Case Report

Alpelisib Treatment for Genital Vascular Malformation in a Patient with Congenital Lipomatous Overgrowth, Vascular Malformations, Epidermal Nevi, and Spinal/Skeletal Anomalies and/or Scoliosis (CLOVES) Syndrome

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A B S T R A C T

Background: Most patients with *phosphoinositide-3-kinase*, catalytic, alpha polypeptide (PIK3CA)-related overgrowth spectrum become symptomatic early in life and need treatment before puberty. Recently, the specific inhibition of PIK3CA pathways has been proposed as a therapeutic option for these patients improving their surgical options and quality of life. Alpelisib, a specific alpha fraction inhibitor, has shown promising results.
Case: A 17-year-old girl presented with severe involvement of her external genitalia with a combined vascular malformation in the context of congenital, lipomatous, overgrowth, vascular malformations, epidermal nevi and spinal/skeletal anomalies and/or scoliosis syndrome, needing frequent blood transfusions for anemia due to vaginal bleeding and use of a crutch for walking. After failure of treatment with rapamycin, compassionate treatment with alpelisib was started with excellent response.
Summary and Conclusion: PIK3CA inhibitors might become a new option of treatment for PIK3CA-related overgrowth spectrum patients.
Key Words: CLOVES syndrome, PROS, Alpelisib, BYL719

Introduction

Phosphoinositide-3-kinase, catalytic, alpha polypeptide (PIK3CA)-related overgrowth spectrum (PROS) designates a heterogeneous group of rare asymmetric overgrowth disorders caused by postzygotic variants in the *PIK3CA* gene. Overgrowth syndromes are characterized by congenital or early childhood-onset hypertrophy, sporadic occurrence, and mosaic distribution. Clinical diagnostic criteria include: adipose, muscle, skeletal, or nerve overgrowth; vascular malformations including large lymphatic malformations; epidermal nevus; macrodactyly; hemimegalencephaly, or focal cortical dysplasia among others.[1]

CLOVES is considered part of the PROS spectrum and its acronym stands for congenital lipomatous overgrowth (CLO), vascular malformations (V), epidermal nevi (E), and scoliosis or spinal deformities (S). Most of these malformations are present at birth and easily recognized. Thoracic lipomatous hyperplasia is a key sign, involving usually back and trunk and presenting with overlying capillary malformations.[2] External genitalia abnormalities are also found in these patients including scrotal lipomatous masses and/or combined vascular malformations affecting labia majora.

Recently, the specific inhibition of *PIK3CA* pathways has been proposed as a therapeutic option for these patients and alpelisib, a specific alpha fraction inhibitor that has shown a safe profile in breast cancer clinical trials, has become an option to improve the quality of life of PROS patients.[3]

We present a case of a patient with severe involvement of external genitalia by a combined vascular malformation in the context of CLOVES syndrome and her management with surgery and preoperative alpelisib treatment.

Case

We present a 17-year-old female patient diagnosed with CLOVES syndrome. Her family history was unremarkable. She was conceived naturally and was born preterm at 36 weeks of gestation with prenatal diagnosis of thoracic wall lymphatic malformation. At birth, she presented with a polimalformative syndrome with overgrowth of both upper and lower left extremities, left thoracic mass compatible with veno-lymphatic malformation, combined capillary-veno-lymphatic malformation in left lower limb, lipomatous mass in right flank and left dorsal region, and syndactyly in both feet, being initially misdiagnosed as Proteus syndrome.

Thoracic mass surgical reduction was performed during the neonatal period, and since then our patient had undergone multiple surgeries throughout her life: multiple interventions for removal of left hemithorax capillary-venous-lymphatic malformation, removal of both lipomas,

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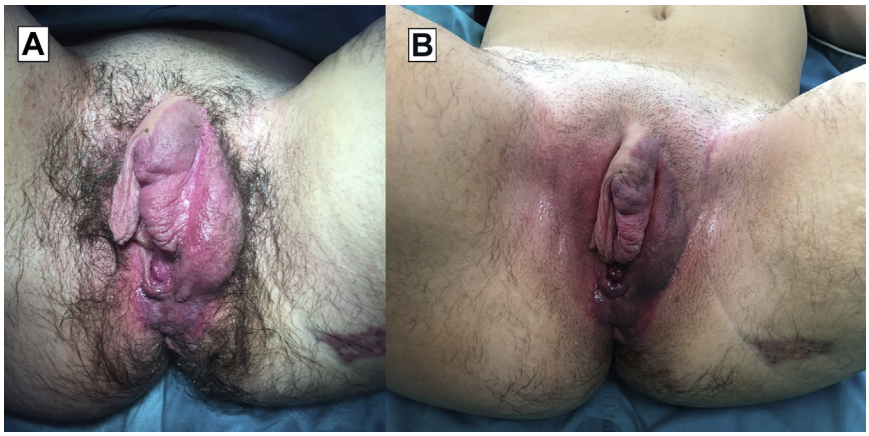

Fig. 1. Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and spinal/skeletal anomalies and/or scoliosis (CLOVES) syndrome with severe involvement of external genital due to a combined vascular malformation. (A) Baseline. (B) One month after alpelisib treatment.

and amputation of first finger of left foot and fifth finger of left hand. Among other complications, she presented with vaginal bleeding due to venous malformations of external left genitalia needing frequent blood transfusions for anemia. Bleeding presented outside her menstruation and hysteroscopy ruled out other causes apart from the venous malformation. She also presented with pulmonary embolism due to deep venous thrombosis at 16 years of age, requiring oral anticoagulation with apixaban (5 mg/d). Besides, she needed a crutch for walking because of severe deformation of the left lower limb.

