Case Report

Antenatal everolimus therapy for fetal cardiac rhabdomyomas in tuberous sclerosis: A case report of tumor regression and seizure-free neonatal outcome

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ABSTRACT

We present an exceptionally rare and high-risk scenario of fetal cardiac rhabdomyoma, with the largest lesion postnatally measuring 3 × 2.4 cm size seldom reported in the literature and traditionally associated with severe complications such as outflow obstruction or hydrops. It was detected at 21+6 weeks' gestation during routine anomaly scanning in a healthy primigravida. Detailed fetal echocardiography revealed three homogeneous, hyperechogenic masses involving the right ventricle and interventricular septum, raising a strong suspicion for tuberous sclerosis complex (TSC). Genetic testing confirmed a pathogenic TSC1 mutation. In a groundbreaking therapeutic intervention, antenatal everolimus was initiated at 24 weeks of gestation, resulting in significant *in utero* tumor regression-an approach not widely documented. Postnatal management included continuation of Everolimus, serial 2D echocardiographic monitoring showing further mass reduction, and seizure control with phenobarbital initiated based on electrographic seizures detected on electroencephalography. This case not only emphasizes the importance of early antenatal detection but also pioneers the potential of *in utero* targeted therapy to alter the natural history of genetic syndromes like TSC.

Key words: Antenatal everolimus therapy, Cardiac rhabdomyoma, Fetal cardiac tumor, *In-utero* tumor regression, Neonatal tuberous sclerosis, Tuberous sclerosis complex

Cardiac rhabdomyomas are the most frequently encountered primary fetal cardiac tumors, with an estimated incidence of 1 in 40,000 live births [1]. These benign hamartomas of striated muscle typically present as non-vascular, homogeneous, hyperechogenic intracardiac masses and are most commonly located in the interventricular septum or ventricular walls [2,3]. With the advent of high-resolution prenatal ultrasonography, diagnosis is now possible, as early as 20 weeks of gestation, allowing for early evaluation and parental counseling [2,3]. Of critical significance is the strong association of multiple cardiac rhabdomyomas with tuberous sclerosis complex (TSC), an autosomal dominant neurocutaneous syndrome resulting from pathogenic mutations in the *TSC1* or *TSC2* genes [3-5]. Conventionally, antenatal management has followed a conservative, observational approach under the assumption of spontaneous postnatal involution [4,6]. Over 80–90% of fetuses with multiple rhabdomyoma are ultimately diagnosed with TSC, making these tumors the earliest recognizable manifestation of the condition [5-7]. TSC affects multiple organ systems, manifesting as cortical tubers, subependymal nodules, hypomelanotic macules, facial angiofibroma, renal angiomyolipoma, and retinal astrocytoma. Long-term sequelae include intractable epilepsy, intellectual disability, autism spectrum disorder, and other neuropsychiatric manifestations [6,7].

Although spontaneous regression of cardiac rhabdomyoma is frequently reported postnatally, up to 60% in some series [1,8,9], their presence during fetal life is not always benign. Tumors can cause arrhythmias, hemodynamic compromise, cardiac outflow tract obstruction, hydrops fetalis, or intrauterine demise [6,10,11]. Recent advances in the understanding of TSC pathophysiology have reshaped this paradigm. Dysregulation of the mammalian target of rapamycin (mTOR) pathway is now recognized as a central molecular mechanism in TSC. Consequently, mTOR inhibitors such as everolimus and sirolimus have emerged as disease-modifying agents capable of inducing regression of cardiac and cerebral lesions, reducing seizure burden, and improving neurodevelopmental outcomes in postnatal settings [5,9,12].

In light of this evolving landscape, we present a rare and impactful case of antenatally diagnosed multiple cardiac rhabdomyoma associated with genetically confirmed TSC, in

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which antenatal Everolimus therapy was initiated at 24 weeks gestation.

CASE REPORT

A 26-year-old primigravida with an unremarkable antenatal history underwent routine second-trimester anomaly scanning at 21+6 weeks' gestation. Fetal ultrasonography revealed three well-defined, homogeneous, hyperechogenic masses arising from the fetal myocardium: one measuring 1.3×1.2 cm in the right ventricular free wall, and two smaller lesions within the interventricular septum and near the left ventricular apex (Fig. 1a). No evidence of hydrops fetalis, pericardial effusion, or associated structural anomalies was noted at that time.

Given the presence of multiple cardiac masses, a presumptive diagnosis of fetal cardiac rhabdomyoma was made. Recognizing the strong association with TSC, amniocentesis was performed, confirming a pathogenic heterozygous mutation in the *TSC1* gene. In view of the size and multiplicity of the lesions and the potential risk of cardiac outflow tract obstruction, a decision was made to initiate antenatal targeted therapy. After multidisciplinary consultation, the mother was started on oral everolimus 2 mg daily beginning at 24 weeks of gestation. Serial fetal echocardiograms demonstrated a gradual reduction in mass dimensions over the following weeks, and no signs of hemodynamic compromise were observed.

