

## Multiple cardiac rhabdomyomas in tuberous sclerosis complex: case report and review of the literature

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### ABSTRACT

Cardiac rhabdomyoma is a benign tumor which constitutes the most common cardiovascular feature of the tuberous sclerosis complex, a multisystem genetically determined neurocutaneous disorder. Cardiac rhabdomyomas can be detected in the prenatal ultrasound, are usually asymptomatic and spontaneously regress within the first three years of life. Less often, the tumors' size, number, and location can produce a mass effect that may lead to blood flow abnormalities or organ dysfunction (heart failure and arrhythmia). In this setting, severe morbidity, and eventually, a lethal outcome despite clinical and surgical treatment may ensue. We describe a fatal case of multiple cardiac rhabdomyomas in a newborn girl. One of the rhabdomyomas was large and unfavorably located, causing significant obstruction of the left ventricular outflow tract. The autopsy identified, in addition to cardiac rhabdomyomas, brain glioneuronal hamartomas (cortical tubers), subependymal nodules and subependymal giant cell tumors, characteristic of the tuberous sclerosis complex. The newborn's family was investigated for the presence of typical clinical symptoms of the complex and image findings showed significant phenotypical variations and a broad symptom spectrum among the family members. This interesting case underscores the variability of tuberous sclerosis complex and the importance of performing a comprehensive postmortem examination in the identification of the cause of death, especially in the setting of familial disease.

### Keywords

Rhabdomyoma; Tuberous Sclerosis; Infant, Newborn; Heart Neoplasms; Neurocutaneous Syndromes.

### CASE REPORT

A 7-day-old girl had been born by cesarean delivery at a gestational age of 39 weeks due to prenatal diagnosis of a cardiac tumor in fetal ultrasound. The mother had attended ten prenatal consultations and had negative serologies to HIV, syphilis, and hepatitis B. Relevant family history comprised the presence of dermatological lesions in the patient's

mother, aunt, and grandfather, and both mother and aunt reported having seizures since childhood.

The newborn's Apgar scores were 7 and 8, and the birth weight was 2745g. Upon initial physical examination, she presented a systolic heart murmur on the left medium sternal border, intensity 3/6. The remaining physical examination was unremarkable.

