Prenatal and Postnatal Management of Congenital Pulmonary Airway Malformation

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Abstract

Congenital pulmonary airway malformation (CPAM) is one of the most common lung lesions detected prenatally. Despite the research efforts made in the past few years, controversy and lack of clarity in the literature still exist regarding nomenclature, classification, pathogenesis and the management of CPAM. Therefore, it is of greatest importance to delineate the natural history of CPAMs and to create a consensus to guide the management and follow-up of these lesions. This review will focus on classification systems, highlighting the most recent advancements in pathogenesis, and current practice in the prenatal diagnosis of CPAM. Strategies of prenatal management and postnatal management will be reviewed. Long-term follow-up, including lung cancer risk, is discussed and an outcome perspective is presented.

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Introduction

Congenital pulmonary airway malformation (CPAM) – previously known as congenital cystic adenomatoid malformation (CCAM) – is a rare developmental malformation of the lower respiratory tract. It is accepted that abnormal airway patterning and branching during lung morphogenesis results in the appearance of lung cysts. Although the exact cellular mechanisms involved in the pathogenesis are unknown, many potential genes have been associated with the formation of lung cysts. Traditionally, Stocker's classification of CPAMs was based on the histopathological cyst diameter [1], but several other classifications have since emerged [2].

CPAM accounts for 95% of congenital cystic lung diseases and is the most common cystic lung lesion diagnosed by prenatal screening at 18–20 weeks of gestation [3]. A commonly quoted incidence of CPAMs is 1 per 25,000–35,000 live births [4]. However, with the advent of prenatal ultrasound (US), it is likely that the true incidence may have been underestimated because previously undiagnosed lesions are now being detected [5]. The management of symptomatic CPAMs is consensually

agreed, whereas the management of asymptomatic CPAMs is still contentious [6, 7]. In this review, CPAM classification systems, pathogenesis, prenatal and postnatal management strategies and long-term follow-up are presented.

Challenging Diagnosis and Classification

The description and classification of congenital lung cysts has evolved over time [1, 2, 8, 9]. CCAM was originally described in 1949 by Ch'In and Tang [10] as a hamartomatous lesion characterised by an overgrowth of terminal bronchioles.

In 1977, three predominant histopathologic types (types I–III) were described by Stocker et al. [1] based on clinical, macroscopic and microscopic criteria. The microscopic features that distinguish CCAM from normal lung include: (i) proliferation of the terminal respiratory structures forming cysts; (ii) polypoid projections of the mucosa; (iii) increased smooth muscle and elastic tissue within cyst walls; (iv) absence of cartilage; (v) presence of mucous-secreting cells, and (vi) the absence of inflammation [1]. Improvements to this classification have been made, with additional types (types 0 and IV) being described [11]. Stocker also proposed changing the name of CCAM to CPAM, since the lesions are cystic in only three of the five types, adenomatoid in only one type, and as they represent malformations affecting different portions of the tracheobronchial tree. The main features of each type are summarised in table 1.

Several other classifications have also been purposed. Langston [8] divided lung cystic lesions into two types: (i) a large-cyst type (equivalent to Stocker's type I), and (ii) a small-cyst type (equivalent to Stocker's type II). A luminal obstruction with the secondary pulmonary dysplastic changes was proposed as a basis for these malformations [8, 12]. Morotti et al. [13, 14] evaluated the cellular composition of different types of CPAM using immunohistochemistry, and divided the CPAMs into two major subtypes: one subtype consisting of CPAMs type I–III that show a bronchiolar-type epithelial differentiation, and the other type consisting of CPAM type IV, showing an acinar-alveolar epithelial differentiation.

Another classification was purposed by Adzick et al. [2] based upon the US appearance of the foetal lesion. Macrocystic lesions contain single or multiple fluid-filled cysts that are 5 mm or larger in diameter and tend to grow slowly and have a favourable prognosis (some fetuses with macrocystic lesions may develop hydrops). Micro-

cystic lesions are smaller than 5 mm in diameter with a homogeneous echogenic appearance, with no visible cystic spaces. When microcystic lesions are large and grow rapidly, they are frequently associated with a mediastinal shift, pulmonary hypoplasia, polyhydramnios and hydrops. They are also frequently associated with a poor outcome [15–17]. This classification is especially useful since it has prognostic value, and can thus provide a practical guideline for the evaluation and treatment of prenatally diagnosed cases.

