

Sirolimus-Induced Regression of Tuberous Sclerosis–Associated Cardiac Rhabdomyoma Causing Left Ventricular Outflow Tract Obstruction



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INTRODUCTION

Cardiac rhabdomyomas (CRs) are histologically benign tumors of the heart that are typically present at birth and account for approximately 60% of pediatric primary cardiac tumors.¹ They are closely associated with tuberous sclerosis (TS), with 81% of patients who have one or more ventricular rhabdomyomas being diagnosed with TS.² Diagnosis of CRs can be made with echocardiography as early as week 15 of gestation.³

Cardiac rhabdomyomas typically have no impact on cardiac function, and most patients are asymptomatic. Therefore, most patients require no intervention as the natural course of CRs is spontaneous regression.⁴ However, CRs may cause hemodynamic instability due to arrhythmias or serious anatomic sequelae including inflow or outflow obstruction.^{4,5} Such symptomatic lesions typically require surgical resection.

Recently, medical therapy with mTOR inhibitors such as sirolimus and everolimus has been found to cause partial or complete involution of TS-associated hamartomatous lesions including CRs and intracranial lesions. Thus, an alternative to surgical intervention now exists for patients with anatomically significant CRs who remain hemodynamically stable and do not require urgent surgical resection.⁶ We present a case of a CR colliding with the aortic valve and causing left ventricular outflow tract (LVOT) obstruction with aortic regurgitation that was adequately treated with sirolimus.

CASE PRESENTATION

A newborn male patient with no significant birth history was found to have a murmur on his initial exam. Otherwise, the patient had an unremarkable newborn nursery course. The patient was scheduled for

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VIDEO HIGHLIGHTS

Video 1: Parasternal long-axis view with color Doppler at initial presentation showing a large rhabdomyoma with LVOT obstruction.

Video 2: Parasternal long-axis view with color Doppler at 6 months after initiation of sirolimus therapy showing regression of rhabdomyoma without any LVOT obstruction.

Video 3: Parasternal long-axis view with color Doppler at 11 months after initiation of sirolimus therapy showing regression of rhabdomyoma without any LVOT obstruction.

Video 4: Parasternal long-axis views showing side-by-side comparison of size of the CR in LVOT after initiation of sirolimus therapy. On the left, at initial presentation, the large CR is seen to cause LVOT obstruction and is colliding with the aortic valve in systole. On the right, after 11 months of sirolimus therapy, a substantial reduction in size of this rhabdomyoma is seen, which is in close proximity to the aortic valve but no longer causing LVOT obstruction.

[View the video content online at www.cvcasejournal.com.](http://www.cvcasejournal.com)

an echocardiogram at an outside facility where tumors were identified. He was then transferred for further evaluation.

On initial presentation, the patient's vital signs were normal, including oxygen saturations of 100% on room air, blood pressure of 89/39 mm Hg, and heart rate of 110 beats per minute. Auscultation of the heart revealed a 3/6 systolic murmur best appreciated at the lower left sternal border. His biological parents and older sister were all healthy, and there was no family history of congenital heart disease, sudden unexplained death, arrhythmias, or TS. Electrocardiography showed normal sinus rhythm with right ventricular hypertrophy, possible biventricular hypertrophy, and nonspecific T-wave abnormalities.

A transthoracic echocardiogram was performed and showed numerous intracardiac rhabdomyomas along the interventricular septum and in both the right and left ventricular apices. Most masses measured around 5.0 mm in diameter (Figure 1). The largest mass measured 11.4 × 7.0 mm. It was located along the left ventricle lateral wall under leaflets of the mitral valve but did not cause resultant left ventricular inflow obstruction.

Another large pedunculated mass measuring approximately 10.3 × 7.5 mm was seen directly underneath the aortic valve within the LVOT causing outflow tract obstruction and turbulence of blood

