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Congenital cystic adenomatoid malformation: clinical features, pathological concepts and management in 172 cases

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Abstract

Objective: Congenital cystic adenomatoid malformation (CCAM) is the most common surgically resected pulmonary malformation in children. This retrospective study was undertaken to present the experience of 172 CCAM cases in a pediatric hospital.

Methods: Published series with a small number of patients reports details of lesions, progress and management. As this study addresses clinical characteristics, progress and surgical procedures in 172 children with CCAM diagnosis, the population includes cases treated and followed up in a pediatric hospital throughout 25 years (1986-2011).

Results: Mean age at diagnosis was 48 months (r = 0.03-213), 52% (n = 90) were male. The most common presenting symptoms were respiratory distress in children under 6 months of age (40%) and recurrent pneumonia in older ones (75%; p = 0.001). Lobectomy was the procedure of choice in the majority. All histological types were found: 1 (70%), 2 (24%), 4 (4%), and 0 and 3 (n = 1). A mixed pattern was observed in nine patients. Associated anomalies were found in 47% of children. The most frequent was sequestration (71%), mostly present in CCAM type 2 (p = 0.001). Severe anomalies were mostly related to type 2 (p = 0.008). A pleuropulmonary blastoma and a bronchioloalveolar carcinoma were also observed. Mortality was 5% (n = 9). Risk factors for mortality were respiratory failure (OR = 25.7 [95%CI 3.2-221]; p = 0.03), sepsis (OR = 9.9 [95%CI 8.2-12]; p = 0.002), respiratory assistance requirements (OR = 9.5 [95%CI 2.3-37]; p = 0.04), and severe associated comorbidities (OR = 3.3 [95%CI 1.2-22]; p = 0.008).

Conclusions: Related anomalies were observed in almost half of the population. Due to the possibility of recurrent infection or development of malignancies, surgical resection should be considered when CCAM is diagnosed. Surgical outcome is favorable with manageable complications.

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Introduction

Congenital cystic adenomatoid malformation (CCAM) of the lung is the most common surgically resected pulmonary malformation in children. The alteration is considered an hamartomatous abnormality of the bronchial tree by some authors, whereas others favor the etiology of an arrest in the development of the fetal bronchial tree with airway obstruction.[1-3] Recent concepts point toward the latter hypothesis.[3]

Definition and classification of these lesions have always been somewhat problematic. In recent years CCAM was classified into five types by Stocker based on clinical and pathological features. He recommended that these be

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termed types 1, 2, and 3, and later added types 0 and 4.[4] Afterward, a unifying pathogenic mechanism based on airway obstruction during development was proposed by Langston and accepted as the basis for these and other associated pulmonary malformations.[3] CCAM was classified into large cyst type (Stocker type 1) and small cyst type (Stocker type 2), both isolated or with systemic arterial/venous connection (intralobar sequestration). Solid form of cystic adenomatoid malformation (Stocker type 3) was proposed as an example of pulmonary hyperplasia.[3]

CCAM are usually detected in neonatal period or in early childhood. With advances in diagnosis, management of CCAM can begin even during the prenatal period. In developing countries a large number of children with congenital lung lesions are initially seen and treated in peripheral hospitals before being referred to tertiary level centers. Diagnosis might be late and initiation of the proper treatment can be delayed.

In children the clinical presentation can range from acute respiratory distress to chronic lung infection localized in a defined area.[5] Some of them may even remain asymptomatic throughout life.

This retrospective study was undertaken to present the experience of 172 CCAM cases in a pediatric hospital. Clinical presentation, localization, frequency of the different pathological types, and related anomalies were described. Management and outcome after surgical intervention were also analyzed.

Patients and methods

A retrospective observational case series study was performed. The population included 172 children treated and followed up at the Children Hospital Dr. Juan P. Garrahan of Buenos Aires, Argentina from August 1987 to March 2011, who underwent surgical lung resection and had histopathological diagnosis of CCAM.

Clinical data considered were: age at diagnosis, sex, perinatal pathology, clinical diagnosis, associated anomalies, localization, and surgical procedures performed, evolution and complications. Imaging with chest x-ray and computed tomography (CT) scan were performed before surgery in all patients. CT angiography was done according to patient's requirement.