Bush [18] suggested a classification of cystic, intermediate or solid congenital thoracic malformation. The distinction between histological subgroups remains important, as some types of cancer are more common in some histologic types of CPAMs [19].

A great controversy exists regarding the correlation between clinical behaviour, prognosis and the CPAM type [20]. Stocker's classification was based upon 38 cases and reflects the pattern of the time since many of the lesions were characterised from autopsied infants with a predominance of type II and type III lesions [1]. Later studies showed that the prognosis of prenatally diagnosed lesions depends on the presence or absence of hydrops [21]. Other prognostic factors [2, 15, 22, 23] include: (i) the size of the lesion and its secondary effects (mediastinal shift, the extent of pulmonary hypoplasia, polyhydramnios, cardiovascular compromise); (ii) the degree of development of the unaffected lung, and (iii) the presence or absence of other congenital anomalies, such as extralobar sequestration, diaphragmatic hernia, pulmonary hypoplasia, cardiovascular malformation, hydrocephalus, skeletal malformation, jejunal atresia, bilateral renal agenesis/dysgenesis and Pierre Robin syndrome [11, 24].

Histopathology and Genetics

Human lung growth starts as a primitive lung bud in early embryonic life and undergoes several morphological stages, which continue into postnatal life. Lung development begins at 3–4 weeks of gestation and occurs in six stages: the embryonic stage (4–7 weeks), pseudoglandular stage (5–17 weeks), canalicular stage (16–26 weeks), sacular stage (24–38 weeks), alveolar stage (36 weeks of gestation to 2 years of life) and microvascular maturation (birth to 2–3 years of age) [25–27]. Morotti et al. [13, 14] postulated that CPAM is caused by a focal arrest in lung development at different stages of the branching of the bronchopulmonary tree: the first subtype (CPAM bronchiolar types I, II and III) at the pseudoglandular stage

Table 1. Pathological features of CPAM [11, 17, 24, 28, 104]

Classification	Type 0	Type I	Type II	Type III	Type IV
Descriptive name	Acinar dysplasia	Multiple large cysts or a single dominate cyst	Multiple evenly spaced cysts (sponge-like appearance)	Bulky firm mass (adenomatoid appearance)	Peripheral cyst type
Frequency, %	1–3	>65	10–15	8	10–15
Typical age at presentation	Birth	In utero, if large, to many years of age, if small	1st month of life	In utero or at birth	Newborn to 6 years, or rarely much later
Presentation	Lungs will not aerate	Newborn: respiratory distress, mediastinal shift Later: incidentally, or cough + fever + infection	Non-pulmonary anomalies may supersede lung anomalies	May be stillborn, or severe neonatal respiratory distress	Respiratory distress ± tension pneumothorax, or infection/pneumonia, or incidental finding
Cyst size (maximum), 0.5 cm		10.0	2.5	1.5	7
Cytdifferentiation		Bronchiolar-type epithelial differentiation			Acinar-alveolar epithelial differentiation
Epithelial lining (cysts)	Ciliated pseudostratified tall columnar with goblet cells	Ciliated pseudostratified tall columnar	Ciliated cuboidal or columnar	Ciliated cuboidal	Flattened alveolar lining cells
Muscular wall thickness of cysts, µm	100–500	100–300	50–100	0–50	25–100
Mucous cells	Present in all cases	Present (33% of cases)	Absent	Absent	Absent
Cartilage	Present in all cases	Present (5–10% of cases)	Absent	Absent	Rare
Skeletal muscle	Absent	Absent	Present (5% of cases)	Absent	Absent
Lobar involvement	All lobes involved	One lobe in 95%; rarely bilateral	Usually one lobe	Entire lobe or lung	Usually one lobe
Location	Proximal tracheobronchial tree	Proximal acinus (bronchial/bronchiolar)	Midacinus (bronchiolar)	Bronchiolar/alveolar duct	Distal acinus (alveolar saccular regions)
Associated anomalies	CV anomalies, renal hypoplasia, focal dermal hypoplasia	Rare (5–12%)	CV anomalies, diaphragmatic hernia, extralobar sequestration, renal agenesis or dysgenesis (7–50%)		No anomalies found to date [24]
Malignancy risk	No	BAC	No	No	PPB
Prognosis	Lethal at birth				

and the second subtype (CPAM type IV) at the saccular stage. Several molecular mechanisms underlying CPAM have been identified and have contributed to a better understanding of its pathogenesis. An increased cellular proliferation and decreased apoptosis in foetal CPAM specimens was demonstrated [28]. However, the authors failed to demonstrate differences in fibroblast growth factor (FGF)-7 expression, a growth factor previously implicated in experimental CPAM [29]. Liechty et al. [30] demonstrated that CPAMs resected in utero by the rapid growth and progression to hydrops had persistently elevated platelet-derived growth factor BB production.