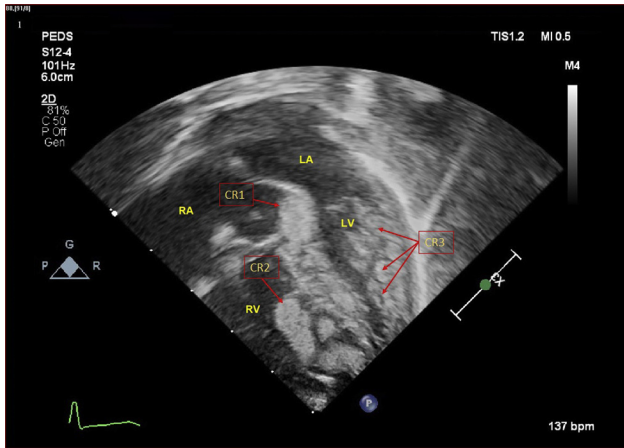


Figure 1 Apical four-chamber view depicting multiple intracardiac and intramyocardial rhabdomyomas in both the right ventricle (RV) and left ventricle (LV). A large intracardiac rhabdomyoma (CR1) is seen in the LVOT in close contact with the aortic valve. A second large intracardiac rhabdomyoma (CR2) is seen in the RV not causing inflow obstruction to the tricuspid valve. Multiple intramyocardial rhabdomyomas (CR3) are seen in the LV lateral wall including a larger mass close to the mitral valve not causing inflow obstruction. LA, Left atrium; RA, right atrium.

flow (Video 1, Figures 2-4). It also appeared to come into contact with both the mitral and aortic valves intermittently (Figure 5). Flow velocity was measured to be 3.25 m/sec with a peak pressure gradient of 42 mm Hg and a mean gradient of 23 mm Hg. Mild aortic regurgitation was also noted with no other suspected causes. There was associated increased left ventricular posterior wall thickness and interventricular septal thickness.

The patient was asymptomatic and hemodynamically stable, but due to the concern for aortic valve injury, the pediatric cardiology team elected to treat the CRs medically with sirolimus. The patient was initially started on 0.6 mg/m² per day. The patient's sirolimus levels were carefully monitored and titrated to consistently be within the therapeutic range of 5-15 ng/mL. Neurology, genetics, and nephrology services were then consulted. A kidney ultrasound revealed several simple cortical cysts bilaterally, and a brain magnetic resonance imaging without contrast revealed multiple subependymal nodules. Given the findings of subependymal nodules and presence of pathognomonic multifocal CRs, the diagnosis of TS was made. The diagnosis was confirmed with genetic testing significant for pathogenic mutation in TS complex 2 gene. Neurology agreed with continuation of sirolimus therapy for treatment of TS-associated hamartomatous intracranial lesions.

Approximately 1 month following the initiation of sirolimus, a repeat echocardiogram was performed. Only two residual rhabdomyomas were identified. One was located within the right ventricle. The other was the rhabdomyoma that had been causing LVOT obstruction. This lesion now measured 5.3 × 6.0 mm, and flow across the LVOT was measured to have a maximum velocity of 1.8 m/sec with a peak instantaneous pressure gradient of only 7 mm Hg (Figures 6 and 7). This was a significant improvement from the initial study. Measurements taken by echocardiogram at 4 months of treatment were similar. The mass continued to gradually decrease in size. At 6 months, it measured 4.6 × 5.8 mm (Video 2), and in the most recent study done at 11 months, the mass had further regressed to 3.0 × 4.7 mm with no LVOT obstruction (Videos 3 and 4, Figure 8). Additionally, the right ventricular apical mass was noted to have completely regressed.

The patient continued with sirolimus therapy. He had normal growth and development during this time without evidence of opportunistic infections. He continued to remain asymptomatic and had no progression of aortic valve pathology. Repeat physical exam revealed

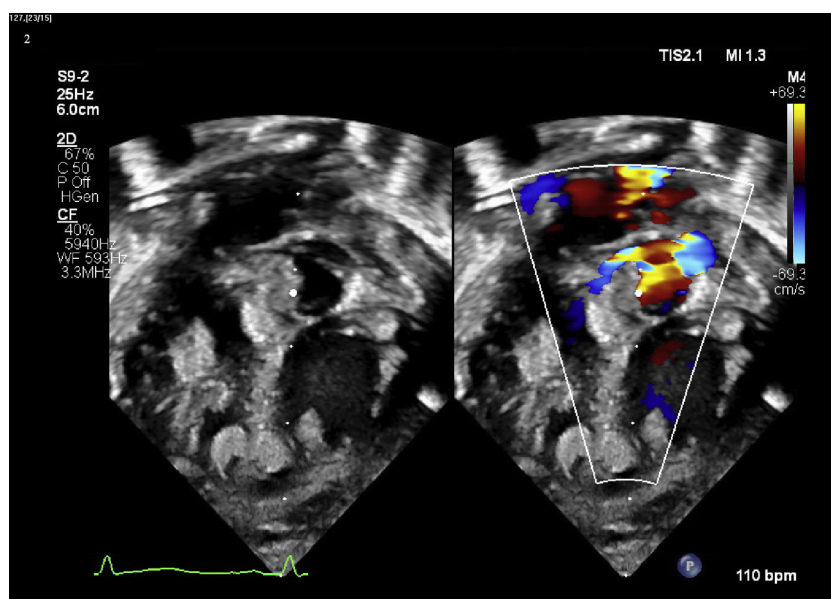


Figure 2 Apical five-chamber view with color Doppler compare on initial presentation. Multiple intracardiac rhabdomyomas are seen in both ventricles. A large CR measuring 10.3 × 7.5 mm is seen obstructing the LVOT and in close contact with aortic valve leaflets in systole.

