# Chapter 12
# Congenital and Developmental Causes of Cystic Lung Disease


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## Abbreviations

| | |
|---|---|
| CCAM | Congenital cystic adenomatoid malformation |
| CHAOS | Congenital high airway obstruction syndrome |
| CLO | Congenital lobar overinflation |
| CNLD | Chronic neonatal lung disease |
| CPAM | Congenital pulmonary airway malformation |
| ELS | Extralobar sequestrations |
| FGFR2 | Fibroblast growth factor receptor 2 |
| FLNA | Filamin A |
| ILS | Intralobar sequestrations |
| miRNAs | Micro-RNAs |
| NKX2–1 | NK2 homeobox 1 |
| PPB | Pleuropulmonary blastoma |
| TBX4 | T-box transcription factor 4 |
| TTF-1 | Thyroid transcription factor 1 |

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## Congenital Cystic Lung Malformations

The widespread use of antenatal ultrasound has led to increased in utero detection of congenital cystic lung malformations. These entities comprise a group of rare but clinically significant developmental abnormalities, including bronchogenic cysts, congenital pulmonary airway malformation, pulmonary sequestration, congenial lobar emphysema, and pulmonary hyperplasia. Although many of these lesions will remain asymptomatic, there is a wide range of clinical complications including hydrops fetalis, airway obstruction, infection, and rarely neoplasia [1]. Treatment of even asymptomatic congenital lung lesions is variable with some managed conservatively, while others surgically resected [2]. Many congenital lung abnormalities detected early in pregnancy will have regressed significantly by birth, further complicating management decisions [3]. While the conventional nomenclature of these malformations infers that congenital cystic lung malformations are distinct lesions, they frequently share common modes of pathogenesis and histological features [4–7]. Specifically, bronchogenic cysts and extralobar sequestration reflect abnormal foregut budding during embryonic development, while congenital cystic pulmonary airway malformations, intralobar sequestration, pulmonary hyperplasia, and congenital lobar overinflation are often related to airway obstruction, with or without secondary dysplastic changes. In an attempt to bring clarity to the origin of these lesions and guide clinical management decisions, revised classifications have been proposed based on the anatomical/pathological findings or imaging appearance of the entities [4, 8–10] (Table 12.1).

### *Bronchogenic Cyst*

Bronchogenic or bronchial cysts arise from anomalous budding of the foregut during development. They present as unilocular fluid or mucin-filled cysts that histologically recapitulate the bronchial structure, without connection to the lung (Fig. 12.1).

Bronchogenic cysts typically occur in the mediastinum or subcarinal area but may be intraparenchymal or even subdiaphragmatic or cutaneous [11, 12]. On radiological imaging, bronchogenic cysts appear as round thin-walled cystic cavities with sharp margins that may have air-fluid levels. They do not communicate with the normal tracheobronchial tree unless they become secondarily infected, which commonly occurs in intraparenchymal cysts. The time of clinical presentation is variable and related to compression of adjacent structures (e.g., trachea, bronchi, esophagus), infection, or rupture. Patients usually present later in life with dyspnea, recurrent coughing, wheezing, dysphagia, or pneumonia, but neonatal presentation or incidental detection on imaging taken for unrelated reasons is not unusual. On pathological examination, bronchogenic cysts consist of a single cyst containing clear or turbid fluid, the latter reflective of secondary infection. Management consists of surgical resection.

**Table 12.1** Langston classification and radiographic classification of congenital lung malformations

| Langston classification[a] |
|---|
| **I. Bronchopulmonary malformations** |
| Bronchogenic cyst |
| Bronchial atresia |
| Cystic pulmonary airway malformation, large cyst type (Stocker type 1) |
| Isolated |
| With systemic arterial/venous connection (hybrid lesion/intralobar sequestration) |
| Cystic pulmonary airway malformation, small cyst type (Stocker type 2) |
| Extralobar sequestration (with/without connection to gastrointestinal tract) |
| Isolated |
| With cystic pulmonary airway malformation, small cyst type (hybrid lesion) |
| **II. Pulmonary hyperplasia and related lesions** |
| Congenital high airway malformation |
| Solid congenital pulmonary airway malformation, small cyst type (Stocker type 3) |
| Polyalveolar lobe |
| **III. Congenital lobar emphysema** |
| **Radiographic Classification[b]** |
| **I. Group 1 (congenital solid/cystic lung malformation)** |
| Cystic pulmonary airway malformation, small cyst type (Stocker type 2) |
| Extralobar and intralobar sequestration |
| Bronchial atresia |
| Bronchogenic cyst |
| Mixed malformation |
| **II. Group 2 (congenital hyperlucent lobe)** |
| Congenital lobar emphysema |
| Polyalveolar lobe |
| **III. Group 3 (congenital small lung)** |
| Lung/lobar agenesis |
| Pulmonary hypoplasia |

[a]Adapted from [4]
[b]Adapted from [10]

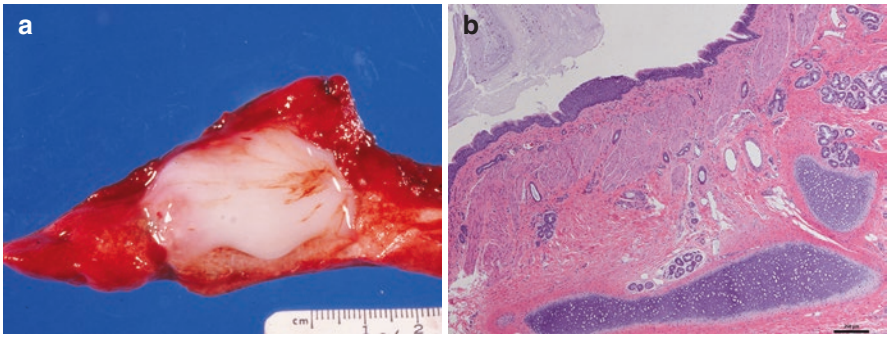


**Fig. 12.1** Bronchogenic cyst. (**a**) An intraparenchymal bronchogenic cyst containing abundant mucus. (**b**) Bronchogenic cysts recapitulate the appearance of the normal bronchus lined by ciliated respiratory epithelium and containing smooth muscle, submucosal glands, and plates of cartilage in the wall (H&E)

