JACC: CASE REPORTS VOL. 3, NO. 13, 2021

CASE REPORT

ADVANCED

HEART CARE TEAM/MULTIDISCIPLINARY TEAM LIVE

Prenatal Pericardiocentesis and Postnatal Sirolimus for a Giant Inoperable Cardiac Rhabdomyoma

Jay Relan, DM,[a] Manish Swami, MD,[b] Anubhuti Rana, MS,[c] Priyanka Chaudhary, MS,[c] Vineeta Ojha, DM,[d] Sowmya Devarapalli, MD,[b] Vatsla Dadhwal, MD,[c] Ankit Verma, MD,[b] Priya Jagia, MD,[d] Anita Saxena, DM[a]

ABSTRACT

We describe the case of an antenatally diagnosed massive cardiac tumor in a fetus requiring cardiorespiratory support immediately following birth. We further discuss the successful management of this case and highlight the importance of a multidisciplinary team in managing such complicated cases. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2021;3:1473–1479) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 23-year-old primigravida was referred at 23 weeks' gestation for an antenatally detected fetal cardiac mass. A fetal echocardiogram revealed a structurally normal heart with a well-circumscribed, round, homogeneously echogenic mass measuring 2.3 × 1.8 cm (**Figure 1,** Videos 1 and 2), involving the interventricular septum and apices of both ventricles. There was mild pericardial effusion (PE) but no inflow/outflow obstruction or hydrops. At 26 weeks' gestation, tumor size increased to 2.9 × 2.3 cm, and there was a large pericardial effusion (PE) (**Figure 1,** Video 3). The family was counseled about the uncertain nature of the tumor and the guarded prognosis due to its rapid growth.

LEARNING OBJECTIVES

- To understand the antenatal and postnatal diagnosis and management options for a hemodynamically significant cardiac rhabdomyoma.
- To emphasize the utility of sirolimus in causing rapid regression of cardiac rhabdomyoma.
- To highlight the role of multidisciplinary expertise for managing complicated cardiac rhabdomyomas.

QUESTION 1: WHAT IS THE DIFFERENTIAL DIAGNOSIS OF CARDIAC MASS IN THE FETUS AND WHAT ADDITIONAL INVESTIGATIONS DO YOU PROPOSE TO DIFFERENTIATE BETWEEN THEM?

Answer 1: The differential diagnosis of fetal cardiac mass, in order of decreasing incidence, includes rhabdomyoma, teratoma, fibroma, myxoma, and hemangioma (1). Rhabdomyomas are the most common primary cardiac tumors in the fetal, infantile, and pediatric age groups and are associated with tuberous sclerosis (TS) in ~50% of patients. They are diagnosed in utero owing to homogeneous

From the [a]Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India; [b]Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India; [c]Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi, India; and the [d]Department of Cardiovascular Radiology and Endovascular Interventions, All India Institute of Medical Sciences, New Delhi, India.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 28, 2021; revised manuscript received June 11, 2021, accepted July 21, 2021.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2021.07.013