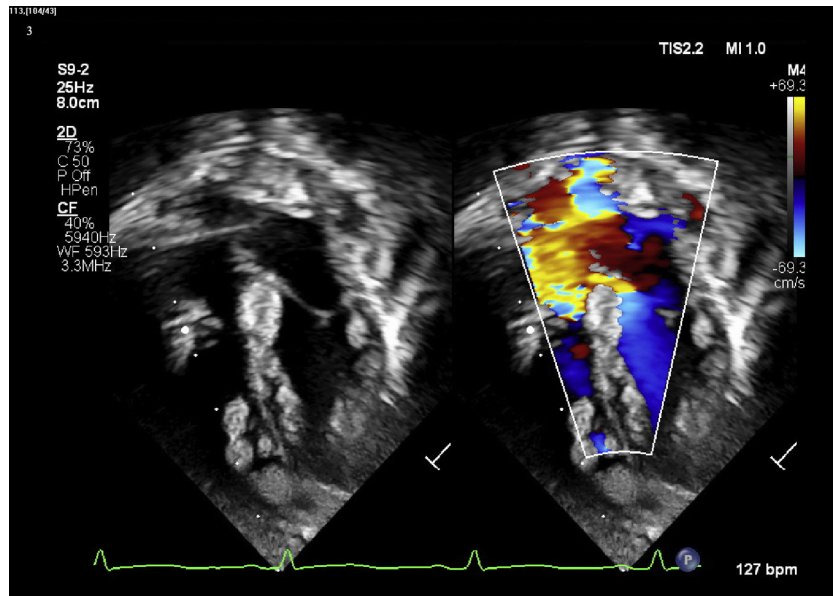


Figure 3 Apical four-chamber view with color Doppler compare on initial presentation. Multiple intracardiac rhabdomyomas are seen in both ventricles. A large CR is seen obstructing the LVOT and in close contact with aortic valve leaflets in systole. Turbulence of color flow is seen around the mass in the LVOT.

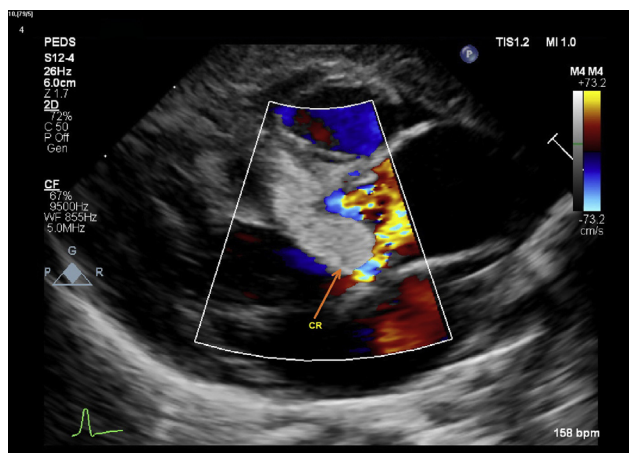


Figure 4 Parasternal long-axis view with color Doppler showing the degree of LVOT obstruction caused in systole by the large CR.

softening of the murmur on auscultation. The patient continues on sirolimus therapy at the time of this writing.

DISCUSSION

The incidence of TS-associated CR is suggested to have a near bimodal distribution. Of children with confirmed TS under the age of 1, 80%-85% are found to have CRs upon imaging with echocardiography. This decreases to 20%-25% of children over the age of 2 in part due to the natural spontaneous regression of CRs with time.⁴ Interestingly, a small series has demonstrated an increased incidence of CR to 40% in patients with TS between 9 and 14 years of age. This is hypothesized to be secondary to hormonal changes.⁷

Serial cardiac imaging, therefore, plays a vital role in the surveillance and management of patients with TS.

