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Review Based Book Chapter

CARDIAC MANIFESTATIONS IN TUBEROUS SCLEROSIS COMPLEX AND PROPOSED PATHOPHYSIOLOGIC MECHANISMS: A CASE REPORT AND LITERATURE REVIEW

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REVIEW BASED BOOK CHAPTER

CARDIAC MANIFESTATIONS IN TUBEROUS SCLEROSIS COMPLEX AND PROPOSED PATHOPHYSIOLOGIC MECHANISMS: A CASE REPORT AND LITERATURE REVIEW

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Abstract

Introduction: Tuberous sclerosis complex (TSC) is a rare autosomal dominant syndrome that presents with complex clinical features and involves multiple human systems. Many manifestations can be associated with severe morbidity and mortality, usually those of the central nervous and cardiovascular system.

Cardiovascular manifestations of TSC: Cardiac rhabdomyoma is often the earliest manifestation TSC, typically appearing during the prenatal period with an incidence between 70% and 90%. Although most are clinically silent, they can lead to serious and potentially life-threatening cardiovascular complications. In the past resolution of rhabdomyomas was considered the natural course of the disease. It has recently been documented re-appearance of the rhabdomyomas in 12-15% of adolescent patients, an issue that increases the risk for future arrhythmias. TSC is a complex arrhythmic disorder associated with conductive effects irrespective of the presence of rhabdomyomas, which requires meticulous cardiac follow-up throughout the patient's life. ECG findings include premature atrial contractions, paroxysmal supraventricular tachycardia, Wolff-Parkinson-White syndrome, sinoatrial nodal re-entrant tachycardia, atrial flutter, junctional rhythm, premature ventricular contractions, ventricular

tachycardia and atrial tachycardia. Arterial aneurysms are another complication of TSC with an incidence which is double compared to the general population and can involve aorta, carotid, axillary, renal, iliac, femoral and pulmonary arteries.

mTOR inhibitor treatment of cardiac complications of TSC: The increasing understanding of the mTOR pathway activation in the pathophysiology of TSC has resulted in a progressive rise in the use of mTOR inhibitors for the management of patients with TSC, including those with rhabdomyomas and refractory arrhythmias.

Case presentation: A fetus with suspected tuberous sclerosis complex presenting with fetal arrhythmias in the absence of rhabdomyomas and various patterns of neonatal and infant arrhythmias treated with Everolimus persisting despite regression of rhabdomyomas

Keywords
Tuberous Sclerosis Complex, Cardiac Rhabdomyomas, m-TOR inhibitors, Everolimus, Sirolimus, Fetal/Neonatal arrhythmias

1. Introduction

1.1 Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is a rare autosomal dominant syndrome that presents with complex clinical features and involves multiple human systems [1, 2]. Many manifestations can be associated with severe morbidity and potentially death. Early recognition of the clinical manifestations of TSC, appropriate lifelong surveillance and timely treatment are crucial given the deleterious influence of the TSC diagnosis and management challenges on the quality of life of the affected children and their caregivers [3]. The incidence of TSC has been estimated and generally is between 1:6000 and 1:10,000 live births [2, 4]. Clinical manifestations are diverse as far as the organs affected, timing of onset, and severity of involvement. TSC is characterized by widespread hamartomas which represent tumors which are benign in origin or abnormal growth of normal tissues [1]. Depending on the location, chronological age of the patient, composition, and progression of the hamartomas, especially those of the nervous and cardiovascular system life-threatening complications may become manifest [2, 3]. The clinical presentation of TSC may follow a dynamic course during life span [2, 4-6].

Updated International Tuberous Sclerosis Complex Diagnostic Criteria were published in 2021 [2, 5]. The International TSC Clinical Consensus Group underlines the importance of independent genetic and clinical diagnostic criteria. In TSC, two specific gene mutations have been identified [1, 2, 4, 6, 7]:

- *TSC1* (9q34) mutation on chromosome 9 which encodes hamartin protein
- *TSC2* (16p13.3) is on chromosome 16 which encodes tuberin protein

Most cases present sporadically, but approximately 1 in 3 patients inherit a defective *TSC1* or *TSC2* gene [6]. TSC shows almost complete penetrance with wide phenotypic variability. The *TSC1* and *TSC2* genes differ in that *TSC1* mutations are mostly nonsense or frameshift, leading to protein truncation, whereas missense mutations, large deletions, or rearrangements are seen more frequently in *TSC2* [6].

Hamartin is expressed in several adult tissues and plays a key role in the regulation of cell adhesion. Tuberin is a GTPase activating protein that regulates the GTP binding and hydrolyzing activity of the Ras superfamily of proteins and helps to regulate cell growth, proliferation and differentiation. Loss of function mutations in *TSC1* or *TSC2* lead to deregulated expression patterns in in the mTOR1 signaling pathway, abnormal production of the end products, and ultimately promote tumorigenesis [7].

TSC pathogenesis is characterized by hyperactivation in the mTOR1 signaling pathway resulting in production of hamartin and tuberin which form a tumor suppressor complex and regulate cell growth and proliferation. The target of these proteins is the mammalian target of rapamycin complex 1 (mTORC1), which is a protein serine/threonine kinase complex involved in many important anabolic and catabolic processes, such as translation, cellular growth, proliferation, stress response, and autophagy [6]. Hamartin and tuberin subsequently bind to a third protein TBC1D7 forming the *TSC protein complex* [6]. *The TSC protein complex* functions as a GTPase-activating protein (GAP) for Rheb (Rat sarcoma-small GTPA protein/Ras homolog enriched in the brain). Ras-specific GTPase-activating proteins (RasGAPs) down-regulate the biological activity of Ras proteins by accelerating their intrinsic rate of GTP hydrolysis. This complex inhibits Rheb activity by promoting the conversion of Rheb-GTP to Rheb-GDP, thereby regulating Rheb's role in the mammalian target of rapamycin

(mTOR) pathway. Thus, without the *TSC protein complex*, the RAS homolog Rheb hyperactivates mTORC1 [6, 7]. This reprogramming inhibits autophagy and favorous anaerobic glycolysis [5].