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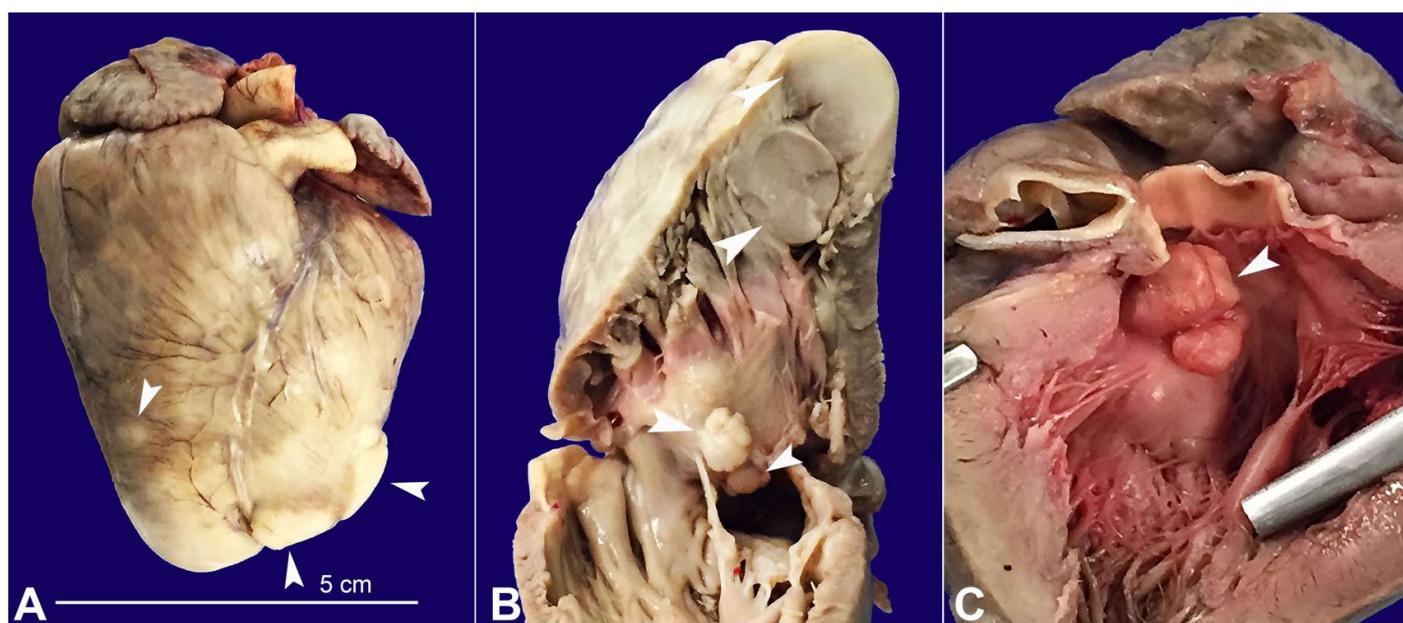
Initially, the patient was hemodynamically stable, without signs of low cardiac output such as hypotension, tachycardia, breathlessness and hypoxemia, alterations in the level of consciousness, cold peripheries, or delayed capillary refill time. Nonetheless, she was kept in the Neonatal Intensive Care Unit (NICU) under rigorous cardiac monitoring. Two echocardiograms were performed and confirmed the presence of multiple tumors in the ventricular walls and interventricular septum. There were two main lesions in the interventricular septum, the largest one located at its basal portion measuring 14X13mm in its longest axis, protruding (8.2mm) into the left ventricular outflow tract, markedly obstructing it. The pressure gradient was approximately 95 mmHg. Rhabdomyomas as the working diagnosis was considered, and surgical intervention was scheduled for the 7<sup>th</sup> day after birth. The physical examination, at this moment, showed normal intensity and regular peripheral pulses at a rate of 162 per minute. The girl's blood pressure was 58/33 mmHg, and her room-air oxygen saturation was 97%. Peripheral perfusion was normal, and no respiratory distress (respiratory rate was 37 breaths per minute) was depicted. The cardiovascular examination demonstrated the persistence of the systolic murmur grade 3/6 at the left sternal border. Pre-op laboratory exams, including

complete blood count, erythrocyte sedimentation rate, C-reactive protein, serum electrolytes, liver, and renal function tests were all unremarkable. However, during anesthetic induction, the patient developed hemodynamic instability, bradycardia, and cardiac arrest. Unfortunately, she died despite the attempts of resuscitation. An autopsy was performed with the informed consent of the family.