ABBREVIATIONS AND ACRONYMS

LV = left ventricular

mTOR = mammalian target of rapamycin

PE = pericardial effusion

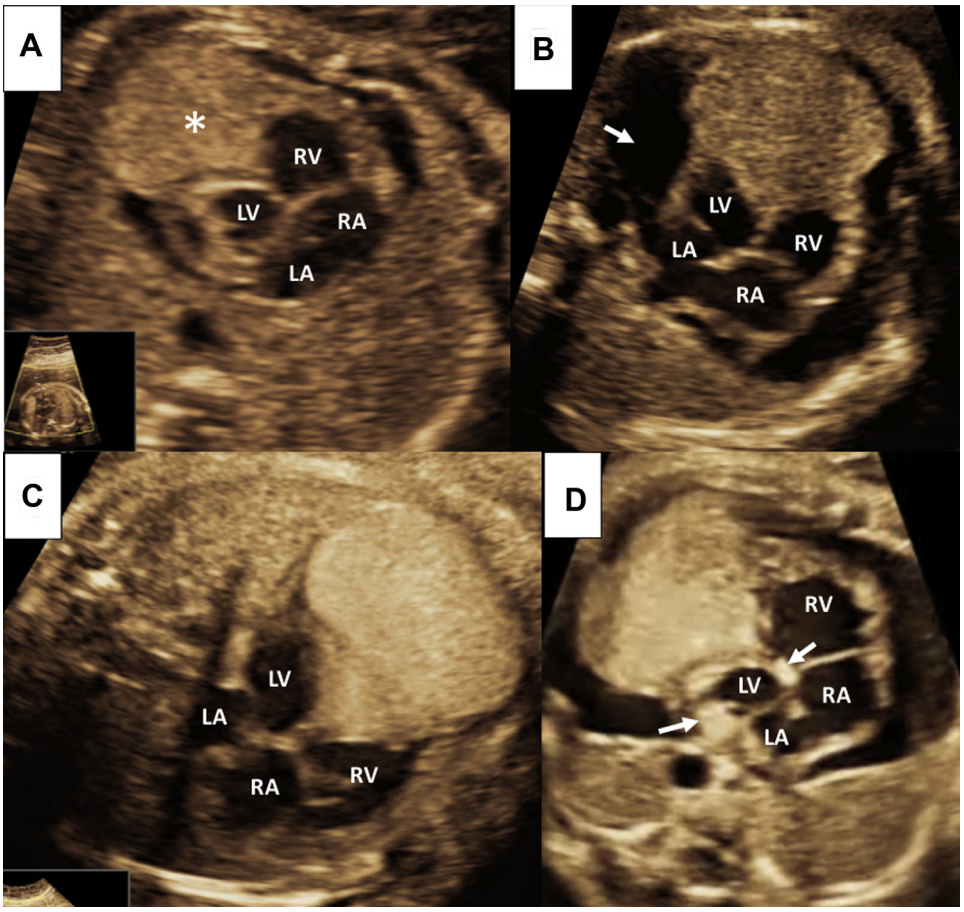
PGE1 = prostaglandin E1

TS = tuberous sclerosis

hyperechogenicity and multifocality (2). In our case, the tumor was homogeneous and hyperechogenic but solitary, leading to a diagnostic dilemma. Moreover, there was no history suggestive of TS in the family. A detailed ultrasound examination revealed no other structural malformation or stigmata of TS. Therapeutic percutaneous pericardiocentesis was performed for impending cardiac tamponade. Microscopic examination revealed few mesothelial cells and no atypia. Echocardiography at 29 weeks' gestation showed a multilobulated 3.3 × 3.1 cm tumor further encroaching into the cavity of the left ventricle (**Figure 1**, Video 4). New small tumors appeared at the lateral mitral annulus and left ventricular (LV) outflow tract, however, without inflow/outflow obstruction. Moreover, cardiac rhythm became irregular owing to frequent ventricular ectopic beats. New tumors were indicative of the tumor being a rhabdomyoma and opened the prospect of initiating transplacental mammalian target of rapamycin (mTOR) inhibitor therapy.

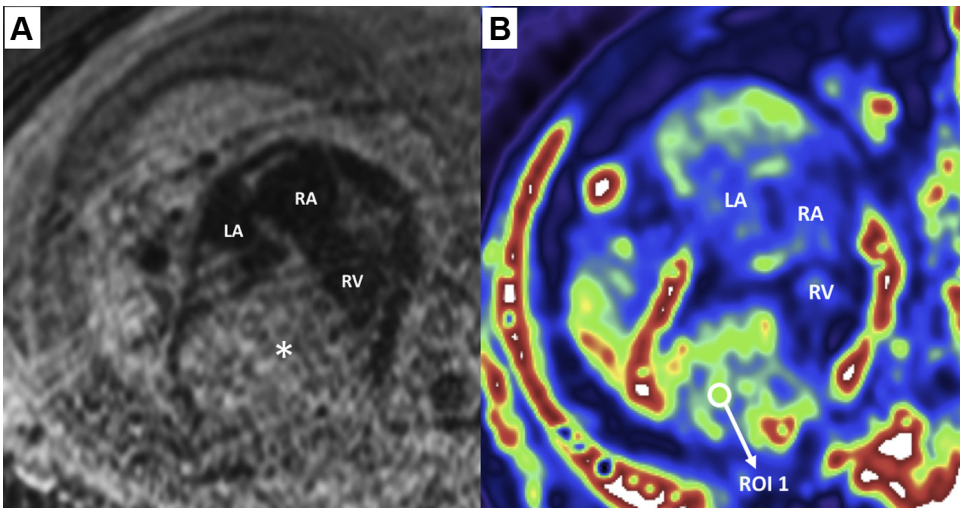
Fetal magnetic resonance imaging (MRI) was performed at this stage to assess the nature of the tumor and to screen for cortical tubers. Performing a fetal cardiac MRI is technically challenging with significant limitations (3), but we found it useful to clarify the diagnosis despite poor spatial resolution. The MRI showed that the cardiac mass was homogeneous and hyperintense on T2 with no intralesional cystic