Thyroid transcription factor 1 regulates early lung development [14] and correlates distinctive patterns of ex-

pression in CPAMs: (i) types I–II presented a similar pattern to that in the pseudoglandular stage and (ii) type IV presented a pattern similar to that in the saccular stage. The glial cell-derived neurotrophic factor is another factor with abnormal expression in the epithelium lining the airways of immature human lungs [31] and could play a role in CPAM. Another potential gene, *Hoxb-5*, is involved in lung branching and has a higher level of expression in resected CPAM specimens, suggesting it has an abnormal temporal and spatial expression in CPAM [32]. Jancelewicz et al. [33] analysed gene expression from laser-dissected epithelium and mesenchyme of human foetal and postnatal CPAMs, and demonstrated an imbalance of the markers of early lung development, namely an

increase in Hoxb-5, TTF1 and FGF9 expression, a decrease in FGF7, and no differences in FGF10 and FGF receptor 2 expression.

Another candidate gene is the fatty acid-binding protein FABP-7 [34], the expression of which is reduced in foetal CPAM specimens. An overexpression of Clara cell marker 10 was also identified [13]. Altered integrin cytoplasmic signalling was also proposed, since integrin and E-cadherin expression patterns were altered in CPAM tissue [35].

SOX2 is a transcription factor with a critical role in lung branching [36]. The overexpression of SOX2 induces the appearance of cyst-like structures [37], and it is expressed in the epithelial lining of cystic lesions in CPAM type II, but not in CPAM type I [37].

Our group [38] was able to evaluate the formation of CPAM-like lesions in response to the overexpression of FGF10 in the mesenchymal compartment of developing foetal rat lung. The overexpression of FGF10 at different locations and developmental stages induced the appearance of localised cystic malformations, ranging from macrocystic malformations lined by predominantly bronchial epithelium, to focal microcystic malformations lined by predominantly alveolar epithelium. The similarity of these lesions to human CPAMs strongly suggests that the overexpression of FGF10 may be one of the most important mechanistic components of the initial events in CPAM formation. However, the initial 'hit' that induces FGF10 overexpression remains to be determined.

The emergence of hybrid lesions has been widely reported in the past few years, leading to speculation of a possible link between these lung malformations [9, 12, 39]. Cass et al. [9] described prenatally diagnosed lung masses that display clinicopathological features of both CPAM and bronchopulmonary sequestration (BPS), suggesting a common embryologic basis for hybrid lesions. Langston [8] postulated that in utero airway obstruction is the basis and the unifying mechanism for congenital lung malformations. It is possible that the level, the completeness and the timing of airway obstruction together with secondary pulmonary dysplastic changes may explain the varied spectrum of hybrid lung malformations.

Diagnosis

Prenatal Diagnosis

Prenatal diagnosis has evolved over the years. Today, routine prenatal US screening complemented with magnetic resonance imaging (MRI) has become increasingly

valuable in detecting CPAMs [40], with an accuracy of 65–91% [41, 42]. Before the advent of prenatal sonography, CPAMs were diagnosed only in symptomatic infants or as an incidental finding. The improvement of prenatal diagnosis has led to the identification of many asymptomatic neonates, creating new management challenges [43]. The major advantage of prenatal diagnosis is the identification of symptomatic neonates [44], prenatal counselling, foetal intervention and birth planning [41].