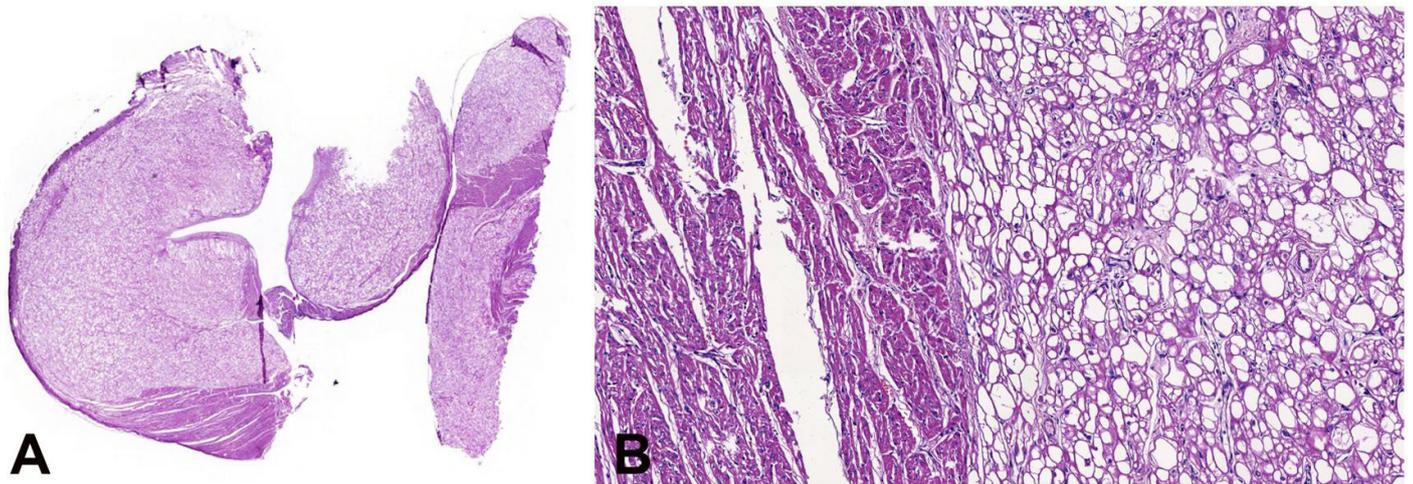
## AUTOPSY FINDINGS

The skin examination was normal. The heart weighed 25 g (average heart weight adapted for age and birth weight:  $19.1 \pm 2.8$ g) and showed nine cardiac nodules diffusely distributed within the atrial and ventricular chambers, measuring from 0.2 to 1.5 cm. They were firm and white, the biggest one had 1.5 cm, was located in the interventricular septum, protruded into the left ventricular outflow tract, and almost entirely obstructed the aortic valve (Figures 1A, 1B, 1C).

Histologically, they were composed of vacuolated cells showing almost "empty" cytoplasm with a centrally placed nucleus and cytoplasmic strands extending to the periphery of the cell – consistent with "spider cells" (Figures 2A, 2B).



**Figure 1.** Gross view of the heart. **A** - Anterior face of the heart showing several whitish nodules (arrowheads); **B** - Right ventricular outflow tract with some of the nodules represented on the cut surface (arrowheads); **C** - Left ventricular outflow tract evidencing subaortic obstruction by the largest rhabdomyoma of the interventricular septum (arrowhead).



**Figure 2.** Photomicrograph of the heart. **A** - Panoramic view of cardiac rhabdomyomas represented by large and clear cell nodules (HE 1x); **B** - Rhabdomyoma composed of a proliferation of large and vacuolated cells with a centrally placed nucleus and cytoplasmic strands extending to the periphery of the cell – “spider cell” (HE 10X).

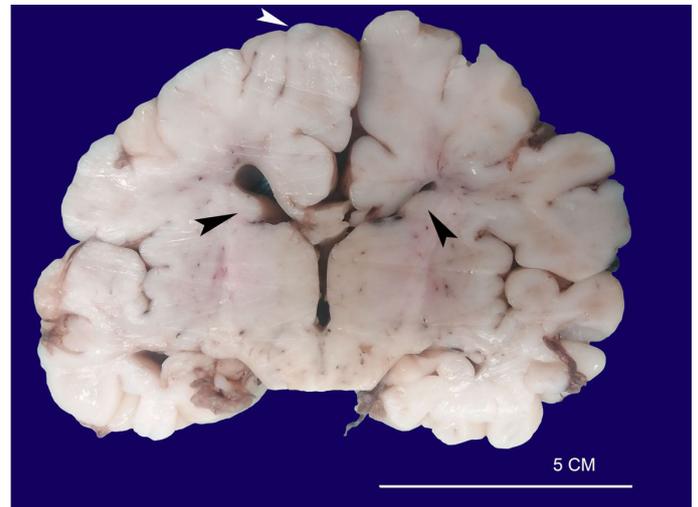
The brain weighed 110g (average brain weight adapted for age and birth weight:  $337 \pm 91$ g). The cut surface revealed multiple glioneuronal hamartomas (cortical tubers) and subependymal nodules along the walls of the lateral ventricle (Figure 3).

