Sonographic diagnosis of fetal cardiac rhabdomyomas and cerebral tubers: a case report of prenatal Tuberous Sclerosis

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Summary

The rhabdomyoma constitutes more than 60% of all cardiac tumors that are diagnosed in the prenatal and postnatal age. In more than 50% of cases, it is the first clinical manifestation of tuberous sclerosis (TS), autosomal dominant genetic condition and multisystem involvement.
Methods: **we report a case of cardiac rabdomyomatosis in twin pregnancy bicorial biamniotic, with suspicion for tuberous sclerosis, diagnosed at our hospital. For the diagnosis of cardiac rhabdomyomas we used the two-dimensional ultrasound, and 3D echocardiography. For the diagnosis of intracranial subependymal nodules an ultrasound and RMN were used. Cesarean section was performed at 34 weeks. The diagnosis of tuberous sclerosis was confirmed at birth by genetic testing.**
Results: **at birth, instrumental examinations have confirmed the ultrasonographic findings and genetic testing for the detection of tuberous sclerosis confirmed the suspected diagnosis. The cardiac lesions regressed spontaneously and the brain showed no progression.**
Conclusion: **the study of the fetal heart ultrasound has allowed an early prenatal diagnosis of cardiac neoplasms, allowing control of their development and their association with other lesions which then actually appeared in the suspicion of a genetic disease much more complex than the Tuberous Sclerosis.**

Key words: fetal cardiac tumor, rhabdomyoma, tuberous sclerosis.

Introduction

The rhabdomyoma constitutes more than 60% of all cardiac tumors diagnosed during the intrauterine life and post-natal age. Sonographically it appears as a nodular multiple lesion, less often unique, hyperechoic, well-defined, oval-shaped, and in more than 50% of cases it is the first clinical manifestation even in the absence of other clinical signs of tuberous sclerosis (TS) (1).
The occurrence of cardiac rhabdomyoma may be associated with fetal hydrops, intrauterine fetal death and sudden infant death.
The rhabdomyomas can be located at any stretch of the ventricular myocardium, less frequently in the atrium or in the subepicardial region of the heart.
The suspicion of cardiac rhabdomyoma is usually placed after the 20th week of gestational age. Diagnosis is made by echocardiography or cardiac magnetic resonance imaging (1).
After birth, the symptoms may change depending on the number, position and size of the intracardiac mass and in relation to any secondary cardiopathy during fetal life.
Major risk factors for their impact on perinatal outcome are gestational age at diagnosis, tumor size, location and number, progression and any intra- or extra- cardiac associated abnormalities.
Macroscopically, the rhabdomyomas occur as nodules of intramyocardial color yellowish-white, circumscribed and non-enveloped; microscopically are hamartomatous lesions and present some positivity for muscle markers such as myoglobin, desmin, actin and vimentin; it can also be observed positive for amartina, tuberin and HMB45.
The cardiac rhabdomyoma usually increases in size until the 32nd week of gestational age only to go through a gradual spontaneous regression (1).
In the study of rhabdomyomas, an ultrasound color Doppler is used only in those cases where it is placed on suspicion of obstruction to spills, to assess the extent of this and the tube patency.
The Tuberous Sclerosis is a genetic disorder with autosomal dominant inheritance and multisystem involvement with variable expressivity. The two genes, TSC1 and TSC2, respectively, are located on chromosome 9 and 16 and encode two proteins: amartina (TSC1) and tuberin (TSC2 gene). Until now, no individual with TS was a carrier of a mutation of the gene is that the TSC1-TSC2 gene, indicating that the de-

fect only TSC1 or TSC2 alone is sufficient to cause the TS.
The incidence of this disease is about 1 in 6.000/10.000 individuals in the general population. Clinical signs may occur in a number of organs and can occur during different periods of life, but generally appear in a precise chronological order (2-4).
To make the diagnosis of tuberous sclerosis at least 2 of the major signs must appear (Tab. 1).
The 45-70% of patients with ST presents sonographically, cardiac rhabdomyomas (2).
The ST rhabdomyomas are usually asymptomatic and do not require specific treatment. In a small percentage of cases (< 1.5%) , due to the large size or location in critical sites it generates problems in fetal, neonatal or exceptionally at a later age.
The follow-up of asymptomatic rabdomyomas or with modest alterations in the flow or rhythm is performed by echocardiography and electrocardiographic monitoring (2).
The renal lesions characteristic of ST are angiomyolipomas, most frequently these are multiple and bilateral and they are associated with the presence of cysts.
The lesions of the central nervous system in the ST are mainly malformations of cortical development: disorders of migration, cell proliferation and differentiation. The lesions of the brain are diagnosed with prenatal ultrasound, but fetal RMN is required to confirm the diagnosis through the detection of cortical tubers and multiple subependymal hamartomas (5).
There still isn't a medical therapy for ST. It tries to treat certain clinical manifestations to prevent complications (3).

