Rapid Regression of Prenatally Identified Intrapericardial Giant Rhabdomyomas with Sirolimus

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INTRODUCTION

Cardiac rhabdomyomas are a common etiology of fetal cardiac tumors and are often associated with tuberous sclerosis. Usually these tumors are benign, small, and located within the ventricular free wall or septum. They typically regress spontaneously with no hemodynamic effect. Here we report an unusual case of prenatally identified intrapericardial giant rhabdomyomas that rapidly regressed postnatally with the use of a mammalian target of rapamycin (mTOR) inhibitor.

CASE PRESENTATION

A 30-year-old woman (G4P2) was referred at 34-6/7 weeks' gestation for a fetus with cardiac masses and a pericardial effusion. The patient had conceived spontaneously. She reported having a personal history of mental disability but no major medical problems. She was adopted, with an unknown family history, and had two healthy children previously. No invasive genetic testing was performed during the current pregnancy.

Fetal echocardiography demonstrated multiple homogenous cardiac masses: one large mass measuring 3 × 4.5 cm on the exterior of the left ventricular free wall in the pericardial space, which appeared to be in continuum across the cardiac apex with a smaller adjacent mass measuring 1.4 × 1.5 cm attached to the right ventricular exterior free wall, and a separate third mass measuring 0.6 × 0.9 cm within the ventricular septal wall (Figures 1 and 2, Video 1). There was also a small to moderate-sized circumferential pericardial effusion. There was no outflow or inflow obstruction, and cardiac structure and function were normal.

Serial fetal echocardiography demonstrated no significant changes. The dimensions of the multiple masses remained stable. Cardiac function continued to remain normal, no inflow or outflow obstruction was seen, and no hydrops was noted. Given the size of the masses in addition to the effusion and concern for hemodynamic instability after delivery, a planned delivery was performed at 39 weeks' gestation, with immediate availability of teams to perform pericardiocentesis, extracorporeal membrane oxygenation, and/or surgical resection if needed.

A male infant was born weighing 3,270 g with Apgar scores of 8, 8, and 9 at 1, 5, and 10 min. He required routine resuscitation and minimal respiratory support (2 L oxygen via nasal cannula). He was hemodynamically stable with good distal perfusion. Postnatal echocardiography confirmed the prenatal findings. This demonstrated a large homogenous mass on the left ventricular exterior free wall, a slightly smaller homogenous mass on the right ventricular exterior free wall, and a mass within the ventricular septum. There were multiple small intracardiac masses within the left and right ventricular myocardium that had not been fully appreciated on the fetal imaging. There was a small pericardial effusion with no evidence of cardiac tamponade or significant cardiac dysfunction (Figures 3 and 4, Video 2).

The patient was admitted to the neonatal intensive care unit for observation and further workup. Magnetic resonance imaging of the brain revealed subependymal nodules and cortical lesions, and magnetic resonance imaging of the abdomen demonstrated angiomyolipomas in both kidneys. This in conjunction with the cardiac tumors was highly suggestive of a diagnosis of tuberous sclerosis and cardiac rhabdomyomas. Genetic testing later was positive for a mutation in the *TSC2* gene, confirming the diagnosis of tuberous sclerosis.

At 1 week of age, the infant was noted to have decreased left ventricular systolic function. The masses within the ventricular myocardium and in the pericardial space were unchanged from birth. We elected to start sirolimus, an mTOR inhibitor, for treatment of the rhabdomyomas. After a week of therapy, there was notable improvement in cardiac function, with diminished size of all the masses. We continued to follow regression of mass size on serial echocardiography. Sirolimus levels were monitored and doses adjusted to remain within therapeutic range with the assistance of our hematology-oncology team. Treatment was discontinued after 4 weeks when left ventricular function had normalized. There were no noted adverse effects during or after sirolimus therapy. Serial posttreatment echocardiography has demonstrated no rebound increase in rhabdomyoma burden (Figures 5 and 6, Video 3). On clinical follow-up 1-month after sirolimus treatment, our patient remains asymptomatic with normal ventricular function.

DISCUSSION

Cardiac tumors are rare, with an incidence ranging from 0.0017% to 0.2% in autopsy series in the literature.[1-3] The first reported prenatal diagnosis of a cardiac tumor came in 1982 at Yale School of Medicine with M-mode echocardiography.[4] Advancements in fetal echocardiography since then have increased the prenatal incidence to 0.05%.[2,5] The differential diagnosis for a primary cardiac tumor in the neonatal population includes, in order of frequency, rhabdomyoma, fibroma, myxoma, teratoma, and hemangioma, with

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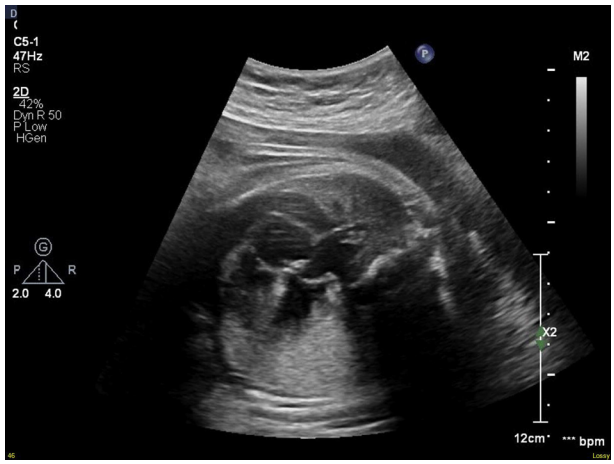

Figure 1 A fetal apical four-chamber view showing large intrapericardial tumors and a pericardial effusion.

