Case Report of Congenital Cystic Adenomatoid Malformation Type III with Lethal Outcome

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CASE REPORT SUMMARY
We present a rare case of congenital cystic adenomatoid malformation (CCAM) type III (mycrocystic) in young, 19 years old primigravida. Diagnosis has been accomplished by ultrasound examination in 26th week of gestation. Hyperechogenic, mycrocystic mass was found in left pulmonary lobe with contra lateral displacement of mediastium, hypoplasia of the right lung and extensive polyhydramnios. Prenatal therapy was based upon a serial of amniodrainage procedures and pharmacological inhibition of amniotic fluid production and uterine activity. Spontaneous preterm labor occurred at 34 weeks of gestation. Diagnosis was confirmed postnatal. Infant was ventilated due to respiratory insufficiency and was operated at the age of 24 hours. Lethal outcome occurred during the second day due to heavy respiratory insufficiency provoked by pulmonary hypoplasia. We discuss about types of a disease, prenatal diagnostic and therapeutic possibilities and pregnancy outcome.

Keywords: congenital cystic adenomatoid malformation, prenatal ultrasound diagnosis, therapy, outcome

1. INTRODUCTION
Congenital cystic adenomatoid malformation (CCAM) of fetal lung is a rare developmental disorder that occurs during the first trimester of pregnancy due to excessive adenomatoid tissue growth of terminal bronchi that suppress normal development of bronchi and alveoli (1). Prenatal diagnosis is based on the ultrasonic display of solid micro or macro cystic hypoechogenic mass in the fetal lungs. If the change is expansive and compresses the surrounding tissues and organs, it is possible to detect a shift of mediastinum structures and/or hypoplasia of the contra lateral lung. Ultrasonic findings in the lungs can be followed by polyhydramnios and non immune fetal hydropsy. Magnetic resonance imaging -MRI helps in distinguishing CCAM from other congenital anomalies of the lungs, provides a detailed view of the changed tissue, and gives an insight into the possible presence of complications (mediastinal shift, compression of the surrounding healthy lung tissue or the contra-lateral lung, lung hypoplasia). MRI with MSCT (multi-slice CT scan) is a diagnostic method of choice after the birth (2, 3, 4, 5, 6, 7, 8). According to the size of the cysts and their distribution CCAM is classified into three types, which correlate with the possible outcome of the disease. The prognosis is good if the changes involve part or one lung, and is particularly beneficial if the resulting spontaneous regression occur during the third trimester of pregnancy. The outcome is unfavorable when changes are present bilaterally, when there is pulmonary hypoplasia and polyhydramnios, and the worst forecast is the phenomena of non immune fetal hydropsy. CCAM therapy is surgical. Prenatal therapeutic possibilities are very limited and rarely performed (lobe resection or toraco-amniotic shunt for mediastinal decompression), and postnatal indicated segmental or lobe resection of the affected lung (2, 9). We present the case of congenital cystic adenomatoid malformation of type III in fetal lung (mycrocystic type) that is diagnosed by ultrasound in the 26th week of pregnancy. Changes are also noticed in the left lung, and the expansive effect of the situation complicated mediastinal shift, compression with subsequent contra-lateral lung hypoplasia and extensive polyhydramnios. Death outcome was present due to respiratory failure shortly after birth and surgery.

2. CASE PRESENTATION
19-year-old pregnant woman (grav 1, para 1) for the first time hospitalized in the 23rd week of gestation because of abdominal pain. Amnamsence during life without difficult illness. Until then, the course of the pregnancy was regular. Blood type 0, Rh positive, indirect antiglobuline test negative, serology for hepatitis A, B and C negative, TPHA-test negative. Was without fever, a physical examination was regular. The cervix swab isolated Candida albicans. Laboratory findings: leukocytes (L) 10.32x10⁹ / L, erythrocytes (E) 3.92x10¹² / L, hemoglobin (Hb) 121 g / L, hematocrit (HCT) 0.34 L / L, platelets (TRC) 201x10¹² / L, C reactive protein (CRP) 3.2 mg / L, erythrocyte sedimentation (SE) 34 mm/3.6 ks, normal microbiological and biochemical findings of urine. Gynecological examination and ultrasound was corresponding to 23 weeks of pregnancy with a little more amniotic fluid, and fetal lung does not change was not detected. Prescribed is spasmolisis, with excluded incidents in acute abdominal pain stopped. Because the findings of Candidae albicans found in the uterine
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cervix, conducted was Plymicol vaginal tablets therapy, and pregnant women was discharged after a week home with the recommendation of taking prenatal multivitamin tablets and compensation for iron.

