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CASE REPORT OPEN ACCESS

Maternal Sirolimus Treatment Reverses Cardiac Rhabdomyoma-Induced Hydrops Fetalis in a Twin Gestation With Tuberous Sclerosis Complex

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ABSTRACT

Cardiac rhabdomyomas are often the presenting sign of tuberous sclerosis complex (TSC). Prior reports have shown that maternal sirolimus treatment can reduce rhabdomyomas. We used maternal sirolimus to reverse hydrops fetalis due to a massive cardiac rhabdomyoma in a twin gestation. This expands the possibilities of prenatal medical treatment in TSC.

1 | Introduction

Cardiac rhabdomyomas are the most common fetal cardiac tumor and are a presenting symptom of tuberous sclerosis complex (TSC) (Davis et al. 2017; Ebrahimi-Fakhari et al. 2018; Northrup et al. 2021). Cardiac rhabdomyomas are benign tumors that grow in the fetal period and then typically regress without intervention in the postnatal period (Jozwiak et al. 2006). However, at times, cardiac rhabdomyomas grow in the fetal period, causing outflow obstruction, arrhythmias, or valvular dysfunction requiring interventions (Aw et al. 2017; Breathnach et al. 2014; Chen et al. 2021; Colaneri et al. 2016; Ebrahimi-Fakhari et al. 2021; Maasz et al. 2023; Nespoli et al. 2021; Ninic et al. 2017; Patel et al. 2018; Sugalska et al. 2021; Weiland et al. 2018; Will et al. 2023). Prior work in TSC has shown that the presence of multiple rhabdomyomas makes a diagnosis of TSC likely (Chen et al. 2019; Jozwiak et al. 2006; Słowińska et al. 2018). As ~60% of individuals with TSC have cardiac rhabdomyomas, prenatal ultrasounds concerning rhabdomyomas are often the first marker of TSC.

Tuberous sclerosis complex is a rare autosomal-dominant genetic condition causing non-malignant tumors throughout the body, skin lesions, epilepsy, and neurodevelopmental concerns. It is caused by mutations in the *TSC1* or *TSC2* gene, though ~10% of cases remain without a known genetic variant identified. Nearly 40% of cases are familial; the rest are sporadic mutations (Northrup et al. 2021). The loss of TSC1 or TSC2 causes overactivation of the mechanistic target of rapamycin (mTOR). Medical treatment with mTOR inhibitors (sirolimus or everolimus) treats many aspects of TSC, including angiofibromas, subependymal giant cell astrocytomas, renal angiomyolipomas, lymphangioleiomyomatosis, and epilepsy (Franz and Krueger 2018). They have also been used off-label to treat arrhythmias and cardiac rhabdomyomas in TSC (Silva-Sanchez et al. 2021) and have been given to mothers to treat critical fetal TSC manifestations

(Cavalheiro et al. 2021; Ebrahimi-Fakhari et al. 2021; Maasz et al. 2023; Qaderi et al. 2024; Will et al. 2023).

Here, we report the reversal of hydrops fetalis induced by cardiac rhabdomyoma with maternal sirolimus treatment. This expands the importance of prenatal diagnosis and targeted medical treatment of genetic diseases.

2 | Presentation

A woman with a monozygotic dichorionic-diamniotic twin pregnancy at 28 weeks and 3 days presented for routine obstetric care. On fetal ultrasound, a mass completely obstructing the left ventricle was detected. In addition, there was a shared vessel between twin A and twin B, making it a high risk for the fetal demise of both twins. Family history was significant for familial long-QT syndrome due to *KNCQ1* mutation. The family was referred to our center and the next day had detailed imaging, counseling, and treatment planning (see Figure 1 for timeline of imaging, treatment, and response).

On initial fetal echocardiograms, twin B was found to have a massive rhabdomyoma in the left ventricle (unable to tell if it was a single mass or multiple masses), causing critical outflow obstruction and pericardial effusions (Figure 2A). Fetal MRI also showed diffuse edema (including cardiac effusions, pleural effusions, and ascites) consistent with hydrops fetalis (Figure 2B). Twin A was found to have several small rhabdomyomas that were non-obstructive (Figure 2A). Neither twin showed cerebral or renal findings of TSC on fetal MRI. However, due to the presence of multiple rhabdomyomas and the twins both with rhabdomyomas, it was thought that TSC was the most likely diagnosis, as the presence of multiple rhabdomyomas gives a >80% risk for TSC (Chen et al. 2019; Słowińska et al. 2018). It is unclear of the utility of prenatal MRI for detecting cerebral and renal TSC manifestations, and other etiologies (e.g., fibromas) were felt to be less likely to have this presentation.