Histologically, the cortical tubers and subependymal nodules were composed by a proliferation of large and atypical neuronal and glial cells (Figure 4A, 4B). One of the subependymal lesions is represented by a subependymal giant cell tumor (SGCT), comprised of a combination of giant cells with glassy, eosinophilic cytoplasm and round nuclei with conspicuous nucleoli, interspersed with spindled cells and fibrillary elements (Figure 4C, 4D). This type of lesion is characteristic of tuberous sclerosis complex (TSC).

No other tumors or hamartomas were identified in the remaining organs.

## FAMILY INVESTIGATION

TSC had not been previously diagnosed in the patient’s mother or the family. The autopsy allowed confirmation of the diagnosis and further investigation of the newborn’s family for TSC symptoms. The mother’s dermatological exam found skin lesions such as angiofibroma, ash-leaf spots, shagreen patches, and periungual fibromas. Her head MRI identified multiple cortical tubers, mostly in the frontal and parietal lobes, and white matter heterotopia and subependymal nodules in the lateral ventricles.

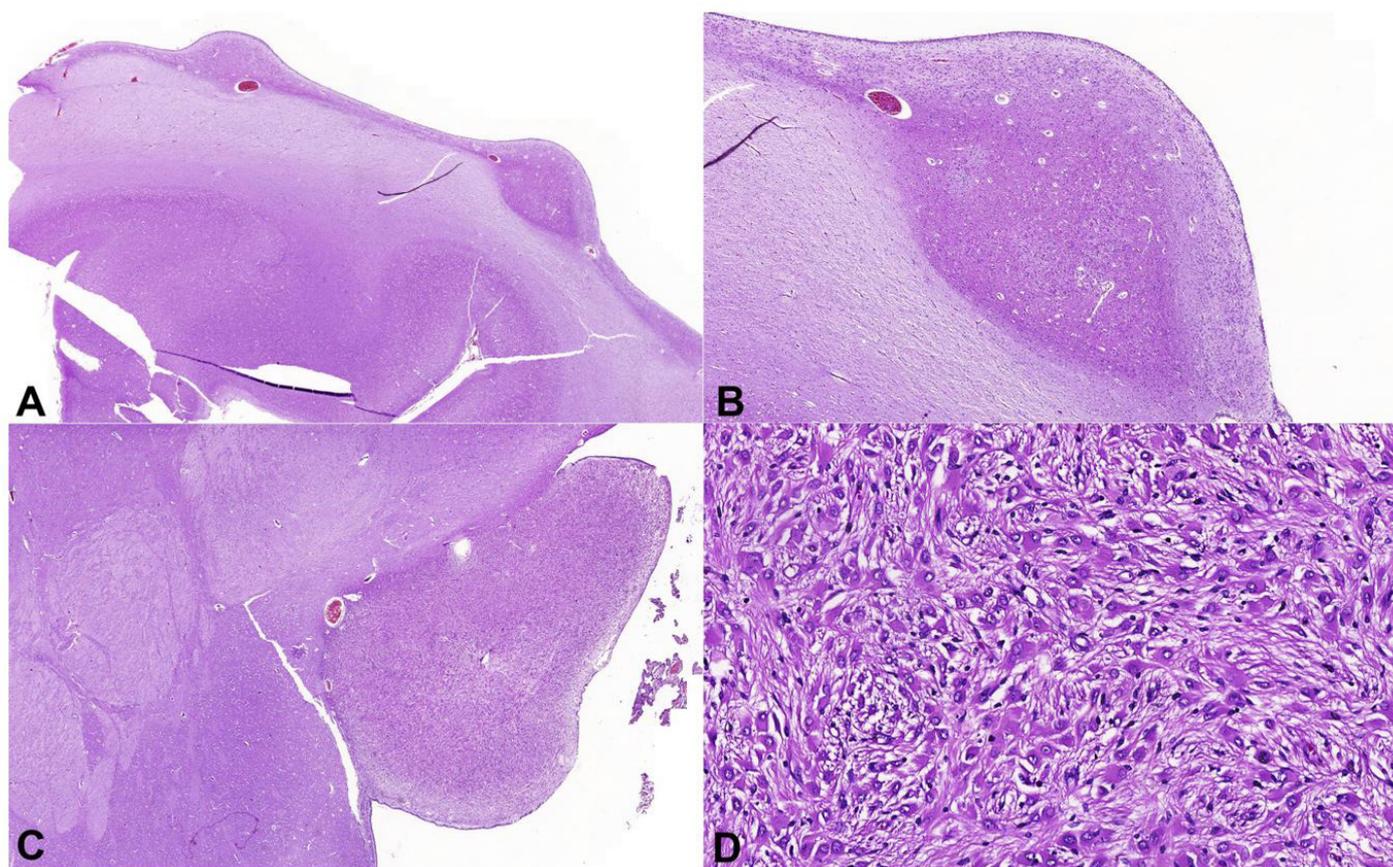


**Figure 3.** Macroscopic aspect of the brain showing cortical tubers (white arrowhead) and subependymal nodular lesions arising in the walls of the lateral ventricles (black arrowheads).

The chest computed tomography (CT) showed bilateral pulmonary cysts associated to small nodules compatible with lymphangiomyomatosis (LAM), while the abdominal CT displayed renal and hepatic hypoattenuating lesions resembling angiomyolipoma, confirmed by kidney biopsy.

## DISCUSSION

Tuberous sclerosis complex (TSC) is a multisystem syndrome clinically characterized by dermatologic lesions, neurologic disorders – mostly seizures – and the



