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Congenital Cystic Lung Lesions: Redefining the natural distribution of subtypes and assessing the risk of malignancy

Jennifer Pogoriler, MD PhD,

Children's Hospital of Philadelphia, Department of Pathology and Laboratory Medicine, Philadelphia, PA

Daniel Swarr, MD,

Division of Neonatology & Pulmonary Biology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Portia Kreiger, MD,

Children's Hospital of Philadelphia, Department of Pathology and Laboratory Medicine, Philadelphia, PA

N Scott Adzick, MD,

Children's Hospital of Philadelphia, Department of Surgery, Philadelphia, PA

William Peranteau, MD

Children's Hospital of Philadelphia, Department of Surgery, Philadelphia, PA

Abstract

Asymptomatic cystic lung lesions – congenital pulmonary airway malformations (CPAMs), sequestrations, and bronchogenic cysts - are commonly diagnosed prenatally. Indications to resect are to eliminate risk of malignancy or infection. CPAMs consist of a spectrum of malformations, with type 1 historically considered the most common. Mucinous cell clusters, seen almost exclusively in type 1, are pre-malignant lesions at risk for progression to mucinous adenocarcinoma. We reviewed and classified 2.5 years of consecutive, prenatally diagnosed lesions as extra lobar sequestration, intralobar sequestration, type 1 CPAM, type 2 CPAM/ bronchial atresia or “other” to determine the distribution of lesion types and risk of malignancy. 184 lesions in 174 patients showed type 1 CPAM to be least common subtype. Type 1 CPAMs had more severe presentation, infrequently had features of obstruction, and usually had cysts ≥ 2 cm. 15/18 type 1 CPAMs had mucinous cell clusters (total risk 8%), with mucous cells outside main cyst in 12/15. No pleuropulmonary blastomas were identified. Additional historic cases were reviewed to further evaluate risk of malignancy. Over 14 years, 28 infants with fetal/type 1 lesions were identified, with clusters of mucinous cells in 75% of cases. A total of 9 pleuropulmonary blastomas were diagnosed in 6 patients over 16 years. Contrary to historical studies, type 1 CPAMs are much less common than type 2, likely related to detection of asymptomatic lesions

Address for correspondence: Jennifer Pogoriler, Assistant Professor of Pathology and Laboratory Medicine at the Children's Hospital of Philadelphia, The Children's Hospital of Philadelphia, Department of Pathology and Laboratory Medicine, 3401 Civic Center Blvd - 5th Floor Main Building Suite 5NW13, Philadelphia PA 19104, Phone: 215-590-1735, Fax: 215 590 1736, pogorilerj@email.chop.edu.

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prenatally. A majority of type 1 CPAMs contain mucinous cell clusters. This data is useful in management of patients in centers that do not resect asymptomatic lesions.

Introduction

Congenital pulmonary airway malformations (CPAMs) consist of a spectrum of cystic or non-cystic lung malformations often associated with bronchial atresia during *in utero* development. Several classifications for these lesions have been proposed using radiologic or pathologic criteria based on cyst size and histology, with the Stocker classification being perhaps the most commonly used in the pathology literature (1). Although the modified Stocker classification includes 5 types, types 1 (large cyst) and 2 (small cyst) are by far the most common in published series. Histologic findings similar to type 2 are often seen in both extralobar (ELS) and intralobar sequestrations (ILS) (2, 3), giving rise to the term “hybrid lesion.” However, continued radiologic and pathologic studies of these specimens have demonstrated that bronchial atresia or other causes of bronchial obstruction are identified in the majority of specimens with type 2 changes, suggesting a common pathogenesis and giving rise to the term “bronchial atresia sequence” to describe lesions whether or not they have a systemic blood supply (4–8).

