Congenital cystic adenomatoid lung malformation: report of two cases and literature review

J. Argeitis[1], *M.D.*; D. Botsis[1], *Assoc. Prof.*; E. Kairi-Vassilatou[2], *Assist. Prof.*; D. Hasiakos[1], *Assist. Prof.*; K. Papakonstantinou[1], *M.D.*; A. Kondi-Pafiti[2], *Assoc. Prof.*

[1]2nd Clinic of Obstetrics and Gynecology and [2]Pathology Department, Aretaieion University Hospital, Athens Medical School, Athens (Greece)

Summary

Congenital cystic adenomatoid malformations of the fetal lung (CCAM) are rare embryonic developmental abnormalities. They are considered as benign hamartomatous or dysplastic lung tumors characterized by overgrowth of the terminal respiratory bronchioles at the expense of the saccular spaces. A minority of cases may not be identified by prenatal imaging techniques and the pulmonary lesions are recognized postnatally. Two cases of congenital cystic adenomatoid malformation of the fetal lung diagnosed in our institution during the last four years are reported. The ultrasonographic and pathologic findings of these cases are discussed.

Key words: Congenital cystic adenomatoid lung malformation; Type II; Ultrasound; Prenatal diagnosis.

Introduction

Congenital cystic adenomatoid malformation of the lung (CCAM) is an extremely uncommon fetal developmental anomaly characterized by an abnormal proliferation of the terminal bronchioles. [1].

CCAM of the lung is usually unilateral and involves part or all of one fetal hemithorax, with up to 15% of cases having bilateral involvement [1]. Polyhydramnios, fetal hydrops and hypoplasia of the contralateral lung may also be present due to compression from the abnormal lung tissue [1]. The cysts within the mass may be macrocystic (cysts ≥ 5 mm) or microcystic (cysts < 5 mm) [2]. The vascular supply for a CCAM mainly arises from the pulmonary vessels. Some communication may exist between the mass and the surrounding normal lung tissue.

The ultrasound differential diagnosis is based on the morphology of the cysts, the location of the lesion, the vascular supply as assessed by color Doppler analysis, and the lesion's effects on adjacent tissues and structures. The differential diagnosis includes various congenital abnormalities of the lung, such as pulmonary sequestration, bronchogenic cysts, diaphragmatic hernia, mediastinum cystic teratoma, and, less commonly, congenital lobar emphysema [2, 3].

In 1949, Chin and Tang [4] first reported a case of CCAM. The current descriptions are founded on studies from Stocker *et al*. [5] and Adzick *et al*. [6]. The Stocker classification is based on certain histologic findings but mainly the cyst dimensions, whereas the Adzick classification is based on the sonographic appearance of the cysts and cyst size. The prognosis varies from spontaneous resolution of the lung lesions in utero to perinatal death or no neonatal morbidity [1]. Sonography is essential for the prenatal diagnosis.

Revised manuscript accepted for publication July 9, 2007

Two cases of congenital cystic adenomatoid malformation of the fetal lung that were diagnosed in our institution during the last four years are presented. The ultrasonographic findings, postmortem pathology and etiology of this entity are discussed and the international literature is reviewed.

Case Reports

Case 1

The first patient was a 27-year-old, gravida 4, nulliparous, rhesus negative woman who was admitted to the 2nd Obsterics and Gynecology Department of Aretaieion Hospital at 24 weeks of gestation suffering from vaginal bleeding and possible spontaneous rupture of the membranes. Her personal history included three spontaneous miscarriages. The course of her pregnancy up to that point had been uneventful.

From the ultrasonographic examination a single fetus was found, fetal movements were normal and the placenta was adhered to the posterior uterine wall. There was a partial placental abruption and a hematoma had formed at the sight of the abruption. The biometric measurements were as follows: fetal biparietal diameter (BPD) 58 mm, head circumference (HD) 199.20 mm, fetal abdominal circumference (FAC) 153.31 mm and fetal femur length (FL) 33.20 mm. Ultrasonographically, the gestational age was calculated to be 20 weeks and four days and the gestational weight was estimated to be 482 g. Amniotic fluid was within normal levels. No fetal anomalies such as congenital diaphragmatic hernia, ascites, pericardial effusion were present. The left lung appeared to be full of small cystic lesions and the maximum diameter of these cysts was approximately 0.5 cm. Displacement of the fetal heart was also recognized. The right lung was not affected. These findings were considered to be a type-II congenital cystic adenomatoid malformation of the lung (Figure 1). During the following days there was a spontaneous rupture of the membranes and a male rhesus-positive fetus was delivered, weighing 465 g. Three hundred micrograms of Rh immunoglobulin (RhIgG) were administered to the mother.

