

Congenital Cystic Adenomatoid Malformation and Intrauterine Cystoamniotic Shunt

Konjenital Kistik Adenomatoid Malformasyon ve İntrauterin Kistoamniotik Şant

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ABSTRACT Congenital cystic adenomatoid malformation (CCAM) represents a spectrum of disease characterized by cystic lesions of the lung. It is a hamartomatous lesion secondary to cessation of bronchiolar maturation with overgrowth of mesenchymal elements and lack of normal alveoli. A 31-year-old woman carrying 22-weeks gestation fetus that has a large left-sided CCAM, severe mediastinal shift, and polyhydramnios admitted to our clinic. Cystic adenomatoid malformation volume ratios (CVR) were 1.76 and 3.37 at 25 and 27 weeks respectively. Thoracoamniotic shunting was performed after two ineffective cyst aspirations at 28 weeks of gestation. Volume reduction in the mass and improvements in mediastinal shift and polyhydramnios were detected thereafter. The woman delivered a female neonate, weighed 3150 gr by cesarean section at 37 weeks and 1 day of gestation. The neonate underwent left lung lower lobectomy by pediatric surgeon at 6th hour after delivery. Postprocedure and postpartum periods of fetus and mother were uneventful.

Key Words: Amnion; cystic adenomatoid malformation of lung, congenital; ultrasonography, prenatal

ÖZET Konjenital kistik adenomatoid malformasyon (KKAM) akciğerin kistik lezyonları ile karakterize olan bir hastalık spektrumunu temsil etmektedir. Konjenital kistik adenomatoid malformasyon normal alveollerin olmadığı, beraberinde mezenkimal elemanların aşırı büyüdüğü ve bronkiyal maturasyonun kesintiye uğramasına sekonder gelişen hamartömatöz bir lezyondur. Kliniğimize 31 yaşında, 22 haftalık fetusunda sol taraflı büyük bir KKAM, şiddetli mediastinal kayma ve polihidramniyoz tespit edilen bir gebe müracaat etti. Kistik adenomatoid malformasyon hacim oranları 25. ve 27. haftalarda sırasıyla 1.76 ve 3.37 idi. Fetusa 28. haftada, daha öncesinde iki defa yapılan etkisiz kist aspirasyonu sonrası torakoamniyotik şant uygulandı. Sonrasında kitle hacminde azalma, polihidramniyoz ve mediasten kaymasında iyileşme görüldü. Anne sezaryen ile gebelik 37 hafta ve bir günlük iken, 3150 gram ağırlığında bir kız bebek doğurdu. Yenidoğana doğum sonrası 6. saatte çocuk cerrahları tarafından sol alt lobektomi uygulandı. Şant işlemi ve doğum sonrasında anne ve yenidoğan problemsiz takip edildi.

Anahtar Kelimeler: Amniyon; akciğerin kistik adenomatoid malformasyonu, konjenital; ultrasonografi, prenatal

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Congenital cystic adenomatoid malformation (CCAM) of the lung is a rare, hamartomatous lesion secondary to cessation of bronchiolar maturation with overgrowth of mesenchymal elements and lack of normal alveoli.¹ The CCAM is almost always unilateral and lobar, generally involving 1 lobe or segment in more than 95% of cases; however, 2 lobes or the entire lung may be involved, and rare bilateral CCAM has been repor-

ted in fewer than 2% of cases.² Congenital cystic adenomatoid malformations communicate with the normal tracheobronchial tree, and their vasculature is typically supplied from the normal pulmonary circulation.^{1,3}

Ultrasonography and magnetic resonance imaging (MRI) are widely used in diagnosis. New imaging techniques ultrafast MRI and three-dimensional color Doppler ultrasound can differentiate CCAM from other lung lesions. The bronchopulmonary sequestration (BPS) and congenital diaphragmatic hernia (CDH) are the most common lung lesions that are confused with CCAM during prenatal evaluation.⁴