Between 10% and 15% of patients with TSC meeting clinical diagnostic criteria have no mutation identified by genetic testing [2, 4, 5, 6]. Mosaic and intronic mutations in TSC1/TSC2 explain the majority of TSC patients with no mutation identified by conventional testing [8]. The clinical diagnosis is now classified simply as either "definite" or "possible" [1]. "Definite" TSC is determined in the presence of 2 major or 1 major with 2 minor features and "possible" TSC in the presence of either 1 major or ≥2 minor criteria [2-4].

Major diagnostic criteria are hypomelanotic macules (≥3 at least 5 mm diameter), angiofibromas ≥3 or fibrous cephalic plaque, ungual fibromas ≥2, shagreen patch, multiple retinal hamartomas, multiple cortical tubers and/or radial migration lines, subependymal nodules ≥2, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lung lymphangiomyomatosis in adult women and angiomyolipomas ≥2 [2] (**Graph**: Clinical manifestations of tuberous sclerosis complex).

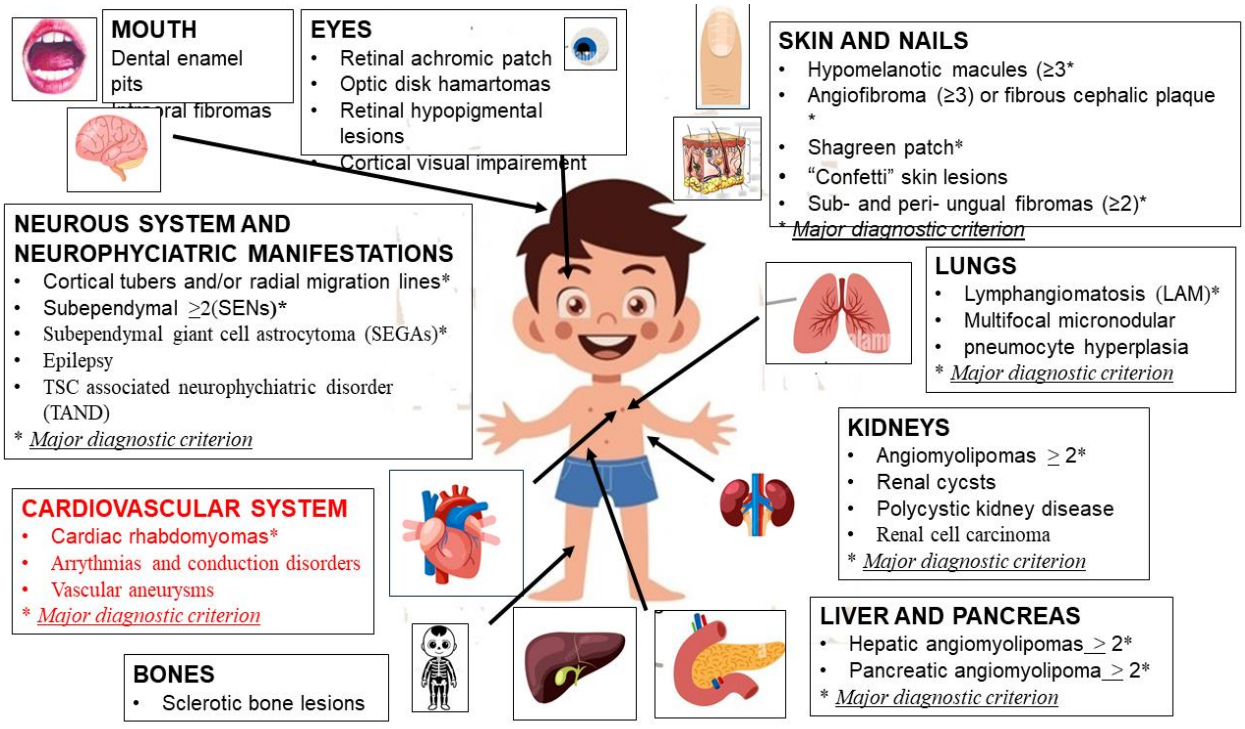


Figure legends Graph: Clinical manifestations of tuberous sclerosis complex

Minor diagnostic criteria are "confetti" skin lesions, dental enamel pits ≥3, intraoral fibromas ≥2, retinal achromic patch, multiple renal cysts, nonrenal hamartomas and sclerotic bone lesions [2] (**Graph**: Clinical manifestations of tuberous sclerosis complex).

Surveillance and management recommendations for individuals with newly suspected or newly diagnosed TSC should include the following [1, 2]:

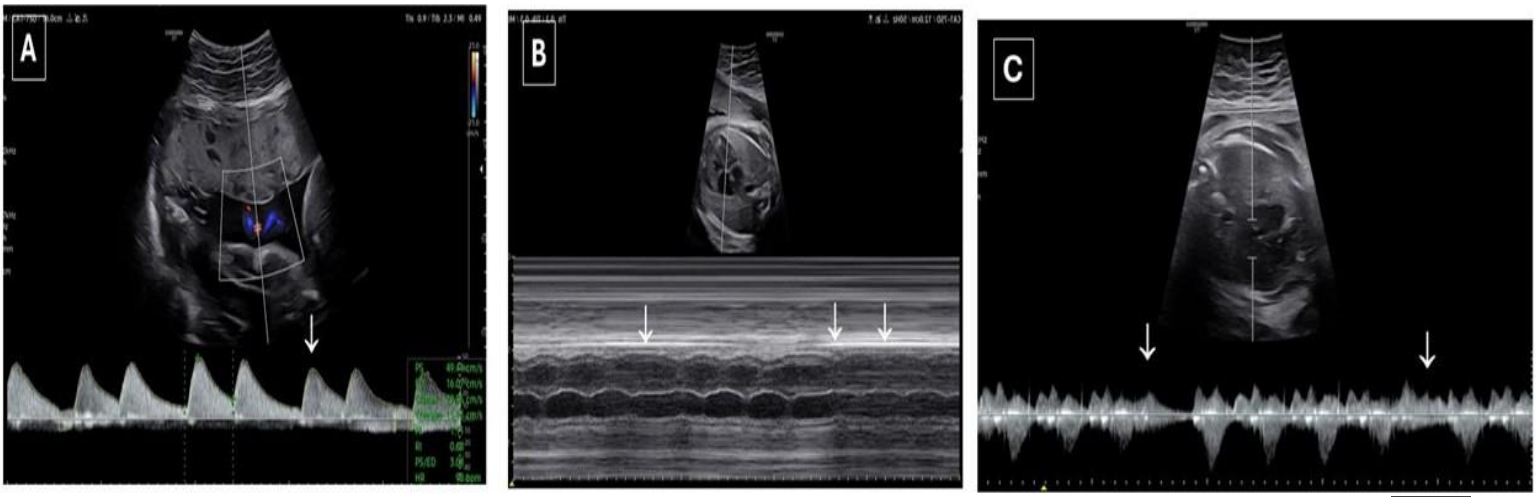
- A three-generation family history to assess additional family members at risk of TSC
- Genetic testing for family counseling or when TSC diagnosis is in question
- MRI of the brain to identify tubers, subependymal nodules, migrational defects, and superependymal giant astrocytoma
- Education of the parents to recognize infantile spasms and focal seizures before they occur
- EEG while awake and asleep. If abnormal, especially if features of TSC are associated neuropsychiatric disorders (TAND), referral to suitable specialists is recommended
- MRI of the abdomen to assess for the presence of angiomyolipomas and renal cysts, screening for hypertension and evaluation of renal function by estimating GFR
- Detailed dermatologic and ophalmologic examination
- When rhabdomyomas are identified antenatally, fetal echocardiography should be performed in the 3rd trimester to detect fetuses at high risk of heart failure after delivery. At least one echocardiogram is recommended in newborns to rule out any haemodynamic impairment
- ECG and echocardiography for cardiac manifestations especially in newborns and children under 3 years old newly diagnosed with TSC
- Evaluation of asymptomatic paediatric patients every 1 to 3 years until regression of rhabdomyomas, whereas more frequent assessment might be necessary for symptomatic ones
- Cardiology consultation at diagnosis and ongoing surveillance, medical or surgical intervention, as indicated

- Referral to a geneticist and neurologist when cardiology makes the initial diagnosis
- Organize a Paediatric to adult transition plan with ongoing cardiology surveillance
- For asymptomatic patients of all ages perform an ECG every 3 to 5 years to monitor for conduction defects, as arrhythmias may occur later in life and perform a 24 to 48-hours Holter monitoring in symptomatic patients
- Evaluation of symptomatic palpitations with cardiac event monitoring
- Concerning cases of syncope should be evaluated with an invasive electrophysiology study

2. Case presentation

A fetus with suspected tuberous sclerosis complex presenting with fetal arrhythmias in the absence of rhabdomyomas and various patterns of neonatal and infant arrhythmias treated with Everolimus persisting despite regression of rhabdomyomas.

A 32-year-old para 2, gravida 2 with gestational diabetes controlled with diet and a previous delivery of a healthy neonate via caesarean section presented at 30 weeks of gestation for a routine fetal scan and arrhythmia was documented in the fetus. **(Figure 1A)** Doppler and M-Mode recorded premature supraventricular non-conducted contractions. **(Figure 1B, 1C)** of notice, hyperechogenic foci were identified in both liver lobes, possibly representing liver hamartomas, raising the suspicion of TSC despite the absence of rhabdomyomas during examination of the feta; heart.



B. M-Mode at 30 weeks across left ventricle and right atrium showing premature supraventricular beats (shown with white arrows: ⬇)

C. Continuous wave Doppler at 30 weeks interrogating inflow (tricuspid flow) and outflow (pulmonary valve) of the right ventricle showing premature supraventricular beats (shown with white arrows: ⬇)

(Figure 2A, 2B) Follow-up every 2-3 weeks showed persistence of the arrhythmia with normal heart anatomy and function and the last prenatal visit was performed at 34 weeks of gestation denoting restoration of normal sinus rhythm associated with normal fetal echocardiography.

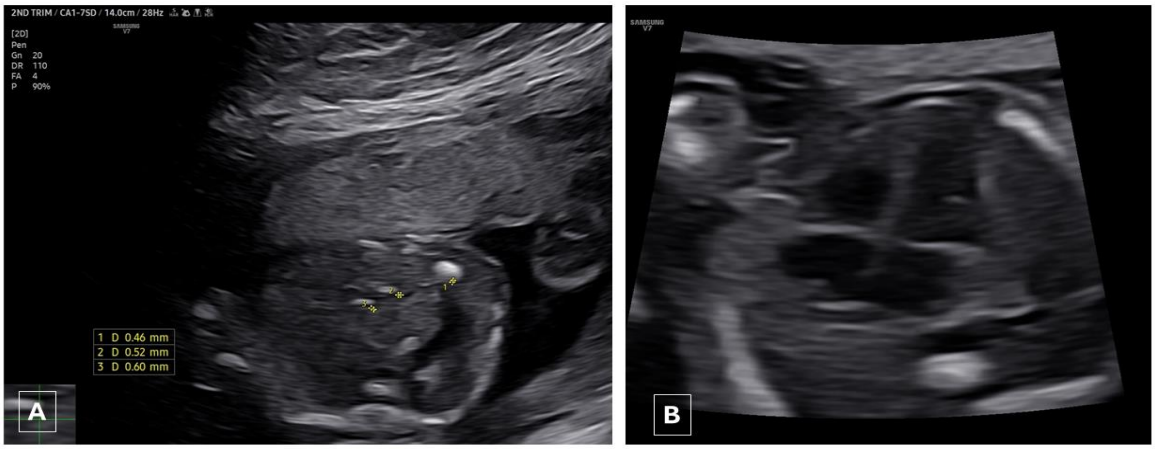


Figure 2: A. Fetal abdominal ultrasound at 30 weeks of gestation showing three hyperechogenic foci in both liver lobes, possibly representing liver hamartomas, raising the suspicion of tuberous sclerosis complex (shown with yellow asterisk *).