## *Congenital Pulmonary Airway Malformation*

Congenital pulmonary airway malformation (CPAM), previously known as congenital cystic adenomatoid malformation (CCAM), is the most common lung malformation of the lower respiratory tract [13]. CPAMs derive their blood supply from the pulmonary artery and drain via the pulmonary veins, with the exception of hybrid lesions (CPAM in pulmonary sequestrations) that have a systemic blood supply. CPAMs occur sporadically with no known genetic predilection. Mechanisms resulting in CPAM formation are debated, but the hypothesis that CPAMs arise from in utero obstruction during development has been substantiated by several studies [5–7].

Historically CPAMs have been categorized into separate subtypes in the Stocker classification, which is based upon cyst size and histological resemblance to segments of the normal respiratory tree, from trachea and large bronchi to peripheral acinar structures [14]. However, with further insights into CPAM pathogenesis, experience with the clinical behavior of this entity and frequent occurrence of hybrid lesions (CPAM in pulmonary sequestrations), the continued utility of the Stocker classification is contested [4]. Stocker type 0 CPAM is now recognized to be acinar dysplasia, a rare diffuse developmental lung disorder associated with mutations in the T-box transcription factor *TBX4* and fibroblast growth factor receptor 2 (*FGFR2*) [15, 16]. Stocker type 3 CPAM resembles pulmonary hyperplasia, and Stocker type 4 CPAM is thought to represent type I pleuropulmonary blastoma (discussed below). Langston divided the most frequent CPAMs into two types: a large cyst type (equivalent to Stocker type 1) and a small cyst type (equivalent to Stocker type 2). This terminology has in part been adapted in the radiographical literature to guide clinical management [17, 18] (see Table 12.1). By histological assessment, the small cyst type is the most common CPAM subtype [19].

Large cyst CPAM presents by radiographical imaging as a solitary lung mass containing variably sized cysts, usually measuring greater than 2 cm. The cysts replace the normal lung parenchyma and may be unilocular or multilocular and septated

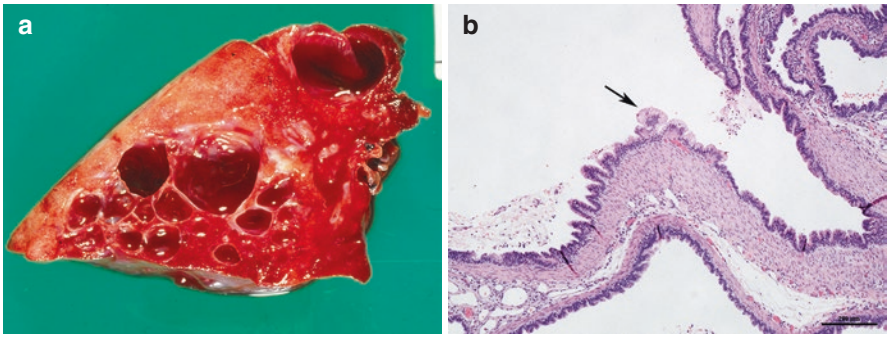


**Fig. 12.2** Congenital pulmonary airway malformation (CPAM), large cyst type. (**a**) Large cyst type CPAM has cysts of variable size, usually measuring greater than 2 cm. (**b**) Microscopically, the cysts are lined by ciliated respiratory epithelium with smooth muscle in the wall; focal mucigenic epithelium is typically seen (*arrow*) (H&E)

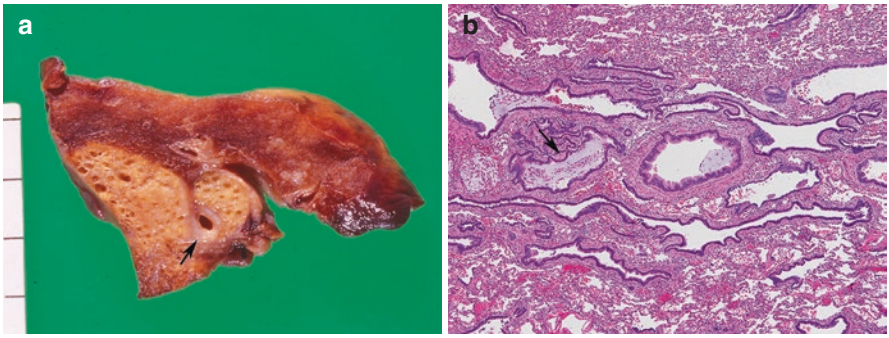


**Fig. 12.3** Congenital pulmonary airway malformation (CPAM), small cyst type. (**a**) Small cyst type CPAM has multiple small cysts admixed with solid areas of parenchyma. A bronchus is present within the lesion (*arrow*). (**b**) Histologic sections show abnormally apposed bronchiole-like structures, many with intraluminal mucus providing evidence of obstruction (*arrow*) (H&E, 100×)

(Figure 12.2a). Histological examination demonstrates that the cysts are lined by ciliated respiratory epithelium, often containing clusters of mucigenic cells [19] (Figure 12.2b). Cartilage is rarely present in the cyst walls.