Cases of cystic lung malformations were historically identified incidentally as part of a postnatal evaluation for other anomalies or following symptomatic presentation including hemodynamic or respiratory compromise in newborns or infection in older infants or children. Now, with near universal prenatal ultrasound, these lesions have been shown to be much more common and to have few associated developmental anomalies (9). Although most lesions decrease in size toward the end of gestation and are asymptomatic at birth, the vast majority of asymptomatic patients still have abnormal postnatal CT findings. The decision to observe or to remove asymptomatic lesions is controversial, but early surgery is well tolerated with less morbidity than in a symptomatic child and will reduce the risk of recurrent infections (10–12). Other arguments in favor of early surgery include allowing compensatory lung growth and removing potential malignancies (either pleuropulmonary blastoma (PPB) or mucinous adenocarcinoma) (13). Our institution is a large referral center for fetuses with congenital lung lesions, and all asymptomatic infants except those with asymptomatic, non-cystic ELS are treated with lobectomy, generally at 6–8 weeks of age (14). Symptomatic fetuses may be offered thoracoamniotic shunt and/or maternal steroids to reduce lesion size or open fetal surgical resection followed by a variety of delivery, resection and postnatal supportive care options (15–17).

Older series of CPAMs suggest that type 1/large cyst lesions are the most common type of CPAM. This subtype may have mucinous cell clusters that contain oncogenic KRAS mutations and may very rarely give rise to mucinous adenocarcinoma—one reason to remove the malformations prior to becoming symptomatic. In our experience type 1 lesions are relatively uncommon, possibly reflecting a historic bias toward symptomatic infants (4, 18–23). Some lesions have mixed features and are difficult to classify using traditional criteria, which consist of combined cyst size, wall thickness, type of epithelial lining, and presence or absence of additional features such as mucinous cells. CPAMs resected during fetal life

do not easily fit the existing classifications (24, 25), and lesions resected in very young infants may still be undergoing some degree of evolution in size and morphology of the cysts.

In the current study we review the histology and associated clinical findings in a large group of prenatally diagnosed cystic lung lesions to determine the distribution of lesion types, their relative risk of malignancy, and the most consistent histologic features for defining these subtypes. The patient population in this study has both symptomatic and asymptomatic lung lesions and is reflective of the increase in diagnosis of asymptomatic lung lesions in the setting of current day routine prenatal ultrasound.

Materials and methods

With institutional review board approval, resected cystic lung specimens from patients with prenatally detected lesions were identified in the pathology files of the Children's Hospital of Philadelphia from January 2013- June 2015. Associated clinical information was obtained by retrospective chart review. Hematoxylin and Eosin stained slides were reviewed blinded to the original diagnosis, gross description, and clinical information. Cases were evaluated for areas of classic Stocker type 1 or type 2 histology (1). Lesions with cysts containing smooth muscle in the wall with pseudostratified epithelium with abundant papillary infoldings and abrupt transitions to thinner alveolar spaces were classified as Stocker type 1 regardless of histologic cyst size. Cases with a single large cyst that did not communicate with smaller airways/alveoli were defined as intrapulmonary bronchogenic cysts. In contrast, cases with more uniform, multiple thin-walled cysts with columnar epithelium were classified as type 2. Lesions without a clear cystic component characterized by dilated bronchioles and enlarged alveoli typical of congenital lobar overinflation/bronchial atresia were included in this group as part of the recognized spectrum of bronchial atresia sequence that is histologically indistinguishable from the spectrum of type 2 CPAM. The presence of bronchiolar-lined dilated cystic spaces unaccompanied by a pulmonary artery were used to define classic type 2 features. Lesions which were received morcellated due to thoracoscopic surgical technique were not inflated and were excluded from detailed histologic analysis other than the presence or absence of mucinous cell clusters.

All cases were evaluated for vessels with a thick-walled systemic appearance, features of airway obstruction (airway mucostasis or foamy macrophages), clusters of mucous cells and any other pathologic diagnosis. Intralobar (ILS) and extralobar (ELS) sequestrations were defined based on surgical findings as lesions with a systemic blood supply either within a given lobe or invested in their own pleura respectively.

After initial blinded review, all cases for which a discrepancy was identified with the original diagnosis were reviewed by two pathologists (JP and PK) for a final classification.

Statistical analysis was performed using chi squared test for categorical data and Kruskal-Wallis test for continuous variables.

