ESC European Society of Cardiology

European Heart Journal - Case Reports (2022) **6**(2), 1–5
https://doi.org/10.1093/ehjcr/ytac068

CASE REPORT
Congenital heart disease

Innocent until proven guilty? Longstanding atrial ectopy preceding cardiac rhabdomyoma diagnosis in tuberous sclerosis complex: a case report

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Received 4 October 2021; first decision 12 December 2021; accepted 27 January 2022; online publish-ahead-of-print 11 February 2022

Background Cardiac rhabdomyoma are the most common cardiac tumour in childhood and are associated with tuberous sclerosis complex (TSC) up to 96% of infant cases. They classically manifest in the foetal and neonatal period, undergo spontaneous regression in the first years of life and are associated with arrhythmia in part due to interruption of normal conduction pathways by the tumour.

Case summary We present a case of a 3-year-old boy with a long-standing history of atrial ectopy who was incidentally found to be in atrial flutter due to a new, rapidly growing cardiac rhabdomyoma impacting ventricular function. The boy was later confirmed with further investigation and TSC1 gene test to have TSC.

Discussion Cardiac Rhabdomyoma does not always present in the infantile period. Any ongoing or new cardiac concern in patient with TSC, even if seemingly minor, should warrant more frequent cardiac evaluation and investigation.

Keywords Paediatric cardiology • Cardiac rhabdomyoma • Tuberous sclerosis complex • Atrial flutter • Case report

ESC Curriculum 2.2 Echocardiography • 5.5 Supraventricular tachycardia • 6.8 Cardiac tumours

Learning points

- *De novo* cardiac rhabdomyoma growth occurs outside of the foetal and neonatal period and can be the presenting feature of tuberous sclerosis complex.
- More frequent surveillance for rhabdomyoma should take place if there are ongoing or new cardiac concerns.

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Handling Editor: Mohammed Al-Hijji
Peer-reviewers: Christoph Sinning; Flemming Javier Olsen; Luis Antonio Moreno-Ruiz
Compliance Editor: Zhiyu Liu
Supplementary Material Editor: Aiste Monika Jakstaite

Introduction

Cardiac rhabdomyoma are the most common cardiac tumour in childhood and are associated with tuberous sclerosis complex (TSC) up to 96% of infant cases.[1] These benign hamartomas classically manifest in the foetal and neonatal period and undergo spontaneous regression in the first years of life often with resolution.[2] They are associated with arrhythmia in part due to interruption of normal conduction pathways by the tumour, creating abnormal atria-ventricular connections and ectopic electrical foci.[3] We present a case of a 3-year-old boy with longstanding atrial ectopy who presented with a new, right atrial tumour causing sustained atrial arrhythmia and impacting ventricular function. Following surgical resection, the diagnosis of cardiac rhabdomyoma was made and the patient later found to have the TSC1 gene mutation.

Timeline

Time	Events
Foetal period	Multiples normal scans
9 months old	Suspicion of cardiac arrhythmia—normal echocardiography
18 months old	Regular follow-up—normal echocardiography
3 years old	Diagnostic of atrial flutter Finding of new massive intracardiac tumour
Day +2 post-tumour diagnostic	Cardiac surgery—extensive excision Histology confirm the rhabdomyoma
Weeks following the surgical excision	Confirmation of the tuberous sclerosis complex diagnosis: brain tubers, renal angiolipomas, TSC1 mutations
4 years old (+1 year post-surgical excision)	Asymptomatic. Normal echocardiography

Case presentation

A healthy 3-year-old male presented for routine paediatric cardiology follow-up. He was initially referred due to the presence of atrial ectopy during a hospital admission for left orchidopexy at 6 months of age. Otherwise, his history was unremarkable with an uneventful antenatal course and normal 20-week anomaly scan. There was no family history of cardiac disease or TSC and no other parental concerns during follow-up except for mild speech delay. At 9 and 18 months, 12-lead electrocardiogram (ECG) were normal and 24-h Holter monitoring noted sinus rhythm with a combined ectopy burden of 11%. Isolated atrial ectopy accounted for 7% of beats and ventricular ectopy 4%. There were no runs of ventricular tachyarrhythmia and the longest run of premature atrial contractions was 3 beats at 158 b.p.m. Echocardiograms performed at the same time as these Holter recordings were normal.

