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"Multiple Cardiac Rhabdomyomas in a Newborn Successfully Treated with a TOR inhibitor: A Case Report"

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ABSTRACT

Introduction:Cardiac rhabdomyomas are the most common primary cardiac tumors in neonates and are strongly associated with tuberous sclerosis complex (TSC). While most lesions regress spontaneously, extensive or multifocal tumors may lead to ventricular dysfunction, arrhythmias, or hemodynamic compromise, prompting consideration of targeted therapy with mammalian target of rapamycin (mTOR) inhibitors.

Case Report:We report a male neonate born at 36 weeks' gestation with prenatally detected intracardiac masses. Postnatal echocardiography revealed multiple large cardiac rhabdomyomas diffusely involving all cardiac chambers, causing marked reduction in ventricular cavity size, biventricular diastolic dysfunction, and moderate pericardial effusion, with preserved outflow tracts. Brain magnetic resonance imaging demonstrated multiple subependymal tubers, confirming the diagnosis of TSC. Everolimus therapy was initiated early in the neonatal period. After three doses, a significant reduction in tumor size and improvement in ventricular function were observed. The infant developed frequent ventricular arrhythmias, which were successfully controlled with low-dose sotalol. Follow-up echocardiography at one month showed marked further regression of the rhabdomyomas and sustained clinical stability.

Discussion:This case illustrates the role of cardiac rhabdomyomas as an early diagnostic marker of TSC and supports the effectiveness of mTOR inhibition in achieving rapid tumor regression in neonates with extensive cardiac involvement. However, the persistence of arrhythmias despite significant tumor reduction suggests that electrical abnormalities may not parallel structural improvement, highlighting the need for continued rhythm surveillance and adjunctive antiarrhythmic therapy.

Conclusion:Early recognition of TSC-associated cardiac rhabdomyomas and prompt initiation of Everolimus can result in rapid tumor regression and functional improvement, potentially avoiding surgical intervention. Comprehensive multidisciplinary follow-up remains essential to address ongoing cardiac and neurological risks and to better define the long-term safety of mTOR inhibitors in neonates.

Keywords: *Cardiac rhabdomyoma -Tuberous sclerosis complex-Neonate-Everolimus-mTOR inhibitors-Cardiac tumors-Ventricular arrhythmia-Prenatal diagnosis.*

INTRODUCTION

Cardiac rhabdomyomas are benign hamartomatous primary cardiac tumors in the pediatric population, affecting up to 0.17% of infants [1]. They were reported in 60% of patients with Tuberous sclerosis complex (TSC) [2–4]. They are among the earliest features of TSC and can appear in utero or in the neonatal period [4].

Given this strong connection, understanding the epidemiology, genetic basis, and relationship between TSC and cardiac rhabdomyomas is essential. TSC is an autosomal dominant genetic disease occurring in 1/6000 live births [3][5], and it may

involve multiorgan hamartomas, especially cardiac rhabdomyomas [2–3]. In addition, 50%–90% of fetuses with a cardiac rhabdomyoma had TSC [1], and there is a 95% chance of confirming the diagnosis with TSC when several cardiac rhabdomyomas exist, making the presence of cardiac rhabdomyomas an early clinical sign that heralds the diagnosis [5]. Diagnosis of cardiac rhabdomyomas is made prenatally at a median of 29 weeks [1], where only 10% of cardiac rhabdomyomas were isolated and 90% were multiple [6]. The majority of cardiac rhabdomyomas regress on their own; however, a few can lead to hemodynamic compromise or arrhythmias, requiring subsequent intervention for treatment or prevention of possible complications [7]. More favorable outcomes were observed in simple cardiac rhabdomyomas compared to TSC-associated cardiac rhabdomyomas despite no significant differences in tumor diameter [1].

In neonates with TSC, cardiac rhabdomyomas have been shown to significantly decrease in size following Everolimus (an mTOR inhibitor), which often eliminates the requirement for surgery and offers a viable alternative when surgery is not an option [8]. This pharmacologic choice in treatment is consistent with the underlying pathophysiology of TSC, where tumor growth is driven by mTOR pathway dysregulation [9][10].

Aside from its cardiac effects, Tuberous sclerosis influences various organ systems, resulting in neurological and psychiatric comorbidities that greatly affect quality of life. TSC can be correlated with other conditions including neuropsychiatric disorders and diffuse hamartomas in retina, liver, and kidney, with various renal complications [5][11]. Thus, the impact is not just physical and psychological, but also social and financial for the individual affected and their family [4].