Histopathological studies

Surgically obtained material was fixed in formaldehyde, paraffin embedded and colored with hematoxylin-eosin, periodic acid Schiff (PAS) and Masson trichrome. In special cases immune histochemistry, CK AE1-AE3, CK20 and surfactant apoprotein A and B were performed using mouse monoclonal anti-surfactant SPA and SPB. After washing with Tris buffer they were incubated with labeled polymer. Staining was conjugated by incubation with 3, 31 diaminobenzidine (DAB).

Statistical analysis

Data were analyzed using a Statistix 8.0 software package (Statistic for Windows; Analytical Software, Tallahassee, Florida). Values were measured as median and interquartile ranges and mean and standard deviation (SD), according to the considered variables. Univariate analysis was applied to analyze features of patients and associated malformations according to CCAM types. Kruskal-Wallis rank test and Fisher's exact test were performed. Multivariate logistic regression model was used to calculate adjusted and unadjusted odds ratios (OR) and 95% confidence intervals (CI) for death. A difference was considered statistically significant if p value was lower than 0.05.

Results

The study included 172 cases of CCAM (89 males). Mean age at diagnosis was 48 months (range between 1 day and 213 months). Eighty-five percent of children with CCAM diagnosis had had prenatal periodical clinical controls; of these, only 14% (n = 24) underwent prenatal ultrasonography screening.

Sixty-five patients (38%) were younger than 24 months of age at the time of diagnosis. Of the children under 6 months of age (n = 63), 49% presented respiratory distress, 40% recurrent pneumonia, and 11% tachypnea. In children older than 6 months (n = 68) repeated infection localized in the same pulmonary area was the most frequent manifestation (75%). Of this last group, 15% of patients presented pleuropulmonary effusion. Diagnosis was an incidental finding in 10% of the study population (Table 1).

All histopathological types according to Stocker classification were found in our series.[4] The majority of the cases corresponded to CCAM type 1 (n = 121, 70%) and type 2 (n = 42, 24%). There were also seven cases (4%) of CCAM type 4. Only one case was observed with CCAM type 3 and type 0, respectively (Table 1).[6]

A mixed pattern in the same resected lobe with features of CCAM type and 1 and 2 was seen in nine cases, with predominance of type 1 in four cases, and type 2 in other four cases. A mixed pattern with characteristics of CCAM type 1 and type 4 was diagnosed in one case. In histopathological studies, 41% of the patients (n = 71) showed signs of chronic pulmonary infection recognized by lymphocytic and plasma cell infiltration of the alveolar walls and peribronchial areas. The alveoli were filled with large foamy macrophages, cholesterol esters and giant cells. Bronchiectasis was recognized in 10% of cases (n = 18), documented by dilated lumen and prominent chronic inflammation within and surrounding airways. These cases

corresponded to those with clinical diagnosis of recurrent pneumonia (Table 1). There was high correlation between pathology and radiological findings.

Right localization predominated (72%). Single lobe disease was more frequently observed (n = 157, 91%). Inferior right lobe was involved in 38% of the patients; inferior left lobe in 24%; superior right lobe in 22%; right middle lobe in 12%, and lingula in 4%. Fifteen patients (9%) showed compromise of more than one lobe: the association of middle and inferior right lobes was the most frequently observed (n = 7). Two cases had all right lobes involved. Bilateral compromise was observed in one patient with CCAM type 1, who showed compromise in all right lobes and inferior left lobe.

Related anomalies were found in 47% (n = 81) of the cases. Of them, the most commonly observed was pulmonary sequestration (n = 58, 71%). This anomaly was more frequent in CCAM type 2 than in type 1 (40.4% vs. 31.5%, p = 0.001). Furthermore, there were more diverse and severe anomalies (great arteries transposition, esophagus atresia, bronchopulmonary foregut malformation, interventricular and interauricular septal defect with severe tricuspid regurgitation, and pulmonary hypertension) related to CCAM type 2 than to the other types (p = 0.008) (Table 2).

There were two cases of malignancies: one patient presented a pleuropulmonary blastoma (PPB) and the other had a bronchioloalveolar carcinoma (BAC) associated to CCAM type 1. There was also one case showing a cluster of intracystic mucinous proliferation associated to CCAM type 1. Two patients with rhabdomyomatous dysplasia were also observed. Both cases were found in CCAM type 2 (Table 1).

