



Atypical mediastinal mass in the fetus: a review of the literature

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Abstract

Objectives Congenital thoracic masses (CTMs) are suspected in presence of solid or cystic thoracic lesions at ultrasound. The common typical fetal CTMs encompass: hyperechogenic lung lesions such as congenital pulmonary airway malformation (CPAM), bronchopulmonary sequestration (PS) and congenital high airway obstruction syndrome (CHAOS); less common solid thoracic masses are mediastinal/pericardial tumors as rhabdomyoma and teratoma.

The aim of our study is to gather the available evidence on cases of atypical CTMs of difficult classification, for which the diagnosis remains often uncertain.

Methods A review of the literature on the prenatal diagnosis of CTMs was performed, focusing on ultrasound features, postnatal manifestation, treatment and neonatal outcome. Inclusion criterion was prenatal diagnosis of CTM cases with difficult classification in six typical categories. A summary of results was carried out.

Results The literature review included six studies in the analysis. Two cases experienced intrauterine fetal death, one with hydrops in rhabdomyoma and another one for a rapid growth of the mass, with autopsies precisising the diagnoses. In two other instances, surgery after birth provided also different histologic diagnoses. All surviving children were asymptomatic at follow-up. One case with rhabdomyoma and another one with atypical pericardial teratoma showed spontaneous regression. Moreover we are presenting our unpublished case of an atypical mass diagnosed as rhabdomyoma or bronchopulmonary sequestration.

Conclusions Some masses may present atypical presentation of a known disease or we may face rare diagnosis for which there is lack of information in the literature. The definitive diagnosis still relies on histologic analysis.

Keywords Fetal echography · Fetal echocardiography · Atypical cardiac mass · Ultrasound · Tumors

Introduction

With the growing utilization of fetal ultrasound, there is a rise in identifying clinically silent anomalies that present diagnostic and management challenges for perinatologists and pediatricians. Congenital thoracic malformations (CTMs) exemplify this, with only a minority showing symptoms early in life while the majority remain asymptomatic, leading to challenges in determining postnatal care for healthy infants with a sonographic or radiologic anomaly.

CTMs are suspected in presence of solid or cystic thoracic lesions at ultrasound examination. CTMs are classified sonographically as solid or cystic lesions [1]. Often the definitive diagnosis is based upon the results of postnatally investigation as histologic examination. Magnetic resonance imaging (MRI) can also be used for doubtful diagnoses.

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Among the most common CTMs there are congenital pulmonary airway malformation (CPAM; otherwise defined as congenital cystic adenomatoid malformation: CCAM), bronchopulmonary sequestration (PS) and congenital high airway obstruction syndrome (CHAOS) and bronchial atresia (BA), less common causes of solid thoracic masses are mediastinal/pericardial tumors as rhabdomyoma and teratoma [1–3], whereas bronchogenic cysts (BC) present anechoic fluid filled appearance [4].

The CCAM are developmental malformations of the lower respiratory tract. According to Stocker's classification [5], CCAM was divided into solid or microcystic, macrocystic with one or more large cysts (>2 cm) and mixed with areas that are solid intermixed with areas containing multiple cysts <2 cm in diameter. During the early third trimester >80% of the microcystic lesions resolve, but in >80% of these cases this is not a true resolution but purely inability to detect the lesion by ultrasound because the normal lungs also become echogenic.

Pulmonary sequestration (PS) [6, 7] is a malformation in which a segment of lung parenchyma develops without tracheobronchial connections and is supported by the systemic circulation rather than the pulmonary one. It is identified sonographically as a homogeneous and hyperechoic lesion in which Color Doppler demonstrates a feeding vessel that arises from the descending aorta. In 75% of cases it is intralobar, making it indistinguishable in appearance from microcystic CPAM. In 25% of cases it is extralobar, located outside the normal lung with its own visceral pleura; in most of these cases there is an associated pleural effusion.

Although these malformations represent the most common causes of hyperechoic CTMs, lesions involving the pericardium or mediastinum such as teratoma or rhabdomyoma cannot be excluded.

Congenital cardiac tumors are rare, with a prevalence of 0.01–0.05% [2, 3].

