PATHOLOGICA 2025;117:33-38;
DOI: 10.32074/1591-951X-1099

Case report

Foetal cardiac rhabdomyoma due to paternal *TSC1* Mutation: a case report and literature review

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Summary

Rhabdomyomas are the most common prenatal cardiac tumours, and are often associated with tuberous sclerosis complex (TSC). They have been shown to grow during foetal development, but may often regress or shrink in early childhood.

In the present case, ultrasonography at 20+2 gestational weeks identified two echogenic masses suspicious of rhabdomyomas in the foetal heart. Neither of these tumours caused significant haemodynamic instability. Genetic testing of DNA extracted from amniocytes revealed a pathogenic variant of the *TSC1* gene, supporting the diagnosis of tuberous sclerosis. The pregnancy was terminated at 21+1 weeks. Pathological examination confirmed the presence of two cardiac rhabdomyomas, histologically characterised by distinctive large vacuolated cells with central nuclei and radial cytoplasmic extensions.

Further research and a multidisciplinary approach are highly recommended to improve management and outcomes of prenatal tumours.

Key words: tuberous sclerosis, rhabdomyoma,cardiac tumours, genetics, histology

Received: September 25, 2024
Accepted: November 14, 2024

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How to cite this article: Nardi E, Silvano A, Ammar O, et al. Foetal cardiac rhabdomyoma due to paternal TSC1 Mutation: a case report and literature review. Pathologica 2025;117:33-38. https://doi.org/10.32074/1591-951X-1099

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder with an estimated incidence of 1:10,000 newborns, characterised by hamartomas in multiple organs such as the skin, central nervous system, heart, lungs and kidney[1]. TSC is caused by a single heterozygous *TSC1* or *TSC2* mutation, and a somatic "second-hit" mutation in the unaffected allele is required for loss of the hamartin-tuberin complex and activation of the mammalian rapamycin complex 1 target (mTORC1), which results in hamartoma development[2]. The loss of heterozygosity for the TSC1 or TSC2 locus has been reported in kidney and cardiac lesions associated with tuberous sclerosis. However, there are conflicting results regarding tuber formation, raising the possibility that some lesions in tuberous sclerosis may be due to haploinsufficiency[3,4].

Diagnosis based on genetic and clinical criteria is generally made in the first 15 months of life. Genetic testing involves the detection of pathogenic *TSC1* and *TSC2* mutations, while clinical criteria involve cutaneous, renal, pulmonary, cardiac and neurological manifestations[1]. Cutaneous lesions may occur at any age and affect over 90% of TSC patients, while neurological and renal sequelae are the main causes of morbidity and mortality[1].

Rhabdomyomas are the most frequently encountered cardiac tumours in children, and can be the first sign of TSC in foetuses and infants[5]. Almost 90% of these tumours are multiple, and common manifestations include hydrops fetalis, left ventricular outflow tract obstruction, arrhythmias, and cardiac shock[6]. The poor neonatal outcome is significantly associated with the size of the tumour (≥20 mm in diameter) and the occurrence of foetal dysrhythmias[7].
Herein, we report a case of foetal cardiac rhabdomyoma due to paternal mutation the *TSC1* gene.