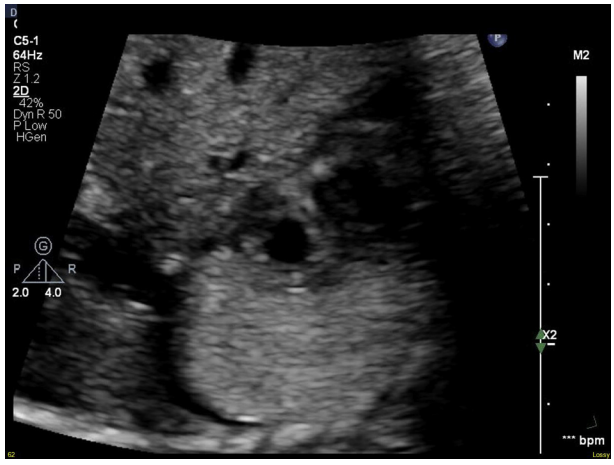

Figure 2 A fetal short-axis view demonstrating a large tumor encompassing the left ventricular free wall.

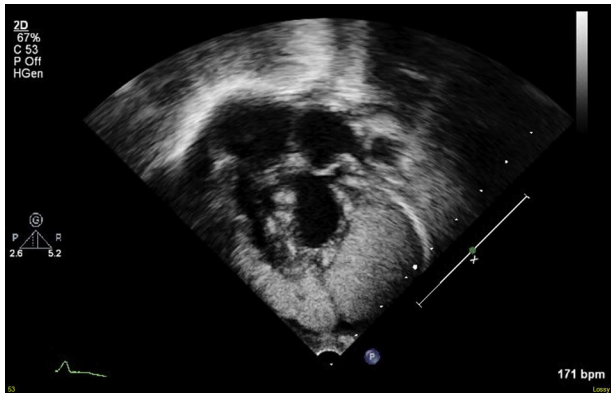

Figure 3 Postnatal transthoracic apical four-chamber view demonstrating giant rhabdomyomas on the exteriors of the left and right ventricular free walls as well as smaller rhabdomyomas in the septum.

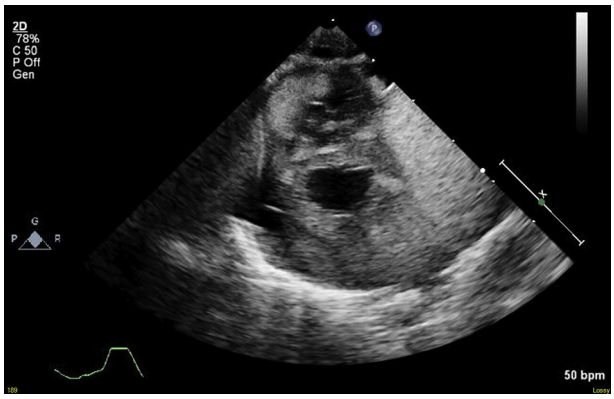

Figure 4 Postnatal parasternal short-axis view showing giant rhabdomyomas encompassing the ventricles with a small pericardial effusion.

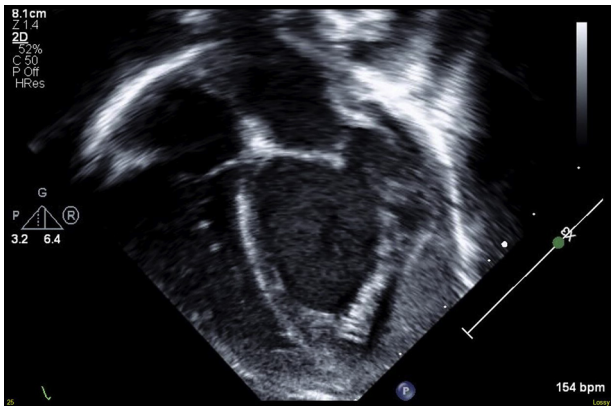

Figure 5 Transthoracic apical four-chamber view completed 1 month after treatment with sirolimus demonstrating significant regression in the rhabdomyomas.