FIGURE 1 Fetal Echocardiogram 4-Chamber View



(A) At 23 weeks' gestation showing large cardiac mass **(asterisk)**. **(B)** At 26 weeks' gestation with large pericardial effusion **(arrow)** causing lung compression. **(C)** Post-pericardiocentesis at 29 weeks' gestation with lobulated tumor. **(D)** At 33 weeks' gestation with multiple tumors **(arrows)** at mitral annuli with large pericardial effusion. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

FIGURE 2 Fetal Cardiac MRI at 29 Weeks Gestation



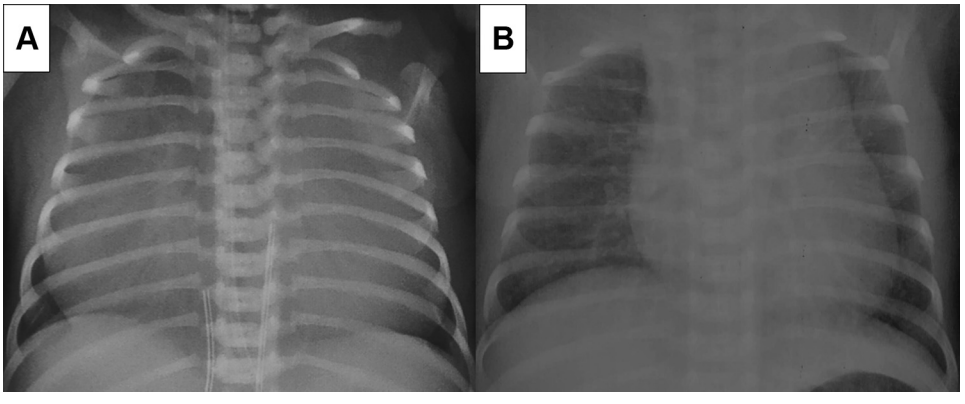
(A) T2-weighted turbo spin echo image showing homogeneously hyperintense mass **(asterisk)**, suggesting a rhabdomyoma. **(B)** T2 mapping image shows high T2 values within the mass at the region of interest 1 (ROI) (200 ms) compared with remote fetal myocardium (~70-80 ms). MRI = magnetic resonance imaging; other abbreviations as in Figure 1.

changes (Figure 2), suggestive of a rhabdomyoma. A fibroma was ruled out as it is hypointense on T2 imaging. There were no cortical tubers.

QUESTION 2: WHAT IS THE NATURAL HISTORY OF ANTENATALLY DIAGNOSED RHABDOMYOMA?

