Case report
Regression of Symptomatic Multiple Cardiac Rhabdomyomas Associated with Tuberous Sclerosis Complex in a Newborn Receiving Everolimus

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Summary
Cardiac rhabdomyoma is the most common primary cardiac tumor, is considered to be a hamartoma of developing cardiac myocytes. Cardiac rhabdomyoma is associated with tuberous sclerosis complex (TSC) in 50–86% of cases. Mutations in TSC-1/TSC-2 genes result in increased mammalian target of rapamycin (mTOR) pathway activation responsible for the hamartomatous lesions of tuberous sclerosis complex. Therapy with mTOR inhibitors is currently under investigation as a treatment option for tumors associated with TSC. In this report we present a case with multiple symptomatic rhabdomyomas associated with tuberous sclerosis complex, deemed to be ineligible for surgical removal, treated with everolimus (mTOR inhibitor). Conclusion: As we observed in our patient, in cases with inoperable symptomatic rhabdomyomas associated with TSC, everolimus, an mTOR inhibitor, may be the treatment of choice, which should be confirmed with additional studies.

Key words: newborn, rhabdomyoma, tuberous sclerosis complex, everolimus.

Introduction
Primary cardiac tumors are extremely rare with a prevalence of 0.0017–0.28% in autopsy series [1]. Cardiac rhabdomyoma, comprising about 60–80% of primary cardiac tumors, is considered to be a hamartoma of developing cardiac myocytes and associated with tuberous sclerosis complex (TSC) in 50–86% of cases [1–4]. TSC is an autosomal dominant neurocutaneous disorder resulting from an inactivating mutation in either the tuberous sclerosis complex-1 (TSC-1, chromosome 9q34, hamartin) or tuberous sclerosis complex-2 (TSC-2, chromosome16p13, tuberin) genes and characterized by slow growing tumors in multiple organs. Mutations in these genes result in increased activation of mammalian target of rapamycin (mTOR) pathway, leading to abnormal cellular proliferation and differentiation, responsible for development of the hamartomatous lesions of TSC [4–7].

Rhabdomyomas are generally asymptomatic or may present with congestive heart failure, arrhythmias, intracavitary obstruction and constitutional symptoms [2]. Because the natural history of the rhabdomyoma is one of regression, most patients can be managed conservatively including frequent monitoring with echocardiography and electrocardiography [8]. Surgical intervention is reserved for patients who have symptoms of severe hemodynamic compromise or intractable arrhythmias. Unfortunately, inoperable multifocal tumors cause a major problem. A chance finding of regression of TSC-associated cardiac rhabdomyoma after receiving everolimus opened a new avenue form mTOR inhibition as a possible novel therapy [6]. In this report we present a newborn infant with multifocal symptomatic and inoperable cardiac rhabdomyomas associated with TSC, who was treated successfully with everolimus.

Case Report
A male infant was born at term to a 25 years old woman by vaginal delivery without any significant
FIG. 1. Echocardiographic appearances of the tumors before treatment (left side) and after 2 months of treatment (right side) are given. Apical four-chamber view demonstrating multiple tumors (a), parasternal short axis view of the tumor located on the mitral valve (b), left ventricular outflow obstruction due to tumor located beneath the mitral valve protruding to outflow tract (c) are seen on the left side. Significant reduction in tumor size (d, e) and relief of left ventricular obstruction (f) are seen on the right side.
antenatal, maternal medical or family history with a birth weight of 3550 g. Apgar scores were 9 and 10 at 1 and 5 min, respectively. He was consulted to pediatric cardiology department because of cyanosis and heart murmur. Physical examination revealed a mild cyanosis (oxygen saturation of 85%), heart rate of 145 beats per minute and respiratory rate of 70 breaths per minute. A grade 2-3/6 systolic ejection murmur best heard at the left sternal border and severe hepatoesophageal were noted. Transthoracic echocardiography demonstrated multifocal echogenic masses, two at left ventricular inflow and outflow tract (24 × 21 mm and 22 × 20 mm, respectively) resulting in mild obstruction, one at cardiac apex (16 × 18 mm), one at right atrium (10 × 10 mm) and multiple milimetric masses on the left and right ventricle free walls (Fig. 1). Neurologic examination, electroencephalography, cranial and abdominal ultrasonography, Wood’s light examination of the skin revealed no lesions in terms of TSC. Cardiac surgeons deemed the masses ineligible for surgical resection. Thus we started everolimus treatment on the second day of age with a dose of 0.25 mg two times per day, 2 days per week. We adjusted the dose in accordance with the dose used in a study by Demir [9]. We monitored complete blood cell count, hepatic and renal function tests, lipid profile, lymphocyte subsets and serum levels of everolimus during therapy. He achieved trough serum everolimus levels that ranged from 3.6 to 7.8 ng/ml (therapeutic levels 5–15 ng/ml).