Histopathology confirmed the above diagnosis of congenital

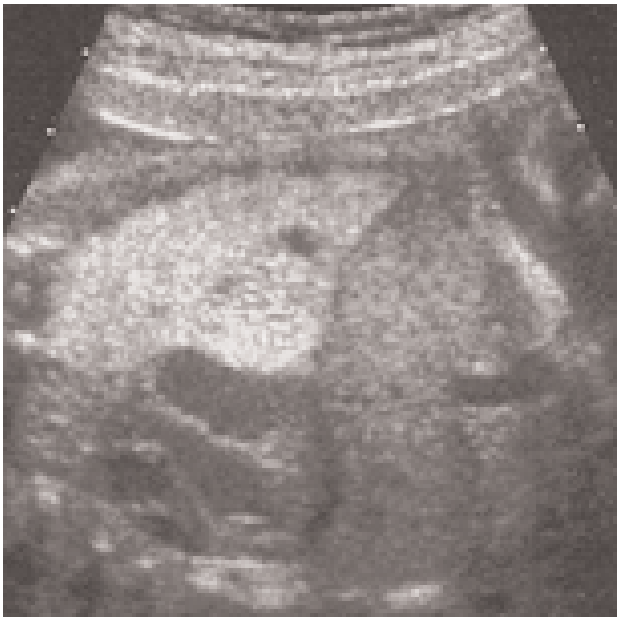

Figure 1. — Cross-section of the fetal thorax. The left lung appears to be full of small cysts. Displacement of the heart to the right. The right lung is not affected.

cystic adenomatoid malformation of the lungs. A retroplacental hematoma and recent infarcts were also confirmed. The cross section of the fetal thorax showed areas that contained cysts of 0.4 to 0.5 cm in diameter, surrounded by normal pulmonary parenchyma. The cysts resembled terminal bronchioles and were lined by ciliated cuboidal to columnar epithelium (Figure 2). Distended alveoli were present between the epithelium-lined cysts (Figure 3). The karyotype results showed 46, XY.

Case 2

The second patient was a 28-year-old, primigravida, rhesus-positive woman who was admitted to the 2nd Obsterics and Gynecology Department of Aretaieion Hospital at the 25th week of gestation with the symptom of spontaneous rupture of the membranes. Her personal history included a tonsillectomy, an appendectomy and hypothyroidism under treatment. The course of her pregnancy up to that point had been uneventful.

From the ultrasonographic examination a single fetus was found, fetal movements were diminished and the placenta was adhered to the anterior uterine wall. The biometric measurements were as follows: BPD 60 mm, HD 205.70 mm, FAC 197.92 mm and FL 41 mm. Ultrasonographically the gestational age was calculated to be 23 weeks and two days and the gestational weight was estimated to be 635 g. Amniotic fluid was absent. No fetal anomalies such as diaphragmatic hernia, ascites, or pericardial effusion were present. Due to the complete absence of amniotic fluid the couple had to terminate the pregnancy, which was carried out by means of misoprostol. A female rhesus-positive fetus was delivered, weighing 639 g.

Histopathology showed a congenital cystic adenomatoid malformation of the lungs, which was classified as type II. The cross section of the fetal thorax showed areas that contained cysts of 0.1 to 0.2 cm in diameter, surrounded by normal pulmonary parenchyma (Figure 4). The cysts resembled terminal bronchioles and were lined by ciliated cuboidal to columnar epithelium. Distended alveoli were present between the epithelium-lined cysts (Figure 5). The karyotype results showed 46, XX.

Discussion

Chin and Tang first described the most common intrinsic intrathoracic lesion that can be defined antenatally, CCAM, in 1947 [4]. Since then, it has been regarded as a rare cause of neonatal respiratory distress, and most of the reported clinical data have derived from postmortem and surgically excised material [5]. Although, the exact incidence of CCAM is unknown, there are reports that estimate the incidence of CCAM to be approximately one in 25,000 pregnancies [7].

