LITERATURE REVIEW AND CASE REPORT OF TWO CLOVES SYNDROME PATIENTS TREATED WITH SCLEROTHERAPY

Saima Ahmad, Ahmed Imran, Abid Ali Qureshi

Department of Radiology, Children Hospital, Lahore, Pakistan.

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Case 1

We present a case of 18 months 18-month-old boy affected by CLOVES syndrome. He was born with C-Section at the 38th week of gestation with a prenatal diagnosis of extensive thoracoabdominal vascular /venous malformation. The lesion was first identified at 6 months of gestation and later on, it increased in size exponentially on a follow-up scan so an elective C-Section was planned. There is no significant family history of the mother, she has another child who has no medical illness. No documentation available regarding Apgar score at birth however baby remained in the ICU for several days. He required advanced resuscitation and mechanical ventilation.

The baby was referred to our department, physical examination at birth revealed large venous and lymphatic malformation involving the left thorax and abdominal region with bluish discoloration overlying hypertrophied growth. MRI and ultrasound of the chest and abdomen confirmed the presence of a large multiloculated mixed intensity lesion of size 6.1 x 2.8 x 10.2 cm with hemorrhage and free fluid along the lateral thorax and an abdominal wall extending from mid thorax to iliac region suggestive of the venous and large macrocytic type of lymphatic malformation with overlying capillary malformation.

On the 18th day of his birth, he received his first sclerotherapy injection for embolization of lymphatic and venous malformation. The sclerosant was bleomycin foam which was prepared with human albumin 20% in equal amounts with air. The weight of the baby was 3 kg so the bleomycin foam dose was adjusted according to the weight of the baby. We have given 3 ml of bleomycin foam (0.5-1mg /kg). After localization of the lesion with ultrasound, the venous outflow was confirmed, and then test contrast injection was given under fluoroscopic guidance, and then 3 ml of bleomycin foam was injected. The procedure was done under sedation as the baby was only 18 days old. To monitor the response of scleroembolization we kept on close follow-ups. There was a significant decrease in the size of the lesion after the first session. The second session was planned 8 weeks after the first session and 5 ml of bleomycin foam was injected percutaneously with the same protocol in the residual lymphatic malformation compartment.

After 3 months of the second session of scleroembolization, there was a total resolution of the lesion. Physical examination was unremarkable, there is slight pigmentation of skin at the previous site of lesion. A follow-up ultrasound was also done to confirm the total resolution of the lesion. We have been following up on this case for the past 1.5 years and there is no recurrence of the lesion. The child has no other illness or any other delayed milestones.

Case 2

A 1-month-old baby girl was referred to our department at the Children's Hospital for assessment of a large lesion involving the right lateral chest, thorax, and abdominal region. The mother belongs to a poor socioeconomic status and, hence did not seek any gynecological advice during pregnancy. The child was born with soft fluctuant swelling involving the right thorax and abdominal area with bluish and purplish

Correspondence : Dr. Saima Ahmad
Department of Radiology,
Children Hospital, Lahore,
Pakistan.
Email: masterinfluencer@gmail.com

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discoloration (Nevi)of overlying skin. Within 1 month time, the swelling increased in size exponentially. She required advanced resuscitation and mechanical ventilation due to septic shock. From the Pediatric ICU, the case was referred for evaluation. An echocardiogram was done which was unremarkable. Ultrasonography was done which showed large cystic swelling and, a fatty component with mixed vascularity on the Doppler. MRI chest and abdomen showed complex soft tissue and cystic mass along the right anterolateral chest wall extending into the upper abdomen with internal fatty components. Post-contrast images showed enhancement of soft tissue components with venous channels suggestive of vascular malformation.

We have planned percutaneous sclerotherapy for the patient on an immediate basis. However, due to the presence of this large chest vascular malformation, she developed progressive respiratory distress, oxygen requirement, and fever. The child died at 30 days of life.

Discussion

A rare, nonheritable sporadic segmental mosaic overgrowth syndrome is called CLOVES syndrome. There have been between 130 and 200 documented occurrences of CLOVES syndrome globally to date. Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and spinal/skeletal deformities are collectively referred to as CLOVES.[1]

The PIK3CA gene, which codes for the catalytic subunit of phosphatidylinositol 3-kinase (PI3K), protein p110 alfa (p110α), is the source of the somatic mutations that cause it. Inappropriate activation of the PIK/AKT/mTOR pathway results in tissue overgrowth and vascular anomalies. Numerous cellular processes, including cell division and development, depend on PI3K signaling. The PIK3CA-related overgrowth spectrum (PROS), which includes CLOVES syndrome, is a group of disorders with varying symptoms that are all brought on by mutations in the PIK3CA gene. Early onset and progressive worsening of PROS symptoms result in a progressively worse quality of life.[2]

Overgrowth syndrome diagnosis and treatment have been difficult for many years. The CLOVES condition has no known treatment. Until recently, patients with CLOVES syndrome were treated palliatively with vascular interventional techniques (sclerotherapy for macrocystic lymphatic malformations, laser therapy for capillary malformations, coil embolization procedures for large venous malformations, superior vena cava filters for central and thoracic phlebectasias), as well as multidisciplinary, staged debulking surgeries for lipomatous and skeletal overgrowths (surgical excision, extremity or finger/toe amputation, surgical correction of scoliosis). Anticoagulant drugs were administered to patients with low-flow anomalies to prevent thromboembolic illness.