Small cyst CPAM is identified as an echogenic mass by ultrasound examination and is comprised of multiple small cysts, which can be heterogeneous in appearance based on the presence of cystic and solid components (Figure 12.3a). Small cyst CPAM may be associated with other congenital anomalies, including cardiovascular and renal malformations as well as diaphragmatic hernia [14]. Bronchial atresia is more frequently identified in small cyst than large cyst CPAM. Features of bronchial atresia are also commonly seen in pulmonary sequestrations with systemic blood supply [4]. Histologically a small cyst CPAM is composed of increased bronchiolar-like profiles lined by cuboidal to ciliated respiratory epithelium that, unlike normal bronchioles, are not accompanied by arteries (see Figure 12.3b).

Rhabdomyomatous differentiation with small bundles of mature skeletal muscle may be present around the cysts and is not reflective of rhabdomyosarcoma. CPAMs resected during fetal life demonstrate significant immaturity akin to the lung during early development and do not fit well into existing classification schemes [20].

The presentation of CPAMs is quite variable; patients may present with respiratory distress in early infancy or remain asymptomatic until later in life. The vast majority of cases are now detected by routine prenatal ultrasound examination. Large lesions typically cause symptoms by compromising alveolar growth during development leading to pulmonary hypoplasia. Mediastinal shift with subsequent development of polyhydramnios and hydrops may develop with rapidly enlarging lesions [21]. Expectant management is appropriate for the nonhydropic fetus, whereas survival of fetuses with hydrops may be dependent on fetal intervention, including thoracoamniotic shunt placement, percutaneous laser ablation, and rarely open fetal surgery [22]. Infants who are symptomatic postnatally are treated with surgical resection, which generally consists of lobectomy or segmental resection. Surgical intervention for a child with an asymptomatic CPAM is controversial. Recurrent infection and a small risk of neoplastic transformation have been cited as reasons for elective resection [19, 23–26]. Reported malignancies are primarily mucinous adenocarcinomas thought to arise from mucigenic epithelium which is frequently present in large cyst CPAM [27, 28]. KRAS mutations have been detected in several cases, similar to precursor adenocarcinoma lesions in the adult lung [29, 30].

## *Pulmonary Sequestrations*

Pulmonary sequestrations are masses of nonfunctioning lung that do not connect to the normal tracheobronchial tree and have a systemic arterial blood supply, usually arising from the thoracic or abdominal aorta [31]. Occasionally, the systemic arterial supply originates from other arteries including the celiac, splenic, intercostal, subclavian, and even coronary arteries [32]. Venous drainage may occur through either a pulmonary or systemic vein. Pulmonary sequestrations are classified as intralobar sequestrations (ILS) when they occur within the visceral pleural lining of the adjacent surrounding lung, and extralobar sequestrations (ELS) when they are separate from the lung and have their own pleural lining. Sequestrations are the second most common lung lesion detected antenatally after CPAM.

ELS comprise the majority of sequestrations and are often identified in utero as a large echo-dense mass that may become smaller relative to the normal lung with advancing gestational age. ELS commonly present with respiratory distress shortly after birth. Antenatal presentation may include polyhydramnios and fetal hydrops. There is a frequent association of ELS with other congenital anomalies, especially diaphragmatic hernia, cardiac abnormalities, and other foregut duplications including bronchogenic cysts [33]. A connection to the gastrointestinal tract may be present (Figure 12.4a). Similar to bronchogenic cysts, ELS are believed to arise from a foregut-derived supernumerary lung bud, but contain distal lung parenchyma [4, 32]. While most are intrathoracic, they can also be found below the diaphragm. On gross