Results

Over a 2 ½ year period we identified 184 surgical specimens from 174 infants with congenital lung lesions. There were 29 (16 %) ELS, 45 (24%) ILS, 81 (44%) type 2/ bronchial atresia sequence specimens, 18 (10%) type 1 CPAM (Table 1), 9 (5%) bronchogenic/foregut cysts and 1 case of diffuse right sided hyperplasia. Two cases were so extensively morcelated that the histology was impossible to interpret regarding type 1 vs type 2. There were no cases of pleuropulmonary blastoma or acinar dysplasia. Overall 11 patients (6.3 %) had more than one separately resected cystic lung lesion including 4 patients with two type 2 lesions, 3 patients with a type 2 lesion and bronchogenic cyst, and 1 patient each with type 2 + ELS, ILS + ELS, ILS + bronchogenic cyst, and ELS + bronchogenic cyst. No patient with a type 1 CPAM had a second lesion. Aside from other cystic lung malformations, other significant developmental anomalies were rare (Table 1) and included congenital diaphragmatic hernia and ventricular septal defects.

The CPAMs were classified as closely as possible according to the Stocker classification, giving preference to microscopic findings over strict cyst size (see below) since the histology was reviewed blinded to the gross description and the radiology findings. Cases with fetal features (immature mesenchyme and cuboidal/columnar alveolar cells) were given a best fit as type 1 or type 2. Features such as thickness of cyst wall and pseudostratified vs columnar type epithelium were generally not helpful as they often varied along the cyst wall and could be seen within the area of dilated bronchus corresponding to a mucocele or within a bronchogenic cyst, leading to confusion with type 1. However, the type 1 CPAMs consistently showed frequent abrupt transitions in the larger cysts between relatively thick walls and alveolar-like sacs (17/18) (Figure 1a) and frequent minute papillary projections (15/18) (Figure 1b). Findings suggestive of airway obstruction (bronchiolar mucous/ muciphages) were rare in type 1 (table 2), although most cases had aspirated squamous cells, consistent with the young age of the patients at the time of resection. The lung tissue surrounding the larger cysts of type 1 showed a variety of features ranging from enlarged alveoli to bronchiolar-like cysts similar to type 2 CPAM to immature mesenchyme with cuboidal to columnar epithelium (1c) to increased numbers of peripheral alveolar spaces (Figure 1d). No case diagnosed as Type 1 had a systemic arterial supply.

In retrospectively reviewing grossly reported cyst size, most but not all type 1 CPAMs had cysts larger than 2 cm, while large cysts were occasionally also seen in each of the other types (Table 2). Among patients with type 1 CPAMs, the majority (15/18, 83%) showed clusters of mucous cells (Table 2). In 3 cases these mucous cell proliferations were restricted to a few small clusters in the large cyst component. However, they usually formed both small papillary projections within the large cysts (Figure 2a) as well as lining the small surrounding spaces (Figure 2b). Given the complex architecture of the surrounding airspaces, it was often impossible to determine whether these represented spread along small convoluted airway-like spaces or spread into the abnormal alveoli, although given their size at least some involvement of alveoli was suspected.

The non-type 1 cases without a systemic blood supply showed a spectrum of findings ranging from classic type 2 CPAM morphology with bronchiolar-epithelium lined cysts

(unaccompanied by pulmonary artery branches) (Figure 3a) to a more subtle parenchymal maldevelopment consisting of prominently dilated bronchioles paired with small pulmonary arteries and with intervening enlarged alveoli as seen in congenital lobar emphysema (Figure 3b). One case resected from a 29 week gestation neonate showed some areas of type 2 with surrounding areas of immature polyalveolar lobe. In many cases there was a spectrum between classic type 2 areas and areas of lobar emphysema, and these specimens were all grouped as type 2/bronchial atresia cases. In morcellated cases these features were often difficult to distinguish, but among intact specimens, 71% showed at least a small focus of bronchiolar-lined cysts. Evaluation of lesions with systemic blood supply (ELS and ILS) revealed the same spectrum of histology described above in both intralobar and extralobar sequestrations with the exception of a single intralobar sequestration that showed no parenchymal abnormality (Table 2). In contrast to type 1 cases, the majority of cases of type 2/bronchial atresia sequence cases and sequestrations showed indirect features of airway obstruction (mucous plugging and muciphages) even if a mucocoele was not identified grossly (Table 2). A single intralobar sequestration (resected from a 34 month old patient) had plexiform arterial lesions.

Although many cases had been signed out descriptively or without subtype designation, factors that led to a discrepancy between review category and original diagnosis included borderline cyst size, fetal/preterm resection with fetal categorization, morcellation, or presence of a “large cyst” that on review was most consistent with a dilated bronchus.