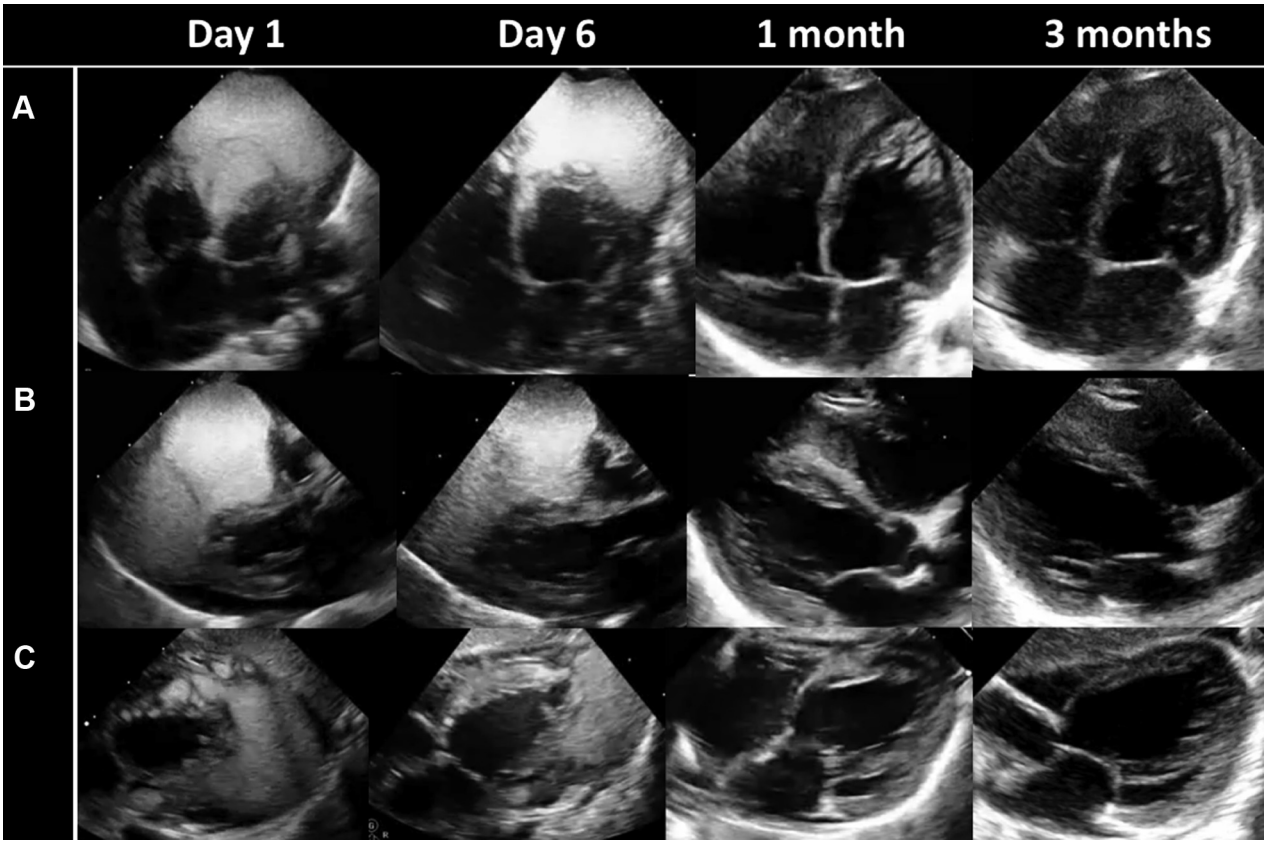
Answer 2: Rhabdomyomas are known to spontaneously regress in ~50% of the cases over the first few years of life (1,4). Thus, most patients are managed conservatively with serial echocardiographic monitoring in utero. Rarely, they result in clinically important problems postnatally such as arrhythmias, ventricular inflow/outflow obstructions, congestive heart failure, and, uncommonly, sudden death (4). Sometimes, congestive heart failure is due to large intramural tumors interfering with ventricular function, as in our case, wherein a giant tumor significantly encroached into the LV cavity.

FIGURE 3 Chest Radiograph



(A) Day 1. **(B)** Day 33.

FIGURE 4 Serial Postnatal Echocardiograms Showing Tumor Regression



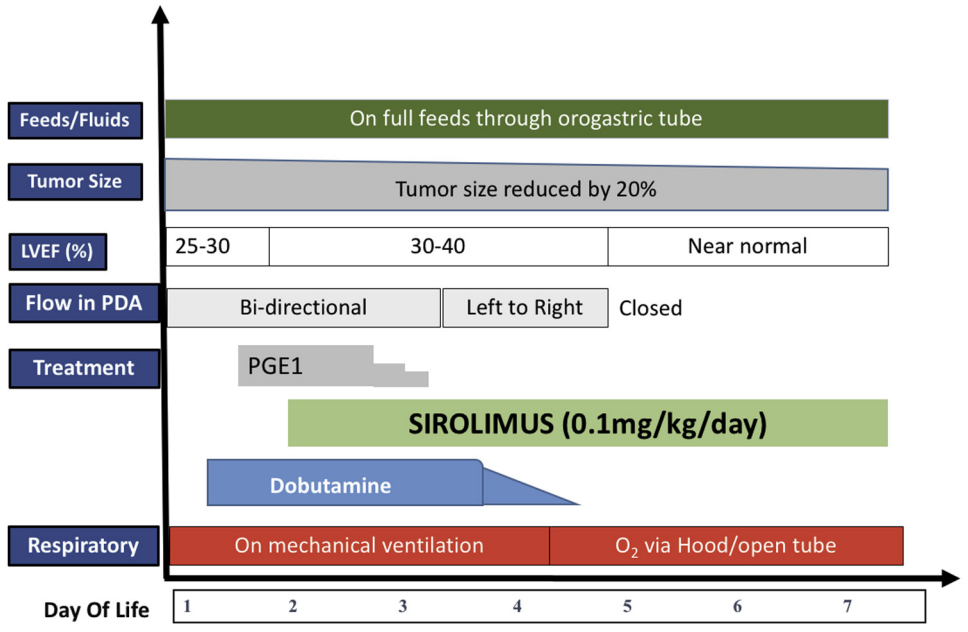
(A) Apical 4-chamber view. **(B)** Parasternal long-axis view. **(C)** Subcostal long-axis view.