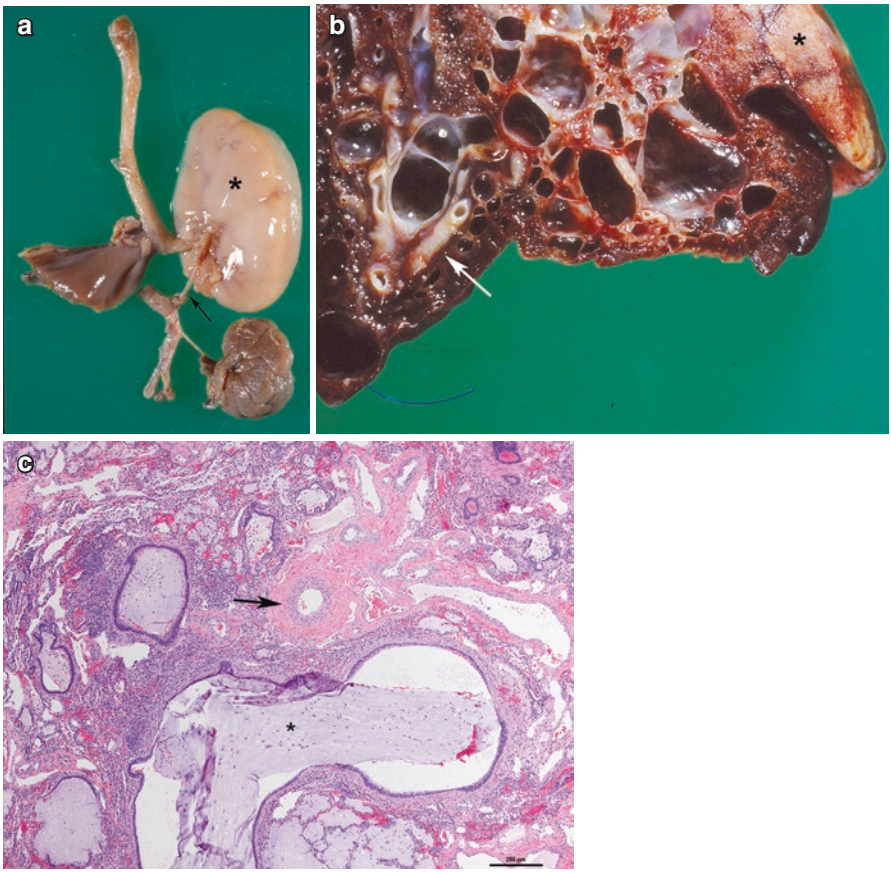


**Fig. 12.4** Pulmonary sequestrations. (**a**) A large extralobar sequestration (ELS) (*) seen below the diaphragm with connection to the distal esophagus (stomach on left) and vascular supply (*arrow*) from the descending aorta; (right kidney lower right corner). (**b**) Intralobar sequestrations (ILS) are usually well-demarcated from the adjacent normal lung (*) and have thick-walled systemic arteries (*arrow*). They often resemble a congenital pulmonary airway malformation (CPAM) with cystic spaces. (**c**) Evidence of proximal airway obstruction is common in both ELS and ILS with dilated airways filled with mucus (*), identical to that seen in bronchial atresia. Arteries with medial thickening reflect systemic blood supply (*arrow*). Depending upon the age of presentation and presence of concurrent infection, inflammation and dense fibrosis may be present (H&E)

examination, ELS resemble an accessory lung lobe with its own pleura and a vascular pedicle containing a systemic artery and a draining vein. Pulmonary sequestrations are composed of lung parenchyma with enlarged and poorly subdivided airspaces, and containing abnormally large thick-walled vessels, reflective of the systemic vascular supply (Figure 12.4b). Notably, bronchial atresia with small cyst CPAM features is extremely common in both ELS and ILS [5, 34]. Depending on the presence of proximal airway obstruction, there may be associated mucus accumulation (Figure 12.4c).

ILS is defined by an isolated nonfunctioning lung segment contained within normal lung and with systemic arterial supply (see Figure 12.4b). Most ILS are located

in the lower lobes. If not detected by routine prenatal ultrasound, they present in childhood or adolescence with cough and recurrent pulmonary infections; in some cases, the lesion is detected as an incidental finding on chest radiograph [35]. Radiographically, ILS typically appears as a dense mass within the pulmonary parenchyma; infection can lead to cystic change with fluid levels.

Historically, there has been debate whether ILS is a congenital or acquired lesion. The late age of presentation and history of recurrent infection support ILS being an acquired lesion. In contrast, the frequent presence of bronchial atresia with CPAM features in ILS supports it being part of a spectrum of congenital lung malformations with or without systemic arterial supply [36].

Due to overlapping pathological features, ILS can be difficult to distinguish from a CPAM or isolated bronchial atresia in the absence of knowledge of an associated systemic arterial supply (Figure 12.4b,c). When infected, ILS may be confused with chronic pneumonia, although in chronic pneumonia there is a normal bronchial connection to the involved lung.

## *Pulmonary Hyperplasia and Congenital Lobar Overinflation*

Pulmonary hyperplasia (also termed polyalveolar lobe) is the result of airway obstruction during development, which blocks outflow of fetal fluid leading to increased alveolar growth. Pulmonary hyperplasia has also been referred to as type 3 CPAM in the Stocker classification [37]. Upper airway obstruction, such as tracheal or laryngeal atresia, affects all lung lobes (also termed congenital high airway obstruction syndrome, or CHAOS) (Figure 12.5a,b), while bronchial atresia and stenosis result in focal hyperplasia (Figure 12.5c).

The pathogenesis of congenital lobar overinflation (CLO) is similar to pulmonary hyperplasia, in that intrinsic or extrinsic compression of an airway results in progressive lobar over expansion, albeit due to alveolar distension by air rather than increased alveolar growth as seen in pulmonary hyperplasia (Figure 12.5d). The underlying cause can be secondary to an intrinsic cartilaginous abnormality with resultant weak or absent bronchial cartilage or extrinsic compression of an airway (e.g., bronchogenic cyst or an enlarged or anomalous pulmonary artery). Intraluminal obstruction from meconium or mucus plugs is another potential etiology. In CLO, the compressed airway acts as a one-way valve, resulting in air trapping postnatally. While CLO may be referred to as congenital lobar emphysema, the term "emphysema" is inaccurate as alveolar wall destruction does not accompany the alveolar expansion.

Pulmonary hyperplasia may manifest in utero with polyhydramnios or fetal hydrops, from compression of venous return to the heart. In both pulmonary hyperplasia and CLO, newborns usually present with respiratory distress [38]. Tension pneumothorax may occur. Radiographical imaging demonstrates progressive hyperinflation or hyperlucency of a lobe. Marked overinflation may lead to compression of the adjacent lung and mediastinal shift, often necessitating lobectomy. In both

