Rapid Regression of Left Ventricular Outflow Tract Rhabdomyoma After Sirolimus Therapy

abstract

The neonatal presentation of cardiac rhabdomyomas varies in severity from severe outflow tract obstruction to minimal cardiac dysfunction. The natural history for these lesions is spontaneous regression in the majority of cases. We describe a newborn boy with severe left ventricular outflow tract obstruction secondary to a large rhabdomyoma. The tumor infiltrated the paraaortic area and extended around the origin of the right coronary artery, making surgical resection challenging. Oral sirolimus therapy resulted in a rapid regression of the tumor and alleviation of outflow tract obstruction within 1 month of treatment. This is the first report of sirolimus therapy in alleviating critical left ventricular outflow tract obstruction in this condition. Pediatrics 2014;134: e1199–e1202
Tuberous sclerosis is a well-recognized autosomal dominant neurocutaneous genetic disorder that arises from a mutation in the TSC1 or TSC2 genes. It is often characterized by the presence of multiple intracardiac rhabdomyomas. The natural history of these lesions in early life has been well defined, with an initial increase in tumor size followed by a progressive decrease in tumor size over time. Occasionally patients present in the neonatal period with severe inflow or left or right ventricular outflow tract obstruction. Such patients occasionally need surgical resection of their tumor to alleviate hemodynamically significant critical outflow tract obstruction. We report such a child in whom an alternative therapeutic strategy was used.

CASE REPORT

A baby boy was born at 38 weeks’ gestation after a prenatal diagnosis of cardiac tumors at 34 weeks’ gestation. On examination the child had no obvious dysmorphic features. His vital signs were normal. The pulses were normal. There was a single first heart sound and split second heart sound, with a 3/6 harsh systolic ejection murmur loudest at the left lower sternal edge, radiating to the left upper sternal edge. There was no organomegaly. There were no visible cutaneous stigmata of tuberous sclerosis. The chest radiograph and electrocardiogram were normal. UV light examination was not performed.

Echocardiogram demonstrated situs solitus with levocardia. There was atrioventricular and ventriculoarterial concordance. The great vessels were normally related. The patent foramen ovale shunted left to right. There were multiple intracardiac tumors, including a large 15- × 12-mm tumor obstructing the left ventricular outflow tract, with a peak velocity of 4.2 m per second and instantaneous gradient measuring 70 mm Hg (Fig 1). There was a left-sided aortic arch with small patent arterial duct shunting left to right. The patient was temporarily treated with a prostaglandin infusion at 5 ng/kg per minute, given concerns about maintaining cardiac output. Cranial and renal ultrasounds were normal. Computed tomography brain scan showed subependymal nodules in both lateral ventricles, diagnostic of tuberous sclerosis. Cardiac MRI was performed to delineate the extent of the tumor. Steady-state free precession imaging demonstrated a large tumor in the left ventricular outflow tract, which invaded the aortic wall and enveloped the right coronary artery. Given the high risk of surgical intervention, it was elected to treat the patient with oral sirolimus (0.5 mg once daily), a mechanism target of rapamycin (mTOR) inhibitor, which was started on day 10 of life and continued for 24 days. The patient was closely monitored with sirolimus levels, electrolytes, liver function tests, and triglycerides. Prophylaxis with co-trimoxazole was used, given the immunosuppression therapy, but there was no episode of infection. The sirolimus level was 26 ng/mL on day 7 of treatment, so the dosage was reduced to 0.4 mg once daily (Table 1).

Serial echocardiography was performed to monitor the tumor size. On day 5 of treatment, the left ventricular outflow tract tumor started to decrease in size (7 mm × 8 mm), and there was a dramatic reduction by day 24 of treatment (5 mm × 4 mm) (Fig 2). The sirolimus was discontinued at that time. The patient was discharged from the hospital and is currently well, with no residual cardiac dysfunction. The tumors increased slightly in size after discontinuation of sirolimus, but the gradient across the left ventricular outflow tract remained stable at most recent follow-up at 8 months of age.