Rhabdomyoma, classically with an intracardiac localization, is the most common cardiac tumor in fetus, infants and children, accounting for 60–86% followed by fibroma, teratoma, myxoma, and haemangioma [2, 3, 8].

Several prenatal imaging findings can help to differentiate between pericardial and mediastinal teratomas. The intrinsic imaging characteristics of pericardial and mediastinal teratoma are identical with both types typically appearing as mixed cystic and solid masses with or without calcifications [9, 10].

Mediastinal teratoma is often a lesion above the heart within the anterior and superior thorax; instead a pericardium teratoma is on the right of the heart. Synchronous movement of the mass with the heart or direct visualization of an attachment to the heart or pericardial effusion are consistent with a pericardial teratoma [11, 12].

However, a correct differential diagnosis is necessary, as the management, prognosis and surgery are different based on the history and histology of the lesions.

The aim of our study is to gather the current available evidence in the literature on cases of atypical congenital thoracic malformations of difficult classification, for which the diagnosis remains often uncertain as well as the perinatal and long-term outcome [13].

Methods

Search strategy, information sources and eligibility

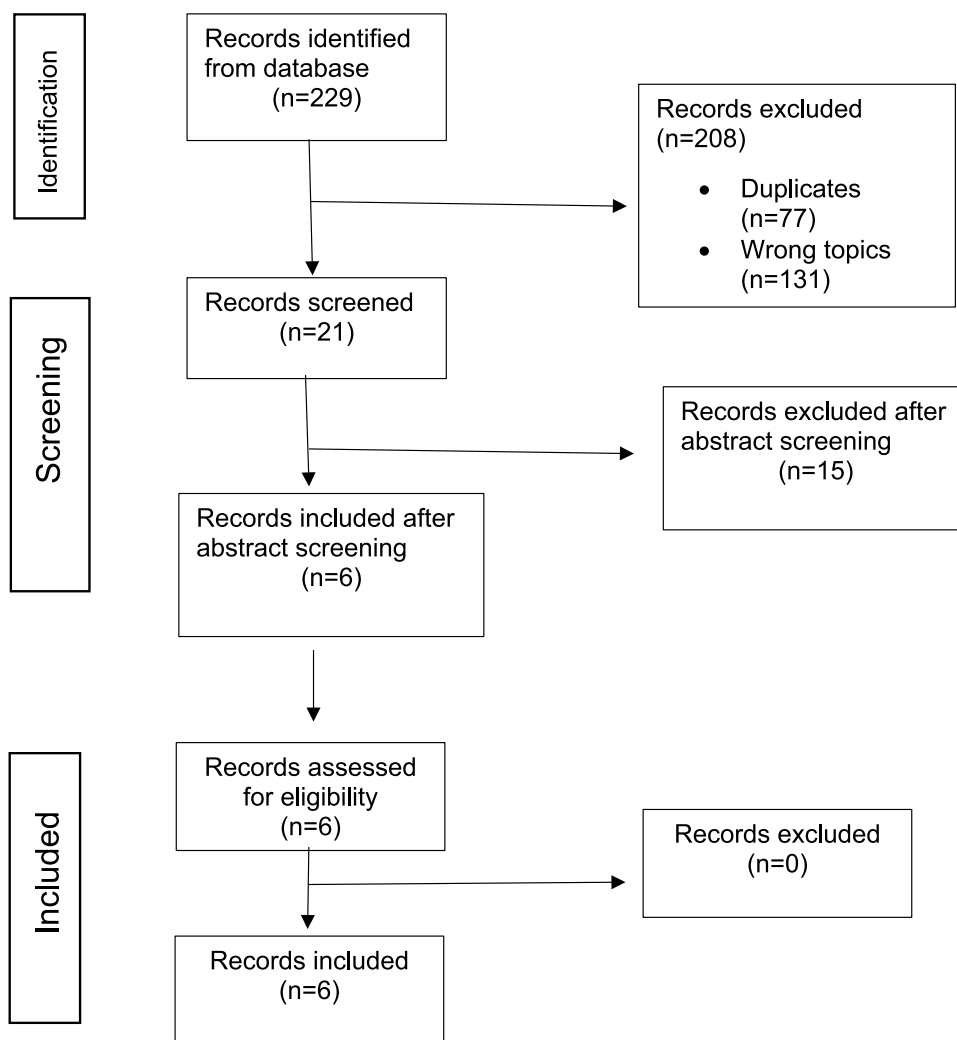
The SCOPUS, PubMed, and EMBASE databases were searched using a combination of the following keywords: atypical OR/AND uncommon OR/AND unusual, fetal OR/AND prenatal OR prenatally, cardiac AND/OR thoracic OR mediastinal, mass AND/OR tumors. This systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Only studies written in English language were considered available from 1987 to 2024, including one unpublished case from our personal experience.