Case report

A 36-year-old woman, primigravida nulliparous, came to prenatal diagnosis service of our Operating Units (Reproductive Medicine, Misericordia Hospital USL 9 Grosseto), with dichorionic and diamniotic twin pregnancy which arose after conception after IVF (three embryos implanted and the age of the donor at the time of egg retrieval was 35 years old), negative medical history proximate and remote, negative obstetric history and negative family history for genetic diseases.
Negative screening for chromosomal was carried out during the first quarter.

Table 1. Diagnostic criteria for the Tuberous Sclerosis

Main features

	Position	Sign	Start	Note
1	Head	Facial angiofibromas or forehead plaque	Children - adult	
2	Toes	Ungueal or periungueal fibromas	Teenager - adult	
3	Skin	Macule Hypomelanotic	Children	More than three
4	Skin	Zigrino patch (connective tissue nuvus)	Children	
5	Brain	Cortical Tuberus	Fetus	
6	Brain	Subependimal Nodules	Children – teenager	
7	Brain	Gyant cell Astrocytoma	Children - teenager	
8	Eyes	Hamartomas of the retina	Newborn	
9	Heart	Cardiac Rabdomyomas	Fetus	Single or multiple
10	Lungs	Linfangioleiomyomatosis	Teenager - adult	
11	Kidney	Renal Angiomyolipomas	Fetus-children-adult	**10** e **11** together count as a major feature

Minor features

	Position	Sign	Note
12	Teeth	Multiple patches to random distribution	
13	Rectum	Rectal Hamartomas	Histological confirmation is suggested
14	Bones	Bones cists	
15	Brain	Cerebral white matter	It's enough radiographic evidence. 5 and 15 together count as a major feature
16	Gums	Fibroids gums	
17	Liver, spleen and other organs	Hamartomas	Histological confirmation is suggested
18	Eyes	Patch acromic of retina	
19	Skin	Lesioni a "confetto"	
20	Kidney	Multiple renal cists	Histological confirmation is suggested

It was monitored by ultrasound according to the protocol adopted for dichorionic twins.
Control at 18 weeks (Fig. 1), the ultrasound examination reveals little focus in one of two fetuses and is shown running in 21 weeks ultrasound morphology.
Morphological ultrasound found in the female fetus the presence in cardiac left ventricular cavity of a hyperechoic focus, which is required for fetal echocardiography.
At 22 +5 weeks of gestation (Fig. 2), the patient undergoes the examination of both fetal hearts showing in the fetus A, male, proper cardiac anatomy and the fetus B, female, the presence of a focus that is described as "endophytic hyperechoic mass, subvalvular, the left ventricle".
At 23 +5 weeks of gestational age a fetal echocardiography in the female fetus has confirmed the previously observed formation, which appears to control the current oblong and measures 5 mm (Fig. 3). This training does not appear to change the transvalvular flow. This was not encountered in other intracardiac or extracardiac anomalies associated.
At 24 +5 weeks of gestational age, the brain, the spine, the neural tube and abdomen are still in the norm; three intracardiac echogenic focuses are found.
At 28 +5 weeks of gestational age (Fig. 4) a new mass

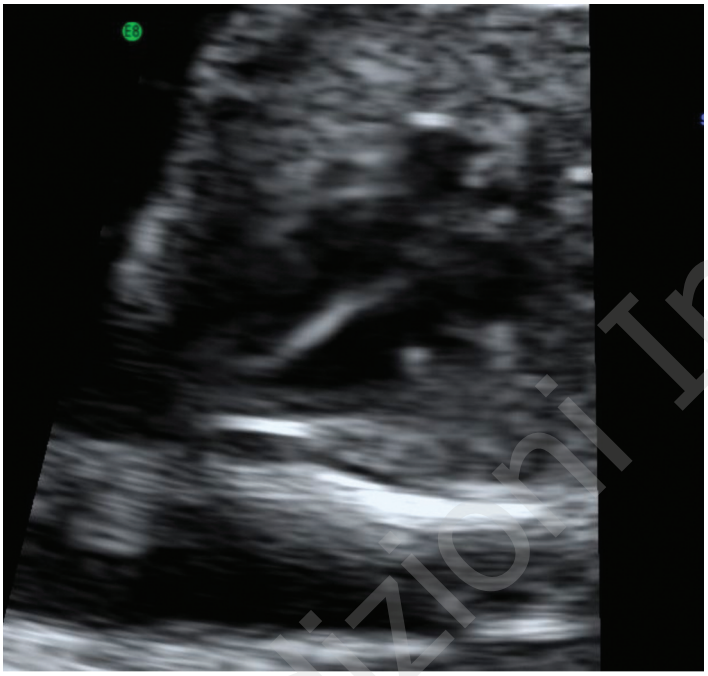

Figure 1. Hyperechoic focus in left ventricular at 18 weeks.