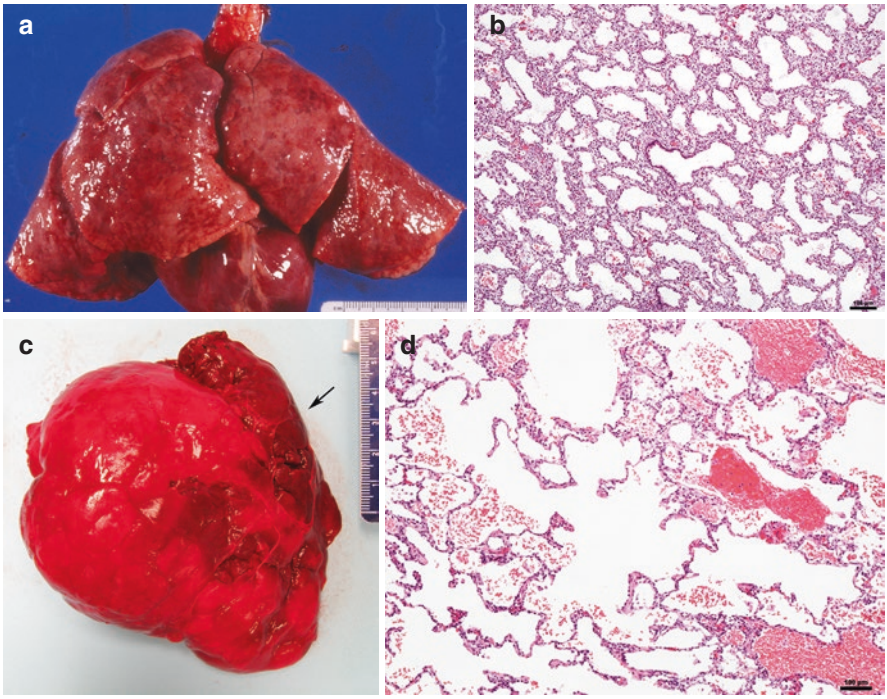


**Fig. 12.5** Pulmonary hyperplasia and congenital lobar overinflation (CLO). (**a**) All lung lobes in an infant with congenital laryngeal stenosis are markedly enlarged (heart lower center). (**b**) Histologically the lungs have a striking increase in alveolar spaces compared to airways, that are often structurally abnormal (H&E). (**c**) Hyperinflation of the right middle lobe in a newborn with severe bronchial compression from a large aortopulmonary window (*arrow* denotes compressed right upper lobe). (**d**) CLO is characterized microscopically by diffuse dilatation of alveoli rather than an increase in alveolar spaces as seen in pulmonary hyperplasia (H&E)

pulmonary hyperplasia and CLO, the involved lung lobes are enlarged, bulky, and sometimes pale (see Figure 12.5a and c).

## Developmental Diffuse Cystic Lung Disease

### *Alveolar Growth Abnormalities Presenting with Cystic Lung Disease*

Alveolar growth abnormalities are characterized by impaired alveolarization with deficient alveolar septation and airspace enlargement that may be misinterpreted as "emphysematous change" on radiographical imaging and pathological evaluation [39]. While impaired lung growth is traditionally considered to occur in the context of prenatal onset pulmonary hypoplasia and chronic neonatal lung disease of

**Table 12.2** Alveolar growth abnormalities presenting as diffuse cystic lung disease

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|---|
| **I. Pulmonary hypoplasia (restriction of prenatal lung growth)** |
| Oligohydramnios (e.g., prolonged rupture of membranes, renal dysfunction) |
| Restriction of thoracic volume (e.g., diaphragmatic hernia, pleural effusions, thoracic deformity from skeletal dysplasia) |
| Central nervous system and neuromuscular disorders resulting in decreased fetal breathing |
| **II. Chronic neonatal lung disease of prematurity (clinical bronchopulmonary dysplasia)** |
| **III. Congenital heart disease** |
| Cardiac anomalies with reduced pulmonary blood flow (e.g., tetralogy of Fallot, pulmonary artery stenosis/atresia, tricuspid atresia) |
| Cyanotic heart disease impairing postnatal alveolarization |
| **IV. Chromosome disorders** |
| Trisomy 21 with deficient postnatal alveolarization (often manifests with subpleural cysts on imaging) |
| Other chromosomal defects |
| **V. Monogenetic disorders** |
| *FLNA* (Filamin A; high phenotypic diversity including brain, cardiovascular, and gastrointestinal anomalies. Radiographical imaging may mimic congenital lobar overinflation) |
| *NKX2.1* (NKX2.1; associated with brain-thyroid-lung syndrome) |
| *DICER1* (DICER1; tumor predisposition syndrome with diverse manifestations most commonly including pleuropulmonary blastoma, cystic nephroma, ovarian Sertoli-Leydig cell tumors, and thyroid nodular hyperplasia/carcinoma. Radiographical imaging may mimic cystic pulmonary airway malformation) |

prematurity (clinical bronchopulmonary dysplasia), it also occurs in infants with congenital heart disease as well as those with chromosomal disorders (Table 12.2) [40].

The majority of cases with pulmonary hypoplasia are secondary to congenital anomalies or pregnancy complications that inhibit lung development. As distension of the lung with liquid and fetal respiratory movements is required for prenatal lung growth, any mechanism that interferes with these processes can result in pulmonary hypoplasia. The severity of the lung growth abnormality depends on the mechanism of hypoplasia and the timing of the insult. Conditions that occur early in pregnancy (renal anomalies) may interfere with airway branching as well as alveolar formation, while later events (premature rupture of membranes) will impact only alveolar formation.

As lung maturation continues after birth, with most alveolarization occurring within the first 2 years of life [41], postnatal events can impact lung growth as well. Postnatal growth abnormalities predominate in infants with chronic neonatal lung disease (CNLD) related to prematurity, which is increasing as the survival of premature infants improves. Radiographical findings are variable based on etiology, age of the infant, and severity of the growth abnormality. Prior treatments involving high concentrations of oxygen and mechanical ventilation resulted in coarse reticular opacities, cystic lucencies, and distorted lung aeration reflecting alternating regions of

