Congenital Parenchymal Lesions of the Lung

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Abstract: Increasing use of ultrasonography during pregnancy has uncovered a range of parenchymal lesions within the lung, some of which will, if left, be a cause of morbidity and occasional mortality. These include congenital cystic adenomatoid malformations (CCAM), bronchopulmonary sequestration (BPS), congenital lobar & segmental emphysema and bronchogenic cysts. Adverse antenatal features include mediastinal shift, caval obstruction, and (rarely) hydrops. This review aims to define current thoughts on these lesions and suggest appropriate management.

Keywords: Cystic adenomatoid malformation, bronchopulmonary sequestration, fetal hydrops, lobectomy.

INTRODUCTION

Congenital parenchymal lung lesions typically arise from disorganised development during embryogenesis whether congenital cystic adenomatoid malformation (CCAM), bronchopulmonary sequestration (BPS) or congenital lobar & segmental emphysema. It is likely that all but bronchogenic cysts share the same abnormal spectrum of developmental malformation [1-5].

The first clinical report of one of these lesions, CCAM, was reported in 1947 by Ch'in and Tang [6]. Bronchopulmonary sequestrations were first termed 'accessory pulmonary lobes' by Rokitansky in 1861, but later renamed 'pulmonary sequestration' by Pryce in 1946 [7, 8]. However, in comparison to infectious (TB and others) causes of pulmonary pathology, such congenital lesions remained a rarity to the practising clinician.

Garrett *et al*. first reported an antenatal diagnosis of a cystic lung lesion using greyscale ultrasound in 1975 [9]. Since that time there has been a huge increase in the detection of these lesions. Early reports in the obstetric literature [10-12] were characterised by large lesions, a marked association with other abnormalities and a poor prognosis. However, as technology evolved it has been increasingly realised that the majority can now be visualised antenatally, and that these are largely small lesions, which are usually asymptomatic in post-natal life. Whether they will remain so for the rest of that individual's life and hence could be left undisturbed is still unknown and controversial.

METHODS

A literature search was carried out using the PubMed, Medline and Google Scholar databases. Search terms included "congenital", "cystic", "adenomatoid malformation", "CCAM", "lung", "bronchopulmonary", "sequestration", "lobar emphysema", "segmental emphysema", "bronchogenic cyst", "lobectomy", "thoracoscopy", "antenatal intervention" and "hydrops". The search was expanded using the "related articles" facility in PubMed and by reviewing references from some of the articles.

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EMBRYOLOGY

The lower respiratory system begins to form during the 4th week of gestation with a median outgrowth from the caudal end of the ventral wall of the primitive pharynx. This, the laryngotracheal diverticulum, elongates to form the lung bud. The tracheoesophageal septum is formed from the fusion of the tracheoesophageal folds separating the foregut from the laryngotracheal diverticulum. Two bronchial buds are formed by the 5th week becoming secondary and tertiary bronchi by 7 weeks. Ultimately there are ~17 branching orders by 24 weeks. Respiratory epithelium is derived from the endodermal lining of the laryngotracheal tube and its mesenchyme gives rise to the connective tissue, cartilage, muscle, and vessels [13].

Parenchymal malformations although superficially heterogeneous in appearance, share a common embryology and may have a significant overlap. Langston [14] proposed that disordered development can be attributed to *in utero* airway obstruction. The level, timing and the completeness of the obstruction producing different patterns of lung malformations. Pathologic evidence exists for this obstructive mechanism, but the mode and timing of these events is currently poorly understood [14].

CCAM are derived from the proliferation of peripheral bronchiolar tissue at the expense of the alveolar tissues during fetal development [6]. Resected fetal CCAM lung specimens shows increased cell proliferation and markedly decreased apoptosis compared to gestational age matched normal lung tissues [2].

The embryological origins of BPS are from supernumery lung buds arising caudal to the main lung buds off the primitive foregut. These then continues to migrate caudally with the oesophagus. If these supernumery lung buds arise before the main lung buds it can be incooperated into the lung pleura making it an ILS, if they form after the main lung buds, these will be invested in its own pleura making it an ELS [15].