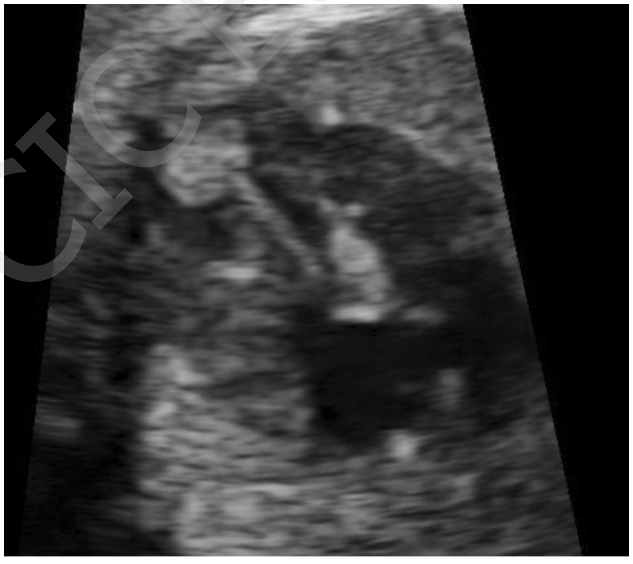

Figure 2. Endophytic hyperechoic mass subvalvular in ventricular left at 22+5 weeks.

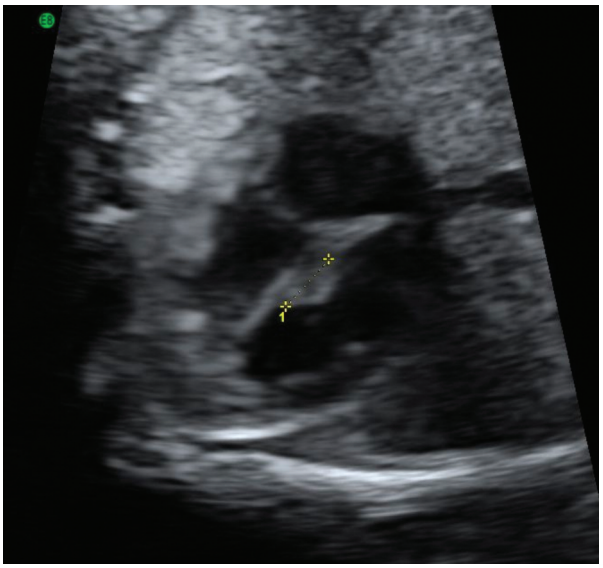

Figure 3. Endophytic hyperechoic mass subvalvular in ventricular left at 23+5 weeks.

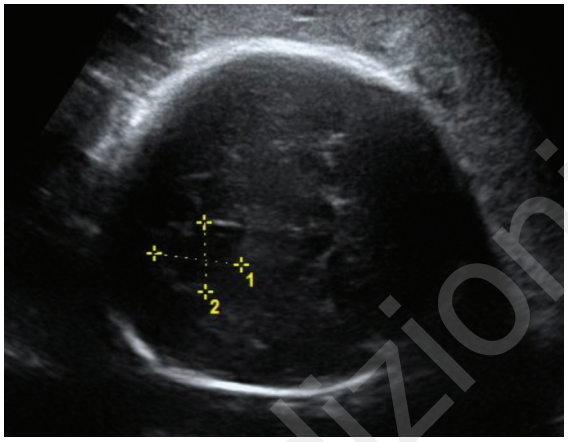

Figure 4. Cerebral mass at 28+5 weeks.

in the head is found, this was not previously highlighted and is described as "training round of the average diameter of 1 cm, anechoic, of regular shape, which is localized in the right hemisphere between the thalamus and the anterior ventricle".

A check up in 4 weeks is suggested.

At 34 +1 weeks a considerable slowdown in the pace of growth in both fetuses was found and again confirmed the three previously described cardiac mass in the female fetus. It also confirmed the intracranial formation associated with marked dilatation of the right cerebral ventricle front and rear. An increase is reported in umbilical artery resistance index of the fetal ductus venosus regular, and reduced fetal active movements (MAF).