The patient was discharged after 6 weeks of age with everolimus, amiodarone and furosemide treatment. Echocardiography revealed significant improvement in findings (Fig. 1). Everolimus was stopped at the end of third month of treatment. Ten months after cessation of everolimus, he had a few short duration of epileptic seizures. Cranial magnetic resonance imaging revealed multiple milimetric subependymal nodules in both of the lateral ventricles. Furthermore he was diagnosed with TSC with aforementioned findings. Our patient is now under near follow-up and has been symptom free for 15 months. He had moderate to severe mental insufficiency, moderate left ventricular dilation and echogenic mass over mitral valve (16 × 12 mm) on the last echocardiographic examination and electrocardiography displayed the features of Wolf-Parkinson-White syndrome.

Discussion

Cardiac rhabdomyoma is the most common primary cardiac tumors, and contrary to knowledge, as cardiac rhabdomyomas are histologically benign tumors, sometimes these may be functionally malign. The natural history of cardiac rhabdomyomas is that of complete or partial regression with consequent resolution of symptoms, although the regression mechanism is not yet well understood. In a series of 154 patients with TSC, partial regression of the cardiac rhabdomyomas was reported in 50% of cases and complete resolution in 18% [8].

Cardiac rhabdomyomas frequently occur in association with TSC, an autosomal dominant–inherited or sporadically occurring disorder characterized by widespread hamartomas that variably involve multiple organs. Mutations in TSC1/TSC-2 genes result in increased activation of mTOR activity, which seems to be responsible for hamartomas in patients with TSC [3, 4, 6, 7]. Kotulska et al. [10] also demonstrated the mTOR dysregulation in cardiac rhabdomyomas associated with TSC.

Therapy with mTOR inhibitors, mimicking the function of hamartin–tuberin complex that is deficient in TSC, is currently under investigation as a treatment option for tumors associated with TSC. Everolimus is an mTOR inhibitor that has been reported to be effective against SEGA in TSC, renal cell carcinoma, neuroendocrine tumors and finally in cardiac rhabdomyomas as case reports [5–7, 9]. Tiberio et al. [6] reported a 7-year-old patient with TSC who received everolimus for SEGAs and subsequently had regression of a previously unchanged large left ventricular cardiac rhabdomyoma. This chance finding opened a new avenue for mTOR inhibition as a possible novel therapy for symptomatic rhabdomyomas. After that, Demir et al. [9] reported a newborn with multifocal cardiac rhabdomyomas resulting in hemodynamic instability, heart failure and cyanosis treated with everolimus.

Our patient had multiple rhabdomyomas which were ineligible for surgery. He had heart failure and mild left ventricular inflow and outflow obstruction. After treatment with everolimus the hemodynamic instability of the patient improved dramatically with significant reduction in size of most of the rhabdomyomas. Size of the residual tumor on mitral valve slightly increased at 10 months after cessation of everolimus without any additional cardiac effects, so we did not start everolimus again.

In conclusion, the reported positive effects of mTOR inhibition on a wide variety of TSC disease manifestations provide the authors to think it as a novel medical therapy for these patients. As we observed in our patient, in cases with inoperable symptomatic rhabdomyomas associated with TSC, everolimus, a mTOR inhibitor, may be the treatment of choice, which should be confirmed with additional studies.

References