

Antenatal ultrasound diagnosis and neonatal results of the congenital cystic adenomatoid malformation of the lung

Diagnóstico ecográfico prenatal y resultados neonatales de la malformación adenomatoidea quística pulmonar

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Abstract

Introduction: Congenital cystic adenomatoid malformation (CCAM) is a rare congenital lung disease, and in the most of cases, prenatal diagnosis is feasible. There are discrepancies regarding prenatal management and postpartum treatment. **Objective:** To analyze prenatally diagnosed CCAM in our hospitals, in order to evaluate ultrasound findings with fetal and postnatal evolution. **Patients and Method:** Retrospective study of all cases diagnosed prenatally by ultrasound between 2005 and 2016 in two reference hospitals. The ultrasounds were performed using high-resolution ultrasound scanners, Toshiba Xario and Voluson 730 Expert Pro, with follow-up from diagnosis to delivery. The variables analyzed included gestational age at diagnosis, the characteristics of the lung lesion, associated malformations, cytogenetic study, the evolution of pregnancy, type of delivery, presence of respiratory distress, need for complementary imaging tests, pediatric clinical course, and necessary postnatal treatments. It was considered a resolution the total disappearance of the lesion in the prenatal ultrasound or that the postnatal chest X-ray showed no lesion. **Results:** 17 cases were prenatally diagnosed. The evolution ranges from the prenatal resolution of the lesion to the persistence after birth. Three patients voluntarily decided to have an abortion due to ultrasound findings of poor prognosis. Of the fourteen remaining cases there were no cases of fetal or neonatal deaths, one case required surgery after birth and four patients had mild symptoms during the first year of life. One case of false negative with neonatal death has been reported which necropsy reported as CCAM type 0. **Conclusions:** This pulmonary malformation presents good prognosis, excluding cases with fetal hydrops. Two-dimensional ultrasound is usually enough for diagnosis and follow-up. Computed tomography is the technique of choice to confirm the resolution of lesions after birth. Surgical treatment is preferable over conservative management, although it is unknown if the potential complications of this disease, even when asymptomatic, justify surgical morbidity.

Keywords:

Congenital cyst adenomatoid malformation;
Prenatal diagnosis;
Lung malformation;
Ultrasound

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Introduction

The congenital cystic adenomatoid malformation of the lung (CCAM) is a rare condition that affects the terminal bronchioles and occurs due to an alteration in embryogenesis between weeks five and seven of gestation¹. The overall frequency is unknown, partly due to the non-universal nature of prenatal ultrasound screening and partly because of the variety of diagnostic classifications and criteria. It is estimated from 1/25 to 1/35,000 live births².

Since the first histological characterization of CCAM in 1977 by Stocker et al¹, other classifications have subsequently been developed such as the *Armed Forces Institute of Pathology* (AFIP)³, which divides these lesions into five groups depending on the cyst size and cell characteristics (Tables 1 and 2). Currently, this classification is the most used although its acceptance is not universal for three reasons: there is some overlap between the types, there are unclassifiable forms and it is not applicable to cases that underwent surgery during the fetal period. Very recently, a radiological classification has been proposed, allowing comparison of results between different studies².

Prenatal diagnosis is possible using ultrasound techniques⁴. The differential diagnosis of fetal thoracic masses includes CCAM, congenital diaphragmatic hernia, bronchopulmonary sequestration, and much less frequently bronchogenic or enteric cysts, neuro-

blastoma, cerebral heterotopia, congenital lobar emphysema, mediastinal cystic hygroma, and unilateral bronchial atresia. The macrocystic CCAM can mimic the stomach and intestines of a hernia⁵. Sequestration, similar in its presentation, as a well-defined homogenous mass, is characterized by having an aberrant nutrient artery that does not present the CCAM. However, these two entities overlap in the CCAM-sequestration complex, having demonstrated the existence of hybrid lesions in surgically treated patients (histologically CCAM and in surgery a systemic artery is seen)^{6,7}.