Stocker et al¹ categorized this lesion into 3 types primarily according to the cyst size. Adzick et al⁵ modified the classification of Stocker et al¹ They defined the lesion as macrocystic or microcystic based on the anatomic characteristics and sonographic appearance of CCAM. The prognosis of the disease is highly variable. The lesions may remain stable or may decrease in size or may have rapid growth pattern which proceeds to nonimmune hydrops and in utero death.⁶ Cystic adenomatoid malformation volume ratio predicts outcome in prenatally diagnosed CCAM of the lung.⁷ Options for the management of the disease are the pregnancy termination, observation with serial ultrasound scan or in utero therapy. In utero resection, fine needle aspiration (single or multiple) and/or thoracoamniotic shunt placement for long term cyst drainage are the recommended therapies for the disease.

We present a case of a large CCAM, treated with thoracoamniotic shunt. The clinical, patholo-

gical features and the surgical outcome were described. We also reviewed the literature.

CASE REPORT

A 31-year-old woman, (gravida 1) admitted to our clinic at 22 weeks of gestation for the routine prenatal evaluation on March 2004. Ultrasonographic examination revealed a large multicystic (5.7 x 4.0 x 3.7 cm) mass in the left lower lobe of the fetal lung, severe contralateral mediastinal shift and polyhydramnios. Amniotic fluid index was 22 cm. The right lung was compressed. Scalp edema, ascites, and placentomegaly were not present. There was a dominant cyst located in the center of lesion. By the color Doppler scan; the vascular supply of the lesion was from pulmonary artery. Venous drainage was to pulmonary vein. The fetal biometric measurements were appropriate for gestational age and no other anatomical abnormalities were detected on detailed ultrasonographic and echocardiographic survey. The cystic adenomatoid malformation volume ratio (CVR) was calculated according to the report of Crombleholme et al.⁷ It was higher than 1.6 during initial evaluation at 22 weeks of gestation. A normal karyotype was determined by cordocentesis. The patient was followed by serial weekly ultrasound scans until 25 weeks of gestation. The lesion and dominant cyst continued to grow and CVR reached to 1.76 at 25 weeks of gestation (Table 1). The dominant cyst was aspirated at 25 and 27 weeks of gestation and 22 ml and 45 ml fluid were obtained respectively. The CVR reached to 3.37 at 27 weeks of gestation. Rapid reaccumulation of fluid in macrocyst following two thoracocentesis was detected. The patient and her family recei-

TABLE 1: Volumes of dominant cyst and cystic adenomatoid malformation (CAM), the values of cystic adenomatoid malformation volume ratio, (CVR) and intrauterine invasive procedures.

Gestational Age (Wk)	Dominant Cyst Volume (ml)	CAM Volume (ml)	CVR	Intrauterine invasive procedures
25	34.3	43.8	1.76	Aspiration of the dominant cyst (22ml)
27	49.1	95.4	3.37	Aspiration of the dominant cyst (45ml)
28	50.6	102.3	3.36	Thoracoamniotic shunt placement
33	2.8	41.8	1.35	
34	2.5	51.1	1.54	
36	2.4	51.3	1.56	

ved prenatal counseling. The patient was also consulted with obstetrician, fetal pediatric surgeon and psychologist. The patient accepted the thoracoamniotic shunt placement. The dominant cyst was shunted to amniotic cavity using a double pigtail silastic catheter (Rocket catheter, Rocket medical, Watford, UK) at 28 weeks of gestation. Shunting was performed in the labor and delivery area, as an outpatient, under continuous ultrasound guidance with intravenous sedation (midazolam, morphine) of the mother and fetus (Figure 1). Following shunt placement, ultrasound was repeated every 2-3 days for 7-10 days to evaluate the therapy progress. The volumes of dominant cyst and CCAM decreased, CVR became <1.6, swallowing function and mediastinal shift improved partially, as a result polyhydramnios resolved following the shunting. When clinical improvement and continued shunt function were documented, the patient was followed with weekly ultrasounds to check for shunt function and reaccumulation of the fluid. Prenatal corticosteroid was not administered to the patient. The fetal hydrops did not develop during the course of pregnancy. Magnetic resonance imaging at 35 weeks of gestation showed; decrease in the volume of macrocystic lesion, contained 3 cysts as large as 2.5 cm in diameter, contralateral mediastinal shift, compressed left middle lobe and right lung (Figure 2 A,B). The patient delivered a female neonate, weighed 3150 g by cesarean section due to nonvertex presentation at 37 weeks and 1 day of gestation. The first and 5th minutes of



