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Longitudinal observation of antenatally detected congenital lung malformations (CLM): natural history, clinical outcome and long-term follow-up

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Abstract

Objective: The objective of the study is to present longitudinal observations in antenatally detected congenital lung malformations (CLM), particularly pulmonary sequestration (PS) and cystic adenomatoid malformation (CAM). **Methods**: Fetuses found to have a CLM on prenatal ultrasound (US) were included in this study and followed up until delivery. In all newborns radiographs and computerized tomography (CT) studies of the thorax were performed. Surgical procedures included sequesterectomy, lobectomy, segmentectomy, and non-anatomic resection. Based on prenatal US findings, intrauterine course, postpartum chest radiographs and CT scans, as well as clinical signs and surgical findings patients were divided into six groups. **Results**: Over a period of 6 years, routine prenatal US revealed suggestion of CLM in a series of 35 consecutive fetuses. In six cases pregnancy was terminated or the fetuses suffered fetal demise. Another four fetuses became symptomatic in utero when sequential scanning revealed hydrops, hydrothorax, and enlargement of cysts or polyhydramnios. Three cases in this group received serial therapeutic amniocentesis and serial puncture of either the hydrothorax or intrapulmonary cysts. After postpartum treatment in the intensive care unit surgical procedures were performed uneventfully and confirmed the diagnosis of CAM, PS or hybrid type lesions. In 11 patients US findings were considered to demonstrate spontaneous resolution of the lesion, but disappearance without sequelae could be confirmed only in six infants. Five infants were shown to have persistent CLM on postpartum CT scans. These infants underwent resection of the lesion within the first year of life. In 11 fetuses CLM were continuously demonstrated during pregnancy with only slight changes in size and structure. Postpartum the infants were asymptomatic and were subjected to a systematic plan of diagnostic work-up and treatment. Surgery in these infants revealed a large number of hybrid type lesions ($n = 5$). In three infants, the primary diagnosis of PS or CAM had to be corrected during the diagnostic and therapeutic work-up. **Conclusion**: CLM are diagnosed antenatally with an increasing frequency and are shown to be quite different from previously applied concepts. The expected clinical outcome is far better than thought to be possible.

Keywords: Prenatal ultrasound diagnosis; Congenital lung malformations; Spontaneous regression; Postpartum multi-slice CT scan; Thoracic surgery

1. Introduction

Routine application of, and general improvements in obstetric ultrasound (US) examination permit a more frequent antenatal diagnosis of congenital lung malformations (CLM), particularly pulmonary sequestration (PS) and cystic adenomatoid malformation (CAM). The abnormalities are detected in earlier stages of pregnancy and sequential scanning to delivery provides an opportunity to observe the natural course and in utero evolution of the anomalies.

A wide range of questions have been raised concerning nomenclature, embryology, pathology, reliable US features, prognostic indicators, spontaneous regression, hidden mortality, treatment options, and likely reasons for surgical

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intervention. The aims of the present study were to address all these aspects in an unselected regional study population and to determine the outcome of treatment in CLM. Many of these issues will be object of the counseling of parents and in planning treatment.

2. Material and methods

Over a 6-year period, a consecutive series of fetuses found to have a CLM on US were included in this study, which was performed at a tertiary care center. The infants were studied in a prospective manner as they were diagnosed. Fetuses were continuously followed to delivery as well as during the postpartum and postoperative period. Data were collected with respect to maternal age, prenatal US findings, prenatal course of the lesion, infant symptoms, physical and radiological examinations, findings from surgical or pathological evaluation, clinical follow-up and infant survival.

2.1. Prenatal diagnosis

Prenatal sonograms were obtained, starting at different stages of pregnancy, using commercially available real-time equipment (mainly a Toshiba PowerStation, SSA-380 A [Otawara, Japan]; 3.5-, 5.0- and 7.5-MHz sector-array transducer). Follow-up sonograms were repeated every 2–4 weeks until delivery to monitor location, size, sonographic appearance, and associated mass effects. Color-Doppler US examination was performed to demonstrate anomalous blood flow from the aorta to the CLM. A complete survey of other field organs was performed to rule out other structural anomalies.