Second followed in the 26th week of pregnancy when the ultrasound examination during suspected fetal malformation of the lung. Patient was without fever, proper blood pressure and pulse. Gynecology finding was adequate to 26 weeks of pregnancy. Cardiologically are registered fetal heart rate around the rate of 140/minute with not coordinated and poor uterine activity. Ultrasound result of head biometry for 26/27 weeks of pregnancy, the placenta back, polyhydramnios, amniotic fluid index (AFI) 36.3 cm. The left lung shown hyperechogenic solid mass with size of 52x39x61 mm, which suppressed the heart and mediastinal structures in the right hemi thorax and the spine, and diaphragm toward abdominal cavity. Right lung was hypo plastic. (Figure 1, 2 and 3) Based on ultrasound findings, we set the diagnosis of congenital cystic adenomatoid lung malformations of type III (micro cystic type). Laboratory at the beginning of the second hospitalization: L 8.16x10↑9 / L, 3.58x10↑12 E / L, Hb 113 g / L, Hct 0:32 L / L, TRC 197x10↑9 / L, prothrombine time (PV) 1.04, PV-INR 0.97, activated partial thromboplastine time (APTV) 24 s, APTV-ratio of 0.96, fibrinogen 4.5 g / L, CRP 4.3 mg / L, positive urine chemical leukocytes esterase in sediments 10-12 leukocytes, 20-25 panted station epithelium 2-3 small epithelial cells, many bacteria and a lot of mucus. With sterile urine culture, TORCH serology was positive on Rubella IgG, IgG Parvovirus B19, Epstein-Barr virus (EBV) VCA IgG, EBNA IgG, remained negative. Degree of purity of the vaginal liquid: II, L +, B +. Carotidype 46, XX, normal female. Because of the clear polyhydramnios, which stretched the uterus and uterine activity, and that pregnant women feel a pain, by the second day of hospitalization is made drainage of the amniotic fluid controlled by ultrasound. Evacuated was 670 ml of amniotic fluid.

Until birth on five occasions was in total evacuated 3310 ml of amniotic fluid (670 ml +630 ml +760 ml +600 ml +650 ml). Immediately upon receiving the intravenous tocolysis with Partusisten started with oral inhibition of amniotic fluid production—Indomethacin. Periodically, on a weekly ultrasound is a controlled amount of amniotic fluid. Biometry of the fetus was for one week more than amenorrhea. Polyhydramnios persisted despite therapy, and the value of amniotic fluid index (AFI) has ranged from 34 to 45 cm. In 32nd week fetus was in a position bottom down. Ultrasound view of fetal lung was unchanged compared to previous findings, the solid mass of 55x45x67 mm dimensions. There were no signs of fetal hydropsy. Daily cardiac monitoring of the fetus registered a clean heart rate and uterine activity lasting, which varied in intensity. Because of the initial inflammatory changes in peripheral veins in the hands of pregnant women, intravenous tocolysis therapy with was replaced after 14 days to oral therapy by Cordipine R. In the 28th week of pregnancy has been induced fetal lung maturation with antenatal corticosteroids (dexametason 24 mg in four doses every 6 hours).

Because of the increased inflammatory laboratory parameters (CRP 70.3 mg / L) in the 31/32 week began antibiotic therapy with Novoci 2x500 mg per os through 7 days, which was followed by normalization of laboratory findings: L 9.79x10↑9 / L, 3.07x10↑12 E / L, Hb 94 g / L, Hct 0:27 L / L, TRC 182x10↑9 / L, CRP 5.6 mg / L.

Preterm, spontaneous, vaginal...
birth and with manual assistance by the Veit-Smellie came in 34th week of pregnancy. Child is born alive, prematurely, female infant with birth weight of 2160 g, birth length 46 cm, Apgar 1/3. At birth has leaked out about 5 liters of amniotic fluid. On the decidua surface of the placenta there was a blood clot which is indicated on placenta abruption, which was confirmed by pathohistological analysis. In addition, the findings described pathohistological placenta weight 500 g, marginal cord insertion, at the intersection of the placenta is mature appearance with visible white sharply restricted areas of 2 cm in diameter, which histologically correspond to transmural chronic myocardial placenta tissue. Placenta tissue is built from the ripe and mature intermediate corial uvula visible with the growing X cells in 30% of them, apparent is inter fibrinoid and intravilos accumulation and calcification disposal. Mother after birth in expected recovery, made ablactating with parlodel tablets, and as healthy discharged from hospital 4th day after birth.

