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ORIGINAL ARTICLE

Management of Congenital Cystic Adenomatoid Malformation and Bronchopulmonary Sequestration in Newborns

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Background: Congenital cystic adenomatoid malformation (CCAM) and bronchopulmonary sequestration (BPS) are major embryonic pulmonary developmental anomalies. Early surgical excision is becoming an increasingly common option. We investigated the clinical features and management of patients with CCAM and BPS at the National Taiwan University Hospital.
Methods: We conducted a retrospective review of neonates diagnosed with CCAM and/or BPS at the Hospital from July 1995 to January 2008. Prenatal examination, postnatal presentation, management and patient outcome were analyzed. We also propose a concise algorithm for the practical management of these conditions.
Results: Sixteen patients were recruited including eight (50%) with CCAM, five (31%) with BPS and three (19%) with mixed-type lesions (CCAM with BPS). Thirteen (81%) patients were diagnosed antenatally at a median gestational age of 20 weeks. Eleven (69%) patients underwent surgical resection before 6 months of age because of respiratory distress or repeated pulmonary infection. There were no surgery-related complications among the seven patients who underwent early surgery within 1 month of age. Five (31%) patients remained asymptomatic and did not undergo surgery. All patients survived with no limitations to daily activity during follow-up periods of 1–8 years.
Conclusion: The high proportion of mixed-type lesions suggests that CCAM and BPS may share the same developmental ancestry. Early surgical resection within 1 month of age is safe in symptomatic patients.

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1. Introduction

Congenital cystic adenomatoid malformations (CCAM) and bronchopulmonary sequestration (BPS) are major categories of congenital pulmonary malformations. CCAM is considered to represent a hamartomatous change in the tertiary bronchioles, and has an incidence of 1 in 25,000 to 35,000 live births.[1,2] BPS has an estimated incidence of 0.15%–1.7% in the general population[3] and is defined as a region of lung parenchyma that lacks a normal connection to the tracheobronchial tree and possesses an anomalous systemic blood supply. Advances in antenatal ultrasonography mean that most cases are now diagnosed prenatally.[4] It is also possible to observe their diverse natural courses *in utero*, from severe hydrops fetalis to total regression. Recent studies have focused on the origin and pathogenesis of CCAM and BPS, emphasizing the developmental anomalies occurring in embryonic pulmonary bud formation. The occurrence of hybrid CCAM/BPS lesions revealed by histopathology suggest the existence of a common origin for CCAM and BPS.[5]

In the present study, we reviewed our experience of neonates with CCAM and BPS. We also emphasize their management and outcome, and propose an algorithm to guide the practical management of these conditions.

2. Materials and Methods

We retrospectively reviewed the medical records of neonates diagnosed with CCAM and/or BPS at the National Taiwan University Hospital from July 1995 to January 2008. The institutional review board at the Hospital gave approval for this review. The diagnosis was based on clinical manifestations, abnormal imaging findings and pathologic confirmation. All patients underwent serial fetal ultrasonography and postnatal chest radiography (CXR) examinations. Computed tomography (CT) scans and magnetic resonance imaging were performed in 13 and 3 patients respectively. A definite diagnosis could only be achieved by histopathology in patients who had undergone pulmonary resection.

The histopathologic definition of CCAM is based on Stocker's classification: type I (single or multiple cysts of >1 cm in diameter, lined by ciliated columnar or pseudostratified epithelium, mucus-secreting cells and prominent cartilage); type II (multiple cysts of <1 cm in diameter, lined by cylindrical to cuboidal epithelium with prominent smooth or striated muscle); and type III (grossly solid, histologically microcystic, lined by cuboidal epithelium, often intricately folded).[6] BPS is described as an ectopic and nonfunctioning pulmonary tissue with its own blood supply, derived either from the systemic or pulmonary artery. It may be composed of different types of lung tissues including bronchi, alveoli, cartilage or ciliated columnar epithelium.[7] A hybrid lesion is a congenital pulmonary malformation manifesting the histopathologic features of both CCAM and BPS.

Data collected from patients' medical records included sex, gestational age, birth weight, clinical features, findings from antenatal ultrasonography and postnatal imaging, management strategies, and outcomes. Statistical data are presented as median (range) and were compared using Mann-Whitney *U* tests. A p value <0.05 was considered significant.