FIGURE 1: Ultrasonographic appearances of the lesion and the dominant cyst before shunting.

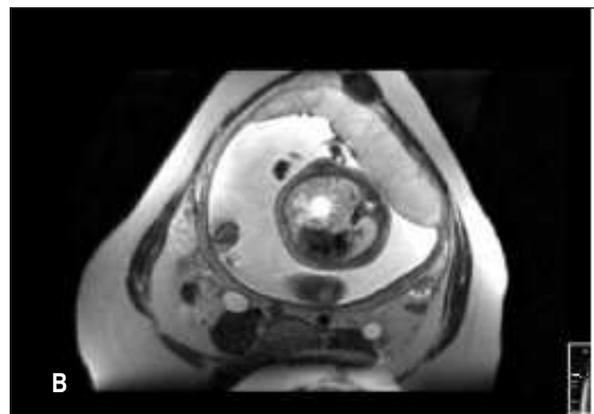


FIGURE 2: (A) Sagittal T2-Weighted magnetic resonance imaging of the lesion. The thoracoamniotic shunt is seen at the bottom of the dominant cyst at the 35 weeks of gestation. (B) Axial T2-Weighted magnetic resonance imaging of the lesion at the 35 weeks of gestation

Apgar scores were 9 and 7 respectively. Spontaneous pneumothorax developed because of the direct communication with the tracheobronchial tree at 10th minute postpartum; therefore tube thoracostomy was placed to the left hemithorax. The neonate with macrocystic CCAM underwent left lung lower lobectomy by pediatric surgeon at 6th hour after delivery. On gross examination, the tumor was multicystic and measured 10x7x2.5