Because of respiratory failure immediately after birth, newborn resuscitation was conducted, during which is placed endotracheal tube, manually ventilated by ambu balloon, with a heart massage and the application of reanimation medications in a total duration of 60 minutes. In the third hour of life the child is moved to the Department of intensive care for newborns Clinic Pediatrics Clinical Hospital Center Zagreb. Child was cool, cyanotic in general, hypoxemic (SO2, about 80% to 100% FiO2), hypotonic (RR 50/24 (33 mmHg), eucardic (154/min). Heart rate was located in the right hemi thorax, rhythmic, with clear tones, noise of left bronchial breathing, impaired breathing on the right, with murmurs on both sides. No other status characteristics. Because of respiratory failure was started breathing guidance with the application of NO (nitrogen oxide II). Laboratory per child admission: pH 7,1, pCO2 8.1 kPa, pO2 4.7 kPa, HCO3 18.9 mmol / L, BE -10.8 mmol / L, lactate 8.8 mmol / L, PV 0.25, APTV> 120 s, fibrinogen 0.9 g / l, 3:44 E x10 ↑ 12 / L, Hb 124 g / L, Hct 38.7 L / L, TRC 104 x10 ↑ 9 / L, 15.3 L x10 ↑ 9 / L, proper blood findings, bilirubin, serum CRP, urea, creatinine normal.

X-ray of the lung and heart showed completely homogenous shadow in right hemi thorax, non homogenous shadow in left hemi thorax with heart and mediastinal structures offset to the right hemi thorax. Shadow of the heart could not be differentiated from the surrounding shadow (Figure 4).

Ultrasound of the heart: the heart is pushed to the right, adequate segments, open foramen ovale with left-right shunt, not completely open Botalli duct (left-right shunt) with a gradient of 20 mmHg, stage II mitral failure, failure of tricuspid with gradient 30 mmHg. Less pericardial and pleural spill. Without cortication. Moderate pulmonary hypertension.

Finding of MSCT (multi-slice CT scan) showed expanded left lung with herniation into the right hemi thorax and displacement of the heart and mediastinum structures in the right hemi thorax. In the left lung there are wide zones of opacity like milky glass, diffuse small cystic lesions, and small areas of consolidation in the lower lobe parenchyma. In the right lung is seen atelectasis in the upper lobe and lower lobe parenchyma is transparent. No spillage in pleural space or pneumothorax. Lumen of trachea is of appropriate lumen and main bronchi, with adequate position of the endotracheal tube.

With regard to the above diagnostic procedure that confirmed the prenatal diagnosis of CCAM, and the child had clinical and laboratory signs of respiratory failure despite mechanical ventilation, decision was to surgically remove the pathologically changed lung with the hope that it will allow expansion of the contra-lateral lung and survival.

In 24th hour of life the child was done left side lung excision. During surgery the left lung was entirely edematous, cystic changed, livid color with mild respiratory movement. Postoperative course was marked by extremely difficult ventilation of the hypo plastic right lung. Death outcome appeared in the 31st hour of life. At the autopsy was confirmed the significant right lung hypoplasia with the left lung weight of 90 grams and 14 grams of the right one. (Figure 5)

Pathohistological findings of left lungs: pleura is smooth and shiny, the slices of the lung is solid, yellow-pink with some small bleeding. (Figure 6) Histologically are found bronchi and alveoli lined with cubic cells. With them there is something bigger space-coated with cylindrical epithelium cor-
responding to bronchial epithelium, but the walls are lacking glands or cartilage, with only a thin layer of smooth muscle. In interstitium there are few blood vessels, of which only some have slightly thickened muscular layer. Pathohistological findings confirmed that this is congenital malformation of the lower respiratory tract (solid type of congenital cystic adenomatoid malformations type III) (Figure 7).

3. DISCUSSION

CCAM is a rare lung disease with the appearance from 1/25000 up to 1/35000 pregnancies. It is hamartomic lesion that occurs because of impaired lung embryogenesis in the first trimester of pregnancy when excessive growth of adenomatoid tissue in terminal bronchi suppresses the normal development of the alveoli and bronchi. This is the most common developmental anoma-

lies of the lungs. It occurs sporadically, with some higher incidence in the male fetuses. In 10% of cases is associated with other fetal malformations: trisomy 18, kidney agenesis, diaphragm herniation and congenital heart disease. Differential diagnosis takes into consideration pulmonary sequestration, bronchogenic cysts, Diaphragmatic hernia, mediastinal cystic teratoma, congenital pulmonary emphysema, cavitated pneumonia, pericardial cysts, etc. (2, 3). Anomaly was first described by Ch’in and Tang 1949 (4), and in 1979 Stocker (5) has defined 3 types of CCAM, depending on the size and distribution of cystic lesions, and were correlated with the possible outcome of the disease. Type I (50% of cases) determined by single or multiple cysts of large diameter (2-10cm), filled with air or liquid content, different wall thickness. This form has a good prognosis. In type II (40% of cases) there are multiple cysts of medium diameter (0.5-2cm), thin walls, and the prognosis is poor in case of association with congenital anomalies of other organs and organ systems. Type III or solid type (10%) has the worst prognosis because of frequently associated with pulmonary hypoplasia and fetal non immune hydropsy, and is characterized by multiple micro cyst formation of up to 0.5 cm in diameter shown by ultrasound as solid mass and are usually localized in the left lower lung lobe.