Study selection, data collection, and outcomes

The PRISMA flowchart of study selection is shown in Fig. 1. Studies were included only when there was evidence of an atypical mass in the thorax or in the mediastinum. We defined as an atypical thoracic mass any lesion that cannot be classified prenatally in the six classical following categories: CPAM, PS, BC, CHAOS; mediastinal/pericardial rhabdomyoma and teratoma; alternatively atypical mass was also defined as a case with prenatal diagnosis in one of these six typical categories but for which the final diagnosis was completely different, giving an opportunity to describe potential differential diagnosis and appearance of rare thoracic masses.

Data concerning the prenatal diagnosis and pregnancy outcomes of atypical congenital thoracic mass were collected and recorded in a dedicated database by two different authors. The data collected were gestational age (GA) at diagnosis, prenatal or postnatal features and diagnostic method, GA at delivery and weight of the newborn, treatment and outcome including final diagnosis, both when this was conclusive or just suspected. Two authors (V.F. and C.P.) reviewed all articles independently and consensus was reached about relevance and inconsistencies. Any doubt and inconsistency were resolved by consulting a senior author (P.C.). This study did not require ethical approval. The patient involved in the research from our

Fig. 1 PRISMA flowchart summarizing study selection and inclusion in review



center provided a signed consent form approving the study and the use of their anonymized data for research purposes.

Study quality assessment

The National Institute of Health (NIH) tool for the quality assessment of Case Series Studies (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>; accessed on 10 December 2022) was used for quality evaluation of the comprised studies (Table 1). This method was recommended by the National Institute for Health and Care Excellence (NICE). The scores were established on the base of questions 1–9: “good” if principal factors were present (1, 6, 7); “fair” if two factors were present; and “poor” if one was present. A comprehensive assessment according to the Agency for Healthcare Research and Quality (AHRQ) was performed, the NICE and NIH standards were assigned to each study.

Results

The review of literature identified 229 studies, of which 223 were excluded and 6 were included in the analysis (Fig. 1) [14–19]. The reasons for calling the mass atypical were different and included: cases with prenatal diagnosis in one of the six typical categories, but for which the final diagnosis was completely different or was atypical for localization and size. The Table 2 shows the data of these six cases. The had a median GA of 31 (range, 21–38) weeks at prenatal diagnosis, which was made using ultrasounds in most cases and also MRI in some of them. Conception was never reported. Four cases were born at term of the pregnancy, two by a cesarean section. Two underwent surgery shortly after birth. Postnatally different diagnostic methods were used as CT scan, MRI and echocardiography and histologic examination. As evident from the table the histologic diagnosis in the two cases operated was different.

In two cases an intrauterine death of the fetus occurred at 24 and 34 weeks of gestation respectively, in one for the

Table 1 Quality assessment of cases series studies by National Institute of Health (NIH)

Author	1. Was the study question or objective clearly stated?	2. Was the study population clearly and fully described, including a case definition?	3. Were the cases consecutive?	4. Were the subjects comparable?	5. Was the intervention clearly described?	6. Were the outcome measures clearly defined, valid, reliable and implemented consistently across all study participants?	7. Was the length of follow-up described?	8. Were the statistical methods well described?	9. Were the results well described?	GRADE AHRQ
Isohata et al. [14]	Yes	Yes	NA	Na	Yes	Yes	Na	Na	Yes	Fair
Catán Valenzuela et al. [15]	Yes	Yes	NA	Yes	Yes	Yes	Yes	No	Yes	Good
Nazir et al. [16]	Yes	Yes	NA	NA	Yes	Yes	Yes	No	Yes	Good
Takeuchi et al. [17]	Yes	Yes	NA	NA	Yes	Yes	NA	NA	Yes	Fair
Guirgis et al. [18]	Yes	No	No	No	Yes	No	Yes	No	No	Fair
Eirich et al. [19]	Yes	No	No	No	Yes	Yes	No	No	Yes	Fair

