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Review Article

Cardiac Rhabdomyomas in Tuberous Sclerosis - A 38 Year Retrospective

Galen N Breningstall[1]* and John Bass[2]

[1]Department of Pediatric Neurology, Gillette Children's Specialty Healthcare, USA

[2]Department of Pediatric Cardiology, University of Minnesota Medical School, USA

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Corresponding author:
Galen N Breningstall, Department of Pediatric Neurology, Gillette Children's Specialty Health Care, 200 E. University Ave, St. Paul, MN 55101, USA, Tel: + 651-245-9075;
Email:
gbreningstall@gillettechildrens.com

ABSTRACT

Cardiac rhabdomyomas occur in 50% of patients with tuberous sclerosis. The vast majority of these are asymptomatic. However, some rhabdomyomas may cause morbidity or mortality through cardiac obstruction. These have classically been treated surgically. Sirolimus now offers hope of non-invasive treatment. Arrhythmias may also occur.

INTRODUCTION

In 1985, Bass, Breningstall and Swaiman published the first incidence study of cardiac rhabdomyomas in tuberous sclerosis [1]. Of 16 consecutive patients, 50% were found to have one or more cardiac rhabdomyomas. 5 were solitary and in 3 there were 2-4 rhabdomyomas. None of the patients were symptomatic. There was male predominance (5/8). All the rhabdomyomas were ventricular, 5/8 in the left ventricle. The rhabdomyomas were intracavitary and intramyocardial. After the recent passing of Dr. Kenneth Swaiman, a very influential figure in pediatric neurology, in his memory, two of the original co-authors performed an overview of the subsequent 38 years' experience with cardiac rhabdomyomas in tuberous sclerosis.

Rhabdomyomas are the most common benign cardiac tumors, often presenting in infancy. Primary cardiac tumors have an incidence of 0.2% and 45% of these are rhabdomyomas. They are typically well circumscribed and nonencapsulated. There is abnormal myocyte architecture which includes vacuolization and "spider cells" [2,3]. There is a strong association of rhabdomyoma with tuberous sclerosis, 30/33 in one series3 and cited as 51—86 % in another4. Multiple cardiac rhabdomyomas are more likely to be related to tuberous sclerosis. 50% continues to be a reasonable estimate of the incidence of cardiac rhabdomyoma in tuberous sclerosis [1,4,5].

Patients with tuberous sclerosis are found to have mutations in the tumor suppressor genes TSC1 coding amartin (9q34) and TSC2 coding tuberin (16p13.3), with disease causing mutations identified in 60-89%. The incidence of tuberous sclerosis is 1:5000 to 1:10000. TSC2 mutations are 50% and TSC1 17% [6,7,8]. One series found 73% TSC2 and 17% TSC1. This series found cardiac rhabdomyomas more frequently in the TSC2 (54%) than the TSC1 (20%) groups. Further, the cardiac rhabdomyoma manifestations were more severe in TSC2 patients, with 4 versus none having heart insufficiency, in one case leading to death [4].

Cardiac rhabdomyoma may be the earliest identified feature of tuberous sclerosis. Prenatal ultrasonography at 22 weeks' gestation may show cardiac rhabdomyoma [9]. Antenatal detection of cardiac rhabdomyoma at 22 weeks with the father and

two brothers of the fetus having tuberous sclerosis, one of the brothers dying as a neonate as surgery was attempted for a large cardiac mass, resulted in pregnancy termination [10]. It is reported that virtually all patients with multiple fetal cardiac rhabdomyomas have tuberous sclerosis [2]. Echocardiography defines cardiac rhabdomyomas. There is markedly increased acoustic density, visualized in at least two views, with evident margins. The papillary muscles and trabeculations found in the right ventricle must be excluded [1].

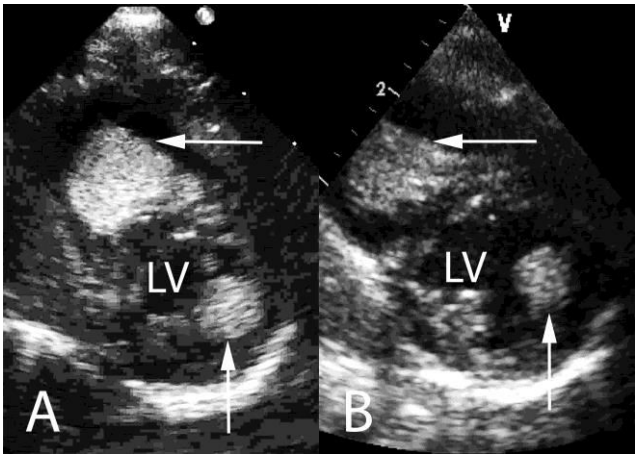

Figure 1: Short axis views of a patient at birth (A) and at 3 years (B) with multiple cardiac rhabdomyomas. The horizontal arrow points to a large intracavitary mass occupying part of the right ventricular cavity. The vertical arrow points to a mass occupying part of the anterior/lateral papillary muscle in the Left Ventricular (LV) cavity. At 3 years of age, there has been minimal change in the tumor masses.