B. Normal 4-chamber view of the fetal heart at 30 weeks of gestation showing absence of rhabdomyomas

(**Figure 3A, 3B)** Family history was unremarkable, and the parents were not consanguineous. The male baby was born at 38+3 weeks of gestation with a birth weight of 3240 g. ECG performed at the nursery showed normal sinus rhythm and a cardiologic evaluation was scheduled on an outpatient basis for further investigation to exclude TSC. At 8 days of age the patient was diagnosed with arrythmia found incidentally on a scheduled paediatric visit for bilirubin measurement. ECG showed atrial tachycardia.

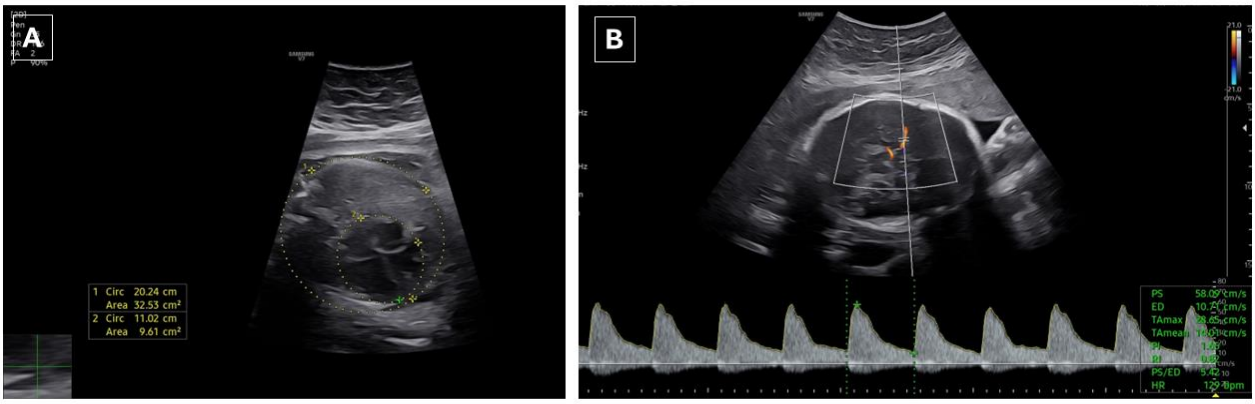


Figure 3: A. Four-chamber view of the fetal heart at 34 weeks excluding the presence of hydrops and rhabdomyomas

B. Middle cerebral artery Doppler at 34 weeks showing resolution of the arrhythmia

(Figure 4A) and echocardiography revealed multiple cardiac rhabdomyomas, a large one at the posterior wall of the right atrium measuring 14x14 mm and another large one in the left ventricle peripherally to the mitral valve measuring 11x4 mm causing no obstruction. **(Figure 4B)** Two small rhabdomyomas were also identified in the lower part of the right and left ventricle.

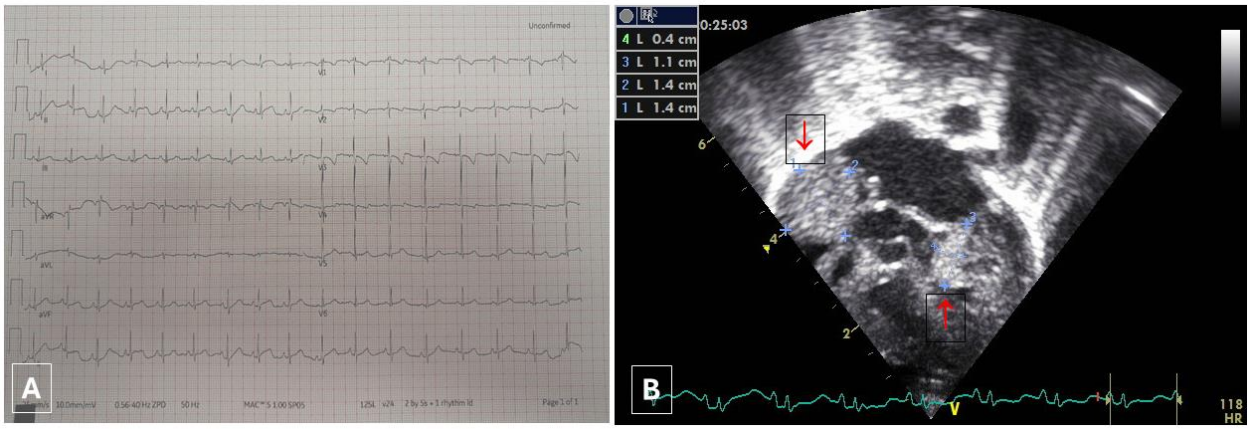


Figure 4: A. ECG at 8 days of life showing atrial tachycardia

B. Transthoracic echocardiography showing a large rhabdomyoma in the right atrium 14x14 mm and another one in the left ventricle close to mitral valve, both shown with red arrows

(Figure 5A, 5B) Brain imaging showed high T1 and low T2 multiple cortical tubers and radial migration lines in the subependymal and periventricular regions. Additionally,

multi-cystic changes were observed in the inferior pole of the left kidney, and a hyperdense lesion measuring 0.6mm was noted in the left lobe of the liver. Due to the presence of adequate major clinical criteria consistent with TSC, genetic testing was not performed.