Commonly, CCAM is a unilateral condition, mainly right, which may involve only one lobe or the entire lung parenchyma. Exceptionally, it has also been observed in the abdomen. It may be associated with polyhydramnios, non-immune fetal hydrops, ascites, mediastinal shift and, less frequently, other structural malformations. Classically, it is stated that the CCAM is not associated with chromosomal abnormalities⁸. The prognosis is variable and includes the possibility of spontaneous intrauterine resolution without observable abnormalities after birth^{4,9-11}. However, mortality due to pulmonary hypoplasia or moderate respiratory symptoms during childhood and even the persistence of lesions that can cause recurrent infections and evolve to malignant processes cannot be excluded^{12,13}. Surgery is usually necessary after birth¹⁴. In the fetal period, corticosteroid treatment, drainage, thoracoamniotic

Table 1. Stocker et al classification

Features	I	II	III
Quantity	1-4 cysts	Multiple	Homogeneous solid echogenic mass of microcysts
Size	3-10 cm	< 2 cm	Millimetric
Histology	Pseudo-stratified ciliated epithelium	Columnar or cuboidal ciliated epithelium	Cuboidal ciliated epithelium

Table 2. The Armed Forces Institute of Pathology Classification

Features	Type 0	Type 1	Type 2	Type 3	Type 4
Frequency	1-3%	65%	20-25%	8%	2-4%
Cyst Size	0.5 cm	10 cm	2.5 cm	1.5 cm	7 cm
Coating of cysts	Ciliated pseudo-stratified, columnar epithelium with goblet cells	Ciliated pseudo-stratified, columnar epithelium	Ciliated, columnar to cuboidal epithelium	Ciliated cuboidal epithelium	Plane
Mucous cells	Always	33%	Absent	Absent	Absent
Presence of cartilage	100%	5-10%	Absent	Absent	Unusual

shunt, and even open surgery have been described for cases that develop hydrops^{6,15}.

The CCAM continues to be the subject of research and discussion since there are disagreements in prenatal management and postpartum treatment, considering the possibility of preventive surgery even in asymptomatic lesions due to the risk of malignancy or developing complications during childhood, 3.2% of those who are born asymptomatic cease to be so^{2,16,17}. The objective of this study is to analyze cases of CCAM diagnosed prenatally in our sphere, with the objective of evaluating and comparing the ultrasound findings and malformations associated with fetal and postnatal evolution.

Patients and Method

We performed a retrospective study of consecutive cases of CCAM diagnosed prenatally by ultrasound between 2005 and 2016 in the two tertiary referral hospitals of Tenerife, the University Hospital of the Canary Islands (2500 deliveries/year) and the University Hospital of the Nuestra Señora de Candelaria (3000 deliveries/year). These hospitals are of reference for the western province of the Canary Islands with a total population of one million inhabitants. Together, per year, they perform 6000 fetal morphological ultrasounds from week 18-20 of gestation, and specialized pediatric consultations receive more than eleven thousand patients.

The ultrasound exams were performed by specialized gynecologists using high-resolution ultrasound scanners: Toshiba Xario and Voluson 730 Expert, following-up from diagnosis to delivery. We included fetal thoracic lesions detected by prenatal ultrasound suggestive of CCAM, with integrity of the diaphragm, which presented a greater uniform echogenicity (microcystic) or containing larger or smaller homogeneous low level internal echoes cysts, or that deviate cardiac axis.

To carry out the study, data from the patients' medical records have been compiled and the ultrasound images have been reviewed. The analyzed variables included gestational age at the time of diagnosis, characteristics of the lung lesion, associated malformations, cytogenetic study, evolution of pregnancy and type of delivery, the presence of respiratory distress, need for complementary imaging tests, pediatric clinical evolution, and necessary postnatal treatments. In the cases in which the patients opted for pregnancy termination (according to the current laws LO 9/1985 and LO 2/2010 article 15b), the report of the subsequent anatomopathological examination has also been obtained. The total disappearance of the prenatal ultrasound le-

sion or that the postnatal chest x-ray showed no lesion was considered as resolution.

Results

In the twelve years reviewed, 17 cases of CCAM were diagnosed prenatally, which are summarized in Table 3 and Figure 1. The average gestational age at diagnosis was 22 weeks (between 16 and 38) and the maternal age ranged from 25 and 39 years. The lung lesions were unilateral in all cases: seven cases in the right lung and ten in the left lung (Figures 2 and 3). The average gestational age at the time of delivery was 39 weeks and there were no cases of preterm birth or intrauterine growth restriction. There were no cases of intrauterine fetal death. In three cases, the patients decided on voluntary pregnancy abortion, one for aneuploidy (46XX/47XXX mosaic) and two of them because of poor prognosis due to severe displacement of the mediastinum. From the remaining 14 patients, nine of them (64.3%) had a vaginal delivery and in five cases (35.7%) a cesarean was performed due to routine obstetric indications.

