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Reporte de caso

Tuberous sclerosis: Prenatal diagnosis, treatment and one-year follow-up. A case report

Esclerosis tuberosa: diagnóstico prenatal, tratamiento y seguimiento de un año. Reporte de caso

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A B S T R A C T

Background: Tuberous sclerosis, occurring in approximately 2 % of pediatric tumors, leads to anomalous masses in various organs (retina, skin, lungs, kidneys, heart, and nervous system). Cardiac rhabdomyomas and brain lesions, causing heart failure and seizures, have shown improvement with Everolimus, a cell growth inhibitor. **Case report:** We present a one-year-old girl with tuberous sclerosis, cardiac rhabdomyomas, and subependymal astrocytoma. The treatments were Everolimus to reduce the lesions. After one year of follow-up, the cardiac and brain lesions decreased in the echocardiograms and MRI, but presences of the arrhytmias (right bundle branch block) were managed with metoprolol and seizures were treated with phenobarbital. No renal or ophthalmological involvement was evident during the one year of follow up. **Conclusion:** The Everolimus treatment (an m-TOR inhibitor) reduces cardiac rhabdomyomas and subependymal astrocytoma in tuberous sclerosis, marking progress in pediatric management.

R E S U M E N

Antecedentes: La esclerosis tuberosa, que se presenta aproximadamente en el 2 % de los tumores pediátricos, origina masas anómalas en varios órganos (retina, piel, pulmones,

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riñones, corazón y sistema nervioso). Los rabdomiomas cardiacos y las lesiones cerebrales, causantes de insuficiencia cardiaca y síndrome convulsivo, han hallado mejoría con Everolimus, inhibidor del crecimiento celular. **Resumen del caso:** Presentamos el caso de una niña con esclerosis tuberosa, rabdomiomas cardiacos y astrocitoma subependimario. Se utilizó Everolimus como tratamiento para reducir las lesiones. Tras un año de seguimiento, se notó disminución de las lesiones cardiacas y cerebrales en ecocardiograma y Resonancia Magnética Nuclear (RMN), pero con presencia de arritmias y bloqueo de rama derecha, manejados con Metoprolol y convulsiones tratadas inicialmente con fenobarbital. No se evidenció afectación renal u oftalmológica hasta el momento. **Conclusión:** El tratamiento con Everolimus (inhibidor del m-TOR) reduce rabdomiomas cardiacos y astrocitoma subependimario en esclerosis tuberosa, marcando avance en su manejo pediátrico.

Introduction

Tuberous sclerosis complex (TSC) is a genetic disorder characterized by the formation of benign tumors, called hamartomas, in various organs, primarily the brain, eyes, kidneys, heart, lungs, and skin (1). Neurological manifestations occur in up to 90 % of patients, often presenting as seizures and intellectual disability (2,3,4). TSC has an estimated incidence of 1 in 6 000 to 10 000 live births and accounts for around 2 % of childhood tumors (5,6,7,8). TSC demonstrates an autosomal dominant pattern of inheritance with complete penetrance but significant variability in clinical expression, even within families (9).

TSC results from mutations in the TSC1 or TSC2 tumor suppressor genes, which encode for proteins that form a complex that inhibits the mammalian target of rapamycin (mTOR) signaling pathway, critical for regulating cell growth and proliferation (9). Loss of TSC1/TSC2 function leads to overactivation of mTOR and subsequent formation of hamartomas in affected organs (9-12). Although TSC behaves genetically like an autosomal dominant condition, mosaicism is common in sporadic cases and influences disease severity (10,12).

Manifestations vary by organ system. Cardiac involvement includes rhabdomyomas (89 %), fibromas, myxomas, pericardial teratomas, and other tumors (2,5,9). These are the most common fetal and infant heart tumors, often causing heart failure, arrhythmias, and obstructions. Subependymal brain nodules may remain unchanged or transform into giant cell astrocytomas (6-20 %); renal angiomyolipomas, cysts, and carcinomas can also develop (5,9).

Prenatal diagnosis is now possible through fetal ultrasonography, detecting up to 70 % of lesions, and fetal MRI (11). Doppler echocardiography assesses cardiac tumors and hemodynamics. Cordocentesis, amniocentesis, and chorionic villus sampling aid chromosomal analysis and mutation detection (4,6). Intracardiac rhabdomyomas frequently regress but may cause arrhythmias, obstructed blood flow, or sudden death (1).

Previously, subependymal giant cell astrocytoma resection was standard given poor chemotherapy/radiation response and malignancy risks. The mTOR inhibitor everolimus has since demonstrated tumor volume reduction by ≥50 % in 35 % of patients (11,12).