The patient with BAC was a newborn with compromise of all right lobes. This child had to be pneumonectomized due to severe respiratory distress. He died due to respiratory insufficiency after surgical resection. The patient with PPB received chemotherapy after surgery. She remains disease-free after 15 years without evidence of tumor recurrence. One of the patients with rhabdomyomatous dysplasia

Table 1 - Children's characteristics according to congenital cystic adenomatoid malformation types

Characteristic	CCAM types					p
	0 (n = 1)	1 (n = 121)	2 (n = 42)	3 (n = 1)	4 (n = 7)	
Age at onset (months)*	0.03	37.6 (11-91)	4 (1-17)	0.03	27.3 (7-40)	0.001
Male sex, n (%)	1 (100)	61 (50.4)	21 (50)	1 (100)	4 (57)	NS
Prenatal diagnosis, n (%)	1 (100)	14 (11.5)	23.8 (10)	0 (0)	0 (0)	NS
Clinic presentation, n (%)						
Recurrent pneumonia	0 (0)	83 (68)	13 (31)	0 (0)	0 (0)	0.001
Respiratory distress	1(100)	13 (10)	16 (38)	1(100)	2 (28.5)	0.001
Tachypnea	0 (0)	4 (3.3)	6 (14.2)	0 (0)	3 (42.8)	0.002
Pleural effusion	0 (0)	10 (8.2)	0 (0)	0 (0)	0 (0)	NS
Asymptomatic	0 (0)	11 (9)	5 (12)	0 (0)	2 (28.5)	NS
Surgery, n (%)						
Lobectomy-bilobectomy	0 (0)	120 (99)	42 (100)	1(100)	7 (100)	NS
Pneumonectomy	1 (100)	1 (0.8)	0 (0)	0 (0)	0 (0)	NS
Pathology, n (%)						
Chronic pulmonary infection	0 (0)	59 (49)	11 (26)	0 (0)	1 (14)	0.01
Bronchiectasis	0 (0)	15 (12.3)	3 (7)	0 (0)	0 (0)	NS
PPB	0 (0)	1 (0.8)	0	0 (0)	0 (0)	NS
BAC	0 (0)	1 (0.8)	0	0 (0)	0 (0)	NS
Mucinous proliferation	0 (0)	1 (0.8)	0	0 (0)	0 (0)	NS
Rhabdomyomatous dysplasia	0 (0)	0 (0)	2 (4.7)	0 (0)	0 (0)	NS
Mortality, n (%)	0 (0)	6 (5)	3 (7)	0 (0)	0 (0)	NS

Kruskal-Wallis rank test and Fisher's exact test were applied.
* Values are expressed in median and interquartile range.
BAC = bronchioloalveolar carcinoma; CCAM = congenital cystic adenomatoid malformation; n = number of individuals; NS = non-significant; PPB = pleuropulmonary blastoma.

Table 2 - Summary of anomalies according to congenital cystic adenomatoid malformation types

	CCAM types				
	0 (n = 1)	**1 (n = 121)**	**2 (n = 42)**	**3 (n = 1)**	**4 (n = 7)**
Congenital thoracic anomalies					
Sequestration, n (%)					
Intralobar	0 (0)	35 (30)	15 (38)	1 (100)	1 (14)
Extralobar	0 (0)	3 (2.5)	2 (4.7)	0 (0)	1 (14)
Pulmonary hypoplasia	0 (0)	3 (2.5)	1 (2.3)	0 (0)	0 (0)
Bronchogenic cyst	0 (0)	3 (2.5)	0 (0)	0 (0)	0 (0)
Congenital lobar emphysema	0 (0)	1 (0.8)	1 (2.3)	0 (0)	0 (0)
Esophageal atresia	0 (0)	0 (0)	1 (2.3)	0 (0)	0 (0)
Bronchopulmonary foregut malformation	0 (0)	0 (0)	1 (2.3)	0 (0)	0 (0)
Cardiovascular anomalies					
Severe*	0 (0)	1 (0.8)	3 (7.1)	0 (0)	0 (0)
Mild†	0 (0)	2 (1.6)	11 (9)	0 (0)	1 (14)
Other anomalies					
Diaphragmatic hernia	0 (0)	6 (5)	0 (0)	0 (0)	0 (0)
Diaphragmatic eventration	0 (0)	0 (0)	1 (2.3)	0 (0)	0 (0)
Congenital lung lymphangiectasia	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)
Pectus excavatum	1 (100)	7 (6)	4 (9.5)	0 (0)	0 (0)
Butterfly vertebra	0 (0)	0 (0)	1 (2.3)	0 (0)	0 (0)
Cervical lymphangioma	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)
Klippel-Feil syndrome	0 (0)	0 (0)	1 (2.3)	0 (0)	0 (0)
Ectopic kidney tissue	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)
Ectopic intestinal tissue	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)