Out of the 14 live newborns, two had mild respiratory distress at birth that was solved with usual support measures. Only one case required neonatal surgery, with resection of the lower lobe of the left lung and confirming the diagnosis of CCAM III through the subsequent anatomopathological study. It was observed one case of total regression of the lesion during the prenatal period and there were three cases (21.4%) of spontaneous resolution after birth, in the remaining cases, the lesions remained stable. There were no cases of postnatal death.

After delivery, different imaging techniques were used to confirm the diagnosis: in six cases chest x-ray, in one case nuclear magnetic resonance (NMR) and in seven cases computed tomography (CT).

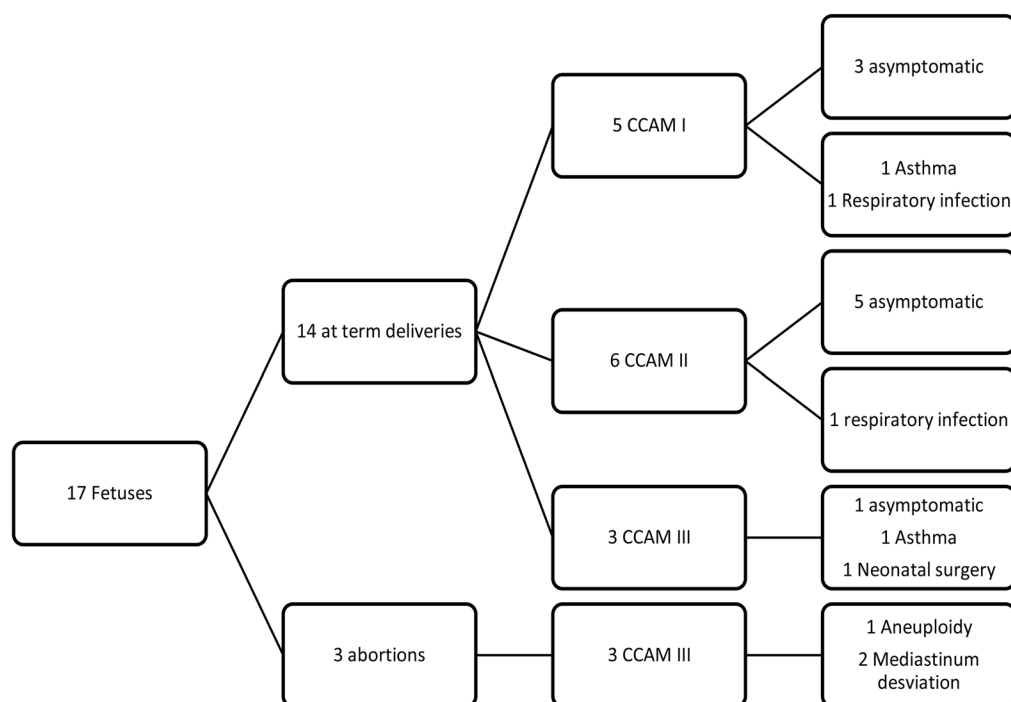
In addition to the 17 confirmed cases of CCAM diagnosed during the 12 years of the study, two false positives were detected: a fetal hydrops from which lung lesion was not confirmed at necropsy after voluntary abortion, and another case that after delivery was diagnosed with cystic lymphangioma. We also had a case of a false negative with suspicion of heart disease on ultrasound at week 20 which finally suffered neonatal death due to refractory respiratory failure and necropsy showed a type 0 CCAM. Considering this false negative and the three voluntary abortions, the final survival rate would be of 77.8%.

During the follow-up, 28.5% of the patients presented non-severe symptoms ranging from rhinitis and bronchial hyperreactivity to bronchospasm, asthma and recurrent respiratory infections.