Table 2 Main characteristics of included cases

Author	GA at diagnosis	Antenatal features and reasons for being atypical	Postnatal diagnostic method and features	Treatment	Delivery, GA and weight at birth	Outcome after 1 year
Isohata et al. [14]	31	US: left lung 4 cm mixed mass microvascular flow (CVR=0.41) MRI: T2-hypointensity Diagnosis: atypical CPAM	Autopsy: CPMT (congenital peribronchial myofibroblastic tumor)	–	VB, 34 + 5 weeks' 2330 g	Intrauterine death for tumor rapid growth
Catán Valenzuela et al. [15]	31 + 5	US: pulmonary lesion hyper-vascularized MRI: intrapulmonary unilobar cystic lesion with high signal in T2 and low in T1 Diagnosis: atypical CPAM	CT (arterial contrast): left hemithorax multilocular cystic mass with air content Genetic test: DICER1 (gene chromosome 14) Histology: pleuropulmonary blastoma type 1	Lobectomy, Chemotherapy	VB, 38 weeks' NA	Asymptomatic
Nazir et al. [16]	38	US: left side chest multicystic lesion, spleen was suspected in the chest Diagnosis: CDH	CT scan: cystic- solid mass in the mediastinum suggests mediastinal teratoma or a CPAM	Surgery Histology: cystic hygroma	Forceps, 40 weeks' NA	Asymptomatic
Takeuchi et al. [17]	21	US: solid bulky iperechoic pericardial mass at LV apex Diagnosis: bulky rhabdomyoma atypical for pericardial localization/size	Autopsy: rhabdomyoma protruded from the epicardial region of the apex into the pericardial cavity	–	VB, 24 weeks' 798 g	Intrauterine death for hydrops fetalis
Guingis et al. [18]	32	US: massive pericardial effusion with an intrapericardial mass Suspected pericardial teratoma atypical for localization and regression	X-ray, echocardiogram Mass and effusion disappeared at follow-up	Conservative	CS, 39 weeks' 4100 g	Asymptomatic
Eirich et al. [19]	32	US: homogeneous epicardial surface mass Suspect of pericardial teratoma	Echocardiogram: exophytic large epicardial mass CT scan biopsy: histology of intrapericardial rhabdomyoma	Oxygen supplementation	CS, 39 weeks' 2926 g	25% size decrease in the neonatal period
Fesslova (2023, unpublished)	19	US: hyperechoic thoracic mass, feeding vessel disappeared at 35 weeks' MRI: mediastinal pericardial mass Suspected PS or atypical rhabdomyoma	US, MRI Mass disappeared at follow-up	Conservative	CS, 37 weeks' 2550	Asymptomatic

NA not available, VB vaginal birth, CS cesarean section, MRI magnetic resonance imaging, CT computerized tomography, CDH congenital diaphragmatic hernia, CPMT congenital peribronchial myofibroblastic tumor, PS extralobar bronchopulmonary sequestration

hydrops in epicardial rhabdomyoma and in the second one for a rapid mass growth. Autopsy allowed to obtain a different diagnosis with respect to the prenatal one. In two cases operated the histologic diagnosis was obtained after surgery and resulted different. In the remaining two cases in which a conservative approach was chosen, the postnatal diagnosis was of an atypical pericardial teratoma in one and of a pericardial rhabdomyoma in the second one. Both cases showed regression after birth.

In two cases the prenatal diagnosis was CPAM: in one case, however, there was an atypical signal in the T2 sequences of the MRI which showed hypointensity and in fact the final histologic diagnosis was congenital peribronchial myofibroblastic tumour (CPMT) [14]; in the other one, although the prenatal ultrasound images were typical for CPAM, the postnatal diagnosis was different: a genetic syndrome due to mutation of the *DICER1* gene and with a compatible histology for pleuropulmonary blastoma type 1 [15].

The six case of the review was diagnosed prenatally as diaphragmatic hernia and only postnatally after a CT scan and surgery the correct diagnosis was the cystic hygroma [16].