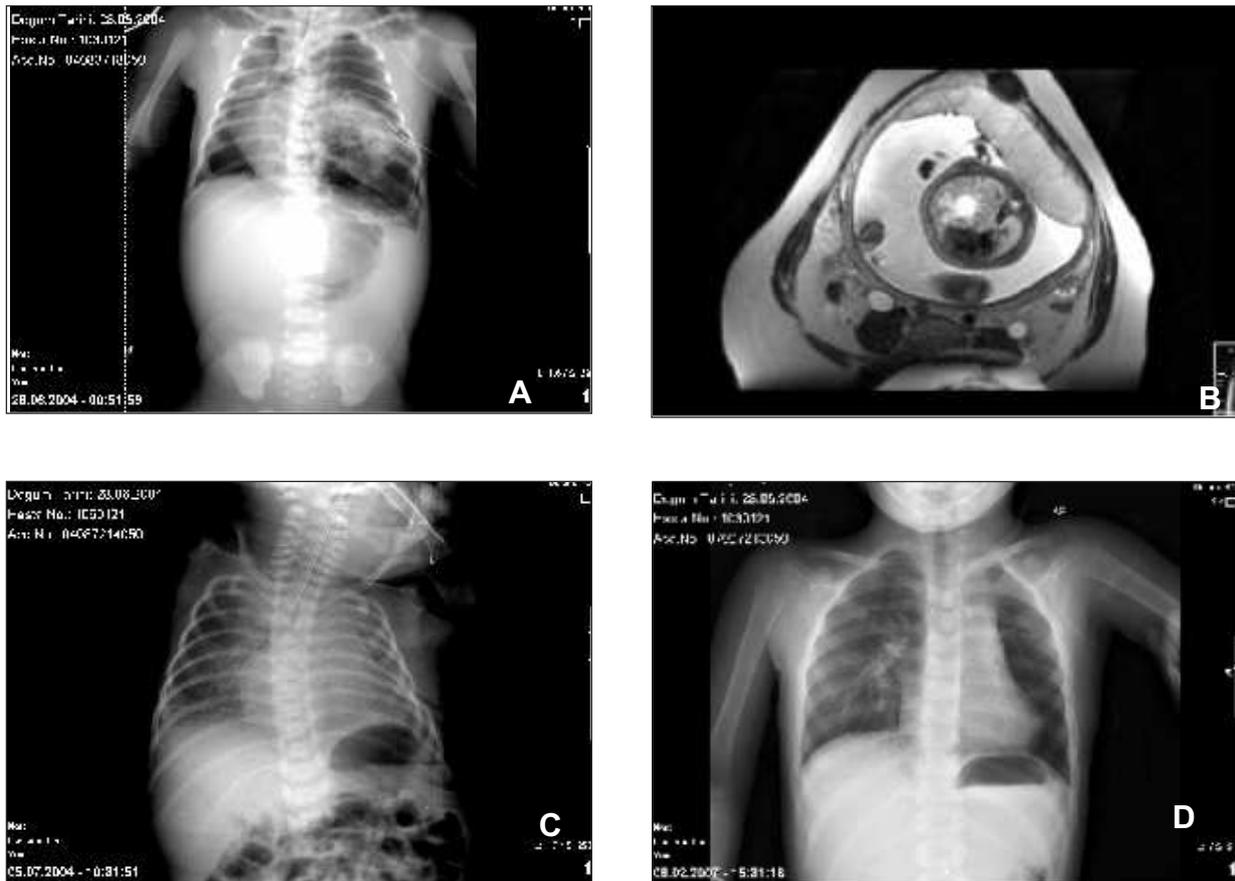


FIGURE 3: (A) Antero-posterior chest X-ray, soon after birth, shows left sided cystic adenomatoid malformation (CAM) mass and thoracoamniotic shunt which was inserted prenatally within the CAM mass. Right sided mediastinal shift due to CAM and endotracheal tube are also seen (B) Chest X-ray, after lobectomy shows pneumothorax of the left side. (C) Chest X-ray just before the removal of lung tubes shows no pneumothorax. (D) Late control chest x-ray demonstrates diminished left lung volume but normal lung markings and aeration.

cm, contained cysts as large as 4.5 in diameter, lined by ciliated columnar epithelium. Mucous glands and smooth muscle tissue were detected in the cyst walls. The surrounding lung parenchyma was congested. Histologically; the lesion was classified as type 1 CCAM. Neither infection nor malignancy was detected in the lesion. The postoperative course of neonate was uneventful. Mediastinal shift improved completely and compensatory expansion of the right lung and the remaining left lung were detected during follow up period (Figure 3 A,B,C,D). Institutional ethic committee and the mother approved the case, to be presented as a report. Now the baby is receiving follow up care and she has no evidence of disease after 32 months of follow up.

DISCUSSION

Congenital cystic adenomatoid malformation is the most common chest lesion, represents 75% of all lung lesions prenatally. It has sporadic inheritance with no recurrence risk. Associated abnormalities may be seen in 3-12%.⁸ The pathogenesis of CCAM is still unclear. Various etiologies such as overgrowth,⁹ hyperplasia,¹⁰ and hamartoma¹¹ have been suggested to describe the pathogenesis of CCAM. However it has been believed by all that the defect occurred at the level of the bronchiole.