Histopathologic classification of CCAM was first described in 1977. Stocker *et al*. classified congenital cystic malformations of the lung into three types based on certain criteria but mainly on the cyst dimensions [5]. All three are characterized by an abnormal proliferation of the terminal bronchioles, increased elastic tissue and polypoid columnar or cuboidal epithelial proliferation:

(A) Congenital cystic adenomatoid malformations of the fetal lung type I: The most commonly seen CCAM lesion is the Stocker type I, which accounts for 50-70% of the diagnosed cases [5]. This defect is composed of single or multiple large cysts (2 to 7 cm in diameter), that are confined to one lobe, and are filled with air or fluid. The cysts are lined by ciliated pseudo-stratified columnar epithelium. The wall of the cysts is quite thick and contains prominent smooth muscle and elastic tissue. Mucous-producing cells can be identified in one-third of the cases and cartilage in the wall can rarely be recognized. Relatively normal alveoli may be seen between the cysts. It is not unusual for these lesions to communicate with the normal bronchial tree. These lesions frequently result in mediastinal herniation. Only 11% of these lesions are complicated with associated anomalies. It has been estimated that 90% of these patients survive. Also the prognosis of the infant is good after the resection of the lesion [5].

(B) Congenital cystic adenomatoid malformations of the fetal lung type II: CCAM Stocker type II lesions are found in 18%-40% of the diagnosed cases, and are characterized by multiple evenly distributed, medium sized cysts (< 1.0 cm in diameter) that resemble terminal bronchioles [5]. The cysts are lined by cuboidal to tall columnar ciliated epithelium. The wall of the cysts has a thin layer of loose connective tissue and contains discontinuous bands of smooth muscle and elastic tissue. Strands of striated muscle fibers can be recognized. Distended alveoli are found between the epithelium-lined cysts. There is no identification of mucous cells and cartilage. CCAM type-II lesions have been associated with a higher incidence (50%) of other congenital anomalies and have a poor prognosis. These congenital anomalies include renal agenesis, bilateral renal dysgenesis, pulmonary sequestration, and congenital heart disease [5].

(C) Congenital cystic adenomatoid malformations of the fetal lung type III: Congenital cystic adenomatoid malformations of the fetal lung type III are identified in about 10% of the cases. These lesions are characterized by a large, bulky lesion with evenly distributed small