In order to further examine risk of malignancy in pediatric cystic lung lesions, the database was searched for cases of PPB between 1997 and 2015 during which time approximately 820 cystic lesions were resected at our institution. A total of 9 cases of PPB arising in 6 patients (~1%) were identified with a median age of resection of 500 days. In 2 cases these had cysts larger than 2 cm. An additional search for type 1/large cyst/mucous cell/goblet cell containing lesions in infants was performed from 2000 to 2013 and identified 53 lesions in 52 patients. Of these, 24 appeared to be bronchogenic cysts or dilated bronchus as part of bronchial atresia. Twenty-nine lesions from 28 patients were confirmed on re-review to be relevant. Three cases had cysts < 1 cm in size, and 2 of these had markedly immature mesenchyme consistent with that described for fetal cases. The others had typical type 1 features. The median age of resection was 2 days. Clusters of mucous cells were seen in 21/28 patients (75%). These were limited to small clusters inside the larger cysts in 6 cases; 14 cases extended into smaller airspaces. Given the immature stroma or abnormal size and shape of surrounding alveoli, it was often impossible to definitively determine whether this involved small airways or “alveoli.”

Clinical signs of severity were markedly more frequent in type 1 patients (Table 1). Prenatal thoracoamniotic shunts had been placed in 5/18 (28%), and there was a trend towards increased use of maternal steroids in this group. The majority of type 1 patients required surgery in the first days of life as well as mechanical ventilation. An EXIT (Ex-utero intrapartum treatment) procedure with resection of a large lung lesion while the infant remained on uteroplacental support was performed in 2 patients both of which had type 1 lesions. Several type 1 patients had pulmonary hypoplasia as a complication of their lung lesion. ECMO was required secondary to postnatal respiratory failure in 5 patients, 3 of

which had type 1 lesions. Two patients (one with a type 1 CPAM, one with diffuse hyperplasia) died in the postoperative period.

A previous study demonstrated squamous cells or debris embedded on the pleural surface following placement of a thoracoamniotic shunt [45]. Among 19 total patients with type 1 lesions that had been treated by thoracoamniotic shunt in our series, 9 (47%) demonstrated this finding (Figure 4). There were no obvious clinical correlations between patients with and without this feature.

Discussion

This work represents the most comprehensive pathologic analysis of a series of congenital cystic lung lesions published to date. With the exception of small, non-cystic ELSs that are not resected at our center, this series is expected to represent the natural distribution of pediatric cystic lung lesion types and may not reflect the distribution of lesions in centers with different surgical practices. The relatively small proportion of prenatally diagnosed type 1 CPAMs contrasts with the original series in infants (1), more recent adult series (21), and recent symptomatic pediatric series (18) in which type 1 was the most common type. Another, smaller recent series (26) of prenatally detected lesions showed fewer type 1 cases. The results of the initial 184 consecutive cases of prenatally diagnosed cystic lesions are overall consistent with the relatively few lesions detected in our larger historic search for these lesions. Our data is consistent with the hypothesis that most type 1 lesions are symptomatic and historically would have been detected postnatally and resected, while the relatively asymptomatic type 2 lesions would have been undetected. This is also consistent with the younger age of patients with type 1 lesions compared to those with type 2 lesions reported to the PPB registry (27) as well as the younger age at the time of resection for type 1 lesions in the current study. The large size of our study also provides a more accurate estimate of the risk of malignancy for the purposes of counseling patient families at centers where lesions are not universally resected.

A number of classification schemes for pediatric cystic lung lesions exist including those based on radiology. Fetal ultrasound divides patients into “micro-” and “macro-” cystic cases based on a 5mm cut-off size (28). The significance of this classification lies in the possibility of treating large macrocystic or microcystic lesions causing or threatening to cause hydrops fetalis with a thoracoamniotic shunt or antenatal steroids respectively and fetal surgical resection for those that fail to respond to these interventions (9, 15, 29, 30). Specific postnatal histologic features do not alter this important prenatal classification but may give us a better understanding of the underlying pathogenic mechanisms. More importantly, pathologic examination allows for evaluation of malignant or premalignant lesions and assessment of their completeness of resection.