CLE is characterised by hyperinflation of one lobe (rarely more), secondary to bronchial obstruction (perhaps

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due to a cartilage defect) and a ball-valve effect [16, 17]. The usual lobes affected are the left and right upper [18, 19].

Bronchogenic cysts arise from defective development of the large airways (trachea/ bronchus) and share the same origin as duplication cysts of the foregut [17, 20]. They appear as thick-walled (smooth muscle, occasionally cartilage) cysts lined by respiratory epithelium [17].

There are murine models replicating CCAM-like lesions and a number of genes have been implicated in its pathogenesis, such as HOXB5, Fgf7 and Platelet derived growth factor B (PDGFB) [21-23]. PDGFB in particular is thought to be involved in branching morphogenesis, mesenchymal proliferation and induction of growth factors and mesenchymal – epithelial interactions. In humans, Liechty *et al*. reported high levels of PDGFB (and PDGF BB protein) in samples of cystic lung lesions, excised from fetuses with hydrops [21, 24].

CONGENITAL CYSTIC ADENOMATOID MALFORMATION (CCAM)

Some recent authors tend to use the term Congenital Pulmonary Airway Malformation (CPAM) as an all-inclusive title but we still favour the original given that the vast bulk of the quoted literature refers to CCAM.

There have been no studies on the incidence or epidemiology of CCAMs but it is the commonest lesion of the spectrum being reviewed. A single lobe is affected in over 95% [3, 5, 7] and can occur in any lobe with a predilection for the basal lobes. Bilateral lesions are uncommon (< 3%) but there is no particular side of preference. About 20% of infants will develop respiratory symptoms within the first month of life [25-27]. Associated anomalies are now observed to be unusual in those that are live-born although they are much more common in those that do not survive intrauterine life.

Colonel JT Stocker of the American Armed Forces, Institute of Pathology developed the most widely accepted post-natal classification of CCAMs describing three types (I – III) [25].

- Type I - large, often unilocular, cysts between 1 – 10cm in diameter with a lining of pseudostratified ciliated epithelium
- Type II – usually multicystic between 0.5 – 2cm in diameter with a lining of columnar epithelium (Fig. **2**)
- Type III – small cysts or solid appearance. Bronchiole like structures lined by ciliated cuboidal epithelium

Two further types (both rare) were added later and designated as Type 0 and type IV to fit in with the older nomenclature [28, 29] (Table **1**).

- Type 0 – (also known as acinar dysplasia). The lungs are small and firm throughout. Bronchial type airway, with abundant mesenchymal cells.
- Type 4 - tends to occurs at the periphery of the lobe and is lined with 'flattened' type 1 and 2 pneumocytes.

The characteristics histological features of CCAM are [25]:

1. Polypoid projections of the mucosa
2. Increased smooth muscle and elastic tissue within cyst walls
3. Absence of cartilage
4. Presence of mucus secreting cells
5. Absence of inflammation.

BRONCHOPULMONARY SEQUESTRATION (BPS)

In these lesions, predominantly solid lung tissue has no communication with the bronchial tree and its blood supply is derived from systemic blood vessels (e.g. the aorta). There is a long-standing division of sequestrations into intralobar and extralobar types dependent on appearance.

- *Intra Lobar Sequestration* – often embedded in normal parenchyma and covered by visceral pleura in continuity with the normal lung. The venous drainage is usually into the pulmonary vein [15].
- *Extra Lobar Sequestration* – invariably solid with its own separate pleural covering, separate from the normal lung.

Most sequestrations are medio-basal in location (left > right) and about 10% are actually located below the diaphragm (Fig. **1**). ELS may be found in association with about 10% of diaphragmatic hernias [3, 30], but other anomalies appear less common (e.g. chest wall anomalies, vertebral deformities, hindgut duplications and congenital heart disease [16, 31, 32]. A peculiar complication, not seen with CCAM, is high-output cardiac failure associated with the sequestration's redundant circulation and a left-to-right shunt.