Table 3. Summary of cases. Clinical findings and neonatal evolution

Case number	Gestational age at diagnosis	Sex	Type of CCAM	Lung	Malformations / Associated chromosomopathies	Outcome
1	20	F	III	Right	Mosaicism 47XXX / 46XX	Abortion
2	21	M	III	Left	Mediastinum deviation	Abortion
3	25	M	I	Left	No	Asymptomatic
4	21	F	II	Left	No	Asymptomatic
5	19	M	II	Right	No	Prenatal resolution
6	20	F	III	Left	Mediastinum deviation	Abortion
7	20	M	III	Left	No	Asthma
8	20	F	III	Left	No	Neonatal surgery
9	30	M	III	Left	No	Postnatal resolution
10	28	M	I	Right	No	Asthma
11	25	F	I	Left	Mediastinum deviation. 46XX inv-dup (15q)	Multiple respiratory infections
12	19	F	II	Left	No	Multiple respiratory infections
13	21	M	I	Right	No	Asymptomatic
14	20	M	II	Left	No	Asymptomatic
15	22	F	II	Left	No	Postnatal resolution
16	37	M	I	Right	No	Postnatal resolution
17	16	M	II	Right	No	Asymptomatic

GE: gestational age. CCAM: Congenital Cystic Adenomatoid Malformation.

**Figure 1.** Flow chart of the clinical course of the patients.

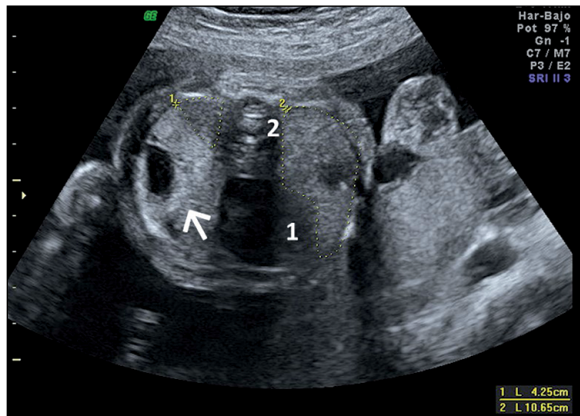


Figure 2. Two-dimensional ultrasound scan of transverse section of the fetal thorax at 25 weeks of gestation. CCAM type I. Case number 11.1: 1: Fetal heart; 2: Fetal spine; Arrow: Macrocyst; Dotted line: Healthy lung parenchyma.

Discussion

In twelve years, 17 cases of CCAM were diagnosed prenatally, which means a prevalence in our sphere of 1.7/10,000 live births. According to the EUROCAT (European Surveillance of Congenital Anomalies), the prevalence of CCAM is 0.87/10,000 births with a higher prevalence in males^{18,19}. In our series, 71% of the infants had a favorable outcome in the postnatal evolution, the worst prognosis corresponded to the type III CCAM.

It is a congenital pulmonary disease that could be detected in ultrasound from week 12¹⁸, however, the average gestational age of ultrasound diagnosis is around 20 weeks²⁰, as shown in our data. A meta-analysis of the King's College group summarizes its own experience, European and global, reporting survival of 97.2%, prenatal resolution in 29.6% and postnatal surgery in 62.7% of a total of 486 fetuses with CCAM and without hydrops²¹. Other authors, from a total of 69 lesions, found two tumors and 16 infections, but their series included both CCAM and lung sequestration and hybrid lesions¹⁷. According to published literature, our experience confirms that CCAM is a pulmonary pathology with a benign outcome and low perinatal mortality, which is not usually associated with morpho-structural growth defects^{10,22}.

In this study, following Stocker's classification, we had a similar number of type II and III CCAM cases (Table 3). There were two cases of chromosomal anomalies (11.7%), much higher than published. Some authors suggest carrying out a karyotype, although in this disease there are only about ten cases reported with trisomies 21, 13 or 18, and these were polymalformed fetuses⁸. In our hospitals, the karyotype is performed

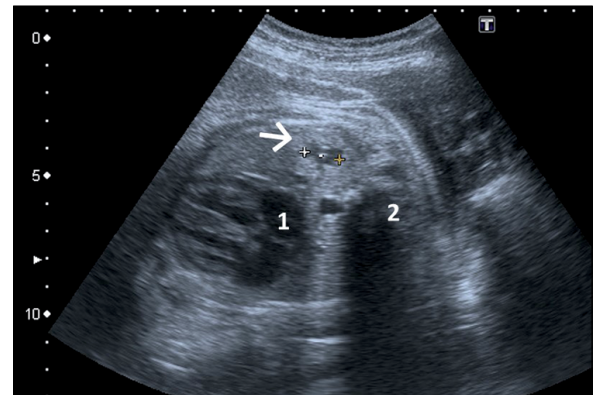


Figure 3. Two-dimensional ultrasound scan of transverse section of the fetal thorax at 19 weeks of gestation. CCAM type II. Case number 12. 1: Fetal heart; 2: Fetal spine; Arrow: Microcyst.

to all major malformation. In our series, 46XX/47XXX mosaic requested an abortion, and duplication-inversion of chromosome 15 was diagnosed at one year of age by CGH array to a girl, due to refractory epilepsy, having been the previous G bands karyotype normal.

