes planus, and brachymetatarsia as well as macrodactyly bilaterally. Patient's medical history was significant for bilateral undescended testicles, which he underwent staged Fowler Stephens orchipexies. Patient received sclerotherapy for the lymphatic malformation of the right flank. Genetic diagnosis for CLOVES disorder is not possible using blood, thus punch skin biopsies were performed over involved tissue from the feet. Concern was raised for the abdominal mass skin breaking down lead the medical team to initiate Sirolimus, an mTOR inhibitor primarily used in cancer therapy, at 3 years, 0 months. He responded well to drug therapy, indicated by marked reduction in the size of his abdominal mass, less bulbous, and more supple feet. His feet have since become less disproportionate and less stiff. However, the overgrowth of his toes (figure 5 and 6) and diastasis between the hallux and second toe, particularly on the right foot (figure 6), remains quite large causing a walking delay. Patient elected to underwent an insertion of 8 plate of left distal medial femur, epiphysiodesis of the left 3, 4, 5 proximal and distal toe phalanges; epiphysiodesis of the right 1 and 3 proximal and distal phalanges; epiphysiodesis of the proximal and distal phalanges of the 2nd toe with hemiepiphysiodesis medially of the middle phalanx.

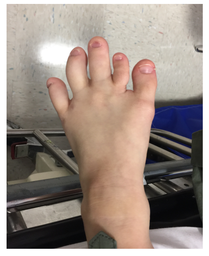

Figure 1: Left foot

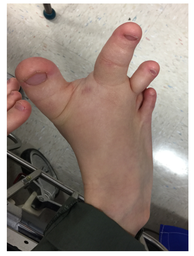

Figure 2: Right foot

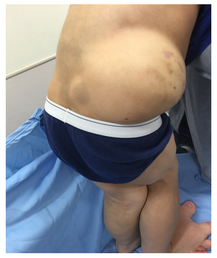

Figure 3: Right sided flank mass prior to Sirolimus

At 3 years, 9 months, he underwent growth inhibition technique on the left distal medial femur using an 8-plate (figure 9). Under C-arm guidance, a small incision was made medially and laterally along the growth plate of the proximal and distal phalanges. A drill was carefully inserted into the growth plate and this was followed by a curette to try to obliterate the growth plate as much as possible (figure 7 and 8). This was done both medially and laterally and then repeated in the distal phalanx. Patient underwent repeat epiphysiodesis of bilateral phalanges at age 4 years, 8 months due to the robustness of this disorder. We elect to leave the metatarsals alone since his feet are too skeletally immature to attempt the procedure.

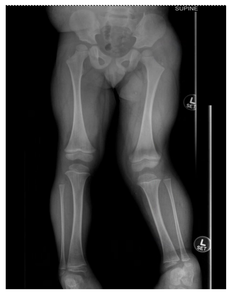

Figure 4: Initial standing film

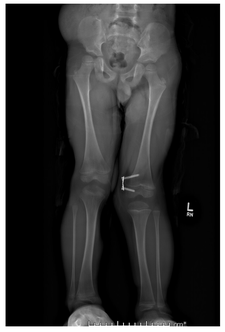

Figure 9: Follow up film

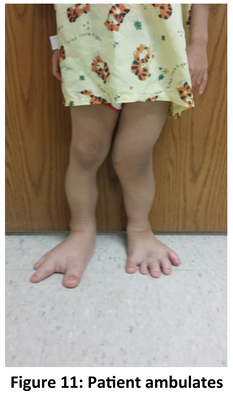

Figure 11: Patient ambulates independently at 24 months follow up

Pre operative XRAYS

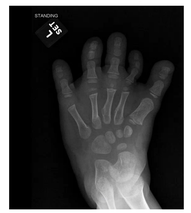

Figure 5: Left foot

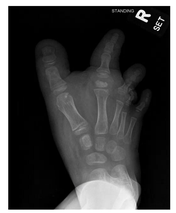

Figure 6: Right foot

Intra operative XRAYS

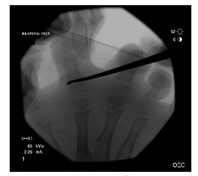

Figure 7: Left 4th toe

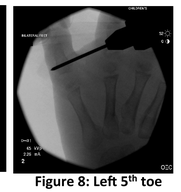

Figure 8: Left 5th toe

Post operative XRAYS

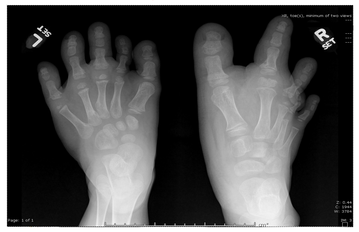

Figure 10: Left and right foot

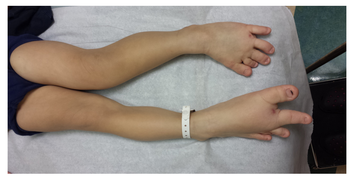

Figure 12: Patient laying supine showing genu valgum and limb length discrepancy

Results and Discussions

- **CLOVES syndrome is a rare congenital disorder characterized by truncal, limb overgrowth, vascular malformations, and skeletal anomalies.**
- **Correct diagnosis requires biopsy of affected tissues.**
- **At 24 months follow up, the abdominal mass has reduced to less than one-quarter the original size. The genu valgum has nearly resolved and his feet have become less disproportionate and less stiff allowing him to ambulate without assistance (figure 11). Most phalangeal growth plates remain open.**
- **The goal of our treatment was to allow his body to catch up to his toes and the use of Sirolimus was very effective in helping his feet and abdominal mass to shrink in size allowing him to walk independently.**
- **While growth inhibition surgery has been successful, epiphyseodesis of toe phalanges has proven challenging. The role for Sirolimus in this disorder has not yet been defined.**
- **Interdisciplinary team management including orthopaedic, podiatric surgery, medicine, interventional radiology, vascular surgery, hematology and neurosurgery is paramount to good treatment outcome.**

References

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