HYBRID LESIONS

This term refers to the overlap between CCAM and sequestration [1, 2]. Several surgical series have shown that some lesions do not fit neatly into the above two categories and have been labelled hybrids. These can present with simultaneous intra-thoracic and intra-abdominal lesions [33]. Features include:

- Anatomical extralobar sequestration with histological appearance more compatible with CCAM.
- ELS and CCAM occurring in the same patient.
- Obvious CCAM-lesions in a lobe but with an accessory systemic blood supply.

CONGENITAL LOBAR & SEGMENTAL EMPHYSEMA

Lobar emphysema tends to involve the upper lobes, to present early with respiratory distress and tracheal and mediastinal displacement. They also appear relatively infrequently in the larger series of antenatally detected series suggesting that their prenatal US appearance is relatively innocuous. Rapid post-natal increase in size suggests a flap-valve effect in the lobar bronchus.

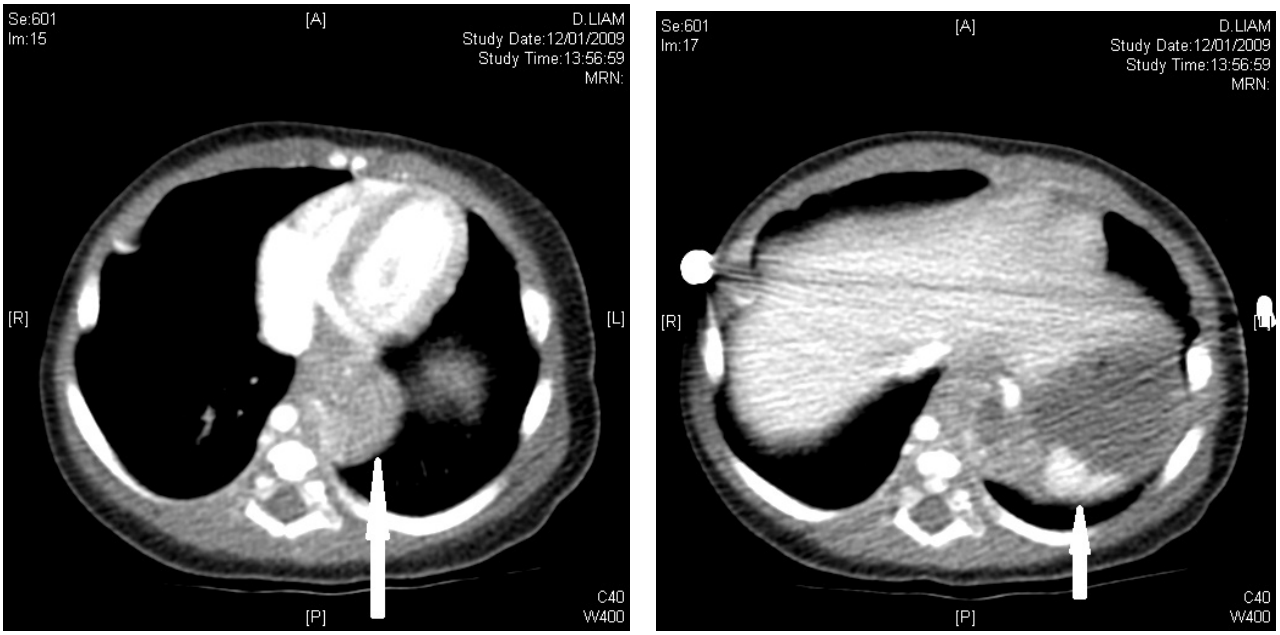

Fig. (1). Sub- diaphragmatic extra-lobar sequestration of lung on left side (arrowed).