Case report

A 21-year-old primigravida, whose pregnancy had remained unrecognised until 15 weeks, underwent an ultrasound examination at 20+2 weeks. The foetus was diagnosed with two echogenic masses suspicious of rhabdomyomas, one measuring 4.0 x 4.5 mm, located in the interventricular septum with a slight protrusion into the left ventricle, and the other measuring 3.5 x 3.7 mm, located between the superior vena cava orifice and the posterior wall of the right atrium. Both tumours were non-obstructive and did not produce significant haemodynamic changes. No other congenital defects were noted.
A previous mutation analysis of the *TSC1* and *TSC2* genes revealed that the father carried the c.1525C > T (p.Arg509X) pathogenic variant in the *TSC1* gene. Therefore, amniocentesis was performed and the c.1525C>T variant was detected by Sanger sequencing on amniocyte DNA. Following the diagnosis of tuberous sclerosis, the woman chose to terminate the pregnancy at 21+1 weeks.
Gross examination showed a phenotypic female. On opening the chest and abdomen, the pericardial sac, heart, lungs, and abdominal organs appeared macroscopically normal. The heart measured 2.9 x 2.0 x 1.8 cm. The two rhabdomyomas appeared as well-circumscribed, firm, grey-brown nodules on the whole heart section. No abnormalities were observed upon the macroscopic examination of, lungs and kidneys.
On opening the skull, no macroscopic alterations were identified.
Microscopically, the tumours were composed of rounded and polygonal cells with eosinophilic cytoplasm containing intracellular glycogen (positive PAS staining); these cells occasionally exhibited central nuclei with radial cytoplasmic extensions toward the cell membrane (so-called "spider cells", Fig. 2 A-C).
The cells demonstrated a strong immunoreactivity to myoglobin confirming the striated muscle characteristics of the neoplastic cells (Fig. 2D).
Microscopic examination revealed a lung parenchyma consistent with the reported gestational age. The nephrogenic cortex was appropriately represented at the renal level and foci of extramedullary erythropoiesis were found in the liver.
A histological examination of the placenta was also carried out showing a severe chorioamnionitis and a maturation of the chorionic villi in accordance with the gestational age.

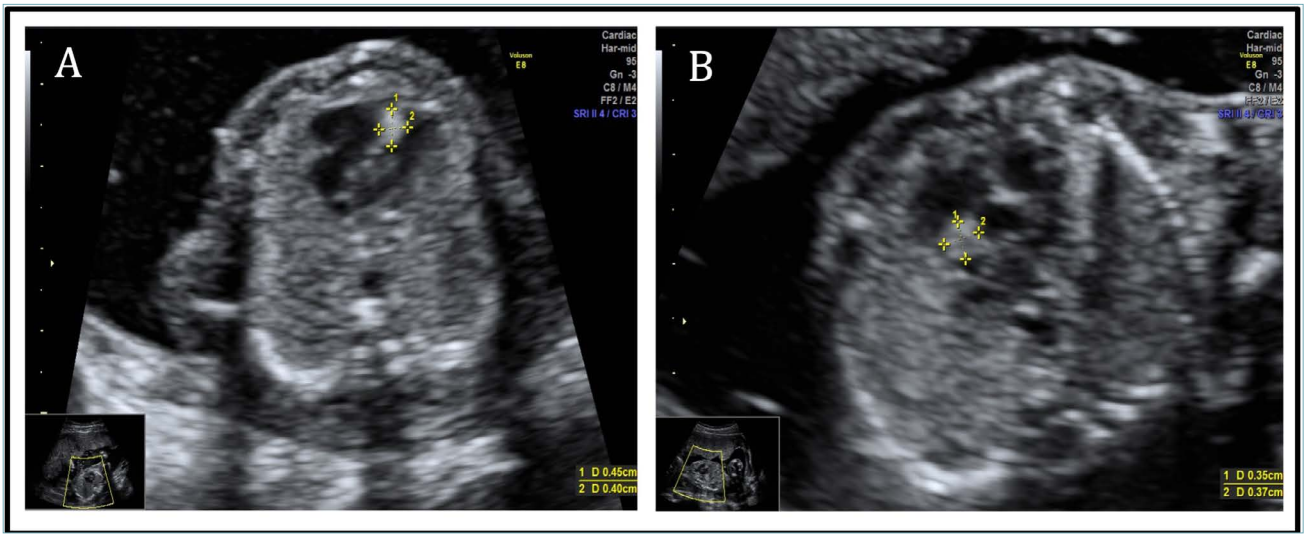

Figure 1. Ultrasound examination at 20+2 weeks. (A): Apical rhabdomyoma of the interventricular septum (4.0x4.5 mm) diagnosed at 20+2 gestational weeks by ultrasound. (B): Right atrial rhabdomyoma between the superior vena cava orifice and the posterior wall (3.5x3.7 mm).