Although clinically very well, at this appointment he was in atrial flutter on his 12-lead ECG. His examination was unremarkable with normal heart sounds and no murmurs heard. Dermal, respiratory, urinary, and visual system were normal as well. Echocardiogram revealed a severely dilated right atrium with a new large mass (6.4 × 3.1 cm) in the right atrium attached to the interatrial septum (see *Figure 1*). The mass was prolapsing through the tricuspid valve into the right ventricle during diastole causing no significant obstruction to inflow but with moderate tricuspid regurgitation through multiple jets. The right ventricular function was reduced (ejection fraction = 39%) but left ventricular function preserved (ejection fraction = 61%). The conventional blood work (including liver enzymes and cardiac biomarkers) was unremarkable. A sedate cardiac magnetic resonance imaging (MRI) demonstrated a heterogeneous, multilobulated right atrial mass but was not able to refine the differential to a single diagnosis. There were few cystic and myxomatous components, no brisk intense early enhancement and no evidence of infiltrative disease (see *Figure 2*).

Given the potential obstruction to inflow, reduced ventricular function and persistent arrhythmia he underwent surgical excision. At the time of surgery, the mass was found to originate from the superior vena cava and right atrial junction (see *Figure 3A*) which were consequently reconstructed in addition to a tricuspid valve annuloplasty.

His post-operative course was uncomplicated. The echocardiogram on post-operative Day 3 showed a good result with a good biventricular systolic function and no residual mass. From a rhythm perspective, the flutter immediately resolved following excision of the mass and he remained in sinus rhythm with no significant ectopy noted on subsequent 24-h Holter monitoring at discharge.

Histology of the tumour revealed large rounded polygonal cells with pathognomonic spider cells confirming the tumour to be a cardiac rhabdomyoma (see *Figure 3B*).

He underwent a brain MRI which revealed multiple cortical and subcortical tubers together with calcified subependymal nodules (see *Figure 3C*). Abdominal ultrasound demonstrated bilateral renal angiolipomas. Subsequent genetic testing confirmed a likely pathogenic variant *TSC1* gene (TSC1.c.1641_1642delAC (p.Pro548Lysfs*15)) according to the ACMG 2015 variant classification guidelines.[4]

Cardiac follow-up at 1 year confirmed good ventricular function on echocardiogram with no recurrence or new tumour growth. Three 24-h Holter monitors throughout the year demonstrated no arrhythmia. He was referred to the TSC clinic at our institution for ongoing follow-up. Routine EEG showed epileptiform discharges from the centro-parietal head regions but he has not had any clinical seizures and did not require seizure medication.

Discussion

We present a case of TSC with cardiac rhabdomyoma growing in size in the first years of life. From the singular history of this patient who had a regular cardiological follow-up for clinically insignificant

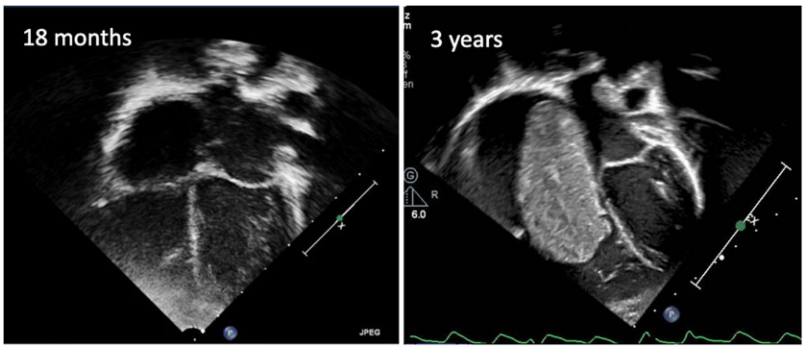

Figure 1 Normal echocardiogram at 18 months old and abnormal echo at 3 years old. Apical four-chamber view demonstrating a new large solitary mass (6.4 × 3.1 cm) originating in the right atrium and protruding through the tricuspid valve.

