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CASE REPORT

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Successful use of sirolimus for refractory atrial ectopic tachycardia in a child with cardiac rhabdomyoma

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Cardiac rhabdomyomas are common in tuberous sclerosis. We report a child who developed rhabdomyoma related arrhythmia refractory to antiarrhythmic drug therapy. Reversion of the atrial ectopic tachycardia was achieved with mammalian target of rapamycin pathway (mTOR) inhibitor sirolimus. As per our knowledge, this is the first time that sirolimus has been successfully used in this setting.

KEYWORDS
arrhythmia, m-TOR inhibitor, rhabdomyoma, sirolimus

1 | INTRODUCTION

Primary cardiac tumors in pediatric population are extremely rare with an incidence ranging between 0.02% and 0.32% (Miyake et al., 2011; Oztunc, Atic, & Gunes, 2015). Cardiac rhabdomyomas (CRs) are the most common pediatric primary tumors. Approximately half of all rhabdomyomas are associated with tuberous sclerosis (TS) where multiple CRs are identified in 70% of the cases (Demir, Ekici, Erdem, Emir, & Bahattin, 2012; Madueme & Hinton, 2011). CRs are usually located within the ventricles, but they may also originate in the atria (Hinton, Prakash, Romp, Krueger, & Knilans, 2014). Although CRs are associated with spontaneous regression in 33%–50% of the cases during the first 2–4 years, they can cause serious cardiovascular complications, including intracavitary obstruction, congestive heart failure, and rhythm disturbances (Demir et al., 2012; Kocabas et al., 2012; Tiberio, Frany, & Phillips, 2011). Arrhythmias have been reported to occur in 16%–47% of all the cases (Hinton et al., 2014; Oztunc et al., 2015). Intramural rhabdomyomas are thought to interrupt the conduction pathways, leading to ectopic electrical foci (Aslan, Sap, Sert, & Odabas, 2014). Because of spontaneous regression, treatment is suggested only in symptomatic patients with rhabdomyomas and in the setting of significant hemodynamic consequences or life-threatening arrhythmias (Kocabas et al., 2012). There is a growing body of evidence for the use of mTOR inhibitors in treating tuberous sclerosis complex (TSC) manifestations, including cardiac rhabdomyoma (CR), but only one referring to the associated arrhythmia (Moavero, Coniglio, Garaci, & Curatolo, 2013; Verhaaren et al., 2003; Yang et al., 2015).

In this study, we report a case of multiple cardiac rhabdomyomas in a 3-year-old child with intractable arrhythmias who was managed successfully with sirolimus treatment.

2 | CASE REPORT

In this report, we present a 3-year-old girl who presented with seizures at the age of 4 months and was diagnosed with TS. Echocardiography examination, performed at the time of diagnosis, revealed the presence of multiple areas of homogenous, well-circumscribed lesions within the base of interventricular septum (IVS), moderator band, and the right ventricle outflow tract. The dimensions ranged from 4 × 4 mm to 4 × 5 mm. Presence of cardiac tumors were initially asymptomatic.

Cardiac arrhythmias appeared at the age of 3 years. Atrial ectopic tachycardia (AET) was diagnosed electrocardiographically (ECG). AET with occasional second degree AV block was confirmed on the 24-hr ECG recording before any drug therapy was initiated. During the episodes of arrhythmia the average heart rate (HR) was 170 bpm (Figure 1a).

Echocardiography was performed before treatment to evaluate ventricular function and cardiac anatomy. Only one tumor lesion, in the interventricular septum close to moderator band was still present. The other two lesions regressed spontaneously. No other visible lesions were detected in the atria suggesting a possibility of the presence of undetected abnormal tissue which could not be detected with a current imaging resolution. Contractility of left ventricle was slightly diminished (EF 55% vs 66% before detected arrhythmia).

The arrhythmia was unresponsive to antiarrhythmic drug therapy (first line amiodarone + digoxin + propranolol, second line quinidine + digoxin + propranolol, DC cardioversion). AET persisted most of the time. Occasionally sinus rhythm was present and lasted for a few seconds. The average HR decreased to 145 bpm (Figure 1b). On the basis of previous report of the use of everolimus in TS patient with life-threatening arrhythmia (Tiberio et al., 2011), we decided to add sirolimus to the current therapy. At 37th days of hospitalization, we started sirolimus therapy with a dose of 1 mg/m^2 twice a day. We also continued antiarrhythmic treatment with quinidine + digoxin + propranolol. Sirolimus use in this setting was approved by the ethical committee and informed content was obtained from the patients parents.

The patient was closely monitored with serum levels of sirolimus, electrolytes, lipid profiles, liver and kidney function tests and blood cell counts. Prophylaxis with cotrimoxazole was used because of the immunosuppressant effects of sirolimus. Blood level of sirolimus reached therapeutic range of 6, 6 ng/ml on day 5. Serial ECGs were performed to monitor heart rate and rhythm. On day 9 of treatment, the HR started to decrease to 100 bpm. However, atrial ectopic rhythm still was present (Figure 2). On day 14 of sirolimus therapy, normal sinus rhythm was noticed for the first time.