For initial screening, the current guidelines recommend that fetal echocardiography be performed for patients with CRs identified on prenatal ultrasound to assess for risk of heart failure after delivery. Echocardiography is also recommended for all patients diagnosed with TS under the age of 3. Once TS is identified, routine echocardiography is recommended every 1-3 years for asymptomatic patients until regression of the CR is documented. More frequent imaging is warranted for patients who have masses causing inflow or outflow obstruction or when masses are in close contact with any of the valves.⁴

Cardiac magnetic resonance imaging (CMR) is often the next imaging modality of choice after echocardiography. It is of highest yield when a solitary cardiac lesion is identified and more specific tissue characterization is needed than can be provided by echocardiography. Multiple intracardiac lesions suggest CRs that are pathognomonic for TS and do not typically require CMR for diagnosis. Cardiac magnetic resonance imaging also plays an important role in surgical planning if surgical resection of the CR becomes necessary. A limitation to performing CMR is the possible need for intravenous administration of contrast and sedation of the patient to obtain adequate images. This is especially a concern for the rare patient who is hemodynamically symptomatic for CR as the hemodynamic instability can be further exacerbated by anesthesia, invasive ventilation, or agitation of the patient. Echocardiography therefore remains the imaging modality of choice for the diagnosis and management of CRs in the majority of patients.⁴

Most patients with TS are found to have a mutation in TSC1 or TSC2, which encode the proteins hamartin and tuberlin, respectively. These proteins together form a tumor suppressor complex that acts as an antagonist to the mTOR pathway. Left unchecked, mTOR leads to unregulated cellular growth and proliferation.⁸

Identification of mTOR inhibitors as a potential treatment for CRs was first made in 2011.⁶ Since then, several cases of rapid regression of CRs in children who received mTOR inhibitor therapy have been reported.^{6,9-12} However, there are very few cases reported in which

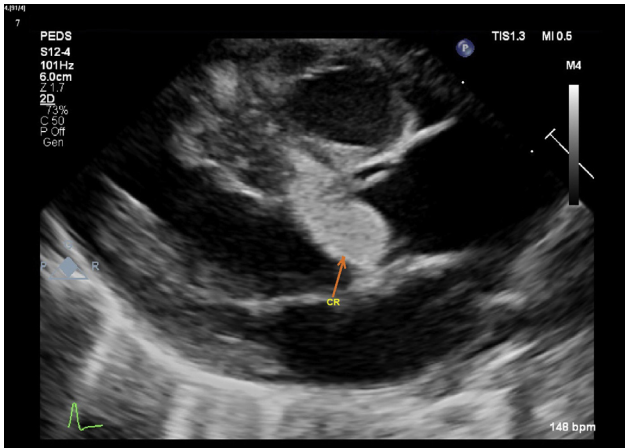


Figure 5 Parasternal long-axis view showing the large CR coming into contact with the aortic valve leaflets during systole.

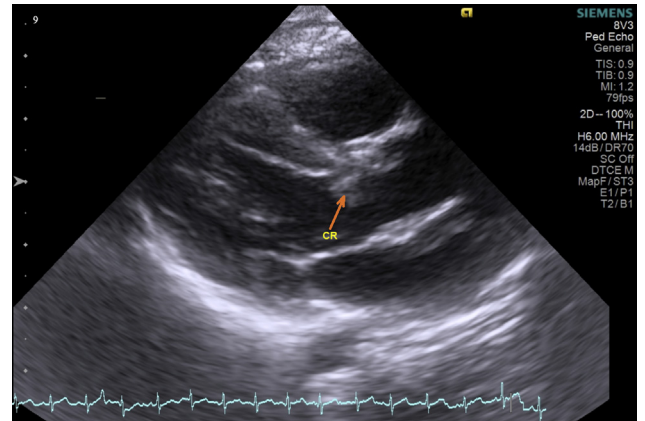


Figure 7 Parasternal long-axis view after 1 month of sirolimus therapy. The CR is still seen in the LVOT but has appreciably regressed in size to 5.3×6.0 mm.

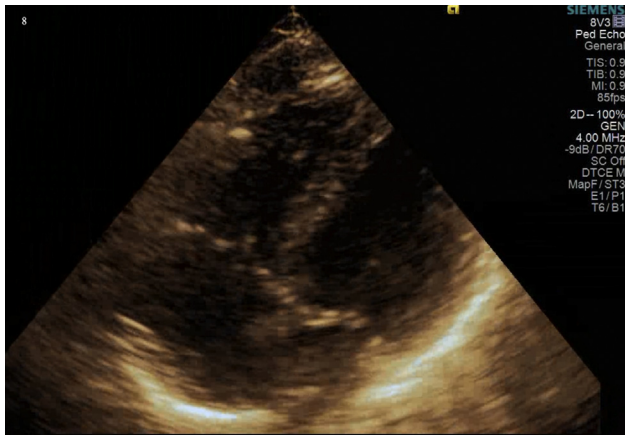


Figure 6 Apical four-chamber view after 1 month of sirolimus therapy. Most other intracardiac rhabdomyomas previously seen have completely regressed.