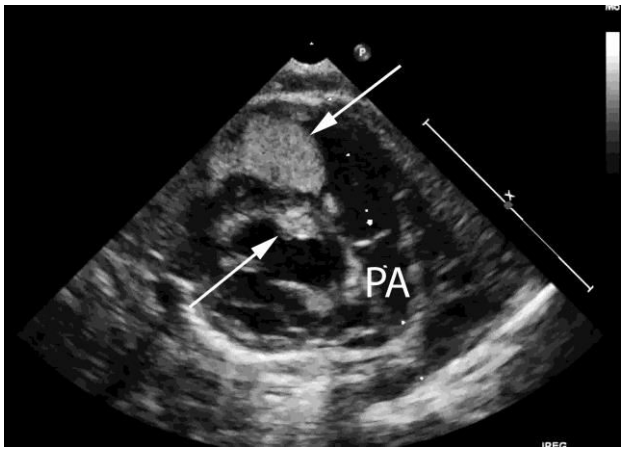

Figure 2: Modified short axis view of a patient at birth with multiple cardiac rhabdomyomas. The upper arrow points to a large intracavitary mass occupying part of the right ventricular cavity. The lower arrow points to a mass on the left ventricular surface of the ventricular septum. The outflow to the Pulmonary Artery (PA) is unobstructed.

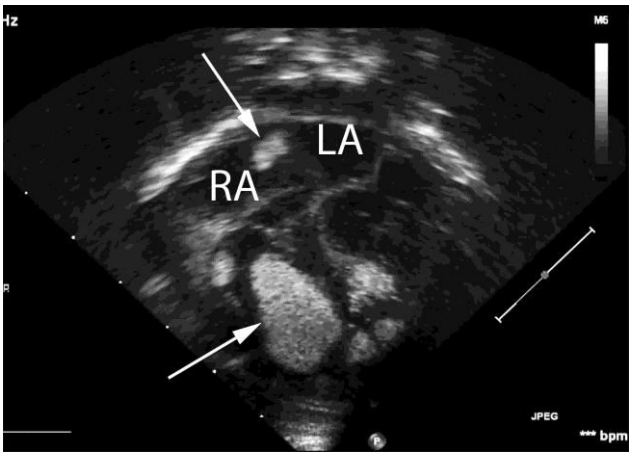

Figure 3: Apical four chamber view of a patient at birth with multiple cardiac rhabdomyomas. The lower arrow points to a large intracavitary mass occupying part of the right ventricular cavity. The upper arrow points to a mass attached to the atrial septum and protruding into the Right Atrial (RA) cavity. Flow from right and Left Atrial (LA) cavities is unobstructed. Although commonly reported at autopsy, it is unusual to visualize atrial rhabdomyomas on cardiac ultrasound.

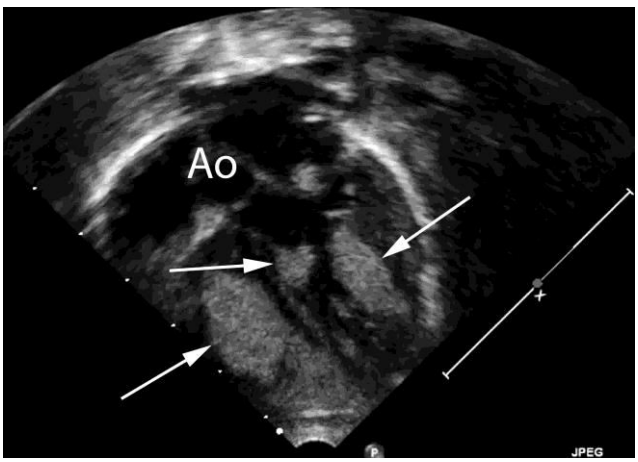

Figure 4: Apical five chamber view of a patient at birth with multiple cardiac rhabdomyomas. The leftward arrow points to a large intracavitary mass occupying part of the right ventricular cavity. The upper left arrow points to a mass on the left ventricular surface of the ventricular septum. The outflow to the aorta (Ao) is unobstructed. The rightward arrow points to a mass occupying part of the anterior/lateral papillary muscle.