Given the systemic nature of TSC and its potential for serious complications, treatment strategies should address both cardiac and non-cardiac manifestations. While treatment is not always necessary for the cardiac rhabdomyomas since they can be asymptomatic, some may still result in clinical symptoms that range from minor to more serious ones, ranging from cardiac arrhythmias and outflow tract obstruction to heart failure, which may necessitate intervention [1][5]. The rhabdomyoma histotype is the most surgically operated on cardiac tumor [12]; however, therapeutic decisions especially in symptomatic neonates increasingly consider non-surgical routes such as pharmacotherapy with Everolimus and close monitoring to avoid adverse events [13].

To appreciate the pharmacological treatment, it is important to understand the pathogenesis of Tuberous sclerosis that may be implicated in the formation of cardiac rhabdomyomas. The protein complex TSC1/TSC2 serves an important function in cell growth regulation and tumor suppression by controlling mammalian target of rapamycin (mTOR); mutations in the TSC1 and TSC2 genes underlie the pathogenesis of Tuberous sclerosis [9].

This mechanism explains the rationale behind treatment via mammalian target of rapamycin inhibitors (mTORi) Everolimus or Sirolimus which target the dysregulated mTOR pathway. In a systematic review and meta-analysis by Mustafa et al. [14], prenatal use of an mTORi demonstrated evidence of cardiac rhabdomyoma size reduction and improvement in the outflow tract obstruction without evidence of demise. Oral sirolimus use in the mother was associated with rhabdomyoma size reduction in the fetus, too [15]. In children, a systematic review by Sugalska et al. [5] demonstrated that cardiac rhabdomyoma size reduction and clinical improvement was achieved in 95.1% and 90.9% of born patients respectively. However, caution was advised with result interpretation due to lack of large cohort studies or randomization [5].

Nonetheless, in fetuses with high mortality risk, treatment with sirolimus both during pregnancy and after delivery was associated with cardiac rhabdomyoma size reduction [15]. Furthermore, statistically significant tumor burden reduction with mTORi has been established for brain and renal manifestations of TSC including subependymal giant cell astrocytomas and angiomyolipomas [13].

CASE REPORT:

We describe here a male newborn with multiple cardiac rhabdomyomas that was admitted to our neonatal intensive care unit. He was born at 36 weeks of gestation via uncomplicated cesarean section without requiring resuscitation. Maternal history was unremarkable, but the pregnancy course was complicated by polyhydramnios and intracardiac mass detected on the morphological scan ultrasound at 26 weeks of gestation.

Shortly after birth, the patient developed respiratory distress requiring intubation and surfactant administration. His physical exam was unremarkable, showing no skin abnormalities, flat and open fontanelles, no palpable abdominal masses, regular heart sounds and minimal subcostal retractions accompanied by tachypnea. His neurological assessment revealed mildly reduced muscle tone with intact primitive reflexes. The chest radiograph was consistent with respiratory distress syndrome along with near complete opacification of the left hemithorax obscuring the cardiac silhouette, which was suspected to be enlarged. An echocardiogram revealed multiple, diffuse rhabdomyomas involving all heart chambers with the largest measuring 6.8 × 3.9 cm at the apex towards the right ventricular (RV) cavity [Figure 1a], in addition to one large rhabdomyoma involving the pericardial space. There was a significant reduction in both right ventricular (RV) and left ventricular (LV) cavity sizes due to tumor burden and biventricular diastolic dysfunction, with patent outflow tracts. A moderate pericardial effusion was also noted. A brain MRI [Figure 2a] showed two subependymal tubers at the foramen of Monro, the largest measuring 4.7 mm on the right. And few bilateral subependymal tubers along the lateral ventricle walls were also noted [Figure 2b]. The presence of multiple cardiac rhabdomyomas and numerous subependymal and lateral ventricle tubers confirmed the diagnosis of tuberous sclerosis complex. Ultrasound of both kidneys, liver, and abdomen was

normal. Additionally, ophthalmological exam did not show any hamartomas in the retina or the optic nerve.