Fetal karyotype analysis was obtained by amniocentesis or chorionic villus sampling in all cases except when the parents rejected the investigations.

2.2. In utero treatment

Termination of pregnancy was offered in the case of severe associated malformations. Fetuses that became symptomatic in utero (e.g., development of hydrops and/or hydrothorax, enlargement of cysts, mediastinal shift or polyhydramnios) underwent different types of in utero treatment (e.g., serial therapeutic amniocentesis, serial puncture of hydrothorax or cysts) as well as induction of preterm delivery.

2.3. Postpartum evaluation

In all live-born infants anterior–posterior and lateral radiographs of the chest were taken immediately after birth, and were evaluated for the presence of midline shift or mass effects, hyperinflation, cystic areas, subtle irregular hyperlucency, or soft tissue opacity.

Computerized tomography (CT) studies of the thorax were performed in the first month of life mainly using a multi-slice CT scanner, MSCT Volume Zoom, Siemens (Erlangen, Germany) with a low-dose protocol ([80 kV, 20 mAs], 4×1 mm collimation, 3 mm axial reconstruction, and 5 mm coronal reconstruction). Intravenous contrast medium (2 ml/kg with an 8 to 10-s delay) was used in the majority of cases, particularly to evaluate anomalous systemic feeding vessels.

2.4. Surgery

Selection of patients for surgical treatment depended on postpartum respiratory distress and/or achievement of patients' clinical stabilization, as well as on postnatal CT results. Surgical procedures included sequesterectomy, lobectomy, segmentectomy, and non-anatomic resection. CLM with a detectable anomalous systemic blood supply received an early planned thoracotomy. The other asymptomatic patients were followed up conservatively and operated on within the first year of life if the lesion was shown to persist on repeat CT scans.

2.5. Final diagnosis and follow-up

The prenatal sonograms, postnatal chest radiographs, and CT scans were reviewed in each case and correlated with postnatal clinical signs and symptoms and findings from surgical or pathological results, including postmortem findings.

Patients were divided into six groups based on prenatal US findings, in utero course, postpartum presentation and treatment of the lesion (Table 1) (1 = termination of pregnancy or fetal demise; 2 = complicated intrauterine course; 3 = confirmed spontaneous regression; 4 = suggested regression with postpartum persistent lesion; 5 = continuously detectable malformations; 6 = wrong diagnoses).

The duration of follow-up (e.g., clinical findings, radiographs, CT scans) ranged from 6 months to 6 years.

3. Results

Over a period of 6 years, routine prenatal US revealed suggestion of CLM in a series of 35 consecutive fetuses at 16–35 weeks gestation (mean gestational age, 21.9 weeks). The mean age of the mother was 25.8 years (range, 19–37 years); 21 fetuses were male and 14 were female.

Twenty-five cases (~71%) were diagnosed prior to 24 weeks and were therefore eligible for elective termination of pregnancy. Twenty-four of the 29 live-born infants (~80%) were largely asymptomatic at birth and could be subjected to a staged diagnostic work-up. The chromosomal analysis was normal in all infants ($n = 27$), and none of the eight infants whose parents had refused antenatal chromosomal

Table 1
Classification of fetuses with antenatally diagnosed CLM ($n = 35$)

Group	Classification	Number of patients
1	Fetal demise	2
	Termination of pregnancy	4
2	Complicated in utero course and complicated postpartum presentation	4
3	Apparently spontaneous regression—postpartum confirmed	6
4	Suspected spontaneous regression—postpartum persistent lesion	5
5	Continuously detectable CLM (partial regression <25%)	11
	Surgical treatment <1 year	(9)
	Clinical and radiological follow-up	(2)
6	Wrong diagnoses	3
	CDH	(1)
	Bronchogenic cyst	(1)
	Duplication cyst	(1)
	Total number	35

CLM, congenital lung malformations; CDH, congenital diaphragmatic hernia.

investigation revealed postpartum evidence of chromosomal anomalies.