QUESTION 3: WHAT ARE THE INDICATIONS FOR TREATING A FETAL RHABDOMYOMA, AND WHAT ARE THE TREATMENT OPTIONS AT THIS STAGE?

Answer 3: The indications for intervention in rhabdomyoma are mass-related symptoms or hemodynamic compromise (5,6). The mere presence of inflow or outflow obstruction does not mandate intervention. Prenatal treatment options include conservative management, off-label mTOR inhibitor therapy (7), pericardiocentesis or shunting, open fetal resection, delivery, and postnatal surgery if pregnancy is advanced (6). Open fetal resection is an uncommonly performed procedure requiring highly specialized expertise. Delivering a preterm infant and performing surgery on cardiopulmonary bypass is also risky, with significant limitations and additional prematurity-related complications.

In our case, mass-related issues mandated fetal intervention. The family was counseled about the options of conservative management and maternal sirolimus therapy. The family agreed on the sirolimus therapy, and baseline investigations were performed. Mild transaminitis was noted, and further investigations revealed asymptomatic acute hepatitis E infection. Hence, sirolimus therapy was deferred. Liver enzyme levels normalized after 10 days, but the patient developed mild coronavirus disease-2019 at 31 weeks' gestation. She was isolated and monitored at a coronavirus disease-2019 dedicated facility. At 33 weeks' gestation, the patient was shifted back, and re-evaluation revealed a tumor of 3.5 × 3.6 × 4.5 cm, with re-accumulation of large PE (**Figure 1,** Video 5). There were multiple small tumors infiltrating the LV wall, in bilateral outflow tracts, but still without obstruction or hydrops. The lungs appeared small and underdeveloped. Therapeutic fetal pericardiocentesis

FIGURE 5 Postnatal Course During First Week of Life



LVEF = left ventricular ejection fraction; PDA = patent ductus arteriosus; PGE1 = prostaglandin E1.

was performed again. The family opted for conservative management instead of sirolimus therapy. No antiarrhythmic agents were administered for ventricular ectopic beats as the heart rate and cardiac output were within normal limits. Ultrasound surveillance was continued for cardiac dysfunction, arrhythmias, and fetal hydrops.

QUESTION 4: WHAT ARE THE ANTICIPATED RISKS AFTER DELIVERY OF THIS FETUS?

Answer 4: At completion of the 37-week gestation period, a multidisciplinary meeting was held, comprising experts from fetal medicine, pediatric cardiology, neonatology, and cardiothoracic surgery, wherein the following anticipated problems were discussed: LV dysfunction, compressed lungs causing respiratory distress, refractory arrhythmias, and prohibitively high surgical risk.