US is the antenatal imaging modality of choice to screen CPAMs, while MRI is an excellent option for the morphological and volumetric evaluation of the foetal lung [6]. CPAMs appear as hyperechoic, heterogeneous tissue with multiple hypoechoic cysts that may differ in size and number on foetal US. MRI returns a higher signal than with a normal lung on T2-weighted images [45]. Depending on the CPAM lesion type, foetal MRI can show a homogeneous or heterogeneous T2-hyperintense lesion containing cystic spaces and vascular architectural distortion [46]. Recently, Epelman et al. [47] recommended a description protocol that includes: (i) anatomical location, (ii) relationship with the bronchial tree, (iii) number of cysts and (iv) size of the largest cyst, among other parameters. US in the second trimester is reliable and accurate in detecting echogenic pulmonary lesions, and differential diagnosis includes CPAM, BPS, bronchogenic or neurenteric cysts, and diaphragmatic hernia [17]. When the US findings are equivocal or the images are difficult to interpret, such as in late pregnancy or with an inaccessible foetal position, MRI should be considered [46]. MRI plays an important complementary role to US since it is able to define the type and extent of these lung lesions, thus guiding prenatal intervention and postnatal care [46].

Colour Doppler US has been suggested as a tool to investigate systemic arterial blood supply. It evaluates the arterial and venous blood flows, allowing prenatal differentiation between CPAM and BPS. While CPAMs derive their blood supply from the pulmonary circulation and drain via the pulmonary veins, BPS has a feeding systemic artery [9]. However, two-dimensional colour Doppler US is not 100% sensitive for identification of the feeding artery [48].

The natural history of prenatal cystic lung lesions varies from complete regression in utero to life-threatening hydrops fetalis. The timing of 'regression' is variable but tends to be in the mid-third trimester, usually at 32–34 weeks of gestation [49].

Hydrops is the strongest prognostic factor and it may be an indication for prenatal intervention [50]. A survival rate of more than 95% of CPAM cases without hydrops

has been reported, whereas death occurred before or after birth in 95% of CPAM cases with hydrops managed expectantly [51]. The development of hydrops is typically limited to those fetuses with very large chest masses with mediastinal shift and vena cava obstruction [15, 46, 52, 53]. Hydrops is commonly associated with ascites, pleural and pericardial effusions, and skin and scalp oedema. Anasarca and placentomegaly appear in advanced cases [54, 55]. Three features were found to be highly specific for foetal hydrops in fetuses with large masses: a mass-thorax ratio of at least 56%, cystic predominance and diaphragm eversion [21]. Gigantic foetal lung lesions have also other pathophysiologic consequences, including oesophageal compression by the thoracic mass, which interferes with amniotic fluid swallowing and results in polyhydramnios [15, 56].

Crombleholme et al. [52] reported a useful tool to stratify the risk of hydrops, the need for foetal intervention and the perinatal survival rate. Sonographic measurement of the CPAM volume ratio (CVR) is an index estimated as the CPAM volume divided by the head circumference. A CVR greater than 1.6 predicts an increased risk for hydrops fetalis, while a CVR less than or equal to 1.6 in the absence of a dominant cyst is associated with a less than 3% risk of hydrops. The growth rate of the lesion, particularly when associated with a macroscopic cyst, is also a risk factor for developing hydrops. Approximately 40% of CPAMs increase in size during pregnancy, with the most rapid growth occurring during 20–26 weeks of gestation, after which growth peaks and plateaus [52, 53]. The gestational age at diagnosis will impact surveillance frequency since microcystic CPAMs tend to regress spontaneously after the growth peak [15], while macrocystic lesions generally do not regress [52].

Postnatal Diagnosis

Imaging evaluation and clinical follow-up after birth is required in all cases to confirm the diagnosis and to initiate adequate treatment [23, 56]. Other imaging techniques like chest X-ray and computed tomography (CT) scan may have a role in postnatal assessment [57].

An apparent involution of lung lesions on serial prenatal US or neonatal chest radiographs can be misleading and does not rule out CPAM persistence on a postnatal CT scan [50, 58]. Prenatal US becomes less sensitive in diagnosing lung cysts with advancing pregnancy due to the loss of the fluid-tissue interfaces. Postnatally, thin-walled cystic lesions are difficult to see on a plain radiograph when uninfected and, thus, a chest CT for definitive diagnosis is strongly recommended in all cases [50,

54, 59, 60]. The radiological image of a CPAM depends on the consistency of the lesion: hyperlucent in multicystic regions (particularly types I and II), radiopaque in solid components (especially type III), or air fluid level in the early neonatal period when the pulmonary fluid is clearing or in infected lesions [61]. On a CT scan, solid CPAMs or those that have cysts filled with fluid will be hyperdense, whereas lesions that are overinflated will have a hypodense appearance [57].