Apart from the patients of group 1 (see Table 2), there were only two minor associated malformations (e.g., chorioid plexus cyst, mitral valve insufficiency). In particular, we failed to detect major cardiac anomalies.

3.1. Group 1 ($n = 6$)

In four fetuses accompanying serious malformations led to a decision to terminate pregnancy (Table 2). Prenatal US revealed bilateral CLM in two fetuses, both being already hydropic on initial scans, at 17 and 19 weeks gestation, respectively. In these fetuses kidney agenesis and high airway obstruction might have interacted negatively with pulmonary development. Two fetuses suffered fetal demise, whereby only in one case fetal demise was considered to be connected with CLM (Table 2).

3.2. Group 2 ($n = 4$)

Four fetuses became symptomatic in utero when sequential scanning revealed the development and progression of hydrops, hydrothorax, mediastinal shift, polyhydramnios, or enlargement of cysts at a mean gestational age of 24 weeks gestation (range, 22–27 weeks). The absence of other structural or chromosomal anomalies prompted the decision to bear the children.

Serial therapeutic amniocenteses were performed in three cases, and two fetuses received serial puncture of either the hydrothorax or intrapulmonary cysts (Table 3). Despite these interventions rapid re-accumulation of fluid and/or progression of negative mass effects led to a delivery before term in three cases at a mean gestational age of 33.7 weeks (mean birth weight 2462 g). The infants experienced respiratory distress and required preoperative treatment in the intensive care unit over a period from 2 days to 4 weeks (Table 3).

Surgical procedures were performed uneventfully (lobectomy [$n = 1$], sequesterectomy [$n = 2$], atypical non-anatomic resection [$n = 1$]). Patient number 4 required urgent intervention on day 2 postpartum due to the child's progressive deterioration. Histopathological examination confirmed the diagnosis in two cases of CAM I, one extrapulmonary sequestration (EPS) and one hybrid type (CAM II/EPS) (Table 3).

The duration of postoperative hospitalization ranged from 9 to 55 days (mean period 26 days). Patient number 3 developed a mild degree of bronchopulmonary dysplasia postoperatively, whereas patient number 4 suffers from recurrent bronchiolitis. Follow-up with multi-slice CT revealed several small residual cystic areas in the preserved apical portions of the left lower lobe.

3.3. Groups 3 and 4 ($n = 11$)

In these patients, serial antenatal US examinations towards the end of pregnancy (36–38 weeks gestation) were considered to demonstrate spontaneous resolution of CLM. Five infants were shown to have a persistent lesion which was not demonstrable on radiographs but could be well depicted on multi-slice CT scans. Resolution without sequelae was confirmed only in six infants on postpartum US, radiographs and CT scans. Depiction of systemic anomalous vascular supply on a CT scan in two infants correlated with the intraoperative findings.

Infants with persistent CLM underwent uneventful resection of the lesion (lobectomy [$n = 2$], segmentectomy [$n = 1$], sequesterectomy [$n = 2$]) at a mean age of 7.4 months of life (range, 4–12 months). Histological evaluation established a final diagnosis of PS in four cases (two EPS, one intrapulmonary sequestration [IPS], and one IPS/CAM II hybrid type) and CAM I in one.

3.4. Group 5 ($n = 11$)

In 11 fetuses, CLM were continuously demonstrated during pregnancy without noteworthy changes in size (<25%) and/or structure, whereas four infants revealed an impressive resolution of the mediastinal shift. All infants

Table 2
Data of CLM-fetuses undergoing termination of pregnancy ($n = 4$) or fetal demise ($n = 2$)