3 | Fetal Course

The family was counseled about a high risk for TSC in both fetuses due to multiple cardiac rhabdomyomas. It was felt that maternal treatment with sirolimus could reduce the cardiac rhabdomyoma in Twin B with no adverse effect on Twin A, as both were expected to have TSC. Additionally, there was no surgical intervention that could be completed at the time to improve outcomes. Our team had discussed before the fetal echocardiogram that we would offer maternal treatment for Twin B even if Twin A did not have findings of TSC since the risk of fetal demise was high for both without intervention. The mother was counseled on the side effects of sirolimus and that this was an off-label use of the medication since there are limited studies. With consent, the mother was started on 3 mg/m^2/day of sirolimus (3 mg twice daily).

Levels were obtained after three doses and weekly thereafter to monitor therapy (Figure 3A). The pharmacokinetic consult service provided recommended dosing to achieve therapeutic drug levels rapidly based on their prior models of sirolimus dosing (Capal et al. 2024; Mizuno et al. 2017). These trough levels were maintained throughout the pregnancy (Figure 3A).

Due to the concern for fetal demise in twin B, the mother was monitored in the hospital for 16 days, and when twin B showed no signs of distress, they were discharged home. At 30 weeks gestation, there was no significant change on the echocardiogram in twin B. In discussion with cardiothoracic surgery, given the gestational age and estimated fetal weight, the postnatal interventional options for twin B were limited at this point (including surgical or mechanical circulatory support options) and continuation of the pregnancy was recommended in the absence of pressing maternal or fetal indications for delivery. After 4 weeks of sirolimus treatment (32 weeks gestation), there was an improvement in the pleural effusions and ascites (Figure 2C), suggesting improved cardiac flow dynamics, but there continued to be flow reversal in the aortic arch on the fetal echocardiogram, indicating critical left

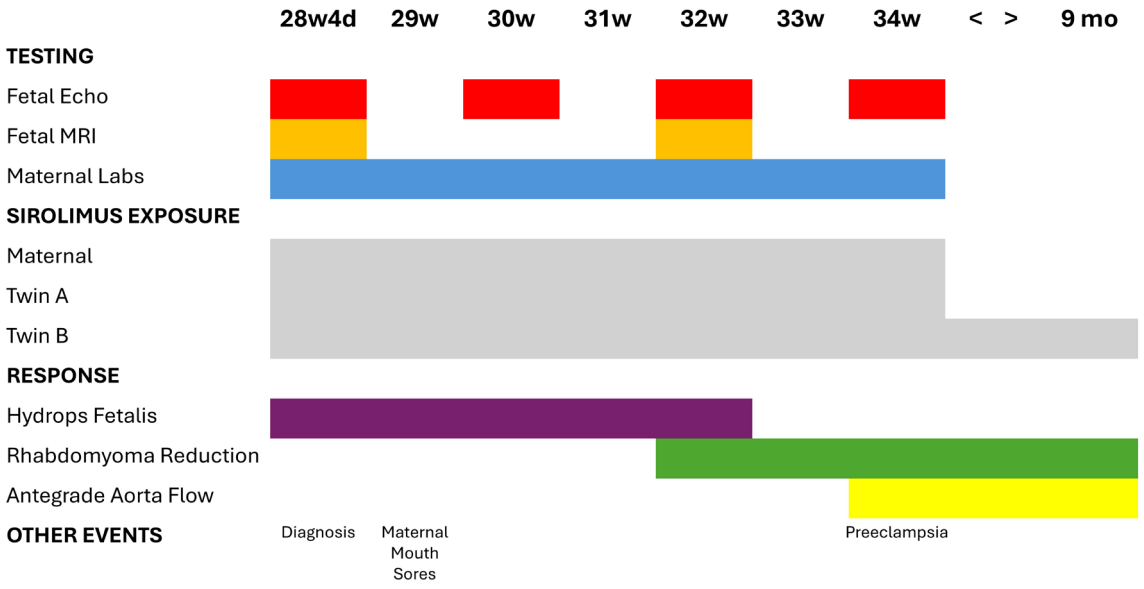

FIGURE 1 | Timeline of events. Testing, sirolimus exposure, response to treatment, and other events during the case. Time is in gestational age (w = weeks, d = days, mo = months).