All children born alive were asymptomatic after 1 year and without recurrence of the disease with a normal growth curve,

We are also reporting an unpublished case of our center with a mediastinal mass that underwent spontaneous regression after birth and that we present below.

Unpublished case

A 27-year-old nulliparous woman was sent at 19 weeks' gestation to our centre for a previous finding at fetal ultrasound of a mediastinal mass behind the left atrium—with an initial supposition of a possible rhabdomyoma. At the first trimester combined screening test an intermediate risk for trisomy 21 was found with biochemical markers (free β HCG and PAPP-A), while soft markers were normal. The non-invasive prenatal test (NIPT) demonstrated a low risk with a fetal fraction of 15%. The couple chose not to perform invasive diagnosis. A fetal echocardiography was performed at our center with a methodology aligned with current major guidelines [20] (Fig. 2, at 19 weeks). The intracardiac anatomy was normal, situs solitus with levocardia, normal atrioventricular valves without regurgitation, normal outflow tracts and great vessels. Aortic and ductal arches were normal and the descending aorta appeared of a normal size and pulsatility. Behind the left atrial wall and the left ventricular posterior wall a huge highly echodense mass was evident, extending toward the apex of the left ventricle, area of 3.0 cm² (circumference of 85.0 mm diameters: 16 × 12 × 22 mm). The mass apparently surrounded

and dislocated the heart (that was slightly rotated toward the left) and it was seen over the heart in different projections. A smallish echo-free cysts was also observed inside the mass with an initial diagnostic supposition at this time of a possible intrapericardial rhabdomyoma or of another atypical thoracic mass. No relevant pericardial or intraabdominal fluids were observed. Complete ultrasound evaluation of the whole fetal anatomy did not reveal additional structural problems, however a feeding vessel from the aorta to the mass was documented raising the suspicion of an atypical extralobar PS in the posterior mediastinum.

The diagnostic conclusion was not clear—in differential diagnosis both an atypical PS or rhabdomyoma were considered. No abnormality was found at the central nervous system MRI, done in view of a hypothesis of rhabdomyoma.

Serial ultrasound scans were performed until the 35 w.g., in the late third trimester a 20% volumetric shrinkage was observed without tracheal compression or deviation. In the latter stages of pregnancy, the blood vessel leading from the aortic arch to the mass was no more distinctly visible (Fig. 3).

An elective cesarean section was performed at 38 weeks and a female neonate was delivered weighing 2550 g, with Apgar score 9–10; breathing and lung function were normal with no ventilation or oxygen supplementation requirement.

A neonatal echocardiography performed a few hours after birth reassessed the presence of the hyperechogenic mass measuring approximately 21 × 16 mm at that point, with no compression on the left atrium or venous pulmonary returns.

At 1 month the features of the mass were unchanged and the baby returned to the country of origin to the attention of the local physicians. Since then good general conditions and a probable reduction of the mass were reported by them.

We have seen the baby again at 5 months—weighing 5 kg, the echocardiography showed inside the heart still a small atrial septal defect (patent oval fossa) with left-to-right shunt, the internal structures of the heart were normal, and around the heart we could not appreciate any retro atrial mass.

Discussion

Various rare tumors can develop in the fetal chest and heart. Congenital cardiac tumors are rare, with a prevalence of 0.01–0.05% [2, 3]. Rhabdomyoma, usually with an intracardiac localization and often with multiple masses, is the most common cardiac tumor in fetuses and infants and children, accounting for 60–86%, followed by fibroma, teratoma, myxoma, and haemangioma [2, 3, 8]. Known is also a frequent association of Rhabdomyoma to tuberous sclerosis (TS), an autosomal dominant condition, and so careful antenatal ultrasonography is required when the parents have