Treatment with oral sirolimus (3 mg/d) was started with adequate tolerance and no side effects. After 12 months of treatment without remarkable improvement, alpelisib (150 mg/d) was initiated under compassionate use after informed consent signing. Baseline blood analysis, genetic tests confirming *PIK3CA* mutation, and magnetic resonance imaging was performed before starting the treatment. One month later, the patient showed significant reduction of the malformation and disappearance of vaginal bleeding (Fig. 1). She related improvement in fatigue and in the ability of walking, without experiencing any side effect (clinical or analytical, assessed according to hepatic and renal function). Quality of life recorded according to Eastern Cooperative Oncology Group and Karnofsky performance status changed from 2 and 60 respectively, to 1 and 80.

The patient was then considered a candidate for surgical debulking and reconstruction of external genitalia during alpelisib treatment, which was successfully performed with minor wound dehiscence as the only complication (Fig. 2).

At present, the patient has been receiving alpelisib for 5 months now, with great improvement in quality of life and ability to walk, with no need of transfusions and without any side effect.

Summary and Conclusion

PROS represent a broad spectrum of disorders caused by postzygotic mosaic mutations in the *PIK3CA* gene, resulting in different patient phenotypes, ranging from isolated macrodactyly to CLOVES syndrome.[1,2,4] Patients with PROS mainly receive supportive care because of debulking and mutilating surgery, sclerotherapy, or pharmacological treatment with variable response. Mammalian target of rapamycin inhibitors like sirolimus have shown good responses with a reasonable side effect profile. Unfortunately, a significant number of patients are do not respond to sirolimus and show a clinical course of progression and remain in a life-threatening condition.[5]

Recent evidence indicates that *PIK3CA* pathway inhibitors undergoing trials in cancer, in which gain of function mutations in *PIK3CA* are observed, can provide a therapy for PROS.[3,6] Research reports highlight the usefulness of selective phosphoinositide-3-kinase (*PI3K*)α inhibitors and mammalian target of rapamycin inhibitors to reduce the size and proliferation of these malformations. PI3Kα inhibitors selectively inhibit the class I *PI3K* catalytic subunit α isoform, showing a wider therapeutic index and fewer off-target toxicity. Among these, alpelisib is the first oral *PI3K*α-specific inhibitor and is undergoing continued testing in

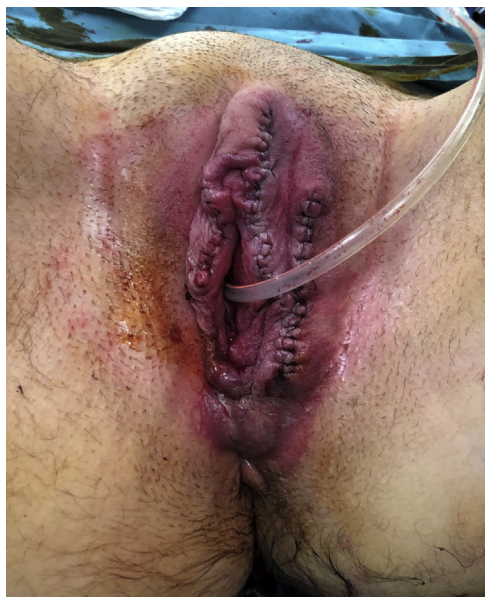

Fig. 2. Result after surgical debulking and reconstruction of external genitalia.

combination with a range of targeted therapies and chemotherapies in multiple phase I and phase II studies involving patients with a diverse range of cancers.[7–9]

Regarding PROS and vascular anomalies, alpelisib has been used to treat 19 patients with PROS who had life-threatening complications or were scheduled for debulking surgery, proving that this drug is able to improve the disease symptoms in all patients. Previously intractable vascular tumors became smaller, congestive heart failure was improved, hemihypertrophy was reduced, and scoliosis was attenuated making previously high-risk contraindicated surgical debulking and reconstruction, lately affordable. In addition, the treatment was not associated with any substantial side effects, proving the first direct evidence supporting *PIK3CA* inhibition as a promising therapeutic strategy in patients with PROS.[3]

In summary, we presented herein a patient with CLOVES syndrome and severe external genitalia involvement who responded to a low dose of alpelisib without any side effects, facilitating additional surgical reconstruction. A more selective inhibition of molecular pathways can be a promising therapeutic option for an appropriately selected group of candidates.

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