Case report

A one-year-old male patient, fifth gestation, with a gestational age of 36.4 weeks based on an ultrasound at 8 weeks and 1 day, without pathological history. However, a detailed anatomical ultrasound at 28 weeks revealed multiple cardiac rhabdomyomas, ventricular asymmetry, tuberous sclerosis, and bilateral hydronephrosis (Figure 1). This was complemented with a neurosonogram that confirmed ventricular asymmetry and severe left ventriculomegaly. A cesarean section was performed on due to preterm labor at 35 weeks and a previous cesarean, and the newborn was admitted to the neonatal intensive care unit due to complex cardiopathy requiring incubator oxygen support. Pediatric echocardiography on [date] reported large rhabdomyomas of varying sizes, approximately 24 x 18 mm in the right ventricle, 27 x 14 mm in the left ventricle, and 7 x 4 mm at the septal level, with a 1.5 mm patent foramen ovale (Figure 2). There was no inflow or outflow obstruction, leading to the decision for expectant management. An electrocardiogram also revealed Wolff-Parkinson-White syndrome. Treatment was initiated with Everolimus and Metoprolol.

The transfontanelar ultrasound on shows nonspecific asymmetry in the volume of the left ventricle with marked prominence of the horn, atrium, and body (Figure 3). MRI on reports a lesion consistent with subependymal astrocytoma, bilateral frontoparietal nodular lesions, and multiple subependymal nodules in the lateral ventricles. However, the patient remains asymptomatic, leading to a decision of expectant management by pediatric neurology. Pediatric ophthalmological assessment on finds no ocular lesions.

The neonate was admitted to the neonatal intensive care unit due to secondary heart failure from an underlying condition requiring inotropic support. A follow-up at 3 months on with a pediatric echocardiogram reveals a progressive reduction in the diameter of cardiac lesions without hemodynamic repercussions (Figure 3). An electrocardiogram shows an intermediate-degree block of the right branch of the His bundle. Management continues with Everolimus, Metoprolol is discontinued and Propanolol is continued.

Neurological follow-up with cerebral MRI on shows a decrease in lesion size compared to the previous scan, and the patient remains asymptomatic with normal neurological development.

At 9 months of age, the patient is readmitted on due to a febrile convulsion and gastrointestinal symptoms. During this hospitalization, antibiotic treatment is administered for gastrointestinal tract infection. The patient is evaluated by Pedia-

tric Neurology, which, considering the underlying condition, subependymal nodulations, and suspicion of astrocytoma, initiates anticonvulsant management with phenobarbital. But in the regular follow-up, recommended modification for Vigabatrin.

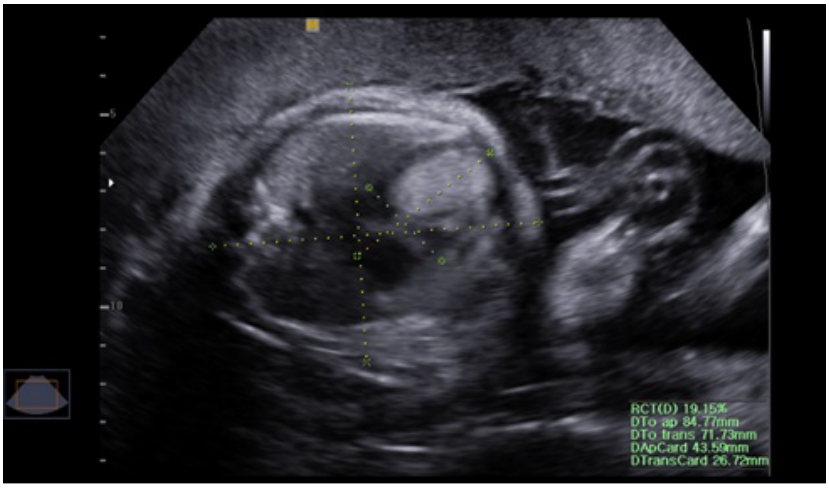

Figure 1. Detailed anatomical ultrasound at 28 weeks shows evidence of multiple cardiac rhabdomyomas, ventricular asymmetry, and bilateral hydronephrosis.