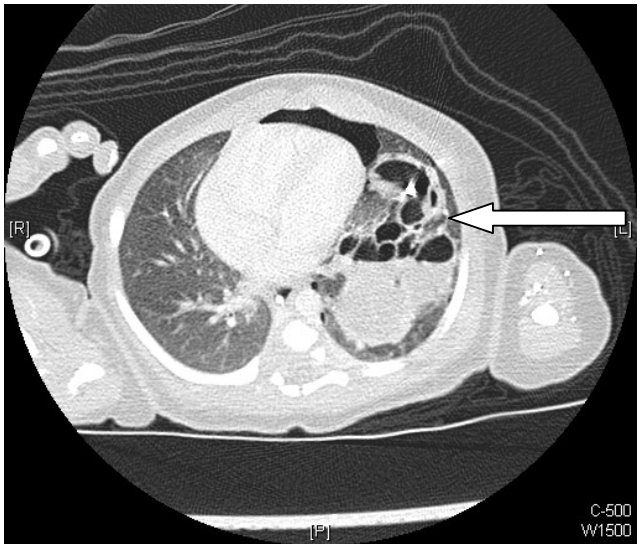

Fig. (2). Legend- Left- sided multicystic Type II CCAM, showing multiple fluid levels (arrowed) and a pneumothorax.

Congenital segmental emphysema (CSE) (sometimes referred to as peripheral bronchial atresia [34]), has been recently described. It is characterised by antenatal detection, early CT imaging showing a solid segmental appearance evolving to a more hyperinflated appearance during early childhood. This volume change appears to be related to the onset of symptoms and surgical excision is suggested.

BRONCHOGENIC CYSTS

Most are found in relation to the trachea and bronchi and hence present as mediastinal cysts. Occasionally detected antenatally, they may be obstructive to neighbouring viscera (e.g. oesophagus) or a focus for secondary infection.

CLINICAL INVESTIGATIONS & PRACTICAL MANAGEMENT

There are two distinct phases – before and after birth.

ANTENATALLY-DETECTED LESIONS

In those countries where ultrasound screening has been established fetal anomaly scanning at about 18 - 20 weeks gestation has been suggested as detecting close to 100% of all parenchymal lung lesions [35, 36]. There is no real way of checking the veracity of this statistic however. Current tools include:

Ultrasound Scan

Precision 3D imaging coupled with colour Doppler ultrasound allows for accurate anatomical definition and an appreciation of its vascular anatomy [26].

MRI Scans

Fetal MRI is gradually gaining in popularity. As there is no known biological risk, this makes it an ideal adjunct to antenatal US, especially with the fast imaging sequence [37]. In practice, most obvious lesions do not need MR imaging as the likelihood of prenatal intervention is small and definitive diagnosis can be left to the post-natal period. It may have a role in areas of diagnostic doubt in trying to differentiate from neuroenteric cysts, diaphragmatic hernia etc. [38-43].

The doyen in this field, Scott Adzick [44], divided cystic lung lesions simply by size into ***microcystic*** (< 5mm) and ***macrocystic*** (>5mm). This reduces the need to define the actual histological diagnosis as a high proportion of microcystic lesions specifically turn out to be things other than CCAM. However identified, only a small proportion (~5%) interfere with normal lung growth and become symptomatic before birth.

Possible symptoms include polyhydramnios [44-46], mediastinal shift and ultimately hydrops (i.e. skin oedema, pleural effusion or ascites [47, 48]). The development of hydrops is probably the only specific adverse indicator of postnatal outcome. Some authors have attempted to define measurement of antenally-detected CCAM volume in relation to head circumference and use this as a basis for prognostication [47, 49]. However this remains controversial and is not widely used outside of the USA [50].

From 6 - 11% of antenatally-detected lesions "vanish" during the 3rd trimester [5, 51, 52]. Generally, these are microcystic rather than macrocystic lesions and may correspond to Stocker type 3 lesions which become isoechogenic to adjacent normal lung tissue at around 32 - 34 weeks gestation. Even obvious lesions with demonstrable hydrops have been reported as regressing, though this remains rare [10, 11, 52]. BPS can also disappear antenatally as they either outgrow their vascular supply or undergo torsion around their vascular pedicle [53, 54]. Similarly, spontaneous antenatal resolution of CLE has been reported in the 3rd trimester [55].

The key point is not to accept this as fact, until appropriate post-natal CT scans have been performed. In our own series, 45% of antenatally "resolved" lung lesions went on to have surgery for real, significant residual lesions [1].

ANTENATAL INTERVENTION

Options for antenatal intervention for complicated lesions include:

- Steroids [49, 56]
- Thoracocentesis and thoraco-amniotic shunts [57, 58]
- Percutaneous transamniotic laser therapy [59-61]
- Fetal lung resection [61, 62].