Fetus no. [GA (weeks), maternal age]	Sonographic diagnosis		Additional findings	Prenatal course	Gross examination	Final diagnosis
	Thorax	Side	Associated malformations	GA at TOP or FD		
(1) [20/21 weeks, 24 years/CA (+)]	CAM II/III	(L)	Severe oligoamnios	Persistent oligoamnios	Sirenomelia	CAM III LLL
	Increased echogenicity		Dolichocephalism	Termination	Ambiguous genitalia	
	Several cystic areas (8 mm ∅)		Dextrocardia	22 weeks	CAM left lower lobe	
			Absence of kidneys (Potter-Syndrome?)	XX, 500 g/32 cm	Renal agenesis	
				Died subpartum		
(2) [19/20 weeks, 21 years/CA (+)]	CAM II/III	(L)	Dextrocardia	Polyhydramnios	Giant harmatous left lower lobe, cysts interspersed dorsally	CAM III LLL
	Increased echogenicity			Termination	Rudimentary left upper lobe	
	Peripheral several small cystic areas			24 weeks		
	Regular right lung			XY, 500 g/28 cm Apgar 2/1/1		
(3) [16/17 weeks, 21 years/CA (+)]	CAM III bil. with a few microcystic areas	(Bil)	Compression of the heart	Oligoamnios	Hydropic fetus	CAM III bil.
			Cervical kyphoscoliosis	Termination	Ascites	
			Ascites	17 weeks	Esophageal atresia type IIIb	
			Hydrothorax	XY, 210 g/18 cm	Tracheal hypoplasia	
			Scalp edema (8 mm)		Craniofacial dysmorphism	
(4) [19 weeks, 32 years/CA (+)]	CAM III, microcystic lesion, enlargement of the lung (>50% of thorax volume)	(R)	Deviation of the heart to the left	Termination	CAM right upper and lower lobe	CAM III RUL and RLL
			Left lung hypoplasia	21 weeks XX, 360 g/27 cm		
(5) [17/18 weeks, 23 years/CA (+)]	CAM III	(Bil)	Compression of the heart	Polyhydramnios	Hydropic fetus	CAM III bil.
	Enormous hyperechogenicity		Gulf ball phenomenon	Fetal demise	Harmatous enlargement of both lungs	
	Enlargement of both lungs		Small bowel hyperechogenicity	22 weeks	Ascites	
			Ascites, hydrothorax	XY, 1046 g/25 cm		
			Scalp edema (7 mm)			
(6) [31 weeks, 21 years/CA (−)]	CAM III	(R)	0	Fetal demise	CAM III right lung	CAM III right lung
	Right lung completely involved (two cystic areas, 16 mm ∅)			35 weeks (nutritive insufficiency)		
				XY, 2080 g/48 cm		

CLM, congenital lung malformations; TOP, termination of pregnancy; GA, gestational age; FD, fetal demise; CA, prenatal chromosomal analysis; CAM, cystic adenomatoid malformation; (R), right-sided lesion; (L), left-sided lesion; (Bil.), bilateral involvement; LLL; left lower lobe; RUL, right upper lobe; RLL, right lower lobe; ∅, diameter.

were asymptomatic after birth and could be monitored in a normal postnatal care unit.

The infants remained asymptomatic until surgery which was performed uneventfully in nine children at a mean age of 3.8 months (range, 1–11 months). Surgery included three lobectomies, three segmental resections, and three sequesterectomies. Intraoperative findings of anomalous systemic vascular supply correlated with the results from prenatal US ($n = 3$) and postpartum performed CT scans ($n = 6$). Histological evaluation established a final diagnosis of two EPS cases, five hybrid type lesions (CAM I/CLE [$n = 1$], IPS/CAM II [$n = 3$], and EPS/CAM II [$n = 1$]), and two cases of CAM I.

Two infants with a postpartum confirmed diagnosis of a mild degree of CAM in the right lower lobe have not been operated on so far. The children are awaiting a final decision, as repeated CT scans showed partial resolution of the lesion during the first months of life.