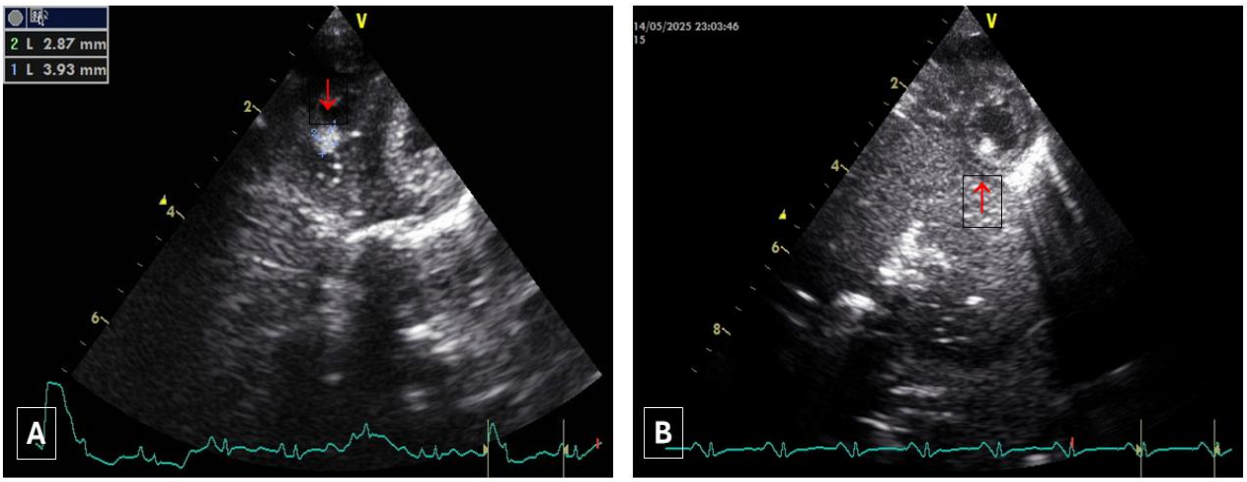


Figure 5: A. Short axis of the neonatal heart showing a small rhabdomyoma in the right ventricle close to the apex (shown with red arrow: ⬇)

B. Short axis of the neonatal heart showing a small rhabdomyoma in the left ventricle close to the apex (shown with red arrow: ⬇)

The patient was treated with Everolimus 0.25 mg/day (1.25 mg/m^2), Propranonol 3 mg/kg/day and Flecainide 6 mg/g/day with no side effects. Echocardiographic follow-up at 6 weeks showed both complete resolution of the cardiac rhabdomyomas and the atrial tachycardia**. (Figure 6A)** ECG and 48-hour holter monitoring recorded ventricular monomorphic extrasystoles isolated and occasional recordings of ventricular couplets and triplets**. (Figure 6B)** Due to high Everolimus blood levels, the medication was administered on alternate days. Flecanide was substituted by Propafenone at 10 mg/kg/day. Everolimus treatment was continued with regular clinical and laboratory monitoring and no adverse effects. During follow-up visits ECG, holter monitoring and transthoracic echocardiogram remained normal and the patient demonstrated normal developmental milestones and appropriate weight gain, with no signs or symptoms of seizures and resolution of renal abnormalities.

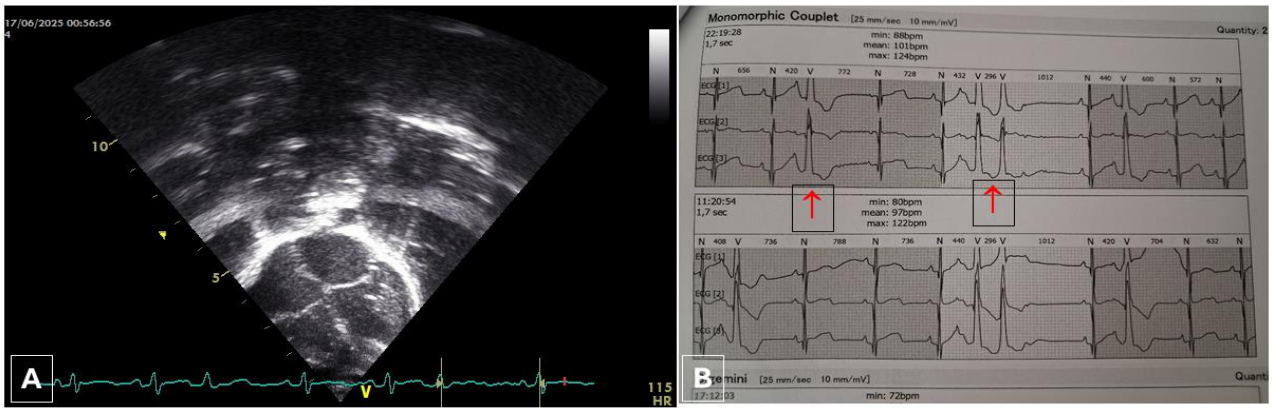


Figure 6: A. Transthoracic echocardiography at 6 weeks showing complete resolution of the rhabdomyomas

B. Holter monitoring at 6 weeks showing monomorphic ventricular extrasystoles with couplets (shown with red arrows: ⬆)

The short-term plan, as the patient is going to immigrate to Ukraine one month after the last visit at four months in our department was to:

1. Continue regular follow-up with a Paediatrician, Paediatric neurologist, and Paediatric cardiologist
2. Continue Everolimus therapy for 3 months, then seek expert opinion to determine the need for continuation of therapy
3. Continue Propafenone treatment up to the age of 12 months

3. Discussion

3.1 Rhabdomyomas in TSC

Rhabdomyomas are the most common primary cardiac tumor in childhood. Between 70% and 90% of children with rhabdomyomas have TSC, and at least 50% of children with TSC develop rhabdomyomas [1]. Cardiac rhabdomyoma, one of the major clinical criteria of TSC is often the earliest manifestation of the disease, typically appearing in most patients during the prenatal period [4]. There is a scarcity of standardized management and follow-up of the cardiac manifestations of TSC in paediatric patients. Rhabdomyomas and a wide spectrum of arrhythmias, which are also occurring later in life, are the most common cardiovascular manifestations in TSC underlying the importance of ongoing lifelong cardiology care [1].

Rhabdomyomas are hamartomas which represent circumscribed tumours characterized by cells of different degrees of vacuolization with a thin fibrous layer, Schiff positive with central nuclei with fine cytoplasmic fibers, distributed towards the periphery, called spider cells [9]. They consist of glycogen-rich atypical cardiomyocytes that differ from both Purkinje fibers and myocardial working cells [3].