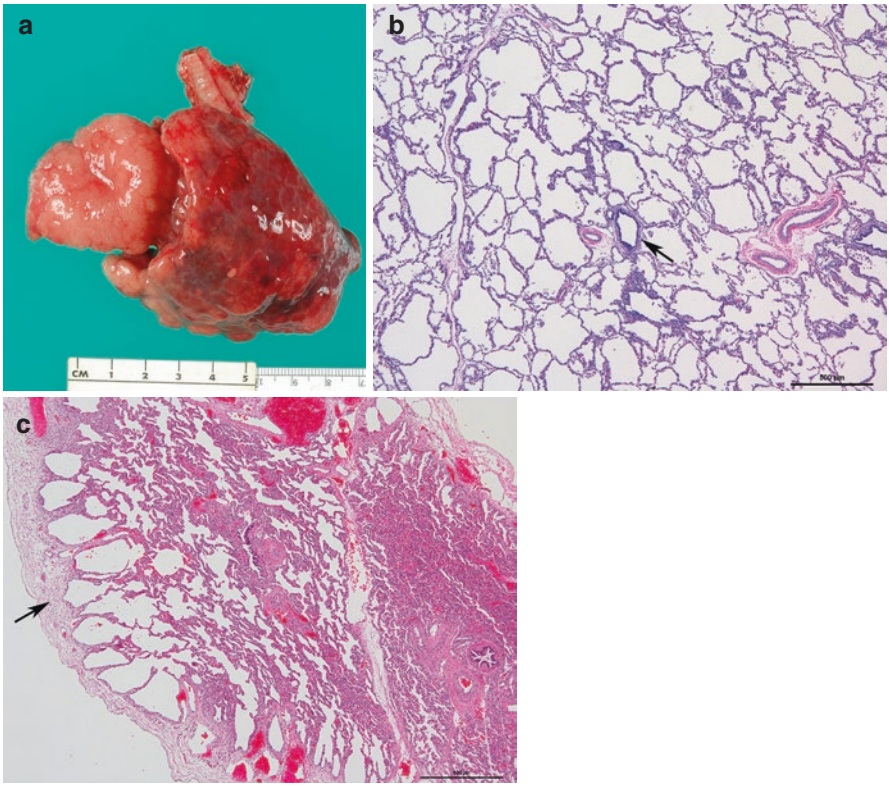


**Fig. 12.6** Deficient lung growth manifesting as cystic lung disease. (**a**) Alternating areas of hyperexpansion and collapse are prominent in the left lung of an 11-week infant with severe pulmonary hypoplasia from bladder outlet obstruction. (**b**) Histologic assessment shows marked enlargement and simplification of alveoli, which normally are smaller in size than bronchioles (*arrow*) (H&E). (**c**) Deficient alveolarization is often most prominent in the subpleural space (*arrow*), as seen in the lungs from an infant with trisomy 21 (H&E)

interstitial fibrosis and atelectasis with hyperinflation on histology [42] (Figure 12.6a). Current neonatal practices including surfactant replacement and refined ventilatory strategies demonstrate more subtle radiographic imaging abnormalities, the most frequent being hyperlucent areas with linear and triangular opacities [43]. The hyperlucent areas correspond to enlarged alveoli and reduced distal vascularization (Figure 12.6b). In general, there is significant variability in the radiographical imaging findings associated with alveolar growth abnormalities, but subpleural cysts along the lung periphery, pulmonary fissures, and bronchovascular bundles can be quite characteristic, particularly in deficient lung growth associated with trisomy 21 [40, 44]. This finding correlates well with the subpleural accentuation of cystically dilated alveoli frequently seen on lung biopsy [45] (Figure 12.6c). The subpleural space is theorized to be the predominant site for late alveolar formation [46, 47].

## *Monogenetic Disorders Presenting with Diffuse Cystic Lung Disease*

Heterozygous loss-of-function mutations in *FLNA*, which encodes the actin cross-linking protein filamin A, cause an X-linked dominant disorder with variable multi-organ involvement, including periventricular nodular heterotopias in the brain, cardiovascular anomalies, Ehlers-Danlos syndrome-like features, intestinal pseudo-obstruction, and pulmonary disease of varying severity [48–50]. Respiratory symptoms are often progressive and accompanied by severe clinical pulmonary hypertension. Age of onset of pulmonary disease associated with *FLNA* mutations occurs over a wide range but frequently presents in the first few months of life [50, 51]. Severe hyperinflation with hyperlucent cystic areas alternating with areas of atelectasis and thickening of the interlobular septa is a common appearance reported on computed tomography (CT) scan [50, 51]. The disorder may also present with severe lobar "emphysema" mimicking the localized lung malformation congenital lobar overinflation. Histologic assessment of lung tissue reveals marked alveolar enlargement and simplification reflective of a lung growth abnormality commonly combined with hypertensive changes of the pulmonary arteries, as well as abnormal muscularization of pulmonary veins and lymphatics [51, 52] (Figure 12.7a). The pathology can be similar to that of other lung disorders with deficient lung growth with pulmonary arteriopathy, which may delay diagnosis, especially in a premature infant, unless clinically suspected [52].

Diffuse cystic lung disease reflective of alveolar simplification can be the primary manifestation of pulmonary disease in individuals with heterozygous mutations in the *NKX2-1* gene (thyroid transcription factor 1, TTF-1). Cystically dilated airspaces may be accompanied by other pathologic findings including alveolar proteinosis, nonspecific interstitial pneumonitis, and fibrous remodeling [53–55]

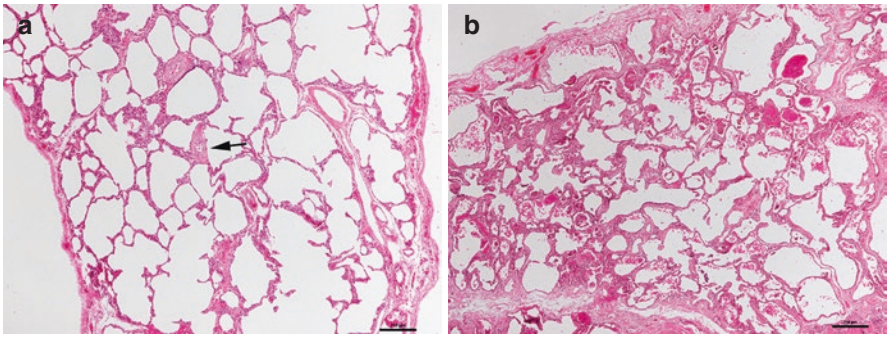


**Fig. 12.7** Monogenetic disorders presenting with diffuse cystic lung disease. (**a**) A term infant with mild hypoplasia of the aortic arch and early onset respiratory distress was found to have a mutation in Filamin-A (*FLNA*) after lung biopsy (H&E). Medial hypertrophy of the pulmonary arteries (*arrow*) accompanies diffuse airspace enlargement. (**b**) Cystic dilatation of alveoli in a young child with an inherited *NKX2.1* mutation (H&E)