Postnatal follow-up should also include the evaluation of associated congenital anomalies and here a CT scan is generally the choice [61, 62]. In asymptomatic patients, a CT scan is advised during the first 3 months of life. It has several advantages, including a faster acquisition, the reduced need for sedation, is less expensive and is very useful in adequate planning of the surgery [47]. Angiography CT can be extremely useful in the differential diagnosis of congenital lung malformations [47]. MRI could be an alternative to a CT scan, but there is no available evidence showing which one is the best technique [60].

After surgical resection or in cases of asymptomatic stable lesions when a conservative ‘wait and see’ approach is adopted, the patient should be followed up until adulthood. The most acceptable imaging technique used in the follow-up is CT and further work is needed to evaluate the potential role of MRI. Although CT is largely accepted, doubts arise on the frequency of the scans, since the benefit of repeated CT scans needs to be balanced against the risks of ionising radiation [47].

Management

Prenatal Management

Prenatal treatment options include the maternal administration of steroids, minimally invasive procedures or open foetal surgery. These interventions aim to alleviate the mass effect, prevent the progression of complications and to improve the outcome for these fetuses [63]. In macrocystic lesions, decompression can be attempted by permanent drainage via a thoracoamniotic shunt (TAS) placement guided by US or single-needle thoracocentesis [64]. In microcystic lesions, open foetal surgery may be indicated [63]. Maternal betamethasone treatment has been suggested to have beneficial effects on large microcystic CPAMs [65–67]. Before a decision for any prenatal intervention is taken, it is recommended to characterise the lesion (macro vs. micro, CVR, hydrops) and to identify associated anomalies by US, echocardiogram and/or MRI [68, 69].

Prenatal Steroids

Resolution of a large CPAM after steroid therapy, initially given for lung maturation, was first described by Higby et al. [70] in 1998. Another group reported the unexpected resolution of hydrops after maternal betamethasone administration [66]. Several others reported the same effect with two standard doses of 12 mg of betamethasone intramuscularly, 24 h apart, showing a decrease in CPAM growth lesions with CVR ≥ 1.4 at 19–26 weeks of gestation [66, 71]. The mechanism of the effect of steroids on CPAM is unknown. Curran et al. [67] hypothesised that steroids stimulate the maturation of the lung cells. Others have speculated that the steroids affect the cell proliferation and apoptosis, thus reducing CPAM growth [72].

Current evidence suggests that in large CPAMs with hydrops, a course of steroids appears to be a reasonable first-line therapy. However, a variable response on maternal betamethasone treatment has also been reported [72, 73]. For a subset of high-risk CPAMs that do not adequately respond to a single course of steroids, multiple courses of antenatal betamethasone may facilitate the stabilisation or regression of CPAM [73]. Whether steroids should also be used in CPAMs without hydrops is more questionable, as the prognosis without intervention is generally good and spontaneous regression may occur [55, 63].

The long-term effects of maternal betamethasone on foetal development are a concern, but there are no studies to support deleterious effects occurring following one or two courses of maternal betamethasone [74]. Betamethasone seems to be a good choice since it does not cause decreased alveolarisation, as compared to dexamethasone [74, 75].

Foetal TAS

Large lesions carry a significant risk of pulmonary hypoplasia and foetal hydrops. These cases can be managed with TAS [17, 51, 63, 76], which has been recommended in severe cases with high-risk hydrops, even before it develops [76]. This issue is still controversial since it is difficult to predict the evolution of a macrocystic lung lesion and there are no randomised studies comparing treatment with the non-treatment of non-hydrotic foetuses.

The criteria for TAS placement are: (i) gestational age <32 and >20 weeks (if performed at less than 20 weeks, it may increase the risks of chest wall deformity); (ii) non-immune hydrops, i.e. pleural effusion (PE) associated with either skin oedema or ascites); (iii) isolated PE without hydrops occupying a large part of the thoracic cavity

($>50\%$) and causing mediastinal deviation, rapidly increasing in size or being associated with increasing polyhydramnios, or rapidly re-accumulating after thoracentesis; (iv) large bilateral PE with a suspicion of pulmonary hypoplasia; (v) macrocystic CPAM with a dominating cyst with a high risk of pulmonary hypoplasia (CVR >1.6 indicates much higher risk), and (vi) the absence of other associated major foetal anomalies detected by US for laboratory analysis [53, 77]. TAS complications include foetal or uterine wall trauma, displacement or occlusion of the catheter, amniotic fluid leakage, infection, premature delivery and foetal demise [77–79]. Squamous metaplasia of the cyst epithelia has also been described [80]. The outcome of TAS has been reported in 68 foetuses with macrocystic CPAMs, two thirds of which were hydrotic [51]. The overall survival rate was 75%: 68% in hydrotic and 87.5% in non-hydrotic foetuses [51].