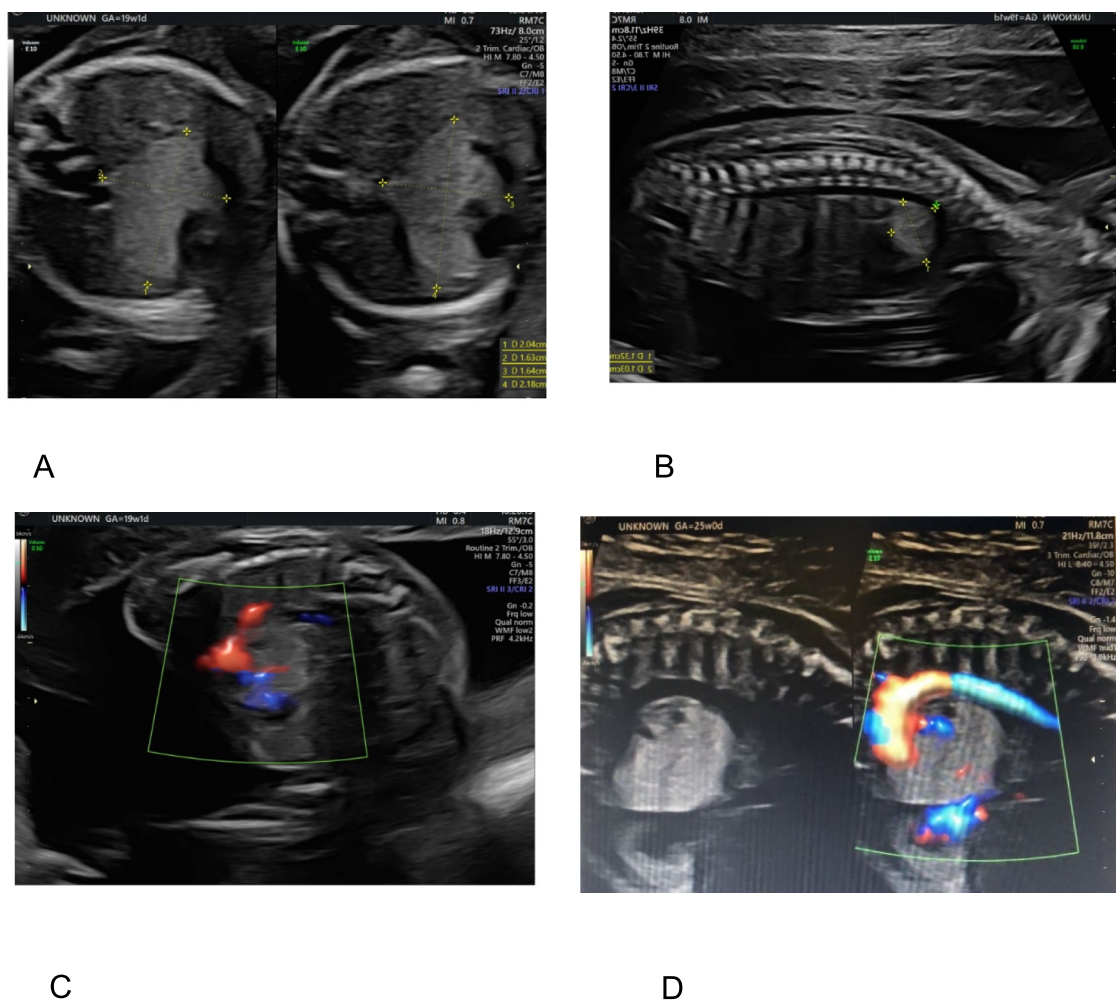


Fig. 2 At 19+1 weeks; homogeneous hyperechogenic thoracic mass measuring $16 \times 12 \times 22$ mm in the posterior mediastinum, adjacent to the left atrium of the heart, in the transverse section (A) and in the

longitudinal section (B). There appears to be a feeding vessel from the aorta to the mass with Color Doppler (C) and Power Doppler (D)

TS [21–23]. Retrocardiac—intrapericardiac position of our unpublished case at serial fetal examinations till birth could state for a rare form of rhabdomyoma. Effectively, in our experience we came through 2 cases with this location, one documented by a biopsy and histologic examination and the second one followed since the fetal life till 12 years [23] and also, in the literature a pericardial localization of rhabdomyoma was reported [24, 25]. Also, for this diagnostic supposition could state the fact of the regression of the tumor is known to occur spontaneously in rhabdomyoma both in presence or absence of TS [24]. Effectively, in our remote fetal case mentioned above [23] the mass progressively reduced completely, with no hemodynamic or rhythm problems. The regression process in rhabdomyoma is thought to be due to apoptosis [25, 26].