(Figure 12.7b). NKX2-1 is a homeobox protein critical for development and function of the lung, brain, and thyroid [56, 57]. Haploinsufficiency of *NKX2-1* due to either gene deletions or loss-of-function mutations results in "Brain-Thyroid-Lung" syndrome with individuals having a variable degree of pulmonary disease, thyroid dysfunction, and neurologic abnormalities [53, 58]. The onset of presentation is often in the newborn period or early childhood with respiratory distress syndrome progressing to interstitial lung disease and frequent pulmonary infections [53]. Recurrent spontaneous pneumothorax has also been reported [53, 54]. CT imaging demonstrates a range of findings from mild to diffuse ground-glass opacities, cysts, infiltrates, and fibrosis. Patient prognosis is variable and dependent upon the extent of lung disease.

The DICER1 tumor predisposition syndrome commonly presents as cystic lung disease. The DICER1 syndrome is an autosomal dominant condition caused by mutations in the *DICER1* gene. DICER1 is required for generation of mature microRNAs (miRNAs) that have essential regulatory roles in multiple processes including development and oncogenesis [59]. Pleuropulmonary blastoma (PPB) is the hallmark manifestation of the DICER1 syndrome and one of the most important causes of DICER1 associated morbidity and mortality [60]. Multiple other benign and malignant neoplasms are seen in the DICER1 syndrome including cystic nephroma, sarcoma and Wilms tumor of the kidney, Sertoli-Leydig cell tumor of the ovary, adenomas and carcinomas of the thyroid gland, embryonal rhabdomyosarcoma, neuroblastoma, pituitary blastoma, and pineoblastoma [60, 61]. Heterozygous germline DICER1 loss-of-function mutations were first identified in PPB in 2009 and have subsequently been identified in >70% of PPB patients [62, 63]. A somatic mutation is acquired in the second allele in DICER1 associated benign and malignant lesions, characteristically occurring in one of five hotspot codons encoding the RNase IIIb domain resulting in a dysfunctional protein [59, 61]. Genetic studies in mice demonstrate that DICER1 loss in the lung epithelium during a particular time frame during embryonic development recapitulates the PPB phenotype, and fibroblastic growth factor FGF9 overexpression in the DICER1 deficient lung epithelium promotes proliferation of the immature mesenchymal cells [64, 65]. Together, mouse models, the natural history of PPB, and tumor sequencing support DICER1 loss during lung development initiating PPB pathogenesis with tumor progression to sarcoma resulting from accumulation of additional oncogenic mutations [66, 67].

PPB manifests as three tumor subtypes representing clinicopathologic progression from a cystic (type I PPB) to a combined cystic and solid malignancy (type II PPB) to a completely solid sarcoma (type III PPB) [68]. PPB primarily affects children with >95% of cases diagnosed by 7 years of age [69]. Median ages of diagnosis are 8, 35, and 41 months for type I, type II, and type III PPBs, respectively, supporting tumor progression over time. Progression from type I to types II and III PPB are well documented in individual patients; however, not all type I PPBs progress to the more malignant subtypes [69]. Lesions with the same multilocular cystic architecture as type I PPB but lacking the primitive mesenchymal cell component that progresses to malignant sarcoma that defines PPB types II and III are identified in children as well as adults with pathologic germline DICER1 mutations [69, 70].

These lesions are presumed to be type I PPBs that have regressed and are designated type Ir PPB. Pulmonary cysts identified in adults with pathologic germline DICER1 variants are not typically resected for oncologic indications but can result in pneumothorax or symptoms related to superinfection [60]. Importantly, there are case reports of pediatric patients with type Ir PPB progressing to type II or III PPB as late as 53 months after diagnosis indicating the need for follow-up, especially when type Ir PPB is diagnosed in a young child [69].

PPB presents with variable clinical symptoms from respiratory distress to nonproductive cough, fever, and chest pain with pneumothorax being a frequent presentation of cystic type I PPB [68, 69]. A primary consideration in the radiological differential diagnosis of cystic PPB is CPAM with intrapulmonary bronchogenic cyst, pneumatocele, and pleuropulmonary synovial sarcoma representing additional considerations [61]. Radiographical features favoring a diagnosis of CPAM include prenatal detection, presence of a systemic feeding vessel, asymptomatic presentation, and hyperinflated lung [71]. These distinguishing features form the basis for an algorithm to identify children at higher risk of PPB to aid in determining cystic lesions that require resection. Two critically important points need to be highlighted regarding the differential diagnosis of cystic PPB and CPAM. First, cystic PPB and CPAM can be clinically and radiographically indistinguishable [71, 72]. Thus, frequent careful follow-up of cystic lesions in children is recommended with development of high-risk features or growth prompting consideration for resection. Second, type I PPB and type 4 CPAM in the Stocker classification system have indistinguishable histologic and radiologic features leading to the conclusion that type I PPB and type 4 CPAM represent the same entity [73–76]. It is therefore critically important that type I PPB not be diagnosed as CPAM to ensure that patients receive appropriate postoperative care and follow-up for malignancy.