EXIT Procedure

The ex utero intrapartum (EXIT) procedure is well described [81–83] and was first developed for reversing tracheal occlusion in foetuses with severe congenital diaphragmatic hernia [84, 85]. An experienced multidisciplinary team is crucial for successful EXIT procedures [86]. The hallmark of the EXIT procedure remains a prolonged uterine relaxation with deep inhalational anaesthesia, leading to preservation of the uteroplacental blood flow and gas exchange [87, 88]. This technique allows a controlled resection of large foetal lung lesions at delivery, limiting complications due to cardiac tamponade and acute respiratory failure [89].

The major indication for EXIT delivery includes the presence of a foetal lung mass with severe mediastinal shift and/or hydrops associated with a persistently elevated CVR (mean 2.2, with a range of 1.0–2.6) after 32 weeks of gestation [69, 89, 90]. Even after resolving hydrops with maternal steroids administration, there is a risk of pulmonary hypoplasia. In some cases, the size of the CPAM remains significantly high with a mediastinal shift and cardiac compression. In these cases, the EXIT procedure may also be indicated and the delivery should be planned for a tertiary care centre [69, 91].

Hedrick et al. [89] reported an overall survival after EXIT lung mass resection of 89%, with the mean gestational age at the EXIT delivery of 35 weeks [89, 92]. Complications are primarily related to a failure to preserve uteroplacental gas exchange or a loss of myometrial relaxation [87]. An advantage is the possibility to start surfactant replacement therapy before delivery [82]. Maternal

postoperative morbidity is comparable to caesarean section under general anaesthesia, with a minimal increased likelihood of maternal anaemia [77].

Prenatal Management Algorithm

A prenatal management algorithm, based on all possible foetal interventions and imaging tools, is proposed (fig. 1).

Postnatal Management

Significant advances in neonatal intensive care have allowed support, either with conventional ventilation or high-frequency oscillation ventilation, optimising oxygen delivery. A postnatal echocardiogram is essential for assessing cardiovascular function and for guiding inotropic support, especially in the case of persistent pulmonary hypertension of the newborn. Extracorporeal membrane oxygenation can be an option in challenging cases despite full cardiorespiratory support.

Surgical versus Conservative Approach

Every patient with CPAM should be evaluated for surgery. If the patient is symptomatic, surgical treatment is recommended. Some newborns with large lesions may even require a neonatal surgical resection in order to save viable lung parenchyma and reverse mediastinal displacement [93].

The management of asymptomatic CPAM remains contentious and no consensus has yet been reached regarding the optimal timing for surgery [4, 15, 94–97]. Some authors adopt an early resection strategy to avoid the onset of symptoms [4, 15, 98, 99] since the safety of lung resection during the infantile period has been proven [41, 98, 100], while others adopt a conservative strategy, recognising the surgical risks and the potential of over-treatment [97, 101–103], and surgery is only purposed after the patient becomes symptomatic with recurrent infections or pneumothorax [100, 104]. Additionally, some authors recognise the potential for spontaneous resolution: in a study of 56 children with an antenatal diagnosis of CPAM, two CPAMs spontaneously resolved postnatally and ten resolved antenatally [104]. The elective and early resection of asymptomatic lung malformations is based on several arguments: (i) an early lobectomy avoids long periods of observation, preventing the need for using ionising radiation in repeated imaging studies and the loss of patients during follow-up; (ii) if no imaging technique is able to confirm the pathological diagnosis; (iii) the possible relation of CPAM with lung malignancy development, and (iv) a potential compensatory lung growth [105].

Long periods of observation increase the risk of complications [15, 106]. In asymptomatic patients following the neonatal period, a 3.2% complication rate was estimated, and occurred at a median age of 7 months [107]. In fact, recurrent infections may impose technical difficulties at the time of lung resection [98, 100, 108]. Furthermore, it has been shown that the infection alone may lead to pulmonary growth impairment [105].