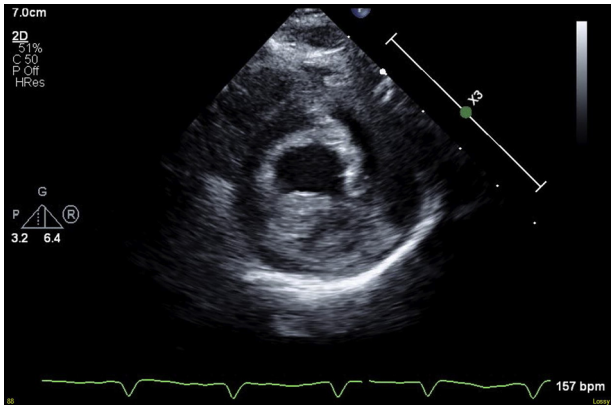

Figure 6 Transthoracic parasternal short-axis view showing a significant decrease in tumor burden 1 month after therapy.

rhabdomyomas accounting for up to 60% to 90% of prenatal cardiac tumors and 80% of postnatal cardiac tumors.[2,3,6]

Cardiac rhabdomyomas are considered benign and typically present as multiple, echogenic, homogenous masses embedded in the ventricular myocardium.[1,6,7] During gestation, the tumors can enlarge significantly and therefore are more readily identified later in gestation. There is a 4% to 6% risk for fetal demise secondary to inflow or outflow obstruction, arrhythmia, or hydrops.[5,8] There is a significant association with tuberous sclerosis, with the incidence reported as high as 80% in patients with fetal rhabdomyomas.[1-3,7] Although tuberous sclerosis follows an autosomal-dominant inheritance pattern, sporadic cases are seen in up to 60% of cases.[9] Thus, in the absence of a family history of tuberous sclerosis, cardiac rhabdomyomas may be the earliest sign of tuberous sclerosis in utero.[5]

Postnatally, rhabdomyomas typically regress spontaneously over the first year of life and are followed expectantly.[7] Survival rates are reported in the 81% to 92% range, with complications related primarily to arrhythmias, inflow or outflow obstruction, or cardiac dysfunction.[1,6,10] In rare instances of cardiac compromise, surgical resection has historically been the only option. More recently, medical treatment with mTOR inhibitors such as everolimus and sirolimus has been increasingly used, with rapid regression of rhabdomyomas.[7,11-13] The mTOR inhibitors act on a protein kinase that regulates cell growth, proliferation, protein synthesis, and transcription and have been used in the treatment of giant cell astrocytomas and renal angiomyolipomas and as immunosuppressants in renal and heart transplantation.[12,14] The treatment can lead to rapid regression of tumors within weeks, though the potential for rebound increase in tumor size to a fraction of the original size after discontinuation of therapy has been reported.[14] mTOR inhibitors essentially allow an alternative, less invasive treatment strategy to surgery.

The location, size, and effect on function of the cardiac rhabdomyomas in our patient made surgical debulking a high-risk option. Thus, we opted for pharmacologic treatment with an mTOR inhibitor. We chose sirolimus because it was available in an oral formulation. In addition, Weiland *et al.*[14] reported a more rapid regression (<1 month) with sirolimus in their small case series compared with reports of tumor regression with everolimus (2–3 months).[14] Both medications have a narrow therapeutic range, requiring frequent monitoring of levels. We saw no adverse effects of the medication, which can include hepatotoxicity, nephrotoxicity, rash, stomatitis, immunosuppression, and hyperlipidemia.[14] Therapy was discontinued as recommended by Weiland *et al.* once the tumors had been sufficiently debulked.

This case was unusual in several respects. Although our patient had some small tumors in the ventricular septum, the location of the large tumors in the pericardium and associated pericardial effusion was highly unusual. Most rhabdomyomas are found in the ventricular septum or free wall, with rare cases reported in the atria, cavoatrial junction, or pericardium.[1,5,10] In a search of the literature, we identified only four other cases that mentioned intrapericardial rhabdomyomas.[5,10,15] Fesslova *et al.*[15] described a similar case of a large, prenatally diagnosed intrapericardial rhabdomyoma measuring 40 × 45 mm. In their case, however, the patient had no hemodynamic compromise postnatally, and spontaneous regression was noted, with the mass measuring 31 × 25 mm at 2 years of age. They also described a case of an intrapericardial rhabdomyoma that was diagnosed postnatally via biopsy. Degueldre *et al.*[10] and Chao *et al.*[5] mentioned one case each of an intrapericardial tumor, but no specifics of the size or outcome were provided.

Our patient developed mild left ventricular dysfunction within the first week of life. Review of the literature reveals numerous reports of large tumors up to 55 mm, most of which self-resolve without hemodynamic effect or need for intervention.[2,5,10] We postulate that because there was no inflow or outflow obstruction from the tumors, they were relatively well tolerated in utero and in the perinatal period. After birth, with an increase in systemic vascular resistance, the excessive tumor burden on the exterior free walls of the ventricles could have acted like "dead weight" on the myocardium, leading to wall stress and mild left ventricular functional impairment. Conversely, left ventricular function improved with regression of the tumor mass.

CONCLUSION

We describe a case of giant intrapericardial rhabdomyomas that regressed with sirolimus therapy. Early prenatal monitoring allowed appropriate postnatal preparation, management, and prevention of significant hemodynamic compromise. Sirolimus should be considered as a treatment strategy in cases of cardiac rhabdomyomas with any hemodynamic impairment.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2018.07.003.

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