STEROIDS

Maternal steroids may be effective in controlling the growth of CCAM [49, 56, 63]. In one series reported by Paranteau *et al*. from Philadelphia there was a 100% survival in fetuses with hydrops when a 100% mortality was expected [63]. This however was not a trial and may for some simply represent the natural course of the CCAM. Nonetheless steroids may be an alternative to open surgery for fetuses with hydrops and large multicystic or predominantly solid lesions. To date, there has been no randomised controlled trial.

THORACOCENTESIS AND THORACO-AMNIOTIC SHUNTS

The first reported thoracoamniotic shunt placement was by Clark in 1987 [12]. Although early reports were disappointing; with improved patient selection, recent results have been much better with up to 70% survival to birth [36,48,57,58,60,62,64]. The main indication is an antenatally-diagnosed symptomatic macrocystic CCAM or for a BPS with significant pleural effusion [59]. In a series of 170 antenatally-diagnosed CCAMs from our institution: 8 fetuses with significant pleural effusion (but non-hydropic) had thoraco-amniotic shunts placed and all survived; 6 others had large dominant cysts which caused significant mediastinal shifts and had cyst-amniotic shunts placed at 22-27 weeks gestation with delivery at 36-39 weeks gestation. All these infants survived and 5 went on to have post-natal surgery. Nine fetuses had hydrops with their CCAM, out of these 4 had macrocystic disease. The 3 fetuses with macrocystic disease who had thoraco-amniotic shunts placed, survived, whereas the one who did not died [59].

Multiple weekly serial aspirations is a less attractive alternative, although, it could be a guide to the need for shunt. A successful outcome form serial aspiration was achieved in a report where the fetus had hydrops secondary to CCAM with multiple large cysts, not amenable to thoracoamnotic shunt and the mother refused fetal surgery [65].

PERCUTANEOUS TRANSAMNIOTIC LASER THERAPY

Solid lung lesions which are causing mechanical compression, mediastinal shift and caval obstruction may be treated by antenatal laser coagulation of the feeding vessels. This may shrink the size of the lesion and in some cases has resulted in complete resolution. In our institution, laser therapy resolved the significant pleural effusion in all 8 fetuses with sequestration and 3 required no post natal surgery as some of the lesions disappeared [59].

FETAL LUNG RESECTION

In 2003, Adzick *et al*. described their series of 175 fetuses with antenatally diagnosed lung lesions. Fetuses with hydrops and large multicystic or predominantly solid lesions had fetal lung resection. Of the 22 who had this, 11 had resolution of their hydrops, return of the mediastinum to the midline and good lung growth within 3 weeks after surgery. The other half died either *in utero* or shortly after birth [44]. Grethel *et al*. reported their series of 294 fetuses over a 15 year period. The survival rates of fetuses with hydrops and no antenatal interventions was 3%, that of their 30 fetuses having had open fetal surgery was 50% and 10 fetuses with thoracoamniotic shunts was 30% [62].

POSTNATAL INVESTIGATION AND MANAGEMENT

Neonatal respiratory distress due to functional diminution in lung volume (usually CCAM but rarely CLE) is actually an uncommon mode of presentation *de novo*, for the reasons outlined above. Those likely to cause such problems should have been detected on antenatal ultrasound and transferred *in-utero* to specialist centres. Nonetheless about 7% of neonates have symptoms at birth and they should proceed to emergency surgery [66]. Substantial ventilatory support or even ECMO postnatally may be required [48, 49], and is associated with about a 7% mortality rate [66].

Later on during infancy and beyond, cystic lesions and even those BPS without apparent communication with the bronchial tree are liable to infection (pneumonia, lung abscess, empyema etc). Our systematic literature review suggested that the median age of symptom development was 10 months and complications and mortality rates following surgery when performed as an emergency was 17% and 3%

respectively. Elective surgery was associated with a 5% complication rate and 0.3% mortality [66].