The potential for compensatory lung growth is one of the main arguments for early lung resection [105, 109–111]. Postnatal lung development consists of three stages: (i) stage I (birth to 1–2 years) with alveolar proliferation and a rapid increase in alveoli number; (ii) stage II (2–3 years) with microvascular maturation and proliferation, and (iii) stage III with late alveolarisation and alveolar maturity [109, 111]. Alveolar multiplication is fastest during the first 2 years of age, then slows at 4 years and stops at around 8 years of age [109, 112]. Stage I is suggested to be the most important period regarding future lung function. Two mechanisms of lung growth can occur after surgery: compensatory alveolar multiplication or overinflation of the remaining parenchyma [113]. A radionuclide imaging study suggested that alveolar multiplication mainly occurs after lobectomy in patients younger than 1 year, while emphysematous overinflation mainly occurs when lobectomy is performed after the age of 1 year [105]. This study also suggested that recurrent and severe infection alone influences pulmonary function. However, a retrospective study showed that age at the time of lobectomy (before vs. after 2 years) did not influence the spirometer results at a mean age of 10 years [113]. If resection is endorsed, most authors agree on surgery during the first year of life. Some authors wait until 6 months of age [114], while others propose a much earlier intervention at 4 weeks of age [68].

Thoracotomy versus Thoracoscopy

A meta-analysis comparing thoracoscopy with the open resection of CPAM suggested no differences between thoracotomy and thoracoscopy regarding overall complications and surgery duration. A reduction in length of hospital stay and in days spent with a chest tube was observed after the minimal invasive approach [115]. The largest study, reviewing 97 lobectomies, revealed longer operative times in thoracoscopic procedures but a shorter hospital stay, better cosmesis and decreased post-operative pain. Larger randomised trials are required in order to compare both approaches. In the current minimal invasive era, data is consistent regarding resection safety and feasibility. In experienced hands, the thoraco-

Fig. 1. Prenatal management algorithm [15, 17, 53, 60, 69, 72]. ECHO = Echocardiogram. * Multiple courses of betamethasone may be an option.

Fig. 2. Genes implicated in CPAM, PPB and BAC [14, 30–35, 127, 137–143]. TTF1 = Thyroid transcription factor 1; PDGF-B = platelet-derived growth factor B; FABP-7 = fatty acid-binding protein 7; GDNF = glial cell-derived neurotrophic factor; Shh = sonic hedgehog; FGFR2b = FGF receptor-2b; FHIT = fragile histidine triad; Rb = retinoblastoma protein; EGFR = epidermal growth factor receptor.

scopic approach can be the approach of choice for CPAM resection.

Lobectomy versus Parenchyma-Sparing Resection

Lobectomy appears to be the best treatment to avoid recurrent pulmonary infection and neoplasia. It is agreed among many surgeons and pathologists that the limit between CPAM and normal parenchyma is impossible to determine [116–118]. Muller et al. [119] demonstrated that preoperative CT is not predictive of extension of the malformation. Therefore, adopting subtotal lobectomy or segmentectomy has the risk of leaving remnants of the CPAM lesion, based only on a CT scan [120]. If the option is surgery, it is necessary to remove all abnormal tissue in order to avoid later infection or malignancy. However, a prospective study will be required to compare the long-term outcome of patients submitted to lobectomy or parenchyma-sparing resection (PSR) in terms of infection risk and neoplasia development. Some authors propose that PSR should be reserved for patients with bilobar or bilateral disease, as PSR is technically feasible and safe, with low postoperative complications [119, 121, 122].

Table 2. Cases of malignant transformation associated with CPAM [4, 118, 124, 145–155]

	CPAM type		
	unspecified ¹	type I	type IV
Bronchioloalveolar carcinoma	2	18	0
Mesenchymal malignancies			
Pulmonary blastoma	8	1	0
Rhabdomyosarcoma	7	1	0
Myxosarcoma	1	0	0
Embryonal rhabdomyosarcoma	7	0	0
Mixed mesenchymal sarcoma	1	0	0
Malignant mesenchymoma	1	0	0
PPB	11	1	2
Total	38	21	2

¹ Unspecified cystic lesions or CPAM type.