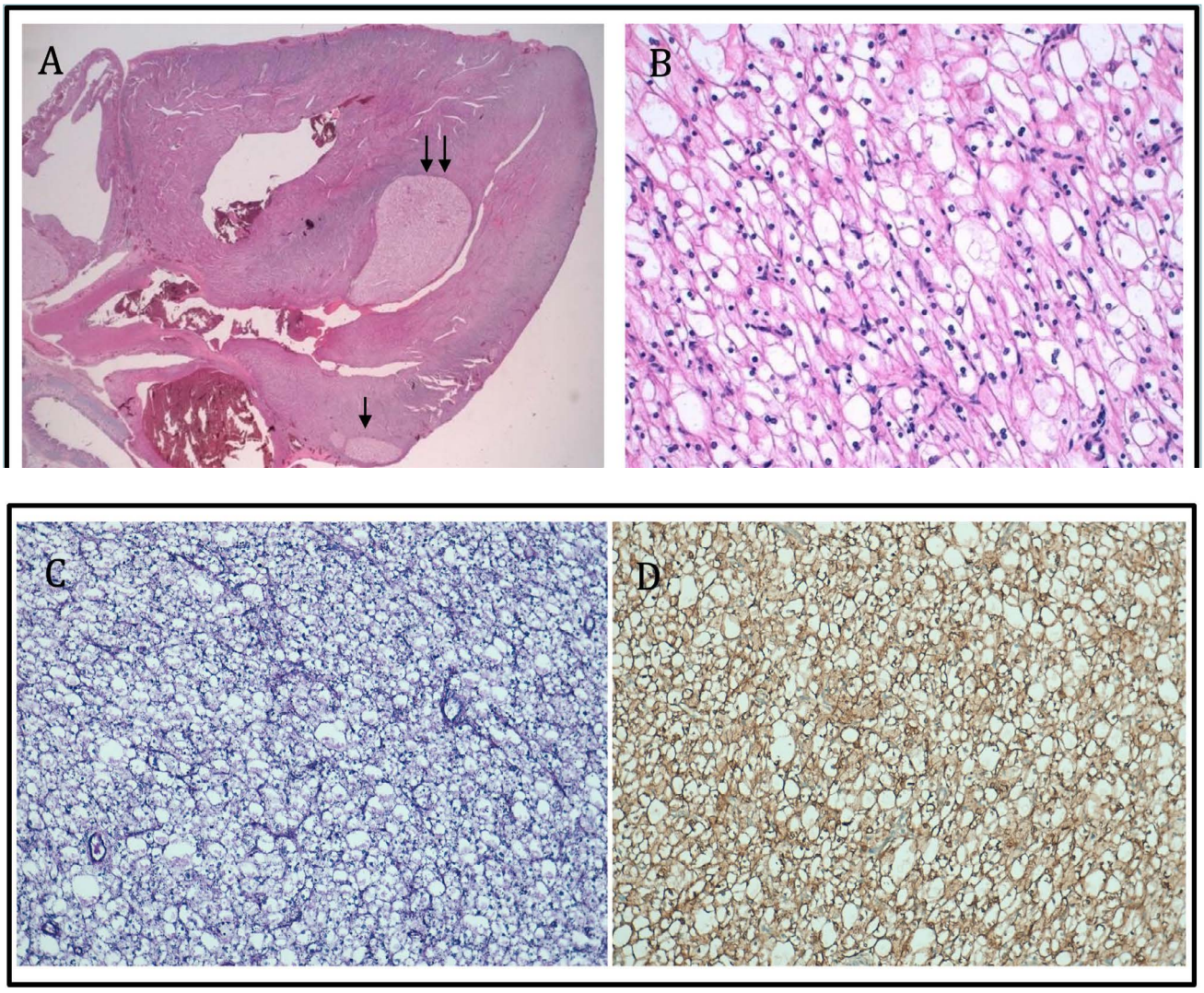

Figure 2. Histology of foetal cardiac rhabdomyoma. (A): Whole heart section showing the two rhabdomyomas; the single arrow indicates right atrial rhabdomyoma between the superior vena cava orifice and the posterior wall, while the double arrows indicate apical rhabdomyoma of the interventricular septum (magnification x2). (B): Cardiac rhabdomyoma composed of distinctive large vacuolated polygonal cells (magnification x10). (C): Positive PAS staining for intracellular glycogen (magnification 20x). (D): Positive myoglobin staining (magnification 20x).