Rhabdomyomas usually appear at 20 to 30 weeks of gestation, and the number and size may increase due to elevated maternal estrogen levels, which might lead to the activation of mammalian target of rapamycin complex 1 (mTORC1) and mTORC2 signaling networks that further increases tumor growth [3, 9]. Spontaneous regression of cardiac rhabdomyomas usually occurs in the first two years of life with the rate of complete regression being variable between 31% and 80% via vacuolar degeneration and apoptosis of the cytoplasm [3, 9]. However, cardiac rhabromyomas have been identified in up to 20% of adults with TSC, but they are usually asymptomatic [5].

Rhabdomyomas might present a large spectrum of clinical and electrophysiological manifestations depending on their number, location and size [3, 9]. They are usually multiple and most often located within the wall of the right or left ventricle (in about 70% of cases) or in the left ventricular outflow tract. These lesions are typically mural, pedunculated, variable in size, and appear hyperechoic on imaging [3, 9]. Nearly 100% of fetuses with multiple rhabdomyomas have TSC, underscoring the practical importance of identifying additional tumours at the time of fetal assessment for diagnosis and prognosis [1].

Although most cases are clinically silent, these tumors can lead to serious and potentially life-threatening cardiovascular complications [1, 3, 9]. Symptomatic rhabdomyomas may present as a heart murmur, arrhythmia, haemodynamic instability and heart failure due to outflow tract or valvular obstruction or compression of the coronaries leading to ischaemia and finally cause syncope (which can be mistaken for "drop attacks" and seizures), or cardiac arrest with sudden death [1, 3]. Treatment of symptomatic rhabdomyoma requires individualized treatment strategy based on the underlying pathophysiology, with involvement of multidisciplinary teams [10]. Of note, death in the fetal and early neonatal period can be due to the obstructive physiology of large masses or incessant ventricular arrhythmias leading to cardiogenic shock [1, 3].

If heart failure is due to obstruction, it may be refractory to treatment, thus surgery is indicated. However, surgical resection of the tumor—traditionally considered the gold standard for relieving obstruction—is often not feasible in small infants and may carry a high risk of morbidity and mortality [10]. In cases of hemodynamic compromise, prostaglandin E may be administered to stabilize the critically ill newborn before transfer to a tertiary center equipped with cardiac intensive care and surgical facilities [1]. However, there are very few reports of surgical management of giant rhabdomyomas in early life.

Developmentally delayed individuals may not be able to report symptomatic palpitations associated with hemodynamically stable sustained tachyarrhythmia and may present with signs and symptoms of heart failure due to tachycardia-mediated cardiomyopathy. Recurrent syncope due to arrythmia may be mistaken for seizures or "drop attacks," and thus the warning signs of impending cardiac arrest may be missed [1].

Rhabdomyomas can also re-present or occur de novo in adolescence in 12-15% especially in girls related to the hormonal changes of puberty [11]. The fact that in some patients rhabdomyomas recur raises the suspicion that spider cells may remain histologically in the macroscopically normal myocardium and potentially serve as the substrate of arrythmia in later life.

3.2 Arrhythmias in TSC

Arrhythmias, in their various forms, have been reported in 30–50% of infants and 5.6% of children and adolescents, depending on age [12]. While arrhythmia is relatively common in individuals with TSC, the range of arrhythmic substrates is wide and not sufficiently specific to form a specific diagnostic criterion. ECG findings include premature atrial contractions, paroxysmal supraventricular tachycardia, Wolff-Parkinson-White syndrome, sinoatrial nodal re-entrant tachycardia, atrial flutter, junctional rhythm, premature ventricular contractions, ventricular tachycardia and atrial tachycardia, as in our case [1].

Conduction defects include sinus node dysfunction, 2nd and 3rd degree atrioventricular block, incomplete and complete right bundle branch block and PR prolongation. Other electrocardiographic abnormalities that have been reported in

these patients include ventricular hypertrophy, non-specific changes of ST interval, dome shaped T waves with or without elevation, Brugada pattern and widened QRS [1].

Isolated atrial or ventricular ectopy may remain without symptoms for a lifetime. Bradycardia, depending on its severity, may remain without symptoms, but may result in fatigue or syncope. Syncope may also have similar presentation to "drop attacks" and other neurologic events seen with TSC. Sustained tachyarrhythmia may result in palpitations or, in some instances, in syncope or cardiac arrest and sudden death [1].

The pathophysiological mechanism for preexcitation and paroxysmal supra-ventricular tachycardias implies the similarity of the hamartomatous cells to normal Purkinje cells in rhabdomyomas located at the atrioventricular junction, where they function as accessory pathways by bypassing the atrioventricular nod [13].

Arrythmias in children without rhabdomyomas have rarely been reported. Although arrhythmias in TSC have been associated with the location of the rhabdomyomas, the underlying mechanisms of arrhythmia in paediatric patients without rhabdomyomas remain unknown [1]. Studies have shown that P-wave duration and dispersion, QT and QTc dispersion, as well as TP-e interval and TP-e dispersion on 12-lead surface ECGs, are significantly greater in TSC patients without rhabdomyomas compared with healthy controls. These findings suggest that such patients may be predisposed to both atrial and ventricular arrhythmias due to prolonged ECG parameters [12].

QT dispersion has been proposed as an indicator of the autonomic tone of the heart. It reflects regional variations in myocardial repolarization and, consequently, the underlying electrophysiological environment. Clinical interest in QT dispersion on the surface ECG is based on the observation that regional heterogeneity of action potential in adjacent cardiac muscle tissue can initiate and sustain ventricular arrhythmias especially in vulnerable myocardium as in patients with TSC [14].

Additionally, structural alterations in the atrial and ventricular myocardium, attributed to alterations of proteinosynthesis associated with TSC mutations hyperactivation in the mTOR1 signaling pathway might result in altered autonomic function and ECG changes [12].