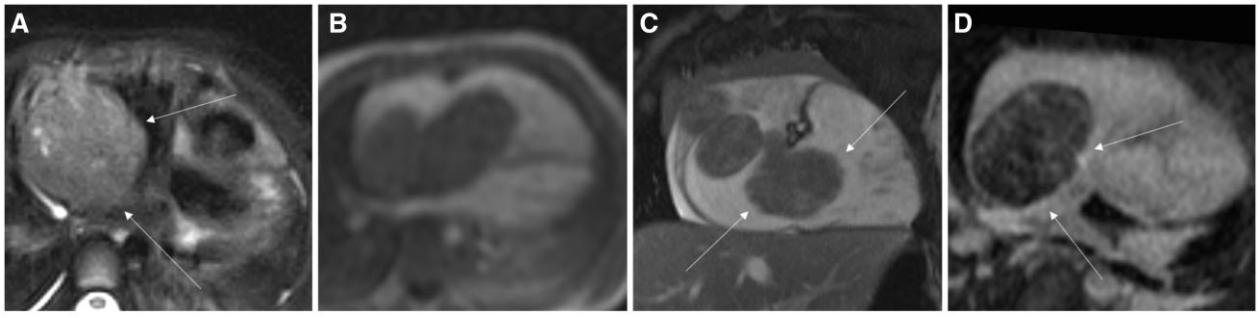

Figure 2 Cardiac magnetic resonance imaging. Pre-operative cardiac magnetic resonance imaging demonstrating a large lobulated right atrial mass that shows heterogeneous mildly hyperintense signal on T2-weighted sequences (*A*), no early enhancement on first pass perfusion (*B*), along with mild heterogeneous enhancement on both post-contrast SSFP cines (*C*) and 3D delayed gadolinium enhancement sequences (*D*).

ectopy, we have confirmation that this cardiac rhabdomyoma appeared *de novo* after 18 months of life and grew significantly during the 3rd year of life of this patient.

The current International Tuberous Sclerosis Consensus Group guidelines concerning echocardiographic surveillance for cardiac rhabdomyoma recommend foetal scanning if there is high suspicion of TSC with imaging later in gestation as tumours can enlarge in the 3rd trimester. At least one postnatal echocardiogram is proposed due to reported haemodynamic compromise after birth. In the absence of inflow/outflow obstruction and ventricular dysfunction, follow-up echocardiography is not recommended in the first year of life but may be considered between 1 and 3 years to document regression. Currently, no further follow-up is recommended once this has occurred unless prompted by new cardiac concerns.[5]

The association between cardiac rhabdomyoma and TSC is due to the mutations in the *TSC1* or *TSC2* genes, leading to disruption of mTOR signalling pathway with resultant tumourigenesis secondary to loss of inhibition of cell growth and proliferation.[1] Recently, exogenous mTOR inhibitors have been used to reduce the size of cardiac rhabdomyomas in haemodynamically significant lesions[6] and there is suggestion that long-term therapy with these medications may alleviate the clinical manifestations of TSC.[7] The predominance of growth of cardiac rhabdomyoma in the foetal period is believed to be due to propagation by trans-placental oestrogen, with regression occurring after this influence dissipates.[8] But it is a misconception that growth is limited to the infantile years. A large multi-national natural history study of TSC found the mean age of cardiac rhabdomyoma diagnosis to be 3.1 years[9] and a previously published literature review observed 20% of diagnoses are made over the age of 6 years, though it is unclear whether these tumours had stabilized since the infant period or presented as *de novo* childhood growth.[10] Although they are the only cardiac tumour known to spontaneously regress,[1] it is incorrect to think regression is the definitive rule. In congruence with other studies, a prospective cohort of 154 TSC patients with cardiac rhabdomyoma noted complete regression in only 18% and partial regression in 50% of patients.[8] Additionally, *de novo* growth outside of the neonatal period does occur with a recent case highlighting a new, rapidly growing cardiac rhabdomyoma in a 2-