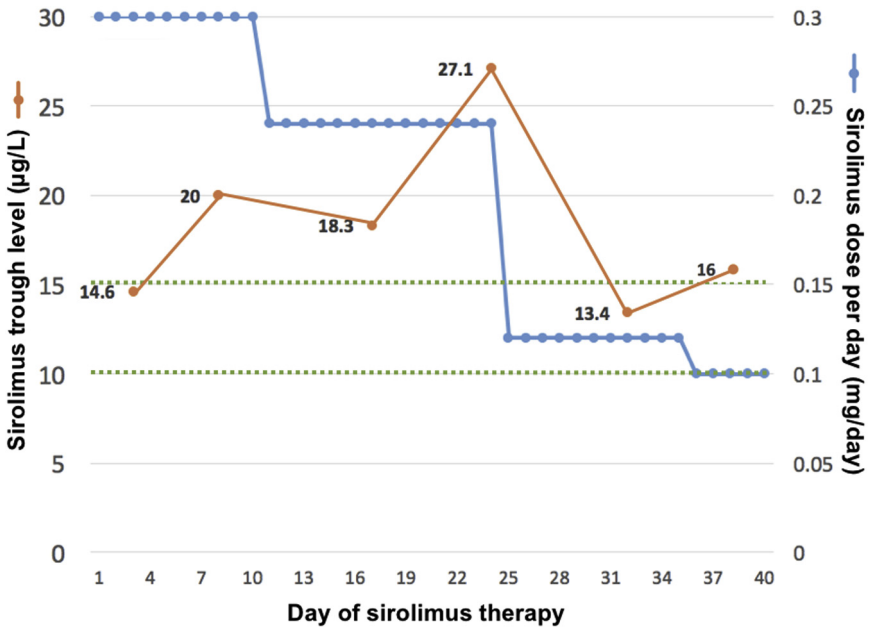
There were concerns regarding circulatory changes after birth. The reduced LV cavity due to tumors had already imposed a diastolic dysfunction, and the postnatal change from parallel-to-series circulation was expected to cause systolic LV dysfunction as well. There was a risk of respiratory compromise due to congestive heart failure caused by ventricular dysfunction with an additional risk factor of bilateral lung compression. In addition, there was a risk of ventricular arrhythmias due to diseased ventricular wall and frequent ventricular ectopic beats.

QUESTION 5: WHAT ARE THE POSTNATAL MANAGEMENT OPTIONS IN THIS CASE, AND HOW WAS THE PATIENT MANAGED?

Answer 5: The postnatal management options in this case are debulking surgery, off-label mTOR inhibitor therapy, and comfort care. Current literature regarding surgical management of multifocal, infiltrating tumors suggests poor outcomes (5). Therefore, debulking surgery was reserved as a measure of last resort. In the last decade, several reports have shown the efficacy of mTOR inhibitors for reduction of cardiac rhabdomyomas (8). However, there are limited data on dose, duration, and safety. mTOR inhibitors are narrow therapeutic drugs with potential complications such as hypercholesterolemia, marrow suppression, and opportunistic infections. The family was counseled accordingly.

An elective caesarean section was performed at 37 weeks' gestation, with preparedness for immediate pericardiocentesis, extracorporeal membrane oxygenation, and/or surgical resection, if needed. A 3,025-g infant was delivered, who cried immediately

FIGURE 6 Sirolimus Trough Levels and Sirolimus Dosage During the First 40 Days of Life



Area between dashed lines **(green)** indicates targeted therapeutic range.

after birth but developed cyanosis and apnea at 1 minute of life, requiring mechanical ventilation. Apgar scores were 4 and 7 at 1 and 10 minutes, respectively. There were no obvious TS stigmata.

A chest radiograph showed gross cardiomegaly and poorly visualized lungs (**Figure 3**). Postnatal echocardiography (**Figure 4**, Videos 6 and 7) showed a structurally normal heart, with the same number and sizes of tumors as noted antenatally, with a 3-mm patent ductus arteriosus shunting bidirectionally and large PE (without tamponade physiology). There was severe LV diastolic and systolic dysfunction, likely due to small ventricular cavity size, and an increase in LV preload and afterload after birth. Dobutamine was started at 5 µg/kg/min to assist the left ventricle, but the infant developed frequent ventricular ectopic beats. The ventricular ectopic beats were managed conservatively by minimizing the dobutamine infusion dose, as permitted by the clinical status of the infant. At 12 h, the infant developed deranged perfusion and hypotension, which improved after starting prostaglandin E1 (PGE1) at 100 ng/kg/min (**Figure 5**).