Loss of TSC1 or TSC2 in cell lines in mouse or human tumours causes endoplasmic reticulum stress and activates the unfolded protein response leading to attenuation of insulin receptor signaling activity and increases the vulnerability to apoptosis. The unfolded protein response (UPR) is a cellular stress mechanism that preserves protein homeostasis within the endoplasmic reticulum by mitigating the accumulation of misfolded or unfolded proteins. While the UPR is primarily cytoprotective, sustained endoplasmic reticulum stress can shift its function toward promoting apoptosis [15-17]. In cardiomyocytes, such stress also disrupts calcium handling—affecting both its release and uptake—which may contribute to the development of cardiac arrhythmias [18].

Oxidative stress and DNA damage are also likely to play a significant role in the pathogenesis of arrythmias in TSC. In paediatric patients with TSC reactive oxygen species are extremely high and represent a crucial factor in the production of arrhythmic substrates by affecting cardiac ion channels and remodeling [10]. The total antioxidant status is significantly reduced, whereas total oxidant status and the oxidative stress index are markedly elevated in patients compared with controls. Moreover, individuals with TSC exhibit significantly greater DNA damage. These findings suggest that increased oxidative stress and consequent DNA damage may play a contributory role in the pathogenesis of TSC [19].

There is an increasing appreciation for latent cardiovascular phenotypes, indicating a need for continued surveillance of these patients. As the natural history of disease in the cardiovascular system is better understood, continued care in adulthood needs to be defined, underscoring efforts to transition care from pediatric to adult cardiology and to maintain surveillance vigilance in adulthood [1]. A lower index of suspicion is required during adolescence, when rhabdomyomas may recur.

Regarding the management of arrhythmias, therapeutic strategies typically include either careful observation or the use of antiarrhythmic medications, depending on the type, frequency, and hemodynamic significance of the arrhythmia. Children with refractory arrhythmias might benefit from catheter or surgical ablation, defibrillators or pacemakers. Catheter ablation appears to have less success than in those without TSC, probably due to the size of the tumour and its possible participation in the arrhythmia mechanism [1]. The increasing understanding of the mTOR pathway

activation in the pathophysiology of TSC has resulted in an increased use of mTOR inhibitors for the management of the patients with TS, rhabdomyomas and refractory arrhythmias with favorable outcomes [3].

3.3 Vascular Manifestations in TSC

Arterial aneurysms in TSC represent a classic but little-known association. They are rare manifestations of TSC and most reports in the literature are case presentations or small series of patients. Aneurysms may develop in the large and medium size vessels and arterial stenotic-occlusive disease and dysplasia may occur in the small vessels. The incidence of aneurysms is twice in TSC patients than in general population and can involve aorta, carotid, axillary, renal, iliac, femoral and pulmonary arteries. The aneurysms associated TSC are usually large and may become manifest early in life because of rapid progression and high risk of rupture and can represent a fatal event if they are not recognized [3]. TSC aneurysmal pathology is characterized by increased proliferation of the smooth muscle cells within the media and disorganized structure also involving the elastic layer [20]. The pathology examination of the aneurysmal wall of a patient with brachial and subclavian arteries aneurysms showed characteristic changes for activation of the mTOR pathway, with the typical important thickening of the aneurysmal wall based on media smooth muscle cell proliferation. TSC patients with intracranial aneurysms are characterized with a higher proportion of large/giant and fusiform intracranial aneurysms and young age, suggesting rapid aneurysmal growth. Furthermore, there is a distinct location pattern of IAs and an inverse sex ratio than in the healthy population, being more common in males [21]. Although rare, healthcare providers should remain vigilant for this cardiovascular complication in patients with TSC and ensure regular monitoring to allow timely detection and surgical intervention when necessary [3].

3.4 mTOR inhibitor treatment of the cardiac complications of TSC

In the past, various therapeutic approaches—primarily symptomatic—have been attempted to mitigate the clinical manifestations of TSC. While all these therapeutic strategies are useful and are still used and indicated, they represent a conservative approach and supportive care. Therefore, they are not fully effective in modifying long-term outcomes of the patients. A new therapeutic approach or a

paradigm shift in the treatment of TSC is the introduction of allosteric inhibitors of mTOR, which allow restoration of metabolic homeostasis in mutant cells, potentially eliminating most of the clinical manifestations associated with TSC. Everolimus, a mammalian target of the rapamycin inhibitor, can reduce hamartomas, correcting the specific molecular defect that causes alterations in various organs, from the central nervous system to the heart [4, 22].

The ORACLE trial (everOlimus for caRdiac rhAbdomyomas in tuberous sCLErosis) was the first randomized clinical trial assessing the efficacy of Everolimus as a specific therapy for symptomatic cardiac rhabdomyoma. ORACLE was a phase II, prospective, randomized, placebo-controlled, double-blind, multicentre protocol trial. Forty children with symptomatic cardiac rhabdomyoma secondary to TSC were randomized to receive either oral Everolimus or placebo for 3 months. The primary outcome was ≥50% reduction in tumour size related to baseline. Secondary outcomes were the effects on arrhythmias, pericardial effusion, intracardiac obstruction, adverse events, progression of tumour reduction and effect on heart failure. The results of this trial were encouraging and represent the first report of evidence-based therapy for TSC with rhabdomyomas [23].

The increasing understanding of the mTOR pathway activation in the pathophysiology of TSC has resulted in a progressive rise in the use of mTOR inhibitors for the management of patients with TSC, including those with rhabdomyomas and refractory arrhythmias [1]. In the absence of comparison clinical trials, selection of a specific mTOR inhibitor in TSC has generally followed the best published evidence for the specific disease manifestation.

A recent systematic review aimed to investigate the difference in cardiac rhabdomyoma size before and after treatment, the effect of therapy on cardiac symptoms and document side effects associated with mTOR inhibitors treatment [11]. A total of forty-one children aged 0 to 18 years with TSC and rhabdomyomas were studied, of whom thirty-three (80.5%) were symptomatic. Patients received treatment with either Everolimus (68.3%) or Sirolimus (31.7%). The studies aimed to achieve targeted Everolimus level in accordance with the EXIST studies which is 5–15 ng/ml [24-26]. The targeted level of sirolimus ranged from 4 to 20 ng/ml, mostly 5–15 ng/mL.