Data are expressed in n (%)
* Severe cardiovascular malformation: great arteries transposition, scimitar syndrome, complex cardiovascular malformation with pulmonary hypertension.
† Mild cardiovascular malformation: interauricular septal defect, interventricular septal defect, tricuspid regurgitation, aortic coarctation, ductus, dextrocardia.
CCAM = congenital cystic adenomatoid malformation; n = number of individuals.

died after surgical procedure due to severe associated cardiovascular malformations. The patient with CCAM type 0 had to be pneumonectomized early in life and despite several complications, he survived and is still alive.

A lobar resection was performed in most patients (n = 170, 99%). Fifteen of these patients were bilobectomies. Two patients were pneumonectomized. Posterolateral thoracotomy approach was used in patients who were under surgery in the first 10 years of the study. Afterward, muscle-sparing thoracotomy and thoracoscopic lobe resection were performed.

Postoperative complications (n = 69, 40%) were pneumothorax (n = 29), atelectasis (n = 14), pleural effusion (n = 14), and wound infections (n = 5). They were all successfully managed by usual means. Eight children had severe complications: sepsis with acute respiratory distress (n = 5) and bronchopleural fistulae (n = 3). The rest of the patients (n = 103, 60%) recovered uneventfully and were doing well over the follow-up period.

Mortality in the postoperative period was 5.3% (n = 9). There was no significant difference of mortality comparing the first and the last 10 years of the study. Children who died were significantly younger than the rest of the population (median = 1.4 months [interquartile range 0.6-6.6] vs. 23 [8.8-77] respectively; p = 0.04). Two of them showed an extended pulmonary compromise and required pneumonectomy. All of them had had severe respiratory symptoms with mechanical assistance requirements. Independent risk factors for mortality in the acute stage were: respiratory failure (OR = 25.7 [95%CI 3.2-221], p = 0.03), sepsis (OR = 9.9 [95%CI 8.2-12], p = 0.002) respiratory assistance requirements (OR = 9.5 [95%CI 2.3-37], p = 0.04) and severe associated co-morbidities (OR = 3.3 [95%CI 1.2-22], p = 0.008).

Discussion

In this series we present 172 confirmed cases of CCAM in a pediatric population diagnosed in a hospital. Most of them showed signs and symptoms early in infancy. Almost half of the population was under 2 years of age at screening. Patients with CCAM type 1 (large cyst type) were diagnosed significantly later than the other cases.

A major issue in a developed world setting is what to do when a congenital thoracic malformation is diagnosed antenatally. However, the experience in a developing country, such as ours, is different.[5] Only 14% of the sample had been prenatally diagnosed. It is worth mentioning that the studied population belonged to a low or very low socioeconomic status and the accessibility to ultrasonography screening was limited. Furthermore, this study encompasses 20 years of experience and the diagnostic screening in the first years of the review was not routinely performed.

Children who do not undergo CCAM resection earlier in life are at risk of recurrent pulmonary infections. In our experience the majority of cases were diagnosed following recurrent pneumonia in a localized area. Respiratory distress was frequently observed in the newborn period. In older children CCAM could be diagnosed as an incidental finding.[7]

All histopathological types were found in our series, CCAM type 1 (large cyst type) being the most frequently described, in accordance with published data.[4]

An interesting finding was the mixed pattern observed in nine cases of CCAM. It is evident that there are difficulties in classifying specimens of mixed types of CCAM, probably due to the fact that many of these types are not individually different from one another. It is possible that the level, completeness and timing of airway obstruction may act together to produce varied patterns of malformations.[3] This particular histopathological observation has been previously reported by one of the authors of our study.[8]

In our series, right localization predominated and single lobe disease was observed more often than multilobar disease. It has been postulated that outcome in the unilateral cases tends to be worse when lesions are on the left.[9] This finding, although suggested in the past, was not supported by our results. All patients who had poor evolution had right compromise. The magnitude of the lesion was also a factor of bad outcome, since all patients with at least three compromised lobes died immediately after surgical resection. Similar findings in fetuses have been previously reported.[10]

There is scarce data available about anomalies associated with CCAM.[11-13] The coexistence of different lesions suggests that a common pathogenetic mechanism may be involved in the development of at least some of these seemingly different lesions.[3] In our series we observed malformations in almost half of the population. More diverse and severe pathologies were related to CCAM type 2 (Table 2).