Different type of classification systems of CCAM have been proposed by different authors. Stocker et al¹ collected 38 cases between 1917 and 1975 and defined three types of CCAM based on

cyst diameter and predominant cell types on histological examination. Type I lesions are composed of relatively well-differentiated bronchi. Cartilage is rarely seen. They tend to be large lesions with one or more cysts that are usually several centimeters in diameter, frequently producing mediastinal compression, lined by a ciliated pseudostratified columnar epithelium. The walls of cysts contain prominent smooth muscle and elastic tissue. Mucus producing cells are present in one-third of cases. Relatively normal alveoli may be seen between the cysts. Prognosis is good. Type II lesions consist of much smaller and more numerous cysts, usually less than 1 cm in diameter, lined by a ciliated, columnar, or cuboidal epithelium. Mucus cells and cartilage are absent and rarely striated muscle fibers may be seen. This group has significant associated anomalies and therefore a poor prognosis. Type III malformation is typically large and homogeneously echogenic, with many tiny cystic lesion. Histologically the mass is composed of regularly spaced, alveolus-like structures lined by ciliated cuboidal epithelium and separated by masses of alveolus-sized structures, lined with non-ciliated cuboidal epithelium. This subgroup also has a very poor prognosis. In a subsequent study Stocker expanded his classification to five types based on the site of origin of the malformation: tracheal, bronchial, bronchiolar, bronchiolar/alveolar duct and alveolar/distal acinar.¹² Adzick et al⁵ proposed a modification of the classification of Stocker et al.¹ based on the anatomic characteristics and sonographic appearance of CCAM. Macrocystic CCAMs have single or multiple cysts of 5 mm or greater in maximal diameter. These lesions are variable in size; however, the macrocysts can be readily seen by sonography. Microcystic CCAMs are more bulk and solid, often appearing homogeneously echogenic because of many fine acoustic interfaces.¹ These lesions correspond to the type II-I CCAM of Stocker et al¹ and may contain a few scattered cysts that are less than 5 mm in diameter. This classification into two types has become the gold standard of in-utero CCAM diagnosis.¹³

Fetal ultrasound, echocardiogram, ultrafast magnetic resonance imaging (MRI) and amniocentesis are used in patients with a known or suspected diagnosis of CCAM for diagnosis or differential diagnosis. Ultrafast MRI and three-dimensional ultrasound Doppler allow more accurate diagnosis and may supply prognostic considerations.¹⁴ In our case we performed firstly detailed and thereafter serial sonographies, color flow Doppler scans and echocardiography to identify nature and behavior of the lesion, its vascular supply and cardiac structure. Therefore MRI may not be needed if you can reach to the accurate diagnosis with sonography.

Congenital cystic adenomatoid malformation must be differentiated from other masses or neoplasms of the lung. A variety of conditions of the lung such as BPS, hybrid lesion CDH, congenital lobar emphysema, tracheal or bronchial atresia, bronchogenic cyst, esophageal duplication cyst, neurenteric cyst and teratoma, may simulate CCAM. Bronchopulmonary sequestration appears to be well-differentiated echodense, homogeneous mass, similar to microcystic CCAM on prenatal ultrasonography and its vascular supply is from aorta. Bronchopulmonary sequestration is 90% left sided and ipsilateral pleural effusion is highly suggestive. Detection by color flow Doppler of a systemic artery arising from the aorta to the fetal lung lesion is pathognomonic feature of fetal BPS.^{8,15} However; if differentiation can not be achieved by color Doppler, ultrafast fetal MRI might help differentiate CCAM from BPS.¹⁶ The diagnosis of a hybrid lesion, which consists of histologic elements of CCAM and BPS, is suggested when a systemic feeding vessel is identified in a complex lesion with cystic and solid components.¹⁷ Intra-abdominal extralobar sequestration is usually located in the upper left abdomen as an echogenic mass, may be confused with suprarenal masses, however diagnosis of BPS is confirmed by the demonstration of systemic feeding artery. There are no diagnostic hallmarks for the specific prenatal diagnosis of an intralobar sequestration. Congenital cystic adenomatoid malformation must be differentiated from CDH which is