With a blended mixture of capillary (low-flow and geographic), venous (superficial phlebectasia), lymphatic (macrocystic, microcystic, or mixed), and arteriovenous malformations with or without arteriovenous fistulae (high-flow), CLOVES syndrome is characterized by complex and combined deposition of vascular tissue. The lesions may be superficial or deeply positioned, solitary or many, localized or widespread. The most prevalent kinds of vascular abnormalities are capillary and lymphatic malformations. Geographic stains, or capillary abnormalities in the appearance of port wine stains, can be seen on the trunk, fingers, palms, soles, or extremities from a dermatological perspective.[3] In one of our cases we had a large lymphatic malformation with a capillary component as well and we treated the case with sclerotherapy using bleomycin which proved to be very effective in dealing with the vascular component of CLOVES Syndrome.

Sclerotherapy was used to treat right anterior abdominal edema in a case of CLOVES Syndrome that was comparable to one that we found in the literature study. Bleeding was to be treated with sclerosing treatment. A volume of roughly 3 milliliters was used to inject sodium tetradecyl sulfate into the enlarged right anterior abdominal wall. After six weeks, the patient returned for a follow-up appointment. There were no bleeding incidents.[4] Similar to our case responded to sclerotherapy very well.

Our patient did not have any therapy-related side effects, suggesting that this treatment may be superior to others. Sirolimus, especially in light of the likelihood that long-term care may be required. Our results suggest that early intervention could result in greater

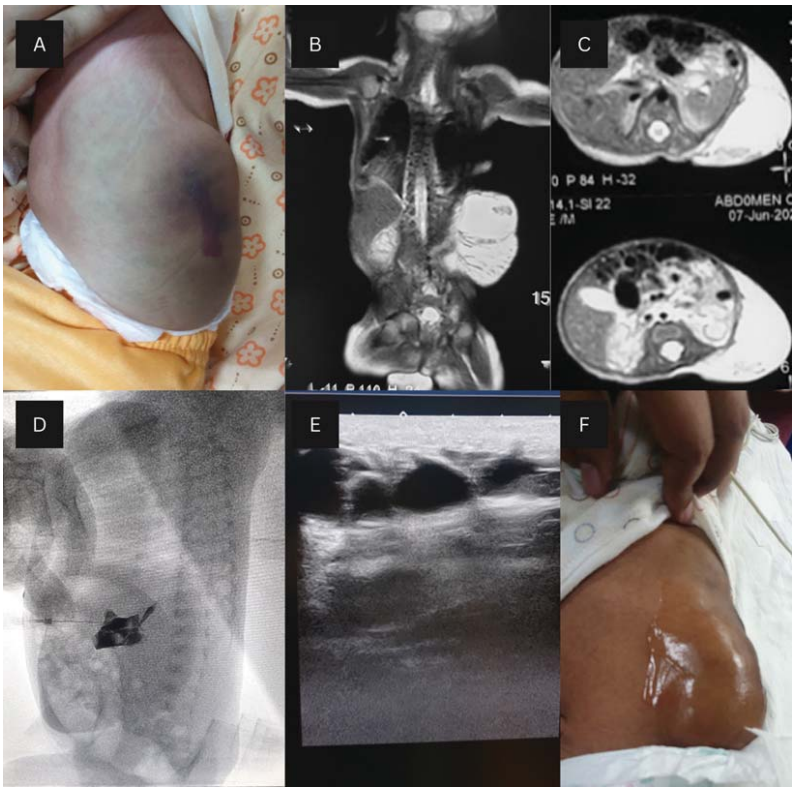

Figure 1: (A) Large swelling (hypertrophied growth) in the left thorax and abdominal region with bluish discoloration (venous and lymphatic component) 18th day at birth. **(B, C)** MRI chest and abdomen showed a large multiloculated mixed intensity lesion of size 6.1 x 2.8 x 10.2 cm with hemorrhage and free fluid from lateral thorax up to iliac region suggestive of venous and large macrocystis type lymphatic malformation with overlying capillary malformation. **(D, E, F)** Fluoroscopic guided image after percutaneous injection with contrast showing opacification of the lesion during sclerotherapy. Follow-up ultrasound and a picture showing marked reduction of the lesion after the first session with sclerotherapy.