IMAGING

A plain chest X-ray of the on the first day of life will give a gross indication of the size of normal lungs or if there is significant mediastinal deviation – however it should not be relied upon to exclude what could be significant parenchymal pathology.

The imaging modality of choice remains the CT scan [5, 52, 67], which will define the volume of lung affected, type of predominant lesion (macro *versus* micro, hyperinflated *versus* solid etc.) associated effusions (BPS and secondary infection) and presence of accessory vessels (BPS and hybrids) etc. Though the correlation certainly of the latter feature with CT imaging has been disputed recently [68].

TO OPERATE OR NOT THAT IS THE QUESTION - MANAGEMENT OF ASYMPTOMATIC CCAMs

Most infants with antenatally-detected lesions are entirely asymptomatic. However a decision needs to be made to try and identify those who may develop symptoms from those where their pathology is minimal and will never cause harm.

There are three possible justifications for "prophylactic surgery":

1. Prevention of chest infection and sepsis
2. Prevention of malignancy
3. Early, rather than delayed, surgery may encourage compensatory lung growth [69].

Some surgeons adopt a "wait and see" approach for all their patients [70, 71]. This allows the remainder of us to judge perhaps the true natural history. Thus, Butterworth *et al*. from Vancouver suggests that spontaneous resolution of CCAM occurs in about 4% [72]. In their series, 2 of 56 children over a 7 year period spontaneously disappeared. One case reportedly was a CCAM occupying the whole of the hemithorax at one point antenatally. However, this had decreased substantially before birth and at the 9 months CT scan the lesion measured 2cm, disappearing by 37 months.

The conservative "do nothing" approach will still involve serial imaging and preferably by CT scan. There are perhaps unrealistic reports of deaths secondary to malignancies caused by CT radiation in childhood with an estimated risk of 1 death in every 1200 CT scans. Obviously this is compounded if there are additional CT scans [73, 74]. Of course, newer CT scanners will have reduced radiation doses [75, 76] and moreover, MRI technology, may at some time be good enough to replace CT in this field [77].

The alternative is to subject any patient diagnosed with a *significant* (however defined) lesion to excisional surgery. We recently reported a systematic review [66] of 41 reports with about 1070 patients. This showed that there was about a 3% incidence of respiratory complication in those treated conservatively following antenatal detection but asymptomatic initially at a median age of 6.9 months. The complication rate for elective surgery for children above 1 months of age was 5% and the mortality was 0.3%. Whereas the complication rate in neonates was 9% with no mortality [66]. There was a 2.8-fold increase in risk of morbidity associated with surgery after symptoms versus elective surgery.

Our preference is to offer elective surgery before 10 months of age, trying to avoid increased anaesthetic risks during the neonatal period.

MALIGNANCY RISK IN CCAM

CCAMs are associated with risk of malignancy not seen in BPS, CLE or bronchogenic cysts. The problem is the quantity of risk is not known with any degree of certainty.

Currently there are a number of case reports linking CCAM in children and (usually) adults with specific lung malignancies such as:

- Pulmonary blastoma [78, 79]
- Pulmonary rhabdomyosarcoma [80, 81]
- malignant mesenchymoma [82]
- bronchioloalveolar carcinoma [83, 84]

There are published cases of blastomas, malignant mesenchymomas and rhabdomyosarcomas arising from congenital cystic lung malformation [78-86]. However, there have been no series of such malignancies, nor series of untreated CCAMs resulting in malignant transformation to gain any idea of the actual risk. Type 1 CCAM is associated with later development of bronchioloalviolar carcinoma (see also Table **1**). But once again the risk of actual malignant transformation is not known.

LUNG GROWTH POST SURGERY

The lung continues to develop up to the age of 2 years in children. It is believed that lung resection at an early age allows for compensatory lung growth. However a retrospective study by Keijzer *et al*. does not convincingly prove this reiterating the need for a randomised controlled trial [69].