**Figure 4.** Photomicrographs of the brain. **A** and **B** - Subependymal nodules (A, HE 1X; B, HE 3X), comprised by a proliferation of neuronal cells and large and atypical glial cells; **C** - Large subependymal lesion (HE 1.44X), comprised by the proliferation of large cells of eosinophilic cytoplasm with moderate pleomorphism (**D**, HE 20X).

development of benign tumors in the brain, heart, and kidneys.<sup>1</sup> It is genetically determined, first by mutations in either the *TSC1* or *TSC2* gene – encoding hamartin and tuberin, respectively, which together form a protein complex that participates in cellular hyperplasia – and second by modifications in a tumor suppressor gene in most hamartomas. The high variability in *TSC1/TSC2* mutation type and position may partially explain the broad range of clinical symptoms observed in TSC patients. However, timing and location of the second hit in the tumor suppressor gene probably have a higher contribution to the variability of clinical symptoms.<sup>2</sup> These mutations are spontaneous in 70% of cases, or they can be inherited in an autosomal dominant manner.<sup>3</sup>

Cardiac rhabdomyomas are the most common cardiovascular manifestation of TSC, present in more than half of the patients. Although these tumors may appear as an isolated affection, they are associated with TSC in the great majority of cases.<sup>4</sup> Despite being

pathologically benign and generally asymptomatic, the tumors' size, number, and location can produce a mass effect and lead to blood flow abnormalities or organ dysfunction (heart failure and arrhythmia). Our case is an example of multiple tumors, one of them with an unfavorable location and big enough to cause significant obstruction of the left ventricular outflow tract. Rhabdomyomas can be detected in 20 to 30 weeks' prenatal ultrasound, and if present, followed with an electrocardiogram (ECG) to evaluate arrhythmia and an echocardiogram every one to three years until the regression is observed, which generally occurs within the first three years of life.<sup>5-7</sup> Unfortunately, tumors that generate hemodynamic instability, as described in this case, can sometimes present poor prognosis and, thereby, require more aggressive intervention.

We reviewed the current literature, which found 31 case reports of cardiac rhabdomyoma and TSC in PubMed (Table 1<sup>8-36</sup>).