Table 3
Data of CLM-fetuses with complicated intrauterine course and in utero treatment ($n = 4$)

Fetus no. (prenatal findings and treatment)	Postpartum presentation and management	Postpartum radiology (ASVS)	Surgery	Pathology	Final diagnosis (complications)
(1) CAM I (L) Macrocystic appearance Slight hydrothorax Dextrocardia, poly-hydramnios Therapeutic amnio-centesis Vaginal del ivery	XX, 3086 g/53 cm Apgar 5/6/intubation Severe respiratory distress Intubation HFV Surfactant	Dextrocardia Mediastinal shift Over-inflation of tumorous LUL, macrocystic areas	Thoracotomy *Lobectomy LUL* Day 5 pp	CAM I LUL Atypical branches of pulmonary artery	CAM I LUL
(2) EPS (L) Increasing hydrothorax Dextrocardia, NIHF Polyhydramnios Therapeutic amnio-centesis Preterm Cesarean section	XX, 1642 g/41 cm Apgar 5/7/intubation Severe respiratory distress Intubation HFV Surfactant Chest tube insertion (50 ml)	Dextrocardia Mediastinal shift Pleural effusion US → ASVS CT → ASVS (AA)	Thoracotomy *Sequesterectomy (L)* 8 weeks pp	EPS (L) Transdiaphragmal ASVS (AA)	EPS (L)
(3) EPS (L) Increasing hydrothorax Mediastinal shift Polyhydramnios Serial hydrothorax puncture (16 ×) and amniocentesis Preterm Cesarean section	XX, 2000 g/44 cm Apgar 5/7/7 Severe respiratory distress Intubation HFV Chest tube insertion (90 ml) Surfactant	Mediastinal shift Dextrocardia Over-inflation LLL US → ASVS CT scan: over-inflation of LLL and mediastinal shift ASVS (TA)	Thoracotomy *Sequesterectomy (L)* Day 8 pp Postoperative infection (puncture and drainage)	EPS (L) + CAM II ASVS (TA)	EPS + CAM II li BPD
(4) CAM I (L) Transient ascites Transient mediastinal shift Enlargement of cysts Serial puncture of cysts (3 ×) Preterm Cesarean section	XX, 3120 g/50 cm Apgar 8/9/9 Mild respiratory distress Deterioration on day 2 pp Intubation (IMV) Urgent surgery	Dextrocardia Mediastinal shift Over-inflation LUL Tumorous LUL CT scan: tumorous LUL	Thoracotomy *Non-anatomic, organ-sparing resection of LLL* Day 2 pp	CAM I LLL	CAM I LLL Residual cysts in rest of LLL Recurrent bron-chiolitis

CLM, congenital lung malformation; ASVS, anomalous systemic vascular supply; LUL, left upper lobe; CAM, cystic adenomatoid malformation; HFV, high frequency ventilation; CT, computerized tomography; US, ultrasonography; EPS, extralobar pulmonary sequestration; IMV, intermittent mandatory ventilation; LLL, left lower lobe; pp, postpartum; BPD, bronchopulmonary dysplasia; (L), left-sided lesion; TA, thoracic aorta; AA, abdominal aorta.

3.5. Group 6 ($n = 3$)

In three patients, the primary antenatal diagnosis of either CAM ($n = 2$) or PS ($n = 1$) had to be corrected during the subsequent diagnostic and therapeutic work-up (see Table 1). The boy with an intrapulmonary bronchogenic cyst was operated on only at the age of 6 years, when he experienced several attacks of serious respiratory infection due to an inflamed intrapulmonary bronchogenic cyst.

In summary, surgical procedures were performed on 18 infants with postpartum demonstrable CLM. Tables 4 and 5 refer to the types of surgical procedure and to the type of lesion. Concerning the location of CLM, there was a clear

Table 4
Survey of surgical procedures applied in operated CLM ($n = 18$)

Number of patients	Seques-terectomy	Lobectomy	Segmen-tectomy	Non-anatomic resection
7	×			
6		×		
4			×	
1				×

CLM, congenital lung malformation.

preponderance of the left side and the lower lobes (Tables 4 and 5). From a pathological point of view, there is a preponderance of hybrid type lesions (six of our 18 operated patients, ~33%) and a remarkable equal distribution between IPS and EPS (see Table 5). The hybrid lesion between CAM I and congenital lobar emphysema (CLE) was interpreted as a singular case.