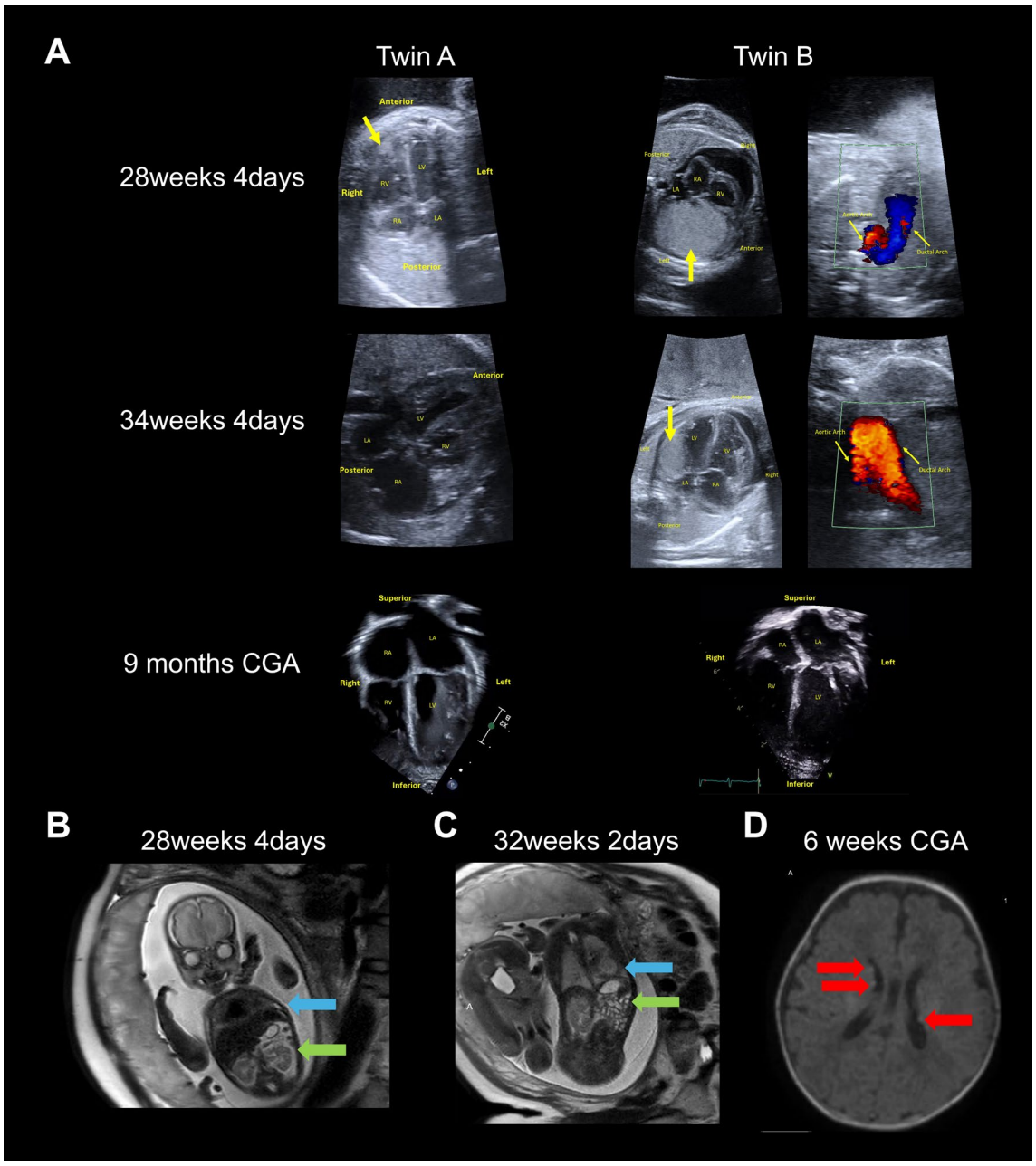

FIGURE 2 | Reversal of edema and rhabdomyomas with sirolimus treatment. (A) Repeat echos and time points related to gestational in age in twin A and twin B. Yellow arrows point to rhabdomyomas in 4 chamber views and to parts of the arch in doppler flow images. (B, C) T1 fetal MRI images of twin B showing pleural effusions (blue arrow) and ascites (green arrow) at presentation (B) and weeks after sirolimus (C). (D) T1 brain MRI images obtained post-birth showing subependymal nodules (red arrows). A dysplastic lesion in the frontal lobe was likely present, but follow-up imaging was thought to be needed to determine fully. CGA, corrected gestational age.

ventricular outflow tract obstruction and prostaglandin dependent heart disease. Arrhythmia was not noted.