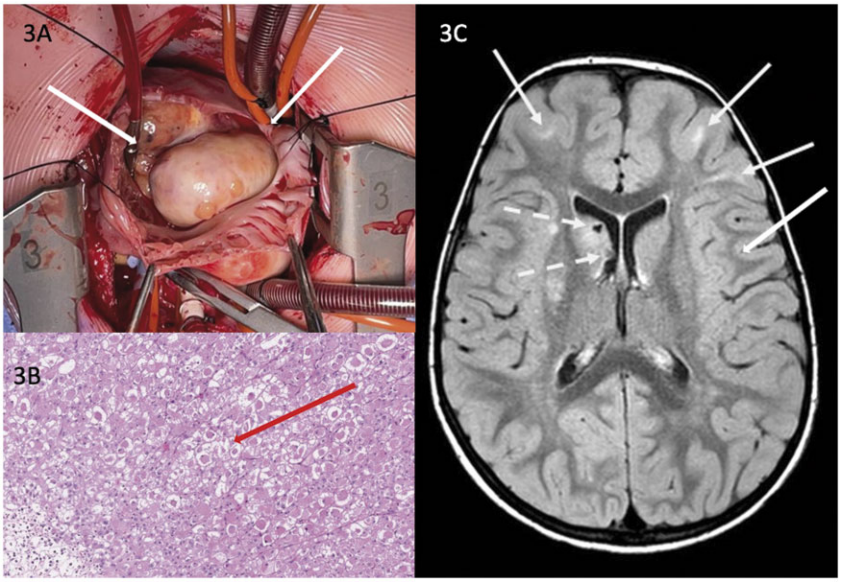

Figure 3 Rhabdomyoma explorations. (*A*) Operative findings: one lobulated soft tissue mass, pale tan in colour measuring 6.5 cm × 5.5 cm × 2.4 cm (arrows). (*B*) Histology: the classic combination of large rounded polygonal cells with strands of cytoplasm extending between nuclei and cell membrane (spider cells)—(haematoxylin and eosin, 10×). (*C*) Axial T2 FLAIR magnetic resonance imaging images of the brain show multiple subcortical tubers (arrows) and calcified subependymal nodules (dashed arrows).

year-old patient following previous surgical resection and documented regression of multiple ventricular rhabdomyomas.[11] Interestingly this new, solitary tumour was located in the right atrium, an uncommon site of origin but the same as our case report.

The theoretical hormonal influence on growth is further supported by the appearance of *de novo* tumours, albeit small and without hemodynamic consequence, in 4% of TSC patients around the time of puberty. Jozwiak *et al.*'s cohort demonstrated new tumour growth in six patients aged 10–15 years, three of which had no prior history of cardiac rhabdomyoma and five of which were female.[8] However, this pathophysiological theory is not applicable in our case due to the patient's atypical age. Another unusual characteristic of this tumour is the demonstration of rapid growth more in keeping with a true neoplasm rather than hamartoma. Such expansile growth is seen in adult cellular cardiac rhabdomyomas which demonstrate cellular proliferation not seen in childhood hamartoma.[12] However, these tumours differ histologically with smaller cell size and fewer vacuolated spider cells which are abundant in childhood cardiac rhabdomyoma. Histology in our case was highly typical of cardiac rhabdomyoma seen in childhood.

Summary

Clinicians must counsel appropriately on the basis of the natural course of any disease. Cardiac rhabdomyomas associated with TSC do not always occur in the foetal and neonatal period, do not universally regress or maintain a stable size, and there is potential for new tumour growth outside of the first years of life. This case highlights the importance of surveillance echocardiography in not only all new TSC diagnoses but throughout childhood and adolescence for all confirmed TSC with even seemingly minor cardiac concerns.

Lead author biography

Alison J. Howell trained in Pediatrics at Great Ormond Street Hospital and is completing her Paediatric Cardiology training at The Hospital for Sick Children, Canada. Her intended subspeciality is Echocardiography with an interest in heart function in repaired congenital heart disease.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

Funding: None declared.

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