Fig. 3. Postnatal management algorithm [3, 116, 118, 119, 144]. ECHO = Echocardiogram; PPHN = persistent pulmonary hypertension of the newborn; ECMO = extracorporeal membrane oxygenation.

Cancer Risk

Although lung cancer associated with CPAM is rare, an increasing number of cases are being reported (table 2). A large review of childhood lung neoplasms demonstrated an association of 8.6% between malignant tumours and CPAMs [114]. A clear link between CPAM and lung cancer is missing, but some molecular pathways

are shared between CPAMs and the two most frequent lung cancers associated to CPAM (fig. 2).

Pleuropulmonary blastoma (PPB) is a dysembryonic malignant sarcoma [104]. Since PPB is a recently recognised entity, many neoplasms previously reported as sarcomas or rhabdomyosarcomas might represent unrecognised PPBs (table 2) [8]. PPBs are classified into

three types based on gross pathologic morphology, and on their radiographic and microscopic characteristics [104, 123]. Type I PPB consists of a cystic lesion, clinically and radiologically indistinguishable from CPAM [104, 123]. Type I PPB may also regress and persist without malignant potential, termed type Ir (regressed). In type II PPB, there are cystic lesion-thickened walls or septa, solid mural nodules and larger tumour excrescences [104, 123]. Type III PPB is a solid high-grade sarcoma [104, 123]. A growing number of mesenchymal malignancies associated with CPAM have been reported, but the relation between PPB and CPAM is not obvious (table 2) [4, 104]. PPB affects mostly young children, including neonates, and is diagnosed at approximately 10 months of age for type I PPB. Most cases appear before the age of 6 years [96, 123, 124]. As in PPB and rhabdomyosarcomas, type II CPAM occasionally exhibits skeletal muscle differentiation [96]. The clinical similarity between the two lesions raises the hypothesis that PPB can develop within a CPAM [96, 107]. In contrast, different PPB types may represent different stages of the same malignant process since recurrences of type I are usually type II or III PPB, and cysts could be a form of PPB rather than a CPAM [123, 125]. Early surgical resection may be advantageous by removing potential malignant tissue, since it is impossible to distinguish CPAM from type I PPB [96, 104, 126]. However, prophylactic resection may not prevent the development of PPB, as there is a case of PPB after resections for bilateral CPAM [118].

CPAM-associated bronchioloalveolar carcinoma (BAC) has been reported, with all the documented cases occurring in patients with CPAM type I (table 2). Unlike PPB, there is a more clear connection between CPAM and BAC [4]. CPAM type I is thought to be a precursor lesion to BAC [127]. Clusters of mucogenic cells are present in 35–50% of type I CPAMs [19]. Atypical adenomatous hyperplasia, atypical goblet cell hyperplasia and chromosomal aberrations have been described in CPAMs type I, supporting their eventual preneoplastic status [126, 128–130]. Mucinous cells within CPAM type I produce gastric mucins similar to those found in BAC and have an increased frequency of KRAS mutations as well as a loss of heterozygosity at the tumour suppressor genes *FHIT*, *p16INK4* and *Rb* [127]. The concept of malignant progression from type I CPAM to atypical goblet cell hyperplasia, or atypical adenomatous hyperplasia to BAC, has been supported by reports in which all the stages are present [131].

Postnatal Management Algorithm

A postnatal management algorithm based on the early surgical treatment of asymptomatic patients has been proposed (fig. 3).

Conclusion

As knowledge about pathogenesis and the natural history of CPAM increases, the pre- and postnatal management of this condition will evolve and improve. Controversy still exists regarding the management and the treatment of asymptomatic patients. The prevention of infection and cancer, the improved restoration of lung volume and fewer complications might favour elective early surgery. The involvement of a multidisciplinary team in the management of these patients is of utmost importance to outline the adequate therapeutic algorithm.

Future Perspectives

Advances in genomic medicine have been applied in many fields of neonatal care and will certainly provide a new array of diagnostic and therapeutic tools [132–135]. Investigations have been performed on human lung cancer, but limited information is available about metabolic perturbations arising in situ from CPAM [133]. Pelizzo et al. [136] suggest that CPAMs have different metabolomic profiles that can be useful for early diagnosis, allowing planned treatment and prognosis during pregnancy. Further investigation of the regulation of these metabolic traits should be done in order to gain a better understanding of the phenotype of foetal lung lesions, specifically in CPAM.

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