4. Discussion

Due to the remarkable advancements in prenatal US, CLM are detected with an increasing incidence. The majority of fetuses with CML are detected coincidentally during the early second trimester. Sequential scanning to delivery provides an opportunity to observe the natural course and in utero evolution of most anomalies [1–6].

Until the last decade, CLM were considered to be rare and to signify an enormous risk of fetal demise or life-threatening respiratory compromise after birth [2,6]. About 14% of fetuses with CAM were stillborn, while 80% were estimated to present with severe cardio-respiratory compromise immediately after birth. In 90% the condition was discovered in the first year of life (70% in the first week) [3,6,7]. Conversely, PS was diagnosed in up to 30% only during investigation of another anomaly (e.g., CDH, cardiac failure) [7–9].

Nowadays, prenatal detected CLM have been proven to be entirely different in many cases from previous concepts of pathogenesis, diagnosis and treatment. Postpartum, the majority of antenatally diagnosed CLM are shown to present completely asymptomatic [3–5,8,10–13]. Later in childhood and adult life, infants with unrecognized CLM may seek medical treatment for progressive respiratory distress, failure to thrive, cardiac failure or recurrent infection of the respiratory tract. Malignant transformation (e.g., pulmonary blastoma, rhabdomyosarcoma) in CAM has been reported in singular cases only [3,7,10].

4.1. Nomenclature and classification

Despite several attempts to do a complete reappraisal the nomenclature and classification of CLM are still ambiguous. Previously applied classification systems mix a number of variable characteristics (e.g., gross appearance, histopathology, sonographic features, radiography, CT scanning, MRI, and surgical findings). Additionally, different terms were used inconsistently in the ante- and postnatal periods and are used to describe overlapping abnormalities [1,3,10,11,14].

CLM are shown to represent a continuum of anomalies of fetal lung development. The term 'bronchopulmonary-foregut malformation', introduced by Gerle et al. [15], takes into account the close communication between the respiratory and the gastrointestinal tract during the first weeks of the embryological development. In 1987, Clements and Warner [16] published the classification system of 'pulmonary malinosculation' which refers to an abnormal congenital connection or opening of one or more of the bronchopulmonary vascular complex. Conversely, Bush [17] recently proposed a more descriptive classification system while avoiding embryologic speculation.

4.2. Hybrid type lesion

Clinicians still continue to differentiate between CAM and PS on the ground of symptomatologic clinical signs and findings from radiology, surgery and pathology [4,7,18]. Contrary to this classical strict distinction, a final diagnosis of a mixed or hybrid type lesion (e.g., PS associated with CAM, predominantly CAM type II in PS) could be made postpartum in up to 15–40% of CLM cases [3,4,9,18]. These lesions were shown to have an anomalous systemic

Table 5
Pathology and location (side and site) of operated CLM ($n = 18$)

Group	Diagnosis						Location						
							Side		Site				
	CAM I	EPS	IPS	CAM II/EPS	CAM II/IPS	CAM I/CLE	Right	Left	EPS	RUL	RLL	LUL	LLL
2 ($n = 4$)	2	1		1				4	2			1	1
4 ($n = 5$)	1	2	1		1		2	3	2	1	1		1
5 ($n = 9$)	2	2		1	3	1	3	6	3		2	1	3
Total number	5	5	1	2	4	1	5	13	7	1	3	2	5

CLM, congenital lung malformations; CAM, cystic adenomatoid malformation; EPS, extralobar pulmonary sequestration; IPS, intralobar pulmonary sequestration; CAM II/EPS hybrid lesion; CAM II/IPS, hybrid lesion; CAM I/CLE, hybrid lesion; CLE, congenital lobar emphysema; RUL, right upper lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.

vessel directly arising from the aorta, whereas histopathological evaluation revealed features of both CAM and PS. Furthermore, the presumed preponderance of intralobar PS (IPS) over extralobar PS (EPS) should rightly be corrected to a nearly equal distribution of IPS and EPS.