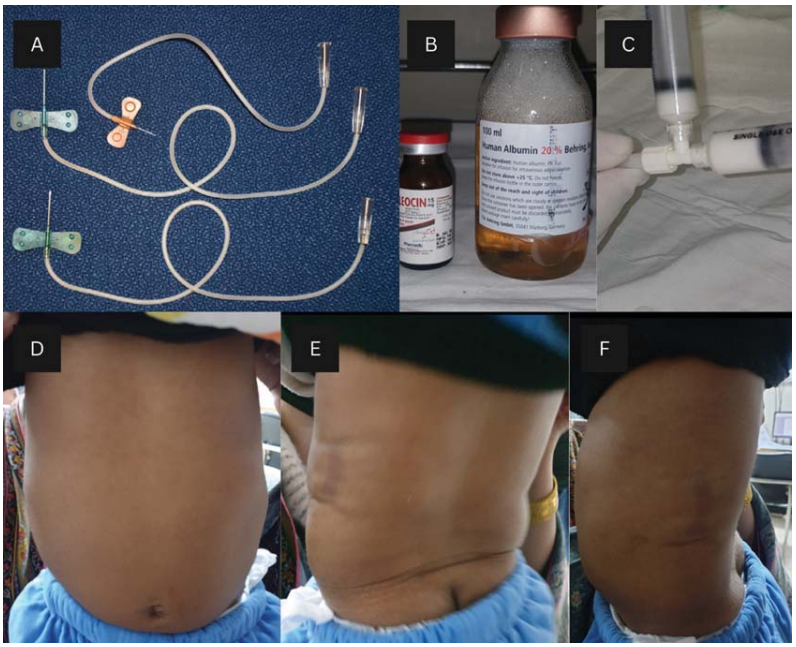

Figure 2: (A, B, C) Butterfly needles (21 G and 24G, human albumin 20%, and bleomycin foam preparation for sclerotherapy) **(D, E, F)** Total resolution of the lesion after 2 sessions of bleomycin foam sclerotherapy.

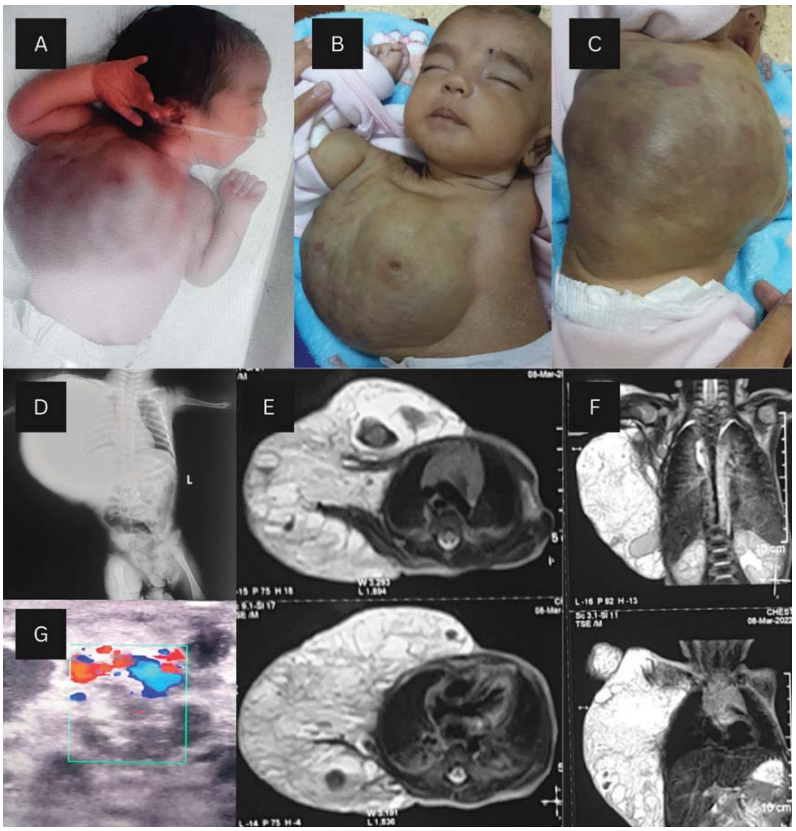

Figure 3: (A, B, C) Lipomatous overgrowth, epidermal nerves (bluish and purplish discoloration) of skin involving the right thorax and abdominal area on Day 1 (A) and day 30 (B, C) at birth. **(D, E, F, G)** MRI of chest and abdomen demonstrating complex soft tissue and cystic mass along the right anterolateral chest wall up to abdomen with internal fatty component. Post-contrast enhancement is suggestive of vascular malformation. Doppler ultrasound showing mixed vascularity.

advantages since it would stop overgrowth earlier without affecting linear growth.

According to this case study, bleomycin sclerotherapy is safe for young children and may even help with their future growth.

Conflict of Interest: None

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