Discussion

An increasing number of foetal cardiac neoplasms, closely related to the gestational age of the foetus[8], have been reported in recent years due to the advancement of prenatal detection techniques. Most tumours are detected by prenatal ultrasound[9] and, once detected, a foetal echocardiography (FE) is required to assess the characteristics of the mass and the impact on cardiac haemodynamics. Although rhabdomyomas may occur anywhere within the cardiac muscle, they usually develop in the ventricles, often as multiple masses[10]. They can grow and increase in number during foetal life, but generally stop growing and often regress or shrink after birth[11]. In the reported case, two rhabdomyomas were observed, one in the apical portion of the interventricular septum and the other in the right atrium between the superior vena cava orifice and the posterior wall. The presence of a rhabdomyoma in the right atrium can lead to cardiac arrhythmias in both antenatal and postnatal periods, resulting in adverse neonatal outcomes[12].

Prenatal genetic testing for TSC is recommended when foetal cardiac rhabdomyomas are identified by ultrasound.

Tuberous sclerosis is a rare genetic disorder charac-

terised by hamartomas in multiple organ systems. Early manifestations, most commonly affecting the heart and brain, can be detected by prenatal imaging. Cardiac rhabdomyomas may be the only finding before other clinical abnormalities appear, and therefore, the diagnosis of TSC should always be considered when they are discovered by foetal ultrasound[7].

A growing number of case reports on the association of foetal cardiac tumours with TSC diagnosis have been reported in the literature[13]. Table I summarises reported cases.

Through targeted exome capture, next-generation sequencing (NGS) and Sanger sequencing, Chen and collaborators[5] recently reported a case of foetal cardi-

Table I. Summary of reported cases of cardiac rhabdomyoma due to *TSC* gene mutation.

Author, year	Weeks and methods of diagnosis	Symptoms	Mother / Foetus management	TSC mutation
Barnes et al., 2018	21 weeks of gestation by foetal echocardiography	Outflow tract obstruction with supraventricular tachycardia and impending hydrops fetalis	Sirolimus administration to the mother with tumor regression in utero. Delivery occurred at 36 weeks of gestation	*TSC1* variant, (c.1781delT, p.Val594Glyfs*35);
Park et al., 2019	21+5 weeks by foetal echocardiography	N/A	Sirolimus administration to the mother began at 23 weeks of gestation; at 29 + 5 weeks no cardiac mass was observed on foetal echocardiography. A male was delivered at 39 weeks of gestation	*TSC2* (c.5108dup, p.Ser1704Valfs*2) transmitted from the mother
Vachon-Marceau et al., 2019	21 weeks of gestation by foetal echocardiography	Tricuspid regurgitation and biventricular systolic and diastolic dysfunction	Sirolimus treatment began at 31+4 weeks and stopped at 36 weeks. Delivery at 39 weeks of gestation	*De novo* variant in the *TSC2* gene
Chen et al., 2020	24 weeks by ultrasound	N/A	Interruption of pregnancy after 24+ 4 weeks' gestation	*TSC2* (c.2294delC, p.Val766Trpfs*4); heterozygous variant in peripheral blood lymphocytes and paternal sperm
Pluym et al., 2020	22 weeks of gestation with foetal echocardiography	Mild narrowing of the left ventricle inflow	Sirolimus treatment began at 28 weeks and stopped at 35 weeks. Vaginal delivery at 36+6 weeks	*TSC2 de novo* variant c.1362-66_1384 del
Dagge et al., 2021	22 weeks of gestation by ultrasound	Supraventricular extrasystoles, obstruction of the right ventricular flow, mild tricuspid insufficiency	Sirolimus treatment began at 27 weeks until delivery. At 39 weeks of gestation, an elective cesarean was performed	*TSC2 de novo* variant (c.1831C>T, p.Arg- 611Trp) diagnosed in the mother. No genetic analysis in the fetus
Will et al., 2023	21 weeks by ultrasound	Insufficiency of the tricuspid valve and reduced contractility of the right ventricle	Sirolimus administration to the mother began at 27 weeks' gestation; the rhabdomyoma shrank with improvement of the ventricular function. Delivery was induced at 39 weeks and 1 day of gestation	*TSC2* (c.5160T>G, p.Asn1720Lys) transmitted from the father
Maász et al., 2023	30 weeks by ultrasound	None	Oral everolimus administration until 36 weeks	*TSC2 de novo* variant (c.3037delG; p.Asp1013IlefsTer3)
Current case	20+2 weeks by ultrasound	The two rhabdomyomas were non-obstructive and haemodynamically insignificant	Interruption of pregnancy after 21+1 weeks gestation	*TSC1* (c.1525C>T, p.Arg509X) transmitted from the father