3. Results

3.1. Patient characteristics and antenatal courses

Sixteen patients (13 males and 3 females) with the diagnosis of CCAM and/or BPS were identified during the study period. The median gestational age was 38 weeks (32–41 weeks) and the median birth weight was 3189 g (1766–4090 g). No patient had any other congenital anomalies or hereditary genetic disorders. One case was a preterm infant and another case was a small-for-gestational-age infant, with a birth weight below the fifth percentile of the Taiwanese birth weight curve.[8] There were eight patients (50%) with CCAM, five (31%) with BPS and three (19%) with hybrid lesions (Table 1). Three (38%) patients had type I CCAM and five (62%) patients had type II CCAM (62%). Three (60%) patients had intralobular BPS and two (40%) had extralobular BPS. The hybrid lesions were often composed of type II CCAM and intralobular BPS. The abnormal lung lesions were mainly located in the left lower lung (8/19, 42%) and the right lower lung (6/19, 32%), followed by the right upper lung (2/19, 11%), the left upper lung (1/19, 5%), the right medial lung (1/19, 5%) and the mediastinum (1/19, 5%).

Prenatal diagnoses were made in 13 cases (81%) at a median gestational age of 20 weeks (20–24 weeks), while the remaining cases were diagnosed within the first postnatal week. The most common sonographic finding was macrocystic or microcystic fetal lung lesion. Serial antenatal sonographic monitoring showed regression of fetal lung lesions in 11 cases (85%), stable lesions in one case (7.5%) and progression in one case (7.5%). No pregnancy-related complications such as hydrops fetalis, polyhydramnios, fetal ascites or fetal pleural effusion were noted among the patients.

Table 1 Demographic data of 16 neonates with congenital cystic adenomatoid malformation (CCAM), bronchopulmonary sequestration (BPS) and hybrid lesions

	CCAM (n=8)	BPS (n=5)	Hybrid lesion (n=3)
Males	7 (88%)	4 (80%)	2 (67%)
Gestational age (wk)*	38 (37–40)	39 (32–41)	39 (38–39)
Birth body weight (g)*	3193 (2732–4090)	2974 (1766–3590)	3198 (2522–3612)
Diagnosed during pregnancy	5 (63%)	5 (100%)	3 (100%)
In utero spontaneous regression	4 (50%)	4 (80%)	3 (100%)
Distribution			
RUL	1 (11%)	0 (0%)	1 (25%)
RML	0 (0%)	1 (20%)	0 (0%)
RLL	4 (45%)	2 (40%)	0 (0%)
LUL	1 (11%)	0 (0%)	0 (0%)
LLL	3 (33%)	2 (40%)	3 (75%)
Mediastinum	0 (0%)	1 (20%)	0 (0%)

*Data presented as median (range). RUL=right upper lung; RML=right medial lung; RLL=right lower lung; LUL=left upper lung; LLL=left lower lung.

Table 2 Postnatal investigation of patients with congenital cystic adenomatoid malformation (CCAM), bronchopulmonary sequestration (BPS) and hybrid lesions*

	CCAM (n=8)	BPS (n=5)	Hybrid lesion (n=3)
Chest radiograph			
Normal	2 (25%)	1 (20%)	0 (0%)
Cystic/hyper-inflated lesion	4 (50%)	0 (0%)	1 (33%)
Ill-defined solid shadow	2 (25%)	4 (80%)	2 (67%)
CT or MRI			
Multicystic lesion	6 (75%)	0 (0%)	2 (67%)
Wedge-shape lesion	2 (25%)	5 (100%)	3 (100%)
Aberrant vessels	0 (0%)	3 (60%)	1 (33%)

*Data presented as n (%). CT=computed tomography; MRI=magnetic resonance imaging.

3.2. Postnatal clinical features and investigations

Seven patients had respiratory distress immediately after birth. They were subsequently diagnosed with CCAM (4 cases), BPS (2 cases) and hybrid lesion (1 case). Another patient with initially asymptomatic CCAM developed dyspnea and mediastinal shift after an episode of acute bronchiolitis at 5 months of age. We routinely performed CXR and CT (or MRI) in patients with fetal lung lesions, even in those with regression and normoechoic changes. All antenatally regressed lesions remained abnormal at postnatal CT scan. Table 2 shows the common radiologic finding of CCAM and/or BPS. CXR was not a sensitive diagnostic tool, and almost 20% of lesions were unidentified by this technique. CT and MRI are standard diagnostic tools which also delineate aberrant vessels. CCAM usually presented as a cystic or hyper-inflated lesion on CXR, and a multicystic/solid lesion on CT scan. BPS always presented as a solid mass in the basal lung region and appeared as a wedge-shape lesion with aberrant vessels on CT scan. Hybrid lesions combined characteristics of both CCAM and BPS. It should be diagnosed more carefully on a histopathological basis.

