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Brief Report

Everolimus treatment of a newborn with rhabdomyoma causing severe arrhythmia

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Abstract Rhabdomyoma is the most common cardiac tumour in children often associated with tuberous sclerosis. Arrhythmia caused by cardiac rhabdomyomas may be the initial sign of tuberous sclerosis. Rhabdomyomas unresponsive to other treatments could be successfully managed with everolimus, which has demonstrated benefit in tuberous sclerosis. We report a case of rhabdomyoma causing severe arrhythmia in a newborn managed successfully with everolimus.

Keywords: Rhabdomyoma; arrhythmia; everolimus

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PRIMARY CARDIAC TUMOURS ARE RARE IN PAEDIATRIC practice, occurring with an incidence of 0.0017–0.02%.[1] Rhabdomyoma is the most common cardiac tumour seen in infants and children.[2] Cardiac rhythm disorders are typical manifestations of rhabdomyomas and seen in 16–47% of all cases.[1] Rhabdomyomas are intimately associated with tuberous sclerosis.[3] Several studies have reported spontaneous tumour regression with full resolution in more than 80% of cases during childhood.[1,4] Owing to the higher incidence of spontaneous regression, surgical intervention after birth should be undertaken when there is cardiac inflow, outflow obstruction, or intractable arrhythmia.[5] Surgery may be challenging in cases with multiple rhabdomyomas in multiple different sites. There are only two previous reports about rhabdomyoma cases that showed regression under medical treatment.[6,7] In the present study, we report a case of multiple cardiac rhabdomyomas causing severe arrhythmia in a newborn who was managed successfully with everolimus treatment.

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Case report

We presented a case of a term female newborn who was born to a primigravida at 38 weeks of gestation. In the delivery room, the newborn presented with supraventricular tachycardia, which was responsive to adenosine treatment. Her physical examination was unremarkable except for a second-degree (II/VI) systolic ejection murmur on the left-sided second intercostal space. Foetal echocardiography at 26 weeks of gestation had revealed focal septal hypertrophy suggestive of rhabdomyoma. Brain MRI was considered to exclude concurrent tuberous sclerosis; however, it was not possible in foetal life. Postnatal echocardiogram demonstrated multiple cardiac masses, which had large extensions along the interventricular septum, subpulmonic area, left atrioventricular junction, mitral papillary muscles, right ventricular anterior wall, and left ventricular posterior wall (Fig 1a and b). There was no evidence of inflow or outflow tract obstruction. No tachycardia was observed during follow-up for 10 days. Electrocardiography showed Wolff–Parkinson–White pattern in sinus rhythm (Fig 1c). After 10 days of asymptomatic clinical course, the newborn again suffered from several episodes of paroxysmal supraventricular tachycardia, which were resistant to direct current

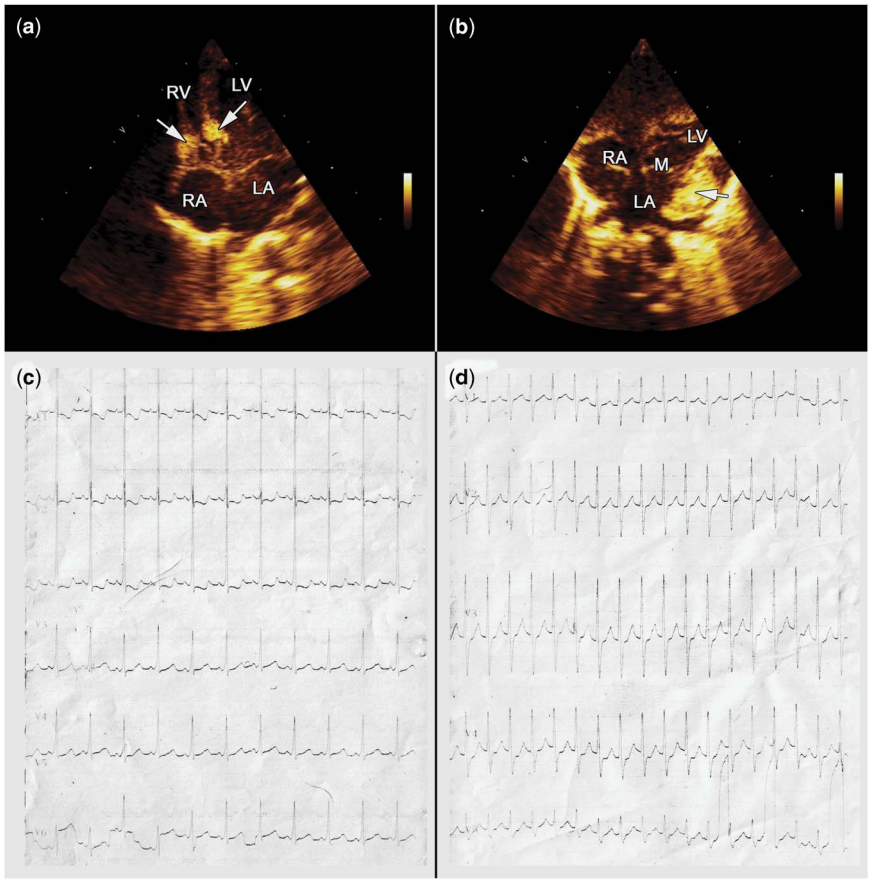

Figure 1.
*(**a**) Masses located on the interventricular septum and right ventricular anterior wall in apical four-chamber echocardiographic view before everolimus treatment (see arrows); (**b**) mass located on the left atrioventricular junction before everolimus treatment (see arrows); (**c**) electrocardiography showing WPW pattern in sinus rhythm; (**d**) electrocardiography showing paroxysmal supraventricular tachycardia. LA = left atrium; LV = left ventricule; M = mitral valve; RA = right atrium; RV = right ventricule; WPW = Wolff–Parkinson–White.*