The incidence of cardiac rhabdomyomas in children < 2 years old was 65%, in children 2-11 years of age 26% and 54% in children 12-15 years.4 The majority of cardiac rhabdomyomas regress with age in numbers and size (31/32) [11]. This series focused on cardiac rhabdomyomas generally, but 93.9% had tuberous sclerosis. In tuberous sclerosis patients with serial echocardiographic studies, the cardiac rhabdomyoma index

fell with each study (2.684, 1.746, 1.141 and .705). Complete spontaneous regression was present in some patients by 6 years of age [12]. Another study found a 50% size reduction of 72.9 ± 53.03 months.13 26/38 patients in another series had regression or disappearance of their rhabdomyomas. 9/38 had no change. 3/38 had growth in the rhabdomyoma and 3 others developed de novo rhabdomyoma on repeat echocardiography (10 - 14 years). 5/6 with new or growing tumors were female and all were of pubertal age [4,13]. Treatment of infantile spasms, which are relatively common in tuberous sclerosis, with corticotropin has been described as increasing rhabdomyoma size [14]. There is a report of a new onset rhabdomyoma occurring at two years of age in a patient who underwent resection of a large rhabdomyoma as a neonate [15].

The location of involvement in one series was 35% right ventricle, 22% left ventricle, 33% intraventricular septum and 5% in each of the atrias [4].

In a series of cardiac rhabdomyomas generally (30/33 with tuberous sclerosis) surgical removal was required in 2 and 3 others had obstructive or regurgitation components to their rhabdomyomas. 3 Heart failure occurred in 5.4% of patients [4]. Standard heart failure pharmacotherapy may be utilized. When inflow or outflow failure occurs, a frequent approach may be closely monitoring, since spontaneous regression may occur over a period of months [2]. A patient is described undergoing surgery at 7 weeks for a progressively enlarging ventricular mass causing outflow obstruction [16]. A baby with an enormous septal and multiple ventricular rhabdomyomas died due to heart failure [11]. Death related to attempted surgery also occurs [10].

The various benign tumors, including cardiac rhabdomyomas, of tuberous sclerosis are caused by disinhibition of the target of the rapamycin (mTOR) protein. mTOR inhibitors are now available as a treatment modality. A patient with TSC2 had multiple cardiac rhabdomyomas detected by fetal ultrasonography at 31 weeks' gestation. Sirolimus (rapamycin/everolimus) treatment resulted in regression of the cardiac rhabdomyomas and, as well, improved seizure control [17]. 3 patients less than 12 months were treated with sirolimus with two having complete response and the other a greater than 50% debulking [18]. 51 patients with cardiac rhabdomyoma were treated with sirolimus. Tumors disappeared in 26 (51%) children, decreased by more than 50% (including 50%) in 15 (29%) children, decreased by less than 50% in 5 (12%) children, and had no change or progressed in 4 (8%) children. Tumors disappeared in 10 of 16 patients in >1-3 years group and in 4 of 11 patients in >3 years group [19]. Four patients were treated with everolimus starting at 2-20 days of age. Compared to 10 historical controls there was an 11.8 times faster tumor regression rate. In 2 patients, a massive left ventricular tumor became inconsequential in size and in 1 the tumor disappeared [13]. In the series treating 51 children with sirolimus, one had a canker sore and nine had dyslipidemia 19.

A patient with a cardiac rhabdomyoma unassociated with tuberous sclerosis with severe right ventricular outflow obstruction had a rapid response to sirolimus [20]. There are numerous additional case reports of successful sirolimus treatment of symptomatic cardiac rhabdomyoma [21-23]. Intrauterine treatment of cardiac rhabdomyomas with sirolimus has also been reported [24]. A recent series of 3 patients, two of whom had rhabdomyomas proceeding to cardiac outlet obstruction, were treated with sirolimus. There was a gradual shrinkage of cardiac rhabdomyomas in all patients. Surgical intervention was not required. This article cites four earlier articles describing transplacental treatment of cardiac rhabdomyomas with sirolimus in individual patients [25-27].

A randomized, placebo-controlled, double-blind study (ORACLE) is in progress to assess everolimus efficacy in tuberous sclerosis patients with symptomatic cardiac rhabdomyomas [29]. 24% of patients had arrythmia documented with 2/8 having Wolf-Parkinson-White Syndrome. In every patient the arrhythmia either disappeared or ameliorated. No patient required pharmacotherapy for arrhythmia [11]. Another series had a 23% arrhythmia incidence. 4 received treatment [4]. In another series an arrhythmia was present in 13/33 with 6 having Wolf-Parkinson-White Syndrome and 4 of these had paroxysmal dysrhythmias. Fetal arrhythmia was noted in one case [3]. The incidence of arrhythmias in the TSC1 and TSC2 patients was similar (16.1 versus 13.3%) [4]. Arrhythmia may be the presenting symptom of tuberous sclerosis. A severe neonatal arrythmia was successfully treated with everolimus [30].