Microscopic criteria for diagnosis of congenital cystic adenomatoid malformations of fetal lung are set by Kwittken and Reiner, 1962 (6). They described the three histological types: in type I, which is the most common, histologically there are large single or multiple cysts covered by ciliar pseudo stratified column epithelium with smooth muscle and elastic tissue in the wall of the cystic formation. Type II defines a number of small cysts lined with cubic and column epithelium. Mucous cells and cartilage are not present. The type III microscopic appear as non cystic extensive lesions that are caused by mediastinal shift, and contain structures resembling to bronchi coated with cular epithelium. The absence of inflammation is one of the diagnostic criteria used in the original description by Kwittken and Reiner. In our case this was a solid type of congenital cystic adenomatoid malformations of type III. Glandular component in CCAM lesions has the potential for malignant transformation. 25% of the pleura-pulmonary blastoma (pleura-pulmonary blastoma) was found in children with CCAM (2, 7).

Diagnosis is made by prenatal ultrasound usually between 16 and 22 weeks, although according to some authors is available from 12 week of pregnancy (8, 9). Our ultrasound diagnosis is set in 26th week of pregnancy. De Santis et al. (10) recommended repeating ultrasound every 20-30 days, and describing the disappearance of changes in the lung as much as 80% of CCAM type III during the last trimester of pregnancy. Vlădărean et al. (2) suggested frequent ultrasound controls, first once a week, then every 2 to 4 weeks, for careful monitoring and evaluation of changes in the lungs. We decided to have frequent ultrasound controls every 7 days, primarily for monitoring the amount of amniotic fluid amniotic fluid index (AFI), and the re-evaluation of lung changes. Compression of the esophagus was creating an extensive background polyhydramnios, which caused symptomatics of threatening premature delivery. Amniotic drainage repeated application of indomethacin and we have tried to reduce the amount of amniotic fluid and reduce its creation, and thus, the tocolysis, to prevent preterm birth. In our case, regression findings on fetal lung does not occur, but the changes affected the whole left lung and was due

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**Figure 6:** View of the left lung after cut.

**Figure 7:** Histological image of the left lung with a diagnosis of cystic adenomatoid malformations: seen is lung parenchyma with few broad areas (bronchi) covered with cylindrical respiratory epithelium, and small spaces (alveoli) with cubic cells. Missing cartilage around the larger space.
to compression of surrounding organs and tissues has been a mediastinal shift and contra-lateral lung hypoplasia. Non immune fetal hydropsy (NIFH), which is explained as a consequence of compression of the heart and lower hollow vein with a reduction in venous return of blood to the heart and heart minute volume, according to De Santis et al (10) and Calvert et al (11) and only the most important negative prognostic factor for CCAM. Since in our case NIFH was not observed, it is an example of possible bad outcomes when there is no NIFH.

Ultrasound prenatal diagnosis is necessary to be supplemented with additional diagnostic tests, magnetic resonance imaging–MRI and MSCT (multislice CT scan). Prenatal and postnatal, MRI provides detailed information about position, extension and change of lung size, and gives insight into the situation and the degree of mediastinal contra-lateral lung hypoplasia. MSCT provides additional postnatal differentiation in non differentiated infected lesion (12). The most important role of good diagnostic process is, of course, planning of treatment. Intrauterine treatment (puncture of pleural fluid and cystic formation, thorax-amiotic shunt, and fetal surgery) and immediate surgery after birth, it is recommended in cases when there are clinical signs of compressive effect on the surrounding tissues and organs. Otherwise, surgical treatment is indicated in the first months of life the child (excision of the lobe, segment and non-anatomical resection) in order to prevent the development of complications (e.g. progressive respiratory symptoms, infection and malignant transformation) (13). In this case is made left side removal of the lung on the first day of life due to severe forms of respiratory failure. Postoperative clinical course was complicated with extremely difficult ventilation of hypoplastic right lung for which soon came the lethal outcome.

4. CONCLUSION
Timely prenatal diagnosis of congenital cystic adenomatoid lung malformations allows monitoring of its natural flow (regression or progression), and detection of complications that arise from compressive effects. Ultrasound takes important place in prenatal diagnosis.

Although the forecast is mostly good due to regression of pulmonary changes on the one hand, and often successful surgery on the other hand, the outcome of patients with prenatally diagnosed cystic adenomatoid lung malformations depends on histology type, the presence of pulmonary hypoplasia and associated anomalies. Adenomatoid lung malformation of type III, which was diagnosed in our case, has the worst prognosis because it is frequently associated with pulmonary hypoplasia and/or fetal non immune hydropsy. Non immune fetal hydropsy is considered to be the worst prognostic sign. In our case, prognosis was determined by complete abstraction of the left lung at the same time with a significant contra-lateral lung hypoplasia.

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