At 34 weeks and 2 days, the mother developed proteinuria and hypertension. Due to the concern for side effects of sirolimus or preeclampsia, she was admitted to the Cincinnati Children's Maternal-Fetal Unit. Her blood pressure continued to increase along with a drop in platelets consistent with preeclampsia (Figure 3B). A repeat fetal echocardiogram showed a reduction in Twin B's cardiac rhabdomyomas and now antegrade flow through the aorta (Figure 2A). It was recommended to proceed with delivery immediately. Both twins were delivered by cesarean section, and twin A needed no additional support. Twin B was placed on prostaglandins but otherwise needed no support at delivery. Twin B was admitted to the Cardiac ICU, where a post-natal echocardiogram confirmed the findings of the fetal echocardiogram earlier that day, and prostaglandins were weaned off. Twin B was transferred to the neonatal ICU after 3 days.

4 | Postnatal Course

Twin B was started on sirolimus 0.8 mg/m^2/day on day 1 of life. Initial levels came back elevated, suggesting decreased clearance,

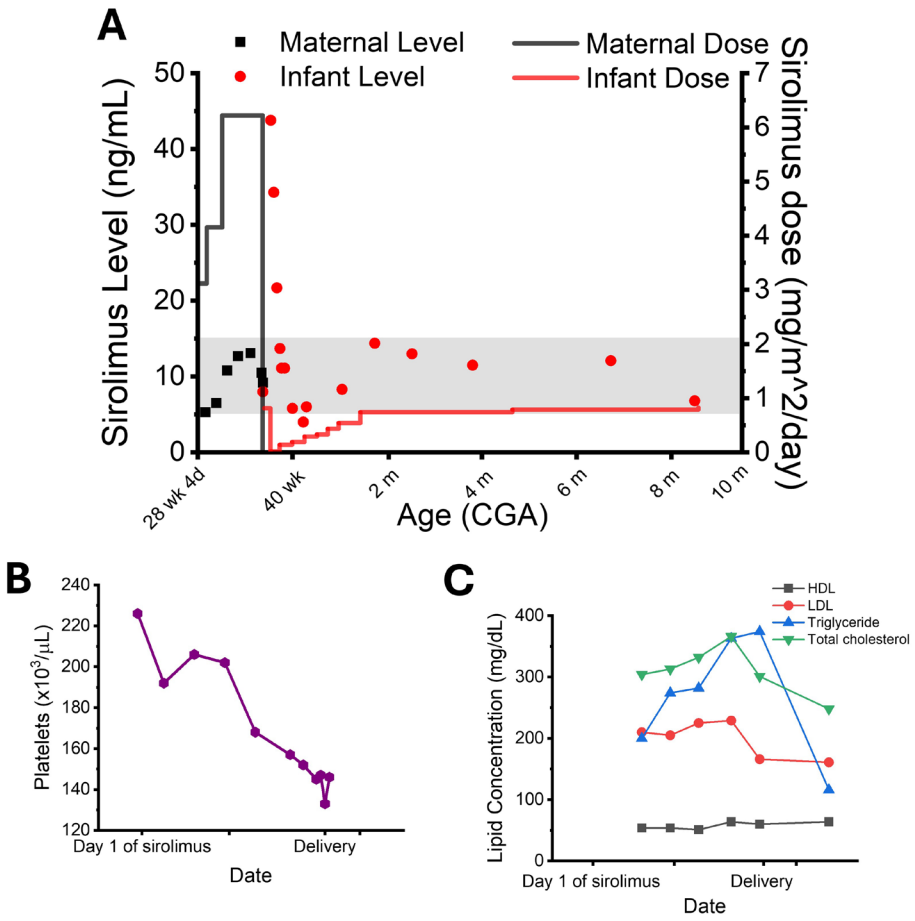

FIGURE 3 | Laboratory results following sirolimus treatment. (A) Trough blood levels and dosing of sirolimus in both mother (black) and infant (red). Notice that the first infant and last maternal levels are nearly identical at birth. Due to unanticipated low clearance after birth, sirolimus was held. Repeat dosing predictions for the infant predicted lower than typical doses but maintained levels. The gray area is the target level zone. (B, C) Maternal platelets (B) and lipids (C) during sirolimus treatment and after delivery. CGA, corrected gestational age.