In the course of next several months, repeated 24-hr ECG recordings were normal. In order to maintain the target plasma level of sirolimus (5–15 ng/ml), we had to increase dose to 2 mg/m^2. Except of a slight increase in serum cholesterol level, no other side effects of sirolimus were detected. There was no episode of infection. During the next 2 months, antiarrhythmic drug therapy was tapered down and discontinued, while the sirolimus therapy remained unchanged. We continued sirolimus therapy beyond the full arrhythmia control because there was a clinical impression of concomitant neurological improvement. ECHO and cardiac MRI were subsequently performed after 6 months. No tumor lesions were found. Nine months after discharge from the hospital, the patient was doing well without any recurrent AET attacks.

Initially, good seizure control was achieved with combined antiepileptic therapy (valproate + topiramate). At the time of starting the therapy with sirolimus, clonazepam was also introduced due to subsequently recorded seizures on EEG. Subsequently, no seizures were registered by parents and all EEGs were with no epileptic discharges. Unfortunately, epileptic discharges were registered again on the EEG performed 10 months later. Also, MRI performed 10 months later still showed multiple cortical tubers, subependymal nodular abnormalities, but no subependymal giant cell astrocytomas (SEGA); there was no progression compared to previous findings. MRI findings did not confirmed our clinical impression of improved neurological improvement beyond seizure control.

3 | DISCUSSION

Tuberous sclerosis complex (TSC) is autosomal dominant genetic disorder characterized by presence of benign, tumor like lesions (hamartomas) in various organs. TSC is caused by mutation in TSC1 or TSC2 genes. Products of these genes, hamartin and tuberin, form a complex that is involved in inhibition of mTOR. mTOR is a protein kinase that regulates protein synthesis, cellular metabolism, differentiation, growth, and migration (Tiberio et al., 2011). Loss of TCS1 or TCS2 genes products lead to activation of mTOR which results in the abnormal cellular proliferation and differentiation, responsible for the hamartomatous lesions of TSC (Tiberio et al., 2011). About 50% of patients with TSC developed rhabdomyomas in the heart. The natural history of these tumors is regression in the first years of life and intervention is rarely necessary. The treatment is suggested only in the symptomatic patients with hemodynamically significant CRs and life-threatening arrhythmias. There is a dilemma whether tumors persist beyond current imaging resolution or completely regress over time. This dilemma is reinforced by the fact that some patients with spontaneously regressed rhabdomyomas on ECHO examination may

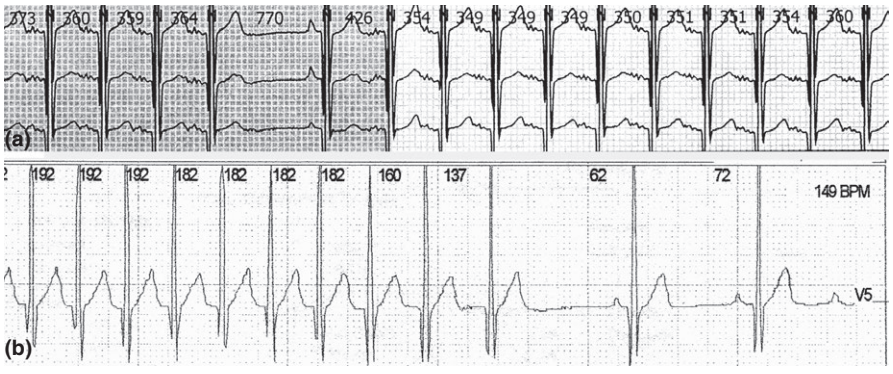

FIGURE 1 (a) Atrial ectopic tachycardia with a second degree AV block before starting antiarrhythmic therapy; (b) Atrial ectopic tachycardia with brief episodes of sinus rhythm during antiarrhythmic therapy