Multiple pathologic classification schemes have been proposed, with perhaps the Stocker classification (1) most commonly referenced in the literature. This classification has been legitimately critiqued because it brings together lesions of distinct etiologies under the heading of CPAM including acinar dysplasia (type 0), pulmonary hyperplasia (type 3) and cystic PPB (type 4) (4). Despite this shortcoming, types 1 and 2 remain as relatively useful

classifications. Type 3 is extremely rare, and while some authors suggest that it reflects hyperplasia of an entire lobe rather than a discrete lesion, the described histology corresponds to a subset of CPAMs described in fetal classification schemes. These lesions resected from pre-term infants may have markedly immature appearing parenchyma. Some of these in our large historic series contain mucous cells. The proposed alternative pathologic terms “large cyst” (type 1) and “small cyst” (type 2) (4) with a cut off of 2 cm, has also been used but can lead to confusion with the macrocystic and microcystic radiology definitions when communicating with clinical colleagues or to confusion of an intraparenchymal bronchogenic cyst with a type 1 CPAM. This scheme may also place undue weight on cyst size as the overriding diagnostic criteria, despite the fact that this gross measurement may depend on degree of inflation, plane of sectioning and prosector attention.

Terminology regarding bronchial atresia, congenital lobar emphysema, and type 2 CPAM is also controversial. Bronchial atresia can be identified in almost all of these cases if detailed microdissection is performed (5, 7), but this is not practical in a busy clinical setting. In our review, a range of morphologies is seen within and between specimens, and unless a specimen is entirely submitted it is impossible to exclude a focus of classic type 2 CPAM. There is currently no known clinical relevance to these distinctions, and many are signed out descriptively in our institution. Similarly, while the designation of “hybrid lesion” may be used for a lesion sharing features of classic type 2 CPAM and sequestration (3), all sequestrations have abnormal parenchymal development on the same spectrum as type 2 CPAM/bronchial atresia, and for the purposes of limiting our categories we did not separate hybrid lesions in this study. Strict definition of ILS requires both a systemic artery and absence of connection to the tracheobronchial tree. However, it was impossible to universally definitively assess this feature in a retrospective pathologic review, so we have more simplistically classified all intralobar lesions with a systemic artery as ILS.

Although cyst size frequently correlated with histology, it was not a perfect predictor of histologic classification and could not predict all cases that should be resected based on the risk of containing pre-malignant mucinous cells. Cyst size presumably changes over time in a developing fetus/growing infant: mucinous cell clusters are seen in a significant number of fetal CPAMs of varying morphology and cyst size (24), though the majority of these lesions presumably would have developed into postnatal type 1 CPAMs if the fetus were stable enough to survive to term. However, in not all of these cases was obvious type 1 histology present and some authors might consider these type 3 lesions. Several cases originally diagnosed as “large cyst” type were reclassified histologically in our study as either bronchogenic cysts or areas of bronchial dilation with adjacent type 2 CPAM (1, 4).

Treatment of asymptomatic lung lesions is often the source of discussion and is variable depending on referral center. Some institutions advocate nonsurgical management with continued observation. (31). However, we and other institutions, recommend surgical resection of the involved lung lobe to prevent infection and exclude malignancy. This recommendation is based on the fact that a proportion of patients with asymptomatic lung lesions will go on to develop symptoms/infections, the incidence of complications from resection of an asymptomatic lung lesion is low, and the complication rate significantly increases following surgical resection after symptom development (12, 32).

Risk of malignancy in this population remains poorly defined. One report suggested that 2/69 asymptomatic cases (2.9%) contained tumors – specifically PPBs (33); however Dicer1 mutation status was not reported, and one of the two cases treated as PPB was a hybrid lesion with “rhabdomyomatous dysplasia.” Scattered skeletal muscle fibers with cross striations have long been reported as a component of some type 2 CPAMs and sequestrations (1, 2). No published evidence has suggested that these findings represent a form of PPB or any other malignancy. No PPBs were identified in our initial cohort, and only rare PPBs in older infants were identified in our larger historic series. PPBs in our institution were extremely rare. While the risk of PPB cannot be entirely dismissed in the prenatal group, it should also not be overestimated in this population, and radiologic and clinical criteria to suggest concern for PPB over CPAM have been published (34).