Some workers incorporate sequestration into the CCAM spectrum.[14] The fact that some sequestrations may contain tissue identical to CCAM emphasize the logic of combining but not separating these two conditions.[15] In some series of CCAM a large proportion, at least 25%, has an associated systemic arterial supply.[16] In our population 34% of the patients had this finding. We also observed that it was mainly related to CCAM type 2, in agreement with previous publications reporting that at least 50% of the cases of sequestration were observed in a small cyst CCAM.[17]

There was one case of PPB associated with macrocystic CCAM. This patient, diagnosed at age of 1, received chemotherapy after surgery and was followed for 15 years without evidence of tumor recurrence. The relationship between CCAM and PPB remains controversial. The earliest manifestation of PPB is a malignant lung cyst in young children, clinically and radiographically indistinguishable from benign congenital lung cysts.[18] Type 4 CCAM are histologically similar to grade 1 PPB, and in the absence of clear-cut sarcomatous differentiation there are few guidelines to distinguish them.[19] Therefore, presence of type 4 CCAM morphology should prompt a thorough search of the cyst wall for evidence of stromal cellularity, with its identification raising concerns regarding malignant transformation or reclassification as a grade 1 PPB.[20]

This evidence justifies resection of all CCAM.[20,21]

There was also one case of BAC, associated with CCAM type 1. This child with BAC died early after birth in the post-surgical period due to respiratory insufficiency, unrelated to the malignant tumor. BAC has been seen both in older children and adults in association with previously unrecognized or unresected large-cyst-type adenomatoid malformations. This relationship is presumed to be related to neoplastic change in the mucigenous epithelium, although it may also be more rarely seen in the small cyst type.[22,23] There were two patients with rhabdomyomatous dysplasia. One died due to severe cardiovascular malformations and the other is still alive. Two main hypotheses regarding the origin of rhabdomyosarcoma arising with CCAM have been suggested. It is possible that it occurs from well-differentiated but poorly organized skeletal muscle fibers present in some subtype of CCAM or by rhabdomyoblastic differentiation of the cambium layer.[23,24]

Lobectomy was the procedure of choice in our series. Few patients required bilobectomy and there were only two cases of pneumonectomy. Most surgeons agree that lobectomy is the best surgical procedure because it is impossible to determine the limit between CCAM and normal parenchyma by direct observation. Some authors have advocated segmental resection for CCAM, but this often results in incomplete resection, persistent bullae and the need for further lobectomy.[25]

Since CCAM poses significant risks of superinfection or malignant transformation, some authors propose surgical resection even in asymptomatic patients. Furthermore, the malignant potential of CCAM in later life has long been recognized.[25-27] Observation may be an option, but patients should be aware of the possibility of adverse course.

Resection should be undertaken if symptoms develop, or if a solid component is found in a previously purely cystic lesion.

At present, there is evidence indicating that some radiological images of the newborn lung simulating CCAM may disappear spontaneously after 1 or 2 years of follow-up.[18] If the regression in size of the CCAM observed during the third trimester of gestation continues postnatally, the patient should be controlled and studies repeated in case of symptom development. While ultrasonography screening may become completely normal before birth, adequate postnatal imaging is required to confirm complete cystic regression.[7]

The mortality observed in our population was lower than that previously reported.[5] Mortality was directly correlated to severe complications in the post-surgical period. Patients who died were significantly younger than the rest of the population and had serious associated malformations. Lesion size has also been proposed as an important predictor of survival.[28] A large lesion may be associated with pulmonary hypoplasia, which can cause respiratory distress after surgery. In our experience half of the patients who showed worse course had more than one lobe compromised.

CCAM is the most common pediatric pulmonary malformation. Our intention was to describe the findings and management in a large group of patients with this pathology. Observation of histological mixed pattern was described, as well as a detailed account of malformations observed in different CCAM types. Malignancy and premalignant lesions were also present in this series.

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