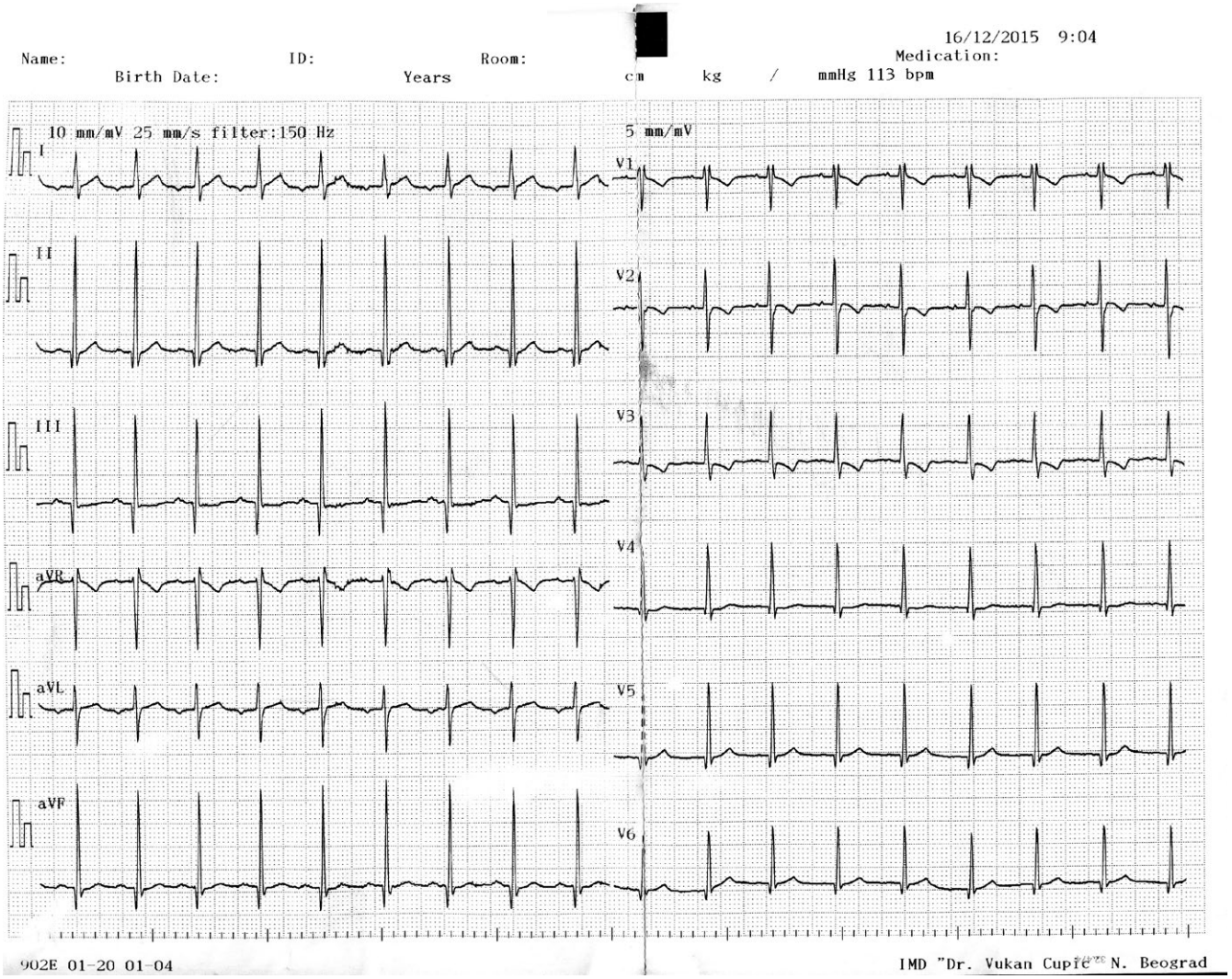

FIGURE 2 Slow atrial ectopic rhythm

continue to have rhythm abnormalities (Madueme & Hinton, 2011). This was the case in our patient who presented with severe arrhythmias suggesting the presence of undetected abnormal tissue.

Mammalian target of rapamycin pathway inhibitors therapy is currently under investigation as a treatment option for tumors associated with TSC. mTOR inhibitors function by forming a complex with the intracellular protein FKBP-12. This complex inhibits mTOR by preventing it from interacting with its cofactor RAPTOR (regulatory associated protein of mTOR) and interrupting further cell signaling downstream, mimicking the function of the hamartin-tuberin complex that is deficient in patients with TSC (Hinton et al., 2014; Oztunc et al., 2015). Because these agents also inhibit lymphocyte and fibroblast proliferation, they are approved for clinical use as immunosuppressive and antiproliferative agents (Tiberio et al., 2011).

There are several reports that describe a rapid regression of rhabdomyomas after therapy with mTOR inhibitors, but there is only one report describing the successful management of intractable, rhabdomyoma-related arrhythmias in newborn with everolimus (Oztunc et al., 2015). In our case, both arrhythmias and rhabdomyomas showed regression after sirolimus treatment. As per our knowledge this is the first report of sirolimus application in this setting. Treatment dosage has been determined on the basis of the previous publications (Breathnach, pears, Franklin, Webb, & McMahon, 2014). No serious side effects were observed during treatment.

We believe that sirolimus could be an effective choice for the treatment of life-threatening TS cardiac manifestations, including drug-resistant persistent arrhythmias. We found this to be the case in the child we treated. Consequently, we suggest that sirolimus therapy may be as effective as everolimus in arrhythmia management in similar situations. Due to its lower price, sirolimus may be more affordable in less-developed countries compared to the more expensive everolimus.

AUTHORS' CONTRIBUTION

All authors have been active participants in the treatment of the patient including participation in the conception, execution, and writing

of the manuscript. Authors confirm: that the work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all coauthors, as well as by the responsible authorities.

CONFLICT OF INTEREST

There is no financial or ethical conflict of interests regarding the contents of the submission.

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