Supporting the diagnosis of rhabdomyoma with an atypical localization of our unpublished case is the fact that in our case the lesion progressively reduced and then completely

disappeared after birth, without hemodynamic or rhythmic problems. Effectively, the rhabdomyoma usually do not regress in pregnancy, but classically after birth. Obviously, we presented the limits of our supposition is the fact that we do not have a progressive postnatal examination of the baby between 1 and 5 months when the mass was no more evident. Our baby did not present signs of TS (on MRI, or clinically). On the other side, we cannot exclude completely a possibility of a PS in differential diagnosis considering the finding of a feeding artery observed at an early stage of pregnancy and that apparently regressed in utero. Effectively, the PS can regress spontaneously in pregnancy, after an embolization/obstruction of the feeding artery and a subsequent necrosis of the mass [6, 7, 27].

In the literature we found other reports of a huge pericardial rhabdomyoma without a hemodynamic compromise and another one that resulted in fetal death, to indicate a variable outcome of cases of R [28, 29]. Also, an isolated

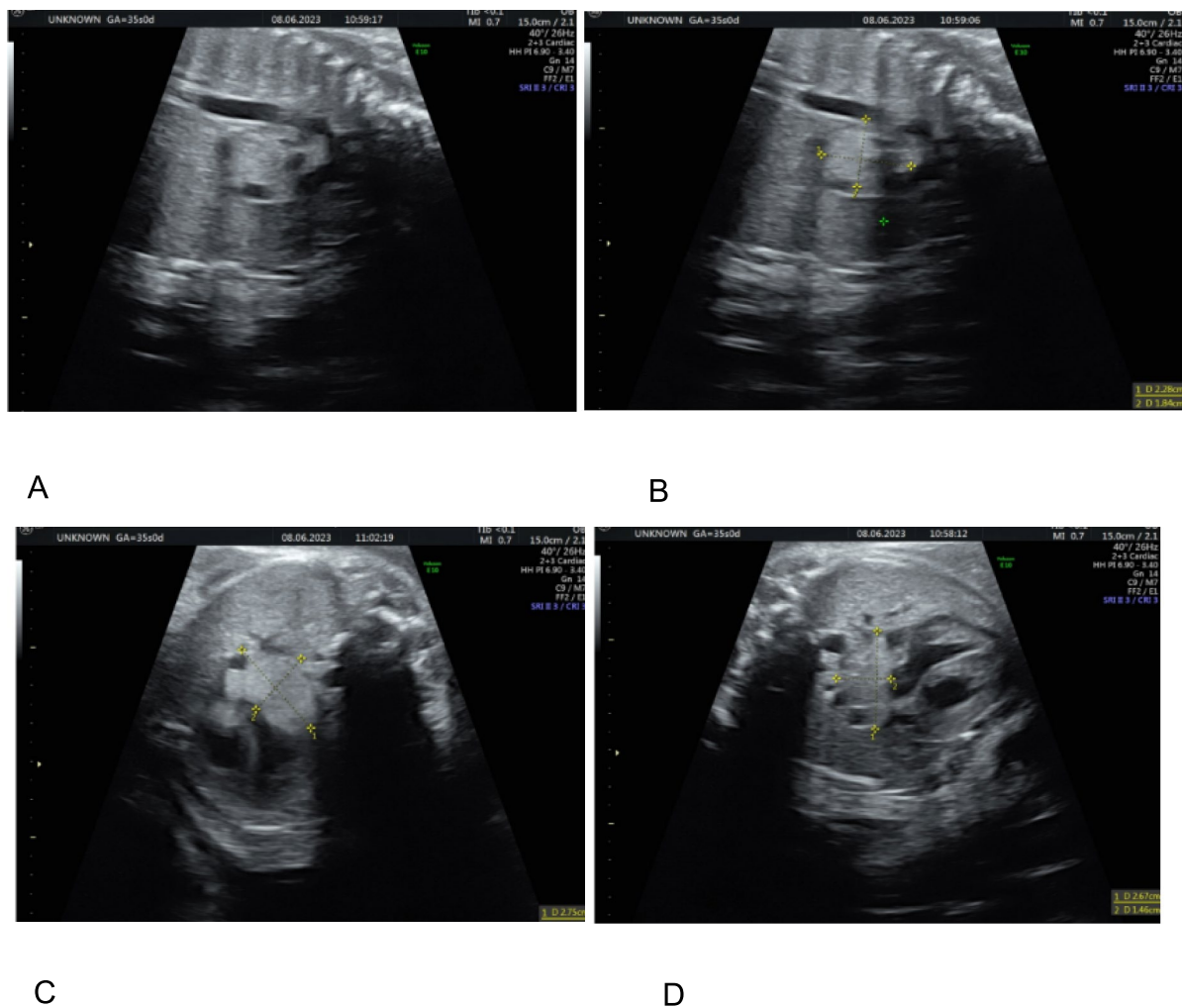


Fig. 3 At 35 weeks; there was a shrinking of the mass. Mid sagittal section, note the relationships that the mass contracts with the descending aorta, the feeding vessels originating from the concavity of the aortic arch/ascending aorta is not clearly visible (**A**, **B**). Cross

section, the mass showed diameters slightly smaller (22×16 mm) than previous measurements and there were no signs of pericardial effusion or hydrothorax (**C**, **D**). The mass is shown surrounded with relative measurements

report concerned a rare prenatally detected thoracic neuroblastoma [30].

In the six cases of the literature review the prenatal diagnoses were 2 CPAM, 1 rhabdomyoma and 2 pericardial teratoma, but also a congenital diaphragmatic hernia. As we reported in the results—the postnatal diagnoses based mainly on histology were often different, to show the difficulty of the diagnosis based upon ultrasound only.

Also, it is evident how it can be difficult the distinction between pericardial and mediastinal teratoma, because both these lesions appear as mixed cystic and solid masses with or without calcifications but mediastinal teratoma is a lesion above the heart within the anterior and superior thorax; while the pericardial teratoma is on the right of the heart [9, 11, 12]. In both these tumors there is usually a pericardial effusion.

Obviously, a correct postnatal differential diagnosis of the thoracic masses is necessary, for the management, prognosis and eventual surgery.

So, in conclusions, this work emphasizes that the diagnosis of thoracic masses is still a challenge.