diagnosed if intrathoracic stomach or bowel loops are identified. Unilateral pulmonary agenesis, in which high airway obstruction occurs, may result in sonographic findings similar to those of a large microcystic CCAM.¹⁸ Congenital airway obstruction syndrome may simulate bilateral CCAM. This condition is secondary to obstruction of the upper airway, causing symmetrical enlargement and increased echogenicity of both lungs because of retention of fetal lung fluid with overdistention of the contralateral lung. Sagittal views of the neck in these cases typically show distended, fluid filled trachea and bronchi, which confirm the diagnosis.⁶

Congenital cystic adenomatoid malformation is a broad spectrum of disease with highly variable outcomes. These lesions may remain stable or may decrease relatively in size with a slower growth rate compared with the uninvolved fetal lung. They may grow slowly over time, maintaining a constant relationship with fetal growth. Alternatively, they may spontaneously regress, decreasing absolutely in size and becoming less apparent during gestation because of echotexture changes. And finally CCAMs may have a rapid growth pattern resulting in nonimmune hydrops and in utero demise. The physiologic mechanism of fetal CCAM is not well known, therefore there are no sonographic or pathologic features that will currently allow us to distinguish between lesions that will regress and those that will progress to hydrops in utero or cause severe cardiorespiratory impairment at birth.¹⁹⁻²² We now know that the single most important predictor of outcome is overall CCAM size. Those that have no growth, partial regression, or even complete resolution are associated with virtually 100% survival. In contrast, large CCAMs that have a rapid or gradual increase in size can cause a direct mediastinal compression that impair cardiac function, obstruction of venous return.²³ Such lesions are far more likely to eventually have full-blown hydrops compared with relatively small lesions with little or no mediastinal shift and absence of cardiac dysfunction.

The sonographic measurement of CVR at presentation in late second and early third trimester is an accurate predictor of outcome in fetuses diagnosed with CCAM. The volume of CCAM is determined by sonographic measurement using the formula for ellipse (length x height x width x 0.52). A CVR was calculated by dividing the CCAM volume by head circumference to correct for fetal size. In fetuses with CVR <1.6 at presentation, 86% did not progress to hydrops. The accuracy of CVR in predicting a favorable outcome is enhanced by eliminating fetuses with a CCAM containing a dominant cyst. In this case, 97% of fetuses with CVR < 1.6 did not have hydrops ($P < .001$).⁷ Presence of dominant cyst appears to be a poor prognostic factor. The survival rate in CCAM without the development of hydrops is 100%. However, if left untreated, CCAMs associated with hydrops almost are uniformly fatal.²⁴ Cystic adenomatoid malformation volume ratio < 1.6 also was found to be significantly correlated with survival because 94% of these fetuses survived. Conversely, CVRs greater than 1.6 were correlated with a poorer outcome with only a 53% survival rate. The CVR might be useful in selecting fetuses that are at risk for hydrops and thus need close ultrasound observation and possible fetal intervention. The CCAM growth usually reaches a plateau by 28 weeks' gestation. It can be recommended that for fetuses less than 28 weeks old, twice weekly ultrasound surveillance if the CVR is greater than 1.6 and initial weekly surveillance for fetuses that have smaller CVR values.¹⁸ In our case the CVR value was 3.36 at 28 weeks and there was a dominant cyst in the lesion therefore we decided to perform thora-coamniotic shunt placement before development of fetal hydrops