4.3. Antenatal ultrasonography

Antenatal US includes direct visual assessment of the thoracic lesion and following mass effects (e.g., pleural effusion, ascites, hydrops fetalis); it also enables the investigator to demonstrate associated anomalies of the fetus [2,4,10,12,13]. Early detection of CLM provides increasing information about the natural history of the disease (e.g., course, regression, side-effects) and prevents irreversible harm to the fetus in cases eligible for in utero treatment [4,10,12].

With improved US resolution and better comprehension of sonographic findings, a number of different sonographic features of CLM were identified. Thus, the accuracy in classifying these lesions on prenatal US has increased from 60 to 90% [4,13,14,18–20].

There is a wide range of sonographic appearances in CLM from subtle to markedly increased uniform echogenicity to lesions containing large echofree areas [14,20]. Microcystic lesions appear more solid due to fine interfaces with the US beam that might create an almost homogenous appearance [14,20].

CLM are predominantly located in the posterior basal segments of lower lobes and only rarely affect middle or upper lobes. Bilateral uniformly increased echogenicity (~2%) has a poor outlook, and some bilateral cases, previously called type III CAM, may in fact have been laryngo-tracheal atresia [14]. Size and volume of CLM as well as associated lung hypoplasia can be evaluated only in a semiquantitative fashion (e.g., computer-assisted planimetry, volumetry, and prenatal ultrafast-MRI) [4,12]. Crombleholme et al. [21] hypothesize that the volume of a CLM could predict whether hydrops would develop.

Color-Doppler US examination can show an anomalous vessel to arise from the thoracic or abdominal aorta and to ramify within the separated lung parenchyma [4,14,20].

Pathophysiological effects on the fetus and the mother (e.g., placenta edema, polyhydramnios) can be demonstrated on prenatal US [12,14,20]. Development of non-immune hydrops fetalis (NIHF) (e.g., skin edema, pleural effusion, ascites, and pericardial effusion) represents one of the most harmful situations during pregnancy with poor outcome for the fetus [2,4]. However, isolated fluid accumulations, such as ascites or pleural effusion only, can occur and are associated with a far better prognosis than in NIHF-complex [1,8,13]. Resolution of mediastinal shift or pleural effusion can be observed independently from the course of the lesion itself.

4.4. Spontaneous regression of CLM

Sequential antenatal US may reveal changes both in size and structure of a lesion. From a sonographic point of view CLM could (1) show progression in size and/or development of NIHF (~6%); (2) remain unchanged in size and sonographic appearance throughout the remainder of the pregnancy; and (3) show decrease in size or even complete disappearance (~30%) [14]. The timing of this phenomenon of 'regression' is variable but tends to be in the mid-third trimester, usually at 32–34 weeks gestation. Several factors appear to be important for a loss of sonographic conspicuity (e.g., loss of fluid/tissue interfaces, resolution of the cystic parts, transient obstruction, acute cessation of systemic blood flow, and torsion of the sequestration) [3,4,11,12,14,19].

Suspected resolution of the US appearances in utero, however, does not necessarily imply complete resolution of the primary pathology. Our study demonstrates that significant abnormalities are shown to persist and thus supports the importance of thorough application of postnatal imaging studies. There exist no studies concerning with the possibility of continuous postpartum regression during the first years of life.

4.5. Differential diagnosis of CLM

A number of pathological entities should be considered in the differential diagnosis of CLM (e.g., congenital diaphragmatic hernia, CLE, tracheal atresia, bronchial atresia, bronchogenic cysts, and gastrointestinal duplication cysts) [2,3,12–14]. Although prenatal US is becoming increasingly sophisticated, diagnostic errors are possible, particularly during the early second trimester. Fetal ultrafast-MRI might provide important information in exceptional cases and might be helpful in establishing a correct differential diagnosis [3,5,13,22–24].