Surveillance recommendations have included obtaining an initial echocardiogram and electrocardiogram. If fetal ultrasonography documents cardiac rhabdomyoma, it is recommended that a fetal echocardiogram be considered to identify patients with a high risk for cardiac failure. It is recommended that asymptomatic patients with cardiac rhabdomyomas have repeat echocardiograms every 1-3 years until regression of the cardiac rhabdomyoma is documented.

An electrocardiogram every 3-5 years is recommended [2]. It is unclear what the yield on such repeat testing might be.

The vast majority of cardiac rhabdomyomas in tuberous sclerosis are incidental findings, like hypopigmented macules, a signature of the disease with no adverse impact. In 38 years of practice in tertiary settings, the pediatric neurologist author has had no patient with tuberous sclerosis symptomatic due to cardiac rhabdomyoma. Nonetheless, some cardiac rhabdomyomas cause symptoms, which may be life threatening. Most commonly, this is cardiac obstruction caused by a large or adversely situated rhabdomyoma. Cardiac surgery in such instances has been utilized, although death may result. More recently, sirolimus treatment has been utilized with apparent favorable effect and good tolerability. It would appear that patients with obstructive cardiac rhabdomyomas, except in cases of immediate jeopardy, should first receive a trial of therapy with sirolimus.

REFERENCES

1. Bass JL, Breningstall GN, Swaiman KF. (1985). Echocardiographic incidence of cardiac rhabdomyoma in tuberous sclerosis. Am J Cardiol. 55:1379-82.
2. Hinton RB, Prakash A, Romp RL, Krueger DA, Knilans TK, et al. (2014). Cardiovascular manifestations of tuberous sclerosis complex and summary of the revised diagnostic criteria and surveillance and management recommendations from the International Tuberous Sclerosis Consensus Group. J Am Heart Assoc. 3: e001493.
3. Bosi G, Lintermans JP, Pellegrino PA, Svaluto-Moreolo G, Vliers A. (1996). The natural history of cardiac rhabdomyoma with and without tuberous sclerosis. Acta Paediatr. 85: 928-31.
4. Jóźwiak S, Kotulska K, Kasprzyk-Obara J, Domańska-Pakieła D, Tomyn-Drabik M, et al. (2006). Clinical and genotype studies of cardiac tumors in 154 patients with tuberous sclerosis complex. Pediatrics. 118: e1146-1151.
5. Yates JR, Maclean C, Higgins JN, Humphrey A, le Maréchal K, et al. (2011). The Tuberous Sclerosis 2000 Study: presentation, initial assessments and implications for diagnosis and management. Arch Dis Child. 96: 1020-1025.
6. Au KS, Williams AT, Roach ES, Batchelor L, Sparagana SP, et al. (2007). Genotype/phenotype correlation in 325 individuals referred for a diagnosis of tuberous sclerosis complex in the United States. Genet Med. 9: 88-100.
7. Niida Y, Lawrence-Smith N, Banwell A, Hammer E, Lewis J, et al. (1999). Analysis of both TSC1 and TSC2 for germline mutations in 126 unrelated patients with tuberous sclerosis. Hum Mutat. 14: 412-422.
8. Jones AC, Shyamsundar MM, Thomas MW, Maynard J, Idziaszczyk S, et al. (1999). Comprehensive mutation analysis of TSC1 and TSC2-and phenotypic correlations in 150 families with tuberous sclerosis. Am J Hum Genet. 64: 1305-1315.
9. Uysal SP, Şahin M. (2020). Tuberous sclerosis: a review of the past, present, and future. Turk J Med Sci. 50: 1665-1676.
10. Crawford DC, Garrett C, Tynan M, Neville BG, Allan LD. (1983). Cardiac rhabdomyomata as a marker for the antenatal detection of tuberous sclerosis. J Med Genet. 20: 303-304.
11. Sciacca P, Giacchi V, Mattia C, Greco F, Smilari P, et al. (2014). Rhabdomyomas and tuberous sclerosis complex: our experience in 33 cases. BMC Cardiovasc Disord. 14: 66.
12. DiMario FJ Jr, Diana D, Leopold H, Chameides L. (1996). Evolution of cardiac rhabdomyoma in tuberous sclerosis complex. Clin Pediatr (Phila). 35: 615-619.
13. Aw F, Goyer I, Raboisson MJ, Boutin C, Major P, et al. (2017). Accelerated Cardiac Rhabdomyoma Regression with Everolimus in Infants with Tuberous Sclerosis Complex. Pediatr Cardiol. 38: 394-400.
14. Hishitani T, Hoshino K, Ogawa K, Uehara R, Kitazawa R, et al. (1997). Rapid enlargement of cardiac rhabdomyoma during corticotropin therapy for infantile spasms. Can J Cardiol. 13: 72-74.
15. Thatte NM, Guleserian KJ, Veeram Reddy SR. (2016). New-onset cardiac rhabdomyoma beyond infancy in a