POST-NATAL SURGERY

Currently, most excisional surgery is performed using conventional techniques. The thoracotomy ($3^{rd}/4^{th}$ or $4/5^{th}$ space) in our opinion should be performed using a muscle-splitting rather than muscle-cutting approach [87]. In general, lobectomy is preferred to segmentectomy or non-anatomical wedge resection as there is a recurrence rate following the latter variations of up to 15% [1, 66]. However, where more than one lobe of the lung is involved (unusual), then lung-sparing surgery has to be performed [88]. Preoperative identification of aberrant vessels is important for prevention of operative morbidity and should aid vascular control before the lobectomy is begun [89]. For those adults not being born in the modern antenatal scans era, identified to have congenital cystic lung lesions, face a risk of these cysts turning malignant. As we are recommending surgical resection for antenatally diagnosed cystic lung anomaly, we would suggest the same for these adults [90].

Table 1. Classification of Congenital Cystic Adenomatoid Malformation

CCAM Type (CPAM)	**(0)**	**1 (1)**	**2 (2)**	**3 (3)**	**(4)**
Description	**Acinar Dysplasia or Dysgenesis**	**Macrocystic**	**Macro or Microcystic**	**Microcystic**	**Unlined Cyst**
Possible airway origin	Tracheal/bronchial	Bronchial/bronchiolar	Bronchiolar	Bronchiolar/alveolar	Distal acinar
Cystic?	No	Yes	Yes – multiple	No	Yes
Adenomatoid?	No	No	No	Yes	No
Proportion of CCAM	<2%	60-70%	15-20%	5-10%	10%
Unique feature	All lobes involved			M > F	Pneumothorax
Associated anomalies	Cardiovascular, renal, dermal		Cardiovascular, diaphragm, renal, sequestration		Familial neoplasia
Lesion size	Small lungs	1 - 10cm	0.5 – 2.0cm	Entire lobe or lung	Large multilocular cysts
Malignancy risk	no	BAC	probable	probable	Pleuropulmonary Blastoma

Notes: BAC - Bronchioloalveolar carcinoma.
Taken from Stocker [25,28], Priest [94] and Bush [95].

THORACOSCOPY

Thoracoscopic procedures are now more regularly being performed. Steven Rothenberg from Denver, Colorado has reported the largest series to date with 97 lobectomies (56 for CCAM, 9 for CLE and 9 for sequestration) and a conversion rate of about 3% [88]. The main difficulty reported during thoracoscopic procedures are the safe control of major vascular structures (Fig. **3**). Comparative studies are few and show little difference in terms of outcome, apart from arguably better cosmesis in the thoracoscopic group [88, 91, 92]. Minimally invasive resection of CCAM results in longer operative time but shorter hospital stay and decreased post-operative pain [88, 89]. Thoracoscopic lobectomy in patients with a history of pneumonia is challenging and a risk factor for conversion to thoracotomy [92, 93].

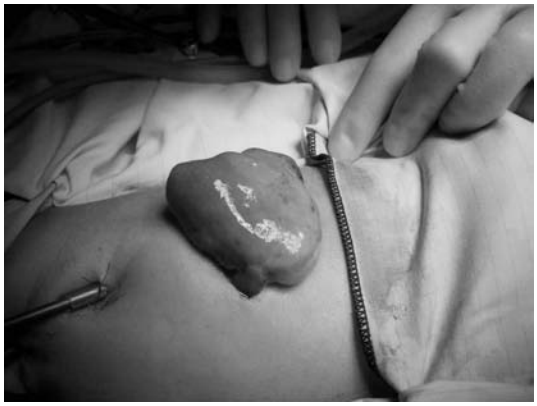

Fig. (3). Lung sequestration excised thoracoscopically.

CONCLUSIONS

While congenital cystic lung lesions (including CCAM etc.) are certainly uncommon they have the potential to cause significant morbidity and mortality. Proper identification of those likely to develop early symptoms is a key part of antenatal detection so that they can be born in an appropriate environment for surgery and respiratory care.

While previous generations of surgeons were only presented with the tip, antenatal detection has now allowed us to consider probably the entire iceberg. Future studies will be directed at those we can safely leave alone and those who have a higher risk of complications – especially malignancy.

ABBREVIATIONS

CCAM = Congenital cystic adenomatoid malformations

BPS = Bronchopulmonary sequestration

CLE, CSE = Congenital lobar & segmental emphysema

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