Fig. 2

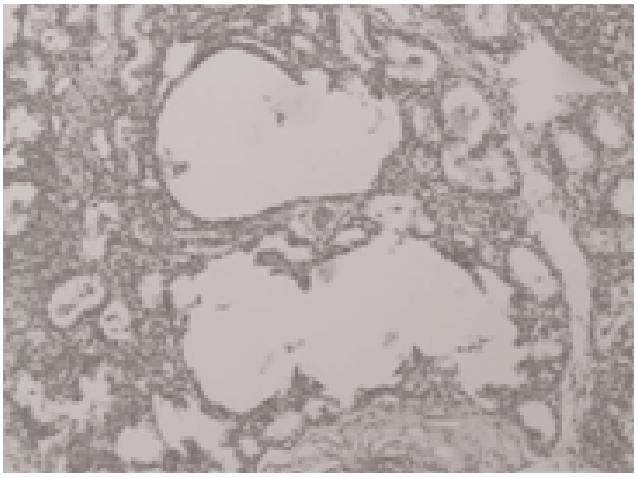

Fig. 3

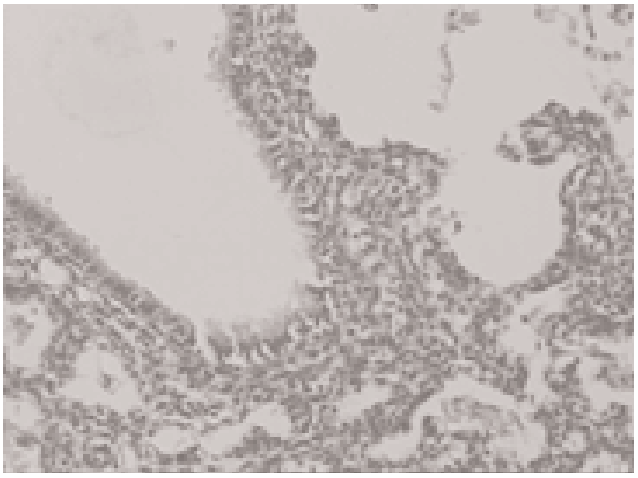

Fig. 4

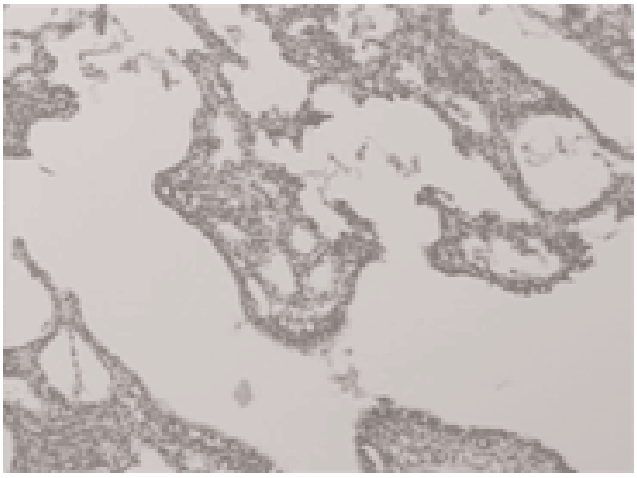

Fig. 5

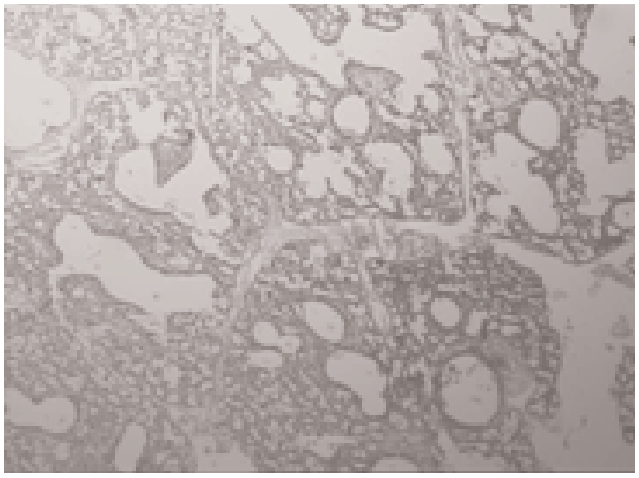

Figure 2. — Histological section of cystic spaces with a respiratory-type columnar epithelium (hematoxylin and eosin x 250).
Figure 3. — Histological section of the fetal lung with many cystic spaces (hematoxylin and eosin x 25).
Figure 4. — Histological section of the fetal lung with bronchiolus-like structures lined with columnar respiratory-type epithelium (hematoxylin and eosin x 250).
Figure 5. — Histological section of the fetal lung with distended alveoli (hematoxylin and eosin x 100).

cysts involving the whole lung or even both lungs. Mediastinal displacement is extremely common. CCAM type-III lesions have the worst prognosis [5].

An expanded concept of CCAM has been presented by Stocker, who has divided CCAM into five different categories based on the site of the defect in the tracheobronchial tree: 1) type 0 - acinar dysplasia, 2) type I - multiple large cysts or a single dominate cyst, 3) type II - multiple evenly spaced cysts, 4) type III - bulky firm mass, 5) type IV - peripheral cyst type.

In our cases the postmortem examination showed a congenital cystic adenomatoid malformation of the lungs, which was histopathologically classified as type II.

Congenital cystic adenomatoid malformations of the fetal lung can lead to pulmonary hypoplasia, mediastinal shift, polyhydramnios and hydrops, especially when the abnormally developed lung tissue reaches large proportions in utero [1, 2]. The development of fetal hydrops is a poor prognostic feature [1, 2]. Fetal hydrops is probably the result of a mass effect by the size of the CCAM on fetal swallowing (due to compression of the fetal esophagus) or decreased venous return following vena cava compression by the pulmonary mass or decreased myocardial contractility due to the extreme mediastinal shift caused by the lesion [1]. In these cases the prognosis of the fetus is adversely affected [1]. Polyhydramnios may also be present due to compression of the fetal esophagus or from increased fetal lung fluid production by the abnormal lung tissue [1]. In our cases there was no development of fetal hydrops, pulmonary hypoplasia, mediastinal shift or polyhydramnios.