patient with tuberous sclerosis complex. Cardiol Young. 26: 396-399.

16. Mohammed F, Tan GC, Hor KN, Arnold M, Wong YP. (2020). A case of surgically resected cardiac rhabdomyoma with progressive left ventricular outflow tract obstruction. Cardiovasc Pathol. 49: 107226.
17. Mao S, Long Q, Lin H, Liu J. (2017). Rapamycin therapy for neonatal tuberous sclerosis complex with cardiac rhabdomyomas: A case report and review. Exp Ther Med. 14: 6159-6163.
18. Lucchesi M, Chiappa E, Giordano F, Mari F, Genitori L, et al. (2018). Sirolimus in Infants with Multiple Cardiac Rhabdomyomas Associated with Tuberous Sclerosis Complex. Case Rep Oncol. 11: 425-430.
19. Pang LY, Zou LP, Huang LL, Gao Y, Ma SF, et al. (2016). Rapamycin in the treatment of cardiac rhabdomyoma associated with tuberous sclerosis complex. Zhonghua Er Ke Za Zhi. 54: 424-427.
20. Nir-David Y, Brosilow S, Khoury A. (2020). Rapid response of a cardiac rhabdomyoma causing severe right ventricular outflow obstruction to Sirolimus in an infant with negative genetics for tuberous sclerosis. Cardiol Young. 5:1-3.
21. Martínez-García A, Michel-Macías C, Cordero-González G, Escamilla-Sánchez KI, Aguinaga-Ríos M, et al. (2018). Giant left ventricular rhabdomyoma treated successfully with everolimus: case report and review of literature. Cardiol Young. 28: 903-909.
22. Doğan V, Yeşil Ş, Kayalı Ş, Beken S, Özgür S, et al. (2015). Regression of symptomatic multiple cardiac rhabdomyomas associated with tuberous sclerosis complex in a newborn receiving everolimus. J Trop Pediatr. 61: 74-77.
23. Colaneri M, Quarti A, Pozzi M. (2016). Everolimus-induced near-resolution of giant cardiac rhabdomyomas and large renal angiomyolipoma in a newborn with tuberous sclerosis complex. Cardiol Young. 26: 1025-1028.
24. Ebrahimi-Fakhari D, Stires G, Hahn E, Krueger D, Franz DN. (2021). Prenatal Sirolimus Treatment for Rhabdomyomas in Tuberous Sclerosis. Pediatr Neurol. 125: 26-31.
25. Barnes BT, Procaccini D, Crino J, Blakemore K, Sekar P, et al. (2018). Maternal sirolimus therapy for fetal cardiac rhabdomyomas. N Engl J Med. 378: 1844-1845.
26. Vachon-Marceau C, Guerra V, Jaeggi E, Chau V, Ryan G, et al. (2019). In-utero treatment of large symptomatic rhabdomyoma with sirolimus. Ultrasound Obstet Gynecol. 53: 420-421.
27. Park H, Chang CS, Choi SJ, Oh SY, Roh CR. (2019). Sirolimus therapy for fetal cardiac rhabdomyoma in a pregnant woman with tuberous sclerosis. Obstet Gynecol Sci. 62: 280-284.
28. Pluym ID, Sklansky M, Wu JY, Afshar Y, Holliman K, et al. (2020). Fetal cardiac rhabdomyomas treated with maternal sirolimus. Prenat Diagn. 40: 358-364.
29. Stelmaszewski EV, Parente DB, Farina A, Stein A, Gutierrez A, et al. (2020). Everolimus for cardiac rhabdomyomas in children with tuberous sclerosis. The ORACLE study protocol (everOlimus for caRdiac rhAbdomyomas in tuberous sCLErosis): a randomised, multicentre, placebo-controlled, double-blind phase II trial. Cardiol Young. 30: 337-345.
30. Öztunç F, Atik SU, Güneş AO. (2015). Everolimus treatment of a newborn with rhabdomyoma causing severe arrhythmia. Cardiol Young. 25: 1411-1414.