Everolimus therapy was initiated at 0.25 mg per dose twice weekly. After 3 doses of the medication, a notable reduction in the size of the cardiac rhabdomyomas was seen on the repeat echocardiogram where the largest mass decreased to 5.1 x 2.9 cm with improvement in the ventricular function. During his stay, he developed several episodes of arrythmias reaching 220 bpm which were self-resolved. Electrocardiography (ECG) showed normal sinus rhythm with normal PR and QT intervals. A 24-hour Holter monitor revealed frequent premature ventricular contractions (PVCs), including couplets, triplets, and an episode of bigeminy for which baby was started on low dose of Sotalol, resulting in the resolution of the premature ventricular contractions. The patient was discharged home on the same dose of Everolimus after two weeks. At a follow-up visit in the cardiology clinic after 1 month, an echocardiography demonstrated a marked reduction in the size of the rhabdomyomas, with the largest measuring approximately 1.8 × 1.6 cm [Figure 1b].

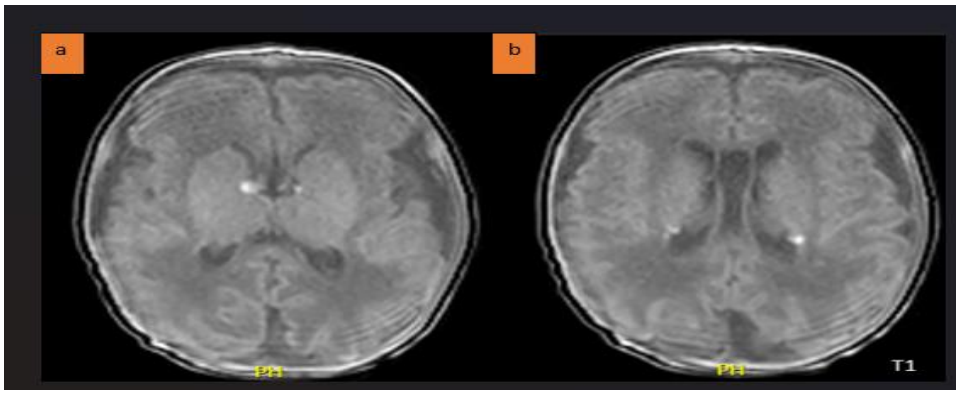

Figure 1a. **Diffuse rhabdomyomas involving all heart chambers with the largest measuring 6.8 × 3.9 cm at the apex towards the right ventricular.** ***Figure 1b.*** **Marked reduction in the size of the rhabdomyomas, with the largest measuring approximately 1.8 × 1.6 cm**

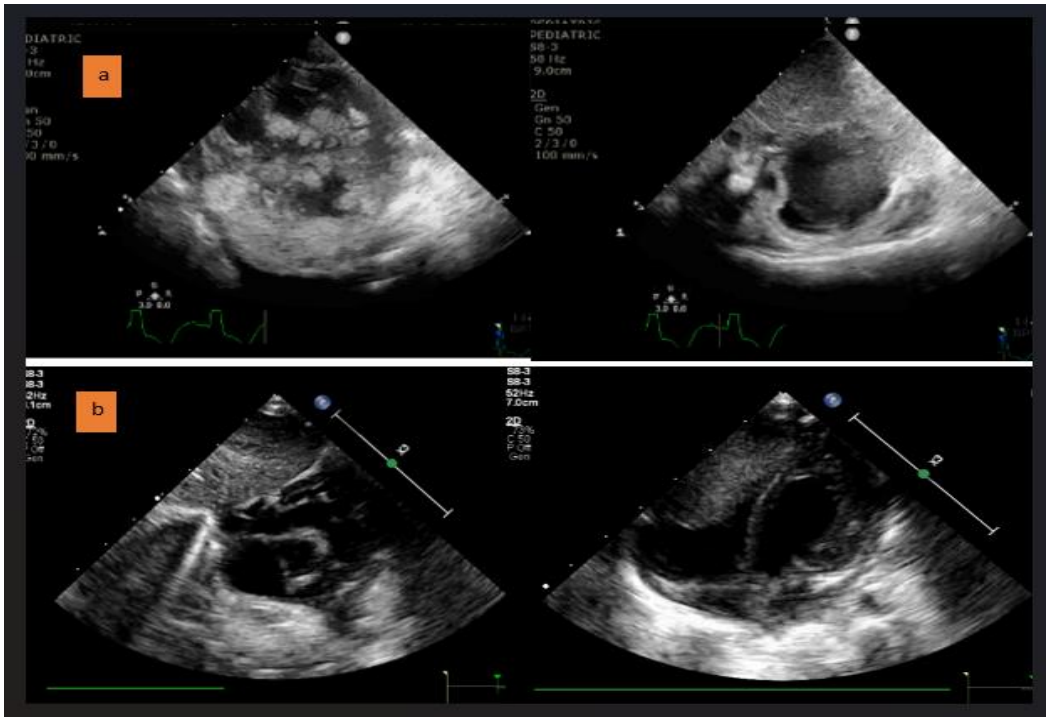

Figure 2**a. Subependymal tubers at the foramen of Monro;** ***Figure 2*****b. Few bilateral subependymal tubers along the lateral ventricle walls**