Recommendations for management depend on the size of the lesion or CVR⁷ development of fetal hydrops, gestational age of fetus, and maternal health. Options for the management of the disease are the pregnancy termination and fetal resection, observation with serial ultrasound scan or in utero therapy. Conservative management is indicated in cases of CCAM without acute polyhydramnios or hydrops.²⁵ If pulmonary maturity is established and hydrops evolves, the fetus should be emergently

delivered by the ex utero intrapartum treatment (EXIT) procedure and the lesion should be resected while the neonate is on the uteroplacental circulation.²⁶ If significant respiratory compromise is present after resection, the fetus can be placed directly on extracorporeal membrane oxygenation (ECMO) support for salvage. Fetuses between 32-34 weeks with evolving hydrops should undergo steroid induced lung maturation followed by ex utero intrapartum strategy, with surfactant administration and surgical resection. Maternal betamethasone might impair CCAM growth in some cases and lead to amelioration of hydrops. In utero therapy should be performed if fetal hydrops evolves, prior to 32 weeks of gestation.²⁷ The decision when to stop observation and consider in utero therapy is not actually well defined. Laberge et al²⁸ proposed intervention for the development of hydrops before 30 weeks, prolonged severe lung compression or severe polyhydramnios. The criteria of prolonged lung compression have not been well defined. In utero resection, fine needle aspiration (single or multiple) and/or thoracoamniotic shunt placement for long term cyst drainage, and laser ablation therapy are included in utero treatment modalities.¹⁴ Fetal thoracentesis alone may not be sufficient for treatment because of rapid reaccumulation of cyst fluid.²⁹ Thoracentesis usually served as a temporizing maneuver before shunt placement or resection. We fulfilled two ineffective cyst aspirations in order to follow the growth nature of the lesion before shunt placement which is a more invasive intervention. Thoracoamniotic shunting is performed in cases with large predominant cyst if there is no a large solid component of the CCAM. Although aggressive fetal therapies like thoracoamniotic shunting can be applied to CCAM, there is no clear consensus regarding their indications? In a prospective cohort study including 33 cases with a prenatal diagnosis of CCAM of the lung thoracoamniotic shunting was offered only in nine macrocystic cases with acute polyhydramnios or hydrops. Four cases were diagnosed postnatally as sequestrations. Of 12 cases complicated by acute polyhydramnios or hydrops, 5 survived (1 type III with spontaneous incomplete

resolution in utero, 4 types I with substantial volume reduction after shunting). The 17 cases without acute polyhydramnios or hydrops were managed conservatively and survived. It has been concluded that conservative management is indicated in cases without acute polyhydramnios or hydrops.²⁵ Thoracoamniotic shunting applied in appropriate cases give rise to the favorable outcomes. In a retrospective study of 10 patients 8 satisfied the in utero fetal treatment criteria (macrocystic CCAM and fetal hydrops) thoracoamniotic shunting has been applied. It has been reported that successful shunting resulted in the prolongation of pregnancy in the 3rd trimester, significant mass volume reduction by %50, resolutions of the hydrops over 7-10 days, and improvement of survival.¹⁴ In a case study Baxter et al³⁰ have managed nine hydropic CCAM pregnancies using thoracoamniotic shunting. The mean pre- and postshunting mass volumes were 46.3 and 18.1 cc, respectively, representing a 61% mean reduction in mass volume following shunt placement. Hydrops resolved following shunting in all cases. The average shunt to delivery time was 13 weeks and 2 days, and fetal or neonatal loss was one of nine (11%). Successful shunt placement was reported in several cases of unilocular CCAM lesions.^{25,31-33}

The application of minimally invasive surgical techniques such as laser therapy to fetal lung lesions appears to be going to be popular in the future. Laser therapy in cases with CCAM has been reported.^{34,35} However the postprocedure outcomes are not satisfactory maybe because of current technical limitations. Experimental animal studies to improve the techniques should be performed before clinical trials.

Thoracoamniotic shunting is feasible approach to macrocystic CCAM of the lung in hydropic fetus. We think that if CVR is higher than cutoff value 1.6 at 28 weeks and continue to increase, shunting may be applied before evolving fetal hydrops in large macrocystic CCAM cases with severe mediastinal shift and polyhydramnios to improve the prognosis.

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