**Table 1.** Case reports of cardiac rhabdomyoma in tuberous sclerosis patients (n = 31)

Case	Age at diagnosis	Arrhythmia	Neurological signs	Skin lesions	Family history	Fatal condition	Multiple tumors
Abu Zahira <sup>8</sup>	ND (birth)	No	Yes	Yes	U	No	Yes
Ninic <sup>9</sup>	PD (4-months)	Yes	Yes (S)	U	U	No	Yes
Hutchinson <sup>10</sup>	AD (34wg)	No	Yes	U	No	Yes	Yes
Thatte <sup>11</sup>	AD	Yes	No	U	Yes	No	Yes
Sadoh <sup>12</sup>	ND	Yes	No	U	No	Yes	Yes
Garg <sup>13</sup>	PD (7-months)	Yes	Yes	Yes	U	No	Yes
Benyounes <sup>14</sup>	PD (10-years)	No	Yes	No	No	No	Yes
Ozeren <sup>15</sup>	AD (32wg)	No	No	Yes	Yes	No	Yes
Chadha <sup>16</sup>	AD (24wg)	U	U	Yes	No	Yes	Yes
Chadha <sup>16</sup>	AD (24wg)	No	No	Yes	No	No	Yes
Tiberio <sup>17</sup>	AD	No	Yes (S)	U	No	No	No
Wortmann <sup>18</sup>	AD (32wg)	No	Yes (S)	No	No	No	Yes
Masoumi <sup>19</sup>	PD (9-years)	Yes	Yes	Yes	Yes	Yes	No
van Baalen <sup>20</sup>	PD (1-month)	No	Yes (S)	No	No	No	Yes
Jóźwiak <sup>21</sup>	PD (2-years)	No	Yes	No	No	No	Yes
Ganame <sup>22</sup>	AD	No	No	No	U	No	Yes
Ganame <sup>22</sup>	ND	No	No	No	U	No	No
Venugopalan <sup>23</sup>	PD (3-months)	Yes	No	No	No	No	No
Mas <sup>24</sup>	AD (36wg)	Yes	Yes (S)	U	U	No	Yes
Sgro <sup>25</sup>	AD (32wg)	Yes	Yes	No	No	No	Yes
Quek <sup>26</sup>	PD (6-years)	Yes	Yes (S)	Yes	No	No	No
Ruggieri <sup>27</sup>	PD (3-years)	No	Yes	No	Yes	No	Yes
Malooof <sup>28</sup>	ND	No	Yes	Yes	Yes	No	Yes
Weig <sup>29</sup>	PD (13-months)	Yes	Yes (S)	Yes	U	No	No
Mehta <sup>30</sup>	ND (birth)	Yes	Yes	No	Yes	Yes	Yes
Scurry <sup>31</sup>	ND	No	Yes	No	No	Yes	Yes
Russell <sup>32</sup>	ND (birth)	No	Yes	U	U	Yes	Yes
Platt <sup>33</sup>	AD	No	No	No	Yes	Yes	No
Guereta <sup>34</sup>	AD (35wg)	Yes	Yes	No	No	Yes	No
Bini <sup>35</sup>	ND	Yes	Yes	U	U	No	Yes
Ohri <sup>36</sup>	ND	No	Yes	No	No	Yes	Yes

AD = antenatal diagnosis (before birth); ND = neonatal (birth - up to 28 days of life) diagnosis; PD = postneonatal diagnosis; wg = weeks of gestation; S = seizure; U = unknown.

In line with our report, we found that 38.7% of the tumors were diagnosed during gestation, and 32.2% were fatal. Family history of TSC was present in 31.8%, and neurological signs were detected in 73.3% of cases. Multiple tumors were more prevalent than isolated lesions, and arrhythmia was a significant finding in 43.3% of the reported cases.