3.3. Management

Surgical resection was performed in seven (88%) symptomatic and four (50%) asymptomatic patients. Timing of surgery in symptomatic patients was primarily based on the severity of respiratory distress and episodes of infection. The median age at surgery was 11 days (5–169 days). Ten patients underwent thoracotomy, while one underwent video-assisted thoracic surgery. Surgical methods included lobectomy (n=8) and sequestrectomy (n=3). Definite histopathologic diagnosis was achieved after surgical resection.

For further analysis, patients who underwent surgery were subdivided into two groups: Group I

Table 3 Comparison of clinical courses of patients undergoing surgery before the age of 1 month (Group I) and after the age of 1 month (Group II)*

	Group I (n=7)	Group II (n=4)	$p^{\dagger}$
Clinical manifestations			
Dyspnea	5 (71%)	3 (75%)	0.90
Mediastinal shift	1 (14%)	1 (25%)	0.67
Infection	0 (0%)	2 (50%)	<0.05
Postoperative ventilator days	1 (0–5)	1 (0–3)	0.92
Postoperative ICU stay (d)	5 (2–12)	6 (2–13)	0.77

*Values expressed as n (%) or median (range); †Mann-Whitney U test. ICU=intensive care unit.

included those who underwent surgery prior to 1 month of age (n=7), and Group II included those who underwent surgery after 1 month of age (n=4; Table 3). Group I patients usually presented with dyspnea immediately after birth but rarely developed infections. Group II patients usually had mild or no respiratory distress after birth, but gradually developed dyspnea and late infection after 1 month of age. There were no surgery-related complications in any patients, indicating that early surgery within 1 month of age was safe. There were no significant differences in postoperative ventilator days or postoperative intensive care unit stay between the two groups.

3.4. Outcome and follow-up

All patients were regularly followed up in the outpatient clinic for 1–8 years. All patients underwent a rehabilitation program conducted by a respiratory therapist and a physical therapist. All patients who underwent surgery remained disease-free and with no limitations of their daily activities. The other five patients who did not receive surgery (2 CCAM, 2 BPS and 1 hybrid lesion) remained asymptomatic during the follow-up periods. There was no malignant transformation in any patient in this case series.

4. Discussion

The fetal respiratory system begins to develop at 3 weeks of gestational age. Abnormal pulmonary development caused by insults to the conducting airway, vascular or lymphatic system at different stages could result in a heterogeneous group of congenital lung malformations.[9] Congenital lung malformations may be detected early by fetal ultrasonography at around 18–20 weeks of gestation.[10] CCAM usually occurs in the pseudocanalicular stage, while BPS develops early in the embryonic stage. However, the concept of classification of congenital lung malformations is currently changing, owing to the detection of further mixed-type lesions, such as hybrid CCAM and BPS lesions.[5] This suggests that these lesions share the same developmental origin, and may represent two ends of a broad pathologic spectrum. There was a high proportion (19%) of hybrid lesions in our case series, identified by the coexistence of accessory blood vessels from the aorta and histopathologic characteristic of CCAM. This finding supports the theory of a common origin for CCAM and BPS.

Serial prenatal sonographic examinations are important for helping to determine the prognosis and necessity for possible intrauterine treatment in patients with CCAM and BPS. Hydrops fetalis in patients with CCAM or BPS consistently indicates a poor prognosis.[11] The degree of hypoplastic lung in a fetus, measured as a ratio <0.25 of lung to thorax transverse area, also suggests a poor prognosis.[12] Polyhydramnios and mediastinal shift representing a significant mass compression effect are warning signs, but are not absolute indicators of a poor prognosis.[1] Although some cystic lesions regress spontaneously, they can usually still be identified in postnatal radiologic evaluations. Postnatal surgical resection is required in up to 45% of lesions with late-gestational resolution.[13] Nine (69%) of our patients with prenatal diagnosis eventually underwent surgical interventions.