More problematic is the risk of mucinous adenocarcinoma arising in type 1 CPAMs. Clusters of mucous cells either lining the large cysts or in the surrounding alveoli were originally reported in 32% of type 1 cases, and multiple cases of mucinous adenocarcinoma (35–37) with metastasis have been reported in young adults and children in association with CPAM type 1. Chromosomal aberrations (38) as well as k-ras mutations (39) have been detected in both the small foci of intracystic “goblet cell hyperplasia” as well as the areas of mucinous adenocarcinoma, supporting the idea that these are precursors to carcinoma. Published terminology regarding these mucinous clusters has been variable and subjective, depending on factors such as whether the mucinous cell clusters are in the large cysts or surrounding alveoli and whether they are “small” or “widespread” and have altered the composition of their mucin (21, 38–40).

The true potential for malignancy is undetermined in neonatal lesions. Oncogenic KRAS mutations can be seen in non-invasive, pre-malignant lesions in various organs, including in atypical adenomatous hyperplasia of the lung (41–43). These lesions may have the potential to become malignant if additional genetic and/or epigenetic changes occur, but they do not necessarily progress to malignancy. Progression/ recurrence/ metastasis has not been reported in infants with complete resection. With the newer lung carcinoma terminology replacing “bronchoalveolar carcinoma”(44), these clusters have been described in recent case reports as mucinous adenocarcinoma in situ (MAIS) in neonates and toddlers (45–47) without evidence of metastasis, as well as in children with extremely small foci (48) of mucinous epithelium. MAIS by definition should be a single, well-circumscribed lesion, while in the majority of our cases multiple (sometimes numerous) foci were present. It was often challenging to determine what compartment the mucinous cells occupied when they were outside the large cysts. In the absence of convincing genetic or histologic criteria to define lesions with metastatic potential, we do not diagnose lung adenocarcinoma in neonates at our institution, although we would recommend complete resection to prevent future risk of malignancy. Genetic or histologic criteria for this diagnosis in older children and adults should be identified.

Our findings of mucous cell clusters in 83% of type 1 lesions in our first series is similar to the 75% of additional historic infantile type 1 lesions is higher than previously published. However, given the relative rarity of type 1 CPAMs, the overall incidence of mucous cell clusters in cystic lung lesions as a whole (15/184, 8%) remains low. It is somewhat

surprising that a greater incidence of mucinous adenocarcinoma associated with type 1 CPAMs have not been reported in adults in the literature. Perhaps because many type 1 lesions are symptomatic, the majority of lesions at risk of developing MAIS are resected early, leaving few type 1 lesions in place in adults. Alternatively, clusters of mucinous cells might regress over time, either due to an intrinsic property of these cells or due to their destruction by repeated inflammatory events.

Additional pathologic findings reported in congenital cystic lung lesions include pulmonary hypertensive changes in many sequestrations (49). We did not identify intimal fibrosis in our patients. We did not attempt to evaluate muscular hypertrophy in the arteries of sequestrations as these are derived from the systemic circulation and a “normal” thickness of a systemic artery feeding into the pulmonary parenchyma is not defined. Plexiform lesions were identified in only a single older patient. Their relative rarity in our series likely reflects the low median age at resection.

The phenomenon of “pleura nodosum” was recently described in a patient with a thoracoamniotic shunt for an extralobar sequestration (50), with the hypothesis that amniotic fluid debris including squamous cells and hair could travel up the shunt into the pleural cavity. We have seen the same phenomenon in 9/19 patients with thoracoamniotic shunts for type 1 lesions. As the type 1 lesions themselves are often full of squamous cells it is impossible to determine in these cases whether the cells are traveling directly from the amniotic space into the pleural cavity or are first traveling through the respiratory tract and lung cyst.

In summary, our findings demonstrate that in the modern practice of widespread fetal imaging, the natural distribution of CPAM types is markedly different than that described for historic, symptomatic cohorts. There is a significant association between type 1 CPAM and severe symptomatic presentation requiring resection in the immediate post-natal period. Although most type 1 CPAMs have mucinous cell clusters, the overall rarity of this subtype makes the presence of these lesions less common. In contrast, asymptomatic lesions are usually on a spectrum encompassing classic type 2 morphology as well as histology that is more classically described in congenital lobar emphysema. This same spectrum is identified in both extra- and intra-lobar sequestrations.

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Figure 1:

Type 1 CPAMs. In addition to cystic spaces with a wall containing smooth muscle, type 1 large cysts showed connections (arrows) to alveolar-type airspaces (a) and epithelium thrown up into prominent papillary projections (b). The airspaces surrounding the main cyst were variable, and besides variations in size and shape sometimes included immature mesenchyme with cuboidal epithelium (c). In other cases (d) the main cyst (lower left) was surrounded by a combination of irregular, smaller cystic bronchiole-like spaces and a peripheral rim of alveoli that were increased for gestational age (36 weeks).