The child developed infantile spasms at 3 months of age, confirmed on interictal EEG with excess intermittent slowing over temporal regions and multifocal independent epileptiform discharges over temporal and frontal regions bilaterally. He was treated with vigabatrin. There was a mutation of C to T at position 4375 (R1459×) on exon 33 of the TSC2 gene.

DISCUSSION

This short report demonstrates that sirolimus may prove helpful in dissolving...
rhabdomyomas in critical locations in the heart of a neonate. Although there are 2 previous reports of everolimus therapy in this setting, the application of sirolimus in the setting of severe neonatal left ventricular outflow tract obstruction with the lesion extending into the region of the right coronary artery has not been previously reported. We elected to use sirolimus because it was available in liquid form, unlike everolimus, and as an mTOR inhibitor and antiproliferative agent it has been used in treating hemangiomas in PHACE syndrome. An initial dosage of 0.5 mg once daily was chosen because it was believed to deliver therapeutic levels that would avoid toxicity and was hoped to demonstrate an antiproliferative effect on the rhabdomyoma, as in a previous report on its use in treatment of hemangiomas. The sirolimus and triglyceride levels were slightly elevated in this patient (Table 1), so the dosage was reduced to 0.4 mg once daily, but this dosage showed effective tumor regression. The potential for early tumor growth in this child and worsening of the gradient across the outflow tract and the coronary involvement complicated matters for this child.

The TSC1 and TSC2 genes form a physical complex that influences the mTOR function. The mTOR is a protein that in humans is encoded by the FRAP1 genes. It is a serine–threonine protein kinase that regulates cell growth, proliferation, protein synthesis, and transcription. Previously, the mTOR inhibitor sirolimus has been used as an immunosuppressant in kidney and cardiac transplant recipients, and more recently everolimus has been used to treat subependymal giant cell astrocytomas and renal angiomyolipomas in patients with tuberous sclerosis.

Sirolimus and everolimus can cause dyslipidemia, deranged liver function tests, and immunosuppression, so careful monitoring of these parameters and prophylaxis with co-trimoxazole are warranted. Target sirolimus levels in the initial period after transplant range from 10 to 15 ng/mL, decreasing to 5 to 10 ng/mL over the medium to longer term. We aimed for a level of 20 ng/mL, which was nontoxic yet demonstrated a significant effect on tumor regression.

Although regression of rhabdomyomas in 2 previous patients receiving everolimus treatment has been reported, this is the first report of sirolimus to intentionally dissolve a critically obstructive left ventricular outflow tract tumor where surgical intervention risk was deemed too high. The rapidity of regression of the tumor within a month of treatment points to the direct effects of the mTOR inhibitor rather than a natural history of regression in this case. There was a slight rebound increase in size of the left ventricular outflow tract tumor after discontinuation of treatment, which has been reported previously. Given the potential for significant side effects with this medication, we would advise therapy only for children with hemodynamically critical cardiac lesions.

**CONCLUSIONS**

Sirolimus therapy has the potential to rapidly accelerate regression of critically located rhabdomyomas in the neonatal heart, where the risk of surgical intervention is deemed too high. The additional benefit of effective nonsurgical management of such tumors is obvious. Close monitoring of the patient and prophylactic antibiotic therapy may optimize outcomes in such cases.

**ACKNOWLEDGMENT**

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### TABLE 1 Biochemical and Hematologic Parameters During Treatment With Sirolimus

<table>
<thead>
<tr>
<th>Time</th>
<th>Sirolimus (ng/mL)</th>
<th>Triglyceride (mmol/L)</th>
<th>Lymphocyte (\times 10^9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>—</td>
<td>1.05</td>
<td>8.2</td>
</tr>
<tr>
<td>Day 7</td>
<td>26</td>
<td>5.32</td>
<td>5.9</td>
</tr>
<tr>
<td>Day 14</td>
<td>22.8</td>
<td>2.29</td>
<td>7.2</td>
</tr>
<tr>
<td>Day 21</td>
<td>—</td>
<td>1.75</td>
<td>3.7</td>
</tr>
</tbody>
</table>

### FIGURE 2

Echocardiogram in the subcostal view demonstrating a significant reduction of the left ventricular outflow tract tumor after treatment with sirolimus. AO, aorta; LV, left ventricle.


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