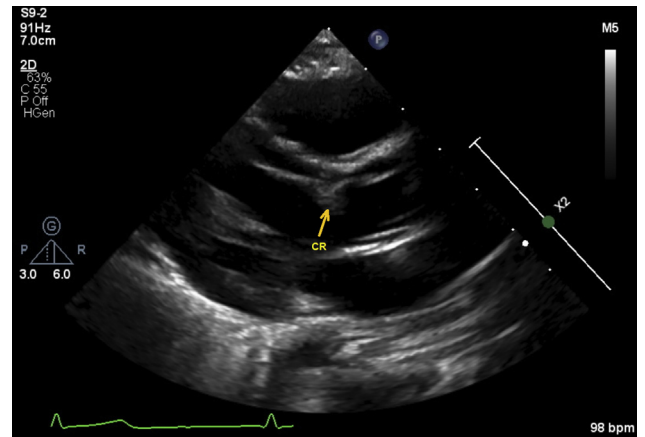


Figure 8 Parasternal long-axis view after 11 months of sirolimus therapy. The CR has significantly reduced in size to 3.0×4.7 mm and is no longer obstructing the LVOT.

mTOR inhibitors were utilized for treatment of CRs having functional impact on the aortic valve and causing left ventricular outflow obstruction without direct need for surgical intervention.

In a study by Kotulska *et al*⁸ it was shown that CRs of children with TS had markedly increased expression of mTOR and decreased expression of hamartin and tuberlin. It was also discovered that there was an increased expression of the proapoptotic protein Bax.⁸ While there is no direct evidence, it cannot be excluded that increased Bax expression plays a role in the natural regression of CRs of children with TS. Likewise, mTOR inhibitors may accelerate the natural regression of CRs by creating more favorable conditions for apoptosis. However, the mechanism of action of mTOR inhibitors on CRs requires further investigation.

It has been suggested that there may be a relationship between sirolimus levels and the rate of CR regression. In several reported cases, supratherapeutic levels of sirolimus were inadvertently reached in neonates being treated for CRs, and the CRs dramatically decreased in size in 5-15 days. Furthermore, the supratherapeutic levels of sirolimus were not associated with any significant acute adverse effects.¹⁰

Likewise, a recent retrospective multicenter study of 17 children who received everolimus starting at an average age of 5 months of age indicated that everolimus is generally safe to use in children under the age of 2. The study used the Common Terminology Criteria of Adverse Events to evaluate drug-related side effects. Grade 1-2 adverse events were reported in 70.6% of children, with recurrent infection being the most common adverse event reported. No grade 3-4 adverse events were noted.¹¹ However, longer-term effects of early infancy mTOR inhibitor therapy have yet to be studied as this therapy is still relatively new and emerging. Of note, dosing, compounding, and obtaining everolimus for neonates remain difficult at the time of writing this report.

The necessary length of treatment with mTOR inhibitors for CRs remains unclear. In most reports, children treated with an mTOR inhibitor are still receiving the therapy by the time the case is published. One explanation is because the mTOR inhibitor is benefiting the patient in more ways than just CR regression/resolution. At least two cases have demonstrated that early cessation of mTOR inhibitor treatment leads to regrowth of the CR.^{10,11} However, one case has reported significant regression of a CR after only 19 days of everolimus therapy and no tumor regrowth at a 5-month follow-up

following the short duration of mTOR inhibitor therapy.¹² This time frame for significant, rapid shrinkage of the lesions appears consistent with our findings of a rapid decline in size with subsequent stabilization despite continued therapy.

Use of mTOR inhibitors is an alternative to surgical intervention for significant CRs in hemodynamically stable patients without the need for urgent intervention. Therefore, reconsideration of surgical criteria in such patients may be warranted. However, optimized medical therapy in regard to dose and duration of treatment remains unclear.

Echocardiogram proves to be the optimal monitoring strategy to visualize both CRs and their respective hemodynamic effects.

CONCLUSION

This case presents a CR causing LVOT obstruction with aortic valve impact that was treated effectively with the mTOR inhibitor sirolimus.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.case.2022.03.009>.

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