The exact mechanism causing congenital cystic adenomatoid lung malformation is not clear, although this abnormality is considered to be the result of hamartomatous changes in the tertiary bronchioles or an arrest in their embryologic development between seven and 17 weeks of gestation [1, 3, 7]. The development of the fetal lung has been subdivided into five distinct periods based on the anatomical changes that occur in lung morphology: embryonic (3-7 weeks), pseudoglandular (7-17

weeks), canalicular (17-29 weeks), saccular (24-36 weeks), and alveolar (36 weeks to maturity). CCAM develops during the pseudoglandular period (7-17 weeks) [1, 3, 7].

The risk of recurrence of congenital cystic adenomatoid lung malformations in future pregnancies appears minimal since this embryonic developmental abnormality represents in most cases as a sporadic non-hereditary lesion [1]. In addition, this malformation is associated with certain genetic syndromes such as trisomy 18 [1]. In the cases we studied the fetal karyotypes were normal.

In the past, years before the advent of prenatal ultrasound imaging, the diagnosis of CCAM was made at autopsy or during investigation of respiratory disease in childhood. Garrett *et al*. made the earliest recorded ultrasound imaging diagnosis of CCAM in 1975 [8]. Improvements in ultrasound technology have led to an increase in the number of cases of CCAM diagnosed prenatally. In addition, the diagnoses are more precise and are made at earlier gestational ages.

The current sonographic descriptions are based on studies from Adzick *et al*. [6]. They classified congenital cystic malformations of the lung into two subgroups based on the sonographic appearances of the cysts and cyst dimensions: macrocystic CCAML, with cysts ≥ 5 mm and microcystic CCAML, with cysts < 5 mm. Reported prenatal prognostic features for CCAM include the size and type of the lesion, laterality, progression or resolution of the cysts, cardiac axis deviation, presentation with or development of hydrops, and findings of other structural anomalies [7]. The microcystic type tends to have a more adverse prognosis. On the other hand, lesions that regress have a better prognosis [7].

Prenatal ultrasound imaging demands special attention to the echogenicity of the lungs to detect fetal lung lesions. Disappearance of the lung lesions with spontaneous resolution in utero has been reported [9]. The initial size of the thoracic lesion may not always be helpful in predicting outcome since shrinkage of the lesion due to decompression of fetal lung fluid through abnormal channels to the bronchi and the gastrointestinal tract has been reported. Another possible explanation is that the pulmonary lesions outgrow their vascular supply and involute [1].

The identification of CCAMs as either cystic or solid is quite practical because it provides more useful categories for determining options and prognosis [6]. The majority of fetuses with CCAM detected antenatally have a good prognosis but continuous surveillance is required due to the unpredictability of growth patterns for CCAM lesions [7].

In the case of lung malformations, associated anomalies and chromosomal aberrations are rare. The rate of associated anomalies is given in the literature as 11% [1]. When other structural anomalies are recognized, a karyotyping analysis should be performed. Organs that may be affected are the kidneys (renal agenesis), the heart (truncus arteriosus communis, tetralogy of Fallot) and the gastrointestinal tract (atresia, diaphragmatic hernia). Hydrocephalus and skeletal malformations may also be found [1].

Pulmonary rhabdomyosarcoma (RMS) and bronchoalveolar carcinoma (BAC) are reported complications of CCAM [10]. Increased cell proliferation, decreased apoptosis and malignant transformation of the glandular component are considered to be carcinogenic mechanisms in CCAM. RMS occurs early in childhood (about 3 years) and should be treated by lobectomy and combination cytotoxic chemotherapy. In contrast, BAC accounts for about 15% to 20% of all lung cancers and its incidence appears to increase. The mean age that this carcinoma occurs is about 50 years; however, in those cases related to CCAM, there is an earlier presentation (about 20 years). In these tumors a prominent mucinous component can be found, and this seems to be particularly prevalent in associated cysts.

Newborn infants with congenital cyst malformations of the lung present varying degrees of respiratory difficulty [1]. Respiratory distress can develop not only from the lung hypoplasia or agenesis, but also because the abnormal cysts can fill with air and compress the adjacent healthy lung tissue after an infant takes its first breaths [6].