We urgently requested a fetal RMN, which confirmed the presence of intracranial mass.

The patient is sent at the Department of obstetric pathology for the induction of lung maturation with corticosteroids and closer monitoring of pregnancy and growth of both fetuses.

Due to the deterioration of Doppler flow, associated with fetal growth reduction (biometry belows to the 5th percentile in both fetuses), 34+4 weeks we decide to perform a cesarean section under spinal anesthesia.

The male fetus was born 1865 gr, and the affected fetus, female, 1830 gr, which was given an Apgar score at minute I and V, respectively, 8 and 9. At birth it is found crying vigorously and spontaneously with good cardiorespiratory adaptation, tone and reactivity appropriate for gestational age.

Postnatal ultrasound of the brain has noted: "mild hyperechogenicity of the periventricular parenchyma with large right ventricle resulting from the merger with the cystic lesion observed in the uterus, presence of a bilateral subependymal nodule near the root of the choroid plexus, as seen in tuberous sclerosis. At the level of the parenchyma of the right ventricle the presence of excess tissue is detected".

Echocardiography detected: "Multiple hyperechoic oval masses, of which, an adherent to the roof of the right atrial dimensions 4x9 mm; 2 in the right ventricle: one at the apex of dimensions 6x10 mm and one smaller in subtricuspidalic region. In the left ventricle there are 5 masses three of which are larger than 7x8 mm 4x6mm, one adherent to the septum average, one at baseline and a posterolateral wall, one at the septum bottom, another one smaller at the top level".

There was no need to perform anticongestive therapy because the heart appeared hemodynamically stable.

The renal ultrasound and ocular fundus examination were negative.

The consulting dermatological clinical examination shows a slightly hyperkeratotic patch, visible in the light of Wood, on the right thigh and some smaller on the right shoulder.

The ultrasound picture is therefore compatible with

cystic evolution confluent necrotic phenomenon in the right cerebral ventricle in patients with subependymal nodules, cardiac rhabdomyomas and skin nodules, all of them compatible with the context of tuberous sclerosis.
Withdrawals are made for genetic testing for the presence of tuberous sclerosis.
The echocardiographic monitoring at 6 months shows spontaneous regression of cardiac masses in number and size.
The post-natal monitoring by RMN of the brain abnormalities shows no progression and it is established, until the eventual positivity of neurological signs and symptoms, to carry out seriated check ups by neurological examination and a check up of the ocular fundus.
The genetic survey carried out after birth confirmed the diagnosis of tuberous sclerosis.

Discussion

The ultrasound in the second trimester allows us to identify formations intracardiac suspicious for malignancy, to be placed in the differential diagnosis with hyperechoic focus, also called "golf ball" (1).
The "golf ball" can be an expression of hyperechogenicity of the papillary muscle.
In the presence of "golf ball" isolated and not associated with other sonographic markers there is an increased risk of aneuploidy and it is a normal variant without clinical relevance for prognosis.
On the contrary, in the case of a positive test combined with suspected heart disease associated or in the presence of other ultrasound markers of aneuploidy, although the finding of a single "golf ball" obligation to conduct investigations of the second level (fetal echocardiography) and any karyotype.
Multiple hyperechogenic intracardiac focus associated with lesions of the cranium morphology or impaired renal pathology are doubt and require a second level control, suspicion of genetic diseases associated with , such as tuberous sclerosis (2,6).
Our case is particularly significant in highlighting how the persence of an echogenic intracardiac focus may be important depending on when it is seen , its permanence or its transformation into multiple focus and the association with other diseases.
The increase of size and the protrusion of the exophytic intracardiac mass during the echocardiography of the 22 week and the appearance of multiple focus to the next check at 23 weeks led us to suspect a tuberous sclerosis (7) and to seek the classic signs associated with brain and kidney, which regularly appeared at 28 weeks, in particular with the presence of the nodule brain.
In suspected ST genetic counseling of couples and subsequent genetic testing for specific disease at birth should be carried out. Checks will be carried out as a specialized RMN and brain TC scan, echocardiogram and echocardiography; renal ultrasonography, ocular fundus examination at birth and at a distance to exclude tuberous sclerosis also very late expressivity and possibly prevent neurological complications (6,7).

Conclusions

We underline the usefulness of ultrasound study of the heart and of the neurocranium in the prenatal suspicion of tuberous sclerosis. This allowed us to address the patient already prenatal to the genetic counseling for the definitive diagnosis during postnatal development.

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