It is evident from the reported cases of the literature that some thoracic masses may fall into the categories of typical thoracic masses in the prenatal period (CPAM, BS, cardiac tumors), but often in the postnatal period—after histologic examination the diagnosis may be different. Also some masses such as rhabdomyoma or teratoma can present in an atypical way in terms of location, size and spontaneous regression.

Furthermore, in interpreting fetal and neonatal chest masses, mediastinal cystic hygroma should be kept in mind as a potential differential diagnosis [16]. Masses close to the

diaphragm may be problematic to diagnose, particularly if they are cystic.

The presumed prenatal diagnosis of a mass gives the possibility to carry out the most possibly correct counseling to the couple, to establish an ultrasound follow-up and to plan the treatment. Obviously, the couple should be informed about a possibility of a different precise diagnosis after the postnatal evaluation.

The optimal approach should be prospective for each specific situation, as for the prognosis and the risks of various management choices. The main objective is to prevent an early premature delivery and fetal compromise, which is relatively frequent in case of thoracic anomalies [31].

Author contributions PI Cavoretto, V. Fesslova: Project development, data collection, manuscript writing. R. Mellone, A. Poloniato: Data collection and manuscript writing. A. Frigiola, M. Candiani, M. Evangelista: critical revision and supervision. C. Poziello: Literature review, manuscript writing and iconography. All authors have read and agreed to the published version of the manuscript.

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Data availability No datasets were generated or analysed during the current study. All data of this study are published in the manuscript, and they are represented by the pictures included and critical analysis of the literature summarized in the text and table. The corresponding author is available to provide further explanations upon reasonable request.

Declarations

Conflict of interest The authors declare no competing interests. Authors declare any personal circumstances or interest that may be perceived as inappropriately influencing the representation or interpretation of the reported research results.

Ethical standards This study was conducted in accordance with the ethical standards for human research established by the Declaration of Helsinki. The patient of the unpublished case series recruited at our center provided a signed consent form allowing their anonymized data to be used for research purposes.

Informed consent Informed consent was not deemed necessary for the patients recruited retrospectively since anonymous data collection was respected. The patient of our clinical case provided a signed consent form for publishing the anonymized data of the clinical case.

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