Regarding imaging techniques, prenatal NMR can not only show the lesion size, but also the size of the remaining normal lung and its relation to the other lung, and it can also allow a differentiation between the CCAM and the congenital diaphragmatic hernia. In our series, it was not necessary to perform prenatal NMR, since the sonographic images did not present diagnostic doubts and there was no suspicion of a diaphragmatic hernia. It has also been described that 3D ultrasound allows visualization of multiple cystic areas < 1 cm that are not visible in 2D mode²³. In the 11 cases diagnosed at the University Hospital of the Canary Islands, complementary 3D ultrasound was used, but no additional information was obtained.

The prenatal resolution of the lesion should not be accepted as evidence of a true disappearance of the pathology: 45% of the lesions considered absent in the Nicolaides series were subsequently subjected to resection due to the existence of persistent lesions on CT²⁴. Radiography is only 60% sensitive, thus most of the authors perform CT at one month of life¹⁷. Therefore, CT is essential to show the presence, location, and size of the mass after birth. In our series, the total pre- or post-natal regression of the lesion was observed in 28.5%, which was subsequently confirmed in some patients by CT. In our center, early or serial CT is avoided in asymptomatic patients due to the need for sedation and the risk of ionizing radiation, although it may be performed in the event of clinical changes or the need for surgery.

Lung lesions, if large, can compress the esophagus,

leading to impaired swallowing, which results in polyhydramnios, compression of the ipsilateral lung leading to pulmonary hypoplasia, and mediastinal shift to the opposite side, causing a deterioration of cardiac venous return that can trigger the development of a hydrops²⁵. In any case, delivery in a tertiary center is recommended, preferably with availability of ECMO⁶.

Subgroups of fetuses with different probabilities of mortality or severe respiratory problems can be predicted based on the combination of polyhydramnios, fetal hydrops and a lung/chest ratio value < 2.5 ²⁶. However, discrimination value of these prenatal predictors is not enough for an appropriate decision making, with the fetal hydrops being the only negative prognostic element in terms of fetal-neonatal mortality^{11,22,27}. From our patients, the three who had prenatal factors of poor prognosis decided abortion of pregnancy (a case of aneuploidy and two cases of severe mediastinal deviation with cardiac dextroposition).

Therapeutic alternatives such as aspiration of the lesion or shunt with thorac-amniotic catheter have been described in those fetuses with a high risk of developing fetal hydrops²⁸ however, these techniques are not available in our sphere, neither the need for them in any case. On the other hand, the use of a single or repeated doses of betamethasone has been studied by several authors and series of small and non-randomized cases have been published (level of evidence III) that demonstrate the resolution of the hydrops and regression of the lesion, avoiding the need for surgery²⁹. Therefore, the option of fetal therapy, already with decades of experience³⁰, is reserved for large lung masses that produce hydrops, prior to week 32 of gestation, performing lobectomy or thoracoamniotic shunt in the case of a dominant cyst. Adzick describes 24 cases of open surgery where there were 11 cases of fetal death⁶.

In our study, one of the cases required surgery after birth, the rest received conservative management, although, in four out of the 14 cases (28.5%), complications such as recurrent infections and bronchospasms have been described.

An extensive review of childhood lung neoplasms revealed that 8.6% of malignancies were associated with previously documented cystic malformations^{12,13}. However, in our study, no cases of malignant progression of the lung lesions were documented, probably due to the short time of postnatal follow-up. Several

studies suggest that surgical management is the best therapeutic option, even in asymptomatic and stable lesions, due to the risk of malignancy and the lack of data about the follow-up period¹⁶.

Conclusion

Given the prenatal diagnosis of a CCAM in the absence of hydrops, the prognosis is favorable. Prenatally, an ultrasound follow-up is necessary and after birth, it is necessary to perform CT despite the fact that the lesion apparently has disappeared. Although postnatal surgical treatment is generally preferred, the question of whether the potential complications of an asymptomatic CCAM justify surgical morbidity has not yet been answered.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

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Authors state that no economic support has been associated with the present study.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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