Current neonatal and pediatric management involves constant observation and stabilization within the neonatal unit. If respiratory distress is present then a computed tomography (CT) examination is performed and surgery is undertaken immediately. Otherwise, the CT examination is performed with the patient under general anesthesia at four to six months of age, and surgery is postponed until the patient is between six and 12 months old. Ten percent of the cases with congenital cystic adenomatoid malformations of the lung present with problems after the first year of life and they do so because of recurrent respiratory tract infections [1]. Thoracotomy with lobectomy is the treatment of choice. If the lesion is more extensive, further limited partial resection may have to be performed to avoid chest wall deformation.

Surgical operations have been performed for the correction of such fetal malformations, even on the fetus in utero [11]. However, if the malformation appears major and ultrasound indicates other associated problems such as hypoplasia of the remaining lung, then a poor outcome is to be expected [1]. In our cases the ultrasound scan that was performed on the first patient detected areas with small cystic lesions that were classified as a type-II congenital cystic adenomatoid malformation of the lung. No cystic lesions or other abnormal ultrasound findings were observed in the second patient. Both patients had to terminate the pregnancy because of spontaneous rupture of the membranes.

In conclusion, we have presented two rare cases of type-II congenital cystic adenomatoid malformations of the fetal lung and described the ultrasonographic and pathologic findings of this entity.

References

[1] Monni G., Paladini D., Ibba R.M., Teodoro A., Zoppi M.A., Lamberti A. *et al*.: "Prenatal ultrasound diagnosis of congenital cystic malformation of the lung: a report of 26 cases and review of the literature". *Ultrasound Obstet. Gynecol.,* 2000, *16,* 159.

[2] Gembruch U., Holzgreve W.: "The fetus with nonimmune hydrops fetalis". In: Harrison M.R., Evans M.I., Adzick N.S., Holzgreve W. (eds.), "The Unborn Patient", New York, WB Saunders, 2000, Vol. 1, 525.
[3] Sakala E.P., Perrott W.S., Grube G.L.: "Sonographic characteristics of antenatally diagnosed extralobar pulmonary sequestration and congenital cystic adenomatoid malformation". *Obstet. Gynecol. Surv.,* 1994, *49,* 647.
[4] Chin K.Y., Tang M.Y.: "Congenital adenomatoid malformation of one lobe of a lung with general anasarca". *Arch. Pathol.,* 1949, *48,* 221-229.
[5] Stocker J.T., Madewell J.E., Drake R.M.: "Congenital cystic adenomatoid malformation of the lung: classification and morphologic spectrum". *Hum. Pathol.,* 1977, *8,* 155.
[6] Adzick N.S., Harrison M.R., Glick P.L., Globus M.S., Anderson R.L., Mahony B.S. *et al.*: "Fetal cystic adenomatoid malformation: prenatal diagnosis and natural history". *J. Pediatr. Surg.*, 1985, *20,* 483-488.
[7] Laberge J.M., Flageole H., Pugash D., Khalife S., Blair S., Filiatraut D. *et al.*: "Outcome of the prenatally diagnosed congenital cystic adenomatoid malformation: a Canadian experience". *Fetal Diagn. Ther.,* 2001, *16,* 178.
[8] Garrett W.J., Kossoff G., Lawrence R.: "Gray scale echography in the diagnosis of hydrops due to fetal lang tumor". *J. Clin. Ultrasound,* 1975, *3*, 199.
[9] MacGillivray T.E., Harrison M.R.: "Disappearing fetal lung lesions". *J. Pediatr. Surg.*, 1993*, 28,* 1321.
[10] Ozcan C., Celik A., Ural Z., Veral A., Kandiloglu G., Balik E.: "Primary pulmonary rhabdomyosarcoma arising within cystic adenomatoid malformation: A case report and review of the literature". *J. Pediatr. Surg.,* 2001, *36*, 1062.
[11] Harrison M.R., Adzick N.S., Jennings R.W., Dunca B.W., Rosen M.A., Filly R.A. *et al.*: "Antenatal intervention for congenital cystic adenomatoid malformation". *Lancet,* 1990, *336*, 965.

Address reprint requests to:
A. KONDI PAFITI, M.D.
Assoc. Prof./Director
Pathology Department
Aretaieion Hospital
76, Vass. Sophias Ave.,
11528 Athens (Greece)
e-mail: akondi@med.uoa.gr