The mother underwent elective lower-segment cesarean section at 38+3 weeks due to obstetric indications. A live female infant was delivered with a birth weight of 2.46 kg. APGAR scores were 7 and 9 at 1 and 5 min, respectively. The neonate exhibited mild tachypnea but maintained excellent oxygenation with four-limb SpO_2 >95%. Cardiovascular and neurological examinations were otherwise unremarkable at birth, with no visible neurocutaneous markers.

Postnatal imaging and workup includes 2D Echocardiography (Day 1): Multiple homogeneous, hyperechogenic masses were identified in the right and left ventricular apices, the posterior wall of the left ventricle, interventricular septum, and subaortic region. The largest lesion measured 3 × 2.4 cm, causing mild right ventricular outflow tract obstruction (Fig. 1b). Cardiac magnetic resonance imaging (MRI) (Day 3): Confirmed multiple intramural masses without pericardial effusion; detailed mapping showed no dynamic flow limitation across valves (Fig. 1b). 3T Brain MRI (Day 4): Revealed multiple cortical tubers and subependymal nodules along the lateral ventricles (Fig. 2a), consistent with central nervous system involvement in TSC. Electroencephalography (EEG): Captured electrographic seizures originating from the right frontal cortex, despite no clinical convulsions (Fig. 2b). Fundoscopic examination: Demonstrated bilateral retinal astrocytomas (Fig. 3), further corroborating the diagnosis of TSC.

Postnatally, Everolimus was continued at a dose of 1 mg/m²/day after adjusting for the neonate's body surface area. The neonate was also started on phenobarbital prophylactically to manage subclinical seizure activity detected on EEG. Serial

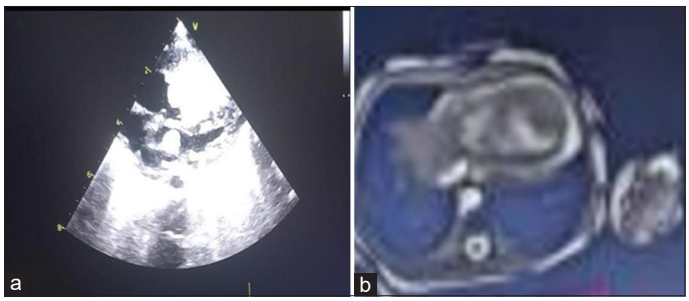

Figure 1: (a) 2D Echo – Multiple homogenous, intra cardiac masses in right and left ventricular apex, left ventricular post wall, inter ventricular septum and sub aortic valve suggestive of rhabdomyoma and (b) Cardiac magnetic resonance imaging - Right ventricular Rhabdomyoma 3 × 2.4 × 2.6 with right ventricular outflow tract obstruction, intra cavitary lesion 95 mm along left ventricular lateral wall and 6 mm lesion in the left ventricular out flow tract causing left ventricular outflow tract obstruction

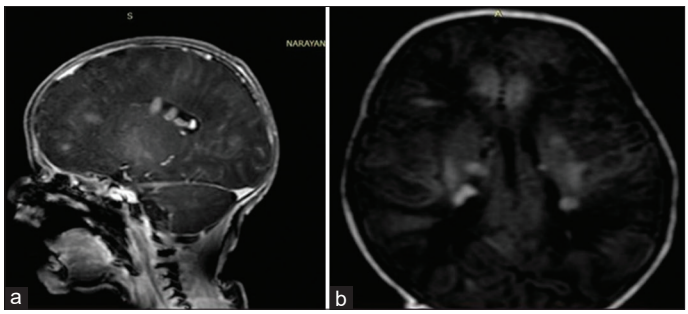

Figure 2: (a) 3T Magnetic resonance imaging brain-multiple foci of cortical thickening in cerebral hemispheres on both sides with periventricular nodule consistent with tuberous sclerosis and (b) Electroencephalography-Electrographic seizures of right frontal region

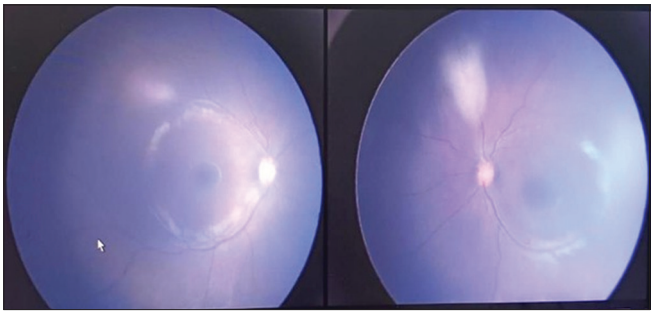

Figure 3: Fundus of eye - bilateral retinal astrocytomas present

echocardiograms over two months demonstrated progressive regression of the intracardiac masses. Importantly, there was no worsening of outflow tract obstruction, no development of heart failure, and no arrhythmias. The neonate remained seizure-free, with no further electrographic abnormalities detected on follow-up EEG. Currently at two months of age, the infant is hemodynamically stable, seizure-free, and thriving on continued multidisciplinary follow-up involving pediatric cardiology, neurology, ophthalmology, and genetics teams.