DISCUSSION:

Our case highlights a unique presentation of a patient with multiple large cardiac rhabdomyomas occupying all chambers and arrhythmias, with significant tumor size reduction evident after use of Everolimus, yet with persistence of arrhythmias.

The case presented further emphasizes the critical role of cardiac rhabdomyomas as an early diagnostic marker of TSC. Our case corroborates this finding, as the newborn presented with diffuse, multiple cardiac rhabdomyomas and subependymal tubers, as two major indicators confirming TSC.

Since TSC might be asymptomatic at birth, early prenatal detection is crucial to avoiding a delayed diagnosis. In this case, prenatal ultrasound at 26 weeks revealed intracardiac masses, raising suspicion for TSC and played a pivotal role in guiding the postnatal diagnostic workup.

The lack of cutaneous manifestations at birth further emphasizes the nevessity of cardiac imaging antenatally and neonatal screening protocols for TSC.

The spectrum of cardiac rhabdomyomas ranges from asymptomatic to potentially fatal consequences. Some cases, like the one described, might result in substantial ventricular dysfunction, pericardial effusion, and arrhythmias, while the majority (~81%) regress spontaneously (1).

In this case, despite significant tumor burden compressing ventricular cavities, the newborn remained hemodynamically stable with normal heart rate and blood pressure. However, the large tumor burden and the presence of pericardial effusion raised concerns for potential obstructive physiology and diastolic dysfunction.The newborn developed frequent premature ventricular contractions (PVCs), including couplets, triplets, and bigeminy, requiring low-dose Sotalol. Literature suggests that arrhythmias in cardiac rhabdomyomas are uncommon but have the potential to be rather serious (16). Among the mechanisms are mechanical compression of cardiac structures or tumor infiltration into the conduction system. The resolution of arrhythmias with antiarrhythmic therapy suggests that while mTOR inhibitors shrink tumor size, adjunctive management of cardiac conduction abnormalities remains necessary.

The rapid tumor size reduction from 6.8 × 3.9 cm to 5.1 × 2.9 cm within three doses of Everolimus, is consistent with findings from systematic reviews demonstrating that mTOR inhibitors lead to tumor regression in ~95% of patients (5). The pathophysiological basis for mTOR inhibitors lies in the dysregulation of the TSC1/TSC2 complex, leading to uncontrolled mTOR activation and aberrant cell proliferation (8). By inhibiting mTOR, Everolimus and Sirolimus restore cell cycle control, reducing tumor size and enhancing cardiac function. However, while tumor size reduction is well-established, long-term safety data on mTOR inhibitors in neonates remains limited. Potential adverse effects include immune suppression, stomatitis, and hyperlipidemia, necessitating careful dose titration and therapeutic monitoring.

Beyond cardiac manifestations, TSC has extensive neurological involvement, as evidenced in this case with multiple subependymal tubers found on brain MRI and possible additional neurological comorbidities such as seizures often refractory to treatment (7), Intellectual disability, autism spectrum disorder (ASD), and behavioral issues. The presence of multiple subependymal tubers suggests a higher likelihood of seizure onset, necessitating early EEG monitoring. Importantly, Everolimus has also been shown to be effective in reducing Subependymal Giant Cell Astrocytomas (SEGAs) and epilepsy burden in TSC patients (4).

Despite advances in TSC management, gaps remain in understanding the long-term effects of mTOR inhibitors in neonates and assesing the impact of early Everolimus therapy on cognitive and behavioral outcomes in TSC patients.

This case underscores the critical role of cardiac rhabdomyomas as a sentinel finding for TSC and highlights the effectiveness of mTOR inhibitors in reducing tumor burden. While Everolimus therapy resulted in rapid tumor regression and improved cardiac function, the presence of neurological involvement reinforces the necessity for comprehensive, long-term surveillance. The successful management of this patient emphasizes the value of early detection, multidisciplinary care, and continued research to improve outcomes for neonates with TSC-associated cardiac rhabdomyomas.

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