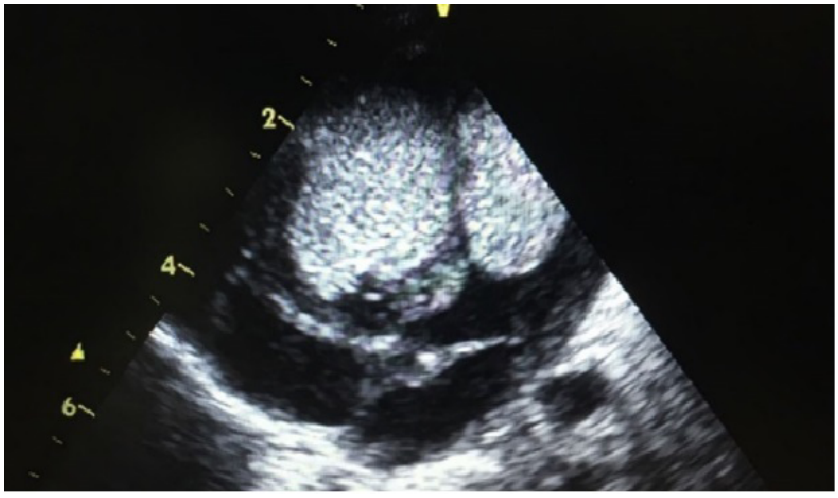

Figure 2. Pediatric echocardiogram (at birth) reveals right ventricle dimensions of approximately 24 x 18 mm, left ventricle dimensions of 27 x 14 mm, septal dimension of 7 x 4 mm, and a 1.5 mm patent foramen ovale; evidence of rhabdomyomas of varying sizes.

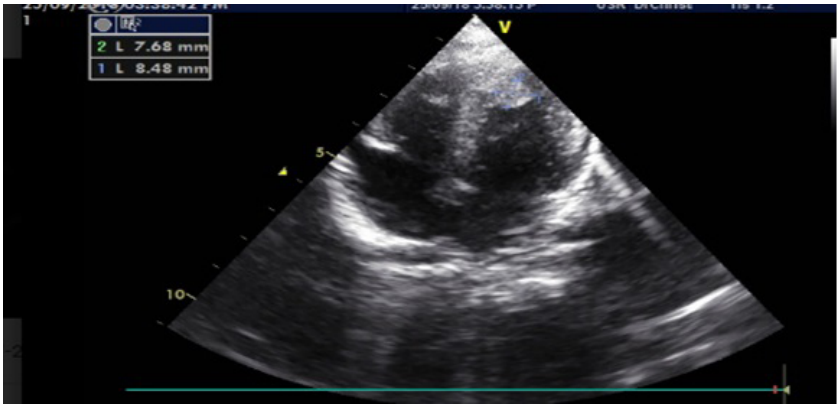

Figure 3. A follow-up pediatric echocardiogram at 3 months reveals an intermediate-degree block of the right branch of the His bundle, with a progressive reduction in the diameter of cardiac lesions.

Discussion

Tuberous sclerosis is a rare pathology, often diagnosed prenatally (12-15), affecting various organs including the brain, eyes, kidneys, heart, lungs, and skin (1,3,5). Intracardiac rhabdomyomas frequently regress but can cause arrhythmias, blood flow obstruction, or sudden death (1-7). Considering the high frequency (89-97 %) of cardiac rhabdomyomas (5,8,9), postnatal echocardiography confirmed right and left ventricular lesions without obstruction in this case. The patient exhibited Wolff-Parkinson-White arrhythmia requiring beta-blockers.

Subependymal giant cell astrocytomas (SEGA) comprise 90 % of tuberous sclerosis intracranial tumors (2,5,9), often diagnosed prenatally or neonatally (15). Prenatal/neonatal ultrasound and MRI are crucial for diagnosis and monitoring (9,14,15). MRI revealed asymptomatic subependymal astrocytomas, nodular lesions, and subependymal nodules. Symptoms often arise between 8-19 years, but neonatal onset occurs (2-5); here, seizures began at 9 months requiring anticonvulsants.

Cardiac rhabdomyomas frequently regress spontaneously (10,13,15). Surgery is reserved for significant ventricular outflow tract obstruction (7). For SEGA, early complete resection is preferred given poor chemotherapy/radiotherapy response and malignancy risks (12-15). The mTOR inhibitor everolimus reduces growth [3) and SEGA volume (16). Costales et al. (12) described everolimus efficacy for SEGA with good response and minimal adverse effects. Here, everolimus reduced cardiac and cerebral lesion size on imaging. Despite follow-up arrhythmia and seizures, no renal or ophthalmologic lesions have been observed to date.

Close monitoring and individualized treatment are important in this heterogeneous disorder, as continued follow-up of treatment response is essential (17). Additional anomalies may emerge, requiring tailored management (16).

Conclusions

Tuberous sclerosis is a rare genetic disorder characterized by the development of noncancerous tumors in various parts of the body. The introduction of mTOR-inhibiting drugs, particularly Everolimus, has shown promise in reducing these tumors with minimal side effects, making it safe for long-term use. Due to the complexity of tuberous sclerosis, comprehensive understanding is crucial, emphasizing careful monitoring and personalized treatment approaches. Ongoing follow-up is essential to identify and address potential additional abnormalities, contributing valuable knowledge to the existing body of research and guiding future clinical practices.

Conflict of Interest. The authors declare no conflicts of interest.

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