DISCUSSION

TSC is a genetically heterogeneous neurocutaneous syndrome resulting from mutations in either the *TSC1* or *TSC2* genes. It

is marked by the development of multisystem hamartomas, prominently involving the heart, brain, kidneys, skin, and eyes. Zhou *et al*. stressed the importance of echocardiographic criteria to distinguish rhabdomyoma from other intracardiac masses such as fibromas or myxomas, a distinction with major implications for counseling and management [2]. For instance, Bader *et al*. described a cohort of prenatally diagnosed cases in which the rhabdomyoma regressed postnatally, avoiding the need for intervention and cardiac rhabdomyoma is often the first detectable manifestation of TSC, especially during fetal life, and serve as crucial prenatal diagnostic markers [3]. The detection of multiple cardiac rhabdomyoma on routine antenatal scans is highly predictive of an underlying TSC diagnosis. Data from the large prenatal series report that over 80–90% of fetuses with multiple rhabdomyoma eventually meet clinical or genetic criteria for TSC [4]. Historically, management has been conservative, often guided by the presumption that rhabdomyoma would regress naturally after birth. However, fatal outcomes due to obstructive lesions have also been reported, highlighting the limitations of a purely expectant approach.

Advances in the understanding of TSC pathophysiology have catalyzed a paradigm shift in management. The mTOR pathway, dysregulated in TSC, serves as a promising therapeutic target. Butany *et al*. conducted a comprehensive review highlighting the emerging pharmacologic alternatives to surgical management, although at the time, use was largely limited to postnatal applications [4]. The introduction of mTOR inhibitors such as Everolimus and Sirolimus has significantly altered the clinical trajectory for many patients. Diwan *et al*. reported one of the earliest successful uses of postnatal Everolimus to reduce cardiac rhabdomyoma size and improve seizure control [5]. A clinical breakthrough was documented by Roberts *et al*., who published a pioneering series on the antenatal use of Everolimus [6]. Their cases demonstrated significant tumor regression *in utero,* although they lacked long-term neurodevelopmental follow-up. Subsequent reports by Garcia and Lee, as well as Lee *et al*., described neonates with life-threatening cardiac obstruction requiring surgical debulking, further underscoring the importance of fetal interventions in severe cases [7,8]. Our case represents a distinctive evolution in this field. Prenatal everolimus was initiated at 24 weeks' gestation, with close multidisciplinary monitoring. Imaging confirmed notable *in utero* regression of the cardiac tumors, and postnatally, the child remained hemodynamically stable with no need for surgical intervention. Electrographic seizures were identified early and managed effectively with phenobarbitone, and no further neurologic deterioration was noted.

The implications of this case are multifold. First, it highlights that fetal cardiac rhabdomyoma can serve not just as diagnostic markers of TSC but as modifiable disease targets. Early initiation of Everolimus may reduce fetal morbidity, prevent cardiac compromise, and alter the trajectory of neurological involvement. This is supported by findings from Santos *et al*., who demonstrated improved neurodevelopmental outcomes with earlier initiation of mTOR inhibitors [9]. Further, Kumar *et al*. and Tan and Wong provided case series where combined antenatal and postnatal Everolimus therapy led to sustained regression of cardiac masses and stabilization of neurological signs [10,11]. Recent studies by Fernandez and Diaz and Zhang and Li have emphasized the utility of fetal and neonatal MRI to track rhabdomyoma and cortical tuber evolution under mTOR therapy, a protocol followed closely in our case with consistent imaging follow-up [12]. Although postnatal spontaneous regression occurs in up to 60% of cardiac rhabdomyoma, during fetal life these tumors can pose significant hemodynamic risks such as outflow tract obstruction, arrhythmias, hydrops fetalis, and intrauterine demise [13-15].

The novelty of our report lies not just in therapeutic timing but also in comprehensiveness. This case integrates antenatal decision-making, imaging, pharmacologic treatment, genetic confirmation, and neuro-ophthalmologic evaluation-all hallmarks of multidisciplinary excellence. To the best of our knowledge, it is among the first detailed Indian case reports to document safe and effective antenatal use of everolimus with robust postnatal follow-up.

CONCLUSION

This groundbreaking case demonstrates that antenatal Everolimus therapy can safely and effectively induce regression of even large (3 × 2.4 cm) fetal cardiac rhabdomyoma, challenging the traditional paradigm of conservative postnatal management. By initiating mTOR inhibition at 24 weeks of gestation, we achieved not only significant tumor reduction but also prevented cardiac complications and improved neurological outcomes - a critical advance for TSC. These findings illuminate a new frontier in prenatal medicine, where targeted molecular therapies may transform outcomes for genetic disorders before birth. We urge the medical community to establish formal guidelines for fetal mTOR inhibitor use through multicenter trials, potentially revolutionizing care for TSC and other congenital conditions.

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