4.6. Timing of treatment in CLM

The goals of antenatal treatment should be to prevent fetal demise and/or irreversible harm to lung development which would result in a disastrous postpartum situation. In our experience intrauterine treatment (e.g., puncture of pleural effusion or cysts, fetal surgery) or urgent postpartum surgical treatment should be recommended only in highly selected fetuses (i.e. progression of mass effects) since the large majority of CLM may be expected to present postpartum without any serious clinical signs and symptoms [4,12].

The aims of postnatal treatment are to improve and stabilize the clinical condition of the child and to prevent sudden lethal deterioration or development of complications (e.g., progressive respiratory symptoms, infection, and malignant transformation) [4,13,14]. The management of completely asymptomatic patients with suggested

decrease in size of the lesion is a controversial issue. Some authors advocate close clinical observation unless symptoms develop, whereas others favor elective resection within the first months of life in every case because of the risks of recurrent infection or malignant transformation [1,7,8,14,22].

4.7. Applied surgical procedures in CLM

In cases with a confirmed diagnosis of CLM an elective removal of PS and CAM should be performed before complications occur. EPS are managed with simple resection of the mass alone. In IPS, management presents more of a challenge, particularly when the patient has suffered repeated periods of infection which may produce dense, vascular adhesions and obliterate normal tissue planes. Lobectomy or segmentectomy will be the best suited procedures in most cases of IPS and CAM (Table 4). The argument for lobectomy is that an elective resection of a single lobe in an infant is very well tolerated [1,4,7–9,11]. Conversely, many reports indicate that methods of partial lobar resection (e.g., segmentectomy and non-anatomic resection) have not been as free of complications as complete lobectomy (e.g., persistent air leak, postoperative infection, higher incidence of recurrence) [4,7,11]. However, segmentectomy of the basal segments of the left lower lobe can be performed even in small infants. Non-anatomic resection has been applied in singular cases to preserve at least parts of a completely involved lung; otherwise surgery could have resulted in pneumonectomy.

The fact that surgery of CLM in the early infancy is well tolerated as well as the possibility of malignant transformation argues against recently reported interventional embolization of the anomalous vessel which also requires general anesthesia and could be difficult to perform in children [12,25].

4.8. Anomalous vascular supply to CLM

All applied surgical procedures must take into account the probabilities of anomalies of the vascular supply to the lung and/or the malformation. The most common vascular anomalies in CLM concern the systemic arterial supply in PS and CAM/PS hybrid type arising from the descending thoracic, abdominal aorta and its major branches. Preoperative depiction of anomalous systemic vascular supply makes surgery, which is often a rather simple procedure, less hazardous. The aberrant arteries may be extremely retractile and are often friable. Hence, at surgery the vessels and the inferior pulmonary ligament must be suture-ligated with care. Otherwise, the vessels can retract into the mediastinum or even into the abdomen and continue to bleed.

Major anomalies of the pulmonary artery branches could be predominantly expected in CAM and IPS. To recognize these varieties could be of great importance if segmentectomy or organ-sparing surgery is intended. Perception of an anomalous venous return during surgery is important because an unnoticed mismatch venous return of the entire right lung could lead to a catastrophic intraoperative situation (e.g., lung infarction) [8,12,18,24].

Prenatal and postpartum US, CT scanning, and MR imaging are non-invasive techniques that have been reported during the last decade to be well suited for evaluating anomalous vascular supply [4,18,24]. Thus, invasive techniques such as arteriography are reserved for exceptional cases.

5. Conclusions

The follow-up of an increasing number of antenatally diagnosed CLM has shown these lesions to be quite different from previously developed concepts in pathogenesis, diagnosis and treatment. The expected outcome is far better than thought to be possible. Therefore, it should be given due attention that prenatal diagnosis of CLM does not automatically mean that an infant should be subjected to pre- and/or postnatal intervention which might be inappropriate or unnecessary. In the case of postpartum confirmed diagnosis early treatment is intended to prevent unexpected deterioration or recurrent infections which could make surgical procedures difficult.

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