The appropriate management of congenital cystic lung disease remains a matter for debate. Based on our experience and a recent literature review, we propose an algorithm for the practical management of patients with these conditions (Figure 1). If prenatal ultrasonographic screening reveals a suspicious fetal lung lesion, a series of ultrasonographic examinations is necessary to evaluate the size, content (microcystic, macrocystic or solid) and distribution of the lesion. Fetal MRI and Doppler ultrasonography provide further delineation of the systemic feeding vessels in BPS.[11] Fetal therapies such as needle aspiration, catheter shunt placement and fetal surgical resection can be applied by centers with expertise, but the effectiveness and the risks associated with surgery should be carefully considered.[14] Because antenatal ultrasonography is not a good predictor of eventual histologic findings, postnatal re-evaluation using standard CXR, CT or MRI scan within a few weeks after birth is strongly recommended.[4] We believe that an increasing number of cases of congenital cystic lung disease

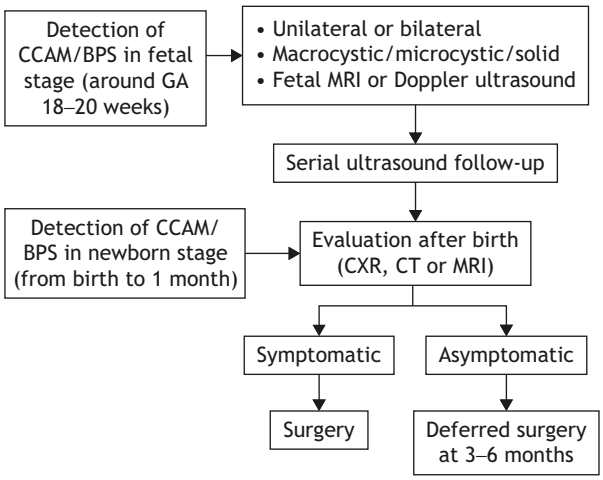

Figure 1 Algorithm for management of congenital cystic adenomatoid malformation (CCAM) and bronchopulmonary sequestration (BPS) in neonates. CT=computed tomography; CXR=chest radiography; GA=gestational age; MRI=magnetic resonance imaging.

could be identified by advanced prenatal examinations. The majority of these lesions will regress or become normoechoic in late pregnancy. However, many cases will remain undiagnosed in the absence of explicit postnatal imaging studies. Our case series supports this fact, as eleven patients (11/16, 69%) were diagnosed during the past 2 years by advanced prenatal ultrasonography and postnatal CT re-evaluation.

Two major factors affect the management of congenital cystic lung disease after birth: the timing of respiratory decompensation and the presence of any associated complications.[15] Improvements in both thoracic surgery and anesthesia in neonates mean that most cystic lesions can now be resected with minimal mortality and morbidity.[16] However, the optimal timing for surgical intervention may vary, depending on the clinical condition. Prompt surgical excision is indicated in patients with significant respiratory distress; however, conservative management for asymptomatic patients remains controversial. We observed different clinical manifestations in the current series: those with surgery before 1 month old presented with marked respiratory distress after birth, whereas the surgical indication shifted to recurrent pulmonary infection after 1 month. This difference must be taken into account when considering the option of surgery.

Initially asymptomatic patients sometimes developed recurrent pulmonary infection with severe respiratory decompensation after the age of 1 month. Reduced maternally transmitted immune protection and exposure to environmental pathogens may predispose these infants to respiratory infections. Although small asymptomatic lesions can regress, there have been an increasing number of reports of malignancy associated with CCAM over the last decade, which cannot be ignored. These associated neoplasms consist mainly of pleuropulmonary blastoma in infants and young children,[17] and bronchoalveolar carcinoma in older children and adults.[18] In addition, a lower incidence of complications and shorter hospital stay have been reported in cases who received surgery while they were still asymptomatic.[16] Early surgical resection of asymptomatic congenital cystic lung lesions at the age of 3–6 months is therefore recommended by several large centers.[19–21] This also allows for compensatory lung growth before lung maturation. Although the current case series was limited in sample size, results regarding the timing of surgery and surgical outcome are compatible with those of other study groups.[19–21]

In the follow-up of patients with cystic lung disease, regular chest CT scans are needed to clearly define the progression or regression of lesions and determine the timing for surgical intervention. In addition, regular vaccinations for *Haemophilus influenza* type B and *Streptococcus pneumoniae* are recommended to avoid life-threatening infections. Pulmonary function tests should also be considered to investigate the long-term outcome in patients who have undergone surgery. These data were unfortunately not available for the patients in the current study, and future studies are needed to investigate this aspect.

In summary, the emergence of mixed-type lesions suggests that CCAM and BPS may share the same developmental origin. Early surgical resection for symptomatic CCAM and BPS within 1 month of age is safe. Surgical resection should also be considered for asymptomatic patients to prevent possible late infection and malignant transformation.

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