Distinguishing pathological features of cystic type I PPB are the multilocular architecture and the frequent well-circumscribed border with adjacent normal lung parenchyma (Figures 12.8a,b) [70]. Key diagnostic histopathological features are collections of small primitive mesenchymal cells within the cyst walls and the cuboidal to flattened epithelial cells resembling normal alveolar epithelial cells lining the septa that separate the cysts (Figures 12.8c,d). The abundance of immature mesenchymal cells varies greatly among cases consisting of a uniform cellular cambium layer underlying the surface epithelium (see Figures 12.8c,d) to very focal, small cellular aggregates requiring examination of multiple tissue sections for identification. Lesions with the same multilocular cystic architecture but lacking a primitive cell component are designated as regressed or nonprogressed PPB type Ir. PPB progression is characterized by expansion of the primitive mesenchymal cells to form a cystic malignancy with a solid sarcomatous component (type II PPB) or an entirely solid sarcoma (type III PPB). The PPB subtype is the strongest predictor of outcome with 5-year overall survival rates of 91%, 71%, and 53% for type I, II, and III PPB, respectively [69]. These outcome data highlight the need to detect and treat PPB in its earliest, most curable, cystic type I stage. To this end, testing to identify at-risk individuals and recommended surveillance strategies have been developed [60].

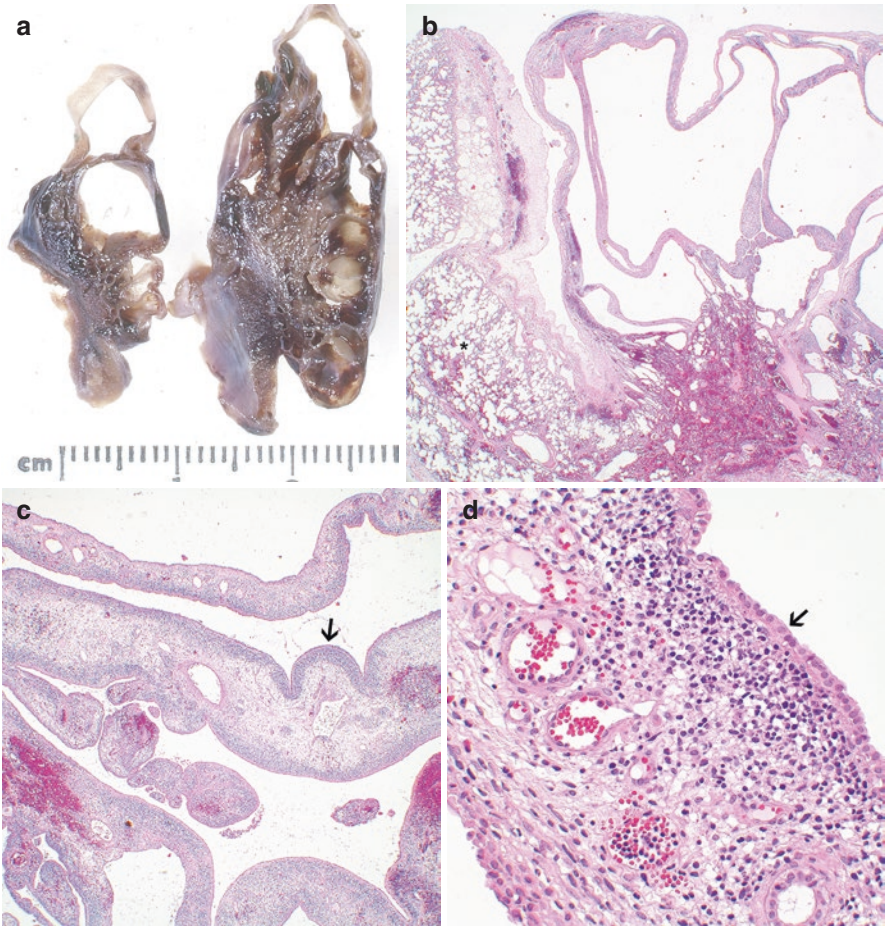


**Fig. 12.8** Type I pleuropulmonary blastoma (PPB). (**a**) Lung tissue resected from a 2-year-old infant presenting with spontaneous pneumothorax containing a multiloculated cystic lesion well demarcated from the adjacent normal lung. (**b**) Microscopic examination confirms the multiloculated architecture and a well-circumscribed border with the adjacent normal lung (*) (H&E, 20×). (**c**) The cyst walls contain a cambium layer of mesenchymal cells underlying the surface epithelium (*arrow*) (H&E, 40×). (**d**) The cambium layer is comprised of small immature mesenchymal cells with the overlying epithelium (*arrow*) comprised of cuboidal cells resembling normal alveolar type 2 epithelial cells (H&E, 400×)

## Conclusion

Diverse congenital and developmental entities present as cystic lung disease including lung malformations, growth abnormalities, and neoplasms. The widespread use of antenatal ultrasound has resulted in congenital lung malformations being increasingly detected in utero providing new challenges in clinical decision-making as well

as opportunities to observe lesion evolution over time. Identification of underlying mechanisms of disease, including airway obstruction and genetic alterations, has provided insights into the pathogenesis of multiple congenital and developmental lesions. A multidisciplinary approach is critical to arriving at a specific diagnosis, with integration of clinical, radiological, pathological, and frequently molecular testing required to optimize patient management.

**Key Learning Points**

- Airway obstruction is the etiology underlying many congenital cystic lung malformations.
- Revised pathology and radiology-based classifications have been developed for congenital cystic lung malformations to encompass pathogenesis and clinical behavior.
- Deficient lung growth can present as diffuse cystic lung disease.
- Genetic conditions can manifest as cystic lung disease.

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