Among neurological conditions, TSC may present with structural brain abnormalities such as glioneuronal hamartomas – also called cortical tubers and found

in at least 80% of TSC patients –, subependymal nodules, seen in about 90% of cases and, with a lower prevalence of 10 to 20%, subependymal giant cell tumors (SGCT).<sup>1,37</sup> Although asymptomatic and with a normal appearance in neurological examination, in this case, the newborn's autopsy identified all of the three brain alterations. The clinical outcome of these tumors, when symptomatic, includes epilepsy or infantile spasms in children younger than 1 year,<sup>38</sup> probably related to cortical tubers, and obstructive

hydrocephalus due to occlusion of the foramen of Monro caused by SGCT in 10% of cases.<sup>39</sup> Intellectual disability, autism spectrum disorders, and behavioral problems can develop in up to 90% of TSC cases, comprising the TSC-associated neuropsychiatric disorders (TAND).<sup>40</sup> An association between infantile spasms and the development of TAND has been described.<sup>41,42</sup>

In this case, not only the newborn's TSC diagnosis was made by the autopsy, but also the family members were examined for the presence of the disease's clinical symptoms because of its genetic basis and the possibility of heritability. Another important aspect of the case is TSC's phenotypical variation among the family. Whereas the newborn presented cardiovascular features, the aunt and grandfather had a history of dermatological lesions, the mother exhibited mostly neurological and dermatological symptoms and had pulmonary, hepatic, and renal image findings. Wide intrafamilial phenotypic variability has been reported,<sup>43,44</sup> and family members may sometimes be affected, yet escape the previous diagnosis because of a milder phenotypic presentation.<sup>45</sup> At times, the disease can only be diagnosed through genetic testing or image findings, leaving the patient otherwise healthy until adulthood, while in other cases it can present clinical symptoms with a broad spectrum of severity. Regarding cardiac rhabdomyomas, they have been reported to be associated with congestive heart failure, arrhythmias,<sup>45,46</sup> or complete cardiovascular collapse and sudden death.<sup>46-48</sup>

Due to the possibility of fatal consequences, symptomatic tumors must be examined. Regarding the heart, prostaglandins can be used to ensure the patency of the ductus arteriosus and systemic blood flow to stabilize the critically ill newborn while waiting for the involution of the rhabdomyoma.<sup>7</sup> Recent reports suggest new clinical treatment modalities with the use of mechanistic target of rapamycin inhibitors, such as sirolimus<sup>49</sup> or everolimus.<sup>17,50</sup> These drugs may induce accelerated tumor regression, therefore avoiding the need for invasive intervention. However, the minority of cases in which they do not spontaneously regress and become life-threatening, due to either left ventricular outflow tract obstruction, right ventricular outflow tract obstruction, mitral valve insufficiency, or intractable arrhythmias, cardiac surgery might be necessary. Operative management

typically involves resection of the intracavitary portion of the tumor without complete excision. As previously stated, the newborn's main tumor was large and caused significant obstruction of the left ventricular outflow tract during systole. Therefore, the newborn was kept under continuous monitorization in the NICU, and surgical resection was planned as soon as possible, in her first week of life, since the mass began to cause hemodynamic compromise and could result in catastrophic cardiovascular collapse. Other authors have reported cases with similar clinical and imaging presentations, in which aggressive surgical management was successful in treating and preventing hemodynamic compromise with good long-term outcomes.<sup>46,51-54</sup> Unfortunately, despite the effort to reverse a life-threatening condition already established, the newborn could not tolerate the additional hypotensive effect of general anesthesia, considering the blood flow compromise caused by the tumor, and did not survive the surgery.

## CONCLUSIONS

The reported case demonstrates that, despite histologically benign, large, and problematically placed cardiac rhabdomyomas may present severe morbidity, and, eventually, a lethal outcome. Thus, we highlight the importance of proper diagnosis and timely adequate management of these tumors in order to prevent the potential of catastrophic cardiovascular collapse. Additionally, this case underscores the variability of TSC and the importance of performing a comprehensive postmortem examination in the identification of the cause of death, especially for a familial disease.

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