so the dosing was reduced to 0.3 mg/m^2/day after holding for 1 week. Weekly labs maintained 10–15 ng/mL levels that have continued postnatally with intermittent pharmacokinetic consults (Figure 3A). The rhabdomyoma has continued to regress in size (Figure 2A). Twin A was not placed on sirolimus postnatally as the postnatal echocardiogram showed minimal size of the rhabdomyomas. Both twins were in the NICU for 4 weeks until discharge. Head and renal ultrasounds were unremarkable, but a skin exam showed hypopigmented macules. Genetic testing revealed a *de novo* pathogenic *TSC1* c.1498C>T mutation in both twins. In addition, both twins had prolonged QT intervals and were positive for the known familial *KCNQ1* variant.

Since discharge from the NICU, both twins have remained seizure-free with normal electroencephalograms at 9 months. Twin B had another NICU stay for a respiratory viral infection requiring oxygen treatment after discharge. At that time, an MRI brain was completed and revealed cerebral manifestations of TSC consisting of several subependymal nodules (Figure 2D). Twin B is mildly delayed in gross motor skills compared to Twin A, and both are in early intervention therapies. Neither twin has demonstrated any arrhythmia related to long QT syndrome, and both remain on treatment with beta-blockade. Twin A has had complete resolution of cardiac tumors, and Twin B has a small residual tumor and an arcade mitral valve with moderate stenosis and mildly stenotic aortic valve with mild stenosis at 9 months of age (Figure 2). Cardiac chamber size and ventricular systolic function remain normal in both twins.

5 | Side Effects

Early in the treatment course, the mother had mouth sores, which were treated with triamcinolone oral paste. Additionally, blood lipid levels were elevated during the treatment and pregnancy (Figure 3C). However, no adjustment to the treatment plan was made based on these findings as it was unclear if the lipid elevation was related solely to pregnancy or to the treatment with sirolimus. The infant has not experienced side effects except elevated lipids.

6 | Discussion

This case confirms that the treatment of cardiac rhabdomyomas with maternal mTOR inhibitors is an important option to consider in fetal TSC. While cardiac dysfunction from rhabdomyomas has been well known in the perinatal period, this report shows a reversal of hydrops fetalis, which from all

causes has a ~50% fatality rate (Tolia et al. 2021). This is the first case we know where hydrops is reversed in TSC, leading to several interesting new areas for prenatal interventions and counseling.

In our situation, the fetal demise of Twin B was deemed to be assured if no treatment occurred, and there were significant concerns about Twin A being able to survive such an event due to shared vasculature. Thus, our medical decision-making was more straightforward as there were no other options for the viability of one, let alone both twins. If Twin A had no findings of TSC, we thought it was likely still to be minimal risk for adverse events based on using mTOR inhibitors for maternal indications and prior case reports of safety (Qaderi et al. 2024; Rose et al. 2024). The finding of small cardiac rhabdomyomas in Twin A made our decision-making easier as we did not have to be concerned about treating an unaffected fetus. This case highlights the need for multidisciplinary discussions and expert involvement, as the outcome may have been different if it were a singleton pregnancy. Currently, it is unknown how far along in cardiac failure that sirolimus treatment can reverse the findings, but certainly, the first signs of hydrops fetalis are not too far, as shown here.

Due to the gravity of twin B, we sought to get to maternal therapeutic sirolimus levels quickly and safely. Our levels were at treatment levels in the first week and maintained using pharmacokinetic modeling. Although prior reports suggested that fetal levels are above maternal levels (Ebrahimi-Fakhari et al. 2021), our levels in the mother and twin B around the time of delivery were nearly identical (Figure 3). Treatment in the immediate postnatal period was affected by decreased clearance of sirolimus in twin B, which will be able to inform future pharmacokinetic models in the preterm infant. Interestingly, this infant is maintained consistently at levels below typical for age with therapeutic sirolimus levels. In a recent phase 1 study of preventative sirolimus in TSC, we saw a wide range of dosing for sirolimus to maintain appropriate levels (Capal et al. 2024), suggesting that personalized dosing of mTOR inhibitors in TSC may be crucial. This may be related to specific pharmacogenetic findings in individuals or due to age-dependent activity in CYP enzymes and other physiological processes (Abduljalil et al. 2020; Emoto et al. 2015).