Owing to significant intramural LV involvement, sirolimus therapy was considered a better alternative to surgical resection. Therefore, we started oral sirolimus at 0.3 mg (0.1 mg/kg/d) as a single daily dose on day 2 after parental consent. Hemogram, liver, renal function tests, and lipid profile were serially monitored over the treatment course. The infant remained stable over the next 2 days, after which patent ductus arteriosus started shunting left-to-right and LV function improved. Hence, PGE1 was stopped. The infant was extubated on day 5 but continued to require oxygen support owing to dyspnea. The ventricular ectopic beats did not recur after cessation of dobutamine infusion. On day 6, echocardiography showed ~20% reduction in tumor size (**Figure 4**). Sirolimus was titrated according to weekly blood levels, with a target trough level of 10 to 15 µg/L (**Figure 6**). Trough levels ranged from 13.4 to 27.1 µg/L during the first 6 weeks. No complication, except self-limiting hypertriglyceridemia, was observed during therapy despite transient supratherapeutic levels of sirolimus during the initial period.

After 3 weeks of sirolimus treatment, there was ~50% tumor reduction, LV function normalized, and the infant was weaned off oxygen. By the end of 1 month, the dose of sirolimus was reduced to one-third of the starting dose to remain in therapeutic range. Results of genetic testing revealed a pathogenic splice variant (c.5161-1G>C) at Intron 40 in the

TSC2 gene, confirming TS. The infant was discharged at 4 weeks.

QUESTION 6: WHAT WAS THE PATIENT'S CLINICAL COURSE AFTER DISCHARGE?

Answer 6: There was significant tumor regression with normalization of LV size and function by 6 weeks of age (Video 8). We continued very low doses of sirolimus, instead of stopping abruptly, to avoid rebound tumor growth (8). The dose was reduced to 0.1 mg every alternate day (0.01 mg/kg/d). Subsequently, no weight adjustment of dose was done to allow self-taper during follow-up. At 3 months' follow-up, the infant was asymptomatic, thriving well, and the tumor size was reduced to ~10% of baseline with no rebound growth despite very low doses of sirolimus (**Figure 1**). We plan to stop the administration of sirolimus at 6 months of age if there is no significant tumor regrowth.

To our knowledge, this case represents the first report of the combined use of antenatal percutaneous pericardiocentesis followed by postnatal sirolimus therapy in a case of inoperable rhabdomyoma with extensive intramural involvement resulting in a favorable outcome.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Anita Saxena, Department of Cardiology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India. E-mail: anitasaxena1956@gmail.com.

REFERENCES

1. Jóźwiak S, Kotulska K, Kasprzyk-Obara J, et al. Clinical and genotype studies of cardiac tumors in 154 patients with tuberous sclerosis complex. *Pediatrics*. 2006;118:e1146–e1151.

2. Zhou QC, Fan P, Peng QH, Zhang M, Fu Z, Wang CH. Prenatal echocardiographic differential diagnosis of fetal cardiac tumors. *Ultrasound Obstet Gynecol*. 2004;23(2):165–171.

3. Marini D, van Amerom J, Saini BS, Sun L, Seed M. MR imaging of the fetal heart. *J Magn Reson Imag*. 2020;51(4):1030–1044.

4. Fesslova V, Villa L, Rizzuti T, Mastrangelo M, Mosca F. Natural history and long-term outcome of cardiac rhabdomyomas detected prenatally. *Prenat Diagn*. 2004;24(4):241–248.

5. Günther T, Schreiber C, Noebauer C, Eicken A, Lange R. Treatment strategies for pediatric patients with primary cardiac and pericardial tumors: a 30-year review. *Pediatr Cardiol*. 2008;29(6):1071–1076.

6. Masmejan S, Baud D, Ryan G, Van Mieghem T. Management of fetal tumors. *Best Pract Res Clin Obstet Gynaecol*. 2019;58:107–120.

7. Pluym ID, Sklansky M, Wu JY, et al. Fetal cardiac rhabdomyomas treated with maternal sirolimus. *Prenat Diagn*. 2020;40(3):358–364.

8. Cleary A, McMahon CJ. Literature review of international mammalian target of rapamycin inhibitor use in the non-surgical management of haemodynamically significant cardiac rhabdomyomas. *Cardiol Young*. 2020;30(7):923–933.

KEY WORDS cardiac tumor, fetal cardiac MRI, fetal rhabdomyoma, mTOR inhibitor, tuberous sclerosis

APPENDIX For supplemental videos, please see the online version of this article.

Go to http://www.acc.org/jacc-journals-cme to take the CME/MOC/ECME quiz for this article.