shock therapy and various pharmacological agents including adenosine, amiodoron, and propranolol (Fig 1d). Subsequently, sotalol and flecanide were initiated together but tachyarrhythmias continued. On the basis of a previous publication, we decided to add everolimus to the current therapy.[6] Everolimus, which is a mammalian target of rapamycin (mTOR) inhibitor, was administered for 4 weeks with the dosage of 0.25 mg two times per day, twice a week. Sotalol and flecainide were continued as the maintenance therapy. The frequency and duration of tachycardia diminished after the 8th day of the everolimus administration. After 15 days of everolimus administration, the masses started to shrink (Fig 2). In order to assess the side effects of everolimus treatment, complete blood cell count, lipid profile, lymphocyte subtypes, and hepatic and renal function tests were studied weekly, but no side effects were observed during the treatment. The patient was also evaluated for the presence of potential tuberous sclerosis. There was no pathological finding in renal ultrasonography; however, cranial MRI showed

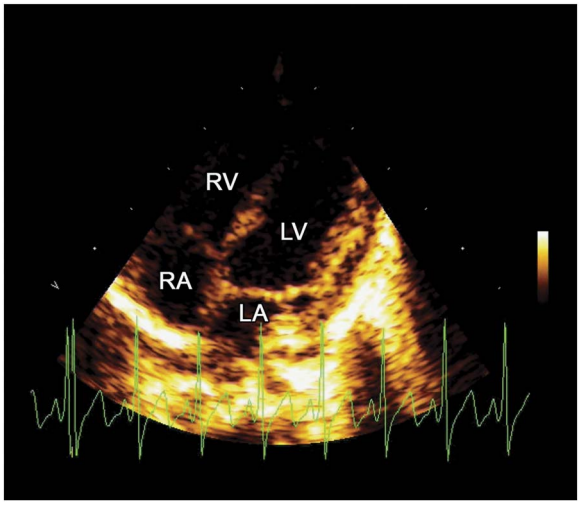

Figure 2.
Two-dimensional apical four-chamber view of echocardiographic images and electrocardiographic monitoring after everolimus treatment. The masses started to shrink and sinus rhythm was observed. LA = left atrium; LV = left ventricule; RA = right atrium; RV = right ventricule.

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multiple tubers. Genetic evaluation for tuberous sclerosis yielded TSC1 gene mutation. Family members were also examined for stigmatas of tuberous sclerosis and no significant clinical findings were detected. At 6 months after discharge from the hospital, the patient was doing well without any recurrent supraventricular tachycardia. Follow-up echocardiographic assessments demonstrated a good left ventricular function and showed small residual masses, which did not cause any haemodynamic compromise.

Discussion

More than 60% of primary tumours of the heart are rhabdomyomas.[2] Although rhabdomyomas may be asymptomatic, they can also cause arrhythmias, inflow–outflow obstructions, and even cardiac failure.[8] Depending on the anatomical location of the tumour, arrhythmia can present with supraventricular and ventricular tachycardias and atrioventricular blocks.[9] As in the present case, Wolff–Parkinson–White pattern has been observed in 1.5% of patients with rhabdomyomas.[1] Management of arrhythmias include medical treatment, catheter ablation, placement of an implantable cardioverter defibrillator, surgical excision, and even heart transplantation.[10]

As in our patient, the presence of multiple rhabdomyomas is usually associated with tuberous sclerosis.[6] Tuberous sclerosis is a genetic disorder that causes hamartamatous lesions in many parts of the body, such as skin, brain, lungs, kidneys, and heart. Mutations in two genes, TSC1 located on chromosome 9q34 and the TSC2 gene located on 16P13, are responsible for most cases of tuberous sclerosis that are inherited as autosomal dominant traits.[11] In our case, TSC1 gene mutation was detected. The TSC1 gene encodes the protein called hamartin and the TSC2 gene encodes the protein tuberin. Tuberin and hamartin form a tumour suppressor heterodimer that inhibits mTOR, which is a protein kinase that regulates the abnormal cellular proliferation and differentiation. Frantic activation of mTOR causes formation of hamartamatous lesions. Solid tumours were previously treated with mTOR inhibitors.[12]

Our patient with multiple cardiac masses and intractable arrhythmias was initially treated with antiarrhythmic drugs, which were unsuccessful in stopping the arrhythmias. The cardiac masses were multifocal with extensive intramural involvement, making surgical resection almost impossible. Previously, Demir et al[6] reported multifocal inoperable cardiac rhabdomyomas that were responsive to everolimus treatment. Tiberio et al[7] reported another case treated with everolimus due to subependymal giant cell astrocytoma in which concurrent cardiac rhabdomyoma showed regression after 13 months of medical therapy. On the basis of these reports, we decided to perform everolimus treatment.

Everolimus is an orally administered inhibitor of mTOR. It is indicated for the treatment of advanced renal-cell carcinoma, neuroendocrine tumours of pancreatic origin, renal angiomyolipoma with tuberous sclerosis complex, and subependymal giant-cell astrocytoma. In our case, both arrthymias and rhabdomyomas showed regression after everolimus treatment. To our knowledge, this is the first case that underwent everolimus treatment for the management of rhabdomyoma-related arrhythmias. Treatment dosage has been determined on the basis of the dosage stated in the study authored by Demir et al.[6] No side effects were observed during treatment. Clinicians should be alert about the well-known side effects of everolimus, such as noninfectious pneumonitis, hyperlipidemia, and opportunistic infections.[13]

In conclusion, cardiac rhabdomyomas that need, but are not suitable for, surgery could be successfully managed with everolimus treatment. Effective dose of everolimus and its side effects in children still require further research.

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Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees.

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