In our case, the mother experienced treatment-related mouth sores and elevated lipids. It was unclear whether the lipids were related to sirolimus or from the third trimester of pregnancy. While she developed preeclampsia, she was able to be weaned off blood pressure medications several weeks after delivery. It is unclear at this time if preeclampsia in this case was related to the known risk factors (advanced age, hydrops fetalis, and twin gestation) or related to sirolimus treatment. However, preeclampsia has not been previously reported as a risk factor for preeclampsia in prior reports (Cavalheiro et al. 2021; Ebrahimi-Fakhari et al. 2021; Maasz et al. 2023; Qaderi et al. 2024; Will et al. 2023). A systematic database of maternal mTOR inhibitor treatment will be beneficial in determining if there is a causal medication relationship. Regardless, the safe delivery of the twins and resolution of the maternal side effects and preeclampsia suggest a favorable profile for sirolimus.

There is little known about how some cardiac rhabdomyomas progress and grow rapidly. Prior work has suggested that estrogen exposure or other circulating hormones may play a role (Jozwiak et al. 2006). However, in this case, we have genetic and environmental identical comparisons between two twins with drastically different rhabdomyoma growth. The only known difference between our twins is that twin B had a hypercoiled umbilical cord on fetal MRI. The clinical significance of this is unclear, and whether the hypercoiling is causative of fetal changes or indicates fetal changes. Regardless, this case highlights a need for further understanding of how to predict when cardiac rhabdomyomas will change rapidly.

Treatment of cardiac rhabdomyomas with mTOR inhibitors has been reported several times. However, it is unclear what time frame we should expect to see clinical changes in the fetus. Specifically, in our case, the first sign of improvement was the improvement in fetal edema, even though we could not see changes in the blood flow dynamics with the heart during the fetal echo. This was followed by small changes in the size of the cardiac rhabdomyomas without the development of anterograde flow of blood through the aorta. Finally, just before delivery, the size of the cardiac rhabdomyoma significantly reduced, and there was anterograde flow through the aorta. Thus, this case suggests that interpreting efficacy based solely on cardiac rhabdomyoma size is inappropriate. Improvement in hydrops fetalis theoretically could have been from changes in other nonimmune hydrops fetalis causes such as twin-twin transfusion and lymphatic obstruction (Rabinowitz et al. 2022). However, neither of these was seen on imaging in our case, making the cardiac response to sirolimus the likely cause of improvement in hydrops fetalis.

Access to prenatal treatment options remains a barrier for many individuals, as this is typically based on surgical expertise. However, medical treatment can occur regardless of location as long as front-line providers (pediatricians, geneticists, TSC specialists, and/or maternal-fetal-medicine) have the support they need to identify cases where prenatal treatment can be considered. In our case, the physical proximity to our institution, including a fetal care center and TSC Center of Excellence, allowed for evaluation and treatment plan implementation within 24 h of the rhabdomyoma being found. Making quick decisions and advocating by local providers with support from TSC experts at a distance is likely to ensure that each family receives timely and optimal counseling and treatment.

While not the focus of this case report, these twins highlight another often overlooked pediatric principle: that patients with autosomal dominant disorders can have other disorders. Here, both twins have TSC and long-QT syndrome. While the TSC was de novo in the twins, the long-QT was inherited in an autosomal dominant fashion. This should encourage providers not to forget to consider a second condition as possible even if there is a known genetic diagnosis.

7 | Conclusion

Here, we showed a reversal of hydrops fetalis caused by obstructive cardiac rhabdomyomas in a twin gestation with both TSC

and long QT syndrome. This report broadens the options for initiating fetal mTOR inhibitor treatment in TSC with positive effects.

Author Contributions

David M. Ritter: conceptualized and curated data, provided methodology, supervised the investigation, wrote the original draft, and edited the manuscript. **Kristin Schneider:** curated data, provided methodology and reviewed and edited the manuscript. **Nkiru Ezeakudo:** curated data and reviewed and edited the manuscript. **Darcy A. Krueger:** supervised, reviewed and edited the manuscript. **Tomoyuki Mizuno:** provided methodology, reviewed and edited the manuscript. **Timothy K. Knilans:** conceptualized data, supervised the care, and reviewed and edited the manuscript. **David N. Franz:** supervised, reviewed and edited the manuscript.

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Disclosure

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Data Sharing

De-identified dosing and blood levels are available upon reasonable request from the corresponding author.

Consent

Parental consent for publication was obtained.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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