Cardiac rhabdomyomas were multiple in 32 children (78%). Treatment with mTOR inhibitor resulted in clinical improvement –defined as reduction in outflow obstruction causing heart failure and/or arrythmias- in 30 of them (90.9%). Reduction of cardiac rhabdomyoma size was reported in 95.1%. Some rhabdomyomas regrew after interruption of treatment, however the size of re-grown of the tumors was still smaller in comparison with the initial size and was usually without recurrence of clinical symptoms. The most common side effects reported in the patients were dyslipidemia (mostly hypertriglyceridemia), recurrent infections, and transient lymphopenia and were mostly mild [11]. Due to the high risk of bias and low quality of data (small studies, significant differences in data reporting within particular studies, and lack of control groups), the meta-analysis or comparison between Sirolimus and Everolimus were not performed [11].

There are no randomized control trials comparing the efficacy and safety of mTOR inhibitors in neonates with rhabdomyomas and there is no established age at when mTOR inhibitors should be initiated, however this is usually done at the end of the first week of life. In addition, there is no consensus on the dosages of TOR inhibitors that should be administered to these infants [27]. In a recent systematic review, the safety and efficacy of TOR inhibitors in neonates with rhabdomyomas was estimated without distinguishing between different treatments. Therefore, a comparison between the effects of Everolimus versus Serolimus was not conducted. Based on the available evidence, it was suggested to use mTOR inhibitors at a low dose, as neonates and infants tend to have high levels due to low activity of drug metabolism [27]. It is advisable to perform the first measurement of Everolimus levels one week after its initiation. The duration of treatment should be individualized and guided by clinical manifestations, hemodynamic alterations, the size of rhabdomyomas and the "rebound" of rhabdomyoma growth post treatment cessation [27]. The duration of treatment was 2.2 months and mTOR inhibitors were used as a life-saving measure in neonates with giant obstructive lesions interfering with ventricular contraction or incessant arrhythmias [27]. All neonates showed rapid reduction of the size of rhabdomyomas during the first month of treatment, associated with hemodynamic improvement and/or resolution of the arrhythmias. However, there is potential of 20 %

for rebound growth of the rhabdomymas after stopping mTOR inhibitors requiring reinstitution of treatment in some cases [28]. Also, 41.6 % exhibited side effects which were mostly mild and dose dependent, such as hyperlipidaemia, mild infections and hematological abnormalities. In 12.5% of these cases the medication was stopped and in the remaining ones it was temporarily suspended or given at a lower dose [27]. Treatment was generally well tolerated without major concerning side-effects.

When initiating therapy with an mTOR inhibitor, baseline laboratory studies should include fasting lipid concentrations, full biochemical panel, cystatin C quantification, urine analysis, and complete blood count with differential [27]. While the combined creatinine and cystatin C equation can add accuracy in GFR calculation, cystatin C is not available in all laboratories, and the creatinine-based equation is adequate for most clinical purposes. These tests should be repeated shortly after treatment is started, in addition to measurements of mTOR inhibitor trough levels and should be rechecked periodically [27]. The approved targeted Everolimus levels is 5-15 ng/ml [28]. Two reports describe that a low-dose therapy with Everolimus and a level of 3–7 ng/ml was sufficient to reduce tumour size [28, 29]. In a very recent case report the authors showed that an even lower Everolimus level of 2–3 ng/ml was enough to diminish tumour size [30]. The authors stated that very low-level Everolimus therapy might also have beneficial effects in cardiac or other tissues, because this directly targets the constantly upregulated mechanistic target of the rapamycin pathway and might lead to a more normalized mechanistic target of the rapamycin pathway activation, while side effects like stomatitis or systemic infections might be lower than reported.

Another recent systematic review and a meta-analysis investigated the natural history of prenatal cardiac rhabdomyoma, including characteristics, progression, and survival and the role of antenatal administration of mTOR inhibitors to the mother and its effect on fetal rhabdomyomas. The 9 studies included in the analysis reporting all together on 11 fetuses with TSC receiving prenatally mTOR inhibitors showed reduction in the size of rhabdomyomas and outflow obstruction with no fetal demise, neonatal death or postnatal cardiac surgery, showing promising results of antenatal administration of mTOR inhibitors [31].

Treatment of symptomatic rhabdomyoma requires individualized treatment strategy based on the underlying pathophysiology, with involvement of multidisciplinary teams. As previously stated, mTOR inhibitors are effective and safe in inducing rapid regression of rhabdomyomas. Although mTOR inhibitors (sirolimus/everolimus) demonstrate great potential in TSC management, two major concerns hamper their generalized application. One is the frequent manifestation of adverse events, such as stomatitis, infections, and menstrual disorders; and the other is the poor response in certain patients [4]. Further studies are warranted, ideally involving multiple international centers with a larger number of patients to clarify the safety and efficacy of m-TOR inhibitors for the cardiovascular complications of TSC, compare the effects of Everolimus versus Sirolimus therapy, define the appropriate dosage and blood levels of the medications and the duration of treatment.

3.5 Learning points-take home message

• TSC is a complex arrhythmic disorder associated with conductive effects irrespective of the presence of rhabdomyomas, which requires meticulous cardiac follow-up throughout the patient's life

• Although arrhythmias in pediatric patients with TSC who have cardiac rhabdomyoma have been frequently identified, arrhythmia in young patients who have TSC without rhabdomyomas has rarely been reported

• Although in the past complete resolution of cardiac rhabdomyomas was considered the natural course of the disease, with physicians focusing on the neurological manifestations, is has recently been documented re-appearance of the rhabdomyomas in 12-15% of adolescent patients, especially girls, an issue that increases the risk for future arrhythmia

• The increasing understanding of the mTOR pathway activation in the pathophysiology of TSC has resulted in a progressive rise in the use of mTOR inhibitors for the management of patients with TSC, including those with rhabdomyomas and refractory arrhythmias

• The use of mTOR inhibitors in neonates with rhabdomyomas at a lower dose to those approved for other manifestations appears to be both efficient and safe in neonates

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