ac rhabdomyoma due to paternal mosaicism in TSC2, with no detectable mutation at this locus in maternal blood samples. Similar to our case, the pregnancy was interrupted at 24+4 weeks of gestation.

TSC is a genetic disorder, resulting in hyperactivity of the mTOR pathway. Given their anti-proliferative effects, mTOR inhibitors can be used in the treatment of foetal masses, representing a potential pharmacological alternative to surgery. In patients with TSC these inhibitors are used to reduce the size of cardiac rhabdomyomas[14]. Treatment, including in-utero therapy, is typically indicated when deterioration in cardiacfunction is observed on foetal echocardiograms[15]. Qaderi et al. reported that in almost all fetuses treated with these drugs, a reduction in rhabdomyoma size was observed[15].

Only a few cases of congenital cardiac rhabdomyoma are associated with *TSC1* mutation[16,8,17,18,19]. Chen et al.[8] showed that out of 37 fetuses in which cardiac tumours were identified by foetal echocardiograms, six had a *TSC1* mutation and 31 a *TSC2* mutation, indicating a close correlation between multiple cardiac tumours and TSC. Uchyiama et al.[18] described two Japanese siblings with cardiac tumours and a *TSC1* intragenic deletion that determined two aberrant transcripts inherited from the father who carried a mosaicism, and was asymptomatic. Mutations in the *TSC2* gene appear to be nearly 3 times more frequent than in *TSC1*, although *TSC1* gene mutations are more common in familial cases with autosomal dominant inheritance[20-22]. This may be attributed to the fact that patients with *TSC1* mutations have less severe symptoms than those with *TSC2* mutations, and therefore their chances of having children and transmitting the mutation are higher[23].

The presence of multiple cardiac rhabdomyomas is a strong predictor of TSC[24,25]. However, to determine whether there is a significant difference in the strength of the association with TSC between cases of multiple or single cardiac rhabdomyomas, larger sample sizes are required.

Genetic screening for *TSC* mutations should be offered to the parents of a foetus following prenatal diagnosis of TSC to estimate the risk of the disease in subsequent pregnancies. A positive genetic diagnosis can help guiding prenatal and postnatal management of these infants.

Conflict of interest statement

The authors declare no conflict of interest.

Funding

The research reported in this publication was supported by Fondazione CRF Firenze Grant number B15F21003630007.

Authors contribution

Conceptualization: FC, EN; Data acquisition: EN, AS, OA; Writing: EN, AS, OA; Review: FG, LP, AM, VS, FC.

Ethical considerations

The present study complied with the Ethical Principles for Medical Research Involving Human Subjects according to the World Medical Association Declaration of Helsinki; all samples were anonymized before histology and immunohistochemistry; no futher ethical approval was necessary to perform the retrospective study.

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