Figure 2:

Mucinous cell clusters were present in most type 1 CPAMs and were composed of either small clusters of cells lining the larger cysts (a) or larger clusters that involved smaller airspaces (b) where it was difficult to determine whether they replaced alveolar epithelium or airway-type epithelium.

Figure 3:

Specimens with type 2 CPAM/bronchial atresia features were on a spectrum from those with (often focal) classic type 2 features (a) with bronchiolar-lined cysts unaccompanied by paired pulmonary arteries, along with extensive areas without cystic spaces (b) that were more accurately described as lobar emphysema with enlarged alveoli and dilated bronchioles, some of which are mucin-filled (top) compared to adjacent normal neonatal parenchyma (bottom).

Figure 4:
A subset of patients with a history of thoracoamniotic shunt had scattered pleural nodules (a) that on higher power contained hair or squamous debris (b) arrows.

Table 1:

Clinical characteristics of patients with congenital cystic lung lesions. Prematurity was defined as <37 weeks gestation. Patients intubated or requiring NICU care for causes other than lung lesion (prematurity or other severe medical conditions) were excluded. EXIT = Ex-utero intrapartum treatment). ECMO = Extracorporeal membrane oxygenation. VSD = ventricular septal defect. CDH = congenital diaphragmatic hernia. NICU = neonatal intensive care unit.

	Type 1	Type 2/bronchial atresia	ILS	ELS	P value
Total lesions	18	81	45	29	
Total patients	18	77	45	29	
Sex (F/M)	7F/11M	35F/42M	25 F/20M	16 F/ 13M	
Location (LUL; LLL; RUL; RML; RLL; other)	2; 4; 4; 2; 4; 2	17; 21; 10; 2; 29; 2	0; 29; 0; 0; 16	22 left; 5 right; 2 other	
Median age at resection (days)	1	58	65	57	<0.0001
Premature	6 (33%)	6 (8%)	9 (20%)	3 (10%)	0.02
Intubation / mechanical ventilation for CPAM	12 (67%)	8 (10%)	0 (0%)	5 (17%)	<0.0001
Required steroids for CPAM	4	5	2		0.2674
Requiring ECMO	3	0	0	2	0.074
Required EXIT	2	0	0	0	0.1846
Required thoracoamniotic shunt	5	0	1	0	0.0002
Other malformations/ serious medical problems	1 (atrial ectopic tachycardia)	5 (mild cerebral ventriculomegaly; foregut duplication cyst; VSD and dysmorphic features; mild coarctation of aorta; hypoplasia of left pulmonary artery and cryptorchidism)	6 (trisomy 21 and choanal atresia; right aortic arch; VSD and aortic arch hypoplasia; neonatal ascites; laryngomalacia; multiple cutaneous hemangioma)	4 (CDH and VSD; CDH and 11 ribs; 11 ribs and pulmonary hypoplasia; Congenital Hyperinsulinism. Right Pelviectasis and Ureterectasis)	
Complications related to lesion	3 pulmonary hypoplasia (1 death), 1 hydrops	None	1 patient with chronic respiratory failure	1 pulmonary hypertension, 1 BPD, 1 hydrops	

Table 2:

Histologic features of congenital cystic lung lesions. Specimens that were received morcellated were only evaluated for the presence of mucinous cell clusters.

	Type 1	Type 2/bronchial atresia sequence	Intralobar sequestrations	Extralobar sequestrations	P value
Largest cyst size (cm)	1–5.5	0–4	0–2.5	0–1.5	
With cysts ≥ 2 cm *	82% (14/17)	7% (4/59)	6% (2/35)	4% (1/25)	< 0.0001
Features of obstruction	(18%) 3/17	(88%) 52/59	86% (30/35)	84% (21/25)	< 0.0001
At least focal well developed bronchiolar-lined cysts		71% (42/59)	63% (22/35)	76% (19/25)	0.4426
Clusters of mucinous cells	83% (15/18)	0	0	0	< 0.0001
Additional pathologic diagnoses			1 plexiform lesion 1 patchy acute pneumonia		